Dr. Atmaram Pawar's .....

PHARMACEUTICS RAPIdex ™

'Optimum Text for Maximum Learning'

PHARMACEUTICS - I

(Savitribai Phule Pune University)

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Dedication ...

Dedicated to

Kaustubh ...

my next generation in pharmacy

... **Dr. Atmaram Pawar**

Preface ...

It is my pride and privilege to present the book Pharmaceutics Rapidex for the students of Savitribai Phule Pune University, my Alma matter from where I have completed my UG, PG and doctoral research.

The success of my first book 'Modern Dispensing Pharmacy, 2004' encouraged me to author a series "Pharmaceutics Rapidex" for my Alma matter. A series authored by a single author would definitely maintain the right link from basic to applied knowledge.

The concept of Pharmaceutics Rapidex is based on the tag line 'Optimum text for Maximum learning'. The aim here is to develop competent pharmacists who can think independently, perform skillfully and be a real asset to the pharmaceutical industry.

Pharmaceutics I is based on the current syllabus of Savitribai Phule Pune University. Optimum text, point-wise description, experiments for practicals and logical sequencing are the main features of the book. The questions for self-study given at the end of every important topic would guide teachers, students and examiners alike.

According to me 'classroom is best place for students to speak wrong things very confidently, because teachers are there to correct them'. Your teachers are also eager to solve your difficulties. Students can feel free to connect with me on p_atmaram@rediffmail.com.

I am especially thankful to Dr. Shivajirao Kadam, the Founder-Dean of Faculty of Pharmaceutical Sciences, Pune University and currently the Vice-Chancellor of Bharati Vidyapeeth University, Dr. B. Suresh President PCI, Dr. K.R. Mahadik, Dr. Anant Paradkar, Dr. S.G. Deshpande, Dr. L.D. Patel, Dr. M.D. Karvekar, and all principals, faculty members of Pune university who have been motivating factors during my professional journey

I am grateful to my publishers, Mr Dineshbhai Furia and Mr. Jignesh Furia of Nirali Prakashan for providing me with the opportunity to write this book. I appreciate the cooperation from Mr. Malik Sheikh for the excellent DTP work, Mrs. Rama Raghu for editing the text, Mrs Mulay for the figures, Mr. Ravindra Walodare for the cover and the entire staff of Nirali Prakashan in bringing out this book in the shortest time period.

Pune **Dr. Atmaram Pawar**

Date : July 2015

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Chapter 1...

Introduction to Pharmaceutics

Syllabus

- Pharmacy as a career.
- Introduction to Pharmaceutics and its various branches - Physical pharmacy, Formulation development, Pharmaceutical engineering, Dispensing Practices etc and scope of each.
- History of pharmacy as a profession and Pharmaceutical Industry in India.
- Code of ethics in pharmacy

Features of the chapter

- Make students aware about pharmacy, its developments and career options.
- Help students understand progress of pharmacy profession.
- Pharmacy code of ethics is supported by interpretations taking into consideration current scenario, acts and regulations.

1.1 INTRODUCTION

Health is a state of complete physical, mental and social well-being and not merely the absence of any illness. However, people confine this definition to illnesses only. Good health is the requirement of all individuals, which is an added dimension to the commonly called basic needs, *'Anna, Vastra, Nivara'* (food, clothes and shelter). Secondly, a healthy community is the strength of a nation, which is the key factor for its economical development. Fortunately, India in the 21st century is considered as the Country of Youth's, a state of healthiness. Therefore, economists believe that India is the healthiest country.

However, people still suffer from infectious diseases like tuberculosis, filariasis, and flu in its different forms like swine flu, bird flu, chicken flu, and many other infectious diseases. Many diseases which were earlier contained by the use of antibiotics are again spreading as multiple drug resistant strains and genetically modified bacteria and viruses are evolving. The

present population is grappling with diseases like diabetes and hypertension by virtue of the changing life-styles. One class of society is deprived of the minimum health facility, whereas others are taking multiple drug treatments. All these complications cannot be solved only by a medical practitioner alone but is only possible with the active participation of a professional who has a thorough knowledge about drug, drug delivery systems, drug effects and side effects.

1.2 PHARMACY AS CAREER

Pharmacy is a paramedical profession that involves manufacturing of quality medicines and their distribution. It also involves supply of medicines to patients while ensuring that their safety and efficacy are not compromised at any stage from production to distribution.

Accordingly, pharmacists as professionals have been involved in many drug and therapy related activities and perform multiple roles in the service of mankind in the way of producing and supplying medicines. Some of the professional roles or career options are as follows:

(a) Pharmacy Education

Pharmacy education is provided at the following levels.

- **Diploma in Pharmacy (12^{th} Science + two years):** A Community Pharmacy oriented diploma programme.
- **B.Pharm:** B.Pharm is a Pharmaceutical technology and industry oriented undergraduate education programme.

  The Bachelor of Pharmacy degree, popularly known as B.Pharm. is a four-year program after 12^{th} Science. D. Pharm (Diploma of Pharmacy) holders are eligible for admission directly into the second year B.Pharm via lateral entry in India.
- **Master of Pharmacy (B.Pharm + two years):** This is a Post Graduate programme in Pharmaceutical sciences and pharmacy practice.
- **Doctor of Pharmacy (Pharm. D.):** This is a patient oriented Post Graduate programme introduced in India from 2008-09. The six-year programme after 12^{th} Science can also be completed within three years after B.Pharm.

  These are the various programmes in pharmacy that needs professional and research oriented teachers.

(b) Research and Development

It includes R&D activities like finding new drug molecules, improving effectiveness of the existing drugs, clinical research, formulation and developments (F&D), novel drug delivery systems (NDDS), drug targeting, nano pharmaceuticals, biotechnology, bioinformatics, etc.

(c) Bulk Drug Manufacturing

It involves manufacturing of active pharmaceutical ingredients (API) from chemical, biological, synthetic or semi-synthetic source.

(d) Industrial Pharmacy

It involves manufacturing of various dosage forms. This activity is further divided into production, packaging, storage, quality assurance and quality control.

(e) Pharmaceutical Marketing

All movements of drug products starting from dispatch section of a manufacturing unit up to its retail sale are covered under marketing activities.

(f) Wholesale Distribution

Wholesale distributors and recognised stockists distribute the medicines to retail pharmacists.

(g) Clinical Testing

Testing of a new drug in humans for its pharmacokinetic (movement of drug in body after administration), pharmacodynamic (type and extent of drug action) and drug safety.

(h) Regulatory Affairs

Pharmacists work as drug inspectors and officers of Food and Drug Administration (FDA) or in Drug Regulatory Affair (DRA) department of Pharmaceutical Company on issues related to licensing for manufacture and sale of drug products, its import and exports, etc. According to the Pharmacy Practice Regulation 2015 following roles of pharmacists are described.

- Pharmacy Practitioner is a registered pharmacist who works as community pharmacist, hospital pharmacist, clinical pharmacist or drug information pharmacist.
- Community pharmacist is a registered pharmacist who works to ensure correct and safe supply of medical products to the general public. They are involved in maintaining and improving people's health by providing advice and information as well as supplying prescription medicines.
- Hospital Pharmacist is a registered pharmacist who works in a hospital pharmacy service, primarily within the public / private sector, where they work collaboratively with other health care professionals to devise the most appropriate drug treatment for patients ensuring safety and cost-effectiveness. Hospital pharmacists take initiative and lead in the design and implementation of various drug policies, health promotion activities and in disease prevention.

- A drug information pharmacist is a registered pharmacist who works in a community pharmacy/hospital pharmacy/teaching hospital/ other health care settings and provides information and advice regarding drug interactions, side effects, dosage and proper medication storage to patients/ physicians/ dentists/ other health care professionals.
- Clinical Pharmacist is a registered pharmacist who provides patient care that optimises the use of medication through evaluation of prescriptions, identification and prevention of adverse events and promotes health, wellness and disease prevention in all health care settings. Clinical pharmacists often collaborate with physicians and other healthcare professionals.

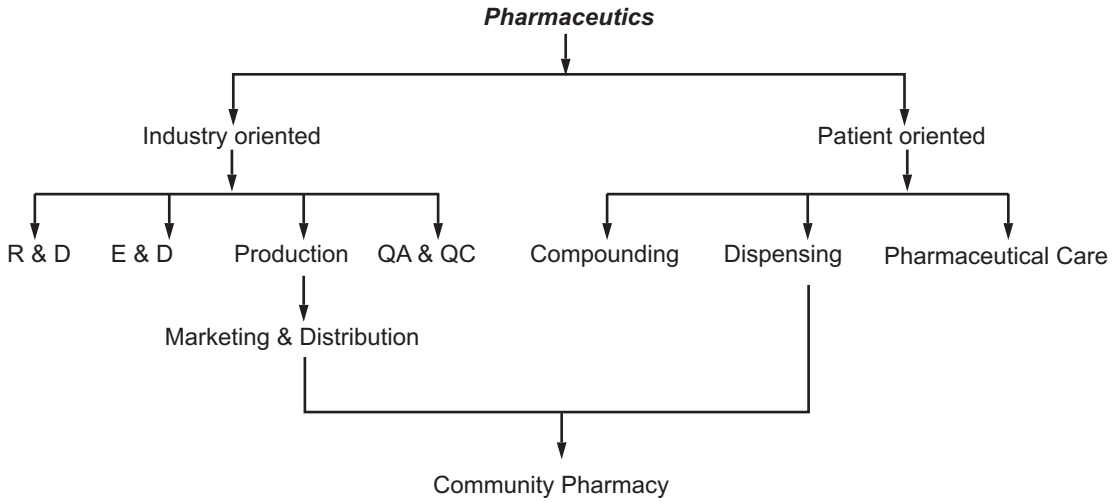
The hospital pharmacist do more managerial task whereas clinical pharmacists are more therapy oriented.

Questions for Self-Study

- Define pharmacy, community pharmacy, clinical pharmacy.
- Write about various education programmes in pharmacy.
- Discuss various career options in pharmacy.

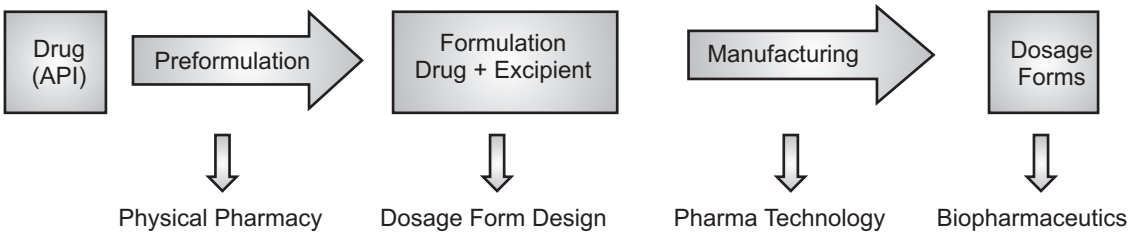
1.3 PHARMACEUTICS

Pharmaceutics is a branch of pharmacy education concerned with the design, development, production and supply of medicinal products.



The functioning of this branch can be categorised into two main sections, viz. industry-oriented and patient-oriented practice.

1. Industrial oriented pharmacy: It mainly involves large-scale manufacturing of pharmaceutical products. The functioning of this area begins with R&D to design new formulations, preformulation studies, pilot-plant scale-up to transfer the product from R&D to large-scale manufacturing, manufacturing procedures, quality assurance and quality control. Drug regulations and drug laws are applicable for manufacturing and sale of the medicines. The industrial Pharmacy needs knowledge of following different subjects:-



Physical Pharmacy: It involves studies of various physicochemical properties of a drug and its excipient and their compatibility with each other. More precisely it is called as pre-formulation.

Dosage form design: Dosage form design, formulation development or pharmaceutical technology are more or less similar terms that explain activities related to design of drug-excipient formula and its conversion in to a suitable dosage form like tablet, capsule, liquid oral, etc. This multitask activity includes manufacturing, quality assurance, quality control and the required men, machinery and method for each of them.

Pharmaceutical engineering: Pharmaceutical engineering involves study of various unit operations like milling, mixing, filtration, drying, etc and unit processes like granulation, filling and packing of dosage forms, etc. It explains the principle of equipments used and the process and parameter for their selection. It also provides knowledge about prevention of corrosion and pollution.

Biopharmaceutics: This branch studies the pharmacokinetics and pharmacodynamic properties of drug/drug product after administration via different routes. Pharmacokinetics explains movement and fate of the drug administered that includes absorption, distribution, metabolism and elimination of drug, factors affecting these processes and thus helps to design a particular dosage form. Pharmacodymanics is related to drug action, drug-receptor interactions and factors affecting drug action.

Microbiology: Microbiology is not a specific branch of pharmacy but it has important applications in pharmacy such as:

- Drug discovery: Antibiotics and vaccines are microbiological or more specifically biotechnology based drug discoveries.

- Preservation, disinfection or sterilisation: To control microbial contamination of the drug product during its manufacture (disinfection and sterilisation of facilities) and in the final form (which involves sterilisation of the product and addition of antimicrobial agents).
- Prevention of communicable diseases: Infectious diseases caused by bacteria (TB), virus (Flu) and other microbial types.

2. Patient oriented pharmacy: Due to pharmacy practice regulation, for the first time the definitions of compounding and dispensing received regulatory status.

- Compounding: It means the preparation, mixing, assembling, packing or labelling of a drug or device as per the prescription or initiative based on the practitioner/ patient relationship with pharmacist in the course of professional practice. In short it is the extemporaneous preparation of drug product for dispensing.
- Dispensing: It means the interpretation, evaluation, supply of drug or device as per a prescription to a patient or patient's agent in a suitable container appropriately labelled for subsequent administration to, or use by, a patient. In simple words, dispensing is supply of compounded as well as manufactured product to the patient ensuring rationality of drug use.
- Pharmaceutical care: It means the provision of drug therapy and other patient care services intended to achieve outcomes related to the care or prevention of a disease, elimination or reduction of a patient's symptoms, or arresting or slowing of a disease process.

Due to the availability of ready to sell manufactured products, practice of compounding is now outdated and is now just an Art of Pharmacy. On the other hand, availability of thousands of drug molecules and their different brands have in turn increased chances of drug related problems and irrational drug use. Thus, dispensing pharmacy has become the primary work of medical stores. This is emerging as Community Pharmacy. Modern Dispensing Pharmacy (MDP), a book authored by me in 2004 is the first Indian book that has focussed on the patient oriented concept of retail pharmacists. It is widely accepted by educationalists and community pharmacists across the nation.

Questions for Self-Study

- Define Pharmaceutics and explain its scope. **(PU 2010)**
- Write scope of pharmaceutical engineering. **(PU 2014)**
- Write role of pharmacists in the field of Pharmaceutical Technology.
- Define: Compounding Pharmacy, Dispensing Pharmacy and Pharmacy Practice.
- Summarise the working of Industrial Pharmacy unit.

1.4 HISTORICAL BACKGROUND AND DEVELOPMENT OF PROFESSION OF PHARMACY AND PHARMACEUTICAL INDUSTRY IN INDIA

For convenience this section is subdivided into development of pharmacy profession, growth of pharmaceutical industry and pharmacy education.

Development of Pharmacy

The word pharmacy is derived from the Greek word *Pharmakon*, which means drug or medicine. Disease is born with man and pharmacist came in to existence when man first used an herbal drug to cure a disease. Egyptian and Greek scholars contributed much in the initial stages. Ebers Paryrus (1550 BC) was the first to attempt systematic classification of medicines. Hippocrates (400 BC) is referred to as Father of Medicine. The God Asclepius and his daughter Hygeia with a sacred serpent together were considered to heal and from them emanated the international symbol of medicine. The Roman physician Dioscorides (65 AD) compiled a list of herbs in De Materia Medica. The ancient Greek physician Galen (131-201 AD) reported methods for preparations of drugs from plants, which are called Galenicals.

In early days, the physician had to deal with diagnosis, compounding and dispensing of medicines. During the second half of the European middle ages, the pharmacist became separated, under name 'Apothecaries'. Thus, the physicians, apothecaries (pharmaceutical chemists) and drug merchants (druggists) were involved in the supply of medicament to the patient. The chemists were related to compounding and druggists were referred to supply or sale of medicines.

Pharmacy is an ancient profession dedicated to providing health care. Several developed and developing countries have been recognising pharmacists as members of the health care team. In India also pharmacy is regarded as a prestigious profession; however, the recognition of the profession is comparatively recent. Before 1984, pharmaceutical education was not considered essential for a person wanting to sell medicines. The 'compounder', a person who was able to read a prescription and assist the physician in compounding, was considered a pharmacy professional. It was only after 1st September 1984 that a diploma in pharmacy was considered a minimum qualification to register as a pharmacist. Therefore, pharmacists having a D.Pharm degree are more in retail drug business. However, due to lack of in-depth knowledge and skills of pharmacy practice, these retail pharmacies remain mere centres of trading. With aim of strengthening pharmacy practice, post graduation in Pharmacy practice (M.Pharm-Pharmacy Practice, M.Pharm-Clinical Pharmacy) was introduced in 1994 and the recent developments like Pharm.D. regulation 2008 and Pharmacy Practice Regulation 2015 are milestone contributions for development of pharmacy profession.

Dr. B. Suresh, President of Pharmacy Council of India is the person behind these important developments. The expertise of clinical pharmacists in hospitals, in clinical trials and in pharmacovigilance is being fully utilised in areas known as 'Pharmaceutical care or Pharmacy Practice'.

Growth of Pharmaceutical Industry in India

Before 1900, Indian science of medicine, Ayurveda, was a system of medicines; however medicines were not produced on industrial scale. India was largely dependent on the UK, France and Germany for pharmaceutical products. In 1901, a small factory 'Bengal Chemicals and Pharmaceutical Works' was established in Calcutta by Acharya Prafulla Chandra Ray. In 1903, Prof. T.K.Gujjar established a small factory in Mumbai, which has grown into the Alembic Chemical Works Ltd at Baroda (1907). After the First World War with the spirit of 'Swadeshi' to compete with inferior quality imported medicines, the Government of India appointed the Drug Inquiry Committee (1931). Lt. Col. R. N. Chopra headed the committee. As per recommendations of this committee, Drug and Cosmetic Act 1940 and its Rules 1945 were enacted.

Role of allopathic medicines, mainly antibiotics was well accepted, this lead to the establishment of Hindustan Antibiotics (HAL) at Pune in the early 1950's and Indian Drugs and Pharmaceutical Ltd (IDPL) at Rishikesh and Hyderabad in the 1960's. The establishment of these pharmaceutical companies has been the milestones in the history of pharmaceutical industry of India. At the time of independence the production of drugs was worth only Rs.10 crores, which was grown significantly due to the Process Protection Patent Act 1970. Manufacturing and export of drugs at great economy by modifying the process of manufacturing accelerated growth of industry and it was about Rs.12000 crores in 1997.

The pharmaceutical industry in India has attained remarkable growth during last decade. This rapid growth can be attributed to the technological advancement and increased export in post GATT (General Agreement on Tariffs and Trade) era. Good Manufacturing Practices (GMP) under revised Schedule M improved quality of drugs. Product Patent Act was accepted by India in 2005, when total production of bulk drug was $ 2.06 billion and formulation at US$ 7.29 billion and the total export during 2004-05 was $ 3.8 billion. Then after, spender progress started with total turnover of India's pharmaceuticals industry in 2008-09 was US$21.04 billion, which stood at US$ 31.9 billion in 2013. The Indian pharmaceutical market is expected to grow to reach US$ 45 billion in 2020. The Indian Pharmaceutical industry is the world's third-largest in terms of volume and 13th in terms of value.

India is the only country after America that has a large number of US FDA approved pharmaceutical formulation units (about 200 units) and due to which export contributes for

almost 50% of total pharma business. Export of generic drug formulations is considered as a major boost. The exports of pharmaceuticals from India grew to US$ 14.6 billion in 2012-13 from US$ 6.23 billion in 2006-07, registering a compound annual growth rate (CAGR) of around 15.2 per cent. The industry holds a market share of US$14 billion in the United States. India has gained recognition as 'Generic Pharmacy of the world".

Among the top pharma companies in India, Ranbaxy 76.86 (all in Rs. billion), Cipla with 69.77, Dr. Reddy's Lab 66.86, Lupin 53.74, Aurobindo Pharma 42.84 are the fastest growing companies as per a report by Corporate Catalyst India; May 2014.

Pharmacy Education in India

In India, knowledge of medicines is very old. The Aryans compiled four Vedas during period of 1500 to 800 BC. The great authors, viz., Charaka, Susruta and Vagbhata compiled their classical books. *Charaka Samhita* is supposed to be the oldest text in *ayurveda*. Susruta, the first surgeon of the world, compiled a great book '*Susrut Samhita*'. Vagbhata wrote '*Ashtanga Ayurveda*' in 7th century AD. During 13th century AD, the Greek-Arab medicine named 'Unani' medicine was introduced in India.

The beginning of Pharmacy education in India is traced back from 1842, when the Portugese started 'Escola Medico de Goa'. The college is now called as Goa College of Pharmacy. At that time the pharmacists were recognised as "Farmaceuticos".

In 1870, Madras Medical College was given permission to conduct licentiate examination for candidates, who wished to work as Chemists and Druggists. In 1894, a two-year pharmacy course after secondary school level was introduced and it was guided by Pharmaceutical Society of Great Britain. However, there were no uniformity in the syllabus and legislation to control the pharmacy education. Professor R. N. Chopra recommended the need of pharmacy-qualified person to perform pharmacy related services and laid down qualifications for diploma and degree pharmacy. As part of the recommendations, the Pharmacy Act 1948 was passed with the objective to regulate the profession of Pharmacy in India and The Pharmacy Council of India (PCI) came into existence in 1949. As part of which, the first educational regulation (E.R.) was introduced in 1953 by the PCI. The Birla Institute of Technology is the first approved institute by PCI to conduct the Diploma in Pharmacy as per ER-53. Since then many changes have been brought about in the education regulations. As per the ER 53, the minimum qualification for a registered pharmacist was two year diploma followed by professional training or one year condensed course for experienced persons. It was subsequently revised and updated in 1972, 1981 and 1991.

As per the ongoing ER 91, 12th science + 2 years diploma is the minimum qualification. For upgradation of professional standards ER 91 introduced many patient orientated subjects

such as health education and community pharmacy, biochemistry and clinical pathology, hospital and clinical pharmacy and drug stores and business management. These subjects are designed to give more professional insight to the students. To keep pace with the working standard of pharmacists worldwide, revision of ER 91 is in progress (ER 2014) with the focus of developing community pharmacists. It includes practice oriented subjects like social pharmacy, community pharmacy, pharmacotherapeutics, etc.

To fulfill the needs of pharma industry, the Chopra committee also recommended a course in degree pharmacy. In 1932, Prof. M. L. Schroff –'The Father of Pharmacy Education in India', initiated pharmaceutical education at the university level in the Banaras Hindu University. Initially, pharmaceutical chemistry was introduced as one of the subjects for B.Sc. A regular three-year B. Pharm course made a beginning from July 1937. It followed with beginning of Department of Pharmacy at different universities like Bombay (1945), Punjab (1947), BITS Pillani (1950), Andhra (1951), Sagar (1956), Nagpur (1956).

In 1940, the first postgraduate programme, Master of Pharmacy, which was a one year programme by research, was stated at B.H.U. In 1954, a one and half year M.Pharm, which was partly by papers and partly by research was introduced by L.M. College of Pharmacy, Ahmedabad. Later Sagar University started two years M. Pharm. Course in 1957.

Currently, pharmaceutical education in India is imparted at three levels: Diploma in Pharmacy (Two years course after 10 + 2 science), Bachelor of Pharmacy (Four years course after 10 + 2 science), and Post Graduate course, Master of Pharmacy (Two years course after B. Pharm). Masters in Pharmacy is available in various branches such as Pharmaceutics, Pharmaceutical Chemistry, Pharmacology, Pharmacognosy, Quality assurance techniques, Pharmaceutical Biotechnology, Biopharmaceutics, Drug regulatory affairs and Practice of Pharmacy. Students who qualify GPAT (Graduate Pharmacy Aptitude Test) examination and admitted to M.Pharm. are entitled for scholarship sanctioned by AICTE. Since 1950s, Doctoral research has been started in various institutes. In the post–GATT era Ph.D. research facilities have also increased significantly.

Though, Indian pharmacy has achieved international recognition in area of industrial pharmacy owing to the development of technology oriented pharmacy graduates, it is at infancy in the area of patient care. The concept of community pharmacy and clinical pharmacy is still not fully developed. The time has come to give impetus to the area of patient oriented pharmacy. With enforcement of Pharm. D Indian Pharmacy has entered in area of pharmacy Practice. Pharm.D. is a six years Post graduate education after 12^{th} science or it can be completed within 3 years after B.Pharm. The visionary thoughts of Dr. B. Suresh, President of Pharmacy Council of India and efforts he has taken for promoting Pharm.D.

education will enable a pharmacist to serve in area of health care, clinical studies and hospital practices.

In addition, Health ministry of India on request of PCI has brought GR of B.Pharm. (Pharmacy Practice)- 2015, which will be a bridge course for D.Pharm. qualified pharmacists , who wish to upgrade their qualification.

Questions for Self-Study

- Write short note: Developments of Profession of Pharmacy. **(PU 2010, 2013)**
- Development of Pharmaceutical industry: A short note. **(PU 2011)**
- Historical Background of Pharmacy Profession : A short note. **(PU 2012)**
- "Pharma sector is most benefited with enforcement of GATT". Explain.
- Describe developments of the education regulations (ER) for Pharmacy education.
- Describe growth of Pharmacy education in India.
- Write historical developments of B.Pharm. education in India.
- Describe current scenario of Pharmacy education in India.
- Explain concepts of Pharmaceutical technology and Pharmacy Practice.
- ❖ Write the history of pharmacy profession and industry in India, also write a note on career opportunities after pharmacy graduation. **(PU 2014)**

1.5 PHARMACY CODE OF ETHICS: SIGNIFICANCE OF LAW AND ETHICS

Laws are rules of legal binding on all persons in a state or nation. Laws are enforced by the government to ensure working in discipline for the betterment of all, for example Drug and Cosmetic act 1940. These are compulsory and expected that everyone must follow them otherwise the illegal act is eligible for some punishment. But, to what extent to follow laws is an individual choice that is governed by willingness of individual, behaviour and moral values. It means that only Law cannot achieve objective of ideal society but it should go parallel with the code of ethics.

Code of ethics can be defined as principles, values, standards or rules of behaviour, stated publically that guide a pharmacy professional to follow procedures, to take decisions and adopt systems in a way that leads to the welfare of its key stakeholders, patient and respects the rights of all those who are involved directly or indirectly in the said operation.

Pharmacists are health professionals who assist individuals in making the best use of medications. Pharmacist is responsible -

- to help people to maintain good health and to avoid ill health
- to promote the responsible use of medicines, and
- to assist patients to gain maximum therapeutic benefit from their medicines.

The codes of ethics guide pharmacists for their daily practice, maintain professional relationships with patients and with other health professionals and society. At all times, pharmacists should strive to provide the best possible care for consumers and patients, with due regard for the limitations of available resources and the principles of equity and justice.

The Pharmacy code of ethics is beneficial for those -

- who want to enter in pharmacy profession. It guides them about the moral commitments of pharmacy profession and serves as a source for gaining required education and skills. As per pharmacy practice regulation 2015, each applicant, at the time of making an application for registration under the provisions of the Act, shall be provided a copy of the duly signed declaration along with copies of Code of Pharmaceutical Ethics and Pharmacist's oath.
- who are in the profession, where code of ethics serves as a basis for self evaluation and peer review, and
- who are outside the profession, it provides public identification and image, and hope of fulfilling the expectations of society on large.

1.6 CODE OF ETHICS STATEMENT FOR PHARMACIST

The Pharmacy Act 1948 has been listing the following statements of code of ethics. The Pharmacy Practice Regulation 2015 also recalls these. Keeping in view the role of modern pharmacist, the author has interpreted these principles in positive sense way back in 2007 (c) Dr. Atmaram Pawar, Handbook for Community Pharmacists, 2007.

1. The appearance of the premises should reflect the professional character of Pharmacy and indicate to the public that the practice of pharmacy is the main purpose of the establishment.
    - Pharmacy is one the vital health professions and the practice of pharmacy is a service provided by registered pharmacists under different designations laid down by Pharmacy Practice regulation viz. Community Pharmacist/Hospital Pharmacist/Clinical Pharmacist/ Drug information Pharmacist.
    - Name of the registered pharmacist along with his registration number, qualification and his/her photograph shall be displayed adjacent to the area where dispensing is carried on in the pharmacy.
    - Registered pharmacist should also comply with a dress code of being dressed formally and wearing clean white coat/apron with a badge displaying the name and registration number.

2. In every pharmacy, there should be a qualified and competent pharmacist to have personal control over the pharmacy and the pharmacist shall be primarily responsible for the observance of proper standards of conduct in connection within it.
    - Community pharmacist is an individual currently registered and who works according to legal and ethical guidelines to ensure the correct and safe supply of medical products to the general public. They are involved in maintaining and improving people's health by providing advice and information as well as supplying prescription medicines.
    - A registered pharmacist should be an honest person, instructed in the art of medicines. He shall keep himself pure in character and be diligent in caring for the sick; he should be modest, sober, patient, prompt in discharging his duty without anxiety; conducting himself with propriety in his profession and in all the actions of his life.
    - A registered pharmacist should uphold the dignity and honour of his profession.
2. Drugs and other ingredients should be purchased from a reputed source.
    - All the medicines should be purchased from a licensed manufacturer/ wholesaler. Further he should ensure that these are properly stocked, if required in air-conditioned warehouse.
3. Price of medicines charged from the customer should be fair and including dispensing and compounding charges without unduly taxing the purchaser.
    - The registered pharmacist, engaged in the practice of pharmacy profession shall give priority to the interests of the patients. The personal financial interests of a registered pharmacist shall not conflict with the medical interests of patients.
4. A pharmacist should not make any attempt to capture the business of fellow competitors that is by offering reduced price, gift, prizes etc.
    - Competition is challenge for business and Pharmacist should accept it by offering professional and value added services as positive effort but not by offering discounts and gifts.
    - Secondly, a registered pharmacist should expose, without fear or favour, incompetent or corrupt, dishonest or unethical conduct on the part of members of the profession.
5. After receiving the prescription, a pharmacist should not show any such emotion on his face as to make the patient lose their faith in the prescriber.

6. Prescription presented for dispensing should not be discussed with patient or others regarding the merits and demerits of their therapeutic efficacy.
7. Pharmacist should neither discuss physician's prescription with customers nor disclose to them the composition of prescription.

   The Pharmacy Act 1948 mentions the above statements. However, over a period of progress and expectations from pharmacists at global level, Pharmacy Practice Regulation 2015 reframed these in the interest of providing effective pharmaceutical care.

   - Every expression and effort made by Pharmacist should lead to building patient's confidence towards the health profession.
   - A registered pharmacist should undertake a pharmaceutical assessment of every prescription presented for dispensing, where he should apply his knowledge to establish the safety, quality, efficacy and rational use of drugs treatments specified by a prescriber. But it should not be discussed with the patient otherwise it may lead to confusion or fear in the mind of the patient.
   - Appropriate information should be provided to the patient or the care giver and, where possible, understanding of this information should be checked.
   - Registered pharmacist should initiate patient counselling that will enhance or optimise drug therapy.
   - Patient confidentiality shall be maintained at all times.
8. Pharmacist is a link between medical professional and public. He should constantly upgrade himself with recent developments in pharmacy and allied fields. He should be expert in the field of pharmacy and should advice physicians, and educate the public to maintain their health.
   - A registered pharmacist should participate in professional meetings as part of Continuing Pharmacy Education programmes, organised by reputed professional academic bodies or any other authorised associations/ organisations and upgrade their knowledge.

- To promote rational use of drugs, the pharmacist shall involve himself in activities such as:
  (i) Preparation of formularies both at the hospital level and at state/ national levels.
  (ii) Critical assessment of promotional materials prepared by the drug companies.
  (iii) Dissemination of evaluated information through authorised sources.
  (iv) Organise educational programmes for health professionals.
  (v) Preparation and dissemination of patient information leaflets.

9. A pharmacist should provide efficient and reasonably comprehensive pharmaceutical services through the medical store or pharmacy.
    - No person other than a Registered Pharmacist should compound, prepare, mix, dispense or supply any medicine on the prescription of a Registered Medical Practitioner.
    - A Registered Pharmacist should review the patient record and each prescription presented for supply for the purpose of promoting therapeutic appropriateness by identifying the following drug related problems and he should take appropriate steps to avoid or resolve these.
        (i) Over utilisation or under utilisation
        (ii) Therapeutic duplication
        (iii) Drug-disease interactions
        (iv) Drug-drug interactions
        (v) Incorrect drug dosage or duration of drug treatment
        (vi) Drug-allergy interactions
        (vii) Correlation of availability of drugs (to avoid artificial shortage of drugs)
        (viii) Clinical abuse/misuse
    - Registered pharmacist should not wilfully commit an act of negligence that may deprive his patients from necessary medical care.
10. A pharmacist should not recommend any particular medical practitioner, unless specially asked for.
    - For promotion of business or for personal benefit pharmacist should not recommend name for any medical practitioner to patients.
11. Self-servicing method should not be allowed, as it would encourage self-medication.
    - Self medication is a serious issue that is leading to individual as well as social ill-health. Antibiotic resistance is the best example of this where patient without rational consume antibiotics. Even OTC medicines should be dispensed by pharmacists only after confirming need to the patient.

1.7 UNETHICAL ACTS

A registered pharmacist should not aid or abet or commit any of the following acts which shall be construed as unethical

1. Advertising

- Soliciting of patients directly or indirectly by registered pharmacist or by pharmacy institutions or organisations is unethical.

- A registered pharmacist should not make use of his name, knowledge or position in any form of advertising or publicity through any mode.
- A registered pharmacist should not give certificate of quality or usefulness to any person or any medicine, therapeutic article, apparatus or appliance or any commercial product.
- Printing of self photograph in the letter head or on sign board of the Pharmacy shall be regarded as acts of self advertisement and unethical conduct.

2. Rebates and Commission

- A registered pharmacist should not give any gift, gratuity, commission or bonus in consideration of or return for the referring, recommending of any patient for sale/dispensing of medicines.
- A registered pharmacist should not directly or indirectly participate in division, transference, splitting or refunding of any fee for dispensing/sale of medicines.

3. Secret Remedies

The dispensing of secret remedies of which he does not know the composition, their use or the manufacture is unethical.

4. Human Rights

The registered pharmacist should not involve or help torture, mental or physical trauma or concealment of torture inflicted by some other person or agency in clear violation of human rights.

Questions for Self-Study

- o Write concept of Law and ethics in Pharmacy.
- o Elaborate the practices of Pharmacists that are considered unethical.
- Write short note on Code of Ethics. **(PU 2014)**
- Enlist various statements of Pharmacy code of ethics.
- ❖ Discuss ethical and unethical pharmacy practice according to Indian acts and regulations.

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Chapter 2...

Pharmacopoeias

Syllabus

- Special emphasis on IP, BP, USP, including history, developments and latest edition.
- Introduction to European pharmacopoeias, Martendale, Merk Index, BPC and Ayurvedic Pharmacopoeia, Materia Medica.

Features of the chapter

- Introduction to various commonly used Pharmacopoeia. To know about its importance.
- Features of current editions of Pharmacopoeia.

2.1 PHARMACOPOEIA

The term pharmacopoeia comes from the Greek word *'pharmakon'* meaning a drug and *'poiea',* meaning 'to make'. It is a legal and official book issued by recognised authorities appointed by the government of each country that describes lists of pharmaceutical substances, formulae together with standards, quality control tests in order to build quality and maintain uniformity.

Pharmacopoeias were developed to improve and maintain the standards and quality of medicinal preparations. In the event of doubt or dispute, the information given in them is considered authoritative and valid. The list of various published pharmacopoeias includes– Argentine, Austrian, Belgian, Brazilian, British, Chinese, Czechoslovakian, Egyptian, European, French, German, Hungarian, Indian, International, Italian, Japanese, Yugoslavian, Mexican, Netherlands, Nordic, Polish, Portuguese, Rumanian, Russian, Spanish, Swiss, Turkish and the United States.

2.2 BRITISH PHARMACOPOEIA AND RELATED BOOKS

2.2.1 British Pharmacopoeia

Antidotarium of Nicholas and Ricettario Fiorentino are the initial books based on the writings of ancient Greek, Roman and Arabian writers. The legal and national pharmacopoeia was published in 1618 with the development of pharmacopoeia Londinensis, and later in 1699 the Edinburgh Pharmacopoeia was published, followed by its English edition in 1839. The Dublin Pharmacopoeia appeared in 1807 and its last edition was published in 1850.

The Medical Act 1858, stressed the need of a single national pharmacopoeia and the first edition of British Pharmacopoeia (BP) appeared in 1864. It is the outcome of the fusion of London, Edinburgh and Dublin pharmacopoeias.

The Indian and colonial addendum was published in 1900, which was appeared as the Government of India edition in 1901.

In the eighth edition (1953), the title of drugs and preparations were in English instead of Latin and the metric system was preferred. The thirteenth edition of BP was published in two volumes in 1980. British Pharmacopoeia 2000 edition was additional companion edition, the British Pharmacopoeia (Veterinary) 2000.

Since 2007 the British Pharmacopoeia comprised of six volumes as viz.- Volumes I and II contain medicinal substances, volume III contains formulated preparations, blood-related products, immunological products, radiopharmaceutical preparations, surgical materials and homoeopathic preparations, volume IV comprises supplementary chapters, Volume V is Veterinary edition and Volume VI is CD-ROM version.

The British Pharmacopoeia (BP) 2015 marks the 150^{th} Anniversary of setting quality standards for medicines and medicinal products in the UK. The squicentenary year copy of the BP 2015 includes a complimentary, commemorative digital facsimile of the BP 1864 - the first edition. This edition also sees the introduction of a USB format which replaces the CD-ROM.

The 2015 edition includes almost 3,500 monographs which are legally enforced by the Human Medicines Regulations 2012. All monographs and requirements of the European Pharmacopoeia are also reproduced in the BP.

Features of BP 2015

- Legally effective from 1 January 2015.
- 39 new BP monographs.
- 144 amended monographs.
- One new BP Supplementary Chapter.

- Three in-year online updates to harmonise with the European Pharmacopoeia Supplements 8.3, 8.4 and 8.5.
- All European Pharmacopoeia monographs integrated (8th Edition as amended by Supplements 8.1 and 8.2).
- USB format - Complimentary 150th Anniversary USB containing a digital facsimile of the BP 1864.

2.2.2 British Pharmaceutical Codex

The British Pharmacopoeia included only well-established drugs and their preparations. With an intention to provide an alternative book for formulations and remedies which were not well established, the council of the Pharmaceutical Society, in 1903, proposed to produce the British Pharmaceutical Codex (BPC). The first edition appeared in 1907 and successive editions in 1911, 1923, 1934, 1949, 1954, 1959, 1963, 1968 and the tenth edition in 1973. The eleventh edition was published in 1979 and since then it is known as – The Pharmaceutical Codex.

The Pharmaceutical Codex comprised general chapters on design, manufacturing and evaluation of various dosage forms and monograph of drug substances along with the up-to-date research work carried out on a particular drug. The Indian edition is available since 2009.

2.2.3 British National Formulary

The British National Formulary (BNF) is a pocket-sized handbook containing essential information about drug, action, uses, dosage forms, adverse reactions, etc. The guidelines on prescribing is very helpful for clinicians that includes special topics like general guidelines, emergency supply of medicines, controlled drug and drug dependence, adverse reaction of drugs and prescribing for children. The BNF evaluates clinical evidence from diverse sources with information validated by a network of clinical experts and published under the authority of a Joint Formulary Committee. The first BNF was published in 1949, followed by the next in 1981. The BNF has been regularly revised twice yearly.

BNF 69 (March 2015) has been revised and revalidated to reflect changes in product availability, emerging safety concerns and shifts in clinical practice.

Some of the significant changes in this edition include:

- Updated general guidance on drugs and driving in response to new regulations in force from March 2015, on risk assessment and treatment in the management of arrhythmias, on assessing cardiovascular risk and modification of blood lipids in the primary and secondary prevention of cardiovascular disease and updates to recommended regimens for prophylaxis against malaria for specific countries.

- Includes new guidance on dose adjustment in renal impairment for atorvastatin and new recommendations on concomitant use of drugs affecting the renin-angiotensin system

Questions for Self-Study

- Define the term Pharmacopoeia.
- Write developments of British Pharmacopoeia.
- When did the Indian edition of the British Pharmacopoeia appear?
- Write about BPC and BNF.
- Write the features of the current edition of the British Pharmacopoeia.
- ❖ What do you mean by Pharmacopoeia? Give an account of various British Pharmacopoeia, British Pharmaceutical codex and British National Formulary.

2.3 INDIAN PHARMACOPOEIA AND RELATED BOOKS

2.3.1 Pharmacopoeia of India

The beginning of the Indian Pharmacopoeia (IP) publication can be traced back to 1841 with the publication of the Bengal Dispensary. The Bengal pharmacopoeia appeared in 1844, edited by William Brooke O'Shaughnessy, which had no legal status anywhere in India. For use in all parts of India, the first official Pharmacopoeia of India, London appeared in 1868, which was edited by Edward John Waring and it contained drugs from BP1964 and some indigenous drugs. The supplement to IP 1868 appeared in 1869. In pre-independence days the British pharmacopoeia was used in India; and the colonial addendum of BP 1898, which was published in 1900 appeared as the Government of India edition in 1901.

The actual process of publishing the first Pharmacopoeia started in the year 1944 under the chairmanship of Col. R. N. Chopra. After almost eight decades, in 1946, the Government of India issued the list known as 'The Indian Pharmacopoeial List'. It was an attempt by India to publish its own book of standards.

In 1945, the Government of India appointed an Indian Pharmacopoeia Committee for preparing the 'Pharmacopoeia of India'. The committee, under the chairmanship of Dr. B. N. Ghosh, published the first edition of IP in 1955. The set of standards are published under the title Indian Pharmacopoeia (IP) which has been modelled over and historically follows from the British Pharmacopoeia. Indian Pharmacopoeia 55 was recognised as a statutory book of standards under the Drug and Cosmetic Act 1940. It is written in English and the official titles of monographs are given in Latin. A supplement to the first edition of IP was published in 1960. In the next edition in 1966, the titles of the monograph were changed to English. The doses were expressed in the metric system. (Many authors of

D.Pharm. and B.Pharm. books that were published even after 1990 have not used the metric system. Modern Dispensing Pharmacy (2004) is the first book to include these modern aspects).

After 19 years, the third edition of IP was published in 1985. It followed with IP 96 along with veterinary supplement. The standards that are in effect since December 1, 2010, is the *Indian Pharmacopoeia 2010 (IP 2010)*. The Pharmacopoeia 2014 was released by Health Minister Ghulam Nabi Azad on November 4, 2013.

The various editions of IP are as follows:

- 1st edition I. P. 1955 was published in the official gazette. Dr. B. N. Ghosh, Chairman
  - Supplement 1960
- 2nd edition I. P. 1966 Dr. B. Mukherji, Chairman,
  - Supplement 1975
- 3rd edition I. P. 1985 Dr. Nityanand, Chairman
  - I Addendum 1989
  - II Addendum 1991
- 4th edition I. P. 1996 Dr. Nityanand, Chairman
  - Addendum 2000
  - Addendum 2002
- 5th edition I. P. 2007 Dr. Nityanand, Chairman
- 6th edition I. P. 2010: Dr. Nityanand Co-Chairman IPC
  - Addendum 2012
- 7th edition I. P. 2014 Dr. B. Suresh Co-Chairman IPC
  - Addendum 2015

For the recent publications, the Secretary of Health ministry as an ex-officio and holds chairmanship of IPC (Indian Pharmaceutical Commission) and expert from pharmacy holds post of Co-chairman IPC and Chairman of Scientific committee, which is technically the person responsible for content and publication of IP.

The Indian Pharmacopoeia 2014 is presented in four volumes. The scope of the Pharmacopoeia has been extended to include products of biotechnology, indigenous herbs and herbal products, veterinary vaccines and additional antiretroviral drugs and formulations, inclusive of commonly used fixed-dose combinations. For the first time, IPC has introduced 19 radiopharmaceutical monographs. Standards for new drugs and drugs used under

National Health Programmes are added and the drugs as well as their formulations not in use now days are omitted from this edition.

The IP 2014 incorporates 2567 monographs of drugs out of which 577 are new monographs consisting of APIs, excipients, dosage forms, herbal products, biotechnology products and radiopharmaceuticals etc.

Features of IP Addendum 2015 to IP 2014

To improve standard of IP at international level and in turn quality of medicines, following changes have been made in addendum 2015.

- General chemical tests for identification of an article have been almost eliminated and the more specific infrared and ultraviolet spectrophotometric tests have been given emphasis.
- The use of chromatographic methods has been greatly extended to cope with the need for more specificity in assays and in particular, in assessing the nature and extent of impurities in ingredients and products.
- Most of the existing assays and related substances tests are upgraded by liquid chromatographic method in view to harmonise with other international pharmacopoeias.
- Keeping in view the essential requirement for harmonisation of analytical methods with those adopted internationally, steps have been taken for monitoring the quality of drug.
- For controlling the microbial quality of all the medicinal product general chapters on microbial contamination in non-sterile products and test for colony forming units have been revised.

2.3.2 National Formulary of India (NFI)

To ease the selection of suitable formulation, the pocket-sized National Formulary of India (NFI) was published in 1960, followed by 1966 and 1979. Like BNF; NFI also is not mandatory document but its aim is to promote rational drug use and serves as a guidelines for a physician and Pharmacist. The latest 4^{th} edition is published in all new format in 2011. A section 'General Advice for Prescribers' elaborate principles of prescription writing, drug selection, drug interactions, dose, adverse drug reactions, patient compliance, etc. It include monographs of 377 drugs and 22 fixed dose combinations explaining their indications, contraindications, precautions, adverse effects and storage. The drugs and formulations included in these are classified on the basis of pharmacological actions.

2.3.3 Indian Pharmaceutical Codex

In 1947, a resolution was passed to compile a 'brochure' to highlight the information and clinical uses of the important indigenous drugs of India. Instead of the brochure, the Indian Pharmaceutical Codex (IPC) was published in 1953.

2.3.4 The Ayurvedic Pharmacopoeia of India

The Ayurvedic Pharmacopoeia of India (API) is the legal document of standards for the quality of drugs, substances and preparations included therein (The Drugs & Cosmetics Act, 1940). This book is included in the first schedule of Drugs and Cosmetic Act, 1940. Manufacturers are required to follow pharmacopoeial standards as these are mandatory requirement under the Act.

It consists of monographs on drugs of plant origin. Pharmacognostical, chemical and Ayurvedic standards of the parts of the plants used in Ayurveda are described in detail in each monograph.

- Each monograph describes macroscopic, microscopic characters along with their chemical standards of identity, permissible limit of foreign matter, purity and strength.
- It also prescribes total ash value, acid insoluble ash, and alcohol soluble extractive, water soluble extractive and chromatographic pattern of TLC.
- The data has been finalised after confirmation of various samples obtained from different agro-climatic zones by the cross-section of experienced scientists in Ayurvedic Pharmacopoeia Committee and after careful scientific scrutiny.
- The standards have been consciously kept modest so that its implementation by the manufacturing companies becomes easily acceptable in order to maintain quality control and batch to batch uniformity.
- Ayurvedic pharmacological properties like Rasa, Guna, Virya, Vipaka, Karma etc. are also mentioned in each monograph along with their therapeutic uses, some of the important classical formulations and therapeutic dose.
- In the end, English equivalents of each Ayurvedic term have been given to make the volume user friendly for all people who work in the area of Ayurveda drugs and who are not conversant with Sanskrit/Ayurvedic terminology.
- Name of the drugs given on the top of each monograph of the drug is in Sanskrit as mentioned in the Ayurvedic classics and/or in the Ayurvedic formulary of India. These names have been arranged in English alphabetical order.
- Synonyms of each drug appearing in each monograph in Sanskrit, English, Hindi, Urdu and other Indian regional languages have been mentioned as found in the classical texts, Ayurvedic Formulary.
- Each monograph begins with an introductory paragraph indicating the part, scientific name of the drug in Latin with short description about its habit, distribution and method of collection, if any.

Questions for Self-Study

- What is Pharmacopoeia? Add note on National Formulary. **(PU 2011, 2013)**
- Which is the first official and unofficial Indian Pharmacopoeia?
- Write the features of the current edition of the Pharmacopoeia of India.
- Mention the different editions of IP.
- Write a note on INF and IPC.
- Write short note on The Ayurvedic Pharmacopoeia of India.
- Write short note on Indian Pharmacopoeia. **(PU 2014)**
- ❖ Give an account of various Pharmacopoeias and formularies officially published in India.

2.4 UNITED STATES PHARMACOPOEIA

The first edition of the United States Pharmacopoeia (USP) was published on December 15, 1820 in both Latin and English. From 1920 to 1942 it was published at ten year intervals, then up to 2000 it was at an interval of five years and from 2002 it has been published annually. The first National Formulary (NF) of the United States appeared in 1888. In 1975, unification of the USP and NF was announced.

The USP22– NF 17, 1990 is the third revision that consolidates USP and NF into a single volume. An electronic version of the USP NF on floppy disks was introduced in 1992. The USP23-NF 18 was published in Mumbai as an Asian edition at the end of 1994 in response to increasing recognition and use of the USP–NF standards by government and pharmaceutical manufacturers in India and other Asian nations.

From 2006 the USP began to publish Spanish edition also. Every year, the next edition of USP gets published. USP 37–NF 32, the latest edition for 2014 was published in English on November 1, 2013 and it was enforced in May 1, 2014. USP 37–NF 32 features more than 4,700 monographs and over 270 general chapters, eight of which are new or revised. The new and revised general chapters include Porosity by Nitrogen Adsorption–Desorption, Vitamin A Assay, Vitamin D Assay, Water Conductivity, X-ray Fluorescence Spectrometry, and more. It also contains more than 100 new or revised monographs, including 50 that are newly modernised.

The major information in the USP-NF includes pharmacy compounding practices, sterile drug products for home use, manufacturing practices for nutritional supplements, radiopharmaceuticals for positron emission tomography compounding, etc. The USP–

equivalence in dissolution behaviour is a widely used tool of quality control and bioavailability of dosage forms. It also contains dissolution or drug release requirements and monographs for a number of successful delayed and extended release formulations. The USP DI electronic database is an informative database which is routinely published every three months.

2.5 EUROPEAN PHARMACOPOEIA

The European Pharmacopoeia is a single reference work for the quality control of medicines in the 37 signatory states and European Union member states. The 1st Edition of the Ph. Eur. was published in 1969 and comprised 120 texts. The 8th Edition, published in July 2013 is currently in force and contains more than 2220 monographs and 340 general chapters illustrated with diagrams or chromatograms and over 2500 descriptions of reagents. It consists of two initial volumes (8.0), with an implementation date of January 1, 2014. Volume 1 contains introductory information, general chapters and reagents, as well as monographs grouped by theme (dosage forms, vaccines, plants, etc.). Volume 2 contains all other monographs as well as an index of the entire contents of the Ph. Eur. The 8th Edition will culminate in a collection of eight non-cumulative supplements (8.1 to 8.8). The supplement 8.5 is enforced from 1st January 2015.

A new edition is published every three years. It is made available in print and electronic (online and USB stick) versions, in both English and French. The online version is also accessible from smartphones and tablet computers. The 9th edition and will therefore come into force on 1st January 2017.

Questions for Self-Study

- Write in brief about the development of the USP.
- What are the specific features of USP regarding dissolution testing?
- Write the features of the current USP.
- What is Pharmacopoeia? Add a note on European pharmacopoeia. **(PU 2014)**

2.6 MARTINDALE: THE EXTRA PHARMACOPOEIA

Martindale: The Extra Pharmacopoeia is the Complete Drug Reference book which provides reliable, unbiased and evaluated information on drugs and medicines used throughout the world. Based on extensive referencing of published information the most clinically relevant and appropriate information is selected. It was first published in 1883. To

date there have been 38 editions of Martindale. The current edition i.e the 38th edition was published in June 2014.

Martindale contains information on drugs in clinical use worldwide, as well as selected investigational and veterinary drugs, herbal and complementary medicines, pharmaceutical excipients, vitamins and nutritional agents, vaccines, radiopharmaceuticals, contrast media and diagnostic agents, medicinal gases, drugs of abuse and recreational drugs, toxic substances, disinfectants, and pesticides.

Martindale aims to cover drugs and related substances reported to be of clinical interest anywhere in the world. It provides a useful source of information for patients arriving from abroad to identify their existing medication, irrespective of their different brand names.

Features of MEP

- Martindale: The Complete Drug Reference is a reference book published by the Pharmaceutical Press.
- It lists about 6,000 drugs and medicines used throughout the world.
- It includes details of over 180,000 proprietary preparations.
- It also includes almost 700 disease treatment reviews.
- Monographs of some toxic substances are also included.
- Lists nearly 5,600 pharmaceutical terms and routes of administration
- Information to enable identification of medicines, the local equivalent and the manufacturer.
- Monographs include Chemical Abstracts Service (CAS), Anatomical Therapeutic Chemical Classification System (ATC) numbers and FDA Unique Ingredient Identifier (UNII) codes to help readers refer to other information systems.
- No other source has breadth of coverage or level of detail making it the ideal first line reference work as well as a trusted source of information for more detailed drug enquiries.
- Recognised and adopted worldwide

2.7 MERCK INDEX

The Merck Index is the definitive reference work for scientists and professionals looking for authoritative information on chemicals, drugs and biologicals. It has been the leading source of information on chemical compounds. The name THE MERCK INDEX is owned by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. It was published from 1889 until 2012, and then the title is acquired by the Royal Society of Chemistry. The current edition is the 15th, published in April 2013.

Monographs in *The Merck Index* typically contain:

- CAS registry number.
- Synonyms of the substance.
- A description of the substance's appearance.
- Melting point and boiling point.
- Solubility in solvents commonly used in the laboratory.
- Citations to other literature regarding the compound's chemical synthesis.
- A therapeutic category, if applicable.
- Caution and hazard information.

The Merck Index contains over 10,000 monographs with information relating to compounds of significance in research, commerce and environmental impact. The 15th edition is fully revised and updated and contains over 500 new monographs since the last edition, molecular weights have been recalculated with the latest IUPAC standards and there are revised periodic table and atomic weight tables.

2.8 ANCILLARY REPUTED DRUG INFORMATION BOOKS

2.8.1 Materia Medica

Materia medica, a text on medical material/substances contains information about the therapeutic properties of substances used for healing. The term derives the title from the work by Ancient Greek physician Pedanius Dioscorides in the 1st century AD. He wrote a five-volume treatise concerning medical matters, entitled *De Materia Medica* in Latin. This famous commentary covered about 600 plants along with therapeutically useful animal and mineral products. It documented the effects of drugs made from these substances on patients. *De materia medica* was the first extensive pharmacopeia, including about a thousand natural product drugs (mostly plant-based), 4,740 medicinal usages for drugs, and 360 medical properties. The book was heavily translated.

Pietro Andrea Mattioli, a renowned botanist and physician, published a translation of De Materia Medica into Italian in 1544. It was later translated into German, French and many other languages.

In India, the Ayurveda is traditional medicine that emphasises plant-based treatments, hygiene, and balance in the body's state of being. Indian Materia Medica includes knowledge of plants, their geographical source, methods for cultivation and storage and shelf life of materials. It also explains directions for making juice, dried powders, infusions and extracts.

Thus BP, IP, API, USP, Ph. Eur., are the primary pharmacopoeia of a particular country and BNF, BPC, INF, US DI, MEP, Merck Index and Materia Medica are various official/authentic drug formularies or drug information sources published by government or non-government organisations.

Questions for Self-Study

- Write note on Materia Medica.
- Write features of Merck Index.
- Write history and objective of The Martindale Extra Pharmacopoeia and enlist features of the current edition.
- Give an account of various authentic drug information sources published by government of Indian, British and other non-government organisations.

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Chapter 3...

Drugs and Dosage Forms

Syllabus

- Definition of Drug, Sources of Drugs.
- Concept of dosage form, rationale for development of dosage form, classification on the basis of nature, route of administration.
- Definition of New Drug as per regulatory aspect.

Features of the chapter

- Understanding difference between Drug, Dosage form, and New Drug.
- Introduction to various current dosage forms with its merits and demerit.
- Dosage forms are supported with examples of marketed products but it is not expected to recite the names of marketed products.
- Concepts of drug delivery and NDDS will be part of Dosage Form Design in Semester II.

3.1 DRUG AND ITS SOURCES

A drug may be defined as a chemical or biological agent intended for diagnosis, mitigation, treatment, cure or prevention of disease in humans or animals. These may exist in solid, liquid, semisolid or gaseous state and administered internally, applied topically, inhaled or injected.

Sources of drug

(a) Natural source: Plant, animals, microorganisms, marine, and arachnoid and amphibian are the various sources of drugs.

- Drugs from plant account for more than 30% of the current human therapy worldwide. Example: Steroids from *Dioscorea* species, reserpine and digitoxin, *Vinca* alkaloids, etc.
- The gland secretions such as insulin, thyroid extract, pituitary serum, antitoxins and vaccines are the leading animal origin drugs.
- Discovery of safe and therapeutically useful Penicillin seconded with discoveries of Tyrothricin, Actinomycin and Streptothricin from microbial origin contributing to modern medicine.

- The antiviral drug Ara-A (Adarabine) and anti-neoplastic agents, Ara-C (Cytarabine) are from marine source.
- Examples from arachnoid and amphibian category include Frog *X. laevis* and *X. borealis*.
- Kaolin, liquid paraffin, like drugs are originated from mineral.

(b) Synthetic drugs: The discovery of new chemical entity (NCE) involves synthesis of molecules in search of desired biological activity or modifications of existing chemical molecule on the basis of quantitative structure activity relationship (QSAR). Allopathic practice is based on use of the synthetic drugs, which is major medical practice, for example aspirin, paracetamol, atenolol, omeprazole etc.

(c) Semisynthetic: Lead nucleous originates from natural source, but can be further improvised by slight chemical modifications to improve effectiveness, eg. Antibiotics.

(d) Biotechnology: Today large number of new biological entities (NBEs) are developed using the genetic engineering, broadly called as Genomics and Proteomics. Medical biotechnology is denoted by RED biotechnology and agricultural developments are denoted by GREEN biotechnology. Present development in RED biotechnology can be categorised in three areas: (a) Cyclooxygenase-2 inhibitors, (b) Chronic diseases like cancer, arthritis, diabetes, Alzheimer's, cholesterol lowering and (c) Proteins and peptides.

- **Plant tissue:** The plant tissue culture is a genetic engineering technique that enables rapid production with improved yield of secondary metabolites which have medicinal value; like alkaloids, glycosides, resins, terpenes, amino acids, polysaccharides, etc. Biogenesis, biotransformation and specific modification of chemical structure of active constituents are also possible.
- **Stempeutics:** A branch related to therapeutic use of stem cells in medicines is termed as 'Stempeutics'. In 1986, bone marrow transplantation was attained first time using stem cells. Embryonic stem cells, adult stem cells and mesenchymal stem cells are three types of stem cells.
  (i) Embryonic stem cells are obtained from growing embryo.
  (ii) Adult stem cells viz., Hematopoietic stem cells obtained from bone marrow and tissue specific stem cells are obtained from heart, nervous and pancreatic tissues.

Mesenchymal stem cells (MSC) are present in most of the postpartum organs like adipose tissue and placenta.

Stem cell therapy opened doors to treat a range of cell-based diseases and to growing medicinally important tissues that can be used for transplantation purposes. Replacing defective cells with healthy ones offer hope of lifelong cure. Thus, stem cells as drugs have a great potential to cure heart problems, Parkinson's diseases, spinal-cord injuries, diabetes, cancer like diseases. A product 'Stempeucel' useful for osteoarthritis is in final stage of clinical trials and would be the first stem cell approved therapy.

3.2 CONCEPT OF DOSAGE FORMS

A drug is a chemical or biochemical which is technically termed as Active Pharmaceutical Ingredient (API). Majority of the APIs are in powder state and a few are liquids and semisolids, whereas gaseous state APIs are very few. For example, Paracetamol, an antipyretic drug has usual adult dose of 500 mg three times a day and for paediatric purpose it is 15 mg/kg body weight. Paracetamol is white crystalline power with bitter taste, which is rarely administered in its pure form. For ease of administration by a particular route, Paracetamol is converted into a suitable dosage form like tablets, liquids or injections.

When a drug component (API) is mixed with suitable non-drug inert components (additives) and produced in a definite physical form of definite size and shape suitable for administration by a particular route of administration, it is called as Dosage Form.

3.2.1 Rational for Designing Dosage Forms

Following are the various reasons that support conversion of drug into dosage forms.

1. A smaller quantity of a pure drug is difficult to weigh and measure accurately, e.g. Haloperidol, an antipsychiatric drug needs to be administered in various doses like 0.25 mg, 1 mg, 1.5 mg, 2 mg, 5 mg, 10 mg and 20 mg.
2. Due to definite size, shape and strength, dosage forms are easy to handle and administer by a particular route of administration, e.g. liquids are easy to swallow, tablets are easy to handle.
3. A unit dosage form provides greater dose accuracy, e.g. Tablets are more accurate than powders and liquids.
4. Dosage forms have improved physicochemical stability, e.g. Hygroscopic drugs in the form of coated tablets are more stable than powder.
5. Dosage forms are less prone to microbial contamination, e.g. Tablets as compared to liquids.
6. Protect drugs from pre-systemic degradations, e.g. Insulin injections, sublingual tablets of nitroglycerine.
7. To minimise harmful effects on the body, e.g. Enteric coated anti-inflammatory drugs, which otherwise, cause gastric irritation.
8. For rapid effect in emergency, e.g. Injections are superior to tablets.
9. To target a drug to its desired site, e.g. Inhalers to target respiratory tract in asthma.
10. For local or systemic action through body cavity, e.g. Eye drops, suppository.
11. For local or systemic action after topical application, e.g. Ointments, creams, gels.
12. To modify onset and duration of action, e.g. Dispersible tablets for rapid onset of action, enteric tablets for delayed onset of action.
13. To improve palpability, e.g. Coloured, sweetened and flavoured preparations.

3.2.2 Types of Dosage Forms

(i) According to sterility

(a) Sterile dosage forms: These are completely free from microorganisms, e.g. Injections and opthalmic preparations.

(b) Non-sterile dosage forms: These are conventional dosage forms like tablets, capsules, liquids, ointments, etc. These are free from pathogenic microorganisms but may contain microorganisms at permissible level and type.

(ii) According to dose accuracy

(a) Unit dosage forms: A pharmaceutical dosage form that contains unit amount of drug is termed as unit dosage form; such dosage forms guarantee the administration of accurate dosage. Tablets and capsules are widely used unit dosage forms.

(b) Bulk or multidose dosage forms: These include bulk powders, granules, liquids, semisolid topical preparations, etc, where a portion is removed from its bulk as a dosage form. Here slight variation in dose is allowed.

(iii) According to physical form and route of administration: Dosage forms can be classified as given in table 3.1.

Table 3.1: Dosage forms according to Route of Administration

No.	Route of administration	Physical State of Dosage Form	Dosage Forms
1.	Oral	Solid	Tablets, Capsules, Pills, Powders, Granules, etc.
		Liquid	Mixtures (Solutions, Suspensions, Emulsions), Syrups, Elixirs, Linctus, Oral drops, etc.
		Semisolid	Oral gels, *Chyavanprash* (Ayurvedic dosage form)
2.	Oral Topical	Solid	Lozenges
		Liquid	Mouth wash, Gargle, Throat Paint, oral spray.
		Semisolid	Oral gel, Dental gel, Medicated tooth paste.
3.	Topical (Dermatological)	Solid	Dusting Powders
		Liquid	Solutions, Spray, Liniments, Lotions, Paints, etc.
		Semisolid	Ointments, Creams, Pastes, Plasters, Gels, etc.

No.	Route of administration	Physical State of Dosage Form	Dosage Forms
4.	Rectal	Solid	Tablets, Soft gelatine Capsule , Suppositories
		Liquid	Enema
		Semisolid	Suppositories, Rectal gel
5.	Vaginal	Solid	Tablets, Pessaries
		Liquid	Solutions, Foams
		Semisolid	Ointment, Pessaries, Gels.
5.	Injections (Parenteral)	Liquid	Injections, IV infusions, Irrigation fluids, Dialysis fluids, Suspensions, Emulsions.
6.	Eye and Ear	Liquid	Ear and Eye drops, Eye Lotions
		Semisolid	Eye ointment, Ear Cones.
7.	Nasal	Solid	Insufflations
		Liquid	Nasal drops, sprays.
		Semisolid	Nasal gels

Questions for Self-Study

- Define dosage form and give its importance. **(PU 2011)**
- Define dosage forms. Discuss in detail the classification of dosage forms.
- Add a note on sustained release and targeted drug delivery system. **(PU 2010, 2013)**
  (Note: Drug delivery system is part of Dosage Form Design at Semester II)
- Write different sources of drug with suitable examples. **(PU 2014)**
- What are areas of drug development in field of RED Biotechnology?
- Explain Tissue Culture / Stem cells as tool of drug design.
- Write reasons to convert a drug into its dosage form.
- Give classification of dosage forms. **(PU 2014)**
- Enlist different routes of drug administration **(PU 2014)**
- Define with examples of term unit dosage forms.
- Differentiate between sterile and non-sterile dosage forms.
- Explain concept of formulating dosage forms and write various types of dosage forms.
- Write short note - Scope of formulation development **(PU 2014)**
  (It is out of scope of the subject but part of DFD at semester II)
- Discuss drug and its sources and rational to design dosage form.

3.3 VARIOUS DOSAGE FORMS

3.3.1 Oral Dosage Forms

A dosage that is administered by oral route to release drug in gastrointestinal tract (stomach/ intestine) is called as oral dosage form.

Merits of Oral Dosage Forms

(i) Ingestion by a natural route.

(ii) Allows self administration.

Demerits

(i) Bioavailability from oral route is comparatively lower than in injections.

(ii) Drug gets distributed in the whole body, non-specific for site of action.

(iii) Some drugs gets degraded in the GI fluid, e.g. Insulin.

(iv) Some drugs irritate GI mucosa thus causing discomfort or ill-effects e.g. Aspirin.

(v) Some drugs undergo first-pass metabolism thus deceasing bioavailability e.g. isosorbit dinitrate.

(A) Oral Solid Dosage Forms

This mainly includes unit dosage forms such as tablets, capsules, etc. Orally administered dosage forms undergo dissolution /disintegration in the stomach to release the medicament, which is then absorbed into the blood to elicit the pharmacological response (systemic effect). Most of the drugs are absorbed better from the upper part of the small intestine. Some medicaments such as antacids, adsorbents, antiseptics and protectives are employed to produce local effects.

Merits of solid dosage forms

(a) Greater accuracy and precision of dose from unit dosage form.

(b) Physicochemically more stable.

(c) Less prone to microbial growth than liquid dosage forms.

(d) Convenient to handle, store and carry as compared to liquid dosage forms.

Demerits

(a) These are difficult to swallow, mainly by paediatric and geriatric patients.

(b) Time required for disintegration and dissolution of solid dosage form may delay its onset of action.

1. Oral Powders

Pharmaceutical powders are solid dosage forms comprising of a mixture of dry powdered drugs intended for internal use. On the basis of composition, route of administration, packaging and physical form, powders can be classified as follows:-

- Bulk powders are packed in jars or pouches and a measuring spoon is provided with it to take the doses. They contain less potent drugs. Proprietary products: Sporlac (Uni Sankyo) which is a digestive; Igol (Raptakos) which is a laxative, Electral (FDC) which is an ORS formula and Inulax Powder (Cadila) which is a laxative.
- Divided powders contain potent drugs, whose dose quantities are critical. These are packed as individual doses.

Merits of oral powders

(a) Flexibility of dose according to the patient's need.
(b) Convenient to administer bulky or large dose drugs.
(c) Due to faster dissolution oral powders can produce rapid onset of action as compared to the other solid dosage forms.

Demerits of oral powders

(a) Powders are inconvenient to handle and administer as compared to tablets and capsules as they spread and adhere in the oral cavity
(b) These are not suitable for oral administration of bitter drugs.

2. Granules

Powders are agglomerated into larger particles called granules. These are suitable for large dose drugs, which are difficult to compound into tablets/ capsules, e.g. Methyl cellulose granules, BPC, is a laxative. Proprietary product: Evacuol (Franco Indian), Cremadiet Granules (Abbot), Husky Granules (KAPL), all are laxatives.

Effervescent granules are granules containing effervescent salts as base. They contain citric acid, tartaric acid, sodium bicarbonate and powdered sugar. Reaction between acid and base in the presence of water liberates carbon dioxide. These are useful to produce flavoured and/or dispersible drug forms. Official examples are effervescent sodium sulphate, BPC, a purgative. Proprietary product: Citro-Soda (Abbot), Husky Granules (KAPL), laxative.

3. Capsules

Capsules are solid unit dosage forms intended for oral administration, usually containing a drug or a mixture of drugs enclosed in a hard or soft water soluble 'shell' of gelatin or any other suitable material. It dissolves or disintegrates in gastric fluid to release the medicament completely. There are two types of capsules, 'hard gelatin' and 'soft gelatin'. Hard capsules are used mostly for encapsulation of solid formulations in the form of powder, beads, pellets or granules, small tablets and capsules. Therefore, they are also called as dry filled capsules (DFC). Soft capsules consist of liquids or solids dissolved or dispersed in suitable base of semisolid constancy. Examples: Chloramphenicol capsule as Chloraxin (CIPLA): Antibacterial; Rifampicin , Antituberculosis as Rifacept (Concept).

Merits of capsules

(a) Suitable to fill drugs having an unpleasant taste.
(b) Provides slippery and easy-to-swallow capsule shell.
(c) Protects the enclosed drug from environmental deterioration.

But capsules are more expensive and are not suitable for hygroscopic and highly water-soluble drugs. If sufficient water is not taken at the time of administration, capsules may adhere to the wall of the oesophagus.

4. Pills

Pills are small spherical or oval shaped solid dosage forms intended for internal use. Most of the pills weigh between 60-300 mg. Sometimes pills are coated to improve the finish, to mask unpleasant taste, to improve stability or to change solubility. Official examples: Compound Phenolphathalein Pills, BPC, as laxative. Proprietary preparations: Yogi Kanthika (Yogi Ayurvedic, M.S.), Kho-Go (Ahilya Ayurvedic, Mumbai).

5. Tablets

Tablets are unit solid dosage forms, prepared by compressing drug powders, with or without diluents. Tablets meant for oral administration are directly swallowed or chewed and swallowed.

Merits of tablets

(a) Convenient to handle, identify and administer
(b) More stable than liquid dosage forms, have longer shelf life
(c) Better accuracy and precision of dose.

Demerits of tablets

(a) Some patients, particularly children, geriatric and the seriously ill, find it difficult to swallow solid dosage forms.
(b) Due to the time required for disintegration and dissolution of tablets, drug absorption and the onset of action is slow as compared to powders and liquid dosage forms. Example: Paracetamol, antipyretic as Tab. Calpol (Burrough Wellcome); Salbutamol sulphate , Anti-asthma, as in Tab. Asthalin (Cipla), Gastro-MPS Chewable Tablet (Cipla) for Gastro- oesophageal Reflux, etc.

Questions for Self-Study

- Define: Granules, capsules.
- Write the principle of effervescent granules.
- Explain in brief: hard gelatin capsules, soft gelatin capsule.
- Why are capsules preferred to powders?
- Distinguish between pills and powders.
- Write demerits of tablets in relation to powder as dosage form.
- Write some important benefits of tablets in comparison to other dosage forms.
- Describe solid dosage forms, their types and applications.
- What are merits of converting drug into dosage form? Give rational to design various solid dosage forms.

6. Oral Liquids

Pharmaceutical liquid dosage forms are solutions (monophasic) or dispersion (biphasic) drugs in a suitable liquid vehicle. Mixture is the synonym for the liquid preparations that are intended for oral administration and consist of dissolved or dispersed drugs. Adult dose of oral liquids is 5 ml or multiples of it and a measure should be provided along with the container.

Merits of Oral Liquids

(i) Liquid preparations are easy to swallow and hence are more useful for paediatric and geriatric patients.

(ii) Bioavailability of dissolved drug is faster than in its insoluble form. The increasing order of bioavailability is Tablets < Capsules < Powders < Suspensions < Solutions.

Demerits of Oral Liquids

(i) A drug in the liquid dosage form is chemically less stable than in its solid dosage form.

(ii) Liquid dosage forms are cumbersome to handle.

(iii) Microorganisms easily contaminate aqueous liquids.

(iv) Though liquids provide flexibility in measuring varied quantity of dose, their accuracy is minimal.

(a) Mixtures: These are aqueous solutions or suspensions for oral administration. The term 'Mixture' or 'liquid' is more applicable to oral liquids that are compounded on small scale. Eg. Magnesium hydroxide mixture BPC, antacid suspension marketed as Milk of magnesia (Parke Davis), eg. Liq. Ciza (Intas), Cisapride for dyspepsia , Liquid Looz Solution (Intas) as Laxative.

(b) Syrups: Syrups are sweet; viscous, nearly saturated aqueous solutions of sucrose containing dissolved drug. Syrup, I.P. which is 66.7 per cent w/w of aqueous solution sucrose is used as vehicles, sweetening agents or flavoured sweetening base to mask bitter or saline taste of drugs. Examples: Paracetamol 125mg per ml as Pacimol Syrup (IPCA).

(c) Elixir: Elixirs are clear, sweetened and flavoured hydro alcoholic solutions for oral use. Drugs with poor water solubility are formulated as monophasic systems using alcohol as co-solvent. Due to the presence of alcohol, elixirs are not preferred for paediatric use. Example: Diphenhydramine elixir, IP, antihistaminic, Broncordil Elixir (USV), Bromhexene Elixir (IPCA) for asthma.

(d) Linctus: Linctuses are viscous syrup based monophasic liquids employed for the treatment of cough with additional property of soothing actions on the inflamed throat. For prolonged action, linctuses should be given undiluted. Eg. Codeine Phosphate as Mits Linctus Codeine Co (Astra-Zeneca) given for Dry cough.

(e) Paediatric Drops: When the dose of oral liquid is less than 5 ml, to ensure dose accuracy it is administered with the help of a dropper. These are especially useful for paediatric patients. The dropper is either graduated in fractions of a millliliter, or is pre-calibrated so that the number of drops delivered by it is equivalent to the prescribed dose. E.g. Metacin Drops (Themis) as an antipyretic, Arovit Drops (Roche) as a multivitamin, Domperon (Cadila) Domperidol for Dyspepsia.

Oral syringes are prefilled syringes for administration of liquids for paediatrics. The syringes are calibrated in fractions of millilitres and adaptor is pushed forward to deliver liquid, eg. Clavotral PD (Astra-Zeneca).

(f) Dry Syrups: Liquid dosage forms are easy to administer to children, but many antibiotics are unstable in water. Therefore, such drugs are formulated as dry powders, which are reconstituted using freshly boiled and cooled water. Dry powders are stable for 2 years and after reconstitution it should be used within 15 days, e.g. Amoxyl (Zydus Cadila) which is an antibiotic .

Semisolid Oral Dosage Form

Oral gels are comparatively thick liquids or semisolids in gel base. Antacids, sucralfate, sodium alginate containing gels are useful for acidity and reflux problems, e.g. Aludrox MH gel (Wyth), Sucrafil O Gel (Fourrts). *Chavanprash*, an ayurvedic nutritional formulation is the best example from this class.

Questions for Self-Study

- Enlist different dosage forms on the basis of increasing order of bioavailability.
- Define the following term: Syrup IP, Elixir.
- Define and classify liquid dosage forms.
- Enumerate the concept of oral drops and oral syringe.
- How do oral drops differ from mixtures?
- Write merits and demerits of pharmaceutical liquids.
- Write rational to design oral liquids and application of individual oral liquid dosage form.
- Discuss concept of design of oral dosage forms taking in account merits and demerits of various oral dosage forms.

3.3.2 Oral Topical Dosage Forms

These are intended for local action in the oral cavity, where prolonged residence of drug in oral cavity is more desirable. Hence, it is recommended not to drink water immediately after administration of such dosage forms.

(a) Oral Topical Solid Dosage Forms

Lozenges: Lozenges are disc, oblong, triangular or rectangular shaped solid dosage forms intended to be sucked; thus the viscous liquid formed in mouth retains medicament for long periods. These are mainly used for treating local infections of the mouth and throat and are occasionally used for slowing down release of drug for systemic action. The drugs routinely incorporated into lozenges include antiseptics, local anaesthetics, antitussives, decongestants, vitamins, etc. Lozenges containing fluoride are used for the prevention of dental caries. Lozenges stimulate oral secretions and thus provide a demulcent and comforting effect in minor throat or mouth irritations.

The lozenge base should ensure integration and slow dissolution of the lozenge. The base mostly includes sugar, glycerine, liquid glucose and adhesives like acacia, tragacanth, gelatin, methyl cellulose or similar materials. Moulded glycero-gelatin lozenges are referred to as pastilles, while compressed lozenges are often referred to as troches.

Official examples: Benzalkonium Lozenges, BPC, for tooth inflammation. Proprietary product: Cofsils (Cipla) cough drops.

(b) Liquids for Local action in Oral Cavity

(1) Gargle: Gargles are clear solutions used for posterior regions of the mouth by agitating the solution with expired air to produce local effect in throat. These are not to be swallowed in large amounts. Proprietary products: Betadine Gargle (Win Medicare), Tantum Rinse (Elder).

(2) Mouthwash: Mouthwashes are clear solutions intended for use in the mouth, in front of the uvula, to cleanse and refresh it. Mouthwashes have more cosmetic value and are used to maintain oral hygiene, whereas gargles are medicated. Like gargles, they are used after dilution with warm water and are not to be swallowed in significant amounts. Proprietary example, Piodin Mouthwash (Biddle Sawyer).

(3) Oral/ Throat Paint: Paints are viscous preparations of medicaments for local action in the mouth (mouth paint), pharynx (throat paint) and gum (gum paint). Proprietary examples: Limaye's Gum Correct (Deccan Dental), Tooche (Litaca), Candid Mouth Paint (Glenmark).

(4) Oral Spray: Sprays are the solutions of drug, which are sprayed on affected area. Kamillosan Mouth Spray (German Remedies), for diseases of oral cavity.

(c) Semisolid Oral Topical Dosage Forms

(1) Oral Gels: Gels are transparent to opaque semisolids, which are a three dimensional colloidal network structure. The solid-like matrix structure formed during storage breaks easily when a bottle is shaken or a tube is squeezed. These gels are useful for application in oral cavity and for teeth cleaning, e.g. Gelora (Reckitt & Colman) for mouth ulcer.

Being greaseless and more porous, a gel allows good release of medicament and therefore also has wider applications in dermatological, nasal, ophthalmic and vaginal administrations.

(2) Medicated Tooth paste is another example from this class; these are used to reduce sensitivity of teeth, e.g. Emoform Tooth Paste (JL Morison) for sensitive teeth.

Questions for Self-Study

- Write characteristics of Lozenges as oral topical dosage form.
- What are the site of drug action from gargle and mouthwash?
- What do you mean by oral paints?
- Write short note on oral topical dosage forms.
- Differentiate between oral and oral topical administration and write principles of solid, liquid and semisolid dosage forms intended for oral topical administration.

3.3.3 Topical (Dermatological) Dosage Forms

The dermatological preparations are intended for application externally on the skin to produce local or systemic effect. These contain medicament or a mixture of medicaments in solution or dispersion form in suitable base, according to which they are called as ointments, creams, pastes, gels or plasters. These produce 'Topical effects' like antiseptic, disinfectant, emollient, cleansing, protective, lubricating, etc. When drug from a dermatological product permeates into blood circulation to produce a systemic effect, these are called as transdermal drug formulations.

Merits of dermatological dosage forms

(i) Useful to provide means of *site-specific local* application of drug on affected area, which avoids unnecessary exposure of other tissues to the drug and thus avoid side effects.

(ii) Transdermal formulations are useful to avoid *first pass metabolism* of drug.

(iii) It is an alternative route of drug administration for drugs that causes gastric irritation.

(iv) Transdermal formulations are convenient for unconscious patients or patients having difficulty in oral administration.

Demerits of dermatological dosage forms

(i) The oily preparations applied on skin are cosmetically less appealing.

(ii) Application with fingertip may contaminate or cause irritation of the affected area.

(a) Topical Solid Dosage Forms

Topical Powders: Dusting powders are applied topically. Medicated dusting powders meant for unbroken skin usually contain astringents (zinc oxide, zinc sulphate), absorbents (starch, kaolin), antiseptics (benzoic acid, povidone iodine, clotrimazole) and volatile oils for cooling and flavouring purpose. Eg. Zinc starch-dusting powder NFI; it is a mixture of astringent and absorbent drug. Surgical dusting powders are sterile and have antibacterial action and are applied on an open wound. Proprietary products: Mycoderm (FDC) for dermatitis, Candid Dusting Powder (Glenmark) antifungal, Abzorb (Crossland) antifungal. Betadine (Win-Medicare) is sterile antibacterial powder.

Since, powders are difficult to spread evenly and have short retention onto the applied area, these are comparatively less used.

(b) Topical Liquids

(1) Solutions: Topical solutions are aqueous, hydro alcoholic or oily preparations, depending on the therapy they can be applied on intact or broken skin. Cresol with Soap Solution, IP, Surgical Chlorinated Soda, BPC. Dettol antiseptic Solution.

(2) Liniments: Liniments are solutions or emulsions having an aqueous or oily base intended for massage on the unbroken skin. They are used as counter irritants and rubefacient, e.g. Liniment Myostal (Solumiks Piramal).

(3) Lotion: Lotions are solutions, suspensions or emulsions designed to apply on the unbroken skin without friction. They are used for topical effect, such as local cooling, soothing, protection, drying or moisturising properties depending upon the ingredients used. These are simple solutions, eg. salicylic acid lotion, suspensions such as calamine lotion or emulsion like benzoyl benzoate lotion. Marketed examples includes Statum-B Lotion (Crossland), antifungal; Zoflut (Cipla), anti-inflammatory.

'Application' is another form of lotion, which is more viscous intended for application on restricted area, e.g. Benzyl Benzoate application as scabicide.

(4) Spray: 'Spray' is solution of drug that is sprayed on the affected area in the form of minute droplets. The uniform application on larger area without direct touch is important advantages of topical spray, e.g. Muscle relaxants like Arjet Spray (Zy. Cadila), Iodex Spray.

(5) Collodions: Collodions are non-aqueous solutions of pyroxylin in ether-alcohol with or without medicament, intended for application on the skin. After application the volatile solvent evaporates leaving protective film on affected area that provide

mechanical protection, water repellent seal for minor cuts and scratches. Its occlusive film, keeps medicament in contact with skin for an extended period of time. Salicylic acid collodion is used as keratolytic agent to remove corns and warts. Proprietary Product: Salactin Paint (NuLife), Keratolytic.

(C) Semisolid Dosage Forms

Semisolid dosage forms are most widely used dermatological dosage forms applied onto the skin to produce local or systemic effect. These are ointments, creams, pastes, gels and plasters.

Merits of semisolids

(i) Retain on the affected area with no or little spreading on healthy skin.

(ii) As compared to solid and liquid dermatological preparations, semisolid dosage forms have better adhesion and prolonged residence after application.

(iii) Semisolid dosage forms are comparatively easy to handle than liquid dosage forms.

Demerits of semisolids

(i) The oily semisolid preparations are sticky and cosmetically less appealing.

(ii) Application with fingertip may contaminate or cause irritation of affected area.

(iii) As compared to solid dosage forms, semisolid preparations are cumbersome to handle.

(iv) These are physico-chemically less stable than solid dosage forms.

(1) Ointments: Ointments are semisolid preparations made with or without medicaments intended for external applications. When applied they flow and spread under applied pressure and adhere to the skin even when pressure is removed, that is these exhibit plastic flow properties. These are prepared dissolving or dispersing the drug in different types of ointment bases, like Petroleum wax, vegetable/mineral oils, wool fat, lanolin, emulsifying ointment, polyethylene glycol bases, etc.

Ointments are cosmetically less appealing because these are oily, sticky, and difficult to apply and remove. Proprietary products: Lobate S (Abbot) as keratolytic and anti-inflammatory, Gentod (Entod), Gentamycin, for antimicrobial action.

(2) Creams: Creams are semisolid emulsions intended for application on the skin or mucous membrane. Creams, due to pseudoplastic flow properties undergo significant thinning under applied pressure and thus show better spreading ability. Creams are of two types, namely oily creams and aqueous creams. The *oily creams* are w/o (water/oil) emulsions which are employed as protective, emollients and cleansing agents. The *aqueous creams* are o/w (oil /water) emulsions. These are useful as water washable bases and for application on open wounds.

Creams are often preferred to ointments because these are less greasy and easier to apply and wash. Moreover, creams interfere less with skin functions and brings better drug-skin contact than ointments. Eg. Calamine cream, IP, Cetrimide cream, IP; Betamil cream (Merk) contains betamethasone as anti-inflammatory, Tinavate (Dabur) tolnaftate as antifungal.

(3) Pastes: Pastes are basically ointments containing high percentage of insoluble solids (usually 20-50 per cent or more). They have good adhesion on skin and form a thick coat. As compared to ointments, they are stiffer, less greasy and more absorptive.

Pastes are more useful for the treatment of oozing lesions as they absorb serous secretions. Due to heavy consistency, they produce a protective barrier on the skin and also retain drug on localised area, without spreading it on to healthy skin. Pastes are less macerating than ointments because of their porous nature, which allows perspiration to escape. E.g. Zinc oxide compound paste, IP, Magnesium sulphate paste, IP. However, due to lack of cosmetic value pastes are not the choice for topical preparation. Tooth pastes are widely used for general hygiene as well as for teeth sensitisation problems.

(4) Topical Gels: As described above gels are viscoelastic in nature and thus easy to spread evenly. These are aqueous, non-staining and easily washable. Being more porous, a gel allows good release of medicament. Due to skin hydration effect of gels it also assists in percutaneous absorption of drug. E.g. Diclonac (Abbot), diclofenac sodium, Infen Gel (Emcure), both are anti-inflammatory in action.

(5) Plasters/Adhesive dressings: Plasters are solid or semisolid masses made by incorporating medicaments in resinous or waxy bases. These bases are melted and spread onto the suitable backing material. They are intended for external application, to provide protection, mechanical support or for local or systemic effects. Medicaments that are usually incorporated in plasters are antiseptics, keratolytics, belladonna extract, capsicum oleoresin, zinc oxide, menthol, thymol etc. When the porous plastic plasters are used, the wound does not become macerated with consequent delay in healing. Waterproof, plastic adhesive plasters are used when complete exclusion of water is desired. Eg.Band-Aid (Johnson & Johnson).

Questions for Self-Study

- Define term topical and transdermal drug formulations.
- Give reason: Powders are the least preferred and gels are the most preferred dermatological dosage forms.
- State differences in the liniments and lotions.

- Write merits of topical spray over topical solutions.
- Describe composition and applications of collidions.
- Differentiate between ointment, cream and paste.
- Write rationale of oral-topical and topical dosage form.
- Enumerate the merits and demerits of dermatological dosage forms over oral dosage forms.
- Write a short note on semisolid dermatological products.
- Discuss various dosage forms that are applied externally on the skin for local and systemic effects.

3.3.4 Dosage Forms For Body Cavities

Body cavities viz. rectum, vagina, nose and ear are used for administration of drug. Mostly, these routes are used for local action in the respective cavity.

Merits of body cavities as route of drug administration

(i) Nasal, ear and rectal routes are used for local action.

(ii) Rectal dosage forms are employed to relive constipation or pain, irritation, itching associated with infections like hemorrhoids and pruritus ani.

(iii) Vaginitis and cervicitis as well as other vaginal infections can be treated with vaginal suppositories.

(iv) Urethral suppositories are used to produce local effect in the treatment of urethral infections.

(v) Dosage forms have been administered via rectum or nose for systemic purpose also, especially to avoid first pass metabolism of drug.

(vi) For drugs that cannot be administered by oral route either because of nausea, vomiting, or in gastrointestinal disturbance or in unconsciousness patients, body cavities are used as alternative route.

(vii) It is useful for infants and geriatric patients who cannot swallow medication.

(viii) Body cavities are the invasive alternative to administer drugs having unpleasant taste and odour.

Demerits of body cavities as route of drug administration

(i) The main limitation is reluctance shown by patients. The administration of suppositories requires privacy.

(ii) Leakage from the body cavities, especially from rectum, vaginal and urethral cavities.

(iii) The absorption of drugs from suppositories is unpredictable.

(iv) Repeated administration of drugs like local anesthetics, dehydrating substances and irritants may cause mucosal damage.

(a) Solid dosage forms for body cavity

(1) Suppositories are solid or stiffened semisolid dosage forms for inserting into body cavities. They melt at body temperature or soften, disintegrate or dissolve in the fluid of the body cavity after being inserted. Suppositories intended for rectum, vagina, urethra, ear or nasal cavity are respectively referred to as suppositories, pessaries, urethral bougies, ear cones, and nasal bougies. These are prepared by moulding method or are compressed in the form of tablets.

Tablets, soft gelatin capsules are administered as suppositories via rectum and as a pessary via vagina. For example, Candid vaginal tablet (Glenmark).

(2) Douche powders are used for cleansing and as antiseptic for vagina, eg. Tantum Vag Douche (Elder).

(b) Liquid dosage forms for body cavities

(1) Nasal drops/Spray: Nasal solutions are aqueous monophasic liquids, rendered isotonic and slightly buffered. Nasal solutions are administered as nasal drops or sprays to relieve nasal congestion, inflammation and to combat infection. E.g. Otrivin Nasal Drops (Novartis), Efcorlin Nasal Drops (Glaxo), Beclate Nasal Spray (Cipla), Recofast Drops/Spray (Shreya).

(2) Eardrops: Eardrops are solutions, suspensions or emulsions of drugs in water, glycerine or propylene glycol intended for instillation into the ear. These are used to remove excess cerumen (ear wax), to treat infection, inflammation or pain and for cleaning and drying the ear. Eg. Soliwax (NuLife), Betnesol Ear Drops (Glaxo).

(3) Enema is widely used liquid for rectal administration. Enemas are aqueous or oily solutions, suspension or emulsions of medicaments intended for rectal administration to cause bowel evacuation or to bring about local or systemic therapeutic action, e.g. Neotomic Enema (USV), Entoforam (Cipla).

(4) Antiseptic liquids are used for washing vagina, these are called as douches or cleansing solutions.

(5) A foam of hydrocortisone acetate for piles is admistered rectally, e.g. Entofoam Aerosol (Cipla).

(c) Semisolid dosage forms for body cavity

(1) Suppositories of cocoa butter or any suitable wax are prepared by moulding method. The melting / dissolution of these release the drug in the rectum. Eg. Bisacodyl suppository, IP, laxative as Dulcolax (German Remedies).

(2) Ointment/ Cream/ Gel: Anti-haemorrhoidal rectal products include Anovit Cream (USV), Pilex ointment (Himalaya), Xylocain gel (Astra-IDL).

The proprietary antifungal and antibacterial dosage forms for vaginal administration are also available, some of these are Candid V gel (Glenmark), GynoTerazoe gel (Johnson & Johnson), Evalon cream (Organon) and pessaries like Betadine Vaginal (Win Medicare).

3.3.5 Injectable Dosage Forms

Injections are sterile and apyrogenic (free from pyrogens) dosage forms administered by slight puncturing of the skin using needle.

Merits of Injections

- Provides immediate effect in emergency.
- Suitable for unconscious or uncooperative patients.
- Suitable for drugs that are not absorbed or degraded in the GIT.

But injections must be administered by trained persons and require asepsis during manufacturing and administration. It is a painful process.

Most injections are solutions, followed by suspensions and emulsions. The large volume injections are administered through vein and are called Intra-Venous fluids. These are available in 500 ml to 1 liter capacity. The small volume injections are meant for injecting at different sites below the skin like Intra-Muscular (IM), Subcutaneous (SC), Intra-arterial etc. Water sensitive drugs are also formulated in the form of sterile dry powder that should be reconstituted with sterile water for injections just before injection.

(Pyrogens are metabolite products of bacteria that raise body temperature if injected in body cavities. Thus the pyrogens are chemicals.)

3.3.6 Ophthalmic Dosage Forms

Like injections, eye drops must be sterile and isotonic but not necessary apyrogenic, therefore, these are classified as a separate class, though these are administered via body cavities.

(1) Eye Drops: These are sterile preparations intended for application in the eye, for local effect on the eye membrane. They mainly include aqueous or non-aqueous solutions or suspensions and ointments. Most of the requirements for ophthalmic preparations are same as that for injections, but they may contain pyrogens. E.g. Ciprobid Eye Drops (Zy. Cadila), GATT Drops (Cadila).

(2) Eye ointments: Sterile, non-irritating ointments having melting or softening point close to body temperature are used to administer in eye. Mixture of yellow soft paraffin, liquid paraffin, wool fat or lanolin is generally used as base for eye ointments. As compared to drops, ointments reside in eye for a prolonged period. Eg. Chloramphenicol eye ointment, IP, as Paraxin (NPIL), Cyclovir Eye Ointment (Zy. Cadila).

Sterile ophthalmic ointments are also filled in soft capsules and these are for single use, called as Eye AppliCaps, e.g. SSZ Applicaps (Gufic), Micoptic (FDC), both are antibacterial and antifungal.

3.3.7 Pulmonary Dosage Forms

Inhalations are liquid preparations of volatile ingredients whose vapours are intended for inhalation after mixing with hot water. The benzoin inhalations and menthol inhalations are solutions of respective volatile substances in industrial methylated spirit. Menthol and eucalyptus inhalation BPC is prepared using light magnesium carbonate as dispersing agent.

Insufflations are powder containing volatile principles, but it is not used in present days.

The metered dose inhalers and dry powder inhalers are the most widely used drug delivery systems from this class, which will be studied in second semester.

Thus, sublingual, transdermal, transnasal, rectal and pulmonary route are used to avoid first pass metabolism. Various drug delivery systems based on this principle will be discussed in higher classes.

Questions for Self-Study

- Define: suppository, pessary and write their applications.
- Describe various sterile dosage forms.
- Define inhalations, eye drops, nasal drops.
- Enumerate various dosage forms that are administered via body cavities.
- Discuss the concept of sterile dosage forms, their requirements and various types of dosage forms.
- Write applications of dosage forms meant for administration via body cavities. Explain their types.
- Write rationale to design dosage form for administration via body cavity and various therapeutic applications, ease of administration and their limitations.

(3) New Drug: Regulatory Concept

Drug, the general definition discussed above is related to active ingredient. However, New Drug as per Drug & Cosmetic Act (D & C Act 1940) can be defined as "*A newly approved*

clinically proven dosage form of Active Pharmaceutical Ingredient(s) by FDA. The approval is based on pharmaceutical, stability and clinical testing (safety and efficacy) a dosage form of - a new API/ new dosage form of the existing API/ new combination of two or more API/ existing drug product for new indication.

Thus, development of new drug is long process that begins with identification of a drug molecule, its characterisation, standardisation and formulation into a suitable dosage form, in-vitro evaluation, stability testing, pre-clinical testing on animals, clinical trials on human and post-marketing testing for safety and efficacy.

Clinical Trials

To understand the development of a new drug, it is essential to know about clinical trials. *Clinical studies can be defined as a systematic study of pharmaceutical product on human subjects in order to verify safety, therapeutic efficacy, biopharmaceutical data, and adverse effects*. Active Pharmaceutical Ingredient (API) is first subjected to toxicological studies in animals (Preclinical testing). In the form of suitable dosage form it is subjected to clinical testing in human. Clinical trial is divided in Phase I, II and III with successive increased number of human volunteers. The phase I is on healthy subjects (less than 20) and Phase II and III on patients. After successful results in Phase III, the Sponsor Company, make form application to FDA as "New Drug Application (NDA)". Considering the safety, efficacy and superiority of drug under study over other existing drugs from same indication, FDA of that country approves the product as New Drug. Phase IV trials are performed during marketing of the 'New Drug' mainly to reveal adverse reactions related to long term use. The New Drug is subject to withdrawal, if it is found to be ineffective and / or unsafe.

Questions for Self-Study

- Write short note: New Drug.
- Describe concept of New Drug development.
- Define term Drug, Dosage form and New Drug.

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Chapter 4...

Pharmaceutical Excipients

Syllabus

- Concept of excipients, Definition and classification with examples,
- Special emphasis on colours, flavours and preservatives used in formulation.

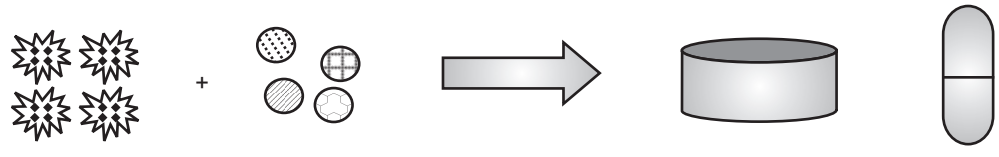
Features of the chapter

- To understand the role of excipients in dosage form design, these are explained according to dosage form.
- Separate section is included for common additives.
- Syrup and Aromatic waters have been used as sweetener and flavouring agents than for their therapeutic value, therefore these are covered in this chapter.

4.1 CONCEPT OF PHARMACEUTICAL EXCIPIENTS

Definition

Drug (API) is rarely administered alone as medicine but it is converted into a suitable dosage form, where the drug is mixed with some non-drug components to attain a particular physical form. Thus, substances which are of little or no therapeutic value but which are added to the formulation in order to ease the production, to maintain physicochemical stability, to improve patient acceptability, modify drug release and/or to improve biopharmaceutical performance of the drug are called pharmaceutical excipients, They are also known as pharmaceutical aids, -additives, - necessities, - adjuncts or adjuvants.



Role of Excipients

- Give body/bulk to the dosage form e.g. diluents in tablets, base of cream .
- Act as solvent or vehicle, e.g. water to dissolve drug, water as external phase in suspension.
- To improve and maintain stability, e.g. suspending agent, binder in tablets, antioxidants.
- To control microbial contamination, e.g. antimicrobial agents.
- To improve palatability, e.g. sweeteners, flavours.
- To improve appearance, e.g. colours.
- To modify drug release, e.g. superdisintegrants in fast dissolving tablets, polymers in sustained release tablets.

Ideal Properties of Excipients

(1) Physiologically inert.

(2) Physico-chemically stable over a wide range of temperature, pH and not chemically reacting with drug or other excipients.

(3) Does not impart any undesired taste, odour or colour to the product.

(4) Must be non-toxic, non-irritant and non-sensitizing.

(5) Should be effective at low concentrations.

(6) Must be free from pathogenic micro-organisms.

(7) Must not interfere with the bio-availability of the drug.

(8) Must be complying with pharmaceutical standards and accepted by regulatory authorities.

(9) Should be available at reasonable cost.

Classification of pharmaceutical excipients

Pharmaceutical additives are classified on the basis of their functions.

(1) Diluents, vehicles or bases: Lactose, water, white soft paraffin etc.

(2) Physical stabilisers: Co-solvents, solubilising agents, suspending or emulsifying agents.

(3) Chemical stabilisers: Antioxidants, buffers.

(4) Preservatives: Methyl paraben, sodium benzoate.

(5) Organoleptic additives : Colouring agents, flavouring agents, perfumes and sweetening agents

(6) Processing aids: Lubricants, antifoaming agents.

(7) Physiological compatibility enhancers: Buffers, tonicity agents.

(8) Auxiliary therapeutic value enhancers: Emollients, protectives, antiseptics.

(9) Special functional excipients: These are mostly used in drug delivery systems like sustained release tablets, anti-cancer injections etc; e.g. Ligands for drug targeting cancer cells, drug release retarding polymers, penetration enhancers.

Questions for Self-Study

- Define and classify pharmaceutical excipients .
- Discuss the concept of pharmaceutical additives with ideal requirements and their role in dosage form.
- Explain the terms drug, additive and dosage form.
- *Define with examples of additive - processing aids, physical stabilisers.*

4.2 EXCIPIENTS USED IN VARIOUS DOSAGE FORMS

4.2.1 Liquid Dosage Forms

Since water is a vehicle for most of the liquids, the additives should preferably be soluble in water.

(1) Diluents, vehicles or bases

(a) Solvents: A liquid used to dissolve drug to produce solution type of dosage form, e.g. Purified water IP.

(b) Vehicle: A liquid used to carry drug and to attain specific volume, e.g. aqueous phase in suspension.

(2) Physical Stabilisers

(a) Co-solvents: Additional water miscible solvent that is used to increase solubility of drug in water to produce solution type of dosage form, e.g. ethanol, propylene glycol, glycerol, polyethylene glycol.

(b) Solubilising agents: Surfactants with HLB value 15-18 used to improve aqueous solubility of drug, e.g. Tween 80.

(c) Complexing, chelating or sequestering agents: Agents used to dissolve metallic drugs by forming complex with them, e.g. ethylenediamine tetra acetic acid (EDTA), citric acid, tartaric acid.

(d) Buffers: To prevent pH dependent precipitation of drug or additives, e.g. carbonates, citrates, acetates, phosphates or tartarates salts like sodium citrate, sodium acetate.

(e) Wetting agents: Agents used to increase wetting of solid surface by main vehicle or solvent, e.g. surfactants with HLB value 8-10, glycerine and polyethylene glycol 400.

(f) Viscosity enhancers: Agents used to increase viscosity of liquid dosage forms, e.g. glycerine, hydrocolloids like gum acacia, Sodium Carboxy Methyl Cellulose (Na CMC).

(g) Suspending agents: Viscosity enhancers used to slower down rate of settling of insoluble drug particles in suspensions, hydrocolloids like gum acacia, tragacanth.

(h) Emulsifying agents: Ampiphilic agents used to improve miscibility of immiscible water and oil phase to produce emulsion, e.g. surface active agents, hydrocolloids.

(i) Crystal growth inhibitors: To prevent crystallisation of sugar in that turn cap locking in syrup based liquids, e.g. glycerine, propylene glycol.

(3) Chemical Stabilisers

(a) Antioxidants: Agents used to prevent oxidative degradation of drugs or additives present in dosage form, e.g. sodium metabisuplhite, and chelating agents like citric acid, tartaric acid, EDTA.

(b) Buffers: To prevent pH dependent decomposition of drugs or additives.

Acidifying agents like citric acid, acetic acid.

Alkalising agents like ammonia solution, diethanol amine.

(4) Preservatives

(a) These are antifungal and antibacterial agents used to prevent and control microbial contamination, e.g. Benzoic acid, sodium benzoate, methyl and propyl paraben.

(5) Organoleptic additives

(a) Colouring agents: Caramel, cochineal, amaranth and other D & C and FD & C colours.

(b) Flavouring agents: Aromatic waters, flavoured syrups, fruit juices, volatile oils, etc.

(c) Sweetening agents: Sucrose, syrups, sorbitol and sodium saccharin.

(6) Processing aids

(a) Antifoaming agents: To prevent foam formation during mixing, e.g. Surfactants (HLB 1.5 – 3).

(b) Dispersing agents: These are adsorbents having good dispersability in liquid phase, used for uniform and quick mixing of solute in solvent/vehicle, e.g. talc, light calcium carbonate.

(c) Clarifying agents: These are adsorbents used to filter-out un-dissolved solid/liquid, e.g. talc, bentonite.

(7) Physiological compatibility enhancers

(a) Tonicity adjusters: To adjust osmotic pressure of dosage form to that of the osmotic pressure of body fluids, e.g. sodium chloride in injections, eye and nasal drops.

(b) Buffers: To adjust pH of dosage form to that of the pH of body fluids.

(8) Auxiliary therapeutic value enhancers

(a) Sorbitol as soothening agents in expectorant syrup or linctus; Gums as mucous membrane protective in antacid suspensions.

(9) Special functional excipients

(a) Permeation enhancers like cationic surfactants, lipoidal carriers.

4.2.2 Semisolid Dosage Forms

(1) Diluents, vehicles or bases

(a) Ointment (semisolid) bases: These are solvents/ vehicles for drugs and impart semisolid consistency to dosage form, e.g. petrolatum, beeswax, vegetable oils, woolfat, emulsifying wax, PEG bases.

(b) Cream bases: Mixture of oils + surfactants + aqueous phase; emulsifying wax.

(c) Paste and Gel bases: Hydrocolloids, thickening agents, clays like bentonite etc.

(2) Physical stabilisers

(d) Hardening agents: Higher melting point waxes like beeswax, petroleum wax.

(e) Wetting / Levigating agents: Liquids used as intervening agents to reduce particle size by wet grinding and to improve dispersion of insoluble drug in base, e.g. glycerine, light liquid paraffin.

(f) Antidrying and antirolling agents: Humectants that hold moisture, e.g. glycerine,

(3) Chemical Stabilisers

(g) Antioxidants: Oil soluble substances like Tocopherol, Propyl gallate, BHA, BHT; Water soluble like sodium bisulphate or chelating agents.

(h) Buffers: sodium citrate, sodium acetate etc.

(4) Preservatives: Methyl paraben, propyl paraben, benzalkonium chloride, phenylmercuric nitrate.

(5) Organoleptic additives: Colours: F & D, FD & C and External D & C colours, titanium dioxide, ferric salts.

(6) Perfumes: Flower oils, artificial flavours.

(7) Processing aids: Antifoaming agents may be used to avoid foaming during mixing of liquid (molten) phases.

(8) Physiological compatibility enhancers: Buffers are added to adjust pH of dosage form to that of the pH of skin e.g. Sodium acetate, Acetate buffer.

(9) Auxiliary therapeutic value enhancers: Humectants, lanolin are used as emollients and moisturisers; waxes are protective.

(10) Special Functional excipients: Permeation enhancers like surfactants, Dimethylsulpoxide (DMSO), menthol etc.

4.2.3 Solid Dosage Forms

(1) Diluents, vehicles or bases: Diluents or fillers are used in solid dosage forms to increase bulk and to improve compression properties, e.g. Lactose, mannitol, dibasic calcium phosphate, etc.

(2) Physical Stabilisers: Binders are used to hold powder mixer in the given shape and impart sufficient strength to tablet without crumbling or powdering, e.g. acacia, PVP-poly vinyl pylloridone, starch paste, etc.

(3) Plasticisers are mixed with polymers to impart viscoelasticity to films for coating of tablet or granules, e.g. PEG, PVP K 30.

(4) Chemical stabilisers: Solids are comparatively chemically less reactive in that they are more stable. Antioxidant type of stabilisers is rarely used.

(5) Preservatives: Due to less moisture content chances of microbial growth are less, but as a preventive measure uncoated tablets, powders and granules may contain preservatives.

(6) Organoleptic additives: Colouring agents like F & D and F D & C colours, sweeteners like mannitol, sucrose, saccharin and flavouring agents like flower/ fruit essence, volatile oils etc. are added to improve the palatability of the drug.

(7) Functional additives: These are of the following types.

(a) Disintegrating agents are used for fragmentation of the tablet in alimentary canal after administration, so as to assist dissolution or release of the drug, e.g. starch, microcrystalline cellulose, primogel .

(b) Special functional additives like drug retarding polymers, where water insoluble (Ethyl cellulose), gel forming (HPMC-Hydroxy Propyl Methyl Cellulose) or pH dependent (CAP-Cellulose Acetate Phthalate) polymers are used to coat granules/ tablet/capsule or mixed with drug powder to extend drug release.

(8) Processing aids: Lubricating agents are mixed with the powdered drug before its compression into tablets to facilitate easy compression. These are of three types:

- **Lubricating agents:** Reduce friction between die wall surface and powdered mass, so as to ease formation of tablet, e.g. magnesium stearate, talc.
- **Glidants:** Reduce inter-particle friction, so as to improve flow of powders, e.g. corn starch, talc.
- **Anti-adherents:** Prevent sticking of tablet/ powder to pouches, e.g. Corn starch, colloidal silica.

(9) Physiological compatibility enhancers: Buffers or alkalising agents are formulated with non-steroidal anti-inflammatory drugs (NSAID) to minimise gastric irritation. e.g. sodium bicarbonate.

4.2.4 Injections

Note: The ingredients used in sterile dosage form should be sterilisable and withstand the conditions of sterilisation process.

(1) Diluents, vehicles or bases: Water for injection and sterile water for injection are most commonly used as solvent for solution type injections or vehicle for suspensions. Oils like cotton seed oil or its emulsion is also used as vehicle for injections.

(2) Physical Stabilisers: Co-solvents like PEG 400, solubilising agents like non-ionic surfactants are used to increase aqueous solubility of drugs.e.g. Tween 80.

(3) Suspending agents, emulsifying agents are also used if injections are biphasic in nature.

(4) Chemical Stabilisers: Antioxidants (water or oil soluble depending on the vehicle) and buffers. Acids and bases are strictly avoided.

(5) Preservatives: Benzalkonium chloride, phenyl mercuric nitrate, chlorobutanol.

(6) Physiological compatibility enhancers: Tonicity adjusters to adjust osmotic pressure of injection to that of osmotic pressure of blood, e.g. sodium chloride; buffers to adjust pH of injection to that of blood (pH 7.4).

(7) Density modifiers are needed in general anaesthetic injections that are meant for injection into the spinal cord. Dextrose is used for this purpose.

(8) Special Functional excipients: Polymers for sustained release, ligands for cell targeting, e.g. PEG or folic used for cancer cell targeting.

Questions for Self-Study

- Enlist additives used in liquid dosage form with examples.
- Enumerate the significance of physical stabilisers in liquid dosage forms.
- Describe the role of tonicity agents in sterile and non-sterile dosage forms.
- Enumerate the significance of processing aids in solid and liquid formulations.
- Define with example- Plasticizers, Anti-oxidants.
- Write vehicles used in liquid and semisolid dosage forms.
- Define pharmaceutical additives and write role of various types of additives used in semisolid dosage forms.
- Give an account of the various types of additives used in pharmaceutical formulations.

4.3 COMMON ADDITIVES

Additives like antioxidants, preservatives and organoleptic additives are commonly used in almost all types of dosage forms, whereas, surfactants, hydrocolloids, polyhydric alcohols and buffers are multifuctional additives used in various types of dosage forms for a specific or general reason, as the case may be. Syrup and aromatic water are discussed as a special note.

4.3.1 Antioxidants

Anti-oxidants are effective when used in soluble form.

- True antioxidants act by suppressing the formation of free radicals in auto-oxidation, e.g. alphatocopherol, butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT), methyl gallate, ethyl gallate, propyl gallate.
- Reducing agents such as sodium sulfite, sodium bisulfite, sodium metabisulfite. These get preferentially oxidised than the drug.
- Synergist antioxidants have little inherent antioxidant activity. These are used in combination with the antioxidants mentioned above. These act by regeneration of anti-oxidant radical or by chelating metals. Their examples include ascorbic acid, tartaric acid, citric acid, hypophosphoric acid, EDTA.

Anti-oxidants suitable for aqueous preparations include sodium bisulfite, sodium metabisulfite, hypophosphoric acid, ascorbic acid, and citric acid. For oily liquids, the oil soluble antioxidants such as alphatocopherol, BHT, BHA, propyl gallate are used. Antioxidant concentration is between 0.01 to 1%.

4.3.2 Preservatives

Preservatives are included in both non-sterile and in sterile preparations respectively to stop the multiplication of microbes present and to minimise further contamination during storage. Water is a good media for microbial growth. In addition to this, presence of sugar and dilute-vegetable extracts provide favourable environment for microbial growth. The preservative should have effective solubility in the aqueous phase, and should remain un-ionised at the pH of preparation. Alcoholic flavours and electrolytes make the environment less favourable for microbial growth.

Preservatives are mainly included in liquid preparations for the fungistatic action. Injections, eye preparations contain antibacterial agents. Based on safety by particular route of administration, following preservatives are commonly selected:-

- For oral solutions, benzoic acid (0.1 to 0.2%), sodium benzoate (0.1 to 0.2%), alcohol (15 to 20%), chloroform (0.25%), glycerine (45%) or preservative system containing 10 : 1 ratio of methyl paraben and propyl paraben (0.1 to 0.2%) are used.

- Dermatological preparations also include preservatives such as phenol (0.5%), cresol (0.3%) and chlorocresol (0.1%).
- Benzalkoniun chloride (0.01%) is suitable for ophthalmic, nasal and otic preparations; phenyl mercuric salts (0.001%) for ophthalmic, nasal and topical preparations and thiomersal (0.01%) for ophthalmic preparations.
- Benzalkonium chloride, phenyl mercuric nitrate, chorobutanol are used in injections.

4.3.3 Colouring Agents

Colours are employed for several reasons

- To give aesthetic appeal and impart pleasing appearance to the preparation. Pleasant and fresh coloured products are more accepted by patients.
- To mask the discoloured, degraded ingredient and thereby to maintain appearance of product. It masks minor defects, un-even surfaces, dull spots etc.
- For identification of the product. Particular shape and colour are mainly used techniques to identity product of particular drug or manufacturer. It is the best tool for identification of medicine by illiterate patients.
- As warning to avoid accidental oral administration, external preparations may be coloured dark or with unusual colour shades like blue, violet, dark brown, etc.

Colours used in pharmaceuticals are categorized as:

(a) Synthetic Colours: Most of these are 'certified'

(i) Colours for Food, Drug and Cosmetics (FD and C)

(ii) Colours for Drug and Cosmetics (D and C)

(iii) Colours for externally applied Drug and Cosmetics (External D and C)

The synthetic colours are available in two forms- Dyes and Lakes. The former are pure colour chemicals that exhibit their colour after getting dissolved in a given solvent, like water, propylene glycol, glycerine etc. Since, dissolved they produce uniform colour intensity and easy to mix with liquids as well as adsorb on powders. However, due to their unsaturated nature, dyes have inferior storage capacities.

To improve stability, the dyes are converted into lakes by adsorbing them on substrate like aluminum hydroxide. The fine powders of lakes are mixed and/ or milled with drug and excipient powders. Thus, lakes are dilute solid forms of dyes. However, lakes have the following advantages and limitations over dyes:-

(a) Lakes produce more stable colour shades.

(b) Unlike dyes, insoluble colours dose not migrate to produce colour variation (mottling).

(c) However, as compared to dyes, more amount of lake is required to produce same colour intensity.

(d) Uniformity of colour shade depends on particle size, extent of dispersion and uniformity of mixing.

The commonly used colours from these classes includes, FD and C Blue No.1 (Brilliant blue FCF), FD and C Red No. 3 (Erythrosine), FD and C Yellow No. 5 (Tartrazine), D and C Blue No. 6 (Indigo), D and C Red. No. 22 (Eosine), D and C Yellow No. 7 (Fluorescein) and their corresponding aluminum lakes.

(b) Natural colours

(i) Vegetable colours: Chlorophyll (green), carotene, curcumin (yellow), caramel (black, brown), riboflavin (yellow), indigo (blue), beet root (red).

(ii) Animal colours: Cochineal (red).

(iii) Mineral colours: Titanium dioxide (opaque), ferric oxides (red, yellow). These are insoluble and restricted to external preparations.

Natural colours are non-uniform in composition; this may be the reason for variation in colour shades. They carry microbes or allow microbial growth.

4.3.4 Flavouring Agents

Flavouring refers to a complex effect of taste, odour and feeling factor and flavouring agents are included to correct these so as to make the preparation more palatable. Because of increased contact with taste buds, taste of the drug is more noticeable in its dissolved state.

Selection of flavours is done on the basis of scientific, artistic and psychological parameters as follows:

(i) To mask the four basic tastes following flavours are recommended.

Salty taste: Vanilla, butter scotch, orange, apricot, mint, raspberry.

Bitter taste: Chocolate, lemon, cherry, strawberry, mint, anise.

Sweet taste: Vanilla and fruity flavours.

Sour taste: Citrus flavour, liquorice, raspberry.

(ii) It is usual to use flavour in association with colour and category of the product, e.g. vitamin preparations are deep red coloured with cherry, strawberry or raspberry flavour.

(iii) Paediatrics prefers chocolate and fruity flavours and sweet taste. Adults prefer sour taste and citrus and intense flavours.

(iv) Viscous flavoured preparation such as flavoured syrup (lemon syrup, orange syrup) or flavour blended with glycerin, sorbitol imparts better mouthfeel effect.

(v) Volatile oils including cinnamon, clove, lemon, orange, peppermint produces aromatic vapours which activate olfactory cells.

(vi) Chloroform and carbon dioxide are desensitising agents which have mild anaesthetic effect on the sensory receptors.

(vii) Stronger flavours such as liquorice extract overshadow the unpleasant taste of medicament.

(viii) Sythetic flavours like eugenol crystals, cinnamaldehyde, benzaldehyde are available in pure synthetic form. Though these are more uniform and stable, it is difficult to imitate flavour of corresponding natural flavours.

4.3.5 Sweetening Agents

These are sweeteners. Though, taste is hardly separated from flavour, it is a separate science as well as art.

Sweeteners are natural or synthetic agents. Some of them are listed below.

(i) **Sugars:** Sucrose, fructose, glucose, invert syrup, syrup.

(ii) **Polyhydric alcohols:** Sorbitol, mannitol, xylitol, glycerin.

(iii) **Artificial sweeteners:** Saccharin, cyclamates, aspartame, acesulfam-K.

(iv) Invert syrup is sweeter than the syrup. Heating or addition of acids in sucrose causes hydrolysis of sucrose into dextrose (glucose) and fructose (levulose). It appears dark in colour due to effect of heat on levulose and may turn amber due to further caramelisation. Invert syrup is more susceptible to fermentation and microbial growth.

(v) **Flavoured Syrups:** Sweet taste is blended with natural flavour in flavoured syrups. These are almost complete flavouring agents due to sweet taste and flavour. The viscous flavoured syrup produces pleasant taste for prolonged period of time for better mouthfeel effect, e.g. Lemon Syrup BPC and Orange Syrup BPC.

(vi) **Artificial Syrup:** Sugar based syrups are caloric and raise the blood sugar level. For diabetic patients carbohydrate based syrups are not recommended. The polyols such as sorbitol, glycerin, propylene glycol or cellulose polymers such as methylcellulose, hydroxyethylcellulose and artificial sweeteners are used in place of sugar. They have low caloric value due to low gastrointestinal absorption. They do not elevate blood glucose level as much as sugars. Cellulose are not hydrolysed and absorbed. Artificial syrups have excellent consistency and sweetness as that of syrup.

4.3.6 Commonly Used Sweetening Agents

Sucrose is the choice of sweetener used to mask taste of salty and bitter drugs. Syrup and liquid glucose imparts body to the liquid. Syrups is the sweetener of choice and a commonly used vehicle (Refer to Unit 4.5.).

Sorbitol 70% w/w is half as sweet as sucrose. Viscosity, humectancy and cooling effect are the qualities of polyhydric alcohols which contribute for mouthfeel effect.

Artificial sweeteners: Saccharin is 500 times sweeter than sucrose. It is water-soluble (sodium salt), is used in liquids at a concentration of 0.02 to 0.5%. Sodium cyclamate in 0.17% concentration is about 30 times sweeter than sucrose but as concentration increases it increases the bitter after taste. Aspartame is 200 times sweeter than sucrose and has less bitter after taste than saccharin. Artificial sweeteners are more suitable for diabetic patients. Non sugar based sweeteners are noncariogenic, non caloric and resist microbial growth.

Questions for Self-Study

- Define and classify antioxidants. Give examples of antioxidants for oral liquids.
- Classify the colouring agents used in pharmaceuticals with examples.
- Enumerate factors affecting selection of preservatives.
- Enumerates reasons for addition of colour in dosage forms.
- Write various approaches to flavour dosage forms.
- Write a short note on flavouring agents.
- Compare between carbohydrates based sweeteners and artificial sweeteners.
- What are excipients? Explain different flavours used in pharmaceuticals. **(PU 2014)**

- Explain the statement 'Flavoured system is a complete flavour solution in designing oral liquid'.
- Describe selection criteria of colouring agents used in pharmaceutical dosage forms.
- Write various types of colouring agents and give examples of colouring agents used in oral liquids.

- Discuss various organoleptic additives used in pharmacy.

❖ Define excipients, how are excipients classified? Add a note on preservatives and colours in Pharmaceuticals **(PU 2014)**

4.4 MULTIFUCTIONAL ADDITIVES

(1) Surfactants: Surface active agents are the amphiphilic chemicals that have both polar and non-polar groups. They have water loving (hydrophilic) and oil loving (lipophilic) properties, which are indicated by HLB (hydrophilic-lipophilic balance) value. Surfactants lower the surface or interfacial tension and therefore have many applications. These are:

- Solubilising agents: Surfactants with HLB value 15 – 18, e.g. Tween 80.
- Wetting agents: Surfactants with HLB value 8 – 10, e.g. Triethanolamine oleate.
- Emulsifying agents: o/w emulsifiers, HLB 8 - 18, e.g. Tween 80; w/o emulsifiers HLB 3 – 6, e.g. Span 80.

- Antifoaming agents: Surfactants with HLB 1.5 – 3, e.g. Span 80.
- Penetration enhancers: Improve contact of drug with skin surface, increase permeability of skin.

(2) Hydrocolloids: These are water loving colloidal systems like gums. These absorb water, swell or form gels. Therefore, these are used as-

- Viscosity enhancing agents, suspending agents or gelling agents.
- Form thick gel layer around the oil droplet, these are useful as oil-in-water emulsifying agents.
- Hydrocolloids are useful as protective and also as bulk laxatives.

These include natural agents like acacia, tragacanth, sodium alginate, clays like bentonite; semisynthetic cellulose derivative like Na CMC, or synthetic hydrocolloids like carbopols.

(3) Polyhydric alcohols: Glycerine propylene glycol, sorbitol are of pharmaceutical interest from this class. These are useful as-

- Co-solvents, viscosity enhancers, and mild sweeteners and preservatives.
- Non-volatile co-solvents these prevent crystallisation of sugar or drug in liquid orals.
- Sorbitol is used for soothening of throat due to its viscosity and cooling effect.
- These are useful in lozenges to form viscous liquid coat in throat.
- Prevent drying of product.
- Act as plasticizers and prevent rolling of semisolids.

(4) Buffers: Adjustment of pH of the pharmaceutical preparation is important for -

- Increasing solubility and chemical stability of the drug and additives.
- Ensuring physiological compatibility of a medicinal product with body.
- Maintaining drug and preservatives in its un-ionized state for better absorption and antimicrobial effect, respectively.

Buffers based on carbonates, citrates, lactates, phosphates, tartarates are included to resist any change in pH, e.g. monobasic sodium acetate, sodium citrate, potassium phosphate, potassium metaphosphate.

Questions for Self-Study

- Enumerate the role of surfactants as pharmaceutical additives.
- Enumerate various uses of hydrocolloids as pharmaceutical excipients.
- Write influence of buffer on quality of dosage form, its performance and effectiveness.
- Write a note on multifunctional additives used in pharmaceutical dosage forms.
- Give an account of common additives and common physicochemical stabilisers used in dosage forms.
- What are pharmaceutical additives? Write types and selection of colouring and flavouring agents.

4.5 SPECIAL NOTES

(1) Syrup

Syrup is sweet; viscous, nearly saturated aqueous solution of sucrose. Syrup IP contains 66.7% w/w of sucrose and Syrup USP is 85% w/v aqueous solution of sucrose. Syrup term is also used to explain dosage form (medicated syrups), which are solution state liquid dosage forms containing dissolved drug in a syrupy base.

Properties of s

yrup as an excipient are listed below:

- Syrup based oral liquids are more palatable due to their mouthfeel effect.
- Due to high osmotic pressure syrups are self-preservatives. The evaporation of the water in a closed container and its subsequent condensation and dropping back of water on the surface of syrup also causes local dilution. In addition, if the syrup is completely saturated, it may undergo crystallisation at low temperature, causing separation of sugar and uneven concentration of sucrose. Thus for extended protection, preservatives like methyl paraben, benzoic acid, sodium benzoate, asorbic acid or alcohol are usually added.
- Due to saturation, syrups have lower solvent capacities than purified water.
- Reducing sugars in syrups prevent oxidation of drugs.
- Syrup is not suitable for diabetic patients and children due to glycogenic properties and tooth decay (cariogenic) properties of sucrose, respectively.

Method of Preparation

(i) Hot Process: Weighed quantity of sucrose is added to purified water and the mixture is heated to get clear solution.

Preparation 4.1

Syrup IP

Sucrose: 66.7 g

Purified water, to make 100.0 g

Principle: It is 66.7% w/w aqueous solution of sucrose. Mixture of sucrose and water to make 100g is heated in a container. If necessary, boiling water is added to adjust the final weight. Hot process is quick but syrup may have amber to dark brown colour. For prolonged storage, it is recommended to add methyl paraben as a preservative.

Method: In a tared vessel, add sucrose in water and dissolve it by heating at a moderate temperature with occasional stirring. Make up to the final weight by adding warm water.

Container and Storage: Pack in glass / plastic bottle. Store in a cool place. Use within two weeks.

Use: Sweetening agent, vehicle for liquid orals.

(i) Cold process by agitation: Agitation of sucrose with water to get solution is a slow process, but it produces colourles and odourless product. This is an alternative process to avoid the use of heat.

(ii) Cold process by percolation: Crystalline or coarse granular sucrose is placed in a percolator. The loosely packed moist cotton is placed in the neck of the percolator and purified water is allowed to pass slowly till sucrose dissolves. Finally sufficient amount of water is passed through the percolator as washing and volume is made. e.g. Syrup USP.

Syrup USP

Sucrose: 85.0 g

Purified water, to make 100.0 ml.

Containers and Storage: Store in glass bottles / jar. Keep container tightly closed in a cool place. Syrups should be used within two weeks of preparation.

(2) Aromatic Waters

Aromatic waters are clear, saturated aqueous solutions of volatile oils or other aromatic substances. These are used as vehicles and flavouring agents and some of these are preservatives. Additionally, aromatic waters have mild therapeutic actions like carminative and stomachic.

Following are the reasons for the use of volatile oils as flavouring agents in diluted form such as aromatic water.

Difficulty in measurement of the required low amount of pure volatile oil.

Difficulty in distribution of oil due to immiscibility and poor solubility of volatile oil in water, e.g. aromatic water,

For the same reason, the volatiles oils are also formulated as emulsions (peppermint oil emulsion) or spirit (chloroform spirit).

In general, aromatic waters have been used as flavouring agents. Chloroform water due to its anodyne action is the choice of vehicle in remedies for colic and diarrhoea. Anis water is used as a vehicle in expectorants. As a vehicle, aromatic waters have limited applications because these are saturated and if a large amount of water-soluble drug is added to it, an immiscible oily layer may separate on top. Double strength chloroform water has preservative action.

Though, aromatic waters are less used for their therapeutic value, most of them have mild carminative and stomachic action and for that these (cinnamon, peppermint, dill, camphor, chloroform) are reported for internal use in dose of 15 to 30 ml per day and concentrated aromatic water in dose of 0.3 to 1 ml. Dose of double strength chloroform water is 5 to 15 ml. But in practice, these are not used for therapeutic purpose.

Types of Aromatic waters

Aromatic water: These are aqueous solutions of 2ml or 2g of volatile principles in 1000ml of purified water. E.g. Camphor water IP, Chloroform water IP, Peppermint water BP. However chloroform water is 0.25ml chloroform /100ml of water.

Concentrated aromatic water: It is forty times stronger than aromatic water and contains alcohol as co-solvent. E.g. Anise water, BPC, Caraway water, BPC, Cinnamon water, BPC, Dill water, IP and Peppermint water, BP

Methods of Preparation

Aromatic waters may be prepared by the following methods

(1) Distillation method: Coarsely ground odoriferous portion of the plant drug is mixed with purified water and the mixture is subjected to steam distillation. Bottom layer of distillate is aromatic water. To obtain a saturated solution, initial distillates are repetitively used as solvents to distil the fresh drug. This process is referred to as cohobation. Depending on the number of cycles, the obtained aromatic waters are known as double or triple distilled aromatic waters. Cohobtion is an expensive and time consuming method but useful when plant source contains a small amount of volatile oils, e.g. orange flowers, rose petals and witch hazel.

(2) Solution method: 1 ml or 1 g of the volatile substance is agitated for 15-30 minutes with 500 ml of water, allowing the resultant mixture to stand for 12 hours, and then filtered through moistened filter paper. The final volume is adjusted with purified water. During the standing, the solution becomes saturated and the layer of insoluble volatile portion is removed by filtration/decantation.

(3) Dispersing method: It is an improved dissolution method, where the rate of dissolution of volatile principles can be increased by adsorbing them on the surface of inert material, like talc, kieselguhr. These agents perform two functions, dispersing agent and filtration aid, where they increase rate of dissolution and the adsorbed un-dissolved volatile principles can be filtered easily.

(4) Dilution method: One part of concentrated aromatic water is diluted with thirty-nine parts of purified water. The aromatic waters prepared by this method contain a small proportion, usually 1.5 % v/v of alcohol.

Preservation and storage: Store in a tightly closed container in a cool place. Protect from light.

Aromatic water mainly contains volatile principles and the concentrated aromatic waters contain alcohol. The evaporation of volatile oil will reduce quality of aromatic water and the alcohol from concentrated waters may leads to separation of oil phase in the form of uneven droplets/ as immiscible layer. The volatile principles are also photolytic. Chloroform in the presence of water and sunlight decomposes with formation of harmful gases like phosgene and hydrogen chloride. Therefore, aromatic waters should be packed in amber coloured bottles and stored in cool and dark place.

Preparation 4.2

Chloroform Water IP

Chloroform: 0.25 ml

Purified water, to make 100 ml

Principle: Solubility of Chloroform is 1 in 200 ml of water, therefore requires careful mixing to dissolve it.

Method

(i) Dissolve chloroform in purified water by shaking for prolonged period of time. If mixture appears turbid, it should be kept aside, shaking occasionally to obtain clear solution. Or

(ii) Triturate chloroform with 5g of talc. Add it into water and shake vigorously for 15 minutes. Filter to get clear solution.

Container and Storage: Chloroform decomposes into harmful gas phosgene and hydrogen chloride on contact with moisture and sunlight; therefore it should be stored in amber coloured bottles and in a dark place.

Use: It was used as vehicle, preservative and to mask unpleasant taste. But in recent days it is not preferred due to safety concerns. Dose: 15-30 ml.

Preparation 4.3

Anis water Concentrated BPC

Anis oil: 2 ml

Alcohol (90%): 70 ml

Purified Water, to make 100 ml

Principle: Anis water concentrated is official preparation of BPC. Anis oil is insoluble in water and soluble in 3 ml of alcohol (90%). The final water contains 60 to 64% alcohol. 1 part of concentrated Anis water is diluted with 39 ml of water to prepare simple anis water.

Method

(i) Dissolve anis oil in alcohol. Gradually add water into it, stirring mixture each time, till to make final volume.

(ii) Add 5g of talc and shake vigorously for 15 minutes. Filter to get clear solution.

Container and Storage: Store in amber coloured bottle, in a cool and dark place.

Use: Flavouring agent in expectorant liquids. Dose: 0.3 to 1 ml.

Preparation 4.4

Dill water Concentrated IP

Dill oil: 2 ml

Alcohol (90%): 60 ml

Purified water, to make, 100 ml

Principle: Dill oil is soluble in an equal amount of alcohol (90%). The method of preparation, containers to be used and storage conditions are same as that of concentrated anis water.

Container and Storage: Store in amber coloured bottle, in a cool and dark place.

Use: Flavouring agent in carminative, stomachic type of liquids. Dose: 0.3 to 1 ml.

Other examples:

Caraway Water Concentrated, BPC/Cinnamon water Concentrated, BPC/ Peppermint water concentrated USP

Caraway oil

Cinnamon oil / Peppermint oil	2 ml
Alcohol (90%)	60 ml
Purified water, to make	100 ml

Camphor Water IP

Camphor	100 mg
Alcohol (90%)	0.2 ml
Purified water, to make	100 ml

Camphor Water Concentrated, BPC

Camphor	4 g
Alcohol (90%)	60 ml
Purified water, to make	100 ml

Preparation 4.5

Aromatic elixir

Orange oil	0.24 ml
Lemon oil	0.06 ml
Coriander oil	0.024 ml
Anise oil	0.006 ml
Syrup	37.5 ml
Alcohol	25.0 ml
Purified water, to make,	100.0 ml
Talc	30g

Principle: Hydro-alcoholic vehicles are useful to prepare solution of poorly water soluble drugs. Such vehicles contain about 25% alcohol. Aromatic elixir is an example of flavoured hydro-alcoholic vehicle used to prepare medicated elixirs. Like aromatic water it is an aqueous solution of aromatic principles, but is concentrated than the aromatic water and also sweet due to presence of syrup. Syrup should be added in several portions into alcoholic solution of oils shaking vigorously after each addition to prevent salting-out of oils. Talc is a clarifying agent that adsorbs the insoluble oil phase and filterers it out. High alcohol content is a reason for caution. The filter paper should be wetted with dilute alcohol to prevent precipitation of oils.

Method

(i) Dissolve the oils in alcohol.

(ii) To this add syrup in several portions shaking vigorously after each addition. Then add sufficient quantity of water in a similar manner.

(iii) Add talc in the mixture and shake vigorously.

(iv) Filter the mixture through filter paper that is moistened with dilute alcohol to obtain clear solution.

Note: As quantity of oil is a fraction of millilitres, it is suggested that mixture of stock solution of oils should be provided. About 0.5 ml of the mixture for 100 ml can be taken.

Container and Storage: Store in amber coloured bottle, in cool and dark place.

Use: Pleasantly Flavoured vehicle.

Questions for Self-Study

- Enlist the composition of Syrup IP and Syrup USP.
- Explain why preservatives are not required in simple syrup IP? **(PU 2010)**
- What are syrups? How is invert syrup prepared and stored? **(PU 2011, 2013, PU 2014)**
- Write types of aromatic waters **(PU 2014)**
- Why are volatile oils used as flavouring agents in the form of aromatic waters?

- Write merits and demerits of syrup as vehicle with special note on preservation of syrups.
- Write a note on aromatic waters. **(PU 2009)**
- What are aromatic waters? How are they preserved? Differentiate between aromatic waters and concentrated aromatic waters. **(PU 2011 & 2013)**

- Give an account of flavouring agents with a special note on aromatic waters.
- What are aromatic waters? Explain the methods of preparation and preservation of aromatic waters. **(PU 2010)**

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Chapter 5...

Performulation Studies

Syllabus

- Concept of pre-formulation,
- Aspects of bulk drug characterisation,
- Solubility and stability studies.
- Importance of each aspect in formulation development.

Features of the chapter

- Conceptualise the importance of different physicochemical properties of drug and excipients in design of dosage form and method to study these properties.
- Attempt is made to create base for study of physical pharmacy.
- New drug development, biological testing and in-depth calculations and numerical is out of scope of the chapter.

5.1 CONCEPT OF PREFORMULATION

Definition

Active Pharmaceutical Ingredients (API) and excipients have their inherent physical and chemical properties like particle size, solubility, pH, chemical reactivity, etc. As a formulation is a mixture of these ingredients, the pharmacists should have in depth knowledge of the properties of every individual ingredient, excipient and their mixtures. For example, to prepare an oral solution of a drug, it must be soluble in water without undergoing hydrolysis. Secondly, the other excipients needed in the formula must also be soluble in water. Moreover they should not cause precipitation of the dissolved drug, chemical degradation of the drug or promote microbial growth. Thus, knowledge of the properties of the ingredient before its formulation into a dosage form assures ease of production and quality of the final product.

Preformulation is defined as studies of physicochemical properties of the drug alone or in its mixture with excipients to generate key information that can be appropriately considered to develop an elegant, economical, stable and therapeutically effective dosage form.

Properties included under preformulation studies are:-

(1) Nomenclature: It includes the basic information about the drug such as compound name, chemical name, molecular structure, molecular weight and batch number.

(2) General appearance: Colour, odour and taste of the drug and the excipient.

(3) Bulk properties: These include primary properties of the API or excipient. Individual powders have characteristic size, shape, crystalline form, solubility, melting point, dissociation constant and partition coefficient; liquid ingredients have viscosity, specific gravity, boiling point, solubility, partition coefficient, etc. In addition to these 'primary / fundamental' properties, they possess 'secondary / derived' properties like bulkiness, flowing ability etc.

(4) Analytical properties: Depending on the chemical nature and functional groups present in the chemical structure, individual ingredients show their peculiar properties like λ_{max} (wavelength at maximum absorption) on colourimetry or UV spectroscopy.

(5) Stability: Individual ingredient has inherent storage stability, which may be affected when mixed with other ingredients.

Objectives of Preformulation

- To understand the fundamental and derived properties of the ingredients, so as to facilitate their selection to obtain a quality product.
- To gain knowledge about drug-excipient incompatibilities.
- To select suitable process for manufacturing of dosage forms and analytical procedure.
- To ensure longer storage stability of the final product.

5.2 BULK CHARACTERISTICS

Majority of the APIs and excipients are available in solid state as powders. Accordingly, the following properties should be studied as preformulation parameters.

5.2.1 Size and Shape

Particle size and shape are the general properties of any powder. Powders may have any irregular shape and may be present as coarse or fine particles. However, pharmaceutical powders with size of 10-40 µm, spherical in shape and with smooth surface are considered as ideal.

Significance of Size and Shape

- The fine powders are bulky, difficult to handle, have poor flow properties, and are more hygroscopic than the coarse powders.
- The needles shaped crystals are difficult to handle.
- Fine powders have more exposure to atmospheric conditions such as oxidation, heat, light and may undergo rapid degradation than coarse powders.
- Milling is the usual technique for reducing size but it may cause further problems such as aggregation and material loss.
- Variations in the particle size and density are the main causes for segregation of powders. Larger and lighter particles move upward against gravity and fine and dense powders settle at the bottom.
- In suspensions, larger and denser powders undergo faster sedimentation than smaller and lighter ones.
- Fine powders have faster rate of dissolution and bioavailability.
- The powders with spherical shape have good flow property and packability than irregular particles.

Methods of studying particle size and shape

- Particle size and shape can be determined by microscopic evaluation like optical microscope, polarizing microscope and scanning electron microscope (SEM).
- In a polarizing microscope, a sample is suspended in a nonsolvent (water/ mineral oil) and observed under the microscope; it reveals the size and shape of an individual particle.
- The larger particles (10 to 1000μm) can be studies by stereomicroscope.
- SEM is useful for smaller particles with diameters ranging from 0.1 to 10μm.

5.2.2 Surface Area

Surface of solids exposed to the atmosphere or environment of the other phase possess higher energy than their inner bulk. Finer the particle size, greater will be the surface area. Surface free energy of solid or surface tension of liquid is directly proportional to the surface area.

Significance of surface area

- Adsorption capacity of a substance increases with the increase in surface area.
- Rate of dissolution and chemical reaction increases.
- Rate of absorption of the drug increases.
- However, due to increased surface energy, fine powders undergo aggregation while immiscible liquids show more separation tendencies.

Method to test surface area: In BET adsorption method, helium or nitrogen is allowed to adsorb on the particle surface, which is then displaced by heating. The amount (molecules) of gas displaced is taken into account for calculation of surface area.

5.2.3 Particle Size Distribution (PSD)

Amount (Wt/%) of particles in a certain size range present in bulk is called as particle size distribution (PSD).

Significance of PSD

- Packing of powder, filling of die cavity of tablet machine or filling of hard gelatin capsule is governed by PSD. Mixture of about 10% fine in coarse powders result in good packing.
- Wider is the PSD of powders, more are the chances of weight variation and drug content of tablets and capsules.
- Wider PSD results in uneven settling of powders in a suspension.

Methods for determining PSD

- Sieving is the commonly used method to determine PSD of the pharmaceutical powders, where unit amount of powder is passed through a set of sieves with decreasing mesh size and the amount retained on each sieve is calculated.
- Microscopy is more specific and accurate but it is a tedious method.
- Instruments based on laser light, light scattering, light blockage, and blockage of electrical conductivity (Coulter Counter) are advanced methods for bulk analysis.

5.2.4 Crystal Characteristics

Solids exist in a definite space lattice arrangement called crystals .The crystals are of the following systems viz. cubic, tetragonal, orthorhombic, monoclinic, triclinic and hexagonal.

- Depending on their outer appearance, the crystals are of six types, these are called crystal habits viz. platy, needle or acicular, bladed, tubular, prismatic, massive or equant.

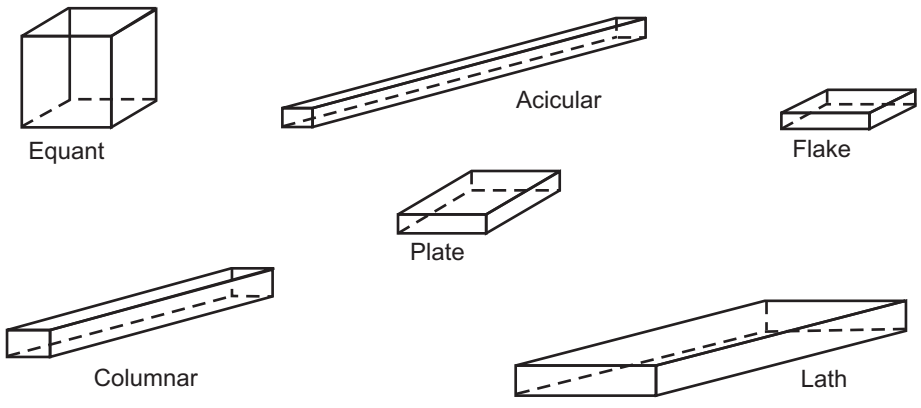


Fig. 5.1: Crystal Habits

- Many drugs having the same internal arrangements can show two or more external structures that give distinct crystal species; these are called as polymorphs.
- Solids that are not ordered in a regular array and have random internal arrangement are called as amorphous solids.
- The term *Enantiotrop* describes reversible change in the type of polymorph obtained by varying temperature or pressure.
- The term *Monotrop* indicates that one polymorph of a substance is always unstable irrespective of temperature and pressure.
- Crystals that entrap solvent are called *clathrates*, *inclusion or pseudopolymorphs*.
- A solvent that is molecularly complexed at a specific site in the crystal is called as a *solvate* or *stoichiometric adduct*.
- When water is the solvent the solvates are called as *hydrates* and can be described as hemihydrate, monohydrate and dihydrate, indicating one-half, one and two molar equivalents of entrapped water, respectively.

Significance of Crystal Properties

- Different crystal properties may show different physical properties such as crystal shape, true density, melting point, and solubility.
- Amorphous forms have more solubility than crystalline forms and anhydrous forms have more solubility that the hydrate forms. Thus, the change in polymorphic state of the drug shows different physical as well as biopharmaceutical properties.
- Due to higher thermodynamic energy, the amorphous forms are comparatively unstable than the corresponding crystalline forms. During storage they can revert to crystalline form, which is a stable form.
- Similarly, unstable polymorph may get converted into stable polymorph.

Methods to study Crystal Characteristics

(i) Microscopy

- Microscopy, particularly single crystal microscope.
- Hot stage microscopy identifies pseudopolymorphs, where heating of crystal under microscopic observation shows release of entrapped solvent in the form of bubbles.

(ii) PXRD

- Powder X-ray diffraction (PXRD) can be used to differentiate crystalline and amorphous nature of drug as well as to check batch-to-batch variability in the crystallinity of the substance. Random orientation of a crystal lattice in a powder sample causes the incident x-rays to scatter at distinct angles (2θ) and in a reproducible pattern of peak intensities. It is characteristic of a specific crystalline species and change in scattering angle (2θ) indicates change in crystal form.
- Peak intensity of PXRD explains crystallinity of sample. Reduction in peak intensity attributes to reduced crystallinity and amorphous forms do not show intense peaks.

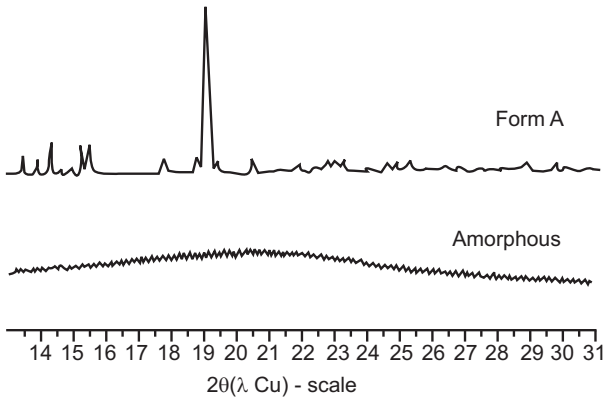


Fig. 5.2: A typical X-ray diffractogram of crystalline and amorphous forms

(iii) Thermal analysis

Thermal analysis is a more advanced tool for powder characterisation.

- DSC (Differential Scanning Calorimetry) measures the heat gain or loss by substances when subjected to heat. A substance absorbs heat when it undergoes melting, boiling, sublimation, vaporisation and desolvation; and it loses heat during crystallisation. A DSC endotherm during heating indicates melting and occurrence of exotherm during cooling cycle is attributed to crystallisation. Polymorphs and solvates show different DSC thermograms. Crystalline form requires more energy to melt producing deeper endotherms than corresponding amorphous forms.
- DTA (Differential Thermal Analysis) measures changes in the weight of a sample as a function of temperature and time, e.g. desolvation and degradation involves weight loss.

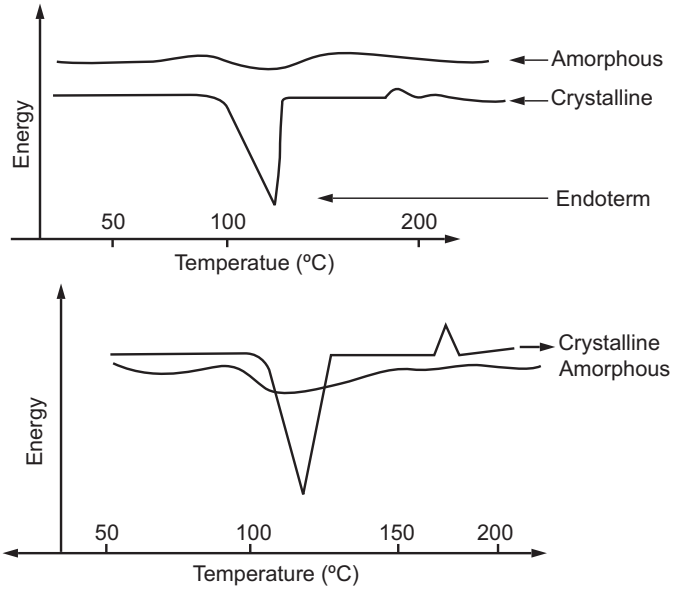


Fig. 5.3: A typical DSC thermogram of crystalline and amorphous form

5.2.5 Melting Point

Melting point is the traditional and well proven method to identify the compound, to test purity, change in crystal property, etc. It also gives an idea about intermolecular cohesiveness that also decides solution properties of a drug. Simple methods using capillary and hot stage microscopy to sophisticated methods like DSC, DTA are useful in determination of melting behavior.

5.2.6 Moisture Content and Hygroscopicity

It indicates the amount of water associated with the substance.

- Many substances carry water either in free or bound form and others have a tendency to adsorb moisture from the surroundings. The amount of moisture adsorbed by a fixed weight of anhydrous sample in equilibrium with the moisture in the air at a given temperature is referred to as equilibrium moisture content.
- Factors like atmospheric humidity, temperature, and surface area affect moisture uptake.
- Deliquescent substances adsorb water to dissolve completely whereas hygroscopic substances adsorb water because of hydrate formation.

Significance of moisture content

- Moisture content has manifold effects on drug stability. It not only increases chances of hydrolysis but also increases sensitivity towards oxidation and thermal degradation.
- The moisture content makes the powder more cohesive, lumpy and sticky.
- It also provides good media for microbial growth.
- On the positive side, controlled amount of moisture acts as a plasticiser and improves tabletting properties of powders.

Methods to test moisture content

- Loss on drying (LOD) is widely used to estimate water content of granules, where the known weight of powder is heated in hot air oven at 60 to 100ºC, till a constant weight is obtained. The difference in weight in percentage is LOD.
- For determination of hygroscopicity, known weight of powder is spread as a thin layer in an open plate and kept in humidity chambers of controlled relative humidity conditions. After specific time the moisture uptake is estimated by any suitable method.
- Analytical methods such as Karl Fischer titration, IR moisture balance, gravimetry, TGA can be used for estimation of moisture content.

5.2.7 Wetting

Wetting is spreading of liquid on a solid surface, mostly by displacing a layer of air from the solid surface.

Significance of wetting

- Wetting is the first step in dissolution. The solvent should cover the solute surface, where presence of air entrapped in pores of the solid surface may oppose or delay it.
- Physical stability of suspensions depends on uniform distribution of insoluble drug particles in bulk of the liquid phase. Poorly wettable solids are difficult to disperse.
- Similarly disintegration and dissolution of the tablet may be slow due to poor wetting of the tablets by the GI fluid.

Method to study wetting properties

- Wettability is measured as a contact angle. Powder of a sample is lightly compressed into a compact. When a drop of liquid is placed on the flat surface of compact of powder, the point where the drop and solid meet forms angle, it is called as contact angle (θ). The low contact angle indicates good wettability, e.g. θ = 0° indicates complete wetting whereas θ = 180° indicates practically a non-wettable substance.

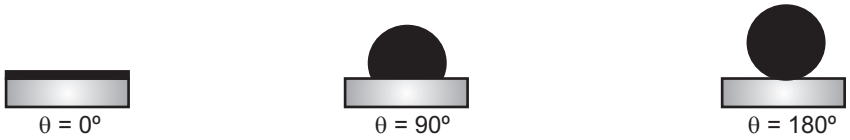


Fig. 5.4: A schematic representation of wetting of solid.

5.2.8 Flow Properties

Other important pharmaceutically important powder properties include powder flow, packability and compressibility. These cohesive properties are influenced by primary properties like size, shape, density and surface properties, therefore categorised as secondary or derived property.

Significance of Flowability

- Powder should easily and continuously flow from hopper into die cavity of tablet machine or into body of the capsule shell; otherwise the weight of the tablets will vary.
- Spherical particles with smooth surface have good flow.
- Fine powders are cohesive and can show poor flow.
- Powders with wider PSD may show un-uniform flow.

Method to study flowability: Angle of repose, flow through orifice, compressibility index, and shear cell are various methods employed for determination of flow property of pharmaceutical powders.

- Angle of repose (ϕ) is the most widely used method, where the powder is passed through an orifice on an horizontal plane surface to form a heap. The angle formed by the inclined portion of the heap on the plane is calculated as angle of repose (tan ϕ). It is equal to twice the powder bed height (h) divided by powder bed diameter (D).

  Tan ϕ = 2 h/ D

  Value of ϕ should be in the range of 20° to 40°.

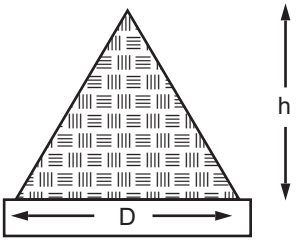


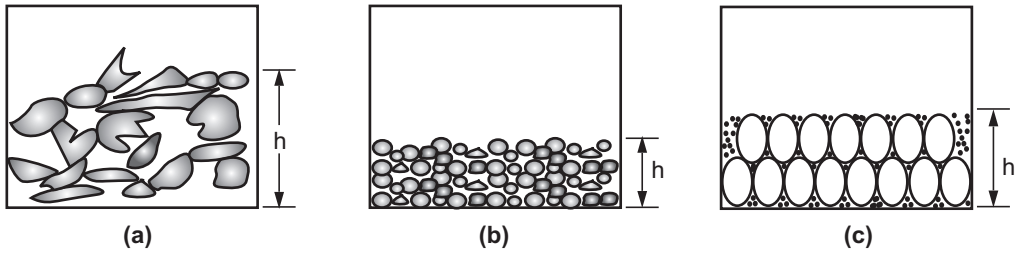
Fig. 5.5: Angle of Repose

5.2.9 Packing Ability

The arrangement of particles in its bulk determines its volume. The increase in density (reduction in volume) under applied pressure is referred to as packability or compressibility.

Significance of Packability

- Bulk density and tap density are the basic methods to determine packability of a powder.
- Bulky powders are voluminous to handle and carry.
- Dense powder produces smaller volume thus requires small die cavity or small capsule to fill it.
- Granules which are denser than powders are easy to compress to form a tablet.



(a) Coarse size and irregular shape (b) Fine Powder (c) Spherical particles + fines

Fig. 5.6: Schematic presentation of packing of same weight of powder

Methods to determine packability

- Bulk density (g/ml) is determined by pouring weighed amount of bulk powder into a graduated cylinder and measuring the volume (v_o).
- Tap density is determined by tapping the graduated cylinder filled with powder for a fixed number of taps until the powder bed volume has reached a minimum (v_t).
- Compressibility index (CI) is also derived from these experiments and its value between 15 to 25% indicates good flow properties.

$$CI = [1 - v_t/v_o] * 100$$

Questions for Self-Study

- Define the terms: polymorphism, crystal habit, clathrates and solvates.
- Which ideal shape a powder should have for tabletting? Why?
- Name the different types of crystal systems and crystal habits.
- What is the difference between working principle of DSC and DTA.
- Explain a method to determine flowability of granules.
- Define bulk density, tap density and compressibility index.
- Explain in detail polymorphism **(PU 2014)**

  (It is short question; detailed explanation is not expected)

- Give importance of particle size as a preformulation parameter.
- What are the merits and demerits of use of micronized drug powders?
- Enlist methods used to study particle size, PSD and surface area of powder and describe any one.
- Give application of DSC as preformulation tool.
- Explain utility of powder X-ray diffractometry in preformulation.
- Explain the different states of crystal containing entrapped moisture.
- Explain the term wettability, its significance and method for testing.
- Give importance of the flow and packing properties of pharmaceutical powders.

❖ Give an account of bulk characterisation of a solid in pre-formulation studies.

5.3 SOLUBILITY AND DISSOLUTION STUDIES

Drug must be in the dissolved state prior to it's absorption. It means that the solubility and rate of dissolution of drug administered dosage form is an important criterion for its bioavailability.

5.3.1 Solubility Testing

(a) Solubility: It is the amount of solute that goes into solution till equilibrium is established between the solute that goes into solution and undissolved solute at constant temperature and pressure. It is expressed as mg ml^{-1}.

Significance of solubility

- As a set rule, drugs should have an aqueous solubility greater than 1% w/v otherwise a potential problem for its absorption may occur.
- When solubility of a drug is less than 10mg/ml, suitable steps should be taken to improve its solubility.
- The drug solubility is also important for design of liquid formulations.

Method to study solubility: A known excess of drug is placed into ampoules containing unit volume of solvent (5ml) and the sealed ampoules are shaken at constant temperature (37°C) for at least 24 hours. Sample is withdrawn, filtered, and concentration of the solute in filtrate is determined by suitable assay.

(a) Intrinsic solubility: It is solubility of the completely unionised drug. It signifies fundamental solubility of the drug (mg ml^{-1}). Extent of ionisation is governed by the pH of the medium, which is considered as variable, which is excluded in determination of intrinsic solubility. It is determined as per general procedure using acidic solvent medium for acidic drugs and basic solvent for basic drugs.

5.3.2 Dissolution Testing

(a) Dissolution rate: The process of transfer of solid solute into solution is dissolution and the dissolution with respect to time is dissolution rate (% drug dissolved / unit time).

Significance of dissolution rate

- It explains the rate of formation of solution and thus decides the rate of absorption in blood.
- It is used to study effect of additives (like polymers) or process parameter (like compression pressure) on the rate of drug release.
- Size reduction of powder or disintegration of dosage forms accelerates dissolution rate.

Test for the determination of dissolution rate: In practice, the dosage form or drug crystals are agitated at constant temperature (37±2°C) using a suitable medium (water, acidic or basic buffers) and in excess amount of the medium (900/ 1000ml) that always maintain unsaturated or sink condition. Periodically, the sample is taken and tested for drug content.

(b) Intrinsic dissolution: It is the rate of dissolution of a drug in a particular medium when surface area of dosage form and volume of solvent are constant when the study is conducted under constant temperature, pressure and agitation.

Significance

- As dissolution proceeds, size of the tablet progressively becomes smaller. The resultant increased surface area accelerates dissolution rate, which is considered as a variable factor. It is the fundamental dissolution rate that depends on the effect of excipient on drug release and solubility of drug in a particular dissolution media, and expressed as mg $cm^{-2}ml^{-1}$.

Test for determination of intrinsic dissolution: The powder is compressed into a disc of known area. The disc is embedded in insoluble wax to coat on three sides and held such that only an uncoated flat surface gets exposed to the dissolution medium. The disc is subjected to dissolution test using a suitable medium and periodically samples are withdrawn to check the amount of the dissolved drug.

5.4 DISSOCIATION CONSTANT (pKa) / pH-SOLUBILITY PROFILE

pKa is the pH at which concentration of ionised and un-ionised species is in equilibrium.

The Henderson-Hasselbalch equation provides an estimate of the dissociation of the drug at a particular pH.

For acidic drugs,

pH = pKa + log [ionised drug] / [unionised drug]

For basic drugs,

pH = pKa + log [uninonised drug] / [ionised drug]

Significance of dissociation constant

- The biological membrane is a matrix composed of hydrophilic proteins embedded in the lipids. As the major portion of the membrane is lipoidal, the drug should have preferential solubility in it, at the same time drug should be sufficiently hydrophilic to enter into systemic circulation. A drug in its unionised form is more lipid soluble and its ionised form is more water soluble.
- For better drug absorption, API should be present in a 'dissolved state' but in its unionised form.
- About 75% of drugs are weak bases, 20% drugs are weak acids and only 5% are non-ionic.
- Thus, the degree of ionisation and solubility of such drugs is governed by the pH of the medium or body fluids.
- Since the pH of the stomach is 1 to 4 and intestinal fluid has pH between 5 to 8, these are better sites for absorption of acidic and basic drugs, respectively. The pH dependent solubility profile suggests the possible sites of drug absorption.
- The weakly acidic drugs (pKa < 4.5) and weakly basic drugs (pKa > 8.5) have better absorption from GI tract as compared to strongly acidic or basic drugs.
- Thus, knowledge of pKa is very useful in determining the site of drug absorption.
- Methods like potentiometric and conductometric titrations are the most useful methods for pKa determination.
- The solubility of a drug can be studied by adding it in excess amount into aqueous phase of definite pH and stirring at constant temperature. Then the sample is withdrawn and assayed.
- If pKa and intrinsic solubility is known, one can calculate the solubility of a drug at a particular pH by Henderson-Hasselbalch equation.

5.5 PARTITION COEFFICIENT

A drug added into a mixture of immiscible liquids distributes between the two phases in a fixed ratio at equilibrium, which is called as the partition coefficient. It reflects the relative aqueous and lipid solubilities of a drug. It also referred by term 'log P value'

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

Significance of Partition coefficient

- Biological membrane is mixture of lipids (lipophilic) and proteins (hydrophilic) components. Though lipid soluble drugs can easily cross the biological membrane, it must have balanced hydrophilic properties to enter in blood circulation. For example, epidermis layer of skin is richer in lipoids whereas underlying layer dermis is more aqueous. Highly lipophilic drugs may have good penetration and prolonged residence in skin layer and but it may have poor partition into systemic circulation.
- Orally administered drug should get dissolved in an aqueous gastric fluid, has to cross lipoidal biological membrane and then enter into aqueous blood circulation.
- Thus, solubility and permeability are the two most important criteria that determine bioavailability of a drug.

Method to estimate partition coefficient: Usually, octanol / water or chloroform / water system is used, where immiscible phases are allowed to saturate with each other before study. Known amount of drug is added in the system and equilibrated by shaking. The phases are separated using separating funnel or using centrifuge and each phase is estimated for drug content.

Common Ion Effect: The solubility of slightly soluble electrolytes (salts) is often influenced by the presence of common ions in the medium; this is termed as common ion effect. The decrease in solubility by this way is called as 'salting out' and increase in solubility is called 'salting in' effect. Except for a few larger anions such as benzoates and salicylates, most of the ions have salting out effect.

Significance: The liquid formulations and injections contain many electrolytes as additives such as sodium benzoate as preservative and sodium chloride as tonicity agent. It is important to study the effects of such salts on solubility of drugs.

Method: The solubility study is carried out in presence of electrolytes.

Questions for Self-Study

- Explain terms solubility, intrinsic solubility, dissolution rate, intrinsic dissolution.
- Write method to determine solubility/ intrinsic solubility.
- Explain salting in and salting out principle of solubility determination.
- Give the importance of partition coefficient as preformulation parameter. **(PU 2014)**
- Write a short note - Solubility studies in preformulation. **(PU 2014)**
- Write the principle and method to study pH-solubility profile of a drug.
- How does the pKa of a drug influence its absorption?

- Explain the statement "Lipid solubility of drug is not the sole criteria for its effective absorption".
- ❖ Discuss importance of solubility related preformulation parameters.
- ❖ Discuss in detail the concept of physicochemical properties involved in preformulation **(PU 2014).**

5.6 ANALYTICAL PROPERTIES

Ultraviolet (UV) spectroscopy, thin layer chromatography (TLC), high pressure liquid chromatography (HPLC), infrared (IR) spectrum are the most common analytical tools useful for identification of a drug and their degraded product. UV and HPLC studies are useful for the development of suitable analytical method for estimation of drug content in dosage form, drug release and drug in body fluids. Analytical techniques are useful to estimate drug interactions and possible stability of dosage form.

5.6.1 Ultraviolet (UV) Spectroscopy

Most of the drugs show absorbance of light at a particular wavelength (λ_{max}), which is attributed to the presence of specific chemical group and unsaturation, called chromophore. UV spectra of a drug are unique and used as identification tool as well as to know about degradation of drug.

5.6.2 Thin Layer Chromatography

TLC is one of the reliable and sensitive tools for identification of pure drug from a mixture of other drugs, additives, impurities or degraded fractions. It involves use of cellulose paper or silica coated glass plate. A standard drug solution and a sample drug solution are separately spotted at the bottom of these plates, which are placed in a chamber containing eluting solvent and closed. The solvent phase moves upward by capillary flux and separates components of the mixture. The distance traveled by a sample (d_{Sample}), relative to the solvent front ($d_{solvent}$) are measured and used to calculate Rf (Relative front) value. Drugs have unique Rf values using a particular eluting solvent. The spots can be separated and analysed.

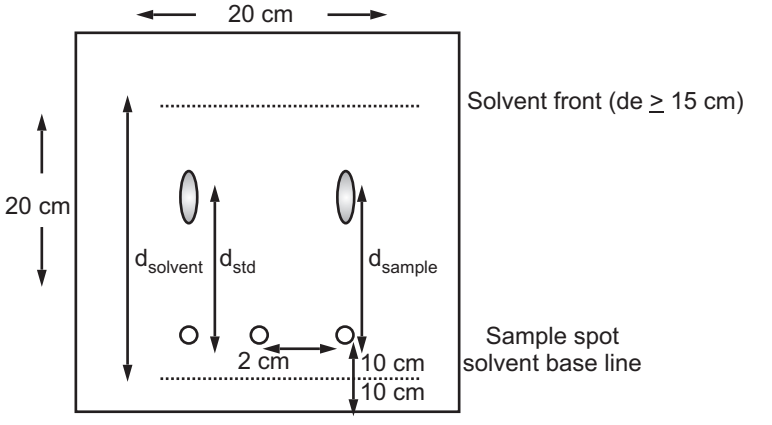


Fig. 5.7: Principle of TLC analysis

5.6.3 High Pressure Liquid Chromatography

It is an advanced form of TLC. HPLC is based on the use of silica filled column in place of silica plate, through which a mobile (mixture of solvent) phase is pumped under high pressure. As compared to TLC, this method requires a small amount of sample, shorter time for separation of components and have high sensitivity and selectivity. The eluted components are assayed.

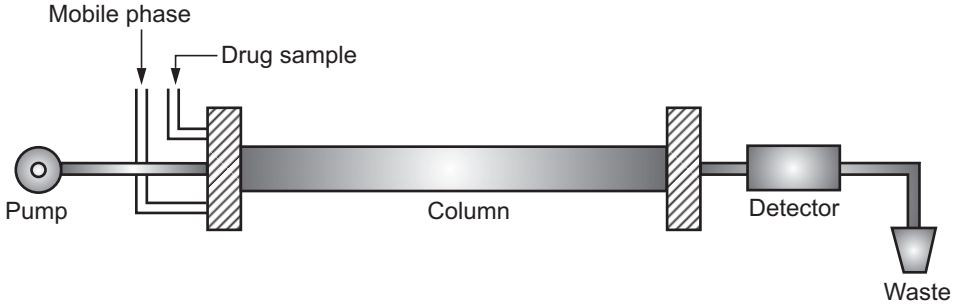


Fig. 5.8: Schematic diagram showing components of HPLC

5.6.4 Infrared (IR) Spectrum

The presence of specific functional groups is responsible for IR peak of drug. Thus, IR spectrum is useful for identification of pure drug; detection of degradation, complex formation, chemical reaction that if occurred in presence of other additives.

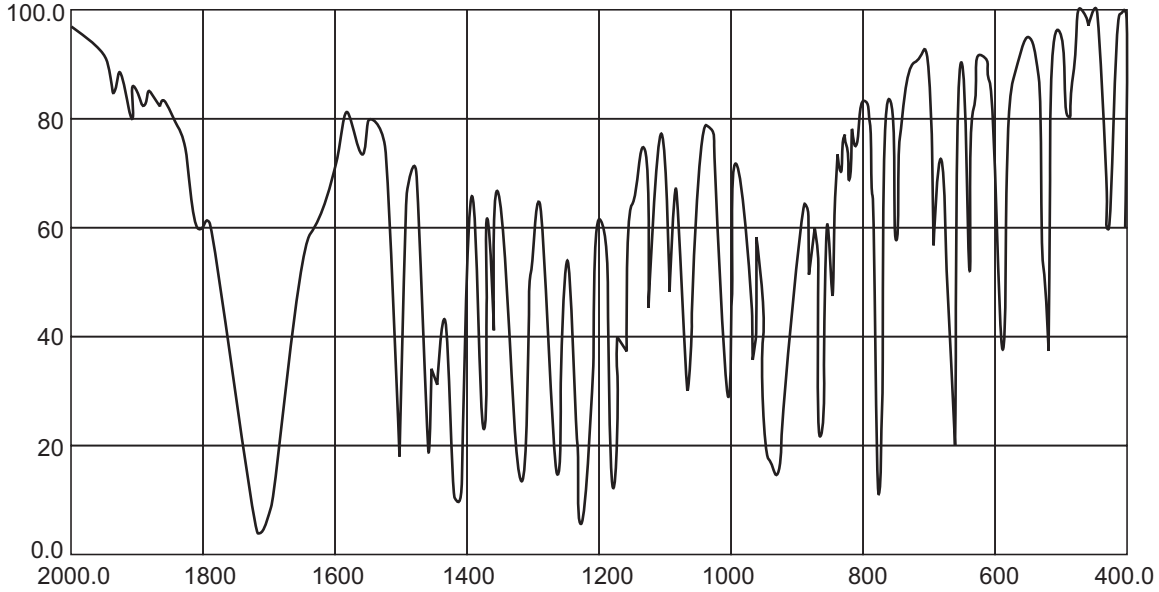


Fig. 5.9: IR spectrum of Ibuprofen

Questions for Self-Study

- Explain how UV and HPLC are used as tool in pre-formulation studies?
- Enlist various important analytical parameters studied as preformulation testing, explain principle of any one.
- Write principle of estimation of drug purity using TLC.

5.7 STABILITY ANALYSIS

Broadly, stability is defined as the ability to retain the original physicochemical properties of the drug under the influence of atmospheric conditions, formulation additives and processing steps. To formulate a dosage form, it is necessary to know the effect of environmental conditions on a drug, excipient and effect of these on each other.

Significance of stability testing

- Effect of atmospheric conditions as well as formulation conditions on physicochemical properties of the drug and excipient provide guidelines for its selection.
- Drug-excipient interactions studies are essential for their selection.
- Processing steps (temperature, pressure), moisture content, pH, ionic strengths also influence the chemical degradation of the drug.

Method of stability testing

- **Accelerated stability testing:** Decomposition of a drug occurs mainly by four processes, viz. hydrolysis, oxidation, photolysis, and metal impurities. At ambient conditions, the time required to degrade may be a few years. Thus, to speed up the process of stability testing it is customary to use stress conditions in the investigation of stability and such testing is called as accelerated stability testing. Since temperature and moisture content are the two main factors responsible for instability, the samples are exposed to different temperatures and humidity like 5°C, 22°C, 37°C and 37°C / 75% RH for period of 4 to 12 weeks.

  The stability testing at accelerated conditions is carried out in following ways:

5.7.1 Solid-State Stability

It is carried out to observe changes in physicochemical properties of solid ingredients.

Significance: The solid state properties of drug like crystal form, melting point, solubility are influenced by moisture content, temperature and atmospheric oxygen.

Methods for Solid State Stability

- For testing, powdered sample is placed in open screw cap vials and subjected to a variety of temperatures and humidity conditions, usually up to 12 weeks. After which, the samples are tested for physicochemical properties like melting point, DSC, DTA, PXRD. FTIR, etc.

- Hydrogen bonding, formation of chemical complexes and similar type of chemical interactions can be easily detected by disappearance of characteristic IR peak or development of new peaks.
- Change in sharpness or shifting of DSC endotherm indicates physical interaction. TLC, HPLC are more useful to check degradation products.
- To check the possibility of degradation by oxidation, the sample is sealed in vials and headspace of the vial is filled with 40% oxygen. It is compared with the sample sealed under inert gas.

5.7.2 Liquid-State Stability

Liquid state stability testing is carried out to find changes in liquid state. Liquid state stability checks effect of solvent, co-solvent, pH, ionic strength, light, temperature, oxygen, etc.

Significance: Rate of chemical reaction is faster in liquid state than in solid state. Secondly, it helps to know drug stability in liquid environment like drug in liquid dosage form, drug in dissolution medium and stability in GI fluid or even stability in blood after injection.

Method for Liquid State Stability

- Sample made in a suitable solvent is sealed in flint glass ampoules and stored at various temperatures, but temperature should not exceed boiling point.
- Drug is mixed with 0.1 N HCl and 0.1N NaOH at 90°C as stress conditions to study effect of acidic and basic conditions and temperature.
- To check the pH of maximum stability, experiments are designed using buffers of different pH.
- Considering physiological compatibility of injections, stability is tested in 0.9% sodium chloride, which is the most suitable fluid to check effect of ionic strength.

5.7.3 Drug-excipient Interactions

To understand the effect of drug-excipient interaction on stability of the formulation, mixtures of these are placed under stress conditions.

Significance

- It helps to select suitable excipient and its concentration.
- It reveals atmospheric or process conditions that affect stability of drug-excipient mixtures.
- One can reduce the number of excipients by using multi-functioning additives.

Method

- Drug and excipient are mixed in realistic proportion to produce physical mixtures. For example, 10 : 1 drug: disintegrant, 20 : 1 drug: lubricant and for other tablet exicipients it is 1 : 1 to 1 : 5.

- Mixtures are sealed in airtight vials and subjected to various stress conditions.
- These can be tested by IR, DSC, DTA to check possibility of physicochemical interaction.

The preformulation study report is one of the important documents that is required to be submitted for approval of new drug (NDA) as well as pre-formulation testing is a routine procedure for designing any new formulation of existing drugs.

Questions for Self-Study

- Define the terms- stability and accelerated stability testing.
- Which are the major factors affecting the stability of pharmaceuticals.
- Enumerate the concept of accelerated stability testing.
- Which are the major factors affecting the stability of a pharmaceutical product ? **(PU 2014)**

  (This question is out of scope of the subject. Importance of stability testing as introduction is scope of the syllabus).

- Write short note: Physicochemical studies in pre-formulation. **(PU 2009)**
- Explain a method to determine solid-state stability of pharmaceutical.
- Write reasons to check liquid-state stability of pharmaceutical.
- Write a note on testing of drug-excipient interactions.
- Write short note on Stability of Solution. **(PU 2014)**

  (Not well defined questions. Liquid state stability is part of preformulation and stability of Solution dosage forms is out of scope of the chapter 'Solution' of the syllabus).

- Give an account of preformulation testing.

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Chapter 6...

Solution State Liquid Dosage Forms

Syllabus

- Definition and types.
- Formulation ingredients. Type of water used in pharmaceutical solutions.
- Formulations like Syrup, Elixir, Aromatic Water, Linctus, ENT preparation and paints, Mouth Wash, Enema.
- Evaluation, in process and finished product quality control.

Features of the chapter

- Objective is to understand formulation design, manufacturing and evaluation of solution type of liquid dosage forms.
- Scope of the chapter is about solutions as a liquid dosage forms and not about 'Solutions' as a physical form. Scope of the chapter is also restricted to solutions other than injections.
- The formulations mentioned under dosage forms are examples for practicals and for understanding the concept. It is not necessary to remember the exact official formula, official books should be used during practicals.
- Syrup and aromatic water are traditional additives, related content is covered in chapter-Excipients.

6.1 SOLUTION STATE LIQUID DOSAGE FORMS

Definition

Solution is a physical form in which the solute is dissolved in solvent. Solution state liquid oral dosage forms can be defined as single phase homogeneous liquid formulations containing drug and additives in dissolved state in suitable vehicle, mostly aqueous phase. The oral solutions are commonly referred as monophasic liquids.

Solution state liquid dosage forms are used for oral administration, application on skin, instillation in body cavities as well as for injections. The injectables and eye preparations are categorised as sterile formulations. The oral liquids are a major class of non-sterile formulations.

These are different from the suspensions and emulsions, which contains insoluble solid or immiscible liquid, respectively, in external liquid phase.

Types of Solution State Liquid Dosage Forms

- Oral liquids: Syrup, elixir, linctus.
- Oral topical liquids: Gargle, mouthwash.
- Liquids for body cavity:
  - **(a) ENT:** Ear drops, nasal drops, throat paints, gargles
  - **(b) Rectal:** Enema.
- Liquids for external use: Liniment, lotion, spray, paint.

Merits of solution state liquid dosage forms

General merits of liquid dosage form including monophasic and biphasic liquids are

(1) Ease of swallowing especially for paediatric patients is a major merit of liquid oral formulations.

(2) High dose drugs for oral administration can be conveniently administered in liquid form than solid dosage formulations.

Merits of solution type of dosage forms are

(1) Dissolved drug has the best absorption than all other oral formulations.

(2) The uniform distribution of dissolved drug as compared by biphasic liquid formulations provides better dose accuracy.

(3) Clarity of the solutions with uniform colour intensity adds to the aesthetic appeal of the product.

(4) The instant mixing and dilution of the solution with gastric content helps to minimise harsh effects of the drugs causing gastric irritation, e.g. potassium chloride, ferrous sulphate.

Demerits of solution state liquid orals

Demerits of liquids dosage form in general are

(1) Liquids filled in bottles are inconvenient to store and carry due to bulkiness and possibility of leakage.

(2) Provide less dose accuracy as compared to unit dosage forms.

(3) Liquid formulation, particularly containing aqueous phase provide suitable media for microbial growth.

Demerits of solution type of dosage form are

(1) Rate of chemical degradation is higher in dissolved state than the insoluble form of the drug like suspensions or solid dosage forms.

(2) Interaction of the dissolved drug with taste buds may intensify the bitterness of bitter tasting drugs.

(3) A number of drugs are insoluble in water, these are either difficult to formulate as solutions or require some additional technique for enhancement of solubility.

Questions for Self-Study

- Define and classify monophasic liquids.
- Enlist the advantages and disadvantages of pharmaceutical liquids.
- Give merits and demerits of solution state liquid dosage forms.

6.2 FORMULATION INGREDIENTS

Solution state liquid dosage forms are clear solutions of drug and additives in a suitable solvent. Therefore, the drug and additives must be selected considering their solubility. In addition to this primary requirement, decision on the type of dosage form to be formulated, the selection formulation ingredient, their stability, effect on bioavailability and acceptance, technical complications etc should be considered to design a formula. This will be covered in higher classes. Let us study, the different types of ingredients required to formulate monophasic liquids.

(1) Drug: Drug that is freely soluble in water is the basic requirement for monophasic liquids.

- The monovalent inorganic molecules are more soluble than polyvalent molecules.
- The weakly acidic or weakly basic drugs may have poor aqueous solubility at a particular pH, however their salts with strong base or strong acid, respectively are more soluble.
- According to the principle of 'like dissolves like' the polar compounds are more soluble in polar solvents like water and alcohol. The salts of are ionisable and more soluble in water than their acidic or basic forms, eg. diclofenac sodium.

(2) Vehicle: The physiological compatibility, non-toxicity, low cost and easy availability are the main reasons to use water as vehicles for medicinal products. Additionally, its wider solvent property is advantageous.

(i) Water: Potable water, distilled water, purified water, aromatic water are the various types of waters. Potable water is palatable and of satisfactory microbiological and chemical

quality for drinking. It is obtained from surface sources like lakes, rivers and streams or from springs and wells. Since it contains uncontrolled amount of minerals that can react with drugs it cannot be used for pharmaceuticals. It may have excessive hardness, extremes of pH, presence of uncontrolled number and types of chemicals and even pathogens.

Distilled water is purified water prepared by distillation. Purified water is recommended for preparations of most of the medicines excluding sterile formulations. Purified water is prepared from tap water by distillation, ion exchange method or by reverse osmosis. Purified water is official in all the pharmacopoeias.

Aromatic waters are flavoured aqueous solutions of aromatic principles. Due to their carminative and stomachic therapeutic properties, aromatic waters are principally used as flavoured vehicles in liquid orals indicated for GI disorders. However, highly soluble electrolytic solutes may salt out immiscible oil phase.

(ii) Syrup: Syrup is the choice of vehicle for paediatric liquids due to its sweetness and viscosity. The latter provides mouth-feel effects and possesses remarkable taste masking properties against bitter and saline drugs.

(iii) Juices: Juice is an aqueous liquid expressed from fruits, flowers or other parts of plants. Enzyme pectinase is added to destroy pectin and then it is filtered. However, these are more susceptible for microbial contamination.

(iv) Alcohol: Alcohol is used in oral liquids as a co-solvent. 95% Alcohol is commonly used for this purpose. However, pharmacological action and toxicity of co-solvents is the major limitation; therefore these should be used in minimum amounts. Instead of using a single co-solvent, blend of two or more co-solvents is preferred.

(a) Alcohol is not recommended for paediatric preparations and for non-alcoholic users. It causes CNS depression and intoxication including visual impairment, slurred speech, muscle incoordination etc., even at low to moderate quantities.

(b) Guidelines for the use of alcohol in paediatric preparations- in products used for children below 6 years the preparations should contain no more than 0.5%, for 6 to 12 years of age the recommended limit is 5% and for children over 12 years of age and adults the limit is 10%.

(c) In external preparations, alcohol may be used as a complete solvent, eg. Aconite liniment. Alcohol in external preparations acts as antiseptic, rubefacient and enhances drug penetration. Rapid evaporation after application produces cooling effect on the inflamed area.

(v) Fixed oils: Fixed oils are obtained from plant and mineral origins are used as a solvent for oil soluble drugs. The oil ingredient may have medicinal value or may be used as

a solvent. But due to unpleasant taste, oily solutions are not accepted and are usually administered in the form of emulsions. The oily topical formulations like methyl salicylate liniment are more useful for massage for rubifacient action. Vegetable and mineral oils are used in topical products as solvent, carrier and for their lubricating, emollient and occlusive effect.

(vi) Polyhydric alcohols: Polyhydric alcohols like glycerine, propylene glycol, sorbital, PEG 400 are used with purified water as co-solvents. Propylene glycol is 1/3rd as intoxicating alcohol and adverse effects are more likely to occur in neonates, children below 4 years of age, pregnant women and patient with hepatic and renal failure. The recommended daily intake is up to 25mg/kg body-weight.

Due to non-volatile nature they prevent crystallisation in syrups. Sorbitol produces cooling effect.

In topical preparations, especially containing alcohol or soaps, glycerine is used to minimise harsh skin irritation. They prevent hardening and drying of the products. The ability to retain drug locally and soothing effects produced by glycerine makes it a vehicle of choice for throat paint. Anhydrous glycerine is used as vehicle in ear drops.

(3) Physical stabilisers (Solubility enhancers): A dissolved drug remaining in its soluble state over the period of shelf-life is the ideal physical stability of monophasic liquids. In addition to use of water soluble salt of drug, following approaches have been successfully used for enhancement of drug solubility in water.

(i) Co-solvents: Use of water-miscible solvents for enhancing aqueous solubility of drug(s) is termed as co-solvency and common co-solvents are glycerine, alcohol, propylene glycol, sorbitol, polyethylene glycol (PEG) etc. Drug possesses good solubility in co-solvents and the total increase in aqueous solubility is greater than the predicted solubility in an individual solvent. The ionisable drugs have good aqueous solubility due to high dielectric constant of water (78). Ideally, the co-solvent system should possess dielectric constant in the range of 25 to 80.

(ii) Surfactants: Enhancing the solubility of poorly soluble drugs using surface active agents is called as solubilisation. Surfactant is used in concentrations above its critical micelle concentration (CMC), therefore it is also termed as miceller solubilisation. Hydrophilic surfactants with HLB values between 15 to 18 are usually used as solubilising agents to improve solubility of drugs in water. The surfactant used should be non-toxic and safe; for this reason non-ionic surfactants are more suitable, e.g. Tween 80, Tween 40, Brij 35, etc. In addition to drug solubility, surface tension lowering property of surface active agents increases drug-membrane contact and permeability.

(iii) Complexing agents: Complexing agents have been used effectively to increase the aqueous solubility of drugs, e.g. the aqueous solubility of riboflavin was increased with increasing concentration of ascorbic acid and sodium ascorbate, poly N vinyl 5 methyl 2 oxazolidone was used for increasing solubility of barbiturates and polyvinylpyrrolidone is used to prepare aqueous solution of iodine. Cyclodextrins (CD) by formation of reversible non-covalent inclusion complexes increase solubility of drugs. The αCD, βCD and γCD are commonly used in pharmacy.

(iv) Solid Dispersion: The mixing of drug in solution of PEG, CD or surfactants and subsequent evaporation to produce amorphous powder is called as solid dispersion. Such drug-excipient mixture may be melted or spray dried to obtain solid dispersion.

(v) Hydrotropes: The increase in solubility of a solute by the addition of alkali metal salts, anionic organic salts, or cationic or non-ionic organic compounds is called as hydrotropic solubilisation. The mechanism of hydrotropic solubilisation involves 'salting-in' through formation of molecular complexes, e.g. sodium benzoate increases solubility of caffeine, sodium acetate and sodium salicylate increases solubility of theophylline, nicotinamide and sodium glycinate is used for paracetamol.

(vi) Buffers: Most of the modern drugs are either weak acids or weak bases and the solubility of which increases with the increase in the degree of ionisation. In general, solubility of acidic drugs increases at pH above its pKa +1 and solubility of basic drug increases at pH below its pKa-1. Thus, adjusting pH is one of the methods for attaining solution state. For oral administration, the dosage form should have pH between 5 to 8. Thus, balance among the drug solubility, stability, physiological compatibility and maximum drug absorption with minimum interactions with other additives is possible by judicious selection of buffer. Buffers based on carbonates, citrates, lactates, phosphates, tartarates e.g. monobasic sodium acetate, sodium citrate, potassium phosphate, potassium metaphosphate are used in liquid dosage forms.

(4) Chemical Stabilisers: Buffers and antioxidants are the two major chemical stabilisers used in liquids. As described above, buffers are used for adjusting drug solubility and chemical stability.

Antioxidants are added in pharmaceutical product to prevent deterioration by oxidation. Water soluble antioxidants like sodium metabisulphite, sodium sulphite are used at a concentration of 0.01 to 1%. EDTA (ethylenediamine tetraacetic acid or edetic), ascorbic acid,

citric acid form complex with metal ions that otherwise catalyse oxidation reactions. These are used alone or in combination with other antioxidants in concentrations of 0.005 to 0.1%.

(5) Preservatives: Water is the main source of microbial contamination and as growth media. Water soluble and orally safe preservatives are used in liquid orals. In liquid orals, benzoic acid and sodium benzoate (0.1 to 0.2%), ascorbic acid and its salt (0.05 to 0.2%) are used in liquids having pH upto 5. A combination of methylparaben (methylhydroxybenzoate) and propylparaben (Propylhydroxybenzoate) in the ratio of 9:1 that is 0.2%: 0.02% w/v is extensively used in typical concentrations of 0.1 to 0.2% up to pH 7.

In addition to these preservatives, preservatives like benzalkonium chloride, phenyl mercuric nitrate are used in products for external use.

(6) Viscosity enhancing agents: In addition to colouring the clear solution, viscosity is increased to gives 'body' to the liquid. The viscous liquids due to their slow pourability also help for accurate measurement of liquid with the help of a 5ml spoon. Flavours built up in viscous liquid prolong the pleasant feel in mouth, called mouthfeel effect. Both natural and synthetic thickening agents have been used for this purpose but the latter gives more reproducible results and is stable. It includes non-ionic hydrocolloids like methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose; ionic hydrocolloids like sodium carboxymethylcellulose, sodium alginate etc. Liquids prepared using syrups may not require additional thickening agents.

(7) Organoleptic additives: The term flavour is the combined effect of taste, odour and feel. Without odour most of the substances would lack their taste appeal; plus association with a colour improves the sense of palatability. Organoleptic additives are employed to promote appearance and palatability of pharmaceutical formulations.

(i) Flavours: These include fruit juice, flower essence and volatile principles from natural or synthetic source. Natural flavours are obtained from aromatic herbs and spices like anise, cardamom, lemon, orange, peppermint, clove, lavender etc. They are available as volatile oils, extracts, tinctures, spirits and aromatic waters. Vanillin, ethyl vanillin cinnamaldehyde are the artificial flavouring agents. The oily principles are used in the form of aromatic water, emulsions (e.g.peppermint water or peppermint oil emulsion) or dissolved in co-solvents. Flavoured syrups like orange syrup, lemon syrup and fruit juices have more pleasing appeal.

(ii) Colours: Selection of colour that matches the flavour is the usual practice to improve palatability of a medicinal product. The water soluble certified colouring agents are colours of choice. For internal use, colours from FD & C and D&C category are used while for topical preparations External D&C and FD& C category

colours are used. Allura red AC (FD&C red #40), (Indigo carmine (FD&C blue #2), Brilliant blue FCF (FD&C blue #1), Fast green FCF (FD&C green #3), Erythrosin (FD&C red #3), (Tartrazine) (FD&C yellow #5), sunset yellow (FD&C yellow #6) are the most exclusively used water soluble colours. Caramel or burnt sugar is used to produce pale yellow to dark brown colours; other colours include natural colours like riboflavin, saffron, indigo, etc.

(iii) Sweetener: Sweetening agents used in medicines are obtained naturally or artificially. These can be categorised as

(a) Sugars: Sucrose, fructose, glucose, invert sugar, syrup.

(b) Polyhydric alcohols: Sorbitol, mannitol, xylitol, glycerine.

(c) Artificial sweeteners: Sodium or calcium saccharin, sodium cyclamates, aspartame, acesulfame-K.

Usually syrup is blended with fruity flavour and matching colour to formulate liquid orals.

(8) Miscellaneous additives: Eye drops, ear and nasal drops like preparations directly come in contact with biological membrane, therefore to make them isotonic, tonicity adjusting agents like sodium chloride are included. Isotonic solutions are less irritant.

Questions for Self-Study

- Give examples of buffers, antioxidants and preservatives used in linctus.
- Write advantages and limitations of water as vehicle for pharmaceutical liquids.
- Which are the methods used to improve drug solubility. **(PU 2012)**
- Describe the aqueous vehicles used in oral solutions.
- Write applications of alcohol and glycerine in oral and external liquid dosage forms.
- Describe non-aqueous solvents used in oral solutions.
- Write role of buffers in monophasic liquids.
- Discuss methods used for improvement of drug solubility. **(PU 2010)**
- Discuss physicochemical stabilizers used in monophasic liquids.
- Enlist examples of colours used in oral solutions.
- Write a short note on Formulation additives in solution. **(PU 2014)**
- Discuss organoleptic additives used in monophasic liquids.
- Define monophasic liquid dosage form. Explain in detail formulation of monophasic liquid dosage form. **(PU 2009)**
- What are solutions? Explain various methods to improve the solubility of poor water soluble drugs. **(PU 2013)**
- Discuss the formulation of solution state liquid formulations.

6.3 TYPES OF SOLUTION STATE LIQUID DOSAGE FORMS

(For convenience the solution state liquid dosage forms are categorised on the basis of route of administration. Some additional types of dosage forms viz, oral solutions, oral drops, gargles, topical paints are also included in this chapter with intention of providing a complete study of a particular dosage form. The liniments and lotions can be formulated as solution, suspensions or emulsions and injections are sterile products; these will be studied under different subjects. Aromatic water is covered under excipients).

6.3.1 For Oral Administration

(1) Syrups

(a) Application of syrup as a dosage form

Syrup is a pleasant means of administration of drugs particularly to children. The sweetness, flavour and mouthfeel produced by syrup reduce any reluctance on the part of the child to take the medicines. Viscosity of the syrup slowers the rate of diffusion of drug and thus the portion of a drug that is actually in contact with taste buds is comparatively very small. Thus the major portion of drug present in the syrup gets carried down the throat. Thus, concealment of disagreeable tasting drug by the syrup is easier way of improving palatability of oral liquids.

(b) Composition of Syrup as dosage form

- The solvent used in syrup type of dosage forms is mostly Syrup IP.
- Drug to be dissolved in syrup should be freely soluble in water. Because of saturation, syrups have low solvent capacity than purified water.
- Due to high osmotic pressure, syrups are self-preservatives. Accordingly, 1 g sucrose preserves 0.54 to 0.63 ml of water. If the water content in the formula is higher than this ratio, other preservatives like methyl paraben, benzoic acid, and sodium benzoate should be included in syrups. Sorbitol, propylene glycol or glycerine can be used as co-solvents; additionally these have the capacity to preserve equivalent amount of water, to minimise evaporation of water, to prevent precipitation of sugar and lend more pleasantness to the liquid.
- Sorbitol syrup USP which contains 64% sorbitol is also mixed with sucrose based syrup to reduce concentration of sucrose.
- In place of syrup IP, invert syrup may be used as a base, which is sweeter than the syrup.
- Artificial syrups, which are devoid of carbohydrates, are the best alternative for diabetic patients.
- Flavoured syrups like orange syrup, raspberry syrup are more pleasant. The pinkish coloured syrups with strawberry, raspberry, orange flavour and sweet are more common.

(c) Precautions and contraindications

Sucrose based syrups are not suitable for diabetic patients and children due to glycogenic properties and cariogenic (tooth decaying) properties of sucrose, respectively.

(d) Method of Preparation of syrups

- **Syrup preparation:** Almost all the oral liquids contain sugar as a sweetener and dissolution of drug in syrup is one of the steps in manufacturing liquids. Sucrose is added in boiled and purified water and gradually heated to get a clear solution or any other method described under chapter 'Pharmaceutical excipients'.
- **Mixing with the aid of heat:** Mixing with the aid of heat assists dissolution of some drugs or additives. Inherent solubility of drug or additives, particle size, surface area, crystallinity and wettability of solute components influence the rate of dissolution. Accordingly, the solution is prepared with or without the aid of heat.
- **Drugs addition:** Heat-stable drugs can be added in the hot syrup, the mixture is allowed to cool and volume is adjusted by adding purified water. Heating also facilitates rapid dissolution of drugs. However, excess heating may cause inversion of syrup.
- **Heat-labile drugs and additives:** Thermolabile drugs, alcohol and volatile ingredients are added in the syrup after its cooling to room temperature.
- **General process:** Usually ¾th of the vehicle is used to dissolve the drug to produce drug concentrate. Part of remaining vehicle is used to obtain additive concentrate, where other soluble and miscible additives are dissolved. The latter is added in the drug solution along with stirring. The resultant solution is subjected to filtration. Volatile additives including flavouring agents are usually added in the solution just before filtration to reduce their evaporation. The remaining amount of solvent is used for rinsing the vessel, passing through filter press and the volume of filtered solution is made using the same.
- **Equipments:** Monophasic liquids are prepared by mixing soluble solids or miscible liquids with another liquid, usually water, to produce a single-phase homogeneous mixture. Such mixing occurs by diffusion, and it is termed as blending. It does not require a high level of shear. Simple stirring is enough for lab scale, and on a large scale, propeller mixers are preferred.
- Jacketed vessels are employed for dissolution with the aid of heat. Drugs are dissolved in a manufacturing vessel and the additive concentrate is made in another small vessel of sufficient capacity.
- The vessels should be of about 10% excess capacity than the actual volume of the product. This can accommodate any increased volume of liquid mixture due to dissolution of drug, heating or air entrapment.

(e) Containers: Plain or amber coloured glass or plastic bottles with closable child resistant closures are used for liquid orals.

- Traditionally, glass bottles are the choice of containers but due to their fragile nature, cost and weight these are replaced by high density polyethylene containers.
- The volume of bottles is generally 30 ml, 45 ml or 60 ml and sometimes it may be 10 to 15 ml or 100, 200 or 450 ml depending on the dose of the liquid medicament.
- A 5ml measuring spoon/calibrated cap is supplied with liquid orals.

(a) Storage conditions: Liquid dosage forms are mostly stored in a cool place (8 to 30^{o}C) and away from direct sunlight.

(b) Label: The composition for drops and syringes should state the drug content per millilitre and for other liquid orals it should be in terms of each 5 ml.

(c) Examples

- Syrup PACIMOL (IPCA), CROCIN (Duphar), FEBREX (Indoco): Paracetamol 125 mg/5 ml. Analgesic, antipyretic.
- FLUZET Syrup (Ranbaxy): Dextromethorphan, paracetamol, phenyleprine HCl, chlorpheniramine maleate as expectorant;
- DEXORANGE (Franco-Indian): Haematinic formula.

Preparation 6.1

Vasaka Syrup IP

Vasaka Liquid Extract	—	50 ml
Glycerin	—	10 ml
Syrup, to make	—	100 ml

Principle: Vasaka is a crude drug. It consists of fresh or dried leaves of *Adhatoda vasica* i.e., Adulsa. Vasaka liquid extract is an alcoholic extract. To avoid precipitation of alcohol soluble components, before mixing with water, it is mixed with glycerine.

Method: Use a tared container. Mix vasaka liquid extract with glycerine. Add syrup to make final volume.

Container and storage: Pack in glass/plastic bottle. Store in tightly closed containers. Use within two weeks.

Category and Dose: Expectorant, 2 to 4 ml.

Label: Alcohol: 15 -18 % v/v.

Precautions: Avoid administering to diabetic patients. It is caloric and cariogenic. It is better to avoid giving it to paediatric patients since it contains 15-18 per cent v/v of alcohol.

Examples:

DANGIDULSA COUGH MIXTURE (Dangi Labs) and TULSIYUKTA ADULSA SYRUP (Amrut Pharma).

Preparation 6.2

Chorpheniramine Maleate Syrup USP

Chlorpheniramine Maleate	40.0 mg
Glycerine	2.5 ml
Syrup	8.3 ml
Sorbitol solution	28.2 ml
Sodium benzoate	0.1 g
Alcohol	6.0 ml
Water, colour, flavour, to make,	100.0 ml

Principle: CPM is H1 receptor antagonist (antihistamine) that has been widely indicated for the treatment of allergic conditions like rhinitis, common cold and nasal decongestion and also in allergic rashes, insect bites etc. It is used alone or in expectorants/cough formulas.

CPM is freely soluble in water and in alcohol. Sorbitol and glycerine are used as viscosity enhancers and for smoothening effect in throat. Syrup is the sweetener and sodium benzoate is the preservative.

Method: Dissolve the drug in sufficient amount of water. Add alcohol, glycerine and sorbitol solution. Add sodium benzoate and stir well to dissolve. Filter the solution, rinse filter paper and adjust final volume with remaining amount of water.

Container and storage: Store in a well closed container in a cool place.

Category: Anti-allergic and dry cough.

Adult: 10 ml, 3 to 4 times a day.

Child: 1-2 years- 2.5 ml twice a day, 2-5 years - 2.5 ml 3 to 4 times a day, 5-12 years - 5 ml 3 to 4 times a day.

Label: Patient should be cautioned not to drive a vehicle or handle heavy machinery as it may cause drowsiness.

Caution: It is dangerous to take this medicine except under medical supervision.

Examples: CAPEX Expectorant (Seagull): CPM with ammonium chloride. PIRITON CS COUGH SUPPRESSANT (GSK): CPM with Dexamethorphan HCl.

(2) Elixir

(a) Application of Elixir

Elixirs are clear sweetened and flavoured hydro-alcoholic solutions for oral use. Drugs with poor water solubility are formulated in elixir form as monophasic systems. The elixirs are less sweet as compared to syrups. Non-medicated elixirs, such as aromatic elixirs and iso-alcoholic elixirs are mainly used as flavoured vehicles.

(b) Composition of Elixir

- Alcohol content in elixirs varies from 10 to 40% depending on the solubility of a particular drug. It should be less than 10% in oral liquids and further less in paediatric dosage forms.
- An amount of alcohol can be reduced using polyhydric alcohols like glycerine or propylene glycol.
- Due to limited solubility in alcohol, sucrose cannot be used in large amounts. In such preparations sodium saccharin can be used.
- Addition of volatile oils as flavouring agents is easier than its incorporation in syrups.
- Preservatives may not be required in elixirs containing more than 10% v/v alcohol.

(c) Precautions and Patient Counselling

- Due to the presence of alcohol, elixirs are not preferred for paediatric use.
- Dilution of elixir with water may leads to precipitation of drug. Therefore, it is recommended to swallow a dose of the elixir followed by drinking of water.

(d) Method of Preparation of Elixir

Elixirs or other alcohol containing solutions are prepared to bring about solution of water insoluble drug with help of alcohol. According to the solubility of drugs, these are dissolved separately either in aqueous phase or alcohol. The resultant drug solution in alcohol is gradually added into the aqueous solution under continuous stirring. Most of the time, elixirs appear cloudy initially due to separation of dissolved drug. Therefore, these should be allowed to stand for sufficient time to attain maximum dissolution till saturation. The separated un-dissolved solid or immiscible liquid is then filtered to get a clear solution. Addition of polyhydric alcohol increases solvent capacity but increases viscosity also. A filter aid like talc may be dispersed in the mixture to assist removal of the un-dissolved components.

Follow the procedure of preparation of syrup without aid of heat. The containers and storage conditions are same as described under syrup.

(e) Examples

- BRONCORDIL ELIXIR (USV): Theophylline 80 mg/ml. It is an antiasthamatic.
- BROMHEXINE ELIXIR (Ipca): Bromhexine HCl 4 mg per 5 ml. It acts as a mucolytic.
- RUBRAPLEX (Sarabhai): Elemental iron 114 mg, and vitamin B. It is used in the treatment of anaemia.

(3) Linctus

(a) Application of Linctus

Linctuses are viscous syrups based monophasic liquids employed for the treatment of cough with additional property of soothing actions on the inflamed throat.

(b) Composition of Linctus

- Linctuses mostly contain a sedative or an expectorant drug and the vehicle has a demulcent or soothing action on the sore mucous membrane of the throat.
- Syrups having an expectorant action, such as Tolu Syrup is most preferred as a vehicle.
- Glycerine and sorbitol syrups are used for their soothing effects.
- Sugar free linctuses can be formulated using polyols or artificial syrup.

(c) Precautions and advice

- Linctuses are sipped and swallowed slowly without the aid of water.
- Do not drink water along with or immediately after administration.
- These should be prescribed with precaution for diabetic patients.

(d) Method of Preparation

Linctuses are prepared using methods described for syrup type of dosage form.

(e) Examples

- COSCOPIN LINCTUS (Biological E): Noscapine, chlorpheniramine maleate, citric acid, sodium citrate, ammonium chloride.
- ZEET LINCTUS (Alembic): Dextromethorphan HBr, guaifenesin, phenyl propalamine HCl.
- MITS LINCTUS CODEINE CO (Astra/Zeneca), COMTUS LINCTUS (Comed) and ZEET LINCTUS (Alembic): Codeine Linctus IP for dry irritating cough.

Table 6.1: Differences in Syrup, Elixir and Linctus

Sr. No.	Syrup	Elixir	Linctus
1.	Nearly saturated aqueous solution of sucrose containing dissolved drugs	Hydroalcohic solution of poorly water soluble drugs	Drug dissolved in viscous syrupy base containing soothing agents.
2.	Sweet and flavoured	Less sweeter than syrup	Sweet with cooling and demulcent effect.
3.	Suitable for drugs having free water solubility. Syrups have poor solvent action than water	Drugs with slight aqueous solubility are formulated using alcohol	Drug should have sufficient solubility in syrup and polyols used in the formula

Sr. No.	Syrup	Elixir	Linctus
4.	Due to palatability it is the choice of liquid for paediatric patients, irrespective of drug category	Not recommended for paediatric use and non-alcoholic patients	Indicated in cough therapy for additional soothing effect on the inflamed throat
5.	Dose of 5ml or few drops is swallowed with water or after mixing in water.	The dose should not be diluted with water. Drink water after swallowing a dose of elixir.	Immediate drinking of water should be avoided

(4) Liquids/Mixtures

(a) Application of Liquids/ Mixture

Solutions for oral administration are also called and as 'Mixture' or 'Liquid'. These are basically for adult patients.

(b) Composition and method of preparation

These include almost all common excipients needed for oral solutions. However, these are comparatively less sweetened, less viscous and clear-light shade in appearance. Oral liquids are prepared as per general method for syrups described above.

(c) Example

- Solution BAMBUDIL (Cipla): Bambuterol HCl, antihistaminic in persistent reversible airways obstruction
- Liquid ASTHALIN Expectorant (Cipla): Salbutamol, Guaifenesin
- FORHEM Liquid (Trigenesis). It is a multivitamin
- CITRALKA (Pfizer): Disodium hydrogen citrate. It is used as urinary alkaliser.

Formulation 6.3

Aqueous Iodine Solution IP	
Iodine	5.0 g
Potassium Iodide	10.0 g
Water, freshly boiled to make & cooled	100.0 ml

Principle: Synonym is Lugol's solution. Iodine is essential for the formation of thyroid hormones. Oral iodine solution is also used as an antidote in alkaloid poisoning. Orally, it irritates the GI tract and should be diluted well with water or milk. Iodine is insoluble in water. Potassium iodide is used to increase solubility of iodine through formation of water-soluble complexes, KI_3.

Method: Dissolve potassium iodide and iodine in sufficient amount of water. Filter the solution. Rinse the beaker with water and filter it in the same solution. Adjust the final volume with remaining water.

Container and storage: Store in iodine resistant container. Cork type of closure must be avoided. Dropper or dosing syringe may be supplied. Store in a tightly closed container. Use within a week.

Category and Dose: Oral as source of iodine, 0.1 to 0.3 ml three times a day daily well diluted with milk or water.

Patient advice: For oral use, dilute with milk or water. Iodine is staining, handle with care. Avoid during pregnancy and in lactating mother. May cause allergic reaction, not dispense to hypersensitive person.

Formulation 6.4

Magnesium Citrate Oral Solution USP	
Magnesium Carbonate	15.0 g
Citric acid anhydrous	30.0 g
Syrup	60.0 ml
Lemon oil	0.1 ml
Sod./Pot. bicarbonate	2.5 g
Purified water, to make	350.0 ml
Talc	5.0 g

Principle: This is an example of solution type of dosage form prepared by chemical reaction, where magnesium citrate, the therapeutically active ingredient is formed as follows:

Magnesium carbonate + Citric acid = Magnesium citrate + carbon dioxide + water.

The composition is commonly referred as 'citrates' is a saline laxative. Palatability of the citrates is a unique criterion for acceptance which develops due to sweetness of syrup, sourness of lemon oil and carbon dioxide. The carbonation is also essential for chemical stability of the product that is further achieved by addition of sodium or potassium bicarbonate.

Sodium/Potassium bicarbonate + Citric acid = Sod./Pot. citrate + Carbon dioxide + water.

To avoid a violent reaction and to minimise loss of carbon dioxide, a tablet of alkali carbonate can be placed in a final container or carbon dioxide can be filled under pressure. Boiling, pasteurisation or even sterilisation is done to control microbial contamination of the product. Refrigeration adds further pleasantness.

Talc acts as a distributing agent to lemon oil and as filter aid.

Method

Add magnesium carbonate to 100 ml of water. To this, add a solution of citric acid made in about 150 ml of water.

(i) Add syrup to the above mixture and boil.
(ii) Triturate lemon oil with talc and add this in hot mixture and stir well.
(iii) Filter the mixture into an air tight type of bottle (beverage bottle is more preferred) with mark of final volume. Add boiled water to make-up the volume.
(iv) Cool the solution and add alkali carbonate. Tight the bottle and shake it to dissolve the alkali carbonate.

Container and storage: Pack in air tight beverage bottle. Store in refrigerator.

Category: Laxative. Dose 200 ml.

(5) Paediatric Drops

(a) Application of oral drops

For paediatric patients, the dose liquid dosage forms is less than 5 ml, therefore for more accuracy these are administered with the help of a dropper. The dropper is either graduated in fractions of a millilitre, or is pre-calibrated so that the number of drops delivered by it are equivalent to the prescribed dose.

Recently, oral syringes have been introduced in place of drops. The prefilled calibrated syringe not only ensures accuracy of dosing but improves ease of administration, handling and storage and minimises product loss and contamination.

(b) Composition of drops

The formulation and method of preparation of Oral drops is almost the same as syrups. However, they contain higher drug content per millilitre. Therefore, for slightly soluble drugs the formulation of drops may contain special additives like polyhydric alcohol, solubilising agents etc to enhance their solubility.

(c) Examples

- METACIN DROPS (Themis): Paracetamol
- AROVIT DROPS (Roche), multivitamin
- CONTUS PAED Drops (Stedman) for cough
- CLAVITROL PD (Astra-Zeneca): antibiotic.

(6) Galenical Preparations (Gripe Water)

(a) Application of Galenical preparation: Galenical preparations contain extracts of crude drugs from plant origin. It may be extract from organised part of a plant like root, bark etc or unorganised product like gum, exudates, oil etc. Depending on pharmacological action of the extracts these are used for various indications usually in the form liquids like Tinctures, Liquid extracts, Asava, Arista, etc.

Gripe water is commercially available solution state liquid dosage of this class.

(b) Composition

These are clear solutions of carminative principles like oils or tinctures of aromatic crude drugs. Alcohol present in tinctures or additionally small amount of alcohol is used to ensure complete solubility aromatic principles. Syrup is generally used as base to improve palatability.

(c) Precautions

Due to alcohol content these are used in paediatric patients with caution.

(d) Method of Preparation

General method for preparation of elixirs.

(e) Examples

Syp. CARMICIDE (Indoco): Each 5 ml of syrup contains sodium citrate 70 mg, citric acid 35 mg, tincture zingiber 0.04 ml, tincture cardamom aromatic 0.04 ml, tincture cinnamon 0.04 ml, Alcohol 0.125 ml.

Formulation 6.5

Gripe Water

Tincture cardamom aromatic BPC	0.8 ml
Tincture cinnamon	0.8 ml
Citric acid	0.7 mg
Sodium citrate	1.4 g
Alcohol (90%)	2.5 ml
Syrup, to make	100.0 ml

Principle: Tincture cardamom aromatic, BPC, contains cardamom oil (0.3 %v/v), caraway oil, cinnamon oil, clove oil (each 1%v/v) and strong ginger tincture (6 %v/v) in alcohol. Citric acid and sodium citrate adds tartness and give natural feel and it acts as an antioxidant. These preparations are effective for digestive disturbances in infants, chronic diarrhoea, flatulent colic due to indigestion and poor appetite. For infants, non-alcoholic preparations can be formulated using volatile oils.

Category and dose: Flatulence and griping in infants and children. Adults, 5-10 ml; Infants, 2.5-5 ml; Children 5-10 ml; three times a day.

Examples:

- CATALYD DROPS (Duckbill): Each 1ml suspension contains, diastase (1 : 800) 50 mg, papain 30 mg, cinnamon oil 0.2 mg, caraway oil 0.4 mg, cardamom oil 0.4 mg.
- VITAZYME DROPS (East India): Each 1 ml contains, fungal diastase (1 : 2000) 20 mg, cinnamon oil 0.2 mg, caraway oil 0.4 mg., cardamom oil 0.4 mg.

Questions for Self-Study

- Write merits and demerits of syrup type of oral liquids.
- Write general composition of medicated syrups.
- Differentiate between elixirs and syrups.
- Define linctuses. Write their usefulness in expectorant formulations.
- Write a short note on paediatric drops.
- Discuss formulation of Linctus. **(PU 2010, 2014)**

- Suggest suitable containers, storage and label conditions for liquid dosage forms.
- Discuss formulation and manufacturing process involved in oral preparations. **(PU 2010)**
- Write short note on syrup as dosage form.

- What are solutions? Explain methods of preparation of solutions and factors affecting rate of solution. **(PU 2011)**
  (Factors affecting rate of solution will be part of chapter 'Dissolution and solubility' under subject Dosage Form Design at Semester II).
- What are the factors affecting rate of solution? Explain the manufacturing process involved in liquid oral preparations? **(PU 2012)**
  (According to the syllabus, Manufacturing of liquid is covered under Pharmaceutics -II).

6.3.2 Oral-Topical Liquids

(1) Mouthwashes and Gargles

(a) Application of Gargles

Gargles are clear solutions used in posterior region of mouth by agitating the solution with expired air to produce local effect in the throat and these are not to be swallowed in large amounts. Gargles are used to relive soreness in mild throat infections and most of these have a deodorant effect.

Application of Mouthwash

Mouthwashes are clear solutions intended to be used in the front of the uvula to clean and refresh the mouth.

They are also used in treating diseased state of oral mucous membrane. Although mouthwashes are considered as a separate class, many of these are used as gargles, either as such or after dilution with warm water. However mouthwashes have more cosmetic value and are used to maintain oral hygiene whereas gargles are highly medicated.

(b) Composition of Mouthwash and Gargles

The commonly used active ingredients include antiseptics, analgesics, astringents and alkalising agents. Astringent helps to restore tune of relaxed throat and also relives dryness

by stimulating salivation. Glycerine is choice of vehicle for gargles, the reasons for which are as follows:

(a) Due to viscosity, it keeps medicament in contact with the membranous lining of the throat for a long period

(b) Acts as a demulcent

(c) Sweet taste of glycerine with aromatic substances in gargle give characteristic flavour and

(d) Aqueous solubility of drugs increases.

The external liquids may be packed in colourless or have brownish, greenish shade for identification.

(a) Precautions and Patient counselling

Since most gargles are concentrated solutions, prescribed amount of it is diluted with warm water for gargling. If gargle is indicated as mouth wash then dilution ratio should be instructed. Not to be swallowed in excess. For external use only.

(b) Examples

Proprietary Preparations: Gargle and mouthwash

- Betadine Gargle (Win Medicare), Wokadine Gargle (Wockhardt): Piodin Mouthwash (Biddle Sawyer): Povidone Iodine.
- Proflo Mouth wash (Sandika Pharma): Sodium fluoride.
- Tantum Oral Rinse (Elder): Benzydamine.

Table 6.2: Difference between gargle and mouthwash

S.N.	Gargles	Mouthwashes
1.	Gargles are used in posterior region of mouth by agitating the solution with expired air to produce local effect in throat.	Mouthwashes are intended to be used in the front of the uvula to cleans and refresh the mouth.
2.	These are used to relive soreness in mild throat infections and most of these have deodorant effect.	These clean and refresh the mouth.
3.	Gargles are comparatively medicated.	Mouthwashes have more cosmetic value.
4.	Gargles after proper dilutions are recommended as mouth wash.	These are comparatively dilute than gargles.

(2) Mouth /Throat/Gum Paints

(a) Application of Paints

Paints are viscous preparations of medicaments for local action in the mouth (mouth paint), pharynx (throat paint) and gum (gum paint). They are applied to the throat with a brush.

(b) Composition of Paints

- Iodine is particularly used in treatment of pharyngitis and tonsillitis, gentian violet in treatment of oral candidiasis (thrush), whereas tannic acid is used to relive a sore throat.
- The common ingredients used in throat paints are anti-infective agents like phenol, iodine, gentian violet, boric acid, borax and astringents like tannic acid.
- Astringent and antiseptic compositions are also used as gum paints to prevent gum infection and for strengthening them.
- Vehicle of choice is glycerine. Because of viscosity, it is prevented from being washed away rapidly by saliva; and thus prolonged action is obtained.

(c) Precautions and Patient counselling

For external use only. Not to be swallowed in large amount. Apply with brush in throat.

Do not drink water immediately after application.

(d) Examples

The Mandl's Paint is official in NFI, in which iodine acts anti-infective, Potassium iodide and alcohol help to dissolves iodine. Mentha oil is the flavour and glycerine is the viscous vehicle used. Proprietary gum and throat paints based on this are:

- Liq. GUMEX (Pharmadent, Valsad): Potassium iodide, iodine, tannic acid, menthol, thymol, camphor, mentha oil, clove oil, zinc phenol sulphonate phenol glycerine.
- SENSOFORM Paint (Warren Pharma): Tannic acid, Potassium iodide, Iodine, thymol, menthol, glycerine.
- Limaye's GUM CORRECT (Deccan Dental), TOOCHE (Litaca),
- CANDID MOUTH PAINT (Glenmark).

Preparation No. 6.6

Borax Glycerine IP

Borax	12.0 g
Glycerine	88.0 g

Principle: Borax is bacteriostatic. Glycerine is a soothing agent and its viscosity keeps drug in contact with the affected part for a prolonged period of time.

Method: Triturate the powdered borax with glycerine to produce smooth dispersion. Warm the mixture using water bath with constant stirring to get solution. Strain if necessary.

Container and storage: Store in fluted bottle. Provide brush. Store in a tightly closed container in a dry place.

Category and Direction to use: Bacteriostatic. For external use only. To be used sparingly.

Patient advice: Do not swallow. If recommended, it may be diluted with glycerine.

Preparation No. 6.7

Tannic acid glycerine Paint IP

Tannic acid	5.0 g
Sodium citrate	0.25 g
Dried sodium sulphate	50.0 mg
Glycerine	19.70 g

Principle: Tannic acid is astringent; sodium citrate and sodium sulphate are antioxidants. Glycerine is viscous sweet vehicle.

Method: Dissolve the powder in 2/3 amount of glycerine by trituration. Make up the weight with remaining glycerine. Store in a cool and dark place.

Category: Astringent for gums, throat. For external use only.

Proprietary similar preparations: LIMAYE'S GUM CORRECT (Deccan Dental), STOLIN GUM ASTRINGENT (Dr. Reddy's).

6.3.3 Liquids Ear, Nose and Throat (ENT)

(1) Ear Drops

(a) Application of Ear drops

Ear drops are solutions, suspensions or emulsions of drugs in water, glycerine or propylene glycol intended for instillation into the ear.

These are used for removal of excessive cerumen (ear wax), to treat infection, inflammation or pain and for cleaning and drying of ear.

(b) Composition of Ear drops

- Mineral oil, vegetable oil and hydrogen peroxide have been commonly used as agents for removal of ear wax.

- Drugs used topically in the ear include analgesics, antibiotics, and anti-inflammatory agents.
- The vehicles most often employed for ear drops are glycerine, propylene glycol and liquid polyethylene glycols. Their viscosity permits the drug to remain in contact with ear canal for a long time. Anhydrous glycerine, being hygroscopic tends to remove moisture from the swollen tissue thereby reducing inflammation and reduce the moisture available for ear infection.
- The presence of moisture, macerated tissue and warm cavity provide ideal conditions for the growth of bacteria and fungi. Secondly, the secretions in the ear are fatty and immiscible with water. For these reasons aqueous solutions are usually not preferred for otic use.
- Ethanol and isopropyl alcohol are also useful solvents for irrigating the ear canal.
- These include preservatives such as chlorobutanol, thiomerosal and combination of methyl and propyl paraben.

(c) Precautions and Patient counselling

The patient is instructed to tilt the head to the side and specified drops are instilled into ear. Cotton plug is placed to retain the medication in ear for 15 to 30 minutes. Also advise the patient to remain in this position for a few minutes so the drops do not run out of the ear. It is also advisable to roll the bottle in hand before administration to make it warm.

(d) Examples

- BETNESOL EAR DROPS (Glaxo Pharma): Betamethasone.
- CHLOROMYCETIN EAR DROPS (Parke-Davis): Chloramphenicol, benzocaine.
- CIPROBID E/E Drops (Cadila Healthcare): Ciprofloxacin.
- GARAMYCIN E/E Drops (Fulford): Gentamycin .

(2) Nasal drops and sprays

(a) Application of Nasal Solutions

Nasal solutions are aqueous monophasic liquids, rendered isotonic and slightly buffered to maintain a pH of 5.5 to 6.5.

Nasal solutions are administered as nasal drops or sprays to relieve nasal congestion, inflammation and to combat infection.

(b) Composition of Nasal Solutions

- It contains drug like antihistaminic, sympathomimetic agents (vasoconstrictors) and antibiotics.

- Oily solutions are not preferred, especially mineral oil has been proved to cause lipoid or oil inspiration pneumonia. Oils also interfere with normal ciliary action.
- A vehicle for nasal solution should be isotonic with mild buffer capacity. It should not modify mucus viscosity and normal ciliary motion.

(c) Precautions and patient counselling

(i) Before using nasal drops, wipe mucous away from the nose.

(ii) Advice the patient to lie down on a flat surface with the head over the edge of bed to keep the head lower than the shoulders. Insert dropper pipette a little way into each nostril and apply prescribed number of drops.

(iii) The patient should remain in this position for few minutes.

(iv) Nasal spray: It should always be administered with the patient in an upright position.

Spraying the solution with the head over the edge of a bed could result in the systemic absorption of drug. The excessive and/or repeated use of these preparations, especial decongestants, can result in a rebound hyperaemia or congestion rebound. This secondary effect is worse than the original congestion. Therefore, the pharmacist should advice the patient to use the nasal drops or spray sparingly, preferably only 2 or 3 times a day. In rebound effect, the patient is advised to withdraw application of solution in only one nostril. The complete withdrawal of the dose may cause total nasal obstruction because of bilateral vasodilatation. Once the rebound congestion subsides in the drug free nostril, within about 1 to 2 weeks, a total withdrawal is then instituted.

(d) Examples

- OTRIVIN Nasal Drops (Novartis), DECON (Cadila Pharma): Xylometazoline HCl in an aqueous isotonic solution.
- EFCORLIN NASAL Drops (Glaxo): Hydrocortisone, naphazoline nitrate.
- 3) Throat Preparations: Gargle and throat paint are used for local action in throat.

6.3.4 Solutions for Rectal Administration

Enema

(a) Application of Enema

Enemas are aqueous or oily solutions, suspension or emulsions of medicaments intended for rectal administration to cause bowel evacuation or to bring about local or systemic therapeutic action.

Enemas can be broadly of two types:

1. Evacuate enemas (cleansing enemas): Evacuate enemas are employed to cleanse the bowel or for x-ray examination of the lower bowel. The volume of evacuate enema to be administered may be as much as one litter.
2. Retention enemas: Retention enemas are used for local or systemic medicinal effects and their volume do not normally exceed 100 ml. These are very much suitable for patients in whom the oral route must be avoided because of age, mental status or physiological condition. They are especially helpful in infants and geriatric patients who have difficulty in swallowing.

(b) Composition of Enema

The cleansing enema contains drugs like soft soap, glycerine, sodium chloride, docusates in solution form. Mesalazine and hydrocortisone are formulated as retention enema for their anti-inflammatory drug action in ulcerative colitis. The latter is available in market as foam.

(c) Precautions and advice

Evacuate enemas should be warmed to body temperature before administration. If the enema is too cold, intestinal cramping may occur, and if is too hot, it may damage the intestinal mucosa. The patient should be guided for use of enema. The patient should lie on one side with knees bent. Lift buttock during administration of enema and he should remain there for 20-30 minutes.

(d) Method of Preparation

Solution of enema is prepared as per general method described above. Enemas should be packed in coloured, fluted, screw capped glass bottles. Recently several plastic squeeze bags with rectal nozzle have been introduced for administration of enema. The unit dose, disposable polythene or PVC bags sealed to a rectal nozzle are more convenient to administer enema.

(e) Examples

Evacuate enemas

- LAXICON ENEMA (Stadmed): Docusates. It is used to provide relief from constipation.
- NEOTOMIC ENEMA (USV): Glycerine, sodium chloride. It is used to provide relief from constipation.

Retention enemas

- LIQ-MESACOL ENEMA (Sun Pharma): Mesalazine. It is used as an anti-inflammatory drug.
- ENTOFOAM (Cipla): Hydrocortisone acetate in aerosol foam. Ulcerative colitis.

Questions for Self-Study

- Differentiate between gargle and mouthwash.
- What are paints? Write composition and applications of some official paints.
- Suggest vehicle for ear drops.
- Discuss formulation and label conditions for ear drops.
- What are nasal drops and nasal sprays? Justify the suitable vehicle and way of instillation of them.
- Write suitable vehicle for ear drops and nasal drops.
- Write patient counselling points for proper use of nasal solutions.
- Differentiate between cleansing enema and medicated enema.
- ❖ Discuss various ENT dosage forms.
- ❖ Define solution. Explain methods of Preparation of Solution. **(PU 2014)**

(Expected is Solution state dosage form. Solution as physical state is part of DFD).

6.3.5 Topical Preparations

Solutions and sprays are applied topically for cleansing, antiseptic, anti-inflammatory purpose. These are not mentioned in the theory syllabus but are mentioned in practical.

Preparation No. 6.8

Tincture Iodine / Weak Iodine Solution IP

Iodine	2.0 g
Potassium Iodide	2.5 g
Alcohol (50%), to make	100.0 ml

Principle: Tincture iodine is a synonym for Weak Iodine Solution IP. Externally, iodine is used as an antiseptic and skin disinfectant to clean superficial wounds. Iodine is soluble in 13 parts of alcohol and alcohol also acts as antiseptic and skin disinfectant. But alcoholic disinfectants are more painful.

Method: Dissolve potassium iodide and iodine in sufficient amount of alcohol (50%). Filter the solution. Rinse the beaker with the alcohol and filter it in the same solution. Adjust final volume with the remaining alcohol.

Container and storage: Store in a fluted iodine resistant container. Closure of cork must not be done. Store in tightly closed container in a cool place. Use within a week.

Category and Dose: Antiseptic and skin disinfectant.

Label: For external use only.

Patient advice: Keep away from open flame.

Preparation No. 6.9

Cresol with Soap Solution I.P

Cresol	50.0 ml
Vegetable oil	18.0 ml
Potassium Hydroxide	10.0 ml
Orange Oil	4.2 ml
Water, freshly boiled and cooled, to make	100.0 ml

Principle: Synonym is Lysol. Cresol is a bactericide and germicide. The presence of vegetable oil, glycerine reduces harsh effect of cresol. Fixed oils, alkali hydroxides or soap and glycerin are good solvents. Soaps make the preparation clear but are of reduced antimicrobial activity. Lysol has been the choice of disinfectant for hospital use.

Method: Dissolve potassium hydroxide in ¼th volume of water. Add vegetable oil and heat on water bath till oil droplets disappear. Add cresol and filter the solution. Rinse the beaker with water and filter it in the same solution and adjust final volume.

Container and storage: Store in amber coloured fluted glass bottle. Store in a tightly closed container away from direct from light. Closure made-up of cork must not be used.

Category and directions for use: It is a popular disinfectant. After dilution it can be used as a disinfectant on utensils, floors, etc.

Label: For External Use Only.

Proprietary preparation: Dettol and Lysol (Reckitt Benckiser) are similar types of proprietary medicines, which contains Chloroxynenol and benzalkonium chloride, respectively.

Preparation No. 6.10

Surgical Chlorinated Soda, BPC Chlorinated lime	1.76 g
Sodium carbonate	3.52 g
Boric acid	0.375 g
Purified water, to make	100 ml

Principle: It has antiseptic and disinfectant properties. Chlorinated lime is an alkaline solution containing 30% available chlorine. It is used as household bleach, disinfectant and deodorant. But it rapidly oxidises on exposure to air. Sodium carbonate and boric acid are widely used in mouthwash and vaginal douches. Boric acid is a buffer and a weak germicide.

Method: Triturate chlorinated lime with boric acid. Then mix it with water. To this add aqueous solution of sodium bicarbonate. Shake the mixture for 20 min, allow it to stand aside for 10 min and then filter.

Container and storage: Store in an air tight container in a cool place.

Category: Topical disinfectant, washing and cleansing agent.

Label: For external use only.

In-Process Quality Control and Quality Control

The solution type of dosage forms should be checked for the following parameters.

(1) General appearance

Principle: It reveals primary integrity and general quality of the product.

Method: Visual observations about the product including colour, odour, taste, consistency, description of container and label.

(2) Clarity

Principle: The solution must be clear in appearance. The samples of liquid are taken from filling lines as well as the final product is tested for clarity.

Method: The un-labelled containers are observed under white and black background under bright light. The coloured particles, dust particle etc are visible against a white background whereas colourless undissolved particles/fibers are visible against the black-background.

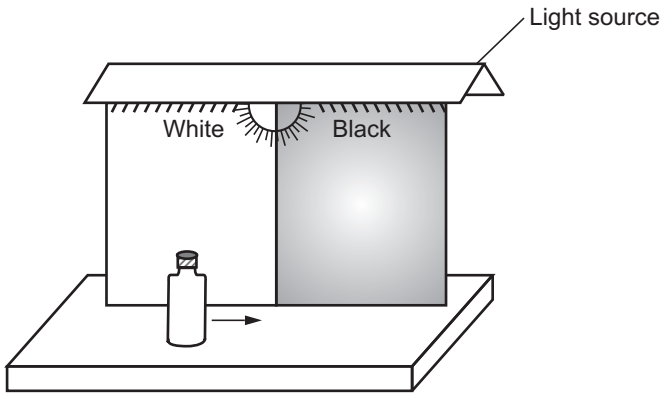


Fig. 6.1: Clarity testing

(3) pH

Principle: The oral liquids should have a pH between 3 to 6 or as stated under monograph/ approved by FDA. The pH of a solution state liquid dosage form is important for the following reasons:-

- Physiological compatibility
- Solubility for drug and additives
- Chemical stability of drug
- Effectiveness of preservative.

Method: The pH of liquid formulations is checked by pH meter.

(4) Density and Specific gravity

Principle: Density is the ratio of weight of liquid in grams to its volume in millilitres at particular temperature. It is denoted as g/cm^3.

Specific gravity is defined as the ratio of specific weight of the liquid dosage form to the specific weight of distilled water, at a particular temperature. It is compared with standard solvent (water).

Significance of density/specific gravity

- The density of solution is higher than water (solvent) due to presence of dissolved drug and additives.
- The specific gravity shows extent of increase in density of solution as compared to water, which is a solvent.
- Thus, using a specific formula, the resultant solution should show same and reproducible density /specific gravity for the randomly selected samples during manufacturing. The inter-batch or intra- batch variation in the values of density / specific gravity indicates un-uniform distribution of drug / additives.
- Air entrapment in liquid during manufacturing/foaming results in lower values of density.

Method: Specific gravity bottle or pycnometer.

(A) Specific gravity bottle is of 20 or 25 ml capacity with capillary stopper. The bottle is filled with liquid to its brim. The excess is wiped.

(i) Capacity of bottle (ml) = Mass of water/0.99602.
The value 0.99602 is the specific gravity of water at 20°C.

(ii) The weight of liquid = Weight of water/liquid in bottle with stopper - Weight of empty dry bottle with stopper.

(iii) Density of liquid dosage form = Weight of liquid (g)/ Volume of liquid (ml).

(iv) Specific gravity of liquid dosage form = Weight of liquid (g) / Weight of water (g).

(B) Pycnometer: For accurate measuring of liquid and to determine density at higher temperatures pycnometer is useful. It is a tube with close-fitted glass stopper with a thin capillary. The excess liquid runs out through it and ensures accurate filling. The remaining measurements are done using sensitive analytical balance.

(5) Viscosity

Principle: Viscosity is resistance to flow. Most of the solution types of liquid follow Newtonian flow, which flow in proportion to applied stress. Viscosity of such fluids in poise can be determined by rate of flow of liquid through a capillary (Ostwald viscometer) or rate movement of a sphere through a liquid (Hoeppler falling ball viscometer).

Viscosity of solutions is intentionally increased to give 'body' to the liquid, to increase mouthfeel effect of flavoured syrups and to control the flow rate so as to pour slowly without loss. However, viscosity should not be too high to make liquids un-pourable.

Method

(A) Ostwald Viscometer

It is official viscometer in IP. The capillary viscometer is a U shaped glass tube with a bulb on each side. The upper level bulb (C) of arm (X) is joined to a bulb at lower level (A) of arm (Y) by a capillary tube. Arm 'X' have two markings (E and F) on upper and lower side of bulb (C). A liquid sample is filled in bulb 'A' through opening of arm 'Y'. It is then sucked up to mark 'E' and held at level by putting thumb on opening of arm 'X'. Slowly, thumb is released to allow flow of liquid from point 'E' to point 'F'. A standard liquid of known density (ρ_1) and viscosity (η_1) and sample of known density (ρ_2) and unknown viscosity (η_2) are tested and the time required to flow standard (t_1) and sample (t_2) between the markings is noted.

$$\eta_2 = \eta_1 (\rho_2 t_2 / \rho_1 t_1)$$

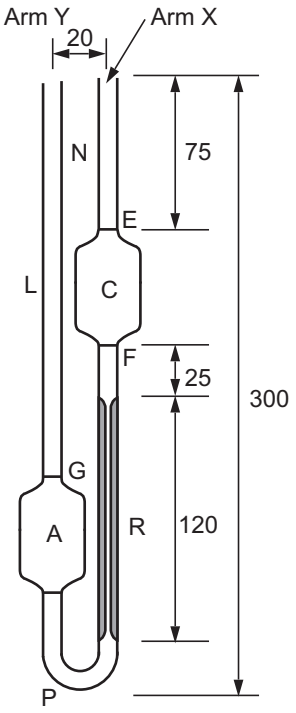


Fig. 6.2: Capillary Viscometer (IP)

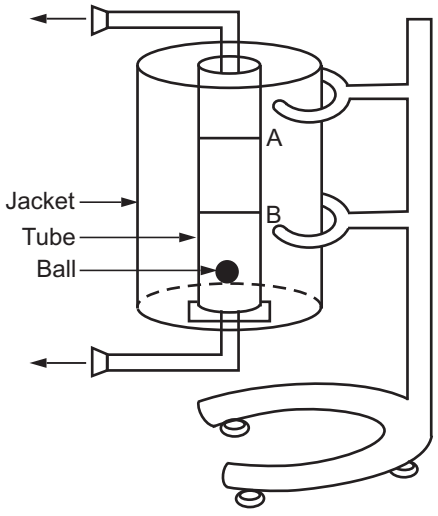


Fig. 6.3: Falling sphere viscometer

(B) Falling sphere viscometer

It works on the principle of resistance created by a liquid of known density for downward motion of a sphere of known density through it.

Method: An apparatus consists of a tube enclosed in a jacketed transparent vessel. Tube is filled with liquid sample of known density (ρ_1) and a metal/glass ball of known density (ρ_2) is placed at the bottom of the tube. The tube is suddenly inverted and time (t) required for the ball to cover the marked distance is noted. The viscosity of sample (η) in poise is calculated as

$$\eta = K (\rho_2 - \rho_1)t$$

Constant K is a function calculated during calibration using standard liquid.

(6) Uniformity of Content

Drug content of oral liquids for adults is expressed as 'mg/5 ml', for paediatric liquids 'mg/ml' and for topical liquids it is expressed in % w/v or %v/v.

Principle: The oral liquid presented in a single dose container and that contain less than 10 mg or 10% of individual API should comply the test for uniformity of content. The smaller drug content increases chances of poor mixing and thus variation in drug content.

Method: The batch which is passed for content of active ingredient(s) is tested for content uniformity. To determine content of active ingredients, 10 containers are randomly selected and each tested for drug content by a suggested analytical method. Drug content within each container and average value of all these is calculated.

- The preparation complies with the test, if all the 10 samples show drug contains between the limits of 85% to 115% of average value.
- The preparation fails to comply with the test if more than 1 of individual value is outside the limits 85 to 115% of average value and if any one individual value is outside the limit of 75 to 125 of the average value.
- If 1 individual value is outside the limit of 85 to 115 % but within the limit of 75 to 125% of the average value, repeat the test using another 20 containers taken at random.
- Then, the preparation complies with the test if not more than 3 individual values out of total 30 containers are outside the limit of 85 to 115% and not more than 1 is outside the limits of 75 to 125% of the average value.

(7) Uniformity of the Volume

Principle: The liquids are filled in bottles, the content of which is poured out to take a dose for administration. A patient should receive the full amount of liquid that is indicated on the label from the container. Smaller the volume of filled content more are the chances of error, therefore as the amount of content in the container increases the acceptance limits becomes closer to the labelled value.

Method: Pour completely the content of each container into calibrated volume measures and determine the volume of the contents of the 10 containers.

- The preparation complies with the test for uniformity of the volume if average net volume of the contents of all 10 samples is not less than the labelled amount, and
- The net volume of the content of any single containers is not less than 91% and not more than 109% of the labelled amount, when labelled amount is less than 50 ml.
- When labelled amount is more than 50 ml and less than 200 ml, the accepted limit is not less than 95.5% and not more than 104.5%.
- When labelled amount is more than 200 ml but less than 300 ml, the acceptance limit is not less than 97% but not more than 103%.

Questions for Self-Study

- Enlist various IPQC and quality control tests for solutions. **(PU 2013)**
- Enlist evaluation parameters for monophasic liquids and explain determination of uniformity of content as per IP.
- Enlist different instruments used to measure viscosity. Discuss any one in detail. **(PU 2009)**
- Define viscosity. Explain how determination of viscosity is important in formulation of solutions.
- Enlist and explain the evaluation parameters of monophasic liquid dosage form. **(PU 2009)**

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Chapter 7...

Concept of Quality Control and Quality Assurance

Features of the chapter

- Concept of Quality Control and Quality Assurance
- Difference between QC and QA
- GPM as tool for QA
- To introduce QA and QC.
- GMP is separate chapter in the second semester. In depth study like validation, documentation, etc will be easy to understand at Final Year of B.Pharm.

7.1 INTRODUCTION

In general, a product or service should meet the overall needs of the user. Fitness to use, cost, easy and timely delivery of the product are the important aspects of a product. The extent to which the product or service successfully serves the purpose of the user is called as fitness to use, which is the most significant factor among these. Fitness to use is commonly known by the broad term "Quality". According to ICH (International Conference on Harmonisation), quality is defined as the degree to which a set of inherent properties of a product, system or process fulfills the requirements of user. For a drug (product) - safety, efficacy, economy and easy availability are considered as quality criteria.

Thus, to attain and produce quality product is the ultimate aim of any organisation. For this, organisations follow certain systems, such as

- **Quality Management System (QMS):** QMS is the highest-level management system, which works to direct and control an organisation to improve quality of their products or services.
- **Good Manufacturing Practices (GMP):** The practice which ensures that products are consistently produced according to the prescribed standards of quality, appropriate for their intended use and specifications.

The quality control and quality assurance are the quality focused activities performed by the respective departments to comply with the requirements and guidelines set under QMS and GMP.

7.2 CONCEPT OF QUALITY CONTROL AND QUALITY ASSURANCE

Quality Control (QC) is the part of GMP, which is concerned with sampling, testing and documentation, and which ensures that all the necessary tests are carried out and judged before the release of a product for sale or use.

QC is a product based approach. After manufacturing the product it is tested for the pharmacopoeial tests like general appearance, drug content, drug release, etc. Confirming the product as "Passed for Quality" is the activity of quality control or else the product is claimed as Rejected.

Thus, QC system is designed to

- Provide routine and consistence checks to ensure integrity, correctness and completeness of the product.
- Identify and address errors and omissions in the product or service.
- Document all QC activities.

Role of QC department

QC personnel are analytical chemists who test the quality of the below mentioned items using various analytical techniques like titrimetry, spectrophotometer, chromatography, etc.

- API and raw materials.
- Drug product - In Process Quality Control (IPQC) and Final Product Quality Control (FPQC).
- Testing of packaging components.
- Re-assay.

7.3 QUALITY ASSURANCE (QA)

QA is a generic and wider term, covering all matters and arrangements, technical, legal, environmental and social that individually or collectively ensures that the product is produced as per quality required for intended use. In simple words, it is an overall management plan to guarantee the integrity of the product.

As explained above, QC is a corrective process to identify the defect whereas QA is proactive and preventive process to avoid defects. QA department implements GMP and other standard operating procedures (SOP) related to manufacturing and quality testing. QA system is designed to

- Establish specific quality building activities before production begins.
- Control factors that influence quality before, during and after production.
- Evaluate and disseminate results.

Role of QA department includes

- Create positive atmosphere and confidence such that quality requirements will be fulfilled.
- Plan and review system for the proper procurement, handling, testing and processing of materials and methods with the aim of 'Doing Right at the First Time'.
- Provide evidence needed to establish quality in work so that good practices are being performed effectively and continuously.
- Work to bring about speedy and operational performance.

Table 7.1: Difference between QC and QA

Sr. No.	Quality Control	Quality Assurance
1.	Focus on testing for quality	Focus on the entire product making process to ensure quality
2.	Begins when product is ready	Begins before start of product manufacture
3.	Product oriented event	Process oriented system
4.	Detects defects and failures	Prevents defects and failures
5.	It involves isolated body or external authority is involved.	It involves all the employee and internal auditors
6.	Result is pass or rejected	Provides opportunity to correct and improve
7.	Rejection leads to loss of efforts, time and money	Minimises loss in time, money and efforts.
8.	Task is more technical consisting of analytical testing and reporting.	The task includes quality by design (QbD) approach, validation, qualification and documentation.

For better understanding

QC is university examination.	QA is internal examinations as continuous activity.
QC is diagnosis of disease	QA is vaccination to prevention of disease and health promotion.

7.4 GMP- ATOOL FOR QA

Schedule M of Drug and Cosmetic Act 1940 provides guidelines and requirements for manufacturing and its related activities. Till the beginning of the 21st century, quality of the final product was the principle requirement. "WHAT" is prepared was more important than "HOW" it was prepared. The cGMP approach based revised schedule M insists on the right process for the right product, while assuring quality has been kept as the focal point. Continuous quality monitoring is accepted as a practice in place of end point analytical report. We will study in detail about GMP in the second semester. As an abstract the following points are sufficient to understand importance of GMP as a tool for QA.

- GMP is the basis for assuring the quality of the pharmaceutical products and its implementation is mandatory even for grant or renewal of license for manufacturing.

- GMP insist on quality requirements for all the components that are involved in the manufacturing of a product, viz. men, machine, method, building, environment, drug laws and documentation of every single and simple activity.
- It believes that working in a systematic way and documentation during working minimises errors and also provides clues for finding faults.
- The building should have adequate working space to allow orderly and logical placement of equipments and materials so as to avoid the risk of mix up between different drugs or with the other components and to avoid cross-contamination.
- All personnel should be healthy and should be trained to maintain a high level of hygiene and the highest level of positive attitude.
- Manufacturing must follow clearly defined procedures in accordance with manufacturing and marketing rules and laws.
- Equipments are so designed and located in order to maintain the uniflow, permit effective cleaning, minimise risk of errors, avoid cross-contamination and mix-up and avoid accumulation of dust.
- Factory should have SOP for each and every process/operation. It should explain stepwise process and should be signed by the concerned authority.
- Validation is the establishment of documented evidence that a system does what it is supposed to do. It involves collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensures that the manufacturing processes are capable of achieving the intended standards consistently. For that, QA department prepares validation protocols and reports. Processes and procedures are established on validation studies and these should be periodically revalidated.
- It looks after everything from the selection of location, construction of building, establishment and setup of equipments, purchase of raw materials, processing steps and operations, quality control to release of finished products.
- Self-assessment and internal audit should be performed routinely by head of GMP team and in addition, performed on special occasions.

Questions for Self-Study

- Define the terms GMP, QA and QC.
- Differentiate between Quality control and Quality Assurance.
- Explain the concept of Quality Assurance in pharmacy.
- Give importance of GMP. **(PU 2010, 2012)**
- Explain cGMP as a tool for quality assurance. **(PU 2011, 2013)**
- Describe the concept of Quality Control and write its limitations.
- Validation parameter of quality analysis. **(PU 2014)**
  (Intention of examiner may be Quality Assurance and not analysis).

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Chapter 8...

Alternative Systems of Medicine

Features of the chapter

- Principles of the system of medicine and dosage forms under the respective systems are covered.
- Ayurvedic dosage forms are explained with storage and stability.

8.1 CONCEPT OF ALTERNATIVE SYSTEM OF MEDICINE

Drugs are basically chemicals obtained through chemical reactions of organic or inorganic compounds or biochemical constituents or products of plants, animals or obtained from minerals, as a pure single entity or a mixture of constituents, having therapeutic value for treatment or cure for diseases. Chemically, synthetic drugs that were introduced in the mid of 20^{th} century are currently being used in the successful treatment and prevention of a large number of afflictions. Their use has been globally acclaimed as the primary system of medicine, termed as allopathic medicine system. However, since the ancient times, traditional medicinal systems are being practiced in several parts of the world; these are together called as Alternative or Complementary Systems of Medicine. Some such important systems are Ayurveda from India, Homeopathy from Germany, Unani from Greece etc. Now a days complementary medicine is used together with allopathic medicines for better treatment of several chronic diseases.

Features of allopathic system of medicine are enlisted below.

- Modern system of medication.
- Majority of API are chemically synthetic molecules.
- API is a pure and single entity.
- Dose dependent toxicity, pharmacokinetics and pharmacodynamics are well established.
- Faster symptomatic relief.
- Validated therapy with reproducible results.
- Comparatively less safe, especially if taken as self medication or without proper diagnosis.

The main features of Alternative Systems of Medicine are follows.

- Traditional systems of medication.
- Based on natural sources like plant, animal and mineral.
- Whole or part of plant/animal or extracts, juices or medicines produced using these according to the principles of particular alternative system are used.
- Instead of mere treating a disease or symptom, it assures of developing a healthy life as a holistic approach.
- Symptomatic relief is slower and needs longer treatment.
- Comparatively safe, but needs further studies about drug interactions and toxicity testing.

8.2 AYURVEDIC SYSTEM OF MEDICINE

The term 'Ayurveda' is a Sanskrit world meaning knowledge of life (*Ayush* = Life and *Veda* = Sacred knowledge or science). Ayurveda explains science of life and not merely science of medicine. It is based on happy and unhappy states of life, explains what is good and bad for a healthy life. This system began and evolved during the Vedic period in India.

Vedas are called '*Apourusheya*' means they are not originally written by men and it was practiced in India traditionally thousands of years ago even before it came into its written form. There are four Vedas viz. Rig Veda, Sama Veda, Yajur Veda and Atharva Veda. Atharva Veda deals with principles of body and diseases, different types of herbs and plants. Ayurveda is called as '*Upaveda'* or deputy veda of Atharva Veda.

Charaka Samhita written by Charaka is supposed to be the oldest text in Ayurveda. Sushruta is considered as the first surgeon of the world and has authored the Sushrut Samhita.

8.2.1 Fundamental Principles of Ayurveda

(1) Tridosha: According to Ayurvedic fundamentals, health is a combination of the three '*Dosha*' viz. '*Vata*, *Pitta* and *Kapha*.

(2) *Panchamahabhuta:* *Doshas* are a combination of two of the five elements called as '*Panchamahabhuta'*.

(3) *Dravya guna rasa viryadi siddhanta*: It is concept of drug properties, the third principle of Ayurveda.

(4) *Tridosha* principle: *Vata*, *Pitta* and *Kapha are* the three basic governing factors of pathophysiology of the body. *Doshas* are body action and function and it is not Marathi word Dosh, which means disorder or impurity.

- When the *Doshas* are not in balance diseases develop. Each *Dosha* compromises of the basic elements - Vayu, Aakash,Agni, Jal and Prithvi (Table 8.1).

Table 8.1 Tridosha Principle of Ayurveda

Sr. No.	Doshas	Elements involved	Function
1.	*Vata*	*Vayu and Akash*	Primary movements
2.	*Pitta*	*Agni*	Heat and energy
3.	*Kapha*	*Jal and Prithvi*	Growth and synthesis

- The *Doshas* act in co-ordination with each other to perform a particular function. For example, chewing of food and their passage into the alimentary tract, churning and mixing with digestive juices is governed by *Vata Dosha*. *Pitta* provides energy for these digestion activities. *Kapha* provides lubrication for movement of food, builds body tissues and promotes growth.
- *Doshas* produce some stable constituents of the body for its normal functioning, called as *Dhatus* (tissues). There are seven *Dhatus* viz. *Rasa* (diagestive juice), *Rakta* (Blood), *Maunsa* (Muscles), *Medha* (Lipids), *Asthi* (Bones), *Majja* (Bone marrow), *Shukra* (Semen). In a healthy body, all these *Dhatus* are formed and function well.
- During physiological and metabolic activity, and from tear and wear of the tissues, some non-useful substances are formed; these are called *Malas*, which mainly include faeces, urine and sweat.

Thus, Ayurveda is based on the balance between *Dosha, Dhatu and Malas*. The critical diagnosis of tridosha and its imbalance gives information about '*Prakruti*' (disease state) of the patient. Pulse reading (*Nadi Pariksha*) is an important criteria in Ayurveda. Observation of the skin, eyes, hair, tongue and '*Malas*' are some other important diagnosis methods.

(1) *Panchamahabuta* Principle: According to Ayurveda every substance in this universe is made up of a combination of the five elements viz., space (*Akasha*), air (*Vayu*), fire (*Teja*), water (*Apa, Jala*), and earth (*Prithvi*). Each of these elements represents particular properties of the substance.

- The earth is solid which is heavy, dense, stable, hard and rough. Due to heaviness such substances have tendency to go downwards and therefore said to act in the lower part of the body. These include laxatives, diuretics. Solid elements are useful for providing shape and strength of body.
- Gas is light and expands to fill space and useful for respiratory tract, lightness, movements, impulses through nervous system, blood circulation action etc.
- Liquids are cold, mobile, unctuous and soft, and useful for plasma, joint lubrication, softness etc.
- Space is soft, light, subtle and smooth and is responsible for the transport of nutrients into cells.
- Fire is hot and controls warmth, digestion assimilation, regeneration and repair of the body tissue etc.

(2) ***Dravya guna rasa viryadi siddhanta:*** In general sense,a drug is a substance that has the desired physical, chemical and biological properties that improve the state of health without side effects or toxic effects. Ayurveda also explains the properties of a drug using similar terms. *Dravya* means drug, *Guna* means physical properties, *Rasa* means chemical composition and accordingly the substances have taste. *Virya* is biological activity of a particular drug and it is based on the chemical composition (*Rasa* property).

For example, *Amla Rasa* (sour taste) is due to Agni and Prithvi elements. These promote Pitta Dosha and increase appetite, digestion, sharpen the senses. *Madhura Rasa* (sweet taste) is due to Prithvi and Jala, which promote growth, strength. Other *Rasas* include *Lavana* (salty), *Katu* (pungent), *Tikta* (bitter), *Kashaya* (astringent).

8.2.2 Disease and Drug Action

Food and season are the two main factors that have great influence on the Dhosha property. According to Ayurveda

- Diseases which are due to imbalance in *Doshas* are called *Adhayatmika* diseases.
- Diseases which may be due to biological and accidental causes are known as *Adhi Bhoutika* and
- Diseases which may be due to natural causes such as time, season, age etc (*Adhi Daivika*).

Drugs are mainly obtained from three sources: plants, animals and minerals. Milk, urine, ghee, honey are the animal origin drugs and iron, calcium, gold etc are the mineral sources of drugs. The different parts of plants like root, bark, leave, seeds, fruits, flowers gums and resins or whole plant are useful as drugs. As discussed above, a particular substance depending on the presence of the basic elements (*Panchmahabhuta)* are used as drug. The knowledge of *Guna, Rasa* and *Veerya* are criteria for the selection of a particular drug to treat a particular disease.

Except *Lepa* (ointments like dosage forms), majority of Ayurvedic drugs are meant for oral administration. The crude drugs are processed mainly for their easy digestion, proper absorption of the biologically active form and for improvement of their physicochemical and microbiological stability.

Questions for Self-Study

- Describe Ayurveda as an alternative system of medicine. **(PU 2012, 2013)**
- Explain different types of diseases as per Ayurvedic principle.
- Explain dridosha principles of Ayurveda.
- Write short note on Panchamahabuta Principle of Ayurveda.
- Explain the essential properties of a drug as per Ayurvedic principles.
- Differentiate between modern system of medicine and alternative system of medicine.
- ❖ Discuss concept of Ayurveda as an alternative system of medicine.
- ❖ Discuss fundamental principles of Ayurveda about disease, drug and therapy.

8.2.3 Ayurvedic Dosage Forms

The source of ayurvedic drug molecules is mainly plants, animals or minerals, which are produced in a particular dosage form by the ayurvedic procedure. The Ayurvedic Formulary of India describes the dosage forms as follows.

(a) Ayurvedic solid dosage forms

Bhasma: Bhasmas are ayurvedic powders obtained by calcinations of metals, minerals and animal origin drugs, by a special process called *puta* (heated with cow dung cakes in pits). E.g. *Tamra Bhasma, Rajat bhasma*.

Storage and stability: Bhasma should not have metallic appearance. It should be a fine powder and should float on water. Bhasmas are stored in glass or earthen containers and have prolonged stability.

Churna: Churna are ayurvedic powder dosage form in which the clean and dried drugs are milled separately and mixed or milled together to produce a fine powder of at least 80 mesh sieve. E.g. *Hingvadi churna, Bhaskara lavana churna*

Storage and stability: Powder should be free from lumps and must be non-hygroscopic. Churnas are stored in airtight containers. They retain potency for one year.

Kvātha Cūrna: Kvātha Cūrna is an ayurvedic coarse powder of certain drugs or combination of drugs that can be used for preparation of decoction or *hima, phānta* etc. E.g. *Astavarga Kvātha Cūrna, Nimbādi Kvātha Cūrna*.

Storage and stability: They should be stored in airtight containers and they retain their potency for one year.

Lavana Ksāra: These are ayurvedic alkaline powders obtained from the ash of drugs (*Lavana*). The ash of drug(s) is mixed with 6 times of its volume of water so as to dissolve soluble salts; the resultant liquid is then evaporated leaving a white powder called Ksāra. E.g. *Palasa khara*, *Vajra ksara*.

Storage and stability: Store in air-tight containers in a dry place. These have prolonged stability.

Lauha: Lauha kalpas are ayurvedic powders prepared by mixing other powdered drugs in loha bhasma. These are administered with prescribed liquids. E.g. *Vidangadi Lauha, Datri Lauha*. These have potency for two years.

Kűpipakva Rasāyana: These are obtained by heating the powder of mineral or metallic origin in a glass flask. After repetitive heat treatments and after cooling the *sindura* deposited at its neck is scrapped and collected. E.g. *Makar Dhuaja, Svarnasindura*.

Storage and stability: They are stored in a tightly closed containers and have prolonged stability.

Parpati: Parpaties are dried flakes of ayurvedic drugs. *Kajjali* is made of purified mercury and sulphur and other drugs are added in it by trituration. The powder mixture is then filled in an iron vessel and heated. Castor leaf (*eranda*) is spread over a shallow pit made up of fresh cow dung. The molten mass is poured on the leaf and covered with another leaf and fresh cow dung is spread in it and gently pressed. After cooling the flakes are collected and powdered. E.g. *Suvrna Parpati, Lauha Parpati*.

Storage and stability: Parpaties are dark in colour. These are stored in glass bottles and have prolonged stability.

Pisti: Pisties are ayurvedic powders prepared by triturating the drug with the specified liquids and exposing to sun or moon light. These are bhasmas prepared without heat therefore also termed as *anagnitpa bhasma*. E.g. *Pravala pisti, Mukta pisti*.

Storage and stability: These are stored in glass bottle and have prolonged stability.

Rasa-Yoga: These are ayurvedic powders or pills containing mineral drugs. The mineral drugs are present in forms such as *bhasma*, *kajjali*. E.g. *Prabhakara rasa, Sutsekhara rasa*.

Sattva: Satva is an ayurvedic powder obtained by maceration of crude drug using water. After straining the sediment is washed repetitively by adding water followed by decantation and finally, it is dried and powdered. E.g. *Guduci Sattva*

Storage and stability: The colour of satva varies from drug to drug. This can be stored in a closed container.

Vati and Gutika: These are the tablets or pills containing drug(s) obtained from plants, animals or minerals. E.g. *Ganghaka vati, Dugdha vati*.

Pills containing plant drugs can be used for two years. Mineral vatis can be used for an indefinite period.

(b) Ayurvedic liquid dosage forms

Āsava and Arista: Āsava and Aristra are ayurvedic liquid preparations produced by fermentation of drug powder or juices with sugar or jaggery, generating alcohol *in situ* that acts as menstrum for extraction of active constituents from the drug. In Āsavas, the decoction of drug (Kasāya) is mixed with boiled sugar or jaggery solution and subjected to fermentation, and in Arista sugar or jaggery solution is first boiled and cooled to which the drug is mixed and subjected to fermentation. Alcohol content of Āsava is more than Arista. E.g. *Lohasava, Vasakasava, Abhayarista, Draksharista*.

Arka: Arka is an ayurvedic liquid preparation produced by distillation of certain liquids or of drugs soaked in water; the resulted liquid may be clear, turbid or slightly coloured according drug. The drug is soaked in water for 24 hrs. before distillation. E.g. *Karpuradyarka, Jatamamsyarka*.

Drāvaka: Drāvaka are ayurvedic liquid preparations obtained by distillation from ash of ayurvedic drugs (*lavanas*) or salts (*Ksaras*), e.g. Sankha Drāvaka.

Storage and stability: Store in glass stoppered bottles. These have prolonged stability.

Ghrita (Snehakalpa): Ghrita are oily liquid ayurvedic preparations that are prepared by boiling ghee with one or more liquid form of drug such as decoction, juice or fine paste of drug(s) (*kalka*). This process increases absorption of the active therapeutic principles of the drug. E.g. *Ashoka Ghrita, Dhanvantara Ghrita*. They are taken internally with prescribed anupan or water or milk. Maintains potency for about sixteen months for internal use.

Taila: Like Ghritas, tailas are oily liquids preparations but it contains oily phase other than ghee and are generally used externally for *abhyanga*. For internal use, they are taken with prescribed *anupan* or water or milk. E.g. *Maha Narayan Taila, Vranraksasa Taila.*

(c) Ayurvedic Semisolid Dosage Forms

Avleha and Pāka: Avaleha or Lehya are ayurvedic semisolid preparations for oral use produced by addition of jaggery, sugar or sugar-candy and boiled with prescribed drug juice or decoction over moderate fire to obtain *Pāka*.. E.g. *Asvagandhadi Lehya, Kalyanaka Guda.* It should be used within one year.

Guggulu: Guggulu are soft, waxy brown coloured exudates obtained after purification (*Sodhana*) from plant *Commiphora mukul.* E.g. *Triphala guggulu, Laksa guggulu*.

Storage and stability: Store in glass or porcelain jars in dry and cool place. Guggulu containing plant drugs maintain potency for about two years. The potency of guggulus containing metal and minerals is further longer.

Lepa: Lepa are semisolid pastes for topical application of ayurvedic drugs, e.g. *Sarsapadi lepa, Grhadhumadi lepa.*

Storage and stability: Store in airtight containers. Lepa containing vegetable drugs should be used with 30 days. Mineral lepa have prolonged stability.

Mandura: These are thick pasty or powder ayurvedic medicines prepared by boiling drug in *gomutra* (cow's urine). Then powders can be added in the paste to get powder medicine. E.g. *Punarnavadi mandura, mandura vataka.*

Storage and stability: They have strong odour of urine. These are stored in air tight containers in dry place and have prolonged stability.

(d) Ayurvedic eye preparations

Vartti-Netrabindu and Anjana: These are ayurvedic preparations for the eye.

Vartties are thin sticks made from soft paste of powder drug in a suitable base, e.g. *Vimala vartti, Tamradi gutika*.

Netrabindu are eye drops prepared by dissolving ayurvedic drugs.

Anjana are very fine powders of ayurvedic drugs to be applied into eye with netra salaka, e.g. *Muktadi Mahanjana*.

Products containing plant drugs should be used within one year.

Questions for Self-Study

- Differentiate between Asava and Arista, and Ghrita and Taila.
- Define Dravaka and Satva.
- Differentiate between Ksara and Satva.
- What is recommended usage life of lepa?
- Name the liquid ayurvedic drug forms.
- Define Ajana and Vartties.
- Enumerate solid ayurvedic forms of drug
- What is the recommended usage life for vaties according to Ayurvedic formulary of India?
- Define mandura with example.
- Write short note on Principle of Ayurveda. **(PU 2014)**
- Describe ayurveda as a system of medicine. **(PU 2012, 2013)**
- ❖ Give and account of ayurvedic dosage forms, their applications, storage and stability.
- ❖ Explain the concept of ayurveda and various ayurvedic dosage forms.

8.3 HOMEOPATHIC SYSTEM OF MEDICINE

8.3.1 Concept of Homeopathy

Homeopathy is a system of therapeutics for treating human beings and animals on the principle of the simile '*Similia similibus curentur*' means 'Let like be treated by likes'. The word Homeopathy is derived from the Greek word *homoios* meaning like or similar and *pathos* meaning suffering or disease. Homeopathy was developed by a German physician Dr.Samuel Hahnemann, in around 1796.

Proving: Dr. Hahnemann observed that a particular preparation given to a healthy individual produce certain symptoms that preparation is effective to treat a disease showing similar symptoms. The symptoms, signs of toxicity produced after administration of a particular preparation in healthy individual are called as 'Proving'. Thus, homeopathic treatment is based on the clinical history of patient, his temperament and personal characteristics, and proving.

Potency of Homeopathic medicine: Dr. Hahnemann experiments proved the apparent increase in the clinical effects of medicines with increase in their dilutions. The prepared dilutions of the extracts are called as *Potentised Remedies* or *Potencies*. In general, dilution of chemicals is considered as reduction in potency but dilution of homeopathic medicines followed by vigorous agitation is considered as true opening up of the natural substances and revealing of hidden powers contained within medicines. Potency is the result of the process of dynamisation, which can be explained as, dilution of solution of solid will cause complete disappearance of the solid state yielding greatest powder. The dilutions or potencies are indicated using term 'x'.

8.3.2 Drugs and Dosage Forms

The homeopathic drugs are obtained from plant, animal and mineral sources as well as synthetic chemicals, such as tincture of plants, salts, metals, venoms from snakes and spiders. The synthetic drugs can also be used but a fresh proving should be carried out. They are prepared by serial dilutions according to homeopathic techniques. These are mainly categorised as –

(a) Mother tinctures

(b) Mother solutions

(c) Triturations.

Substances in the liquid vehicles can be made into mother tinctures by suitable processes of extraction (maceration / percolation) or the chemical is dissolved in a suitable solvent to produce mother solutions. Solutions are usually made in water, alcohol or a mixture of it and very rarely in glycerin or syrup. Substances that are insoluble in vehicle are triturated with inert diluents to produce triturates. The object of trituration is to reduce the dry drug to the finest possible powder. The drug powder is mixed with portion of milk sugar and triturated using mortar and pestle. The first trituration prepared using 1:1 parts of drug: sugar milk is further diluted with three parts and then five parts of milk sugar. It produces '1x' potency. In short it is:

1 part drug: 1 part milk sugar + 3 parts milk sugar + 5 parts milk sugar.

The triturates can be converted in to liquid potencies by dissolving such '6x' potency triturate in fifty parts by volume of purified water, to which fifty parts by volume of dispensing alcohol is added.

(a) Oral Dosage Forms: The mother tinctures and mother solutions are dispensed after mixing with water, adsorbing on porous globules, sugar milk or on tablet triturates or tablets. The triturates are dispensed as such or in the form of tablets.

- **Tinctures or solutions with purified water:** According to physician's direction drops of purified water are added in required amount of medicine. Though the aqueous mixtures have good penetration (absorption) power, it has poor storage qualities.
- **Tinctures or solutions with milk sugar:** A specific predetermined number of drops of the medicine are poured on measured quantity of milk sugar. Due to chances of partial dissolution of milk sugar this method is not suitable for aqueous or alcoholic solutions. Mother tinctures are mixed by trituration with sugar milk using mortar and pestle. The trituration should be done for an hour so as to get completely dry powder.
- **Tinctures or solutions dispensed with globules:** While saturating globules with medicines, it is necessary to pour sufficient quantity of medicine on the globules to saturate them. Drain out the excess liquid after proper saturation of globules. These medicated globules should be kept for 48 hours and then they become ready for use.
- **Tinctures or solutions dispensed with tablets:** The tablets are more advantageous for administration and handling than the globules. In this method the required drops of medicine are poured carefully on tablets.
- **Triturates:** The triturates can be dispensed by wrapping in new-white paper or to improve handling and administration these are moulded in tablet triturates.
- **Tablet Triturates:** The powder triturates are mixed with 50% alcohol and paste is made. It is moulded in tablet triturates using moulds. The tablet triturates is allowed to dissolve orally or in a tea-spoonful of water.

(b) External Applications: Treatment of disease by internal drug administration is specialty of Homeopathy and there is no definite principle for external applications. The principle says that there is no separation between internal and external disease and external symptoms are the outward reflections of internal problems. Only external application can never treat the diseases completely but external applications are the choice for cleansing, dressing, injuries, lacerations, burns, accidental cases, etc. The mother tincture is mixed with various liquid or semisolid vehicles to get dosage form. The homoeopathic dosage forms include glycerols, liniments, lotions, ointments, cerates, opodeldocs (applications), poultices, plasters, oils and rectal, vaginal and urethral injections.

Some important Principles of dispensing homoepathic medicines: Proving, individualisation, single drug, minimum dose are the basic principles of Homeopathy.

According to these, the following points should be considered for proper dispensing of medicines.

1. Drugs are dispensed according to Proving of drug and clinical diagnosis and patient history of patient.
2. Smallest possible dose should be administered initially. After observing toxic symptoms and relief the dose may be increased or stopped.
3. Avoid administration more than one medicament at a time.
4. Repeat the dose only when improvement is observed till recovery ensures or different groups of symptoms arise.
5. Nothing should be taken at least half an hour before or after taking the medicine.

8.4 UNANI SYSTEM OF MEDICINE

Unani medicine was developed in Arabian civilisation, therefore called as Arab medicines. In India, the Unani medicine took its shape during the reign of Allaudin Khilji (1290-1321 AD). Unani system is based on the Hippocratic theory of four humours, viz. blood, phlegm, yellow bile and black bile and Pythagorian theory of four proximate qualities, viz. hot, cold, moist and dry. The balance and distribution of these decides state of health of individual, it is called as Temperament (*Mizaj*). According to temperament person is categorised as hot (*Mizaj-e-har*), cold (*Mizaj –e- barid*), dry (*Mijaz-e-yabis*), and moist (Mizaj-e-rath). Galen described the humours as Sanguine, Phlegmatic, Melancholic and Choleric. These are based on proximate qualities or states of matter, which are result of combination elements.

Table 12.3: Unani Concept of Healthy Life

Sr. No.	Galen's concept	Humour	Pythogorian state	Elements involved
1.	Sanguine	Blood	Hot and moist	Air
2.	Phlegmatic	Phlegm	Cold and moist	Water
3.	Melancholic	Yellow bile	Hot and dry	Fire
4.	Choleric	Black-bile	Cold and dry	Earth

The imbalance in humours is the output of improper digestion of food. Improving digestion and the removal of toxins formed by digestion is thought to cause restoration of humours. The abnormal temperament resulting into disease is treated by Unani drug. The Hakeems diagnose their patients by examining urine, stools and sputum and by pulse reading. The family history, individual life style and emotions are also taken into consideration. Some of the traditional treatments include body cleansing by purgation,

vomiting or bleeding. Like Ayurveda, this system also aims at a healthy body on the whole by eradicating the root cause and not just relief from symptoms.

Unani drugs consist of the drugs of plant, animal and mineral origin. Use of animal drugs like animal organs, flesh, hair, hoofs, excreta or bones is widespread. Unani drugs are formulated as Saffoof (powder), Sharbat (syrup), Mazoom (mixture of powder and honey), Laooq (mixture of powder and syrup), Joshanda (decoctions), Khaisanda (infusion), Marham (ointment), Kohal (for eyes) and Shiaf and Battis (suppository and pessary).

8.5 SIDDHA SYSTEM OF MEDICINE

Siddha system has its origin in the ancient Dravidian culture, the pre-ayurvedic period. This system spread in south India, Sri Lanka, Malaysia and Singapore, the regions where the Dravidians migrated. Like Ayurveda, the Siddha system is also based on Triguana (three) principles, i.e. *Vata, Pitta* and *Kapha* and five basic elements, viz., earth, water, sky, fire and air. The diagnosis is made by examination of pulse reading, speech, tongue, body, colour, faecal matter, urine and eyes.

Siddha medicines also have its origin in plants, animals and minerals. Use of mercury, silver, gold, sulphur, zinc, alum, borax, and arsenic is well documented. Powders (Churna), oils (Tailam), Bhasmas, Ghrta are some of the dosage forms of Siddha drugs. Siddha demands some restrictions during therapy like avoiding eating of chicken, mango, coconut, groundnut and tobacco as well as no sex and daytime sleeping.

Questions for Self-Study

- Explain in brief the concept of Homeopathy.
- Explain the terms Proving and Potentiation of Homeopathic medicines.
- Describe Homeopathy as a system of medicine. **(PU 2010, 2011)**
- Describe Unani and Siddha as alternate systems of medicine. **(PU 2010, 2014)**

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