

Industrial Pharmacy I

for Fifth Semester Bachelor of Pharmacy

As per the latest syllabus prescribed by
Pharmacy Council of India for Bachelor of Pharmacy Course



Gaurav Agarwal
Atul Kaushik

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to

My Grandfather Sh. Rajendra Kumar Gupta
and Grandmother Smt. Premwati



—Gaurav Agarwal

Preface

This book *Formulative Pharmacy* is designed specifically as per PCI (Pharmacy Council of India) B.Pharmacy fifth semester students. This book covers wide areas and contains a comprehensive description of existing knowledge of pharmaceutics. The book is a thoughtful compilation backbone of pharmaceutics. The text not only deals with the basic concepts but also emphasizes technical and practical aspects of the subject. The book is primarily intended as textbook for students of pharmacy for degree and diploma courses. Being an interdisciplinary subject, it is today covering a wide-range of interest both among the students and teaching communities. Taking this increasing interest into account, this book gives a comprehensives introduction to the subject.

The book contains numerous specimens, vivid illustrations, tables, diagrams and flow diagrams to present the ideas. The distinguishing feature is ample question bank at the end of the book. The structure and the content of the book have changed to reflect modern thinking and current university curricula throughout the world. The distinguishing feature is practical related to subject at the end of the book. In spite of great care there might be some mistakes and deficiencies. I will be grateful for giving suggestions to improve. So go through the content and mail to me at *gbitsian@rediffmail.com*

Gaurav Agarwal

Atul Kaushik

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I express my gratitude to my Father Er.VK Agarwal and my Mother Asha Agarwal for there all time blessings and moral support.

Last but not the least, I express my love to my wife Shilpi for her all time inspiration, and dedication. She is always a constant source to motivation in bring out this achievement!

To my numerous students, whom I cannot possibly name individually, I thanks for their class interactions which have been the guiding spirit in selection of the subject matter and its logical arrangement.

Gaurav Agarwal

I would like to acknowledge the large heartedness of my family and colleagues. My family was supportive from the beginning and encouraged me to write this book. I would like to appreciate the critical eyes and viewpoints of my friends Pallavi, Shilpa, Raju and Praveen who read the drafts and kept me on the correct path. I thank Dr Ravindra Tiwari, who spent a good deal of time in writing the text for the chapters. I would also like to thank Dr Amit Antarkar and Dr Rakesh Kumar Bhasin, who have always been inspirational to me.

This book is dedicated to all the students to whom I have taught in IFTM, Moradabad and ITS, Ghaziabad. I hope the students of pharmaceutics will appreciate this book.

At last I would like to thank the Almighty.

Atul Kaushik

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Chapter
1

Preformulation

DEFINITION

Preformulation (pre + formulation, i.e. prior to formulation) as the name depicts before initiating formulation development, preformulation is the step to understand physiochemical properties (physical and chemical properties) of drug substance. Preformulation studies help the formulation scientist to develop in-depth understanding about physiochemical parameters of drug substance, which leads to design optimum drug delivery system without significant barriers during development. In other words, preformulation studies describes as the process of optimizing the delivery of drug through determination of physiochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form.

"It is defined as phase of research and development in which preformulation scientist characterize physical and chemical properties of new drug molecule in order to develop safe, effective and stable dosage form."

Before beginning the formal preformulation programs the preformulation scientist must consider the following factors:

i. The amount of drug available.
ii. The physicochemical properties of the drug already known.
iii. Therapeutic category and anticipated dose of compound.

Objectives of Preformulation Studies

The primary objectives of preformulation studies are as follows:

i. Establish the identity and physiochemical parameters of a new drug substance.
ii. Establish chemical stability profile of drug substance.
iii. Bulk characterization
iv. Establish drug substance compatibility with common excipients
v. To establish relation between physiochemical properties of drug substance and formulation stability. Preformulation studies give preliminary idea about selection of excipients, which makes the formulation stable.
vi. Establish relation between physiochemical properties of drug substance and bioavailability. Preformulation studies give preliminary idea about selection of excipients, selection of particle size and morph of drug substance, which can affect bioavailability of drug.

vii. Preformulation studies give preliminary idea about selection of manufacturing process. For example, if drug substance has fine particle size than it is advisable to use granulation process instead of direct compression because there is possibility of blend non-uniformity, if direct compression method is used.

PHYSICAL PROPERTIES

Crystallinity and Polymorphism

Crystal habit and internal structure of a drug can affect bulk and physiochemical properties which ranged from flowability to chemical stability.

A single compound can have several different crystal habits depending upon the environment for growing crystals. Changes with internal structure usually alter the crystal habit, for example, conversion of a sodium salt to its free acid form produce both a change in internal structure and crystal habit (Table 1.1 and Fig. 1.1).

Polymorphism

When a substance exists in more than one crystalline form, the different forms are designated as polymorphs and the phenomenon as polymorphism. Polymorphism also influences biopharmaceutical behavior of drug. A pure more soluble B form of chloramphenicol palmitate is more bioavailable after oral administration as compared to less soluble pure A form and their mixture.

Amorphous (from the Greek, A: without, morphé: shape, form) solid is any non-crystalline solid in which the atoms and molecules are not organized in a definite lattice pattern. Amorphous forms are typically prepared by rapid precipitation, lyophilization or rapid cooling of liquid melts. Since amorphous forms are usually of higher thermodynamic energy than corresponding crystalline forms, solubility as well as dissolution rates are generally greater. Polymorphisms are of two types:

1. **Enantiotropic:** It is the one which can be reversibly change into another form by altering the temperature or pressure, e.g. sulphur.
2. **Monotropic:** It is the one in which transition from one morph to another form is irreversible.

Depending upon their relative stability, one of the several polymorphic forms will be physically more stable than others. Stable morph represents lowest energy state, has highest melting point and least aqueous solubility. The remaining polymorphs

TABLE 1.1: Various types of crystal system

Sr. No.	*Crystal system*	*Angle of axis*	*Length of axis*	*Example*
1	Cubic (regular system)	$\alpha = \beta = \gamma = 90°$	$a = b = c$	NaCl
2	Tetragonal	$\alpha = \beta = \gamma = 90°$	$a = b \neq c$	Nickel sulfide
3	Orthorhombic	$\alpha = \beta = \gamma = 90°$	$a \neq b \neq c$	$KMnO_4$
4	Monoclonic	$\alpha = \gamma = 90°$ and $\beta \neq 90°$	$a \neq b \neq c$	Sucrose
5	Triclinic (asymmetric)	$\alpha \neq \beta \neq \gamma \neq 90°$	$a \neq b \neq c$	$CuSO_4$
6	Trigonal (rhombohedral)	$\alpha = \beta = \gamma \neq 90°$	$a = b = c$	Sodium nitrate
7	Hexagonal	$\alpha = \beta = 90°$ and $\gamma = 120°$	$a = b \neq c$	$AgNO_3$

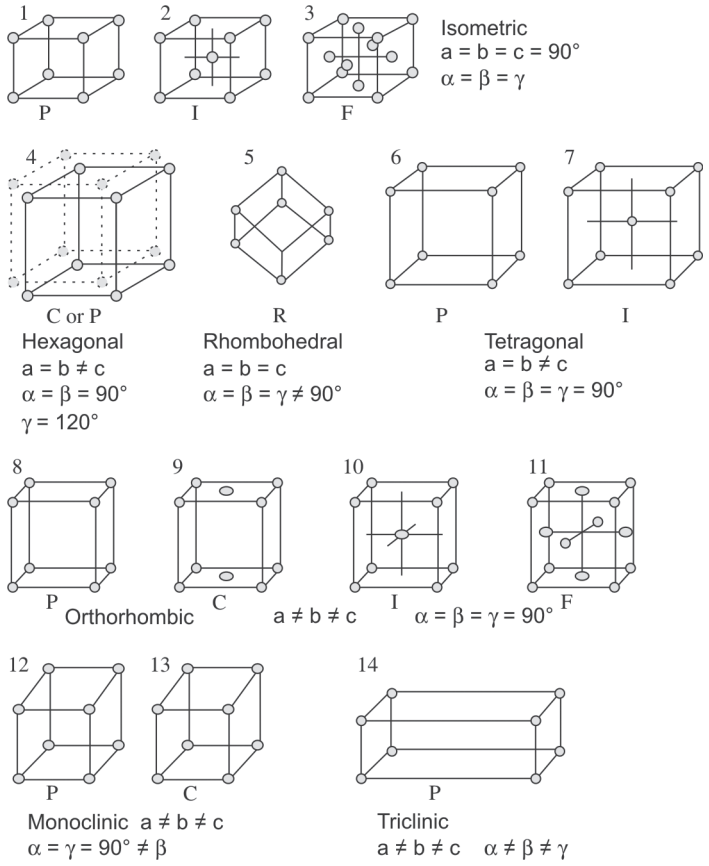


Fig. 1.1: Different types of crystal systems

are called metastable forms, which represent the higher energy state, have low melting point and high aqueous solubility. Because of their higher energy state, the metastable forms have a thermodynamic tendency to convert to the stable form.

Order of dissolution: Amorphous > Metastable > Stable

Detection: Morph compound can be detected by following techniques

- Optical crystallography
- X-ray diffractions
- Differential scanning calorimetry

Pseudopolymorphism

A crystalline compound may contain either a stoichiometric or non-stoichiometric amount of crystallization solvent.

Non-stoichiometric adducts such as inclusion or catharses, involve entrapped solvent molecules within the crystal lattice. Usually this adduct is undesirable, owing to its lack of reproducibility and should be avoided for development.

Stoichiometric adducts, commonly referred as solvates is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal

lattice. The solvate can exist in different crystalline form called pseudopolymorph and phenomenon called pseudopolymorphism.

When the incorporated solvent is water, the complex is called a hydrate and the term hemihydrate, monohydrate and dihydrate describes various hydrate forms. A compound not containing any water is called anhydrous compound. Generally the anhydrous form of a drug has a greater aqueous solubility than the hydrates. This is because the hydrates are already in interaction with water and, therefore, has less energy for crystal break-up in comparison to anhydrates (thermodynamically higher energy state) for further interaction of water, e.g. ampicillin and theophylline anhydrous form have more aqueous solubility. Pseudopolymorphs should be identified since most polymorphs can be obtained by changing the recrystallizing solvent. Solvents inducing polymorphic changes are water, methanol, ethanol, acetone, chloroform, n-propanolol, isopropyl alcohol, n-butanol, n-pentanol, benzene and toluene.

These hydrates water and solvates (e.g. methanolate, ethanolate) have been confused with the true polymorphism. The distinction between these false forms and true polymorphs can be obtained by observing the melting behaviour of the compound dispersed in silicon oil using hot stage microscopy. Pseudopolymorphs will evolve a gas (steam or solvent vapour) causing bubbling of the oil while, true polymorphs merely melt. The temperature at which the solvent volatilizes will be close to the boiling point of the solvent and can be used for identification.

PARTICLE SIZE DISTRIBUTION

Bulk flow, formulation homogeneity, and surface-area controlled processes such as dissolution and chemical reactivity are directly affected by size, shape and surface morphology of the drug particles. In general, each new drug candidate should be tested for particle size distribution during preformulation.

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also in some instances, on their biopharmaceutical behavior. It is generally recognized that poorly soluble drugs showing a dissolution-rate limiting step in the absorption process will be more readily bioavailable, when administered in a finely subdivided state rather than as a coarse material. Gibbs Kelvin has explained the relationship between particle size and solubility.

Gibbs Kelvin relation: It is relationship between particle size and apparent solubility of a drug.

$$\log \frac{S_r}{S_\alpha} = \frac{2\gamma_{SL} M}{2.303\ RT\ \rho r}$$

Where, S_r = apparent solubility of a drug
S_α = true equilibrium solubility
γ_{SL} = interfacial energy that exists between solid and liquid
r = radius of particle
M = molecular weight
R = gas constant
T = absolute temperature
ρ = density of the solid

In case of tablets, particle size distribution influences the flow and the mixing efficiency of powders and granules. Particle size distribution can also be a factor in stability; fine materials are relatively more open to attack from atmospheric oxygen, humidity, and interacting excipients.

Methods of Particle Size Determination

1. Simple method—microscopy with help of light microscope and sieving. Sieving method needs comparatively large sample of bulk material, thus this method is less useful at preformulation stage due to lack of bulk material (Table 1.2).
2. Instrument based on light scattering—ROYCO.
3. Instrument based on light blockage—HIAC.
4. Instrument based on blockage of electrical conductivity path—Coulter counter.
5. Based on rate difference of sedimentation of different particle—Anderson pipette method.

POWDER FLOW PROPERTIES

Assessment of flow properties of a drug powder is important to the formulator. When limited amount of drug are available then can be evaluated simply by measurement of:

a. Bulk density; and
b. Angle of repose.

Bulk Density

Bulk density of the drug substance is very useful in having some idea as to the size of final dosage form. Carr's compressibility index and Hausner Index can be used to predict the flow property based on density measurement (Tables 1.3 and 1.4).

TABLE 1.2: Common techniques for measurement of particle size

S. No.	*Technique*	*Particle size (um)*
1	Microscopic	1–100
2	Sieve	>50
3	Sedimentation	>1
4	Permeability	>1
5	Centrifugal	<50
6	Light scattering	0.5–50

TABLE 1.3: Grading of the powder for their flow properties, according to Carr's index

Consolidation index (Carr index in %)	*Flow*
5–15	Excellent
12–16	Good
18–21	Fair to passable
23–35	Poor
33–38	Very poor
>40	Very very poor

TABLE 1.4: Compressibility and flow ability of pharmaceutical excipients

Material	*% compressibility*	*Flow*
Celutab	11	Excellent
Emcompress (DCP)	15	Excellent
Starch-1500	19	Fair passable
Lactose monohydrate	19	Fair passable
Maize starch	26–27	Poor
Dicalcium phosphate dihydrate (coarse)	27	Poor
Magnesium sterate	31	Poor
Titanium dioxide	34	Very poor
Dicalcium phosphate dihydrate (fine)	41	Very poor

Carr's index (%) or consolidation index

$$= \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner index} = \frac{\text{Tapped density}}{\text{Poured density}}$$

Fluff (poured) density is the ratio of mass of powder to the fluff volume. Fluff volume is the volume occupied by a certain mass, when gently poured into a measuring cylinder.

Tapped density is the ratio of mass of powder to the tapped volume. Tapped volume is the volume occupied by the same mass of powder after a standard tapping of a measure.

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane (Fig. 1.2).

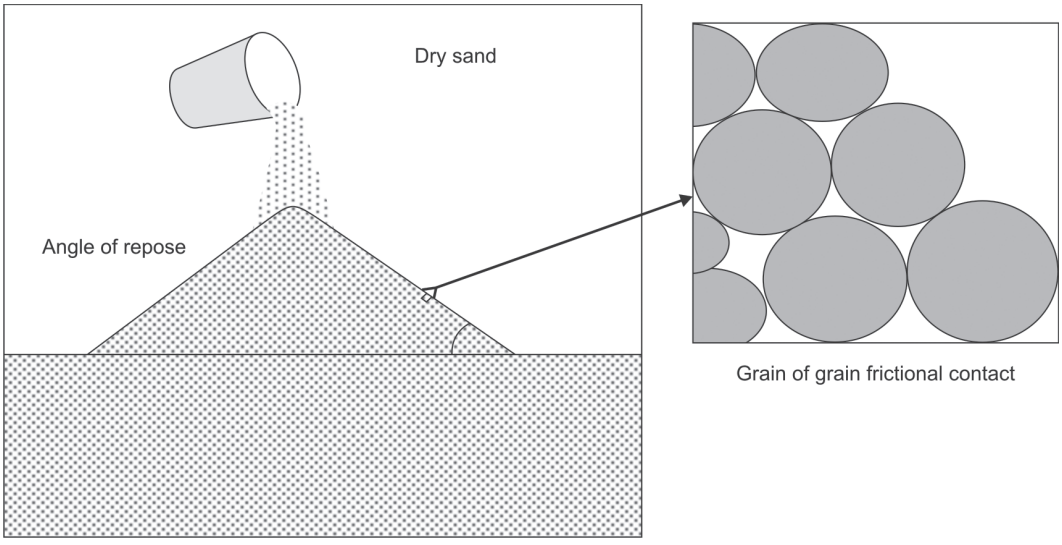


Fig. 1.2: Angle of repose of dry sand

$$\tan \theta = \frac{h}{r}$$

$$\theta = \tan^{-1} \frac{h}{r}$$

where, θ = angle of repose, h = height of pile, and r = radius of the base of pile.

The lower the angle of repose, the better the flow property. Certain observations are made (Tables 1.5 and 1.6)

i. Decrease in particle size leads to a higher angle of repose.
ii. Lubricant at low concentration decreases the angle of repose. At high concentration, this enhances the angle of repose.
iii. Fines (passed through 100 meshes) increase the angle of repose.

SOLUBILITY

Solid drugs administered orally for systemic activity must dissolve in the gastrointestinal fluids prior to their absorption. Thus the solubility and rate of dissolution of drugs in GIT fluids could influence the rate and extent of their absorptions (Fig. 1.3).

A compound having good aqueous solubility over the pH range 1–7 at 37°C does not usually exhibit bioabsorption problem.

Analytical methods useful for solubility measurements include HPLC, UV spectroscopy, fluorescence spectroscopy and gas chromatography. For most drugs, reverse phase HPLC offers an efficient and accurate means of collecting solubility data. Its major advantages are direct analysis of aqueous samples, high sensitivity and specific

TABLE 1.5: Relationship between angle of repose (θ) and powder flow

Angle of repose (θ degrees)	*Flow*
<25	Excellent
25–30	Good
30–40	Passable
>40	Very poor

TABLE 1.6: Angle of repose of some pharmaceutical excipients

Substance	*Angle of repose (θ°)*
Calcium state NF	10
Dextrose	25
Lactose USP (granular grade)	15
Lactose (spray dried) USP	20
Magnesium oxide	20
Microcrystalline cellulose USP (granular grade)	15
Starch NF	15
Stearic acid NF	15
Talc USP	15
Sodium bicarbonate USP	20

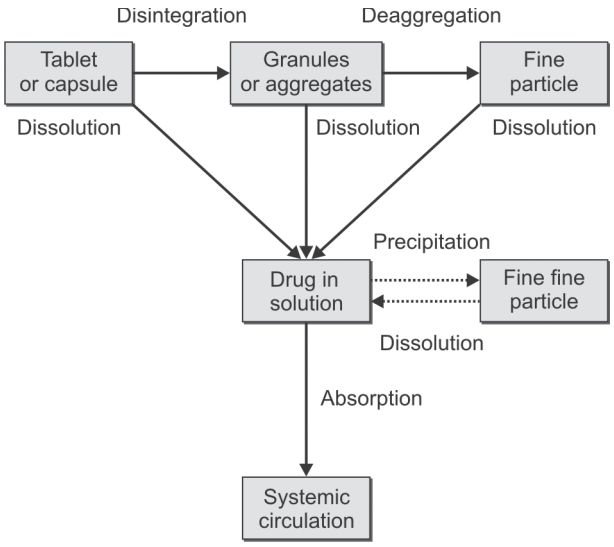


Fig. 1.3: Solubility or dissolution as critical step during absorption

determination of drug concentration due to chromatographic separation of drug from impurities or degradation products.

Intrinsic Solubility (C_0)

An increase in solubility of a new drug in an acidic solution compared with its aqueous solubility suggests that drug is a weak base. However, weak acidic drug has good solubility in alkali solution. An increase in both acidic and alkaline solubility suggests either amphoteric or zwitterion behaviour; in this case there will be two pKa, one acidic and one basic. No change in solubility shows non-ionizable behaviour of molecule with no measurable pKa. Here, solubility cannot be changed with change in pH of the solution.

Intrinsic solubility (true solubility) C_0 is the solubility due to unionized form of drug. When the purity of drug sample can be assured, then the solubility value obtained in acid for a weak acid or alkali for a weak base can be assumed intrinsic solubility.

The solubility should ideally be measured at two temperatures:

a. 4 or 5°C to ensure good physical stability.

b. 37°C to support biopharmaceutical evaluation.

pH

The degree of ionization and therefore the solubility of acidic and basic compound depend upon the pH of the media. The saturation solubility for such compounds at a particular pH is sum total of solubility of ionized and unionized forms.

$$S_t = [BH^+] + [B]$$

BH^+ is protonated species (salt species), B is free base, S_t = total molar solubility.

The pH at which both base and salt species are simultaneously saturated is defined as the pH_{max}

$$S_t, pH = pH_{max} = [BH^+]_S + [B]_S$$

Where the subscript (s) denotes saturation.

For weak bases in the pH region, where the solubility of protonated form is limiting the molar solubility is

$$S_t,\ pH < pH_{max} = [BH^+]_S + [B]$$

Similarly, the solubility in pH region where free base is limiting is expressed as:

$$S_t,\ pH > pH_{max} = [BH^+] + [B]_S$$

Corresponding equation for acidic compound:

$$S_t\ pH < pH_{max} = [AH]_S + A^-$$

$$S_t\ pH > pH_{max} = [A^-]_{S+}[AH]$$

Since ionizable compounds may be available in free or salt form, one could use either in solubility experiments, e.g. phenazopyridine is available in free base and hydrochloride salt. The solubility behaviour of phenazopyridine free base over pH range 1 to 10 shows that phenazopyridine, with pKa of 5.2, exhibits maximum solubility at pH 3.45 (pH_{max}). If pH of the phenazopyridine solution changed from pH 3.5, solution will become supersaturated and drug will precipitate.

pKa DETERMINATION (DISSOCIATION CONSTANT)

The amount of drug that exists in unionized form is related to dissociation constant (pKa) of drug and pH of the fluid at the absorption site. The dissociation constants of both acidic and basic drugs are expressed by pKa values. Lower the pKa of an acidic drug represents strong acid while, higher the pKa of basic drug represents strong base. Thus, from the knowledge of pKa of the drug and pH at the absorption site (or biological fluid), the relative amount of ionized and unionized drug in solution at a particular pH and the percent of drug ionized at this pH can be determined by **Henderson–Hasselbalch equation**

For weak acid:

$$pH = pKa + \log \frac{\text{Ionized drug concentration}}{\text{Unionized drug concentration}}$$

$$\% \text{ drug ionized} = \frac{10^{pH-PKa}}{1+10^{pH-PKa}} \times 100$$

For weak base:

$$pH = pK_a + \log \frac{\text{Unionized drug concentration}}{\text{Ionized drug concentration}}$$

$$\% \text{ drug ionized} = \frac{10^{PKa-pH}}{1+10^{PKa-pH}} \times 100$$

Above equations can be used

i. To determine the pKa: pKa is that pH at with ionized and unionized drug concentration is same. Buffer, temperature, ionic strength and co-solvent affect the pKa value and should be controlled during pKa determinations.
ii. To determine solubility at any pH provided that the intrinsic solubility (C_0) and pK_a are known.
iii. To determine percentage ionization.

PARTITION COEFFICIENT

Partition coefficient (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

$$P_{o/w} = (C_{oil}/C_{water})_{equilibrium}$$

For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of *in vivo* absorption, it does provide a means of characterizing the lipophilic/hydrophilic nature of the drug.

Since, biological membranes are lipoidal in nature, the rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule. The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water. Drugs having values of P much greater than 1 are classified as lipophilic, whereas those with partition coefficients much less than 1 are indicative of a hydrophilic drug. Although, it appears that the partition coefficient may be the best predictor of absorption rate, the effect of dissolution rate, pKa, and solubility on absorption must not be neglected.

Applications of Partition Coefficient

Partition coefficient (solvent water quotient of drug distribution) has a number of applications which are relevant to preformulation.

i. Solubility both in aqueous and in mixed solvent.
ii. Drug absorption *in vivo.*
iii. Partition chromatographic (like HPLC and TLC) analytical method development.
iv. Extraction of crude drugs.
v. Recovery of antibiotics from fermentation broth.

Dissolution

The dissolution rate of the drug is only important where it is rate limiting step in the absorption process.

An equation which describes the process of drug dissolution is the Noyes–Whitney equation.

$$\frac{dC}{dt} = KS(C_s - C_t)$$

where $\frac{dC}{dt}$ = rate of dissolution,

K = dissolution rate constant,

S = surface area of the dissolved solid,

C_t = concentration at time 't', and

C_s = saturation solubility.

The constant 'K' has been shown to be equal to D/h, where D is the diffusion coefficient of the dissolving solid and 'h' is the thickness of the diffusion layer (Fig. 1.4). The diffusion layer is a thin stationary film of solution adjacent to the surface of the solid. The layer is saturated with drug. Thus, the drug concentration in the layer is equal to C_s. The term C_s–C_t represents the concentration gradient between the diffusion layer and the bulk solution. In dissolution rate limited absorption C_t is negligible, then equation becomes:

$$\frac{dC}{dt} = \frac{DSC_s}{h}$$

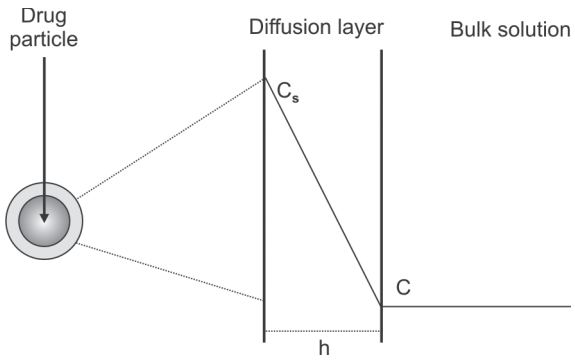


Fig. 1.4: Dissolution of drug particle according to Noyes–Whitney equation

CHEMICAL PROPERTIES

Chemical instability normally results from either of the following reaction:

i. Hydrolysis
ii. Oxidation
iii. Photolysis
iv. Racemization
v. Polymerization

Hydrolysis

The most likely cause of drug instability is hydrolysis, partially in solid dosage form. Hydrolysis may be defined as the reaction of a compound with water. It is of two type ionic and molecular form of hydrolysis.

***Ionic hydrolysis*:** It occurs with salt of weak acids, e.g. potassium acetate and bases of codeine phosphate interact with water to give alkaline and acidic solution respectively.

***Molecular hydrolysis*:** Slower irreversible process involving cleavage of the drug molecule. This form of hydrolysis is mainly responsible for the decomposition of pharmaceutical products ester, e.g. the local anesthetic amethocaine and benzocaine and amines.

It involves nucleophilic attack of labile groups, e.g. Lactam > Ester > Amide > Imide. When this attack is by a solvent other than water then it is known as **solvolysis.** It generally follows second order kinetics as there are two reacting species, water and API. In aqueous solution, water is in excess, the reaction is first order. A number of conditions catalyzes the breakdown.

i. Presence of OH^- ion
ii. Presence of H_3O^+ ion
iii. Presence of divalent metal ion is quicker than molecular ion
iv. Ionic hydrolysis (protolysis)
v. Heat
vi. Light
vii. Solution polarity and ionic strength
viii. High drug concentration

Prevention of Hydrolysis

1. **pH adjustment:** Most of the potent drugs are weakly acidic or weakly basic,which are more soluble when ionized so their instability will increase.

Remedy: The hydrolysis can be prevented by

i. Formulating the drug solution close to its pH of optimum stability.
ii. Addition of water miscible solvent in formulation.
iii. Optimum buffer concentration to suppress ionization.

2. **Addition of surfactant:** Nonionic, cationic and anionic surfactant stabilizes the drug against base catalysis.
3. **Salts and esters:** The solubility of pharmaceuticals undergoing ester hydrolysis can be reduced by forming less soluble salts or ester of drug, e.g. phosphate ester of clindamycin.
4. **Store with desiccants.**
5. **By use ofcomplexing agent.**

Oxidation

It is a very common pathway for drug degradation in liquid and solid formulation. Oxidation occurs in two ways:

1. Auto-oxidation.
2. Free radical chain process.

Auto-oxidation

It is defined as a reaction of any material with molecular oxygen which produces free radicals. These radicals are highly unsaturated and readily take electron from other substance causing oxidation. For auto-oxidation to occur in solid molecular oxygen must be able to diffuse through the crystal llattice to liable sites. Hence crystal morphology and packing are important parameters for determining oxidation kinetics.

Free Radical Chain Process

a. Initiation

$$\text{Activation RH X} \xrightarrow{\text{Light, Heat}} R^{\cdot} + H^{\cdot}$$

b. Propagation

$$R^{\cdot} + O_2 \longrightarrow RO_2^{\cdot}$$

$$RO_2^{\cdot} + RH \longrightarrow ROOH + R^{\cdot}$$

c. Decomposition

$$ROOH \longrightarrow RO^{\cdot} + OH^{\cdot}$$

d. Termination

$$RO_2^{\cdot} + X^{\cdot} \longrightarrow \text{Inactive product}$$

$$RO_2^{\cdot} + RO_2^{\cdot} \longrightarrow \text{Inactive product}$$

Functional groups prone to oxidation are:

i. Alkenes
ii. Substituted aromatic groups (toluene, phenols, anisole)
iii. Ethers
iv. Thioethers
v. Amines.

Factors affecting oxidation process

i. Oxygen concentration
ii. Light
iii. Heavy metals particularly those having two or more valence state, (e.g. copper, iron, nickel, cobalt)
iv. Hydrogen and hydroxyl ion
v. Temperature.

Prevention of oxidation

1. Reducing oxygen content: Oxidative degradation of drug takes place in an aqueous solution, so the oxygen content can be decreased by boiling water.
2. Storage in a dark and cool condition.
3. Addition of an antioxidant: They act by acting as reducing agent and chain inhibitors of radical induced decomposition (Table 1.7).
4. Addition of chelating agent: It forms complexes with trace amount of heavy metal ion and inactivate their catalyzing activity, e.g. EDTA, citric acid, tartaric acid.
5. Adjustment of pH: To optimum stability in order to reduce oxidation potential of the system.
6. Changing solvent: Solvent other than water may have catalyzing effect on oxidation reaction when used in combination with water or alone, e.g. aldehydes, ethers, ketones may influence free radical reaction.

Photolysis

Photolysis catalyze oxidation and to some extent hydrolysis. This energy associated with the radiation increases as its wavelength decreases, so that the energy of UV > visible > IR and is independent of temperature (Table 1.8).

TABLE 1.7: List of antioxidants along with their examples

Antioxidant	
Oil soluble	*Water soluble*
Free radical acceptor and inhibit free radical chain	Oxidized itself and prevent Oxidation of drug
Examples	
Hydroquinone	Sodium meta bisulphate
Propyl gallate	Sodium bisulphite
Butylated hydroxy anisole (BHA)	Acetyl cysteine, ascorbic acid
Butylated hydroxy toluene (BHT)	Sodium thiosulfate, sulphur dioxide
Lecithin	Thioglycolic acid
α-tocopherol	Thioglycerol

TABLE 1.8: Energy associated with different radiations

Types of radiation	*Wavelength*	*Energy (Kcal mol^{-1})*
UV	50–400	287–72
Visible	400–750	72–36
IR	750–10,000	36–1

When molecules are exposed to electromagnetic radiations they absorb light (photons) at characteristic wavelengths which causes an increase in the energy state of the compound. This energy can:

i. Cause decomposition
ii. Be retained or transferred
iii. Converted to heat
iv. Result in emission of light at a new wavelength (fluorescence, phosphorescence)
v. Natural sunlight lies in the wavelength range 290–780 nm of which only the higher energy (UV) (290–320 nm) cause photo degradation of drugs.

These photolysis can be prevented by suitable packing, i.e. using amber coloured glass bottles, card board outers and aluminium foil overwraps and blisters.

Racemization

The inter conversion from one isomer to another can lead to different pharmacokinetic properties (ADME) as well as different pharmacological and toxicological effect, e.g. L-epinephrineis 15 to 20 times more active than D-form, while activity of racemic mixture is just one half of the L-form. It follows first order kinetics. It depends on temperature, solvent, catalyst and presence or absence of light.

Polymerization

It is a continuous reaction between molecules. More than one monomer reacts to form a polymer For examples:

- Darkening of glucose solution is attributed to polymerization of breakdown product [5-(hydroxyl methyl) furfural].
- Polymerization of HCHO to para-HCHO which crystallizes out from the solution.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

BCS as a tool is used in drug product development. BCS classifies API in one of four categories depending on its solubility and permeability as they pertain to oral dosing. The drugs are classified in BCS on the basis of following parameters:

1. Solubility
2. Permeability
3. Dissolution

1. **Solubility:** It is based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 6.8. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.
2. **Permeability:** It is based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. A drug substance is considered highly permeable when the extent of absorption in humans is determined to be 85% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose.

3. **Dissolution:** An immediate release product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 15 minutes using USP Dissolution apparatus 1 at 100 RPM or Apparatus 2 at 50 RPM in a volume of 900 mL or less in the following media: 0.1 N Hydrochloric acid simulated gastric fluid, pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid. According to the biopharmaceutics classification system, drug substances (Fig. 1.5) are classified as follows:

Class I. High permeability, high solubility: Example is metoprolol. These drugs are well absorbed and their absorption rate is usually higher.

Class II. High permeability, low solubility: Example is glibenclamide, bicalutamide, The bioavailability of those products is limited by their solubilization rate, i.e. solubility is less.

Class III. Low permeability, high solubility: Example is cimetidine. The absorption is limited by the permeation rate but the drug is solubilize very fast.

Class IV. Low permeability, low solubility: Example is hydrochlorothiazide. Those compounds have a poor bioavailability. Generally they are not well absorbed and have low solubility.

STABILITY STUDIES

The stability studies are done to determine shelf-life of the product, excipient-API compatibility and API vulnerability to degrade by oxidation, hydrolysis, isomerisation, polymerization, decarboxylation, moisture, heat and light. Properly conducted stability studies must also include an examination of specific decomposition products by appropriate techniques to establish identity and relative toxicity of the decomposition products and the concentrations in which they are formed. Stability studies should not only take the account of the physical state in which the compound is likely to be used, but also the immediate biological environment likely to be met on administration. The substance for tablet, encapsulation and preparation of suspension, should be examined primarily in solid state. Substances for injection, which must be subjected to some form of sterilization procedure, must be examined particularly for

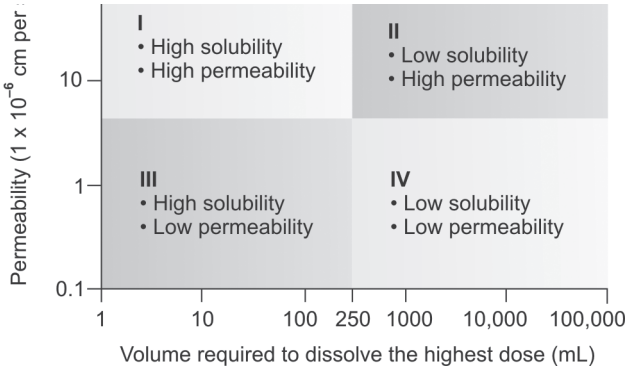


Fig. 1.5: Biopharmaceutical classification system; classes I, II, III and IV

stability at elevated temperature for possible hydrolysis or rearrangement in aqueous media and effects of exposure to CO_2 and light. Similarly, all substances intended for oral administration must be chemically stable to the pH and enzymatic conditions likely to be met in the gastrointestinal tract.

Hence, stability studies must be conducted on the drug substance in the solid state over a range of temperature, at varying degrees of humidity, and in both light and dark. Also, if a product is to be used in multiple dose form in the tropics with fluctuation in temperature, which should be stored ideally in cool or refrigerated conditions, then the stability tests should include a study of the effects of fluctuating temperature. Stability studies are an integral part of the drug development program and are of the most important area in the registration of pharma products. Stability assessment started with studies on the substance to determine degradation products and degradation pathway. Stability studies can influence the specification, limits and control method for drug.

The physico-chemical parameters, presence of additives and storage conditions, which may affect the stability of drugs, have received considerable attention in the field of pharmaceutics. The formulation of a stable dosage form is essential for the patient's safety and drug efficacy.

In the ICH harmonized tripartite guidelines on stability testing of new drug substances and products fundamental recommendation are summarized. According to the ICH guideline, long term and accelerated stability studies (least 6 months) have to be carried out (Table 1.9).

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. These studies include both solution and solid state experiments under conditions typical for the handling, formulation, storage and administration of a drug candidate.

Stability analysis can be done by:

i. UV spectroscopy
ii. Thin layer chromatography (TLC)
iii. High performance liquid chromatography (HPLC)
iv. Differential scanning calorimetry (DSC)

TABLE 1.9: Long term, accelerated and where appropriate, intermediate storage conditions for the drug substances

Study	*Storage conditions*	*Time period*
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	Long term stability will decide shelf life of the product
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* Long term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition. Intermediate stability sample analysis is to be conducted, if accelerated stability study fails. 12 months of intermediate stability data (with no significant impact in long term) gives confidence for extension of shelf life uptill 18 months.

At least 6 months of accelerated data or 6 months intermediate data and 12 months of long term data required for filing (submission) of the product for US and Europe market.

DRUG EXCIPIENT COMPATIBILITY STUDIES

The successful formulation of a stable and effective solid dosage forms depend on the careful selection of the excipients which are added to facilitate administration, promote the consistent release and bioavailability of drug and protect it from degradation. Incompatability between excipient and drug substance can be detected by:

1. Differential scanning chromatography.
2. By evaluating organoleptic characterstics like change in color.
3. By checking purity of drug substance using HPLC method.

1. **Differential scanning chromatography:** Differential scanning chromatography can be used to investigate and predict any physiochemical interaction between components in a formulation and therefore can be applied to the selection of suitable chemically compatible excipients. For example, in one of the studies, compatibility of Oxcarbazepine (OXC) with excipients was done using DSC analysis. DSC compatibility studies were carried out by comparing the thermal curve of pure OXC with the curves obtained from pure OXC at 1:1 w/w individual mixtures with each excipient under consideration.

   The DSC curve of OXC was typical of a pure crystalline substance, showing a sharp endothermic peak at its melting point, with an onset temperature of 221.13ºC. No significant degradation was seen to occur before 240ºC.

   Inference: OXC was found to be compatible with microcrystalline cellulose, starch and talc. Interaction between OXC and mannitol, monohydrate lactose, colloidal silica, magnesium stearate and sodium lauryl sulfate (SLS) was observed and the extent of interaction varied from only a shift in the OXC melting endotherm to total abolition of the peak (Table 1.10).

2. **By evaluating physical characteristics like change in color:** This is the simplest method, where mixtures of drug substance and excipients are charged for 2 and 4 weeks at accelerated condition (40°C/75% RH) under fixed ratios and change in color is evaluated. For example, in one of the studies, physical compatibility study was done with cephalaexin, observation tabulated below.

   Inference: Based on physical compatibility study, cephalexin seems to be compatible with excipients listed in Table 1.11.

3. **By checking purity of drug substance using HPLC method:** Formulation scientist can use HPLC method to detect impurities generated because of incompatibility between excipients and drug substance. This is the most effective method for

TABLE 1.10: DSC data on drug and excipients

Sample	*Melting endotherm onset (°C)*
OXC	221.13
OXC/microcrystalline cellulose	223.66
OXC/Starch	218.81
OXC/talc	224.50
OXC/mannitol	208.63
OXC/Colloidal silica	206.11
OXC/lactose	199.40
OXC/magnesium stearate	206.64

TABLE 1.11: Physical compatibility studies

Composition	*Description*		
	Initial	*2 weeks*	*4 weeks*
Cephalexin	White to off white powder	No color change	No color change
Cephalexin + microcrystalline cellulose	White to off white powder	No color change	No color change
Cephalexin + lactose	White to off white powder	No color change	No color change
Cephalexin + HPMC15cps	White to off white powder	No color change	No color change
Cephalexin + HPMC K4M	White to off white powder	No color change	No color change
Cephalexin + HPMC K100M	White to off white powder	No color change	No color change
Cephalexin + HPMC K15M	White to off white powder	No color change	No color change
Cephalexin + colloidal silicon dioxide	White to off white powder	No color change	No color change
Cephalexin + magnesium stearate	White to off white powder	No color change	No color change

evaluating incompatibility. Similar to physical compatibility studies, mixtures of drug substance and excipients are charged for 2 and 4 weeks at accelerated condition (40°C/75% RH) under fixed ratios. After two and four weeks, mixtures are evaluated with respect to impurities generated because of interaction between excipients and drug substance.

Conclusion

Preformulation studies properly carried out have a significant part to play in anticipating formulation problem and identifying logical paths in both liquid and solid dosage form technology. The need for adequate drug solubility cannot be overemphasized. The availability of sufficient solubility data should allow the selection of the most appropriate salt for development.

Stabilities studies in solution will indicate the feasibility of parenteral or other liquid dosage forms and can identify methods of stabilization. In parallel, solid state stability by DSC, TLC and HPLC and in the presence of tablet and capsule excipient will indicate the most acceptable vehicles for solid dosage formulations.

Finally by physiochemical property of drug the scientist can assist the synthetic chemist to identify the optimum molecule, provides the biologists with suitable vehicle to elicit pharmacological response and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

ISOLATED KEY POINTS

- Preformulation studies begin when a new chemical entity shows sufficient pharmacological promise and it may be a viable candidate for studies in man
- Aim: To establish the physicochemical properties of a new drug (API)
  To establish the data on drug–excipient compatibility
  To establish its (API) kinetic rate profile

- Some commonly evaluated parameters in preformulation: Organoleptic properties, purity, particle size, particle shape, particle surface area, solubility, dissolution, partition coefficient, ionization constant, crystal properties, polymorphism, density, hygroscopicity, flowability, wettability and stability.
- Purity studies are essential during preformulation. Techniques used for characterizing purity—thin layer chromatography (TLC), high pressure liquid chromatography and gas chromatography (GC).
- Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. Size and shape also influences the dissolution of poorly soluble drugs, which in turn influences bioavailability.
- Microscopy is the simplest technique of estimating size ranges and shapes, e.g. light microscope and electron microscope. Anderson pipette methodis based on the rate difference of sedimentation of different particles, but techniques like this are seldom used due to their tedious nature. Seiving methods are also used to measure particle size. Instruments based on light scattering (Royco), light blockage (HIAC) and blockage of electrical conductivity path (coulter counter) are also available.
- Common techniques for measuring fine particles of various sizes (in μm) are:
  Microscopic: 1–100 μm, sieve >50 μm, sedimentation >1 μm, elutriation 1– 50 μm,
  Centrifugal <50 μm, permeability >1 μm, light scattering micrometer 0.5–50 μm.
- The solubility of drug is an important physicochemical property because it effects the rate of drug release into dissolution medium and consequently, the bioavailabilty of the drug and therapeutic efficiency of the pharmaceutical product.
- Common solvents used for solubility determination are benzyl alcohol, isopropyl alcohol, surfactant (like tween and sodium lauryl sulfate) aqueous solution, castor oil. Peanut oil, sesame oil and buffer at various pHs, polyethylene glycols, propylene glycol, glycerin, sorbitol, ethyl alcohol and methanol.
- Intrinsic solubility: The solubility should ideally be measured at two temperatures, i.e. 4°C and 37°C. The minimum density of water occurs at 4°C, this leads to a minimum aqueous solubility and at 37°C to support biopharmaceutical evaluation.
- pKa determination: It is the negative logarithm of dissociation constant. It describes about the chemical nature of API. It is mainly determined by using the **Henderson–Hasselbalch equation.**
  For acidic compounds,
  $$pH = pKa + \log (\text{unionized drug})/(\text{ionized drug})$$
  For basic compounds,
  $$pH = pKb + \log (\text{ionized drug})/(\text{unionized drug})$$
- Partition co-efficient: It is defined as the ratio of unionized drug distributed between the organic and aqueous phases at equilibrium. P o/w = (C oil/C water) equilibrium. Partition coefficient (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. If P much greater than 1 are classified as lipophilic, whereas those with partition coefficient much less than 1 are indicative of a hydrophilic drug.
- Many drug substance can exist in more than one crystalline from with different space lattice arrangements. This property is known as polymorphism. Polymorphs generally have different melting points, X-ray diffraction patterns and solubility even though they are chemically identical.

- Powder flow properties can be evaluated by measurements of bulk density and angle of repose. Changes in particles size and shape are generally very important.
- Knowledge of absolute and bulk density of the drug substance is very useful in having some idea on the size of final dosage form, the density of solids also of affects their flow properties. Carr's compressibility index can be used to predict the flow properties based on density measurement.

$$\text{Carr's index (\%) or consolidation index} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \times 100$$

- Angle of repose: The maximum angle which is formed between the surface of a pile of powder and horizontal surface is called the angle of repose.
- Elevated temperature studies: The elevated temperatures commonly used are 40ºC, 50ºC and 60ºC with ambient humidity. The samples are stored at highest temperature are observed weekly for physical and chemical changes and compared to an appropriate control. If a substantial change is seen, samples stored at lower temperature are examined. If no changes are seen after 30 days at 60ºC, the stability prospects is excellent.
- Photolytic stability: Many drugs fade on light exposure. Though the extent of degradations may be small and limited to the exposed surface area, it leads to aesthetic problem. Exposure of drug to 400 and 900 foot-candles of illumination for 4 and 2 week periods respectively is adequate to provide some idea of photosensitivity. Resulting data may be useful in determining if an amber colored container is required or if color masking dye should be used in the formulation.
- Stability to oxidation: Drug's sensitivity to oxidation can be examined by exposing it to atmosphere of high oxygen tension. Usually a 40% oxygen atmosphere is used for rapid evaluation. Results may be useful in predicting whether antioxidant is required in the formulation or final product should be packaged under inert atmospheric conditions.
- Compatibility studies: The knowledge of drug excipients interaction is useful for the formulation to select appropriate excipients.

PRACTICE QUESTIONS

Long Answer Type Questions

1. What do you understand by the term preformulation? Discuss in brief about the objectives of preformulation studies.

2. Enumerate the various factors involved in preformulation studies? Discuss in detail about organoleptic properties?

3. Write short notes on following in context to preformulation studies.

a. Bulk characterization

b. Gibbs Kelvin relation

c. Crystallinity and polymorphism

4. Discuss in detail about physiochemical parameters related to preformulation.

5. How solubility and pKa play role in preformulation studies?
6. Discuss in brief the significance of pKa determination and dissociation constant in preformulation studies?
7. Make a chart for drug X, which is to be formulated in the form of tablet and carry out its preformulation studies?
8. What are various methods of drug excipient compatibility studies? Give brief explanation of each method.
9. Write in brief note on stability studies?
10. Write short notes on: (a) Contact angle, (b) surface area, (c) young's equation.

Objective Type Questions

1. Gibbs–Kelvinis relationship exists between _____ and apparent solubility of a drug.
2. When a substance exists in more than one crystalline form than the phenomenon is called _____ .
3. Preformulation studies includes all the studies except the following factor.
   a. The amount of drug available.
   b. The physicochemical properties of the drug already known.
   c. Therapeutic category and anticipated dose of compound.
   d. Route of drug administration
4. The primary objectives of preformulation studies are as follows:
   a. Establish the identity and physiochemical parameters of a new drug substance.
   b. Establish chemical stability profile of drug substance.
   c. Establish drug substance compatibility with common excipients
   d. Preformulation studies give preliminary idea about selection of excipients, which makes the formulation stable.
   e. All of the above
5. Stability analysis can be done by:
   a. IR
   b. High performance liquid chromatography (HPLC)
   c. Differential scanning calorimetry (DSC)
   d. All
6. Match the following based on particle size determination:

S. No.	*Instrument*		*Principle*
1	Anderson pipette	a	Based on light scattering
2	ROYCO	b	Based on rate difference of sedimentation of different particle
3	HIAC	c	Instrument based on blockage of electrical conductivity path
4	Coulter counter	d	Based on light blockage

7. Match the following based on grading of the powder for their flow properties and Carr index

S. No.	*Carr index*		*Flow*
1	5–15	a	Poor
2	18–21	b	Very poor
3	23–35	c	Excellent
4	33–38	d	Good

8. Match the following between angle of repose (θ) and powder flow

S. No.	*Angel of repose (θ) (degrees)*		*Flow*
1	< 25	a	Very poor
2	25–30	b	Excellent
3	30–40*	c	Good
4	> 40	d	Poor

ANSWERS

1. Particle size **2.** Polymorphism **3.** d
4. e **5.** d **6.** 1—b, 2—a, 3—d, 4—c
7. 1—c, 2—d, 3—a, 4—b **8.** 1—b, 2—c, 3—d, 4—a

Chapter
2

Tablets

Tablets and capsules, on the other hand, currently account for well over two-third of the total number and cost of medicines produced all over the world. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia, pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet. All medicaments are available in the tablet form except where it is difficult to formulate or administer.

Ideal Characteristics of Tablet

A well-prepared tablet should possess the following qualities:

1. It should, within permitted limits, contain the stated dose of drug.
2. It should deliver its dose of drug at the site and at the speed required.
3. Its size, taste, and appearance should not detract from its acceptability by the patient.
4. A tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
5. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
6. Should have the chemical and physical stability.
7. The tablet must be able to release the medicinal agents in a predictable and reproducible manner.

Advantages of the Tablet

1. They are unit dosage form which provides the greatest dose precision and the least content variability.
2. Cost is lowest of all oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Delayed release product is possible by enteric coating.

7. Objectionable odour and bitter taste can be masked by coating technique.
8. Suitable for large scale production.
9. Greatest chemical and microbial stability over all oral dosage form.
10. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.
11. Sustained release product is possible by polymer matrix or coating.

Disadvantages of Tablet

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.
5. Slow onset of action as compared to parenterals and liquid orals.
6. Patients undergoing radiotherapy cannot swallow tablet.

CLASSIFICATION OF TABLETS

(A) Tablets Ingested Orally

These tablets are meant to be swallowed intact along with a sufficient quantity of drinking water. Exception is chewable tablet. This is the most popular type of tablet dosage form andover 90% of the tablets manufactured today are ingested orally. The different types of tablet ingested orally are mentioned below.

1. Compressed tablet, e.g. paracetamol tablet
2. Multiple layer tablet
3. Sustained release tablet
4. Delayed release tablet, e.g. enteric coated bisacodyl tablet
5. Sugar coated tablet, e.g. multivitamin tablet
6. Film coated tablet, e.g. metronidazole tablet
7. Chewable tablet, e.g. antacid tablet

Compressed tablets (CT): These tablets are uncoated and made by compression of granules. These tablets are usually intended to provide rapid disintegration and drug release. These tablets contain drugs, which after swallowing get disintegrated in the stomach and its drug contents are absorbed in the gastrointestinal tract and distribute in the whole body.

Multiple layer tablets: These tablets consist of two or more layers of materials compressed successively in the same tablets. The colour of each layer may be the same or different. The tablets having layers of different colours are known as "multicoloured tablets". These tablets are prepared to separate incompatible ingredients physically. A special type of tablet making machine is used which provides two compressions.

Sustained release tablets: These tablets are used to get a sustained action of medicament. These tablets when taken orally release the medicament in a sufficient quantity as and when required to maintain the maximum effective concentration of the drug in the blood throughout the period of treatment. Controlled release of drug helps in getting the desired degree of action. These tablets are gaining popularity these days.

Enteric coated tablets: These are compressed tablets meant for administration by swallowing and are designed to bypass the stomach and get disintegrated in the intestines only. These tablets are made to release the drug undiluted and in the highest concentration possible within the intestine. These type of dosage forms are formulated for those drugs, which causes gastric irritation or degrade in acidic media (in stomach).

Sugar coated tablets: The compressed tablets having a sugar coating are called "sugar coated tablets". Sugar coating is done to mark the bitter and unpleasant odour and the taste of the medicament. The sugar coating makes the tablet elegant and it also safe guards the drug from atmospheric effects.

Film coated tablets: The compressed tablets having a film coating of some polymer substance, such as hydroxypropyl cellulose, hydroxyl propylmethyl cellulose and Polyvinyl alcohol. The film coating protects the medicament from atmospheric effects. Film coated tablets are generally tasteless, having little increase in the tablet weight.

Chewable tablets: These tablets are chewed in the mouth and broken into smaller pieces. In this way , the disintegration time is reduced and the rate of absorption of the medicament is increased, e.g. aluminum hydroxide tablets and phenolphthalein tablets.

(B) Tablets Used in Oral Cavity

These tablets released the drug in oral cavity and gives localize action. These tablets bypass first-pass metabolism, decomposition in gastric environment and gives rapid onset of action. The different types of tablet used in oral cavity are mentioned below.

1. Buccal tablet, e.g. vitamin C tablet
2. Sublingual tablet, e.g. vicks menthol tablet
3. Troches or lozenges
4. Dental cone

Buccal tablets: These tablets are to be placed in the buccal pouch or between the gums and lips or cheek where they dissolve or disintegrate and are absorbed directly without passing into the alimentary cannel, e.g. tablets of ethisterone.

Sublingual tablets: These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT, e.g. tablets of glyceryl trinitrite.

Lozenge tablets and troches: These tablets are designed to exert a local throat effect. These tablets are commonly used to treat sore throat or to control coughing in common cold. They may contain local anesthetics, antiseptic, antibacterial agents, astringents and antitussives. They are prepared by compression at a high pressure or by the molding process and generally contains a sweetening agent, a flavouring agent and the substance, which produces a cooling effect along with medicaments.

Dental cones: These are relatively minor compressed tablets meant for placing them in the empty sockets after tooth extraction. They prevent the multiplication of bacteria in the socket following such extraction by using slow-releasing antibacterial compounds or to reduce bleeding by containing the astringent. These tablets contain an excipient like lactose, sodium bicarbonate and sodium chloride, etc. These cones generally get dissolve in 20 to 40 minutes time.

(C) Tablets Administered by other Route

These tablets are administered by other route hence the drugs are avoided from passing through gastrointestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application. The different types of tablet administered by other routes are mentioned below.

1. Implantation tablet
2. Vaginal tablet, e.g. clotrimazole tablet

Implantation tablets: These tablets are placed under the skin or inserted subcutaneously by means of minor surgical operation and are slowly absorbed. These may be made by heavy compression but are normally made by fusion. The implants must be sterile and should be packed individually in sterile condition. Implants are mainly used for administration of hormones such as testosterone and deoxycorticosterone etc.

Vaginal tablets: These tablets are meant to dissolve slowly in the vaginal cavity . The tablets are typically ovoid or pear shaped to facilitate retention in the vagina. This tablet form is used to release steroids, antibacterial agents, antiseptics or astringents to treat vaginal infections. The tablets are often buffered to promote a pH favorable to the action of a specified antiseptic agent. They contain excipients, such as lactose or sodium bicarbonate.

(D) Tablets used to Prepare Solution

These types of tablets get dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used. The different types of tablet used to prepare solution are mentioned below.

1. Effervescent tablet, e.g. Dispirin tablet (Aspirin)
2. Dispensing tablet, e.g. Enzyme tablet (Digiplex)
3. Hypodermic tablet

Effervescent tablets: These tablets when added in water produce effervescence. So they dissolved rapidly in water due to the chemical reaction which takes place between alkali bicarbonate and citric acid or tartaric acid or combination of both. These tablets are to be protected from atmospheric moisture during storage. So, these tablets should be stored in well-closed air tight containers.

Dispensing tablets: This type of tablets is intended to be added to a given volume of water to produce a solution of a given concentration. These tablets contain excipient which gets dissolved quickly to form a clear solution. These tablets are highly toxic if taken orally by mistake. So, great care must be taken in the packaging and labeling of such tablets in order to prevent their misuse.

Hypodermic tablets: These are compressed tablets which are composed of one or more drugs with readily water soluble ingredients. These tablets are dissolved in sterile water or water for injection and administered by parental route. So, special precautions are needed to be taken during their preparation. These tablets however are not preferred nowadays as there are chances that the solution prepared from hypodermic tablets may be a non-sterile.

Tablet Excipients

Excipient means any component other than the active pharmaceutical ingredient(s) intentionally added to the formulation of a dosage form. Many guidelines exist to aid in selection of non-toxic excipients such as IID (inactive ingredient database), GRAS (generally regarded as safe), Handbook of Pharmaceutical Excipients and others. Excipients play an important role in formulating the dosage form, determining its quality and bioavailability. Excipients perform a variety of functions (Table 2.1).

TABLE 2.1: Excipients and their functions

Excipients	*Functions*
Diluents or fillers	To increase the required bulk of the tablet when the active drug is less to produce tablets of adequate weight and size.
Binders or granulating agents or adhesives	Binders are added to tablet formulations to add cohesiveness to powders, thus providing the necessary bonding to form granules.
Disintegrants	A disintegrant is added to give bursting effect or breakup of the tablet, when placed in an aqueous environment.
Lubricants	Lubricants are added to reduce the friction during tablet ejection from die cavity.
Antiadherents	Antiadherents are added to reduce sticking or adhesion of tablet granulation or powder to the faces of the punches or to the die wall.
Glidants	Glidants are intended to increase the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between the particles.
Dissolution retardants	Dissolution retardants decrease the dissolution rate of active pharmaceutical ingredient(s).
Dissolution enhancers	Dissolution enhancers increase the dissolution rate of active pharmaceutical ingredient(s).
Adsorbents	Adsorbents are capable of retaining large quantities of liquids without becoming wet; this helps many oils, fluid extracts and eutectic melts to be added into tablets.
Buffers	Buffers are added to maintain the pH to get improved stability and bioavailability.
Antioxidants	Antioxidants are added to maintain product stability by preventing API (active pharmaceutical ingredient) oxidation.
Preservatives	Preservatives are added to prevent the growth of micro-organisms.
Colours	Colours are added to mask the colour of drugs and impart better colour.
Flavours	Flavours are added to make them palatable enough in case of chewable tablet by improving the taste.
Sweeteners	Sweeteners are added to tablet formulation to improve the taste of chewable tablets especially in case of bitter tasting drugs.
Wetting agents	Wetting agents are added to help wetting of the API (active pharmaceutical ingredients). This will eventually help in dissolution of API.

Diluents

In order to formulate an adequate size and shape and have content uniformity, the tablet size should be kept above 2–3 mm and weight of tablet should be above 50 mg. Many potent drugs have low dose (for e.g. diazepam, clonidine hydrochloride) in such cases diluents provide the required bulk of the tablet. Generally diluents vary from 5 to 85%, they are also called fillers. Diluents provide better tablet properties like.

i. Improved cohesion
ii. Facilitate direct compression
iii. Increase flow of powders.
iv. To adjust weight of tablet as per die capacity

An ideal diluent should have following properties:

i. Should not react with the drug substance and other ingredients
ii. Should not have any therapeutic pharmacological activity
iii. Should be easily reduced in size to match the particle size distribution of the active pharmaceutical ingredient
iv. Should not support microbiological growth
v. Should not interfere with the bioavailability of active pharmaceutical ingredient, until it is intended to increase bioavailability
vi. Should not impart any colour to the formulation.

Tablet diluent or filler may also be classified on the basis of their solubility in water as soluble and insoluble. Selection of diluent should be done after considering properties of diluent such as: Compactibility, flowability, solubility, disintegration qualities, hygroscopicity, lubricity and stability (Table 2.2).

TABLE 2.2: List of tablet diluents

S. No.	*Diluents*	*Properties*
1.	Calcium carbonate	Insoluble in water
2.	Dibasic calcium phosphate	Insoluble in water and good flow properties
3.	Tribasic calcium phosphate	Insoluble in water
4.	Calcium sulfate	Insoluble in water
5.	Microcrystalline cellulose	Good compression properties and also act as disintegrant
6.	Sucrose	Freely soluble in water, sweet taste and hygroscopic
7.	Dextrose	Hygroscopic and reducing sugar
8.	Mannitol	Freely soluble in water having less moisture content and being polyol it helps in stability of the drug
9.	Sodium chloride	Freely soluble in water and used in solution tablets
10.	Xylitol	Good taste
11.	Lactose monohydrate	The most commonly used diluent. With primary and secondary amines undergo Maillard reaction
12.	Starch	Also acts as disintegrating agent and binder. It may give soft tablets
13.	Starch, pregelatinzed	Also acts as disintegrating agent and binder

Binders

Binder is one of an important excipient to be added in tablet formulation. In simple words, binders or adhesives are the substances that promote cohesiveness. It is utilized for converting powder into granules through a process known as granulation. Types of binder and probable concentration of use are tabulated in Tables 2.3 and 2.4.

TABLE 2.3: Types of binders

Natural binders	*Synthetic/semisynthetic polymer*
Acacia	Methyl cellulose
Tragacanth	Ethyl cellulose
Gelatin	Hydroxy propyl methyl cellulose (HPMC)
Starch paste	Hydroxy propyl cellulose (HPC)
Pregelatinized starch	Sodium carboxy methyl cellulose
Alginic acid	Polyvinyl pyrrolidone (PVP)
Cellulose	Polyethylene glycol (PEG)
Sucrose	
Liguid glucose	

TABLE 2.4: Binders used in the wet granulation process

Sr. No.	*Binder*	*Concentration (% w/w)*
1.	Acacia mucilage	Up to 20
2.	Algnic acid	1–5
3.	Carbomer	5–10
4.	Carboxymethylecellulose calcium	5–15
5.	Carboxymethylecellulose sodium	5–15
6.	Polyethylene oxide	5
7.	Povidone	0.5–5
8.	Sodium alginate	1–3
9.	Starch paste	5–25
10.	Starch, pregelatinized	5–10
11.	Sucrose (syrup)	Upto 70
12.	Hydroxyethyl cellulose	2–6
13.	Hydroxypropyl cellulose—low substitute	5–25
14.	Hydroxypropylmethyl cellulose	2–7
15.	Magnesium aluminum silicate	2–10
16.	Maltodextrin	2–10
17.	Methyl cellulose	1–5

Direct Compression Binders

Due to ease of manufacture, product stability and high efficiency, the use of direct compression for tableting has increased. For direct compression, directly compressible binders are required which should exhibit adequate powder compressibility and

flowability. Direct compression binders should be selected on the basis of compression behavior, volume reduction under applied pressure and flow behavior in order to have optimum binding performance. The choice and selection of binders is extremely critical for direct compression tablets. Because of their properties, this category of binders also act as diluent (Table 2.5).

TABLE 2.5: Commonly used directly compressible binders

DC binder	*Class*
Avicel (PH 101)	Microcrystalline cellulose
SMCC (50)	Silicified microcrystalline cellulose
UNI-PURE(DW)	Partially pregelatinized starch
UNI-PURE (LD)	Low density starch
DC Lactose	DC lactose anhydrous
DI TAB	Dibasic calcium phosphate dihydrate

Disintegrants

Disintegrants are added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which causes this process are known as disintegrants (Fig. 2.1).

Mechanism of Tablet Disintegration

The tablet breaks to primary particles by one or more of the mechanisms listed below:

1. By capillary action
2. By swelling
3. Because of heat of wetting
4. Due to disintegrating particle/particle repulsive forces
5. Due to deformation
6. Due to release of gases
7. By enzymatic action

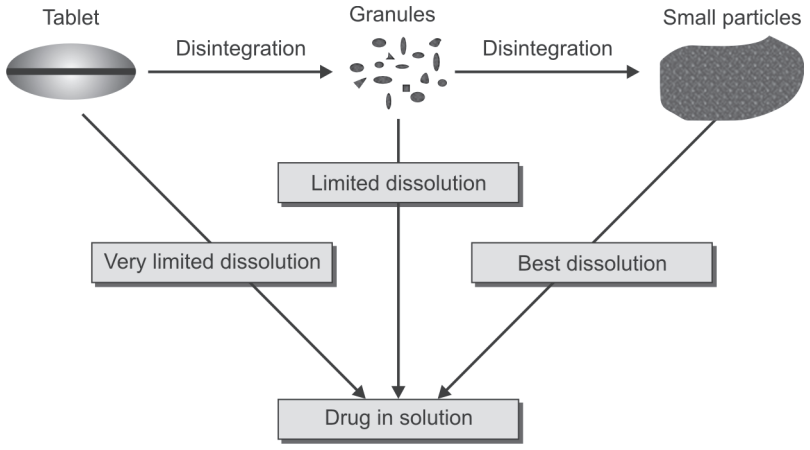


Fig. 2.1: Tablet disintegration and subsequent drug dissolution

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down (Fig. 2.2).

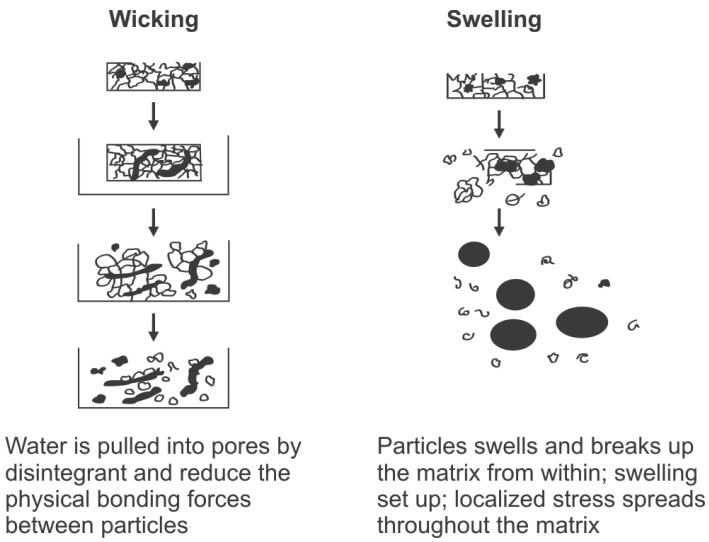


Fig. 2.2: Disintegration of tablet by wicking and swelling

Methods of Adding Disintegrants

Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (after granulation i.e. extragranular) or at the both processing steps. Extragranular fraction of disintegrant (usually, 50% of total disintegrant requires) facilitates breakup of tablets to granules and the intragranular addition of disintegrants produces further erosion of the granules to fine particles (Table 2.6).

TABLE 2.6: List of disintegrants

Disintegrants	*Probable concentration (% w/w)*	*Special comments*
Starch	5–20	Higher amount is required, poorly compressible
Sodium starch glycolate	2–8	Super-disintegrant
Microcrystalline cellulose	10–20	Good flowproperties and directly compressible
Crosscarmellose sodium (AC-Di-Sol®)	2–8	Super-disintegrant
Alginic acid	1–5	Acts by swelling
Na alginate	2.5–10	Acts by swelling
Crosspovidone	2–8	Super-disintegrant

STARCH

Starch is widely used in tablet manufacturing. The mechanism of action of starch is wicking and restoration of deformed starch particles in contact with aqueous fluid leads to disintegration. The concentration of starch used is also very crucial part. If it is below the optimum concentration then there are insufficient channels for capillary action and if it is above optimum concentration then it will be difficult to compress the tablet.

Pregelatinized Starch

Pregelatinized starch is produced by the hydrolyzing and rupturing of the starch grain. It is a directly compressible disintegrants and its optimum concentration is 5–10%. The main mechanism of action of pregelatinized starch is through swelling.

Modified Starch

To have a high swelling properties and faster disintegration, starch is modified by carboxy methylation followed by cross-linking, which is available in market as cross-linked starch. One of them is SSG (sodium starch glycolate). Even low and substituted carboxymethyl starches are also marketed as Explotab and Primojel. Mechanism of action of this modified starches are rapid and extensive swelling with minimum gelling. Concentration used is 2–8%.

Cellulose and its Derivatives

Sodium carboxy methylcellulose (NaCMC) has highly hydrophilic structure and is soluble in water. But when it is modified by internally cross-linking we get modified cross-linked cellulose, i.e. croscarmellose sodium which is nearly water insoluble due to cross-linking. It rapidly swells to 4–8 times its original volume when it comes in contact with water.

Microcrystalline Cellulose (MCC)

MCC exhibit very good disintegrating properties because MCC is insoluble and act by wicking action. The moisture breaks the hydrogen bonding between adjacent bundles of MCC.

Alginates

Alginates are hydrophilic colloidal substances, which has high sorption capacity. Alginic acid is insoluble in water, slightly acidic in reaction. Hence, used in only acidic or neutral granulation.

Superdisintegrants

They are effective at low concentration and have greater disintegrating efficiency and they are more effective. Superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration. Example, croscarmellose sodium, crospovidone and sodium starch glycolate (Fig. 2.3).



Fig. 2.3: Mechanism of super disintegration by swelling

ANTIFRICTION AGENTS

Lubricants

Lubricants are the agents that act by reducing friction between the tablet constituents and the die wall during compression and ejection. Lubricants should be incorporated in the final mixing step, after granulation is complete. When hydrophobic lubricants are added to a granulation, they form a coat around the individual particles (granules), which may cause an increase in the disintegration time and a decrease in the drug dissolution rate. Surface area is important parameter for deciding lubricant efficiency. Lubricants with high surface area are more sensitive to changes in mixing time than lubricant with low surface area. Therefore, lubricant mixing time should be kept minimum. Tooling used to compress the tablet is important for deciding type and level of lubricant used. Additional lubricant is often added to the tablet formulations that are to be compressed with curved face punches. Further, the amount of lubricant increases as the particle size of the granulation decreases but its concentration should not generally be more than 1% w/w. Lack of adequate lubrication produces binding which can results in tablet machine strain and can lead to damage of lower punch heads, lower cam track, die seats and the tooling itself, it may also yield tablets with scratched edges and are often fractured at the top edges.

Classification of Lubricants

Lubricant are classified according to their water solubility, i.e. water insoluble and water soluble (Table 2.7).

Water Insoluble Lubricants

Water insoluble lubricants are most effective and used at reduced concentration than water soluble lubricants. Since these lubricants function by coating, their effectiveness is related with their surface area, extent of particle size reduction, time, procedure of addition and length of mixing.

Water Soluble Lubricants

Water soluble lubricants are used when a tablet is completely soluble or when unique disintegration and dissolution characteristics are required. Tablet containing soluble lubricant shows higher dissolution rate than tablet with insoluble lubricants.

Physical mixture of soluble lubricants (like sodium lauryl sulfate (SLS) or magnesium lauryl sulfate) with insoluble lubricant (like stearates) can lead to optimum lubricity, tablet strength and disintegration.

TABLE 2.7: List of lubricants

Sr. No.	*Lubricant*	*Probable concentration in tablet (%w/w)*	*Comments*
1.	Calcium stearate	0.5–2	Water insoluble
2.	Fumaric acid	5	Water soluble
3.	Glyceryl behenate	0.5–4	Water insoluble
4.	Glyceryl palmitostearate	0.5–5.0	Water insoluble
5.	Hydrogenated vegetable oil	1–6	Water insoluble
6.	Magnesium lauryl sulfate	1–2	Soluble in warm water
7.	Magnesium stearate	0.25–5	Water insoluble and excellent lubricant. However, it reduces tablet strength, prolongs disintegration and dissolution.
8.	Polyethylene glycol 4000 or 6000	2–5	Soluble in water and moderately effective, also known as macrogols
9.	Sodium lauryl sulfate	1–2	Water soluble and moderate lubricant
10.	Starch	2–10	Moderate lubricant
11.	Stearic acid	1–3	Water insoluble
12.	Talc	1–10	Insoluble in water but not hydrophobic
13.	Zinc stearate	0.5–2	Water insoluble

Antiadherents

Some material have strong adhesive properties towards the metal of punches and dies or the tablet formulation containing excessive moisture which has tendency to result in picking and sticking problem. Therefore, antiadherents are added, which prevent sticking to punches and die walls. Talc, magnesium stearate and corn starch have excellent antiadherent properties (Table 2.8).

Glidants

Glidants are added to the formulation to improve the flow properties of the material, which is to be fed into the die cavity. Starch is a popular glidant because it has additional value of disintegrant. Concentration of starch is common up to 10%, but beyond this it

TABLE 2.8: List of antiadherents

Antiadherent	*Concentration (%w/w)*	*Comment*
Talc	1–5	Lubricant with excellent antiadherents properties
Cornstarch	3–10	Lubricant with excellent antiadherents properties
Sodium lauryl sulfate	<1	Antiadherents with water soluble lubricant
Stearates	<1	Antiadherents with water insoluble lubricant

TABLE 2.9: Glidant and their concentration used

Sr. No.	*Glidant*	*Concentration in tablet (%)*
1.	Calcium silicate	0.5–2
2.	Cellulose, powdered	1–2
3.	Magnesium carbonate	1–3
4.	Magnesium oxide	1–3
5.	Magnesium silicate	0.5–2
6.	Silicon dioxide, colloidal	0.05–0.5
7.	Starch	2–10
8.	Talc	1–10

will worsen the flow of material. Talc is a glidant which is superior to starch; its concentration should be limited because it hinders dissolution and disintegration. Silaceous material like colloidal silica, i.e. syloid, pyrogenic silica (0.25%), hydrated sodium silicoaluminate (0.75%) are also successfully used to induce flow (Table 2.9).

MISCELLANEOUS EXCIPIENTS

Wetting Agents

Wetting agents in tablet formulation helps in water absorption and thereby helps in disintegration and drug dissolution. Addition of sodium lauryl sulphate (SLS) is known to enhance the dissolution. SLS improves permeation of drug through biological membrane by destroying the path through which drug has to pass and thus minimizing the path length for the drug to travel. Wetting agents are mainly added when hydrophobic drug is to be formulated.

Dissolution Retardants

Dissolution retardants are incorporated when controlled release of drug is required. Waxy materials like stearic acid and their esters can be used as dissolution retardants. Even high viscosity polymers like hydroxypropyl methyl cellulose and insoluble polymer like ethyl cellulose act as dissolution retardants.

Dissolution Enhancers

They are the agents which decreases the molecular forces between ingredients to enhance the dissolution of solute in the solvent. Examples like fructose and povidone are used as dissolution enhancer.

Adsorbents

Adsorbents are the agents that can retain large quantities of liquids. Commonly used adsorbents in pharmaceuticals are anhydrous calcium phosphate, starch, bentonite, kaolin, magnesium silicate, magnesium oxide and silicon dioxide. Generally the liquid to be adsorbed is first mixed with the adsorbent prior to incorporation into the formulation.

Buffers

Buffers are added to maintain a required pH because a small change in pH can cause great changes in the stability of drug. Examples are sodium bicarbonate, calcium carbonate and sodium citrate.

Antioxidants

Antioxidants are added in tablet formulation to protect drug from undergoing oxidation. Antioxidants undergo oxidation in place of drug or they block the oxidation reaction. Most commonly used antioxidants include ascorbic acid and their esters, alpha-tocopherol, ethylene diamine tetra acetic acid, sodium metabisulfite, sodium bisulfite, butylated hydroxy toluene (BHT) and butylated hydroxy anisole (BHA).

Preservatives

Preservatives prevent the growth of microorganisms in tablet formulation. They are generally used when the moisture content is bit high, i.e. beyond 4%. Parabens (p-hydroxy benzoate) like methyl, propyl, benzyl and butyl are used as preservatives.

Coloring Agent

They are used to overcome colors of active ingredient, for brand image in the market and to enhance the aesthetic appearance of the product to have better patient acceptance. Most widely used colorants are dyes and lakes which are FD and C and D and C approved. The list of permitted colors is published under the authority of government. The following is the list of colors permitted under Drugs and Cosmetics Act, 1940.

1. **Natural colors:** Annato, carotene, chlorophyll, cochineal, curcumin, red and yellow oxides of iron, titanium dioxide.
2. **Artificial colors:** Caramel
3. **Coaltar colors:**
   - Black: Napthol blue black 20470
   - Blue: Brilliant blue FCS 42090
     Indigocarmine 73015
   - Brown: Resorcin brown 20170
   - Yellow: Sunset yellow FCF 15185
     Quinoline yellow SS 4700
   - Green: Fast green FCF 42053
     Quinazoline green 61565
     Green S 44090
     Alizarin cyanine green F 61570
   - Orange: Orange G 16230
   - Red: Amaranth I.N. 16185
     Erythrosin 45430
     Sudan III 26100
     Fast red E 16045

4. **Lakes:** These are those colors in which dyes are absorbed generally on aluminium hydroxide. The lakes consist of 15 to 40% of adsorbed dyes and are insoluble in water.

Flavoring Agents

Flavors are commonly used to improve the taste of chewable tablets as well as mouth dissolving tablets. Flavors are incorporated either as solids (spray dried flavors) or oils or aqueous (water soluble) flavors. The flavor of a pharmaceutical formulation is a very important characteristic has important effect on success or failure of a commercial product can be interlinked with the quality of its flavor. In the traditional context the term flavor was equated with odorific qualities of a product though in the modern concept a flavor includes initial impact, mouth feel and after impact of the preparations. The flavor should ultimately be in consonance with the taste as well as the colour of the product. They should also cater to specific liking of patient population (Tables 2.10 and 2.11).

TABLE 2.10: Matches between tastes and flavors

Taste	*Flavor/flavors*
Alkaline	Mint, chocolate, vanilla, custard
Acid (sour)	Lemon, orange, anise, liquorice, raspberry, cherry, strawberry
Bitter	Anise, mint, fennel, chocolate, spicy, cherry
Metallic	Grape, lemon, burgundy
Salty	Citrus flavors, maple, raspberry, fruity, melon
Sweet	Fruity, vanilla, maple, honey

TABLE 2.11: Matching flavors and colors

Flavors	*Colours*
Raspberry, cherry, strawberry, apple, rose	Pink to red
Chocolate, honey, molasses, walnut, caramel	Brown
Lemon, lime, orange, custard, cherry	Yellow to orange
Banana, mint, pistachio	Green
Mint, vanilla, spearmint, jasmine, banana	White to off white
Grape, liquorice, violet	Violet or purple
Blueberry, mixed fruit, plum, liquorice	Blue

Sweetening agents: Sweeteners are added primarily to chewable tablets (Table 2.12).

Amongst the other sweetening agents listed above saccharin and cyclamates have had an era of popularity chiefly because very small amounts of these substances can make formulations appreciably sweet. Saccharin can be easily synthesized starting with toluene. Saccharin is also marketed as saccharin or saccharin sodium in which the hydrogen group in NH group is replaced by Na and which in crystalline form also has two molecules of water crystallization. Sodium saccharin can easily prepared by dissolving saccharin in equimolecular quantities of sodium hydroxide solution followed by crystallization. Sodium saccharin is nearly 200 times more soluble in water in comparison to saccharin. Saccharin is reputed to be nearly 450 times sweeter than

TABLE 2.12: List of sweetening agents used in tablet formulations

Sweetening agent	*Relative sweetness compared to sucrose*
a. L-Aspartyl-1-phenylalanine	250
b. Cyclamate	40
c. Dextrose	0.75
d. D-fructose	1.73
e. Glycerrhizin	50
f. Lactose	0.16
g. Maltose	0.32
h. Mannitol	0.6
i. Saccharin	450
j. Sorbitol	0.5
k. Sucrose	1
l. Xylitol	1

sucrose in dilute solutions. Cyclamates are the sodium or potassium salts of cyclohexesulfonic acid.

Both saccharin and the cyclamates have been very popular with the pharmaceutical and food manufacturers. At one time these compounds were considered to be absolutely safe but some recent reports have turned the tables against them. Some countries have banned the use of these compounds while some others in process of doing so because they are found to be carcinogenic. Hence, before including these sweeteners in a preparation the manufacturer should check up the law regarding their use.

Tablet Manufacturing/Formulation of Tablets

Tablets are made by compressing a formulation containing a drug or drugs with excipients on stamping machine called presses. Blend of drug and excipients is contained in a die and a compressing force of several tonnes is applied to it by means of punches. The shape of the die governs the cross-sectional shape of the tablet and the distance between the punch tips at the point of maximum compression governs its thickness. Regardless of whether tablets are made by direct compression or granulation, the first step, milling and mixing, is the same; subsequent step differ. Numerous unit processes are involved in making tablets, including particle size reduction and sizing, blending, granulation, drying, compaction, and (frequently) coating. Various factors associated with these processes can seriously affect content uniformity, bioavailability, or stability (Fig. 2.4)

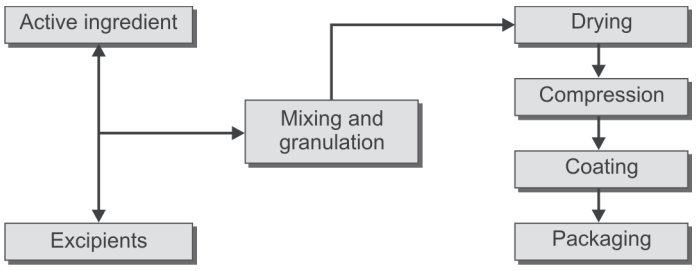


Fig. 2.4: Various steps in tablet manufacturing

Dispensing

Dispensing is the first step in tablet manufacturing process. Dispensing may be done by:

1. Manually: Purely manual by hand scooping from primary containers and weighing each ingredient by hand on a weigh scale.
2. Manual weighing with material lifting assistance like vacuum transfer and bag lifters.
3. Automated dispensaries with mechanical devices such as vacuum loading system and screw feed system.

Issues like weighing accuracy, dust control (laminar air flow booths, glove boxes), cross-contamination and material movement into and out of dispensary should be considered during dispensing.

Size Reduction

The size reduction is an important step in the tablet manufacturing. In manufacturing of tablet, the mixing or blending of several solid ingredients of pharmaceuticals is easier and more uniform when the ingredients are approximately of same size. This provides a greater uniformity of dose. A fine particle size is essential in case of lubricant mixing with granules for its proper function.

Advantages of size reduction in tablet manufacture are as follows:

i. It increases surface area, which increases dissolution rate and bioavailability.
ii. Increases tablet content uniformity.
iii. Better particle size distribution of dried granules and proper mixing.
iv. Better flow properties of powders and granules.

Granulation

Granulation is defined as a size enlargement process which converts small particles into physically stronger and larger particles. Granulation method can be broadly classified into two types: Wet granulation and dry granulation. The process of granulation is essentially one of size enlargement, and it serves several purposes in the tablet manufacturing process:

1. It improves flow by increasing particle size, since large particles flow more readily than small ones, reduces dust and static generation.
2. It improves compression characteristics, adding to the cohesive strength of the tablet.
3. Once a homogeneous mixture has been achieved, segregation is prevented, since particles that are stuck together cannot separate.
4. It reduces dust.

Ideal Characteristics of Granules

The ideal characteristics of granules include uniformity, good flow, and compactibility, spherical shape, narrow particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1 and 2%), and addition of binder.

The effectiveness of granulation depends on the following properties:

i. Particle size of the drug and excipients
ii. Type of binder

iii. Volume of binder
iv. Wet massing time
v. Amount of force applied to distribute drug, binder and moisture
vi. Drying rate

Types of Granulation Process

1. Wet granulation
2. Dry granulation

Wet Granulation

The most widely used process in pharmaceutical industry is wet granulation. This is the traditional method of pretreatment of solids prior to tableting. Despite its complexity and inherent disadvantages, even now about half the tablets produced worldwide are manufactured by this process. Its essence is that particles of active ingredient, with a diluent if necessary, are stuck together using an adhesive, the latter usually being water-based. The result is a granular product which flows more readily and has an improved ability to flow during compression. Wet granulation process simply involves mixing of wet powder mass with a granulating liquid, wet sizing and drying.

Important steps involved in the wet granulation (Fig. 2.5)

i. Mixing of the drug(s) and excipients
ii. Preparation of binder solution
iii. Mixing of binder solution with powder mixture to form wet mass
iv. Coarse screening of wet mass using a suitable sieve (coarse sieves: 6–12 mesh size screens).

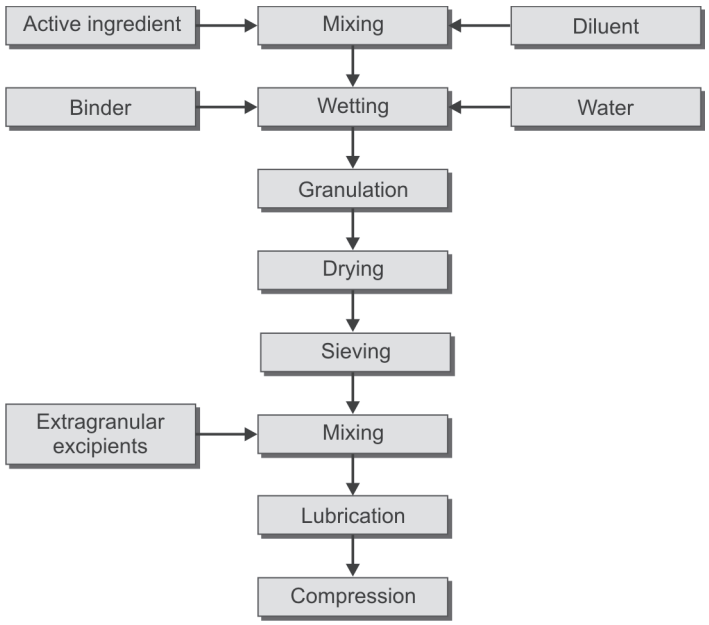


Fig. 2.5: Tablet manufacture (wet granulation process)

v. Drying of moist granules.
vi. Screening of dry granules through a suitable sieve (generally 14–30 mesh size screens).
vii. Mixing of screened granules with disintegrant, glidant, and lubricant.

Disadvantage of wet granulation

The various disadvantage of wet granulation are:

i. It is an expensive process because of labor, time, equipment, energy and space requirements.
ii. Loss of material during various stages of processing.
iii. Not suitable for moisture sensitive and thermo-labile drugs.
iv. Multiple processing steps add complexity and make validation and control difficult.

Dry Granulation

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is less frequently used methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation.

1. Slugging, where the powder is precompressed and the resulting tablet or slug are milled to yield the granules.
2. To precompress the powder with pressure rolls using a machine such as chilosonator.

Advantages

The main advantages of dry granulation or slugging are that it uses less equipment and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

i. For moisture sensitive material
ii. For heat sensitive material
iii. For improved disintegration since powder particles are not bonded together by a binder

Disadvantages

i. It requires a specialized heavy duty tablet press to form slug.
ii. It does not permit uniform color distribution.
iii. More dust is formed than wet granulation, increasing the chances of contamination.

Steps in dry granulation (Fig. 2.6)

i. Milling of drugs and excipients
ii. Mixing of milled powders
iii. Compression into large, hard tablets to make slug
iv. Screening of slugs
v. Mixing with lubricant and disintegrating agent
vi. Tablet compression

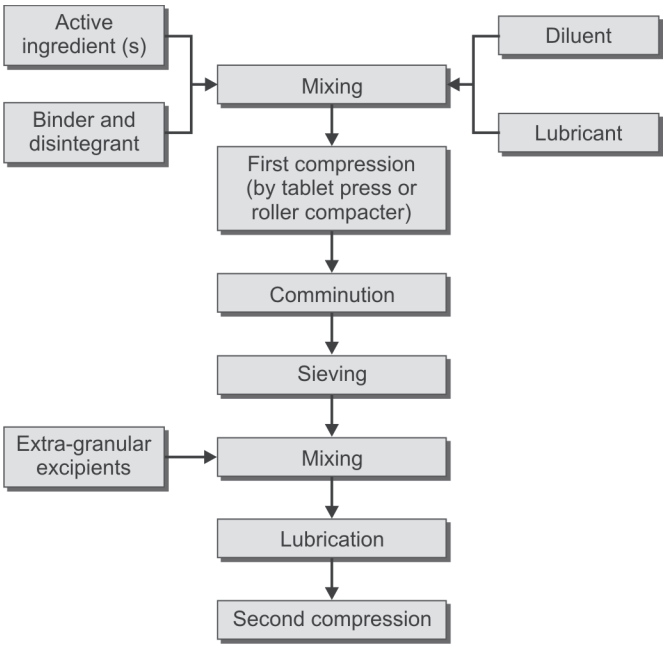


Fig. 2.6: Tablet manufacture (dry granulation process)

Two main dry granulation processes

Slugging process: Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

Factors affecting slugging

i. Compressibility or cohesiveness of the matter
ii. Compression ratio of powder
iii. Density of the powder
iv. Machine type
v. Punch and die size
vi. Slug thickness
vii. Speed of compression
viii. Pressure used to produce slug

Roller compaction: The compaction of powder by means of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules.

Formulation for dry granulation: The excipients used for dry granulation are basically same as that of wet granulation or that of direct compression. With dry granulation it is often possible to compact the active ingredient with a minor addition of lubricant and disintegrating agent. Fillers that are used in dry granulation include the following examples: Lactose, dextrose, sucrose, MCC, calcium sulphate, etc.

Drying: Drying is a one of the important step in the formulation. It is important to keep the residual moisture low enough to prevent product deterioration and ensure free flowing properties. The commonly used dryer includes fluidized bed dryer, vacuum tray dryer, microwave dryer, spray dryer, freeze dryer, turbo-tray dryer, pan dryer, etc.

Mixing or blending: The powder/granules blending are involved at stage of pre-granulation and/or postgranulation stage of tablet manufacturing. For optimum mixing, blending time and blending speed are to be evaluated. The various blenders used for blending are: Double cone blender, container blender, tumbling blender, agitated powder blender, bin blender, etc.

Direct compression (without granulation): The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required. Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression. Thus offering advantage particularly in terms of speedy production. Because it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

Advantages over wet granulation process: The variables faced in the processing of the granules can lead to significant tableting problems. Properties of granules formed can be affected by viscosity of granulating solution, the rate of addition of granulating solution, type of mixer used and duration of mixing, method and rate of dry and wet blending. The above variables can change the density and the particle size of the resulting granules and may have a major influence on fill weight and compaction qualities. Drying can lead to unblending as soluble API migrates to the surface of the drying granules.

i. Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API with necessary excipients.
ii. Decreases processing time, reduced labor costs, fewer manufacturing steps, and less number of equipment are required, less process validation, reduced consumption of power.
iii. Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive APIs.
iv. Particle size uniformity.
v. Provides stability against the effect of aging.
vi. The chances of batch-to-batch variation are negligible.
vii. Chemical stability problems for API and excipient would be avoided.

Disadvantages

i. Problems in the uniform distribution of low dose drugs.
ii. High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression. For example, aluminium hydroxide, magnesium hydroxide.
iii. The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flowability.
iv. Many active ingredients are not compressible either in crystalline or amorphous forms.
v. Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.
vi. Non-uniform distribution of color, especially in tablets of deep colors.

Manufacturing steps for direct compression (Fig. 2.7): Direct compression involves comparatively few steps:

i. Sizing of drug and excipients.
ii. Mixing of drug and excipients.
iii. Tablet compression.

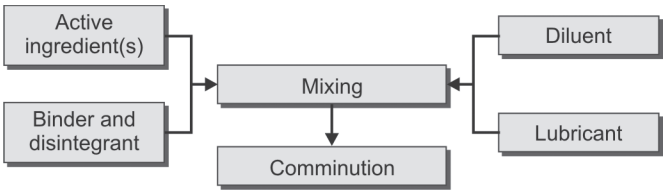


Fig. 2.7: Tablet manufacture (direct compression process)

TABLE 2.13: Comparison between wet granulation, dry granulation and direct compression

Wet granulation	*Dry granulation*	*Direct compression*
1. Milling and mixing of drugs and excipients	1. Milling and mixing of drugs and excipients	1. Milling and mixing of drugs and excipients
2. Preparation of binder	2. Compression into slugs	2. Compression of tablet
3. Wet massing by addition of binder solution	3. Milling and screening of slugs and compacted powder	
4. Screening of wet mass	4. Mixing with extra-granular excipients and lubricant.	
5. Drying of the wet granules	5. Compression of tablet	
6. Screening of dry granules		
7. Mixing with extra-granular excipients and lubricant		
8. Compression of tablet		

Compression

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press, refer to Fig. 2.8) or by multi station machine (rotary press).

The compression is divided into mainly three steps.

Step 1. Filling

The lower punch falls within the die, leaving a cavity into which particulate matter flows under the inuence of gravity from a hopper. Though, tablets are usually described in terms of weight, the die is filled by a volumetric process. The volume is determined by the depth to which the lower punch descends in the die. Unless this volume is filled reproducibly on each occasion, then the mass of the tablet will vary, and with it the drug content of each tablet. Therefore, uniform filling is essential. However, it must be borne in mind that the die cavity has a cross-section of only a few millimetres, and only a fraction of a second is available for filling each die. It is therefore necessary that the particles must flow easily and reproducibly.

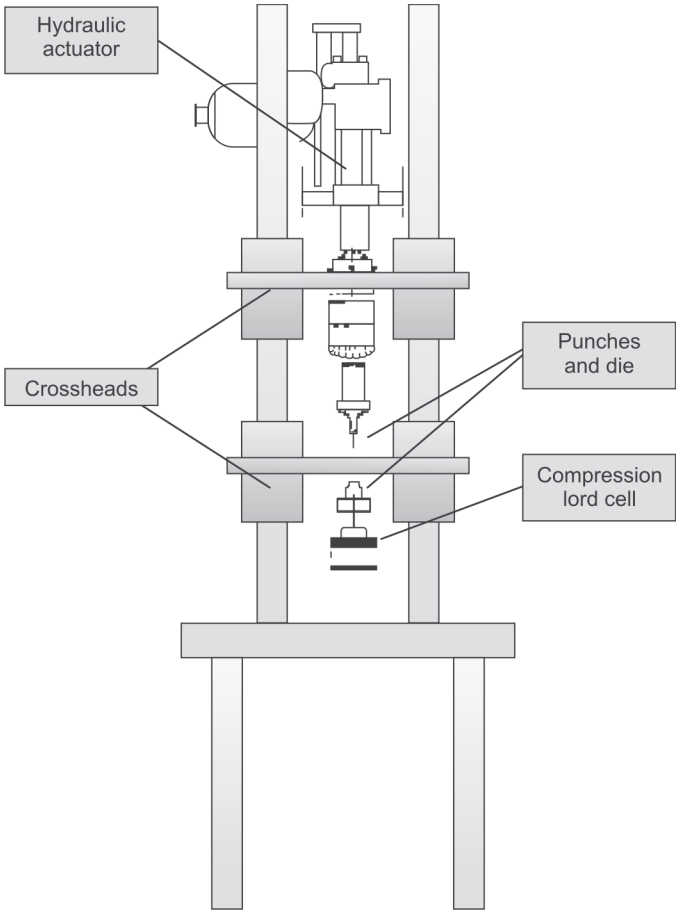


Fig. 2.8: Schematic diagram of a compression machine

Step 2. Compression

The upper punch descends, and its tip enters the die, confining the particles. The distance separating the punch faces decreases, either by movement of the upper punch alone or by movement of both punches as in rotary presses. The porosity of the contents of the die is progressively reduced, and the particles are forced into ever-closer proximity to each other. This process is facilitated by the particles fragmenting and/or deforming. Once the particles are close enough together, interparticulate forces then cause the individual particles to aggregate, forming a tablet. The magnitude of the force is governed by the minimum distance separating the punch faces. Hence, a second essential property of the particles is that they flow under the inuence of a compressive force.

Step 3. Ejection

The upper punch is withdrawn from the die, and so the force being applied to the tablet is removed. As the upper punch leaves the die, the lower punch moves upwards, pushing the tablet out of the die.

Common stages occurring during compression (Fig. 2.9)

Stage 1: Top punch is withdrawn from the die by the upper cam. Bottom punch is low in the die so powder falls in through the hole and fills the die.

Stage 2: Bottom punch moves up to adjust the powder weight—it raises and expels some powder

Stage 3: Top punch is driven into the die by upper cam and bottom punch is raised by lower cam. Both punch heads pass between heavy rollers to compress the powder.

Stage 4: Top punch is withdraw by the upper cam. Lower punch is pushed up and expels the tablet. Tablet is removed from the die surface by surface plate (scraper).

Stage 5: Return to stage 1.

Compression Equipment and Tablets Tooling

Compression machine can be single punch machine (stamping press) or by multi-station machine (rotary press). Tablet presses are designed with following basic components:

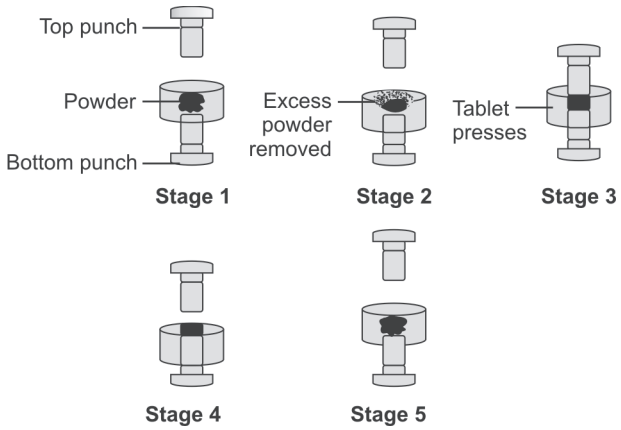


Fig. 2.9: Various stages during compression

1. Tablet compression machine hopper
2. Feeder system
3. Tablet press punches
4. Tablet press die system
5. Tablet press turret
6. Tablet press machine cam tracks
7. Tablet press filling station and weight control
8. Compression rollers
9. Tablet press ejection cam.

1. Tablet Compression Machine Hopper

The tablet compression process starts from here. It is at this point that you will put all powder you intend to compress into tablets. Tablet press hoppers come in a wide range of shapes and designs. Whatever the shape, it should be such that the material can flow seamlessly into the tablet compression chamber. Again, since it is one section that is in direct contact with the material, it is made of stainless steel (Fig. 2.10).



Fig. 2.10: Hopper

Depending on the design of a tablet press machine, you can fill the powder manually or using other automated systems. While designing hopper, it is to ensure there is a consistent flow of powder from the hopper to compression systems. Here are major concerns that we have addressed so far:

i. Hoppers may feature optimal flow angles to facilitate flow, especially where it is nearly impossible to adjust formulation.
ii. Some hoppers may feature vibratory rods. This is done carefully to enhance product flow and to prevent possible product separation.
iii. At any given point, the design of these tablet compression machine parts aims to eliminate possible feeder starvation.

2. Feeder System

This yet another critical part of the tablet compression process. Remember, at any given time, the design of the system should be such that it allows an accurate and consistent amount of powder to flow to the punch and die system. Tablet press machine feeder system is made up two critical components:

Feeder housing: Material from the hopper will enter the die system through the housing. The feeding process should be consistent and accurate to produce high quality tablets. The feeding housing is made of stainless steel 316 since it is in contact with the product. Also, the product must not stick on the feeder housing as it will cause inconsistencies during the feeding process.

Feed peddles: Quite a number of high speed rotary tablet press machines have a feed peddles. The feed peddles ensures consistent and accurate material feeding into the die systems. Without a feed peddle, especially if the machine is operating at a high speed, there could be chances of some dies being filled half way. This may result in tablets with varying thickness or the degree of compaction.

3. Tablet Press Punches

This is yet another critical part of the tablet compression machine parts. Normally, you can choose from simple to complex shapes of tablet press punches. The design and shape of a press punch tool design have a direct impact on the tablet quality. Under normal circumstances, these tablet compression parts are subjected to abrasive environments and exposed to extremely high pressure. Therefore, they require high quality material and if possible with a special coating to prevent sticking or wear (Fig. 2.11).

To produce the desired tablets, punches move within the die, thereby compressing powder into the desired tablets. The tablet press machine consists of:

Upper punch system: Like the name suggests, the tablet press upper punches are on the upper section of the rotary system. They move vertically, in and out of the die bore as you can see in Fig. 2.11.

Lower punch system: The lower punches are on the lower section of the rotary system of the tablet press machine. During the tablet compression process, the lower punches remain within the die bore throughout the entire cycle.

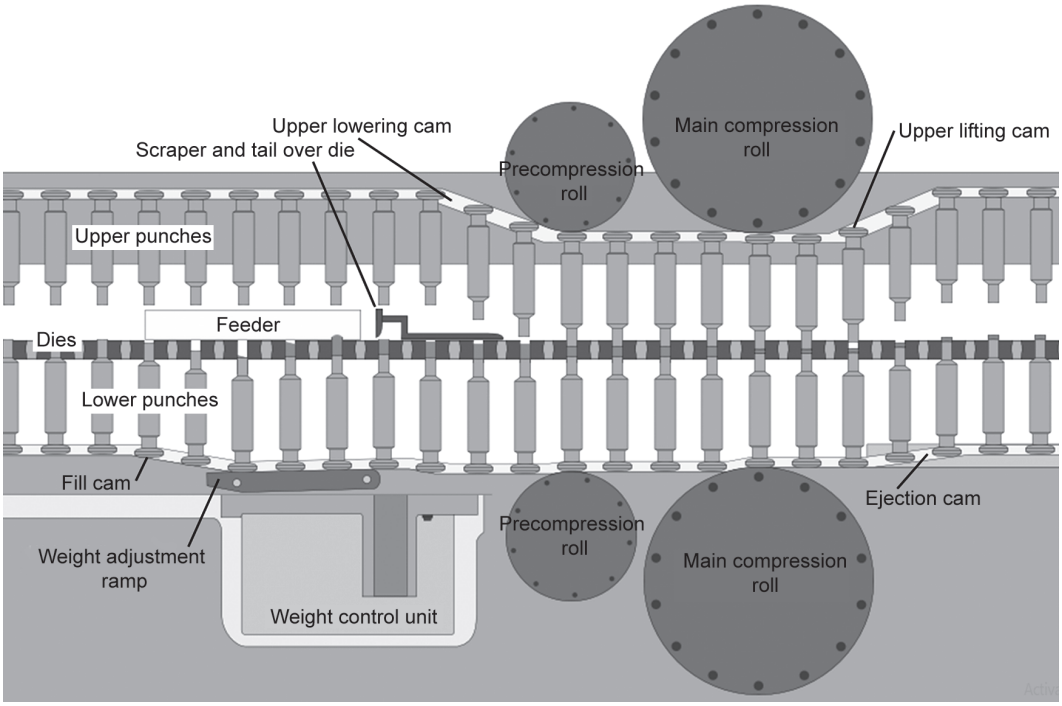


Fig. 2.11: Compression process with components of compression machine

4. Tablet Press Die System

Normally, whenever we talk about the tablet press punch then the next component that comes in mind is the die system. As I had mentioned earlier, the movement of tablet press machine punches, takes place within the die bore or cavity. Therefore, the punch and die must be machined together to ensure compatibility. It is in the die cavity that the powder is compressed into desired tablets of definite thickness and size (Fig. 2.12).

It is the die cavity that determines both the thickness and size of a tablet. Like the punches, a die system should have the following key features:

i. Clean impression on every punch
ii. Prevent chipping or damaging of tablets
iii. Feature anti-corrosion protection
iv. Have non-stick treatment

Other critical features we consider whenever we are machining a tablet press die system include: Tapering angle; this is a critical aspect since it allows excess air to escape, while minimizing the tablet ejection force and frictional heat. Other technical specifications include die height, chamfer, die bore and die diameter.

5. Tablet Press Turret

There have been a lot of developments in the recent past as far as designing these tablet compression machine parts is concerned. As a matter of fact, turrets are the heart of tablet press tooling.

The rotating turrets have holes that host the die system of a tablet making machine. They are precisely machined to the required rotational tolerances and dimensions.

Every bore on its surface ensures the die and punch are fully aligned for optimal tablet making process.

Again, to guarantee efficiency and reliability, there is always need to allow for any necessary adjustments as far as the dynamisms in tablet compression processes are concerned. Therefore, it is for this reason that tablet press manufacturers are shifting from traditional turrets that were basically dies and punches, to segmented turrets that have segmented sections and punches. A segmented rotary turret design increases production, while minimizing possible downtime during the manufacturing process. Furthermore, this new design allows for increased number of tablet compression stations and fast part changeover.

Remember, it is the tablet press machine turret that determines the number of stations. This helps to determine the production capacity of the machine for every complete rotation of the turret.



Fig. 2.12: Dies of different sizes

6. Tablet Press Machine Cam Tracks

Cam tracks are other critical tablet compression machine parts that play an integral role in ensuring seamless tableting process. The main work of the cam tracks is to guide the upper and lower punches in different stages in the tablet compression process. That is, as the turret rotates, it is the cam trucks that move the punches in an up and down motion. This helps to control filling, compression and ejection of already processed tablets.

For example, as the upper cam withdraws top punches from the die, powder flows in filling the cavity. On the other hand, the lower cam track pushes the bottom punches upwards within the die cavity. This makes the die to be overfilled by material, allowing for accurate adjustment of the die content. Again, to achieve a maximum compression force, the upper cam track drives the top punch and the lower cam adjusts the bottom punch. With the tablet compressed to the desired specifications, the upper cam withdraws top punches. On the other hand, the lower punches move upwards to expel the compressed tablets with the help of lower cam. In short, you can see that upper and lower cam tracks play an integral role at every tablet compression stage in these machines. It is a simple process that must be precisely controlled to achieve the desired tablet size and weight.

7. Tablet Press Filling Station and Weight Control

With the help of different movements of the cam systems, material will flow into the die cavity depending on the position of the punches. In most cases, tablet press machine manufacturers use servo motors to control movement of the cam track for accurate dosing. This is due to their high precision and ease of integration to other computerized systems of other machine parts (Fig. 2.13).

A critical procedure in this section of tablet compression process in the weight control, by controlling the depth fill, tableting machine can easily regulate the content within its die cavity. Normally, with the help of lower cam track, the bottom punch moves upwards to a predetermined height. This ensures the die cavity is filled to a required depth before any compression process begins. At times, as the bottom punch

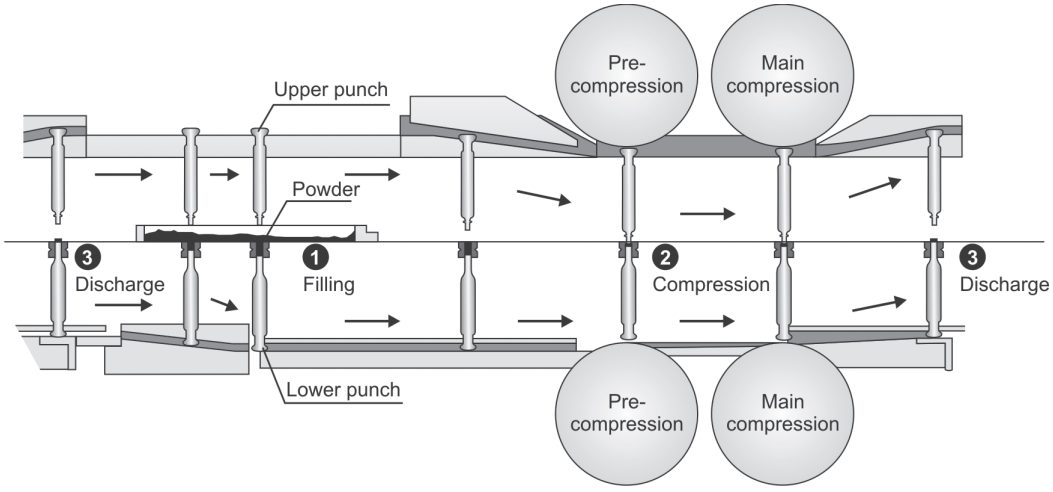


Fig. 2.13: Process illustrates the filling process, compressing to tablet discharge

moves up, the excess powder may overflow. Therefore, to avoid wastages, the excess powder automatically moves to the next die cavity, which is just about to be filled. To achieve these, all the other components must coordinate smoothly for a seamless tableting process.

8. Compression Rollers

The idea is to ensure only powder is compressed to the desired shape and size. However, at times you may find air within the powder particles. To achieve this, tablet compression machines feature a series of rollers that exert a sufficient amount of force to compress the powder. That is, they expel air first before the compression process begins. Most machines have two sets of rollers.

Pre-compression rollers: These are the very first rollers in rotary tablet press. Basically, these rollers apply a small amount of force on the upper and lower punches. This gives the initial compression force. The aim of this process is to remove air that could be in the die or powder particles. Any air within the die cavity or powder particles will obviously result in low quality tables. This process is necessary for the reason that, any powder in the machine's hopper may have air between its particles.

Main compression rollers: Main compression rollers exert a predetermined amount of force (final compression force) for the formation of tablets. The compression force at this stage is higher than the pre-compression force. It is important that the rollers remain stable with no vibration during the entire process. This is to ensure consistency of the tablets' thickness and size.

9. Tablet Press Ejection Cam

Again, the ejection cam is located just after the main compression rollers. Like the other cam tracks, ejection cams are also critical aspects of tablet compression machine parts. Without them, there is no way you will access the already processed tablets. Remember, after compression, the tablet is always fixed within the die systems (space between lower and upper punches).

Toolings: Tooling set includes three components:

i. Upper punch
ii. Lower punch
iii. Die

A lower punch fits into the die from the bottom and an upper punch, having a head of the same shape and dimensions, which enters the die cavity from the top after tablet material fills the die cavity.

Parts of punches and dies (Fig. 2.14)

1. **Head:** The end of the punch that guides it through the cam track of tablet machine during rotation.
2. **Outside head angle:** The area in touch with the roller prior to head flat, while compression.
3. **Inside head angle:** This is the area, which pulls down the lower punches after ejection and lifts the upper punches after compression.

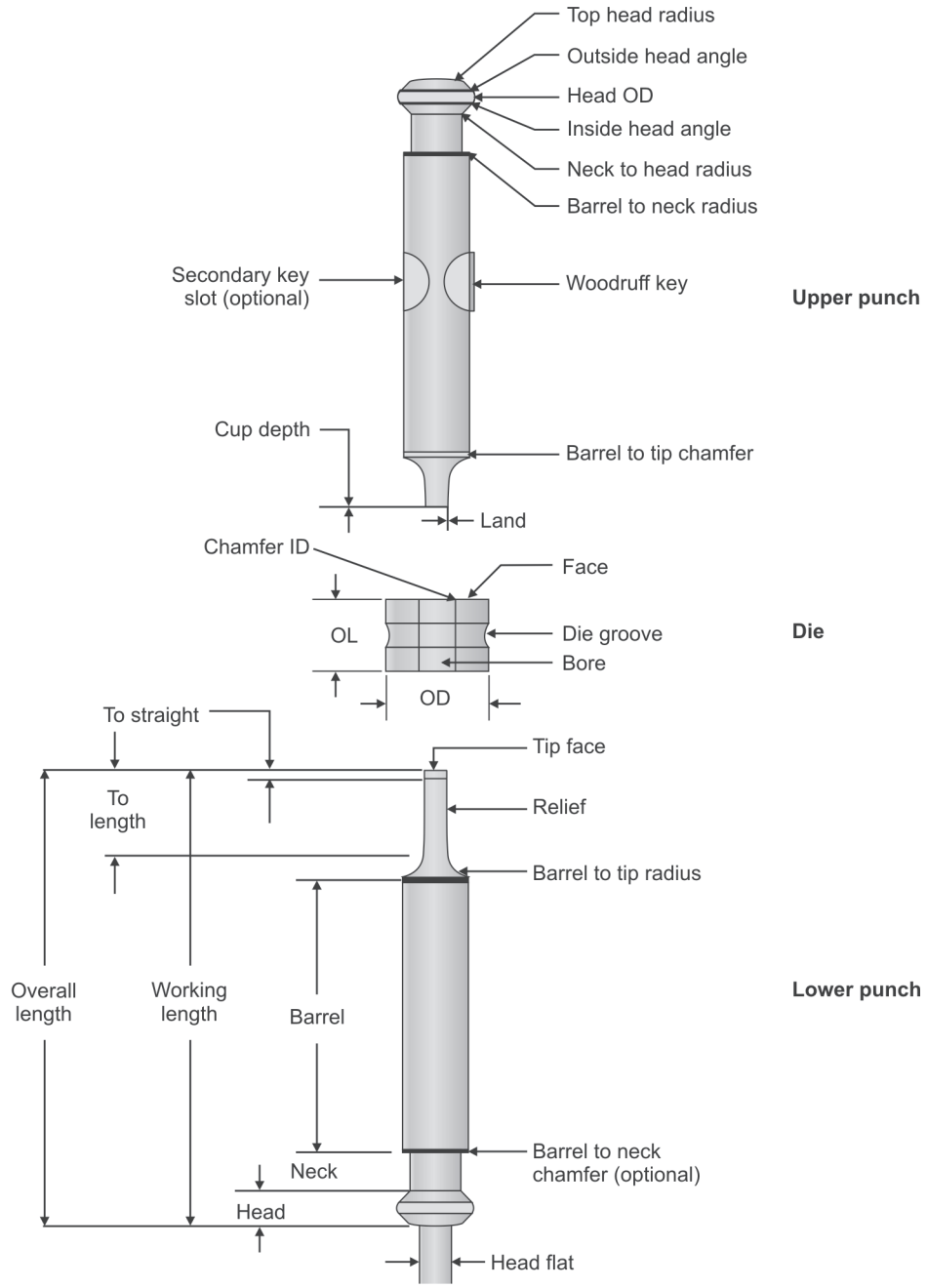


Fig. 2.14: Tooling set schematic diagram (OD: Outer diameter, ID: Inner diameter, OL: Outer length, IL: Inner length)

4. **Neck:** The relived area between head and barrel, which provides clearance for the cams.
5. **Barrel:** The area guides the punch (while going up and down) with reference to turret guides.
6. **Tip:** This determines size, shape and profile of the tablet.

7. **Tip face:** This area of the punch is where the tablets formed. Good surface finish is required for better quality.
8. **Working length:** This distance between bottom of the cup and the head flat is called working length.
9. **Overall length:** Distance between top of the cup and the head flat.
10. **Key angle:** The relationship of the punch key to the tablet shape. The keys position is influenced by the tablet shape, take-off angle and turret rotation.

Type of tooling set (Fig. 2.15)

i. Based on tablet shape
ii. Based on barrel diameter
iii. Based on material of construction (MOC)

Based on tablets shape: Based on the punches tip, tooling can be of following types:

i. Flat faced
ii. Flat faced beveld edge
iii. Shallow concave (round/oval/capsule shaped)
iv. Standard concave (round/oval/capsule shaped)
v. Deep concave (round/oval/capsule shaped)
vi. Extra deep cup
vii. Double radius
viii. Tall and pill

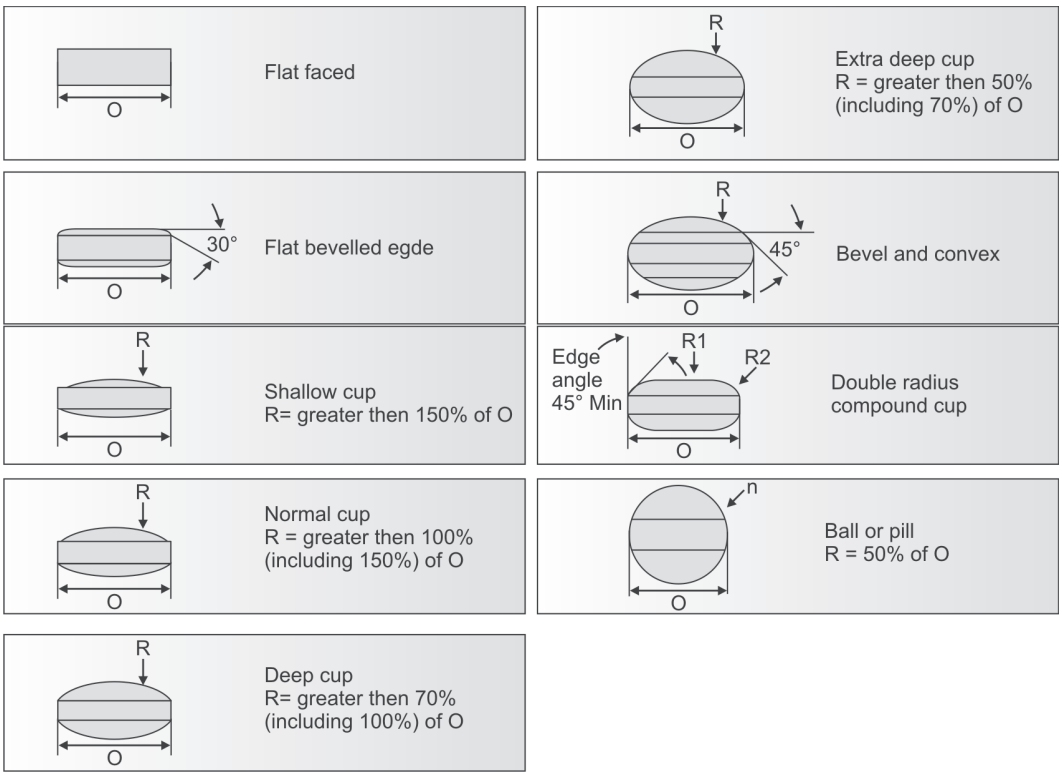


Fig. 2.15: Various types of punches based on tablet shape required

Based on punch barrel diameter and outer diameter of die: Based on based on punch barrel diameter and outer diameter of die, tooling can be of following types (Table 2.14):

1. B tooling
2. D tooling
3. BB tooling
4. DB tooling

Based on tablet weight, type of tooling selected, usually for small tablet, B-type tooling preferred.

TABLE 2.14: Type of tooling based on punch barrel diameter and outer diameter of die

Tooling type	*Punch barrel diameter*	*Outer diameter of die*
D	25.4 mm	38.10 mm
B	19.0 mm	30.16 mm
BB	19.0 mm	24.00 nm
DB	25.4 mm	30.16 mm

Based on material of construction (MOC): Material of construction is very important from tool finishing and strength perspective, but better finishing and quality incur extra cost. Thus, based on requirement MOC gets finalized. MOC can be:

1. High carbon high chromium (HCHC)
2. Oil hardened non-shrinking steel. Steel can be of different grades.

Compression and Processing Problems

A manufacturing chemist faces number of problems during tablet manufacture. Majority of defects are due to inadequate fines or inadequate moisture in the granules ready for compression or due to faulty machine setting. These manufacturing problems requires an in-depth knowledge of granulation processing and tablet presses, and is acquired only through an in-depth study and a vast experience.

The manufacturing problems found in tablets along-with their causes and related remedies are discussed below. These manufacturing problems are due to:

I. Tableting process
II. Excipient
III. Machine

Tableting process problems are as follows

i. Capping
ii. Lamination
iii. Cracking

Excipients related problems are as follows

i. Chipping.
ii. Sticking
iii. Picking
iv. Binding
v. Mottling

Defect related to machine:

Double impression

Capping: 'Capping' is defined as, when the upper or lower segment of the tablet separates horizontally, either partially or completely from the main body of a tablet and comes off as a cap, during ejection from the tablet press, or during subsequent handling (Table 2.15).

Cause: Capping is usually due to the air-entrapment in a compact during compression, and subsequent expansion of tablet on ejection of a tablet from a die (Table 2.16).

TABLE 2.15: Causes and remedies of capping related to granulation

Sr. No.	*Causes*	*Remedies*
1.	Large amount of fines in the granulation	Remove fines through 100 to 200 mesh screen
2.	Too dry or very low moisture content	Moisten the granules. Add hygroscopic substance, e.g. sorbitol, methyl-cellulose or PEG-4000
3.	Not properly dried granules	Dry the granules properly
4.	Less amount of binder	Increasing the mount of binder or by adding dry binder like gum acacia, powdered sorbitol, PVP, hydrophilic silica or powdered sugar
5.	Less or improper lubricant	Increase the amount of lubricant or by changing the lubricant

TABLE 2.16: Causes and remedies of capping related to dies, punches and tablet press

Sr. No.	*Causes*	*Remedies*
1.	Improper finished dies	Polish dies properly
2.	Deep concave punches or beveled-edge faces of punches	By using flat punches
3.	Lower punch remains below the face of die during ejection	By proper setting of lower punch during ejection
4.	Sweep-off blade is not adjusted properly	By adjusting sweep-off blade properly
5.	High speed of turret	Reduce speed of turret

Lamination: 'Lamination' is the separation of a tablet into two or more distinct horizontal layers.

Cause: Air-entrapment during compression and subsequent release on ejection, which worsen by high speed of turret (Tables 2.17 and 2.18).

TABLE 2.17: Causes and remedies of lamination related to granulation

Sr. No.	*Causes*	*Remedies*
1.	Oily or waxy materials in granules	By adding adsorbent or absorbent
2.	High amount of hydrophobic lubricant, e.g. magnesium-stearate	By using less amount of lubricant or changing the lubricant

TABLE 2.18: Causes and remedies of lamination related to dies, punches and tablet press

Sr. No.	*Causes*	*Remedies*
1.	Rapid relaxation of the peripheral regions of a tablet during ejection from die wall cavity	By using tapered dies, i.e. upper part of the die bore having an outward taper of 3°–5°

Chipping: 'Chipping' is defined as the breaking of tablet edges during ejection of tablet from the press or handling and coating process (Tables 2.19 and 2.20).

Cause: Incorrect machine settings, especially improper ejection.

TABLE 2.19: Causes and remedies of chipping related to granulation

Sr. No.	*Causes*	*Remedies*
1.	Sticking on punch faces	Drying the granules properly or increasing the amount of lubricant
2.	Too dry granules	Moisten the granules and by adding hygroscopic substances

TABLE 2.20: Causes and remedies of chipping related to dies, punches and tablet press

Sr. No.	*Causes*	*Remedies*
1.	Groove of die damaged at compression point	Polish to open end and replacing the die
2.	Center of the die wider than ends	Polish the die to make it cylindrical
3.	Edge of punch face turned inside/inward	Polish the punch edges
4.	Concavity is high to compress properly	Reducing concavity of punch faces and using flat punches

Cracking: Small, fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as 'cracks' (Tables 2.21 and 2.22).

Cause: It is due to rapid expansion of tablets, especially when deep concave punches are used.

TABLE 2.21: Causes and remedies of cracking related to granulation

Sr. No.	*Causes*	*Remedies*
1.	Large size of granules	Reducing granule size and by adding fines
2.	Granules are very dry	Moisten the granules properly and add proper amount of binder
3.	Granulation too cold	Compress at room temperature

TABLE 2.22: Causes and remedies of cracking related to dies, punches and tablet press

Sr. No.	*Causes*	*Remedies*
1.	Tablet expands on ejection due to air entrapment	Using tapered die
2.	Deep concavities during ejection	Using special take-off

Sticking and filming: 'Sticking' refers to the tablet material adhering to the die wall. Filming is a slow form of sticking and is largely due to excess moisture in the granulation (Tables 2.23 and 2.24).

Cause: Improperly dried or improperly lubricated granules.

TABLE 2.23: Causes and remedies of sticking related to granulation

Sr. No.	*Causes*	*Remedies*
1.	Granules not dried properly	Drying the granules properly
2.	Less or improper lubrication	Increasing or changing the lubricant
3.	Too much binder	Reduce the amount of binder
4.	Soft or weak granules	Optimize the amount of binder and granulation technique
5.	Oily materials	Modify mixing process. Add an absorbent

TABLE 2.24: Causes and remedies of sticking related to dies, punches and tablet press

Sr. No.	*Causes*	*Remedies*
1.	Concavity too deep for granulation	Reducing concavity
2.	Too little pressure	Increase pressure
3.	Compressing too fast	Reducing the speed of compression

Picking: 'Picking' is the term used when a small amount of material from a tablet is sticking to and being removed off from the tablet-surface by a punch face. The problem is more frequent on the upper punch faces than on the lower ones. The problem becomes more severe when tablets are repeatedly manufactured in same station because of the more and more material getting added to the already stuck material on the punch face (Tables 2.25 and 2.26).

Cause: When punch tips have engraving or embossing letters, as well as the granular material is improperly dried.

TABLE 2.25: Causes and remedies of picking related to granulation

Sr. No.	*Causes*	*Remedies*
1.	Excessive moisture in granules	Dry properly the granules
2.	Less or improper lubrication	Increase lubrication; use colloidal silica as a 'polishing agent', so that material does not cling to punch faces
3.	Low melting point substances, may soften from the heat of compression and lead to picking	Add high melting-point materials. Use high meting point lubricants
4.	High amount of binder	Reduce the amount of binder or by changing the type of binders
5.	Too warm granules when compressing	Compress at room temperature. Cool sufficiently before compression

TABLE 2.26: Causes and remedies of picking related to dies, punches and tablet press

Sr. No.	*Causes*	*Remedies*
1.	Rough or scratched punch faces	Polish faces to high luster
2.	Embossing or engraving letters on punch faces such as B, A, O, R, P, Q, G	Designing letter as large as possible and coating the punch faces with chromium to produce a smooth and non-adherent face
3.	Pressure applied is not enough	Increase pressure to optimum

Binding: 'Binding' in the die, is the term used when the tablets sticks, seize or tear in the die. A film is formed in the die and ejection of tablet is hindered. With excessive binding, the tablet sides are cracked and it may crumble apart (Tables 2.27 and 2.28).

Cause: Binding is usually due to excessive amount of moisture in granules, lack of lubrication and use of worn dies.

TABLE 2.27: Causes and remedies of binding related to granulation

Sr. No.	*Causes*	*Remedies*
1.	High moisture content in granules	Dry the granules properly
2.	Insufficient or improper lubricant	Increase the amount of lubricant
3.	Too coarse granules	Reduce granular size, add more fines, and increase the quantity of lubricant
4.	Granular material too warm, sticks to the die	Reduce temperature
5.	Granular material very abrasive and cutting into dies	Using wear-resistant dies

TABLE 2.28: Causes and remedies of binding related to dies, punches and tablet press

Sr. No.	*Causes*	*Remedies*
1.	Poorly finished dies	Polish the dies properly
2.	Rough dies due to abrasion, corrosion	Changing the granulation
3.	Too much pressure in the tablet press	Reduce pressure

Mottling: 'Mottling' is define as the unequal distribution of colour on a tablet, with light or dark spots standing out in an otherwise uniform surface (Table 2.29).

Cause: Major cause of mottling is coloured drug, whose colour differs from the colour of excipients used for granulation of a tablet.

TABLE 2.29: The causes and remedies of mottling

Sr. No.	*Causes*	*Remedies*
1.	A coloured drug used along with colourless or white-coloured excipients	Using appropriate colourants
2.	A dye migrates to the surface of granulation while drying	Changing the solvent system, and binder reducing drying temperature and using a smaller particle size
3.	Improperly mixed dye	Mixing properly and reducing size to prevent segregation

Double impression: 'Double impression' involves only those punches, which have a monogram or other engraving on them (Table 2.30).

Cause: During compression, the tablet receives the imprint of the punch. Also when the lower punch freely drops and travels uncontrolled for a short distance before riding up the ejection cam to push the tablet out of the die, now during this free travel, the punch rotates and at this point, the punch may make a new impression on the bottom of the tablet, resulting in 'double impression'. If the upper punch is uncontrolled, it can rotate during the short travel to the final compression stage and create a double impression.

TABLE 2.30: The causes and remedies of mottling

Sr. No.	*Causes*	*Remedies*
1.	Free rotation of either upper punch or lower punch during ejection of a tablet	Preventing punch rotation

Packaging

'Blister packs' are a common form of packaging used for a wide variety of products. They are safe and easy to use and they allow the consumer to see the contents without opening the pack. This saves the cost of different tools and to change the production machinery between products. Sometimes, the pack may be perforated so that individual tablets can be detached. This means that the expiry date and the name of the product have to be printed on each part of the package. The blister pack itself—must remain absolutely flat as it travels through the packaging processes, especially when it is inserted into a carton.

Bottles packs are also available. Usually bottles are made up of HDPE (high density polyethylene).

Quality Control Test for Tablets

For establishing the quality of a tablet product, the fundamentals remain the same, i.e. to ascertain that the product delivers the intended active ingredient in an accurate and reproducible manner. Therefore, tablet testing are broadly divided into three aspects.

1. Confirmation of the nature of the active ingredient and the product (identity, quantity, impurities, integrity, etc.).
2. Establishing pharmaceutical availability of the active moiety both *in vitro* and *in vivo* in humans and, if required, also in animals.
3. Establishing stability profile to achieve shelf life.

In this category, one seeks to establish whether the tablets are within specifications, for example, the nature of the active ingredient (identication), expected amount (assay), purity (related compounds), and uniformity of the amount of drug from tablet to tablet (uniformity of dosage units). Commonly these testing procedures are described in pharmacopeias under a specic name, for example, the names given in parentheses are referred to as the USP (US Pharmacopeia). In addition to these tests, some other tests such as friability, hardness, disintegration, etc. are also conducted and are described below. Although a number of procedures could be described for individual tests, most emphasis will be given to procedures described in the pharmacopeias because these are usually relatively simpler to conduct and are generally recognized around the

world. The various quality control test prescribed in pharmacopeias regarding the quality of pharmaceutical tablets are diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characteristics of tablets.

General Appearance

The general appearance of tablets, its visual identity and overall 'elegance' effects the consumer acceptance. The general appearance test involves characteristics like tablet's size, shape, color, taste, surface textures and consistency.

Size and Shape

The shape and dimensions of compressed tablets are determined by the type of tooling during the compression process. Tablet thickness, size and shape are consistent from batch to batch or within a batch only when tablet granulation is consistent in particle size and particle size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in good working condition. The thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information of the variation between tablets. Weigh individually 20 units selected at random and calculate the average weight. Not more than two of the individual weights deviates from the average weight by more than the percentage given in the pharmacopeia and none deviates by more than twice that percentage. IP/BP and USP limits for tablet weight variation is given in Table 2.31.

Organoleptic Properties

The color of the product should be uniform in a single tablet, tablet to tablet and from batch to batch. Non-uniformity of coloring not only lack aesthetic appeal but could be associated by the consumer with non-uniformity of content and general poor product quality. The eye cannot differentiate small differences in color hence reflectance spectrophotometry, and micro reflectance photometer have been used to measure color uniformity. Taste is also important especially chewable tablets for this companies utilize taste panels to judge the preference of different flavors and flavor levels in the development of a product. Taste preference is however subjective and the control of taste in the production of chewable tablets is usually based on the presence or absence of a specified taste.

Assay

Quantitative test, in this 10–20 tablets are ground and the active ingredient is dissolved or extracted in a suitable solvent using the described procedure. The concentration of the extracted solution is determined using a specic and validated spectroscopic or

TABLE 2.31: Weight variation parameters

Average weight (USP)	*Average weight (IP/BP)*	*Percentage difference*
130 mg or less	80 mg or less	10
More than 130 mg through 324 mg	More than 80 mg through 250 mg	7.5
More than 324 mg	More than 250 mg	5

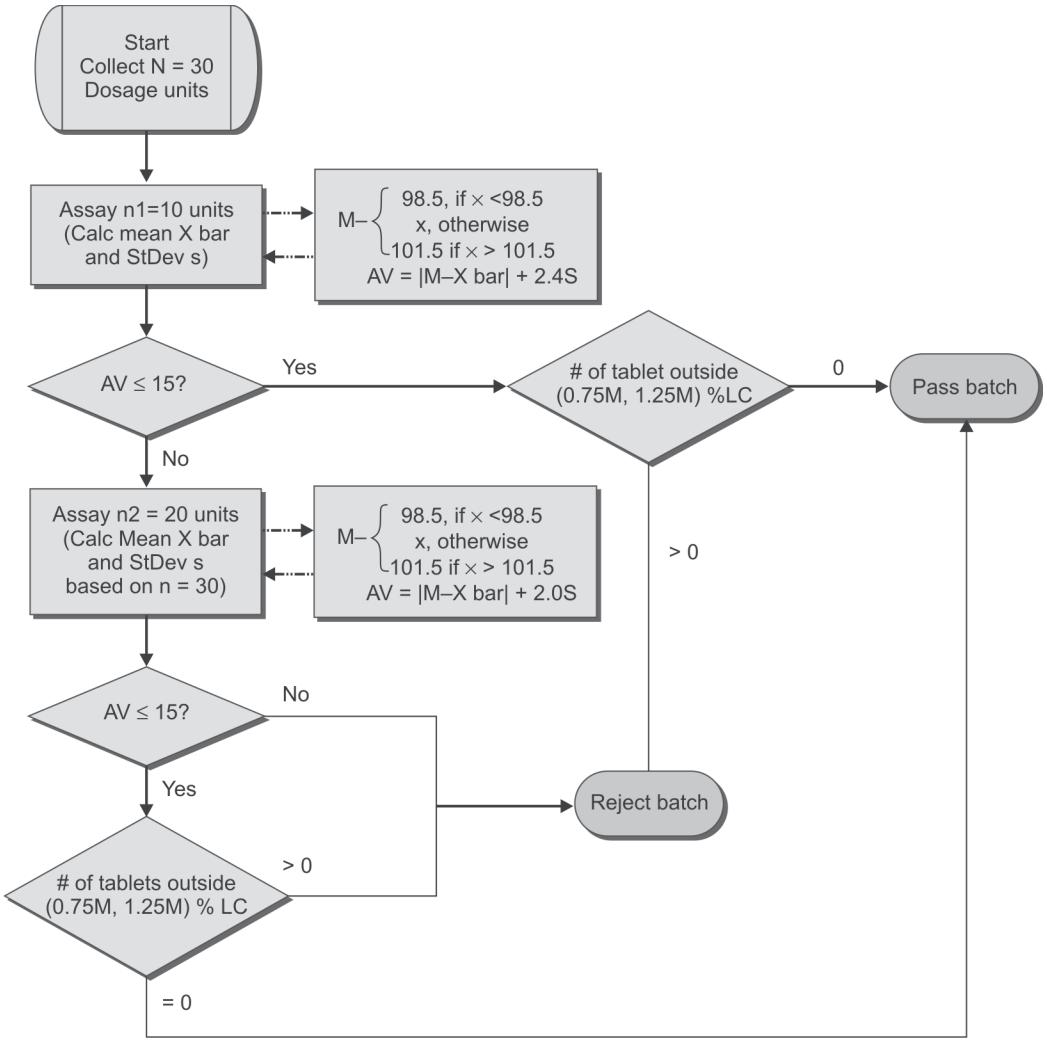
chromatographic method against a solution of reference standard. These results are reported as percent of expected/labeled value. Although the specifications for assay results differ from product to product, generally the expected range for individual active ingredient is to be within 90–110% of the labeled amount.

Uniformity of Dosage Form

This test is done to make sure that every tablet should contain the same amount of active ingredient with little or no variation within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets. Uniformity of dosage form can be established by weight variation and content uniformity (Flowchart 2.1).

Weight variation criteria is adopted for uncoated tablets or film coated tablets, when content of drug substance (DS) is more than equal to 25%w/w and weight of tablet is more than equal to 25 mg. For other tablets, a content uniformity criterion is adapted.

Flowchart 2.1: Showing content uniformity criteria



The requirements for dosage uniformity (as per USP) are met if:

The acceptance value of the first 10 dosage units is less than or equal to L1%.

If the acceptance value is greater than L1%, test the next 20 units, and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1%, and no individual content of any dosage unit is less than [1 (0.01) (L2)] M nor more than [1 + (0.01)(L2)] M as specified in the calculation of acceptance value in the USP <905>. L1 is 15.0 and L2 is 25.0.

Calculate the acceptance value (AV) by the formula:

$$AV = |M - X| + ks$$

S = Standard deviation

k = Acceptability constant (K = 2.4 (Case 1, number of tablets = 10) and K = 2 (Case 2, number of tablets = 30).

M value depends on mean assay value of samples, if mean value (X) is 98.5% ≤X ≤101.5 %, then M = X and AV = ks

When mean (X) < 98.5%, then M = 98.5

$$AV = 98.5 - X + ks$$

If mean (X) 101.5%, then M 101.5

$$AV = |M - X| + ks$$

Hardness or Crushing Strength

The resistance of tablets to **capping**, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its **hardness**. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrally to the tablet. Hardness, which is now more appropriately called crushing strength determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10–20 kg). **Tablet hardness** have been associated with other tablet properties such as density and porosity. Hardness generally increase with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression (Fig. 2.16).

Tablet Disintegration

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. The disintegration test is carried out using the disintegration tester which consists of a basket rack holding

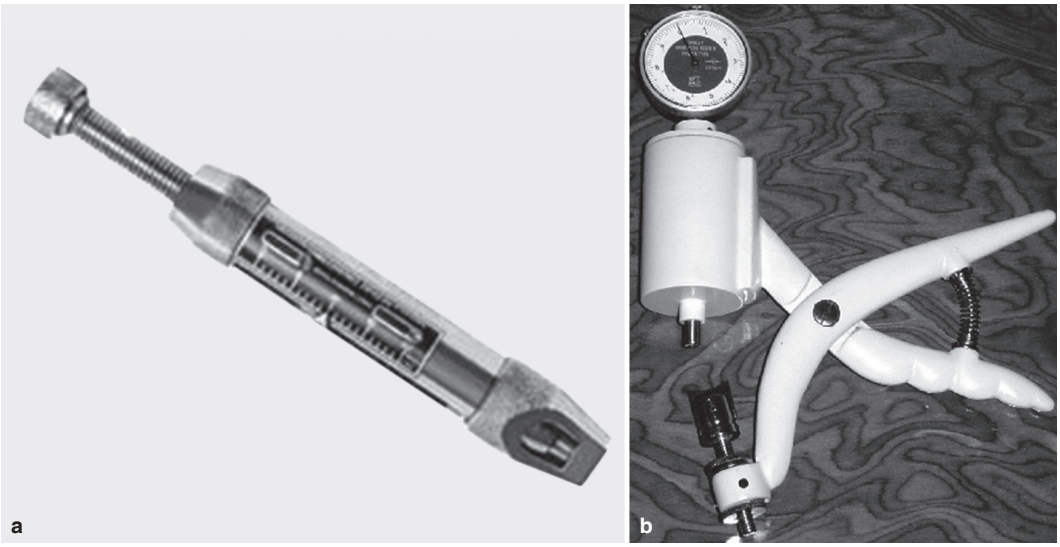


Fig. 2.16a and b: Tablet hardness tester: (a) Monsanto type, (b) Pfizer type

6 plastic tubes, open at the top and bottom, the bottom of the tube is covered by a 10-mesh screen. The basket is immersed in a bath of suitable liquid held at 37ºC, preferably in a 1L beaker. For compressed uncoated tablets, the testing fluid is usually water at 37ºC but some monographs direct that simulated gastric fluid be used. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets. For most uncoated tablets, the BP requires that the tablets disintegrate in 15 minutes (although it varies for some uncoated tablets) while for coated tablets, up to 2 hours may be required. The individual drug monographs specify the time disintegration must occur to meet the pharmacopoeial standards. Each of the pharmacopeia like the USP, BP, IP, etc. each have their own set of standards and specify disintegration tests of their own. USP, European pharmacopeia and Japanese pharmacopeia have been harmonized by the International Conference on Harmonization (ICH) and are interchangeable. The disintegration test is performed to find out the time it takes for a solid oral dosage form like a tablet or capsule to completely disintegrate. The time of disintegration is a measure of the quality. This is because, for example, if the disintegration time is too high; it means that the tablet is too highly compressed or the capsule shell gelatin is not of pharmacopeial quality or it may imply several other reasons. And also if the disintegration time is not uniform in a set of samples being analyzed, it indicates batch inconsistency and lack of batch uniformity.

Disintegration Test Apparatus

The disintegration test is conducted using the disintegration apparatus. Although there are slight variations in the different pharmacopeias, the basic construction and the working of the apparatus remains the same. The apparatus consists of a basket made of transparent polyvinyl or other plastic material. It has 6 tubes set into the same basket with equal diameter and a wire mesh made of stainless steel with uniform mesh size is fixed to each of these six tubes. Small metal discs may be used to enable immersion of the dosage form completely. The entire basket-rack assembly is movable by

reciprocating motor which is fixed to the apex of the basket-rack assembly. The entire assembly is immersed in a vessel containing the medium in which the disintegration test is to be carried out. The vessel is provided with a thermostat to regulate the temperature of the fluid medium to the desired temperature (Fig. 2.17).

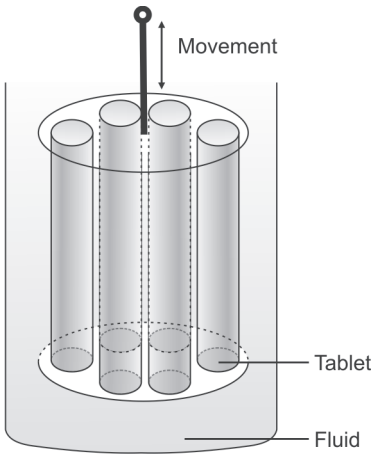


Fig. 2.17: Schematic representation of disintegration test apparatus

Disintegration Test Method

The disintegration test for each dosage form is given in the pharmacopeia. There are some general tests for typical types of dosage forms. However, the disintegration test prescribed in the individual monograph of a product is to be followed. If the monograph does not specify any specific test, the general test for the specific dosage form may be employed. Some of the types of dosage forms and their disintegration tests are:

1. **Uncoated tablets:** Tested using distilled water as medium at 37+/–2°C at 29–32 cycles per minute; test is completed after 15 minutes. It is acceptable when there is no palpable core at the end of the cycle (for at least 5 tablets or capsules) and if the mass does not stick to the immersion disc.
2. **Coated tablets:** The same test procedure is adapted but the time of operation is 30 minutes.
3. **Enteric coated/gastric resistant tablets:** The test is carried out first in distilled water (at room temperature for 5 min; USP and no distilled water per BP and IP), then it is tested in 0.1 M HCL (up to 2 hours; BP) or stimulated gastric fluid (1 hour; USP) followed by phosphate buffer, pH 6.8 (1 hour; BP) or stimulated intestinal fluid without enzymes (1 hour; USP).
4. **Chewable tablets:** Exempted from disintegration test (BP and IP), 4 hours (USP).

These are a few examples for illustration. The disintegration tests for capsules, both hard and soft gelatin capsules are also performed in a similar manner. Also, the USP also provides disintegration tests for suppositories**,** pessaries, etc.

Friability Test

This test is intended to determine the friability of uncoated tablets, tablets are subjected to abrasion and shock by utilizing a plastic chamber by mechanical shock or attrition. The strength of a tablet plays a very important role in its marketing and dissolution. The mechanical strength of tablet or granules can be determined by its hardness and friability test. Measuring the hardness of a tablet is not a reliable indicator for tablet strength as some formulations when compressed into very hard tablets tend to 'cap' or lose their crown portions on attrition. Such tablets tend to powder, chip and fragment. The commonly used friabilator in laboratories is Roche Friabilator.

Roche friabilator: This instrument consists of a plastic chamber for placing the tablets which is attached to a horizontal axis. The drum has an inside diameter of 287 mm

and is about 38 mm in depth, made of a transparent synthetic polymer with polished internal surface. A set of pre weighed tablets (if one tablet weigh 650 mg or less then approx 6.5 g of total weight should be taken and for more than 650 mg/tablet weight, 10 tablets should be taken) are placed in the plastic chamber revolving at 24–25 rpm for 4 min. The tablets are subjected to combined effects of abrasion and shock. The tablets are dropped at a distance of six inches on each revolution. If the tablet size or shape becomes irregular adjust the drum so that base forms an angle of about 10 degrees with bench top and the tablets fall freely when drum is rotated. The instrument is operated for 100 revolutions after which the tablets are dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1% of weight are considered acceptable. Most effervescent tablets and some chewable tablets undergo high friability weight loss which is an indication for the special stack packing that is required for these types of tablets. In case of hygroscopic tablets a humidity-controlled environment (relative humidity less than 40%) is required for testing. The tablets roll or slide and fall onto the drum wall or onto each other. Usually, a sample of 10 tablets are tested at a time, unless tablet weight is 0.65 g or less, where 20 tablets are tested. After 100 turns, the tablet samples are evaluated by weighing. If the reduction in the total mass of the tablets is more than 1%, the tablets fail the friability test. Generally, the test is done once. If cracked, cleaved, or broken tablets are obvious, then the sample also fails the test (Fig. 2.18).

Friability is affected by various external and internal factors like:

1. Punches that are in poor condition or worn at their surface edges, resulting in 'whiskering' at the tablet edge.
2. Friability test is influenced by internal factors like the moisture content of tablet granules and finished tablets.

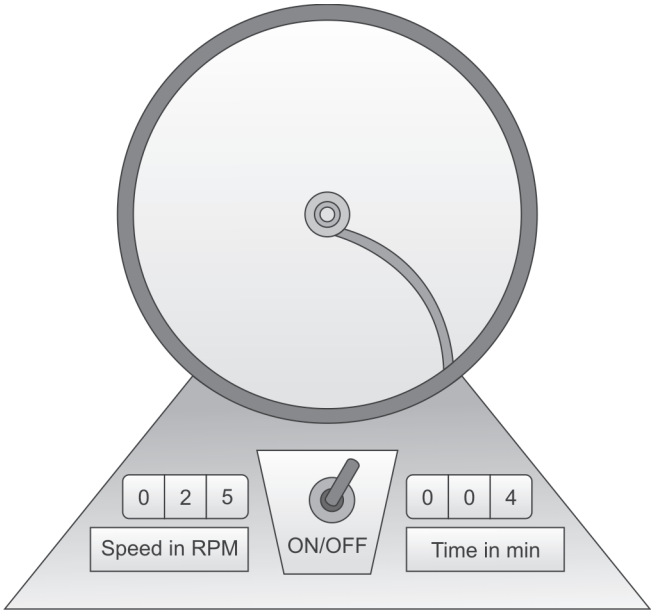


Fig. 2.18: Schematic representation of Roche friabilator

Dissolution

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. It is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. Dissolution is considered one of the most important quality control tests performed on tablet and is used for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence. The dissolution test measures the amount of time required for certain percentage of the drug substance in a tablet to go into solution under a specified set of conditions. It describes a step towards physiological availability of the drug substance, but it is not designed to measure the safety or efficacy of the tablet being tested. It provides *in vitro* control procedure to eliminate variation among production batches. The dissolution medium must be aqueous and the pH of the medium should be controlled and should simulate *in vivo* conditions (Fig. 2.19).

i. Dissolution testing is widely used in the pharmaceutical industry for optimization of formulation and quality control.
ii. To identify the critical manufacturing variable, like the binding agent effect, mixing effects, granulation procedure, coating parameters and comparative profile studies.
iii. To comply with guidelines set in the scale up and post approval changes (SUPAC) and ICH.
iv. Routine assessment of production quality to ensure uniformity between production lots.
v. Assessment of 'bioequivalence', that is to say, production of the same biological availability from discrete batches of products from one or different manufacturers.
vi. Prediction of *in vivo* availability, i.e. bioavailability (where applicable).

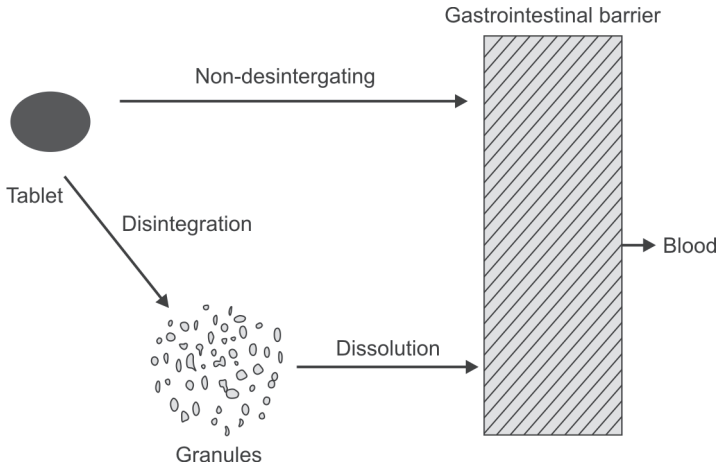


Fig. 2.19: Schematic diagram of the dissolution process

Procedure

Ensure that the equipment has been calibrated within the past 6–12 months. Place the volume of dissolution medium, as stipulated in the individual monograph, in the vessel; assemble the apparatus and place it in the water-bath; allow the temperature of the dissolution medium to reach 37 ± 0.5°C and remove the thermometer. When apparatus "Paddle" is used, allow either one tablet or one capsule of the preparation to be tested to sink to the bottom of the vessel before starting the rotation of the blade, taking care that no air bubbles are present on the surface of the dosage form. In order to stop the dosage form from floating, anchor it to the bottom of the vessel using a suitable device such as a wire or glass helix. When apparatus "Basket" is used, place either one tablet or one capsule of the preparation to be tested in a dry basket at the beginning of each test. Lower the basket into position before rotation. Immediately start rotation of the blade or basket at the rate specified in the individual monograph. Withdraw a sample from a zone midway between the surface of the dissolution medium and the top of the rotating blade or basket, not less than 10 mm below the surface and at least 10 mm from the vessel wall, at the time or time intervals specified.



Fig. 2.20: Dissolution test apparatus

The apparatus "Paddle" (Fig. 2.20) consists of a cylindrical vessel of suitable glass or other suitable transparent material with a hemispherical bottom and a nominal capacity of 1000 ml. The vessel is covered to prevent evaporation of the medium with a cover that has a central hole to accommodate the shaft of the stirrer and other holes for the thermometer and for devices for withdrawal of liquid. The stirrer consists of a vertical shaft with a blade at the lower end. The blade is constructed around the shaft so that it is flush with the bottom of the shaft. When placed inside the vessel, the shaft's axis is within 2 mm of the axis of the vessel and the bottom of the blade is 25 ± 2 mm from the inner bottom of the vessel. The upper part of the shaft is connected to a motor provided with a speed regulator so that smooth rotation of the stirrer can be maintained without any significant wobble. The apparatus is placed in a water-bath that maintains the dissolution medium in the vessel at 37 ± 0.5 °C.

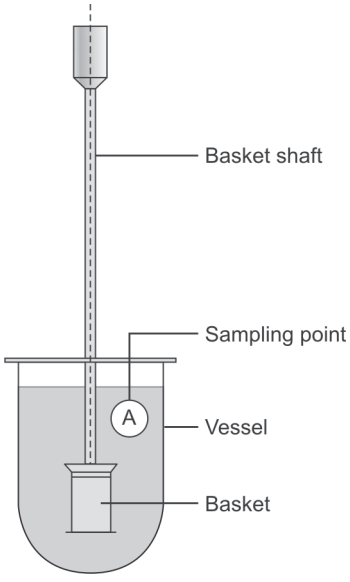


Fig. 2.21: Basket type dissolution test apparatus

The apparatus "Basket" (Fig. 2.21) consists of the same apparatus as described for "Paddle", except that the paddle stirrer is replaced by a basket stirrer. The basket consists of two parts. The top part, with a vent, is attached to the shaft. It is fitted with three spring clips, or other suitable attachments, that allow removal of the lower part so that the preparation being examined can be placed in the

basket. These three spring clips firmly hold the lower part of the basket concentric with the axis of the vessel during rotation. The lower detachable part of the basket is made of welded-seam cloth, with a wire thickness of 0.254 mm diameter and with 0.381 mm square openings, formed into a cylinder with a narrow rim of sheet metal around the top and the bottom. If the basket is to be used with acidic media, it may be plated with a 2.5 µm layer of gold. When placed inside the vessel, the distance between the inner bottom of the vessel and the basket is 25 ± 2 mm.

Test conditions: The following specifications are given in the individual monographs:

i. The apparatus to be used
ii. The composition and volume of the dissolution medium
iii. The rotation speed of the paddle or basket
iv. The preparation of the sample and reference solutions
v. The time, the method, and the amount for sampling of the test solution
vi. The method of analysis and
vii. The limits of the quantity or quantities of active ingredient(s) required to dissolve within a prescribed time.

Dissolution media: If a buffer is added to the dissolution medium, adjust its pH to within ±0.05 units of the prescribed value. Prior to testing, if necessary, remove any dissolved gases that could cause the formation of bubbles.

Dissolution buffer pH 1.3: Dissolve 2 g of sodium chloride reagent in 800 ml of deionized water, adjust the pH to 1.3 with hydrochloric acid (~70 g/l), and dilute to 1000 ml with water.

Dissolution buffer pH 2.5: Dissolve 2 g of sodium chloride reagent in 800 ml of deionized water, adjust the pH to 2.5 with hydrochloric acid (~70 g/l), and dilute to 1000 ml with water.

Dissolution buffer pH 3.5: Dissolve 7.507 g of glycine reagent and 5.844 g of sodium chloride reagent in 800 ml of deionized water, adjust the pH to 3.5 with hydrochloric acid (~70 g/l), and dilute to 1000 ml with water.

Dissolution buffer pH 4.5: Dissolve 6.8 g of potassium dihydrogen phosphate reagent in 900 ml of deionized water, adjust the pH to 4.5 either with hydrochloric acid (~70 g/l) or sodium hydroxide (~80 g/l), and dilute to 1000 ml with water.

Dissolution buffer, pH 6.8: Dissolve 6.9 g of sodium dihydrogen phosphate reagent and 0.9 g of sodium hydroxide reagent in 800 ml of water, adjust the pH to 6.8 with sodium hydroxide (~80g/l) and dilute to 1000 ml with water.

Dissolution buffer, pH 6.8, 0.25% SDS: Dissolve 6.9 g of sodium dihydrogen phosphate reagent, 0.9 g of sodium hydroxide R and 2.5 g of sodium dodecyl sulfate R in 800 ml of water R, adjust the pH to 6.8 with sodium hydroxide (~80 g/l) and dilute to 1000 ml with water R.

Dissolution buffer pH 7.2: Dissolve 9.075 g of potassium dihydrogen phosphate R in deionized water to produce 1000 ml (solution A). Dissolve 11.87 g of disodium hydrogen phosphate R in sufficient water to produce 1000 ml (solution B). Mix 300 ml of solution A with 700 ml of solution B.

Gastric fluid, simulated: Dissolve 2.0 g of sodium chloride R and 3.2 g of pepsin R in 7.0 ml of hydrochloric acid (~420 g/l) TS and sufficient water to produce 1000 ml. This test solution has a pH of about 1.2.

Intestinal fluid, simulated: Dissolve 6.8 g of potassium dihydrogen phosphate R in 250 ml of water, mix, and add 190 ml of sodium hydroxide (0.2 mol/l) and 400 ml of water. Add 10.0 g of pancreatin R, mix, and adjust the resulting solution with sodium hydroxide (0.2 mol/l) to a pH of 7.5 ± 0.1. Dilute with sufficient water to produce 1000 ml.

The requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to the following table, unless otherwise specified in the individual monograph.

Stage	*Samples tested*	*Acceptance criteria for immediate release formulation*
S_1	6	Each unit is not less than Q + 5%
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than Q-15%
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q; not more than 2 units are less than Q-15%; no unit is less than Q-25%

Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the released labelled content of active ingredient as a percentage as specified in the individual monograph; both the 5% and 15% values in the acceptance table are percentages of the labelled content so that these values and Q are in the same terms.

Stage	*Samples tested*	*Acceptance criteria for extended release formulation*
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units (L1 + L2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units (L1 + L2 + L3) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

For extended release formulation, range is defined for time points.

Stage	*Samples tested*	*Acceptance criteria for delayed release formulation in acidic media*
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units (A1 + A2) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units (A1 + A2 + A3) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

For delayed release, resistance of enteric coating is checked in acidic media.

ISOLATED KEY POINTS

- Sublingual tablet is designed to dissolve in small quantity of saliva and used when immediate action within few minutes is desired.
- Implants are inserted into subcutaneous tissue by surgical procedures where they are very slowly absorbed over a period of a month or a year.
- Excipients are any component other than active pharmaceutical ingredient(s) intentionally added to the formulation of a dosage form.
- Excipients play a crucial role in determining the final suitable dosage form and determining the bioavailability.
- Various excipients used in tablet formulation are diluents, binders, disintegrants, lubricants, antiadherents, glidants, wetting agents, dissolution retardants, dissolution enhancers, absorbents, buffers, antioxidants, chelating agents, preservatives, colours, flavours, sweeteners, etc.
- Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size.
- Microcrystalline cellulose (MCC) is perhaps the most widely used direct-compression Binder added in tablet formulation to have required flow property and compressibility of powders.
- Wet granulation, dry granulation/slugging, direct compression are major granule manufacturing methods.
- Disintegrants are added to tablet to induce breakup when it comes in contact with aqueous fluid.
- Disintegration by capillary action or by swelling is the major mechanism for disintegrants.
- Lubricants are added to reduce the friction during compression.
- Glidants improve the flow property of material/granules.
- Only FD&C, D&C approved colourants can be incorporated into tablet formulation.
- Direct compression is one of the most advanced technologies to prepare tablets.
- Wet granulation has been and continues to be the most widely used agglomeration process.
- In the dry granulation process granulation takes place without utilizing liquid.

Tablets Problems

- Capping and lamination are the defects arising as a result of air-entrapment in the granular material.
- Cracking is due to rapid expansion of tablets, when deep concave punches are used
- Sticking, picking and binding are the imperfections related to more amount of binder in granules.
- Mottling is an imperfection arising due to more than one factor: a coloured drug, dirt in granules or the use of an oily lubricant.
- Double-impression is related to a machine defect: It is caused by the free rotation of punches that have some engraving on the punch-faces.

PRACTICE QUESTIONS

Long Answer Type Questions

1. Define the term "Tablets"? Name the different categories of excipients used in the preparation of compressed tablets.
2. Define the term "Excipient". Enlist the various excipients used in the formulation of tablet?
3. Name of the various diluents commonly used in the formulation of a tablet.
4. Why is a binding agent required in certain types of tablets?
5. Give a list of the granulating agents which are commonly used in the moist granulation method.
6. What are the various tests usually employed for the purpose of evaluation of tablets?
7. What materials, are commonly used in the enteric coating of tablets.
8. Name the materials commonly used in film coating of tablets.
9. What are the various type of lubricants used as excipients in compressed tablets?
10. What are advantages and disadvantages of a tablets?
11. Give the advantages of film coating of tablets.
12. How does a disintegrating agent help to disintegrate a tablet in the stomach.
13. Mention the properties of an ideal enteric coating material.
14. Why are tablets still considered to be a formulation of choice among oral preparations?
15. Give in brief the various steps involved in the manufacturing of compressed tablets.
16. Describe the various stages,construction and working of a "single–punch tablet making machine".
17. Discuss in brief the various tests which are generally done to maintain the quality control of tablets.
18. Discuss in brief the common defects which can occur in compressed tablets. How can such defects be removed.
19. Write short notes on the following:
    i. Effervescent tablets
    ii. Enteric coated tablets
    iii. Multiple compressed tablets
    iv. Hypodermic tablets
    v. Lozenges
    vi. Sustained action tablets
    vii. Sublingual tablets
20. Write short notes on:
    a. Disintegration test
    b. Dissolution test
    c. Excipients used in tablet formulation
    d. Common defects which occurs in compressed tablets.

Objective Type Questions

1. Precompression can be used to solve the problem:
i. Capping and lamination ii. Mottling
iii. Picking and sticking iv. Double impression

2. Picking and sticking problems may be observed due to:
i. Excess glidant ii. Excess diluent
iii. Insufficient lubrication iv. Insufficient compression

3. Engraving or embossing or debossing on the upper punch tip like small enclosed areas in the letters like "D", "O" or "Q" may result in:
i. Sticking ii. Picking
iii. Mottling iv. Tablet breaking

4. Unequal distribution of colour on tablet surface is called:
i. Mottling ii. Sticking
iii. Picking iv. Chipping

5. Using bright coloring agent that will mask all the color variations of the ingredients in the formula helps in avoiding:
i. Picking ii. Capping
iii. Mottling iv. Sticking

6. The reason for mottling may be:
i. Double impression
ii. Migration of dye to the surface of granulation during drying
iii. Improper mixing
iv. Excess lubrication

7. Bridging/arching and rat-holing of granules at the bottom of the hopper results in:
i. Poor mixing ii. Poor flow
iii. Mottling iv. Capping

8. The processing problem of tablets that can be revealed by friability test is:
i. Picking ii. Capping and lamination
iii. Mottling iv. Sticking
v. None of the above

9. In general the disintegration time of uncoated compressed tablet is _____ .

10. According to IP the shape of a tablet is defined as _____ .

11. The film coating of tablets protects their medicaments from _____ .

12. The vaginal tablets are _____ or _____ shaped to facilitate _____ in the vagina.

13. The dry cota tablet machine is used for the manufacturing of _____, _____ and _____ tablets.

14. The film coating of tablets is done to make them _____ before sugar coating.

15. In capping, there is _____ or _____ removal of _____ or _____ portion of the tablet.

16. In picking the material is _____ or _____ by the upper punch form the _____ surface of the tablet.

17. The enteric coated tablets are made to get disintegrated in the _____ .

18. The tablets are tested for their mechanical strength in order to ensure that they can withstand _____ handling and _____ .

19. Lozenges are so designed as the exert a local effect in the _____ or _____ .

20. Buccal tablets are placed between the _____ and _____ or check so that they are dissolved and _____ directly.

21. Match the following:

Column I	*Column II*
A. Sugar coating of tablet	(i) Is done to disintegrate it in the intestine
B. The disintegration technique in not required	(ii) For sugar coating, film coating and enteric coating
C. Pan coating technique is used	(iii) In lozenge tablets and chewable tablets
D. The enteric coating of tablet	(iv) Is done to mask the unpleasant odour and taste of the medicament

ANSWERS

1. i, **2.** iii, **3.** ii, **4.** i, **5.** iii, **6.** ii, **7.** ii, **8.** ii, **9.** 15 mts
10. Circular with flat or convex faces
11. Atmospheric effect
12. Ovoid, pear, retention
13. Multiple compressed, multicoloured press coated
14. Water proof
15. Partial, complete, top, bottom
16. Removed, picked up, upper
17. Intestine
18. Normal risk, transportation
19. Mouth, throat
20. Gum, lips, absorbed
21. A—(iv); B—(iii), C—(ii), D—(i)

Chapter
3

Coating of Tablets

Coating is defined as tablets covered with one or more layers of mixture of various substances such as natural or synthetic resins, gums, inactive and insoluble filler, sugar, plasticizer, polyhydric alcohol, waxes, authorized coloring material and sometimes flavoring material. Coating may also contain active ingredient. Substances used for coating are usually applied as solution or suspension under conditions where vehicle evaporates.

Tablet coating is the application of coating composition to moving bed of tablets with concurrent use of heated air to facilitate evaporation of solvent.

Advantages of Tablet Coating

i. Prevent irritation of esophagus and stomach
ii. Prevent bad taste
iii. Prevent inactivation of drug in the stomach
iv. Improve drug effectiveness
v. Prolong dosing interval in the form of sustain release or prolong release dosage form
vi. Improve dosing interval
vii. Better patient compliance
viii. Prevent the active drug from moisture
ix. Prevent dust formation
x. Reduce influence of atmosphere
xi. Improve drug stability
xii. Prolong shelf life
xiii. Overcome bad taste
xiv. Improve product identity
xv. Improve appearance and acceptability

Types of Tablet Coating Process

1. Sugar coating
2. Film coating
3. Enteric coating
4. Specialized coating

1. SUGAR COATING

The sugar coating protects the drug from the atmosphere and provides a barrier to objectionable taste. The coating is water soluble and quickly dissolves after swallowing Sugar coating helps in taste masking, smoothing the tablet core, coloring and modified release. The disadvantages of sugar coating are:

1. It requires more time and expertise.
2. It increases size and weight, which eventually increases the shipping cost.

Sugar coating process involves following steps:

i. Sealing/water proofing: Provides a moisture barrier and harden the tablet surface.
ii. Subcoating: Increases the bulk and round off the tablet edges.
iii. Grossing/smoothing: Smoothes the subcoated surface and increases the tablet size
iv. Coloring: Gives color to the tablet
v. Polishing: Gives characteristics gloss.

Sealing

It is also called water proofing; it provides a moisture barrier and hardness to the surface of the tablet in order to minimize attritional effects. The sealants are generally water-insoluble polymers/film formers applied from an organic solvent solution. The quantities of material applied as a sealing coat will depend primarily on the tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly across the surface of every tablet in the batch. Therefore one or more further application of resin solution may be required to ensure that the tablet cores are sealed effectively.

Common materials used as a sealant include Shellac, cellulose acetate phthalate (CAP), polyvinylacetate phthalate (PVAP), hydoxylpropyl cellulose, hydoxypropyl-methylcellulose (HPMC), etc.

Subcoating

It is the actual sugar coating process and provides the rapid buildup necessary to round up the tablet edge. It also acts as the foundation for the smoothing and color coats. The methods used for subcoating are:

i. The application of gum based solution followed by dusting with powder and then drying.
ii. The application of a suspension of dry powder in gum/sucrose solution followed by drying.

Thus subcoating is a sandwich of alternate layer of gum and powder. It is necessary to remove the bulk of the water after each application of coating syrup (Tables 3.1 to 3.3).

TABLE 3.1: Gum-based solution used for subcoating

Ingredient	*%w/w**
Gelatin	3
Gum acacia (powdered)	8
Sucrose (powdered)	45
Distilled water	to 100

TABLE 3.2: Dusting powder used for subcoating

Ingredient	*%w/w**
Calcium carbonate	40.0
Titanium dioxide	5.0
Talc, asbestos free	25.0
Sucrose (powdered)	28.0
Gum acacia (powdered)	2.0

TABLE 3.3: Suspension used for subcoating

Ingredient	*%w/w**
Sucrose	40.0
Calcium carbonate	20.0
Talc, asbestos free	12.0
Gum acacia (powdered)	2.0
Titanium dioxide	1.0
Distilled water	25.0

*Note: Percentage can change based on formulation scientist discretion.

Smoothing

It is also called grossing, in this process smoothing and filing of the irregularity on the surface generated during subcoating is done. If the subcoating is rough with high amount of irregularities then the use of grossing syrup containing suspended solids will provide better texture it also help in increasing the bulk of tablet. Smoothing is generally done by application of a simple syrup solution (approximately 60–70% sugar solid). This syrup generally contains pigments, starch, gelatin, acacia and opacifier.

Color Coating

This stage is very important in the successful completion of a sugar coating process and involves the multiple application of syrup solution (60–70% sugar) containing the desired coloring matter. Mainly soluble dyes were used in the sugar coating to achieve the desired color, since the soluble dye will migrate to the surface during drying. But nowadays the insoluble certified lakes are more frequently used.

Polishing

Polishing is achieved by applying the mixture of waxes like beeswax, carnuaba wax, candelila wax or hard paraffin wax to tablets in polishing pan.

2. FILM COATING

Film coating is deposition of a thin film of polymer over the tablet core. Conventional pan equipment may be used but nowadays more sophisticated pieces of equipment are employed to have a high degree of automation and coating time. Firstly the polymer is dissolved in the solvent. Other additives like plasticizers and pigments are added. Resulting solution (or suspension) is sprayed onto a rotated tablet bed. Continuous

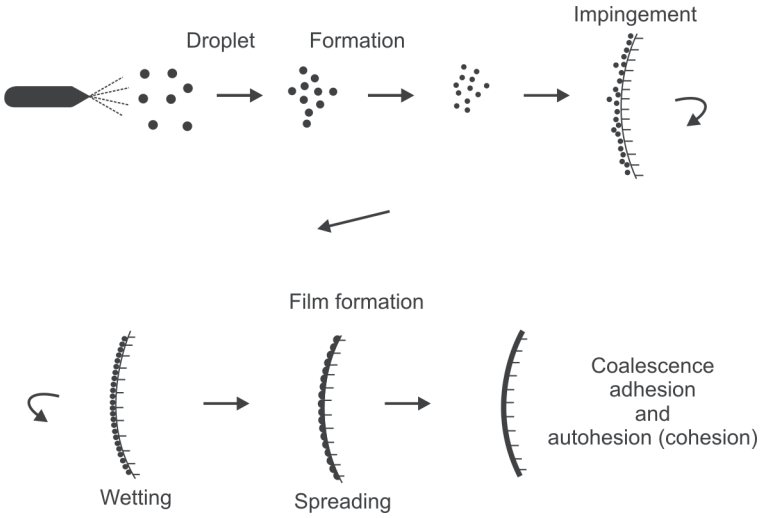


Fig. 3.1: Film coating process

drying is done which cause removal of the solvent, giving thin deposition of coating material over the tablet (Fig. 3.1).

Generally spray process is used in preparation of film coated tablets. Accelacota is the prototype of perforated cylindrical drum providing high drying air capacity. Fluidized bed equipment has made considerable impact where tablets are moving in a stream of air passing through the perforated bottom of a cylindrical column. For fluidized bed coating, very hard tablets (hardness > 20 N) have to be used. Film coating is more favored over sugar coating (Table 3.4).

TABLE 3.4: Difference between film coating and sugar coating

Features	*Film coating*	*Sugar coating*
Tablet appearance	Usually not as shiny as sugar coat type	Rounded with high degree of polish
Tablet weight increase	2–3%	30–50%
Tablet logo or 'break lines'	Possible	Not possible
Process stages	Usually single stage	Multistage process
Operator training required	Easy training of operator	Moderate

Coating Material

Materials used in film coating are:

1. Film formers, which may be enteric or non-enteric (Table 3.5)
2. Solvents
3. Plasticizers
4. Colorants
5. Opaquant—extenders
6. Miscellaneous coating solution components

TABLE 3.5: Some commonly used film former polymers

Non-enteric polymers	*Enteric polymers*
Hypromellose (HPMC)	Hypromellose phthalate
Hydroxyethyl cellulose	Polyvinyl acetate phthalate
Hydroxyethylmethyl cellulose	Cellulose acetate phthalate
Carboxymethylcellulose sodium	Polymethacrylates
Hydroxypropyl cellulose	Shellac
Ethyl cellulose	
Polyethylene glycol	

Film Formers

An ideal film former should have the following characteristics.

i. Soluble in solvent of choice for coating preparation
ii. Should give elegant looking product
iii. High stability against heat, light, moisture, air and the substance being coated
iv. No inherent color, taste or odor
v. Nontoxic and should have no pharmacological activity
vi. High resistance to cracking
vii. Compatible to printing procedure

Hydroxy propyl methyl cellulose (HPMC): It is a polymer of choice for air suspension and pan spray coating systems because of solubility characteristic in gastric fluid, organic and aqueous solvent system.

Advantages of HPMC as film forming agaent are:

1. It does not affect tablet disintegration and drug availability.
2. It is cheap, flexible, highly resistant to heat, light and moisture.
3. It has no taste and odor, color and other additives can be easily incorporated.

Disadvantage: When it is used alone, the polymer has tendency to bridge or fill the debossed tablet surfaces. Hence, mixture of HPMC and other polymers is used.

Ethyl cellulose (EC): It is completely insoluble in water and gastric fluids. Hence it is used alone or in combination with water-soluble additives like HPMC. Unplasticized ethyl cellulose films are brittle and require film modifiers to obtain an acceptable film formulation. Aqua coat is aqueous polymeric dispersion utilizing ethyl cellulose. These pseudolatex systems contain high solids, low viscosity compositions that have coating properties quite different from regular ethyl cellulose solution.

Hydroxy propyl cellulose (HPC): It is soluble in water below 40°C (insoluble above 45°C), gastric fluid and many polar organic solvents. HPC is extremely tacky as it dries from solution system. It is used for sub-coat and not for color or glass coat. It gives very flexible film.

Sodium carboxy methyl cellulose: It is available in medium, high and extra high viscosity grades. It is easily dispersed in water to form colloidal solutions but it is insoluble in most organic solvents and hence not a material of choice for coating solution based on organic solvents. Films prepared by it are brittle but adhere well to tablets. Partially dried films of are tacky. So coating compositions must be modified with additives.

Polyethylene glycols (PEG): Lower molecular weights PEG (200–600) are liquid at room temperature and are used as plasticizers. High molecular weights PEG (900–8000 series) are white, waxy solids at room temperature. Combination of PEG waxes with CAP gives films that are soluble in gastric fluids.

Acrylate polymers: Acrylate polymer with good solubility in acidic media and poor solubility in above pH 5 marketed under the name of Eudragit E. Acrylates with brand name RL and RS have poor solubility, thus used as coating material for sustained release formulation. These materials are available as organic solution (12.5% in isopropanol/acetone), solid material or 30% aqueous dispersion.

Solvents

Solvents are used to dissolve or disperse the polymers and other additives and convey them to substrate surface. Ideal solvent should have the following characteristics:

i. Should be either dissolve/disperse polymer system.
ii. Should easily disperse other additives.
iii. Only small concentration of polymers (2–10%) is required.
iv. Should be colorless, tasteless, odorless, inexpensive, inert and nontoxic.
v. Rapid drying rate.
vi. Should not cause environmental pollution.

Mostly solvents are used either alone or in combination with water, ethanol, methanol, isopropanol, chloroform, acetone, methylene chloride, etc. Water is most frequently used it is economic and easily available. For drugs sensitive to water, non-aqueous solvents are used.

Plasticizers

Plasticizers are simply relatively low molecular weight materials which have the capacity to alter the physical properties like glass transition temperature of the polymer to render it more useful in performing its function as a film-coating material. They are generally used in concentration (8–10%).

When solvent is removed, most polymeric materials tend to pack together in 3-D honey comb arrangement. "Internal" or "External" plasticizing technique is used to modify quality of film. Combination of plasticizer may be used to get desired effect.

Commonly used plasticizers are castor oil, PG, glycerin, lower molecular weight (200–400 series)PEG, surfactants, etc. For aqueous coating PEG and PG are more used while castor oil and spans are primarily used for organic-solvent based coating solution. External plasticizer should be soluble in the solvent system used for dissolving the film former and plasticizer. The plasticizer and the film former must be at least partially soluble or miscible in each other (Table 3.6).

TABLE 3.6: Some common plasticizers

Polyols	*Organic esters*	*Oils/glycerides*
Glycerol	Phthalate esters	Castor oil
Propylene glycol (PG)	Citrate esters	Fractionated coconut oil
Polyethylene glycol (PEG)	Triacetin	Acetylated monoglycerides

Colorants

These materials are generally used as ingredients in film-coating formulae to contribute to the visual appeal of the product, but they also improve the product in other ways. They are used in concentration (2.5–8%).

For proper distribution of suspended colorants in the coating solution requires the use of the powdered colorants (<10 microns). Most common colorants in use are certified FD and C or D and C colorants. These are synthetic dyes or lakes. Lakes are choice for sugar or film coating as they give reproducible results. Concentration of colorants in the coating solutions depends on the color shade desired, the type of dye, and the concentration of opaquant-extenders. If very light shade is desired, concentration of less than 0.01% may be adequate on the other hand, if a dark color is desired a concentration of more than 2.0% may be required. The inorganic materials (e.g. iron oxide) and the natural coloring materials (e.g. anthocyanins, carotenoids, etc.) are also used to prepare coating solution. Magenta red dye is non-absorbable in biologic system and resistant to degradation in the gastro (opaque color concentrate for film coating) and intestinal track (Table 3.7).

TABLE 3.7: Some common colorants

Organic dyes and their lakes	*Inorganic colors*	*Natural colors*
Sunset yellow	Iron oxide red, black	Carmine
Erythrosine	Titanium dioxide	Anthocyanine
Tartrazine		Riboflavine

Opacifier

These are very fine inorganic powder used to provide more pastel colors and increase film coverage. These inorganic materials provide white coat or mask color of the tablet core. Colorants are very expensive and higher concentration is required. These inorganic materials are cheap. In presence of these inorganic materials, amount of colorants required decreases. Most commonly used materials are titanium dioxide, silicate (talc and aluminum silicates), carbonates (magnesium carbonates), oxides (magnesium oxide) and hydroxides (aluminum hydroxides).

Miscellaneous Coating Solution Component

Flavors, sweeteners, surfactants, antioxidants, antimicrobials, etc. may be incorporated into the coating solution (Table 3.8).

TABLE 3.8: General formula for film coating

S. No.	*Ingredients*	*Percentage (%w/w)*	*Comments*
1.	Polymer	50–80%	This gives tensile strength
2.	Plasticizer	8–12%	Provide flexibility to coat
3.	Opacifying agent and coloring agent	10–12%	Colorant sufficient to provide desired shade

3. ENTERIC COATING

Enteric coatings are those which remain intact in the stomach (and exhibit low permeability to gastric fluids) but break down readily, once the dosage form reaches the small intestine. This type of coating is used to protect tablet core from disintegration in the acid environment of the stomach and is used because of following reasons:

i. To maintain the activity of drugs those are unstable when exposed to the gastric environment (e.g. erythromycin and pancreatin).
ii. To minimize either nausea or bleeding that occurs with those drugs that irritate the gastric mucosa (e.g. aspirin and certain steroids).
iii. To prevent irritation of stomach by certain drugs like sodium salicylate.
iv. Delivery of API into intestine.
v. To provide a delayed release.

Generally two types of enteric layer systems are used

One layer system: The coating formulation is applied in one homogeneous layer, which can be white-opaque or colored. In this only one application is needed.

Two layer system: To prepare enteric tablets of high quality and pleasing appearance the enteric formulation is applied first, followed by colored film. Both layers can be of enteric polymer or only the basic layer contains enteric polymer while top layer is fast disintegrating and water-soluble polymer.

Ideal properties of enteric coating material are listed below:

i. Resistance to gastric fluids.
ii. Permeable to intestinal fluid.
iii. Compatibility with most coating solution components and the drug substratance.
iv. Formation of continuous film.
v. Nontoxic, cheap and ease of application.

Polymers used for enteric coating are as follows:

Cellulose Acetate Phthalate (CAP)

It is widely used in industry. It is reconstituted colloidal dispersion of latex particles. It is composed of solid or semisolid polymer spheres of CAP ranging in size from 0.05–3 microns. Cellulose acetate trimellitate (CAT) developed as an ammoniated aqueous formulation showed faster dissolution than a similar formulation of CAP.

Disadvantages of CAP

1. It dissolves above pH 6 only, delays absorption of drugs.
2. It is hygroscopic and permeable to moisture in comparison with other enteric polymer.
3. It is susceptible to hydrolytic removal of phthalic and acetic acid changing film properties.
4. CAP films are brittle and usually used with other hydrophobic film forming materials.

Acrylate Polymers

Eudragit L and *Eudragit S* are two forms of commercially available enteric acrylic resins. Both of them produce films resistant to gastric fluid. *Eudragit L* and S are soluble in

intestinal fluid at pH 6 and 7 respectively. Eudragit L is available as an organic solution, solid or aqueous dispersion. Eudragit S is available only as an organic solution and solid.

Hydroxy Propyl Methyl Cellulose Phthalate

HPMCP 50, 55 and 55S (also called HP-50, HP-55 and HP-55S) is widely used. HP-55 is recommended for general enteric preparation while HP-50 and HP-55S for special cases. HP-50 and HP-55 polymers dissolve at a pH 5 and 5.5 respectively.

Polyvinyl Acetate Phthalate

It is similar to HP-55 in stability and pH dependent solubility.

4. SPECIALIZED COATING

Compressed Coating

This type of coating requires a specialization tablet machine. Compression coating is not widely used. It has advantages in some cases in which the tablet core cannot tolerate organic solvent or water and yet needs to be coated for taste masking or to provide delayed or enteric properties to the finished product and also to prevent incompatibility by separating incompatible ingredients.

Electrostatic Coating

Electrostatic coating is an efficient method of applying coating to conductive substrates. A strong electrostatic charge is applied to the substrate. The coating material containing conductive ionic species of opposite charge is sprayed onto the charged substrate. Complete and uniform coating of corners and adaptability of this method to such relatively nonconductive substrate as pharmaceutical is limited.

Dip Coating

Coating is applied to the tablet cores by dipping them into the coating liquid. The wet tablets are dried in a conventional manner in coating pan. Alternative dipping and drying steps may be repeated several times to obtain the desired coating. This process lacks the speed, versatility, and reliability of spray-coating techniques. Specialized equipment has been developed to dip-coat tablets, but no commercial pharmaceutical application has been obtained.

Vacuum Film Coating

Vacuum film coating is a new coating procedure that employs a specially designed baffled pan. The pan is hot water jacketed and it can be sealed to achieve a vacuum system. The tablets are placed in the sealed pan and the air in the pan is displaced by nitrogen before the desired vacuum level is obtained. The coating solution is then applied with airless spray system. The evaporation is caused by the heated pan and the vapour is removed by the vacuum system. Because there is no high-velocity heated air, the energy requirement is low and coating efficiency is high. Organic solvent can be effectively used with this coating system with minimum environmental or safety concerns.

Factors Affecting Coating

Air Capacity

This value represents the quantity of water or solvent that can be removed during the coating process which depends on the quantity of air flowing through the tablet bed, temperature of the air and quantity of water that the inlet air contains.

Surface Area of Tablet

It plays an important role for uniform coating. The total surface area for unit weight decreases significantly from smaller to larger tablets. Application of a film with the same thickness requires less coating composition. In the coating process only a portion of the total surface is coated.

Coating Efficiency of Machine

Tablet coaters use the expression "coating efficiency" a value obtained by dividing the net increase in coated tablet weight by the total nonvolatile coating weight applied to the tablet. Ideally 90–95% of the applied film coating should be on the tablet surface. Coating efficiency for conventional sugar coating is much less and 60% would be acceptable. The significant difference in coating efficiency between film and sugar coating relates to the quantity of coating material that collects on the wall.

Equipment used for coating are:

1. The conventional coating pan
2. The perforated coating pan
3. The fluidized bed coater

1. Conventional Pan System

It consists of a circular metal pan mounted somewhat angularly on a stand and is rotated on its horizontal axis by a motor. Heated air is directed into the pan and onto the tablet bed surface, and is exhausted by means of ducts positioned through the front of the pan (Fig. 3.2).

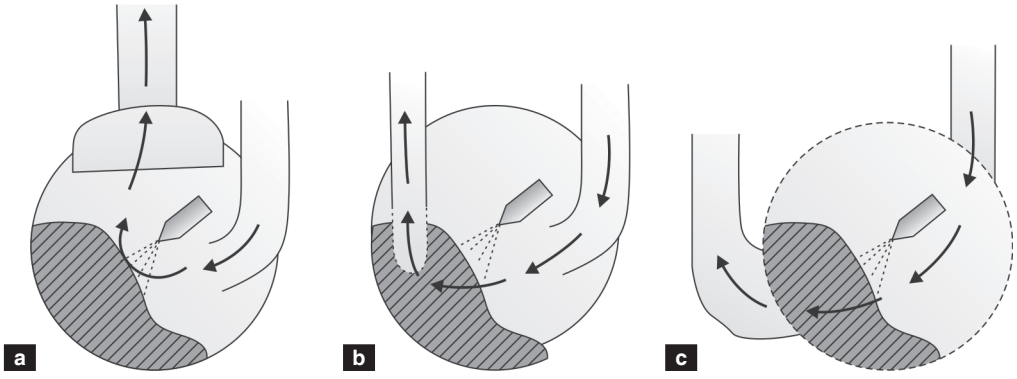


Fig. 3.2: (a) Conventional coating pan, (b) Upgraded conventional coating pan, (c) Side vented coating pan

Characteristic features of conventional pan system: Generally, the energy required for evaporating the moisture from the coating layers is derived from the drying air. The duration of the coating process as well as the quality of the end product thus crucially depend on the efficiency of heat and mass transfer. Increasing the heat and mass transfer either directly (for example by increasing temperature and rotation speed or implementation of perforations) or indirectly by improving the drying air supply can improve drying efficiency. With the conventional drying method, the drying air is blown across the surface of the core bed. As only the surface of the core bed is exposed to the drying air, insufficient drying of core materials and impaired spraying processes might occur. Hence, different drying gadgets have been developed, of which the two conventional ones are:

i. Immersion sword
ii. Immersion tube

Immersion sword

With the immersion sword system, drying air is introduced through a perforated metal sword device that is immersed in the tablet bed. The drying air flows upward from the sword through the bed. Since the air is more intimately mixed with the wetted tablets, a more efficient drying environment is provided in Fig. 3.3.

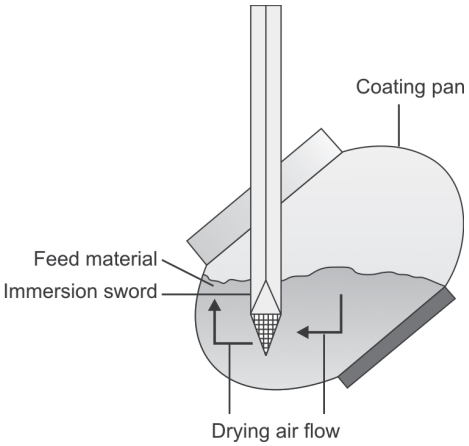


Fig. 3.3: Immersion sword system

Immersion Tube

In this type of system the immersed tube delivers the heated air, and a spray nozzle is built in the tip of the tube. During this operation, the coating solution is applied simultaneously with the heated air from the immersed tube. The drying air flows upward through the tablet bed and is exhausted by a conventional duct. Both the immersion sword and immersion tube systems are adaptable to conventional coating pans. Relatively rapid processing times have been reported for both film and sugar coating with this system (Fig. 3.4).

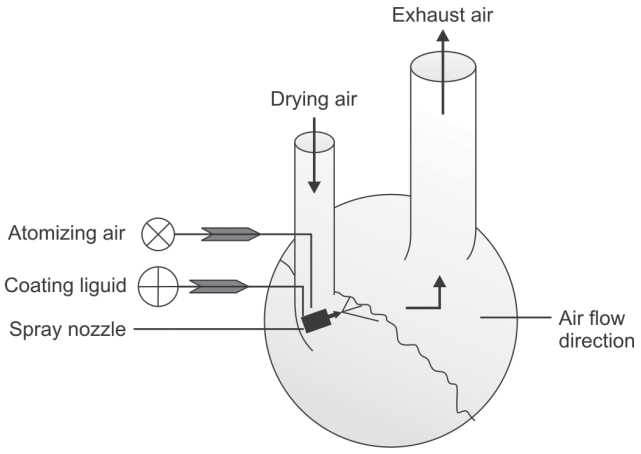


Fig. 3.4: Immersion tube system

2. Perforated Coating System: Accela-cota and Driacoater Systems

Accela-cota: In Accela-cota and Hi-coater systems, drying air is directed into the drum, is then passed through the tablet bed, and is exhausted through perforation in the drum (Fig. 3.5).

Driacoater: The driacoater introduces drying air through hollow perforated ribs located on inside periphery of the drum. As coating pan rotates the ribs dip into the tablet bed, and dying air passes through and fluidizes the tablet bed. Air is exhausted from back of the pan. For hard sugar coating, driacoater with perforated multisided drums are used. The machines are capable to handle sugar and sugar free solutions (sorbitol, xylitol, malitol, isomalt, etc.), glazing and polishing solutions as well as aqueous suspensions. Automatic loading and unloading, inside pan cleaning and fully automatic process capabilities characterize this driacoater with batch sizes from 625 ltr to 3750 ltr (Fig. 3.6).

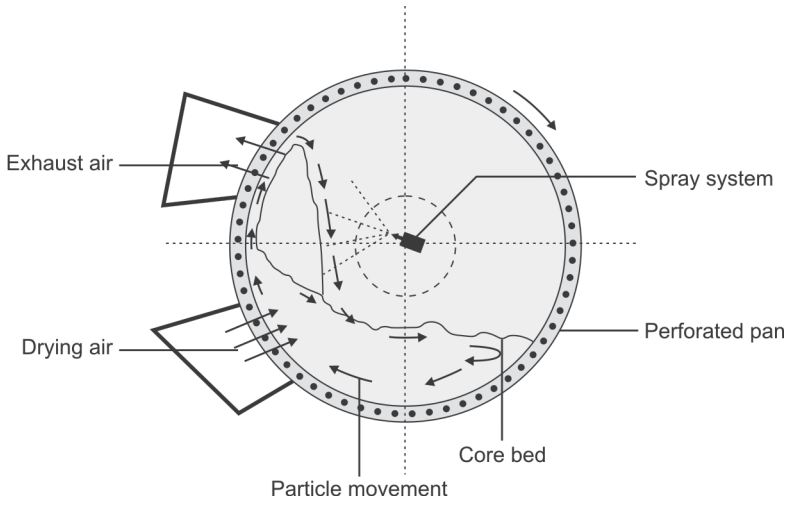


Fig. 3.5: Showing accela-cota

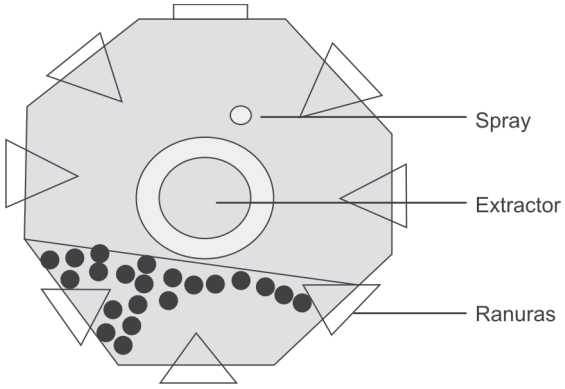


Fig. 3.6: Driacoater

3. Fluidized Bed Dryer (FBD)

A fluidized bed consists of fluid-solid mixture that exhibits fluid-like properties. The bed can be considered to be an inhomogeneous mixture of fluid and solid that can be represented by a single bulk density (Fig. 3.7).

Advantages

i. Uniform, continuous product coating.
ii. Aqueous or organic coatings can be applied.
iii. Coating and drying take place in one machine.
iv. The coating process and the filling and emptying of the machine can be carried out in complete isolation and without product spreading into the environment.
v. When using organic solvents, the process machines can be made inert and used with a solvent recovery system.

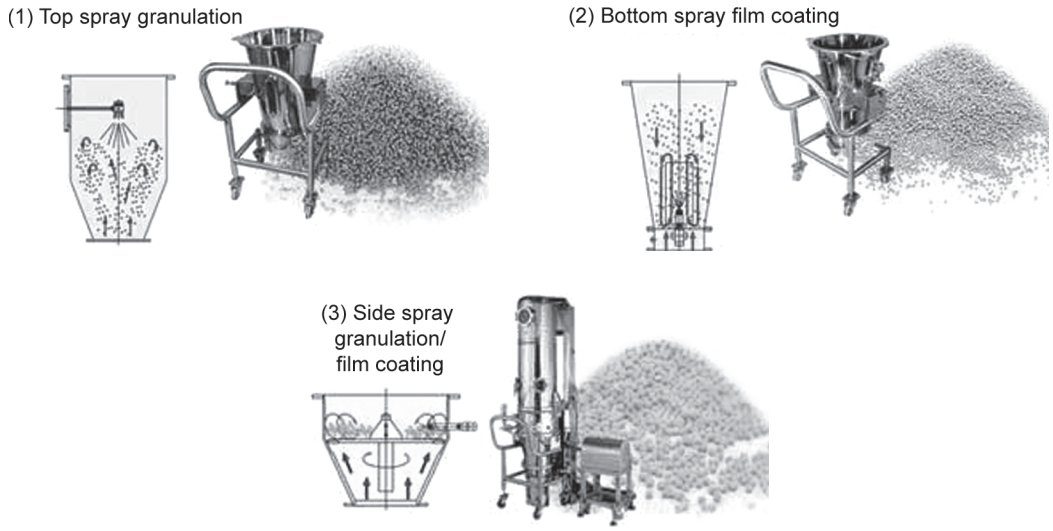


Fig. 3.7: Fluidized bed dryer

Principle of Operation

With fluid bed coating, particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating. The various types of fluid bed systems are:

1. Top spray coating
2. Bottom spray coating (wurster coating)
3. Tangential spray coating (rotor pellet coating)

Top Spray Coating

This process is used for general coatings right up to enteric coating. With top spray coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate (Fig. 3.8).

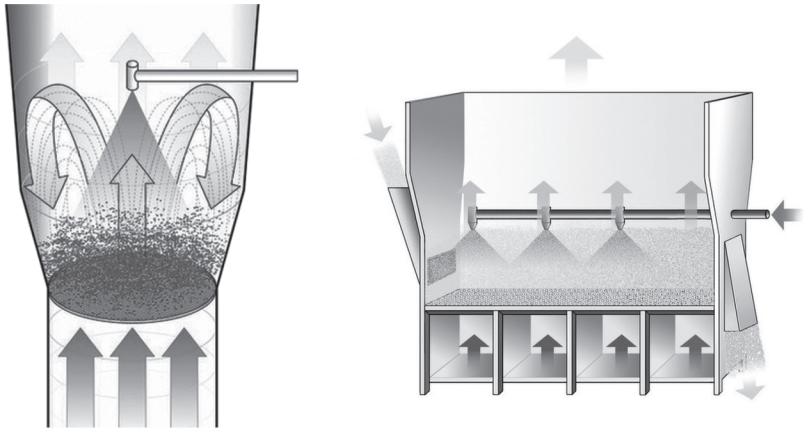


Fig. 3.8: Top spray coating in the fluid bed dryer

The coating liquid is sprayed into the fluid bed from above against the air flow (countercurrent) by means of a nozzle. Drying takes place as the particles continue to move upwards in the air flow. Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform. Coating in the continuous fluid bed is particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones. The dry, coated particles are continuously extracted.

Bottom Spray Coating (Continuous Fluid Bed)

When the hot air flows through the bottom screen of container and coating column, it will generate the siphonage principle. Convection is created through the strong force from bottom toward top. The granules will then fall down and will be sucked into the coating column again, while the bottom spray gun will spray towards top to achieve coating purpose. Particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow (Fig. 3.9). Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones whereby spraying can take place from below in the form of a bottom spray. The dry, coated particles are continuously extracted.

Tangential Spray Coating (Rotor Pellet Coating)

The cores (seeds) are placed on the turntable and hot air is blown upward between the turntable and the granulation area. The passage of air causes the cores to roll on the turntable; at the same time, the coating solution is sprayed on the rolling cores through the pump and spray gun. The process involves simultaneous coating and drying of the cores, layer after layer, until the repeated actions achieve the desired coating thickness or granule size. Powder coating is achieved by charging powder and spray binder at the same time.

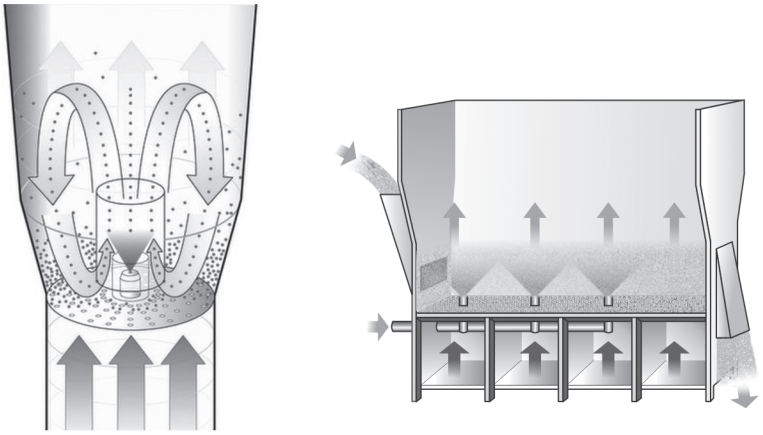


Fig. 3.9: Bottom spray coating in the fluid bed dryer

Powder and binder are combined to form the required layer, thus the repeated layer after layer actions can achieve the desired granule size or coating thickness. Ideal for coatings with high solid content. The product is set into a spiral motion by means of a rotating base plate, which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays concurrently into the powder bed. Very thick film layers can be applied by means of the rotor method (Fig. 3.10).

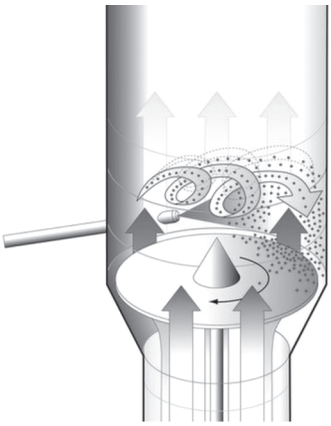


Fig. 3.10: Tangential spray coating in the fluid bed dryer

DEFECTS IN TABLET COATING

Orange Peel Effect

A surface defect resulting in the film being rough and non-glossy. Appearance is similar to that of an orange peel off (Table 3.9)

TABLE 3.9: Causes and rectification of orange peel/roughness

Sr. No.	*Causes*	*Rectification*
1.	Rapid drying	Optimizing drying conditions
2.	High solution viscosity	Decreasing viscosity of solution

Cratering

It is due to film coating whereby volcanic-like craters appears on the tablet surface.

The coating solution penetrates into the tablet, generally at the crown where the surface is more porous, causing localized disintegration of the core and disruption of the coating (Table 3.10).

TABLE 3.10: Causes and rectification of cratering

Sr. No.	*Causes*	*Rectification*
1.	Inefficient drying.	By optimizing drying conditions
2.	Higher rate of application of coating solution	Increase viscosity of coating solution to decrease spray application rate and decreasing the rate of application

Picking

It is defined as when isolated areas of film are pulled away from the surface, when the tablet sticks together and then apart. This is due to localize over wetting, which produces wet tablet bed, where adjacent tablets can stick together and then break apart (Table 3.11).

TABLE 3.11: Causes and rectification of picking

Sr. No.	*Cause*	*Rectification*
1.	Inefficient drying	Use optimum and efficient drying conditions or increase the inlet air temperature
2.	Higher rate of application of coating solution	Decrease the rate of application of coating solution by increasing viscosity of coating solution

Pitting

It is defect whereby pits occur in the surface of a tablet core without any visible disruption of the film coating.

This happens when temperature of the tablet core is greater than the melting point of the materials used in the tablet formulation (Table 3.12).

TABLE 3.12: Cause and rectification of pitting

Sr. No.	*Causes*	*Rectification*
1.	Improper drying (inlet air) temperature	Changing the drying (inlet air) temperature such that the temperature of the tablet core is not greater than the melting point of the batch of additives used

Blistering

It is defined as the detachment of film from the substrate leading to formation of blister (Table 3.13).

TABLE 3.13: Cause and rectification of blistering

Sr. No.	*Cause*	*Rectification*
1.	High temperature during drying effecting the strength, elasticity and adhesion of the film	Use mild drying condition

Chipping

It occurs when the film becomes chipped and dented, this occurs generally at the edges of the tablet (Table 3.14).

TABLE 3.14: Cause and rectification of chipping

Sr. No.	*Cause*	*Rectification*
1.	High degree of attrition during coating process	Increasing hardness of the film by using high molecular weight polymer. Reduce pan RPM

Blooming

In this the coating becomes dull immediately or after prolonged storage at high temperatures.

It is due to collection of low molecular weight ingredients on the surface added in the coating formulation. Generally the ingredient is plasticizer (Table 3.15).

TABLE 3.15: Cause and rectification of blooming

Sr. No.	*Cause*	*Rectification*
1.	Use of high concentration and low molecular weight plasticizer	Decreasing plasticizer concentration and increasing molecular weight of plasticizer

Cracking/Splitting

In this the film either cracks across the crown of the tablet (cracking) or splits around the edges of the tablet (splitting).

This happens when internal stress in the film exceeds tensile strength of the film (Table 3.16).

TABLE 3.16: Cause and rectification of cracking/splitting

Sr. No.	*Cause*	*Rectification*
1.	Use of higher molecular weight polymers	Use lower molecular weight polymers or polymeric blends. Changing the plasticizer and concentration

Blushing

It is described as whitish specks or haziness in the film.

It is thought to be due to precipitated polymer aggravated by the use of high coating temperature (Table 3.17).

TABLE 3.17: Causes and rectification of blushing

Sr. No.	*Causes*	*Rectification*
1.	High coating temperature	Decrease the drying air temperature
2.	Use of sorbitol along with hydroxy propyl cellulose, hydroxy propyl methyl cellulose, methyl cellulose and cellulose ethers, in formulation which causes largest fall in the thermal gelation temperature	Avoiding use of sorbitol with hydroxy propyl cellulose, hydroxy propyl methyl cellulose, methyl cellulose and cellulose ethers

Color Variation

There is variation in color of the film (Table 3.18).

TABLE 3.18: Cause and rectification of color variation

Sr. No.	*Cause*	*Rectification*
1.	Inadequate mixing, uneven spray pattern, insufficient coating, migration of soluble dyes-plasticizers and other additives during drying	By geometric mixing, using different plasticizers and using mild drying conditions

Logo-filling/Logo-bridging

Logo-filing is described as filling of logo while coating, while logo-bridging happens when coating film get detached from tablet core at the end and forms bridge. Logo-filling happens due to coating polymer deposition in the embossing, which covers the logo and tablets lost their identity (Table 3.19).

TABLE 3.19: Cause and rectification of infilling

Sr. No.	*Cause*	*Rectification*
1.	Spray drying due to increase temperature High spray rate High percentage coating	Decrease inlet temperature to reduce spray drying Optimize spray rate and percentage coating

Twinning

This is the term for two tablets that stick together, and its a common problem with capsule shaped tablets. It can be solved by balancing the pan speed, reducing the spray rate or increasing the pan speed.

EVALUATION OF COATED TABLETS

Evaluation of coated tablets requires evaluation of both the coatings and the coated tablets. Physical characterization of the coating system should include particle size, preparation time and viscosity because each affects the handling and use of the powdered on step coating systems. Large particles minimize dust and short process time have obvious advantages. Low viscosity enables to create a coating with high ratio of solids, which lead to faster tablet coating. Once tablets are coated they should be evaluated for:

i. Gloss
ii. Opacity
iii. Color uniformity
iv. Disintegration
v. Adhesion time
vi. Logo-bridging and logo-filling
vii. Film strength and flexibility

ISOLATED KEY POINTS

- The sugar coating involves several steps like, sealing, subcoating, color coating and printing.
- Sugar coating process yields elegant and highly glossed tablet.
- Film coating is deposition of a thin film of polymer surrounding the tablet core.
- Film coating is more favored than sugar coating because weight increase is 2–3%, single stage process, easily adaptable to controlled release, it retains color of original core, high adaptability to GMP, automation is possible, etc.
- Accelacota and fluidized bed equipment are widely used for film coating.
- Materials used in film coating include film formers, solvents, plasticizers, colorants, opaquant-extenders, surfactant, antioxidant, etc.
- Widely used film formers are hydroxypropyl methyl cellulose (HPMC), methyl hydroxy ethyl cellulose (MHEC), ethyl cellulose (EC), hydroxypropyl cellulose (four grades available, i.e. K-15, K-30, K-60 and K-90), Eudragit RS, Eudragit E are used for film coating. Eudragit L and S are used for enteric coating. Eudragit RL, Eudragit RS, Eudragit S are available as organic solution.
- Quality of film can be modified by plasticizer. Commonly used plasticizers include PG, glycerin, low molecular weight PEG, castor oils, etc. Castor oil and spans are more used for organic-solvent based coating solution while PE and PEG are used for aqueous coating.
- FD and C or D and C certified colorants are used. Lakes are choice for film coating as they give reproducible results. Colorants are expensive and higher concentration is required. So materials like titanium dioxides, silicates, and carbonates are used to provide more pastel colors and increase film coverage.
- Enteric coating is used to protect tablet core from disintegration in the acid environment of stomach to prevent degradation of acid sensitive API, prevent irritation to stomach by certain drugs, delivery of API into intestine and to provide a delayed release components for repeat action.
- Polymers used for enteric coating are cellulose acetate phthalate (CAP), acrylates (Eudragit L and Eudragit S, hydroxy propyl methyl cellulose phthalate (HPMCP 50, HPMCP 55 and HPMCP 55S) and polyvinyl acetate phthalate.
- Polymers like modified acrylates, ethyl cellulose, etc. are used for the same.

Coating Problems and Remedy

- Blistering is due to entrapment of gases in or underneath the film due to overheating either during spraying or at the end of the coating run. Remedy is by mild drying.
- Chipping is related to higher degree of attrition associated with the coating process. Increase in molecular weight grade of polymer can solve this problem.
- Cratering is related to penetration of the coating solution into the surface of the tablet. Decrease in spray application rate and use of optimum and efficient drying conditions can solve this problem.
- Pitting is defect in which temperature of the tablet core is greater than the melting point of the materials used in tablet formulation. Dispensing with preheating procedures at the initiation of coating and modifying the drying temperature can solve this problem.

- Infilling is because of bubble/foam formation during air spraying of a polymer solution. Addition of alcohol or use of spray nozzle capable of finer atomization can solve this problem
- Orange peel/roughness is related to inadequate spreading of the coating solution before drying. Remedy is by decrease in viscosity of coating solution.
- Cracking is seen when internal stresses in the film exceeds tensile strength of the film. This is common with higher molecular weight polymers or polymeric blends. Remedy is by using lower molecular weight polymers.
- Color variation is because of improper mixing, uneven spray pattern, insufficient coating or migration of soluble dyes during drying. Geometric mixing, mild drying conditions and reformulation with different plasticizers can solve this problem.
- Blooming or dull film is generally because of higher concentration and lower molecular weight of plasticizer. Remedy is by using lower concentration and higher molecular grade of plasticizer.

PRACTICE QUESTIONS

Long Answer Type Questions

1. Define the term tablet coating? Give various advantages of tablet coating?
2. Enumerate the various types of tablet coating technique? Why sugar coating is done?
3. Discuss in detail the various steps involve in sugar coating with suitable examples of substances use?
4. Write short notes on:
   a. Binder solution used for subcoating
   b. Dusting powder used for subcoating
   c. Suspension used for subcoating.
5. What is film coating? Why is it done? Give difference between film coating and sugar coating?
6. Discuss in detail about various materials used in film coating with suitable examples?
7. Write short notes on (with reference to coating of tablets)
   a. Plasticizers
   b. Colorants
   c. Solvents used
   d. Film forming polymers.
8. What is enteric coating? Give its significance? How enteric coating is done explain it with the help of suitable examples?
9. Write short notes on specialized coating techniques
   a. Compressed coating
   b. Dip coating
   c. Vacuum film coating
10. Enumerate various factors affecting coating? List at least two equipment used for coating?
11. Discuss in brief about conventional pan coating system with the help of neat and labeled diagram?

12. Discuss in brief about immersion sword and immersion tube coating system with the help of neat and labeled diagram?
13. What is FBD? Give its advantages?
14. Write principle of operation of FBD? Describe top spray, bottom spray and tangential spray FBD in detail with neat and labeled diagram?
15. Enumerate various problems in tablet coating? How these problems can be resolved?
16. Give various methods of evaluation of coated tablets?

Objective Type Questions

1. _____ coating is used to protect tablet core from disintegration in the acid environment of the stomach.
2. Which of the following is not the property of enteric coating material listed below?
i. Resistance to gastric fluids
ii. Permeable to intestinal fluid
iii. Give immediate release
iv. Formation of continuous film
3. Which of the following is not a type of fluid bed system?
i. Top spray coating
ii. Horizontal spray coating
iii. Bottom spray coating (Wurster coating)
iv. Tangential spray coating (rotor pellet coating)
4. Match the following:

S. No.	*Coating problems*		*Cause*
1.	Blistering	a	Higher degree of attrition during coating process
2.	Chipping	b	Penetration of the coating solution into the surface of tablet
3.	Cratering	c	Inadequate spreading of the coating solution before drying
4.	Orange peel	d	Entrapment of gases in or underneath the film

5. Match the following:

S. No.	*Sugar coating processes*		*Functions*
1.	Sealing/water proofing	a	Increases the bulk and round off the tablet
2.	Subcoating	b	Smoothes the subcoated surface and increases the tablet size
3.	Grossing/smoothing	c	Provides a moisture barrier and harden the tablet surface
4.	Polishing	d	Give characteristics gloss

ANSWERS

1. Enteric
2. iii
3. ii
4. 1—d, 2—a, 3—b, 4—c
5. 1—c, 2—a, 3—b, 4—d

Chapter
4

Liquid Orals

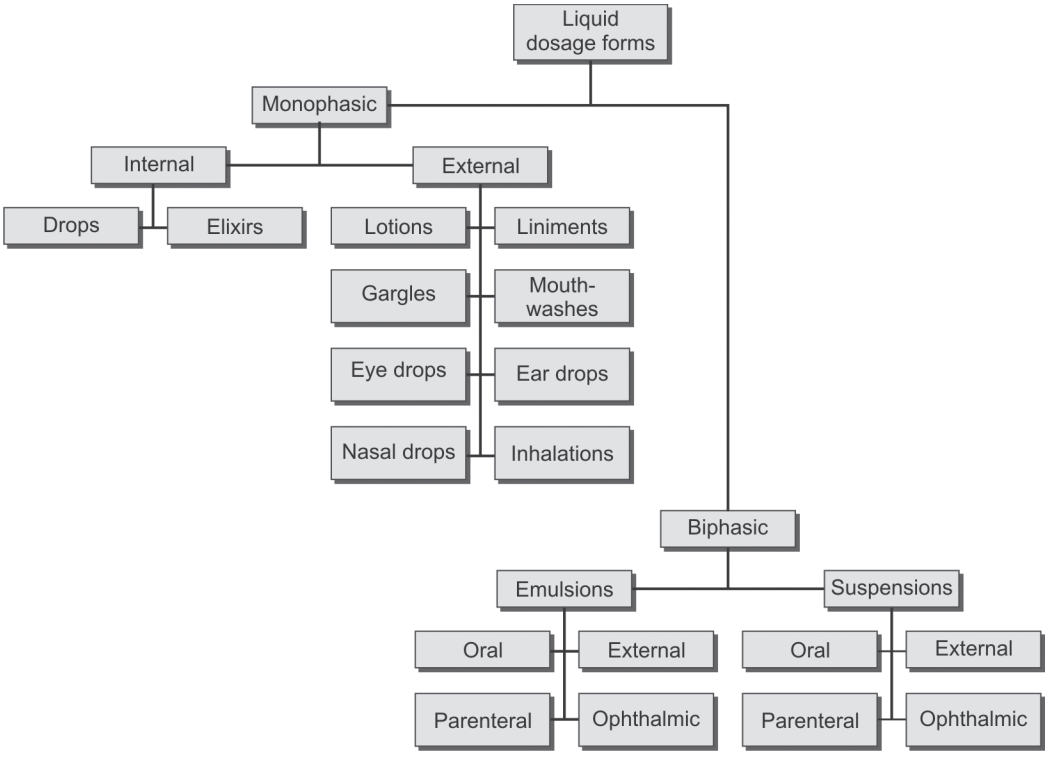
Liquid dosage forms commonly used in pharmaceutical practice are either monophasic or biphasic. Monophasic systems are characterized by the presence of a single homogeneous phase, e.g. solution, mixtures, elixirs, tinctures, syrups, ear drop, nasal drops, etc., whereas biphasic liquid dosage forms consist of two distinct phases, e.g. emulsions and suspensions. Liquid preparations may be broadly classified under two categories (Flowchart 4.1).

1. Internal liquid preparation:

A. Monophasic liquid preparations

a. Syrups
b. Elixirs
c. Solutions
d. Linctuses

Flowchart 4.1: Different types of liquid dosage form



B. Biphasic liquid preparations
   a. Suspension (mixture) b. Emulsion

2. External liquid preparations:

A. Topical (applied on the skin)
   a. Lotions b. Liniments
   c. Throat paints d. Collodions

B. Instilled into body cavities
   a. Douches b. Enemas
   c. Ear drops d. Nasal drops
   e. Nasal sprays f. Inhalations

C. Used in mouth
   a. Gargles b. Mouthwashes

ADVANTAGES AND DISADVANTAGES OF LIQUID DOSAGE FORMS

Advantages

1. They are more effective than solid dosage forms as this eliminates the dissolving step of solid drug in the GIT.
2. It is easy to swallow than solid dosage form especially in case of geriatric and pediatric populations.
3. Certain drugs have to be administered in liquid form only. It may be due to the large dose of the drug that is difficult to administer in solid dosage form.
4. Some drugs cause gastric irritation when administered in solid dosage form, e.g. potassium iodide and bromide. Hence they are to be administered in liquid dosage form.

Disadvantages

1. They undergo deterioration and loss of potency more frequently than solid dosage forms.
2. They show many flavoring and sweetening problems. It is difficult to mask the bitter taste and unpleasant odor of some drugs.
3. Many incompatibility problems occur between the dissolved ingredients of the dosage form.
4. More chances for microbial contamination of the product as water provide a major means for mold and bacterial growth. Hence preservatives added. But the liquid dosage forms with preservatives are not intended for neonates as the antimicrobial preservatives cause serious acute and long-term adverse affects. (Due to presence of water microbial contamination of product occurs hence preservatives are added.)
5. Inaccuracy of measuring dose may occur. It needs an accurate measuring device for administration.
6. These are bulkier to carry than solid dosage forms. There are chances for breakage of the container.

EXCIPIENTS USED IN LIQUID DOSAGE FORM

Excipients play an important role in formulating a dosage form. These are the ingredients which along with active pharmaceutical ingredients make up the dosage

forms. In most of the formulations these are present in a greater proportion with regards to active pharmaceutical ingredient, as it forms about the bulk of the formulation, it is necessary to select an excipient which satisfies the ideal properties for a particular excipient. Pharmaceutical excipients are substances other than the pharmacologically active drug which are include in the manufacturing process or are contained in a finished pharmaceutical product dosage form. Excipients act as protective agents, bulking agents and can also be used to improve bioavailability of drugs in some instances. Excipients as like other active pharmaceutical ingredients need to be stabilized and standardized. Excipient quality plays a vital role in assuring safety, quality and efficacy of dosage forms.

1. ***Vehicle:*** Vehicles, in pharmaceutical formulations, are the liquid bases that carry drugs and other excipients indissolved or dispersed state. Pharmaceutical vehicles can be classified as under
   - **a. Aqueous vehicles:** Water, hydro-alcoholic, polyhydric alcohols and buffers. These may be thin liquids, thick syrupy liquids, mucilages or hydrocolloidal bases
   - **b. Oily vehicles:** Vegetable oils, mineral oils, organic oily bases or emulsified bases.
2. ***Buffering agents:*** These are the agents which are added to maintain different ranges of pH of the solution. They resist the change in pH of the solution, e.g. Sorenson's modified phosphate buffer, sodium acetate buffer.
3. ***Isotonicity modifiers:*** These are the agents added to maintain the isotonicity of the solutions similar to that of various body cavities. These are mainly added for ophthalmic solutions, injectable solutions and solutions applied for mucous membrane, e.g. dextrose and 0.9% NaCl solution.
4. ***Viscosity modifiers:*** In order to increase the residence time of the aqueous based solutions that are intended for skin, eye, and ears, some jelling agents, in low concentrations are added to increase the viscosity of the product. Syrups may also be added to increase the viscosity of the product. They also improve palatability and ease of pourability of the product, e.g. hydroxypropyl methylcellulose, hydroxyethyl cellulose, methylcellulose, polyvinyl alcohol, and polyvinyl-pyrrolidine.
5. ***Preservatives:*** Preservatives are substances added to various pharmaceutical dosage forms and cosmetic preparations to prevent or inhibit microbial growth. An ideal preservative would be effective at low concentrations against all possible micro-organism, be non-toxic and compatible with other constituent of the preparation and be stable for the shelf-life of the preparation.
   - i. Ethanol (>10%v/v)
   - ii. Propylene glycol (15–30%v/v)
   - iii. Glycerin (>20%v/v)
   - iv. Benzoic acid and sorbic acid (0.1%–0.5%w/v)
   - v. Chloroform water BP (0.25%v/v)
   - vi. Methyl, ethyl, propyl and butyl parabens (up to 0.2%). Generally combination of parabens is used in the formulations in order to achieve a higher total concentration and to be active against a wider range of microorganisms.
   - vii. Quarternary ammonium compounds: Benzalkonium chloride (0.002–0.02%) shows optimal activity over the pH range of 4 to 10.

6. ***Antioxidants:*** Antioxidants are currently used as efficient excipients that delay or inhibit the oxidation process of molecules. These are agents used to prevent the products like vitamins, essential oils and fats from oxidation. The oxidation reaction may be due to heat, light and heavy metals. To prevent from heat and light, they should be stored at cool temperature and in light resistance container respectively. EDTA or citric acid is mostly used to prevent oxidation by heavy metals like Fe, Cu, other antioxidants used are ascorbic acid, citric acid, propyl and octyl esters of gallic acid, tocopherols, sodium metabisulfite, and sodium sulfite.
7. ***Sweetening agents:*** These are the agents added to mask the bitter taste of the active ingredient. For example, aspartame, sucralose and sodium saccharin
   i. Sucrose is widely used sweetening agent.
      a. Advantages: Colorless, highly water soluble, stable over a wide pH range (4–8), increase the viscosity, masks both salty and bitter taste, has soothing effect on throat.
      b. Disadvantages: Prolonged usage of the product with sucrose cause dental caries and it is also not suitable for diabetic patients.
   ii. Polyhydric alcohols such as sorbitol, mannitol and glycerol also act as sweeteners and can be used for diabetic preparations.
8. ***Flavors:*** These are the agents added to mask the unpleasant taste or odor and make the preparation more acceptable to take. If it is from natural source, it is classified as natural and if synthesize by artificial means then categorized as artificial flavor. Artificial flavors are cheaper, more readily available and more stable than natural products.

   Examples of natural flavors are Fruit juices (raspberry), extracts (liquorice), spirits (orange and lemon), syrups (black current), tinctures (ginger), and aromatic water (anise and cinnamon).
9. ***Coloring agents:*** These are the agents added to enhance the appearance of the preparation. They should be non-toxic, non-irritant and should not show any therapeutic activity. Both natural and artificial coloring agents are available.

   Natural coloring agents: These include materials extracted from plants and animals, e.g. carotenoids, chlorophylls, saffron, red beet root extract, caramel, and cochineal.

   Synthetic colors: Azo compounds. These are widely used as they give wide range of bright and stable colors.
10. ***Wetting agents and surfactants:*** Wetting agents are routinely used in pharmaceutical formulations, especially in liquid dosage forms to create a homogeneous dispersion of solid particles in a liquid vehicle. The use of a wetting agent allows removal of adsorbed air and easy penetration of the liquid vehicle into pores of the particle in a short period of time. For an aqueous vehicle, alcohol, glycerin, and PG are frequently used to facilitate the removal of adsorbed air from the surface of particles. Whereas for a non-aqueous liquid vehicle, mineral oil is commonly used as a wetting agent. Typically, hydrophobic API particles are not easily wetted even after the removal of adsorbed air. Hence, it is necessary to reduce the interfacial tension between the particles and the liquid vehicle by using a surface active agent. For example, sodium lauryl sulfate is one of the most commonly used surface-active agents. Such surfactants, when dissolved in water, lower the contact angle of water and aid in spreadability of water on the particles surface to displace the air layer at the surface and replace it with the liquid phase. Wetting agents have a hydrophilic-lipophilic balance (HLB) value between 7 and 9.

SOLUTIONS

Solutions are the homogenous mixtures in which one or more active ingredients are dissolved in a one or mixture of solvents which may be aqueous or non-aqueous in nature. These are the oldest dosage forms used in the treatment of patients, which afford rapid and high absorption of soluble active ingredients.

Advantages and Disadvantages of Solutions

Advantages

i. Easier to swallow: Especially for pediatrics, geriatrics and unconscious people.
ii. Quick onset of action: As it eliminates the step of disintegration and dissolution.
iii. Flexible dosing.
iv. No need to shake the container.
v. Can be designed for different routes of administration.

Disadvantages

i. Difficult to mask the unpleasant taste and odor of active ingredient.
ii. Needs a measuring device (like graduated bottle caps, or a spoon) to measure accurate dose on administration.
iii. Less stable than solid dosage forms.
iv. Bulky, difficult to transport and they are prone to breakages.

Important Aspects of Solution Preparation

Different solutions are prepared with different methods, different additives and different drugs. Two main aspects considered majorly while preparing the solution are solubility and stability of the active ingredient in the solution.

Solubility: The solubility of the active ingredient in the formulation is a major aspect and the following points are to be checked before preparing a solution.

a. The solubility of the drug in the solvent system
b. Quantity of the drug to be dissolved
c. Dissolution time of the drug in that solvent
d. Whether the drug remains in solution or precipitate.
e. pH of the solvent required for dissolution

Stability: The following stability parameters to be considered for solution stability

a. The physical stability of the solution towards temperature fluctuations and photosensitivity should be considered
b. The chemical stability with respect to the additives and shelf life should be considered.
c. The microbiological stability of the solutions is considered and there is need for addition of preservative.

Major signs of instability are:

a. Color change
b. Precipitation or crystal growth appearance
c. Microbial growth
d. Chemical gas formation

Methods of Preparation of Solutions

Solutions are prepared by the following methods.

a. Simple solution
b. Solution by chemical reaction
c. Solution by extraction

a. Simple solution: In this the solute is dissolved in a suitable solvent either by stirring or heating. Other additives may be added along with the solvent in order to enhance the stability and solubility of the active ingredient. For example, in the preparation of Strong Iodine Solution USP (Lugol's solution), KI is added to the mixture of iodine and water, as it forms more soluble polyiodides ($KI{\cdot}I_2$ $KI{\cdot}2I_2$ $KI{\cdot}3I_3$ $KI{\cdot}4I_4$).

b. Solution by chemical reaction: In this two or more solutes react with each other to form solution in a suitable solvent. For example, calcium carbonate and lactic acid used in the preparation of calcium lactate mixture.

c. Solution by extraction: Plant or animal products are prepared by suitable extraction process. Preparations of this type may be classified as solutions but more often, are classified as extractives.

BIPHASIC LIQUIDS EMULSION AND SUSPENSION

Emulsion

A **pharmaceutical emulsion** is a two-phase liquid preparation consisting of two or more immiscible liquids in which small globules of one liquid are dispersed uniformly throughout the other liquid. The liquid that is dispersed as small globules is called the dispersed phase or internal phase or discontinuous phase and the other liquid is called the dispersion medium or external phase or continuous phase.

Emulsion is a thermodynamically unstable liquid preparation containing at least two immiscible liquids, in which one liquid phase is dispersed as globules (dispersed or internal phase) in other liquid phase (continuous or external phase) stabilized with the aid of an emulsifying agent (Fig. 4.1). General types of pharmaceutical emulsions include lotions, liniments, ointments, creams, and vitamin drops.

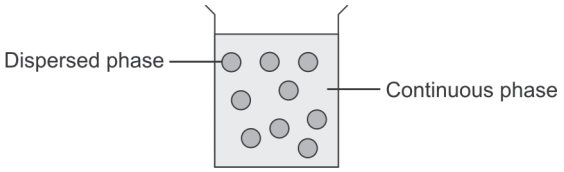


Fig. 4.1: Dispersed phase and continuous phase of an emulsion

Advantages and Disadvantages of Emulsions

Advantages

i. Unpalatable drugs can be administered in palatable form.
ii. Oil sensation of oil soluble drugs can be masked as aqueous phase can easily disperses the flavors in it.
iii. Improve the rate of absorption of drugs.
iv. Two incompatible ingredients can be included one in each phase of an emulsion.

Disadvantages

i. The emulsion should be shaken every time prior to administration.
ii. It needs an accurate measuring device for measuring the dose for administration.

iii. Proper storage conditions are required.
iv. Bulky and difficult to transport and may prone to breakage.
v. Easily contaminated by microorganisms that leads to emulsion instability.

Types of Emulsions

1. Macroemulsion or simple emulsion
2. Microemulsion

1. ***Macroemulsions (simple emulsions):*** In this type of emulsion one phase of emulsion gets dispersed in the other phase generally water in oil (w/o type) or oil in water (o/w type) (Fig. 4.2 and Table 4.1). The size of the droplets is approximately 5 μm.
Oil in water (o/w): In this the oil droplets are dispersed in a continuous aqueous phase. This emulsion is generally formed if the aqueous phase constitutes more than 45% of the total weight. In this a hydrophilic emulsifier is used. The globule size is 0.25 to 10 microns. These are generally used for oral administration.

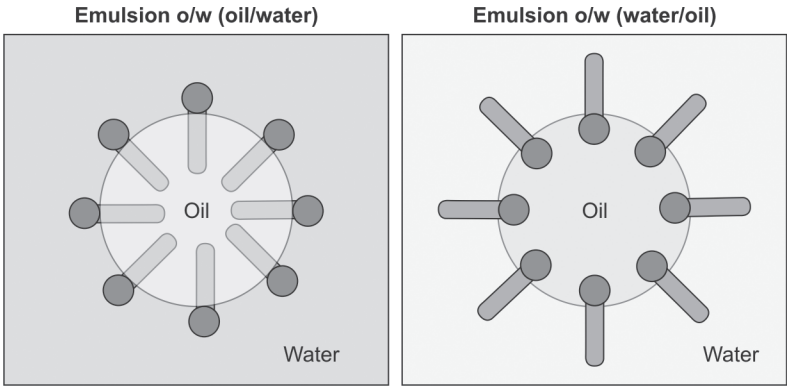


Fig 4.2: A simple emulsion: o/w type and w/o type

TABLE 4.1: Difference between o/w and w/o emulsions

S. No.	*Oil in water emulsion (o/w)*	*Water in oil emulsion (w/o)*
1.	Water is the dispersion medium and oil is the dispersed phase	Oil is the dispersion medium and water is the dispersed phase
2.	They are non greasy and easily removable from the skin surface	They are greasy and not water washable
3.	They are used externally to provide cooling effect, e.g. vanishing cream	They are used externally to prevent evaporation of moisture from thesurface of skin, e.g. cold cream
4.	Water soluble drugs are more quickly released from o/w emulsions	Oil soluble drugs are more quickly released from w/o emulsions
5.	They are preferred for formulations meant for internal use as bitter taste of oils can be masked.	They are preferred for formulations meant for external use like creams
6.	O/W emulsions give a positive conductivity test as water is the external phase, which is a good conductor of electricity	w/o emulsions go not give a positive conductivity test as oil is the external phase which is a poor conductor of electricity

Water in oil (w/o): In this the aqueous phase is dispersed in a continuous oily phase. This emulsion is generally formed if the oily phase constitutes more than 45% of the total weight and a lipophobic emulsifier is used. These are generally used for cosmetics. These are employed for treatment of dry skin and emollient applications.

2. ***Microemulsions:*** These are the clear, homogenous emulsions in which one insoluble liquid is dispersed in a second liquid. Droplets size range 0.01 to 0.1µm. These are generally referred to as solubilized systems or transparent emulsions or micellar solutions as they appear as true solutions to the naked eye. Microemulsions are believed to be thermodynamically stable. These are used for drug administration and toiletry products.

Test for Identification of Emulsion

1. ***Dilution test:*** In general the emulsion will be diluted only with its continuous phase. Hence o/w can be diluted with water and w/o can be diluted with oil. So, when oil is added to o/w emulsion or when water is added to w/o emulsion, separation of internal and continuous phase occurs. This test is used for liquid emulsions (Fig. 4.3).
2. ***Dye solubility test:*** In general water soluble dye (e.g. amaranth dye or methylene blue) will be taken up by the aqueous phase where as oil soluble dye (e.g. scarlet dye) will be taken by oily phase. When it is observed microscopically that water soluble dye is taken up by the continuous phase, it is o/w emulsion. If the dye is not taken up by the continuous phase, test is repeated with oil soluble dye. If it is taken up by the continuous phase, it can be confirmed as w/o emulsion. This test can fail if ionic emulsions are present (Fig. 4.4).

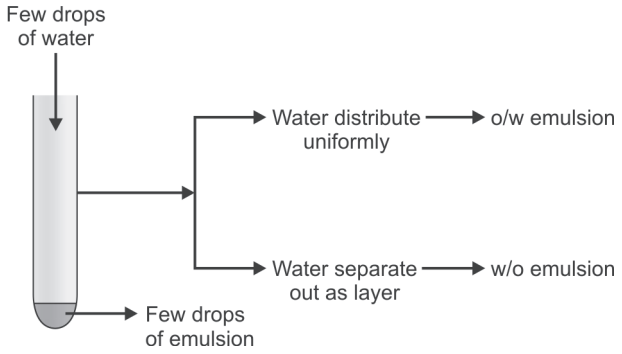


Fig. 4.3: Dilution test for liquid emulsions

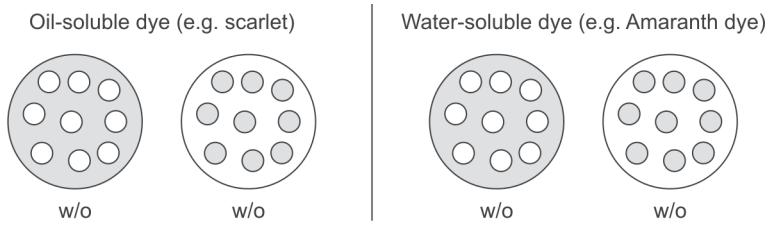


Fig. 4.4: Microscopic examination of type of emulsion by dye solubility test

3. ***Conductivity test:*** Water is a good conductor of electricity where as oil is non-conductor of electricity. When a pair of electrodes connected to a lamp and an electrical source are dipped into emulsion and on pressing the key the bulb glows it means the given emulsion is o/w type emulsion and if the lamp does not glow, it means the given emulsion is w/o type emulsion (Fig. 4.5).

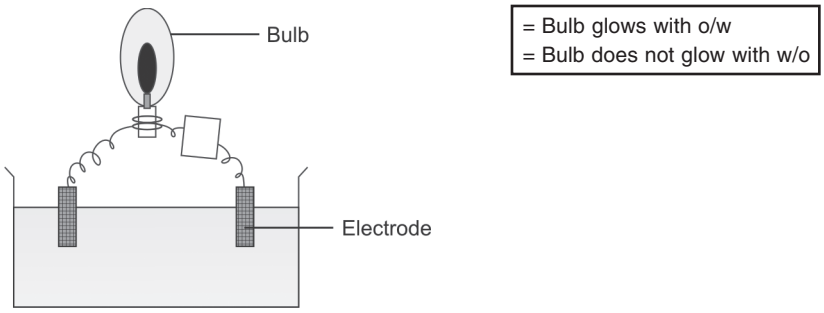


Fig. 4.5: Conductivity test for determination of type of emulsion

4. ***$CoCl_2$ filter test:*** To a filter paper impregnated with $CoCl_2$ and dried (blue), o/w emulsion is added. It changes to pink. It may fail if emulsion is unstable or breaks in presence of electrolyte.
5. ***Fluorescence test:*** Since some oils fluoresce under UV light, o/w emulsions exhibit no fluorescence whereas, w/o emulsion exhibits fluoresce. But this test is applicable for oils that have fluorescent property.

Emulsifying Agents

These are the substances added to an emulsion to prevent the coalescence of the globules of the dispersed phase and hence maintain the stability of emulsion. They are also known as emulgents or emulsifiers. HLB method is indicative of emulsification behavior. A HLB value of 3–6 is used for w/o emulsion and HLB value of 8–18 is used for o/w emulsion. An emulsifying agent mainly acts by the following mechanisms;

- *Reduction in interfacial tension:* Thermodynamic stabilization.
- *Formation of a rigid interfacial film:* Mechanical barrier to coalescence.
- *Formation of an electrical double layer:* Repulsion of individual droplets.

Ideal requirements of emulsifying agent:

a. It should be able to reduce the interfacial tension between the two immiscible liquids.
b. It should be physically and chemically stable, inert and compatible with the other ingredients of the formulation.
c. It should be non irritant and non-toxic when used in required concentrations.
d. It should be organoleptically inert, i.e. should not impart any color, odor or taste to the preparation.
e. It should be able to form a coherent film around the globules of the dispersed phase and should prevent the coalescence of the droplets of the dispersed phase.
f. It should be able to produce and maintain the required viscosity of the preparation.

Method of Preparation of Emulsion

While preparing the acacia emulsions for extemporaneous use, primary emulsion formula must be used. Based on the nature of the oil different formulas are there (Table 4.2).

TABLE 4.2: Formula for preparation of primary emulsion

Nature of oil	*Examples*	*Ratios of ingredients*		
		Oil	*Water*	*Gum*
Fixed oil	Castor oil, Almond oil, Arachis oil	4	2	1
Mineral oil	Liquid paraffin	3	2	1
Volatile oil	Turpentine oil, Peppermint oil	2	2	1
Oleo gum resin	Male fern extract	1	2	1

Preparation techniques of emulsions: The preparation techniques for emulsion can be divided into laboratory scale productions and large-scale productions.

Laboratory scale techniques: Techniques used on laboratory scale are:

1. Continental or dry gum method
2. Wet gum method
3. Bottle or Forbes bottle method
4. Auxiliary method
5. In situ soap method

Continental method or Dry gum method: The continental method is used to prepare the initial or primary emulsion from oil, water and an emulsifier (gum usually acacia) in 4:2:1 ratio. The 4 parts of oil and 1 part of gum represent their total amount for the final emulsion.

Method: In this 1 part of gum (acacia) is triturated with 4 parts of oil in a motor, until the powder is thoroughly wetted. Then 2 parts of water is added all at once and the mixture is vigorously and continuously triturated until a creamy white primary emulsion is formed. Additional water may be incorporated after the primary emulsion is formed. Solid substances (like active ingredients, preservatives, colors and flavors) are added as a solution to the primary emulsion, oil soluble substances in small amounts may be incorporated directly into the primary emulsion. Any substance which might reduce the physical stability of the emulsion, such as alcohol (which may precipitate the gum) is added at the end in order to avoid breaking the emulsion. When all agents have been incorporated, the emulsion should be transferred to a calibrated vessel, and the final volume is made with water, then homogenized or blended to ensure uniform distribution of ingredients.

Example: Cod liver oil emulsion

Cod liver oil	50 ml
Acacia	12.5 gm
Syrup	10 ml
Flavor oil	0.4 ml
Purified water	up to 100 ml

Method: Weigh accurately all the ingredients. The cod liver oil is placed in dry mortar. Add acacia and mix it quickly. Add 25 ml of water and immediately triturate

to form thick white, homogenous primary emulsion. Add flavor and mix. Add syrup and mix. Add sufficient water to make the final volume.

Wet gum method or English method: In this method the proportion of oil and water and emulsifier (gum) are in the ratio of 4:2:1, but the order and technique of mixing is different from dry gum method. In this 1 part of gum is triturated with 2 parts of water to form mucilage. To these 4 parts of oil is slowly added in portions, while triturating. After all the oil is added, the mixture is triturated for several minutes to form the primary emulsion. Then other ingredients are added as in continental method. In general the English method is more difficult to perform successfully, especially with more viscous oils, but it results in a more stable emulsion.

Bottle method: This method is used to prepare emulsions with volatile oils, or oleaginous substances of very low viscosities. This method is a variation of dry gum method. 1 part of powdered acacia (or other gum) is placed in a dry bottle and 4 parts of oil are added. The bottle is capped and thoroughly shaken. The time of mixing the gum and oil should be less as the gum will tend to imbibe the oil and will become water proof. To this required volume of water is added all at once and shaken thoroughly until the primary emulsion is formed.

Auxiliary method: A hand homogenizer is used to improve the emulsion prepared by other methods. In this the emulsion is passed through a very small orifice, and hence reduces the dispersed droplet size to about 5 microns or less.

In situ soap method: This contains oils such as olive oil and oleic acid along with lime water (calcium hydroxide solution, USP). These are called calcium soaps. It is prepared by mixing equal volumes of oil and lime water.

Example: Nascent soap which consists of oil phase as olive oil/oleic acid and lime water as aqueous phase. Olive oil can be replaced by other oils but oleic acid must be added. Lime water [$Ca(OH)_2$] should be freshly prepared. The emulsion formed is w/o type emulsion.

Packaging of Emulsions

These are generally packaged in wide mouthed containers made of plastic, glass and metal. Parenteral emulsions are generally stored in glass vials or glass ampoules or glass bottles. Disposable syringes are generally made of plastic material. The stoppers used are made up of elastomeric materials. Metallic containers are used for packaging of topical emulsions. This protects the emulsion from light. Table 4.3 represents the type of packaging of pharmaceutical emulsions.

Expiry Date of Emulsions

The preparation should be discarded after the expiry date.

TABLE 4.3: Packaging of pharmaceutical emulsions

Emulsion Type	*Bottle Type*	*Typical size*
Oral emulsions	Amber flat medical bottles	50 ml, 100 ml, 150 ml, 200 ml, 300 ml and 500 ml
External emulsions	Amber fluted medical bottles	50 ml, 100 ml and 200 ml

Labeling Requirements of Emulsions

The labeling of pharmaceutical emulsions is important for ease of patient administration. They are as follows.

- Shake well before use
- For external use only: In case of external emulsions that are not intended for oral use
- Do not freeze
- Protect from direct sunlight.

Suspensions

Suspensions are class of liquid dosage forms in which the finely divided solid particles (internal phase) are dispersed uniformly in a liquid dispersion medium (external phase). The internal phase consisting of insoluble solid particles having a range of size (0.5–5 microns) which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent. The external phase (suspending medium) is generally aqueous in some cases it may be an organic or oily liquid for non-oral use. The formulation, manufacturing, stability and packaging are the important aspects to be considered in the designing of pharmaceutical suspensions.

Advantages and Disadvantages of Suspension

Advantages

i. Insoluble derivatives of certain drugs are more palatable than soluble forms and these derivatives are formulated in the form of suspensions.
ii. Some insoluble derivatives of drugs are more stable in aqueous solvents than in the soluble salts.
iii. Suspension can improve chemical stability of certain drug, e.g. procaine penicillin G.
iv. Suspended insoluble powders are easy to swallow. Bulky powders such as kaolin BP and chalk BP can be administered in suspension form which acts as adsorbents of toxic substances in the gastrointestinal tract.
v. Drug in suspension exhibits higher rate of bioavailability than other solid dosage forms. The decreasing order of bioavailability of drug in the dosage form is as follows: Solution > Suspension > Capsule > Compressed Tablet > Coated tablet.
vi. Duration and onset of action can be controlled, e.g. protamine zinc-insulin suspension.
vii. Suspension can mask the unpleasant/bitter taste of drug, e.g. chloramphenicol palmitate.

Disadvantages

i. They should be shaken well prior to administration.
ii. Physical stability, sedimentation and compaction can causes problems.
iii. Care should be taken while handling and transport due to its bulky nature.
iv. Formulation of an ideal suspension is difficult.
v. Uniform and accurate dose cannot be achieved unless suspension is packed in single dosage form.

Classification of Suspensions

Based on route of administration

a. Oral suspensions
b. Parenteral suspensions
c. Topical suspensions

Based on proportion of solid particles

a. Dilute suspension (2 to 10%w/v solid)
b. Concentrated suspension (50%w/v solid)

Based on electro-kinetic nature of solid particles

a. Flocculated suspension
b. Deflocculated suspension

Based on size of solid particles

a. Colloidal suspension (<1 micron)
b. Coarse suspension (>1 micron)
c. Nano suspension (nm range)

Reasons for the formulation of a pharmaceutical suspension

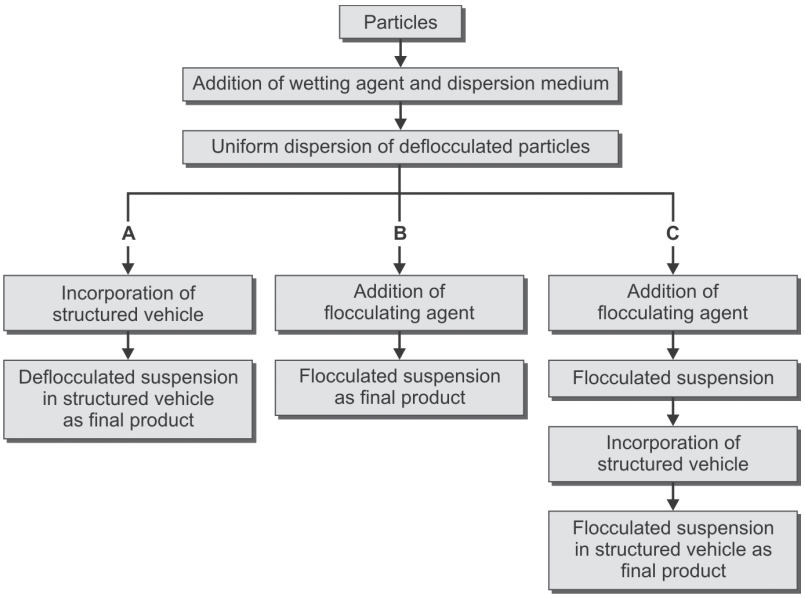
i. The drug is insoluble in the vehicle
ii. To mask the bitter taste of the drug
iii. To increase the stability of the drug
iv. To make the drug sustained or controlled release

Method of Preparation

The preparation of suspension includes three methods:

1. Use of controlled flocculation
2. Use of structured vehicle
3. Combination of both, i.e. use of controlled flocculation and structured vehicle (Flowchart 4.2).

Flowchart 4.2: Method of preparation of suspension



Important Considerations in Formulation of a Suspension

During the formulation of a suspension, the properties both the dispersed phase and dispersion medium should be known well in order to obtain a good suspension. The route of administration, intended application and possible adverse effects of the material should be well studied, and then it is selected for formulating into a suspension. The following are the most important factors that are to be considered during formulation a pharmaceutical suspension.

Nature of the suspended material: The suspended particles should possess low interfacial tension so that they are easily wetted by water and hence can be suspended easily. Particles with high interfacial tension are not wetted easily. In this case surfactants are used which reduces the interfacial tension of the particles and increases their wettability.

Size of the suspended particles: As per the Stroke's law, the sedimentation rate decreases when the particle size is reduced. It is given by the equation;

$$\text{Rate of sedimentation, } V = \frac{d^2(\rho_1 - \rho_2)\, g}{18\eta o}$$

where, V = terminal velocity of sedimentation (cm/s)
d = diameter of the particle (cm)
η_o = viscosity of the suspending medium
g = acceleration due to gravity
ρ_1 and ρ_2 = densities of the suspending particles and the medium respectively.

Factors Affecting Sedimentation

Particle size diameter (d): Sedimentation velocity (v) is directly proportional to the square of diameter of particle (d).

$$V \propto d^2$$

Density difference between dispersed phase and dispersion media ($\rho_1 - \rho_2$): The velocity of sedimentation is directly proportional to the difference between the dispersed phase and dispersion medium.

$$V \propto (\rho_1 - \rho_2)$$

Generally the density of the suspended particles is greater than dispersion medium. But in certain cases particle density is less than dispersion medium, so suspended particle floats and hence uniform dispersion of the particles is difficult. If density of the dispersed phase and dispersion medium are equal, the rate of settling becomes zero.

Viscosity of dispersion medium (η_o): Sedimentation velocity is inversely proportional to viscosity of dispersion medium.

$$V \propto 1/\eta_o$$

Increase in viscosity of medium decreases settling, so that the particles achieve good dispersion system. But increase in viscosity should not be such that it gives rise to problems like pouring, syringeability and redispersibility of suspension.

Flocculated and Deflocculated Suspension

Flocculated suspensions: In flocculated suspension, formed flocs (loose aggregates) will cause increase in sedimentation rate due to increase in size of sedimenting particles. Hence flocculated suspensions sediment more rapidly. Here the sedimentation depends not only on the size of the flocs but also on the porosity of flocs.

Deflocculated suspensions: In deflocculated suspension, individual particles are settling. Rate of sedimentation is slow, which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation. This phenomenon called 'caking' or 'claying'. In deflocculated suspension larger particles settle fast and small particles in supernatant liquid so supernatant appears cloudy (Table 4.4 and Fig. 4.6).

TABLE 4.4: Difference between flocculated and deflocculated suspensions

Flocculated	*Deflocculated*
1. Particles forms loose aggregates and form a network like structure	1. Particles exist as separate entities
2. Rate of sedimentation is high	2. Rate of sedimentation is slow
3. Sediment is rapidly formed	3. Sediment is slowly formed
4. Sediment is loosely packed and does not form a hard cake	4. Sediment is very closely packed and a hard cake is formed
5. Sediment is easy to redisperse	5. Sediment is difficult to redisperse
6. Suspension is not pleasing in appearance	6. Suspension is pleasing in appearance
7. The floccules stick to the sides of the bottle	7. They do not stick to the sides of the bottle

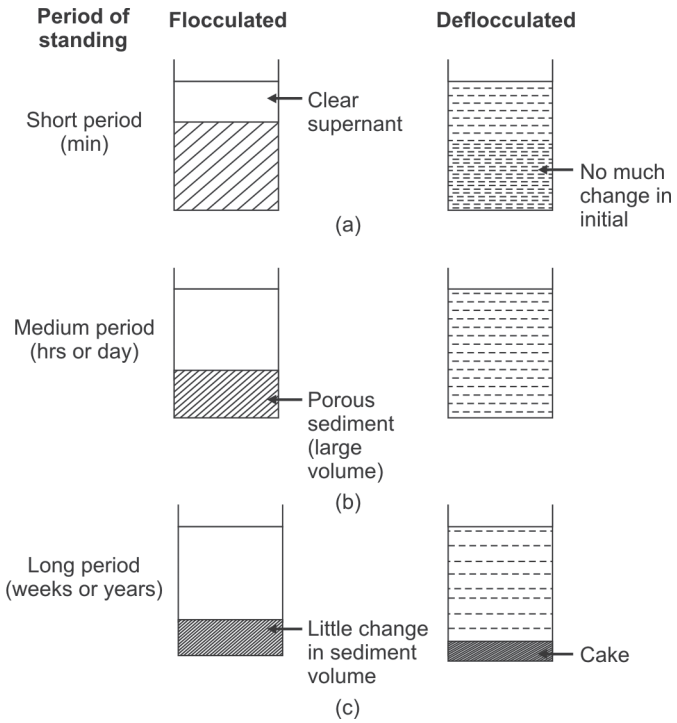


Fig. 4.6: Rate of sedimentation of deflocculated and flocculated suspensions

Stability Problems with Suspension

The following are some problems which are associated with the stability of suspension during their storage and shelf life.

1. Caking and poor redispersibility
2. Cap locking
3. Color change
4. Crystal growth
5. Deflocculation
6. Rapid settling
7. Change in particle size
8. Foaming

EVALUATION TESTS OF LIQUID DOSAGE FORMS

1. Particle size determination of dispersed particles in a suspension: The particle size of the suspension is to be determined as it affects the drug absorption and larger size of the particles cause irritation in case of parenteral suspensions. The particle size can be determined by the following methods.

a. **Optical microscopy:** Particle size can be measured microscopically by sizing and counting, but for a statistically valid analysis, millions of particles must be measured. This is impossibly arduous when done manually, but now-a-days automated analysis of electron micrographs is commercially available. Instruments such as the Retsch camsizer can perform this analysis using standard camera technology.

b. **Coulter counter method (electroresistance counting methods):** In this the momentary changes in the conductivity of a liquid passing through an orifice is measured when individual non-conducting particles pass through. The particle count is obtained by counting pulses, and the size is dependent on the size of each pulse.

c. **Acoustic spectroscopy or ultrasound attenuation spectroscopy:** In this method ultrasound is employed for collecting information on the particles that are dispersed in fluid. Dispersed particles absorb and scatter ultrasound similarly to light. It turns out that instead of measuring *scattered energy versus angle*, as with light, in the case of ultrasound, measuring the *transmitted energy versus frequency* is a better choice. The resulting ultrasound attenuation frequency spectra are the raw data for calculating particle size distribution. It can be measured for any fluid system with no dilution or other sample preparation. Calculation of particle size distribution is based on theoretical models that are well verified for up to 50% by volume of dispersed particles.

d. **Laser diffraction methods:** In this "halo (dark portion)" of diffracted light is produced when a laser beam passes through a dispersion of particles either in air or in a liquid. The angle of diffraction increases as particle size decreases. This method is particularly good for measuring sizes between 0.1 and 3000 μm. A particular advantage is that the technique can generate a continuous measurement for analyzing process streams.

2. Tests for solutions

a. **Clarity of the solution:** Retention of clarity of solution is a main concern regarding stability of solution. In this a microscopic light is projected though a diaphragm

into the solution. The solution will remain clear if there are no undissolved particles. The solution appears hazy due to the scattering of light by undissolved particles. Light scattering instruments are most widely used to test the clarity of the solution.

b. Test for particulate matter in solutions: Solutions should be essentially free from particulate matter that can be observed on visual inspection. Particulate matter includes mobile, randomly sourced, extraneous substances, other than gas bubbles that cannot quantified by chemical analysis due to less amount and of their heterogeneous compositions. It can be determined by the following two methods.

i. Light obscuration method

ii. Microscopic method

i. *Light obscuration method:* This method applies for solutions, including solutions constituting from sterile solids, for which the test for particulate matter is specified in the individual monograph. The product meets the requirements of the test if the average numbers of particles present in the units tested does not exceed the appropriate value listed in Table 4.5.

TABLE 4.5: Light obscuration particle count test

	Diameter	*Diameter*
	≥10 µm	≥25 µm
Number of particles	50 per ml	5 per ml

If the average number of particles exceeds this limit, the test article is subjected to microscopic method.

ii. *Microscopic method:* This method is employed when some particles are not exactly detected by the light obscuration method. This test enumerates the subvisible particles essentially solid particulate matter present in the otic and ophthalmic solutions. The test sample is collected on a micro-porous membrane filter. The product meets the requirements of the test if the average number of particles present in the units tested does not exceed the appropriate value listed in Table 4.6.

TABLE 4.6: Microscopic method particle count test

	Diameter	*Diameter*	*Diameter*
	≥10 µm	≥25 µm	≥50 µm
Number of particles	50 per ml	5 per ml	2 per ml

3. Test for sterility: This is used to test the presence of micro-organisms in the sterile liquid dosage form intended for parenteral administration. The following tests are performed to determine the sterility of the liquid formulation.

a. Membrane filtration method

b. Direct inoculation (immersion) method

a. Membrane filtration method: In this the test product is first passed through a size exclusion membrane capable of retaining the micro-organisms. The concept is that the microorganisms will collect on the surface of a 0.45 micron pore size filter. The filter is rinsed and then the membrane is transferred to appropriate test medium as specified in the monograph.

b. Direct inoculation (immersion) method: In this the test article is directly inoculated into the test medium and then the medium is incubated for the growth of microorganisms. The test media generally used include fluid thioglycollate medium (FTM) and soybean casein digest medium (SCDM). FTM is selected based upon its ability to support the growth of anaerobic and aerobic microorganisms. SCDM is selected based upon its ability to support a wide range of aerobic bacteria and fungi (i.e. yeasts and molds).

Incubation time: In both the methods the test medium after the transferring of the test solution is to be incubated for 3 days in case of bacteria and 5 days in case of fungi and then the growth is compared with that of standard. If no growth is observed then the sample passes the test and it meets the GMP requirements. Table 4.7 outlines the requirement for sterility testing as per USP.

TABLE 4.7: Volume of product to be tested

Volume/container	*Minimum quantity to test in each media*
<1 ml	The entire contents of each container
1–40 ml	Half the contents of each container but not <1 ml
41–100 ml	20 ml
>100 ml	10% of the contents of the container, but not <20 ml

4. Test for pyrogens: Pyrogens are the endotoxins produced by micro organisms which are responsible for increase in body temperature. This test is designed to limit to an acceptable level the risks of febrile reaction in the patient to the administration, by injection, of the product concerned. The following tests are performed to check the presence of pyrogens in the liquid dosage forms intended for parenteral administration.

a. Rabbit test, and

b. LAL test

a. Rabbit test: Unless otherwise specified in the individual monograph, 10 ml of the test solution per kg of body weight has to be injected into an ear vein of each of three rabbits, completing each injection within 10 minutes after start of administration. Assure that the test product is protected from contamination. Perform the injection after warming the test product to a temperature of 37 ± 2°C. Record the temperature at 30 minute intervals between 1 and 3 hours subsequent to the injection.

Test interpretation: Consider any temperature decreases as zero rise. If no rabbit shows an individual rise in temperature of 0.5°C or more above its respective control temperature, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.5°C or more, continue the test using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.5°C or more and if the sum of the eight individual maximum temperature rises does not exceed 3.3°C, the material under examination meets the requirements for the absence of pyrogens.

b. LAL test: Limulus amebocyte lysate (LAL) is an aqueous extract of blood cells (amoebocytes) from the horseshoe crab, *Limulus polyphemus*. LAL reacts with bacterial endotoxin or lipopolysaccharide (LPS), which is a membrane component of gram negative bacteria. This reaction is the basis of the LAL test.

Method: Blood is removed from the horseshoe crab's pericardium and the blood cells are separated from the serum using centrifugation and are then placed in distilled water, which causes them to swell up and burst ("lyse"). This releases the chemicals from the inside of the cell (the "lysate"), which is then purified and freeze-dried. To test a sample for endotoxins, it is mixed with lysate and water. Coagulation occurs if endotoxins are present.

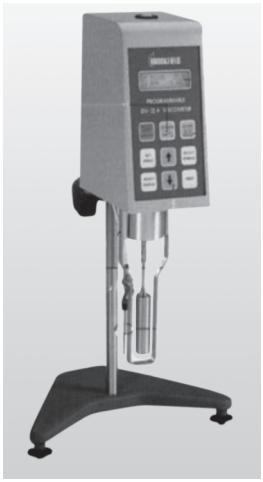


Fig. 4.7: Brookfield viscometer

5. Viscosity measurement: The flow of fluids through the bottle is influenced by viscosity of the product. In order to have a better flow and to maintain residence time in the ear, the viscosity of the formulation should be checked under controlled temperature. In general, viscosity is measured by Brookfield viscometer, cone and plate viscometer.

Brookfield viscometer: It measures the shearing stress on a spindle rotating at a definite, constant speed while immersed in the sample (Fig. 4.7). The degree of spindle lag is indicated on a rotating dial. This reading multiplied by a conversion factor based on spindle size and rotational speed, gives a value for viscosity in centipoise.

Cone and plate viscometer: It used a cone of very shallow angle in bare contact with a flat plate (Fig. 4.8). With this system the shear rate beneath the plate is constant to a modest degree of precision and deconvolution of a flow curve; a graph of shear stress (torque) against shear rate (angular velocity) yields the viscosity in a straight forward manner.

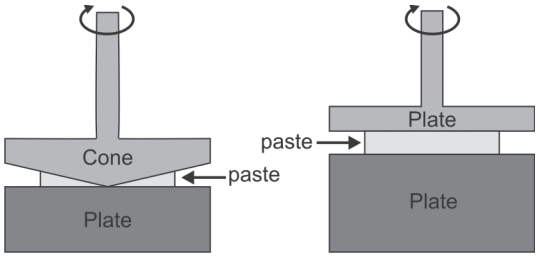


Fig. 4.8: Cone and plate viscometer

6. Test for antimicrobial effectiveness: Generally an antimicrobial agent is used in multiple dose units of liquid formulations to protect the product from microbial contamination that may occur during the suck back of an unreleased drop, when the pressure is released after withdrawal of the product. So there is need to check the efficacy of the antimicrobial agent against these microorganisms. In this cultures of *Candida albicans, Aspergillus niger, Escherichia coli, Pseudomonas aeuroginosa, Staphylococcus aureus* are used. In this a standardized inocula of microorganisms is prepared with a count of 105–106 per ml and added to the test product. They are incubated for 28 days at 20–25°C and observed for the preservative action at 7, 14, 21 and 28 days. The products preservative action is found to be effective if it satisfies the following:

- There should be reduction of no more than 0.1% of viable bacteria with that of initial concentrations by day 14th.
- There should be decrease in concentration of viable yeasts and molds when compared to initial by day 14th.
- The concentration of remaining viable organisms should be lower as designated at the end of 28th day.

Cidaltest: This is another test employed to determine antimicrobial agent efficacy. In this the formulation is tested against 5–14 species of microorganisms including gram –ve, gram +ve, bacteria, and fungi in previously standardized inoculums. Cidal times (growth of microorganisms) are measured within 24, 48 and 72 hours of contact.

ISOLATED KEY POINTS

- Solutions can be formulated for different routes of administration orally: Syrups, elixirs, drops in mouth and throat: Mouth washes, gargles, throat sprays. In body cavities: Douches, enemas, ear drops, nasal sprays. On body surfaces: lotions.
- *Advantages of solutions:* (1) Easier to swallow therefore easier for children, old age, unconscious people. (2) More quickly effective than tablets and capsules. (3) Homogenous therefore give uniform dose than suspension or emulsion which need shaking. (4) Dilute irritant action of some drugs (aspirin, Kl, KBr) minimize adverse effects in the GIT like KCl.
- *Disadvantages of solutions:* (1) Bulky therefore difficult to transport and store. (2) Unpleasant taste or odours are difficult to mask. (3) Needs an accurate spoon to measure the dose. (4) Less stable than solid dosage forms. Major signs of instability: colour change, precipitation microbial growth chemical gas formation.
- *Additives used in solutions:* (1) Buffers, (2) isotonicity modifiers, (3) preservatives, (4) antioxidants, (5) sweetening agents, (6) flavours and perfumes.
- *Methods of preparation of solutions:* (a) Simple solution, (b) solution by chemical reaction, (c) solution by extraction.
- An emulsion is mixture of two immiscible liquids. By definition, an emulsion contains tiny particles of one liquid suspended in another.
- *Emulsion types:* Oil-in-water (o/w) and water-in-oil (w/o).
- Methods of emulsion preparation: Dry gum method. The continental method is used to prepare the initial or primary emulsion from oil, water, and a hydrocolloid or "gum" type emulsifier (usually acacia). The primary emulsion, or emulsion nucleus, is formed from 4 parts oil, 2 parts water, and 1 part emulsifier.
- *Wet gum method:* In this method, the proportions of oil, water, and emulsifier are the same (4:2:1), but the order and techniques of mixing are different. The 1 part gum is triturated with 2 parts water to form a mucilage; then the 4 parts oil is added slowly, in portions, while triturating.
- *Bottle method:* This method may be used to prepare emulsions of volatile oils, or oleaginous substances of very low viscosities.
- *Auxiliary method:* An emulsion prepared by other methods can also usually be improved by passing it through a hand homogenizer, which forces the emulsion through a very small orifice, reducing the dispersed droplet size to about 5 microns or less.
- A pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent. The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non-oral use.

- Classification based on: (1) General classes: Oral suspension, externally applied suspension and parenteral suspension, (2) Based on proportion of solid particles: Dilute suspension (2 to10% w/v solid) and concentrated suspension (50% w/v solid), (3) Based on electrokinetic nature of solid particles: Flocculated suspension and deflocculated suspension, (4) Based on size of solid particles: Colloidal suspension (<1 micron), coarse suspension (>1 micron) and nano suspension (ng).
- Bioavailability is in following order, Solution > Suspension > Capsule > Compressed Tablet > Coated tablet. Duration and onset of action can be controlled, e.g. protamine zinc-insulin suspension. Suspension can mask the unpleasant/bitter taste of drug, e.g. chloramphenicol palmitate.
- Theory of suspensions by Stoke's equation $V= 2r^2(\rho s - \rho o)\ g/9\eta$ Where, V = sedimentation velocity in cm/sec r = radius of particle ρs = density of disperse phase ρo = density of disperse media g = acceleration due to gravity η = viscosity of disperse medium.
- Factors affecting sedimentation particle size radius (r) $V \propto r^2$. Density difference between dispersed phase and dispersion media $(\rho s - \rho o)\ V \propto (\rho s - \rho o)$. Generally, particle density is greater than dispersion medium but, in certain cases particle density is less than dispersed phase, so suspended particle floats and is difficult to distribute uniformly in the vehicle. If density of the dispersed phase and dispersion medium are equal, the rate of settling becomes zero.
- In flocculated suspension, formed flocks (loose aggregates) will cause increase in sedimentation rate due to increase in size of sedimenting particles. Hence, flocculated suspensions sediment more rapidly. In flocculated suspension the loose structure of the rapidly sedimenting flocs tends to preserve in the sediment, which contains an appreciable amount of entrapped liquid. The volume of final sediment is thus relatively large and is easily redispersed by agitation.
- In deflocculated suspension, individual particles are settling, so rate of sedimentation is slow which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation.
- Surfactants decrease the interfacial tension between drug particles and liquid and thus liquid is penetrated in the pores of drug particle displacing air from them and thus ensures wetting.
- Ideal requirements of packaging material it should be inert. It should effectively preserve the product from light, air, and other contamination through shelf life. It should be cheap. It should effectively deliver the product without any difficulty.

PRACTICE QUESTIONS

Long Answer Type Questions

1. What are the different types of liquid dosage form? Give their advantages and disadvantages?

2. Define the term solutions? Give classification of solution based on the route of the administration?

3. Discuss in detail about various additives used in the formulation of solution?

4. Write short notes on following with respect to liquid dosage form
   A. Viscocity enhancer B. Preservatives
   C. Anti-oxidant D. Flavours and perfumes
   E. Colouring agent
5. What are emulsion? Give their advantages and disadvantages?
6. What are different types of emulsions? How we can determine the type of emulsion?
7. Discuss in detail about various types of emulsion with suitable examples?
8. Write in brief about various test used to differentiate between various types of emulsion?
9. Give various methods of preparation of emulsion with suitable example?
10. What are biphasic liquid dosage forms? Compare and contrast between suspension and emulsion?
11. What is a suspension? Give advantages and disadvantages of suspension?
12. What are important factors which are to be kept in mind while formulating a suspension? Give pharmaceutical application of suspension?
13. Discuss in brief about various theories of suspension? Compare and contrast between flocculated and deflocculated suspension?
14. Discuss in brief about quality control methods, packaging and labeling of suspension?
15. Give detailed evaluation test used for liquid dosage form?

Objective Type Questions

1. Match the following

S. No.	*Type of water*		*Specification*
1.	Potable water	a	Water prepared by distillation, by ion exchange resin method, or by reverse osmosis.
2.	Purified water	b	Safe drinking water
3.	Aromatic waters	c	Clear saturated solutions of volatile oils, or other aromatic or volatile substances
4.	Sterile water	d	Free from microbes

2. Match the following

S. No.	*Type of agents*		*Example/functions*
1.	Buffering agents	a	Improve palatability and ease pourability of the product
2.	Isotonicity modifiers	b	0.9% NaCl solution
3.	Viscosity modifiers	c	Propyl paraben
4.	Solubilizing agents	d	Resist the change in pH
5.	Preservatives	e	Enhances the solubility of the active ingredient in the solvent

3. Match the following

S. No.	*Type of agents*		*Example*
1.	Antioxidants	a	Raspberry and ginger
2.	Sweetening agents	b	BHA, BHT
3.	Flavors	c	Carotenoids, chlorophylls
4.	Coloring agents	d	Aspartame

4. Which of the following is false regarding preservative
   a. Effective against broad spectrum of microorganisms
   b. Stable for its shelf life
   c. Should be highly toxic
   d. Should not affect the stability of the active ingredient
   e. Free of taste and odor
5. When the two phases are immiscible like oil and water they form _____ and when two phases are different, like one is solid and other is liquid they form _____ .
6. In o/w emulsion, _____ is in disperse phase whereas _____ is in continuous phase.
7. Emulsifying agents reduce _____ between two phases.
8. Emulsions meant for external use should be _____ type.
9. Soaps formed from monovalent base produce _____ emulsion and soaps from divalent base produce _____ emulsion.
10. Bottle method is used for preparation of emulsions of _____ and _____ oils.
11. When the two phases are immisicble like oil and water they form _____ and when two phases are different like one is solid and other is liquid they form _____ .
12. The particle size of the suspended drug particles in the suspension should be in the range of _____ to _____ micron.
13. The suspensions which are instilled into the eye should be free from _____ particles.
14. The fine particle size of solid in suspension give a _____ rate of _____.
15. The particles form _____ and from a _____ like structure in case of flocculated suspension.
16. The flocculating agent reduces the _____ and improved the _____ of sold particles.
17. In non-flocculated suspension, the particle exists as _____ .

ANSWERS

1. 1—b, 2—a, 3—c, 4—d
2. 1—d, 2—b, 3—a, 4—e, 5—c.
3. 1—b, 2—d, 3—a, 4—c
4. c
5. Emulsion, suspension
6. Oil, water
7. Interfacial tension
8. o/w type
9. O/w, w/o
10. Volatile, non-viscous
11. Emulsion, suspension
12. 0.5, 5 micron
13. Gritty
14. Faster, dissolution
15. Loose aggregated, net work
16. Surface tension, dispersion
17. Separate entities

Chapter
5

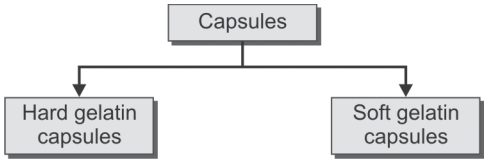
Capsules

The word capsule is derived from the Latin word capsule meaning small box. In pharmacy capsule is described as an edible package made from gelatin or other suitable material which is filled with medicines to produce a unit dosage form mainly for oral use.

Or

"The capsule may be considered as a container drug delivery system that provides a tasteless and odorless dosage form without need of secondary coating steps as may be required for tablets".

There are two types of capsules, "hard" and "soft". The hard capsule is also called "two piece" as it consists of two pieces in the form of small cylinders closed at one end; the shorter piece is called the "cap" which fits over the open end of the longer piece, called the "body". The soft gelatin capsule is also called "one piece". Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odors can be masked by the tasteless gelatin shell. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilized dosage forms.



Advantages of Capsules

i. Capsules mask the taste and odor of unpleasant drugs and can be easily administered.
ii. They are attractive in appearance.
iii. They are slippery when moist and, hence, easy to swallow with water.
iv. As compared to tablets less excipient are required.
v. The shells are physiologically inert and get easily and quickly digested in the gastrointestinal tract.
vi. They are economical and easily available.
vii. The shells can be opacified (with titanium dioxide) or colored, to give protection from light.
viii. They have better shelf life and bioavailability as compared to tablets.

Disadvantages of Capsules

i. The drugs which are hygroscopic absorb water from the capsule shell making it brittle and hence are not suitable for filling into capsules.
ii. The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such lead to irritation of stomach.

HARD GELATIN CAPSULES

Hard gelatin capsule shells are used to manufacture most of the commercially available medicated capsules. They are also commonly employed in clinical drugs trials to compares the effects of investigations of drugs also. They are made from a mixture of gelatin and water as they are clear and colorless and essentially tasteless. They may be colored with various FD and C and ID and C dyes and may be made opaque by adding agents such as titanium dioxide.

Advantages of Hard Gelatin Capsules

1. Hard gelatin capsules have better bioavailability than tablets.
2. They are easier to formulate.
3. Modern filling equipment makes possible the multiple ingredients or drug filling in the same capsule which offers the possibilities to overcome incompatibility by separating the ingredients with in the same capsule.
4. Hard gelatin capsules are uniquely suitable for the blinding clinical tests and are widely used in the preliminary drug studies.

Disadvantages of Hard Gelatin Capsules

1. Filling equipment is slower than tableting process.
2. More costly as compared to tablet formulation.
3. Not suitable for administration of extremely soluble material such as KCl and KBr. Since the sudden release of such compounds in the stomach could result in gastric irritation.
4. Not suitable for en-capsulated for highly hygroscopic material. As hygroscopic materials may dry the capsule shell to excessive brittleness.

Raw Materials Used

The raw materials used in the manufacture of both hard and soft gelatin capsules are similar. Both contain gelatin, water, colorants as main ingredient and other pharmaceutical aids.

1. Gelatin: Gelatin is the major component of the capsules and is the raw material of choice because of ability of its solution to form a gel solid at a temperature just above ambient temperate conditions, which enables a homogeneous film to be formed rapidly on a mould pin. Gelatin is a translucent brittle solid substance, colorless or slightly yellow, nearly tasteless and odorless, which is created by prolonged boiling of animal skin connective tissue or bones. There are two types of gelatin:

Type A: It produced by acid hydrolysis and is manufactured mainly from pork skin.
Type B: It produced by alkaline hydrolysis and is manufactured from animal bones.

Type A gelatin is derived from an acid-treated precursor and exhibits an isoelectric point in the region of pH 9, whereas type B gelatin is from an alkali-treated precursor and has its isoelectric zone in the region of pH 4.7. Capsules may be made from either type of gelatin, but mostly a mixture of both types is used considering availability and cost. Blends of bone and pork skin gelatins of relatively high strength are normally used for hard capsule production. The bone gelatin produces a tough, firm film, but tends to be hazy and brittle. The pork skin gelatin contributes plasticity and clarity to the blend there by reducing haze or cloudiness in the finished capsule.

Gelatin is used because of following characteristics:

i. It is non-toxic, widely used in foodstuffs and acceptable worldwide.
ii. It is readily soluble in biological fluids at body temperature.
iii. The gelatin films are homogeneous in structure, which gives them strength.
iv. It is good film forming material, producing a strong flexible film.
v. The wall thickness of a hard gelatin capsule is about 100 micrometer.
vi. Solution of higher concentration 40% w/v is mobile at 50°C.

The major disadvantage of gelatin for hard capsules is that it may undergo cross-linking.

Production of gelatin: On a commercial scale, gelatin is made from by-products of the meat and leather industry, mainly pork skins, pork and cattle bones, or split cattle hides. Contrary to popular belief, horns and hooves are not commonly used. The raw materials are prepared by different curing, acid, and alkali processes, which are employed to extract the dried collagen hydrolysate. The entire process takes several weeks. The flowchart for gelatin production has been shown in Fig. 5.1.

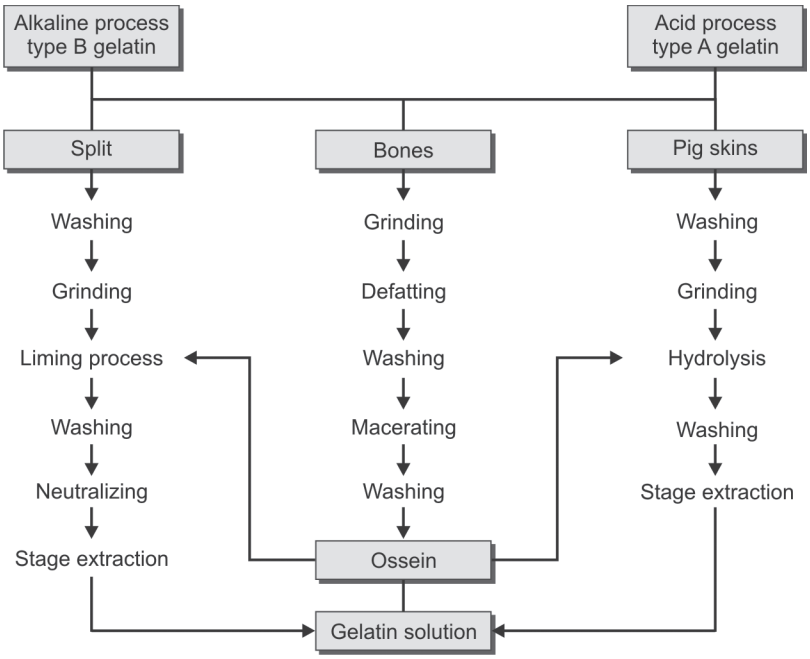


Fig. 5.1: Flowchart for gelatin production process

2. Colorants: Color is used principally to identify a product in all stages of its manufacture and use. The colorants that can be used in capsules are of two types:

1. Water soluble dyes
2. Insoluble dyes, the dyes used are mostly synthetic in origin and can be subdivided as:
   a. Azo dyes
   b. Non azo dyes, most dyes used currently are the non azo class and the three wildly used are:
      a. Erythrosine (E-127)
      b. Indigo (E-132)
      c. Quinoline yellow(E-104)

To make a range of colors dyes and pigments are mixed together as solutions or suspensions. The two types of pigments used are:

- Iron oxides—black, red and yellow
- Titanium dioxide which are white and used to make the capsule opaque.

Capsules are colored by the addition of colorants to the gelatin solution during the manufacturing stage.

3. Pharmaceutical aids: Preservatives and surfactants are added to the gelatin solution during capsule manufacture to aid in processing. Gelatin solutions are an ideal medium for bacterial growth at temperatures below 55°C. Preservatives are added to the gelatin and colorant solutions to reduce the growth of microorganisms. The materials used as preservatives include: Sodium bisulfite or metabisulfite, sorbic acid or the methyl propyl esters of para hydroxy-benzoic acid, and the organic acids, benzoic and propanoic acids.

Some hard gelatin capsules may contain 0.15% w/w of sodium lauryl sulphate which functions as wetting agent, to ensure that the lubricated metal moulds are uniformly covered, when dipped into the gelatin solution. Unpleasant tastes and odors of drugs are effectively masked by the practically tasteless capsule shell, which dissolves or is digested in the stomach after about ten to twenty minutes.

Properties of empty capsule: Empty capsules contain a significant amount of water that acts as a plasticizer for the gelatin film and is essential for their function. The standard moisture content specification for hard gelatin capsules is between 13% and 16% w/w. This value can vary depending upon the conditions to which they are exposed that is at low humidity, they will lose moisture and become brittle, and at high humidity, they will gain moisture and soften. The moisture content can be maintained within the correct specification by storing them in sealed containers at controlled temperature.

Capsules are readily soluble in water at 37°C. When the temperature falls below this, their rate of solubility decreases. At below about 30°C, they are insoluble and simply absorb water, swell and distort. This is an important factor to take into account during disintegration and dissolution testing.

Types of materials for filling into hard gelatin capsules

Dry solids: Powders, pellets, granules or tablets.

Semisolids: Suspensions or pastes.

Liquids: Non-aqueous liquids.

CAPSULE SIZES

The empty capsules are available in various sizes. They are numbered according to the capacity of the capsules. The number starts from 000 and goes up to 5. The approximate capacity of a capsule with respect to its number is given in Table 5.1 and the various sizes are shown in Fig. 5.2.

TABLE 5.1: Capsules number and its approximate capacity

Capsule number	*Approximate capacity in mg*	*Actual volume in ml*
000	950	1.37
00	650	0.95
0	450	0.68
1	300	0.50
2	250	0.37
3	200	0.30
4	150	0.21
5	100	0.13

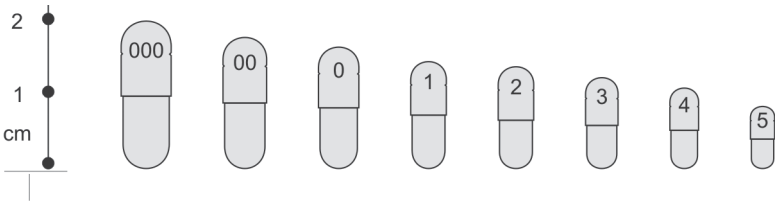


Fig. 5.2: Size of hard gelatin capsules

Excipients used in the filling of capsules

While filling solid medicaments in powder form into the body of a hard gelatin capsules, the following additives are also included in the formulation:

1. **Diluents:** The diluent is needed in certain cases where the quantity of the medicament is too small in bulk to get it filled in the smallest available capsule size. In such cases, diluent is added to bring the medicament up to the desired bulk. The commonly used diluents are lactose, mannitol, sorbitol, starch, etc. The quantity of the diluent to be incorporated depends on the medicament and the capsule size.
2. **Absorbents:** Sometimes the medicaments are physically incompatible with each other, e.g. eutectic substance or hygroscopic substances. In such cases, absorbents, such as oxides and carbonates of magnesium and calcium and kaolin are added to the powered drug. These inert material acts as a protective absorbent.
3. **Glidants:** To ensure a regular flow of power into the automatic capsule machine glidants are mixed with the medicaments. The various glidants used for the purpose are talc, magnesium stearate and calcium stearate.
4. **Antidusting compounds:** During the filling of capsules by an automatic filling machine, a lot of dust comes out of the machines. The dust is inhaled by the operator of the machine. It can pose a serious health hazard especially when the dust of the potent drugs is inhaled by the workers. To avoid this, some antidusting components, like edible oils, are added to the formulation.

5. **Wetting agents:** Which improve water penetration for poorly soluble drugs, e.g. Sodiumlauryl sulfate.
6. **Disintegrants:** Which produce disruption of the powder mass, e.g. crospovidone and sodium starch glycolate.

Shell manufacture: Completely automatic machines are used for the production of hard gelatin capsules shells. The manufacturing machines having two parts:

1. On one half the capsule cap is made.
2. On the other capsule body is made.
3. The thickness of the gelatin walls must be strictly controlled.
4. The caps are slightly larger in diameter than the bodies.

The moulds commonly referred to pins are made of stainless steel and mounted on metal strips called bars. The small the capsule the higher is the output. The sequence of manufacturing process is as follows:

Dipping → Rotation → Drying → Stripping → Trimming → Joining → Sorting → Painting

Dipping

- Pairs of stainless steel pins lubricated, are dipped into the dipping solution to form caps and bodies simultaneously
- The pins are at ambient temperature, 22°C whereas the dipping solution is at 50°C in heated jacketed heating pan
- The dipping time to cast the film is about 12 seconds

Rotation

- After dipping, the pins are withdrawn from dipping solution. They are elevated and rotated until they are facing upward
- This helps distribution of the gelatin over the pins uniformly and to avoid the formation of bead at the capsule ends
- After rotation they are given a blast of cool air to set the film

Drying

- The racks of gelatin coated pins then pass into a series of four drying ovens
- Drying is mainly done by dehumidification by passing large volumes of dry air over the pins
- Temperature elevation of few degrees are permissible to prevent film melting
- Drying also must be too rapid to prevent case hardening
- Under drying leave film sticky for subsequent operations
- Over drying must be avoided as this could cause the films to split on the pins due to shrinkage or at least make them brittle for later trimming step

Stripping

- A series of bronze jaws strip the cap and body portions of the capsules from the pins

Trimming

- The stripped caps and bodies are delivered to collects in which they are firmly held
- As the collects rotate the knives are brought against the shells to trim them to the required length

Joining

- The cap and body portions are aligned concentrically in channels, and the two portions are slowly pushed together
- The entire cycle takes about 45 minutes, about 2/3 of which is required for the drying step alone

Sorting

- The moisture content of capsules as they are ejected from machine will be in the range of 15–18% w/w
- During sorting, the capsules passing on a lighted moving conveyor are observed visually by inspector
- Any defective capsules spotted are thus manually removed

Painting

- In general, capsules are printed prior to filling as they are easy to handle
- Generally printing is done on offset rotary presses having capabilities as high as ¾ million capsules per hour
- Available equipment can print axially along the length or radially around the circumference of capsules.

CAPSULE SHELL FILLING

Hand operated hard gelatin capsule filling machines: Hand operated and electrically operated machines are in practice for filling the capsules but for small and quick dispensing hand operated machines are quite economical. A hand operated gelatin capsule filling machine consists of the following parts and is shown in Fig. 5.3.

1. A bed with 200–300 holes
2. A capsule loading tray
3. A powder tray
4. A pin plate is having 200 or 300 pins corresponding to the number of holes in the bed and capsules loading tray
5. A lever
6. A handle
7. A plate fitted with rubber top.

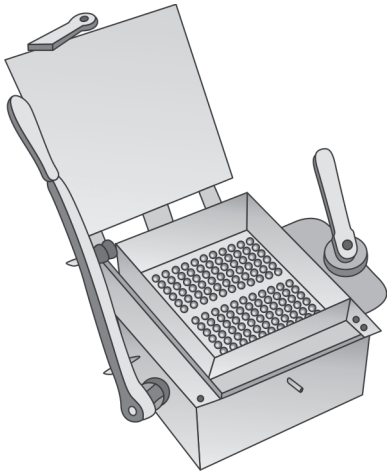


Fig. 5.3: Hand operated hard gelatin capsule filling machine

All parts of the machine are made up of stainless steel. The machines are generally supplied with additional loading trays, beds, and pin plates with various diameters of holes so as to fill the desired size of the capsules. These machines are very simple to operate, can be easily dismantled and reassembled.

Working: The empty capsules are filled into the loading tray which is then placed over the bed. By opening the handle, the bodies of the capsules are locked and caps separated in the loading tray itself which is then removed by operating the lever. The weighed amount of the drug to be filled in the capsules is placed in powder tray already kept in position over the bed. The powder is spread with the help of a powder spreader, so as

to fill the bodies of the capsules uniformly. Collect excess of the powder on the platform of the powder tray. Lower the pin plate and move it downward so as to press the powder in the bodies. Remove the powder tray and place the caps holding tray in position. Press the caps with the help of plate with rubber top and operate the lever to unlock the cap and body of the capsules. Remove the loading tray and collect the filled capsules in a tray. With 200 hole machine about 5000 capsules can be filled per hour and with 300 hole machine 7500 capsules can be filled per hour. On large-scale manufacturing various types of semiautomatic and automatic machines are used. They operate on the same principle as manual filling, namely the caps are removed, powder filled in the bodies, caps replaced and filled capsules are ejected out. With automatic capsule filling machines powders or granulated products can be filled into hard gelatin capsules. With accessory equipment, pellets or tablets along with powders can be filled into the capsules. A process flow diagram for automated capsule filling is shown in Fig. 5.4.

Filling capsules with a semisolid mass: If the material to be placed into hard gelatin capsules is a semisolid, it can be encapsulated by either forming a pipe or pouring a melt (Fig. 5.5).

1. **Pipe:** If the material is sufficiently plastic, it can be rolled into a pipe with a diameter slightly less than that of the inner diameter of the capsule in which it will be enclosed. The desired quantity of material is cut using a spatula or knife, the length determining the weight of the material enclosed. The pieces may be dusted with corn starch (check patient allergies) prior to individual insertion into the capsules.

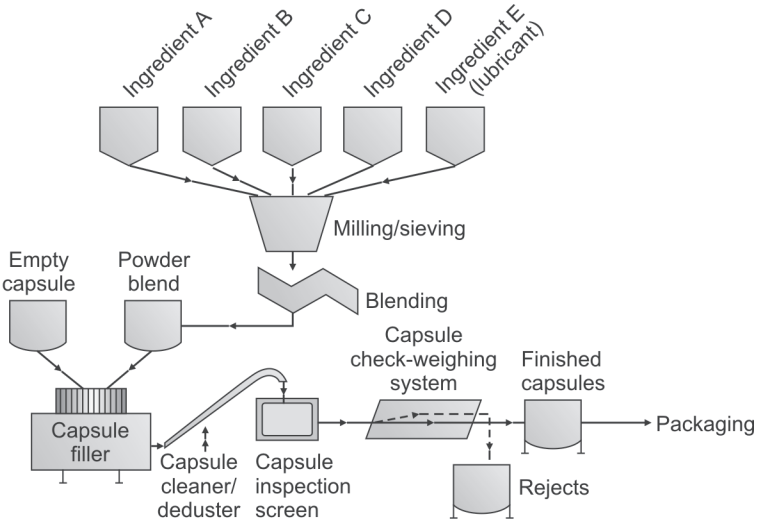


Fig. 5.4: Process flow diagram for automated capsule filling

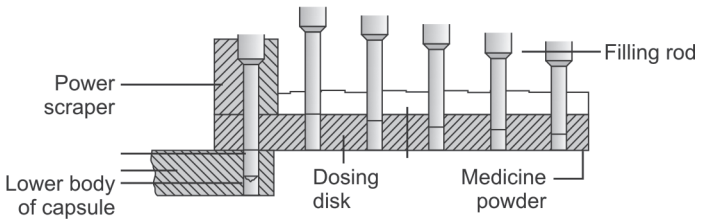


Fig. 5.5: Schematic diagram for capsule filling

If a material is too fluid to be worked as described, it may be necessary to add corn starch or some similar material to yield a more firm consistency. The quantity to be added can be determined empirically.

2. **Semisolid pour:** If the material is too firm to roll into a pipe but its melting point is satisfactory, it can be melted and poured into the capsule bases, cooled, and the caps replaced. This method also can be used to enhance the bioavailability of drugs, which are poorly soluble and exhibit bioavailability problems. For this purpose, the drug is added to a melt of a material such as polyethylene glycol (PEG). The mixture is heated and stirred until the powder is either melted or thoroughly mixed in the PEG. The melt is cooled to just above the melting point of the PEG and poured into the capsule shells as described. When this method is used, the desired quantities can be measured using a pipette, syringe, or calibrated dropper to deliver the volume to the individual capsules.

LIQUIDS IN HARD GELATIN CAPSULES

Liquids can be prepared in hard gelatin capsules, if the gelatin is not soluble in the liquid to be encapsulated; alcoholic solutions and fixed and volatile oils work well. It may be necessary to determine the solubility of gelatin in the liquid by experimentation. The liquid can be measured accurately using a pipette (micropipette) or a calibrated dropper and dropped into the gelatin base, taking care not to touch the opening. The gelatin caps can be touched, open end down, on a moist towel to soften the gelatin at the opening of the caps or a cotton swab dipped in warm water can be rubbed around the edge of the capsule cap to soften. The cap is placed over the base containing the liquid with a slight twist and the softened edge of the cap should form a seal with the base to prevent leakage. Prior to packaging, these capsules should be placed on a clean, dry sheet of paper and observed for leakage. Another method of sealing makes use of a warm gelatin solution that is painted around the capsules and the inside of the caps prior to placing on the base.

Industrial scale filling: The machines for industrial-scale filling of hard gelatin capsules come in great variety of shapes and sizes, varying from semi- to fully automatic and ranging in output from 5000 to 15000 per hour. Automatic machines can be either continuous in motion, like a rotary tablet press, or intermittent, where the machine stops to perform a function and then indexes round to the next position to repeat the operation on a further set of capsules. The capsule filling process is illustrated in Fig. 5.6.

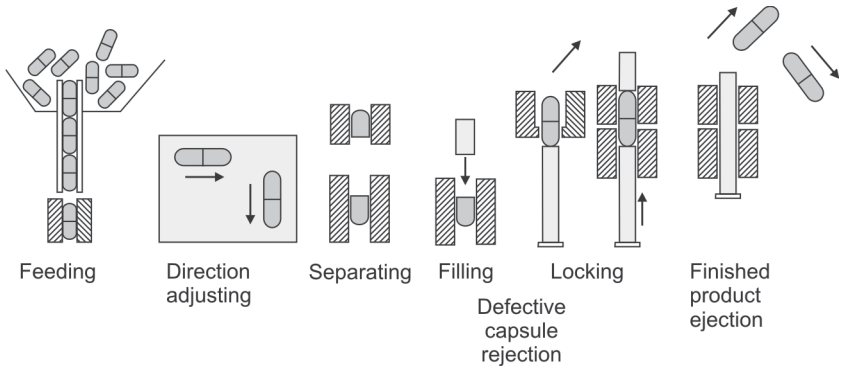


Fig. 5.6: Capsule filling process

The dosing systems can be divided into two groups

Dependent: Dosing systems that use the capsule body directly to measure the powder. Uniformity of fill weight can only be achieved if the capsule is filled completely, e.g. Auger filling.

Independent: Dosing systems where the powder is measured independently of the body in a special measuring device. Weight uniformity is not dependent on filling the body completely. With this system the capsules can be part filled, e.g. dosator.

Difficulties in filling capsules

1. **Deliquescent or hygroscopic powders:** A gelatin capsule contain water, which is extracted or taken up by a hygroscopic drug and renders the capsule very brittle which leads to cracking of the capsule. The addition of an adsorbent like magnesium carbonate, heavy magnesium oxide or light magnesium oxide overcomes this difficulty provided the capsules are packed in tightly closed glass capsule vials.
2. **Eutectic mixtures:** Certain substances when mixed together tend to liquefy and form a pasty mass due to the formation of a mixture which has a lower melting point than room temperature. For filling these types of substances each troublesome ingredient is mixed with an absorbent separately then mixed together and filled in capsules. The absorbents used are magnesium oxide and kaolin. Another method in dealing with such type of difficulty is that the substances are mixed together so as to form a eutectic mixture, then an absorbent like magnesium carbonate or kaolin is added.
3. **Addition of inert powders:** When the quantity of the drug to be filled in capsules is very small and it is not possible to fill this much small amount in capsules then inert substance or a diluent is added so as to increase the bulk of the powder, which can be filled easily in capsules.
4. **Use of two capsules:** Some of the manufacturers separate the incompatible ingredients of the formulation by placing one of the ingredients in smaller capsule, and then placing this smaller capsule in a larger capsule containing the other ingredients of the formulation.
5. **Filling of granular powder:** Some powders which lack adhesiveness and most granular powders are difficult to fill in the capsules by punch method because they are not compressible and flow out of the capsule as soon as they are lifted from the pile of powder into which they are punched. To overcome this difficulty the non-adhesive powders should be moistened with alcohol and the granular powders should be reduced to powder before filling into capsules.

Alternative Material for Hard-Shell Capsules

Several materials have been examined as a substitute for the gelatin in two-piece hard capsules. Hydroxypropylmethyl cellulose (HPMC) has become a successful alternative material for two-piece capsules and is actually on the market in the world. HPMC capsules have been developed for both pharmaceutical products and dietary supplements. QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products.

SOFT GELATIN CAPSULES

A soft gel (a soft gelatin capsule) is a solid capsule (outer shell) surrounding a liquid or semi-solid center (inner fill). An active ingredient can be incorporated into the outer shell, the inner fill, or both. The formulation of drugs into soft gelatin capsules has gained popularity throughout the past decade due to the many advantages of this dosage form. The bioavailability of hydrophobic drugs can be significantly increased when formulated into soft gelatin capsules. Many problems associated with tableting, including poor compaction and lack of content or weight uniformity, can be eliminated when a drug is incorporated into this dosage form. Improved stability of drugs that are highly susceptible to oxidation can be achieved when formulated into a soft gelatin capsule. Gelatin soft capsules are made from gelatin and water but with the addition of a polyhydric alcohol, such as glycerol or sorbitol, to make them flexible. Sorbitol is less hygroscopic than glycerol. Gelatin soft capsules usually contain a preservative too, such as beta-naphthol. They are most suitable for liquids and semisolids and are widely used, in spherical and ovoid forms for vitamin preparations, such as cod liver oil, vitamins A and D and multiple vitamins. They are available in variety of shapes and sizes as shown in Fig. 5.7.

1. Spherical—0.05–5 ml
2. Ovoid—0.05–7 ml
3. Cylindrical—0.15–25 ml
4. Tubes—0.5–0 ml
5. Pear shaped—0.3–5 ml

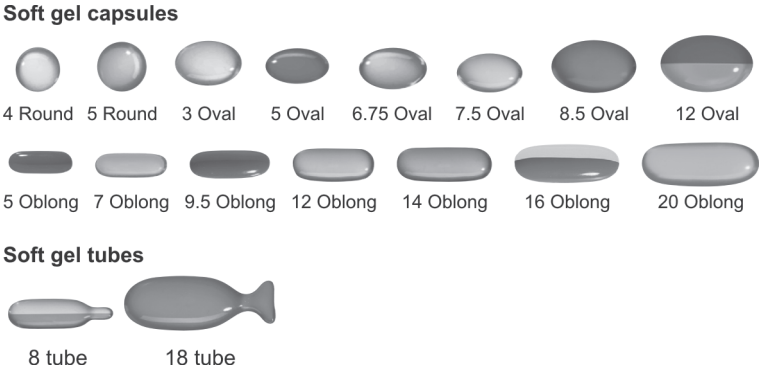


Fig. 5.7: Soft gel capsules and tubes

Advantages of soft gel capsules

1. Ease of use—easy to swallow, no taste, unit dose delivery, temper proof.
2. Versatile
   i. Accommodates a wide variety of compounds filled as a semisolid, liquid, gel or paste.
   ii. Wide variety of colors, shapes and sizes.
   iii. Immediate or delayed drug delivery—can be used to improve bioavailability by delivering drug in solution or other absorption enhancing media.

Disadvantages of soft gel capsules

1. Requires special manufacturing equipment

2. Stability concerns with highly water soluble compounds, and compounds susceptible to hydrolysis
3. Limited choices of excipients/carriers compatible with the gelatin

Content of a softgel capsule is a liquid, or a combination of miscible liquids, a solution of a solid(s) in a liquid(s) or a suspension of a solid(s) in a liquid(s). Liquids are an essential part of the capsule content. Only those liquids that are both water miscible and volatile cannot be included as major constituents of the capsule content since they can migrate into the hydrophilic gelatin shell and volatilize from its surface. Water, ethyl alcohol and emulsions fall into this category.

There are a large number of liquids that do not fall into the above category and thus can function as active ingredients, solvents or vehicles for suspension type formulations. These liquids include aromatic and aliphatic hydrocarbons, high molecular weight alcohols, esters or organic acids. The mostly widely used liquids for human use are oily active ingredients such as vegetable oils (soybean oil), mineral oil, non-ionic surface active agents (polysorbate 80) and PEG (400 and 600) either alone or in combination.

There are three primary types of inner fill materials:

1. **Neat substances, especially oily liquids, for example:** Cod liver oil capsules.
2. **Solution fills:** Actives dissolved in a carriers like:
   - Oils such as soybean oil and Miglyol 812 (neutral oil, triglycerides of medium chain fatty acids).
   - Olyethylene glycols: Especially PEG 400–600.
   - Other solvents: Any other solvent, which does not degrade or solubilize the gelatin shell, i.e. dimethyl isosorbide, surfactants, diethylene glycol monoethyl ether.
   - Water or alcohol: up to 10% w/w (if needed for solubility).
   - Glycerin: 1 to 4% w/w (to retard the migration of the glycerin out of the shell into the fill).
   - Polyvinylpyrrolidone: Up to 10% w/w used in combination with PEG (can increase drug solubility, and also improve stability by inhibiting drug recrystallization).
3. **Suspension fills:** Active dispersed in a carrier.
   a. Suspensions can accommodate about 30% solids.With higher solid content (more than 30%) viscosity and filling become a problem.
   b. Suspensions can be heated up to 35ºC to decrease viscosity during the filling process.
   c. Suspended solids must be smaller than 80 mesh—Mill or homogenize before filling to prevent needles from clogging during filling.

Materials to be filled: As stated earlier, it is possible to fill liquids, semi-solids as well as solids into soft gelatin capsules. The liquids that are packaged are generally of the following kinds:

1. Vegetable or aromatic oils, hydrocarbons, ethers, esters, alcohols and organic acids, which are water immiscible;
2. Polyethylene glycols and non-ionic surfactants which are water miscible;
3. Water miscible and relatively non-volatile compounds such as glycerin, propylene glycol (up to 5–10% of total liquid), isopropyl glycol, etc.

The liquid combinations for encapsulation in soft gelatin capsules must be able to flow by gravity at about 35°C or less. In general, liquids ranging in viscosity from 0.2

to 3000 cps at 25°C, can be encapsulated without any difficulty, liquids which cannot be capsulated are water (more than 5%), alcohols, ketones, acids, amines, esters, etc. These liguids can leak through the capsule shell. Liquids with pH below 2.5 or above 7.5 should also be avoided since acidic liquids cause hydrolysis of the shell and alkaline ones cause tanning, which affects solubility characteristics of the shells.

Solids that are not sufficiently soluble in liquids or in combinations of liquids are capsulated as suspensions. Most organic and inorganic solids or compounds may be capsulated. Such materials must be 80 mesh or finer in particle size, owing to certain close tolerances of the capsulation equipment and for the maximum homogeneity of the suspension. Many compounds cannot be capsulated, owing to their solubility in water and thus their ability to affect the gelatin shell, unless they are minor constituents of a formula or are combined with a type of carrier (liquid or solid) that reduces their effect on the shell. Examples of such solids are strong acids (citric), strong alkalies (sodium salts of weak acids), salts of strong acids and bases (sodium chloride) and ammonium salts. Also, any substance that is unstable in the presence of moisture (e.g. Aspirin) would not exhibit satisfactory chemical stability in soft gelatin capsules.

Base adsorption of solids to be suspended in soft gelatin capsules: Base adsorption is expressed as the number of grams of liquid base required to produce a mixture when mixed with one gram of solid(s). The base adsorption of a solid is influenced by such factors such as the solids particle size and shape, its physical state (fibrous, amorphous, or crystalline), its density, its moisture content, and its lipophilic or hydrophilic nature.

In the determination of base adsorption, the solid(s) must be completely wetted by the liquid base. For glycol and nonionic type bases, the addition of a wetting agent is seldom required, but for vegetable oil bases, complete wetting of the solid(s) is not achieved without an additive. Soy lecithin, at a concentration of 2 to 3% by weight of the oil, serves excellently for this purpose, and being a natural product, is universally accepted for good drug use. Increasing the concentration above 3% appears to have no added advantage.

A practical procedure for determining base adsorption and for judging the adequate fluidity of a mixture is as follows. Weigh a define amount of the solid (40 g is convenient) into a 150 ml teared beaker. In a separate 150 ml beaker tared beaker, place about 100 g of the liquid base. Add small increments of the liquid base to the solid, and using a spatula, stir the base into the solid after each addition until the solid is thoroughly wetted and uniformly coated with the base. This should produce a mixture that has a soft ointment like consistency. Continue to add liquid and stir until the mixture flows steadily from the spatula blade when held at a 45-degree angle above the mixture. The base adsorption is obtained by means of the following formula.

Weight of the base/weight of the solid = base adsorption

The base adsorption is used to determine the "minim per gram" factor (M/g) of the solid(s). The minim per gram factor is the volume in minims that is occupied by one gram (S) of the solid plus the weight of the liquid base (BA) required making a mixture. The minim per gram factor is calculated by dividing the weight of the base plus the gram of solid base (BA + S) by the weight of the mixture (W) per cubic centimeter or 16.23 minims (V). A better formula is:

$$\mathbf{(BA + S) \times V/ W = M/g}$$

Thus lower the base adsorption of the solid (s) and higher the density of the mixture, the smaller the capsule will be. This also indicates the importance of establishing specifications for the control of those physical properties of a solid mentioned previously that can affect its base adsorption. The final formulation of a suspension invariably requires a suspending agent to prevent the settling of the solids and to maintain homogeneity prior to, during, and after capsulation. The nature and the concentration of the suspending agent vary. In all instances the suspending agent used is melted in a suitable portion of the liquid base, and the hot melt is added slowly, with stirring, into the bulk portion of the base, which has been pre-heated to 40 degrees prior to the addition of any solids. The solids are then added, one by one, with sufficient mixing between additions to ensure complete wetting. Incompatible solids are added as far apart as possible in the mixing order to prevent interaction prior to complete wetting by the base.

Example of suspension fills include drug suspended in the following carriers

1. Oily mixtures

a. Soybean oil with beeswax (4–10% w/w) and lecithin (2–4% w/w). The lecithin improves material flow, and imparts some lubrication during filling. Add enough beeswax to get a good suspension, but avoid creating a non-dispersible plug.

b. Gelified oil (e.g. gel oil SC), a ready to use system composed of soybean oil, a suspending agent, and a wetting agent.

2. Polyethylene glycol

i. PEG 800–1000 for semi-solid fills

ii. PEG 10,000–100,000 for solid fills

iii. Or mixtures of the above (heat up to 35ºC to make fluid enough for filling).

3. Optional ingredients that can be added in the suspension fill

i. Surfactant: Sorbitol derivatives such as polysorbate 80 or lecithin.

ii. For hydrophobic drugs dissolved or dispersed in an oily matrix, a surfactant of HLB 10 will increase the dispersibility of the product in aqueous fluids and also may improve bioavailability.

Large-Scale Manufacture

Rotary capsule machine: This machine has two, side-by-side cylinders in each of which half-moulds are cut. These cylinders, like the rollers of a mangle, rotate in contrary direction and as they are mirror images the moulds come together precisely during rotation. Two ribbons of gelatin are fed between the rollers and, just before the opposing rollers meet, jets of medicament press the gelatin ribbon into the moulds, filling each half.

The moment of pressure follows, immediately sealing the two halves together to form a capsule. These rotary machines are capable of producing between 25000 and 30000 capsules an hour with an accuracy of dosage of approximately ± 1 percent. An automated soft gelatin encapsulation machine is shown in Fig. 5.8.

Seamless gelatin capsules: Another method of making soft capsules takes advantage of the phenomenon of drop formation. The essential part of the apparatus consists of two concentric tubes. Through the inner tube flows the medicament and, through the surrounding outer tube, the gelatin solution. The medicament, therefore, issues from

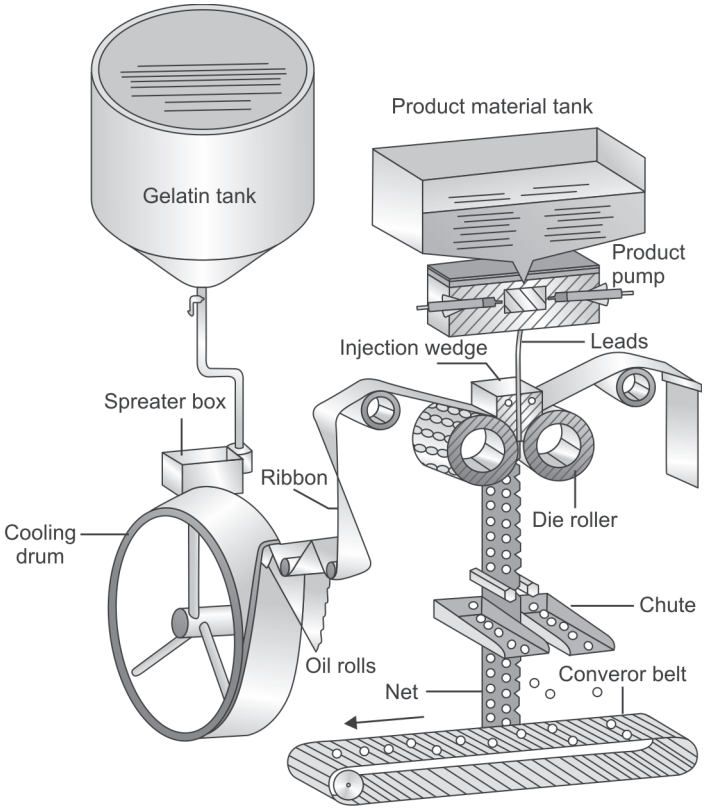


Fig. 5.8: Automatic soft gelatin encapsulation machine

the tube surrounded by gelatin and forming a spherical drop. This is ensured by allowing the drop to form in liquid paraffin in which the gelatin is insoluble. Regular induced pulsations cause drops of the correct size to be formed by lowering the temperature. The capsules are than subsequently degreased and dried.

Ingredients Used in Formulation of Soft Gelatin Capsules

Gelatin shell formulation: Typical soft gels are made up of gelatin, plasticizer, and materials that impart the desired appearance (colorants and/or opacifiers), and sometimes flavors.

Plasticizers: These are used to make the softgel shell elastic and pliable. They usually account for 20–30%. The most common plasticizers used in softgels is glycerol, although sorbitol and propylene glycol are used frequently often in combination with glycerol. The amount and choice of the plasticizer contribute to the hardness of the final product and may even affect its dissolution or disintegration characteristics, as well as its physical and chemical stability. Plasticizers are selected on the basis of their compatibility with the fill formulation, ease of processing, and the desired properties of the final soft gel, including hardness, appearance, handling characteristics and physical stability. One of the most important aspects of softgel formulation is to ensure that there is minimum interaction or migration between the liquid fill matrix and the soft gel shell. The choice of plasticizer type and concentration is important in ensuring optimum compatibility of the shell with the liquid fill matrix.

Water: The other essential component of the soft gel shell is water. Water usually accounts for 30–40% of the wet gel formulation and its presence is important to ensure proper processing during gel preparation and softgel encapsulation. Following encapsulation, excess water is removed from the softgels through controlled drying. In dry gels the equilibrium water content is typically in the range 5–8% w/w, which represents the proportion of water that is bound to the gelatin in the soft gel shell. This level of water is important for good physical stability, because in harsh storage conditions softgels will become either too soft and fuse together, or too hard and become brittle.

Colorants/Opacifiers: Colorants (soluble dyes, or insoluble pigments or lakes) and opacifiers are typically used in the wet gel formulation. Colorants can be either synthetic or natural, and are used to impart the desired shell color for product identification. An opacifier, usually titanium dioxide may be added to produce an opaque shell when the fill formulation is a suspension, or to prevent photodegradation of light-sensitive fill ingredients. Titanium dioxide can either be used alone to produce a white opaque shell or in combination with pigments to produce a colored opaque shell. The difference between hard gelatin and soft gelatin capsule is shown in Table 5.2.

TABLE 5.2: Difference between hard gelatin and soft gelatin capsules

Hard gelatin capsules	*Soft gelatin capsules*
The hard gelatin capsules shell consists of two parts: (a) Body, (b) Cap	The soft gelatin capsule shall becomes a single unit after sealing the two halve of the capsules.
They are cylindrical in shape.	They available in round, oval and tube like shapes.
The contents of a hard gelatin capsule usually consist of the medicament or mixture of medicaments in the form of powder, beads or granules.	The contents of soft gelatin capsules usually consist of liquids or solids dissolved or dispersed in suitable excipients to give a paste–like consistency.
These are prepared from gelatin titanium dioxide, colouring agent and plasticizer.	These are prepared from gelatin plasticizer (Glycerin or sorbitol) and a preservative.
Capsules are sealed after they are filled to ensure that the medicaments may not come out of the apsule due to rough handling.	Filling and sealing of soft gelatin capsules are done in a combined operation on machines.

QUALITY CONTROL OF CAPSULES

Whether capsules are produced on a small scale or large scale all of them are required to pass not only the disintegration test, weight variation test and percentage of medicament test but a visual inspection must be made as they roll off the capsule machine onto a conveyor belt regarding uniformity in shape, size, color and filling. As the capsules moves in front of the inspectors the visibly defective or suspected of being less than the perfect are picked out. The hard and soft gelatin capsules should be subjected to quality tests for their standardization. Quality control should be carried out during all stages of manufacturing operation which is the primary requirement of good manufacturing practices as per Schedule M. In official books the following quality control tests are recommended for capsules.

1. Standard for content of active ingredients: This test determines the amount of active ingredient by the method in the assay. For example, assay of indomethacin capsules.

- To a quantity of the mixed contents of 20 capsules equivalent to 50 mg of indomethacin, add 10 ml of water in a volumetric flask 100 ml.
- Stand for 10 minutes, shaking occasionally.
- Add 75 ml of methanol shake well and add sufficient methanol to produce 100 ml and filter if necessary.
- To 5 ml of the filtrate, add sufficient of a mixture of equal volumes of methanol and phosphate buffer (pH-7.2) to produce 100 ml in a volumetric flask.
- Measure the absorbance of the resulting solution at λ_{max} = 318 nm.

Q. Calculate the content of indomethacin, taking 0.193 as the value of E_1%. Limit is 90–110% of the labeled amount.

Calculations:

- Weight of 20 capsules = W_1
  Weight of empty shells = W_2
  Weight of contents = $W_1 - W_2 = W_3$
- Amount of drug = 20 capsule × 25 mg each → W_3
  50 mg → X
- Abs. = 0.452
- Concentration = $\frac{\text{Abs. volume of last flask}}{E_1\% \times 100} = \frac{0.452}{0.193} \times \frac{100}{100}$
- Theoretical amount of indomethacin:
  50 ⟶ 100 ml
  x ⟶ 5 ml
  x = 2.5 mg% because we completed the volume to 100
- % of drug = $\frac{\text{Concentration} \times 100}{\text{Amount of indomethacin}} = \frac{2.34 \times 100}{2.5} = 93.6\%$

2. Empty hard capsules: According to Japanese Pharmacopoeia, the test called 'purity' uses five capsules which are tested individually. Each is placed in a 100 ml conical flask and shaken vigorously after adding 50 ml of water at 37°C throughout the test. The capsule passes the test if it completely dissolves within 10 minutes giving odorless, neutral or slightly acidic pH.

3. Uniformity of weight: This test applies to all types of capsules and it is to be done on 20 capsules.

i. Weigh an intact capsule.
ii. Open the capsule without losing any part of the shell and remove the contents as completely as possible.
iii. Weigh the shell.
iv. The weight of the contents is the difference between the weighing.
v. Repeat the procedure with a further 19 capsules selected at random.
vi. Determine the average weight.

Limit is not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in Table 5.3, and none deviates by more than twice that percentage. Results are recorded in Table 5.4.

TABLE 5.3: Limit of uniformity of weight

Average weight of capsule content	*Percentage deviation*
Less than 300 mg	10
300 mg or more	7.5

TABLE 5.4: Record of limit of uniformity of weight

Capsule Number	*Weight of intact capsules (A)*	*Weight of empty shell (B)*	*Weight of contents = A – B*
1			
2			
—			
—			
—up to 20			
Total weight			**X**

Average weight = X/20,Upper limit = average weight + (Average weight × % error)
Lower limit = average weight – (Average weight × % error)

4. Content uniformity: Hard capsules containing below or less than 25 mg of the drug contents should meet content uniformity requirements. Assay 10 capsules individually and calculate the acceptance value.

The requirement is met if the acceptance value of 10 capsules is less than or equal to 15%. If acceptance value is greater than 15% then, test the next 20 units and calculate the acceptance value. The 30 capsules if less than or equal to 15% and no individual unit is $1 - 25 \times 0.01$ nor more than $1 + 25 \times 0.01$.

Calculation of acceptance value =

(Reference value – mean of individual contents) + acceptability constant × sample standard deviation

Acceptability constant: 2.4 (for 10 capsules)

Acceptability constant: 2 (for 30 capsules)

Refer Tablet chapter for details

5. Disintegration: Disintegration is the state in which no residue except fragments of capsule shell, remains on the screen of the test apparatus or adheres to the lower surface of the disc. The disintegration test determines whether tablets or capsules disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions.

The disintegration of capsules is different from those of tablets because the determination of end point is difficult owing to the adhesive nature of shell. The shell pieces after disintegration may agglomerate forming large mass of gelatin taking more time to dissolve and may adhere to the mesh thus, blocking the holes.

According to USP, place one dosage unit in each of the tubes of the basket with water or any other specified medium (depends on individual monograph) maintained at 37 + 2°C. Attach a removable wire cloth with a plain square weave of 1.8–2.2 mm of mesh aperture and a wire diameter of 0.60–0.655 mm to the surface of upper rack of the basket assembly. Observe the capsules for a time limit (specified in individual monograph), at the end of prescribed time, all of the capsules must have been disintegrated excluding the fragments from the capsule shell. If 1 or 2 capsules fail, the test should be repeated on additional of 12 capsules. Then, not fewer than 16 of the total 18 capsules tested should disintegrate completely.

According to the BP (for both hard and soft capsules)

i. Introduce one capsule into each tube and suspend the apparatus in a beaker containing 600 ml water at 37° C.
ii. If hard capsules float on the surface of the water, the discs may be added.
iii. Operate the apparatus for 30 minutes; remove the assembly from the liquid.
iv. The capsules pass the test if
    a. No residue remains on the screen of the apparatus, or
    b. If a residue remains, it consists of fragments of shell, or
    c. Is a soft mass with no palpable core.
    d. If the disc is used, any residue remaining on its lower surface should only consist of fragments of shell.

6. Dissolution: Place each of the capsules in the apparatus 1, excluding air bubbles from the surface of the capsule. Operate immediately at specified rate within specified dissolution medium at 37 + 0.5°C. Aliquots should be withdrawn at specified time points mentioned in individual monograph. The requirements are met if the quantity of active ingredients dissolved conforms the following:

1. At stage 1 (S1): When 6 capsules are tested, amount of each of the dissolved content should not be less than Q + 5%.
2. At stage 2 (S2): When 6 capsules are tested, the average of 12 (both from step 1 and 2) should be equal to or greater Q and no capsule should by less than Q – 15%.
3. At stage 3 (S3): When 12 capsules are tested, the average of 24 capsules (all 1,2 and 3 steps) should be equal to or greater than Q and not more than two units are less than Q – 15% and no unit is less than Q – 25%.

Note: Q1 and Q2 as mentioned in the monograph.

For details of this test refer to Tablet Chapter, this test is same for tablets and capsules.

7. Raw materials: The gelatin of the capsule shells should be assayed for various physical properties like bloom strength, viscosity and its loss (by atomic force microscopy). Chemical tests like purity, microbial properties, and limits for heavy metals like arsenic, ash content should be determined. The colorants should also be checked for purity, limits for heavy metals, color properties, dye content, subsidiary dye content and color value.

8. Machine output: The manufacturing machine's output should be monitored continuously via the dimensional correctness during each lot production. The color of the capsules should be checked against a standard strip; in case of any changes the

gelatin solution should be adjusted by adding standardized dye solutions which can be ensured via thin layer chromatography.

9. Sorting of defects: After electronic or manual inspection, they are sampled by quality control inspectors. The results should meet the inspection plan, if not the capsules should be resorted or rejected depending upon frequency of faults.

10. Printing inspection: Quality inspectors sample the lot and are inspected for quality of print. The results will again be compared with the inspection plan and in case if it does not match then, either capsules should be resorted or rejected depending upon number of faults present.

11. Final inspection: After the capsules are placed in final containers, samples are checked for various parameters like dimensions, physical defects and color. These samples are also subjected to various microbial tests also.

"Quality is not the step that can be incorporated at last, it is mandatory and should be inbuilt into the products" to, make this happen, apart from all these mandatory tests certain other tests can be performed.

Packaging and Storage of Capsules

Capsules should be packed in a well-closed glass or plastic containers and stored in a cool place. These type of containers have advantage over cardboard boxes that they are more convenient to handle and transport and protect the capsules from moisture and dust. To prevent the capsules from rattling a tuft of cotton is placed over and under the capsules in the vials. In vials containing very hygroscopic capsules a packet-containing desiccant like silica gel or anhydrous calcium chloride may be placed to prevent the absorption of excessive moisture by the capsules. Generally capsules have a longer shelf in unopened glass bottles than in strip-packs but this is reversed, once a bottle has been opened. Nowadays, capsules are strip packaged which provide sanitary handling of medicines, ease in counting and identification. Empty gelatin capsules should be stored at room temperature at constant humidity. High humidity may cause softening of the capsules and low humidity may cause drying and cracking of the capsules. Storage of capsules in glass containers will provide protection not only from extreme humidity but also from dust. Storage of filled capsules is dependent on the characteristics of the drugs they contain. Semisolid filled hard gelatin capsules should be stored away from excessive heat, which may cause a softening or melting of the contents. The capsules are finally packed for shipment in moisture proof liners preferably heat sealed aluminum foil bags in card board cartons.

Capsule Administration

Capsules of the size number 5 to number 0 generally are not too difficult to swallow. Many patients may have difficulty swallowing the number 00 and number 000 capsules. If this occurs, the patient may be advised to place the capsule on the back of the tongue before drinking a liquid, or to place the capsule in warm water for a few seconds prior to taking to make it slide over mucous membranes easily. The pharmacist may suggest an alternative dosage form, e.g. smaller capsules or a liquid or rectal preparation.

Special Types of Hard Gelatin and Soft Gelatin Capsules

Altered release: The rate of release of capsule contents can be varied according to the nature ofthe drug and the capsule excipients. If the drug is water-soluble and a fast release is desired, the excipients should be hydrophilic and neutral. If a slow release of water-soluble drug is desired, hydrophobic excipients will reduce the rate of drug dissolution. If the drug is insoluble in water, hydrophilic excipients will provide a faster release; hydrophobic and neutral excipients will slow its release. A very rapid release of the capsule contents can be obtained by piercing holes in the capsule to allow faster penetration by fluids in the gastrointestinal tract, or by adding a small quantity of sodium bicarbonate and citric acid to assist in opening the capsule by the evolution of carbon dioxide. About 0.1 to 1% of sodium lauryl sulfate may be added to enhance the penetration of water into the capsule and speed dissolution. If slower release of the active drug is desired, it can be mixed with various excipients, such as cellulose polymers (methylcellulose) or sodium alginate. In general, the rate of release is delayed as the proportion of polymer or alginate is increased relative to water soluble ingredients, such as lactose. It should be mentioned that it is difficult to predict the exact release profile for a drug and to obtain consistent results from batch to batch. Further, reliable, consistent blood levels and duration of action can only be proved with controlled bioequivalence studies. In addition, many medications exhibit narrow therapeutic indices as the toxic and therapeutic doses are very close. Therefore, extemporaneous attempts to alter release rates to this extent should be avoided.

Coating of capsules: Coatings have been applied extemporaneously to enhance appearance and hide conceal taste, as well as to prevent release of the medication in the stomach (enteric coated products). Most coating of capsules requires considerable formulation skill and quality control equipment found in manufacturing facilities. Capsules can be coated to delay the release of the active drug until it reaches a selected portion of the gastrointestinal tract. Materials found suitable include stearic acid, shellac, casein, cellulose acetate phthalate and natural and synthetic waxes; the basis of their use is their acid insolubility but alkaline solubility. Many of the newer coating materials are time–erosion-dependent rather than acid–base-dependent, i.e. they erode over time on exposure to gastrointestinal contents rather than over a pH gradient. There are, in addition, a number of newer materials with predictable pH solubility profiles.

Enteric-coated capsules: Enteric-coated capsules resist disintegration in the stomach but break up in the intestine. They have largely been superseded by enteric-coated tablets. Types of coating used commercially include cellulose acetate phthalate and mixtures of waxes and fatty acids and/or their esters. Enteric coating may be given to following categories of drugs:

i. For substances that irritate the gastric mucosa or are destroyed by the gastric juice, and for medicaments, such as amoebicides and anthelmintics that are intended to act in the intestine.
ii. Which interfere with digestion, e.g. tannins, silver nitrate and other salts of heavy metals.
iii. Which are required to produce delayed action of the drug.

Sustained release capsules: The traditional method of taking a dose three or four times a dayleads to periods of excess and deficiency in blood concentration of the medicament. One way of correcting this, and at the same time, reducing the number of doses per day, is to administer a capsule containing numerous coated pellets that release the drug successively over a long period. The finely powdered drug is first converted into pellets, usually by attaching it to sugar granules with an adhesive. The pellets are then treated with protective coatings that delay release of the drug, each batch receiving a different thickness. The batches are mixed thoroughly and suitable doses are filled into capsules. For example, a mixture might contain 30 percent of uncoated pellets, for immediate release of drug, 30 percent each of coated pellets that release at 4 hours and 8 hours, and 10 percent of neutral pellets, used solely to fill the capsule. Each batch may be colored differently to simplify identification and facilitate control of mixing.

Liquid filled hard gelatin capsules: It is generally accepted that many of today's NCEs (New Chemical Entities) are poorly water soluble and the classical methods, such as reduction in particle size are no longer adequate to achieve satisfactory drug adsorption from a solid oral dosage form. One of the most promising strategies to deliver these insoluble compounds is using dissolved systems like using lipids, liquids or semi-solids to formulate new products. Two piece hard shell capsules are one of the most logical approaches when choosing the best dosage form to deliver these new liquid formulations. The new technology of packaging liquids in hard gelatin capsules is considered a major breakthrough. It can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in-house formulations when only small quantities of drug substance is available. The process can be scaled-up and also kept in-house similar to the operations of tableting or powder/pellet filling of hard gelatin capsules.

Rectal capsules: Soft gelatin capsules may be used as substitutes for rectal and vaginal suppositories. Various shapes and sizes are used for this purpose. They are generally wider at one end which is inserted first; the movement of the sphincter muscles forces the capsules forward into the rectum. Liquids or solids can be filled into rectal capsules but the base in which the medicaments have been incorporated must be non-toxic, non-irritant and compatible with the capsule shell.

Capsules for packing of ophthalmic ointments: It is very important that the ophthalmic ointments should be sterile and free from irritant effect. Therefore, they must be packed in such a manner that the product remains sterile until whole of it is used up. The best method to keep the preparation free from contamination during use is to pack it in single dose containers. Nowadays soft gelatin capsules are very commonly used for filling ophthalmic ointments. These capsules are meant for single application to the eye. Just before application, the capsule is punctured with a sterile needle, the contents instilled into the eye and the shell discarded.

Recent Updates in Capsule Technology

1. ***New products by Capsugel:*** Capsugel has introduced **Oceancaps capsules**, these capsules made from all natural fish gelatin derived from farm-raised fish, they have the same characteristics as traditional gelatin capsules, including appearance, machinability, mechanical properties, hygroscopic and oxygen properties, chemical stability, and versatility. Plus, they are odorless and tasteless.

Licaps new 000 size capsules are ideal for maximizing liquid dosage with a fill capacity of 1000 mg to 1400 mg depending on the density of the liquid fill material. This two-piece capsules has been specially designed to be sealed for secure containment of liquids and semi-solids without banding. Available in both gelatin and HPMC (hydroxypropyl methylcellulose) capsules they are available in a variety of colors to meet your specific needs.

2. ***New product by NATCO Pharma:*** Hyderabad based NATCO Pharma Limited has launched Lukatret—a medicine used in the treatment of a rare form of leukemia. Lukatret (Tretinoin—all transretinoic acid) available in the form of 10 mg capsules (in a pack of 100 capsules) is used in the treatment of acute promyelocytic leukemia (APL). Lukatret is a treatment option for remission induction in newly diagnosed, relapsed and/or refractory, chemotherapy non-responsive patients and for patients where anthracycline based chemotherapy is contraindicated. Use of Lukatret results in differentiation and clinical remission.
3. ***New products by Banner Pharmacaps Inc.:*** Banner Pharmcaps has developed an Enteric Softgel called Entericare, with enteric properties built into the shell matrix of the capsules for delivering very potent (small quantities) as well as drugs that require larger quantities and provide sustained delivery for more than an 8 to 12 hours period.
4. ***New product by Shionogi Qualicaps:*** QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products.

ISOLATED KEY POINTS

- Capsules are solid dosage forms in which drug substance is enclosed within hard or soft soluble shell.
- The shells are generally formed from gelatin.
- Capsules are of two types: (1) Hard gelatin capsules, (2) Soft gelatin capsules.
- Hygroscopic drugs are not suitable for filling into capsules, because they absorb water present in capsule shell makes shell very brittle and ultimately lead to crumble into pieces for human use, empty capsules ranging in size from 000 the largest to 5 the smallest.
- Generally, hard gelatin capsule are used to encapsulate between 65 mg and 1 gram. Capsule size.
- Gelatin is heterogeneous product derived by hydrolytic extraction of animal's collagen. The sources of gelatins including animal bones, hide portions and frozen pork skin.
- There are two basic types of gelatin Type A derived from acid treated precursor that exhibits an iso electric point at pH-9. It is manufactured mainly from pork skin. Type B derived from alkali treated precursor that exhibits an iso electric point at pH-4.7. It is manufactured mainly from animal bones.
- Steps involved in making empty gelatin capsules: (1) Dipping, (2) spinning, (3) drying, (4) stripping, (5) trimming and joining, (6) polishing.
- Soft gelatin capsules are one piece, hermetically sealed, soft gelatin shells containing a liquid, a suspension, or a semisolid. Soft gelatin is mainly composed of gelatin, plasticizers, preservative, colouring and opacifying agents, flavoring agents and sugars.

- The shape of soft gelatin capsule are round, oval, oblong, tube.
- Soft gelatin capsules are manufactured by four methods: (1) Plate process, (2) rotary die process, (3) reciprocating die, (4) accogel machine.
- Whether capsules are produced on a small scale or large scale all of them are required to pass not only the disintegration test, weight variation test and percentage of medicament test but a visual inspection.
- Quality control test of capsules: (1) Standard for content of active ingredients, (2) empty hard capsules, (3) uniformity of weightm, (4) content uniformity, (5) disintegration, (6) dissolution, (7) raw materials, (8) machine output, (9) sorting of defects, (10) printing inspection, (11) final inspection, capsule stability.
- Capsules should be packed in a well-closed glass or plastic containers and stored in a cool place.

PRACTICE QUESTIONS

Short Answer Type Questions

1. Define the term "capsule"?
2. Name the different ingredients used in the preparation of hard gelatin capsules?
3. What are the various excipients used in the filling of hard gelatin capsules?
4. What are the various ingredients used in the preparation of soft gelatin capsules?
5. What is the approximate capacity in mg of a capsule having number 000, 00, 0, 1, 2, 3, 4, 5?
6. What is the output of a hand—operated capsule filling machine, having 200 holes and 300 holes?
7. What is the output of a rotary machine?
8. What percentage deviation in weight is allowed in the pharmacopoeia of a capsule weighing 358 mg?
9. Name the various types of glidants used along with medicaments in filling the hard gelatin capsules.
10. Name the various tests which can be carried out for the purpose of maintaining the quality control of capsules.
11. What are the materials commonly used in the enteric coating of capsules.
12. Name the various diluents which are mixed with the medicament before filling it into capsules.
13. Write the advantages and disadvantages of a capsule.
14. Described in brief about hard gelatin capsule.
15. Explain the term soft gelatin capsule.
16. How will you differentiate between a hard gelatin capsule and soft gelatin capsule.
17. Explain the packaging and storage of capsules.

Long Answer Type Questions

1. What are hard gelatin capsules? Described the construction and working of a capsule filling machine (hand operated).
2. Write in brief about a soft gelatin capsule. Explain the construction and working of a rotary machine with the help of neat diagram.

3. What are the various tests recommended by the IP for evaluation of capsules.
4. Describe the various types of excipients used in filling of hand gelatin capsules.
5. Write short note on the following: (a) Hard gelatin capsule, (b) soft gelatin capsule, (c) enteric coated capsule, (d) sustained release capsule, (e) rectal capsule.
6. What are the various sizes of hard gelatin capsules? Explain it with the help of suitable diagram.
7. Compare and contrast hard gelatin capsule and soft gelatin capsules.

Objective Type Questions

1. Micro-capsules provide the _____ form.
2. The hygroscopic/eutectic substance is filled into capsules by mixing _____ as absorbents.
3. The lubricants _____ the angle of repose but excess quantities of lubricants _____ the angle of repose.
4. In general the disintegration time of hard gelatin capsules is _____ minutes.
5. The glidants such as _____ are used to ensure a _____ of power into the automatic capsule machine.
6. Match the following:

Column I	*Column II*	
A Glidant	(i)	Required when quantity of medicament is small
B Protective coating on drug particles	(ii)	Used in enteric—coated capsule
C Soft capsule	(iii)	Used to fill medicament in the form of powder, beads or granules
D Diluent	(iv)	Required to ensure a regular flow of powder into an automatic capsule machine
E Cellacephate	(v)	Used in a sustained release capsule
F Hard capsule	(vi)	Needed to fill liquid or paste

7. The word capsule is derived from the Latin word capsule meaning _____ .
8. The hard capsule is also called "two piece" as it consists of two pieces, the shorter piece is called the _____ which fits over the open end of the longer piece, called the _____ .
9. Which of the following is not true for hard gelatin capsules?
   i. Capsules mask the taste and odor of unpleasant drugs
   ii. They are slippery when moist and, hence, easy to swallow with water
   iii. They are suitable for hygroscopic drugs
   iv. The shells can be opacified (with titanium dioxide) or colored, to give protection from light.
10. The major component of the capsules is _____ .
11. Type A gelatin capsule is produced by _____ and is manufacture mainly from pork skin, while Type B is produced by _____ and is manufacture from animal bones.

12. Match the following:

S. No.	*Ingredient*		*Example*
1.	Diluents	a	Crospovidone
2.	Glidants	b	Lactose
3.	Wetting agents	c	Talc
4.	Disintegrants	d	Edible oils
5.	Antidusting compounds	e	SLS

13. Which of the following is not true for soft gelatin capsules.

i. Easy to manufacture
ii. Accommodates a wide variety of compounds filled as a semisolid, liquid, gel or paste.
iii. Available in wide variety of colors, shapes and sizes
iv. Immediate or delayed drug delivery—can be used to improve bioavailability by delivering drug in solution or other absorption enhancing media.

14. _____ is expressed as the number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s).

ANSWERS

1. Sustained released dosage
2. Oxides and carbonates of magnesium and calcium and kaolin
3. Decrease, increase
4. 28–30 mts
5. Talc, magnesium, stearate and calcium stearate, regular flow
6. A (i), B (v), C (vi), D (i), E (ii), F (iii)
7. Small box
8. Cap, body
9. 3
10. Gelatin
11. Acid hydrolysis, acid hydrolysis
12. 1—b, 2—c, 3—e, 4—a, 5—d
13. 1
14. Base absorption

Chapter
6

Pellets

Pharmaceutical pellets are agglomerates of fine powder particles, nearly spherical or cylindrical in shape with a narrow particle size distribution. Pellets range in size, between 0.5 and 1.5 mm, though other sizes could be prepared, depending on the processing technique.

Advantages of pellets

i. Good flowability due to uniform size and spherical shape. This enables uniform and accurate filling of the capsules.
ii. High physical integrity, meaning flow with minimal friction and dust generation.
iii. Superior properties for coating due to spherical shape, low area to surface volume, smooth surface and ability to withstand mechanical stress.
iv. Because pellets disperse freely in the GI tract, they invariably maximize drug absorption, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering drug bioavailability.
v. Pellets also reduce variations in gastric emptying rates and overall transit times. Thus, intra- and inter-subject variability of plasma profiles, which are common with single unit regimens, are minimized.
vi. The ability to produce pellets with a high drug loading is one of the claimed advantages of the process of extrusion/spheronization.
vii. When formulated as modified-release dosage forms, pellets are less susceptible to dose dumping than the reservoir-type, single unit formulations.
viii. Pellets also allow the combined delivery of two or more bioactive agents that may or may not be chemically compatible, at the same site or at different sites within the gastrointestinal tract.
ix. In addition pellets have a low surface area-to-volume ratio and provide an ideal shape for the application of film coatings. The specific surface area of pellets having a defined particle size is smaller due to the spherical shape and smooth surface. This allows the use of less film forming polymer to achieve a required film thickness and reduces coating process.
x. Pellets are frequently used in gastric resistant or modified release forms. Recently, coated pellets are compressed to rapidly disintegrating tablets. For those purposes small pellets with the mean diameters below 0.5 mm are most suitable. Such pellets can be produces by the direct pelletization methods.

METHODS OF PREPARING PELLETS

Following are the methods for preparing pellets (Fig. 6.1).

Compaction and drug layering are the most widely used pelletization techniques in pharmaceutical industry. Of all techniques, extrusion and spheronization is the most popular method. Other pelletization, such as globulation, balling and compression are also used in the development of pharmaceutical pellets although on a limited scale. The extrusion-spheronization process has become the method of choice for developing multiunit, pellet-based formulations. Extrusion/spheronization is a multi-step process used to make uniformly sized spherical particles. It is used primarily to produce multiparticulated for controlled drug release applications.

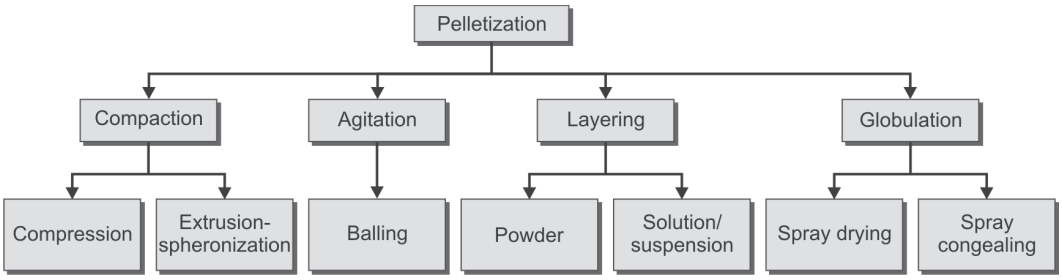


Fig. 6.1: Various methods of pelletization

I. Balling (Agitation)

This technique is not popular in the pharmaceutical industry as a pelletization process, probably due to the constraints of particle size distribution and content uniformity.

The **first phase**, known as the nucleation region, involves the random collision and subsequent coalescence of the primary particles to provide well-formed nuclei. The sizes of the nuclei depend on the sizes of the primary particles, the moisture content, the viscosity of the binding liquid, and the wettability of the substance.

Followed by the **transition region**, where particles collide with each other and unite in a preferential molten, or where smaller particles are crushed and layered on large particles. This mechanism in this region is, therefore, size dependent; fines that are produced through attrition or crushing are picked up by large pellets. Production of fines and subsequent coalescence and layering continues until a time is reached when the number of favorable collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets.

At this point, the **third phase**, known as the ball growth region, is reached. In this region surface abrasion becomes marked; as a result, layering becomes the predominant mechanism of growth, i.e. spherical agglomeration (Fig. 6.2) or emulsion solvent diffusion (Fig. 6.3). During the process, the tumbling action in the pelletizers allows the particles to re-orientate themselves and form dense pellets of appreciable strength. The strength of the uncured pellets is directly related to the surface tension of the binding liquid which in turn affects the suction potential that develops into the pellets.

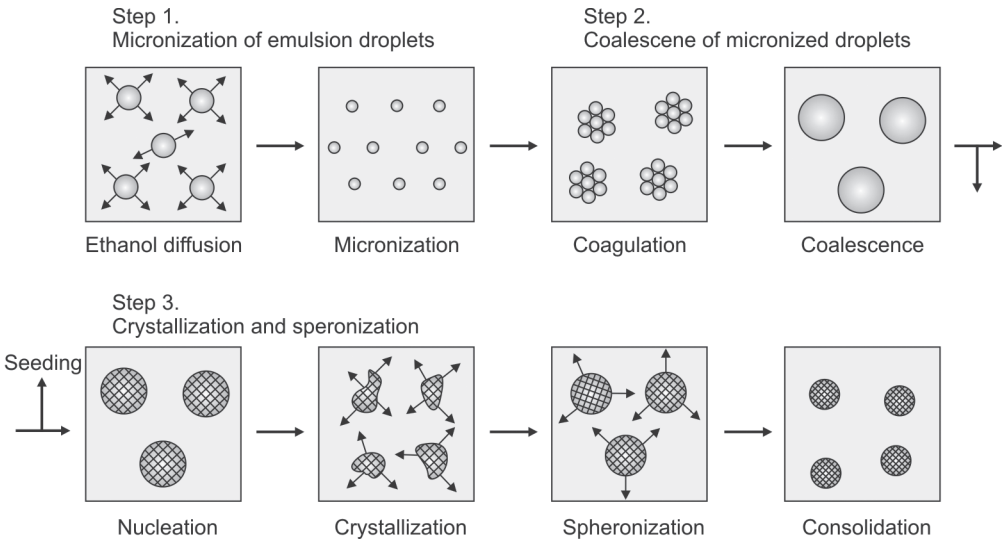


Fig. 6.2: Pellet growth mechanisms (spherical agglomeration)

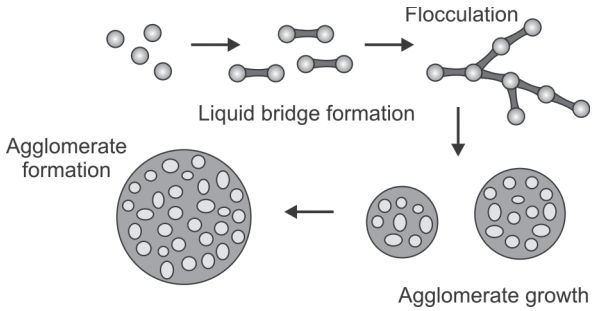


Fig. 6.3: Pellet growth mechanisms (emulsion solvent diffusion)

II. Drug Layering

Pelletization by layering involves the deposition of successive layers of drug moieties from solution or suspension.

Spraying: In solution/suspension layering, the drug particles are dissolved or suspended in the binding liquid; a hardening binder may or may not be added in the binding liquid. Once this formulation is sprayed, the droplets, which owe their existence to the surface tension of the liquid, spread out on the nuclei, and drying follows.

Wetting and distribution: Spreading depends on the droplet wetting characteristics, the wettability of the material, and the thermodynamics.

Layering/Solidifying: As the liquid evaporates, the dissolved substances crystallize out. On further evaporation, these crystals and the particles they are initially suspended in the binding liquid are drawn toward each other and toward the starter seeds by capillary forces. This leads to the formation of solid bridges among the particles. Strength of the solid bond depends on the properties of the binder, other additives in the formulation and the active ingredient.

Pellets formation: This phenomenon of spraying and drying and the subsequent formation of solid bridges are repeated until the desired size of pellet is achieved.

In powder layering, liquid saturation is low and irrespective of the solubility of the active in the binding liquid, complete dissolution does not occur. Typically, a binder solution is first sprayed onto the nuclei, followed by the addition of powder. The moist nuclei tumble in the rotating pan or disc, pick up powder particles, and form layers of small particles that adhere to each other and the nuclei by means of capillary forces developed in the liquid phase. As additional binding liquid is sprayed, layering of more powder on the nuclei continues until the desired pellet sizes are achieved. On drying, the binder and other dissolved substances crystallize out and the liquid bridges are partially replaced by solid bridges (Fig. 6.4).

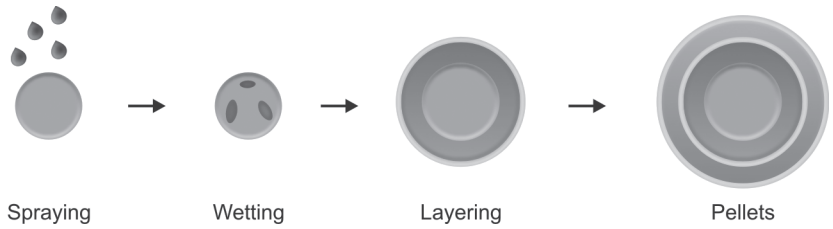


Fig. 6.4: Layering process

III. Globulation

It is a process where hot melts, solutions, or suspensions are atomized to generate spherical particles or pellets. In globulation, atomization produces solid particles directly from the liquid phase through evaporation or cooling and subsequent solidification of hot melts, solution and suspension.

Spray drying: During spray drying, the atomized droplets are contacted by a hot gas stream and evaporation of the liquid is initiated, which involves simultaneous heat- and mass transfer and depends on the temperature, humidity, and transport properties of the air surrounding the droplet. As more and more liquid evaporates, surface saturation conditions are reached and formation of solid begins. These particles are initially held together by capillary forces developed by the liquid phase and are gradually replaced by solid bridges. Continuation of the process leads to the formation of a porous layer or crust on the surface of the droplets and thickness of the crust increases through both evaporation and subsequent crystallization of the dissolved material that may include active drug, hardening binder or any other excipients which have solubility in the binding liquid. The rate controlling mechanism is the diffusion of the liquid through the expanding crust, followed by convective transport from the surface of the shell. In crosslinking technique, the polymer is rigidized by chemical reaction with the crosslinking agents such as aldehydes, calcium chloride, etc.

Spray congealing: During spray congealing, the atomized droplets are cooled below the melting point of the vehicle. The particles are held together by solid bonds formed from the congealed melts. Due to the absence of solvent evaporation during most spray congealing processes, the particles are generally nonporous and strong and remain intact upon agitation. The processing conditions play a very significant role in the development of good quality pellets, it is the physical forces that first bond the

primary particles together and initiate the pelletization process. The propensity and strength of these physical forces depend to a large extend, upon the physicochemical properties of the formulation components. Therefore, the physical forces coupled with the elementary growth mechanisms ultimately determine the strength and performance of pellets and should be taken into account during the design and development of pellet dosage forms.

IV. Extrusion and Spheronization (Compaction)

Extrusion-spheronization is the most preferred method when it comes to manufacturing of spherical pellets of uniform size and shape. It has various advantages like easy operation, high throughput with low wastage, narrow particle size distribution, less friable pellets, ease of film coating, better controlled release profile, etc. Given below, is the description of the processing steps involved in extrusion-spheronization.

MANUFACTURING PROCESS

The manufacturing process includes series of unit operations which are associated with a number of individual processing and formulation variables. The process flow is described in Fig. 6.5.

a. Mixing and Granulation

Mixing is usually carried out in the same equipment which is used for granulation. However, if continuous granular is being used then a separate mixer is required like twin shell blender, high shear mixer and planetary mixer. Mixing is a crucial step as it has effect on the quality of granulation, which in turn, produces spherical pellets. Using high shear mixers may cause evaporation of the granulating fluid. During granulation a wet plastic mass is prepared. It is somewhat similar to conventional granulation techniques, but the major difference between the two is that the granulation done for compression requires uniform dispersion of the granulation fluid and the amount of fluid required is also less. The granulation end point of the extrusion-spheronization process is determined by the behaviour of the wetted mass during the

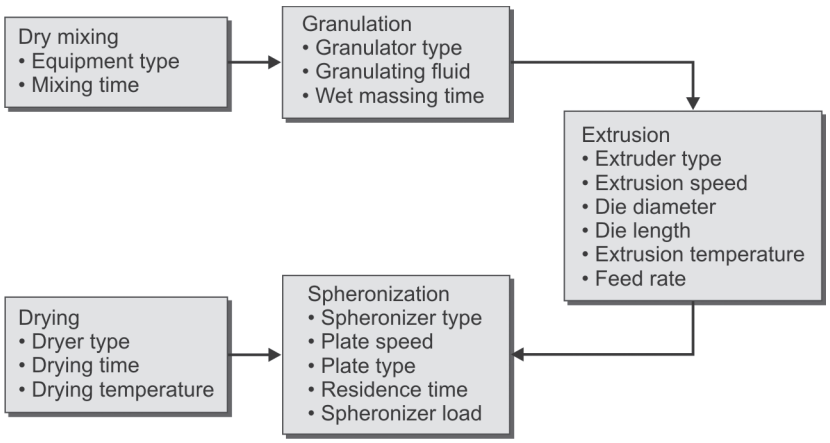


Fig. 6.5: Process flow diagram of the extrusion–spheronization

extrusion process. The water solubility of the drug plays an important role in determining the granulation end point. An insoluble drug has problems in wetting during the granulation step. It also tends to release moisture which migrates on surface during extrusion-spheronization, which might cause agglomeration.

The granulation parameters were:

1. Dry mixing (time)
2. Addition of water or binder solution (time)
3. Rotor used (time)
4. Chopper used (time)
5. Granulation end point (ml)
6. Racking

b. Extrusion

It is an integral part of spheronization process. Extrusion is a unit operation which applies pressure to a mass until it passes through dies to produce rod-shaped particles called extrudates. The diameter of these dies controls the diameter of the extrudate. The weights of the extrudates make them break at similar lengths. The wet mass must have inherent fluidity, so that it flows during the process and must be self-lubricating as it passes through the die. It should possess a degree of rigidity in order that the shape imposed by the die is retained. Furthermore, it should be brittle and have plasticity that would enable it to be spheronized, but not so friable as to cause disintegration into fines. Extruders come in many varieties but can generally be divided into three classes based on their feed mechanism. They include those that rely on a screw, gravity or a piston to feed the wet mass into the extrusion zone. Screw feed extruders include the (a) axial or end plate, (b) dome, and (c) radial type, while gravity feed extruders include (d) cylinder, (e) gear, and (f) radial types. The screw and gravity-feed types are used for development and manufacturing with the radial varieties being the most popular for pharmaceutical applications (Fig. 6.6).

During the spheronization process, the rod-shaped particles round off and form uniformly sized spheres. Thus, a spheronizer device consists of a vertical bowl with fixed side walls, and a rapidly rotating friction plate. The friction plate has a grooved surface to produce frictional forces. The plate has two kinds of geometric patterns: A



Fig. 6.6: The fuji paudal laboratory marumerizer spheronization

cross-hatched or a radial pattern. In cross-hatched geometry, the grooves intersect each other at 90° angles, whereas, the other pattern is a radial geometry, in which grooves emanate from the centre. A cross-hatched is more frequently used. The rotational speed of the friction plate can range from 100–2000 rpm. The spheronization of a product can take 2–10 minutes (Fig. 6.7).

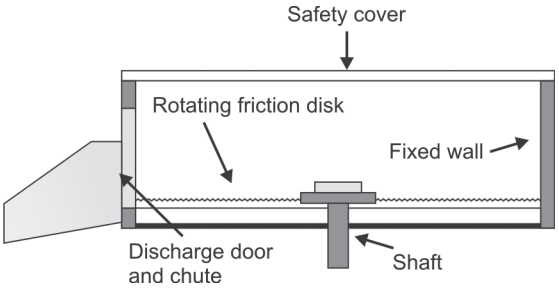


Fig. 6.7: Basic configuration of a spheronizer

In principle the basic machine consists of a rotating friction disk, designed to increase friction with the product, which spins at high speed at the bottom of a cylindrical bowl. The spinning friction disc has a carefully designed groove pattern on the processing surface. This is most often crosshatched, but several sizes and other types are available (Fig. 6.8).

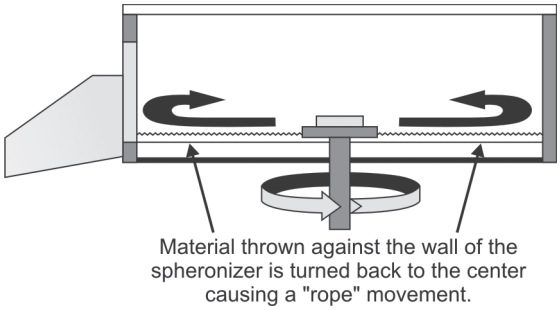


Fig. 6.8: Movement of granules inside spheronizer

Extrudates are charged to the spheronizer and fall on the spinning disc. At first, the cylindrical extrudate segments are cut into segments with a length ranging from 1 to 1.2 times the diameter. These segments then collide with the bowl wall and they are thrown back to the inside of the friction plate. Centrifugal force sends the material to the outside of the disc. The action of the material being moved causes the extrudate to be broken down into pieces of approximately equal length relative to the diameter of the extrudate. These cylindrical segments are gradually rounded by the collisions with the bowl wall, the plate and each other.

The ongoing action of particles colliding with the wall and being thrown back to the inside of the plate creates a "rope-like" movement of product along the bowl wall (Fig. 6.9). The continuous collisions of the particles with the wall and with the friction plate gradually turn the cylindrical segments into spheres, provided that the granules are plastic enough to allow the deformation without being destroyed. It is essential

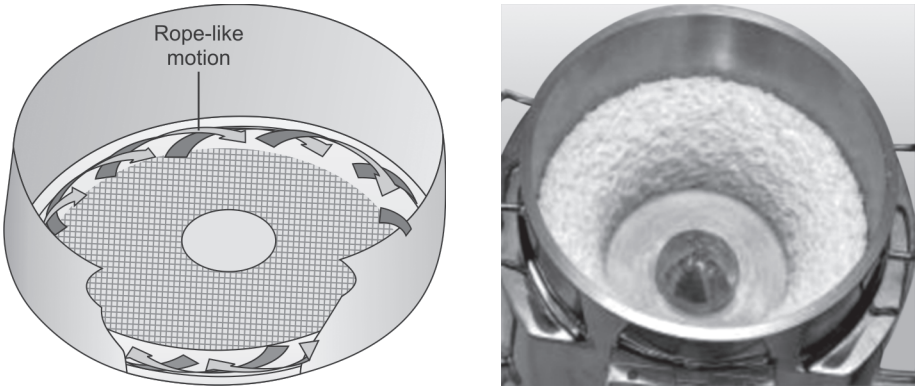


Fig. 6.9: Granules creating a "rope-like" movement inside spheronizer

that this rope movement is present for an optimal spheronization. When the particles have obtained the desired spherical shape, the discharge valve of the chamber is opened and the granules are discharged by the centrifugal force. The design principle of the spheronizer is relatively simple, but additions and adaptations are available have widened the range of applications and greatly improved the flexibility of the machines.

c. Drying

Drying stage is required in order to achieve the desired moisture content. Any kind of dryer can be used for drying of pellets. The choice mainly depends upon the pellet property. The main differences in the dryer are because of the difference in the rate of evaporation of water. The tray drier is the slowest. Other dryers which operate at elevated temperatures include the fluidized bed dryer, forced circulation oven, or a microwave oven. Tray drying is a slow process which can lead to migration of drug towards the surface, or its recrystallization. Fluid bed drying is more rapid, which minimizes the effect of migration. The increase drug concentration at the surface can increase the rate of dissolution. The smoothness of surface is also reduced which may cause problems in film coating. The choice of dryer determines the final pellet quality.

d. Screening

Screening is an essential step to achieve desired particle size distribution. For this purpose, sieve analysis is done. The pellets of desired size range are selected. It may be range from 0.5 to 1.5 mm.

FORMULATION REQUIREMENT AND VARIABLES

1. Pelletization material: Suitable formulation for spheronization is critical in determining the properties of the pellets produced. Varying types of material behaviors are required during each of process steps. The materials must form a wet plastic mass, deform during extrusion, and also round-off to form uniform sized spherical pellets during spheronization. A minimum amount of granulating fluid should migrate on the surface of extrudates. During spheronization process, they should not grow in size due to agglomeration, and must be obtained as separate entities without much sticking. The excipients must be sphere forming at both low and high concentrations. Thus, the choice of excipients is crucial. Microcrystalline cellulose (MCC) is incorporated in most formulations, since, it provides the proper rheological properties to the wetted mass for successful extrusion-spheronization. MCC is referred to as golden standard for extrusion-spheronization, as it has good binding properties that provide cohesiveness to the wetted mass. It has the ability to absorb and retain a large quantity of water, due to its large surface area and high internal porosity. Thus, the two main functions of MCC are:

a. Controlling the movement of water through the wet powder mass during extrusion
b. Modifying the rheological properties of the mass, so that it is extruded easily.

Due to these properties the MCC-based pellets have a good sphericity, low friability, high density, smooth surface and more robustness. Three models have been proposed to study the behavior of MCC during extrusion-spheronization:

i. **Liquid saturation model:** The liquid saturation model describes the relationship between the amount of powder and the granulating liquid, based on different

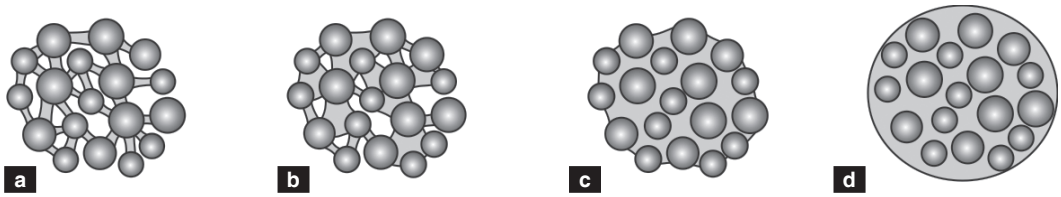


Fig. 6.10a to d: Different stages of saturation for liquid bonds in granules: (a) Pendular state; (b) Funicular state; (c) Capillary state; (d) Droplet state

liquid saturation stages: Pendular, funicular, capillary, and droplet stage, as shown in figure. Liquid when added to a powder, occupies the void spaces between the individual powder particles. Liquid saturation or voidage saturation(S) is defined as the relative amount of liquid in the wetted powder. It can be calculated as ratio of the volume of liquid to the total volume of voids. Different levels of liquid saturation are related to different states of liquid, i.e. below 1.5 is pendular state, between 0.25 and 0.8 is funicular state, above 0.8 is capillary state, and beyond 1 is the droplet state (Fig. 6.10a to d).

ii. **The sponge model:** It was proposed that each particle of MCC behaves as a porous molecular sponge, and is able to retain water in a manner similar to a sponge. A part of water in MCC is absorbed in the pores inside the cellulose fibres, and a part is located between the fibres. Under the pressure of extrusion, water is partly squeezed out from the internal structures, and acts as a lubricant. Water can also be taken back in, after releasing the extrusion pressure, and the volume will increase, which will make them appear dry and brittle. Brittleness would facilitate the breaking of extrudates during spheronization.

iii. **The crystallite-gel model:** According to this model, gel is formed during extrusion with MCC. In the presence of water, the MCC tends to break down into smaller subunits because of shear during granulation and extrusion. Thus, single crystallites are obtained, which are able to form gel and immobilize water. Over a particular range of water, suitable plasticity and deformability is obtained and therefore, extrusion and spheronization occurs successfully.

2. ***Amount of granulation liquid:*** It is a significant factor for pelletization. It is required to provide plasticity and cohesiveness to the powder, so as to extrude the wet mass, and to spheronize it. The rheological properties of the extrudate and the final spheronized pellets are highly governed by the liquid content of wetted mass. Only a narrow range of liquid content should be there to obtain pellet of acceptable quality. Below this specific narrow moisture content range, plasticity of the extrudate is inadequate, which leads to increase in extrusion pressure, power consumption and temperature. Not only this, fines production is also enhanced. When the moisture content exceeds the specific moisture content range, it leads to lower levels of extrusion parameters. Excessive water on surface of spheronized pellets leads to agglomeration because of coalescence of pellets. The pellets are large, round and the size distribution is broad. Hence, in order to control the process, the moisture content at the end of liquid addition can be controlled using moisture content using infrared moisture sensor, or by an indirect method such as measuring power consumption and torque on the friction plate.

3. Composition of granulating liquid: Water is the most commonly used granulating fluid. Various other liquids like alcohol or water/alcohol mixture have been reported. The use of solvents like isopropyl alcohol, ethyl ether and dilute acetic acid has also been reported.

4. Fraction of drug: The fraction of drug that can be added in the pellets, and its effect on the process and product properties, depends on the physico-chemical properties of the drug. On increasing fraction of the drug, the concentration of pelletization aid decreases which can cause problems in production of pellets with desired properties.

5. Particle size of drugs: Drugs with small particle size may adhere to the wall of the product container and cause hindrance in rope-like motion which is required for spheronization. The effect may increase if high fraction of drug is to be incorporated into pellets.

PROCESS CONSIDERATIONS AND VARIABLES

1. ***Extrusion speed:*** The total output of the extrudate is mainly dependent upon extrusion speed. It has been reported that surface impairments like roughness and shark-skinning can be produced with high extrusion speed. These surface impairments can lead to pellets of poor quality, as the extrudate breaks unevenly during the initial stages of spheronization process. As a result, an increase in ferns production and wide particle size distribution is observed.
2. ***Extrusion screen:*** The extrusion screen has two major parameters, i.e. the thickness of the screen and the diameter of the perforations. The properties of the pellets can be altered by changing these parameters. On increasing the diameter of the openings, the pellets with a larger diameter are produced. Differences in extrudate quality may also be attributed to different screen thicknesses. The screen with low thickness produce rough and loosely bound extrudate while the screen with high thickness forms smooth and well bound extrudate.
3. ***Extrusion temperature:*** The control of temperature during extrusion is important, in view of the importance of the moisture content. A rise in temperature during extrusion leads to evaporation of granulation liquid, which alters moisture content. This can lead to differences in quality of extudate at the beginning of the batch as well as at the end of the batch. In the case of Avicel pH 101, evaporation of water during extrusion is possible because most of the water is available as free water. High temperature may be a cause of damage to the thermolabile drugs and excipients. For example, Nica extruder (gravity feed radial extruder) do not generate much heat during extrusion.
4. ***Spheronization speed:*** Spheronization speed of the spheronization plate should be same throughout the process. Spheronization speed affects the size of the pellets. Studies revealed that faster speed of the friction plate together with longer residence time brings about rounder pellets. Effect of spheronization speed was pronounced on moisture loss during the process, shape of pellets and their density. Hasznos et al showed that faster speed and longer time increased the moisture loss during the process. Moisture loss can, thus, reduce plasticity which can cause problem in rounding-off into spheres. Many researchers have reported the effect of disk speed on the density of pellets. Increase in either disk speed or residence time, resulted in an increase in density.

5. ***Spheronization time:*** Spheronization time has an impact on the densification of pellets. Particles become more denser and spherical with time. An increase in spheronization time results in pellets with narrow size distribution, higher sphericity, lower friability, smooth surface, reduced pore volume and higher tensile strength.
6. ***Spheronization load:*** It has been noted that larger load reduces the size of pellets, and at the same time, narrow size distribution is obtained.
7. ***Drying technique:*** Drying technique affects the properties of the final pellets. Usually the pellets are dried on the fluid bed or tray dried. Use of microwave oven in the final phase of production of pellets has also been reported.

CHARACTERIZATION OF PELLETS

These methods are used to evaluate the quality of pellet. The aim of pelletization process is to produce spherical pellets of acceptable size and size distribution. Thus, it is important to determine the size, the size distribution and the shape of the pellets, as these parameters are crucial for uniform filling in hard gelatin capsules, and success of the coating process.

1. ***Determination of the size and size distribution:*** The size of pellets can be determined using a variety of parameters like particle size distribution, mean diameter, geometric mean diameter, inter quartile range, mean particle width and length. Particle size range should be as narrow as possible. This ensures least variation in coating thickness, and also facilitates blending process, if blending of different types of pellets is to be done. Particle size analysis in most cases is carried out by sieve analysis using sieve shaker. The reasons for its excessive usage are simplicity, low costs and less time consumption. The procedure involves mechanical shaking of sample through a series of sieves and weighing these sieves before and after the shaking. The critical parameters of this method include sieve loading, type of motion (vibration or tap), intensity, duration. Microscopic techniques like optical microscopy are used to measure diameters of pellets. The size and size distribution of the pellets produced was determined by agitation for 10 min with sieve shaker. A sieve shaker (Jayant laboratory instruments), vibrating at 1 mm amplitude was used. Pellets were put on the top of the sieve with series of openings ranging from 1 mm (BSS sieve no. 16), 0.853 mm (BSS sieve no. 18), 0.71 (BSS sieve no. 22) to 0.5 (BSS sieve no. 30). The results were taken as percentage of weight retained on each sieve size. The fraction of pellets sieved from BSS sieve no. 18 to BSS sieve no. 22 was reported as usable yield.
2. ***Shape and surface roughness:*** One of the most important characteristics of a pellet is its sphericity. Shape can be determined using image analysis system. Photo-micrographs of pellets are taken with a digital camera linked with a microscope system. Each individual pellet is characterized by mean Feret diameter (FD), i.e. the average of 180 calliper measurements with angle of rotation of 1°, aspecxt ratio (AR), i.e. the ratio of longest Feret diameter and its longest perpendicular diameter. The shape of pellets was examined with light microscope (Olympus microscope) at 10× magnification, connected to a camera. Major and minor axes of 50 particles of each composition were measured. The sphericity factor, the ratio of major and minor axes of pellets was determined as mean of 50 measurements.

$$\text{Roundness} = \pi/(d_{max}/2)^2$$

3. ***Bulk density and tapped density:*** The bulk density and tapped density were determined from the weight of a 40 g sample charged into a 100 ml graduated cylinder, and the volume was recorded. The pellets were tapped 1250 times until a constant volume was obtained and tapped density was calculated. Both densities were averaged from three determinations. Bulk density was calculated as: M/V_0, Where M is weighed mass and V_0 is unsettled apparent volume. Tapped density was calculated as: M/V_f, where M is weighed mass and V_{fis} final tapped volume.
4. ***Hausner ratio:*** The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by the formula:

$$H = \rho T/\rho B$$

Where ρB is the freely settled bulk density of the powder, and ρT is the tapped bulk density of the powder. The tap density was determined by using tap density tester (Electrolab, Aarkey Labtronix (India) Delhi). The Hausner ratio is used as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

5. ***Carr's index:*** The Carr's index is an indication of the compressibility of a powder. The Carr index is related to the Hausner ratio, another indication of flowability, by the formula:

$$C = 100 \times (1 - 1/H)$$

Carr's index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

6. ***Moisture analysis:*** The moisture content of the dried pellets was analyzed with a moisture content analyser (Mettler Toledo Ltd., Switzerland). Two grams of pellets were used for the test. The percentage loss of moisture during the test was determined. The results were calculated as mean value of three measurements.
7. ***In vitro dissolution testing:*** The drug release profile of pellets is an important characteristic of pellets. The dissolution characteristics can be influenced by different factors such as physical characteristics, wettability, penetration ability, the disintegration and the swelling process of the dosage form. Dissolution process can be either reaction limited or diffusion limited, depending which step in the process is slower. It is determined either by USP apparatus I or USP apparatus II. Release of drug from solid dosage form often constitutes a determining step in the *in vivo* absorption process. It is used in conjunction with *in vivo/in vitro* correlation to establish quality control parameter.

ISOLATED KEY POINTS

- Pelletization can be defined as an agglomeration process that converts fine powders or particles of bulk drugs and excipients into small, free flowing, more or less spherical units, called pellets. This technique enables the formation of spherical beads or pellets with a mean diameter usually ranging from 0.5 to 2.0 mm.
- Therapeutic advantages
  - Pellets can disperse freely throughout an area of the gastrointestinal tract
  - Pellets reduce peak plasma fluctuations and minimize potential side effects
  - Avoiding the irritant effect of some drugs on the gastric mucosa
  - Modified-release multiparticulate delivery systems are less susceptible to dose dumping than single-unit dosage form.

- Disadvantages: Often pellets cannot be pressed into tablets because they are too rigid. In that case, pellets have to be encapsulated into capsules.
  - The production of pellets is often an expensive process and/or requires highly specialized equipment.
  - The control of the production process is difficult (e.g. the amount of water to be added is critical for the quality of the pellets and overwetting can occur very easily).
- Pelletization techniques are spray-drying, solution and suspension layering, fluid-bed granulation, spray congealing, dry powder layering, extrusion/spheronization.
- Extrusion is necessary first step in the extrusion-spheronization process.
- The size of the sphere are determined by the diameter of the extrudate used.
- Spheronization is a process of forming a spherical particles from different rod shapes, by extrusion, that has a diameter ranging from 0.5 to 1 mm.
- The size of the spheres are determined by the diameter of the extrudate used for the spheronization process. For example, in order to obtain spheres with a diameter of 1 mm, a 1 mm screen is used on the extruder.
- Key spheronization factors are disc speed and load, disc groove geometry, disc diameter and speed, retention time.
- During processing of pellets three mechanical forces cause particle movement, mixing, and granulating.
- During spraying-drying, a drug is solution or suspension is sprayed, with or without excipients, into a hot-air stream, generating dry and highly spherical particles.

PRACTICE QUESTIONS

Long Answer Type Questions

1. What are various methods of preparing pellets? Briefly explain each method?
2. What are the advantages of preparing pellets?
3. What are the various manufacturing process along with the instrument used for manufacturing pellets?
4. Explain extrusion-spheronization process? Discuss process parameters needs to consider while extrusion-spheronization process?
5. Write in detail about characterization of pellets?

Objective Types Questions

1. _____ can be defined as an agglomeration process that converts fine powders or particles of bulk drugs and excipients into small, free flowing, more or less spherical units called pellets with a mean diameter usually ranging from _____ .
2. Which of the following is not a pelletization techniques?

i. Spray-drying ii. Solution and suspension layering
iii. Accela cota iv. Fluid-bed granulation

ANSWERS

1. Pelletization, 05.–2.0 mm **2.** iii

Chapter
7

Parenteral Products

DEFINITION

Parenteral (derived from Greek word, *para enteron,* beside the intestine) dosage forms of drugs are injected directly into body tissue through one or more layer of skin and mucous.

Parenteral preparation are introduced directly in to body fluid system composing:

a. The intra- and extra-cellular fluid compartment
b. The lymphatic system
c. The blood circulatory system

As highly protective barriers get avoided so introduction of microorganism and toxic agents is very dangerous. Considering this parenteral formulation should be as perfect as possible with respect to the following:

a. Purity
b. Freedom for toxicity
c. Freedom from contamination

Advantages

i. Quick onset of action: 15–30 seconds for IV, 3–5 minutes for IM and subcutaneous.
ii. 100% bioavailability for IV injection.
iii. Suitable for drugs not absorbed by the gut or those that are too irritant (anti-cancer).
iv. One injection can be formulated to last days or even months, e.g. Depo-Provera, a birth control shot that works for three months.
v. IV can deliver continuous medication, e.g. morphine for patients in continuous pain, or saline drip and glucose for people needing fluids and nutrients.
vi. Useful for unconscious and vomiting patient.
vii. Suitable for drugs, which are inactivated by GIT fluid or enzymes.

Disadvantages

i. Onset of action is quick, hence more risk of addiction when it comes to injecting drugs of abuse.
ii. Patients are not typically able to self-administer, needs trained person.
iii. Belonephobia, the fear of needles and injection.
iv. If needles are shared, there is risk of HIV and other infectious diseases.
v. It is the most dangerous route of administration because it bypasses most of the body's natural defenses, exposing the user to health problems such as hepatitis, abscesses, infections, and undissolved particles or additives/contaminants.

vi. If not done properly, potentially fatal air boluses (bubbles) can occur.
vii. In cases of toxicity retrieval of the drug is very difficult.

Classifications

Parenteral dosage forms can be categorized in to six categories (Table 7.1)

i. Solutions ready for injection.
ii. Dry, soluble products ready to be combined with a solvent just prior to use.
iii. Suspensions ready for injection.
iv. Dry, insoluble products ready to be combined with a vehicle just prior to use.
v. Emulsions.
vi. Liquid concentrates ready for dilution prior to administration.

TABLE 7.1: Various types of injections

Organs	*Injection type*
Skin	Intradermal, subcutaneous
Organs	Intracavernous, intravitreal, transscleral
Central nervous system	Intracerebral, intrathecal/intraspinal, epidural, intracisternal
Circulatory	Intravenous, intracardiac
Musculoskeletal	Intramuscular, intraosseous, intra-articular, intraperitoneal
	Intra-arterial

Routes of Administration

Intradermal (in or into the skin): An intradermal injection is given into the skin. It is used for skin testing some allergens, and also for Mantoux test for tuberculosis.

Subcutaneous: Under the skin. "Subcutaneous" implies just under the skin. With a subcutaneous injection, a needle is inserted just under the skin (Fig. 7.1). A drug (for example, insulin) can then be delivered into the subcutaneous tissues. After the injection, the drug moves into small blood vessels and the bloodstream. The subcutaneous route is used with many protein and polypeptide drugs such as insulin which, if given by mouth, would be broken down and digested in the intestinal tract. The amount of medication is around 1 ml, given by holding the needle at 45 degree angle while piercing the skin, skin is pinched tight, insert needle so that hub of needle shaft touches the skin, aspirate to check the location of needle. If blood is aspirated, withdraw the needle

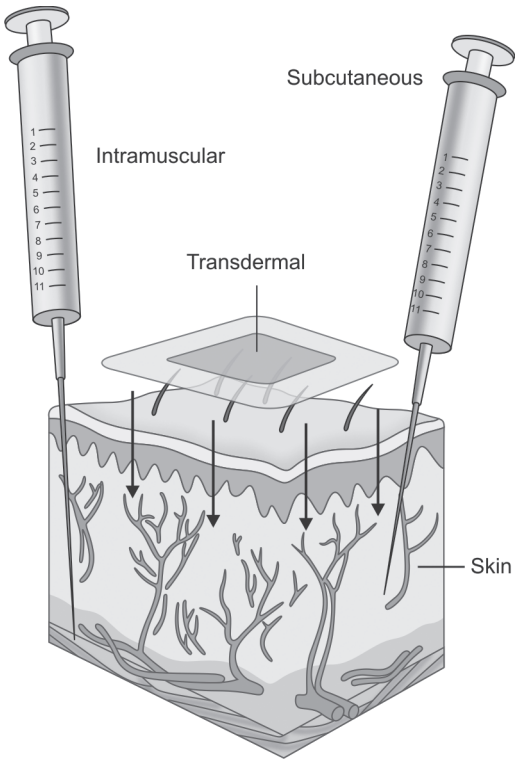


Fig. 7.1: Types of injections

and try at other site, if not gently push the medication into subcutaneous tissue, withdraw needle and gently massage the area to help in absorption never massage insulin or other drug which stains the skin.

Intracavernous: An intracavernous (or intracavernosal) injection is an injection into the base of the penis. This injection site is often used to administer medications to check for or treat erectile dysfunction in adult men.

Intravitreal: Intravitreal (intravitreal is a route of administration of a drug, or other substance, in which the substance is delivered via an eye. "Intravitreal" literally means "inside an eye") (Fig. 7.2).

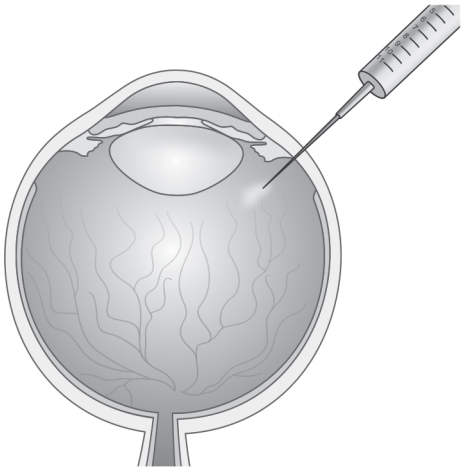


Fig. 7.2: Intravitreal injection

Transscleral (trans- + sclera + -al) Injected in to sclera. (Sclera: The white of the eye. It is the tough outer coat of the eye that covers the eyeball except for the cornea.)

Intracerebral (L, intra + cerebrum, brain, pertaining to the area or substance within the cerebrum): Injected in cerebrum.

Intrathecal (Latin intra—"inside", Greek theka "capsule", "hull") is an adjective that refers to something introduced into or occurring in the space under the arachnoid membrane of the spinal cord). Injection of a substance through the theca of the spinal cord into the subarachnoid space.

Epidural: Injection of an anesthetic substance into the epidural space of the spinal cord in order to produce epidural anesthesia (Fig. 7.3).

Intraosseous infusion (into the bone marrow) is, in effect, an indirect intravenous access because the bone marrow drains directly into the venous system. This route is occasionally used for drugs and fluids in emergency medicine and pediatrics, when intravenous access is difficult.

Intracisternal: It is given between the first and second cervical vertebrae. It is used to withdraw cerebrospinal fluid for diagnostic purposes.

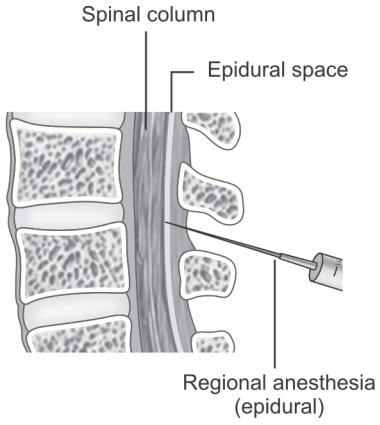


Fig. 7.3: Epidural injection

Intravenous: Intravenous therapy or IV therapy is the giving of substances directly into a vein. The word intravenous simply means "within a vein".

Intracardiac: Intracardiac (into the heart),Injection given into the heart, e.g. adrenaline during cardiopulmonary resuscitation, nowadays not commonly performed.

Intramuscular: Intramuscular injection into a muscle, e.g. many vaccines, antibiotics, and long-term psychoactive agents.

Intra-articular (Origin: Intra-+ L. Articulus, joint), drug injected with in joints (Fig. 7.4).

Intraperitoneal (infusion or injection into the peritoneum) intraperitoneal injection or IP injection is the injection of a substance into the peritoneum (body cavity). IP injection is more often applied to animals than humans, e.g. peritoneal dialysis.

Intra-arterial (Arterial-arteries) injected into arteries, e.g. vasodilator drugs in the treatment of vasospasm and thrombolytic drugs for treatment of embolism.

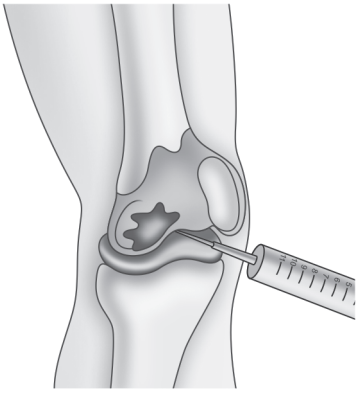


Fig. 7.4: Intra-articular injection

The most common routes of parenteral administration are intravenous (IV), subcutaneous (SC), and intramuscular (IM).

Classification on Injections on the Basis of Injection Volumes

Pharmacopoeias classify injectables into two on the basis of injection volumes:

i. Small-volume parenterals (SVPs)
ii. Large-volume parenterals (LVPs).

Small-volume parenterals (SVPs): The US Pharmacopeia (USP) defines SVPs as containing less than 100 ml.

Large-volume parenterals (LVPs): The US Pharmacopeia (USP) defines LVPs as containing more than 100 ml.

SVPs given rapidly in a small volume are known as a bolus. SVPs may also be added to LVPs, such as 5% dextrose and 0.9% sodium chloride infusion/injection, for administration by intravenous infusion. The selection of bolus or infusion will depend on the pharmacokinetics of the drug, and the distinction is not very clear. Infusions can be as brief as 15 minutes or may continue for several days. Usually infusions are formulated as a concentrate, which will subsequently be diluted by the practitioner or pharmacist prior to administration. Intramuscular or subcutaneous injections are almost always administered as a bolus. Usually volume of injection administered through subcutaneous route is less than 1 to 1.5 ml and for intramuscular route no more than 2 ml.

Preformulation Studies of Parenteral Formulation

Characterization of Drug Substance

The drug substance attributes that were considered during product development are:

i. The drug substance solubility
ii. The drug substance stability
iii. The particle size of the drug substance
iv. The compatibility between the excipients and the drug substance

The drug substance solubility: Solubility is one of the most important physicochemical properties studied during pharmaceutical preformulation. Solubility is the maximum

TABLE 7.2: US Pharmacopoeia (USP)—definitions of solubility

Descriptive term	*Parts of solvent required for 1 part of solute*
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble	10,000 and over

concentration that can be attained by a solute in a specific solvent. pH effects on solubility also can be of particular utility in the preparation of parenteral solutions (i.e. intravenous). The US Pharmacopoeis (USP) gives following definitions of solubility (Table 7.2).

Factors that can affect solubility

a. Nature of the drug substance
b. Particle size
c. Solvent system
d. pH of solution
e. Temperature
f. Solubilizing agents
g. Complexing agents

The drug substance stability: Drug substance stability has big commercial and safety related impact on the project. A highly unstable protein drug cannot be placed in anything but a highly preserved and protected parenteral form.

The particle size of the drug substance: The particle size of a new drug substance is a critical parameter. Appropriate particle size is required to achieve control sedimentation and flocculation in parenteral suspensions and it affects solubility for parenteral solution.

The compatibility between the excipients and the drug substance: The drug excipients shall be evaluated by forced degradation and stability studies at various temperature/humidity conditions. After force degradation studies, we can trace out whether drug substance undergo oxidation/reduction/hydrolytic or thermal degradation. Whereas the choice of excipients starts with the stages of formulation, some excipients are historically used in specific drug formulations; for example, if the newly discovered drug is a cephalosporin for use as an intravenous product, compatibility with arginine or sodium carbonate would be advised as these are the most commonly used active excipients used for solubilization.

Components of Parenteral Formulation

The components of the product to be accumulated and selected include:

1. Vehicles
2. Additives/solute
3. Isotonicity

Vehicles: Majority of the injections are diluted so vehicle makes highest portion of the injection. Vehicles are categories into following headings:

i. Aqueous vehicles
ii. Water-miscible vehicles
iii. Nonaqueous vehicles

Aqueous vehicles: The vehicle of greatest importance is water, i.e. water for injection (WFI). Usually aqueous vehicles are isotonic vehicles to which a drug may be added at the time of administration. *For example,* sodium chloride injection, ringer's injection, dextrose injection, dextrose and sodium chloride injection, and lactated ringer's injection.

Water for injection: The USP monograph states: "Water for injection (WFI) is water purified by distillation or reverse osmosis." WFI is produced by either distillation or 2-stage RO. It is usually stored and distributed hot (at 80° C) in order to meet microbial quality requirements and should not be used after 24 hours of storage (Table 7.3).

TABLE 7.3: Specifications of water for injection

Parameter	*Unit*	*USP 24*	*Ph. Eur.*
TOC	ppb	500	500
Conductivity	µS/cm@20°C	—	<1.1
Conductivity	µS/cm@25°C	<1.3	—
Dry residue	%	—	<0.001
Nitrate (NO_3)	ppm	—	<0.2
Heavy metals	ppm as Pb	—	<0.1
Aerobic bacteria	CFU/100 ml	<10	<10
Bacterial endotoxins	EU/ml	<0.25	<0.25

Water-miscible vehicles: A number of solvents that are miscible with water *is used* in the formulation of parenterals as cosolvent. These solvents are used primarily to affect the solubility of certain drugs and to reduce hydrolysis. Most common cosolvents used in the approved parenteral products are glycerin, ethanol, propylene glycol, polyethylene glycol, and N, N-dimethylacetamide.

Non-aqueous vehicles: The most important group of nonaqueous vehicles are the fixed oils. The fixed oils used in parenteral must be of vegetable origin because of following characteristics:

i. They will be metabolized,
ii. Remain liquid at room temperature, and
iii. Will not become rancid readily.

The USP also specifies limits for the degree of unsaturation and free fatty acid content. Examples of fixed oils are corn oil, cotton seed oil, peanut oil, and sesame oil. Fixed oils are used particularly as vehicles for certain hormone preparations and poorly soluble drugs for intramuscular administration can be formulated in a nonaqueous vehicle; this can have the additional benefit of providing a slow release of the active moiety. The label must state the name of the vehicle so that the user may beware in case of known sensitivity or other reactions to it.

Additives/solutes: The requirement of purity of medical compound used in an injection often makes it necessary to take special purification. Factors to be consider for the quality of solute:

i. Purity
ii. Freedom for toxicity
iii. Freedom from contamination (microbial and pyrogen contamination)
iv. Solubility of compound
v. Freedom from gross dirt.

Added substances: The USP includes in this category all substances added to a parenteral preparation to improve or safeguard its quality. An added substance may:

i. Effect solubility, as does sodium benzoate in caffeine sodium benzoate injection.
ii. Provide patient comfort, as do substances added to make a solution isotonic or near physiological pH.
iii. Enhance the chemical stability of a solution, as do antioxidants, inert gases, chelating agents and buffers.
iv. They may preserve the preparation against microbial growth.

Antimicrobial agents

i. The USP states that antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to preparations contained in multiple-dose containers (Table 7.4).
ii. They must be present in adequate concentration at the time of use to prevent the multiplication of microorganisms inadvertently introduced into the preparation while withdrawing a portion of the contents with a hypodermic needle and syringe.
iii. The USP provides a test for antimicrobial preservative effectiveness to determine that an antimicrobial substance or combination adequately inhibits the growth of microorganisms in a parenteral product.
iv. Compatability studies of the microbial agents should be performed before using them into the formulation.

TABLE 7.4: Preservative used and their concentration

Preservative	*Typical concentration (%)*
Benzyl alcohol	1–2
Chlorbutanol	0.5
Methylparaben	0.1–0.18
Propylparaben	0.01–0.02
Phenol	0.2–0.5
Thiomersal	<0.01

Buffers: Buffers are used primarily to stabilize a solution against pH, which result in to reduction in the chemical degradation that might occur if the pH changes. Buffer systems employed should normally have low buffering capacity as if buffering capacity of product is high it may disturb significantly the body's buffering systems when injected. In addition, the buffer range and effect on the activity of the product must be evaluated carefully. A parenteral product should be formulated with a pH close to

TABLE 7.5: Buffers used in parenteral products

Buffer	*pH range*
Acetate	3.8–5.8
Ammonium	8.25–10.25
Ascorbate	3.0–5.0
Benzoate	6.0–7.0
Bicarbonate	4.0–11.0
Citrate	2.1–6.2
Diethanolamine	8.0–10.0
Glycine	8.8–10.8
Lactate	2.0–4.1
Phosphate	3.0–8.0
Succinate	3.2–6.6
Tartrate	2.0–5.3
Tromethamine (TRIS. THAM)	7.1–9.1

physiological, unless stability or solubility considerations preclude this. Often, the pH selected for the product is a compromise between the pH of maximum stability, solubility, and physiological acceptability (Table 7.5).

Antioxidants: Antioxidants are required to preserve products because of the ease with which many drugs are oxidized. Antioxidants are included in parenteral formulations, although their use is now in decline, and EU guidelines discourage their use unless no other alternative exists. A preferred method of preventing oxidation is simply to exclude oxygen; this is usually achieved by purging the product with nitrogen and creating a nitrogen head space within the container. Examples are metal chelator, such as disodium edentate (0.05%) and an antioxidant compound, such as ascorbic acid or sodium metabisulfite (1%, and 0.3%, respectively).

Isotonicity: Tonicity agents are used in many parenteral and ophthalmic products to adjust the tonicity. However, not all preparations need to be isotonic. The agents most commonly used are electrolytes and mono- or disaccharides.

METHOD OF PREPARING PARENTERAL SUSPENSION AND SOLUTION

Two basic methods are used to prepare parenteral suspension or solution.

Method 1

Step 1. Aseptically combining sterile powder and vehicle.

Step 2. This method involves dispersing or dissolving sterile milled active ingredients in to sterile vehicle system (solvents + necessary excipients).

Step 3. Aseptically milling the resulting suspension as required.

Step 4. Aseptically filling the milled suspension or solution into suitable containers.

For example, this process is used to prepare penicillin G suspension. As shown in Fig. 7.5.

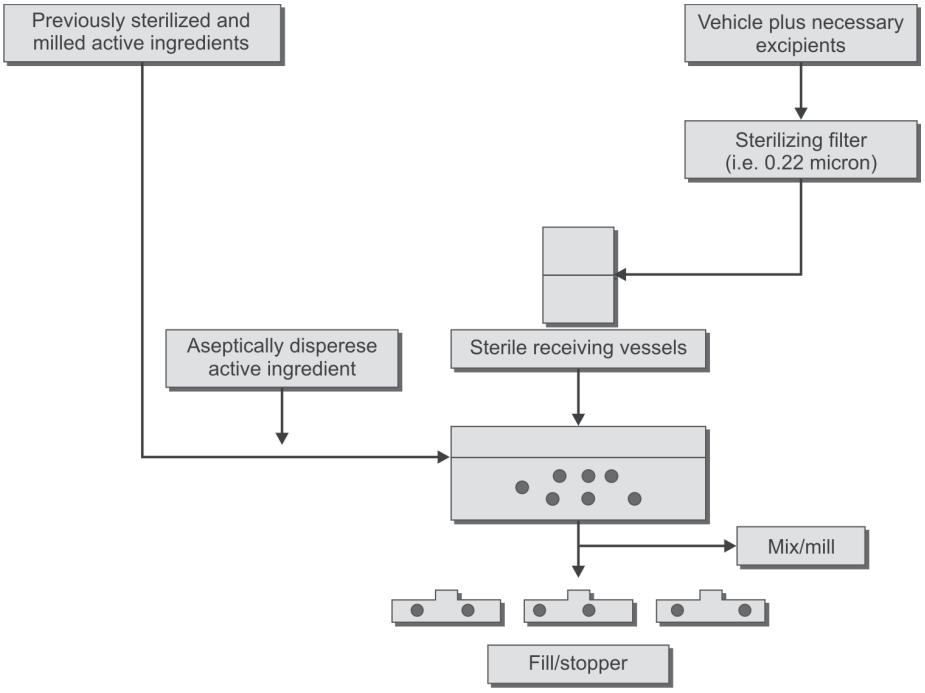


Fig. 7.5: Method 1 of preparing parenteral suspension and solution

Method 2

In situ formation of parenteral suspension:

Step 1. *In situ* crystal formation by combining sterile solutions (Fig. 7.6).

Step 2. In this method active ingredients are dissolved in suitable solvent system.

Step 3. A sterile vehicle system or counter solvent is added to step 2 solution that causes active ingredient to crystallize.

Step 4. The organic solvent is aseptically removed, the resulting suspension is aseptically milled as necessary and then filled in suitable container.

Important unit operations involved during parenteral preparation

There are five critical steps involved in preparation of parenteral products:

1. Compounding of product
2. Filtration
3. Filling
4. Sealing—ampoules and vials
5. Sterilization

1. Compounding

In general following steps are involved:

1. Preparation of master formula (MF).
2. All the excipients and active substance should be weighed accurately.
3. Dispensing must be done by weight as weight can be taken more accurately than volume.

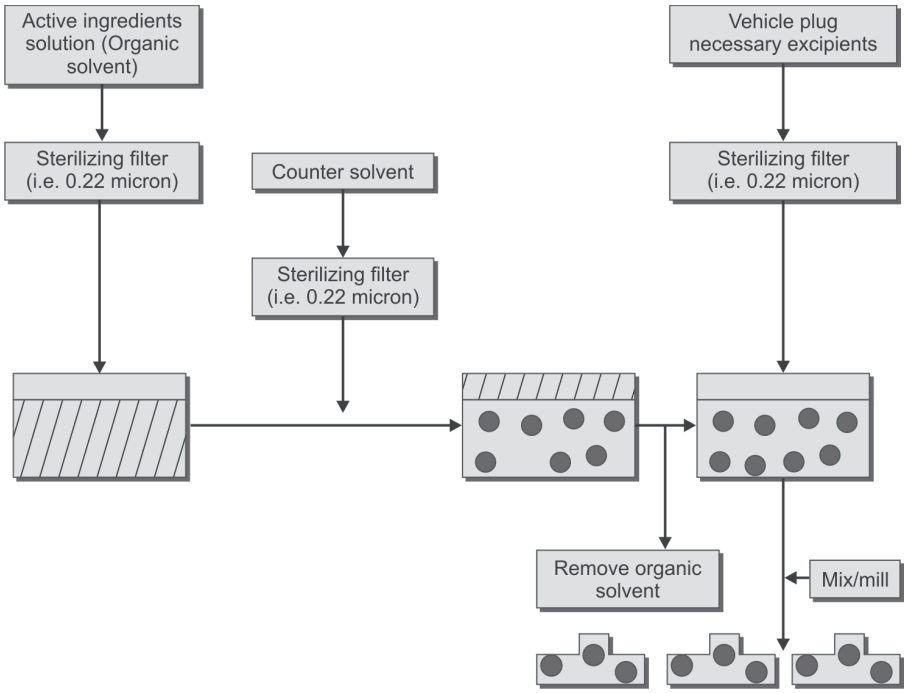


Fig. 7.6: Method 2 of preparing parenteral suspension

4. During calculation for the amount of active drug substance to be taken, assay and Water content of drug substance is to be taken in to consideration.
5. Mixing time: The order of mixing of ingredients may affect the product significantly, particularly those of large volume, where attaining homogeneity requires considerable mixing time.

2. Filtration

The main purpose of filtration are:

1. Getting clarity of parenteral solution: Removal of particulate matter having particle size more than 0.2 µm in size.
2. Remove microorganism (cold sterilization).

Filters are thought to function by one or usually, a combination of the following:

i. Sieving or screening,
ii. Entrapment or impaction,
iii. Electrostatic attraction.

Sieving or screening: When a filter retains particles by sieving, they are retained on the surface of the filter.

Entrapment or impaction: Entrapment occurs when a particle smaller than the dimensions of the passageway (pore) becomes lodged in a turn or impacted on the surface of the passageway.

Electrostatic attraction: Electrostatic attraction causes particles opposite in charge to that of the surface of the filter pore to be held or adsorbed to the surface. Membrane filters used for parenteral preparation should be non-shedding and non-reactive to

components of parenteral preparation. The most common membranes are composed of cellulose esters, nylon, polysulfone, polycarbonate, polyvinylidene difluoride, or polytetrafluoroethylene (teflon).

Each filter in its holder should be tested for integrity before and after use, particularly if it is being used to eliminate microorganisms. This integrity test usually is performed as the *bubblepoint test*.

3. Ampoule Filling

Aseptic filling must be exercised to prevent contamination, particularly when there is no terminal sterlization. This unit operation is carried out under blanket of HEPA filtered laminar flow in an aseptic area. Filling machine is provided for repetitively forcing a measured volume of the liquid through the orifice of a delivery tube that is introduced into the container. For large volumes the quantity delivered usually is measured in the container by the level of fill in the container and the force required to transfer the liquid being provided either by gravity or by pump (like pressure and a vacuum pump) or both.

The narrow neck of an ampoule limits the clearance possible between the delivery tube and the inside of the neck. Since a drop of liquid normally hangs at the tip of the delivery tube after a delivery, the neck of an ampoule will be wet as the delivery tube is withdrawn, unless the drop is retracted. Therefore, filling machines should have a mechanism by which this drop can be drawn back into the lumen of the tube.

Features of ampoule filling machines

i. Most ampoule fillers are characterized with fast changeover time to accommodate a variety of ampoules in terms of shapes and size.
ii. These machines require minimal maintenance and are very easy to clean. They should easily be demountable for cleaning and sterilization.
iii. Another feature is the installation of speed adjusting equipment and 'no ampoule no fills' capability to ensure that unfilled ampoules are not packed.
iv. Check weight mechanism of the machine helps to maintain consistency in each batch.
v. Sealing is done either by laser sealing system or conventional gas flame.

Solid filling: Sterile solids, like antibiotics, are more difficult to subdivide evenly into containers than are liquids as the rate of flow of solid material is slow and often irregular. Some sterile solids are subdivided into containers by individual weighing using filling machines.

4. Sealing

Ampoules—filled containers should be sealed as soon as possible to prevent the contents from being contaminated by the environment. Ampoules are sealed by melting a portion of the glass neck. Two types of seals are employed normally:

a. Tip-seals (bead-seals)
b. Pull-seals.

a. Tip-seals: Those made by melting sufficient glass at the tip of the ampule neck to form a bead of glass and close the opening.

b. Pull-seals: Those made by heating the neck of a rotating ampule below the lip, then pulling away the tip to form a small, twisted capillary just prior to being melted closed.

Manual pull

Sealing of ampoules: Using a twin-jet burner (Fig. 7.7), adjust the platform height and flame intensity.

Try an empty ampoule first before sealing your products. Position the ampoule between the flames. Grip the end of the neck with a blunt-nosed forceps and when the glass is soft enough, pull off the top of the ampoule vertically and gently. Leave the tip in the flame for a second or two longer and then remove. The tip should now be smoothly and evenly rounded (Fig. 7.8) ampoules should have a reliable seal which can be readily leak tested. A good seal will not deteriorate during the lifetime of the product.

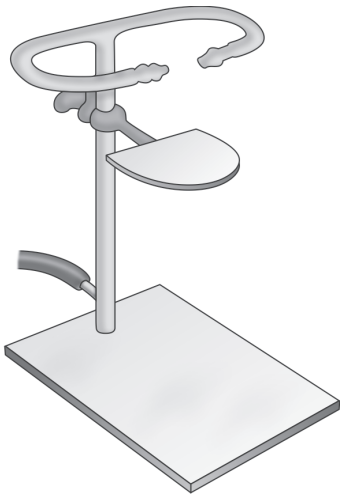


Fig. 7.7: Twin jet burner

Sealing of vials and bottles: These are sealed by closing the opening with a rubber closure (stopper). This must be accomplished as rapidly as possible after filling and with reasoned care to prevent contamination of the contents. Rubber closures are held in place by means of aluminum caps. The caps cover the closure and are crimped under the lip of the vial or bottle to hold them in place (Fig. 7.9). The closure cannot be removed without destroying the aluminum cap; it is tamperproof. Therefore, an intact aluminum cap is proof that the closure has not been removed intentionally or unintentionally. Such confirmation is necessary to ensure the integrity of the contents as to sterility and other aspects of quality.

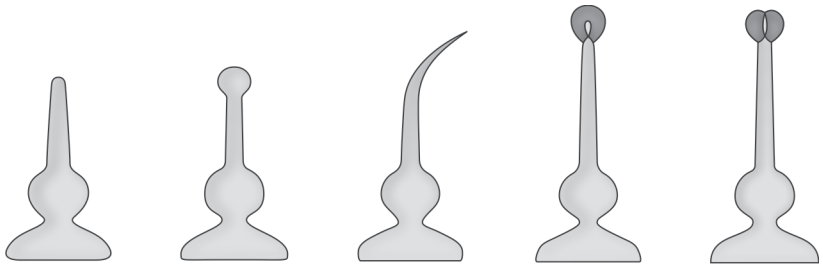


Fig. 7.8: (a) Good seal; (b to e) Faulty ampoules seal



Fig. 7.9: Vials of heparin, where closures was held in place by means of aluminum caps

5. Sterilization and Disinfection

Sterilization can be achieved by means of (Fig. 7.10):

i. Physical treatment
ii. Chemical treatment
iii. Physiochemical treatment

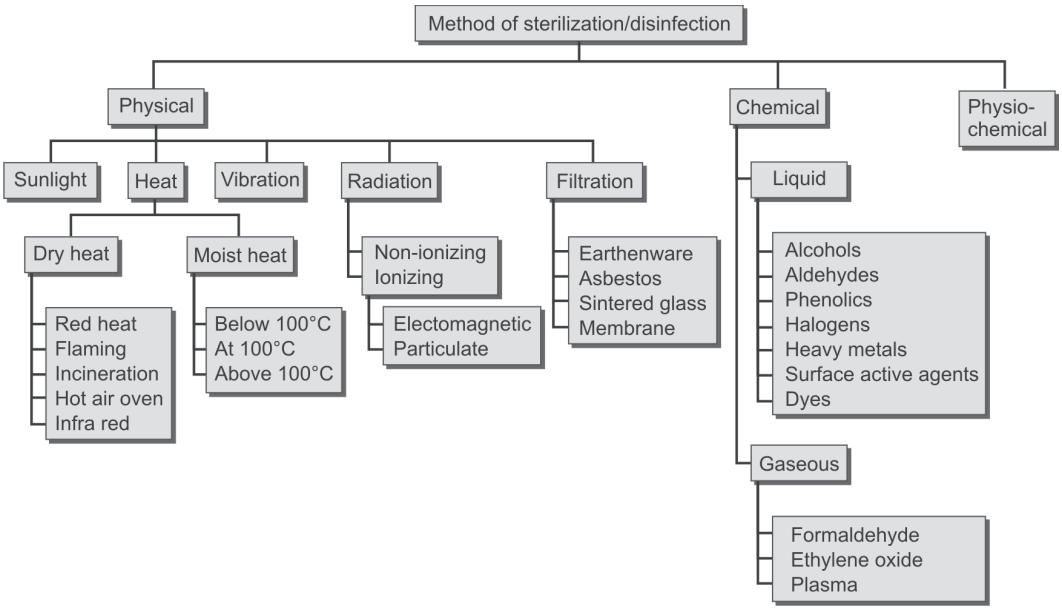


Fig. 7.10: Classification of various methods of sterilization/disinfection

Disinfection is the process of elimination of most pathogenic microorganisms (excluding bacterial spores) on inanimate objects. Disinfection can be achieved by physical or chemical methods. Chemicals used in disinfection are called disinfectants. Different disinfectants have different target ranges, not all disinfectants can kill all microorganisms. Some methods of disinfection such as filtration do not kill bacteria, they separate them out. Sterilization is an absolute condition while disinfection is not. The two are not same. Sterilization can be effectively achieved at a temperature above 100° C using an autoclave. Water boils at 100° C at atmospheric pressure, but if pressure is raised, the temperature at which the water boils also increases. In an autoclave the water is boiled in a closed chamber. As the pressure rises, the boiling point of water also raises. At a pressure of 15 lbs inside the autoclave, the temperature is said to be 121° C. Exposure of articles to this temperature for 15 minutes sterilizes them. To destroy the infective agents associated with spongiform encephalopathies (prions), higher temperatures or longer times are used; 135° C or 121° C for at least one hour are recommended.

Advantages of steam: It has more penetrative power than dry air, it moistens the spores (moisture is essential for coagulation of proteins), condensation of steam on cooler surface releases latent heat, condensation of steam draws in fresh steam.

Different Types of Autoclave

Simple "pressure-cooker type" laboratory autoclave, steam jacketed downward displacement laboratory autoclave and high pressure pre-vacuum autoclave.

Lyophilization

Lyophilization (freeze drying) is the removal of water from frozen material. It is an excellent method for preserving microbes and heat-sensitive materials such as proteins, plasma, etc.

Water is removed from frozen samples mainly by sublimation, water is converted from the frozen state into vapor, thus bypassing the liquid phase. The rate of sublimation depends on vapor pressure, which is affected by the system vacuum and sample temperature. The frozen sample absorbs heat, causing water in the sample to enter the vapor phase and migrate into the instrument atmosphere where it is removed by refreezing on the condenser. Drying first occurs at the surface of the sample. As drying proceeds, water is removed from deeper layers of the sample and the drying rate slows. Three steps are involved in lyophilization.

1. Freezing: The sample is placed in a freezing vial/flask. The purpose is to completely freeze the sample.
2. Primary drying: Approximately 90% of the total water in the sample (essentially all of the free water and some of the bound water) is removed by sublimation.
3. Secondary drying: Bound water is removed by desorption, resulting in a product that has <1–3% residual water. This step requires time about one-third to half the time needed for primary drying.

Three basic formats for freeze drying

1. Manifold drying is the most commonly used method. Drying flasks or ampules are attached to individual ports on a central manifold. The samples are usually frozen by the shell method, and are quickly attached to the manifold and placed under vacuum to prevent melting. Room temperature provides heat for the sample. This method is useful for relatively small volumes.
2. The batch method is used when large numbers of similar-sized containers are simultaneously freeze dried, e.g. serum vials. A tray system is used instead of a manifold. Heating elements in the trays supply the heat. Most batch systems have a mechanism to seal the vials before they are exposed to air.
3. The bulk method is used for large volumes of a single sample. The sample is poured into special trays, frozen, and then dried in a lyophilizer. Bulk dried samples cannot be sealed while in the instrument. Exposure to air before packaging may affect shelf life.

Characteristics of the finished product: Freeze dried products have from <1–3% residual water content and are very hygroscopic. The stability of the freeze-dried product depends on moisture, oxygen, and temperature. A good seal prevents exposure of the sample to moisture and oxygen. It is best to freeze dry samples in vials and seal them under vacuum. Storage at high temperatures reduces shelf life. Refrigeration or freezing is best for long-term storage.

Quality control/evaluation tests for parenteral preparations

A. Pyrogen test

B. Test for particulate matter

i. Light obstruction particle count test

ii. Microscopic particle count test

C. Test for sterility of ophthalmic products
D. Leak test

Test for pyrogens: It is used to check for the presence of pyrogens in the parenteral formulation. Two general tests are performed.

i. Rabbit test, and
ii. LAL test

Rabbit test: The pyrogen test is designed to limit to an acceptable level the risks of febrile reaction in the patient to the administration by injection of the product concerned. Unless otherwise specified in the individual monograph, inject into an ear vein of each of three rabbits 10 ml of the test solution per kg of body weight, completing each injection within 10 minutes after start of administration. The test solution is *either* the product, constituted if necessary as directed in the labeling, *or* the material under test treated as directed in the individual monograph and injected in the dose specified therein. Assure that all test solutions are protected from contamination. Perform the injection after warming the test solution to a temperature of 37 ± 2°. Record the temperature at 30-minute intervals between 1 and 3 hours subsequent to the injection.

Test interpretation: Consider any temperature decreases as zero rises. If no rabbit shows an individual rise in temperature of 0.5° or more above its respective control temperature, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.5° or more, continue the test using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.5° or more and if the sum of the eight individual maximum temperature rises does not exceed 3.3°, the material under examination meets the requirements for the absence of pyrogens.

LAL test: Limulus amebocyte lysate (LAL) is an aqueous extract of blood cells (amoebocytes) from the horseshoe crab, limulus polyphemus. LAL reacts with bacterial endotoxin or lipopolysaccharide (LPS), which is a membrane component of gram-negative bacteria. This reaction is the basis of the LAL test.

Method: Blood is removed from the horseshoe crab's pericardium and the blood cells are separated from the serum using centrifugation and are then placed in distilled water, which causes them to swell up and burst ("lyse"). This releases the chemicals from the inside of the cell (the "lysate"), which is then purified and freeze-dried. To test a sample for endotoxins, it is mixed with lysate and water, if endotoxins are present coagulation occurs.

Particulate evaluation: Parenteral solutions should be essentially free from particulate matter which can be observed on visual inspection. This test describes the physical tests performed to enumerate extraneous particles with specific size ranges. Particulate matter includes mobile, randomly sourced, extraneous substances, other than gas bubbles that cannot quantified by chemical analysis due to less amount and of their heterogeneous compositions.

Methods

i. Light obscuration method
ii. Microscopic method

Light obscuration method: This method applies for ophthalmic solution including solutions constituting form sterile solids, for which the test for particulate matter is specified in the individual monograph. The parenteral product meets the requirements of the test if the average numbers of particles present in the units tested does not exceed the appropriate value listed in Table 7.6. If the average number of particles exceeds this limit, the test article is subjected to microscopic method.

TABLE 7.6: Light obscuration particle count test

Test	*Diameter*	*Diameter*
	≥10 µm	≥25 µm
SVI	6000	600/container
LVI	25	3/ml

Microscopic method: This method is performed when some particles are not exactly detected by the light obscuration method. This test enumerates the sub visible particles essentially solid, particulate matter present in the parenteral preparation. The test sample is collected on a micro porous membrane filter. The USP injection meets the requirements of the test if the average number of particles present in the units tested does not exceed the appropriate value listed in Table 7.7.

TABLE 7.7: Microscopic method particle count test

	Diameter	*Diameter*
	≥10 µm	≥25 µm
SVI	3000	300/container
LVI	12	2/ml

Sterility Test

This is used to test the presence of micro-organisms in the test solution. It is done by 2 methods:

i. Membrane filtration method
ii. Direct inoculation (immersion) method

Membrane filtration method: In this the test solution is first passed through a size exclusion membrane capable of retaining the microorganisms. The concept is that the microorganisms will collect on the surface of a 0.45 micron pore size filter. The filter is rinsed and then the membrane is transferred to appropriate test medium as specified in the monograph.

Direct inoculation (immersion) method: In this test article is directly inoculated into the test medium and then the medium is incubated for the growth of microorganisms, if present.

Test media: The test media are fluid thioglycollate medium (FTM) and soyabean case in digest medium (SCDM). FTM is selected based upon its ability to support the growth of anaerobic and aerobic microorganisms. SCDM is selected based upon its ability to support a wide-range of aerobic bacteria and fungi (i.e. yeasts and molds).

Incubation time: In both the methods the test medium after the transferring of the test solution is to be incubated for 3 days in case of bacteria and 5 days in case of fungi and then the growth is compared with that of standard. If no growth is observed then the sample passes the test and it meets the GMP requirements.

The following table outlines the requirement for sterility testing as per USP. The requirement for sterility testing as per USP (Table 7.8).

TABLE 7.8: The requirement for sterility testing as per USP

Volume/container	*Minimum quantity to test in each media*
<1 ml	The entire contents of each container
1–40 ml	Half the contents of each container but not <1 ml
41–100 ml	20 ml
>100 ml	10% of the contents of the container, but not <20 ml

CONTAINER FOR PARENTERAL PRODUCTS

The container closure system is an intrinsic part of the parenteral product and is essential to delivery and handling of the pharmaceutical product. It defines the closure, protection, and functionality of a container while it ensures the safety and quality of the drug product over the product shelf life. Changes to components and materials, suppliers, and processing flow are also part of product life cycle. The selection of container is based on:

a. Composition of container
b. Composition of solution
c. Treatment to which it is to be subjected.

Container types

a. Plastic
b. Glass

Plastic

Thermoplastic polymers have been established as packaging materials for sterile preparations such as large-volume parenterals, ophthalmic solutions and small volume parenteral.

Advantages of plastic

i. Not breakable
ii. Less weight
iii. Flexible

Sterilization technique used for plastic containers: Ethylene oxide or radiation sterilization may be employed for the empty container with subsequent aseptic filling.

Disadvantages of plastics

i. Permeation of vapors and other molecules in either direction through the wall of the plastic container, e.g. permeation of volatile constituent and water.
ii. Leaching of constituents from the plastic into the product, e.g. constituent of plastic like plasticizer and antioxidant migrate into the product.

iii. Sorption (absorption and/or adsorption) of drug molecules or ions on the plastic material, e.g. sorption of insulin, vitamin A acetate, and warfarin sodium has been shown to occur on PVC bags.
iv. Not as clear as glass therefore inspection of contents is difficult.

Glass

Three types of: (Types I, Type II, and Type III) glass containers are all suitable for parenteral (injection or intravenous) preparations as specified by the US Pharmacopoeia on the basis of chemical durability tests.

Type I glass: Type I glass bottles are made from borosilicate, which have has a highly resistant composition and releases the least amount of alkali. It is commonly used for pharmaceutical or fine chemical products that are sensitive to pH changes.

Type II glass: Type II glass containers are made from commercial soda lime glass that has been de-alkalized to obtain a great improvement in chemical resistance by treating the interior surfaces at a high temperature to eat away the alkali on or near the glass surfaces. The undesirable characteristic of Type II glass is that the treating etches the surface, causing a frosted (snowy) appearance.

Type III glass: Type III glass bottles and containers are made of untreated commercial soda-lime glass and has average or somewhat above average chemical resistance.

Type NP glass: Untreated glass containers made of ordinary soda-lime glass. This glass cannot be used for parenteral preparations.

USP tests for determining glass type:

i. The powdered glass test
ii. The water attack test.

The water attack test is used only for Type II glass and is performed on the whole container, because of the dealkalized surface.

The powdered glass test is performed on powdered glass, which exposes internal surfaces of the glass compound. The results are based upon the amount of alkali titrated by 0.02 N sulfuric acid after an autoclaving cycle with the glass sample in contact with a high purity distilled water. Thus, the powdered glass test challenges the leaching potential of the interior structure of the glass while the water attack test challenges only the intact surface of the container.

Uses

i. Type I glass will be suitable for all products.
ii. Type II glass may be suitable, for example, for buffered solution, has a pH below 7, or is not reactive with the glass.
iii. Type III glass usually will be suitable principally for anhydrous liquids or dry substances.

Physical shapes: Ampoules and vials sizes are up to 100 ml and bottles can be of larger size (up to 1000 ml). The physical shapes of glass container can be (Fig. 7.11).

i. Ampoules
ii. Vials
iii. Glass bottles

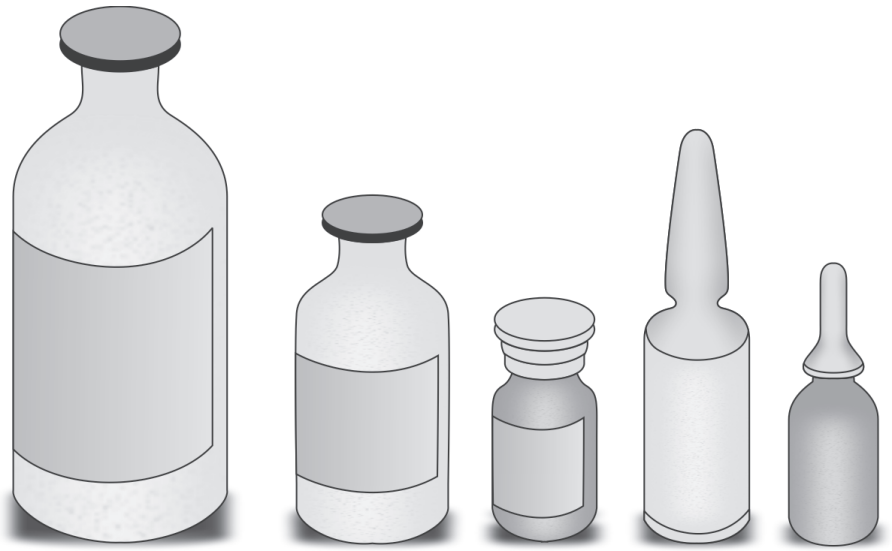


Fig. 7.11: Ampoules and vials

Desired Characteristics of Glass Container

i. Glass containers should be strong enough to withstand the physical shocks of handling and shipping and the pressure differentials that develop, particularly during the autoclave sterilization cycle.
ii. The container also must be transparent to permit inspection of the contents.
iii. Preparations that are light-sensitive must be protected by placing them in amber glass containers or by enclosing flint glass containers in opaque cartons labeled to remain on the container during the period of use. As amber color bottles can have impeachable iron, which can leach to parenteral preparation. To avoid leaching of iron silicon coating can be given over amber color glass.

CLOSURE FOR PARENTERAL PRODUCTS

Rubber Closures

Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders are made of materials obtained by vulcanisation (cross-linking) of macromolecular organic substances (elastomers), with appropriate additives. The elastomers are produced from natural or synthetic substances by polymerisation, polyaddition or polycondensation. The nature of the principal components and of the various additives (for example, vulcanisers, accelerators, stabilisers, pigments) depends on the properties required for the finished article. Rubber closures may be classified in 2 types.

Type I closures are those which meet the strictest requirements and which are to be preferred.

Type II closures are those which having mechanical properties suitable for special uses (for example, multiple piercing), cannot meet requirements as severe as those for the first category because of their chemical composition (Table 7.9).

TABLE 7.9: Components of rubber

Ingredient	*Examples*
Elastomer	Natural rubber (latex) butyl rubber neopene
Vulcanizing (curing) agent	Sulfur, peroxides
Accelerator	Zinc dibutyldithicarbamate
Activator	Zinc oxide, stearic acid
Antioxidant	Dilaryl thiodipropionate
Plasticizer, lubricant	Paraffinic oil, silicon oil
Fillers	Carbon black, clay, barium sulfate
Pigments	Inorganic oxides, carbon black

Criteria for Selecting Closure

The closures chosen for use with a particular preparation are such that:

i. The components of the preparation in contact with the closure are not adsorbed onto the surface of the closure and do not migrate into or through the closure to an extent sufficient to affect the preparation adversely.
ii. The closure does not yield to the preparation substances in quantities sufficient to affect its stability or to present a risk of toxicity.
iii. The closures are compatible with the preparation for which they are used throughout its period of shelf life.
iv. The closures are washed and may be sterilized before use.

Packaging, Labeling, and Storage of Injections

Containers for injections, including closures, must not interact physically and chemically with the preparation.

A. **Single-dose container:** A single dose container is a hermetic container holding a quantity of sterile drug intended for parenteral administration as a single dose, and which when opened cannot be re-sealed with assurance that sterility has been maintained.
B. **Multiple-dose container:** A multiple-dose container is a hermetic container that permits withdrawal of successive portions of the contents without changing the strengths, quality, or purity of the remaining portion.

The labels on containers of parenteral products must state

1. The name of the preparation.
2. For liquid preparation, the percentage content of the drug or amount of the drug; for dry preparation—the amount of the active ingredient present and the volume of liquid to be added to the dry preparation to prepare a solution or suspensions.
3. The route of administration.
4. Statement of storage conditions and expiration.
5. The name of the manufacturer and distributor.
6. The identifying lot number.

ISOLATED KEY POINTS

- Parenteral (derived from Greek word, *para enteron,* beside the intestine) dosage forms of drugs are injected directly into body tissue through one or more layer of skin and mucous.
- Intradermal (in or into the skin): An intradermal injection is given into the skin. It is used for skin testing some allergens, and also for Mantoux test for tuberculosis.
- Subcutaneous: Under the skin. "Subcutaneous" implies just under the skin.
- Intracavernous: An intracavernous (intracavernosal) injection is an injection into the base of the penis. This injection site is often used to administer medications to check for or treat erectile dysfunction in adult men.
- Intravitreal: Intravitreal (intravitreal is a route of administration of a drug, or other substance, in which the substance is delivered via an eye. "Intravitreal" literally means "inside an eye").
- Transscleral (trans- + sclera + -al) injected in to sclera. (Sclera: The white of the eye. It is the tough outer coat of the eye that covers the eyeball except for the cornea.)
- Intracerebral (L, intra + cerebrum, brain, pertaining to the area or substance within the cerebrum)—injected in cerebrum.
- Intrathecal—injection of a substance through the theca of the spinal cord into the subarachnoid space.
- Epidural—injection of an anesthetic substance into the epidural space of the spinal cord in order to produce epidural anesthesia.
- Intraosseous infusion (into the bone marrow)—this route is occasionally used for drugs and fluids in emergency medicine and pediatrics when intravenous access is difficult.
- Intracisternal: It is given between the first and second cervical vertebrae—used to withdraw cerebrospinal fluid for diagnostic purposes.
- Intravenous: Intravenous therapy or IV therapy is the giving of substances directly into a vein. The word intravenous simply means "within a vein".
- Intracardiac: Injection given into the heart, e.g. adrenaline during cardiopulmonary resuscitation, nowadays not commonly performed.
- Intramuscular: Intramuscular injection into a muscle, e.g. many vaccines, antibiotics, and long-term psychoactive agents.
- Intraarticular: Drug injected with in joints.
- Intraperitoneal, injection of a substance into the peritoneum (body cavity).
- Intra-arterial: Injected in to arteries.
- The most common routes of parenteral administration are intravenous (IV), subcutaneous (SC), and intramuscular (IM).
- Small-volume parenterals (SVPs): The US Pharmacopeia (USP) defines SVPs as containing less than 100 ml.
- Large-volume parenterals (LVPs): The US Pharmacopeia (USP) defines LVPs as containing more than 100 ml.
- Components of parenteral formulation are vehicles, additives/solute, isotonicity modifier.
- The vehicle of greatest importance is water, i.e. water for injection (WFI).
- "Water for injection (WFI) is water purified by distillation or reverse osmosis." WFI is produced by either distillation or 2-stage RO.

- Buffers are used primarily to stabilize a solution against pH, which result into reduction in the chemical degradation that might occur if the pH changes.
- Antioxidants are required to preserve products because of the ease with which many drugs are oxidized. Example are metal chelator, such as disodium edentate (0.05%) and an antioxidant compound, such as ascorbic acid or sodium metabisulfite (1%, and 0.3%, respectively).
- Tonicity agents are used in many parenteral and ophthalmic products to adjust the tonicity.
- There are five critical steps involved in preparation of parenteral products are compounding of product, filtration, filling, sealing—ampoules and vials, sterilization.
- Ampoules: Filled containers should be sealed as soon as possible to prevent the contents from being contaminated by the environment. Ampoules are sealed by melting a portion of the glass neck. Two types of seals tip-seals (bead-seals) and pull-seals.
- Lyophilization (freeze drying) is the removal of water from frozen material. It is an excellent method for preserving microbes and heat-sensitive materials such as proteins, plasma, etc.
- Three steps are involved in lyophilization are freezing, primary drying and secondary drying.
- Disinfection is the process of elimination of most pathogenic microorganisms (excluding bacterial spores) on inanimate objects.
- Sterilization can be effectively achieved at a temperature above 100°C using an autoclave.
- Quality control/evaluation tests for parenteral preparations are pyrogen test, test for particulate matter, light obstruction particle count test, microscopic particle count test, test for sterility of ophthalmic products, leak test.
- Presence of pyrogens in the parenteral formulation by two tests rabbit test and LAL test.
- Rabbit test: The pyrogen test is designed to limit to an acceptable level the risks of febrile reaction in the patient to the administration, by injection, of the product concerned.
- Limulus amebocyte lysate (LAL) is an aqueous extract of blood cells (amoebocytes) from the horseshoe crab, limulus polyphemus. LAL reacts with bacterial endotoxin or lipopolysaccharide (LPS), which is a membrane component of gram-negative bacteria.
- Parenteral solutions should be essentially free from particulate matter which can be observed on visual inspection.
- Sterility test is used to test the presence of micro-organisms in the test solution. It is done by two methods membrane filtration method and direct inoculation (immersion) method.
- Membrane filtration method: In this the test solution is first passed through assize exclusion membrane capable of retaining the micro-organisms.
- Direct inoculation (immersion) method: In this the test article is directly inoculated into the test medium and then the medium is incubated for the growth of micro-organisms, if present.

- Container types for parenteral are plastic and glass.
- Types I, Type II, and Type III glass containers are all suitable for parenteral (injection or intravenous) preparations as specified by the US Pharmacopoeia on the basis of chemical durability tests.
- Type I glass bottles are made from borosilicate, which have has a highly resistant composition and releases the least amount of alkali.
- Type II glass containers are made from commercial soda lime glass that has been de-alkalized to obtain a great improvement in chemical resistance by treating the interior surfaces at a high temperature to eat away the alkali on or near the glass surfaces.
- Type III glass bottles and containers are made of untreated commercial soda-lime glass and has average or somewhat above average chemical resistance.
- Untreated glass containers made of ordinary soda-lime glass. This glass cannot be used for parenteral preparations.
- USP tests for determining glass type are powdered glass test and water attack test.
- Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders.
- Containers for injections, including closures, must not interact physically and chemically with the preparation.
- A single dose container is a hermetic container holding a quantity of sterile drug intended for parenteral administration as a single dose, and which when opened cannot be re-sealed with assurance that sterility has been maintained.
- A multiple-dose container is a hermetic container that permits withdrawal of successive portions of the contents without changing the strengths, quality, or purity of the remaining portion.

PRACTICE QUESTIONS

Long Answer Type Questions

1. Define the term parenteral products? Give their advantages and disadvantages?
2. Give classification of parenteral products with the help of suitable examples, based on their route of administration?
3. Give classification of parenteral products with the help of suitable examples on the basis of their injection volumes?
4. Discuss in brief the various factors which can effect solubility of parenteral drugs?
5. Write in detail about the various components of parenteral formulation?
6. Name some common apparatus used for the production of water for injections?
7. Write short notes on:
   a. Non-aqueous vehicles used for parenteral
   b. Specification for purified water
   c. Water miscible vehicles
   d. Solutes

8. Write short notes on (reference to parenteral products)
   a. Antimicrobial agents
   b. Preservatives
   c. Buffers
   d. Anti-oxidant
9. Describe in detail about the various types of containers used for parenteral formulation.
10. What are the desired characteristics of parenteral container?
11. Write in brief about rubber closures and their criteria of selection for parenteral products?
12. Write in brief about the test done for parenteral closures?
13. Describe the methods used for preparation of parenteral suspension?
14. Describe the methods used for preparation for parenteral solution?
15. Enlist various important operations involved during formulation of parenteral preparation?
16. Give the classification of various methods of sterilization for parenteral products?
17. Write short notes on:
    a. Packaging of parenteral
    b. Labeling of parenteral
18. What is lyophilization? Give basics of lyophilization?
19. Enumerate various factors affecting efficiency of lyophilization?
20. Describe the evaluation test done for parenteral formulations?

Objective Type Questions

1. _____ dosage forms of drugs are injected directly into body tissue through one or more layer of skin and mucous.
2. The US Pharmacopeia (USP) defines small volume parenteral (SVPs) which contains _____ and large-volume parenterals (LVPs) containing _____ .
3. _____ is the removal of water from frozen material. It is an excellent method for preserving microbes and heat-sensitive materials such as proteins, plasma, etc.
4. The two USP tests for determining glass types are _____ and _____
5. Match the following:

S. No.	*Parenteral dosage form*		*Route of administration*
1.	Intradermal	a	Inside an eye
2.	Subcutaneous	b	Into the skin
3.	Intravitreal	c	Under the skin
4.	Intracavernous	d	Into the epidural space of the spinal cord
5.	Intrathecal	e	Into the base of the penis
6.	Epidural	f	Through the theca of the spinal cord
7.	Intraosseous infusion	g	Into the bone marrow
8.	Intravenous	h	Into the peritoneum
9.	Intra-articular	i	Within a vein
10.	Intraperitoneal	j	With in joints

6. Match the following:

S. No.	*Type of glass*		*Material used*
1.	Type I glass	a	Treated soda lime glass
2.	Type II glass	b	Ordinary soda-lime glass
3.	Type III glass	c	Untreated soda lime glass
4.	Type NP glass	d	Highly resistant borosilicate glass

7. Which of the following is the evaluation tests for parenteral preparations?
a. Pyrogen test and test for particulate matter
b. Light obstruction particle count test and microscopic particle count test
c. Test for sterility of ophthalmic products and powder attack test
d. a and b
e. All of the above

ANSWERS

1. Parenteral
2. Less than 100 mL, more than 100 ml
3. Lyophilization (freeze drying)
4. Powdered glass test, water attack test
5. 1—b, 2—c, 3—a, 4—e, 5—f, 6—d, 7—g, 8—I, 9—j, 10—h.
6. 1—d, 2—a, 3—c, 4—b
7. d

Chapter
8

Ophthalmic Preparations

Eye is unique and very precious organ. It is considered as window of the soul. We can enjoy and viewed the whole world only with this organ. There are many eye ailments which affect this organ and can loss the eye sight also. Therefore, many ophthalmic drug delivery systems are available. These are classified as conventional and newer drug delivery systems. Most commonly available ophthalmic preparations are eye drops and ointments. But these preparations when instilled into the cul-de-sac are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage. Only a small amount is available for its therapeutic effect resulting in frequent dosing.

"Ophthalmic products are the sterile products meant for instillation in to the eye in the space between eyelid and the eyeball. These products must be sterile ophthalmic products includes eye drops, eye lotion, eye ointment, eye suspension, contact lens solution."

Topical administration for ocular therapeutics is ideal because of smaller doses required compared to the systemic use, its rapid onset of action and freedom from systemic toxicity topically applied ocular drugs have to reach the inner parts of the eye and transcorneal penetration is believed to be the major route for drug absorption. Corneal absorption is much slower process than elimination. To optimize topical ocular drug delivery system prolonged contact time with the corneal surface and better penetration through cornea is necessary.

PHYSIOLOGY OF EYE

The eyeball has three regions namely outer most core which comprises transparent cornea and white opaque sclera, middle which contains iris anteriorly, the choroids and the ciliary body posteriorly and the last layer contains retina which is an extension of central nervous system. Ophthalmic preparations are generally act at cornea and this region acts as the gate way for these formulations. The penetration of drugs through the cornea is dependent on the stroma epithelium of the cornea. This layer is of bilipid layer, i.e. fat-water-fat structure and thus control passage of drugs. The aqueous humor and the vitreous humor constitute fluid systems in the eye. This fluid escapes through the posterior part and anterior part (Fig. 8.1).

The ocular drugs applied topically are intended for the local action or for penetration into the anterior chamber and thus distributes to whole tissues of the eye. Some of the characters required for optimizing the ocular drug delivery system are:

i. Good corneal penetration
ii. Prolong contact time with corneal tissue

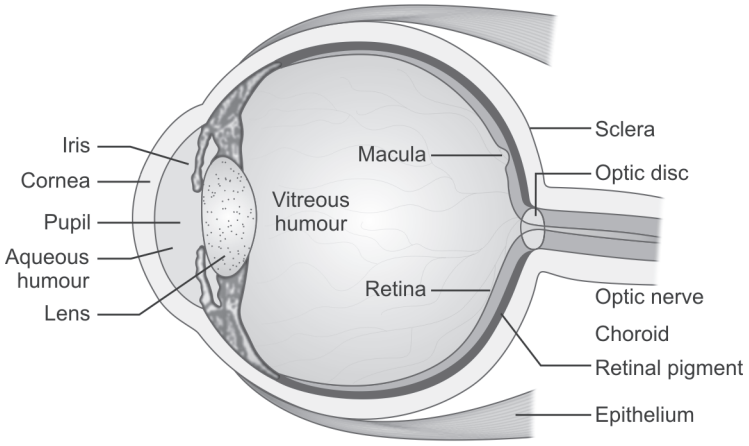


Fig. 8.1: Physiology of eye

iii Simplicity of instillation for the patient
iv. Sterility of the product
v. Non-irritative and comfortable form (viscous solution should not provoke lachrymal secretion and reflex blinking)
vi. Appropriate rheological properties and concentrations of the viscous system.

Characteristics of Ideal Ophthalmic Formulations

i. Ophthalmic solutions should be free from foreign particles.
ii. Opthalmic suspensions are to be prepared for insoluble drug particles. They should be redispersed on shaking the container.
iii. There should not be any leakage from the finished dosage form of ointment and it should be free from larger particles and it must meet the requirements of metal particles.

For achieving the drug delivery through the eye, different methods were followed like:

1. Using different grades of polymers
2. Preparation of viscous gels
3. Colloidal preparations
4. Using erodible and non-erodible inserts which prolong the drug retention time at cornea.

Various Types of Ophthalmic Products

1. Eye drops
2. Eye lotions
3. Contact lens solution
4. Eye ointments

Eye drops: These are the aqueous or oily solutions or suspensions that are instilled into the conjuctival sac of the eye. These are used as anaesthetics, anti-inflammatory

agents, antiseptics, diagnostic agents, mitotics, mydriatics and artificial tears, e.g. atropine sulphate eye drops BPC, hyoscine eye-drops BPC, physostigmine eye drops BPC. Requirements for an ideal eye drops product are

i. Should be sterile in condition
ii. Absence of foreign particles
iii. They should not cause any pain and irritation

Ophthalmic solutions are the most common dosage form for delivering the drug to the eye. As it is solution all the ingredients are completely soluble and there is almost no physical inference with the eye sight. The disadvantage of these solutions is the contact time of drug is less with the absorbing tissue. Efforts have been made to improve this contact time by including the viscosity enhancing agents but their use is restricted to low viscosities only because the drops can be dispensed through the eye droppers and to minimize the blurring the vision. Generally the viscous solutions produce residue on eye lashes and around eye if they are spilled during dispensing. It can be easily removed by wiping with moist cloth to closed eye.

Eye-lotions: These are the aqueous solutions that are used in undiluted condition for bathing the eye in first aid or in home, e.g. sodium chloride eye lotion.

Contact lens solutions: These are the aqueous solutions intended for lubricating, cleaning and hydrating contact lenses, e.g. thimerosal contact lens solution.

Eye ointments: These are placed in the conjunctival sac or applied to the margins of the eyelids, e.g. bacitracin ophthalmic ointment.

Recent Advances in Ophthalmic Drug Delivery

New ophthalmic delivery system includes ocular in-serts, collagen shields, ocular films, disposable contact lens and other novel drug delivery systems like liposomes and nanoparticles. Newer trend is a combination of drug delivery technologies for improving the therapeutic response of a non-efficacious drug. This can give a superior dosage forms for topical ophthalmic application.

Formulation Consideration for Ophthalmic Products

All ophthalmic products are required to be sterile and free from extraneous particulate matter. Solutions used during surgery should not contain any preservative. Ophthalmic preparations should be checked for the following properties:

1. Foreign particles
2. Viscosity
3. Tonicity
4. pH of preparations
5. Sterility
6. Surface activity

Foreign particles: All the ophthalmic products should be clear and free from foreign particles, fibers and filaments. Ophthalmic solutions should be clarified very carefully by passing through bacteria proof filters such as membrane filters, sintered glass filters. The particle size of the eye suspension should be in an ultrafine state of subdivision to

minimize irritation. A separate filter should be used for different ophthalmic products in order to avoid the contamination.

Viscosity: In order to prolong the contact time of the drug in the eye, various thickening agents are added in the ophthalmic preparations. Polyvinyl alcohol (1–4%), polyethylene glycol, methyl cellulose, carboxy methyl cellulose is some of the commonly used thickening agents. These agents improve the viscosity of the preparation. An ideal thickening agent should possess the following properties:

i. It should be easy to filter.
ii. It should be easy to sterilize.
iii. It should be compatible with other ingredients.
iv. It should possess requisite refractive index and clarity level.

Thickening agents are not included in the formulation of eye drops and eye lotions, which are required to be used during or after surgery due to some possible adverse effects on the interior of the eye.

Tonicity: Ophthalmic products should be isotonic with lachrymal secretions to avoid discomfort and irritation. It has been observed that eye can tolerate a range of tonicity from 0.5 to 2% NaCl. There are certain isotonic vehicles which are used to prepare ophthalmic products like 1.9% boric acid, sodium acid phosphate buffer.

pH of the preparations: pH plays an important role in therapeutic activity, solubility, stability and comfort to the patient. Tears have a pH of about 7.4. Eye can tolerate solution having wide range of pH provided they are not strongly buffered, since the tear will rapidly restore the normal pH value of the eye. There are times, when formulator needs to make balance between stability and manufacturability point of view, e.g. alkaloid salt solutions are stable at pH 2–3 but this pH is irritant to eye. The alkaloids get precipitated at pH above 7 and create a number of formulation problems.

Sterility: Ophthalmic preparations must be sterile when prepared. *Pseudomonas aeroginosa* is very common gram-negative bacteria which is generally found to be present in ophthalmic products. It may cause serious infections of cornea. It can cause complete loss of eye sight in 24–48 hrs. To maintain sterility in multi-dose container, containing ophthalmic products, a suitable preservative is added. The preservative should be non-toxic, non-irritant and should be compatible with medicaments. The ophthalmic products are generally sterilized by autoclaving, filtration through bacteria proof filters and addition of bactericides at low temperature.

Surface activity: Vehicles used in ophthalmic preparations must have good wetting ability to penetrate cornea and other tissues. Certain surfactants or wetting agents added which are found suitable for ophthalmic products. It should not cause any damage to the tissue of eye. Benzalkonium chloride, polysorbate 20, polysoabate 80, dioctyl sodium sulpho succinate, etc. are some of the surfactants which are commonly used.

METHODS OF PREPARATION OF OPHTHALMIC PRODUCTS

Eye Drops

Eye drops are sterile aqueous or suspensions of drug that are instilled into the eye with a dropper. They usually contain drugs having antiseptic, antianesthetic, anti-

inflammatory, mydriatic or meiotic properties. In the formulation of eye drops following things are done:

i. Drug
ii. Preservative
iii. Sterilization
iv. Isotonicity modifier
v. Buffer
vi. Viscosity
vii. Container
viii. Label

i. Drug: These contains drug of various categories including antiseptic, anti-inflammatory agent, mydriatric or meiotic properties.

ii. Preservative: Eye drop should be sterile and should contain preservatives to avoid microbial contamination when the container is open. The preservative for ophthalmic use includes benzalkonium chloride, chlorbutanol, phenylmercuric acetate, phenylmercuric nitrate, etc.

iii. Sterilization: Eye drops are sterilized by autoclaving at 121°C for 15 minutes or by bacteria filter to avoid thermal degradation; for example—preservative chlorbutanaol hydrolyzes at high temperature.

iv. Isotonicity modifier: All the solutes including drug contribute to the osmotic pressure of the eye drop, therefore, isotonicity of the formula should be calculated and it is adjusted with sodium chloride, for example—sodium chloride 0.9% and boric acid 1.9% are iso-osmotic.

v. Buffer: The buffer should be added to maintain balance between comfort, solubility, stability and activity of drug. For example, the hydrolyzed chlorbutanol forms hydrochloride acid making the drop acidic, whereas certain drug like pilocarpine hydrochloride are acidic. On the other hand certain drug such as alkaloids shows precipitation at lachrymal pH. Boric acid, monobasic sodium phosphate are the common buffers for eye drop.

vi. Viscosity: The size of drop and its residences in eye depends on viscosity of eye drops. Methylcellulose, hydroxypropyl methylcellulose and polyvinyl alcohol are common viscosity enhancer.

vii. Container: The commonly used container for ophthalmic solutions or suspension is multi-dose container (5 ml, 10 ml). Glass container is supplied with sterile plastic dropper. Plastic bottles are with built-up nozzle.

viii. Label: Not for injection. For external use only. Shake well before use (if it is suspension).

Method of preparation: The eye drops are prepared in 4 stages. These stages are as under:

A. Preparation of bactericidal and fungicidal vehicle: The aqueous or oily vehicle is used in preparation of eye drops. The aqueous vehicle may support bacterial or fungal growth, so one of the following bactericide may be used to prepare the eye drops: Phenyl mercuric nitrate/acetate—0.002%, benzalkonium chloride—0.01%, chlorhexidine acetate—0.01%.

B. Preparation of solution of medicaments and adjuvant: The medicaments are dissolved in the aqueous vehicle containing suitable antimicrobial agent. The adjuvants are also dissolved in the vehicle at a stage to form a stable preparation.
C. Clarification: The eye drops are clarified by passing the solutions through membrane filter having pore size of 0.8 µm. The clarified solution is immediately transferred in to final containers and sealed to exclude microorganisms.
D. Sterilization: The eye drops are sterilized by autoclaving or heating with bactericide at 98° to 100°C for 30 minutes, or filtration through bacteria proof filter.

Containers: The eye drops should be packed in neutral glass containers or in suitable plastic containers. In olden days the eye drops are stored in vertically fluted amber colored glass bottles fitted with a bakelite cap carrying a dropper. The bottle must confirm to limit test for alkalinity of glass. Nowadays neutral glass small bottles having capacity of 4 ml to 8 ml are used. It has two poly propylene screw caps, one for attaching a silicone rubber teat to the container and the other for covering the teat. The plastic squeeze bottles having ridged plastic cap and polythene friction plug containing baffle that produces uniform drops are also used these days. These are very handy. These bottles are sterilized by gaseous sterilization method.

Eye Lotion

Eye lotions are the sterile aqueous solutions used for washing of the eyes. The eye lotions are supplied in concentrated form and are required to be diluted with warm water immediately before use. They are usually applied with a clean eye-bath or sterilized fabric dressing and a large volume of solutions is allowed to flow quickly over the eye. Eye lotions should be isotonic and free from foreign particles to avoid irritation to the eye. They are required to be prepared fresh and should not be stored for more than two days as the lotion may get contaminated include sodium chloride, sodium bicarbonate, boric acid, borax or zinc sulphate.

Formulation of eye lotion: Eye lotions are simple solution. They are iso-osmotic with tears because they cause much greater dilution of the lachrymal fluid and hence are more likely to cause discomfort if not adjusted. The eye lotion should be sterile because the large volume is used to prevent irritation of the eyes. While removing the irritation from the eye, it become more susceptible to infection. The eye lotions are sterilized by autoclaving or by passing through bacteria proof filters. Sodium chloride eye lotion and sodium bicarbonate eye lotion are commonly used to remove foreign substance from the eye.

Preparation of eye lotion: To prepare and submit ml of sodium chloride eye lotion BPC.

Rx
Sodium chloride 9 gm
Purified water to produce 1000 ml.

Method: Dissolve sodium chloride in purified water and made the final volume by adding more of purified water. Filter through sintered glass filter grade 4. The eye lotion is transfer to the bottle. Close and sealed the bottle sterilizes it by auto-claving.

Eye Ointments

Eye ointments are sterile preparation meant for application to the eye. These are prepared under aseptic conditions and packed in sterile collapsible tubes which keep the preparation sterile until whole of it is consumed. Nowadays eye applicaps are available which contain only one application of the eye-ointment preparation:

Formulation of eye ointments: The ointment based for an eye-ointment must be no-irritating to the eye. The eye ointment base should melt near to the body temperature, so as to permit the diffusion of the drug through the lachrymal secretions of the eye. For the preparation of eye-ointment the base used are Yellow soft paraffin 80 g liquid paraffin 10 g wool fat 10 g.

Methods of preparation of eye ointments: Melt wool fat, soft paraffin on a water bath. Add liquid paraffin. Filter through coarse filter placed in heated funnel. It is sterilized by dry heat method (160°C for 2 hours). Incorporate the medicament with the eye ointment base. Pack in sterile containers.

Eye Suspension

Ophthalmic suspensions are also easily placed into the eye. In general, suspensions produce a longer effect than do solutions. Suspensions do have one disadvantage; it is difficult to ensure that the suspension does not contain particles large enough to produce eye irritation. Eye suspensions are not commonly used as compared to eye drops. They are prepared only in those cases, when the drug is insoluble in the desired vehicle or unstable in liquid form.

Contact Lenses

Contact lenses are usually made from polymethyl-methacrylate, a hard hydrophobic plastic, but some softer hydrophilic lenses have been developed and are coming to use.

Types of contact lenses

1. Hard contact lenses
2. Soft contact lenses

Hard contact lenses: Wearers of hard contact lenses generally use two solutions.

A wetting solution, which is used primarily for treating the lenses before insertion.

A storage solution, which is used for overnight cleansing, soaking and storage.

Wetting solutions, because of its hydrophobic nature, polymethyl methacrylate is poorly wetted by the lachrymal fluid and requires moistening with a wetting agent to render the surface hydrophilic and make insertion easy and comfortable. Unlike most eye-drops, contact lens solutions are used daily for years and, therefore, they should be exceptionally bland. They may contain

i. A wetting agent
ii. An antimicrobial agent
iii. A substance for adjusting the osmotic pressure
iv. A buffering agent
v. A thickening agent

vi. Storage solutions
vii. A mixture of antimicrobial agents

i. **Wetting agent:** A wetting agent polyvinyl alcohols, which are strongly hydrophilic, and polysorbate 80, a non-ionic surfactant in which hydrophilic groups predominate, are examples. Polyvinyl alcohols are obtained from polyvinyl acetate by hydrolysis and may contain traces of the parent compound from which irritating amounts of acetic acid may be liberated at neutral or alkaline pHs. Hence, solutions are often adjusted to a pH between 5 and 6. Polysorbate 80, at concentrations of 0.5 percent and above, inactivates benzalkonium chloride and chlorhexidine acetate and at lower concentrations may increase or decrease their activity according to the conditions. Thus, it is to be used in optimum amount with appropriate antimicrobial agents.
ii. **An antimicrobial agent:** Prolonged use of solutions containing the concentrations of antimicrobial agents recommended for eye-drops may cause irritation or allergic reactions. Consequently, lower levels are used in lens solutions, e.g. benzalkonium chloride 0.004 percent, chlorhexidine acetate 0.005 to 0.006% and chlorbutol 0.3 to 0.4 percent. Using more than one antimicrobial agent is a way of reducing the concentration of each and, at the same time, maintain an acceptable level of preservative activity. For example, disodium edentate (0.1 to 0.2%) may be combined with benzalkonium chloride, benzalkonium chloride and chlorbutol or benzalkonium chloride and chlorhexidine acetate. Studies show that phenyl ethyl alcohol enhances the activity of all bactericides commonly used in eye solutions and is not inactivated by up to 1% of polysorbate 80; but so far this compound has not been used in wetting solutions.
iii. **A substance for adjusting the osmotic pressure:** It is desirable to adjust wetting solutions to approximately the same osmotic pressure as lachrymal secretion by adding sodium chloride alone or with potassium chloride. Wearing contact lenses seems, by interfering with corneal metabolism, to increase the sensitivity of the eye to solutions that are not iso-osmotic with tears.
iv. **A buffering agent:** Hypromellose eye drops BPC, which is sometimes used as a contact lens solutions, is buffered to pH 8.4 to 8.6 with boric acid and borax. Sodium bicarbonate 2%, an early contact lens solution, has a pH of about 8.2 and is well tolerated.
v. **A thickening agent:** Comfort is significantly increased if the solution contains a substance that raises the viscosity, e.g. polyvinyl alcohols or the cellulose derivatives. The thickener must be compatible with the preservative(s) and produce a clear solution that does not interfere with vision. Generally, the vehicle for lens solutions is properly stored purified water; tap water is unsuitable because it contains salts, that may cause deposits, and chlorine, which may be irritating.
vi. **Storage solutions:** Hydrophobic lenses attract hydrophobic substances from the eyelids, fingers, etc. and, therefore, require cleaning after use. After removal they are wetted with the wetting solution and rubbed between well-scrubbed fingers until they appear clear after rinsing with purified water. Then they are stored in a soaking solution intended to continue the cleaning process and prevent dehydration. Storage solutions usually contain non-ionic surface active agent to aid cleaning.

vii. **A mixture of antimicrobial agents:** The concentrations can be greater than in wetting solutions because storage solutions are not used in the eye. The solution is changed every few days because the preservatives may be partially inactivated by organic debris.

Soft contact lenses: These are soft flexible type of lenses. Certain medicaments from wetting and storage solutions are strongly absorbed by the soft contact lenses. Due to these reason patients wearing soft lenses should be advised to remove them before instilling eye drops. For cleaning soft contact lenses are heated in 0.9% sodium chloride solution. The wetting and storage solutions formulated for hard lenses must never be used. Special proprietary storage solutions are available. Wetting is not a problem because of the hydrophilic nature of lens. Contact lens solutions should be sterile.

EVALUATION TESTS FOR OPHTHALMIC PREPARATIONS

1. Particle size determination
2. Test for clarity of ophthalmic solutions
3. Test for pH of the solution
4. Test for particulate matter
   i. Light obstruction particle count test
   ii. Microscopic particle count test
5. Test for sterility of ophthalmic products
6. Pyrogen test

Particle Size Determination

The desired particle size of the suspension is 5–10 µm or less. Eyes show sensitivity to the particle size of 20 µm or more. The particle size of the ophthalmic suspension is to be determined as it affects the drug absorption and larger size of the particles cause irritation to the ocular tissue.

1. **Optical microscopy:** Particle size can be measured microscopically by sizing and counting, but for a statistically valid analysis, millions of particles must be measured. This is impossibly arduous when done manually, but automated analysis of electron micrographs is now commercially available. Instruments such as the Retsch Camsizer can perform this analysis on the run using standard camera technology.
2. **Sieve analysis:** In this the particles of a powder mass are placed on screen made of uniform apertures. By the application of some type of motion to the screen the particles of larger size retain on the screen and smaller ones pass through other screens. Sieves measuring particle size of 5 µ are available now with the introduction of electroformed screens.
3. **Coulters counter method (electroresistance counting methods):** In this the momentary changes in the conductivity of a liquid passing through an orifice is measured when individual non-conducting particles pass through. The particle count is obtained by counting pulses, and the size is dependent on the size of each pulse.

   Technique advantages: Very small sample aliquots can be examined.

   Technique disadvantages: Sample must be dispersed in a liquid medium as some particles may (partially or fully) dissolve in the medium altering the size distribution.

The results are only related to the projected cross-sectional area that a particle displaces as it passes through an orifice. This is a physical diameter, not really related to mathematical descriptions of particles (e.g. terminal settling velocity)

4. **Acoustic spectroscopy or ultrasound attenuation spectroscopy:** In this method ultrasound is employed for collecting information on the particles that are dispersed in fluid. Dispersed particles absorb and scatter ultrasound similarly to light. It turns out that instead of measuring *scattered energy versus angle*, as with light, in the case of ultrasound, measuring the *transmitted energy versus frequency* is a better choice. The resulting ultrasound attenuation frequency spectra are the raw data for calculating particle size distribution. It can be measured for any fluid system with no dilution or other sample preparation. Calculation of particle size distribution is based on theoretical models that are well verified for up to 50% by volume of dispersed particles.
5. **Laser diffraction methods:** These depend upon analysis of the "halo" of diffracted light produced when a laser beam passes through a dispersion of particles in air or in a liquid. The angle of diffraction increases as particle size decreases. This method is particularly good for measuring sizes between 0.1 and 3,000 µm. A particular advantage is that the technique can generate a continuous measurement for analyzing process streams.

Tests for Clarity of Ophthalmic Solutions

1. **Clarity of the solution:** Retention of clarity of solution is a main concern regarding stability of solution. In this a microscopic light is projected though a diaphragm into the solution. The solution will remain clear if there are no undissolved particles. If not the solution appears hazy due to the scattering of light by undissolved particles. Light scattering instruments are most widely used to test the clarity of the solution.
2. **Test for particulate matter in ophthalmic solutions:** Ophthalmic solutions should be essentially free from particulate matter which can be observed on visual inspection. This test describes the physical tests performed to enumerate extraneous particles with specific size ranges. Particulate matter includes mobile, randomly sourced, extraneous substances, other than gas bubbles that cannot quantified by chemical analysis due to less amount and of their heterogeneous compositions.

Methods

i. Light obscuration method
ii. Microscopic method

Light obscuration method: This method applies for ophthalmic solution including solutions constituting form sterile solids, for which the test for particulate matter is specified in the individual monograph. The ophthalmic product meets the requirements of the test if the average numbers of particles present in the units tested does not exceed the appropriate value listed in Table 8.1.

TABLE 8.1: Light obscuration particle count test

	Diameter	*Diameter*
	≥10 µm	≥25 µm
Number of particles	50 per ml	5 per ml

If the average number of particles exceeds this limit, the test article is subjected to microscopic method.

Microscopic method: This method is performed when some particles are not exactly detected by the light obscuration method. This test enumerates the subvisible particles essentially solid, particulate matter present in the ophthalmic solutions. The test sample is collected on a micro porous membrane filter. The ophthalmic product meets the requirements of the test if the average number of particles present in the units tested does not exceed the appropriate value listed in Table 8.2.

TABLE 8.2: Microscopic method particle count test

	Diameter		
	≥10	≥25	≥50
Number of particles	50 per ml	5 per ml	2 per ml

Test for Sterility

This is used to test the presence of micro-organisms in the test solution. It is done by two methods.

i. Membrane filtration method
ii. Direct inoculation (immersion) method

Membrane filtration method: In this the test solution is first passed through asize exclusion membrane capable of retaining the micro-organisms. The concept is that the microorganisms will collect on the surface of a 0.45 micron pore size filter. The filter is rinsed and then the membrane is transferred to appropriate test medium as specified in the monograph.

Direct inoculation (immersion) method: In this the test article is directly inoculated into the test medium and then the medium is incubated for the growth of micro-organisms if present.

Test media: The test media are fluid thioglycollate medium (FTM) and soybean casein digest medium (SCDM). FTM is selected based upon its ability to support the growth of anaerobic and aerobic microorganisms. SCDM is selected based upon its ability to support a wide range of aerobic bacteria and fungi (i.e. yeasts and molds).

Incubation time: In both the methods the test medium after the transferring of the test solution is to be incubated for 3 days in case of bacteria and 5 days in case of fungi and then the growth is compared with that of standard. If no growth is observed then the sample passes the test and it meets the GMP requirements. The following table outlines the requirement for sterility testing as per USP. The requirement for sterility testing as per USP (Table 8.3).

TABLE 8.3: The requirement for sterility testing as per USP

Volume/container	*Minimum quantity to test in each media*
<1 ml	The entire contents of each container
1–40 ml	Half the contents of each container but not <1 ml
41–100 ml	20 ml
>100 ml	10% of the contents of the container, but not <20 ml

Test for Pyrogens

It is used to check for the presence of pyrogens in the ophthalmic formulation. Two general tests are performed.

i. Rabbit test, and
ii. LAL test

Rabbit test: The pyrogen test is designed to limit to an acceptable level the risks of febrile reaction in the patient to the administration, by injection, of the product concerned. Unless otherwise specified in the individual monograph, inject into an ear vein of each of three rabbits 10 ml of the test solution per kg of body weight, completing each injection within 10 minutes after start of administration. The test solution is *either* the product, constituted if necessary as directed in the labeling, *or* the material under test treated as directed in the individual monograph and injected in the dose specified therein. Assure that all test solutions are protected from contamination. Perform the injection after warming the test solution to a temperature of 37 ± 2°. Record the temperature at 30-minute intervals between 1 and 3 hours subsequent to the injection.

Test interpretation: Consider any temperature decreases as zero rise. If no rabbit shows an individual rise in temperature of 0.5° or more above its respective control temperature, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.5° or more, continue the test using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.5° or more and if the sum of the eight individual maximum temperature rises does not exceed 3.3°, the material under examination meets the requirements for the absence of pyrogens.

LAL test: Limulus amebocyte lysate (LAL) is an aqueous extract of blood cells (amoebocytes) from the horseshoe crab, *Limulus polyphemus*. LAL reacts with bacterial endotoxin or lipopolysaccharide (LPS), which is a membrane component of gram-negative bacteria. This reaction is the basis of the LAL test.

Method: Blood is removed from the horseshoe crab's pericardium and the blood cells are separated from the serum using centrifugation and are then placed in distilled water, which causes them to swell up and burst ("lyse"). This releases the chemicals from the inside of the cell (the "lysate"), which is then purified and freeze-dried.

To test a sample for endotoxins, it is mixed with lysate and water; endotoxins are present, if coagulation occurs.

Test for Ophthalmic Gels, Suspensions and Ointments

Viscosity measurement: By Brookfield viscometer and cone and plate viscometer.

The flow of fluids through the dropper or tube is influenced by viscosity of the product. In order to have a better flow and to maintain residence time in the eye, the viscosity of the formulation should be checked under controlled temperature.

Brookfield viscometer: It measures the shearing stress on a spindle rotating at a definite, constant speed while immersed in the sample. The degree of spindle lag is indicated on a rotating dial. This reading multiplied by a conversion factor based on spindle size and rotational speed, gives a value for viscosity in centipoise (Fig. 8.2).

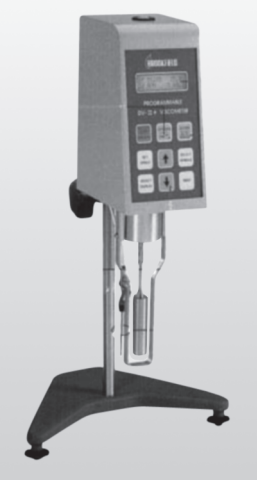


Fig. 8.2: Brook-field viscometer

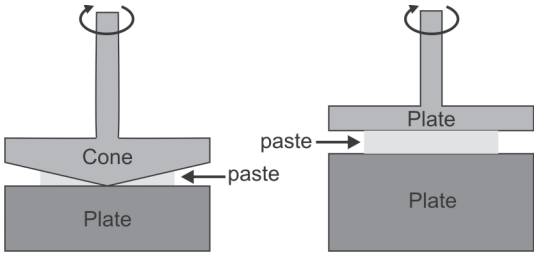


Fig 8.3: Representation of cone and plate, plate and plate viscometers

Cone and plate viscometer: It used a cone of very shallow angle in bare contact with a flat plate. With this system the shear rate beneath the plate is constant to a modest degree of precision and deconvolution of a flow curve; a graph of shear stress (torque) against shear rate (angular velocity) yields the viscosity in a straight forward manner (Fig. 8.3).

Consistency measurement: It is the measure of penetration of an object into the product to be examined in a container with a specified shape and size. In this the test sample is placed on the base of the penetrometer such that its surface is perpendicular to the vertical axis of penetrating object. The temperature of the penetrating object is maintained at 25+/–0.5°C and then its tip is adjusted such that it just touches the surface of the sample. The penetrating object if released and hold it for 5 sec. then the penetrating object is clamped and the depth of penetration is measured. The test is repeated for 2 remaining containers (Fig. 8.4).



Fig: 8.4: Penetrometer

Texture analysis: It is primarily concerned with the evaluation of mechanical characters when the material is subjected to controlled force which cause deformation of the sample. Texture analyzer which is used to detect ointment flow characteristic, e.g. brookfield CT3 texture analyser. In this the sample is subjected to controlled forces in compression using a probe or in tension using grips. The resistance of the sample material to these forces is measured by a calibrated load cell and is expressed in either gram of newton. These forces are a function of the properties of the sample and the parameters of the test method (Fig. 8.5).

Gel strength: Gels have gained wide acceptance as semisolid dosage forms. It has been postulated that the strength rather than the viscosity of a gel layer plays a major



Fig. 8.5: Brookfield CT3 texture analyser

role in determining the amount of drug release from hydrophilic matrices. Recent advances have occurred in the development of an optimal apparatus to characterize gel strength. The apparatus consists of a sample holder placed on an electronic microbalance connected to a computer. A probe is lowered into the sample by means of a motor equipped with a speed transformer, and the force required to penetrate the gel is measured. The increase in force with time is a function of the mechanical resistance of the sample to the penetration of the probe. Because the lowering speed is known, the displacement covered by the probe as a function of time is calculated and used to compute the gel-strength parameter or mechanical resistance of the gel system.

Sachet or tube extrusion force measurement: In this the device quantifies the force required to extrude the contents from either tube or sachet style packaging that allows the manufacturers to tests the force required to extrude the content of a sachet or tube at regular intervals over a long period of time, throughout its shelf-life.

Test for antimicrobial effectiveness: Generally an antimicrobial agent is used in multiple dose units of ophthalmic products for from microbial contamination that may occur during the suck back of an unreleased drop, when the pressure is released after withdrawal of the product. Organisms like *Pseudomonas* and *Staphylococcus* species cause eye infections mostly. So there is need to check the efficacy of the antimicrobial agent against these microorganisms. In this cultures of *Candida albicans, Aspergillus niger, Escherichia coli, Pseudomonas aeuroginosa, Staphylococcus aureus* are used. In this a standardized inocula of microorganisms is prepared with a count of 10^5–10^6 per ml. This is used to test the preserved formula. They are incubated for 28 days at 20–25°C and observed for the preservative action at 7, 14, 21 and 28 days. The products preservative action is found to be effective if it satisfies the following:

i. There should be reduction of no more than 0.1% of viable bacteria with that of initial concentrations by day 14th.
ii. There should be decrease in concentration of viable yeasts and molds when compared to initial by day 14th.
iii. The concentration of remaining viable organisms should be lower as designated at the end of 28th day.

Cidal test: This is another test employed to determine antimicrobial agent efficacy. In this the formulation is tested against 5–14 species of microorganisms including gram –ve, gram +ve, yeast, and fungi in previously standardized inoculums. Cidal times (growth of microorganisms) are measured within 24, 48 and 72 hours of contact.

CONTAINERS

1. **Single dose containers:** It is minimum unit and consists of a disposable, pliable, tube-like applicator made from polypropylene by ultrasonic sealing. It has a nozzle protected by a cap. It is generally enclosed in a heat-sealed envelope.
2. **Multiple application containers:** The traditional container for eye drops is a glass bottle carrying in the cap a dropper fitted with a teat. The containers are amber colored container to provide protection from light, made from neutral or treated soda glass, screw capped bottle with separate droppers.

LABELLING

Comply with the general requirements for labelling, following information is mentioned on the label clearly.

1. Name and concentration of medicaments.
2. Name and concentration of antimicrobial agent.
3. Date after which the product is not intended to be used.
4. Discard the contents at a specified time after opening (about one month).
5. If any discomfort or irritation discontinue use of the eye drop.
6. 'For external use only'.

ISOLATED KEY POINTS

- Ophthalmic products are the sterile products meant to instillation into the eye in the space between eyelid and the eyeball.
- These products must be sterile ophthalmic products include eye drops, eye lotion, eye ointment, eye suspension, contact lens solution".
- The eyeball has three regions, namely outer most core which comprises transparent cornea and white opaque sclera, middle which contains iris anteriorly, the choroids and the cilliary body posterioirly and the last layer contains retina which is an extension of central nervous system. Ophthalmic solutions should be free from foreign particles.
- Various types of ophthalmic products are: (1) Eye drops, (2) eye lotions, (3) contact lens solution, (4) eye ointments.
  - Eye drops: These are the aqueous or oily solutions or suspensions that are instilled into the conjuctival sac of the eye. These are used as anaesthetics, anti-inflammatory agents, antiseptics, diagnostic agents, mitotics, mydriatics and artificial tears, e.g. atropine sulphate.
  - Eye lotions: These are the aqueous solutions that are used in undiluted condition for bathing the eye in first aid or in home, e.g. sodium chloride eye lotion.
  - Contact lens solutions: These are the aqueous solutions intended for lubricating, cleaning and hydrating contact lenses, e.g. thimerosal contact lens solution.
  - Eye ointments: These are placed in the conjunctival sac or applied to the margins of the eyelids, e.g. bacitracin ophthalmic ointment.

- Ophthalmic preparations are checked for the following properties:
  – Foreign particles, viscosity, tonicity, pH of preparations, sterility, surface activity
  – In the formulation of eye drops following things are done drug, preservative, sterilization, isotonicity modifier, buffer, viscosity, container, label.
- Eye lotion are the sterile aqueous solutions used for washing of the eyes. The eye lotions are supplied in concentrated form and are required to be diluted with warm water immediately before use.
- Eye ointments are sterile preparation meant for application to the eye. These are prepared under aseptic conditions and packed in sterile collapsible tubes which keep the preparation sterile until whole of it is consumed.
- Ophthalmic suspensions are also easily placed into the eye. In general, suspensions produce a longer effect than do solutions.
- Contact lenses are usually made from polymethyl-methacrylate, a hard hydrophobic plastic, but some softer hydrophilic lenses have been developed and are coming to use.
- Types of contact lenses hard contact lenses, soft contact lenses:
  – Wearers of hard contact lenses generally use two solutions. A wetting solution, which is used primarily for treating the lenses before insertion. A storage solution, which is used for overnight cleansing, soaking and storage
  – Soft contact lenses are soft flexible type of lenses. Certain medicaments from wetting and storage solutions are strongly absorbed by the soft contact lenses.
- Evaluation tests for ophthalmic preparations are particle size determination, test for clarity of ophthalmic solutions, test for pH of the solution, test for particulate matter, light obstruction particle count test, microscopic particle count test, test for sterility of ophthalmic products, pyrogen test.
- Generally an antimicrobial agent is used in multiple dose units of ophthalmic products for from microbial contamination that may occur during the suck back of an unreleased drop, when the pressure is released after withdrawal of the product
- Organisms like *Pseudomonas* and *Staphylococcus* species cause eye infections mostly.
- *Cidal test:* This is another test employed to determine antimicrobial agent efficacy.
- *Single dose containers:* It is minimum unit and consists of a disposable, pliable, tube-like applicator made from polypropylene by ultrasonic sealing. It has a nozzle protected by a cap. It is generally enclosed in a heat-sealed envelope.
- *Multiple application containers:* The traditional container for eye drops is a glass bottle carrying in the cap a dropper fitted with a teat.

PRACTICE QUESTIONS

Long Answer Type Questions

1. What are ophthalmic products? What should be the characteristics of an idea ophthalmic product?
2. Give physiology of eye with the help of a heat and labeled diagram?
3. Enlist the various types of ophthalmic products, give their examples?
4. How ophthalmic products bio-availability can be increase by controlled drug delivery system?

5. What are the recent advancement in ophthalmic products? Give their examples?
6. What are the various test employed for ophthalmic solutions?

Objective Type Questions

1. Ophthalmic preparations generally act at _____ which acts as the gate way for these formulations
2. Contact lenses are made up of the most widely used material _____ .
3. The desired particle size of the suspension for the preparation of ophthalmic preparation is _____ .
4. To check for the presence of pyrogens in the ophthalmic formulation the two general tests done are _____ .
5. LAL stands for _____ and it is an aqueous extract of blood cells (amoebocytes) from _____ .
6. Pyrogens are _____ they are _____ in nature, which is a membrane component of Gram _____ bacteria.
7. Which of the following is not the characters required for optimizing the ocular drug delivery system?
   i. Good corneal penetration.
   ii. Prolong contact time with corneal tissue.
   iii. Hypertonicity of the the solution
   iv. Sterility of the product
8. Which of the following is not an ophthalmic product?
   i. Spects and sunglasses
   ii. Eye lotions
   iii. Contact lens solution
   iv. Eye ointments
9. Which of the following are the evaluation tests for ophthalmic preparations?
   i. Particle size determination and test for clarity of ophthalmic solutions
   ii. Test for pH of the solution and test for particulate matter
   iii. Test for sterility of ophthalmic products and pyrogen test
   iv. All of the above

ANSWERS

1. Cornea
2. Polymethyl-methacrylate
3. 5–10 μm or less
4. Rabbit test and LAL test
5. Limulus amebocyte lysate, horseshoe crab, limulus polyphemus.
6. Bacterial endotoxin, lipopolysaccharide, negative
7. iii
8. i
9. iv

Chapter
9

Cosmetics

Cosmetics are substances used to enhance the appearance or odor of the human body. They are generally mixtures of chemical compounds, some being derived from natural sources, many being synthetic.

In the US, the food and drug administration (FDA) which regulates cosmetics, defines cosmetics as "intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions." This broad definition includes, as well, any material intended for use as a component of a cosmetic product. All cosmetics are formulated as solids, semi-solids or liquids. Their formula design is very similar to drug dosage forms.

Classification of Cosmetics

1. Skin cosmetics
2. Hair cosmetics
3. Nails cosmetics
4. Oral hygiene cosmetics

LIPSTICKS

Lipsticks also termed as lip cosmetics are widely used by women. Lipsticks are basically dispersions of coloring matter in a base consisting of a suitable blend of oils, fats, and waxes suitably perfumed and flavored, moulded in the form of a stick and enclosed in a case (Fig. 9.1). A lipstick should have the following characteristics:

1. It should cover the lips adequately with some gloss and last for long time
2. It should make the lips soft
3. The film must adhere firmly to the lips without being brittle and tacky
4. It should have high retention of color intensity without any change in shade
5. It should be completely free from grittiness and be non-drying
6. It should be non-irritating to the skin of lips



Fig. 9.1: Lipsticks

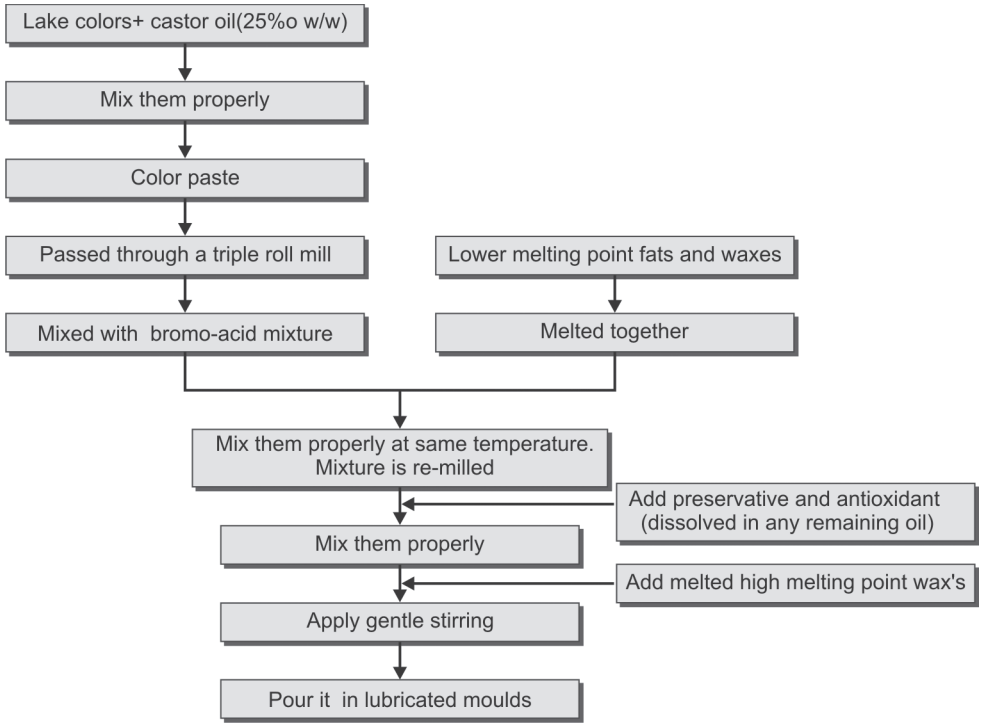
Formulae of Lipstick

Ingredients	*%w/w*
Carnauba wax	3–4
Candelilla wax	4–6
Ozokerite wax	3–4
Beeswax	4–6
Lanolin	6–8
Castor oil	40–60
Isopropyl myristate	4–6
Halogenated fluorosceins	1–3
Lake colors	15–19
Propyl-p-hydroxy benzoate	0.1–0.5
Perfume	0.6–0.8

Method of Preparation

1. The lake colors are first dispersed by mixing with suitable quantity (as 25% w/w) of castor oil.
2. The color paste obtained is passed through a triple roll mill until it is smooth and free from agglomerates and gritty particles. If titanium dioxide is used in the formula, the same is also made into a paste similarly and mixed with the color mix (Flowchart 9.1).

Flowchart 9.1: Manufacturing process of lipsticks



3. The color mixture is then mixed with the bromo-acid mixture.
4. All the ingredients of the base are identified and arranged in order of increasing melting point. The lower melting point fats and waxes are next melted together and mixed with colors and bromo mixtures at the same temperature. This mixture is re-milled until perfectly smooth.
5. The preservative and antioxidant are dissolved in any remaining oil and added to the mix.
6. The high melting point waxes are now melted and added to the bulk at the same temperature.
7. The perfume is finally added and the mass stirred thoroughly but gently to avoid entrapment of air.
8. The mass should not be melted after the high melting point waxes have been added.
9. Gentle stirring is continued until the mass is homogeneous and it is then poured in lubricated moulds.

COLD CREAM

Cold cream is water in oil type of emulsion. Cold cream is called cold cream because breaking up of emulsion on application to skin leads to evaporation of water giving cooling effect. Cold cream is primarily used to prevent excessive drying of skin. It has emollient action and prevents dehydration of skin. The key chemical constituent of cold cream is bees wax (Fig. 9.2).

Bees wax, spermacitin, paraffin wax are used as thickening agent and also provide fatty acid soap formation during the preparation of cold cream. Non-ionic and ionic emulsifiers are also used to supplement borax bees wax emulsion adding increase flexibility and stability to emulsion.

Example of emulsifiers that can be used alone or in combination are Sorbitol fatty acid esters and other co-emulsifier that can be used are glyceryl stearate, cetyl alcohol, stearyl alcohol, phosphate fatty alcohols and fatty alcohol sulphate.



Fig. 9.2: Cold cream

Since this preparation contains both oil and water. It is susceptible to microbial attack. Hence a cold cream preparation should also be preserved by adding preservatives (Table 9.1 and Flowchart 9.2)

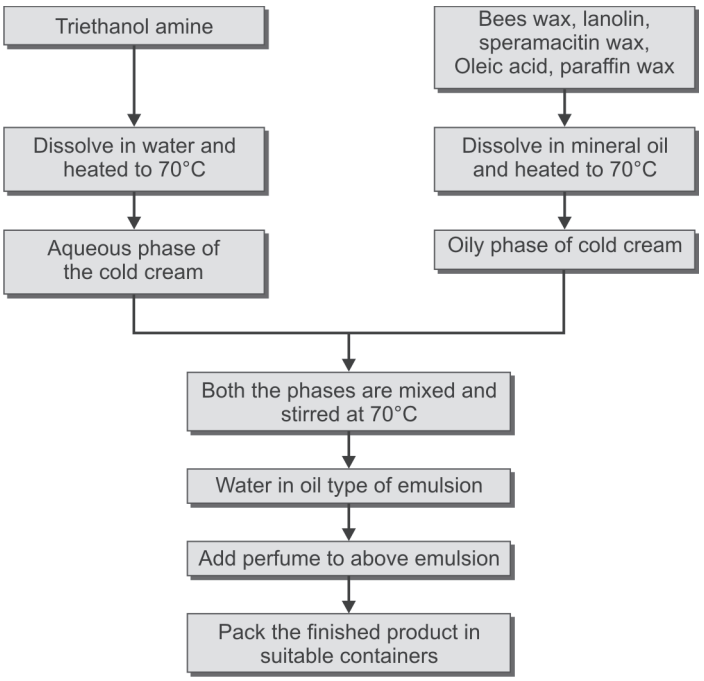
Marketed cold cream pro ducts are

i. Pond's cold cream
ii. Charmis cold cream
iii. Nivea cold cream

TABLE 9.1: Different formulas of making cold cream

Ingredients	*Cold cream formula 1* *Qty in gm*	*Cold cream formula 2* *Qty in gm*	*Cold cream formula 3* *Qty in gm*	*Cold cream formula 4* *Qty in gm*	*Cold cream formula 5* *Qty in gm*
Bees wax	14	—	4	18	30
Cetyl alcohol	2	4	—	—	—
Stearyl alcohol	2	2	—	—	—
Mineral oil	53	53	18.5	60.5	46
Lecithin	2	—	—	—	—
Borax	1	—	0.25	1	1
Water	26	20	37	—	6
Olive oil	—	8	20	—	—
Lanolin	—	4	37.5	—	6
Glyceryl monostearate	—	1	—	—	—
Sodium lauryl sulphate	—	1	—		—
Spermacitin	—		1	—	—
Oleic acid	—	—	—	—	1
Triethanol amine	—	—	—	—	1
Stearic acid	—	—	—	—	6.5
Glycerin	—	—	—	10	1
Perfume	Quantity sufficient	Quantity sufficient	Quantity sufficient	Quantity sufficient	Quantity sufficient
Methylparaben	0.18	0.18	0.18	0.18	0.18
Propylparaben	0.02	0.02	0.02	0.02	0.02

Flowchart 9.2: Steps to make cold cream



Method of Preparation

Step 1. Triethanol amine was weighed according to formula and dissolved in given quantity of water and heated to 70°C in a suitable pharmaceutical grade container. This would make the aqueous phase of the cold cream.

Step 2. Bees wax, lanolin, speramacitin wax, oleic acid, paraffin wax are next weighed as per formula and then dissolved in mineral oil and heated to 70°C. This makes the oily phase of cold cream water in oil emulsion.

Step 3. Now this is the most important step and requires experience and skill to execute. At 70°C, both the phases are mixed and stirred to form water in oil type of emulsion. It is important to stir continuously while adding aqueous phase to the oily phase to get stable water in oil emulsion. Keep stirring till the temperature comes down to room temperature.

Step 4. Sufficient quantity of perfume is added before packing the finished product to suitable wide mouth labeled containers.

VANISHING CREAM

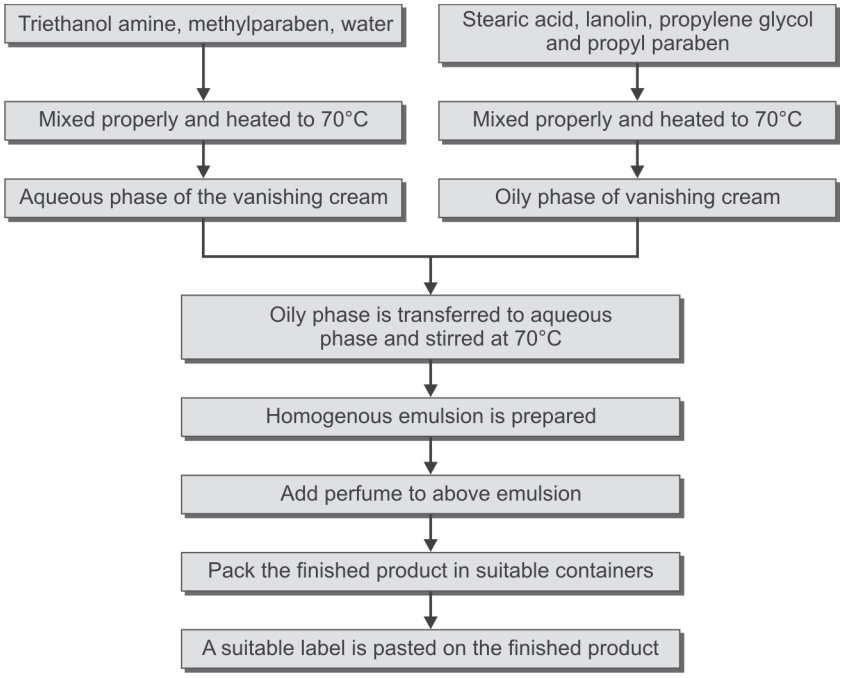
As name indicates vanishing creams, these creams are disappeared after applied and rubbed onto the skin. Vanishing cream is oil in water emulsion, oily phase in composed of stearic acid which gives a shiny and pearly appearance to vanishing cream. Emulsion is formed *in situ* by reaction of stearic acid with either alkali or triethanol amine to form stearate soap.

Vanishing cream differs from cold cream in having smaller quantity of oily phase; hence it is easy to rub on skin and leaves non-greasy film on skin with glow. This combined with evaporation of water, gives cooling effect. Since creams contain large proportion of water it tends to dry near the top of container. To prevent drying near the rim large quantity of humectants about 15% weight/weight is added to vanishing cream (Table 9.2 and Flowchart 9.3).

TABLE 9.2: Two different formulas of vanishing cream

S. No.	*Ingredients*	*Formula 1 % w/w*	*Formula 2*
1.	Stearic acid	20%	25%
2.	Triethanol amine	—	1.35%
3.	Lanolin	—	4%
4.	Propylene glycol	—	5%
5.	Potassium hydroxide	1%	—
6.	Sodium hydroxide	0.133%	—
7.	Glycerin	5%	—
8.	Methylparaben	0.18%	0.18%
9.	Propylparaben	0.02%	0.02%
10.	Perfume quantity sufficient to make it pleasing	Qs to make it pleasing	
11.	Water quantity sufficient to make	100%	

Flowchart 9.3: Procedure for making vanishing cream



Marketed preparation based on vanishing cream formula is

i. Fair ever
ii. Naturally fair
iii. Fair and lovely

Method of Preparation

Step 1. The oil soluble ingredients such as stearic acid, lanolin, propylene glycol and propylparaben are mixed and heated to 70°C in a suitable container generally borosilicate glass apparatus is used in when making on lab scale. For large-scale production stainless steel containers are used. This makes the oily phase of vanishing cream.

Step 2. The water soluble ingredients such as triethanol amine, methyl paraben and water are mixed and heated to 70°C simultaneously in another suitable container. This makes the aqueous phase of the vanishing cream.

Step 3. When both phases are at 70°C, oily phase is transferred to aqueous phase in small portions with continuous stirring in manner that a homogenous emulsion is formed. Now, once the transfer is complete, it is allowed to come at room temperature all the while being stirred.

Step 4. Perfume is added just before the finished product is transferred to suitable container for the consumers.

Step 5. A suitable label is pasted on the finished product.

SUNSCREEN

Sunscreen, also known as **sunblock** and **suntan lotion**, is a lotion, spray, gel or other topical product that absorbs or reflects some of the sun's ultraviolet (UV) radiation and thus helps protect against sunburn. Diligent use of sunscreen can also slow or temporarily prevent the development of wrinkles and sagging skin. Depending on the mode of action, sunscreens can be classified into physical sunscreens (i.e. those that reflect the sunlight) or chemical sunscreens (i.e. those that absorb the UV light).

Medical organizations such as the American Cancer Society recommend the use of sunscreen because it aids in the prevention of squamous cell carcinomas. Many sunscreens do not block UVA radiation, which does not primarily cause sunburn but can increase the rate of melanoma and photodermatitis. The use of broad-spectrum (UVA/UVB) sunscreens can address this concern.

Sunscreen use can help prevent melanoma and squamous cell carcinoma, two types of skin cancer. There is little evidence that it is effective in preventing basal cell carcinoma.

Minimizing UV damage is especially important for children and fair-skinned individuals and those who have sun sensitivity for medical reasons.

Measurement of Protection

The sun protection factor (SPF rating, introduced in 1974) is a measure of the fraction of sunburn-producing UV rays that reach the skin. For example, "SPF 15" means that 1/15th of the burning radiation will reach the skin, assuming sunscreen is applied evenly at a thick dosage of 2 milligrams per square centimeter (mg/cm^2). A user can determine the effectiveness of a sunscreen "by multiplying the SPF factor by the length of time it takes for him or her to suffer a burn without sunscreen. Thus, if a person develops a sunburn in 10 minutes when not wearing a sunscreen, the same person in the same intensity of sunlight will avoid sunburn for 150 minutes if wearing a sunscreen with an SPF of 15. It is important to note that sunscreens with higher SPF do not last or remain effective on the skin any longer than lower SPF and must be continually reapplied as directed, usually every two hours.

The SPF is an imperfect measure of skin damage because invisible damage and skin aging are also caused by ultraviolet type A (UVA, wavelengths 315–400 or 320–400 nm), which does not primarily cause reddening or pain. Conventional sunscreen blocks very little UVA radiation relative to the nominal SPF; broad-spectrum sunscreens are designed to protect against both UVB and UVA. According to a 2004 study, UVA also causes DNA damage to cells deep within the skin, increasing the risk of malignant melanomas. Even some products labeled "broad-spectrum UVA/UVB protection" have not always provided good protection against UVA rays. Titanium dioxide probably gives good protection, but does not completely cover the UVA spectrum, as early 2000s research suggests that zinc oxide is superior to titanium dioxide at wavelengths 340–380 nm.

Different sunscreen ingredients have different effectiveness against UVA and UVB. The SPF can be measured by applying sunscreen to the skin of a volunteer and measuring how long it takes before sunburn occurs when exposed to an artificial sunlight source. In the US, such an *in vivo* test is required by the FDA. It can also be measured *in vitro* with the help of a specially designed spectrometer. In this case, the

actual transmittance of the sunscreen is measured, along with the degradation of the product due to being exposed to sunlight. In this case, the transmittance of the sunscreen must be measured over all wavelengths in sunlight's UVB–UVA range (290–400 nm), along with a table of how effective various wavelengths are in causing sunburn (the *erythemal action spectrum*) and the standard intensity spectrum of sunlight. Such *in vitro* measurements agree very well with *in vivo* measurements. Numerous methods have been devised for evaluation of UVA and UVB protection. The most-reliable spectrophotochemical methods eliminate the subjective nature of grading erythema.

The ultraviolet protection factor (UPF) is a similar scale developed for rating fabrics for sun protective clothing. According to recent testing by *Consumer Reports*, UPF ~30 is typical for protective fabrics, while UPF ~6 is typical for standard summer fabrics.

Sunblock typically refers to opaque sunscreen that is effective at blocking both UVA and UVB rays and uses a heavy carrier oil to resist being washed off. Titanium dioxide and zinc oxide are two minerals that are used in sunblock. For total protection against damage from the sun, the skin needs to be protected from UVA, UVB, and also IRA (infrared A light) roughly 35% of solar energy is IR.

Active Ingredients of Sunscreen

In addition to moisturizers and other inactive ingredients, sunscreens contain one or more of the following active ingredients, which are either chemical or mineral in nature:

i. Organic chemical compounds that absorb ultraviolet light.
ii. Inorganic particulates that reflect, scatter, and absorb UV light (such as titanium dioxide, zinc oxide, or a combination of both).
iii. Organic particulates that mostly absorb UV light like organic chemical compounds, but contain multiple chromophores that reflect and scatter a fraction of light like inorganic particulates. An example is Tinosorb M. The mode of action is about 90% by absorption and 10% by scattering.

Generally aromatic molecules conjugated with carbonyl groups are the active ingredients. This general structure allows the molecule to absorb high-energy ultraviolet rays and release the energy as lower-energy rays, thereby preventing the skin-damaging ultraviolet rays from reaching the skin. So, upon exposure to UV light, most of the ingredients (with the notable exception of avobenzone) do not undergo significant chemical change, allowing these ingredients to retain the UV-absorbing potency without significant photodegradation. A chemical stabilizer is included in some sunscreens containing avobenzone to slow its breakdown; examples include formulations containing Helioplex and AvoTriplex. The stability of avobenzone can also be improved by bemotrizinol, octocrylene and various other photostabilisers. Most organic compounds in sunscreens slowly degrade and become less effective over the course of several years if stored properly, resulting in the expiration dates calculated for the product.

Usage of Sunscreen

The dose used in FDA sunscreen testing is 2 mg/cm^2 of exposed skin. If one assumes an "average" adult build of height 5 ft 4 inch (163 cm) and weight 150 lb (68 kg) with a 32 inch (82 cm) waist, that adult wearing a bathing suit covering the groin area

should apply approximately 30 g (or 30 ml, approximately 1 oz) evenly to the uncovered body area. This can be more easily thought of as a "golf ball" size amount of product per body, or at least six teaspoonfuls. Larger or smaller individuals should scale these quantities accordingly. Considering only the face, this translates to about 1/4 to 1/3 of a teaspoon for the average adult face.

Some studies have shown that people commonly apply only 1/4 to 1/2 of the amount recommended for achieving the rated sun protection factor (SPF), and in consequence the effective SPF should be downgraded to a square root or 4th root of the advertised value. A later study found a significant exponential relation between SPF and the amount of sunscreen applied, and the results are closer to linearity than expected by theory.

HAIR COSMETICS

To study and design hair preparations it is very much essential to have knowledge of hair. Hair is one of the vital parts of the body. They are also known as epidermal derivatives as they originate from the epidermis during embryological development. Hair production is a process of mutual involvement of both dermis and epidermis and originate from hair follicles. Hair follicles extend deep into the dermis, typically projecting into the underlying subcutaneous layer. The base of the hair follicle, called hair papilla, is a peg of connective tissue containing capillaries and nerves.

The hair follicle is composed of multiple layers with the outermost continuous with the epidermis and the innermost being the cortex surrounded by its cuticle, which gives rise to the shaft that extends above the cutaneous surface (Fig. 9.3). The hair

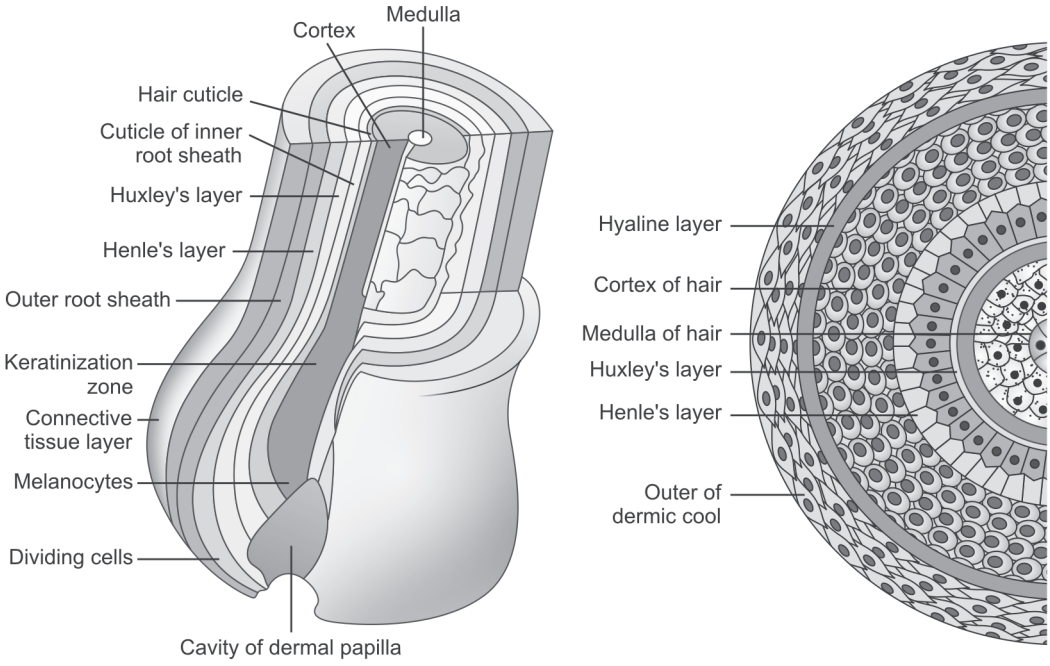


Fig. 9.3: Schematic structure of hair

follicle is positioned at an angle with its base in the subcutaneous fat. A muscle is attached to the side of the follicle and runs to the upper dermis, forming an obtuse angle. When the muscle contracts, the hair rises, resulting in goose bumps. The sebaceous gland, located above the attachment of the muscle, connects to the pilar canal through a duct.

The hair shaft is a very porous structure and softens rapidly with wetting. The hair is most brittle when dry, a time when it is most susceptible to mechanical injury. Fibrous proteins fill the cortical cells and are surrounded by a matrix protein, and these are locked together by disulfide bonds. The hair shafts can be damaged by sunlight, especially lightly colored hair, and by chemicals used to bleach or color the hair. Reduction of disulfide bonds is commonly done to straighten or permanently curl hair. This results in cumulative injury and must be done with care to avoid breakage.

Functions of Hair

1. Hair on the head protects the scalp from ultraviolet light, cushion round the head and insulates the skull.
2. Eyebrows protect the eye from small foreign particles and insects. Also it diverts sweat from the eyes.
3. The hairs, guarding the entrances to nostrils and external ear canals filter the air and help prevent the entry of foreign particles.
4. Body hair helps in evaporation of perspiration and draining of external water from the body.

SHAMPOO

The functions of a shampoo are expected to be various. A good an acceptable shampoo should have the following characteristics:

i. It should be effectively and completely remove dust or soil, excessive sebum or other fatty substances from the hair and other residual substances of hair dressings or settings or other materials.
ii. It should effectively wash the hair.
iii. The shampoo should be easily removed by rinsing with water.
iv. It should leave the hair non-dry, soft, lustrous with good manageability and less fly away.
v. It should impart a pleasant fragrance to the hair.
vi. It should not have any side effects or causes irritation to skin or eye.

Types of Shampoo

1. Powder shampoos
2. Clear liquid shampoos
3. Liquid cream or lotion shampoos
4. Solid cream/gel shampoos
5. Oil shampoos
6. Miscellaneous including anti-dandruff medicated shampoos

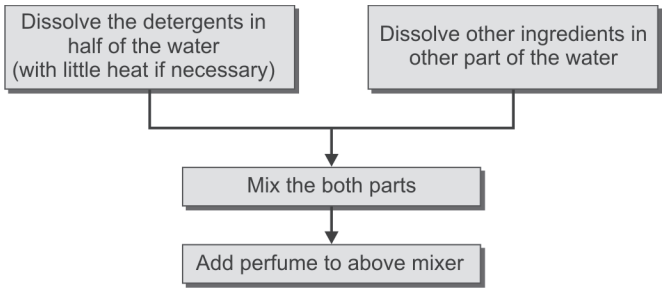
Formulae of Clear Liquid Shampoos

Ingredients	*%w/w*
Triethanolamine lauryl sulphate	40–50
Coconut monoethanolamide	1–3
Water	50–56
Perfume	q.s
Color	q.s
Preservative	q.s

Manufacturing Process

In clear liquid shampoos the detergents are first dissolved in half of the water with little heat if necessary. Other ingredients are added to other part of the water and then mixed with the first part. The perfume is added at last (Flowchart 9.4)

Flowchart 9.4: Manufacturing process of clear liquid shampoos



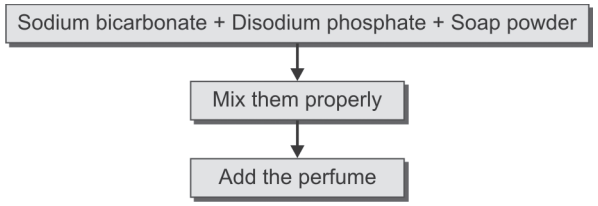
Formulae of Solid Cream/Gel Shampoos

Ingredients	*gm/batch*
Sodium lauryl sulphate	15–25
Coconut monoethanolamide	0.5–1.5
Propylene glycol monostearate	1–3
Stearic acid	3–7
Sodium hydroxide	0.5–1
Water	65–75
Perfume	q.s

Manufacturing Process

Mix water, oleic acid and sodium lauryl sulphate paste and heat to 60°C. Slowly add triethanolamine with continuous stirring. Add perfume after cooling to 35°C (Flowchart 9.5).

Flowchart 9.5: Manufacturing process of gel shampoos



HAIR DYES

Hair coloring or **hair dyeing** is the practice of changing the hair color. The main reasons for this are cosmetic: To cover gray or white hair, to change to a color regarded as more fashionable or desirable, to restore the original hair color after it has been discolored by hair dressing processes or sun bleaching.

Types of Hair

Humans have between 90 and 150 thousands of hair fibers on the scalp that grow 1 cm/month (0.37 mm/day) and the normal amount of hair lost is between 50 and 100 fibers per day. The hair diameter varies from 15 to 110 μm, depending on the race. The various types of hairs are:

i. Caucasian hair is usually thin and fine, may have waves, and is circular under the cross-section view (ellipticity of 1.25).
ii. The African hair type (wavy to curly) has a larger diameter, with a slightly oval cross-section (ellipticity of 1.75).
iii. Mongolian hair also has a larger diameter but varies from flat to wavy with a cross-section similar to Caucasian hair (ellipticity of 1.35).

Hair dying systems are divided into two main categories according to the color durability after the application on hair strands. The four most common classifications are ***permanent***, ***demi-permanent***, ***semi-permanent*** **and** ***temporary***.

Permanent

Permanent hair color generally contains ammonia and must be mixed with a developer or oxidizing agent in order to permanently change hair color. Ammonia is used in permanent hair color to open the cuticle layer so that the developer and colorants together can penetrate into the cortex. The developer or oxidizing agent comes in various volumes. The higher the developer volume, the higher the "lift" will be of a person's natural hair pigment. Someone with dark hair wishing to achieve two or three shades lighter may need a higher developer whereas someone with lighter hair wishing to achieve darker hair will not one as high. Timing may vary with permanent hair coloring but is typically 30 minutes or 45 minutes for those wishing to achieve maximum color change.

Demi-permanent

Demi-permanent hair color is hair color that contains an alkaline agent other than ammonia (e.g. ethanolamine, sodium carbonate) and, while always employed with a developer, the concentration of hydrogen peroxide in that developer may be lower than used with a permanent hair color. Since the alkaline agents employed in demi-permanent colors are less effective in removing the natural pigment of hair than ammonia these products provide no lightening of hair's color during dyeing. As the result, they cannot color hair to a lighter shade than it was before dyeing and are less damaging to hair than their permanent counterpart. Demi-permanents are much more effective at covering gray hair than semi-permanents, but less so than permanents.

Demi-permanents have several advantages as compared with permanent color. Because there is essentially no lifting (i.e. removal) of natural hair color, the final color

is less uniform/homogeneous than a permanent and, therefore, more natural looking; they are gentler on hair and therefore safer, especially for damaged hair; and they wash out over time (typically 20 to 28 shampoos), so root regrowth is less noticeable and if a change of color is desired, it is easier to achieve. Demi-permanent hair colors are not permanent but the darker shades in particular may persist longer than indicated on the packet.

Semi-permanent

Semi-permanent hair coloring involves little or no developer, hydrogen peroxide or ammonia, and is thus less damaging to hair strands. The reduced amount of developer, whether peroxide or ammonia, means that hair previously damaged by applying permanent color or permanent reshaping is less likely to be damaged during the color application process.

Semi-permanent hair color uses compounds of low molecular weight than are found in temporary hair color dyes. These dyes penetrate the hair shaft only partially, because of the reduced amount of developer used. For this reason, the color will survive repeated washing, typically 4–5 shampoos or a few weeks, before undergoing significant fading or washing out entirely.

Semi-permanents may still contain the suspected carcinogen p-phenylenediamine (PPD) or other related colorants. The US environmental protection agency reported that in rats and mice chronically exposed to PPD in their diet, the PPT appears to simply depress body weight of the animals, with no other clinical signs of toxicity observed in several studies.

The final color of each strand of hair will depend on its original color and porosity. Because hair's color and porosity across the head and along the length of a hair strand, there will be subtle variations in shade across the entire head. This gives a more natural-looking result than the solid, all over color of a permanent color. Because gray or white hairs have a different starting color than other hair, they will not appear as the same shade as the rest of the hair when treated with semi-permanent color. If there are only a few grey/white hairs, the effect will usually be enough for them to blend in, but as the gray spreads, there will come a point where it will not be disguised as well. In this case, the move to permanent color can sometimes be delayed by using the semi-permanent as a base and adding highlights. Semi-permanent color cannot lighten the hair.

Temporary Color

Temporary hair color is available in various forms including rinses, shampoos, gels, sprays, and foams. Temporary hair color is typically brighter and more vibrant than semi-permanent and permanent hair color. It is most often used to color hair for special occasions such as costume parties and Halloween. The pigments in temporary hair color are high molecular weight and cannot penetrate the cuticle layer. The color particles remain adsorbed (closely adherent) to the surface of the hair shaft and are easily removed with a single shampooing. Temporary hair color can persist on hair that is excessively dry or damaged in a way that allows for migration of the pigment to the interior of the hair shaft.

Natural Hair Coloring

There are many natural ways to color the hair instead of having to use color that contains several chemicals especially some that may cause irritation to the skin. A lot of the natural hair coloring can be simply done at home. Natural hair coloring alternatives can be done by the use of natural herbs such as henna. Different types of herbs can be used to achieve a certain color. Indigo or black walnut powder and dried gooseberry lead to a black or dark color and chamomile and calendula lead to a darker blond. Teas such as black or hibiscus that are made from black tea leaves and hibiscus flowers are also natural ways to color the hair, henna and derivatives are also used for hair coloring, especially in South East Asia, to achieve a dark Orange-reddish hue. Although many of the natural hair coloring can be done at home, there are products on the market that come as a kit that can be purchased or salons that use natural ingredients in their hair color.

ORAL HYGIENE COSMETICS

Maintenance of health of the teeth and gums well is very important for having good general health. Health of teeth and gum of a person is an indication of his general health. So, it is necessary to take care of health of teeth and gums. Various preparations are used for cleansing and maintenance of good health of teeth, gum and oral cavity. The products, termed as dentifrices, are used to keep the teeth clean, shiny and to inhibit the formation of unpleasant odour in mouth and freshen the breath.

TOOTHPASTE

Toothpastes are most popular, valuable and widely used preparations for cleansing the teeth. It has largest share of dental cleansing and care preparations. Though they are expensive than tooth powders but still they are more preferred. Toothpastes are preferred because of the following reasons:

i. Easy to take measured quantity and spread on the toothbrush.
ii. No spillage or wastage.
iii. Attractive consistency.
iv. Proper distribution in mouth.

Formulae of Toothpaste

Ingredients	*%w/w*
Calcium carbonate	50–60
Sodium lauryl sulphate	0.5–1.5
Glycerine	20–26
Gum tragacanth	1–2
Water	17–20
Saccharine	0.1–0.3
Flavour	q.s
Preservative	q.s

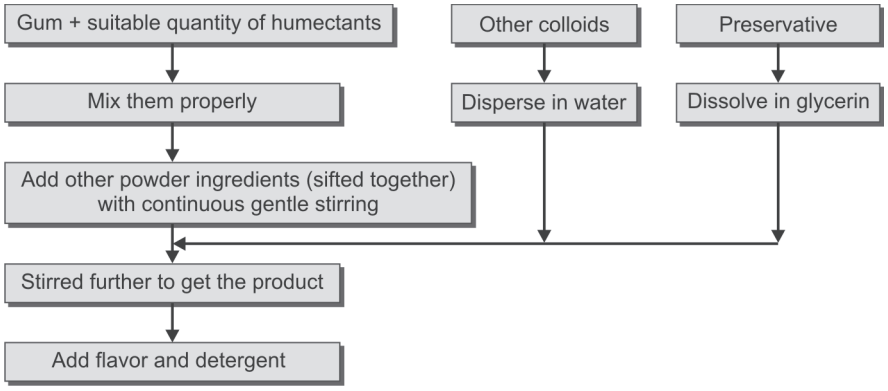
Manufacturing Process

These preparations are preferably made in stainless steel mixer container. It can be done in a planetary mixer or similar mixer used for semisolid preparations. Small scale batch can be made in a glass container.

The gum is mixed with a suitable quantity of humectant, without any water for proper dispersion. Chloroform or alcohol can also be used for dispersion of binding agents. Other colloids may be dispersed in water. Preservative can be dissolved in glycerin or water. Methylcellulose should be mixed with cold water, but ethyl cellulose should be dispersed in warm water. Other powder ingredients are sifted together and added gradually to mucilaginous mixture with continuous gentle stirring. Then aqueous media is mixed and stirred further to get the product. Flavour and detergent should be added at the last (Flowchart 9.6).

In an alternative method the binder is premixed with solid abrasives and other powders and then poured in a suitable mixer (dough-type mixer) along with aqueous solution of the humectant, preservative, sweetening agent and mixing is done. After obtaining a homogeneous paste, flavour and detergent are added.

Flowchart 9.6: Manufacturing process of toothpaste



ISOLATED KEY POINTS

- Cosmetics arise from a greek word kosmeticos which means adorn. If any material used for beautification or improvement of appearance is known as cosmetics. In other words they may be applied to skin, hair and nails for the purpose of covering colouring, softening, cleansing, nourishing, setting and protection.
- Classification of cosmetics cosmetics skin, hair, nail, hygenic powder, compact creams, lotion, colourants hair remover, hair conditioner, shampoos, hair dyes, lotion eyelash (mascaras), eyebrow pencils, eyelid inside (kohls), face powder, compact powder, body powder, prickly heat powder, cold cream, vanishing cream, all purpose cream, cleansing cream, foundation cream, emollient cream, astringent lotion, lipsticks, rouges, nail lacquers, lacquer removers, nail polish, cuticle removers, dental powders, paste dentifrices lotion, mouthwash, bath soaps.

  Skin is the heaviest single organ of the body combine with the mucosal lining of the respiratory, digestive and urogenital tract. A square centimeter of skin covers 10 hair follicles, 12 nerves, 15 sebaceous gland, 100 sweat gland. PH of the skin varies from 4 to 5.6.

- Function of the skin: Protection from external stimuli like chemicals light, heat and cold, radiation. It regulate the body temperature. It controlling blood pressure. It acts as a barrier for invasion of various microorganism. It has bactericidal, fungicidal activities due to presence of sebum secretion. It has important role in the synthesizes of Vit D_3—calcitriol.
- The human skin consist of mainly three layers, i.e. epidermis, dermis and subcutaneous.
- Epidermis: It is multilayer. It varies in thickness depends on cell size and area soles, palm—0.8 mm eyelid–0.06 mm. The epidermis comprise 5 distinct layers stratum corneum (horny layer) stratum lucidum stratum granulosum (granular layer) stratum spinosum (prickly cell layer) stratum germinativum (basal layer).
- Stratum corneum: It consists of epidermal cells lipophilic nature. The membrane provides about 10–15 layers of flattened keratinized dead cells. It is 10 um when it is dry. But it can take up moisture up to 15–20%. When occlusive dressing/cream applied over the skin prevent the evaporation of water. It plays a role in controlling the percutaneous absorption of chemical substance.
- Stratum lucidum: It is thin translucent layer stratum granulosum: It is consist of keratin protein. Stratum spinosum: It consist of flattened polygonal cells. Stratum germinativum: It consist of melanocytes.
- Dermis/corium: It consist of dense network of structural protein fibres—collagen mucopolysaccharide—ground substance. It is about 0–0.3 mm thickness. It contains blood vessels, lymphatic vessels, nerve ending.
- Subcutaneous: It consists of fat rich areolar tissue. It is otherwise called superficial fascia. It is quite elastic. Large arteries and vein are present.
- Lipgloss is a sheer form of lipstick that is in a liquid form.
- Lipstick, lip gloss, lip liner, lip plumper, lip balm, lip conditioner, lip primer, and lip boosters. Lip stains have a water or gel base and may contain alcohol to help the product stay on the lips. The idea behind lip stains is to temporarily saturate the lips with a dye, rather than covering them with a colored wax. Usually designed to be waterproof, the product may come with an applicator brush or be applied with a finger.

PRACTICE QUESTIONS

Long Answer Type Questions

1. What do you understand by the term cosmetics? Elaborate in detail about the applications of cosmetics in the healthcare systems?
2. What do you mean by the word "Lipsticks"? How you will prepare it. Write in detail about the precautions taken while manufacturing Lipsticks?
3. Write the ideal formula to prepare the Lipsticks?
4. What do you mean by the term "Cold creams"? Discuss its role in cosmetology.
5. Define cold creams? Discuss its manufacturing process with the with the help of suitable flowcharts.
6. Cold cream is o/w or w/o type emulsion? Explain with the formula.
7. How vanishing creams are different from cold creams?
8. Define shampoo? Explain its manufacturing process?

9. Discuss in brief:
   a. Clear liquid shampoo
   b. Gel shampoos
   c. Oil shampoos
   d. Antiseptic/antidandruff shampoo

10. Write in detail about the role of dentifrices?

Short Answer Type Questions

1. Substances which are intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions are called _____ .

2. There are various layers of cells within the epidermis, the outermost layer of skin is called _____ .

3. Vanishing creams are _____ type emulsion, as name indicates these creams get _____ after applied and rubbed on to the skin.

4. _____ contain fragrance, but they also block the pores to stop the discharge of perspiration while _____ allows the release of perspiration, but prevents odor by combating it with antiseptic agents, which kill odor-causing bacteria.

5. Hairs _____ are used after shampooing the hair, to render the hair more lustrous, easy to comb, and free from static electricity when dry.

6. Which of the following is false in context to function of skin?
   a. Protects the body against physical injury and microbes
   b. Homeostasis
   c. Provides protection from UV light.
   d. Vitamin E synthesis and biotransformation of some chemicals.

7. Cold cream is:
   a. w/o emulsion
   b. o/w emulsion
   c. Provides protection from UV light
   d. Forms a dry layer on skin.

8. To remove the makeup and foundation bases cream used is:
   a. Vanishing cream
   b. Cleansing cream
   c. Moisturizer
   d. Cold cream

9. Which of the following is not the function of hair?
   a. Hair on the head protects the scalp from ultraviolet light, cushion round the head and insulate the skull.
   b. Eyebrows protect the eye from small foreign particles and insects.
   c. Body hair helps in biochemical synthesis of vitamins.
   d. The hairs, guarding the entrances to nostrils and external ear canals filter the air and help prevent the entry of foreign particles.

10. Which of the following is not an oral hygiene cosmetic?
   a. Dentifrices
   b. Toothpaste
   c. Gargle
   d. Mouth wash

ANSWERS

1. Cosmetics
2. Stratum corneum (horny layer)
3. o/w, disappeared
4. Antiperspirants, deodorant
5. Conditioners
6. d
7. a
8. b
9. c
10. c

Chapter
10

Pharmaceutical Aerosols

An aerosol is a pressurized dosage forms containing one or more therapeutic active ingredients which upon actuation emit a fine dispersion of liquid and/or solid materials in a gaseous medium contain smaller than 50 μm.

Advantages

i. The medication can be delivered directly to the affected area in a desired form, such as spray, steam, quick breaking foam or stable foam.
ii. Product can be maintained free of contamination. Substances that get spoiled by oxygen or moisture can be maintained.
iii. Irritation produced by the mechanical application of topical medication is reduced or eliminated.
iv. Ease of convenience of application.
v. Application of medication in thin layer.

Disadvantages

i. Aerosol packs must not be subjected to heat.
ii. Toxicity of propellants.
iii. Catalytic oxidation of drugs such as ascorbic acid and epinephrine has been caused by traces of metal from valve parts of container.

Components of aerosol product: An aerosol product consists of the following component parts (Fig. 10.1)

1. Propellant
2. Product concentrate
3. Containers
4. Valves and actuator

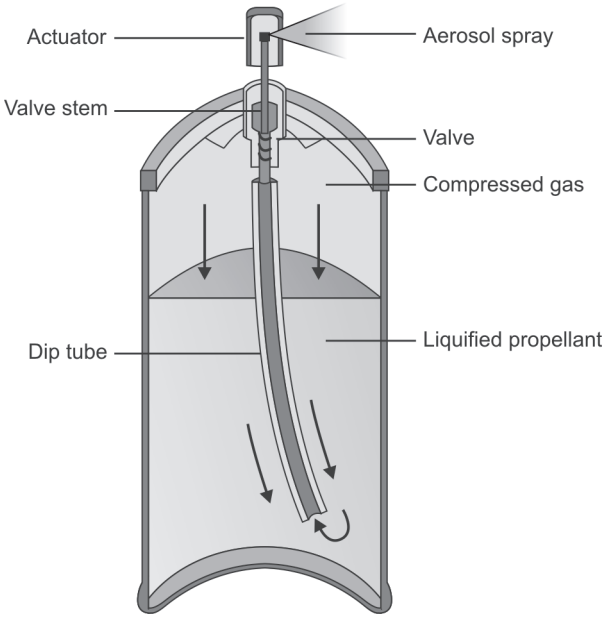


Fig. 10.1: Components of aerosol

PROPELLANT

A propellant is a chemical with a vapour pressure greater than atmospheric pressure at 40°C. The

propellant is the driving force (or you could say, the 'Engine'), behind the aerosol. Propellant is a material that is used to **move ("Propel")** an object. The material is usually expelled by gas pressure through a nozzle. The pressure may be from a compressed gas, or a gas produced by a chemical reaction. The exhaust material may be a gas, liquid, plasma, or before the chemical reaction, a solid, liquid or gelled. The propellant supplies the necessary pressure within an aerosol system to expel material from the container, and in combination with other components, to convert the material into the desired physical form. The mixture of propellants is frequently used to obtain the desirable pressure, delivery and spray characteristics.

Desired Characteristics of Aerosol Propellant

i. It should be non-toxic
ii. Inert and unreactive in the formulation
iii. Chemically should be stable under a range of conditions
iv. It should be of high purity
v. Acceptable taste and odour

Types of propellants commonly used in pharmaceutical aerosols include

1. Chlorofluorocarbons
2. Hydrocarbons
3. Hydrochlorofluorocarbons and hydrofluorocarbons
4. Compressed gases.

Chlorofluorocarbon (CFC) Propellants

For many years, the chlorofluorocarbon (CFC) propellants P-11, P-12, and P-114 were used in aerosol products. Their use has been severely curtailed due to their role in depleting the ozone layer of the atmosphere. Since January 1996, worldwide production of these CFCs has been reduced to only the amount needed for aerosols used in the treatment of asthma and chronic obstructive pulmonary disease. Alternatives to P-12, i.e. P-134a and P-227 have now been developed and are being incorporated in aerosol formulations. Currently, there are not alternatives for P-11 and P-114. Small amounts of P-11 are required in most aerosol suspensions to make slurry of the active drug and other ingredients. It also is used to dissolve surfactants in some formulations (Fig. 10.2).

P-11, P-12, and P-114 are the CFCs for oral, nasal, and inhalation aerosols. These particular chlorofluorocarbon propellants have relatively low toxicity and inflammability. If water is present, P-12 or a mixture of P-12 and P-114 are used.

The numerical designations for fluorinated hydrocarbons propellants have been designed so the chemical structure of the compound can be determined from the number. The system consists of three digits.

i. The digit at the extreme right refers to the number of fluorine atoms in the molecule.

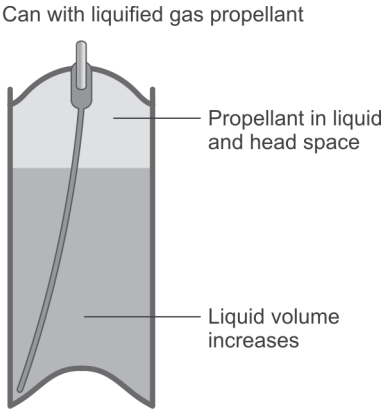


Fig. 10.2: Propellant in a container

ii. The second digit from the right represents one greater in the number of hydrogen atoms in the molecule.
iii. The third digit from the right is one less the number of carbon atoms in the molecule; if this third digit is 0, it is omitted and a two digit number is used.
iv. The capital letter "C" is used before a number to indicate the cyclic nature of a compound.
v. The small letters following a number are used to indicate decreasing symmetry of isomeric compounds. The most symmetrical compound is given the designated number, and all other isomers are assigned a letter (i.e. a, b, etc.) in descending order of symmetry.
vi. The number of chlorine atoms in a molecule may be determined by subtracting the total number of hydrogen and fluorine atoms from the total number of atoms required to saturate the compound.

When a liquefied gas propellant or propellant mixture is sealed in an aerosol container with the product concentrate, equilibrium is establish between the propellant which remains liquefied and a portion that vaporizes and occupies the upper portion of the container. The pressure at this equilibrium is referred to as the vapor pressure (expressed as psia) and is a characteristic of each propellant at a given temperature. Since the vapor pressure is exerted equally in all directions and is independent of the quantity of liquefied phase present, the pressure forces the liquid phase up the dip tube and out of the container when the valve is actuated. As the propellant reaches the air, it evaporates due to the drop in pressure and leaves the product concentrate as airborne liquid droplets or dry particles. As the liquid is removed from the container through the dip tube, the equilibrium between the propellant's liquefied phase and vapor phase is rapidly re-established. Thus, the pressure within the container remains virtually constant and the product may be continuously released at an even rate and with the same propulsion. In the case when there is no dip tube in the container, the container is used in the inverted position so that the liquid phase will be in direct contact with the valve. When the valve is actuated, the liquid phase is emitted and immediately reverts to the vapor phase in the atmosphere.

Hydrochlorofluorocarbons (HCFC) and Hydrofluorocarbons (HFC)

The hydrochlorofluorocarbons (HCFC) and hydrofluorocarbons (HFC) differ from CFCs in that they may not contain chlorine and have one or more hydrogen atoms. These compounds breakdown in the atmosphere at a faster rate than the CFCs resulting in a lower ozone depleting effect.

P-22, 142b, and 152a are used in topical pharmaceuticals. These three propellants have a greater miscibility with water and, therefore, are more useful as solvents compared to the other propellants. They are also slightly more flammable than the other propellants but this is not perceived as a disadvantage.

Hydrocarbons

The hydrocarbons are used in topical pharmaceutical aerosols because of their environmental acceptance and their low toxicity and non-reactivity. They are also useful in making three phase (two layer) aerosols because of their density being less than 1 and their immiscibility with water. The hydrocarbons remain on top of the aqueous

layer and provide the force to push the contents out of the container. However, they are flammable and can explode. They contain no halogens and, therefore, hydrolysis does not occur making these good propellants for water based aerosols.

Propane, butane, and isobutane are the most commonly used hydrocarbons. They are used alone or as mixtures or mixed with other liquefied gases to obtain the desired vapor pressure, density, and degree of flammability. The flammability hazard has been substantially reduced by using mixtures of propellants and with the development of newer types of dispensing valves (i.e. vlave with vapor tap).

Compressed Gases

Gases such as nitrogen, nitrous oxide, and carbon dioxide have been used as aerosol propellants for products dispensed as fine mists, foams, or semi-solids. But due to their low expansion ratio, the sprays are fairly wet and the foams are not as stable as produced by liquefied gas propellants. However, using a compressed gas that is insoluble in the product concentrate (e.g. nitrogen) will emit the product concentrate in essentially the same form as it was placed in the container (Fig. 10.3).

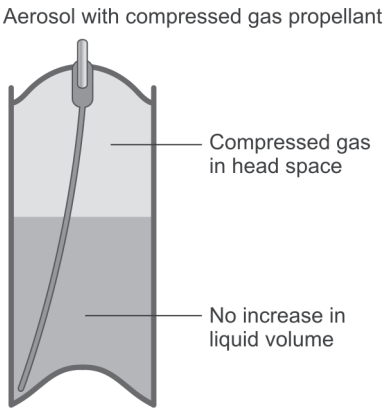


Fig. 10.3: Compressed gas propellant

The pressure of the compressed gas contained in the head space of the aerosol container forces the product concentrate out of the container. But unlike aerosols prepared with liquefied gas propellants, there is no propellant reservoir. So higher gas pressures are required in these aerosols and the pressure diminishes as the product is used. These gases have been used for the most part to dispense food products, dental creams, hair preparations, and ointments.

Other Types of Propellants

Liquefied petroleum gas (LPG): The LPG grade aerosol propellant consists of high purity hydrocarbons derived directly from oil wells, and as a by-product from the petroleum industry. They consist of a mixture of propane, isobutane and n-butane. These propellants are used in most aerosols today, and have been used for many years in household aerosol products.

Di-methyl ether (DME): This is an alternative liquefied propellant, and is more common in personal care products, and some air fresheners.

Chlorofluorocarbons (CFCs): These liquefied propellant gases used to be very common prior to the discovery that they were affecting the ozone layer. They are no longer used in consumer aerosols in the western world. They are however permitted in inhalation aerosols, as used in the treatment of asthma.

PRODUCT CONCENTRATE

The product concentrate is the active drug combined with additional ingredients or co-solvents required to make a stable and efficacious product. The concentrate can be

a solution, suspension, emulsion, semisolid, or powder. The propellant provides the force that expels the product concentrate from the container and additionally is responsible for the delivery of the formulation in the proper form (i.e. spray, foam, semisolid).

CONTAINERS

Aerosol containers are generally made of **glass, metals (e.g. tin plated steel, aluminum, and stainless steel), and plastics.** The selection of the container for a particular aerosol product is based on its adaptability to production methods, compatibility with the formulation, ability to sustain the pressure necessary for the product, the design and aesthetic appeal, and the cost.

Glass containers would be the preferred container for most aerosols. Glass presents fewer problems with respect to chemical compatibility with the formulation compared to metal containers and is not subject to corrosion. Glass is also more adaptive to design creativity and allows the user to view the level of contents in the container.

However, glass containers must be precisely engineered to provide the maximum pressure safety and impact resistance. Therefore, glass containers are used in products that have lower pressures and lower percentages of propellants. When the pressure is below 25 psig and less than 50% propellant is used, coated glass containers are considered safe.

To increase the resistance to breakage, plastic coatings are commonly applied to the outer surface of glass containers. These plastic coatings serve many purposes: (1) Prevent the glass from shattering into fragments if broken; (2) absorb shock from the crimping operation during production thus decreasing the danger of breakage around the neck; (3) protect the contents from ultraviolet light; (4) act as a means of identification since the coatings are available in various colors. Glass containers range in size from 15 to 30 ml and are used primarily with solution aerosols. Glass containers are generally not used with suspension aerosols because the visibility of the suspended particles presents an aesthetic problem. All commercially available containers have a neck finish which adapts easily to metered valves.

Tin-plated steel containers are light weight and relatively inexpensive. For some products the tin provides all the necessary protection. However, when required, special protective coatings are applied to the tin sheets prior to fabrication so that the inside of the container will be protected from corrosion and interaction between the tin and the formulation. The coating usually is an oleoresin, phenolic, vinyl, or epoxy coating. The tin plated steel containers are used in topical aerosols.

Aluminum is used in most MDIs and many topical aerosols. This material is extremely light weight and is less reactive than other metals. Aluminum containers can coated with epoxy, vinyl, or phenolic resins to decrease the interaction between the aluminum and the formulation. The aluminum can also be anodized to form a stable coating of aluminum oxide. Most aluminum containers are manufactured by an impact extrusion process that makes them seamless. Therefore, they have a greater safety against leakage, incompatibility, and corrosion.

Aluminum containers are made with a 20 mm neck finish that adapts to the metered valves. For special purposes and applications, containers are also available that have neck finishes ranging from 15 to 20 mm. The container themselves available in sizes ranging from 10 ml to over 1,000 ml.

Stainless steel is used when the container must be chemically resistant to the product concentrate. The main limitation of these containers is their high cost.

Plastic containers have had limited success because of their inherent permeability problems to the vapor phase inside the container. Also, some drug–plastic interactions have limited the efficacy of the product (Table 10.1).

TABLE 10.1: Types of containers used in aerosls

Pressure limitations of aerosol containers		
Container material	*Maximum pressure (psig)*	*Temperature (°F)*
Tin-plated steel	180	130
Uncoated glass	<18	70
Coated glass	<25	70
Aluminum	180	130
Stainless steel	180	130
Plastic	<25	70

VALVE ASSEMBLY

The effectiveness of a pharmaceutical aerosol depends on achieving the proper combination of product concentrate formulation, container and valve assembly. The valve mechanism is the part of the product package through which the contents of the container are emitted. The valve must withstand the pressure required by the product concentrate and the container, be corrosive resistant and must contribute to the form of the emitted product concentrate.

The primary purpose of the valve is to regulate the flow of product concentrate from the container. But the valve must also be multifunctional and regulate the amount of emitted material (metered valves), be capable of delivering the product concentrate in the desired form, and be easy to turn on and off. Among the materials used in the manufacture of the various valve parts are plastic, rubber, aluminum, and stainless steel (Fig. 10.4).

The basic parts of a valve assembly are:

1. **Actuator:** The actuator is the button which the user presses to activate the valve assembly and provides an easy mechanism of turning the valve on and off. In some actuators, mechanical breakup devices are also included. It is the combination of the type and quantity of propellant used and the actuator design and dimensions that determine the physical form of the emitted product concentrate.
2. **Stem:** The stem supports the actuator and delivers the formulation in the proper form to the chamber of the actuator.
3. **Gasket:** The gasket, placed snugly with the stem, serves to prevent leakage of the formulation of the valve is in the closed position.
4. **Spring:** The spring holds the gasket in place and also is the mechanism by which the actuator retracts when pressure is released thereby returning the valve to the closed position.
5. **Mounting cup:** The mounting cup which is attached to the aerosol container serves to hold the valve in place. Because the undersigned of the mounting cup is exposed to the formulation, it must receive the same consideration as the inner part of the

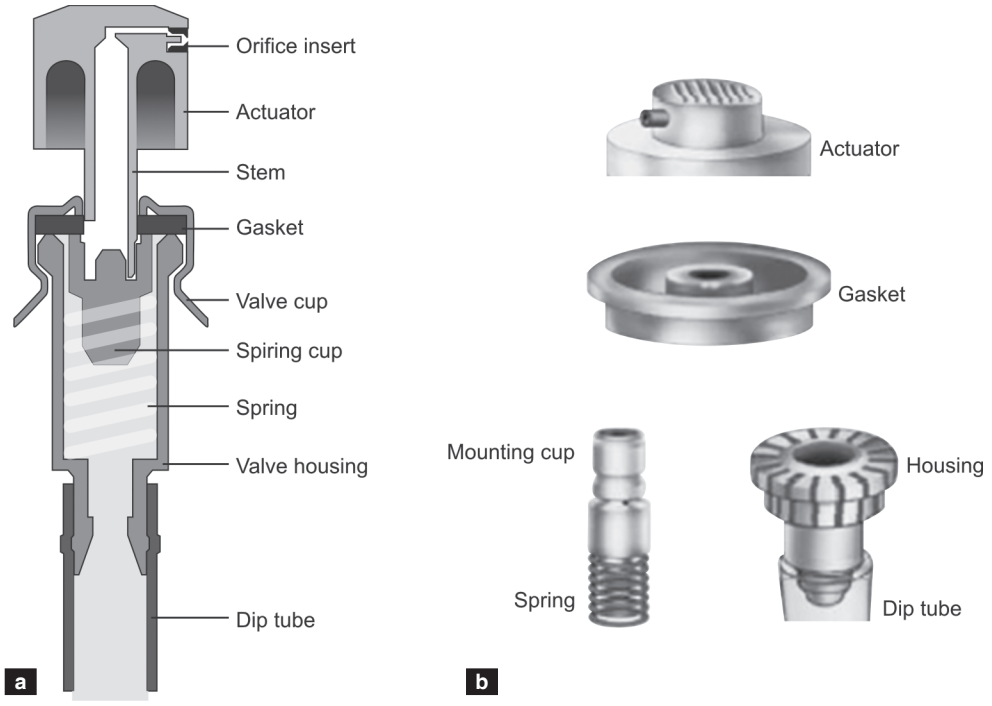


Fig. 10.4a and b: Basic parts of valve assembly

container with respect to meeting criteria of compatibility. If necessary, it may be coated with an inert material to prevent an undesired interaction.

6. **Housing:** The housing located directly below the mounting cup serves as the link between the dip tube and the stem and actuator. With the stem, its orifice helps to determine the delivery rate and the form in which the product is emitted.
7. **Dip tube:** The dip tube which extends from the housing down into the product concentrate serves to bring the formulation from the container to the valve. The viscosity of the product and its intended delivery to rate dictate the inner dimensions of the dip tube and housing for a particular product.

Spray valves are used to obtain fine to coarse wet sprays. Depending on the formulation and the design of the valve and actuator, the particle size of the emitted spray can be varied. The spray is produced as an aerosol solution passes through a series of small orifices which open into chambers that allow the product concentrate to expand into the proper particle size.

Vapor tap valves are used with powder aerosols, water based aerosols, aerosols containing suspended materials, and other agents that would tend to clog a standard valve. This valve is basically a standard valve except that a small hole has been placed into the valve housing. This allows vaporized propellant to be emitted along with the product concentrate and produces a spray with greater dispersion. These valves are used with aqueous and hydroalcoholic product concentrates and hydrocarbon propellants.

Foam valves have only one orifice that leads to a single expansion chamber. The expansion chamber also serves as the delivery nozzle or applicator. The chamber is the appropriate volume to allow the product concentrate to expand into a ball of foam.

Foam valves are used for viscous product concentrates such as creams and ointments because of the large orifice and chamber. Foam valves also are used to dispense rectal and vaginal foams. If the size of the orifice and expansion chamber is appropriately reduced, a product concentrate that would produce foam will be emitted as a solid stream. In this case, the ball of foam begins to develop where the stream impinges on a surface.

Metered dose inhaler (MDI) valves (metering values) are used to accurately deliver a dose of medication. Metered valves are used for all oral, inhalation, and nasal aerosols. The metered valves reproducibly deliver an amount of product concentrate accurately from the same package and also allow for the same accuracy between different packages.

Two basic types of metering valves are available; one for inverted use and the other for upright use. Generally the valves for upright use are used with solution type aerosols and contain a thin capillary dip tube. Suspension or dispersion aerosols use the valve intended for inverted use that does not contain a dip tube. In general valves should retain the material in the metering chamber for fairly long periods. However, it is possible for the material in the chamber to slowly return back to the container. The degree to which this occurs depends on the construction of the valve and length of time between actuations of the valves. Some valves have been fitted with a "drain tank" to overcome this problem.

Methods of Manufacturing

Two methods are used to manufacture aerosols:

i. Cold fill process
ii. Pressures fill process.

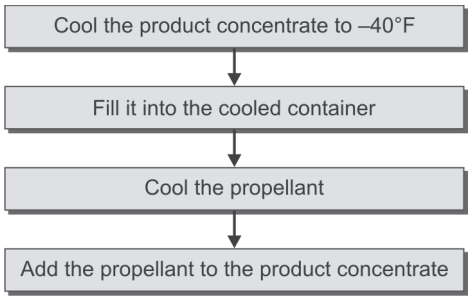
Cold fill process: The cold fill process takes advantage of the property that some ingredients will liquefy when cooled, and the pressure fill process uses the property that some ingredients will liquefy when placed under pressure.

In the cold fill process, both the product concentrate and the propellant must be cooled to temperatures between –30°C and –60°C where they will remain liquefied. The cooling system may be a mixture of dry ice and acetone or an elaborate refrigeration system. The chilled product concentrate is quantitatively added to the equally cold aerosol container and then the liquefied gas is added. The heavy vapors of the cold liquid propellant will generally displace the air present in the container. When filling is complete, the valve assembly is inserted into the container and crimped into place. The container is then passed through a water bath of about 55°C to check for leaks or distortion in the container.

Aqueous solutions cannot be filled by this process since the water will turn to ice in the low temperatures. For nonaqueous systems, some moisture usually appears in the final product due to the condensation of atmospheric moisture within the cold containers (Flowchart 10.1).

Pressure fill process: Pressure filling is carried out essentially at room temperature. The product concentrate is placed in the container, the valve assembly is inserted and crimped into place, and then the liquefied gas, under pressure, is added through the valve. The entrapped air in the package might be ignored if it does not interfere with

Flowchart 10.1: Method of manufacture by cold fill method



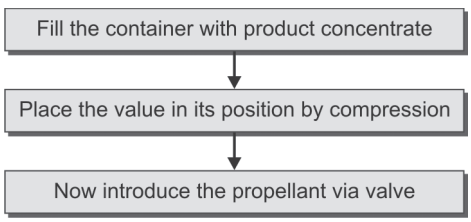
the stability of the product, or it may be evacuated prior to filling or during filling. After the filling operation is complete, the valve is tested for proper function. This spray testing also rids the dip tube of pure propellant prior to consumer use. Pressure filling is used for most pharmaceutical aerosols. It has the advantage that there is less danger of moisture contamination of the product and also less propellant is lost in the process (Flowchart 10.2).

Aerosols are used to deliver active drugs to the pulmonary airways, the nasal passages, or the oral cavity. They are also used to administer drugs topically and into body cavities such the vagina and rectum. Pulmonary, nasal, and oral administration is intended to achieve either local or systemic therapeutic effect, while topical, vaginal, and rectal administration is only intended for local effect. Inhalation therapy (i.e. drug delivery to the pulmonary airways and nasal passages) was once accomplished using nebulizers or atomizers that were cumbersome to use and restricted to institutional or home use. The development of the metered dose inhaler in the mid 1950s provided the convenience of portability with the accuracy of dosing.

Successful inhalation therapy requires that the formulation emit droplets or particles that are the optimum size. Large particles (about 20 μm) deposit in the back of the mouth and throat and are eventually swallowed rather than inhaled. Particles in the 1 to 10 μm range will reach the bronchioles. Very small particles (0.6 μm) penetrate to the alveolar sacs but have limited retention since a large fraction of the particles are exhaled in the breath. The most therapeutically effective particle size range appears to be between 3 and 6 μm. Therefore, it is important that the aerosol system produce most of its particles between approximately 1 and 10 μm.

MDIs are the most commonly used product for inhalation therapy and is also one of the most difficult dosage forms to administer properly. One of the most critical maneuvers during administration is to coordinate the actuation of the aerosol with the patient's inspiration. The mouthpiece adapter on the aerosol package has been

Flowchart 10.2: Method of manufacture by pressure fill method



repeatedly modified since the mid 1970s in an attempt to help patients receive the correct dosage when this coordination is not performed correctly. Larger adapters (sometimes called tube spacers) permit the propellant to completely evaporate before the aerosol reaches the patient. This results in a reduced particle size and velocity. The reduced particle size improves the depth to which the drug will penetration into the lungs and the lower velocity decreases the amount of drug that will impact on the back of the throat. The biggest disadvantages of these larger adapters are the cost, difficulty to clean, and inconvenience to use because of their size.

Nasal aerosols deliver the drug directly to the nasal mucosa. The most common nasal aerosols contain steroids used to treat nasal congestion, sneezing, and running nose associated with hay fever, allergies, and rhinitis. Such products use steroids such as beclomethasone dipropionate, triamcinolone acetonide, dexamethasone sodium phosphate, and budesonide. Aerosols used to deliver drugs to the oral cavity generally administer the product sublingually. One such product is a sublingual nitroglycerin formulation that is sprayed under the tongue and delivers 0.4 mg of nitroglycerin per actuation.

Topical aerosol formulations are available for local anesthetics, antiseptics, germicides, first aid preparations, and spray on protective films. These aerosol deliver particles that are larger and more course than the inhalation aerosols. Topical aerosols deliver the active drug in the form of a powder, a wet spray, a stream of liquid, or an ointment like product.

Vaginal and rectal foams are available that contain estrogens, contraceptives, and anti-inflammation agents. These products are packaged in containers that have an application device which is filled with foam when the valve is actuated and then the device is placed in the vagina or rectum and the foam is instilled with the device plunger.

EVALUATION TEST AND QUALITY CONTROL OF AEROSOLS

Evaluation Tests

Pharmaceutical aerosols can be evaluated by testing flammability and combustibility, physico-chemical, performance and biological tests. Aerosols are pressurized packages and many tests are necessary to ensure proper performance of the package and safety during the use and storage evaluation of aerosol includes following tests:

A. Flammability and combustibility
   1. Flash point
   2. Flame projection

B. Physiochemical characteristics
   1. Vapour pressure
   2. Density and weight
   3. Moisture content
   4. Identification of propellants
   5. pH
   6. Viscosity

C. Performance
   1. Aerosol valve discharge rate
   2. Spray pattern

3. Dosage with metered valves
4. Net contents
5. Foam stability
6. Particle size determination
7. Leakage test

D. Biological testing
1. Therapeutic activity
2. Toxicity studies
3. Extractable substances

A. Flammability and Combustibility

Flash point: **"Standard tag open cap apparatus"** is used for determination of flash point (Fig. 10.5). For this the formulation is chilled to temperature of –25°F and transferred to the test apparatus. The temperature of test sample liquid increase slowly, and the temperature at which the vapors of propellant ignite is taken a "flash point". It is calculated for flammable component, which in case of topical hydrocarbon propellants.

Flame projection

i. Flame test indicates the effect of an aerosol formulation on the extension of an open flame (Fig. 10.6).
ii. Aerosol product is sprayed for 4 sec into open flame.
iii. Depending on the nature and type of formulation, the fame is extended to some length and exact length was measured with ruler.

B. Physicochemical Characteristics

Vapour pressure: Vapour pressure is determined by pressure gauges or elaborately through use of a water bath, test gauges and other special equipment. Variation in pressure indicates the presence of air in headscape. Variation in pressure indicates the presence of air in the headscape. For accurate measurement of vapour pressure in aerosol container **can punctuating device** is used.



Fig. 10.5: Flash point tag open cap apparatus



Fig. 10.6: Flame projection test apparatus

Density of aerosol system: It is determined by **hydrometer or a pycnometer** (Figs 10.7 and 10.8)

i. This method is useful for nonaerosols modification to accommodate the liquefied gas preparation.
ii. In which a pressure tube is fitted with metal fingers and hoke valve of apparatus, which under pressure the liquids are introduced.
iii. The hydrometer is kept in to the glass pressure tube. Some sufficient amount of sample is added through the valve to cause the hydrometer to rise half way up the length of the tube. The density can be read directly from the apparatus.

Moisture content: Karl Fischer method or gas chromatography method used.

Identification of propellants: Gas chromatography or IR spectrophotometry methods are used for identification of propellants and also to indicate the proportion of the each component in a blend.

pH: pH meter is used

i. A pH range of 9 to 10.5 is optimal for unlined steel containers.
ii. A pH range of 4.5 to 8.5 is optimal for aluminum containers.
iii. pH less than 8 problematic for unlined steel containers.
iv. pH can drift over product lifetime.

Viscosity: There are many types of test equipment and methods for determining product viscosity. They all tend to involve either rotational friction or capillary extrusion practices. Variations in viscosity can have dramatic effects on the following:

i. Time and effort spent compounding and filling.
ii. CO_2 absorption.
iii. Spray pattern.
iv. Foam stability.
v. Spray out appearance.
vi. Low temperature usability.

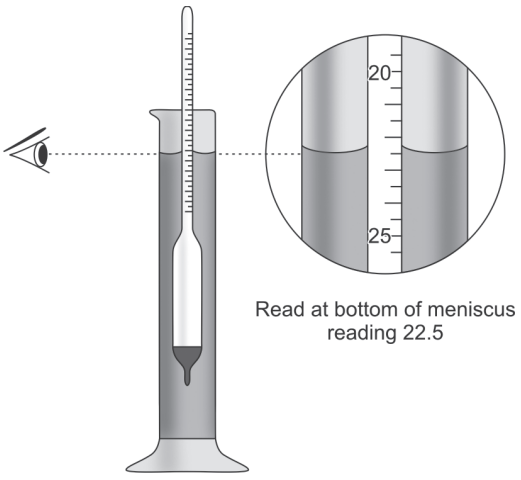


Fig. 10.7: The hydrometer



Fig. 10.8: The pycnometer

C. Performance Test

Aerosol valve discharge rate: It is determined by taking an aerosol with known weight and discharging the contents for given time using standard apparatus. Again reweigh the container, the difference in weight per time release or dispensed is discharge rate. It is expressed as gram per seconds.

Spray patterns: For this, the method involves the impingement of sprays on a piece of paper, which is treated with dye-talc mixture. Based on the nature and type of the aerosol, an oil soluble dye or water soluble dye is used. When the particles reach the paper it causes the dye to go into solution and to be absorbed onto the paper. It gives a record of the spray pattern.

Dosage with metered valves: Several points to be considered, reproducibility of dosage each time the valve is dispersed and amount of medication actually received by the patient. Reproducibility has been determined by assay technique and amount of active ingredient is determined. Another method for determination of active ingredient that accurate weighing of filled container then remove contents by dispersing and reweigh the container can and difference in weight divided by number of doses, gives the average dosage (Fig. 10.9).

Net contents: Weight method used. The tared cans are placed on to the filling line and weighed; the difference in weight is equal to the net contents. The other method is a destructive method and consists of weighing of a full container, and dispensing the contents. The contents are then reweighed. The difference in weight gives the amount of contents present in the container.

Foam stability: The life of a foam ranges from a few seconds (for quick breaking foam) to one hour or more depending on the formulation and type of foam. The methods used to determine the foam stability is **visual evaluation**. Visual evaluation is the time for a given mass to penetrate the foam, time for given rod that is inserted into the foam to fall.

Particle size determination: Particle size can be determined by cascade impactor and light scattering decay methods.



Fig. 10.9: Spray pattern

i. **Cascade impactor:** Cascade impactor works on the projected through a series of nozzle and glass slides at high velocity. First the larger particles become impacted on the lower velocity stages and then the smaller particles impacted at high velocity stages. The size ranges from 0.1 to 30 u (microns).
ii. **Light scattering decay:** Light scattering method is used to determine the particle size. The aerosol product settle in turbulent condition, Here the particle size is measured by the change in light intensity of Tyndall beam.

Leakage test: Leak test is done by checking the crimping of the valve must be available to prevent defective containers. This is accomplished by measuring the crimp's dimension and ensuring that they meet specifications. Final testing of valve closure is done by passing filled containers through water bath.

D. Biological Testing

The final phase of testing of aerosols involved in a comprehensive research and development program for pharmaceutical aerosols must involve biological testing. These are similar to tests performed for non-aerosol pharmaceuticals.

Therapeutic activity: For inhalation aerosols: Therapeutic activity is depends on the particle size. For ropical aerosols: It is determined by applying the active ingredients topically to test areas and the amount of therapeutic active ingredients absorbed is determined.

Toxicity: For inhalation aerosols: Inhalation toxicity is studied by exposing test animals to vapor sprayed from aerosol container. For topical aerosols: Irritation on the skin and chilling effects are checked. When aerosol is topically applied, thermistor is used to determine the change in skin temperature for a given period of time.

Extractable substances: The pressurized inhalers and aerosols are normally formulated with organic solvents as the propellant or the vehicle. The leaching of extractables from the elastomeric and plastic components into the formulation is a potentially serious problem. Hence the composition and the quality of materials used in the manufacture of the valve components (e.g. stem, gaskets, housing, container, etc.) must be carefully selected and controlled. The container compatibility with formulation components should be thoroughly checked, so as to prevent distortion of the valve components and to minimize changes in the medication delivery, discharge rate, leaks and impurity profile of the drug product over time. The extractable profiles of a representative sample of each of the elastomeric and plastic components of the valve should be established under specified conditions and should be correlated to the extractable profile of the placebo or aged drug product, to ensure quality and purity of the drug product. Extractable substance which may include poly nuclear aromatics, nitrosamines, antioxidants, plasticizers, vulcanization accelerators and monomers, etc., should be identified and minimized wherever possible.

QUALITY CONTROL OF AEROSOL

Quality control of aersol includes the testing of:

i. Propellents
ii. Valves, actuator, dip tubes

iii Containers
iv. Weight checking
v. Leak testing
vi. Spray testing

1. **Propellents:** Following are the parameters tested for propellants (Table 10.2).

TABLE 10.2: Tested parameters for propellants

S. No.	*Parameters*	*Tested by*
1.	Identification	Gas chromatography
2.	Purity	Moisture, halogen, non-volatile residue determination

2. **Valves, actuator, dip-tubes:** The object of this test is to determine magnitude of valve delivery and degree of uniformity between individual valves. Standard test solutions were proposed to rule out variation in valve delivery (Table 10.3).

TABLE 10.3: Tested parameters for valves

Ingredients (%w/w)	*Test solution "A"*	*Test solution "B"*	*Test solution "C"*
Iso propyl myristate	0.10%	0.10%	0.10%
Dichlorodifluoromethane	49.95%	25.0%	50.25%
Dichlorotetrafluoroethane	49.95%	25.0%	24.75%
Trichloromonofluoromethane	24.9%	—	—
Alcohol USP	—	49.9%	—
Specific gravity	1.384	1.092	1.388

Testing procedure

i. Take 25 valves and placed on containers.
ii. Filled with specific test solution.
iii. Actuator with 0.020 inch orifice is attached.
iv. Valve is actuated to fullest extent for 2 sec.
v. Repeat this for total 2 individual deliveries from each 25 test units.

Valve delivery per actuation in µL = Individual delivery wt in mg/specific gravity of test solution.

Valve acceptance limit is shown in Table 10.4.

Acceptance criteria: Of 50 deliveries (25 × 2 delivery). If 4 or more are outside limits valves are rejected, if 3 delivery are outside limits, another 25 valves are tested, lot is rejected if more than 1 delivery outside specification.

3. **Containers:** Containers are examined for detects in lining. From QC aspects, exposed metals are measured for their degree of conductivity of electric current. While, glass containers examined for flaws.

TABLE 10.4: Valve acceptance limit

S. No.	*Deliveries*	*Limits*
1.	54 µL or less	± 15%
2.	55 to 200 µL	± 10%

4. **Weight checking:** It is done by periodically adding tared empty aerosol container to filing lines, which after filling with concentrate are removed and weighed. Same procedure is used for checking weight of propellants.
5. **Leak test:** It is done by measuring the crimp's dimension and comparing. Final testing of valve closure is done by passing filled containers through water bath.
6. **Spray testing:** It is done to clear dip tube of pure propellant/concentrate and to check for defects in valves and spray pattern.

ISOLATED KEY POINTS

- A pharmaceutical aerosol is defined as a system that depends on the power of a compressed or liquefied gas to expel the contents from the container or pressurized dosage form, containing one or more active ingredients, which upon actuation emit a fine dispersion of liquid and solid materials is gaseous medium.
- Components of aerosol package: (i) Propellant; (ii) container; (iii) valve and actuator; (iv) product concentrate.
- Propellants; propellant is responsible for developing the proper pressure within the container, and it expels the product when the valve is opened and aids in the atomization or foam production of the product.
- Types of propellants; A. liquid gas propellant are chloroflurocarbons, trichloro-monofluromethane, dichlorofluoromethane, dichlorotetrafluoroethane, hydro-carbons, butane.
- Compressed gas propellant: (1) Nitrogen, (2) oxygen. (3) carbondioxide.
- Containers they must be stand at pressure as high as 140 to 180 psig. Types of containers: (1) Tin plate containers consists of sheet of steel plate that has been electroplated on both sides with tin. (2) Aluminium containers greater resistance to corrosion. Light weight. Good for light sensitive drugs. (3) Stainless steel container limited for smaller size extremely strong and resistant to most materials pressure stand. (4) Glass containers available with plastic or without plastic coating compatible with many additives no corrosion problems can have various shape because of molding not for light sensitive drugs.
- Valves and actuator; valves are imporatant for aerosols containers as they help in expelling the contents from the container.
- With the help of actuator present on the valve, the foam product present in the container can dispensed in the form of spray or wet stream. The type of product formed, i.e. foam, spray or wet stream depends on tha proper selection of propellant during formulation.
- Actuators to ensure that aerosol product is delivered in the proper and desired form. Different types of actuators spray actuators foam actuators solid steam actuators mist actuators.
- Metered dose inhalers (mdis) metered dose inhalers (mdis) are pharmaceutical delivery systems designed for oral or nasal use, which deliver discrete doses of aerosolized medicament to the respiratory tract, e.g. salbutamol 100–200 µg, terbutaline sulphate 250–500 µg, sodium chromoglycate 5 mg. The metering valve is place in inverted position.
- Manufacture of pharmaceutical aerosols: (1) Pressure filling apparatus; (2) cold filling apparatus; (3) compressed gas filling apparatus.

- Pressure filling product concentrate is placed in aerosol container. Valve assembly is inserted. Liquified gas (propellant) is metered under pressure by means of pressure burette into the container. The desired amount of propellant is allowed to flow through the aerosol valve into the container under its own vapor pressure. When the pressure is equalized between the burette and the container, the propellant stops flowing. Additional propellant is added with compressed air (N_2, CO_2, NO) to increase pressure of the propellant in the container. Trapped air inside the container was evacuated.
- Cold filling the principle of cold filling method requires the chilling of all components including concentrate and propellant to a temperature of –30 to –40°F. This temprature is necessary to liquify the propellant gas. The cooling system may be a mixture of dry ice and acetone or refergiration system. First, the product concentrate is chilled and filled into already chilled container followed by the chilled liquefied propellant. The heavy vapour of the cold liquid propellant generally displace the air in the container.
- Compressed gas filling product concentrate is placed in the container. Valve assembly is inserted. Air is evacuated from the container by a vacuum pump. Compressed gas is passed into the container. When pressure is equal to the pre-determined and regulated pressure, the gas flow stops.
- Evaluation of pharmaceutical aerosols:
  1. Flammability and combustibility—(i) flame projection, (ii) flash point
  2. Physicochemical characteristics—(i) vapour pressure, (ii) density, (iii) moisture
  3. Identification of propellants performance—(i) aerosol valve discharge rate, (ii) spray patterns, (iii) dosage with metered valves, (iv) net contents, (v) foam stability, (vi) particle size determination, (vii) leakage
  4. Biological testing—(i) therapeutic activity, (ii) toxicity.
- Spray pattern spray the product on the coated (dye + talc) paper. Depending upon the nature of aerosol water/oil soluble dye is used.

PRACTICE QUESTIONS

Long Answer Type Questions

1. Define the term aerosols? What are their advantages and disadvantages?
2. What are different components of an aerosol product? Discuss in brief the significance of each product?
3. What are propellants? Discuss in detail the use of various types of propellants?
4. Explain how the name of trichloromonofluoromethane (CCl_3F) is derived?
5. Discuss in detail the various methods used for the manufacture of aerosol?
6. Write short notes on the following:
   a. Compressed gases
   b. Product concentrates
   c. Basic parts of a valve assembly
   d. Containers
   e. Meterd dose inhaler
7. Write down the full forms of the followings:
   1. CFC
   2. HFC
   3. HCFC

Objective Type Questions

1. _____ are defined as the products containing therapeutically active ingredients dissolved, suspended or emulsified in a propellant or a mixture of solvent and propellant and intended for oral or topical administration into body cavities.
2. An aerosol formulation consists of two major components firstly the _____ and the _____ .
3. MDIs stands for _____ .
4. _____ is responsible for developing the proper pressure within the container of the aerosol and it expels the product when the valve is opened and aids in the atomization or foam production of the product.
5. _____ are pharmaceutical delivery systems designed for oral or nasal use, which deliver discrete doses of aerosolized medicament to the respiratory tract. Types of aerosol system there are four types of aerosol system: Solution system/ two phase system water based system/three phase system suspension or dispersion system foam system aqueous stable foam non-aqueous stable foam quick breaking foam thermal foam.
6. Net content is the difference in the weight of _____ and _____ of the container in an aerosol system.

ANSWERS

1. Aerosols
2. Product concentrate, propellant
3. Metered dose inhaler
4. Propellant
5. MDI (metered dose inhaler)
6. Gross weight, tare weight

Chapter
11

Packaging Material Science

After the manufacturing of drugs, it is essential that these should be stored properly. The stability of drug during its storage depends on so many factors as they are in direct contact with the containers and closures. So improper packing and poor quality of containers may lead to deterioration of the products. Pharmaceutical container has been defined as a device that holds the drug and it may or may not be in direct contact with the pharmaceutical preparations. Closures are the devices by means of which containers can be opened and closed.

"Packaging is the science, art and technology of enclosing or protecting products for distribution, storage, sale, and use. Packaging also refers to the process of design, evaluation, and production of packages. Packaging can be described as a coordinated system of preparing goods for transport, warehousing, logistics, sale, and end use".

PACKAGING TYPES

i. Primary packaging is the material that first envelops the product and holds it. This usually is the smallest unit of distribution or use and is the package, which is in direct contact with the contents.
ii. Secondary packaging is outside the primary packaging—perhaps used to group primary packages together.
iii. Tertiary packaging is used for bulk handling, warehouse storage and transport shipping.

FUNCTIONS OF PACKAGING

To efficiently preserve products, and to distribute and market them safely and effectively the functions of packaging are listed below:

1. **To protect the product from the environment:** Majority of the pharmaceutical products have a limited shelf life, due to interaction with their environment. This may occur during the manufacturing process, manufacturing an intermediate product, the shipping process, storage, marketing by the consumer. Products may need to be protected from many hazards components in the environment like presence of dust, microbes, yeasts and bacteria in the atmosphere.
2. **To protect the environment from the product:** Many products may be harmful to the environment, causing an adverse reaction with the environment.
3. **To maintain the product in the state in which it was produced:** Many products are manufactured to a degree of consistency that is necessary for their effective

use. For example, creams created for skin application on tender skin would be unacceptable if they were allowed to go hard and thus have an abrasive action on application. The manufacturer makes all products with a view to their final use, and any deterioration could render the product unacceptable.

4. **To safely transport the product:** Transportation through a modern transport and storage system, either within a country or via a worldwide distribution network, demands modern packaging. The journey hazards are numerous with pelletized storage; movement by fork trucks or conveyor belts; road, sea or air transport and variations in temperature and/or humidity. All potential hazards need to be thought when the product is going to arrive safely to the consumer.
5. **To identify the brand:** The majority of products and companies have a brand identity; the valuation of companies may differ significantly according to a commercial rating of their brand image. Brand loyalty amongst consumers is highly valued by the brand owners; since advertising is expensive, a strong brand loyalty can minimize the need for advertising.
6. **To sell the product to the consumer:** The pack here serves two vital purposes—to sell the product to the consumer, and to allow the consumer to recognize the product for a repeat purchase.
7. **To inform the consumer about product use:** A further function of packs is to inform the consumers of the appropriate ways to use the product and to warn them of the dangers that may exist in use. Packs also provide other information, such as ingredients lists, storage conditions, shelf life and manufacturer name.
8. **To warn the consumer of dangers:** Some products, if used incorrectly, are dangerous; thus, the pack can also be used to give warnings. Again, these warnings may be a legal requirement, or they may be placed on the pack by a concerned.
9. **To attain and maintain a cost-effective unit:** Packaging needs to be cost-effective, it must be usable and safe for the consumer, and also efficient to produce and safe to transport.
10. **To protect the consumer:** The packaging may need to have the additional requirements of 'tamper evidence'. In general, it is accepted that ideally, tamper-evident features must be seen by the consumer at the time of purchase. Tamper evidence is of no use if the consumer is unaware of the feature and how it works. Thus, any tamper-evident feature must be easily seen and easily used. Additional protection for the consumer may be required by law for certain products, such as those that could be dangerous if used incorrectly, for example, bleach or other products that may require a child-resistant cap, or warnings for blind consumers.

DESIRABLE QUALITIES OF GOOD CONTAINERS

i. The containers must be neutral towards the material which is stored in it.
ii. The containers must not react physically or chemically with the substance stored in it.
iii. It should help in maintaining the stability of product against the environment factors which cause its deterioration.
iv. It should be made of materials which can withstand wear and tear during normal handling.

v. It should be able to withstand changes in pressure and temperature. This is required in case of sterilization of parenteral products along with its container and closure.
vi. The material used for making the container should be non-toxic.
vii. The container can be labeled easily.
viii. The container must have a pharmaceutically-elegant appearance.
ix. The closure of the container must be easily removable and replaceable.

Types of Containers

Containers are divided into following types on the basis of their utility.

1. **Well closed containers:** A well-closed containers protects the contents from loss during transportation, handling, storage or sale, etc.
2. **Single dose containers:** These containers are used to supply only one dose of medicament and hold generally parenteral products, e.g. ampoules and vials.
3. **Multi-dose containers:** These containers allow the withdrawal of dose at various intervals without changing the strength, quality or purity of remaining portion. These containers hold more than one dose and are used for injectables, e.g. vials.
4. **Light resistant containers:** These containers protect the medicament from harmful effects of light. These containers are used to store those medicaments which are photosensitive.
5. **Airtight containers:** These are also called hermetically sealed containers. These containers have airtight sealing or closing. These containers protect the products from duct, moisture and air.
6. **Aerosol containers:** These containers are used to hold aerosol products. These containers have adequate mechanical strength in order to bear the pressure of aerosol packing.

MATERIALS USED FOR CONTAINERS

The containers used for pharmaceutical products are usually made from the following basis materials:

1. Glass
2. Plastic
3. Metal
4. Paper and board

Glass

Glass has always been a standard means for pharmaceutical packaging. Its physical characteristics of clarity and impermeability coupled with its inert chemical nature made it the standard starting point for package development. However, glass is not totally inert. Glass, depending on its composition, can impart hydroxyl ions to a solution; some of the chemicals used in its manufacture are leachable.

Glass Composition

The chemical materials used to make glass are sand, soda ash, and limestone. The composition of glass varies and it depends on the specific purpose for which it is used. Silicon, aluminum, boron, sodium, potassium, calcium, magnesium, zinc and barium are generally used in the preparation of glass. These materials are readily available and easily obtained from naturally occurring mineral deposits found all over the world.

Traces of other materials are added to impart clarity and hardness. Lead (Pb) provides brilliance and clarity but makes glass relatively soft and alumina (Al_2O_3) is a common addition to increase hardness and durability. Other trace materials are used to reduce seeds and blisters in glass, for example, arsenic trioxide (As_2O_3) and sodium sulfate (Na_2SO_4). A short list of the advantages and disadvantages of glass as a package is as follows:

Advantages

i. They are transparent.
ii. They are available in various shapes and sizes.
iii. They can withstand the changes in temperature and pressure during sterilization.
iv. They are cheap and easily available.
v. Amber colored glass can protect the photosensitive medicaments from light during their storage.
vi. They are neutral towards the medicament stored.
vii. They are impermeable to moisture and atmospheric gases.
viii. They provide good protection power.
ix. They can be easily labeled.
x. They can be sealed hermetically or by removable closures.

Disadvantages

i. Glass is fragile, hence easily broken down when dropped or knocked.
ii. Glass containers are heavy, which increase the cost of its transportation from one place to another.
iii. Major problem is glass containers may release alkali to aqueous preparation.

Types of glass: Glass of the following types are available commercially for making containers.

1. **Lime-soda glass:** It is composed of SiO_2, MgO and Al_2O_3. Lime-soda glass can be manufactured easily. Further, it is not so expensive. It is used for preparing containers which are meant for storage of solid medicaments. It is however not suitable as a container material for storage of parenteral products because:
   i. It liberates alkali in aqueous preparations.
   ii. On repeated use its surface loses some of its brilliance.
   iii. It is not resistant to sudden changes in temperature.
   iv. Flakes separate more easily as compared to other types of glass.
2. **Borosillicate glass:** It is composed of SiO_2 (80%), B_2O_3 (12%) Al_2O_3 (6%) and mixture of Na_2O, CaO and other oxides (2%). It is chemically more inert than lime-soda glass. It is a highly resistant glass.
3. **Sillicone treated glass:** Glass is treated with silicon so that it can be used for preparing containers to store alkali sensitive products.
4. **Sulphured glass:** It is a cheaper variety of glass used for construction of containers for parenteral products. The soda-lime glass is exposed to moist SO_2 at about 500°C to get sulphured glass. It does not liberate alkali.
5. **Neutral glass:** It is composed of SiO_2 (72–75%), B_2O_3 (7–10%), Al_2O_3 (4–6%), Na_2O (6–8%), BaO(2–4%) and K_2O (0.5–2%). It is resistant to alkalis, weather and can also withstand autoclaving. It is the capacity to filter out UV radiations.

6. **Amber colour glass:** Amber colour glass container is used for storage of photosensitive pharmaceutical products because it has the capacity to filter out UV radiations. Some preparation are very sensitive to lead or arsenic, for such preparations only containers made from glass free from lead or arsenic should be used. Containers for injectable preparations must be made from uncoloured glass. However, for substance which are highly sensitive to light coloured glass may be used but it should be transparent to permit visual inspection of its contents.

Types of Glass used for Pharmaceutical Packaging

There are four types of glass used in pharmaceutical containers. The glass performance grades or "Types" used in pharmaceutical packaging are defined precisely in the USP as type I, type II, type III, and NP glass (1). Type I glass is borosilicate glass. Type II glass is very high-quality soda lime glass. The last two are lower grades of soda lime glass and approximate glass found in packaging food and other consumer products. Their performance characteristics are listed in the USP as type III glass and NP or nonparenteral glass. Both type III glass and NP glass are acceptable for food packaging. NP glass has a highest specification for leachable components in USP's standardized test. Two limited applications for type NP glass are in packaging oral or topical products. It is not a material normally used in primary drug packaging (Tables 11.1 and 11.2).

TABLE 11.1: Types of glass

Type of glass	*Main constituents*	*Properties*	*Uses*
Type I Borosilicate glass, e.g. pyrex, borosil	SiO_2–80% B_2O_3–12% Al_2O_3–2% Na_2O + CaO–6%	Can withstand high temperature • Resistant to chemical substances • Reduced leaching action	• Laboratory glass apparatus • For injections, and • Water for injection
Type II Treated soda-lime glass	Made of soda-lime glass	• The surface of the glass is fairly resistant to attack by water for a period of time • Sulfur treated more chemically resistant	• Used for alkali sensitive products • Infusion fluids, blood and plasma • Large volume container
Type III Regular soda-lime glass	SiO_2 Na_2O CaO	• It contains high concentration of alkaline oxides and imparts alkalinity to aqueous substances, • May crack due to sudden change of temperature	• For all solid dosage forms (e.g. tablets, powders) • For oily injections
Type NP Non-parenteral glass or general purpose soda-lime glass			• For oral and • Topical purpose • Not for ampoules
Coloured glass	Glass + iron oxide	• Produce amber colour glass	• For photosensitive products

TABLE 11.2: Glass pigment colors

S. No.	*Metal compounds*	*Colours*
1.	Iron oxides	Greens, browns
2.	Manganese oxides	Deep amber, amethyst
3.	Cobalt oxide	Deep blue
4.	Gold chloride	Ruby red
5.	Selenium compounds	Reds
6.	Carbon oxides	Amber/brown
7.	Antimony oxides	White
8.	Sulfur compounds	Amber/brown
9.	Copper compounds	Light blue, red

Plastic

Plastics play a large and important role in packaging of pharmaceutical products plastic materials can be the primary, secondary and tertiary packaging material. They can be part of a composite structure of materials or an adjunct to another material to improve its properties. They can be used as the sealant, adhesive, or coating material between a wide variety of metal and paper materials. Plastic containers are very commonly used in pharmaceutical packaging because of the following advantages:

i. They are light in weight and can be handled easily.
ii. They are poor conductor of heat.
iii. They have sufficient mechanical strength.
iv. They can be transported easily.
v. They are unbreakable.
vi. They are available in various shapes and sizes.
vii. They are resistant to inorganic chemicals.
viii. They have good protection power.
ix. There are no changes of formulation of flakes as it comes in glass containers.

Disadvantages of plastics

i. They are permeable to water vapour and atmospheric gases.
ii. They cannot withstand heat without softening or distorting.
iii. They may interact with certain chemical to cause softening or distortion.
iv. They may absorb chemical substances, such as preservatives for solution.
v. They are relatively expensive.
vi. Special type of gum or adhesive required for labeling.

Depending upon the properties following plastic materials are used

Polyethylene: The basic material of polyethylene (PE) can be classified into several different forms and grades, ranging from the linear-low-density (LLDPE), through to low density (LDPE), medium-density (MDPE) and high-density (HDPE) polyethylene, each having its own specific attributes and manufacturing qualities.

LDPE is usually used for closures in the food and beverage markets since the flexibility of the material gives a good snap and reuse facility. Where tougher materials are required, the preference is for HDPE materials. HDPE materials also have better organoleptic properties and are often chosen for sensitive products.

Polypropylene: This is a common material used for closure applications, because it possesses most of the good properties of the PE range within a single material. Polypropylene (PP) makes very good hinge lids, with a good repeat performance over many closure applications; it is widely used in food, beverage, cosmetic and pharmaceutical products. There are two basic types of materials:

1. Homopolymers which have high rigidity and low impact strength.
2. Copolymers which are more flexible and perform better at low temperatures.

Due to the high rigidity of PP, due care must be given to the seal integrity when PP is used in the closure and other polymers are used in the container; in these circumstances, the use of a liner material in the cap should be considered.

Polystyrene: Similar to most other plastics materials, polystyrene (PS) is also available in more than one type. General-purpose polystyrene (GP) can be formed with high clarity, and thus it can be used for glass clear' applications. However, in this form it is very brittle and liable to shatter if it is subjected to rough treatment. Another type of polystyrene is *high impact polystyrene* (HIPS), which also has a good gloss and clarity. PS has been used for vacuum-formed trays, where the low oxygen barrier properties can be exploited to retain the red colour for meats. However, because of its brittle nature, it is liable to tearing on closing machines. With the many other materials available, the use of PS is declining in the closure industry.

Other plastics materials: Many other materials are available for closure designer to give the material the specific properties. For example, there is *acrylonitrile butadiene styrene* (ABS), which has the ability to withstand elevated temperatures without distortion; this is used for steam-sterilizable products.

In addition, one may consider nylon—this comprises a family of products that may be chosen on account of their particular attributes; for example, they are often used for cosmetics closures, since they have good scratch resistance; they may also be used for further finishing operations, such as electroplating. Another such material is *ethylene vinyl acetate* (EVA), which is mainly used as a lining material when the sealing function of the closure is paramount (Table 11.3).

TABLE 11.3: Different types of plastic materials used for preparing pharmaceutical containers

Material	*Advantages*	*Disadvantages*	*Typical uses*
High density polyethylene (HDPE) r = 0.955 g/cc	Inert, low cost, low water vapour transmission, tough	Semi-opaque, transfer of taste ingredients, absorb dilute solutions	Detergents, bleaches, milk, foods, cleansing powders, drugs and cosmetics
Low density polyethylene (LDPE) r = 0.920 g/cc	Squeeze property, inertness, low cost	Relatively poor barrier to non-polar molecules and high water vapour transmission	Cosmetics, personal products, foods
Polystyrene r = 1.05 g/cc	Clarity, stiffness, low cost	High water vapor transmission, susceptibility to cracking, poor impact	Dry drugs, petroleum jelly
Rigid polyvinylchloride (PVC) r = 1.35 g/cc	Clarity, stiffness, O_2-barrier, retention of non-polar molecules	10–12 additives may be present, difficult to process, susceptible to organic solvent	Shampoo, bath oil, detergent

(*contd.*)

TABLE 11.3: Different types of plastic materials used for preparing pharmaceutical containers (*contd.*)

Material	*Advantages*	*Disadvantages*	*Typical uses*
Polypropylene r = 0.90 g/cc.	Inert, low cost	Low temperature brittleness, high concentration of stabilizer is present	Drugs, cosmetics, syrups, juices
Polyamide (Nylon 6,10) r = 1.10 g/cc.	Good barrier for non-polar molecules, tough, good O_2-barrier, sterilizable	High cost, water absorption	Foods, drugs, cosmetics, aerosols
Polycarbonate r = 1.20 g/cc.	Very tough, clear, sterilizable	Cost, susceptibility to solvent cracking, poor barrier for water and O_2	Drugs, cosmetics
Acrylic polymers (PMMA=Polymethyl methacrylate) r = 1.10 g/cc.	Clarity, good for oils O_2	Poor water vapor transmission, poor barrier for	Drug cosmetics
Polyethylene terephthlate (PET)	Excellent strength, good barrier for gas and aroma		Bottle for carbonated waters, mineral waters mouth washes, cosmetics

Metal

Aluminum and tin plate are commonly use metals for pharmaceutical packaging. They are used to make cans, tubes and pouches. Almost all metal can need to coat or paint the metal with an organic lining to separate the product from bare metal. A wide variety of organic coatings were first to be adapted to seal or insulate the metal from the product.

The metal containers have the following advantages

i. They are sturdy.
ii. They are impermeable to tight, moisture and gases.
iii. They can be made into rigid unbreakable containers by impact extrusion.
iv. They are light in weight as compare to glass containers.
v. Labels can be printed directly on to their surface.

The metal containers have the following disadvantages

i. They are expensive.
ii. They may shed metal particles into the pharmaceutical product.
iii. They are not generally used for extemporaneous dispensing.
iv. They react with certain chemicals or drugs.

Aluminum, tin and lead are used for construction of collapsible tubes. The collapsible tubes are available in different sizes. In pharmaceutical industry the collapsible tube made from tin are preferred because they are compatible with a wide range of products. However, they are quite costly. The collapsible tubes made from aluminum are light in weight and are mostly used for toothpastes and creams. These are less costly than collapsible tubes made from tin. Lead tubes are the cheapest among all metal collapsible tubes but are not used for pharmaceutical packing due to the risk of lead poisoning. If the product is not compatible with bare metal, the interior of the collapsible tube can be coated with wax-type formulation or with resin solutions. Wax linings are used as

lining material for aluminum tubes. The epoxides and vinyls are used as lining material for aluminum tubes which gives better protection to the product filled in it.

The metal containers are also used for bulk packaging of tablets, capsules, powders and food materials, etc. Metal foil may be used for wrapping individual suppositories or pessaries. However, it is mainly used in strip packaging or blister packaging.

Paper and Board

Paper and board are used in various forms for packaging of pharmaceutical products. They are used for preparing outer containers, such as cartons, boxes, envelops and drums, to provide additional mechanical protection to other containers, e.g. strip and blister packs of tablets, capsules, suppositories and pessaries may be packed in an outer paper board carton. Collapsible tubes of ointments, creams and gels as well as liquid medicines in sizes 500 ml and below, may be packed in another paper board carton, slide paper board boxes suitable lined may be used for extemporaneous dispensed suppositories, pessaries and powders.

Package Validation

The packaging of the medical device must insure the integrity of the device, shield and protect it from mechanical damage, insure the sterile barrier is intact, and in some cases the package must act as a dispenser, a holder, or a fixture for the device. This is why the packaging must meet the same rigorous proof of performance required by a validation procedure. Maintenance of sterility is the primary concern of most agencies and is the most common defect created by exposing a medical device to general conditions found in the distribution chain including handling, dropping, or possible mishandling.

The vibration of packages by over the road vehicles and airplanes can significantly damage the device and the packaging. Common defects created by shipping and handling include slits, cuts, pinholes, tears, fractured thermoform clamshells, crushing, and deformation that may call the integrity of the package or the packaging into question.

Distribution Testing

After a package is produced, it must be tested and proven to survive the transportation and distribution environment. This means the package must protect the product through all the drops, vibrations, and other stresses normally associated with transportation and storage testing to answer these questions usually involves the following procedures:

i. **Drop testing:** Drop testing is just what the name implies and is carried out from a specified height on all sides of a package and on the corners.
ii. **Compression testing:** A compression test squeezes the package in a manner similar to it being placed on the bottom of a stack or at the bottom of a pallet.
iii. **Loose load vibration and shock testing:** Loose load vibration and shock testing subjects the package to being vibrated at a frequency and bounced multiple times. This simulates typical truck shipment.
iv. **Random vibration profile testing:** A random vibration profile subjects the package to the multiple frequencies, it would undergo during shipment.

EVALUATION OF PRIMARY PACKAGING MATERIAL

The following test are done for the evaluation of primary packaging

i. Leakage test
ii. Hydrolytic resistance collapsibility
iii. Residue on ignition
iv. Buffering capacity
v. Light transmission
vi. Water vapour permeation
vii. Heavy metals and nonvolatile residue

EVALUATION OF SECONDARY PACKAGING MATERIAL

The following test are done for the evaluation of secondary packaging

i. Testing of paper and board.
ii. Air permeability: Permeability is the mean air flow through unit area under unit pressure difference in unit time, under specific conditions.
iii. Tensile strength: The maximum tensile force per unit width that a paper or board will withstand before breaking.
iv. Cobb test: This measures the mass of water absorbed by 1 cm^2 of the test piece in a specified time under a head of 1 cm of water. It is determined by weighing before and after exposure to the water.
v. Specific tests for cartons compression: Assessment of the strength of the erected package, thereby estimating the degree of protection that it confers on the contents.
vi. Crease stiffness: Also called the crease recovery test. It is the ability to regain its former position when the bending force is removed. The increase and decrease in the inherent board stiffness after folding is measured.

QUALITY CONTROL TEST OF PACKAGING MATERIALS

A. Test for Hydrolytic Resistance (Limit of Alkalinity)

Because none of the glasses used for pharmaceutical containers is completely free from extractable alkali a test for its absence is impractical and limit tests must be used:

1. **Crushed glass test:** This test is done on all types of glass containers except surface treated glass (i.e. Type-II, sulfured or siliconed surface). The container is crushed and sieved to produce uniform particle size of which a definite weight is taken. Control of particle size and weight of powder ensures that a constant surface area is exposed to the solution.

   The measured amount of glass powder is then taken in a resistant glass beaker; measured amount of distilled water was added, autoclaved for 1/2 an hour at 121°C. The water was then cooled and filtered. Filtrate is titrated with standard H_2SO_4.
2. **Whole container test:** In case of surface treated glass container the intact container is taken, filled with distilled water and exposed to the autoclaving condition. The extracts from several containers are pooled and titrated with standard HCl (according to IP) (Table 11.4).

TABLE 11.4: Types of glass and tests

Type	*Description*	*Test used*	*Size (ml)*	*Limits*
				Volume of 0.05 N H_2SO_4 to neutralize the extract from 10 g of glass (ml)
I	Highly resistant Borosilicate glass	Crushed glass	All	1.0
II	Treated soda-lime glass	Whole container	100 or less Over 100	0.7 0.2
III	Soda -lime glass	Crushed glass	All	8.5
NP	General purpose soda-lime glass	Crushed glass	All	15.0

B. Metal Containers for Eye Ointments

Metal collapsible tubes comply with the following test for metal particles.

Empty tubes are taken, filled with ointment base, sealed and kept overnight. Now, a metal bacteriological filter assembly fitted with a suitable filter paper was taken and heated to the melting range of the ointment base.

Ointment bases from all the tubes squeezed at a certain rate, pooled and passed through the heated filter under vacuum. The filter paper is washed with chloroform. The filter paper is dried and observed with magnifying glass under oblique light. The observations are noted as follows:

Particles 1 mm and above	50
Particles 0.5 mm to 1 mm	10
Particles 0.2 mm to 0.5 mm	2
Particles less than 0.2 mm	Nil
Total score	**62**

The lot of tube passes the test if the total score is less than 100 points. If the score is above 150, the lot fails. If it is between 100 and 150 the test is repeated again with 50 more tubes. This time the lot will pass if total 100 tubes give 150 points.

C. Plastic Containers

i. **Leakage test:** Ten containers are filled with water, fitted with the closures and are kept inverted at room temperature for 24 hours. There should be no signs of leakage from any container.

ii. **Collapsibility test:** This test is applicable to containers which are to be squeezed in order to remove the contents. The container, by collapsing inwards during use, yields at least 90% of its nominal contents at the required rate of flow at ambient temperature.

iii. **Transparency test:** A 16-fold dilution of a standard suspension is prepared so as to give an absorbance of 0.37 to 0.43 at about 640 nm.

Five empty containers were filled to their nominal capacity suspension in each container is detectable when viewed through the containers, as compared with a container of the same type filled with water.

iv. **Water vapor permeability test:** Five containers are filled with nominal volume of water and heat sealed with aluminium foil-polyethylene laminate or other suitable seal. Each container is accurately weighed and allowed to stand for 14 days at a relative humidity of 60 ± 5% and a temperature between 20 and 25°C.

After 14 days, it is weighed again. The loss in weight in each container is not more than 0.2%.

Other tests include

- Tests for barium, heavy metals, tin, zinc, etc.
- Test on extracts: Specified volume of extracting medium is taken in it. Plastic of specified surface area is cut and extracted. With the extract following tests are carried out:

i. Appearance of the extract—must be colourless
ii. Light absorption
iii. Non-volatile matter
iv. Residue on ignition
v. Heavy metals
vi. Buffering capacity
vii. Oxidisable substances

ISOLATED KEY POINTS

- Packaging is the science, art and technology of enclosing or protecting products for distribution, storage, sale, and use. Packaging also refers to the process of design, evaluation, and production of packages. Packaging can be described as a coordinated system of preparing goods for transport, warehousing, logistics, sale, and end use.
- Primary packaging is the material that first envelops the product and holds it.
- Secondary packaging is outside the primary packaging–perhaps used to group primary packages together.
- Tertiary packaging is used for bulk handling, warehouse storage and transport shipping.
- Well-closed containers: A well-closed containers protects the contents from loss during transportation, handling, storage or sale, etc.
- Single dose containers: These containers are used to supply only one dose of medicament and hold generally parenteral products, e.g. ampoules and vials.
- Multi-dose containers: These containers allow the withdrawal of dose at various intervals without changing the strength, quality or purity of remaining portion. These containers hold more than one dose and are used for injectables, e.g vials.
- Light-resistant containers: These containers protect the medicament from harmful effects of light. These containers are used to store those medicaments which are photosensitive.
- Air-tight containers: These are also called hermetically sealed containers. These containers have air-tight sealing or closing. These containers protect the products from duct, moisture and air.

- Aerosol containers: These containers are used to hold aerosol products. These containers have adequate mechanical strength in order to bear the pressure of aerosol packing.
- The containers used for pharmaceutical products are usually made from the following basis materials glass, plastic, metal, paper and board.
- Lime-soda glass: It is composed of SiO_2, MgO and Al_2O_3 lime-soda glass can be manufactured easily. Borosillicate glass: It is composed of SiO_2 (80%), B_2O_3 (12%) Al_2O_3 (6%) and mixture of Na_2O, CaO and other oxides (2%). It is chemically more inert than lime-soda glass. It is a highly resistant glass.
- Sillicone-treated glass: Glass is treated with silicon so that it can be used for preparing containers to store alkali sensitive products.
- Sulphured glass: It is a cheaper variety of glass used for construction of containers for parenteral products. Neutral glass: It is composed of SiO_2 (72–75%), B_2O_3 (7–10%), Al_2O_3 (4–6%), Na_2O (6–8%), BaO(2–4%) and K_2O (0.5–2%). It is resistant to alkalis, weather and can also withstand autoclaving. It is has the capacity to filter out UV radiations.
- Amber colour glass: Amber colour glass container is used for storage of photo-sensitive pharmaceutical products because it has the capacity to filter out UV radiations.
- Type I: Borosilicate glass, e.g. pyrex, borosil can withstand high temperature—resistant to chemical substances, reduced leaching action, laboratory glass apparatus—for injections and for water for injection.
- Type II: Treated soda-lime glass—made of soda lime glass—the surface of the glass is fairly resistant to attack by water for a period of time used for alkali sensitive products—infusion fluids, blood and plasma—large volume container.
- Type III: Regular soda-lime glass it contains high concentration of alkaline oxides and imparts alkalinity to aqueous substances may crack due to sudden change of temperature for all solid dosage forms (e.g. tablets, powders), for oily injections.
- Type NP: Non-parenterals glass or general purpose soda-lime glass—for oral and topical purpose, not for ampoules.
- Coloured glass: Glass + iron oxide—produce amber colour glass—can resist radiation from 290–450 nm—for photosensitive products.
- Plastic materials can be the primary packaging material, the material that contacts the product being protected often referred to as the primary package, or they can be used in other parts of the
- Metals like aluminum, tinplate, and steel are the three primary metals used to make metal cans.
- Paper and board are used in various forms for packaging of pharmaceutical products. They are used for preparing outer containers , such as cartons, boxes, envelops and drums, to provide additional mechanical protection to other containers, e.g. strip and blister packs of tablets, capsules, suppositories.
- Test done for the evaluation of primary packaging are leakage test, hydrolytic resistance collapsibility, residue on ignition, buffering capacity, light transmission, water vapour permeation, heavy metals and non-volatile residue.

- For quality control of packaging materials the following test are done

i. Crushed glass test
ii. Whole container test
iii. Leakage test
iv. Collapsibility test
v. Transparency test
vi. Water vapor permeability test

PRACTICE QUESTIONS

1. Define the term pharmaceutical packaging? What are the various types of packaging?
2. Give function so packaging? What are the desirable qualities of good container?
3. Enlist various types of containers, give there examples?
4. write short notes on:
   a. Glass
   b. Plastic
   c. Metal
   d. Paper and board
5. What are the various types of glass used for pharmaceutical packaging?
6. Give advantages and disadvantages of plastic as a pharmaceutical packaging material.
7. Give advantages and disadvantages of metal as a pharmaceutical packaging material.
8. Enumerate various package validation methods.
9. Give evaluation methods of primary and secondary package.
10. Discuss in detail about various package testing methods.

Objective Type Questions

1. Packaging protects products during _____ and use.
2. _____ is the material that first envelops the product and holds it, while _____ is used for bulk handling, warehouse storage and transport shipping.
3. _____ containers hold more than one dose and are used for injectables, e.g vials.
4. Light resistant containers protect the medicaments which are _____ .
5. Air-tight containers are also called _____ .
6. The containers used for pharmaceutical products are usually made from materials like _____ .
7. Match the following:

S. No.	*Type of glass*		*Example of glass*
1.	Type I	a	Regular soda-lime glass, e.g. tablets, powders
2.	Type II	b	Borosilicate glass, e.g. pyrex, borosil
3.	Type III	c	Treated soda-lime glass—made of soda lime glass
4.	Type IV	d	NP—non-parenteral glass

8. Which of the following test is not done for quality control of packaging materials

i. Crushed glass test
ii. Whole container test
iii. Leakage test
iv. Disintegration test
v. Transparency test

ANSWERS

1. Distribution, storage, sale
2. Primary packaging, tertiary packaging
3. Multi-dose
4. Photosensitive
5. Hermetic containers
6. Glass, plastic, metal, paper and board
7. 1—b, 2—c, 3—a, 4—d
8. iv

Chapter
12

Experiments in Formulative Pharmacy

Object: To perform pre-formulation studies for preparing granules

Theory: *Granulation* is a method for, improving the flowability of powder drugs. It includes converting the powder of the drug into agglomerates of small particles (free flowing coarse powder) to be administered as such or to be tabulated or encapsulated. Granulation also allows the addition of flavoring and coloring agents and produces an easily handled. Granules can be manufactured by dry granulation (by compaction or slugging) or wet granulation (using aqueous solvent or non-aqueous solvent).

Selection of granulation process depends on physiochemical characteristic of active pharmaceutical ingredients (API). Physiochemical properties of API need to be evaluated before preparing granules are:

1. Aqueous stability: If API is prone for hydrolytic degradation, then dry granulation is preferred.
2. API content is high and flow is poor: Granulation (dry or wet) over direct blending.
3. API content is high and bulk density is very low: Granulation (dry or wet) over direct blending.
4. API content is low and particle size distribution is fine: Wet granulation process is preferred for better mixing.
5. API is poorly soluble: To improve solubility of API, wet granulation process can be used by dissolving API (along with soluble polymer) in solvent and loading over diluent.
6. API is hygroscopic and deliquescent: Wet granulation process not preferred.

Experiments for Evaluating Physiochemical Properties before Granulations

Determination of API PSD (particle size distribution) by sieve analysis:

Apparatus required

i. Stack of sieves including pan and cover
ii. Balance (with accuracy to 0.01 g)
iii. Mechanical sieve shaker

Test procedure

1. Take sample of about 100 g of any API.
2. Prepare a stack of sieves. Sieves having larger opening sizes (i.e. lower numbers) are placed above the ones having smaller opening sizes (i.e. higher numbers).

S.No	Sieve number	Opening size (mm)
1.	12	1.680
2.	16	1.180
3.	20	0.850
4.	30	0.600
5.	40	0.425
6.	60	0.250
7.	80	0.180
8.	100	0.150
9.	140	0.106
10.	200	0.075

(**Note:** Number of sieves can be reduced or increased)

3. Weigh all sieves and the pan separately (fill in column 3).
4. Pour the sample into the stack of sieves from the top and place the cover, put the stack in the sieve shaker and fix the clamps, adjust the time on 10 to 15 minutes and get the shaker going.
5. Stop the sieve shaker and measure the mass of each sieve + retained sample (fill in column 4).

1 Sieve #	*2 Sieve size (mm)*	*3 Mass of each sieve (g)*	*4 Mass of each sieve + retained sample*	*5 Mass of sample retained-Wn (g) Coln 4–Coln 3*	*6 Percentage on each sieve Rn Coln. 5/Wt (100 gm)*100*	*7 Cumulative percent retained S Rn*
12	1.680					
16	1.180					
20	0.850					
30	0.600					
40	0.425					
60	0.250					
80	0.180					
100	0.150					
140	0.106					
200	0.075					

Calculation

Column 5 = Column 4–Column 3

Column 6 = Column 5/(Total mass in step 1 = 100 gm)

Calculate the cumulative percent of sample retained on the 7th sieve, = **S** Rn

Make a graph by keeping cumulative percentage retained on y-axis and PSD on x-axis.

Determination of API Hygroscopicity

Apparatus required

i. Glass weighing vessel
ii. Desiccators with 80% RH (prepared by saturated solution of ammonium chloride or ammonium sulphate)
iii. Weighing balance.

Procedure

1. Place the API in the vessel (Petri dish, weight m_1) and weigh (vessel + API weight, m_2).
2. Place the vessel in a desiccator at 25 °C containing a saturated solution of ammonium chloride or ammonium sulphate or place it in a climatic cabinet set at 25 ± 1 °C and 80 ± 2 percent relative humidity.
3. Allow to stand for 24 hr and take weight (sample + vessel + moisture weight, m_3).
4. Calculate the percentage increase in mass using the expression:

$$\frac{m_3 - m_2}{m_2 - m_1} \times 100$$

The result is interpreted as follows:

i. Deliquescent: Sufficient water is absorbed to form a liquid.
ii. Very hygroscopic: Increase in mass is equal to or greater than 15 percent.
iii. Hygroscopic: Increase in mass is less than 15 percent and equal to or greater than 2 percent.
iv. Slightly hygroscopic: Increase in mass is less than 2 percent and equal to or greater than 0.2 percent.

Evaluation of API Flow

API flow can be evaluated using angle of repose and Hausner ratio or compressibility index.

Angle of Repose

Apparatus required

- Funnel
- Funnel holder

Procedure

1. Pour API through the funnel from a fixed height on a level surface allowing powder to make the heap.
2. Care should be taken to prevent vibration as the funnel is moved. The funnel height should be maintained approximately 2–4 cm from the top of the powder pile.
3. Measure the height of the pile from the peak to the ground by using the ruler.
4. Measure the horizontal distance from the middle of the pile to the edge was measured by using the ruler. (Width = Diameter of circle/2).
5. The equation tan 1 (height/width) had been used to find the angle of repose.

Inference: Flow properties evaluated against the angle of repose. Flow property corresponding angle of repose given below.

Flow property	*Angle of repose (degrees)*
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	45–55
Very poor	56–65
Very, very poor	>66

Flow property corresponding angle of repose.

Hausner ratio and compressibility index: These two parameters deduced from bulk density and tap density.

Procedure for measuring bulk density and tap density:

Bulk density (untapped density)

1. Takea 250 ml clean and dry graduated measuring cylinder.
2. Take about 20 g to 25 g of test sample and carefully transfer into the above cylinder with uniform flow.
3. Carefully level the test sample and note down the occupied volume (V_1) to the nearest ml.

Calculate the untapped density as follows.

$$\text{Untapped density} = \frac{\text{Weight of the test sample taken in g}}{\text{Volume of the test sample before tapping in mL}}$$

Tapped density

1. Fix the above measuring jar in the place provided in the bulk density apparatus.
2. Switch on the instrument for tapping and enter the No. of taps as 10 and start.
3. After 10 taps stop the instrument, remove the cylinder from the instrument and note down the occupied volume (V_2) of the test sample in ml.
4. Again perform 500 taps and measure the occupied volume (V_3). Again perform 750 taps and measure the occupied volume (V_4).

Calculate the difference between first tapping and second tapping by the following formula.

If the difference in volume is more than 2% when compared to the occupied volume after the first tapping, again repeat the tapping with No. of taps as 1250.

Calculate the tapped density as follows.

$$\text{Tapped density} = \frac{\text{Weight of the test sample taken in g}}{\text{Volume of the test sample after tapping in mL}}$$

Compressibility (Carr's) index and Hausner ratio calculation:

$$\text{Compressibility index} = 100 \times [(\rho_{tapped} - \rho_{bulk})/\rho_{tapped}]$$

$$\text{Hausner ratio} = (\rho_{tapped}/\rho_{bulk})$$

Inference: Flow properties evaluated against the compressibility index and Hausner ratio. Flow property corresponding compressibility index and Hausner ratio given below.

Compressibility index (%)	*Flow character*	*Hausner ratio*
Less than 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
More than 38	Very, very poor	More than 1.6

Flow property corresponding compressibility index and Hausner ratio.

Biopharmaceutical classification system (BCS) solubility: Solubility of highest strength in 250 ml of media (media across pH range: pH 1.2 to pH 6.8).

Procedure

1. Take API equivalent to highest strength.
2. Prepare 3 solutions (0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer). These media is to be prepared as per USP.
3. Add API equivalent to highest strength in each media and shake vigorously.

Result: If clear solution forms in all the three media than BCS solubility of API is good.

Object: To prepare and submit 100 gm of effervescent granules of sodium citrotartarate.

Theory: *Granulation* is a method for improving the flow ability of powder drugs. It includes the converting the powder of the drug into agglomerates of smaller particles (free flowing coarse powder) to be administered as such or to be tabulated or encapsulated. Granulation also allows the addition of flavoring and coloring agents and produces an easily handled, attractive, palatable product. Granules can be prepared in different forms.

1. **Non-effervescent granules** that contain in addition to the drug other additives such *as sugar, lactose, starch,* etc. All ingredients are moistened and made as a wetted mass with a granulating agent such water, starch mucilage, gelatin and sucrose solutions or dilutions of alcohols. The mass is then pressed through a sieve of appropriate size and the resulting granules dried. The granules should be uniform in size as possible.
2. **Effervescent granules** that effervesce on addition to water, and **usually contain mixture *of citric, tartaric acids with bicarbonate soda* and** usually some medicaments and occasionally sugar. They are dissolved in water for purposes of administration and taken during effervescence or immediately thereafter.

The effervescent granules are popular in use due to the pleasant taste of carbonated solution and to psychological effect.

A mixture of acids will be used because tartaric acid produces *a chalky* friable granules and citric acid is *too sticky to be manipulated.* It is desired that *citric acid and tartaric acid* are to be used in the *ratio of 1:2* respectively.

Observation table

S. No.	Ingredients	Quantity for 1000 gm	Quantity for 100 gm
1.	Sodium bicarbonate	450	45
2.	Citric acid	170	17
3.	Tartaric acid	250	25
4.	Sucrose	130	13

Note: For preparation of effervescent granules, citric acid should be powdered just prior to use. Sodium bicarbonate should be powdered and dry. Other ingredients should be dried to 100°C until they cease to loss weight. All ingredients should be passes through sieve No. 60. The effervescent mixtures of this kind react very rapidly when added to water and in many cases part of the draught is lost due the violence of the effervescence.

Procedure

1. All the ingredients are finely powdered and passed through sieve No. 60.
2. Magnesium sulfate must be exsiccated by heating in a clean dry porcelain dish on direct-flame till completely dry.
3. The powders are mixed homogenously, massed with 95% ethanol. The produced dough is passed through a sieve No. 10.
4. The resultant granules are dried in hot air oven at 40°C for 4 hours.

Category: Effervescent tablet.

Storage: Store in a cool and dry place, away from sunlight.

Direction: To be dissolved in water before use.

Use: As an antacid.

Object: To prepare and compress 30 tablets each contains 0.9 g sodium chloride by direct compression method.

Theory: A compressed tablet is unit dosage form prepared by compression under several hundred kilograms of pressure per square centimeter, granulated medicinal or powdered substances into a, discoid shape by means of dies. Tablets usually consist of several materials in addition to the medicament that they convey to the patient. These components have different functions. Although all of them furnish bulk or volume to the tablets, they are usually classified according to the principle function in *the tablet.* Therefore, the word diluent or bulking agent applies only to those substances that usually make up the major portion of the tablet. Substances that bind powders together and make then cohesive are the "binders".

Tablet ingredients: Materials that help the tablet to break up and dissolve to release the medicament are the disintegrates. In order for granules to flow from a hopper on the tablet press to the die and for consistent and uniformly fill, substances called "glidants" are added to the formula. Once the tablet has been compressed, it will not release from the die unless a "lubricant' is present in sufficient amount. Sometimes the compressed tablet leaves a film on the punches and "anti-adhesives" are needed to

prevent this. The last three substances frequently have interrelated properties. Ingredients sometimes added but not essential for tabletting are dyes, flavors, sweetness, adsorbents, and buffers.

A compressed table is a unit dosage form prepared by compressing medicinal substance in a powder or granular form under several hundred kilograms of force per square centimeter into the required shape by means of punches and dies. There are approximately 360 official tablets. Tablets usually consist of several materials in addition to the drug called *excipients.* These excipients are classified according to their principle function they exert in the tablets.

Diluents, fillers: These substances are added to increase the volume of tablet, e.g. lactose, sorbitol, sucrose.

Binders or adhesives: These are substances that bind all the powder together to make them as cohesive paste. Binders may be added in a dry or in solution form. Binders are either polysaccharides polymeric material. Examples of binder used are gum acacia, gelatin and cellulose derivatives.

Disintegrants: These are materials that help tablet break up into small particles in the gastrointestinal tract, e.g. starch, alginates, cellulose derivatives, and lactose.

Lubricants: These are agents that reduce the friction between the tablet edges and die wall during the election cycle. They are usually added at the very last step before compression. They present on the granules surfaces and in between them and the Parts of the tablet press. *Example:* Magnesium stearate, stearic acid, talc.

Glidants: These are those substances which improve the flow characteristics of granulation, for example, talc.

Anti-adherents: These are materials used to prevent tablet sticking to the faces of punches and die walls. *Example:* Talc.

Other table components: These are coloring agents, flavors, sweeteners and adsorbents, etc.

Observation table

S. No.	*Ingredients*	*Quantity used*
1	Sodium chloride	0.9 g

Procedure

1. Screen sodium chloride crystals through a No. 16–22 sieve. This step is necessary to breakdown lumps and to produce a uniform granular powder.
2. Adjust the tablet machine to 1/2 gm size tablet.
3. Fill the sodium chloride into the feeder (hopper) of tablet machine whose dosing unit has been adjusted for compressing tablets having weight 0.5 gm. Check on the weight of the tablets every now and then adjust the machine accordingly. One tablet dissolved in sufficient water for injection and the volume completed to 100 ml.

Category: Tablet.

Storage: Store in a cool and dry place, away from sunlight.

Direction: To be swallowed with water.

Use: Tablets used in preparation of isotonic solutions.

Object: To prepare and compress 20, tablets each contains sodium bicarbonate by wet granulation method.

Theory: A compressed tablet is unit dosage form prepared by compression under several hundred kilograms of pressure per square centimeter, granulated medicinal or powdered substances into a discoid shape by means of dies. Tablets usually consist of several materials in addition to the medicament that they convey to the patient. These components have different functions. Although all of them furnish bulk or volume to the tablets, they are usually classified according to the principle function in *the tablet*. Therefore, the word diluent "or" bulking agent applies only to those substances that usually make up the major portion of the tablet. Substances that bind powders together and make then cohesive are the "binders".

Tablet ingredients: Materials that help the tablet to break up and dissolve to release the medicament are the disintegrates. In order for granules to flow from a hopper on the tablet press to the die and for consistent and uniformly fill, substances called "glidants" are added to the formula. O*n*ce the tablet has been compressed, it will not release from the die unless a "lubricant' is present in sufficient amount. Sometimes the compressed tablet leaves a film on the Punches and "anti-adhesives" are needed to prevent this. The last three substances frequently have interrelated properties. Ingredient sometimes added but not essential for tabletting are dyes, flavors, sweetness, adsorbents, and buffers.

A compressed table is a unit dosage form prepared by compressing medicinal substance in a powder or granular form under several hundred kilograms of force per square centimeter into the required shape by means of punches and dies. There are approximately 360 official tablets. Tablets usually consist of several materials in addition to the drug called *excipients.*

These excipients are classified according to their principle function they exert in the tablets.

Diluents, fillers: These substances are added to increase the volume of tablet, e.g. lactose, sorbitol, sucrose.

Binders or adhesives: These are substances that bind all the powder together to make them as cohesive paste. Binders may be added in a dry or in solution form. Binders are either polysaccharides polymeric material. Examples of binder used are gum acacia, gelatin, cellulose derivatives.

Disintegrants: These are materials that help tablet break up into small particles in the gastrointestinal tract. *Examples:* Starch, alginates, cellulose derivatives, and lactose.

Lubricants: These are agents that reduce the friction between the tablet edges and die wall during the ejection cycle. They are usually added at the very last step before compression. They present on the granules surfaces and in between them and the Parts of the tablet press. *Example:* Magnesium stearate, stearic acid, talc.

Glidants: These are those substances which improve the flow characteristics of granulation, for example, talc.

Anti-adherents: These are materials used to prevent tablet sticking to the faces of ft punches and die walls. *Example:* Talc.

Other table components: These are coloring agents, flavors, sweeteners and adsorbents, etc.

Observation table

S. No.	*Ingredient*	*Quantity*
1.	Sodium bicarbonate	300 mg
2.	Peppermint oil	0.003 ml
3.	Acacia powder	3%
4.	Acacia mucilage	qs (25%)
5.	Magnesium stearate	0.25%; 0.75%
6.	Talc purified	1%

Procedure

1. Acacia mucilage is prepared by dissolving 5 gm of powdered acacia in 10 ml of water and stirring until the acacia is dissolved then complete to 20 ml warm water.
2. Sodium bicarbonate mixed with powdered acacia.
3. The pervious mixture moistened with the acacia solution.
4. Wet mass is pressed through a sieve 0.84 mm.
5. Granules are dried at temperature not exceeding 60°C and sieved to remove powder and small granules.
6. Peppermint oil is added. The oil is dissolved in little alcohol and sprayed on the dry granules, which are continually turned over during the process.
7. Finally, lubricants are added and the whole are shaken in a dry way.
8. Granulation is transferred to the hopper of tablet machine adjusted for compression of tablets having calculated final compression weight.

Category: Tablet.

Storage: Store in a cool and dry place, away from sunlight.

Direction: *To be swallowed with water.*

Use: Used as gastric antacid, in treatment of systemic acidosis. It can be used locally on the skin in the form of moist paste or solution. In this form, it is an effective antipruritic.

Object: To perform various evaluation tests of tablets.

Theory: Tablets are evaluated by a variety of methods.

A. Unofficial tests

1. Tablet hardness: The tablets must be hard enough to withstand mechanical stress during packaging, shipment, and handling by the consumer. Section <1216> of the USP 24/NF19 outlines a standard tablet friability test applicable to manufactured tablets. Most compounding pharmacy would not have the apparatus specified in Section <1216>. However, there are several hand operated tablet hardness testers that

might be useful. Examples of devices are the Strong Cobb, Pfizer, and Stokes hardness testers. The principle of measurement involves subjecting the tablet to an increasing load until the tablet breaks or fractures. The load is applied along the radial axis of the tablet. Oral tablets normally have a hardness of 4 to 8 or 10 kg; however, hypodermic and chewable tablets are much softer (3 kg) and some sustained release tablets are much harder (10–20 kg).

Experiment: **Determination of tablet hardness**

Using a hardness tester (Monsanto), determine the hardness of the four (4) different types of tablets supplied. Use an average of three measurements for each determination and comment on your results.

Tablet type	*Hardness 1*	*Hardness 2*	*Hardness3*	*Mean hardness*

Results

2. Friability test: This test is designed to measure the ability of the tablet to withstand handling and transportation.

Procedure: Using Roche Friabilator

1. Take 20 tablets dedust and weigh them (wo).
2. Place tablets in friability drum, switch on the apparatus adjusting the timer to 4 min, and the speed at 25 rpm.
3. At the end of the operation the tablets are removed, de dusted and re-weighed (w). should any tablet break the batch is rejected.
4. Friability B is expressed as a percentage loss in weight
   $B = 100 (1 - (w/wo))$
5. If value of B is 1.0% or less, the batch is accepted.

B. Official standards (USP)

Experiment: **Tablet disintegration:** Disintegration is an essential attribute for tablets intended for administration by mouth, except those intended to be chewed before being swallowed and except some types of sustained release tablets.

Disintegration (for uncoated tablets): This test is provided to determine compliance with limits on disintegration stated in the individual monograph. Disintegration does not imply complete solution of the tablet or even its active constituent. Complete disintegration is defined as that state in which any residue of the tablet remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

Procedure

1. Place one tablet in each of the six tubes of the basket, add a disk to each tube
2. Operate the apparatus, using water maintained at (37 + 2)°C as the immersion fluid unless another fluid is specified in the individual monograph.
3. At the end of the time limit specified in the individual monograph, left the basket from the fluid and observe the tablets: All of the tablets have disintegration

completely. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets: Not less than 16 of the total of 18 tablets tested disintegrate completely.

II. Tablet dissolution: Disintegration time determination is a useful tool for production control, but disintegration of a tablet does not imply that the drug has dissolved. A tablet can have a rapid disintegration time yet be biologically unavailable. The dissolution rate of the drug from the primary particles of the tablet is the important factor in drug absorption and for many formulations is the rate-limiting step. Therefore, a dissolution time is more indicative of the availability of a drug from a tablet than the disintegration test. Even though this is an important parameter to measure.

Place the stated volume of dissolution medium in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the dissolution medium to 37 ± 0.5°C and remove the thermometer. Place one tablet in the apparatus, and operate at the specified rate of the monograph. At the time specified, withdraw a sample and perform the analysis as in the monograph. Repeat the test with additional tablets.

Unless otherwise specified in the individual monograph and the requirements are met if the quantities of active ingredient dissolved from the tablets tested conform to the accompanying acceptance table.

S. No.	*Stage*	*Number*	*Tested*	*Acceptance criteria*
1.	S1	6		
2.	S2	6		
3.	S3	12		

Acceptance table: Each tablet is not less than Q + 5%, for S1 (six tablets)

Average of 12 tablets (S1 + S2) is equal to or greater than Q, and no unit is less than Q – 15%. Average of 24 tablets (S1 + S2 + S3) is equal or greater than Q and not more than two tablets are less than Q – 15% and no tablet should be less than Q – 25%.

The quantity Q, is the amount of dissolved active ingredient specified in monograph expressed as a percentage of the labeled content.

Dissolution test for aspirin tablets (uncoated)

Medium : 0.05 M acetate buffer having pH of 4.5; 500 ml.

Time: 30 min, Q: 75%.

RPM: 50

Apparatus type: Paddle

Assay procedure

1. At the time specified, 2 ml aliquot is pipetted out through a Millipore filtration unit and placed in a 50 ml volumetric flask. Then add 2 ml dissolution medium to the dissolution vessel.
2. After adjusting volume to 50 ml with 0.1 N sulfuric acid, the absorbance of each solution is measured at 228 nm.
3. The amount of aspirin dissolved (C) = (Absorbance × Conc. factor × Dil. factor × Dissolution medium volume) = (Absorbance × 0.02 × 25 × 500) mg.

4. Percentage of Aspirin dissolved at time specified = C/Label Claim × 100 = C/325 × 100.

Object: Evaluation of capsule dosage forms (BP)

Theory

Disintegration test: The disintegration test determines whether tablets or capsules disintegrate within a prescribed time when placed in an aqueous medium under the prescribed experimental conditions.

Disintegration is the state in which no residue, except fragments of capsule shell, remains on the screen of the test apparatus or adheres to the lower surface of the disc, if a disc has been used.

Procedure

1. Introduce one capsule into each tube and suspend the apparatus in the beaker containing water.
2. If the hard capsule floats on the top of water, the disc may be added.
3. Operate the apparatus. Record the time. Remove the assembly from the liquid. The capsules pass the test if no residue remains on the screen of the apparatus.
4. The capsules should disintegrate within 30 minutes, unless otherwise justified.

Uniformity of weight: This test is to be done on 20 capsules.

Procedure

1. Weigh an intact capsule.
2. Open the capsule without losing any part of the shell and remove the contents as completely as possible. Weigh the shell.
3. The weight of the contents is the difference between the two weightings.
4. Repeat the procedure for further 19 capsules selected at random.
5. Determine the average weight.
6. Compare the average weight to the table below, to determine the % deviation permitted.
7. Calculate the upper and lower limits at the % deviation stated, and at double that percentage.
8. Compare the individual weights of the capsule contents to the upper and lower limits calculated at the % deviation stated, and at double that %.
9. Limit: Not more than two capsules of the individual weights deviate from the average weight by more than the % deviation listed in the table, and none deviates by more than twice that %.

Average weight of capsule content (mg)	*% deviation*
Less than 300	10
300 or more	7.5

Results of disintegration test: Time recorded for the capsules to break into particles and pass to the liquid medium = _____ minutes.

Results of weight variation test

Average weight of the contents = (total wt. of the contents/20)

% deviation permitted (from the table) =

Upper limit (at % deviation) = av. Wt. + (%/100 × av.wt.)

Lower limit (at % deviation) = av. Wt. – (%/100 × av.wt.)

Upper limit (at double % deviation) = av. Wt. + (double%/100 × av.wt.)

Lower limit (at double % deviation) = av. Wt. – (double%/100 × av.wt.)

Capsule No.	*Wt. of intact capsule*	*Wt. of the empty shell*	*Wt. of the content*	*Comparison at % deviation*	*Comparison at double % deviation*
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					
13.					
14.					
15.					
16.					
17.					
18.					
19.					
20.					
			Σ =		

Object: To perform film coating of dummy tablets.

Equipment required

1. Tablet compression machine
2. Coating machine
3. Vessel
4. Stirrer

Observation table: Formula of dummy core tablets

Ingredients	*Category*	*mg/tablet*
Lactose/microcrystalline cellulose*	Diluent	186
PVP/HPMC	Binder	6
Crosscarmellose sodium/crospovidone	Disintegrant	6
Magnesium stearate	Lubricant	2
Total		200 mg

*Either one or mixture of the diluents can be used. Use diluent with good flow.

Observation table

Sr. No.	*Ingredient name*	*Composition*	*Activity*
1.	Hydroxypropyle cellulose 2910 (E-3 or E-5)	91.5%	Film-forming agent (polymer)
2.	Triacetin**	8.0%	Plasticizer
3.	Talc	0.5%	Anti-tacking agent

** Plasticizer can be change to PEG-400

Procedure

A. Core tablets

1. Sift all core ingredients through suitable sieve.
2. Mix ingredients of step 1 for 10 minutes.
3. Compress step 2 blend using compression machine with suitable punches at appropriate hardness.

Note: Tablet compressed should be concave (not flat) for proper rolling during coating.

B. Preparation of coating dispersion

1. Dispense quantity of coating material based on batch size and percentage coat.
2. Mix all the coating ingredients.
3. Sift it through suitable sieve and blend them for 5–10 minutes.
4. Disperse step 3 blend in water using stirrer. Water quantity is to be taken to make dispersion with solid concentration of 10–15% w/w.
5. Keep step 4 dispersion on stirring for 45–60 minutes.
6. Pass step 5 dispersion through filter, if required. This step can be avoided, if dispersion is uniform without lumps.

C. Coating

1. Pre-warming
   a. Pre-warm core tablets in coating pan in inching mode (or slow rpm) keeping inlet temperature around 50–65°C. Till product temperature reaches 40°C.
   b. Take average weight of 50 tablets.
2. Coating
   a. Coat core tablet using coating dispersion by keeping following parameters:
   Equipment name: Ganscoater GAC275.
   Note: Coater can be neocota, accelacota any other with different capacity.

% damper position: 100% open (both inlet and outlet), for small equipment like GAC275. This is to get required air flow (CFM). For larger capacity, CFM can be arranged based on requirement.

Pump RPM: 1–15 (depend on desired spray rate)

Pan RPM: 01–15 (to get desired rolling)

Inlet temperature: 50–65°C (to evaporate water)

Exhaust temperature: 40–55°C

Bed temperature: 40–52°C

Inlet temperature is set, bed and exhaust temperature are the output. Inlet temperature is set based on spray rate, CFM and polymer coating base (like for said experiment, it is HPMC).

Pan load: 500 g (based on equipment capacity and tablet shape/size)

Gun nozzle: 1 mm

Atomization pressure: Set to get desired droplet.

Pattern pressure: To get desired spray pattern. For some spray system this is not available.

b. Check weight gain and stop the process, once desired weigh gain achieved.

3. **Curing:** Dry the coated tablets for 5–10 minutes at slow rpm.
4. Evaluated tablets with respect to physical attributes (like appearance, DT, hardness, thickness, average weight gain, individual tablet weight variation).

   Note: In general for film coating, weight gain is 3 ± 1.5% (1.5–4.5%).

Object: To evaluate glass containers by conducting vacuum leak test (blue dye test)

Theory: Ampoule pack is one of the most common packing available in the market. Sealing of ampoule is the most critical aspect of Ampoule packing. If sealing does not happen properly and moisture penetrates inside the blister, it can impact drug product (tablet and capsule) stability. Blue dye leak test is one of the common in-process test for checking proper sealing of blisters.

Apparatus and material required

1. Ampoule
2. Blue dye
3. Desiccator
4. Vacuum pump
5. Absorbent cloth

Procedure

1. Fill 1/3 of the volume of the vacuum desiccator with water and add few drops of methylene blue and mix to give a light blue colour.
2. Place the ampoule to be leak tested into the desiccator containing a blue dye solution.
3. Place a wire mesh and a weight on top of the blisters ensuring blue dye solution covers the blisters.
4. Slide the lid on to the desiccator.
5. Turn vacuum valve “ON” of the leak tester and ensure vacuum regulator valve is fully open.
6. Close the vacuum release valve on the desiccator.

7. Use the regulating valve to adjust vacuum until guage reads minus 60 kPa by slowly closing the vacuum regulator valve.
8. When correct pressure is reached, maintain exposure time for 60 seconds, look for bubble flows in the desiccator, which may indicate leakers.
9. Turn "OFF" the vacuum valve and fully open the vacuum regulator. Release the vacuum on the desiccator (Fig. 12.1). Turn "OFF" the vacuum pump.
10. Wait for another 60 seconds as recovery time to allow blue dye to enter faulty blister.
11. Take sample out and rinse with water.
12. Visually inspect each ampoule that none contains blue dye.
13. For non-clear blisters, thoroughly dry the external face of the ampoule with an absorbent cloth, then pop each tablet out and inspect both tablet and the pocket.

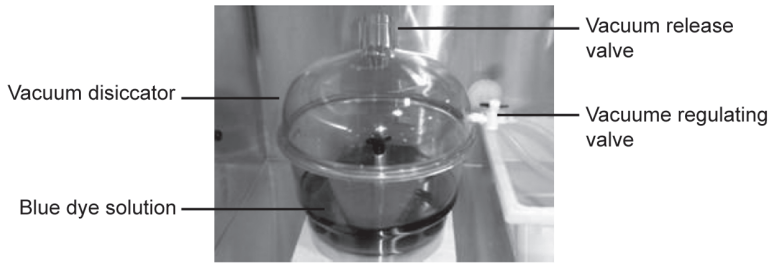


Fig. 12.1: Vacuum leak testing assembly

Result: If leak test fails, then ampoule sealing is not proper. Proper measures should be taken for proper sealing.

Object: To prepare pellets of active pharmaceutical ingredient (API) using extrusion spheronization process.

Theory: Pellets are defined as small, free flowing, spherical, or semispherical units made up of fine powders of bulk drugs and excipients by variety of processes. The extrusion-spheronization is commonly used in pharmaceutical industry to make pellets. The manufacturing process includes series of unit operations which are associated with a number of individual processing and formulation variables. The process flow is described in Fig. 12.2.

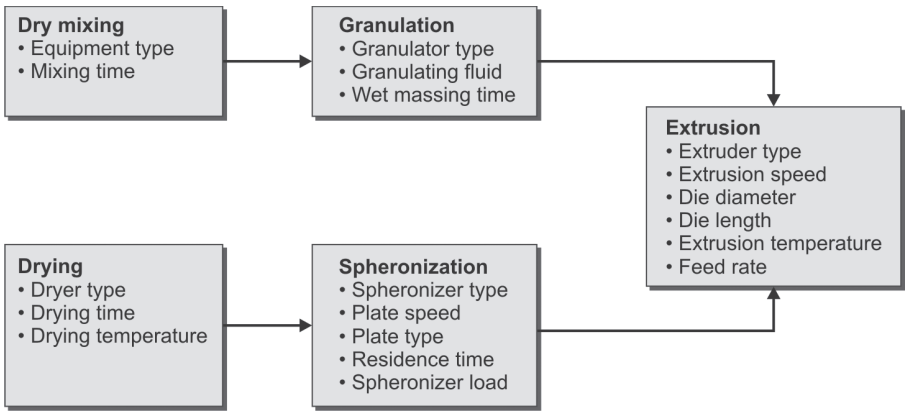


Fig. 12.2: API using extrusion spheronization process

Process flow diagram of the extrusion-spheronization process, showing the process and formulation variables for each unit operation.

Experiments are conducted, where parameters can be optimized to formulate pellets with narrow PSD and good sphericity.

Excipients used: List of excipients along with their category

S. No.	*Drug and excipients*	*Category*
1.	Model drug	API
2.	Microcrystalline cellulose	Diluent
3.	HPC (hydroxypropylcellulose)	Binder

Equipment used: List of equipment used along with their source

S. No.	*Equipment/apparatuses*	*Company*
1.	Extruder (single screw radial extruder, diameter of die: 1 mm)	Fuji Paudal Co Ltd, Tokyo, Japan
2.	Spheronizer (plate of regular cross hatch geometry)	Fuji Paudal Co Ltd, Tokyo, Japan
3.	Rapid mixer granulator	Sainath Boilers and Pneumatics, Mumbai
4.	Fluidized bed dryer	Retsch, Germany Scientific Works Pvt. Ltd., New Delhi
5.	Sieve Shaker	Jayant Scientific, India
6.	British Standard Sieves (BSS)	Jayant Scientific, India
7.	Digital vernier calipers	Absolute Digimatic, Mitutoyo, Japan
8.	Digital moisture analyzer	Mettler Toledo HB43, Switzerland
9.	Electronic balance (Afcoset F-3000)	The Bombay Burman Trading House Corp. Ltd.
10.	Mechanical stirrer and speed regulator	Remi Motors Ltd, Mumbai
11.	Tapped Density Tester	Electrolab, India

Note: Equipment type and company can be different, based on availability and pellets geometry required.

Preparation of pellets: Summary of experiments: Batches of pellets were prepared by microcrystalline cellulose (avicel pH 101) as spheronizing agent. HPC-L (Hydroxypropylcellulose) was used as binder. Purified water was as used as a granulating fluid and a liquid binder. Pellets were prepared by extrusion-spheronization method. Process variables have huge impact on the pellet properties.

Observation table

S. No.	*Ingredients*	*Category*	*%w/w*
1.	Model drug	API	10–40%
2.	MCC-101	Diluent	55–85%
3.	HPC	Binder	1–5%
4.	Water (get evaporated after drying)	Binder solvent	30%–50% w/w of dry mix (fluid uptake)

MCC is preferred diluent for extrusion-spheronization process. Different binder can be used. Concentration of API, binder, diluent and water can be changed, based on formulator discretion.

Manufacturing process

1. Dispense API and diluent.
2. Mix them in rapid mixture granulator for suitable time (dry mix).
3. Make binder solution in water.
4. Granulate step 2 mixture using step 3 binder solution by keeping following parameters

S. No	*Processing variables*	*Parameters*
1.	Mixing time of the premix in RMG	2–5 min
2.	Binder addition time (dosing speed)	20–40 ml/min
3.	Impeller run in RMG	2–5 min
4.	Chopper run in RMG	1–3 min

Set parameters can be changed based on formulator discretion. Parameters given above are just for reference purpose.

5. Make extrudes of step 4 wet mass by keeping following parameters:

S. No.	*Processing variables*	*Parameters*
1.	Extruder speed	30–50 rpm
2.	Extruder roller mesh size (diameter of die)	1 mm

Set parameters can be changed based on formulator discretion. Parameters given above are just for reference purpose.

6. Makes pellets from extrudes of step 5 using spheronizer.

S. No	*Processing variables*	*Parameters*
1.	Spheronization speed	400–800 rpm
2.	Spheronization time	3–7 minutes

Set parameters can be changed based on formulator discretion. Parameters given above are just for reference purpose.

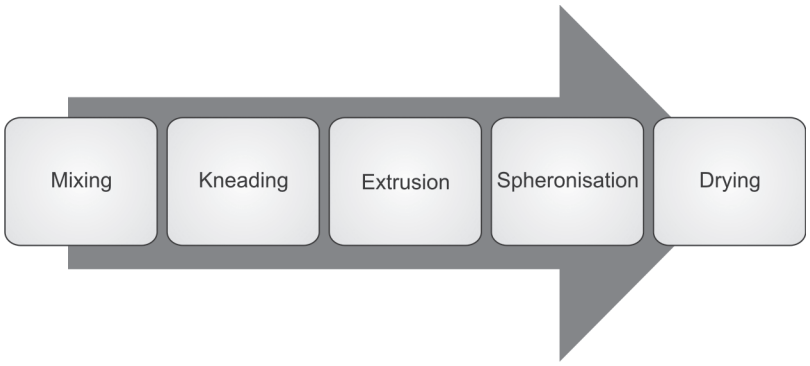
7. Dry step 6 pellets.

Processing variables that were kept during formulation

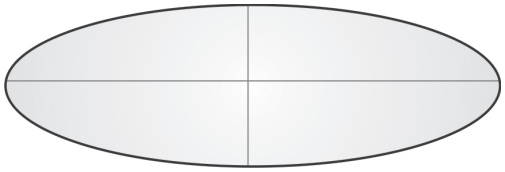
S. No.	*Processing variables*	*Parameters*
1.	Drying temperature of pellets in fluidized bed dryer	50–60°C
2.	Drying time in fluidized bed dryer	30–60 min
3.	Loss of drying of the pellets	Not more than 2.5% w/w

Set parameters can be changed based on formulator discretion. Parameters given above are just for reference purpose.

Flowchart 12.1: Manufacturing process



8. Final pellets can be evaluated with respect to particle size distribution (by sieve), sphericity (by aspect ratio), bulk density, tap density and dissolution.



Aspect ratio (AR) = d_{max}/d_{mi}

Where, d_{max} and d_{min} were the longest and shortest diameters measured.

Result: Aspect ratio close to 1 means spherical. Ideal pellets should have narrow particle size distribution (PSD) and good sphericity.

Object: To prepare and submit 25 gm of cold cream.

Theory: Cold creams are typically beeswax-borax emulsions. They are so-called as cold cream because on application to skin the evaporation of water leads to cooling effect. When a solution of borax is added to molten beeswax emulsifying agent is formed because of wax acid and borax, i.e. wax acid is saponified by borax forming Na-soap (i.e. Na-soap of wax acid). This agent is formed at the interface between oil and water, which emulsifies the mineral oil in water. It is because of beeswax, cream is able to contain appreciable amount of water. These are typically white creams of higher-class free form greasiness, which has firm consistency and on application they liquefy and spread easily.

This cream can be either o/w type (or) w/o type depending upon the ratio of water phase. 45% is considered to be the critical level of water phase, cream-containing water less than 45% is w/o type and cream with water phase more than 45% is o/w type of emulsion. Percentage of beeswax used ranges from 5 to 15% and borax 5–6% of wt of beeswax. Lesser amount of beeswax gives softer cream and higher amount give stiffer cream. Cold cream has got a neutral pH.

Both w/o and o/w emulsion can be obtained by beeswax-borax which depends upon.

i. Ratio of oil to water phase.
ii. Temperature of preparation.
iii. Amount of beeswax saponified.
iv. Other ingredient present.

Observation table

S. No.	Ingredients	Quantity given	Quantity taken
1.	Beeswax	80 gm	2 gm
2.	Mineral oil	490 ml	12.25 ml
3.	Soft paraffin	70 gm	1.75 gm
4.	Cetyl alcohol	10 gm	0.25 gm
5.	Borax	4 gm	0.1 gm
6.	Water	346 ml	8.65 ml
7.	Perfume	QS	QS

Procedure: Take 2.16 gm beeswax, 1.89 gm of soft paraffin, 0.27 gm of cetyl alcohol 13.2 ml mineral oil in a clean dry vessel and heat on water bath to 80°C. Dissolve borax in water in another vessel and heat simultaneously with the oil phase to 70°C. Add the aqueous phase to oil phase slowly with rapid stirring. Continue stirring slowly after the additions of aqueous phase until the cream has cooled to about 50°C. Add the perfume, mix well. Weigh out 25 gm of cream and fill into jar. At the time of filling the cream, it should have cooled to 40°–42°C.

Category: Humectants.

Storage: Store in a cool and dry place.

Direction: "For external use only".

Uses: To prevent loss of water for dry skin especially during winter and skin smoothener.

Object: To prepare and submit 25 gm of vanishing cream.

Theory: A cream, which spreads easily and seems to disappear rapidly when applied on the skin, is termed as vanishing cream. Vanishing creams are composed of emollient esters, which have little apparent film on the skin. Low percentage of oil phase is chosen for the above-mentioned reasons. Traditional formula of vanishing cream is based on the stearic acid. The acids melt above the body temperature and crystallize in suitable form so as to be immiscible providing a non-greasy film stearic acid to impart attractive appearance to cream.

Stearic acid makes the cream very white and because of this vanishing cream contains partially saponified stearic acid, free stearic acid and water. Cream made with sodium hydroxide is harder than made with potassium hydroxide. Borax also can be used and these creams are white in colour, but the product has the tendency to become greasy. Glycerin is used as humectant that attracts moisture and hydrates the stratum corneum. Glycerin also prevents the cream from drying up. Lanoline is used in modern formula as emollient. Tri-ethanolamine stearate is used as emulsifier, which is obtained by reaction between tri-ethanol amine and stearic acid.

Observation table

S. No.	Ingredients	Quantity given	Quantity taken
1.	Stearic acid	200 gm	5 gm
2.	Glycerin	60 ml	1.5 ml
3.	Potassium hydroxide	4 gm	0.1 gm
4.	Triethanolamine	12 ml	0.30 ml
5.	Water qs	1000 ml	25 ml
6.	Preservative	0.2 gm	0.005
7.	Perfume	Adequate	Adequate

Procedure: Melt 5.4 gm of stearic acid by heating along with glycerin to about 70°C on a water bath. Dissolve 0.108 gm of KOH in water. Add Tri-ethanol amine, preservative and warm the aqueous solution to 70°C on water bath.

Add the aqueous phase to the oil phase and stir continuously all the time until the cream has formed. When it has cooled to 50°C add the perfume, mix well. Transfer to a clean mortar and triturate well until a cream of pearslescent luster is obtained. Weigh out 25 gm of cream and fill into suitable container.

Category: Cosmetic.

Storage: Store in a cool and dry place.

Direction: " For external use only".

Uses

1. Used as base for free powder and other makeup.
2. Used as emollient.
3. It gives better appearance to skin and also used for oily skin.

Object: To prepare and submit 20 ml of benzalkonium chloride eye drop.

Theory: Eye drops are aqueous or oily solutions or suspensions for instillation into the eye. They should be sterile and prepared under conditions appropriate for the preparation of sterile products (aseptic conditions). The method of sterilization is stated in each monograph. For aqueous solutions, water for injection should be used.

Eye drops should be prepared in a vehicle which is bactericidal and fungicidal. They should be isotonic with lachrymal secretions (which is equivalent to 0.9% NS).

Dropper plastic bottles are suitable for packing eye drops. Label should instruct the patint to discard the unused eye drops no longer than one month after opening the container.

The following care is to be taken while preparing the eye drop first of all it is to be sterilize by heating at 98° to 100°C for 30 min. It is to be store in airtight containers, below 25°C and used within three months and it should be protected from light.

Observation table

S. No.	Ingredients	Quantity given	Quantity taken
1.	Benzalkonium chloride solution	0.02 ml	0.004 ml
2.	Disodium edetate	50 mg	10 mg
3.	Sodium chloride	900 mg	180 mg
4.	Water for injection qs	100 ml	20 ml

Procedure

1. Mix benzalkonium chloride solution, disodium edetate and sodium chloride in about 2/3 the amount of vehicle (water for injection).
2. Transfer to a cylinder and complete to volume with water for injection.
3. Transfer into a suitable container and fix a red label.

Category: Eye drop.

Storage: Store in a cool and dry place, away from sunlight.

Direction: *"Keep out of the reach of children" always close the stopper after use.*

Use: As an antiseptic with bactericidal and bacteriostatic activities

Object: To prepare and submit 20 ml *of chloramphenicol eye drop.*

Theory: Eye drops are aqueous or oily solutions or suspensions for instillation into the eye. They should be sterile and prepared under conditions appropriate for the preparation of sterile products (aseptic conditions). The method of sterilization is stated in each monograph. For aqueous solutions, water for injection should be used.

Eye drops should be prepared in a vehicle which is bactericidal and fungicidal. They should be isotonic with lachrymal secretions (which is equivalent to 0.9% NS).

Dropper plastic bottles are suitable for packing eye drops. Label should instruct the patient to discard the unused eye drops no longer than one month after opening the container.

The following care is to be taken while preparing the eye drop first of all it is to be sterilize by heating at 98 º to 100 ºC for 30 min. It is to be store in airtight containers, below 25 ºC and used within three months and it should be protected from light.

Observation table

S. No.	*Ingredients*	*Quantity given*	*Quantity taken*
1.	Chloramphenical	500 mg	100 mg
2.	Disodium edetate	50 mg	10 mg
3.	Sodium chloride	900 mg	180 mg
4.	Water for injection qs	100 ml	20 ml

Procedure: Same as benzalkonium chloride eye drop.

Category: Eye drop.

Storage: Store in a cool and dry place, away from sunlight.

Direction: *"Keep out of the reach of children". Always close the stopper after use.*

Use: As a wide spectrum antibiotic used for the treatment of acute bacterial infection of the external eye.

Object: To prepare and submit 10 ml of shampoo.

Theory: Shampoo may be defined as a preparation containing surface-active agents, which are used to remove dirt, oil and debris from the hair, scalp without affecting the natural gloss of hair. It also helps to keep the hair fragrant, lustrous, soft and

manageable. Shampoo is prepared by dissolving detergents in suitable liquid along with other ingredients like cleansing, flavoring agent and preservatives. An ideal shampoo should have following properties.

1. It should remove dirt, grease (oil) debris from the hair and scalp.
2. It should be non-toxic.
3. It should be non-irritant.
4. It should provide sufficient fragrance to the hair after its use.
5. It should effective in small amounts.
6. It should be easily removed by washing with water.
7. It should make the hair soft and shining.

All the fatty acids oil content, which reacts with potassium hydroxide and form soap. In this preparation glycerol is used as solubilising agent and methyl paraben used as preservative.

Observation table

S. No.	*Ingredients*	*Quantity given*	*Quantity taken*
1.	Coconut oil	140 gm	1.4 gm
2.	Olive oil	30 ml	0.3 gm
3.	Castor oil	30 ml	0.3 gm
4.	Potassium hydroxide	47 gm	0.47 gm
5.	Glycerol	20 ml	0.2 gm
6.	Methylparaben	1.8 gm	0.018 gm
7.	Perfume	0.2 gm	0.002 gm
8.	Water qs	1000 ml	10 ml

Procedure: In a beaker heat coconut oil, olive oil and castor oil with potassium hydroxide and a little quantity of water on a water bath at 70°C. Take remaining quantity of water in another beaker, add glycerol, preservative and perfume, dissolve them thoroughly. Mix both the liquids to form a clear solution.

Category: Cleaning agent.

Storage: Store in a narrow mouthed, well-closed plastic container.

Direction: To be applied on wet hair.

Uses: To rinse out the dirt and give gloss to hair.

Object: To prepare and submit 10 gm of lipstick.

Theory: Lipstick is defined as a preparation, which is applied on lips to impart colour and make them more attractive. It is a dispersion of colored material in base, which is a blend of oil, fat and waxes. Lipstick is generally prepared in 3 steps:

1. Preparation of component blends
2. Mix of various blends to give the lipstick mass
3. Molding of the mass and flaming.

In the first step all the colour present are grounded using mills and mixed with oil or solvent to give uniform dispersion. Simultaneously other mix of the entire wax

base is heated and the wax base is prepared. Oil blend and wax blend are mixed to give lipstick mass. During mixing temperature of oil blend and wax blend should be almost same in order to prevent thickening of wax in oil. The mass obtained is then poured into lipstick mould in the step 3. Before pouring the mass is warmed to about 40°C. This is done to avoid flow of mass during setting of lipstick. Mass is overflown to prevent dispersion in the center of stick. When mass has just cooled the excess is removed off. Moulds are then cooled until the lipstick has completely settled. Mould is then opened and lipstick is then subjected to immediate flaming. Flaming is done after the placing of lipstick into its container. This helps to give the lipstick a smooth and glossy look. An ideal lipstick should have the following properties.

i. It should non-irritant and non-toxic.
ii. It should not dry on storage.
iii. It should maintain the lip colour long period after its application.
iv. It should be free from gritty particles.
v. It should be easily applicable and removable after its application.
vi. It should not break during use.

Observation table

S. No.	*Ingredients*	*Quantity given*	*Quantity taken*
1.	Bees wax	150 gm	1.5 gm
2.	Paraffin wax	100 gm	1 gm
3.	Cetyl alcohol	50 gm	0.5 gm
4.	Perfume	Adequate	Adequate
5.	Castor oil qs	700 ml	7 ml
6.	Coloring agent	Adequate	Adequate

Procedure: Take paraffin wax and beeswax in a china dish and heat it up to 70°C on a water bath. In a beaker take caster oil and heat up to 70°C and mix into melted mixture and add perfume and coloring agent. Immediately pour the molten mass into the lubricated mould, allow it to cool by placing moulds on ice cubes. And then cut the surface using sharp knife. Remove the sticks from the mould and place it in the lipstick case and label it.

Category: Cosmetic.

Storage: Store in a cool and dry place.

Direction: To be applied on lips.

Uses: As a cosmetic to make lips attractive.

Glossary

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness.

Active ingredient: An active pharmaceutical ingredient (API) is the chemical substance contained in a pharmaceutical, which is responsible for its therapeutic effect.

Aerobic microorganism: A microorganism that utilizes oxygen as the final electron acceptor during metabolism: A microorganism that will grow primarily in the presence of oxygen.

Aerosol: Air suspension of solid or liquid particles having a volume median diameter of less than 50 µm. The small size of the droplets or particles allows entry to the body via the respiratory tract and readily contaminates clothing, skin and eyes.

Agglomeration: Adherence of particles into a larger mass due to moisture, static charge or chemical or mechanical binding.

Aggregation: Accumulation or collection of particles in to larger units.

Amorphous: Solid substances that are not crystals.

Anaerobic organism: A microorganism that does not utilize oxygen as the final electron acceptor during metabolism: Microorganism that will grow only in the absence of oxygen.

Analgesic: A medication that reduces or eliminates pain.

Analytical procedure: The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

Anemometer: Anemometer is an instrument used to measure air flow velocity.

Angle of repose: Angle of repose is the greatest angle form the horizontal that a heap of material will remain stationary.

Antacid: An agent that counteracts or neutralizes acidity.

Antiemetics: Drugs used to treat nausea and vomiting.

Antiflatulent: Any agent that reduces intestinal gas.

Antineoplastics: Drugs used to treat cancer.

Antipyretic: A medication that reduces body temperature or pain.

ANDA: An application to market a generic drug in the USA. The application does not contain extensive preclinical (pharmacology and toxicology) or clinical data. Instead an ANDA for a typical tablet or capsule relies on therapeutic equivalence to the innovator product (reference listed product), together with an extensive CMC section.

Aseptic filling: The part of aseptic processing where a presterilized product is filled and/or packed in to sterile containers and closed.

Bar code: A way of labelling a product with a description and batch information using a series of lines of various thickness that is read by a scanner.

Batch (Lot): A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Binder: An excipient used to increase powder cohesiveness, which increases the bonding strength of the final product. In wet granulation, they help to form agglomerates.

Bioavailability: A measure of the fraction of a drug that enters the systemic blood circulation after oral administration. The usual measure is the ratio of the AUC of two different formulations of the same drug, corrected for dose.

Bioequivalence: A high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse effects, or both.

Biological indicator (BI): A population of microorganisms inoculated onto a suitable medium (e.g. solution, container or closure) and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process. The challenge microorganism is selected based upon its resistance to the given process. Incoming lot D-value and microbiological count define the quality of the BI.

Biopharmaceutical classification system (BCS): A system of classification of drugs based on their solubility and their permeability through the gut wall. The system was introduced by Professor Gordon Amidon in 1995. A soluble drug is one whose highest dose is soluble in 250 ml or less of aqueous media over the pH range 1 to 7, 5. A permeable drug is one that is more than 90% absorbed from the human gut. Permeability may be determined using *in vitro* model systems. The BCS classes are Class 1: High solubility and high permeability. Class 2 = Low solubility and high permeability. Class 3 = High solubility and low permeability. Class 4 = Low solubility and low permeability.

Biowaiver: An exemption from the need to perform a clinical bioequivalence study under certain circumstances. Biowaivers are possible in the USA, in Europe and in Japan, but the requirements for achieving a biowaiver differ in these countries. In the USA and Europe the biowaiver is potentially available for rapidly dissolving formulations of BCS Class 1 drugs.

Bronchodilators: Drugs that open up the bronchial tubes within the lungs when the tubes have become narrowed by muscle spasm. Bronchodilators ease breathing in diseases such as asthma.

Bulk density: The mass per unit volume of a material under specified conditions of pressure.

Cap: The upper part of a two piece capsule. It is slightly larger in diameter and shorter than the body.

Caplet: A tablet shaped like a capsule to ease swallowing.

Child resistant packaging: Child resistant packaging is a special type of packaging used to reduce the risk of children ingesting dangerous items. This is often accomplished by the use of a special safety cap.

Chipping: 'Chipping' is defined as the breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations.

Clean area (clean room): An area (or room) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Coating: The process of applying a coat to a tablet or other dosage form. Coatings are applied for a number of reasons from aesthetic (colour, identification and ease of handling or swallowing) to highly functional (delayed and modified release). Aesthetic coatings are typically based on low viscosity grades of HPMC or PVA, whereas functional coatings are typically based on methacrylic acid copolymers or cellulose derivatives such as ethylcellulose.

Code of federal regulations (CFR): CFR is the codification of the general and permanent rules and regulations. CFR can be called administrative law and is published by federal government of united states.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Critical area: Area where sterilized products or containers/closures are exposed to the environment (i.e. aseptic preparation and filling).

Cross-contamination: Contamination of a material or product with another material or product.

CTD: A harmonised layout for the structure and content of application dossiers applicable to the USA, the European Union and Japan. The CTD has 5 modules of which module 3 (Quality) contains the chemical and pharmaceutical section of the dossier.

D value: Decimal reduction value (for biological indicators). The time in minutes required to secure inactivation of 90% (one log) of the test organisms under stated exposure conditions.

Decongestants: Drugs that reduce swelling of the mucous membranes, that line the nose by contracting blood vessels, thus relieving nasal stuffiness.

Delayed release: A drug product (typically oral) that is not intended to release the drug substance immediately after ingestion. The delay is commonly related to change of pH in the gastrointestinal tract ("enteric coating") or less commonly may relate to a specific time after ingestion when the drug is released. Enteric coating is achieved by coating with polymers that are poorly soluble in low pH media (for example, gastric fluid), but are soluble in media with pH values typically found lower in the intestine. Methacrylic acid copolymers are very commonly used for delayed release coatings as they can be supplied in grades that dissolve at different pH values.

Depyrogenation: A process used to destroy or remove pyrogens.

Desiccant: A highly hygroscopic substance used to absorb moisture in bottles, vials, blisters and other packing.

Die: A circular machine tool with a central cavity in which powders or granular solids are compacted into tablet between the upper and lower punches of a tablet press.

Diluent: A component of a tablet or capsule, usually present to add bulk to the dosage form. The most commonly used diluents include lactose, microcrystalline cellulose and native or pregelatinised starches. Dibasic calcium phosphate and mannitol are also used.

Direct compression: A means of producing a tablet without granulation. The active ingredient is blended with excipients, typically at least a filler-binder, a disintegrant and a lubricant and then the blend is compressed on a tablet machine. The filler-binders are usually special grades of excipients (for example, spray dried lactose) exhibiting good flow and compaction properties to enable the DC process.

Disintegrant: An excipient that facilitates the disintegration of a tablet or other dosage form in contact with water or gastrointestinal fluid. Traditionally starch was used, but in general today's

formulations utilise a so called superdisintegrant such as croscarmellose sodium or sodium starch glycolate. Superdisintegrants are typically cross-linked hydrophilic polymers that strongly attract water. The presence of the cross-links allows swelling, but prevents dissolution of the polymer and generation of high viscosity gels.

Disintegration: The process by which a solid oral dosage form breaks up in water when measured in a standard apparatus.

Dissolution: The process by which drug dissolves out of a dosage form and is made available for absorption from the gastrointestinal tract. *In vitro* measurements are made in a range of apparatus types. The requirements for different types of dosage forms are given in each pharmacopoeia.

Diuretics: Drugs that increase the quantity of urine produced by kidney.

DOP test: Dioctyl Phthalate test is a test which used to check the HEPA filter integrity.

Dosage form: A pharmaceutical product type (e.g. tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug master file (DMF): A DMF is a means of providing data on a processing facility, drug substance, packaging material or excipient confidentially to FDA. The data in a DMF can be accessed by FDA in support of an NDA upon provision of a letter of access (a letter from the DMF holder to the NDA applicant authorising FDA to access the DMF during their review of a particular NDA). In Europe there is no DMF system for excipients and in Japan there is a recently introduced system.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Dry granulation: A means of granulation (size enlargement) of a powder using a compaction step followed by milling. The most common means of dry granulation in pharmaceutical industry is roller compaction, although the older process of slugging is still sometimes used. Anhydrous lactose is the most suitable form of lactose for these processes because it tends to retain compactability after the dry granulation process.

Endotoxin: A pyrogen (e.g. lipopolysaccharide) derived from the cell wall of gram-negative bacteria. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.

Enteric coat: A delayed release coating, usually designed to delay release of the drug from the dosage form until it has reached an area of the gastrointestinal tract of a specified pH. Methacrylic acid copolymers are very commonly used.

Excipient: A component of a drug product other than the API, that is intentionally added to the dosage form to enable processing into patient friendly medicines, to control the rate at which the API dissolves from the dosage form, to aid drug stability and other reasons. For solid oral dosage forms, main classes of excipients include diluents or filler-binders, disintegrants, glidants, lubricants, coating materials, and stabilising agents.

Exotoxin: An exotoxin is a toxin secreted by bacteria. An exotoxin can cause damage to the host by destroying cells or disrupting normal cellular metabolism. They are highly potent and can cause major damage to the host. Exotoxins may be secreted or similar to endotoxins may be released during lysis of the cell.

Expectorant: Drugs that stimulate the flow of saliva and promotes coughing to eliminate phlegm from the respiratory tract.

Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used

Extended release: A form of modified release dosage form in which the dissolution rate of the drug from a medicine is controlled over an extended period of time, usually to reduce the frequency at which a patient has to take the medicine. A number of means of effecting extended

release is possible, the most common being barrier coating (with for example, acrylate polymers), inclusion of hydrogel polymers (for example, hydroxypropyl methyl cellulose) and construction of osmotic pumps.

Factory acceptance test (FAT): Factory acceptance test is test conducted at the vendors premises, to verify that the equipment/system operates according to the specifications.

Finished product: Finished product is a product that has undergone all stages of production, including packaging in its final container and labelling.

Fixed dose combination (FDC): Fixed dose combinations (FDCs) refer to products containing two or more active ingredients used for a particular indication(s).

Fluid-bed dryer (FBD): A device that dries powder using mechanical force and/or airflow to evaluate and aerate it, increasing interstitial particle spacing and driving off moisture.

Fluid-bed granulation: The process of spraying solution onto aerated powders to form granules.

Friabilty: A measure of the resistance to abrasion and breakage of tablets during a standardised test involving tumbling tablets in a rotating drum. Details of the equipment and test protocol are found in all main pharmacopoeia. A limit of not more than 1% weight loss is generally taken to be a satisfactory measure of friability.

Generic drug: A drug for which the patents protecting the originator product have expired (or may be challenged). Generic products are pharmaceutically equivalent to a reference listed drug (same drug substance, same route of administration, same dosage form and same strengths) and are also therapeutically equivalent (typically bioequivalent for oral solid dosage forms).

Glidants: Glidants are execipients used to promote powder flow by reducing inter particle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction (e.g. talc).

Granulation: Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Granulation process is an inevitable step in tablet manufacturing as it improves flow property and compressibility of powder mass intended for compression.

HEPA filter: High efficiency particulate air filter with minimum 0.3 micron particle retaining efficiency of 99.97%.

Hygroscopicity: A material's ability to absorb moisture from its surroundings.

ICH: International conference on harmonization.

Immediate (primary) pack: It is that constituent of the packaging that is in direct contact with the drug substance or drug product, and includes any appropriate label.

Immediate release: Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

Impermeable containers: Containers that provide a permanent barrier to the passage of gases or solvents, e.g. sealed labelling tubes for semi-solids, sealed glass ampoules for solutions.

Investigation new drug application (INDA): It is an application which is filed with FDA to get approval for legally testing an experimental drug on human subjects in the USA.

Lamination: The presence of weak planes in a compressed tablet normal to the direction of compaction. On subsequent handling or processing it is possible for the tablet to separate into layers along these weak planes. Lamination may have the same causes as capping, or it may also be a result of under lubrication of the tablet compression mix.

Laxatives: Laxatives (purgatives, aperients) are foods, compounds and/or drugs that facilitate or increase bowel movements. They are most often used to treat constipation.

LD50: The dose of a material which results in 50% mortality in an animal test.

Leachable: Leachables are chemical entities, both organic and inorganic, that migrate from components of a container closure system or device into a drug product over the course of its shelf-life.

Long term testing: Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labelling.

Lubricant: An excipient that is used in tablet and capsule formulations to allow ejection of the compressed tablet from the die, or the capsule plug from the dosator. Lubricants also act as anti-adherents to prevent sticking of the tablet to the tablet punches during compression. By far the most commonly used lubricant is magnesium stearate, although less hydrophobic materials such as sodium stearyl fumarate are now available. Other lubricants include calcium stearate and mixtures of talc and stearic acid. Options to minimise the need for tablet lubrication include the use of coated punches in compression and tablet machine developments that add very small quantities of lubricants directly to the punches during tableting.

Lyophilization: A process by which material is rapidly frozen and dehydrated under high vacuum.

Marketing authorisation application (MAA): It is an application (to the relevant authority; typically the UK's MHRA or the European Commission's Committee for Medicinal Products for Human Use (CHMP) to market a drug or medicine. The US food and drug administration equivalent of marketing authorisation application (MAA) is a new drug application (NDA).

Milling: The process of de-agglomerating or reducing the particle size of powders manually or by machine.

Modified release: Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

Mottling: 'Mottling' is the term used to describe an unequal distribution of colour on a tablet, with light or dark spots standing out in an otherwise uniform surface.

New drug application (NDA): The process by which a pharmaceutical company requests permission to manufacture and sell a new drug in the USA. The NDA differs from the ANDA in that it contains extensive data on safety and efficacy of the proposed new drug.

New molecular entity: An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or non-covalent-bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Noncondensable gas: Gases which cannot be liquefied by compression under the range of conditions of temperature and pressure used during the operating cycle.

Nonviable: A term used in reference to particulates, which are not capable of living, growing or developing and functioning successfully—"unable to divide".

Orally disintegrating tablet (ODI): An ODT is a dosage form designed to disintegrate or dissolve quickly in the mouth without the need for water and without chewing. In general the tablet should disintegrate within 30 seconds when tested using standard pharmacopoeial disintegration apparatus, or another correlated disintegration test method.

Orange book: "The Orange Book" is actually the US Food and Drug Administration's (FDA) official listing of approved drug products with therapeutic equivalences. "Orange Book" is published by the FDA's centre for drug evaluation and research (CDER).

Orphan drugs: "Orphan drugs" are medicinal products intended for diagnosis, prevention or treatment of life-threatening or debilitating rare diseases. They are "orphans" because the pharmaceutical industry has little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare conditions.

Overage: Increased content of drug substance, usually due to loss of potency on storage.

Over fill: Increased volume of drug product to account for loss during delivery.

Over the counter drugs (OTC): A drug product that is safe and effective for use without a prescription.

Oxygen transmission rate (OTR): The amount of oxygen that passes through packaging film or foil over a unit of time and under specific environmental conditions.

Paragraph 4 filings: A type of ANDA submitted during the patent term of the originator product. The filing asserts that either the patents supporting the originator product are invalid or that they are not applicable to the product that is the subject of the ANDA.

Performance qualification (PQ): The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Pharmacopoeia: Pharmacopoeia is a book or encyclopedia of drugs standards, their formulas, methods for making medicinal preparations and other related information's which is published under the jurisdiction of government body.

Picking: A imperfection caused by powders sticking to a punch surface during tabletting.

Pilot scale batch: A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Placebo: A product which stimulates the marketable product but has no active ingredient present.

Polymorphic forms: Different crystalline forms of the same drug substance. These can include hydration products (also known as pseudo-polymorphs) and amorphous forms.

Precision: The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: Repeatability, intermediate precision and reproducibility. Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

Preventive action: Action to eliminate the cause of a potential non-conformity or other undesirable potential situation.

Primary batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Probiotics: Probiotics are live microorganisms or microbial mixtures administered to improve the patient's microbial balance, particularly the environment of the gastrointestinal tract and the vagina. Probiotics have demonstrated an ability to prevent and treat some infections. Probiotics can be bacteria, moulds or yeast. Commonly used bacterial strains are Lactobacillus and Bifidobacterium. Commonly used yeast strain is *Saccharomyces boulardii*.

Pure steam: Steam whose condensate complies with the ompendia monograph, water for injection (WFI).

Pyrogen: Substance which induces febrile reactions in a patient.

Quality assurance (QA): The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality by design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Range: The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

Raw material: A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference listed drug (RLD): The listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. A generic drug must exhibit therapeutic equivalence to the RLD.

Relative humidity: The ratio of the actual water vapour pressure of the air to the saturated water vapour pressure of the air at the same temperature expressed as a percentage. More simply put, it is the ratio of the mass of moisture in the air, relative to the mass at 100% moisture saturation, at a given temperature.

Reproducibility: Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Robustness: The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Roller compaction: A dry granulation process in which a powder blend is passed through rollers under pressure to form a ribbon. The ribbon is milled into granules, optionally blended with extragranular excipients and recompressed into tablets or filled into capsules.

Scale up: The process of converting a small volume process to large volume production

Screening: The process of reducing agglomerates, sorting particles by size and removing oversized particles and contaminants using a woven metal screen or perforated plate.

Semi-permeable containers: Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Slugging: A form of dry granulation, somewhat similar to roller compaction. In slugging however a powder blend is first compressed on a tablet machine and the resulting, usually large, tablets (slugs) are milled, optionally reblended with more excipients, and recompressed into tablets. Alternatively the milled slugs are sometimes filled into capsules.

Spore: A bacterial form highly resistant to adverse conditions.

Stability: Ability of a material to maintain a stated property value within specified limits for a specified period of time, when stored under specified conditions.

Standard operating procedure (SOP): An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Sterile: Free of any viable organisms (absence of life).

Sterility assurance level (SAL): Probability of a single viable microorganisms occurring in an item.

Sticking: Adhesion of a powder to the faces of a punch during tablet compaction. Causes are various and include low melting components in a compression mix, inadequate drying of a granulation, and inadequate lubrication of the compression mix. Additionally poor punch maintenance can contribute to sticking. The remedies are generally evident from the causes, but if low melting components cannot be excluded from a formulation then specially coated tablet punches may be a solution. Occasionally changes to the punch design (for example, reducing the depth of concavity) may alleviate the problem.

Stress testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (*see* ICH Q1B) and specific testing on certain products (e.g. metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Stress testing (drug substance): Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Super heated steam: Steam whose temperature, at a given pressure, is higher than that indicated by the equilibration curve for the vaporization of water.

Supplement: A supplement is an application to allow a company to make changes in a product that already has an approved new drug application (NDA). CDER must approve all important NDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are still met.

Surfactant: A substance that decreases the surface tension of a liquid.

Sustained release: A method of drug delivery by which API release occurs over an extended period after administration. The method reduces dosing frequency compared to a traditional method such as immediate release.

Teratogenicity: The occurrence of structural malformations in a developing foetus when a substance is administered during pregnancy.

Terminal sterilization: A process whereby product is sterilized with its sterile barrier system.

Tincture: A medicine consisting of an extract in alcohol solution.

Twininng: The bonding of tablets with large, flat surfaces during the coating process.

Uniformity of dosage forms: A measure of the degree of uniformity of the amount of active substance in individual dosage units (for example, individual tablets or capsules). For uncoated tablets, film coated tablets and hard capsules containing at least 25 mg of drug substance and the drug substance is at least 25% of the dosage form, then variation in weight may be used as a measure of uniformity. For other solid oral dosage forms then individual unit assays are necessary. Specific details are given in major pharmacopoeia.

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Validation master plan (VMP): Validation master plan is a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning.

Viable: Capable of living

Viscosity: The measurement of a materials resistance to flow.

Water for injection (WFI): Water, which is intended for use in the preparations of parenteral solutions. WFI is produced by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms.

Wet granulation: A means of granulation of powders using water or other liquid to agglomerate powders into granules, and drying the granules. The process fixes API and excipients into a granular form that helps to prevent segregation of the components, that aids flow of there powders, and allows the incorporation of binders to improve compactability. The granulation step and the drying step may be performed consecutively (typically using high shear granulation and fluid bed drying) or concurrently (typically using fluid bed granulation). Continuous wet granulation is increasingly being used to aid throughput in pharmaceutical processing factories.

Yield, expected: The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, theoretical: The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

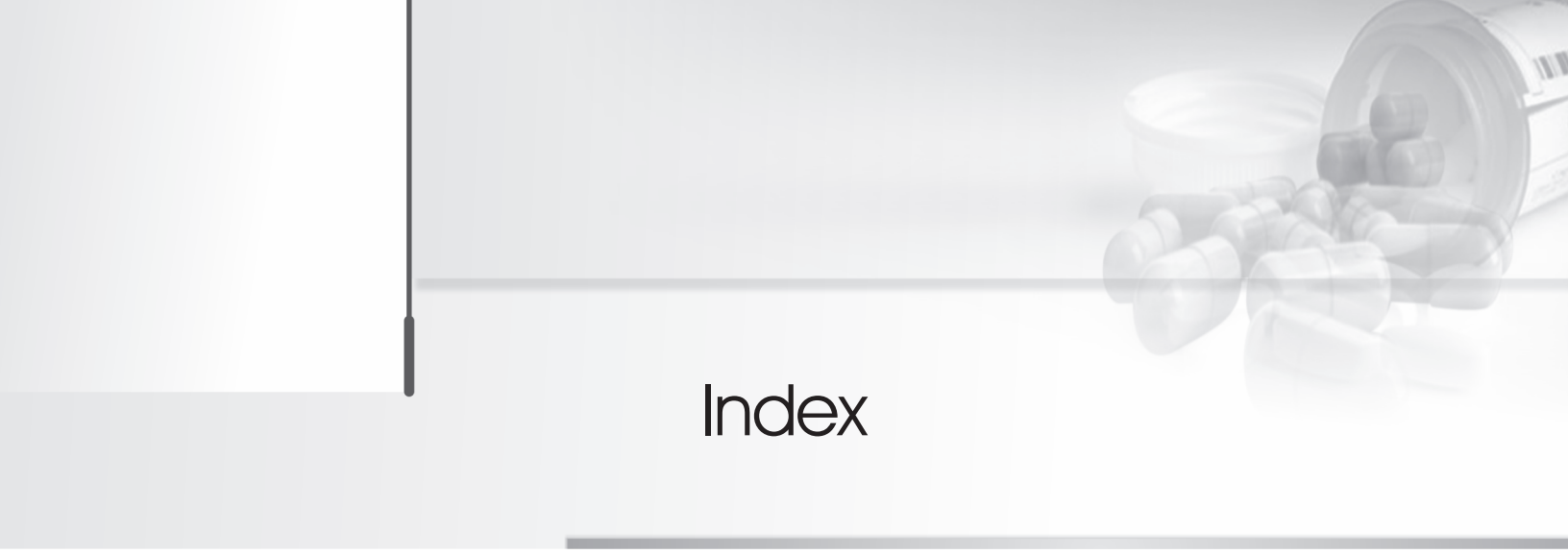
Z-value: The number of degrees of temperature change necessary to change the D-value by factor of 10.

Appendix

UNITS AND CONVERSION FACTORS

Length	1 inch	= 0.0254 m
	1 ft	= 0.3048 m
Area	1 ft^2	= 0.0929 m^2
Volume	1 ft^3	= 0.0283 m^3
	1 gal Imp	= 0.004546 m^3
	1 gal US	= 0.003785 m^3 = 3.785 litres
	1 litre	= 0.001 m^3
Mass	1 lb	= 0.4536 kg
	1 mole	molecular weight in kg
Density	1 lb/ft^3	= 16.03 kg m^{-3}
Velocity	1 ft/sec	= 0.3048 m s^{-1}
Pressure	1 lb/m^2	= 6894 Pa
	1 torr	= 133.3 Pa
	1 atm	= 1.013 x 10^5 Pa = 760 mm Hg
	1 Pa	= 1 N m^{-2} = 1 kg m^{-1} s^{-2}
Force	1 Newton 1 lb ft s^{-2}	= 1 kg m s^{-2} = 1.49 kg m s^{-2}
Viscosity	1 cP	= 0.001 N s m^{-2} = 0.001 Pa s
	1 lb/ft sec	= 1.49 N s m^{-2} = 1.49 kg m^{-1} s^{-2}
Energy	1 Btu	= 1055 J
	1 cal	= 4.186 J
Power	1 kW1 W	= 1 kJ s^{-1} = 1 J s^{-1}
	1 horsepower	= 745.7 W = 745.7 J s^{-1} = 0.746 kW
	1 ton refrigeration	= 3.519 kW
Temperature units	(°F)	$T_{(°F)} = T_{(°C)} \times 9/5 + 32$
	(°K)	$T_{(K)} = T_{(°C)} + 273.15$
Heat-transfer coefficient	1 Btu ft^{-2} h^{-1} $°F^{-1}$	= 5.678 J m^{-2} s^{-1} °C
Thermal conductivity	1 Btu ft^{-1} h^{-1} $°F^{-1}$	= 1.731 J m^{-1} s^{-1} $°C^{-1}$
Constants	Π	3.1416
	e (base of natural logs)	2.7183
	R	8.314 kJ $mole^{-1}$ K^{-1}
		or 0.08206 m^3 atm $mole^{-1}$ K^{-1}

(M) Mega = 106, (k) kilo = 103, (H) Hecto = 102, (m) milli = 10^{-3}, (μ) micro = 10^{-6}



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