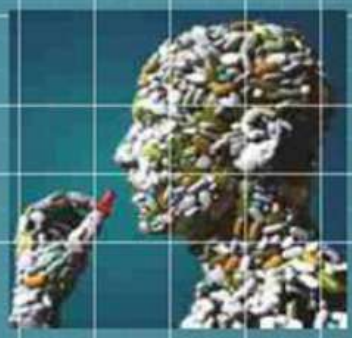
As Per PCI Regulations

First Year B. Pharm. • Semester-I

PHARMACEUTICS-I

Dr. Sanjar Alam
Prof. (Dr.) Jagannath Sahoo
Ms. Shikha Sharma



NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

A Text Book Of

PHARMACEUTICS - I

As Per PCI Regulations

FIRST YEAR B. PHARM.
Semester I

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Preface

It gives us immense pleasure to present to pharmacy students our book entitled **"Pharmaceutics I"**. Writing a book is inspiring, often exciting, and sometimes very challenging work.

Pharmaceutics plays a vital role in formulation development and evaluation of various dosage forms. This book will mainly guide students to get knowledge about origin and scope of pharmacy, various pharmacopoeias, prescription and drug incompatibilities, conventional dosage forms, pharmaceutical calculation and basics of Pharmaceutics. All the contents are discussed in detail and suitable examples are explained whenever required. This book is highly useful for understanding of principle(s) and methods involved in formulation of various dosage forms in a simplest way. The book contains calculations and important questions related to the topics to fulfill the requirements of students.

We are grateful to Dr. Farhan J. Ahmad for his constant encouragement and suggestions given during completion of this book.

We record our sincere thanks to Dr. R.K. Khar, Dr. Javed Ali, Dr. Puspendra Kumar, Mr. Nitesh Chauhan, Dr. Aftab Alam, Dr. Mandeep Kumar Arora, Dr. Shadab Md. Dr. Javed Ahmad, Dr. Ruchi Tiwari, Dr. Manish, Mrs. Richa Goel, Mrs. Parul Grover, Ms. Priya Bansal, Mrs. Deepti Katiyar, Mr. Surya Prakash, Mr. Sheikh Murtuja, Mr. Shadab Siddiqui, Mr. Pankaj Sharma, and Mr. Amit for constant encouragement and suggestions betterment of this book.

We appreciate the co-operation and interest taken by Shri Dinesh Furia, Shri Jignesh Furia and Ms. Roshan Khan of Nirali Prakashan, Pune in bringing out this book.

We will be grateful to all the teachers and students who will be kind enough to point out our mistakes that have escaped our attention. Suggestions for future improvement are always welcome.

Dr. Sanjar Alam
Prof. (Dr.) Jagannath Sahoo
Ms. Shikha Sharma

Syllabus

UNIT – I **(10 Hours)**

- **Historical Background and Development of Profession of Pharmacy:** History of profession of Pharmacy in India in relation to pharmacy education, industry and organization, Pharmacy as a career, Pharmacopoeias: Introduction to IP, BP, USP and Extra Pharmacopoeia.
- **Dosage Forms:** Introduction to dosage forms, classification and definitions.
- **Prescription:** Definition, Parts of prescription, handling of Prescription and Errors in prescription.
- **Posology:** Definition, Factors affecting posology. Pediatric dose calculations based on age, body weight and body surface area.

UNIT – II **(10 Hours)**

- **Pharmaceutical calculations:** Weights and measures – Imperial and Metric system, Calculations involving percentage solutions, alligation, proof spirit and isotonic solutions based on freezing point and molecular weight.
- **Powders:** Definition, classification, advantages and disadvantages, Simple and compound powders – official preparations, dusting powders, effervescent, efflorescent and hygroscopic powders, eutectic mixtures. Geometric dilutions.
- **Liquid Dosage Forms:** Advantages and disadvantages of liquid dosage forms. Excipients used in formulation of liquid dosage forms. Solubility enhancement techniques

UNIT – III **(8 Hours)**

- **Monophasic Liquids:** Definitions and preparations of Gargles, Mouthwashes, Throat Paint, Eardrops, Nasal drops, Enemas, Syrups, Elixirs, Liniments and Lotions.
- **Biphasic Liquids:**
- **Suspensions:** Definition, advantages and disadvantages, classifications, Preparation of suspensions; Flocculated and Deflocculated suspension and stability problems and methods to overcome.
- **Emulsions:** Definition, classification, emulsifying agent, test for the identification of type of Emulsion, Methods of preparation and stability problems and methods to overcome.

UNIT – IV **(8 Hours)**

- **Suppositories:** Definition, types, advantages and disadvantages, types of bases, methods of preparations. Displacement value and its calculations, evaluation of suppositories.
- **Pharmaceutical Incompatibilities:** Definition, classification, physical, chemical and therapeutic incompatibilities with examples.

UNIT – V **(7 Hours)**

- **Semisolid Dosage Forms:** Definitions, classification, mechanisms and factors influencing dermal penetration of drugs. Preparation of ointments, pastes, creams and gels. Excipients used in semi solid dosage forms. Evaluation of semi solid dosages forms

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Contents

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Unit...1

HISTORICAL BACKGROUND, DOSAGE FORMS, PRESCRIPTION AND POSOLOGY

♦ **OBJECTIVES** ♦

- **To know about the historical background and development of pharmacy profession.**
- **To understand the scope of pharmacy.**
- **To know about various Pharmacopoeias – IP, BP, USP etc.**
- **To understand various types of conventional dosage forms and their classification.**
- **To understand the handling of prescription and how to calculate the dose of a paediatric patient based on body surface area, age etc.**

1.1 HISTORY OF PHARMACY

Origin and Development of Pharmacy

Pharmacy (from the Greek 'pharmakon' = drug) is the health profession that links the health sciences with the chemical sciences, and it is charged with ensuring the safe and effective use of medication.

It was in 9th century in the civilized world around Baghdad that the profession of pharmacy started acquiring shape. It slowly spread to Europe as alchemy and finally developed into chemistry. The artisans of Mesopotamia, Egypt and China carried out the first known chemical process. However, in the 19th century it completely sprouted out from medicine and started developing as a separate profession. This happened only when the role of pharmacist as a compounder of medicines were identified and differentiated from physician whose role was accepted as the therapist. The practice in those times was restricted to compounding, dispensing medication, and manufacturing medicaments in bulk lots not for general sale. The medicament commonly produced was simple elixirs, spirits, and powders in contrast to the complex pharmaceutical remedies of the present era.

1. **Before the Dawn of History:** In earliest times, medicine was based on **magic and religion.** Sumerians living around 4,000 BC believed that **demons were the cause of illness**. In many cultures, **physicians were priests**, and sometimes considered as gods.

2. **Pharmacy in Ancient Babylonia:** The earliest known record of the art of apothecary (the forerunner of the pharmacist) is in Mesopotamia at about 2600 B.C Babylonian healing practitioners combined the responsibilities of **priest, physician, and pharmacist**
3. **Pharmacy in Ancient China:** In ancient China (2000 B.C.) legend tells that Emperor Shen Nung investigated the medical properties of hundreds of herbs. He recorded 365 native herbal drugs in the first pen T'sao. (Book called "the Great Herbal")
4. **Days of the Papyrus Ebers:** One of the earliest known records written around 1500 B.C. was the Ebers Papyrus named by George Ebers. It contains 800 prescriptions using 700 drugs, of particular note in the papyrus is inclusion of quantities of substances, which were largely missing from Babylonian clay tablets.

   Many modern dosage forms are also referred to in the Ebers Papyrus as gargles, inhalations, suppositories,
5. **Greeks period:** Around 600 B.C. the Greeks integrated science into mythological thinking. They began thinking logically about disease rather than believing spiritual explanations. The Romans conquered the Greeks and the medical and pharmaceutical cultures merged, it is known as the **Greco-Roman era.**
   * Charaka and Sushruta, Indian pharmacist and physician, wrote *Charak Samhita* and *Sushruta Samhita*, respectively
6. **Roman period:** Pharmacopoeia: Maker of remedies.

   Pharmacotritae: Drug Grinders, **Unguentarii:** Makers of ointments.

   Pigmentarii: Maker of cosmetics, **Pharmacopolae:** Seller of drugs.
7. **Arabian period:** Major advances in this era are Formularies: The continuation of documentation of drug information. They also had different drug forms which are now used: Syrups, Conserves, Confections and juleps.
8. **Empiric Era:** Pharmacopoeia's were used to protect public health. Roots, Bark, Herbs Flowers etc. were used and controlled by the government. They questioned the toxicological affects on the human body. Created interest in testing of drugs and how they affected the body. In 1751 Benjamin Franklin started the first hospital.
9. **Pharmacy today and tomorrow:** Pharmacy, with its heritage of 50 centuries of service to mankind, has come to be recognized as of the great professions.
   - **Prescription** is a written paper for a drug product by a licensed prescriber to treat a patient.
   - **Prescriptions** filled increased by **27%** while the number of **pharmacists** increased by **15%.**
   - **Pharmacology:** The study of drugs (from the Greek *pharmakon* means drug).

- **Pharmacognosy:** The study of physical, chemical, biochemical and biological properties of drugs as well as drugs from natural sources.
- **Pharmacopoeia:** An official listing of drugs and issues related to their use.
- **Pharmaceutical:** study of or about drugs; also, a drug product.
- **Panacea:** A cure-all (from the Greek *panakeia).*
- **Materia Medica:** A dictionary of medicinal plants.

1.2 PHARMACY AS A CAREER

Pharmacy (from the Greek 'pharmakon' = drug) is the health profession that links the health sciences with the chemical sciences, and it is charged with ensuring the safe and effective use of medication.

Scope of Pharmacy

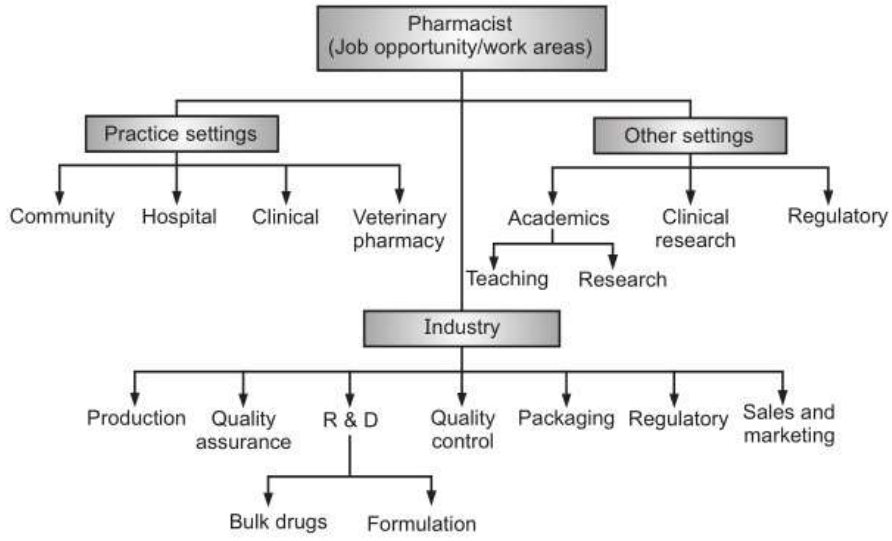


Fig. 1.1: Scope of Pharmacy

The scope of pharmacy practice includes more traditional roles such as compounding and dispensing medications, and it also includes more modern services related to patient care, including clinical services, reviewing medications for safety and efficacy, and providing drug information.

Types of Pharmacy Practice Areas

Pharmacists practice in a variety of areas including retail, hospitals, clinics, nursing homes, drug industry and regulatory agencies. Pharmacists can specialize in various areas of practice including hematology/oncology, infectious diseases, nutrition support, drug information, critical care, pediatrics, etc.

Wholesale Pharmacy

It offers opportunities to a limited number of pharmacists to run wholesale business of drugs and medicines. The wholesalers serve as an intermediary between manufacturer and retailer.

Industrial Pharmacy

Pharmaceutical industry offers opportunity to pharmacist of all educational levels. It provides job to a pharmacist in the following fields:

I. Production

II. Analytical and Quality Control

III. Research and Development and New drug discovery

IV. Medico-marketing and sales clinical trials

V. Clinical Trials.

I. Production: In production, the pharmacist works as manufacturing chemist. He has to supervise the production of various types of pharmaceutical formulations, packaging, labeling and storage. Pharmacists with bachelor degree in pharmacy are absorbed as manufacturing chemist.

II. Analytical and Quality Control: A manufacturing unit needs the service of analytical chemists in its analytical laboratory to do testing of raw materials and finished goods manufactured by it. Pharmacists with bachelor degree in pharmacy get job of analytical chemist.

III. Research and Development and New drug discovery: Mostly Pharmaceutical Industries have their own separate Research and Development unit. A pharmacist having Doctorate or master degree in pharmacy is ideally suited for Research and Development department in pharmaceutical industries.

Research and development unit engage in the following fields:-

(a) Synthesis of new compounds to be used as drugs, cosmetics, excipients, industrial chemicals etc.

(b) Isolation and purification of active principles of plant and animal tissues, determination of their chemical composition and its synthesis.

(c) Preparation of drugs in suitable dosage forms and its testing to find the bioavailability of drugs.

(d) The physical, chemical and biological standardization of drugs.

(e) Research on pharmacokinetics, pharmacodynamics and toxicology of new drugs.

(f) The stability of dosage form during its storage and finding its expiry date.

IV. Medico-marketing and sales: Pharmaceutical marketing means the performance of pharmaceutical business activities that direct the flow of pharmaceutical formulations and services from producer to consumers. Sale team consists of medical representatives, sale representatives, field officers, area managers, regional managers and sales managers. Pharmacist with bachelor degree in pharmacy, having an aptitude for sale, is best fitted in this field, because there is lot of scope of promotion.

V. Clinical Trials: Now a day there is enough openings in clinical trials. India has been recognized as the best place in the world to carry out clinical trials before launch of new drug molecule in the market.

Pharmacy Education (Academics)

Due to rapid growth of pharmaceutical industry and expansion of health services in the country, there is steep increase in the number of pharmacy teaching institutions in the country. In order to fulfill the demand, there is need for qualified and experienced faculty members. So there is more scope for fresh pharmacy graduates to be absorbed as faculty members in these teaching institutions.

Community Pharmacy

A pharmacy or drug store is the place where most pharmacists practice the profession of pharmacy. A **community pharmacy** is a healthcare facility that is able to provide pharmacy services to people in a local area or community. A community pharmacy dispenses medicine and typically involves a registered pharmacist with the education, skills and competence to deliver professional services to the community.

Hospital Pharmacy

Hospital pharmacists work in a hospital pharmacy service, primarily within the public sector. They are experts in the field of medicines and are not only responsible for the dispensing of prescriptions but also the purchase, manufacture and quality testing of all medicines used in a hospital. Many hospital pharmacists are qualified to prescribe in their own right.

Hospital pharmacists are medicine experts and tasks may include:-

- Checking prescriptions to ensure that there are no errors and that they are appropriate and safe for the individual patient.
- Providing advice on the dosage of medicines and the most appropriate form of medication, for example, tablet, injection, ointment or inhaler.
- Participating in ward rounds, discussing treatments with patient's relatives.
- Ensuring medicines are stored appropriately and securely.

Clinical Pharmacy

Clinical pharmacists provide a direct patient care service that optimizes the use of medication and promotes health, wellness, and disease prevention. Clinical pharmacists care for patients in all health care settings but the clinical pharmacy movement initially began inside hospitals and clinics. Clinical pharmacists often collaborate with physicians and other healthcare professionals to improve pharmaceutical care.

Veterinary Pharmacy

Veterinary pharmacies, sometimes called animal pharmacies may fall in the category of hospital pharmacy, retail pharmacy. Veterinary pharmacies stock different varieties and different strengths of medications to fulfill the pharmaceutical needs of animals

1.3 INTRODUCTION TO PHARMACOPOEIA

1.3.1 Pharmacopoeia

Derived from Greek words **'Pharmakon'** means **drug** and **'Poeia'** means **to make**.

The books containing the standards for drugs and other related substances are known as pharmacopoeias and formularies. Collectively these books are known as **Drug Compendia**.

The pharmacopoeias contain a list of drugs and other related substance regarding their source, descriptions, tests, formulae for preparing the same, action and uses, doses, storage conditions etc.

It is a legal and official book issued by recognized authorities usually appointed by Government of each country.

These books are revised from time to time as to introduce the latest information available as early as possible after they become established.

Classification

The drug compendia are classified as:

(1) Official compendia.

(2) Non-official compendia.

(1) Official compendia: Official compendia are the compilation of drugs and other related substances which are recognized as legal standards of purity, quality and strength by government agency of respective countries of their origin. Official compendia include:

(a) British Pharmacopoeia.

(b) British Pharmaceutical Codex.

(c) Indian Pharmacopoeia.

(d) United State Pharmacopoeia.

(e) National Formulary.

(2) Non-official compendia: The books other than official drug compendia which are used as secondary reference sources for drugs and other related substances are known as non-official drug compendia. These include

(a) Merck Index.

(b) Remington's Pharmaceutical Sciences.

(c) The United States Dispensary.

1.3.2 Indian Pharmacopoeia

The development of IP was started with an aim to promote public health by bringing out authoritative and officially accepted standards for quality of drugs including active pharmaceutical ingredients, excipients, dosage forms and medical devices for use by health professionals, patients and consumers.

- In pre-independence days, British Pharmacopoeia was used in India.
- In 1946 Government of India issued one list known as 'The Indian Pharmacopoeial list' which was used as supplement to British Pharmacopoeia.
- Committee under chairmanship of Sir R. N. Chopra alongwith other nine members prepared 'The Indian Pharmacopoeial list'.
- It was prepared by Department of Health, Government of India, Delhi in 1946.
- In 1948 Government of India appointed an Indian Pharmacopoeia committee for preparing 'Pharmacopoeia of India'.
- Tenure of this committee was five years.

In 1955 first edition of Indian Pharmacopoeia committee under chairmanship of Dr. B. N. Ghosh was published.

- It is written in English and official titles of monographs given in Latin.
- 1960 - Supplement to this edition was published

In 1966 Second edition of IP was published under the chairmanship of Dr. B. Mukherji.

- Official titles of monographs given in English.
- Doses were expressed in Metric system.
- Formulations of the drugs were given immediately after the monograph of drugs.
- 1975 - Supplement to this edition was published.

In 1985, third edition of IP was published with two volumes and nine appendices.

- 261 new monographs have been added.
- Addendum I to IP was published in 1989 were 46 new monographs added and 126 amended.
- Addendum II was published in 1991 were 62 new monographs added and 110 amended.

In 1996 Fourth edition of IP was published under the chairmanship of Dr. Nityanand.

- It has been made effective from 1st December 1996.
- It covered 1149 monographs and 123 appendices.
- It includes 294 new monographs and 110 monographs have been deleted.
- Addendum I has been made effective from 31st December 2000 were 42 new monographs have been added.
- Addendum II has been made effective from 30th June 2003 were 19 new monographs have been added.
- The veterinary supplement to IP 1996 contains 208 monographs and four appendices.

In 2007, fifth edition of IP was published and addendum to this edition was published in 2008.

- IP 2007 is presented in three volumes.
- Volume one contains general notices and general chapters.
- Volume two and three contains general monographs on drug substances, dosage forms and Pharmaceutical aids.

In 2010, sixth edition of IP was published.

- The 6th edition of the Indian Pharmacopoeia 2010 is published by the Indian Pharmacopoeia Commission (IPC), Ghaziabad.
- This edition was effective from 1st September, 2010.
- The Indian Pharmacopoeia 2010 is presented in three volumes.
- Volume I contains the Notices, Preface, the Structure of the IPC, Acknowledgements, Introduction, and the General Chapters.
- Volume II contains the General Notice, General Monographs on Dosage Forms and Monographs on drug substances, dosage forms and pharmaceutical aids (A to M).
- Volume III contains Monographs on drug substances, dosage forms and pharmaceutical aids (N to Z).
- Monographs on Vaccines and Immunosera for Human use, Herbs and Herbal products, Blood and blood-related products, Biotechnology products and Veterinary products.
- The number of monographs of Excipients, Anticancer drugs, Herbal products and antiretroviral drugs has been increased in this edition.
- A chapter on NMR and chapter on microbial contamination also updated.

In 2014, seventh edition of Indian Pharmacopoeia was published.

- The seventh edition of the Indian Pharmacopoeia (IP 2014) is published by the Indian Pharmacopoeia Commission (IPC) on behalf of the Government of India, Ministry of Health and Family Welfare by Ghulam Nabi Azad.

- The Indian Pharmacopoeia 2014 is presented in four volumes.
- The scope of the Pharmacopoeia has been extended to include additional anticancer drugs and antiretroviral drugs and formulations, products of biotechnology, indigenous herbs and herbal products, veterinary vaccines.
- The IP 2014 incorporates 2550 monographs of drugs out of which 577 are new monographs consisting of APIs, excipients, dosage forms and herbal products etc.

1.3.3 British Pharmacopeia

- First edition of BP was published in 1864.
- It consists of two sections:
  Part I: Materia Medica and
  Part II: Preparation and compounding.
- Second edition of BP was published in 1867.
- Third edition of BP was published in 1884.
- Fourth edition of BP was published in 1898.
- Next edition of BP was published in 1914.
- Next edition of BP was published in 1953.
- In this edition titles of drugs and preparations were in English instead of Latin and metric system.
- It has been published annually.
- In BP 2007 monographs has been introduced for material specifically used in preparation of Traditional chinese medicines.
- BP 2008 contains approximately 3100 monographs for substances, preparations and articles used in practice.
- It has been made effective from 1st January 2008.
- BP 2007, 2008, 2009 were given in six volumes i.e. volume I to volume VI.
- Volume I and II contains medicinal substances.

- Volume III contains formulated preparations, blood related products, immunological products, radiopharmaceutical preparations, surgical materials and homoeopathic preparations.
- Volume IV contains supplementary chapters, IR spectra etc.
- Volume V contains veterinary.
- Volume VI contains CD ROM version.

The British Pharmacopoeia 2010

- Medicines and Healthcare products Regulatory Agency (MHRA), has published the British Pharmacopoeia (BP) 2010.
- The British Pharmacopoeia (BP) is the official collection of standards for UK medicinal products and pharmaceutical substances. Published annually the BP contains monographs for pharmaceutical substances, formulated preparations and other articles used in the practice of medicine.
- The standards in the BP 2010 are legally effective in the UK from 1st January 2010.
- The BP has been providing authoritative, official standards for pharmaceutical substances and medicinal products since 1864. Today, it is used in almost 100 countries worldwide and remains an essential reference.

New to the British Pharmacopoeia 2010

- 40 monographs for formulated preparations, including veterinary medicines and standards used for unlicensed formulations.
- BP contains new and revised monographs for herbal medicinal products and for homeopathic stocks and mother tinctures.
- The BP 2010 comprises four volumes of the BP 2010 and a single volume of the BP (Veterinary) 2010.

The British Pharmacopoeia 2013

- Six volume printed edition including the BP (Veterinary) 2013.

New for British Pharmacopoeia 2013

- 41 new BP monographs.
- 40 new European Pharmacopoeia monographs.
- 619 amended monographs.
- 6 new and 1 amended Infrared Reference Spectra.

The British Pharmacopoeia 2014

- The only official source of British pharmaceutical standards.
- Produced by the British Pharmacopoeia Commission Secretariat of the Medicines and Healthcare Products Regulatory Agency (MHRA), and updated annually.
- The 2014 edition includes almost 3500 monographs which are legally enforced by the Human Medicines Regulations 2012.

- The BP 2014 has five volumes of the British Pharmacopoeia 2014 and a single volume of the British Pharmacopoeia (Veterinary) 2014, along with a fully searchable CD-ROM and online access.

New for British Pharmacopoeia 2014

- Legally effective from 1 January 2014.
- 40 new BP monographs.
- 272 amended monographs.
- Three new Supplementary Chapters.
- Four new BP (Vet) monographs.
- One new BP (Vet) Supplementary Chapter.

1.3.4 United State Pharmacopoeia

The United States Pharmacopoeia and National Formulary (USP-NF) is an official public standards–setting authority for all prescription and over–the–counter medicines and other health care products manufactured or sold in the United States.

USP also sets recognized standards for food ingredients and dietary supplements. These standards help to ensure the **quality, purity, strength,** and **consistency** of products made for public consumption.

USP's standards are recognized and used in more than 130 countries around the globe. USP's work is aided by the participation and oversight of volunteers representing pharmacy, medicine, and other health care professions as well as academia, government, the pharmaceutical and food industries, health plans, and consumer organizations.

The United States Pharmacopoeia was originally published in 1820 under the authority of the United States Pharmacopoeial Convention and the National Formulary was published in 1888 under the guidance of American Pharmaceutical Association.

In 1974 the National Formulary was purchased by the United States Pharmacopoeial Convention and from 1980 onwards only one official book of drug standards was published under the heading, The United States Pharmacopoeia and The National Formulary (USP-NF).

The United States Pharmacopoeia–National Formulary (USP–NF) 2009 is a book of public pharmacopoeial standards.

It contains standards for medicines, dosage forms, drug substances, excipients, medical devices, and dietary supplements.

USP–NF in English is available in print, online, and CD formats.

The USP–NF is a three volume combination of two official compendia, the United States **Pharmacopoeia (USP) and the National Formulary (NF)**

Monographs for drug substances and preparations are featured in the USP.

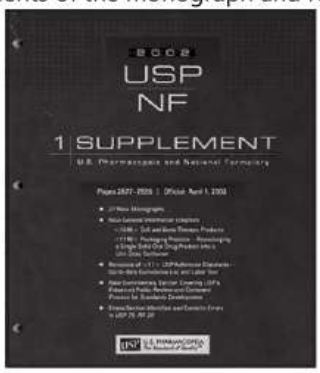
Monographs for dietary supplements and ingredients appear in a separate section of the USP.

Excipient monographs are in the NF.

A monograph includes the name of the ingredient or preparation; the definition; packaging, storage, and labeling requirements; and the specification.

The specification consists of a series of tests, procedures for the tests, and acceptance criteria. These tests and procedures require the use of official USP Reference Standards.

Medicinal ingredients and products will have the stipulated strength, quality, and purity if they conform to the requirements of the monograph and relevant general chapters.



1.3.5 Extra Pharmacopoeia

The Extra Pharmacopoeia was first produced in 1883 by William Martindale and is still known as "Martindale".

This is an authorized reference book on drugs and is used throughout the world.

It provides all sorts of latest information on drugs and medicines.

The Extra Pharmacopoeia is prepared by consulting the pharmacopoeias of other countries.

The twenty-eighth edition was published in December 1982.

The twenty-ninth edition was published in January 1989, by direction of the council of The Royal Pharmaceutical Society of Great Britain and prepared in the Society's Department of Pharmaceutical Sciences.

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.

1.4 INTRODUCTION TO PHARMACEUTICAL DOSAGE FORM

Dosage forms are the safe, effective and stable terms in which medication will be delivered into the body. Dosage forms are essentially pharmaceutical product which are marketed for use typically involving a mixture of active drug components and excipients (non-drug components). These dosage forms are classified in a number of ways as mentioned below by which drug molecules are delivered to the site of action.

1. Form wise: (i) Solid dosage form
   (ii) Liquid dosage form
   (iii) Semi-solid dosage form
2. Route wise: (i) Oral dosage form
   (ii) Topical dosage form
   (iii) Parenteral dosage form
3. Release rate: (i) Sustained release
   (ii) Prolonged release
   (iii) Controlled release
   (iv) Targetted drug delivery

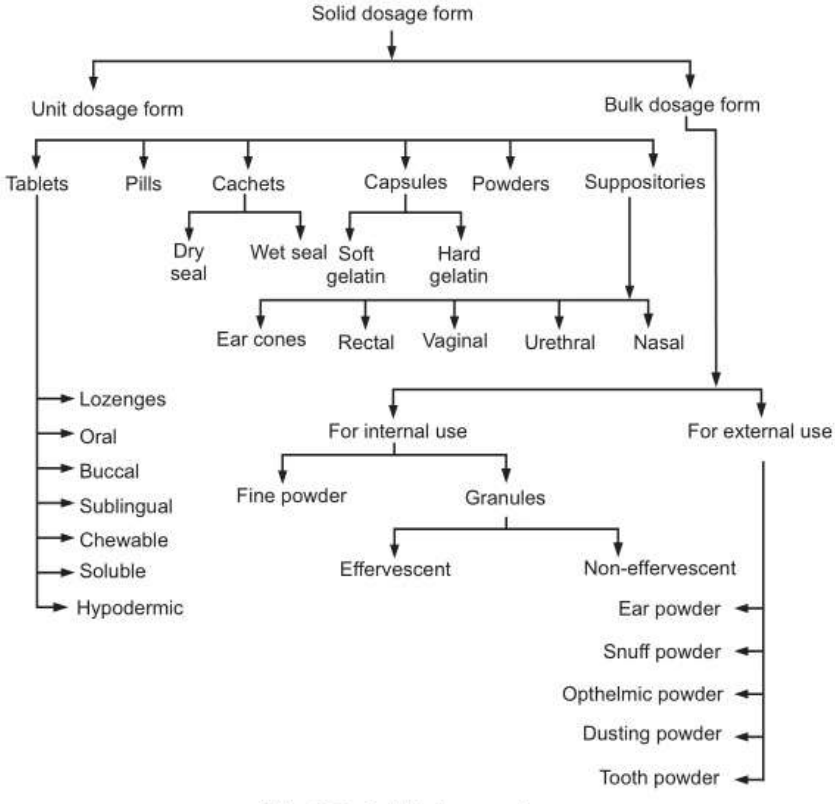


Fig. 1.2: Solid dosage form

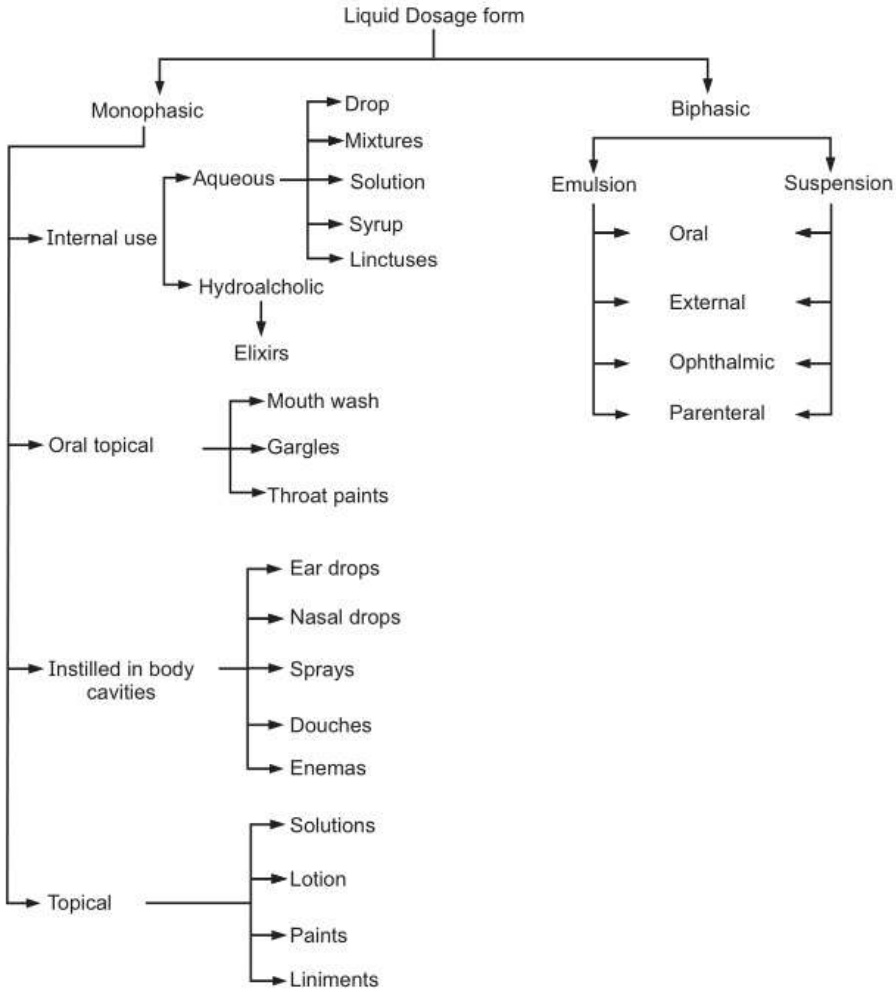


Fig. 1.3: Liquid dosage form

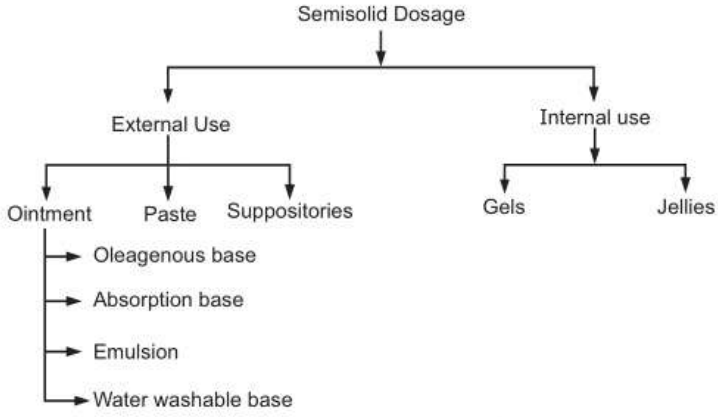


Fig. 1.4: Semi-solid dosage form

1. Aromatic water: They are saturated aqueous solution of volatile oils or other aromatic or volatile substances. e.g. Camphor water, concentrated Peppermint water.

Mainly used as flavouring agent. They are prepared by:-

A. Distillation. e.g. Strong rose water, orange flower water.

B. Solution method. e.g. Dill water, pepper water, camphor water.

C. Alternate solution method. e.g. Volatile oil is thoroughly mixed with an inert adsorptive agent (talc, kiesulguhr), then one litre of purified water is added and agitated for 10 minutes. The solution is filtered until a clear filtrate is obtained.

e.g. Concentrated peppermint water.

2. Cachets: They are solid dosage form meant for oral administration of nauseous and disagreeable drug substances. These are moulded from rice paper, a material made by pouring a mixture of rice flour and water between two hot polished revolving cylinders upon which water evaporates and a sheet of wafer is formed. In the filling of cachet, the medicament is placed between two pieces of a cachet which are then either wet sealed or dry sealed. Cachets are made in a variety of size holding from 0.2 to 2 grams of powder of medium density. Before administration they are softened by immersion in water for a few seconds and then taken with a draught of water.

3. Tinctures: Tinctures are sweet viscous liquid oral preparation containing medical substances which have demulcent, sedative or expectorant preparation. The simple solution or administrations containing a high proportion of syrup and glycerin have demulcent effect on the mucous membrane of the throat e.g. Codeine tincture. They are alcoholic or hydro alcoholic solution of chemicals or soluble constituents of crude drugs. e.g., orange tinctures, ipecacuanha tincture, cardamom tincture. Tincture contains 20-90% alcohol and spirits, containing volatile substances only.

They are prepared by

(a) Simple dilution of stronger preparation

(b) Maceration

(c) Percolation

4. Spirits: Spirits are alcoholic or hydro alcoholic solution of volatile oils which are used internally for their medicinal values and flavoring agent. Spirit may also applied externally or used by inhalation. e.g., Aromatic spirit of ammonia. They are prepared by

(a) Simple dissolution

(b) Maceration

(c) Chemical reaction

(d) Distillation

5. Proof spirits: They are defined as mixture of alcohol and water which is 51°F weight $12/13^{th}$ of an equal volume of water. The strength of alcoholic preparation are medicated by degrees, over proof (o/p) or under proof (u/p). Any alcoholic solution which contain 57.1% v/v alcohol is a proof spirit and said to be 100 proof.

6. Elixirs: Elixirs are clean liquid, oral alcoholic preparation contain potent and nauseous drugs which are plenty flavoured and usually attractive coloured. They are more stables than mixture.

Classification

(a) Non medicated elixir e.g. Compound benzaldehyde elixir.

(b) Medicated elixir e.g. Chlorpheniramine, Chloral hydrate

7. Syrups: Syrups are concentration aqueous preparation of sugar or sugar substances with or without flavoring agent and medical substances.

(a) Medicated Syrup

(b) Flavoured Syrup

Syrup IP is 66.7% w/w solution of sucrose where as syrup USP is 85% w/v or 64.74% w/w solution of sucrose in purified water.

8. Droughts: Droughts are oral liquid preparation meant to take as a single dose. A single dose of mixture is usually known as draught.

(a) Male fern drought

(b) Paraldehyde drought: oxidizes to acetic acid on storage leads to death.

9. Drops: Drops are liquid oral preparation of potent drugs or vitamin which are given in to original form without dilution.

10. Ear drops: They are liquid preparations meant for instillation in to ear. In these preparations, the drug is usually dissolved or suspended in a suitable solvent such as propylene glycol, polyethylene glycol, glycerol, alcohol and water or a mixture of these. Aqueous vehicle is generally not preferred because the secretions in the ear are fatty in nature and as such these do not mix with water.

11. Eye drops: They are aqueous and oily solutions or suspensions of one or more active ingredients for instillation in to the eye sac. These are sterile free from foreign particles and irritating effect. They contain auxiliary substance such as isotonicity agent, buffers, antioxidant, stabilisers and preservatives.

Fig. 1.5

They are Categorised in to number of various types:

1. Liquid preparation for application to the surface of eye. e.g., Eye drops, lotions.
2. Semisolid dosage forms eg., Ointment, Cream, gels.
3. Parenteral products for sub-conjunctival or Intraocular injection.
4. Solid dosage form intended to be placed in contact with surface of eye e.g., ocusert.

12. Ointments: Ointments are semisolid preparation indented to adhere to the skin or certain mucous membranes. They are usually solutions or dispersions of one or more medicaments in non-aqueous bases.

Ointment bases are often anhydrous and include fats, oils and waxes of animal vegetable or mineral origin.

Fig. 1.6

13. Eye Ointment: These are sterile semi-solid preparations of homogeneous appearance intended for application to the conjunctiva or margins of eyelids. They contain one or more active ingredients dissolved and dispersed in a suitable base like soft paraffin, liquid paraffin and wool fat. They contain suitable amount of antioxidant, stabilizers and antimicrobial preservatives.

14. Gargles: Gargles are aqueous solution used to prevent or treat infection. They are usually available in concentrated form with direction for dilution with warm water before use. They are brought into intimate contact with mucous membrane of throat and are allowed to remain in contact with it for few second, before they are thrown out of mouth. Phenol or thymol may be present in low concentrations which exert mild anaesthetic effect. KCl is included in gargle preparation for its weak astringent effect. Gargle differs from mouth washes because they are light medicated oral mixture which is to be diluted with water before use.

e.g. Phenol gargle, $KClO_3$ gargles.

(a) (b)

Fig. 1.7

15. Creams: Creams are viscous semisolids are usually o/w emulsions (aqueous Creams) or w/o emulsions (oily creams). Creams are usually pseudoplastic and exhibit low yield values. The microstructure of o/w cream may comprise several phases, such as viscoelastic gel with fixed water, dispersed oil, free water and crystalline material from fatty alcohol. Rigidity can be increased by incision of higher concentration of agent which is usually admixture to acetyl and stearyl alcohol and a surfactant.

(a) (b)

Fig. 1.8

16. Gels: Gels are transparent or translucent semisolid or solid preparations, consisting of solution of one or more active ingredients in suitable hydrophilic or hydrophobic bases. They are made with aid of suitable gelling agent. Usually gel exhibit pseudo plastic flow properties and those made with synthetic or semi-synthetic polymers with a high degree of cross have relatively high yield value and low viscosity.

17 Pastes: They are semi-solid preparations for topical application that differ from similar product in containing higher proportions of finely divided medicaments. They are much stiffen than ointment and are used principally as absorbents, antiseptics properties or to smooth broken skin surfaces. Pastes usually consist of finely ground insoluble powder dispersed in hydrocarbon or water miscible bases. Bases used are liquid paraffin/glycerol. They show dilatant properties and has high yield value.

18. Poultices: It consists of moistened masses of vegetable materials or clay that are sometimes heated before application.

Penetration enhancers: e.g. Sulphoxides, amides, surfactants, pyrrrolidones, calcium thioglycerate, propylene glycol.

19. Tablets: Solid unit dosage from intended to be administered in to the oral cavity. They are prepared either by moulding or by compression methods. Tablets are swallowed whole and some after being chewed, some are dissolved or dispersed in water before administration and some are retained in the mouth where the active ingredients are liberated.

Fig. 1.9

20. Capsules: Capsules are solid dosage form usually containing one dose of drug enclosed within a small water soluble shell of a suitable form of gelatin. They are of two types hard gelatin and soft gelatin capsules. Hard gelatin capsules are generally used for filling solid medicaments although liquid can also be filled by incorporating suitable excipients in the formulation. They contain a body and a cap made up of gelatin, water plasticizer and preservatives.

Soft gelatin capsules are used for filling solids, liquids as well as semisolids. The shell of soft gelatin capsules are formed, filled and sealed. They contain large amount of plasticizers as compared to hard gelatin capsules which provide flexibility to the shell.

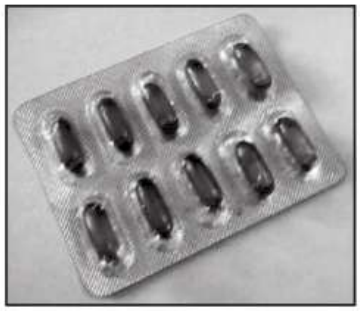


Fig. 1.10

21. Pastilles: Pastilles are solid medicated preparations intended to dissolve slowly in the mouth similar to troches and lozenges. The main difference being that pastilles are comparatively softer. These generally consists of a glycerol and gelatin containing the medicament in solution or suspension. Acacia and sugar are sometimes used when hard pastilles are desired. e.g. Squill pastilles, Menthol and Eucalyptus pastilles.

22. Pessaries: Pessaries are solid dosage forms meant for introduction in to the vagina where they melt or dissolve and exert a local action. Pessaries are prepared either by moulding or by compression. Moulded pessaries are usually cone shaped and prepared in a manner similar to suppositories and hence are also known as vaginal suppositories. Compressed suppositories prepared by compression are available in a variety of shapes and sizes and are also known as vaginal tablets. e.g. Pessaries of Clotrimazole, Nystatin, Ichthammol.

23. Pills: Pills are small, round solid dosage forms containing one or more active ingredients meant for oral administration. Pills are formerly the most extensively used oral dosage form but they have been largely replaced by compressed tablets and capsules.

e.g. Phenolphthalein pills, hexylresorcinol pills.

24. Paints: Paints are solutions or dispersions of one or more active ingredients intended for application to the skin or mucosa of mouth and throat usually with the help of a soft brush or a cotton swab. Skin paints often have a volatile solvent such as alcohol that evaporates quickly to leave a dry or resinous film of medicament. Throat paints are generally more viscous due to a high content of glycerine which being sticky, adheres to the affected area and prolongs the contact time and hence action of the medicament. For example, compound paint of iodine also known as Mandl's paint, crystal violet paint etc.

25. Linctuses: They are viscous, sweet, liquid oral preparations that are usually prescribed for the relief of cold. They consist of simple solutions or admixture containing a high amount of syrup and sometimes, glycerine which in addition to give sweet taste to the preparation have a demulcent action on the mucous membranes of the throat. For best results, linctuses should be used without dilution and sipped and swallowed slowly to ensure prolonged contact with the mucous membrane of the throat. E.g. Codeine linctus, tolu linctus.

26. Liniments: They are liquid or semi-liquid preparations meant for application to unbroken skin by friction or applied on lint or other suitable material and placed on the affected part. They may be alcoholic or oily or soapy solutions or emulsions. Alcoholic liniments are used generally for their rubefacient, counterirritant, mildly astringent, and penetrating effects. The oily or soapy liniments are milder in their action but are more useful when massage is required. Liniments should never be applied to the skin areas that are broken or bruised. E.g. camphor liniment, turpentine liniment.

Fig. 1.11

27. Lotions: Lotions are liquid or semi-liquid preparations meant for application to unbroken skin without friction. They are either dabbed on the skin or applied on a suitable dressing and covered with water proof material to reduce evaporation. An evaporating vehicle like alcohol may be used when a cooling effect is desired on application to the skin. Lotions generally contain antiseptic, astringent, anaesthetics, germicides, protectives or screening agent for prevention or treatment of various skin diseases. e.g. calamine lotion, hydrocortisone lotion.

28. Lozenges: Lozenges are solid dosage forms containing medicaments in a sweetened and flavoured base intended to dissolve slowly in the mouth. The base may be a hard sugar candy, glycerinated gelatins or a combination of sugar with sufficient gum to give it form. Lozenges do not disintegrate in the mouth but dissolve slowly liberating the active ingredients which may be an antiseptic, local anaesthetic, antibiotic, antihistaminic, antitussive, analgesic or a decongestant. They are also known as Troches.

Fig. 1.12

29. Mouth washes: Mouth washes are aqueous solutions containing one or more active ingredients for use in contact with the mucous membrane of the oral cavity usually after dilution with warm water. They contain additives such as alcohol, glycerine, synthetic sweeteners, surfactant, flavouring and colouring agents. They are used for cleansing, refreshing, deodorising, and antiseptic action. They may be either acidic or basic in their reaction and in some instances are fairly effective in reducing bacterial concentration and odours in the mouth for short periods of time.

Fig. 1.13

30. Nasal drops: They are solutions, suspensions or emulsions containing active ingredients intended for instillation in to the nostrils usually with the help of a dropper. Nasal drops are mostly based on aqueous vehicles although oily drops are not common. Oily vehicles are usually not preferred since the oil may retard the ciliary action of the mucosa and may even cause lipoid pneumonia if drops of the oil enter the lungs.

Fig. 1.14

31. Nasal sprays: They are suspensions or solution of drugs intended for spraying in to the nostrils. The chief uses of nasal sprays are to relieve nasal congestion and inflammation and to treat infections. They are intended to be retained in the nasal tract, they are usually viscous and coarse since fine droplets tend to penetrate further in to the respiratory tract. These preparations are usually supplied in pressurized containers or plastic squeeze bottles.

1.5 PRESCRIPTION

What is a Prescription?

A prescription is a legal document or order written by a qualified health care professional for diagnosis, prevention or treatment of a specific patient's disease.

- Is written by a licensed practitioner
- Is written as part of a proper physician-patient relationship
- Is a legal document, "prima facie" evidence in a court of law.

(**Note:** A prima-facie case is a lawsuit that alleges facts adequate to prove the underlying conduct supporting the cause of action and thereby prevail.)

Definition

Literally, "Recipe" means simply "Take...." and when a medical practitioner writes a prescription beginning with "R_x", he or she is completing the command.

It is probably originally directed at the pharmacist who needed to take a certain amount of each ingredient to compound the medicine (rather than at the patient who must "take/consume" it).

Types of Prescription forms

1. **Private prescription form:** This type of prescription generally written on a form that includes name, address and qualification of prescriber. R_x is written to indicate this is prescription form. This is issued by private prescribers.
2. **National Health Service (NHS) prescription form:** It is only issued for NHS patients i.e. patient suffering from certain disease and is issued by Government Prescribers.

1.5.1 Parts of the Prescription

1. Date
2. Patient Information
3. Superscription
4. Inscription
5. Subscription
6. Signa
7. Signature lines, signature, degree, brand name indication
8. Prescriber information
9. DEA (Drug enforcement administration) if required
10. Refills
11. Warnings/label

1. Date

- All prescriptions expire after one year. In case of narcotics and other habit forming drugs the date prevents the misuse of the drugs by the patient. It helps a pharmacist to know when the medicine were last dispensed if the prescription is brought for redispensing.

2. Patient Information

- Name
- Address
- Age
- Weight (optional, but useful – especially in paediatrics)
- Time (used only with inpatient medication orders)

3. Superscription

Represented by symbol R_x, traditional symbol for prescription which is always written before writing prescription. This is derived from latin word 'recipe' which means to take. Instruction given to pharmacist as well as patient to take the medicine as prescribed. Another theory proposed by some scholars is that it drives from the symbol for the god Jupiter. The connection to healing was via prayers that a specific treatment would be effective and the individual would get better.

4. Inscription

This is the main body of prescription which includes the name and quantity of medicine which are prescribed. This is written in English language. All medicines are written in separate line along with their required quantity needed to treat the disease.

What is the pharmacist to take off the shelf?

Drug Name
Dose = Quantity of drug per dose form
Dose Form = The physical entity needed, i.e. tablet, suspension, capsule
Simple versus compound prescriptions
Manufactured versus compounded prescriptions
Clarity of number forms 0.2, 20 not 2.0 (Zeros lead but do not follow!)

5. Subscription

These are instructions given to the pharmacist for dispensing the number of doses to the patient and how the medicine has to be taken before meal or after meal.

What is the pharmacist to do with the ingredients?

Quantity to be dispensed (determines amount in bottle) Dispense # 24.
For controlled substances write in numbers and letters (like a bank cheque)
i.e., 24 (twenty four)
Any special compounding instructions.

6. Signa, Signatura or Transcription

Sig – write, or let it be labelled (Latin terms: Signa or signatura)
Instructions for the patient

- Route of administration
  Oral, nasally, rectally, etc
  Take by mouth …, Give, Chew, Swallow whole, etc.
- Number of dosage units per dose
  Take one tablet, Give two teaspoonfuls, etc.
- Frequency of dosing
  every six hours, once a day …

- Duration of dosing
  for seven days, … until gone,...if needed for pain.
- Purpose of medication
  for pain, for asthma, for headache, etc.
  VERY IMPORTANT to include purpose as this reduces errors!
  "As directed by physician"
- Special instructions (shake well, refrigerate etc.)
- Warnings

7. **Refills or renewal Instruction**
   Indicate either no refills or the number of refills you want (do not leave it blank). Determines maximum duration of therapy.
8. **Signature, address and registration of Prescriber**
   This makes the prescription a legal document. Signature, prescriber registration number is necessary especially in case of habit forming drugs. Prescriber must write "brand necessary," "brand medically necessary," or "DAW" (Dispense as Written) to get non-generics.

Doctor's Name
Qualification (e.g MBBS, MD)
Regn. No. ..... (ALLOPATHY)
Full Address, Contact : (Telephone No., E-mail etc.)
Date
Name of the Patient _____
Address _____
Age & Sex _____ Weight _____
R_X
(1) Name of Medicine _____
Strength, dosage instruction, duration & total quantity _____

(2) - do -
(3) - do –

Doctor's signature
Stamp

DISPENSED
Date : _____ Pharmacist : _____
Name of Pharmacy : _____
City

Postal Address/E-mail/Mobile

1.5.2 Handling of Prescription

The following procedures should be adopted by the pharmacist while handling the prescription for compounding and dispensing:

(i) Receiving.
(ii) Reading and checking.
(iii) Collecting and weighing the materials.
(iv) Compounding, labelling and packaging.

I. **Receiving:** The prescription should be received by the pharmacist himself /herself. While receiving a prescription from a patient, a pharmacist should not change his/her facial expression that gives an impression to the patient that he/she is confused or surprised after seeing the prescription.

II. **Reading and checking:** Reading the prescription and checking for -

(a) Legality

(b) Legibility

(c) Completeness and correctness

(a) Legality: A prescription is legal when:

- It is written (can also be typed) by a R.M.P (Registered medical practitioner).
- Signed by the R.M.P.
- It has all the information required to be contained with respect to parts of prescription.

(b) Legibility: Legibility is a problem requiring alertness and critical judgment on the part of the pharmacist. Careless handwriting and similarity in spelling of names of different drugs add to the difficulty.

e.g. Prednisone and Prednisolone, Digoxin and Digitoxin. When handwriting is illegible, the best thing to do is to contact the physician over the phone and confirm.

(c) Completeness and correctness: The prescription serves as a vehicle for communication from the licensed practitioner to the pharmacist about the pharmaceutical care of the patient. Details to be checked are (i) Physician's details. (ii) Patient's details. (iii) Product details.

Checking the product details will include checking Name of the product, Dosage form, Strength/potency of the medicine, Total amount to be dispensed and its availability Dosage and directions for use, Frequency of administration.

III. **Collecting and weighing the material:** Before compounding a prescription all the materials required for it should be collected from the shelves or drawers and kept in the left hand side of the balance. After measuring each material should be kept on the right hand side of the balance. After compounding the prescription the materials are replaced back to the shelves / drawers where from they were collected. While compounding the label of every container of material should be checked thrice in the following manner:

- When collected from the shelves/drawers.
- When the materials are measured.
- When the containers are replaced back to the shelves/drawers.

IV. **Compounding, labeling and packaging:** Only one prescription should be compounded at a time. Compounding should be done on a clean table. All equipment required should be cleaned and dried. The preparation should be prepared according to the direction of the prescriber or as per methods given in pharmacopoeia or formulary and are according to established pharmaceutical art of compounding. The compounded medicament should be filled in a suitable container with appropriate label depending upon the quantity and use. While delivering the prescription to the patient, the pharmacist should explain the mode of administration, direction for use and storage.

1.5.3 Sources of Errors in Prescriptions

1. **Abbreviation:** In most of the prescriptions abbreviated terms are used by the prescriber that leads to major errors during interpretation by the pharmacists. For example: 'SSKI' is the abbreviated term of 'Saturated Solution of Potassium Iodide'. It is preferable to avoid this types of misleading abbreviations.
2. **Name of the drugs:** Names of some drugs (especially the brand names) either looks or sounds alike. So any error in the name of a drug will lead to major danger to the patient. e.g. Althrocin – Eltroxin, Acidin – Apidin etc
3. **Strength of the preparation:** Drugs are available in the market in various strengths. So a drug must not be dispensed if the strength is not written in the prescription. For example, Paracetamol tablet 500 mg should not be dispensed when no strength is mentioned in the prescription.
4. **Dosage form of the drug prescribed:** Many drugs are available in more than one dosage forms e.g. liquid, tablets, injections or suppositories. The dosage form intended for the patient must be mentioned in the prescription to reduce ambiguity.
5. **Dose:** If unusually high or low dose is mentioned in the prescription then it must be consulted with the prescriber. Some time a sustained release (SR) dosage form is prescribed thrice or more times daily. Actually Sustained Release dosage forms should be given once or twice a day.
6. **Instructions to the patient:** Sometimes the instruction for a certain preparation is either omitted or mentioned partially. The quantity of the drug to be taken, the frequency and timing of administration and route of administration should be mentioned clearly so that it is easy for patients to take medicine.
7. **Incompatibilities:** It is essential to check that there is no pharmaceutical or therapeutic incompatibilities in the prescription. If more than two medicines are prescribed then it is the duty of the pharmacist to see whether their interactions will produce any harm to the patient or not. Certain drugs has interactions with food. The pharmacist has to advise the patient about it. For example: Tetracycline should not be taken with milk or antacid.

1.5.4 Abbreviation used in Prescription

Abbreviation	Latin	English
tsp		teaspoon
troch.	trochiscus	lozenge
trit.	triturate	grind to a powder
tr, tinc., tinct.	tinctura	tincture
TPN		total parenteral nutrition
top.		topical
tinct.	tinctura	tincture
Tbsp		tablespoon
tal., t.	talus	such
tab.	tabella	tablet
t.i.w.		3 times a week
t.i.d., t.d.	ter in die	3 times a day
t.d.s., TDS	ter die sumendum	3 times a day
syr.	syrupus	syrup
susp.	suspensio	suspension
supp.	suppositorium	suppository
sum.	sumat [or] sumendum	let him take [or] let it be taken
subQ		subcutaneously
stat	statim	immediately
st.	stet	let it stand (for example, for settling)
SSRI		selective serotonin reuptake inhibitor [or] sliding scale regular insulin
SSI		sliding scale insulin or sliding scale regular insulin
SQ		subcutaneously
sol.	solutio	solution

... Contd.

SOB		shortness of breath
SL, s.l.	sub lingua	sublingually, under the tongue
sing.	singulorum	of each
sig.	signa, signetur	write (write on the label)
sem.	semen	seed
SC		subcutaneous
s.s., SS	semisse	one-half [or] sliding scale
s.o.s., si op. sit	si opus sit	if there is a need
s.i.d.	semel in die	once a day
s.a.	secundum artem	according to the art (accepted practice or best practice)
s.	signa	write (write on the label)
S	sine	without (usually written with a bar on top of the "s")
Rx, R_x, RX, ℞, ℟	recipe	take (often effectively a noun meaning "prescription"—medical prescription or prescription drug)
RL, R/L		Ringer's lactate
rep., rept.	repetatur	repeats
rep.	repetatur	let it be repeated
QWK		every week
q4PM		at 4 pm (can replace "4" with other numbers)
q.v.	quantum volueris [or] quod vide	at will [or] which see
q.s.	quantum sufficiat (subjunctive), quantum sufficit (indicative)	as much as suffices; a sufficient quantity
q.q.h.	quater quaque hora	every 4 hours
q.q.	quaque	every, each

... Contd.

q.p.m.	quaque die post meridiem	every evening (every day after noon)
q.o.d.	quaque altera die	every other day
q.n.	quaque nocte	every night
q.l.	quantum libet	as much as is requisite
q.i.d.	quater in die	4 times a day
q.h.s.	quaque hora somni	every night at bedtime
q.h.	quaque hora	every hour
q.d.s.	quater die sumendus	4 times a day
q.d.p.m.	quaque die post meridiem	once daily in the evening
q.d.a.m.	quaque die ante meridiem	once daily in the morning
q.d./q.1.d.	quaque die	every day
q.a.m.	quaque die ante meridiem	every morning (every day before noon)
q.a.d.	quaque alternis die	every other day
q.1 h, q.1°	quaque 1 hora	every 1 hour (can replace "1" with other numbers)
Q	quaque	every, per
pulv.	pulvis	powder
pt.	perstetur	continue
ppt.	præparata	prepared
pig./pigm.	pigmentum	paint
Ph.Int.	Pharmacopoeia Internationalis	International Pharmacopoeia
Ph.Eur.	Pharmacopoeia Europaea	European Pharmacopoeia
Ph.Br., BP	Pharmacopoeia Britannica	British Pharmacopoeia
Per	per	by or through
part. æq.	partes æquales	equal parts
p.v., PV	per vaginam	vaginally
p.r.n., PRN	pro re nata	as needed
p.r., PR	per rectum	rectally
p.o.	per os	by mouth *or* orally
p.m.	post meridiem	evening or afternoon

... Contd.

p.c.h.s., pc&hs	post cibum et hora somni	after meals and at bedtime
p.c.	post cibum	after meals
p.	perstetur	continue
o 2, o_2		both eyes
Oz		ounce
OPD		once per day
omn. hor.	omni hora	every hour
omn. bih.	omni bihora	every 2 hours
o.u.	oculus uterque	both eyes
o.s.	oculus sinister	left eye
o.n.	omni nocte	every night
o.m.	omni mane	every morning
o.d.	omni die	every day (once daily) (preferred to "qd" in the UK)
o.d.	oculus dexter	right eye
NTE		not to exceed
NS		normal saline (0.9%)
NPO, n.p.o.	nil per os	nothing by mouth
non rep.	non repetatur	no repeats (no refills)
noct.	nocte	at night
NMT		not more than
nebul, neb.	nebula	a spray (such as for insufflation)- nebulizer
MSO_4		morphine sulfate
MS		morphine sulfate or magnesium sulfate
mod. præscript.	modo præscripto	in the manner directed
mL		millilitre
mit., mitt.	mitte	send
mist.	mistura	mixture

... *Contd.*

min.	minimum [or] minim [or] minutum	minimum [or] minim [or] minute
$MgSO_4$		magnesium sulfate
mg/dL		milligrams per deciliter
mg		milligram
mEq		milliequivalent
mcg		microgram
max.	maximum	maximum
mane	mane	in the morning
m.d.u.	more dicto utendus	to be used as directed
M., m.	misce	mix
lot.	lotio	lotion
liq.	liquor	solution
lin	linimentum	liniment
lb.	libra	pound
lat. dol.	lateri dolenti	to the painful side
LAS		label as such
l.c.d.	liquor carbonis detergens	coal tar solution
kg		kilogram
IVPB		intravenous piggyback
IU		international unit
IT		intrathecal
IP		intraperitoneal
inf.	infusum	infusion (extraction) / intravenous infusion
ind.	indies	daily
IN		intranasal
IJ, inj.	injectio	injection
iii	tres tabuletta	three tablets
ii	duo tabuletta	two tablets
ID		intradermal

... Contd.

IBW		ideal body weight (for dosing based on clearance estimation)
i.v.p., IVP		intravenous push
i.v., IV		intravenous
i.m., IM		intramuscular
i	unus tabuletta	one tablet
hor. tert.	horis tertiis	every third hour
hor. intermed.	horis intermediis	at intermediate hours
hor. decub.	hora decubitus	at bedtime
hor. alt.	hora alternis	every other hour (every second hour; at alternate hours)
habt.	habeat	let him have
h.s.	hora somni (at the hour of sleep)	at bedtime [or] half-strength
h, hr, hor.	hora	hour
H		hypodermic
gutt.	gutta(e)	drop(s)
gtt(s)	gutta(e)	drop(s)
gr.	granum	grain
garg.	gargarisma	gargle
g, gm		gram (modern SI symbol is g, not gm)
ft.	fiat	make; let it be made
fl., fld.	fluidus	fluid (usually meaning specifically liquidin health care)
f.s.a.	fiat secundum artem	make according to art
f.m.	fiat mistura	make a mixture
f.h.	fiat haustus	make a draught
f. pil.	fiat pilula	make a pill
f.	fiat	make; let it be made
exhib.	exhibiatur	let it be given

... *Contd.*

ex aq.	ex aqua	in water
et	et	and
EOD		every other day
emuls.	emulsum	emulsion
elix.	elixir	elixir
e.m.p.	ex modo prescripto	as directed (in the manner prescribed)
DW		distilled water [or] dextrose in water (intravenous sugar solution)
DTO		deodorized tincture of opium
DS		double strength
dL		deciliter
div.	divide	divide
disp.		dispersible [or] dispense
dim.	dimidius	one-half
dil.		dilute
dieb. alt.	diebus alternis	every other day; on alternate days
det.	detur	let it be given
decoct.	decoctum	decoction
DC, dc, D/C, disc		discontinue [or] discharge
DAW		dispense as written (i.e., no generic substitution)
da	da	give
D5W, D_5W		dextrose 5% in water (intravenous sugar solution)
D5NS		dextrose 5% in normal saline (0.9%) (intravenous sugar solution)
D5LR		dextrose 5% in lactated Ringer's solution(intravenous sugar solution)
D10W, $D_{10}W$		dextrose 10% in water (intravenous sugar solution)

... Contd.

d.t.d.	dentur tales doses	give of such doses
d. in p. æ.	divide in partes æquales	divide into equal parts
D, d.	die [or] dosis	days [or] doses
cyath. vinos.	cyathus vinosus	a wine-glassful
cyath.	cyathus	a glassful
cuj.	cujus	of which
CST		continue same treatment
cr., crm		cream
cpt.	capiat	let him take (let the patient take)
contin.	continuetur	let it be continued
comp.	compositus	compound
colet.	coletur	let it be strained
cochl. parv.	cochleare parvum	a scant spoonful (a teaspoonful)
cochl. mod.	cochleare modicum	a modest spoonful (a dessert-spoonful)
cochl. mag.	cochleare magnum	a large spoonful (a tablespoonful)
cochl. infant.	cochleare infantis	a small spoonful (a teaspoonful)
cochl. ampl.	cochleare amplum	an ample spoonful (a tablespoonful)
cochl.	cochleare	spoonful
cib.	cibus	food
cf.	confer	compare
cap., caps.	capsula	capsule
cap.	capiat	let him take (let the patient take)
c.v.	cras vespere	tomorrow evening
c.n.	cras nocte	tomorrow night
c.m.s.	cras mane sumendus	to be taken tomorrow morning
c.m.	cras mane	tomorrow morning
c.c.	cum cibo	with food [or] cubic centimetre
c, c.	cum	with (usually written with a bar on top of the "c")

... Contd.

bucc.	bucca	buccal (inside cheek)
BSA		body surface area
BS		blood sugar
BP, Ph.Br.	Pharmacopoeia Britannica	British Pharmacopoeia
bol.	bolus	as a large single dose (usually intravenously)
BNF		British National Formulary
BM		bowel movement
bis ind.	bis indies	twice a day
bis in 7 d.	bis in septem diebus	twice a week
bis	bis	twice
bib.	bibe	drink
BDS, b.d.s.	bis die sumendum	twice daily
b.t.		bedtime
b.i.d., b.d.	bis in die	twice daily
ATC		around the clock
aq. ferv.	aqua fervens	hot water
aq. dest.	aqua destillata	distilled water
aq. com.	aqua communis	common water
aq. bull.	aqua bulliens	boiling water
aq.	aqua	water
amt		amount
amp.	ampulla	ampule (ampul, ampoule)
alt. h., alt. hor.	alternis horis	every other hour; at alternate hours
alt. d., alt. dieb.	alternis diebus	every other day; on alternate days
agit.	agita	agitate (stir or shake)
admov.	admove admoveatur	apply [or] add add; let there be added
add.	adde addatur	add let there be added
ad.	adde addatur	add let there be added

... *Contd.*

ad us.	ad usum	according to custom
ad lib.	ad libitum	Latin, "at one's pleasure"; as much as one desires; freely
AAA		apply to affected area
aa, āā, ĀĀ	ana	of each
a.u.	auris utraque	both ears
a.m.	ante meridiem	morning, before noon
a.l., a.s.	auris laeva, auris sinistra	left ear
a.d.	auris dextra	right ear
a.c.h.s., ac & hs	ante cibum et hora somni	before meals and at bedtime
a.c.	ante cibum	before meals
@		at
>		greater than
<		less than

1.6 POSOLOGY

The word posology is derived from the Greek words **'posos'** meaning how much and **'logos'** meaning science**.** So **posology** is a branch of medical science which deals with dose or quantity of drugs which can be administered to a patient to get the desired pharmacological actions.

1.6.1 Factors Affecting Posology

The following are some of the factors which influence the dose.

1. Age: The pharmacokinetics of many drugs changes with age. So while determining the dose of a drug, the age of an individual is of great significance. Children and old people need lesser amount of drug than the normal adult dose, because they are unable to excrete drugs to that extent as adults. Children can tolerate relatively larger amounts of belladonna, digitalis and ethanol, whereas elderly patients are more sensitive to some drug effects. For example, hypnotics and tranquillizers which may produce confusion states in them.

2. Gender: Women do not always respond to the action of drugs in the same manner as it is done in men. Morphine and barbiturates may produce more excitement before sedation in women. Special care should be taken when drugs are administered during menstruation, pregnancy and lactation. There are certain drugs which on administration to the mother are capable of crossing the placenta and affecting the foetus e.g. alcohol, barbiturates, narcotic and non-narcotic analgesics etc.

3. Body weight: The average dose is mentioned either in terms of mg per kg body weight or as a total single dose for an adult weighing between 50-100 kg. However, the dose expressed in this fashion may not apply in cases of obese patients, children and malnourished patients. It should be calculated according to body weight.

4. Route of administration: Intravenous doses of drugs are usually smaller than the oral doses, because the drugs administered intravenously enter the blood stream directly. Due to this reason the onset of drug action is quick with intravenous route and this might enhance the chances of drug toxicity. The effectiveness of drug formulation is generally controlled by the route of administration,

5. Time of administration: The presence of food in the stomach delays the absorption of drugs. The drugs are more rapidly absorbed from the empty stomach. So the amount of drug which is very effective when taken before a meal may not be that much effective when taken during or after meals. The irritating drugs are better tolerated if administered after meals for example, iron, arsenic and cod-liver oil should always be given after meals.

6. Environmental factors: Daylight is stimulant, enhancing the effect of stimulating drugs and diminishing the effect of hypnotics. Darkness is sedative. Hypnotics are more effective at night. The amount of barbiturate required to produce sleep during day time is much higher than the dose required to produce sleep at night. Alcohol is better tolerated in cold environments than in summer.

7. Emotional factors: The personality and behaviour of a physician may influence the effect of drug especially the drugs which are intended for use in a psychosomatic disorder. The females are more emotional than males and requires less dose of certain drugs.

8. Presence of disease: Drugs like barbiturates may produce unusually prolonged effect in patients having liver cirrhosis. Streptomycin is excreted mainly by the kidney may prove toxic if the kidney of the patient is not working properly.

9. Accumulation: The drugs which are slowly excreted may built up a sufficient high concentration in the body and produce toxic symptoms if it is repeatedly administered for a long time e.g. digitalis, emetine and heavy metals. This occurs due to accumulative effect of the drug.

10. Additive effect: When the total pharmacological action of two or more drugs administered together is equivalent to sum of their individual pharmacological action, the phenomena is called as an additive effect. For example, combination of ephedrine and aminophylline in the treatment of bronchial asthma.

11. Synergism: When two or more drugs are used in the combination their action is increased. The phenomena is called synergism.

12. Antagonism: When the action of one drug is opposed by the other drug on the same physiological system is known as drug antagonism. The use of antagonistic responses to drugs is valuable in the treatment of poisoning e.g. milk of magnesia is given in acid poisoning where alkaline effect of milk of magnesia neutralise the effect of acid poisoning.

13. Idiosyncrasy: An extraordinary response to a drug which is different from its characteristic pharmacological action is called idiosyncrasy. The word idiosyncrasy has now been replaced by the term drug allergy. For example, small quantity of aspirin may cause gastric haemorrhage and a small dose of quinine may produce ringing in the ears.

14. Tolerance: When an unusually large dose of a drug is required to elicit an affect ordinarily produced by the normal therapeutic dose of the drug, the phenomenon is termed as drug tolerance. e.g., smokers can tolerate nicotine, alcoholic can tolerate large quantity of alcohol.

15. Metabolic disturbances: Changes in water electrolyte balance and acid base balance, body temperature and other physiological factor may modify the effects of drugs. Salicylates reduce body temperature only in case an individual has rise in body temperature. They have no antipyretic effect if the body temperature is normal.

1.6.2 Formulae used in Calculations of Pediatric Dose

1. **Clark's formula:**

   Child's dose = weight in (lbs)/150 × Adult dose

   Child's dose = weight in (kg)/70 × Adult dose

2. **Dilling's formula:** Used for calculating dose of child from 12-20 years of age.

   Child's dose = Age in years /20 × Adult dose

3. **Fried's formula:** Used for calculating dose of an infant upto 24 months of age.

   Child dose = Age in months /150 × Adult dose

4. **Young's formula:** Used for calculating dose of child from 1-12 years of age.

   Child dose = Age in years/Age + 12 × Adult dose

5. **Cowling's formula:** Child's dose = Age at next birthday/24 × Adult dose

6. **Bastedo's Formula:** Child's dose = Age in Years/ 30 × Adult dose

7. **Calculation based on body surface area:**

   Child's dose = body surface area of the child/1.73 sq. m × Adult dose

SOLVED EXAMPLES

Example 1.1: Calculate the dose for a child of 6 years old for olanzapine by young's formula when adult dose of the drug is 150 mg.

Solution: Child dose = A/A + 12 × Adult dose

6/6 + 12 × 150 = 50 mg

Example 1.2: How will you calculate a dose for a child of 5 years old by Dilling's formula when adult dose of the drug is 1 gm.

Solution: Child Dose = A/20 × Adult dose

= 5/20 × 1 = 0.25 gm

Example 1.3: Calculate the dose of a child of 18 month old by Fried's formula when the adult dose is 500 mg.

Solution: Child Dose = Am/150 × Adult dose where Am is the age of child in month.

= 18/50 × 500 = 60 mg.

Example 1.4: How will you calculate a dose for a child 7 years old by Cowling's formula when the adult dose is 300 mg.

Solution: Child Dose = A/24 × Adult dose

where A = age of child at next birthday in years

8/24 x 300 = 100 mg.

Example 1.5: Calculate the dose for a child of 5 years old whose weight is 22 pounds and adult dose is 600 mg.

Solution: Child Dose = W/150 × Adult dose

where, W is the weight of child in pound.

= 22/150 × 600 = 88 mg.

Example 1.6: Calculate a dose for a child of 5 years old whose surface area is 1.5 m^2 whose adult dose is 40 mg.

Solution: Child Dose = S.A /1.73 × Adult dose

where, S.A. = Body surface area of child in m^2

= 1.5/1.73 × 40 = 34.7 mg

QUESTIONS

Short Answer Questions

1. Define compendia.
2. Define community pharmacy
3. Define prescription.
4. Define superscription.
5. What is sos, tid and AAA?
6. What is dispensing?
7. What is inscription?
8. Define posology.
9. Define idiosyncrasy.
10. Define the term additive effect.
11. Define the term tachyphylaxis.
12. Write clark's formula.
13. Write down the editions of I.P.
14. What is materia medica?
15. Classify official and non official compendia.

Long Answer Questions

1. Write a note on International Pharmacopoeia.
2. Define pharmacopoeia. Explain the salient features of latest edition of IP.
3. Write in detail about origin and development of pharmacy.
4. Write a note on Pharmaceutical education.
5. Discuss and explain about various scope of pharmacy.
6. Write a note on B.P.
7. Write a note on U.S.P.
8. Write in brief on extra pharmacopoeia.

9. What is prescription? Explain various parts of prescription in detail.
10. Discuss handling of prescription and sources of errors in prescription.
11. Define Posology. What are the factors that affect the drug dose?
12. Write down the formulae for the determination of child dose based on age of child.
13. Describe in detail classification of dosage forms.
14. Write Fried's and Dilling's formula to calculate child dose.
15. Why the dose of a drug given i.v is smaller than the dose given orally ?

❑❑❑

Unit...2

PHARMACEUTICAL CALCULATIONS, POWDERS & LIQUID DOSAGE FORMS

♦ OBJECTIVES ♦

- **To understand various pharmaceutical calculations.**
- **To know about powders, different types of powders, their preparation, advantages and disadvantages.**
- **To know liquid dosage forms , their advantages and disadvantages.**
- **To understand about the use of excipients in liquid dosage forms.**
- **To know about solubility enhancement method.**

2.1 PHARMACEUTICAL CALCULATION

Metrology

While dispensing of drug it is desirable for a pharmacist to have thorough knowledge regarding weights and measures which are used in calculations.

There are two types of system for weights and measures:

1. Imperial system
2. Metric system

1. Imperial System

This is an old system of weights and measures.

Weight is a measure of the gravitational force acting on a body and is directly proportional to mass.

The imperial system is divided in two parts for the purpose of measurement of weights. These are

(a) Avoirdupois system.

(b) Apothecaries system.

(a) Avoirdupois System: Primary unit of weight is pound (LB) and all measures of mass are derived from the imperial standard pound thus,

(a) 1 pound (lb) = 16 ounce (oz)

(b) 1 pound = 7000 grains

(c) 1 ounce (oz) = 7000/16 = 437.3 grains

Here only weight is primarily used for compounding.

437.5 grain = 1 oz = 28.35 gm

7000 grain = 1 lb = 16 oz = 454 gm

1 kg = 2.2 lb

1 gr = 64.8 mg

(b) Apothecary System: Comprised of both volume and weight. It is used for compounding and for preparing concentration for dilution. In this system, weight is measured in grain and volume in Minim.

(i) Volume:

1 teaspoonful (tsp) = 5 milliliters (ml) = 1 dram = 5 cubic centimeters (cc)

1 tablespoonful (tbsp) = 15 milliliters (ml)

29.57 milliliters (ml) = 1 fluid ounce (fl oz)

473 milliliters (ml) = 1 pint (pt) = 16 fluid ounce (fl oz)

946 milliliters = 1 quart = 2 pints

3784 milliliters = 1 gallon = 8 pints = 128 fl oz

(ii) Weight:

1 grain = 64.8 mg

1 ounce = 31.1 gm = 480 grain

2. Metric System

The metric system is used for the measurement of weight and capacity. The metric system in India was implemented from 1st April 1964 in pharmacy profession. This system was used the Indian pharmacopoeia. The metric system is an alternative system of measurement used in most countries, as well as in the United States. The metric system is based on joining one of a series of prefixes, including kilo-, hecto-, deka-, deci-, centi-, and milli-, with a base unit of measurement, such as meter, liter, or gram.

Measurement of weight in metric system: A kilogram is the standard unit for measurement of weight and all other measures are derived from it.

1 kilogram (kg) = 1000 grams

1 gram = 1000 mg

1 milligram (mg) = 0.001 gram

1 microgram (mcg) = 0.000,001 gram

1 hectogram (hg) = 100 grams

1 decagram (dag) = 10 grams

1 decigram (dg) = 0.1 gram

1 centigram (cg) = 0.01 gram

Measurement of volume or capacity: for measuring volume litre is used as the standard unit and the remaining measures can be derived from it.

1 litre (lt) = 1000 millitre (ml)

Convert the following apothecary problems using the ratio and proportion method:

1. 2,000 gr = 4.167 oz (AP)
2. 500 gm = 16.077 oz (AP)
3. 500 mg = 7.716 gr
4. 100 fl oz = 6.25 pt
5. 500 fl oz = 3.906 gal
6. 4.5 oz (AP) = 139.95 gm
7. 3 gr = 194.4 mg
8. 20,000 ml = 5.284 gal
9. 3 pt = 1,419 ml
10. 119 ml = 4.024 fl oz
11. 2.5 gal = 320 fl oz
12. 5,000 gr = 10.417 oz (AP)
13. 25 pt = 3.125 gal
14. 1,500 ml = 3.171 pt
15. 6 fl oz = 177.42 ml
16. 0.75 gal = 2,838.75 ml
17. 1,000 gr = 2.083 oz (AP)
18. 3.25 gal = 26 pt
19. 350 gr = 22,680 mg
20. 2.5 oz (AP) = 1,200 gr
21. 1.5 tsp = 7.5 ml
22. 12.5 ml = 2.5 tsp
23. 1.5 fl oz = 44.355 ml
24. 500 mg = 7.716 gr
25. 500 fl oz = 3.906 gal
26. 375 ml = 12.682 fl oz
27. 24 fl oz = 1.5 pt
28. 275 gm = 8.842 oz (AP)
29. 500 ml = 33.333 Tbsp
30. 1 drop = 0.05 ml
31. 1 tsp = 5 ml
32. 1 tbsp = 15 ml
33. 1 wineglass ful = 60 ml
34. 1 tumbler ful = 240 ml
35. 1 inch = 2.54 cm
36. 1 pint = 473ml
37. 1 gallon = 3785 ml
38. 1 quart= 946 ml

2.2 CALCULATION OF ISOTONOCITY

1. Freezing Point Method

The lachrymal secretion contains several solutes in it and has a freezing point of –0.52°C. All solutions, which freeze at –0.52°C, will be isotonic with the lachrymal fluid. Human blood plasma also freezes at this temperature and hence solutions having freezing point at – 0.52°C will be isotonic with blood plasma as well.

Adjustment of tonicity is simplified if the freezing points of the medicament and the inert salt (adjusting substance) are known for various strengths of their solutions. Freezing points are usually expressed in terms of 1% solutions and one can calculate the quantity by multiplying the freezing point with the factor.

The following equation is useful:

Freezing point of tear secretion Freezing point of drug + freezing or human Blood plasma = point of the adjusting substance.

Therefore, the amount of adjusting substance required may be calculated from the equation $W = \frac{(0.52 - a)}{b}$

Where,

W = Weight in g, of the added substance in 100 ml of the final solution;

a = Depression of the freezing point produced by the medicament already present in solution, calculated by multiplying the value for the medicament by the strength of the solution expressed as a percentage w/v; and

b = Depression of the freezing point of water produced by 1% of the adjusting substance.

Example 2.1:

How much boric acid is required to render 200 ml of eyewash containing 1% boric acid are to be dispensed.

(F.P. of 1% boric acid at – 0.29°C and F.P. of 1% solution of sodium chloride = – 0.58°C).

Applying the above equation:

Thus the working formula for 200 ml of the eyewash will be:

Boric acid (1%, for 200 lL) = 1 g × 2 = 2 g.

Sodium chloride (0.39%, for 200 ml) = 0.39 × 2 = 0.78 g.

Purified water q.s. 200 ml.

Solution:

However if the pharmacist has been asked to supply 200 ml of eyewash of boric acid, the calculation will be as follows:

Lowering of 0.29°C in F.P. is caused by 1 g of boric acid

Lowering of 0.52°C in F.P. will be caused by 1.8 g of boric acid

Therefore, 1.8 g of boric acid is required to make 100 ml of eyewash and the working formula will be : Boric acid (1.8%, for 200 ml) = 1.8 × 2 = 3.6 g. Purified water, q.s. 200 ml.

2. Molecular Weight Method

Freezing point of a solute depends on the concentration of the solute dissolved therein. Greater the concentration of the solute, lower is the freezing point. In other words, it depends on the number of ions (more correctly, the number of effective ions), the weight of the substance and its molecular weight. The concentration for 0.9% solution of sodium chloride can be expressed in the following manner:

Percentage w/v of adjusting substance required = 0.03 m/n

Where n = No. of effective ions (n)

m = molecular weight of substances (m)

Since 0.9% solution of sodium chloride (normal saline) is isotonic with body fluids, 0.03 will be the isotonicity or tonicity factor for tear secretion and blood plasma as well. Thus quantities for making eye solutions can be calculated by equating the value of 0.03 with the tonicity contributed by the drug and the additive(s).

The following equation is employed for calculating the quantity of the additive(s):

$$\text{Quantity of additive} = (g/m) \times n$$

where g, n and m denote the weight in gram, effective ion concentration and molecular weight of the medicament, respectively. Effective ionic concentration can be ascertained from the following generalizations;

n = 1 for non-ionizable substances, e.g. dextrose

n = 1.5 for partially ionizable solutes in two ions, e.g. silver nitrate

n = 2 for highly ionizable solutes in two ions e.g. sodium chloride

n = 2 for partially ionizable solutes in three ions, e.g. sodium sulfate

Example 2.2:

Find the concentration of sodium chloride required to produce a solution isoosmotic with blood plasma.

Solution:

Molecular weight of sodium chloride = 58.5

Sodium chloride is ionizing substance and hence it gets dissociated into two ions.

Therefore, the formula used is

$$W = 0.03\ m/n$$

$$= \frac{(0.03 \times 58.5)}{2}$$

$$= 0.88\ g/100\ ml$$

3. Sodium Chloride Equivalent Method

This is the simplest method and is based on the sodium chloride equivalents of various drugs. Sodium chloride equivalent of a drug represents the amount of sodium chloride equivalent to 1 g of the drug. The method avoids tedious calculation.

It can be memorized that 0.27 g of sodium chloride makes 30 ml of a 0.9% solution and that 4.1 grain of sodium chloride makes 1 fl oz. of a 0.9% solution.

This was given by Mellen & Seltzer, also called tonicic equivalent.

* The sodium chloride equivalent of a drug is the amount of sodium chloride that is equivalent to (i.e. has same osmotic effect as 1 g or other weight unit of the drug.

It is represented by "E". E_{value} can be calculated for number of drugs.

It can be calculated from Liso or freezing point depression value.

For solution containing 1 g of drug in 1000 ml or (1L) of solution the molar concentration is

$$c = 1\ g/Mwx_1$$

$$\Delta T_f = Liso\ 1\ g/Mwx_1$$

Now E is the weight of NaCl with "same freezing point depression" of 1 g of the drug and for NaCl solution containing E grams of drug per 1000 ml.

$$\Delta T_f = 3.4E/58.45 \text{ (Liso of NaCl = 3.4)}$$

$$Liso\ 1\ g/Mwx_1 = \frac{3.4E}{58.45}$$

$$E = \frac{17 \times Liso}{Mw}$$

Example 2.3:

Calculate the number of gram of sodium chloride, which should be added to 120 ml of 0.5% solution of pilocarpine hydrochloride to make it isotonic.

Solution:

Weight of pilocarpine hydrochloride contained in the prescription = 120 × 0.5% = 0.6 g Sodium chloride equivalent of pilocarpine hydrochloride = 0.22.

Hence, the amount of sodium chloride represented by pilocarpine hydrochloride contained in the prescription = 0.6 x 0.22 = 0.132 g.

120 mL of 0.9% sodium chloride would contain 120 × 0.9 = 1.08 g of sodium chloride.

This is the amount of sodium chloride required to make 120 ml of isotonic solution in absence of pilocarpine hydrochloride.

Hence, the number of g of sodium chloride required = 1.08 g – 0.132 g = 0.948 g

Example 2.4:

Calculate the number of gram of sodium chloride needed to render 30 ml of physostigmine salicylate solution isotonic.

Solution:

Weight of physostigmine salicylate contained in the prescription = 30 × 0.5 = 0.15 g.

Sodium chloride equivalent of Physostigmine salicylate = 0.14

Hence, Physostigmine salicylate present in the prescription is equivalent to:

$$0.15 \times 0.14 = 0.0210 \text{ of sodium chloride.}$$

30 ml of a solution containing 0.9% sodium chloride will contain 30 × 0.9% = 0.27 g of sodium chloride if sodium chloride alone is present in the prescription.

Number of gram of additional sodium chloride needed = 0.27 g – 0.0210 g = 0.2490 g

Example 2.5:

Calculate the amount of sulphate as barium sulphate from sodium sulphate.

Solution:

Solution of sodium sulphate (Na_2SO_4) is treated with solution of barium chloride ($BaCl_2$) to get precipitates of barium sulphate ($BaSO_4$). The precipitates are then washed, dried and ignited to get free from impurities and then weighed.

$$Na_2SO_4 + BaCl_2 \rightarrow BaSO_4 + 2N$$

Molecular weight of $BaSO_4$ = 233.42 g

Molecular weight of SO_4^- = 96.06 g

Suppose obtained weight of BaSO4 precipitates = X g

233.42 gm of $BaSO_4$ = 96.06 gm of SO_4^- ions

$$BaSO_4 = \frac{96.06}{233.42}$$

= 0.411 g of SO_4^- ions

Suppose 25 ml solution is consumed, then

25 ml solution contains = 0.411 g of SO_4^- ions

1000 ml solution conatins = (0.411 x 1000)/25 = 16.44 g of SO_4^- ions

Example 2.6:

Calculate the amount of zinc oxide from zinc sulphate.

Solution:

A solution of zinc sulphate is boiled to convert it into zinc carbonate by adding solution of sodium carbonate. Sodium carbonate is added to precipitate zinc completely as zinc carbonate. Precipitates of zinc carbonate is boiled for few minutes to convert it into zinc oxide and collected in a tarred Gooch crucible. Precipitates are washed with hot water until it gets free from alkali and then dried, ignited and weighed to a constant weight.

$$ZnSO_4 + Na_2CO_3 \rightarrow ZnCO_3 + Na_2SO_4$$

$$ZnCO_3 \rightarrow ZnO + CO_2$$

$$ZnSO_4 = ZnCO_3 = ZnO$$

$$ZnSO_4 = ZnO$$

Molecular Weight of $ZnSO_4$ = 168 gm

Molecular Weight of ZnO = 81.38 gm

81.38 gm of ZnO = 168 gm of $ZnSO_4$

1 gm of ZnO = ?

$$= \frac{168 \cdot 1}{81.38}$$

= 1.984 gm

Example 2.7:

Calculate the amount of Boric acid from Borax.

Solution:

Borax is an alkaline substance, and reacts with conc. HCl to form Boric acid. Boric acid is freely soluble in boiling water and precipitated out in cold water. To get high grade of Boric acid, Borax is treated with conc. HCl as it is volatile in nature and would not left any residual traces on crystal surface of Boric acid.

Weigh and dissolve 5 gm of Borax in 15 ml of distilled water. Add 7 ml of conc. HCl, mix thoroughly with glass rod and mark the original volume with glass rod. Evaporate the solution till the volume reduces to half of the original volume. Allow to cool at room temperature. Keep it aside for few minutes and add ice water. Filter the residue under suction and dry it in air. Weigh the compound preparation.

$$Na_2B_4O_7 \cdot 10H_2O \rightarrow 4H_3BO_3 + 5H_2O + 2NaCl$$

Molecular weight of Borax = 381.37 gm, Molecular weight of Boric acid = 61.83 gm

Practical yield: X gm

381.37 gm of Borax = 4 × 61.83 gm of Boric acid

X gm of Borax = ?

= (4 x 61.83) /381.37

= 0.674 g of Boric acid

4. Percentage Solutions:

The concentration of a solution is often expressed as the percentage of solute in the total amount of solution. For the extremely dilute solutions the concentration unit parts per million (ppm) is often used. Since, the amounts of solute and solution present can be stated in terms of either weight or volume.

A percentage solution is an weight or volume of something per 100 ml or 100 g of a solution. Percentage means rate per hundred.

50% means 50 parts in 100 of same kind = 50/100 = 0.5

There are three types of percentage solution:

1. Percentage weight by volume (w/v).
2. Percentage volume by volume (v/v).
3. Percentage weight by weight (w/w).

Percent weight in volume w/v: number of gram of a constituent in 100 ml of solution or liquid preparation.

Percent volume in volume v/v: express number of ml of a constituent in 100 ml of a solution or preparation.

Percent weight in weight w/w: express number of gram of a constituent in 100 gram of a solution or preparation.

(a) Percentage Weight by Volume w/v:

$$\text{Concentration (expressed in \%)} = \frac{\text{Quantity or volume of solute}}{\text{Quantity or volume of preparation}}$$

Example 2.8:

How many grams of dextrose are required to prepare 4000 ml of 5% solution?

Solution:

Let the quantity of solute be X

Using the formula

$$\text{Concentration} = \frac{\text{Quantity of solute}}{\text{Quantity of solution}}$$

$$5\% = \frac{X}{4000}$$

Therefore

$$X = \frac{4000 \times 5}{100}$$

$$= 200 \text{ gram of dextrose}$$

Example 2.9:

What is the percentage (w/v) of solution of urea if 80 ml contain 12 g?

Solution:

Let the percentage of urea be X.

Using the formula,

$$\text{Concentration} = \frac{\text{Quantity of solute}}{\text{Quantity of solution}}$$

$$X\% = \frac{12}{80}$$

Or

$$\frac{X}{100} = \frac{12}{80}$$

Or

$$X = \frac{12 \times 100}{80}$$

$$= 15\%$$

Example 2.10:

How many ml of 3% solution can be made from 27 g of ephedrine sulphate?

Solution:

Volume of preparation = X

$$\text{Concentration} = \frac{\text{Quantity of solute}}{\text{Quantity of solution}}$$

$$3\% = \frac{27}{X}$$

Or, $$\frac{3}{100} = \frac{27}{X}$$

Therefore, $$X = \frac{27 \times 100}{3} = 900 \text{ ml}$$

(b) Percentage Volume by Volume v/v:

$$\text{Concentration} = \frac{\text{Volume of solute}}{\text{Volume of preparation}}$$

$$\text{Specific gravity} = \frac{\text{Given weight}}{\text{Volume required}}$$

Example 2.11:

How many ml of liquefied phenol should be used in compounding the following prescription?

Liquid Phenol - 2.5%

Calamine lotion – 240 ml

Solution:

Using the formula,

$$\text{Concentration} = \frac{\text{Volume of solute}}{\text{Volume of preparation}}$$

$$2.5\% = \frac{X}{240}$$

$$X = \frac{2.5 \times 240}{100} = 60 \text{ ml}$$

Example 2.12:

For preparing 250 ml of lotion, 4 ml liquid phenol is used. What was the (v/v)% of liquefied phenol in solution?

Solution:

Using the formula,

$$\text{Concentration} = \frac{\text{Volume of solute}}{\text{Volume of preparation}}$$

$$X\ \% = \frac{4}{250}$$

$$\frac{X}{100} = \frac{4}{250}$$

Or, $$X = \frac{4 \times 100}{250}$$

$$= 1.6\%$$

Example 2.13:

What is the % strength (v/v) of a solution of 800 g of a liquid with a specific gravity of 0.8 in enough water to prepare 4000 ml.

Solution:

$$\text{Specific gravity} = \frac{\text{Weight given}}{\text{Volume required}}$$

$$\text{Volume required} = \frac{\text{Weight given}}{\text{Specific gravity}} = \frac{800}{0.8} = 1000$$

$$\text{Concentration} = \frac{\text{Volume of solute}}{\text{Volume of preparation}}$$

$$= \frac{1000}{4000}$$

$$\frac{X}{100} = \frac{1000}{4000}$$

$$X = 25\%\ v/v$$

(c) Percentage Weight/Weight (w/w):

$$\text{Concentration} = \frac{\text{Weight of solute}}{\text{Weight of preparation}}$$

Example 2.14:

How many grams of phenol should be used to prepare 240 g of 5% (w/w) solution in water?

Solution:

$$\text{Concentration} = \frac{\text{Weight of solute}}{\text{Weight of preparation}}$$

$$5\ \% = \frac{X}{240}$$

$$X = \frac{5 \times 240}{100} = 12\ g$$

Example 2.15:

How many grams of a drug substance are required to make 120 ml of a 20% w/w solution having specific gravity of 1.15.

Solution:

$$\text{Volume of solution} = 120 \text{ ml}$$

$$\text{Weight} = ?$$

$$\text{Volume} = \frac{\text{Weight}}{\text{Specific gravity}}$$

$$\text{Weight} = 120 \times 1.15 = 138 \text{ g}$$

$$\text{Concentration} = \frac{\text{Weight of solute}}{\text{Weight of preparation}}$$

$$20\% = \frac{X}{138}$$

$$X = \frac{20 \times 138}{100} = 27.6 \text{ g}$$

Example 2.16:

How many grams of a drug substance should be dissolved in 240 ml of water to make a 4% (w/w) solution.

Solution:

$$100\% - 4\% = 96\% \text{ (by weight) of water}$$

240 ml of water weighs 240 g

$$\text{Using formula Concentration} = \frac{X}{240}$$

$$\frac{4}{96} = \frac{X}{240}$$

$$X = 10 \text{ g}$$

Example 2.17:

How should you prepare 100 ml of a 2% (w/w) solution of a drug substance in a solvent having specific gravity of 1.25 ml.

Solution:

100 ml of water weighs 100 g

$$\text{Specific gravity} = \frac{\text{Weight}}{\text{Volume}}$$

$$1.25 = \frac{X}{100}$$

$$X = 125 \text{ g is weight of 100 ml solvent}$$

$$\text{Concentration} = \frac{\text{Weight of solute}}{\text{Weight of solution}}$$

$$2\%\ (w/w) = \frac{X}{125}$$

$$\frac{2}{98} = \frac{X}{125}$$

$$X = \frac{2 \times 125}{98} = 2.55\ g$$

Dissolve 2.55 g of drug in 125 g of solvent.

Alcohol Dilutions:

Dilute alcohols are made from 95% alcohol which contains 95 parts by volume of ethyl alcohol and 5 parts by volume of water.

Following changes occur when alcohol gets mixed with water.

(a) There is sudden rise in temperature.

(b) There is contraction in volume.

Appearance of turbidity in the solution because solubility of air is more in alcohol than in water. When alcohol is diluted with water, minute bubbles of air get evolved from the alcohol and make the solution turbid.

So when the alcohol is diluted with water, it is necessary to cool the mixture to about 20°C and then final volume is made up.

The formula used is:

Quantity of stronger solution to be used X concentration of alcohol used

= Quantity required to prepare X Concentration of alcohol required.

Example 2.18:

If 500 ml of a 15% solution are diluted to 1500 ml, what will be the percent strength?

Solution:

Using the above formula

$$500\ ml \times 15\% = 1500\ ml \times X\%$$

$$7500 = 1500X$$

$$\frac{7500}{1500} = \frac{1500X}{1500}$$

$$X = 5\%$$

Example 2.19:

If 2000 gm of ointment contain 75 gm of hydrocortisone, what is the percentage strength (w/w) of the ointment?

Solution:

$$\frac{75\ gm\ (\text{Active ingredient})}{2000\ gm\ (\text{Total amount})} = \frac{1}{X\%}$$

Divide to solve for X.

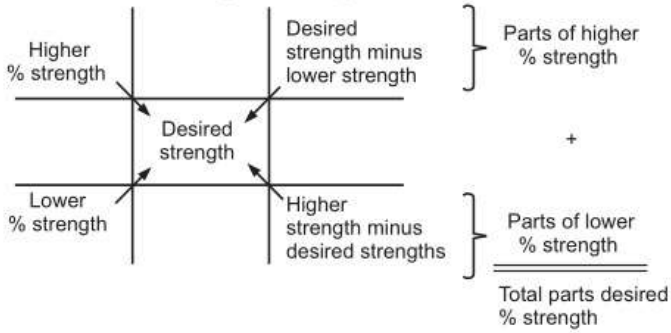
$$\frac{2000}{75} = X$$

$$X = 0.0375$$

$$X = 3.75\ \%$$

Alligation Method:

When the calculation involves mixing of two similar preparations of different strength, in order to prepare intermediate strength, the alligation method is used.



Example 2.20:

What would be the percentage strength of alcohol obtained by mixing 200 ml of 12%, 150 ml of 10%, 100 ml of 5%. (Based on Alligation method).

Solution:

$$200\ ml \times 12\% = 2400$$

$$150\ ml \times 10\% = 1500$$

$$100\ ml \times 5\% = 500$$

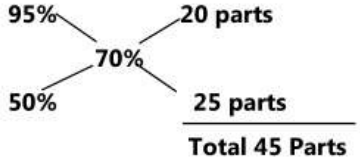
$$450\ ml\ of\ X\% = 4400$$

Or $$X = 9.78\%$$

Example 2.21:

How much 95% alcohol and how much 50% alcohol will be needed to attain 450 ml of 70% alcohol? (Based on Alligation Alternate)

Solution:



Volume of 95% alcohol required is $20 \times \frac{450}{45}$ = 200 ml.

Volume of 50% alcohol required is $25 \times \frac{450}{45}$ = 250 ml.

2.3 PROOF SPIRIT

Proof spirit: Proof spirit is defined as a mixture of absolute alcohol and water which has 57.1% v/v ethyl alcohol. The strength of alcoholic preparations are indicated by degrees 'over proof' and 'under proof' for excise purpose. Proof spirit is that mixture of alcohol and water which at 51° F weighs 12/13th of an equal volume of water. In India 57.1 volume of ethyl alcohol is considered to be equal to 100 volumes of proof spirit. This means that alcoholic solutions containing 57.1%v/v alcohol is a proof spirit which is said to be 100 proof. So any strength above proof strength is expressed as over proof (O.P.) and any strength below proof strength is expressed as under proof (U.P.)

Formula for calculation of over proof and under proof:

(i) 57.1% v/v alcohol = 100 volume of proof spirit.
Therefore, 1% v/v alcohol = 100/57.1 = 1.753 volume of proof spirit.

(ii) So multiply the given percentage strength of alcohol by 1.753 and deduct from the product.

(iii) If the result is positive it is known as over proof.

(iv) If the result is negative, it is known as under proof.

Conversion of percentage strength in to proof strength: Multiply percentage strength v/v with 100/57.1 i.e. 1.753 and substract the resulting product from 100.

Example 2.22:

Find out the proof strength of alcohol which is 90%v/v and 30%v/v.

Solution:

90% v/v = 90 × 1.753 = 157.77

Thus, proof strength = 157.77 – 100 = 57.77° O/P (Over proof)

30% v/v = 30 × 1.753 = 52.59.

Thus, proof strength = 52.59 – 100 = – 47.41 i.e. 47.41° U/P (Under proof)

Conversion of proof strength in to percentage strength: Add 100 to over proof and substract 100 for under proof spirit, and divide the resulting product by 1.753.

Example 2.23:

Find out the percentage strength corresponding to 40° O/P and 25° U/P.

Solution:

$$40° \text{ O/P} = \frac{100 + 40}{1.753} = 79.86\% \text{ v/v.}$$

$$25° \text{ U/P} = \frac{100 - 25}{1.753} = 42.79\% \text{ v/v.}$$

2.4 POWDER

A powder is a homogeneous mixture of more or less finely divided particle or material in dry form. It is a solid dosage form of medicament which are meant for internal and external uses. They are present in crystalline and amorphous form.

Advantages

- They impart flexibility with regard to a wide selection of drugs.
- They are stable when compared to other dosage forms.
- They show rapid therapeutic effect.
- Ease in administration to all categories of patients.
- They are economical because they do not require special technique or machinery.
- Chances of incompatibility are less.

Disadvantages

- Drugs having bitter, nauseous and unpleasant taste cannot be dispensed in powdered form.
- Deliquescent and hygroscopic drugs cannot be dispensed in powdered form.
- Drugs which get affected by atmospheric conditions are not suitable for dispensing in powder form.

General Method of Preparation

- The crystalline substances are powdered separately and then weigh the required quantity of each ingredient.
- Mix all ingredients in ascending order of their weight. Mix thoroughly to obtain homogeneous mixture.
- Weigh required number of powders and wrap in the papers.
- The hygroscopic and deliquescent and volatile substance requires to be double wrapped.
- The inner wrapper should be wax paper so as to prevent volatilization.

Types of powders

1. Divided Powders
   (a) Simple Powder
   (b) Compound powder
2. Bulk Powder
   (a) Dusting Powder
   (b) Effervescent Powder
   (c) Dentifrices
   (d) Insufflations
   (e) Douche Powder
   (f) Snuffs

1. **Divided Powder:** These are unit dose powders normally packed properly.

(a) **Simple powder:** Contains only one ingredient either in crystalline or in amorphous form. Then finely divided powder is weighed wrapped as individual dose.

(b) **Compound powder:** Contains two or more than two substances which are mixed together and then divided into individual doses.

2. **Bulk powders:** Powder supplied in bulk quantities are applied by the patient according to his need. They are preferably provided in sifter type container.

2.4.1 Dusting Powder

A powder is used on skin to relieve irritation or absorb moisture and to keep skin soft and comfortable. Dusting powders are used externally for local application not intended for systemic action. They are applied to various part of body as lubricants, protectants, absorbents, antiseptics, astringent and antiperspirant.

Dusting powders always should be dispensed in a very fine state of subdivision to enhance effectiveness and minimize irritation.

When necessary they may be passed through 80, 100, number sieves.

Characteristics of dusting powder

(i) Dusting powder should be homogeneous in nature.
(ii) It should have non-irritable property.
(iii) It should be Free flowing.
(iv) Powder should have good spreadibility.
(v) Dusting powder should have good adsorption and absorption property.
(vi) Dusting powder usually contains substances as zinc oxide, starch, magnesium, carbonate, light magnesium oxide, boric acid, talc, kaolin, etc.
(vii) Dusting powder should not be applied to broken skin.

Formula:

R_x

Zinc oxide	-	20 gm
Salicylic acid	-	5 gm
Starch	-	25 gm
Talc	-	50 gm

Labelling: FOR EXTERNAL USE ONLY.

2.4.2 Effervescent Powder

They are specially prepared solid dosage form of medicament meant for internal use. They contain medicament (API) mixed with citric acid, tartaric acid and sodium bicarbonate. Saccharine may be added as sweetening agent. Before administration the desired quantity is dissolved in water, the acid and bicarbonate react together producing effervescence (releasing CO_2). This mixture should be taken while effervescing.

Preparation

1. Fusion method 2. Wet method

(a) Fusion method: In this method, all the ingredients are placed in a porcelain dish and kept in water bath, they releases water and this moisture supports to produce a hard mass. This mass is passed through 20 number sieve. Granules obtained are dried (60°C in oven). Then the granules are collected and sieved again. Leading to fine granules.

(b) Wet method: Ingredients are wet with alcohol (non-aqueous solvent) and follow the same procedure.

Formula

R_x

Sodium Bicarbonate	-	35 gm
Citric acid	-	25 gm
Tartaric acid	-	15 gm
Anhydrous sodium carbonate	-	25 gm

Storage: It should be packed in wax paper and doubly wrapped.

Fig. 2.1

Hygroscopic powder: A hygroscopic substance absorbs water from the atmosphere. It may absorb enough to clump together, but a deliquescent substance absorbs so much water from the atmosphere that it actually forms a liquid.

Deliquescence, the process by which a substance absorbs moisture from the atmosphere until it dissolves in the absorbed water and forms a solution. Deliquescence occurs when the vapour pressure of the solution that is formed is less than the partial pressure of water vapour in the air.

Problem Encountered in Powder Formulation

1. Hygroscopic and Deliquescent Powder

Problem 1: Absorption of moisture from air leading to partial or complete liquefaction.

Solution:

(A) Applied in a granular form to decrease the exposed surface to air.

(B) Packed in aluminium foil or in plastic film packets.

(C) Addition of light magnesium oxide to reduce the tendency to damp.

(D) Addition of adsorbent materials such as starch.

Examples:

- Halide salts (Example: Sodium Iodide).
- Certain alkaloids (physostigmine HCl).

2. Efflorescent Powders

When some substances are exposed to air, they lose water to the atmosphere, thereby reducing in weight. Solids that behave in this way are those with water of crystallization. The molecules of water of crystallization are partially or completely lost to the atmosphere, thereby making them to lose their crystalline forms.

Example: $Na_2SO_4 \cdot 10H_2O$ loses all its water of crystallization when exposed to air; $Na_2CO_3 \cdot 10H_2O$ loses 9 of its molecules of water of crystallization; and $FeSO_4 \cdot 7H_2O$ loses all its molecules of water of crystallization.

Some crystalline substances liberate water of crystallization wholly or partly on exposure to humid atmosphere or during trituration and thus become wet or liquefy. Example of such substances include caffeine, citric acid, ferrous sulphate etc. This difficulty may be overcome by using either corresponding anhydrous salt or an inert substance may be mixed with effloresent substance before incorporating with other ingredients.

Problem 2: Crystalline substances which during storage loose their water of crystallization and change to powder (to be efflorescent). The liberated water convert the powder to a paste or to a liquid.

Solution:

Using the anhydrous form, and treating it in a manner similar to hygroscopic powders.

Examples: Alum- atropine sulfate-citric acid-codeine phosphate.

Eutectic Mixtures

A eutectic mixture is defined as a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower melting point than either of the components. Eutectic mixtures, can be formed between Active Pharmaceutical Ingredients (APIs), between APIs and excipient or between excipient; thereby providing a vast scope for its applications in pharmaceutical industry. Eutectic mixture formation is usually governed by the following factors:

(a) The components must be miscible in liquid state and mostly immiscible in solid state.

(b) Intimate contact between eutectic forming materials is necessary for contact induced melting point depression.

(c) The components should have chemical groups that can interact to form physical bonds such has intermolecular hydrogen bonding etc.

(d) The molecules which are in accordance to modified Vant Hoff's equation can form eutectic mixtures.

Certain substances such as menthol, thymol, camphor, phenol, salol etc. when mixed in a particular proportion tend to liquefy due to reduction in their respective melting points.

Such mixture are known as eutectic mixtures. Greek meaning of eutectic is easy melting.

The phenomenon of eutectic formation has also been used in pharmaceutical practice to improve the dissolution behaviour of certain drugs.

For example: Aspirin-acetaminophen (37% and 63% respectively), Urea – acetaminophen (46% and 54% respectively) dissolve more rapidly than the drug alone or their simple mixtures.

Problem 3: Mixture of substances that liquefy when mixed, rubbed or triturated together. The melting points of many eutectic mixtures are below room temperature.

Solution:

(A) Using inert adsorbent such as starch, talc, lactose to prevent dampness of the powder.

(B) Dispensing the components of the eutectic mixture separately.

Examples: Menthol, thymol, phenol, salol, camphor etc.

Applications of Eutectic Mixtures in Pharmaceutical Industry

During pre formulation stage, compatibility studies between Active Pharmaceutical ingredients and excipient plays a crucial role in excipient selection. Testing for eutectic mixture formation can help in anticipation of probable physical incompatibility between drug and excipient molecules. Eutectic mixtures are commonly used in drug designing and delivery processes for various routes of administration. During manufacturing of pharmaceutical dosage form, it is extremely necessary to anticipate the formation of eutectics and avoid manufacturing problems if any. For example, during tablet compaction the heat produced in the punch and die cavities may lead to fusion or melting of tablet powder compacts leading to manufacturing defects. Thus, knowledge of eutectic points of powder components may help to avoid these problems. During pharmaceutical analysis, understanding of eutectic mixtures can help in the identification of compounds having similar melting points. Compounds having similar melting points, as a rule will have different eutectic point with a common other component. This knowledge could be used to identify compounds like Ergotamine, Allobarbital etc. The listed drugs can be distinguished by their tendency to form eutectic mixtures with Benzanilide.

Geometric Dilution

Geometric dilution is a pharmaceutical process that thoroughly mixes a small amount of a drug with an appropriate amount of a diluent, an inert substance that thins or binds the drug. It ensures equal distribution of the drug throughout the resulting compound, according to the UNC Eshelman School of Pharmacy.

The method used depends on the types of substances used, such as a fluid or powder, and the form, such as an ointment or tablet, of the compound. Two commonly used geometric dilution methods include trituration, which can be used to combine powders or mix a powder into an ointment, and the liquid aliquot method, which involves combining fluids to create a solution, as explained by the UNC Eshelman School of Pharmacy.

Trituration, which involves reducing a substance to particle size, requires the use of a mortar and pestle to grind together equal parts of substances in small-batch quantities, adding the same amount of each substance and repeating the process until the entire amount of both substances has been mixed together. The liquid aliquot method involves dissolving a quantity of the drug in a small quantity of an appropriate solvent, often water or alcohol, to reach a desired volume, according to the UNC Eshelman School of Pharmacy. The aliquot, which is the desired amount of the concentrated drug solution, is then added to a larger amount of solution to make up the total volume of the prescription.

Methods of Geometric Dilution

Geometric dilution is the process of diluting something based on its measured size. Most often, scientists and doctors employ this method when combining fine powders of unequal amounts to ensure equal distribution. Bakers sometimes use geometric dilution to equally combine the dry ingredients in a mixture. The process involves slowly combining the products in a small portion at a time.

(a) Two Powders (Standard)

The two-powder method requires a mortar and pestle. Take the powder of the smaller amount and place it in the pestle. Then add the other powder but only of equal amount to the lesser powder, leaving the rest outside the mixture. Fully triturate, or finely grind, the powder with the mortar so that it is completely mixed. Add an amount of the remaining powder equal to that in the pestle. Repeat the triturating process. Continue until all of the powder has been combined. In baking, the addition method is the same but you do not grind the powders; just mix them.

(b) Powder in Ointment

The same method used for two powders can be utilized when mixing a powder into an ointment. During the initial step you mix in the same amount of ointment as there is of the powder. Use the mortar to fully grind the powder into the ointment, ensuring uniformity. Add ointment of equal amount to the mixed ointment until you have fully combined the ointment with powder.

(c) Liquid Aliquot Method

The liquid aliquot method is similar to trituration but works with fluids instead. The theory is that the liquids need to be combined equally, but you might need to mix more together than you actually need. You calculate the total volume of the drug you wish to give and your end amount of fluid. Then give the measurement of how the drug is available you mix it with the appropriate amount of solution. You then draw up in a syringe the amount of mixed fluid you need to give to the patient.

(d) Radar Geometric Dilution

An entirely different type of geometric dilution is that of radar or radio waves. This process requires you use geometry to cross cut the radar waves making them less effective. Developed as a way to interfere with foreign signals, this form of dilution tends to be used most by the military. The dilution angles can be calculated to protect your radar from being discovered or to "jam" the enemy's radar. Jamming the other radar can help to keep you safe or eliminate communications aiding in a sneak attack.

2.4.3 Dentifrices (Tooth Powder)

- Dentifrices are bulk powders used to clean teeth.
- They contain a soap or detergent (for cleaning action), mild abrasive and an anti-cryogenic agent.
- Mild abrasion can be provided by using finely precipitated Calcium Carbonate, Sodium Chloride, Magnesium Chloride etc.
- A strong abrasive substance should not be used as it may cause damage to the tooth.
- They are applied with the help of tooth brush for cleaning the surface of teeth.

Formula

R_x

For 100 gm tooth powder

Hard soap, fine powder - 5 gm

Precipitated calcium carbonate - 94 gm

Saccharine sodium - 2 gm

Peppermint oil - 4 gm

Fig. 2.2

2.4.4 Insufflations

- These are finely divided powders introduced into body cavities such as the ear, nose, throat, tooth sockets and vagina.
- An insufflators is employed to administer these products.
- It sprays the powder into a stream of finely divided particles all over the site of application.
- Pressure aerosols also have been employed as a means of administering insufflations, especially for potent drugs.

Fig. 2.3

2.4.5 Snuffs

These are finely divided solid dosage form of medicament which are inhaled into nostrils for its antiseptic, bronchodilator and decongestion actions. Traditionally, it is sniffed or inhaled lightly after a pinch of snuff is either placed onto the back surface of the hand, held pinched between thumb and index finger, or held by a specially made "snuffing" device. Snuff comes in a range of texture and moistness, from very fine to coarse, and from toast (very dry) to very moist.

2.5 LIQUID DOSAGE FORM

The use of liquid pharmaceuticals has been justified on the basis of ease of administration and rapid and efficient absorption of drug.

Dosage forms meant either for internal, external or parenteral use may be sub-classified into monophasic or biphasic liquid dosage forms. The monophasic liquid dosage forms consists of either true or colloidal solutions or solubilised system. All these consists of only a single phase and may have either aqueous or non-aqueous solvents as the base. Biphasic dosage forms are represented by emulsions and suspensions and consist of two immiscible phases, the continuous phase and the dispersed phase. The continuous phase in both is a liquid, the dispersed phase in emulsions is also a liquid while in case of suspensions, the dispersed phase consists of a finely divided solid. The classification of liquid dosage form is given in Fig 2.4. and the comparison of characteristics of various liquid dosage forms are shown in Table 2.1.

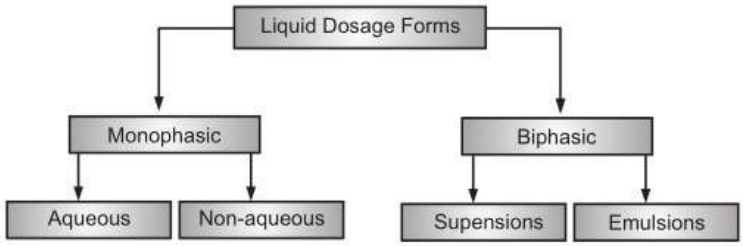


Fig. 2.4: Classification of Liquid Dosage Forms

Table 2.1: Comparison of characteristics of various liquid dosage forms

Characteristic	Solutions	Suspensions	Emulsions
	Monophasic system in which solute is dispersed molecularly in a suitable solvent	Biphasic system composed of finely divided insoluble solid suspended in a liquid medium	Biphasic system in which one liquid is dispersed throughout another liquid in form of minute droplets
Thermodynamic Stability	Thermodynamically stable on storage	Unstable, undergo caking on storage	Unstable, undergo creaming on storage
Homogeneity	Homogenous system No dose variation	Heterogenous system Dose variation	Heterogenous system Dose variation
Hydrolytic Stability	Most susceptible to hydrolysis	Less	Least
Appearance	Clear dispersions	Cloudy	Greasy/Smooth
Pharmacokinetics	Rapid onset of action	Slowest onset of action	Slower onset of action
Viscosity	Low viscosity	High viscosity	Highest viscosity

2.5.1 Advantages of Liquid Dosage Forms

The presentation of drugs as liquid dosage form offers the following advantages:

(i) The drug is more readily available for absorption from liquid dosage forms as compared to solid dosage form. By providing the drug in solution, the dissolution phase of the absorption process can be surpassed, providing faster therapeutic response.

(ii) The doses of drugs can be easily adjusted according to the need of the patient. If the dose of active ingredient is to be altered, a simple adjustment to the quantity of solution to be taken is all that is required.

(iii) Liquids are easier to swallow than tablets or capsules and are therefore especially suitable for children, elderly, intensive care and psychiatric patients.

(iv) Gastric irritation due to certain drugs like potassium chloride and when administered as a solid dosage form is avoided or reduced on administration as a liquid dosage form because of the immediate dilution by gastric content.

(v) Drugs with large doses can be easily administered as liquid dosage form.

(vi) Distribution of drug in liquid dosage forms is better than solid dosage forms.

(vii) Liquid dosage forms are more economical to produce than solid dosage forms.

(viii) Liquid dosage forms can be designed to administer via number of routes. Parenteral preparations, douches for vaginal use, cutaneous (for use on skin) preparations and ophthalmic preparations can all be liquids.

Disadvantages of Liquid Dosage Forms

There are also some disadvantages associated with the use of liquid preparations:

(i) Drugs are usually less stable in liquid dosage forms as compared to solid dosage forms like tablets and capsules, particularly if they are susceptible to hydrolysis.

(ii) Liquids, especially aqueous preparations, are susceptible to microbial contamination.

(iii) Masking the unpleasant taste of a drug in solution is more difficult than when the drug is in a solid dosage form.

(iv) Liquid preparations are usually bulky and therefore inconvenient to store and carry. Liquid dosage forms are always much larger and more bulky than solid formulations. Coupled with this is the fact that pharmaceutical liquids are packed in glass bottles, which are prone to breakage.

(v) Administration of the correct dose is less precise since it depends on the ability of the patient to measure the correct dose using a suitable measuring device such as a spoon or a dropper.

(vi) Measuring device is to be supplied to the patients for accurate dose administration. This will have cost implications and in addition the counselling is required for its use.

(vii) Suspensions and emulsions have the added drawback that they must be thoroughly shaken to allow accurate dosing.

2.5.2 Excipients used in Formulation of Liquid Dosage Forms

Sweetening agent: Sweeteners are indispensable components of many liquid oral dosage forms, especially those containing bitter or other unacceptable tastes. In fact, sweetening agents may comprise large portions of solid content in most liquid oral dosage forms. Sweeteners are often classified as either nutritive (caloric) or non-nutritive (non-caloric). Non-caloric sweetening agents are preferred for diabetic patients, as ingestion does cause increase in systemic glucose concentrations. Some of the most commonly used sweeteners include sucrose, sorbitol, mannitol, liquid glucose, honey molasses, saccharin, aspartame, sucralose, and acesulphame-K. The types and concentrations of sweeteners for

common prescription liquid medications are reported by Hill, Flaitz, and Frost. Sucrose is the most widely used sweetener, with a long history of use. It is a white crystalline powder, soluble in water and alcohol. It inhibits the growth of microorganisms in solution at sucrose concentrations above 65 wt% by reducing the water-activity coefficient. Official simple syrup is an 85%w/v solution of sucrose in water. During the preparation of sucrose solution, care should be taken to avoid charring and caramelization caused by heat. Sucrose is chemically and physically stable in the pH range of 4.0–8.0. It is frequently used in conjunction with sorbitol, glycerin, and other polyols, which reduces its tendency to crystallize.

One of the manifestations of the sucrose crystallization is ''cap-locking,'' which occurs when sucrose crystallizes on the threads of the bottle cap and interferes with opening. Liquid glucose is an extremely viscid substance that imparts both body and sweetness to liquid formulations. It is obtained by the incomplete hydrolysis of starch and consists chiefly of dextrose, dextrins, maltose, and water. It imparts a characteristic odour and flavour to the formulation in similar fashion to honey and molasses, but to a lesser degree. Although liquid glucose is not a pure chemical entity, its method of manufacture can be well controlled, and batch to batch variability is usually not significantly problematic. The same is not true of honey and molasses, in which quality depends on uncontrollable natural factors.

Saccharin (Sweet' N Low) is a non-nutritive synthetic sweetening agent. It has approximately 500 times the sweetening power of sucrose, depending in extent on the strength of the solution. The relative sweetening power is greatest in dilute solution. Saccharin is a sucrose substitute for diabetics, the obese, and others who do not wish to ingest sucrose. It is commonly found in its sodium salt form, which is more palatable than saccharin and comparatively free of unpleasant after taste. Sodium cyclamate is another synthetic sweetening agent that is approximately 30 times as sweet as sugar. However, its use as an artificial sweetener is banned in the U.S.A. because of the possible toxicity of its metabolite cyclohexylamine. Aspartame, is 200 times sweeter than sucrose and, unlike saccharin, has no aftertaste. Its aqueous solubility is adequate for formulation purposes. It is stable in the solid form, but its stability in solution depends on temperature and pH. It hydrolyzes to aspartylphenylalanine and diketopiperazine, with a loss in sweetness by aspartame synergistic with saccharin, sucrose, glucose, and cyclamate. In addition, its taste can be improved by adding sodium bicarbonate, gluconate salts, and lactose.

Newer non-caloric sweetening agents have come to market in the last decade. Sucralose (Splenda) is approximately 600 times sweeter than sucrose and differs from sucrose by the substitution of three chlorines for hydroxyl groups. Sucralose is heat stable and stable over a wide pH range affording its utility in formulations prepared at high temperatures. Acesulphame-K is approximately 200 times sweeter than sucrose and is commonly used concomitantly with aspartame to synergistically enhance overall sweetening. This sweetener is also heat stable. Furthermore, Monoammonium glycyrrhizinate has even been used in liquid oral preparations.

Viscosity controlling agents

It is sometimes desirable to increase the viscosity of a liquid, either to serve as an adjunct for palatability or to improve pourability. This can be achieved by increasing the sugar concentration or by incorporating viscosity controlling agents such as polyvinylpyrrolidone or various cellulosic derivatives (e.g., methylcellulose or sodium carboxymethylcellulose). These compounds form solutions in water that are stable over a wide pH range. Methylcellulose and carboxymethylcellulose are available in a number of different viscosity grades. Carboxymethylcellulose may be used in solutions containing high concentrations of alcohol (up to 50%) without precipitating. It is precipitated, however, as an insoluble salt of a number of multivalent metal ions such as AT^{++} , Fe^{+++} and Ca^{++}. Methylcellulose polymers do not form insoluble salts with metal ions, but can be salted out of solution when the concentration of electrolytes or other dissolved materials exceed certain limits. These limits may vary from about 2 to 40%, depending on the electrolyte and the type of methylcellulose involved.

Viscosity inducing polymers should be used with a degree of caution. They are known to form molecular complexes with a variety of organic and inorganic compounds, and in so doing, influence the activity of these compounds. It is conceivable that highly viscid systems that resist dilution by gastrointestinal fluids might impede drug release and absorption.

Buffers

During storage of liquid preparations, degradation of the product, interactions with container components or dissolution of gases and vapors causes change in their pH level, which can be prevented by addition of buffer. A suitable buffer system should have adequate buffer capacity to maintain the pH level of the product. Commonly used buffer systems are phosphates, acetates, citrates, and glutamates. Although buffers ensure pH stability, the buffer system can affect other properties such as solubility and stability. The ionic strength contributions of the buffer systems can affect stability. Buffers can also act adversely as general acid or general base catalysts and cause degradation of the drug substance. Therefore, before selecting any buffer system, the effect of buffer species should be studied.

Antioxidants

Various drugs in solution are subject to oxidative degradation. Oxidation is defined as a loss of electrons from a compound leading to change in the oxidation state of the molecule. Such reactions are mediated by free radicals or molecular oxygen, and are often catalyzed by metal ions. Moreover, oxidation often involves the addition of oxygen (or other electronegative atoms like halogens) or the removal of hydrogen. Drugs possessing favorable oxidation potential are especially vulnerable to degradation. Agents with an oxidation potential lower than that of the drug in question are called **antioxidants**. Additionally, certain properties of the selected primary packaging (such as polymer degradation, oxygen transmission rates, impurities, etc.) can readily lead to oxidation of drug molecules in solution and hence may require the addition of antioxidants to maintain

product stability. They are added to solutions alone or in combination with a chelating agent or other antioxidants and function by being preferentially oxidized and gradually consumed or by blocking an oxidative chain reaction where they are not consumed.

Salts of sulfites are the most common antioxidants in aqueous solutions and their antioxidant activity depends on their final concentration and the final pH level of the formulation. Generally, sodium metabisulfite is used at low pH, sodium bisulfite at near neutral pH, and sodium sulfite is used at basic pH. A combination is often used since single antioxidant may provide incomplete protection. Certain compounds (e.g., citric and ascorbic acids) have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those that block oxidative reactions. Often, chelating agents such as edetic acid derivatives such as ethylene diamine tetra acetate (EDTA) are used in formulations containing trace amounts of heavy metals that would otherwise catalyze oxidative reactions. Moreover, synthetic phenolic compounds, such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) serve as hydrogen atom donors and can successfully prevent oxidation of oils and fats in oral liquid formulations.

Flavours

Flavouring can be divided into two major categories: selection and evaluation. Much has been written on both phases of pharmaceutical flavoring, but selection remains a totally empiric activity.

The four basic taste sensations are salty, bitter, sweet, and sour. Some generalizations concerning the selection of flavours to mask specific types of taste have been suggested by Janovsky and by Wesley. (Table 2.2)

Table 2.2: Flavour Selection

Taste Sensation	Recommended Flavour
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint combinations, passion fruit, mint spice, anise.
Sweet	Fruit and berry, vanilla.
Sour	Citrus flavors, liqorice, root beer, raspberry.

A combination of flavoring agents is usually required to mask these taste sensations effectively. Menthol, chloroform, and various salts frequently are used as flavour adjuncts. Menthol and chloroform are sometimes referred to as de-sensitizing agents. They impart a flavour and odour of their own to the product and have a mild anesthetic effect on the sensory receptor organs associated with taste. Monosodium glutamate has been widely used in the food industry, and to a lesser extent, in pharmaceuticals, for its reported ability to enhance natural flavors. A carefully selected panel reported this substance to be effective in reducing the metallic taste of iron containing liquids, as well as the bitterness and after

taste of a variety of other pharmaceutical preparations. It cannot be used in pediatric products.

Chemburkar and Joslin have reported that the partitioning of parabens into flavouring oils from aqueous systems depends on the concentration of the flavouring oil, the nature and concentration of the additives, and pH.

Wesley's Pharmaceutical Flavor Guide contains suggestions for flavoring over 51 types of pharmaceutical preparations. It and many similar reports provide some guidance for the formulation chemist, but the final selection must result from a trial and error approach. Inherent in this approach is what is referred to as taste fatigue. Repeated samplings of strong tasting substances soon result in decreased flavour acuity, and therefore, impaired ability to evaluate flavour properly. Preliminary flavoring should be carried out on diluted samples. This is done by preparing flavoured vehicles and adding increments of the medicament or other formulation components responsible for the taste problem. The concentration at which the taste of the medicament is perceptible is referred to as the *minimum threshold level*. The vehicles that are most effective in masking low levels of drug are candidates for full-strength flavour evaluation.

Flavour evaluation techniques have progressed to a much greater extent than flavour selection. Taste panels can be useful in selecting one of several candidate formulations. This subject, as well as other flavour considerations, has been surveyed in an excellent book assembled by Arthur D. Little, Inc.

Preservative

In recent years, adequate preservation of liquid products has increased in importance. Reports of clinical complications arising from microbial contamination of oral and topical products have originated in several European countries and the United States. Numerous product recalls and tightened regulatory and compendia limits have re-emphasized the need for die formulator to carefully and thoroughly consider all aspects of the preservative system chosen for a particular formula. In addition to presenting a health hazard to the user, microbial growth can cause marked effects on product stability.

Numerous sources of contamination exist. Including among these are raw materials, processing containers and equipment, the manufacturing environment, operators, packaging materials, and the user.

Manufacturing techniques to minimize microbial contamination are presented under the heading "Manufacturing Considerations." The remainder of this section deals with preservative systems for liquid products.

An ideal preservative can be qualitatively defined as one that meets the following three criteria:

1. It must be effective against a broad spectrum of microorganisms.
2. It must be physically, chemically and microbiologically stable for the lifetime of the product.
3. It must be non-toxic, non-sensitizing, adequately soluble, compatible with other formulation components, and acceptable with respect to taste and odour at the concentrations used.

No single preservative exists that satisfies all of these requirements for all formulations. The selection of a preservative system must be made on an individual basis, using published information and "in house" microbiologic studies for guidance. Frequently, a combination of two or more preservatives are needed to achieve the desired antimicrobial effect.

The antimicrobial agents that have been used as preservatives can be classified into four major groupings: acidic, neutral, mercurial, and quaternary ammonium compounds. Table 2.3 lists some representative members of these groupings and the concentration ranges at which they have been used.

Table 2.3: Some Pharmaceutically Useful Preservatives

Class	Usual Concentration (%)
Acidic	
Phenol	0.2-0.5
Chlorocresol	0.05-0.1
O-phenyl phenol	0.005-0.01
Alkyl esters of parahydroxybenzoic acid	0.001-0.2
Benzoic acid and its salts	0.1-0.3
Boric acid and its salts	0.5-1.0
Sorbic acid and its salts	0.05-0.2
Neutral	
Chlorobutanol	0.5
Benzyl alcohol	1.0
o-phenylethyl alcohol	0.2-1.0
Mercurial	
Thiomersal	0.001-0.1
Phenylmercuric acetate and nitrate	0.002-0.005
Nitromersol	0.001-0.1
Quaternary Ammonium Compounds	
Benzalkonium chloride	0.004-0.02
Cetylpyridinium chloride	0.01-0.02

The phenols are probably the oldest and best known pharmaceutical preservatives, but are little used in oral pharmaceuticals, owing to their characteristic odour and instability when exposed to oxygen. The more useful members of the series, for this application, are

the parahydroxy-benzoic acid esters, and the salts of benzoic and sorbic acid. They are adequately soluble in aqueous systems and have been demonstrated to possess both antifungal and antibacterial properties.

Frequently, a combination of two or more esters of parahydroxybenzoic acid are used to achieve the desired antimicrobial effect. Methyl and propyl parahydroxybenzoic acid, for example, are often used together in a ratio of 10 to 1, respectively. The use of more than one ester makes possible a higher total preservative concentration, owing to the independent solubilities of each, and according to some researchers, serves to potentiate the antimicrobial effect. The solubilities of a series of parabens have been studied at four temperatures. The solubilities are expressed in terms of ideal, actual, and excess free energies.

The remaining three classes of preservatives have been widely used in ophthalmic, nasal, and parenteral products, but have been little used in oral liquids. The neutral preservatives are all volatile alcohols, and their volatility introduces odour problems as well as concern for preservative loss on aging. The mercurials and quaternary ammonium compounds are excellent preservatives. They are, however, subject to a variety of incompatibilities, with mercurials being readily reduced to free mercury and the quaternary compounds being inactivated by a variety of anionic substances. The incompatibilities common to these and other preservatives are discussed by Lachman.

Syrups containing approximately 85% sugar resist bacterial growth by virtue of their exosmotic effect on microorganisms. Syrups that contain less than 85% sucrose, but a sufficient concentration of polyol (such as sorbitol, glycerin, propylene glycol, or polyethylene glycol) to have an exosmotic effect on microorganisms, similarly resist bacterial growth. It is possible, however, for surface dilution to take place in a closed container as a result of solvent evaporation followed by condensation, with the condensate flowing back onto the liquid surface. The resulting diluted surface layer makes an excellent medium for bacterial and fungal growth. These products, therefore, should be designed so that even after dilution, they do not support microbial growth. This can be done either by incorporating a sufficient concentration of preservative, so that a diluted sample of the product resists microorganism growth, or by including approximately 5 to 10% ethanol in the formulation. The vapour pressure of ethanol is greater than that of water and normally vaporizes to the surface of the liquid and the cap area, preventing, or at least minimizing, the potential for microorganism growth as a result of surface dilution.

An effectively designed preservative system must retain its antimicrobial activity for the shelf-life of the product. To ensure compliance with this precept, the preservative characteristics of the product in its final form (including formulation and package) must be studied as a function of age. The best method of demonstrating preservative characteristics is by microbiologic evaluation.

To determine whether a specific organism is hazardous, one must consider the nature of the product and its dose, the state of health of the user, and clinical reports on the frequency and severity of infections caused by the microorganism.

The FDA distinguishes between organisms that are "always objectionable" and "usually objectionable." The former designation is based on only two factors: pathogenicity of the organism and site of use. The latter designation is based on an additional determinant, the state of health of the user. The official compendia are continually reevaluating their standards based on the latest FDA data and guidelines.

Specific organisms generally recognized as undesirable in oral liquids include *Salmonella* species, *Escherichia coli, Enterobacter* species, *Pseudomonas* species (commonly *P. aeruginosa*), proteolytic species of *Clostridium* and *Candida albicans*. Some liquid pharmaceuticals (i.e., ophthalmic solutions) must be processed aseptically and rendered sterile.

Chemical analysis for the antimicrobial constituent frequently provides a helpful guide but can be misleading. Molecular interactions involving preservatives and commonly used pharmaceutical adjuvants, such as surfactants and cellulose derivatives, have been observed. For example, it has been shown that Tween 80 interacts to a significant extent with the methyl and propyl esters of parahydroxybenzoic acid, and that the preservative surfactant complex is essentially devoid of antibacterial activity. Chemical analysis for the parahydroxybenzoate esters would not differentiate between the unbound substance (microbiologically active) and the bound substance (microbiologically inactive).

2.6 SOLUBILITY

Solubility is defined as amount of solute that can be dispersed molecularly in the given amount of solvent under standard conditions of temperature, pressure and pH. The following questions related to solubility must be resolved before formulating solution dosage form:

(a) Will the drug(s) dissolve in the vehicle?
(b) How much drug will dissolve?
(c) How long will dissolution take?
(d) What is optimum pH for dissolution?

To determine the solubility of solute in solvent following points are to be considered:

(a) Temperature must be controlled.
(b) The solute and the solvent should be pure.
(c) A saturated solution of the solute should be prepared before withdrawing the sample for analysis.
(d) A proper method of separation of saturated solution from the undissolved solute.
(e) Dissolved solute should be determined adequately by the suitable method of analysis.

Method of determination: An excess powder is added in the solvent to achieve the saturated solubility and constant stirring is given for long duration at required temperature till the equilibrium is achieved. There should be few amount of undissolved solute should be present in order to ensure that the solvent is saturated. The aliquot of the saturated solution is taken separated from the undissolved solute by specific method. Generally speaking,

filtration is the common method employed for most of the studied. Further the quantity of the drug dissolved or the solubility of the solute in the solvent is determined by the analyzing the sample by suitable method.

Table 2.4

Terms	Expression of solubility Part by volume of solvent required to dissolve 1 part by weight of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or insoluble	Greater than 10,000

During compounding of a solution the solids will need to go through a dissolution phase, so it is worth remembering that rate of dissolution generally increases with:

(1) Effective stirring (2) Lower viscosity

(3) Increasing temperature (4) Decreasing particle size

2.7 TECHNIQUES OF SOLUBILIZATION

In liquid pharmaceuticals solutions sometime the active drug is poorly soluble or insoluble in desired solvent and could not able to achieve the required concentration of formulation. In such cases, it is required to increase the solubility of that material in the solvent by a suitable technique. Solubilization is the technique by which the desired solubility of a poorly water-soluble substance is achieved. Since, water is the most commonly used solvent in pharmaceutical liquids, the following techniques have been aimed at increasing the solubility of a drug substance in water.

Pharmaceutical Approach

1. pH Adjustments

Most of the drugs are either weak acids or weak bases. The aqueous solubility of a weak acid or a weak base is greatly influenced by the pH of the solution. Hence, the solubility of drug that is either a weak base or a weak acid may be altered by adjusting the pH of the solution. The solubility of a weak base can be increased by lowering the pH of its solution whereas the solubility of a weak acid can be improved by increasing the pH. pH adjustment for improving the solubility can be achieved in two ways:

(a) Salt formation.

(b) Addition of buffers to the formulation.

However, pH adjustments should be done judiciously since other factors such as stability, bioavailability, etc. can also be affected by a change in pH.

e.g. Gatifloxacin is insoluble in water at higher pH but the same drug get solubized at the lower pH and attends maximum solubility below the pH of 5. Hence the parenteral preparation of Gatifloxacin is formulated at the pH of 3.5 to 5.5.

e.g. The solubility of various chemotherapeutic agents such as Methotrexate, Fluorouracil, Cytrabine etc. also gets affected by the alteration in pH changes.

2. Cosolvency

Cosolvency is the technique of increasing the solubility of poorly soluble drugs in a liquid by addition of a solvent miscible with the liquid in which the drug is also highly soluble. Cosolvents such as ethanol, glycerol, propylene glycol or sorbitol decreases the interfacial tension or alter the dielectric constant of the medium and increases the solubility of weak electrolytes and non-polar molecules in water. Example: Formulation of Diazepam injection using propylene glycol as cosolvent.

3. Complexation

In certain cases, it may be possible to increase the solubility of a poorly soluble drug by allowing it to interact with a soluble material to form a soluble intermolecular complex. It is however essential that the complex formed is easily reversible so that the free drug is released readily during or before contact with biological fluids. A number of compounds, such as nicotinamide and Beta-cyclodextrin, have been investigated as possible agents to increase the solubility of water insoluble drugs.

e.g. Interaction of Iodine with Povidone to form water soluble complex and preparation of Itraconazole injection by forming inclusion complex of itraconazole with hydroxy propyl beta cyclodextrin.

4. Surface active agent

A surface active agent is a substance which reduces the interfacial tension between the solute and the solvent to form thermodynamically stable homogeneous system. The mechanism involved in this solubilization technique involves micelle formation and due to formation of stable system it is widely used in pharmaceutical formulations. When a surfactant having a hydrophilic and a lipophilic portion is added to a liquid, it first accumulates at the air/solvent interface; further addition leads to its dispersion throughout the liquid bulk. At a certain concentration known as the Critical Micelle Concentration (CMC), the dispersed surfactant molecules tend to aggregate into groups of 100 to 150 molecules known as micelle.

In aqueous medium, the surfactant molecule orient in such a manner that their hydrophilic portion faces the water while the lipophilic portion resides in the micelle interior. An insoluble compound added to the surfactant liquid either enters the micelle interior, gets adsorbed onto the micelle surface, or sits at some intermediate point depending on its polarity, thus effecting solubilization.

Surface active agents should be non-toxic and stable, possess good solubilizing power, and be compatible with other formulation ingredients. If they are intended for oral use, they should also have an agreeable taste and odour. Surfactants that are used as solubilising

agents generally have HLB values in excess of 13. Examples include polysorbate-80, polyoxyl 40 stearate, sodium lauryl sulphate and PEG-40-Castor oil (Cremophor).

e.g.: Fat soluble vitamins A, D, E and K, antibiotics like griseofulvin and chloramphenicol and analgesics such as aspirin and phenacetin have been solubilized by using surface active agents.

5. Hydrotropism

Hydrotropism is the term used to describe the increase in aqueous solubility of a drug by the use of large concentrations (20% to 50%) of certain additives. The exact mechanism for hydrotropism is not clear although complexation, solubilization or cosolvency have been suggested as the probable mechanisms. Hydrotropism is rarely applied to pharmaceutical formulations, as the increase in aqueous solubility is generally inadequate.

e.g.: Increase in solubility of caffeine and theophylline by addition of sodium benzoate and sodium salicylate respectively.

6. Micronization

Surface area and particle size are inversely related to each other. Smaller the drug particle, larger the surface area and greater is the solubility. A decrease in particle size achieved through micronization, will result in higher solubilization of drug.

e.g.: Micronization of poorly aqueous soluble, but non-hydrophobic drugs such as griseofulvin and chloramphenicol results in enhanced solubility.

7. Solid Solutions

Solid solutions are prepared by melting of physical mixture of solute, a poorly water soluble drug and solid solvent, a highly water soluble compound or polymer followed by rapid solidification. Solid solutions are also called as molecular dispersions or mixed crystals. When such binary system comprising of drug dispersed in a solid solvent is exposed to water, the soluble carrier dissolves rapidly leaving the poorly water soluble drug in a state of microcrystalline form with increased surface area resulting in enhanced solubility.

e.g.: Griseofulvin from succinic acid solid solution dissolves 6 to 7 times faster than pure griseofulvin and Digitoxin-PEG 6000 solid solution showed enhanced solubility.

Chemical Modification

Solubility of a substance can be improved by chemically modifying the substance. For example, aqueous solubility can be improved by increasing the number of polar groups in a molecule. This is often achieved by salt formation; for instance, alkaloids are poorly soluble in water whereas alkaloidal salts are freely soluble in it. Alternatively, a molecule may be modified to produce a new chemical entity or prodrug. The aqueous solubility of chloramphenicol sodium succinate, for example, is about 400 times greater than that of chloramphenicol. Prodrugs, however, must revert to parent molecule after administration.

Stability

In addition to the solubility of the medicament, other considerations regarding physical, chemical and microbiological stability of the preparation will need to be taken into consideration.

QUESTIONS

Short Answer Questions

1. What do you understand by term over and under proof?
2. Define alcohol dilution.
3. Define proof spirit.
4. What is geometric dilution?
5. Define isotonic solution.
6. What are dusting powder?
7. Define dentrifices.
8. Classify compound powder.
9. What are catches?
10. Name bulk powdes which are used externally.
11. Define sifting.
12. Define hygroscopic and deliquescent powders.
13. Define insufflations.

Long Answer Questions

1. What are the methods to adjust tonicity?
2. How 80% alcohol is prepared from 90% and 30% alcohol?
3. How much of a 50% w/v solution would be required to prepare 550 ml of a 0.8% w/v solution?
4. How many proof gallons are contained in 60 wine gallons of 90% v/v alcohol?
5. How much water should be mixed with 600 ml of 80% alcohol to make 65% v/v alcohol?
6. Define Proof spirits. Find the strength of 70% and 30% alcohol in terms of proof spirits.
7. Define and classify powders.
8. Define Eutectic mixtures.
9. Write in detail about effervescent and efflorescent powders with examples.
10. What are the methods of preparation of powder?
11. What are different solubility enhancement techniques?
12. Explain the advantage and disadvantage of liquid dosage forms.
13. What are the excipients used in the preparation of liquid dosage forms?

❑❑❑

Unit...3

MONOPHASIC & BIPHASIC LIQUIDS

♦ OBJECTIVES ♦

- **To understand about various monophasic liquid dosage forms like gargles, syrups, elixirs, lotion, liniment, nasal drops, ear drops etc.**
- **To understand biphasic liquid dosage forms like suspension and emulsion.**
- **To understand suspensions, types of suspensions and stability of suspensions.**
- **To know about emulsions, classification of emulsion.**
- **To understand the various test to identify type of emulsion.**
- **To know the method of preparation of emulsion and stability of emulsion.**

3.1 MONOPHASIC LIQUIDS

The compounding of solution retains an important place in therapeutics owing to the simplicity of preparation and rapid absorption of soluble medicinal products. Solutions are of particular value for paediatrics, geriatrics and psychiatric patients who have difficulty in swallowing solid dosage forms and in cases where individualized dosages are required. Dosage forms meant either for internal, external or parenteral use may be sub-classified into monophasic or biphasic liquid dosage forms. The monophasic liquid dosage forms consist of either true or colloidal solutions or solubilised system. All these consist of only a single phase and may have either aqueous or non-aqueous solvents as the base.

3.1.1 Gargles

Gargles are aqueous solution used to prevent or treat infection. They are usually available in concentrated form with direction for dilution with warm water for use. They are brought into intimate contact with mucous membrane of throat and allowed to remain in contact with it for few seconds, before they are thrown out of mouth. They are used to relieve soreness in mild throat infection. Phenol or thymol is used as antibacterial agent in gargles. Phenol or thymol may be present in low concentrations which exert mild anaesthetic effect; KCl is included in gargle preparation for its weak astringent effect, and stimulation the flow of saliva, which released drugs. Gargle differs from mouth washes in that they are light medicated oral mixture be diluted with water before use.

For example: Phenol gargle, $KClO_3$ gargles.

Storage: Gargles should be dispensed in clear, fluted glass bottles. Coloured bottles are required to be used if gargles need protection from sunlight.

Labeling: For EXTERNAL USE ONLY.

NOT TO BE SWALLOWED.

Formula: Phenol gargle

R_x

Phenol glycerin – 5 ml

Amaranth solution - 1 ml

Purified water - q.s. to 100 ml

This gargle may be prepared by mixing amaranth solution (1% w/v in chloroform water) with a small quantity of water and adding Phenol glycerin (16% w/w phenol and 84% w/w glycerin) to it. The solution is stirred and made up to volume with purified water. The gargle is meant to be diluted with equal quantity of warm water before use.

Uses: Antibacterial effect, astringent effect, mild anaesthetic effect.

Packaging: Pack in flip flop bottles, water proof packing.

3.1.2 Mouth Wash

These are aqueous solutions with a pleasant taste to clean, deodorize the buccal cavity. Mouthwashes have refreshing, antiseptic and antibacterial activity and prevent Halitosis.

They may also contain alcohol, glycerin, synthetic sweeteners, surfactants, flavouring and colouring agents. They may be either acidic or basic in their reaction and in some instances are fairly effective in reducing bacterial concentration and odours in the mouth for short periods of time.

For example: Compound sodium chloride mouth wash, Zinc chloride mouth wash, Fluoride mouth wash.

Storage: Keep in cool and dry place, Dispense in clear, fluted bottles.

Labeling: FOR EXTERNAL USE ONLY

- Not to be swallowed in large amount
- Pack in narrow mouth bottle

Formula: R_x

Zinc sulphate and zinc chloride mouth wash B.P.C.

Zinc sulphate – 20 g

Zinc chloride – 10 g

Oilute hydrochloride acid – 10 ml

Compound tartarzine solution – 10 ml

Chloroform water to produce – 1000 ml

The preparation may be made by dissolving Zinc sulphate and Zinc chloride in small quantity of Chloroform solution. To this is added dilute hydrochloric acid and compound tartrazine solution and the final volume is made up with water.

Zinc sulphate and Zinc chloride included in the preparation acts as astringents. Chloroform water acts as the flavouring agent and preservative while tartrazine serves as the colour. Zinc sulphate usually contains a small quantity of oxychloride which may make the solution turbid. This however disappears on addition of dilute hydrochloric acid.

3.1.3 Throat Paint

Solution or dispersion of one or more active agents.

- Throat paints are viscous liquid preparations used for mouth and throat infections.
- Glycerin is commonly used as a base because being viscous it adheres to mucous membrane for a long period.
- Glycerin prolongs the action of medicaments.
- Glycerin also provides sweet taste to preparation.

For example: Boroglycerin, Phenol glycerin throat paint.

Storage: Throat paint should be stored in airtight container and in cool place.

Labeling: For EXTERNAL USE ONLY.

Not to be swallowed.

Formula: R_x

Potassium iodide - 2.5 gm

Iodine - 1.25 gm

Alcohol – 4 ml

Water - 2.5 ml

Peppermint oil - 0.4 ml

Glycerin – 100 ml

Dissolve the potassium iodide in water. Add the iodine and stir until completely dissolved.

Dissolve peppermint oil in alcohol 90% in a small container and transfer it into iodine solution.

Transfer paint into a measuring cylinder and make up the volume to q.s.

- Paint are applied with soft brush.

Packing: A wide mouth, fluted, light resistant, screw car glass bottle is used and dispensed in amber coloured bottle.

3.1.4 Ear Drops

Ear drops are liquid preparations meant for instillation into the ear. In these preparations, the drug is usually dissolved or suspended in a suitable solvent such as propylene glycol, polyethylene glycol, glycerol, alcohol and water or a mixture of these. Aqueous vehicle is generally not preferred because the secretions in the ear are fatty in nature and as such these do not easily mix with water.

Ear drops are generally used for their cleansing, pain relieving and antiseptic actions. The main classes of drugs include analgesics like benzocaine, antibiotics like neomycin and chloramphenicol and anti-inflammatory agents such as cortisone and dexamethasone. Wax softening agents include hydrogen peroxide and sodium bicarbonate. Ear drops are usually supplied in amber coloured, glass bottles with a teat and dropper closure or plastic squeeze bottles.

Example : Chloramphenicol Ear Drops

Chloramphenicol - 5 g

Propylene glycol q.s to 100 ml

Chloramphenicol ear drops may be prepared by dissolving Chloramphenicol in sufficient quantity of Propylene glycol and finally making up the final volume with it.

3.1.5 Nasal Drops

Nasal drops are liquid preparations intended for instillation into the nostrils usually with the help of a dropper. Nasal drops are mostly based on aqueous vehicles although oily drops (containing liquid paraffin of suitable viscosity) are not uncommon. Oily vehicles are generally not preferred since the oil may retard the ciliary action of the mucosa and may even cause lipoid pneumonia if drops of the oil enter the lungs. Nasal drops are generally formulated to resemble the nasal secretions as closely as possible. Thus, these are usually isotonic and slightly buffered to maintain a pH of 5.5 to 7.5. Additionally, the preparation is made slightly viscous with the help of thickening agents like methyl cellulose to match its viscosity with that of the nasal secretions.

Commercial nasal preparations usually contain decongestants, antibiotics, antihistamines and drugs for asthma prophylaxis. Examples include Ephedrine Nasal drops, Phenylephrine Nasal drops, etc.

Nasal drops are usually supplied in amber coloured fluted bottles with rubber teat and dropper closure.

Example : Ephedrine Nasal Drops

Ephedrine Hydrochloride - 0.5 g

Chlorbutol - 0.5 g

Sodium Chloride - 0.5 g

Purified water q.s to 100 ml

The drops may be prepared by first dissolving Chlorobutol in small quantity of hot water followed by cooling the solution to room temperature. Other ingredients are then dissolved in the solution, which is filtered and the final volume is made up with water. These drops are used as decongestant with Ephedrine acting as the active medicament. Chlorobutol acts as the preservative while Sodium chloride is added to make the solution iso-osmotic with nasal secretions.

3.1.6 Nasal Sprays

Nasal sprays are suspensions or solution of drugs intended for spraying in to the nostrils. The chief uses of nasal sprays are to relieve nasal congestion and inflammation and to treat infections. They are intended to be retained in the nasal tract, they are usually viscous and coarse since fine droplets tend to penetrate further in to the respiratory tract. These preparations are usually supplied in pressurized containers or plastic squeeze bottles.

3.1.7 Enemas

Enemas are liquid preparations meant to be introduced into the rectum for cleansing, therapeutic or diagnostic purposes. Evacuation enemas are rectal injections employed to evacuate the bowel in constipation or before an operation. e.g., Enema of soap, Sodium phosphate enema, Olive and arachis oil enema, etc. Retention enemas are usually employed to influence the general system by absorption or to affect locally the seat of disease. They may possess anthelmintic (quassia), nutritive, sedative (chloral hydrate), or anti-inflammatory (corticosteroids) properties, or they may contain radio-opaque substances (barium sulphate) for X-ray examination.

Large volume enemas are administered from a douche can and should be warmed to body temperature before use. Small volume enemas are available in polythene or polyvinyl chloride bags sealed to a rectal nozzle and these are more convenient for personal administration since the patient has simply to insert the nozzle and squeeze the bag.

3.1.8 Syrups

Syrups are sweet viscous concentrated aqueous solution of sucrose in purified water.

Simple syrup I.P contains 66.7%w/w sucrose in purified water (100 ml)

Simple syrup USP contains 85%w/v sucrose in purified water (100 m.)

Medicated Syrup: Contains a therapeutic or medicinal agent e.g. Cough syrup.

Flavoured Syrup: Contains flavouring agent but no medicinal substances e.g. Cherry syrup.

Advantages

1. Syrup retards oxidation because it is partly hydrolyzed into its reducing sugar such as laevulose and dextrose.
2. It prevents decomposition of vegetable substances. Syrup has high concentration of sugar having high osmotic pressure which prevents the growth of bacteria, fungi, microbes. It acts as a self preservative.
3. They are palatable due to the sweetness of sugar. It is a valuable vehicle for the administration of nauseous and bitter substances.
4. Syrups are good demulcents and soothing agents and hence they are of special value in cough syrup.
5. Syrups have good patient compliance.

Concentration of sucrose in sugar based syrup is very important. A dilute solution may lead to growth of micro-organisms whereas saturated solution may lead to crystallization of same part of sucrose. Both syrup concentrations as per IP and USP gives stable syrup. Syrup containing various concentrations of sucrose needs antimicrobial preservative.

Fig. 3.1

Method of Preparation

The choice of particular method depends on the physical and chemical characteristics of the substance being used.

1. Hot Process

This method is used when active constituents is neither volatile nor heat labile.

Procedure

- Weighed sucrose is taken in beaker.
- Purified water is added.
- Heated on water bath (less than 70°C) till a solution is obtained.
- Product is filtered.
- Volume is made upto q.s.

Excessive heat may leads to inversion of sucrose.

2. Percolation

- Sucrose is placed in percolator.
- Water is passed through sucrose slowly.
- Neck of percolator is packed with cotton.
- Rate of percolation regulates rate of dissolution.
- After complete dissolution final volume is made upto q.s.

3. Agitation Without Heat

Procedure for heat labile constituents

- Sucrose and other ingredients are weighed properly.
- Dissolved in purified water.
- Kept in a bottle of about twice the volume of syrup followed by continuous agitation.
- Prepared syrup volume is made upto q.s.

4. Addition of Medicating or Flavouring Liquid to Syrup

This method is used when fluid extracts, tinctures or the other liquids are to be added to syrup.

- Alcohol is added to dissolve the resinous or oily substances.
- Alcohol acts as a preservative also.

Formulation of Syrup

1. **Vehicle:** Syrups are prepared by using purified water.
2. **Adjuncts:** The following adjuncts are generally added to improve the formulation of syrup.

- **Chemical Stabilizer:** Glycerin, sorbitol, propylene glycol is added in small quantity to syrup to prevent the crystallization.
- **Colouring agent:** Many syrup are attractively coloured with coal tar dyes such as amaranth, compound tartarazine and Green S.
- **Flavouring agents**
  (i) Tinctures: Lemon and ginger tincture
  (ii) Fruit juice: Cherry, Raspberry
  (iii) Essence: Vanilla, orange

Preservatives: Syrups are self preservative. Generally, Benzoic acid, Sodium benzoate, Methyl paraben etc.

Storage: Stored in well dried, completely filled and well stoppered bottle in a cool dark place. Store at a temperature not exceeding 25°C.

3.1.9 Elixir

Elixirs are defined as clear, aromatic, sweetened, hydroalcolohic liquids intended for oral us

- They provide a palatable means of administering potent or nauseous drugs.
- Elixirs are less sweet and less viscous then syrup may contain less or no sucrose.
- Elixirs are more stable than syrups and hence preferred over syrup.
- Elixirs contain 4-40% of alcohol (ethanol).
- They may contain glycerin and syrup for increasing the solubility of medicaments or for sweetening purpose.
- Elixirs may also contain suitable flavouring and colouring agents.
- Preservatives are not needed in elixirs as alcohol content is sufficient to act as preservative.

Types

Non-medicated: Not contain medicament and used as flavoring agent.

For example: Aromatic elixir.

Medicated: Which contain a potent drug such as antibiotics, antihistamines, sedatives.

Fig. 3.2 : Paracetamol Elixir

Method of Preparation

- Elixirs are prepared by simple dissolution with agitation or by mixing two or more liquids.
- Ingredients are dissolved in their respective solvents. For example alcohol soluble ingredients in alcohol and water soluble in water.
- Alcoholic strength is maintained by adding the aqueous solution to the alcoholic solution.
- The mixture is then made upto the desired volume (q.s.).
- At this stage the product may not be clear due to separation of some of the flavouring agent because the alcoholic strength is reduced.
- Then elixir allowed to stand for some time here the oil globules starts precipitating.
- Then elixir is filtered.
- Talc can be added to absorb the excess of oils.
- Filtration gives clear product.

Formulation of Elixir

1. **Vehicles:** The elixirs are usually prepared by using water, alcohol, glycerin, sorbitol, and propylene glycol. Certain oils are easily soluble in alcohol where alcohol is used as cosolvent. 30-40% of alcohol may be used to make a clear solution.
2. **Adjuncts**
   - **(a) Chemical stabilizer:** The various chemicals or special solvents are used in many elixirs to make suitable elixir. E.g. For neomycin elixir – citric acid is added to adjust pH.
   - **(b) Colouring agent:** Amaranth, compound tartrazine dyes are used for colouring purpose.
   - **(c) Flavouring agent:** Black current syrup, raspberry syrup, lemon syrup etc.
   - **(d) Preservatives:** Alcohol 20% or more propylene glycol or glycerol as a vehicle is used as preservative. Chloroform desirable strength, benzoic acid may also be used.

Container: Elixirs are dispense in well filled, well closed air tight or glass bottles having screw caps.

Storage: Store in cool and dry place, protected from sunlight.

Formula:

R_x

Lemon oil	-	0.025 ml
Syrup	-	375 ml
Talc	-	30 gm
Purified water	-	q.s. to 1000 ml

3.1.10 Liniment

- Liquid or semi-liquid preparation meant for application to the skin.
- The liniments are usually applied to the skin with friction and rubbing of skin (on the affected area).
- The liniment may be alcoholic or oily solution or emulsion.
- In alcoholic preparation, alcohol helps in the penetration of medicament to the skin and also increases its counter irritant effect and rubefacient action.
- In oily liniments, arachis oil is commonly used which spreads more easily on the skin.
- Some lubricants may contain soap which helps in easy application of liniment on skin.
- Liniment should not be applied on broken skin because it may cause excessive irritation.
- Liniment contain medicament possessing analgesic action, rubefacient, counter irritant properties and applied in joint pain, muscle pain etc.

Should be dispensed in colored fluted bottle.

Labelling: FOR EXTERNAL USE ONLY

Storage: Stored in tightly closed container.

Formulation: Turpentine liniment

Soft soap – 9 gm

Camphor – 5 gm

Turpentine oil – 65 ml

Purified water - q.s. to 100 ml

Note: Rubefacient: Dilates blood vessels.

Counter irritant: Causes superficial inflammation to cure deep inflammation.

3.1.11 Lotions

- Lotions are liquid preparations meant for external use without friction.
- They are applied direct to the skin with the help of some absorbent material, such as cotton wool, gauze soaked in it.
- Lotions are not applied to broken skin it may cause excessive irritation. The insoluble matter should be divided very finely for preparing lotions. Bentonite as a suspending agent is added to it.
- Lotions are applied for antiseptic action, astringent action, germicidal action e.g. Calamine lotion.
- Alcohol is sometimes included in aqueous lotions for its cooling and soothing effect e.g. salicylic acid lotion.

Fig. 3.3

Preparation: Lotions are prepared by triturating the ingredients to a smooth paste and then adding the remaining liquid phase with trituration.

Storage: Lotions should be stored in well closed and in air tight container.

Lebelling: FOR EXTERNAL USE ONLY

Formula: Calamine lotion

R_x

Calamine – 15 gm

Zinc oxide – 5 gm

Bentonite – 3 gm

Sodium citrate - 0.5 gm

Glycerin – 5 ml

Liquid phenol - 0.5 ml

Rose water - q.s. to 100 ml

3.2 BIPHASIC LIQUIDS

3.2.1 Emulsion

- An emulsion is liquid preparation containing two immiscible liquids, one of which is dispersed as globules (dispersed phase = internal phase) in the other liquid (continuous phase = external phase).
- Droplets ranging in diameter (0.1-100 um).
- Emulsion is thermo dynamically unstable and is stabilized by presence of emulsifying agent (emulgent or emulsifier).
- Emulsion no more official in I.P.
- Emulsion protect the drug which are susceptible to hydrolysis and oxidation. It also provide prolonged action of medication.
- In the form of an o/w emulsion, ephedrine has more prolonged effect when applied to nasal mucosa , than when used in an oily solution.

3.2.2 Types of Emulsion

Primary emulsion containing one internal phase, for example,

- oil-in-water emulsion (o/w)
- water-in-oil emulsion (w/o).

Secondary emulsion also called multiple-emulsion contains two internal phases, for instance,

- o/w/o
- w/o/w.

It can be used to delay release or to increase the stability of the active compounds.

3.2.3 Test for Emulsion

Dilution test: Addition of water to a w/o emulsion and oil to o/w emulsion would crack the emulsion and lead to separation of the phases.

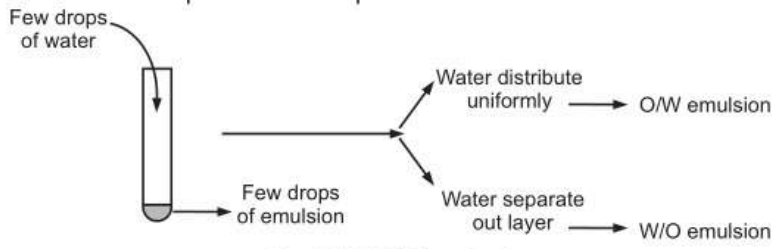


Fig. 3.4: Dilution test

Conductivity test: When current is passed to an emulsion which is connected to a voltage bulb, the bulbs glows if it is o/w emulsion since water is good conductor of electricity and when the bulb does not glow it is w/o emulsion because oil is non-conductor of electricity.

i.e. o/w = current flow

w/o = current do not flow

o/w = current not flow (when purified water instead of portable water is taken)

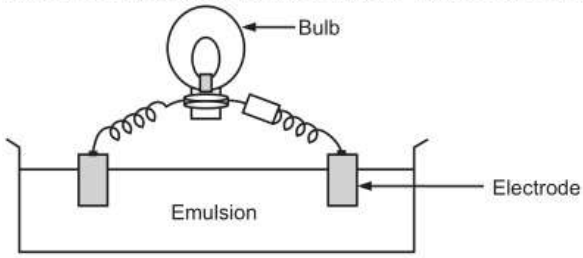


Fig. 3.5: Conductivity test

Dye test: Water-soluble dye will dissolve in the aqueous phase whereas oil-soluble dye will dissolve in the oil phase. For example: Amaranth (o/w Emulsion), Scarlet/Sudan (w/o Emulsion).

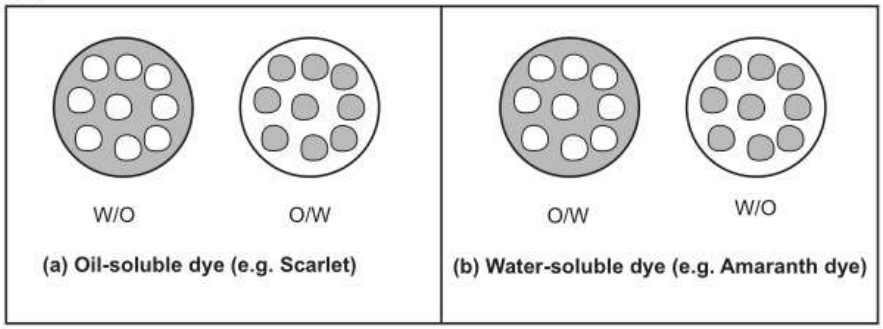


Fig. 3.6: Dye test

Fluorescent test: Oils give fluorescence under UV light, while water does not. Therefore, O/W emulsion shows spotty pattern while W/O emulsion fluorescence.

Filter paper test: o/w emulsion should spread out rapidly when dropped on to filter paper, in contrast w/o will migrate slowly.

Cobalt chloride test: filter paper soaked in cobalt chloride ($COCl_2$) solution and allowed to dry, turn blue to pink on evaporation to o/w emulsion.

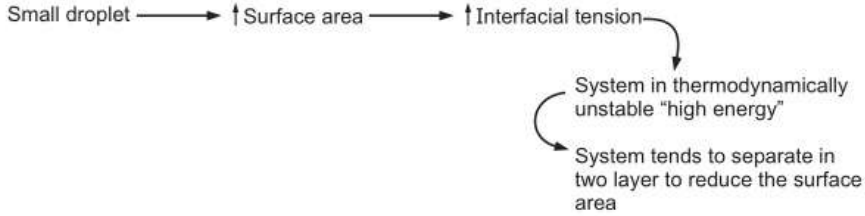
Pharmaceutical applications of emulsions

- To mask the bitter taste of the drugs.
- o/w emulsion is convenient means of orally administration of water-insoluble liquids.
- o/w emulsion facilitates the absorption of water-insoluble compounds comparing to their oily solution preparations (e.g. vitamins).
- Oil-soluble drugs can be given pareneterally in form of oil-in water emulsion. (e.g. Taxol)
- Emulsion can be used for external application in cosmetic and therapeutic uses.

3.2.4 Theories of Emulsification

- In case of two immiscible liquids, cohesive force between the molecules of each separate liquid exceeds adhesive force between two liquids. This is manifested as interfacial energy or tension at boundary between the liquids.

  Therefore, to prevent the coalescence and separation, emulsifying agents have been used.

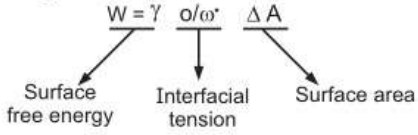


Surfactant: Adsorbed at oil/water interface to form monomolecular film to reduce the interfacial tension. e.g., Tween and Spans.

Hydrophillic colloids: Forming a multimolecular film around the dispersed droplet. e.g., Acacia.

Finely divided solids: They are adsorbed at the interface between two immiscible liquid phases to form particulate film. e.g., Bentonite and veegum.

(a) Monomolecular adsorption:



Surface active agent (SAA) is molecule which have two parts, one is hydrophilic and the other is hydrophobic. Upon the addition of SAA, they tend to form monolayer film at the oil/water interface.

The functions of surface active agents to provide stability to dispersed droplets are as follows:

- Reduction of the interfacial tension.
- Form coherent monolayer to prevent the coalescence of two droplet when they approach each other.
- Provide surface charge which cause repulsion between adjust particles.

Bancroft rule

As per bancroft rule, the emulsifying agent being used in an emulsion should be favourable to the external phase of the emulsion.

So even though there may be a formula that is 60% oil and 40% water, if the emulsifier chosen is more soluble in water, it will create an oil-in-water system.

The Hydrophilic-Lipophilic Balance (HLB) of a surfactant can be used in order to determine whether it is a good choice for the desired emulsion or not.

In Oil in Water emulsions, use emulsifying agents that are more soluble in water than in oil (High HLB surfactants).

In Water in Oil emulsions, use emulsifying agents that are more soluble in oil than in water (Low HLB surfactants).

(b) Multimolecular adsorption

	Polysaccharides	Amphoterics	Synthetic or semi-synthetic polymers
Colloids	Acacia Agar Alginic acid Carrageenan Guar gum Karraya gum Tragacanth	Gelatin	Carbomer resins Cellulose ethers Carboxymethyl chitin PEG-n (ethylene oxide polymer)

Hydrophilic colloids form multimolecular adsorption at the oil/water interface. They have low effect on the surface tension.

- Their main function as emulsion stabilizers is by making coherent multi-molecular film. This film is strong and resists the coalescence. They have, also, an auxiliary effect by increasing the viscosity of dispersion medium.

(c) Solid particle adsorption

Finely divided solid particles are adsorbed at the surface of emulsion droplet to stabilize them. Those particles are wetted by both oil and water (but not dissolved) and the concentration of these particles form a particulate film that prevent the coalescence.

Finely divided soilds	Bentonite Hectorite Kaolin Magnesium aluminium silicate Montorillonite Aluminium hydroxide Magnesium hydroxide Silica

Emulsion Stability

The process by which an emulsion completely breaks is generally considered to be governed by four different droplet loss mechanisms, i.e.

- Brownian flocculation,
- Creaming,
- Sedimentation flocculation and disproportionation.

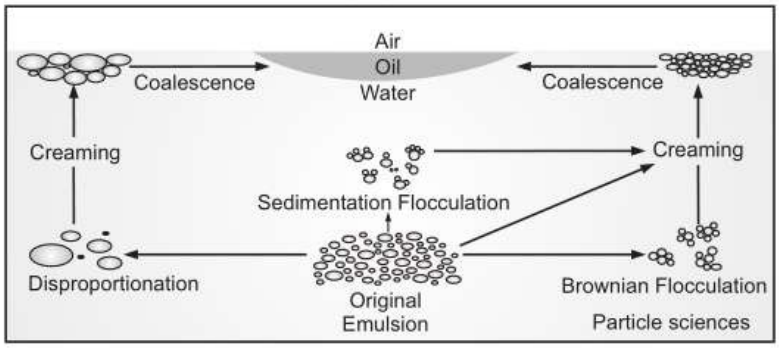


Fig. 3.7: Mechanism leading to coalescence of an oil in water emulsion

Creaming – upward and downward

- Creaming derives its name from the most commonly known example of a de-emulsification process.
- The separation of milk into its cream and skim milk components. Creaming is not an actual breaking but a separation of the emulsion into two emulsions, one of which (the cream) is richer in the disperse phase than the other. Creaming is the principal process by which the disperse phase separates from an emulsion and is typically the precursor to coalescence.
- The creaming rate (or settling rate for disperse phases more dense than the continuous phase) can be estimated from the Stoke's equation:

$$\upsilon = 2r^2 (\rho - \rho_0) g/9\eta$$

where, υ is the creaming (settling) rate, r is the droplet radius, ρ is the density of the droplet, ρo is the density of the dispersion medium, η is the viscosity of the dispersion medium (continuous phase) and g is the local acceleration due to gravity.

Flocculation

- The aggregation of droplets to give 3-D clusters without coalescence occurring. Importantly, all droplets maintain their own integrity and remain as totally separate entities. It results when there is a weak, net attraction between droplets and arises through various mechanism.

- Flocculation may be subdivided for convenience into two general categories: that resulting from sedimentation aggregation and that from Brownian motion aggregation of the droplets.

Disproportionation or Ostwald ripening

- It is dependent on the diffusion of disperse phase molecules from smaller to larger droplets through the continuous phase.
- The pressure of dispersed material is greater for smaller droplets than larger droplets as per the Laplace equation.

Coalescence

- A few globules tend to fuse with each other and form bigger globules.
- In this process, emulsifier film around the globules is destroyed to some extent.

Breaking

- Complete separation of phases, irreversible process.

  Phase Inversion

  In phase inversion o/w type emulsion changes into w/o type and vice versa. It is a physical instability.
- It may be brought about by the addition of an electrolyte, by changing the phase volume ratio or by temperature changes, by changing chemical nature of emulsifier

  Phase inversion can be minimized by using the proper emulsifying agent in adequate concentration, and by storing the emulsion in a cool place.

3.2.5 Preparation of Emulsions

Preparation of emulsions depends on the scale at which it is produced.

- **On small scale** mortar and pestle can be used but its efficiency is limited. To overcome this drawback small electric mixers can be used although care must be exercised to avoid excessive entrapment of air.
- **For large scale** production mechanical stirrers are used to provide controlled agitation and shearing stress to produce stable emulsions.
- The methods commonly used to prepare emulsions can be divided into two categories:

(A) Trituration Method

This method consists of dry gum method and wet gum method.

(1) Dry Gum Method

In this method, the oil is first triturated with gum with a little amount of water to form the primary emulsion. The trituration is continued till a characteristic 'clicking' sound is heard and a thick white cream is formed. Once the primary emulsion is formed, the remaining quantity of water is slowly added to form the final emulsion.

(2) Wet Gum Method

As the name implies, in this method first gum and water are triturated together to form a mucilage. The required quantity of oil is then added gradually in small proportions with thorough trituration to form the primary emulsion.

Once the primary emulsion has been formed remaining quantity of water is added to make the final emulsion.

(B) Bottle Method

This method is employed for preparing emulsions containing volatile and other non-viscous oils. Both dry gum and wet gum methods can be employed for the preparation.

As volatile oils have a low viscosity as compared to fixed oils, they require comparatively large quantity of gum for emulsification.

In this method, oil or water is first shaken thoroughly and vigorously with the calculated amount of gum. Once this has emulsified completely, the second liquid (either oil or water) is then added all at once and the bottle is again shaken vigorously to form the primary emulsion. More of water is added in small portions with constant agitation after each addition to produce the final volume.

Formulae for Primary Emulsion

Dry gum method or continental method

	Oil	Gum	Water
For fixed oil	4	1	2
For volatile	2	1	2
Oleo resins	1	1	2

3.2.6 Evaluation of Emulsion

Stability testing of emulsions involves determining stability at long term storage conditions, accelerated storage conditions, freezing and thawing conditions. Stress conditions are applied in order to speed up the stability testing.

1. The stress conditions used for speeding up instability of emulsions include:
   - Centrifugal force, Agitational force, Aging and temperature.
2. Physical parameters are evaluated to assess the effect of any of the above stress conditions:
   (a) Phase separation
   (b) Viscosity
   (c) Electrophoretic properties
   (d) Particle size and particle count

1. Determination of particle size and particle count: Determination of changes in the average particle size or the size distribution of droplets is an important parameter used for the evaluation of emulsions. It is performed by optical microscopy, sedimentation by using Andreasen apparatus and Coulter counter apparatus.

2. Determination of viscosity: Determination of viscosity is done to assess the changes that might take place during aging. Emulsions exhibit non-newtonian type of flow characteristics.

The viscometers which should be used include cone and plate viscometers.

3. Determination of phase separation: This is another parameter used for assessing the stability of the formulation.

Phase separation may be observed visually or by measuring the volume of the separated phases.

4. Determination of electrophoretic properties: Determination of electrophoretic properties like zeta potential is useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

Types of Surfactants

- Anionic
- Cationic
- Non-ionic
- Ampholytic

(a) Anionic: Monovalent, polyvalent and inorganic soaps sulphates and sulphanotes, alkali soaps includes sodium, potassium and ammonium salts are lauric, myristric, palmitic, stearic and oleic acid are water soluble which forms o/w emulsion.

Metallic soaps like calcium or magnesium salts are fatty acid are water insoluble and tend to form w/o emulsion. Organic soaps forms o/w emulsion. Sulphated alcohols such as sodium lauryl sulphate form o/w emulsion.

Sodium dioctyl sulphosuccinate is frequently used sulphonates di-(2-ethyl hexyl) sodium sulphosuccinate called Aerosol OT.

(b) Cationic emulgent: They are commonly used in lotion and cream due to their remarkable bactericidal property. For example: domiphen bromide, cetyl pyridium bromide, benzalkonium chloride, cetyl trimethyl ammonium bromide.

(c) Non-ionic emulgents: For example: Glyceryl ester, fatty acid esters of sorbitol, and their poly oxyethylene derivative, polyoxyethene glycol esters and Sorbitan fatty acid esters e.g. Sorbitan mono palmitate (span-40) are non-ionic and oil soluble promoting w/o emulsion.

Polyoxyethylene sorbitan monopalmitate (tween 40) are hydrophilic, water soluble derivative promotes o/w emulsion.

(d) Amphoteric: N-dodecyl, N, N- dimethyl betaine, lecithin.

PEG esters such as polyoxy ethylene glycol 400 monostearate are widely used to prepare emulsified lotion and creams.

Natural emulgents: Most commonly used is acacia. Others are Gelatin which is amphoteric in nature, Lecithin (phospholipid) and Cholesterol.

Acacia and gelatin: Form interfacial monolayer.

Lecithin and cholesterol: Form interfacial mono molecular layer.

Lecithin is a phospholipids and form o/w emulsion, Darken on storage.

Cholesterol form: w/o emulsion.

Finely dispersed solids: Colloidal clays such as bentonite, veegum, oxide, silica gel, aluminium hydroxide, Magnesium oxide. Magnesium hydroxides are most commonly used finely dispersed solids which act by forming particular particulate film around dispersed globules.

- **Bentonite** produce both o/w and w/o type of emulsion depending on order of mixing.
- **Veegum** is also as an emulgent for o/w emulsion but it is chiefly used as an stabilizer in cosmetic creams and lotion.
- **Auxilairy emulgents** are incapable of forming stable emulsion. Have thickening property. Thus, consistency of an o/w emulsion prepared by using acacia. It can be increased by tragacanth or agar which act as auxiliary emulsion.

List of antioxidants (0.001-0.1%)

- Gallic acid
- Propyl Gallate
- Ascorbic acid
- Sulphites
- alpha -Tocopherol
- Butylated hydroxyl toluene
- Butylated hydroxyl anisole
- Ascorbyl palmitate

3.2.7 Preservative used in Emulsion

Type	Example	Characteristic
Acid and acid derivatives	Benzoic acid Sorbic acid Propionic acid Dehydroacetic acid	Antifungal
Alcohols	Chlorobutanol Phenoxy- 2-ethanol	Eye prep. Synergism
Aldehydes	Formaldehyde, Glutaraldehyde	Broad spectrum
Formaldehyde Derivatives	Hexamethylene tetramine Mono and de- methyl ol dimethyl hydantoin	Broad spectrum
Phenolic	Phenol,Cresol,chlorothymol p-phenyl phenol p-chlorometaxylenol Methyl-p-hydroxybenzoate Propyl-p-hydroxybenzoate Benzyl-p-hydroxybenzoate Butyl -p-hydroxybenzoate	Broad spectrum
Quaternaries	Chlorhexidine Benzethonium chloride Benzalkonium chloride Cetyl pyridinium chloride Cetyl Methyl ammonium bromide	Broad spectrum
Mercurials	Phenyl mercuric acetate Sodium Ethyl mercuric Thiosalicylate	Broad spectrum

3.3 SUSPENSIONS

- Suspensions are biphasic, heterogeneous system in which finely divided insoluble solid particles (disperse phase) are dispersed or suspended in a vehicle (dispersion medium).

- The diameter of disperse phase may range from 0.5 µm to 100 µm.
- Systems in which particle size is below than this range are called colloidal (1 nm – 0.5 µm diameter).
- Suspension can be used as oral dosage form, applied topically to skin or given parenterally.

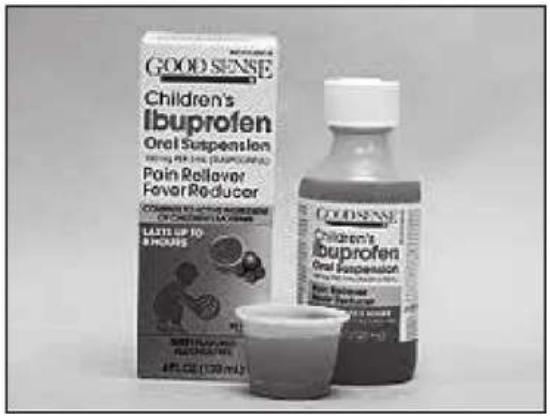


Fig. 3.8

3.3.1 Properties of Good Suspensions

1. The dispersed particles should settle slowly and should redisperse immediately on shaking.
2. The product should remain sufficiently homogeneous for atleast the period between shaking the container and removing the required dose.
3. The viscosity of suspension should be such that it can be easily removed from container and transferred to site of application without any difficulty.
4. The sediment produced on standing should not form a hard cake.
5. Suspension particles should be small and uniformly sized in order to give a smooth, elegant product free from grittiness.
6. The suspension should be physically and chemically stable during handling and storage conditions.
7. It should have good syringibility in case of parenteral suspension.
8. It should produce thixotropic property, gel to sol upon shaking and sol to gel on storage.

Advantages of Suspensions

1. Insoluble drug may be made more palatable (masking bitter taste).
   For example: Chloramphenicol.
2. Insoluble drug can be prepared in a more stable manner. For example: Procaine penicillin G.

3. Suspensions results in more bioavailability compared to any other dosage form.

   Solution > Suspension > Capsule > Compressed tablet > Coated tablet.

4. Duration and onset of action can be controlled. For example: Protamine Zinc-insulin injection.
5. Lotion leaves a cooling layer of medicament on skin.
6. It can be prepared for both immediate and sustained drug release preparations.

Disadvantages of Suspensions

1. Suspensions require shaking before use, to ensure uniformity of dose.
2. If suspension is not shaken well, accuracy of dose gets affected.
3. Improper storage condition can affect the disperse system.
4. Sufficient care must be taken during handling and transport.

3.3.2 Classification

1. **Based on general classes:**
   - **Oral Suspensions –**

   e.g. Paracetamol suspension

   Antacid suspension

   Antibiotic suspension

   Anthelminitics suspension

   Laxative suspension

   - **Topical suspensions –** (Externally applied)

     E.g.- Calamine lotion.

   - **Parenteral suspension –** e.g. Cholera vaccine, insulin, Zinc suspension.

2. **Based on proportion of solid:**
   - **Dilute suspension –** (2 to 10% w/v solid)

     E.g. Cortisone acetate, Prednisolone acetate.

   - **Concentrated suspension –** (50% w/v)

     E.g. Zinc oxide suspension.

3. **Based on deteriorate nature of solid particles**
   1. Flocculated
   2. Deflocculated

Flocculated suspension	Deflocculated suspension
1. Particles exist as loose aggregates.	1. Particles exist as separate entity.
2. Rate of sedimentation is high.	2. Rate of sedimentation is low.
3. Sediment formed rapidly.	3. Sediment formed slowly.
4. Consist of loosely packed particles possessing a Scaffolding like structure a hard dense cake does not form and the sedimentation can easily redispersed.	4. Sediment becomes very closely packed as the repulsive forces between the particles are overcome a hard cake is formed which is difficult to redisperse.
5. Elegant preparation are obtained due to uniform distribution of loosely bonded flocs.	5. Unsightly preparation result due to the formation of sedimentation.

4. Based on size of solid particles

1. Colloidal suspension – (< 1 micron)
2. Coarse suspension – (> 1 micron)
3. Nano suspension – (10 ng less than 1 mm)

3.3.3 Applications of Suspensions

1. Suspension is usually applicable for drug which is insoluble or poorly soluble e.g. Prednisolone syrup.
2. To prevent degradation of drug or to remove stability of drug e.g. Oxytetracycline suspension.
3. To mask the bitter drug. e.g. Chloramphenicol palmitate.
4. Topical application e.g. Calamine lotion is used.
5. Parenteral applications for control rate of drug absorption e.g. Penicillin procaine.
6. Vaccine as immunizing agent e.g. Cholera vaccines.
7. X-Ray contrast agent e.g. Barium Sulfate for examining alimentary canal.

Theoretical consideration of suspensions

I. Particle size control
II. Wetting
III. Sedimentation
IV. Brownian movement
V. Electrokinetic
VI. Aggregation

1. Particle size: It should be in range. Too large and too small should be avoided. Large particles will settle fast at bottom of container. Too fine particles can form cake.

2. **Sedimentation:** Means settling of particles on floccules occur under gravitational force in liquid dosage form.

$$V_{sed} = \frac{d^2 (\rho_s - \rho - 0)\, g}{18\eta_0}$$

d = Diameter of particle
ρ_s = Density of disperse phase
g = Acceleration due to gravity
η_0 = Viscosity of disperse medium in poise
V_{sed} = Sedimentation velocity in cm/sec
ρ_o = Density of disperse medium

Stoke's law only applies to:

1. Spherical particle in a very dilute suspension (0.5 to 2 gm/100 ml).
2. Particles which freely settle.
3. Particles with no physical or chemical attraction.

Sedimentation volume for flocculated suspension

$$F = \frac{V_u}{V_o}$$

F = Sedimentation volume
V_u = Final volume
V_o = Original volume before settling

F is the ratio of ultimate volume of sediment to the original volume of sediment before settling.

When $F < 1 \rightarrow V_u < V_o$
$F = 1 \rightarrow V_u = V_o$

System is in flocculated equilibrium, no clear supernatant liquid on standing.

When $F > 1 \rightarrow V_u > V_o$

That means sediment volume is greater than original volume due to the network of flocs formed in suspension and so loose and fluffy sediment.

3. **Degree of flocculation:** It is the ratio of sedimentation volume of the flocculated suspension, F to the sedimentation volume of deflocculated suspension F_∞

$$\beta = \frac{F}{F_\infty}$$

$$\beta = \frac{(V_u/V_o) \text{ flocculated}}{(V_u/V_o) \text{ deflocculated}}$$

The minimum value of β is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.

4. Brownian movement

- Prevents sedimentation by keeping the dispersed material in random motion.
- Brownian movement depends upon density of dispersed phase, the density and viscosity of disperse medium.
- Kinetic bombardment of particles by the molecules of suspending medium will keep particles suspending provided that their size is below critical radius.
- Brownian movement can be observed if particles are of 2 to 5 mm and when density of particle and viscosity medium is favourable.

Brownian Movement is given by

$$D_i^2 = RTt/N_3\pi\eta r$$

R = Gas constant

T = Temperature

t = Time

N = Avogadro number

η = Viscosity of medium

r = Radius of particle

5. Electrokinetic parameter

(δ) Zeta potential: The zeta potential is defined as the difference in potential between the surface of tightly bound layer (shear plane) and electro neutral region of solution.

- The potential located at the shear plane is known as the zeta potential.
- It has a practical application in the stability of disperse systems since the potential governs the degree of repulsion between adjacent, similarly charged, dispersed particles.
- If zeta potential is reduced to a certain value, the attractive force exceed the repulsive force and the particles came together leading to flocculation. If zeta potential increased repulsion occurs.

6. Formulation of Suspension:

It involves the following ingredients:

1. **Medicament:** Drug with non-aqueous solubility.
2. **Flocculating agent:** The particle should be well dispersed in a vehicle. Dispersion can be improved by adding a surfactant, electrolyte or a polymer. It act as a deflocculating agent.
   - **(a) Electrolytes:** As flocculating agent by reducing the electric barrier between the particles due to a decrease in zeta potential
     - Forms a bridge between adjacent particles.
     - Particles links in loose manner

     E.g. Sodium salts of acetate, phosphates, citrates.

(b) Surfactant: Non-ionic surfactant acts by reducing surface tension or by forming bridges between particles.

Ionic surfactant also cause flocculation by neutralization of charge on each particle, thus resulting in flocculated system (also depends which type of charge is present on particles)

(c) Polymers: The linear branches chain molecules of polymer forms a gel network within the system, which becomes absorbed onto the surface of dispersed particles thus holding in flocculated state. E.g. Starch, alginates, cellulose derivative, carbamers, tragacanth.

3. **Deflocculating agent:** Prevent flocculation by reducing viscosity and is called as dispersant. An agent for thinning suspensions or slurries. They are low molecular weight anionic polymers. e.g.: polyphosphates, lignosulphonates, and water soluble synthetic polymers.
4. **Suspending agents:** They are hydrophilic colloids which forms colloidal dispersion with water and then acts by increasing viscosity of external phase.
   - Reducing rate of sedimentation of particles.
   - Particles remain suspended for long time.
   - Easier to withdraw accurate dose.

They are also known as Thickening agents.

E.g. Tragacanth BP – 0.2% conc.

BP compound tragacanth – 2.0%

Bentonite BP – 2-3%

3.3.4 Types of Suspending Agents

1. Natural polysaccharides

(a) Acacia: Protective colloid and suspending agent used in preparation containing resinous tincture that precipitates on addition of water.

(b) Tragacanth: Better than acacia, used to suspend heavy indiffusible substances.

(c) Alginates: 1-5% Viscous in nature immediately after preparation but the viscosity decreases within 24 hours.

Alginate mucilage must not be heated above 60°C due to polymerization its viscosity is lost.

2. Semi-synthetic derivative

(a) Methyl cellulose – 0.5 to 2% (sol to gel, gel to sol)

(b) SCMC – 0.25%-1% (oral, external, IV)

(c) Microcrystaline cellulose – insoluble in water, but show a good dispersion.

- Used in combination with MC, HPMC to flocculate dispersion.

3. **Inorganic agents**
   (a) Bentonite – 3% for external use.
   (b) Magnesium aluminiun silicate (veegum) – 5%.
4. **Synthetic compound**
   (a) Carbamers – 0.5% conc.
   (b) Colloidal silicon dioxide – 4% for external use.
5. **Wetting agents:** These substances reduces the surface tension between solid particles and liquid medium. This is achieved by the solid liquid interface in such a way that the affinity of the particles towards the surrounding medium is increased, there by helping in the penetration of liquid into the particles, thus resulting in good suspension (0.5%), for example: Spans and tweens etc.
6. Preservative substances which protect substance from bacterial growth. They should be stable and compatible. e.g. Benzoic acid, methyl and propyl paraben, EDTA.
7. **Organoleptic agent**
   (a) Flavouring agent – e.g. Vanilla, Strawberry, Banana.
   (b) Sweetening agent – Sucrose, Sodium saccharin, Aspartame.
   (c) Coloring agent – Sunset yellow, Tartrazine, Erythrosine.
   (d) Perfumes – Rose water and Lavender oil.
8. **Chemical stabilizers:** To maintain the stability of formulation. e.g. Citric acid, disodium diedetate, sodium citrate.

3.3.5 Manufacturing and Dispensing of Suspension

1. **Suspension containing diffusible solids**
   - Drug is finely powdered with other ingredients.
   - $3/4^{th}$ of vehicle is added to make cream.
   - Addition of rest of vehicle.
   - Volume is makeup.
   - Suspension is labelled properly and corked

     e.g. Light kaolin, light Magnesium carbonate, Sodium bicarbonate, Peppermint water.

     Labelling: Shake well before use.
2. **Suspension containing indiffusible solids:** Prepared by using compound tragacanth and Tragacanth mucilage (mixture of tragacanth, ethanol and chloroform water) e.g., Aspirin, Chalk, Phenobarbitone, Zinc oxide.

Note: Formulation method of suspension using

1. Tragacanth mucilage
2. Compound tragacanth powder

The procedure is same as that of diffusible solid additional point is step one where drug is also triturated with suspending agent with the addition of vehicle in small quantity and then reset procedure is same.

3. **Suspension containing precipitate forming liquid:** Liquid preparation containing resinous matter when mixed with water show precipitation of resin, which stick to the walls of container and tolu tincture. To prevent this compound tragacanth or Tragacanth mucilage is used e.g. Myrrh, Tolu, Lobelia.
4. **Suspensions containing poorly wettable solids:** Some substances like sulfur and Hydrocortisone are both insoluble in water and poorly wettable by it.

   In these type of suspension, a suitable wetting agent is added which is adsorbed at the solid liquid interface in such a way that the affinity of particles for surrounding medium is increased which interparticular forces are decreased.

   E.g. Sulfur lotion – quilliar tincture is used as suspending agent.
5. Suspension produced by chemical reaction – e.g. $MgSO_4 + (NaOH)_2 + Na_2SO_4$

   For preparing milk of magnesia suspension (antacid). Precipitate is produced by chemical reaction.

3.3.6 Evaluation of Suspension

(1) Sedimentation method

(2) Rheological method

(3) Electrokinetic method

(4) Micromeritic method

Sedimentation Volume

Sedimentation volume of the formulations was determined using the following formula.

$$F = \frac{V_u}{V_o}$$

F = Sedimentation volume,

V_u = Ultimate settled height of suspension,

V_o = Original height of the suspension before settling

Ease of Redispersibility

The suspension was allowed to settle in a measuring cylinder. The mouth of the cylinder was closed and was inverted through 180° and the number of inversions necessary to

restore a homogeneous suspension was determined. If the homogeneity of the suspension was attained in one inversion, then the suspension was considered 100% easily redispersible. Every additional inversion decreases the percentage of ease of redispersibility by 5%.

Viscosity determination (Rheological parameter)

The viscosity of all formulations was determined by using Brookfield digital viscometer. The measurements were carried out using spindle number-3 (disc type) rotating at 10, 20, and 100 rpm. The temperature was maintained at 30°C

Particle size distribution

Using optical microscope particle size distribution studies were carried out.

1. Eye piece micrometer was calibrated using stage micrometer,
2. Sample was uniformly suspended in paraffin oil.
3. A slide of above suspension was prepared, placed under microscope and measured the size of the particles.

Electro kinetic method

Measurement of Zeta-potential using Micro electrophoresis.

Apparatus and Zeta Plus (Brook haven Instruments Corporation, USA).

It shows the stability of a disperse system.

Zeta potential

The zeta potential of the formulated suspensions was determined using a Zeta Plus (Brookhaven Instruments Corporation, USA).

Approximately 1 mL of suspension was transferred into a plastic.

Cuvette using a pipette and diluted with distilled water.

The Brookhaven zeta potential software was used for the Parameters set to a temperature of 25°C and refractive index (1.33)

The zeta potential of the formulation is determined on day 0, 7, 14, 21 and day 28 post formulation.

Packaging of Suspensions

Pharmaceutical suspensions for oral use are generally packed in **wide mouth container** having adequate space above the liquid to ensure proper mixing.

Parenteral suspensions are packed in either glass ampoules or vials.

Ideal Requirements of Packaging Material

- It should be inert.
- It should effectively preserve the product from light, air, and other contamination through shelf life.
- It should be cheap.
- It should effectively deliver the product without any difficulty.

Materials Used For Packaging

Generally glass and various grades of plastics are used in packaging of suspension.

Glass

Generally soda lime and borosilicate glass are used in preparation of non-sterile suspensions.

Amber glass does not allow U.V. light to pass through. Amber characteristics can be developed in the glass by addition of various types of additives.

Disadvantages of Glass Materials

- They are fragile.
- They are very heavy as compared to plastic so handling and transport is difficult.
- Most important disadvantage of glass that glass constituents get extracted into the product.

Plastic

Due to the negative aspects of glass, plastic material significantly use of plastic as packaging material for sterile as well as non-sterile pharmaceutical suspension increased.

Advantages of Plastic Material

Materials used: Polyethylene, Poly Vinylene Chloride, Polystyrene, Polycarbonate etc.

Closure and Liners

With an exception of ampoules all containers required elastomeric closure.

Factors affecting in selecting closure

- Compatibility with product
- Seal integrity
- It should be stable throughout the shelf life

Factors affecting in selecting liner

- Chemical resistance
- Appearance
- Gas and vapour transmission
- Removal torque
- Heat resistance
- Shelf life
- Economical factors

STORAGE REQUIREMENTS & LABELLING

Labelling

- Shake well before use.
- Do not freeze.
- Protect from direct light (for light sensitive drugs).
- In case of dry suspensions powder the specified amount of vehicle to be mixed may indicated clearly on label.

MULTIPLE CHOICE QUESTIONS

1. All of the following liquids are for internal use except
   (a) Syrup (b) Elixir
   (c) Aromatic water (d) Liniment
2. β-cyclodextrin increases the solubility and stability of poorly soluble drugs by
   (a) Cosolvency (b) Solubilization
   (c) Complexation (d) Chemical modification
3. Additives are substances which are included during formulation of dosage form but
   (a) Do not have any therapeutic activity of their own.
   (b) Have therapeutic activity of their own
   (c) Both
   (d) None of the above
4. Aromatic waters are prepared by
   (a) Distillation (b) Maceration
   (c) Condensation (d) Triple maceration
5. Which of the following surfactants is used as a wetting/solubilizing agent?
   (a) Polysorbate 80 (b) Sodium lauryl sulphate
   (c) PEG-40-castor oil (d) All of the above
6. Liniment is a
   (a) Non-greasy semisolid preparation
   (b) Semi-liquid preparation applied to unbroken skin
   (c) Complex mix of drug with Al^{3+} and Ca^{2+}
   (d) Semisolid preparation applied to broken skin
7. Elixirs are
   (a) Alcoholic preparations (b) Hydroalcoholic preparations
   (c) Aqueous preparations (d) Non-alcoholic preparations
8. Which of the following is not used as solvent in oral formulation of liquid?
   (a) Ethanol (b) Ethylene glycol
   (c) Propylene glycol (d) Glycerin

Answer Key

1. (d)	2. (b)	3. (a)	4. (a)	5. (d)	6. (b)	7. (b)	8. (b)

QUESTIONS

Short Answer Questions

1. Define gargles
2. Define nasal drops.
3. Explain the term Co-solvent with example.
4. Write down the formula for simple syrup I.P and U.S.P.
5. Define creaming.
6. Define sedimentation volume.
7. Define degree of flocculation.
8. Define drought.
9. What should be the pH of nasal drops?
10. Give four monophasic liquid dosage form which is used for internal use.
11. What is the role of glycerine in throat paints?
12. What is the range of particle size in suspension?
13. Write down two emulsifying agents.
14. Define wetting agents.
15. What is primary emulsion?
16. What is cracking?
17. What is phase inversion?

Long Answer Questions

1. What are Elixirs? Give method of its preparation and examples.
2. Define syrup IP and give its method of preparation storage and use.
3. Write short notes on – (a) Ear drops (b) Enemas (c) Throat paint.
4. Classify monophasic and biphasic liquid dosage forms.
5. Differentiate between lotion and liniment.
6. Differentiate between gargles and mouthwash.
7. Write down the advantages and disadvantages of suspension.
8. Define suspension. Write a note on method of preparation of suspension.
9. Define emulsifying agent. Write the ideal properties of emulsifying agents.
10. Write in brief about method of preparation and evaluation of an emulsion.
11. Describe various factors influencing stability of emulsion.
12. Differentiate between flocculated and deflocculated suspension.
13. Discuss various test to identify the type of emulsion.
14. Write a note on stability of suspension.

❑❑❑

Unit...4

SUPPOSITORIES & PHARMACEUTICAL INCOMPATIBILITIES

♦ **OBJECTIVES** ♦

- **To understand the term suppository.**
- **To know various types of suppositories and suppository base.**
- **To understand the advantages and disadvantages of suppositories.**
- **To know the method of preparation and evaluation of suppositories.**
- **To understand displacement value and its calculation.**
- **To understand the various pharmaceutical incompatibilities.**

4.1 INTRODUCTION TO SUPPOSITORIES

Suppositories are solid dosage form of medicament which is made for insertion into the body cavities. They may be Conical or ovoid medicated solids intended for insertion into several cavities of the body other than mouth are known as Suppositories. This term was derived from the Latin word suppositus, meaning "to place under." They may be inserted in the rectum, vagina, and to a lesser extent, the urethra for local or systemic effects. Rectal and urethral suppositories usually employ vehicles that melt or soften at body temperature, whereas vaginal suppositories, sometimes called *pessaries*, are also made as compressed tablets that disintegrate in the body fluids exert localized or systemic effects.

4.2 TYPES OF SUPPOSITORIES

1. **Rectal suppositories:** These are meant for insertion into the rectum for producing systemic effect. The rectal suppositories meant for adults usually weigh 2 gm and are torpedo shape, whereas the suppositories made for children are much smaller in size as compared to the adult suppositories. Children's suppositories weigh about 1 gm.

   The rectal suppositories which are used for systemic effects may contain analgesics, antispasmodic, transquillizers and sedative effects. Other than other these are used for antiseptic action, local anaesthetic action, for lubricating, soothing purposes.

   The rectal suppositories are used for evacuating bowel by irritating mucous membrane of rectum or by lubricating the membrane.

2. **Vaginal suppositories:** The vaginal suppositories are also known as Pessaries. They are meant for insertion into the vaginal cavities. They weigh about 3-5 gm and are molded in globular or oviform shape or compressed on a tablet press into conical shapes. The vaginal suppositories are larger than the rectal suppositories. They are used for their local action in vagina.
3. **Urethral suppositories:** These are also called as bougies and are of pencil shape. The urethral suppositories are meant for insertion into the urethra. The urethral suppositories intended for males weigh 4 gm each and are 100-150 mm long and those for females are 2 gm each and 60-75 mm in length.
4. **Nasal suppositories:** The nasal suppositories are also called as nasal bougies or buginaria. The nasal suppositories are meant for introduction in to nasal cavity. They are usually prepared with glycerogelatin base. They have similar shape as that of the urethral bougies. They weigh about 1 gm and have length of 9-10 cm.
5. **Ear cones:** Ear cones are used for insertion into the ear. They are also known as Aurinaria. They are used rarely. For preparation of ear cones generally theobroma oil is used as base. They are prepared in urethral bougies mould and cut according to size.

Advantages

1. Suppositories can exert local effect on rectal mucosa.
2. It is used to promote evacuation of bowel.
3. It avoid any gastrointestinal irritation.
4. Suppositories can be used in unconscious patients (e.g. during fitting).
5. Suppositories can be used for systemic absorption of drugs and avoid first-pass metabolism.
6. Babies or old people who cannot swallow oral medication.
7. It is useful for post operative people who cannot be administered oral medication.
8. A very suitable dosage form for people suffering from severe nausea or vomiting.

Disadvantages of Suppositories

1. Suppositories have a problem of patient acceptability.
2. In some cases, the total amount of the drug must be given will be either too irritating or in greater amount than reasonably can be placed into suppository.
3. Incomplete absorption may be obtained because suppository usually promotes evacuation of the bowel.
4. Suppositories are not suitable for patients suffering from diarrhoea.

4.3 IDEAL PROPERTIES OF SUPPOSITORIES BASES

1. It should melt at body temperature or dissolves in body fluids.
2. It should be good in appearance.

3. It should be non-toxic and non-irritant.
4. It should be compatible with any medicament.
5. Suppositories should releases medicament readily.
6. It should be easily moulded and removed from the mould. It shrinks sufficiently on cooling to release itself from the mold without the need for mold lubricants.
7. It should be stable to heating above the melting point.
8. It should be easy to handle and should retain its shape while handling.
9. It should be stable on storage such that it does not change colour, odour, or drug release pattern.
10. Acid value is below 0.2, saponification value ranges from 200 to 245, and iodine value is less than 7.
11. The "water number" is high, i.e., a high percentage of water can be incorporated in it.

4.4 TYPES OF BASES

1. Fatty Bases.
2. Water Soluble or Miscible Bases.
3. Emulsifying Bases.

4.4.1 Fatty Bases

1. Theobroma oil
2. Emulsified theobroma oil
3. Hydrogenated bases

They are designed to melt at body temperature.

1. Theobroma Oil (Cocoa butter)

It is a mixture of glyceryl esters of different unsaturated fatty acids.

Cocoa Butter is a triglyceride, yellowish white, solid, brittle fat, smells and taste like chocolate. Its melting point is between 30-35°C, its iodine value is "between" 34-38 and its acid value is not higher than 4, because cocoa butter can melt and rancid. So it must be stored in cool dry place protected from light.

Overheating changes its physical characteristics and it has a tendency to adhere to the mold when solidified. It may exist in four crystalline states.

α Form: This form is obtained by suddenly cooling the melted mass to 0°C. Its melting point is 24°C.

β Form: This form is obtained when cocoa butter is melted at 35 to 36°C and slowly cooled. It melts at 18 to 23°C.

β' Form: It reverts back to 3 forms and melts at 34 to 35°C.

γ Form: It is obtained by pouring a cool (20°C) cocoa butter into a container before it is solidified and cooled at deep freeze temperature. It melts at 18°C.

All the four forms are unstable and are converted to stable form over a period of several days. Thus, extreme care should be exercised while melting and cooling cocoa butter. As in general, the minimal use of heat during the melting process is recommended.

To overcome drawbacks of cocoa butter, emulsified theobroma oil, hydrogenated palm kernel and soyabean oils have been suggested.

Advantages

(a) A melting range of 30 - 36°C (solid at room temperature but melts in the body).
(b) Readily melted on warming, rapid setting on cooling.
(c) Miscible with many ingredients.
(d) Non-irritating.

Disadvantages

(a) Polymorphism: When melted and cooled it solidifies in different crystalline forms, depending on the temperature of melting, rate of cooling and the size of the mass.
(b) If melted at not more than 36°C and slowly cooled it forms stable beta crystals with normal melting point.
(c) If over-heated then cooled it produce unstable gamma crystals which melt at about 15°C or alpha crystals melting at 20°C.
(d) Cocoa butter must be slowly melted over a warm water bath to avoid the formation of the unstable crystalline form.
(e) Adherence to the mould.
(f) Softening point too low for hot climates.
(g) Melting point reduced by soluble ingredients.
(h) Rancidity on storage.
(i) Poor water-absorbing ability: Improved by the addition of emulsifying agents.
(j) Leakage from the body.

2. Emulsified Theobroma Oil

When large quantities of aqueous solutions are required to be incorporated then emulsified theobroma oil as a base can be used. There are many agents which are used to form emulsified theobroma oil, for example: 2-3% cetyl alcohol, 4% glyceryl monostearate, 10% lanette wax, 4% bees wax, and spermaceti up to 12% can be utilised for emulsified theobroma oil suppositories.

3. Hydrogenated Oils

They are used as a substitute to theobroma oil, many hydrogenated oils are used as a substitute, for example, coconut oil, palm kernel oil, hydrogenated edible oil, a mixture of oleic acid and stearic acid. They are known as synthetic fat bases.

Advantages

The synthetic fat bases have advantages over theobroma oil are as follows:

- Their solidifying points are unaffected by overheating.
- Because of the lower content of unsaturated fatty acids they have good resistance to oxidation.
- The difference between melting and setting points is small. Hence, they set quickly, the risk of sedimentation of suspended ingredients is low.
- Lubrication of mould is not necessary because they contract significantly on cooling.
- They are marketed in a series of grades with different melting point ranges, which can be chosen to suit particular products and climatic condition.
- They produce colourless, odourless and elegant suppositories.
- They contain a proportion of w/o emulsifying agents, and therefore, their water-absorbing capacities are good.

Disadvantages

- Brittle if cooled rapidly, avoid refrigeration during preparation.
- The melted fats are less viscous and more fluid than theobroma oil because of that there is a greater risk of drug particles to sediment during preparation.

4.4.2 Water Soluble or Water Miscible Base

(i) Glycero Gelatin

It is a mixture of glycerin and water which is made into a stiff jelly by the addition of gelatin. The proportion of gelatin can be varied according to the intended use of the preparation.

Gelato-glycerin bases dissolve in the body fluids liberating contained medicaments Gelato-glycerin Mass BP which contains 14% gelatin, 70% glycerin and water. USP formula contains 20% gelatin together with 70% of glycerin.

For dispensing purposes, good quality powdered gelatin should be used. In order to control the consistency, glycerin can be partially or wholly substituted by propylene glycol and polyethylene glycols. The incompatibility of some medicaments can be avoided by the use of either Pharmagel A (cationic) or Pharmagel B (anionic). Glycerin suppositories being liable to mould growth, preservatives should be added.

Disadvantages

(a) Physiological effect: osmosis occurs during dissolving in the mucous secretions of the rectum, producing a laxative effect.
(b) It can cause rectal irritation due to small amount of liquid present.
(c) Unpredictable solution time.

(d) **Hygroscopic:** So, they should be packaged in tight containers and also have dehydrating effects on the rectal and vaginal mucosa leading to irritation.
(e) Microbial contamination likely.
(f) Long preparation time.
(g) Lubrication of the mould is essential.

(ii) Soap Glycerin

In this case, soap is employed instead of glycerin for hardening. Sodium stearate can incorporate up to 95% of glycerin. Sodium stearate (soap) is produced in-situ by interaction of sodium carbonate with stearic acid. Soap glycerin suppositories are however hygroscopic.

(iii) PEG Bases

Different mixtures of polyethylene glycols are marketed under the trade names of Postonals, Carbo waxes and Macrogols.

Most of the drugs commonly administered in suppository form are compatible with these bases. Polyethylene glycols are however incompatible with phenols and reduce the antiseptic effects of quaternary ammonium compounds.

4.4.3 Emulsifying Bases

Massa Esterinum, Witepsol and Massupol are the trade names under which the emulsifying bases are marketed.

1. **Massa Esterinum** is a mixture of the mono-, di- and tri-glycerides of the fatty acids having the formula $C_{11}H_{23}COOH$ to $C_{17}H_{35}COOH$.
2. **Witepsol** bases consist of hydrogenated triglycerides of lauric acid with added monoglycerides. These are available in nine grades.
3. **Massupol** consists of glyceryl esters namely of lauric acid and addition of very small quantity of glyceryl monostearate.

All these bases are free from the drawbacks of cocoa butter and do not require lubrication of mould.

Water-dispersible bases essentially consist of surfactants. They melt at body temperature. Some formulae of dispersible bases containing surfactants are outlined below.

Glyceryl monostearate 10, Glyceryl monostearate 15, Tween 60, 40.

4.5 METHODS OF PREPARATION

Suppositories can be prepared by one of three methods:

1. Hand Rolling

- It is the simplest and oldest method of suppository preparation and may be used when only a few suppositories are to be prepared in a cocoa butter base. It has the advantage of avoiding the necessity of heating the cocoa butter.

- By triturating grated cocoa butter and active ingredients in a mortar a plastic-like mass is prepared. The mass is formed into a ball in the palm of the hands, then rolled into a uniform cylinder with a large spatula or small flat board on a pill tile. The cylinder is then cut into the appropriate number of pieces which are rolled on one end to produce a conical shape.
- The suppository "pipe" or cylinder tends to crack or hollow in the center, especially when the mass is insufficiently kneaded and softened.

2. Compression Molding

Compression molding is a method of preparing suppositories from a mixed mass of grated suppository base and medicaments which is forced into a special compression mould using suppository making machines. The suppository base and the other ingredients are combined by thorough mixing. The base softens because of the friction in the process. A mortar and pestle can be used for small scale. On the other hand the large scale manufacturing involves mechanically operated kneading mixers and a warmed mixing vessel. In the compression machine, the suppository mass is placed into a cylinder which is then closed. After that from one end pressure is applied to release the mass from the other end into the suppository mould or die. When the die is filled with the mass, a movable end plate at the back of the die is removed and when additional pressure is applied to the mass in the cylinder, the formed suppositories are ejected. The end plate is returned, and the process is repeated until all of the suppository mass has been used. When active ingredients are added, it is necessary to omit a portion of the suppository base, based on the density factors of the active ingredients.

3. Fusion Moulding

Fusion Moulding process involves the following steps:

- Firstly melting the suppository base.
- Then the drug is either dispersed or dissolved in the melted base.
- The mixture is then removed from the heat and poured into a suppository mould.
- The melt is allowed to congeal.
- Now the suppositories are removed from the mould.

Suppository Moulds

Small scale moulds are capable of producing 6 or 12 suppositories in a single operation. Industrial moulds produce thousands of suppositories per hour from a single moulding.

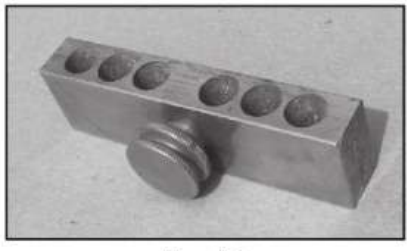


Fig. 4.1

Calibration of the Mould

The calibration of mould is necessary because the size of the suppositories remains same from a particular mould but there weight varies because the density of the different types of bases and the medicaments used are different. The first step is to prepare moulded suppositories from base material alone. The suppositories are combined and average weight is recorded. To determine the volume of the mould, the suppositories are melted in a calibrated beaker, and the volume of the melt is determined.

Lubricants used in Mould

Cocoa butter and glycero-gelatine bases are required lubrication of moulds. This is prevent sticking of bases to the wall of moulds cavity. It is also useful in easy removal of suppositories from the moulds. The lubricants forms a film between the wall of mould cavity and base of suppositories so, it prevent adhering of bases to the moulds. The nature of lubricants should be different from nature of bases.

Lubricant must be compatible with medicament or adjuncts. In industry silicone fluid is used as lubricant. Mould is lubricated using a pad of gauze or muslin or with a small fairly stiff brush. Cotton wool is not used because some fibres adhere to the mould. Excess of lubricant can be removed by inverting the mould on a clean white tile.

Following lubricants may be used for the preparation of theobroma oil suppositories.

Examples:

(a) For cocoa butter bases

Alcohol(90%)- 50 ml

Glycerol - 10 ml

Soft soap - 10 gm

(b) For glycerol-gelatin base

Liquid paraffin or Arachis oil is used as lubricant

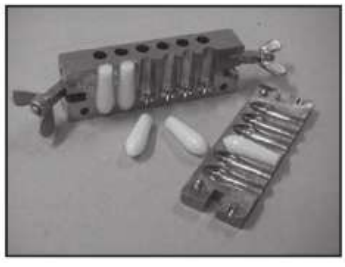


Fig. 4.2

Packaging

Suppositories must be packed in such a manner that they do not touch each other.

Poorly wrapped and packaged suppositories can lead to staining, breaking or deformation by melting caused by adhesion. Suppositories usually are foiled in tin or aluminium, paper or plastic strips. Overwrapping is done with hand or machine.

Hand packing yields a non-uniform products so machine are utilised to overcome this problem and machines can wrap 8000 suppositories per hour.

Storage

Suppositories should be protected from heat, preferably by storing in the refrigerator.

Polyethylene glycol suppositories and suppositories enclosed in a solid shell are less prone to distortion to temperature slightly above body temp.

Labelling

Suppositories should be labelled as:

(a) "STORE IN A COOL PLACE"

(b) "FOR EXTERNAL USE ONLY"

(c) "NOT TO BE TAKEN ORALLY".

4.6 EVALUATION TESTS FOR SUPPOSITORIES

1. Test of Appearance

All the suppositories should be uniform in size and shape. They should have elegant appearance. Individual suppositories should be examined for cracks and pits due to entrapment of air in the molten mass.

2. Breakage Test (Test of physical strength)

The tensile strength of suppositories is measured in this test to assess their ability to withstand the rigors of normal handling.

The apparatus used is called as breaking test apparatus. It consists of a double-wall chamber. Through the walls of the chamber, water is pumped. The inner chamber consist of a disc which holds the suppositories. To this disc, a rod is attached. The other end of the rod consists of another disc on which weights are placed.

Procedure

On the first disc the test suppository is placed. On the second disc a 600 g weight is placed. At 1 minute interval, 200 g weights are added till the suppository crumbles. All the weights used are added which gives the tensile strength. Likewise, few more suppositories are tested and the average tensile strength is calculated. Tensile strength indicates the maximum force which the suppository can withstand during production, packing and handling. Large tensile strength indicates less tendency to fracture.

3. Test of Dissolution Rate

It is the amount of dosage form that gets dissolved in body fluid in unit time. It is a measure of the rate of drug release from the suppository.

Two types of apparatus are available for testing the dissolution rate. They are:

(a) Suppository dialysis cell: Lipophilic suppositories are tested using suppository dialysis cell, which is also called as modified flow-through cell.

(b) Stationary basket: Rotating paddle apparatus (USP dissolution test apparatus). Hydrophilic suppositories are tested using stationary basket - rotating paddle apparatus.

4. Test of Melting Range

Both macromelting range and micromelting range are determined as follows:

(a) Macromelting range

It is a measure of the thermal stability of the suppository. It is the time taken by the entire suppository to melt in a constant temperature water bath. The test is conducted using the tablet disintegration apparatus. The suppository is immersed in a constant water bath. Finally, the melting range is recorded.

(b) Micromelting range

The melting range of the fatty base is measured in capillary tubes.

5. Liquefaction time (softening)

Softening time is the time for which the suppository melts completely at a definite temperature. This test measures the softening time of suppositories which indicates the hardness of the base.

Liquefaction temperature/time test was done using fabricated instrument. A big pipette was taken having a narrow opening on one side and broad opening on another side. The pipette was dipped in hot water maintained at 35 ± 0.2°C so that narrow end faces towards hot water. The sample suppository was introduced from the top of the pipette through broad end and carefully pushed down its length until it reaches narrow end. A glass rod was then inserted so that it rests over the suppository. The temperature at which the glass rods just come down was noted, that represents the liquefaction temperature. The time at which glass rod reaches to narrow end after complete melting of suppositories represents the liquefaction time.

Test of uniformity of drug content

This test is to assess the uniformity of the mixed suppository mass. Different suppositories are assayed for the drug. All the suppositories should contain the same labelled quantity of the drug.

Test of drug uptake

Both *in-vitro* and *in-vivo* tests should be conducted to assess the amount of drug absorbed into the systemic circulation.

(a) *In-Vitro* test

The test conditions should be similar to those inside the human body. The dissolution apparatus is used which consists of simulated gastric and simulated intestinal fluids. Definite number of suppositories are placed in the apparatus. Aliquot portions of the dissolution medium are withdrawn at definite intervals of time and drug uptake is measured using a U.V. spectrophotometer.

(b) *In-Vivo* test

This test is carried in animals or human volunteers. The suppository is placed in the intended body cavity. At regular intervals of time, blood samples are collected and the amount of drug present is determined.

Stability Problems of Suppositories

Blooming: During storage cocoa butter suppositories sometimes show deposition of white powder on the surface. This result in suppositories of disagreeable appearance.

Hardening: During storage, the suppositories made of fatty bases become hard. Hardening is occurs due to crystallization of bases. This also effect the melting and rate of absorption of drugs.

4.7 DISPLACEMENT VALUE

A suppository mould is filled by volume, but the suppository is formulated by weight.

The volume of a suppository from a particular mould is uniform but its weight can vary when a drug is present due to difference in densities between the drug and base.

The quantity of the drug which displaces one part of the base is called as displacement value.

The displacement values of some of the medicament used in suppositories with reference to cocoa butter are given below:

Drug	Displacement value
1. Aminophyllin	1.5
2. Boric acid	1.5
3. Castor oil	1.0
4. Tannic acid	1.0

The displacement value of a given medicament may be determined as follows:

1. Prepare and weigh 6 suppositories containing theobroma oil for other base) = a gram.

2. Prepare and weigh 6 suppositories containing, say 40% medicament = b gram.
3. Calculate the amount of theobroma oil present in medicated suppositories.

$$\frac{60}{100} \times b = c \text{ gram}$$

4. Calculate the amount of medicament present in the medicated suppositories.

$$\frac{40}{100} \times b = d \text{ gram}$$

5. Calculate the amount of theobroma oil displaced by d gram of medicament = (a – c) gram.
6. Displacement value of medicament = $\frac{d}{a - c}$.

Example: Calculate the displacement value of ZnO in theobroma oil suppositories containing 40% of ZnO and is prepared in a 1 g mould. The weight of eight suppositories is 11.74 g.

Solution: Weight of eight suppositories containing theobroma oil = $1 \times 8 = 8$ g

Weight of 8 suppositories containing 40% of ZnO = 11.74 g

Amount of theobroma oil present is 8 suppositories = $60/100 \times 11.74 = 7.044$ g

Amount of medicament present in 8 suppositories = $\frac{40}{100} \times 11.77 = 4.696\%$

Amount of theobroma oil displaced by 4.696 g of medicament (a – c) = 8 – 7.044 = 0.956.

Displacement value = $\frac{4.696}{0.956} = 4.912$

4.8 PHARMACEUTICAL INCOMPATIBILITIES

Incompatibilities is the result of prescribing or mixing two or more substances which are antagonist in nature and an undesirable product is formed which may affect the safety, purpose or appearance of the preparation. It is usually unintentional.

It may occur *in-vitro* between drugs and other components during preparation, storage or administration.

Incompatibility may be:

(a) Pharmaceutical/Physical Incompatibility.
(b) Therapeutic Incompatibility.
(c) Chemical Incompatibility.

4.8.1 Physical Incompatibility

In this type of incompatibility a visible physical change takes place. An unacceptable, non-uniform, unpalatable product is formed. It is a result of insolubility and immiscibility, precipitation, liquefaction, adsorption and complexation of solid materials.

The changes which occur due to physical incompatibilities can be corrected by one or more methods: Order of mixing, alteration of solvents, change in the form of ingredients, alteration of volume. Emulsification and addition of suspending agent, addition, substitution or omission of therapeutically inactive substances.

Examples of physical incompatibility.

1. Immiscibility

Immiscibility is the result of the mixture of two or more immiscible liquid or an immiscible solid with a liquid. Acceptable liquid product can be obtained by emulsification or solubilization.

R_x

Olive oil- 30 ml

Water up to 120 ml

Make an emulsion use a suitable emulsifying agent.

Methods of Rectifying Immiscibility

Immiscibility can be overcome by:

- Vigorous shaking / stirring.
- Emulsification or solubilization for example, Fats soluble Vitamins, Certain antibiotics like Chloramphenicol, Amphotericin B, Analgesics like Aspirin, Acetanilide and phenacetin many alkaloids and glycosides etc. are made soluble by the technique of solubilization.

2. Insolubility

Liquid preparation with indiffusible solids (e.g. Sulphamethoxasole, phenacetin, Zinc oxide, calamine etc.) a suspending agent is required to uniform distribution of the solids in the liquid phase for sufficiently long time so as to facilitate accurate measurement of dose.

R_x

Sulphamethoxazole - 4.0 g
Trimethoprim - 0.8 g
Sodium CMC - 0.5 g
Purified water - q.s to 100 ml
Prepare a solution.
Sulphamethoxazole and Trimethoprim are indiffusible in water. To make them diffusible a suspending agent is used.

Methods of Rectifying Insolubility

Cosolvency: for example, we may use alcohol, propylene glycol, syrups.

Complexation: for example, formation of tri-iodide complex, complexation of caffeine with Sodium Benzoate.

Hydro trophy: for example, Hyoscyamine with tween.

Solubilization: for example, Fats soluble vitamins, certain antibiotics.

3. Precipitation

A solubilised substance may precipitate from solution if a non-solvent (i.e. a solvent in which the drug is insoluble) is added to the solution. Alcoholic solution of Resins and water is equal to precipitated Resins Aqueous dispersion of Hydrophillic colloids and polysaccharide mucilage plus high concentration of Alcohol or salts is equal to precipitated colloids. But significant amount is tolerated if well diluted and added in small amount with vigorous stirring.

4. Liquefaction

Some low melting point solids sometimes liquefy when mixed together due to the formation of eutectic mixture or liberation of water. e.g: Menthol, Thymol, Camphor, Phenol, Naphthol and chloral hydrate when mixed together forms eutectic mixtures.

The eutectic forming ingredient may either be dispensed separately or these may be mixed separately with enough quantity of adsorbent powder like magnesium carbonate or Kaolin to form free flowing product.

Example

R_x

Menthol = 2.0 g

Camphor - 2.0 g

Ammonium carbonate - 20.0 g

Make a powder.

In this case, if the ingredients are mixed together, they shall liquefy due to formation of a eutectic mixture. Hence, to dispense them in the form of a powder, it is necessary to mix them separately with sufficient quantity of a suitable adsorbent like magnesium carbonate. Then they are mix together to obtain a powder.

Methods of Rectifying Liquefaction

By the use of absorbent like kaolin, light magnesium carbonate.

Techniques to Rectify:

Order of mixing.

Alteration of solvent.

Change in the form of ingredients.

Alteration of volume.

Emulsification.

Addition of suspending agents.

Addition/Substitution/omission of therapeutically inactive substance.

4.8.2 Chemical Incompatibilities

Chemical incompatibilities is said when a chemical interaction takes place among the ingredients of a prescription. Such interactions may take place immediately upon compounding then these are termed as immediate incompatibilities. It is due to oxidation-reduction, acid base hydrolysis or combination reactions. These reactions may be noticed by effervescence, decomposition, colour change. It may be as a result of chemical interactions between the ingredients of a prescription and a toxic or inactive product may be formed.

Chemical incompatibilities are of two types:

(a) Tolerated: This reaction can be minimized by applying some suitable order of mixing or mixing the solution in dilute form but no change in the active ingredients of the preparation.

(b) Adjusted: The reaction is prevented by addition or substitution of one of the reacting substances with another of equal therapeutic value but does not affect the medicinal value of the preparation.

E.g. of Chemical Incompatibilities: Alkaloidal Incompatibility.

1. Alkaloidal Salt with Alkaline Substances, Iodies, Salicylates

Most alkaloidal salts are soluble in water but alkaloidal bases practically insoluble in water and are freely soluble in organic solvents. When an alkaline substance like aromatic spirit of ammonia, solution of ammonia, ammonium bicarbonate, sodium bicarbonate, borax, etc., is added to an alkaloidal salt solution the free alkaloid may be precipitated. However they are not always precipitated, because all alkaloids are slightly soluble in water and other added substances.

(a) Example

R_x

Strychnine hydrochloride solution - 5 ml

Aromatic spirit of ammonia - 3 ml

Purified water to 100 ml make a mixture

Strychnine HCl used in the mixture is an alkaloidal salt, whereas aromatic spirit of ammonia is an alkaline substance. On reaction between the two, insoluble strychnine is precipitated. since the precipitate formed is diffusible, the incompatibility may be taken care by suitable formulation. In this case, strychnine HCl solution should be dissolved in half the required quantity of water while aromatic spirit of ammonia should dissolved in the remaining portion of water. The two portion should be mixed slowly.

(b) Gas formation

Gas may be evolved due to chemical reaction between the ingredients of a formulation.

Example: Carbonates or bicarbonates with an acid or acidic drug resulting in the evolution of carbon dioxide. Reaction of sodium bicarbonate, borax and glycerol.

R_x

Sodium bicarbonate - 1.5 g

Borax - 1.5 g

Phenol - 0.75 g

Glycerin - 25 ml

Water to - 100 ml

Prepare a spray

(c) Colour change

The colour of most of the dyes used in formulations is influenced by their ionization which in turn depends on the pH of the solution. Colour change due to change in pH can be prevented by properly buffering the vehicle or by preventing reaction that cause formation of free acid or base in the medium.

R_x

Sodium salicylate - 4 g

Sodium bicarbonate - 4 g

Peppermint water to - 60 ml

Make a mixture

Sodium salicylate gets oxidized in presence of sodium bicarbonate and the mixture darkens on storage. This alkaline catalyzed oxidation may however be prevented by the use of a suitable antioxidants like 0.1% sodium meta-bisulphite.

2. Ionic Reactions

The therapeutic or pharmaceutical properties of many organic compounds are usually associated with a large cation or anion. Interaction of such ions of opposing types may yield compounds which may totally lack the useful properties of the interacting molecules. For instances, Cream prepared using cationic emulgents may crack if mixed with a cream prepared using an anionic emulgents. Similarly an anionic solubilizers may lower the antimicrobial activity of a cationic medicament or preservative.

3. Explosive Combination

Oxidizing agents are chemically incompatible with reducing agent and a combination of the two in a formulation may lead to an explosive reaction. For example, if potassium chlorate is prescribed with an oxidisable substance like Sulphur, tannic acid, etc. and the two are triturated or heated together, there is a fair chance of an explosive reaction taking place. In such case, it is better to dispense the components separately or if it is necessary to mix them together, the mixing should be done very lightly.

Some chemical incompatibility:

(a) All oxidizing agents, such as potassium chlorate, chromic acid, potassium permanganate, silver oxide, are liable to explode when combined with organic matter, and such oxidizable inorganic matter as sulfur or carbon.

Strong nitric acid and its preparations produces effervescence with preparations containing tannin, or with oil of turpentine, sometimes with explosive violence.

(b) Hypophosphites are liable to explode when heated above 100°C, or when combined with oxidizing substances such as nitrates, chromates or permanganates.

(c) Iodine is liable to explode when treated with ammonia or with oil of turpentine.

- **Cementation of ingredients:** In some cases all or part of the ingredients of a prescription may set into a mass cement-like hardness.
- Separation of an immiscible liquid when certain organic chemicals are decomposed by certain reagents, such as the decomposition of chloral, by the action of an alkali into chloroform. (Some authors consider the formation of chloral alcoholate as a chemical incompatibility).
- Development of heat or cold.
- Other types of chemical changes, like polymerization, substitution and addition.
- Hydrolytic changes (hydrolysis).
- Invisible changes (This is most likely overlooked).
- Development of poisonous substances (may also be considered under therapeutic incompatibilities).

Types of Chemical Changes

1. **Oxidation:** Oxidation is defined as loss of electrons or gain of oxygen. Auto-oxidation: It is a reaction with oxygen of air which occur spontaneously without other factors. Pre-oxidants: are substances catalyze oxidation process i.e. metals, some impurities.
2. **Hydrolysis:** A chemical reaction in which water is used to break down a compound; this is achieved by breaking a covalent bond in the compound by inserting a water molecule across the bond.
3. **Polymerisation:** In polymerization, small repeating units called monomers are bonded to form a long chain polymer.
   e.g.: Formaldehyde Paraformaldehyde (Polymer: white precipitate). To avoid this formaldehyde must be stored in suitable temperature and addition of methanol 15%. Ampicillin in high temperature forms polymers which cause allergy.
4. **Isomerization:** It means conversion of drug to its isomer. Isomers have identical molecular formulae and a different arrangement of atoms.

4.8.3 Therapeutic Incompatibility

It may be the result of prescribing certain drugs to the patient with the intention to produce a specific degree of action but the nature or the intensity of the action produced is different from that intended by the prescriber.

Therapeutic Incompatibility occurs due to the following reasons: It may be due to the administration of:

(a) Overdose.
(b) Improper or wrong dosage form.
(c) Contraindicated drug.
(d) Synergistic and antagonistic drugs.
(e) Drug interactions.

(a) Over dose: Many therapeutical incompatibility results from errors in writing the prescription. The most serious type is over dose of a dosage form. This is the duty of pharmacist to check the dose which is written in the prescription before dispensing the medicine to patient.

R_x

Codeine phosphate - 0.5 gm

Make powders.

It is a unintentional incompatibility. The pharmacist wants to give 5 mg and yet prescribes 500 mg. This is the example of overdose medication. The prescription should be given back to prescriber for necessary correction.

(b) Wrong dosage form: There are some drugs which have almost similar names and there are possibilities of dispensing wrong drug. Many drugs are available in different dosage forms hence if the dosage form is not clearly mention on the prescription it becomes difficult for the prescriber to dispense the medicine. Examples prednisone and prednisolone, digoxin and digitoxin.

(c) Contraindicated Drugs: There are certain drugs which may be contraindicated in a particular disease. Penicillin and sulphonamides are not prescribed for those patients who are allergic to it also corticosteroids are never prescribed in peptic ulcer condition. The drugs which will excrete into milk are never prescribed in lactating mothers. e.g. Phenytoin, Phenobarbitone, chloramphenicol etc.

(d) Drug interaction: The effect of drug is changed by either prior administration or simultaneous administration of another drug.

R_x

Tetracycline Hydrochloride - 250 gm

Directions for Pharmacist

Make Capsules.

To Take 10 capsules every six hours with milk.

Tetracycline is inactivated by the milk due to the presence of calcium in it. Avoid administration of tetracycline with milk to prevent the formation of insoluble complex.

(e) Synergism: Many drugs shows synergistic effect, when two drugs are given together the effect of each drug is increased, this is known as synergistic effect. Synergism is usually intentional as the prescriber has given the combination of two drugs which increases the activity of the drugs.

Aspirin and Paracetamol increases analgesic activity Penicillin and streptomycin increases antibacterial activity.

R_x

Amphetamine sulphate - 20 mg

Ephedrine sulphate - 100 mg

Simple syrup up to - 100 ml

Make a mixture.

Both are sympathomimetic drugs cause additive effect. Hence of individual drugs dose should be reduced to avoid the therapeutic incompatibility.

(f) Antagonism: When two drugs are given together and one drug opposes the pharmacological activity of another drug it is known as antagonism.

R_x

Aspirin - 0.6 g

Probenecid - 0.5 g

Aspirin and probenecid both are anti-gout agents. When prescribed together their combination produces neutralization effect.

QUESTIONS

Short Answer Questions

1. What are suppositories?
2. What do understand by term bougies?
3. What is the importance of calibration of mould?
4. What are the various lubricants used to lubricate the mould?
5. What is displacement value?
6. What are pessaries?
7. Define synergism.
8. What is antagonism?
9. Define liquefaction.
10. Define saponification value.
11. What are the different type of incompatibility?
12. Define chemical incompatibility.
13. Define adjusted incompatibility.
14. What is tolerated incompatibility?

Long Answer Questions

1. What are the ideal properties of suppository bases?
2. Define suppositories and its various types.
3. Discuss various methods of preparing suppositories.
4. What are the advantages and disadvantages of theobroma oil as suppository base.
5. What are the evaluation methods of suppositories?
6. Write in brief about displacement value.
7. How will you find displacement value of the medicament?
8. What do you understand by the term Pharmaceutical Incompatibility.
9. Write different methods to correct physical incompatibility.
10. Differentiate between tolerated and adjusted incompatibility.
11. Discuss the chemical incompatibility.
12. Explain contraindicated drugs and drug interaction.
13. Write in detail about therapeutic incompatibility.

❑❑❑

Unit...5

SEMI-SOLID DOSAGE FORMS

♦ OBJECTIVES ♦

- **To know the definition of various semi-solid dosage forms like ointment, creams, pastes etc.**
- **To understand the ideal properties of semi-solid dosage forms.**
- **To deal with the advantages and disadvantages of semisolid dosage forms.**
- **To understand the classification of semi-solid dosage forms.**
- **To identify the method of preparation and evaluation of ointment cream pastes and gels.**
- **To know the use of excipients in semi-solid dosage forms.**

5.1 INTRODUCTION

Definition: Semi-solid dosage forms are dermatological preparations intended to apply externally on the skin to produce local or systemic effect e.g. ointments, creams, gels and pastes. They contain one or more active ingredients dissolved or uniformly dispersed in a suitable base and any suitable excipients such as emulsifiers, viscosity increasing agents, antimicrobial agents, antioxidants, or stabilizing agents. Semisolids can adhere to the application surface for sufficiently long periods before they are washed off. This property helps prolong drug delivery at the application site. Novel semisolids are non-greasy since they are made up of water washable bases. Hence, they cause less irritation to skin and are superior to conventional semisolid dosage form.

5.2 IDEAL PROPERTIES OF SEMI-SOLID DOSAGE FORMS

1. **Physical Properties**
   (a) They should have smooth texture.
   (b) They should be elegant in appearance.
   (c) They should be non-dehydrating.
   (d) They should be non-gritty in nature.
   (e) Semi-solid dosage forms possess non-greasy and non-staining property.
   (f) They are non-hygroscopic in nature.

2. **Physiological Properties**
   (a) They should be non-irritating.
   (b) They should not alter skin functioning.
   (c) They should be easily miscible with skin secretion.
   (d) They should have low sensitization effect.
3. **Application Properties**
   (a) They should be easily applicable with efficient drug release.
   (b) They should possess high aqueous washability.

5.3 CLASSIFICATION

Types of Semi-solid dosage form

1. Ointments
2. Creams
3. Pastes
4. Gel
5. Poultices
6. Plasters

Ointments: Ointments are semisolid preparations meant for external application to the skin or mucous membrane. They usually contain a medicament or medicaments dissolves, suspended or emulsified in the base.

Creams: Creams are viscous emulsions of semisolid consistency intended for application to the skin or mucous membrane and **o/w** type and **w/o** type.

Pastes: Pastes are the preparations which contains a large amount of finely powdered solids such as starch and zinc oxide. These are generally very thick and stiff.

Jellies: These are thin transparent or translucent, non-greasy preparations. They are similar to mucilages because they are prepared by using gums but they differ from mucilages in having jelly like consistency.

Gels: These are jelly-like semisolid dispersions of drug meant to be applied on the skin.

Suppositories: These are meant for insertion in to the body cavities other than mouth. They may be inserted in to rectum, vagina or urethra.

Poultices: These are also known as cataplasms. They are soft viscous wet masses of solid substances.

Plasters: These are semi-solid masses applied to the skin to enable prolonged contact of drug with the skin. or Substances intended for external application, made of such materials and consistency as to adhere to the skin and thereby attach as dressing.

Mechanism of Skin Permeation

The skin itself has two main layers, the epidermis, which is the outermost layer of the skin, covering the dermis that is the active part of the skin, holding the hair muscles, blood supply, sebaceous glands, and nerve receptors. There is a fat layer underneath the dermis. The skin is a very heterogeneous membrane and has a variety of cell types, but the layer that

controls the penetration of drugs is called the stratum corneum and, despite its thickness of only 15–20 μm, it provides a very effective barrier to penetration. The permeation of the drug through the skin has several routes: transcellular, intercellular, and appendageal (through eccrine (sweat) glands or hair follicles) (Fig. 5.1).

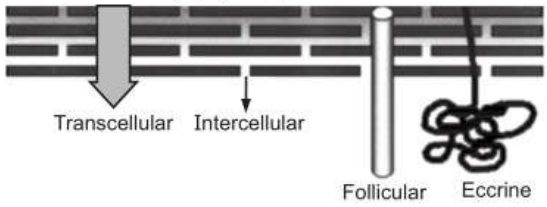


Fig. 5.1: Schematic representation of the different possible routes of penetration through the skin.

Since, the appendages occupy a very low surface area, this means of permeation is less significant under normal conditions. Nevertheless, in iontophoretic delivery this route is more significant. The intercellular spaces consists of a mixture of lipids–ceramides, free fatty acids and their esters, and cholesterol and its sulphates that are structured in bilayers. Recent developments in spectroscopic techniques give interesting insights at the molecular level that may explain the impermeability of the skin by repeated partition and diffusion across structured bilayers. Transdermal drug permeability is influenced mainly by three factors: the mobility of the drug in the vehicle, the release of the drug from the vehicle, and drug permeation through skin. Therefore, the researchers are challenged to come up with formulations that increase the permeability of the drug without irreversibly changing the skin barrier function. Various potential mechanisms to enhance drug penetration through the skin include directly affecting the skin and modifying the formulation so the partition, diffusion, or solubility are altered. Here we will present briefly these potential mechanisms that are interconnected with each other.

1. Direct Effect on the Skin

(a) Denaturation of intracellular keratin or modification of its conformation causes swelling and increased hydration.

(b) Affection of desmosomes (known as macula adherens- cell structures specialized for cell to cell adhesion) that maintain cohesion between corneocytes (dead cells of the stratum corneum).

(c) Modification of lipid bilayers reduces resistance to penetration.

(d) Altering the solvent properties of the stratum corneum to modify drug partitioning.

(e) Use of solvent that can extract the lipids in the stratum corneum and decrease its resistance to penetration.

2. Modification of the Formulation

(a) Super saturation state produced by volatile solvent that leaves the active substance in a more thermodynamically active state.

(b) Choosing the enhancer molecules in the vehicle that are good solvents for the active ingredient and which enhance permeation through the skin; this way the partition of the drug into the stratum corneum will be improved.

(c) The diffusion of the active ingredient through the skin may be facilitated by using enhancers that create liquid pools within the bilayers like oleic acid, or disturb the bilayers uniformly as do the Azone® molecules (1-dodecyl azacyclo heptan-2-one or lauro capram) is the first molecule specifically designed as a skin permeation enhancer. Azone® serves as surfactant and enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents.

5.4 FACTORS INFLUENCING DERMAL PENETRATION OF DRUGS

5.4.1 Physiological and Pathological Condition of Skin

(a) Reservoir effect of the horny layer: The horny layer is thickest on palms and soles and thinnest on the face; penetration rate increases with decreased thickness of horny layer.

(b) Skin condition: The permeability of the skin is affected by age, disease, climate and injury. For example, absorption occurs rapidly in children and if the dermis is exposed by a wound or burn.

(c) Skin hydration: The hydration of keratinized cells is raised by covering the area with a moisture-proof plastic film to prevent evaporation of perspiration. Hydration increases the drug penetration.

(d) Skin age: The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug.

(e) Blood flow: Changes in peripheral circulation can affect transdermal absorption.

(f) Skin temperature: The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

(g) Regional skin site: Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

(h) Species variation: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

(i) Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

5.4.2 Physico-Chemical Properties of Active Substances

(a) Molecular characteristic of drug: Molecular weight upto 400 daltons can easily penetrate through the skin surface.

(b) Drug concentration: The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

(c) Solubility and partition coefficient: Highly lipid soluble molecules enters through hair follicles. Moderately lipid soluble molecules penetrates directly across the horny layer.

(d) Crystal structure/polymorphism: The metastable polymorph is much more soluble than its stable form, so the release of drug in metastable state is much more faster than stable form.

(e) Dissociation constant (pKa): If a drug is ionized in the surrounding pH of the dermis then the penetration of the ionic species are restricted by electrostatic interactions. Degree of ionization depends on the pKa of the drug.

e.g. Methyl salicylate and methyl nicotinate penetrate much faster than salicylic acid and nicotinic acid respectively.

(f) Partition coefficient: The optimal partition coefficient (K) is required for good action.

Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

(g) Diffusion coefficient: Penetration of drug depends on diffusion coefficient of drug.

At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

5.4.3 Effects of Vehicles

The vehicles may enhance the penetration of a drug in one or more of the following ways:

(a) By ensuring good contact with the surface of the body.

(b) By increasing the degree of hydration of the stratum corneum.

(c) By penetrating the epidermis.

(d) By directly altering the permeability of the skin.

5.4.4 Effects of Additives

(a) Surfactants increases the penetration because they are surface active agents which reduces the surface tension e.g., quaternary ammonium compounds, alkali soaps etc

(b) Humectants increases the solubility of active ingredients. To elevate its skin preparation and to elevate the hydration of the skin e.g., glycerine, polyethylene glycol etc.

(c) Penetration enhancers- Penetration can be improved by addition of penetration enhancers like methanol, oleic acid etc.

Classification of Semi-solid Bases and their Selection

There are four classes or types of bases which are differentiated on the basis of their physical composition.

These are:

1. Oleaginous bases
2. Absorption bases
3. Emulsifying base (Water in oil emulsion bases and Oil in water emulsion bases)
4. Water soluble bases

1. Oleaginous Bases

These bases are fats, fixed oils, hydrocarbon or silicones. They are anhydrous, non-washable, does not absorb water. They should not be applied to infected skin. They are used as protectants, emollients, vehicles for hydrolysable drugs. Examples: White Petrolatum, White Ointment.

2. Absorption Bases

The term absorption base is used to denote the water absorbing or emulsifying property of these bases and not to describe their action on the skin.

These bases are generally anhydrous substances which have the property of absorbing (emulsifying) considerable quantities of water but still retaining their ointment-like consistency.

The absorption bases are of two types: i) Non-emulsified bases ii) Water in oil emulsion bases.

The non-emulsified bases absorb water and aqueous solution producing w/o emulsion e.g. Wool fat, wool alcohol, bees wax and cholesterol.

The water in oil emulsion is capable of absorbing more water and have the properties of non-emulsified bases. Example: Hydrous wool fat (lanolin).

3. Emulsifying Bases

These are anhydrous, hydrophilic, absorbs water and non-water removable, with low thermal conductivity and occlusive. They have the same properties as the absorption bases. They are used as emollients, cleansing creams, vehicles for solid, liquid, or non-hydrolyzable drugs. Examples: Cold Cream type, Hydrous Lanolin, Rose Water Ointment, Hydrocream, Nivea.

Oil in water emulsion bases

These bases are anhydrous, water soluble, absorb water and water washable. They are either Carbowaxes Polyethylene Glycols (PEGs) or hydrated gums (Bentonite, gelatin, cellulose derivatives). They are used as drug vehicles. Examples: PEG Ointment, Polybase™.

4. Water Soluble Bases

Water soluble does not contain oily substances and are called greaseless base and are completely soluble in water. Examples:

(A) Polyethylene glycol (PEGs), polyoxyl 40 stearate and polysorbates.

(B) Macrogols: They are mixture of water and polycondensation products of ethylene oxide.

They are of three types: (i) Solid Macrogols (ii) Liquid Macrogols (iii) Semisolid Macrogols.

Advantages

(a) They are water soluble and washable.

(b) They are non-greasy, non-staining, non or less occlusive, lipid free in nature.

(c) They are relatively inert.

(d) They do not allow mould growth.

Disadvantages

They may dehydrate skin and hinder percutaneous absorption.

Selection of the appropriate base based on:

1. Dermatological factors
2. Pharmaceutical factors

Dermatological Factors

(a) Absorption and Penetration: 'Penetration' means passage of the drug across the skin i.e. cutaneous penetration, and 'absorption' means passage of the drug into blood stream. Medicaments which are soluble in oil and water are most readily absorbed through the skin. Whereas animal and vegetable fats and oils normally penetrate the skin. Animals fats, e.g. lard and wool fat when combined with water, penetrates the skin. o/w emulsion bases release the medicament more readily than greasy bases or w/o emulsion bases.

(b) Effect on the skin: Greasy bases interfere with normal skin functions i.e. heat radiation and sweating. They are irritant to the skin. o/w emulsion bases and other water miscible bases produce a cooling effect due to the evaporation of water.

(c) Miscibility with skin secretion and serum: Skin secretions are more readily miscible with emulsion bases than with greasy bases. Due to this the drug is more rapidly and completely released to the skin.

(d) Compatibility with skin secretions: The bases used should be compatible with skin secretions and should have pH about 5.5 because the average skin pH is around 5.5. Generally, neutral ointment bases are preferred.

(e) Non-irritant: All bases should be highly pure and bases specially for eye ointments should be non-irritant and free from foreign particle.

(f) Emollient properties: Dryness and brittleness of the skin causes discomfort to the skin therefore, the bases should keep the skin moist. For this purpose water and humectants such as glycerin, propylene glycol are used. Ointments should prevent rapid loss of moisture from the skin.

(g) Ease of application and removal: The ointment bases should be easily applicable as well as easily removable from the skin by simple washing with water. Stiff and sticky ointment bases require much force to spread on the skin and during rubbing newly formed tissues on the skin may be damaged.

2. Pharmaceutical factors

(a) Stability: Fats and oils obtained from animal and plant sources are prone to oxidation unless they are suitably preserved. Lard which is obtained from animal origin rancify rapidly due to oxidation and gives bad odour. This type of reactions are called rancidification. Soft paraffin, simple ointment and paraffin ointment are inert and stable. Liquid paraffin is also stable but after prolonged storage it gets oxidized. Therefore, an antioxidant like tocopherol (Vitamin E) may be incorporated. Other antioxidants those may be used are Butylated Hydroxy Toluene (BHT) or Butylated Hydroxy Anisole (BHA).

(b) Solvent properties: Most of the medicaments used in the preparation of ointments are insoluble in the ointment bases therefore, they are finely powdered and are distributed uniformly throughout the base.

(c) Emulsifying properties: Hydrocarbon bases absorbs very small amount of water. Wool fat can take about 50% of water and when mixed with other fats can take up several times its own weight of aqueous solution. Emulsifying ointment, cetrimide emulsifying ointment and cetomacrogol emulsifying ointment are capable of absorbing considerable amount of water, forming w/o creams.

(d) Consistency: The ointments produced should be of suitable consistency. They should neither be hard nor too soft. They should withstand climatic conditions. Thus in summer, they should not become too soft and in winter not too hard to be difficult to remove from the container and spread on the skin. The consistency of an ointment base can be controlled by varying the ratio of hard and liquid paraffin.

5.5 METHODS OF PREPARATION

1. Trituration method
2. Fusion method
3. Emulsification Method:
   (a) Preparation of oil and aqueous phases
   (b) Mixing of the phases
   (c) Cooling the emulsion
   (d) Homogenization
4. Chemical reaction method.

1. **Trituration Method:** It is the most commonly used for the preparation of semisolid. When base contains soft fats and oils, or medicament is insoluble or liquid, then this method is used with spatula or motar and pestle.

2. **Fusion Method:** The ingredients of the base are melted together and properly mixed to obtain a uniform product. Initially, the ingredient of high melting point is melted. Then remaining ingredient of the base are added in the decreasing order of their melting points and melted with constant stirring. The above mixture is removed from the water bath and stirred in order to cool it. If the drug is soluble in the base, then its powdered form is added to the molten base. Liquid or semisolid are added at a temperature of 40°C. Insoluble additives are added in small quantities with proper stirring, when the thickening of the base starts. Localized cooling of the molten base and vigorous stirring should be avoided to prevent aeration of the ointment.

3. **Emulsification Method**

Preparation of Oil and Aqueous Phases: Place the ingredients of the oil phase into the stainless steel steam-jacketed kettle and melt them whilst mixing. Filter the oil phase through several layers of cheese cloth to remove any foreign matter. Heat the emulsion mixing kettle to the temperature of the oil phase. This avoids congealing of higher melting component. Transfer the oil phase into the emulsion mixing kettle. Dissolve the ingredient of the aqueous phase in purified water and filter the solution. A soluble drug which is thermostable may be added to the aqueous phase in this step.

The phases are usually mixed at a temperature of 70 to 72°C, because at this temperature intimate mixing of the liquid phases can occur. The properties of some emulsions depend on the temperature at which the phases are mixed.

Three ways of mixing the phases: 1. Simultaneous blending of the phases. 2. Addition of the discontinuous phase to the continuous phase. 3. Addition of the continuous phase to the discontinuous phase.

Equipments used for mixing of phases:

Agitator mixers: Sigma mixer and planetary mixer.

Shear mixers: Triple roller mill and Colloidal mill.

4. **Chemical reaction:** This method is used to prepare several types of ointments. This method involves both fusion and mechanical mixing. Best example of this method is Iodine ointment.

Chemical Reaction Method Procedure for iodine ointment: Powder iodine in a mortar and pestle and add it to arachis oil taken in a flask. Heat the mixture to 50°C with occasional stirring until greenish black colour appears. Add yellow soft paraffin to the above mixture and heat it to 40°C with mixing. Cool the Ointment.

5.6 PREPARATION OF OINTMENTS

An ointment should be:

(a) *Uniform throughout* i.e. it contains no lumps of separated high melting point ingredients of the base, there is no tendency for liquid constituents to separate and insoluble powders are evenly dispersed.

(b) *Free from grittiness*, i.e. insoluble powders are finely subdivided and large lumps of particles are absent. Methods of preparation must satisfy this criteria.

Two mixing techniques are frequently used in making ointments:

1. Fusion, in which ingredients are melted together and stirred to ensure homogeneity.
2. Trituration, in which finely-subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base or one of its ingredients followed by dilution with gradually increasing amounts of the base.

5.6.1 Ointments Prepared by Fusion Method

When an ointment base contain a number of solid ingredients such as white bees wax, cetyl alcohol, stearyl alcohol, stearic acid, hard paraffin, etc. as components of the base, it is required to melt them.

The melting can be done in two methods**:**

Method-I

The components are melted in the decreasing order of their melting point i.e. the higher m.p. substance should be melted first, the substances with next melting point and so on. The medicament is added slowly in the melted ingredients and stirred thoroughly until the mass cools down and homogeneous product is formed.

Advantage

This will avoid over-heating of substances having low melting point.

Method-II

All the components are taken in subdivided state and melted together.

Advantage

The maximum temperature reached is lower than Method-I, and less time was taken possibly due to the solvent action of the lower melting point substances on the rest of the ingredients.

Cautions

(i) Melting time is shortened by grating waxy components (i.e. bees wax, wool alcohols, hard-paraffin, higher fatty alcohols and emulsifying waxes) by stirring during melting and by lowering the dish as far as possible into the water bath so that the maximum surface area is heated.

(ii) The surface of some ingredients discolours due to oxidation e.g. wool fats and wool alcohols and this discoloured layers should be removed before use.

(iii) After melting, the ingredients should be stirred until the ointment is cool, taking care not to cause localized cooling, e.g. by using a cold spatula or stirrer, placing the dish on a cold surface (e.g. a plastic bench top) or transferring to a cold container before the ointment has fully set. If these precautions are ignored, hard lumps may separate.

(iv) Vigorous-stirring, after the ointment has begun to thicken, causes excessive aeration and should be avoided.

(v) Because of their greasy nature, many constituents of ointment bases pickup dirt during storage, which can be seen after melting. This is removed from the melt by allowing it to sediment and decanting the supernatant, or by passage through muslin supported by a warm strainer. In both instances the clarified liquid is collected in another hot basin.

(vi) If the product is granular after cooling, due to separation of high M.P. constituents, it should be remelted, using the minimum of heat, and again stirred and cooled.

Example

(i) Simple ointment B.P. contains

Wool fat	-	50 g
Hard paraffin	-	50 g
Cetostearyl alcohol	-	50 g
White soft paraffin	-	850 g

Type of preparation: Absorption ointment base.

Procedure

Hard paraffin and cetostearyl alcohol on water-bath. Wool fat and white soft paraffin are mixed and stirred until all the ingredients are melted. If required decanted or strained and stirred until cold and packed in suitable container.

(ii) Paraffin ointment base

Type of preparation: Hydrocarbon ointment base.

(iii) Wool alcohols ointment B.P.

Type of preparation: Absorption base.

(iv) Emulsifying ointment B.P.

Type of preparation: Water-miscible ointment base.

(v) Macrogol ointment B.P.C

Type of preparation: Water soluble ointment base.

Formula: Macrogol 4000
Liquid Macrogol 300

Method: Macrogol 4000 is melted and previously warmed liquid macrogol 300 is added. Stirred until cool.

5.6.2 Ointment Prepared by Trituration

This method is applicable in the base or a liquid present in small amount.

(i) Solids are finely powdered are passed through a sieve (# 250, # 180, #125).

(ii) The powder is taken on an ointment-slab and triturated with a small amount of the base. A steel spatula with long, broad blade is used. To this additional quantities of the base are incorporated and triturated until the medicament is mixed with the base.

(iii) Finally, liquid ingredients are incorporated. To avoid loss from splashing, a small volume of liquid is poured into a depression in the ointment an thoroughly incorporated before more is added in the same way. Splashing is more easily controlled in a mortar than on a tile.

Examples

(i) Whitfield ointment (Compound benzoic acid ointment B.P.C.)

Formula:

Benzoic acid, in fine powder	-	6 gm
Salicylic acid, in fine powder	-	3 gm
Emulsifying ointment	-	91 gm

Method: Benzoic acid and salicylic acid are sieved through No. 180 sieves. They are mixed on the tile with small amount of base and levigated until smooth and dilute gradually.

(ii) Sulphur ointment I.P.

Sublimed sulphur – 10 g

Simple ointment – 90 g

Prepare an ointment.

Method: Sublimed sulphur is sieved through no. 180 sieves. Then sublimed sulphur is triturated with small amount of simple ointment. Then the remaining amount of simple ointment is added and the mixture is levigated until smooth and homogenous mass is obtained.

5.6.3 Ointment Preparation by Chemical Reaction

Chemical reactions were involved in the preparation of several famous ointments of the past, e.g. Strong Mercuric Nitrate Ointment of the 1959 B.P.C.

(a) Ointment containing free iodine

Iodine is only slightly soluble in most fats and oils.

Iodine is readily soluble in concentrated solution of potassium iodide due to the formation of molecular complexes $KI{\cdot}I_2$, $KI{\cdot}2I_2$, $KI{\cdot}3I_2$ etc.

These solutions may be incorporated in absorption-type ointment bases.

Example, **Strong Iodine Ointment** (British Veterinary Pharmacopoeia) is used to treat ringworm in cattle. It contains free iodine. At one time this type of ointments were used as counter-irritants in the treatment of human rheumatic diseases but they were not popular

because they stain the skin a deep red colour. Due to improper storage the water dries up and the iodine crystals irritate the skin, hence glycerol is some times added to dissolve the iodine-potassium iodide complex instead of water.

Example: Strong Iodine Ointment.

Iodine – 4 g
Woolfat - 4 g
Yellow soft paraffin – 76 g
Potassium iodide – 4 g
Water – 12 g

Procedure

(i) KI is dissolved in water. I_2 is dissolved in it.
(ii) Wool fat and yellow soft paraffin are melted together over water bath. Melted mass is cooled to about 40°C.
(iii) I_2 solution is added to the melted mass in small quantities at a time with continuous stirring until a uniform mass is obtained.
(iv) It is cooled to room temperature and packed.

Use: Ringworm in cattle.

(b) Ointment containing combined iodine

Fixed oils and many vegetable and animal fats absorb iodine which combines with the double bonds of the unsaturated constituents, e.g.

$$CH_3{\cdot}(CH_2)_2{\cdot}CH = CH{\cdot}(CH_2)_7{\cdot}COOH + I_2CH_3{\cdot}(CH_2)_2{\cdot}CHI\ CHI{\cdot}(CH_2)_7{\cdot}COOH$$

Oleic acid Di-iodostearic acid

Example: Non-staining Iodine Ointment B.P.C.

Iodine – 5 g
Arachis oil – 15 ml
Yellow soft paraffin - q.s. to 100 g

Method

(a) Iodine is finely powdered in a glass mortar and required amount is added to the oil in a glass-stoppered conical flask and stirred well.
(b) The oil is heated at 50°C in a water-bath and stirred continually. Heating is continued until the brown colour is changed to greenish-black; this may take several hours.
(c) From 0.1 g of the preparation the amount of iodine is determined by B.P.C. method and the amount of soft paraffin base is calculated to give the product the required strength.
(d) Soft paraffin is warmed to 40°C. The iodized oil is added and mixed well. No more heat is applied because this causes deposition of a resinous substance.
(e) The preparation is packed in a warm, wide-mouthed, amber colour, glass bottle. It is allowed to cool without further stirring.

5.6.4 Preparation of Ointments/Cream by Emulsification

An emulsion system contain an oil phase, an aqueous phase and an emulsifying agent.

For o/w emulsion systems the following emulsifying agents are used:

(i) Water soluble soap
(ii) Cetyl alcohol
(iii) Glyceryl monostearate
(iv) Combination of emulsifiers: triethanolamine stearate + cetyl alcohol
(v) Non-ionic emulsifiers: glyceryl monostearate, glyceryl monooelate, propylene glycol stearate

For w/o emulsion creams the following emulsifiers are used:

(i) Polyvalent ions e.g *magnesium, calcium and aluminium* are used.
(ii) Combination of emulsifiers: *bees wax + divalent calcium ion*

The viscosity of this type of creams prevent coalescence of the emulsified phases and helps in stabilizing the emulsion.

Example: Cold cream

Procedure

(i) Water immiscible components e.g. oils, fats, waxes are melted together over water bath (70°C).
(ii) Aqueous solution of all heat stable, water soluble components are heated (70°C).
(iii) Aqueous solution is slowly added to the melted bases with continuous stirring until the product cools down and a semi-solid mass is obtained.

Note: The aqueous phase is heated otherwise high melting point fats and waxes will immediately solidify on addition of cold aqueous solution.

5.7 PASTE

Pastes are semisolid preparations for external application containing a high proportion of finely powdered medicaments. They are stiffer and are usually employed for their protective action and for their ability to absorb serous discharges from skin lesions. They do not melt at ordinary temperature they form a coating over the affected area. Pastes are used as protective, antiseptic, and soothing dressings.

5.7.1 Differences Between Pastes and Ointments

(i) Pastes generally contains a large amount (50%) of finely powdered solids. So they are often stiffer than ointments.
(ii) When applied to the skin pastes adhere well, forming a thick coating protects and soothes inflamed and raw surfaces and minimizes the damage done by scratching in itchy conditions such as chronic eczema. It is comparatively easy to confine pastes to the diseased areas whereas ointments, which are usually less viscous, tend to spread on to healthy skin, and this may result in sensitivity reactions if the preparations contain a powerful medicament such as dithranol.

(iii) Because of the powder contents pastes are porous; hence, perspiration can escape. Since, the powders absorbs exudate, pastes with hydrocarbon base are less macerating than ointments with a similar base.

(iv) They are less greasy than ointments but since their efficacy depends on maintaining a thick surface layer they are far from attractive cosmetically.

(v) Most of the pastes are unsuitable for treating scalp conditions because they are difficult to remove from the hair.

5.7.2 Methods of Preparation

Like ointment, pastes are prepared by trituration and fusion methods. Trituration method is used when the base is liquid or semisolid.

Fusion method is used when the base is semisolid and/or solid in nature.

Preparation 1.

Name: Compound Zinc Paste

Formula:

Zinc oxide, finely sifted	-	25 g
Starch, finely sifted	-	25 g
White soft paraffin	-	50 g

Type of preparation: Paste with semi-solid base prepared by fusion and trituration.

Procedure

(a) Zinc oxide and starch powder are passed through No. 180 sieve.

(b) Soft paraffin is melted on a water bath.

(c) The required amount of powder is taken in a warm mortar, triturated with little melted base until smooth. Gradually rest of the base is added and mixed until cold.

Preparation 2.

Name: Zinc and Coal tar Paste B.P.C.

Formula: Zinc oxide, finely sifted - 60 g
Coal tar- 60 g
Emulsifying wax – 50 g
Starch- 380 g
Yellow soft paraffin – 450 g

Type of preparation: Paste with semi-solid base prepared by fusion.

Procedure

Method-I

(a) Emulsifying wax is melted in a tarred dish (70°C).

(b) The coal tar is weighed in the dish. Stirred to mix.

Soft paraffin is melted in a separate dish (70°C) and about half is added to the tar-wax mixture; stirred well. Remainder is added; stirred again until homogeneous.

Allowed to cool at about (30°C) and zinc oxide (previously passed through 180 mesh) and starch, in small amount with constant stirring. Stirred until cold.

Method-II

Wax and paraffin melted together, mixed well and stirred until just setting. Powders are mixed on a slightly warm tile and the tar is incorporated. This method eliminates the risk of over heating.

5.8 GELS

Gels are transparent semisolid preparation meant for external application to the skin or mucous membrane. Gels are semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules in an liquid vehicle appear jelly like by the addition of a gelling agent.

These are organic hydrocolloids or hydrophilic inorganic substances.

They contains Tragacanth, Sodium Alginate, Pectin, Starch, Gelatin, Cellulose Derivatives, Carbomer, and Poly Vinyl Alcohol Clays. These are numerous gelling agents varying in gelling ability.

Clear gels are microemulsions in which the diameter of the dispersed phase globules is in the range of 10 to 60 nm. These emulsions are thermodynamically stable. Microemulsions are transparent as the globule diameter of the disperse phase is less than the wavelength of light.

Microemulsions can be distinguished from other types of gels by the vibrations or 'ringing' that occurs when the emulsion is subjected to impact.

Procedure of Clear Gel

- Gel is prepared by mixing a suitable thickening agent with an aqueous vehicle.
- The drug is dissolved in an aqueous vehicle and the thickening is added by triturating in a mortar.
- The trituration is carried out until a homogenous preparation is formed.

Ingredient: Quantity for 50 gm –

Sodium Carboxy methyl cellulose (thickening agent) - 2.5 gm

Glycerol (binding agent) - 1.5 gm

Preservative - 0.05 gm

Colour - 0.0005 gm

Purified water (vehicle)

To make - 50 gm

Method: Dissolved methyl paraben in water by heating. Add SCMC to glycerine and stir thoroughly. Add this mixture to the aqueous vehicle and stir in a uniform, homogenous preparation is formed. Add the dye colour and stir. Transfer to a suitable container.

Evaluation of Gel

The various evaluation parameters involved the assessment of the properties of the gels are be as follows:

1. **Yield Value:** It is a measure of the force required to extrude the material from the deformable bottle tube. It can be determined by the use of an instrument called the Penetrometer. Penetrometer consist of a metal needle that pierces through the system and the distance of penetration of the needle is measured, from which the yield value may be calculated.
2. **Spreadability:** The Spreadability test is performed to determine the extent of Spreadability of gels based on their rheological properties.
3. **Stability:** This test is known as the shipping test and is performed to determine the extent of stability of gels at varying temperature, which the product may experience while exporting to other countries.

5.9 EXCIPIENTS USED IN SEMISOLID DOSAGE FORMS

1. **API:** Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Active pharmaceutical ingredient is any part of drug which produces any effect.
2. **Preservatives:** To stop microbial growth preservatives are added. Preservatives for ointment includes: p-hydroxy benzoates, phenol, benzoic acid, sorbic acid, methyl paraben, propyl paraben, quaternary ammonium compounds, mercury compounds etc. The preservatives should not react with any of the component of the formulation. Plastic containers may absorb the preservative and thereby decreasing the concentration of preservative available for killing the bacteria.
3. **Humectants:** such as, glycerin, propylene glycol and sorbitol may be added to prevent the loss of moisture from the preparation.
4. **Emulsifying agents:** Like polysorbate, anionic emulsifying agents etc. are added if required.
5. **Antioxidant:** Some ingredients like wool fat and wool alcohols are susceptible to oxidation. Therefore, a suitable antioxidant may be incorporated to protect the active ingredients from oxidation.
6. **Organoleptic agents:** suitable colouring agent – (amaranth, brilliant blue etc.) flavouring agent (vanilla , strawberry, raspberry) are added.

   Ointment must be stored at an optimum temperature otherwise separation of phases may take place in the emulsified products which may be very difficult to remix to get a uniform product.

5.10 EVALUATION OF SEMI-SOLID DOSAGE FORMS

1. **Content uniformity of drug:** A known weight of ointment is taken and assayed for amount of the drug.
2. **Penetration:** A weighed quantity of ointment is rubbed over skin for a given period of time and unabsorbed ointment is collected and weighed. The differences in weights represent the amount absorbed.
3. **Rate of release of medicament:** To assess rate of release of medicament, small amount of the ointment can be placed on the surface of nutrient agar contained in a Petri dish. If the medicament is bactericidal the agar plate is previously seeded with a suitable organism like *S. aureus*. After a suitable period of incubation, the zone of inhibition is measured and correlated with the rate of release.
4. **Absorption of medicament into blood stream:** Ointment should be evaluated for the rate of absorption of drug into the blood stream. This test can be run *in-vivo* only. Definite amount of ointments should be rubbed through the skin. Under standard conditions and medicaments are estimated in the blood plasma or urine.
5. **Irritant effect:** In general no ointment should possess irritant effect on the skin or mucous membranes the tests for irritancy can be carried out on the skin and eyes of rabbits or the skin of human beings. The irritant effect can also be judged to a certain extent by injecting the ointment into thigh muscles and under the abdominal skin of rats. Reaction are noted at intervals of 24, 48, 72 and 96 hours. Lesions on cornea, iris, conjunctiva are used for judging the irritancy to the eyes. Presence of patches on the skin within 2 weeks indicate irritancy to pressing skin.
6. **Consistency test:** Using penetrometry.

Procedure

Preparation of test sample: Three methods (A, B, C).

A: Carefully and completely fill three containers without forming air bubbles. Level it if necessary to obtain a flat surface.

B: Apply a suitable shear to the samples for 5 minutes carefully and completely fill three containers without forming air bubbles. Level it if necessary to obtain a flat surface.

C: Melt three samples carefully and completely fill three containers without forming air bubbles. Level it if necessary to obtain a flat surface.

Determination of Penetration

Place the test sample on the basis of the penetrometer. Verify that its surface is perpendicular to the vertical axis of the penetrating object. Bring the temperature of the penetrating object to 25 ± 0.5°C and then adjust its position such that its tip just touches the surface of the sample. Release the penetrating object and hold it free for 5 sec. Clamp the penetrating object and measure the depth of penetration. Repeat the test with two remaining containers.

1. **Rheology:** The rheology or viscosity should remain constant. As creams are normally non-Newtonian in nature, the viscosity can be measured using viscometers used for such liquids. Rheologic measurements are utilized to characterize the ease of pouring from a bottle, squeezing from a tube, maintaining product shape in a jar etc.
2. **Sensitivity:** As various types of ingredients are used with occasional use of antiseptics hormones etc. there is a possibility of sensitization or photosensitization of the skin. This test is normally done by patch test. The test sample is applied along with a standard market product at different places and effect is compared after a period of time.

5.11 IN-SITU GEL

It is a drug delivery system which is in a solution form before the administration in the body but it converts in to a gel form after the administration.

There are various routes such as oral, ocular, vaginal, rectal, intravenous, intraperitoneal etc.

Advantages

- They have ease of administration.
- In-situ gel shows improved local bioavailability.
- They possess reduced dose concentration and reduced dosing frequency.
- It allows improved patient compliance and comfort.
- It can be administered by unconscious patients.
- Drug gets released in a sustained and controlled manner.
- Natural polymers have inherent properties of biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities.
- Synthetic polymers usually have well-defined structures that can be modified to yield tailorable degradability and functionality.
- In-situ gels can also be engineered to exhibit bioadhesiveness to facilitate drug targeting, especially through mucous membranes, for non-invasive drug administration.
- In-situ gels offer an important "stealth" characteristic in-vivo, owing to their hydrophilicity which increases the in-vivo circulation time of the delivery device by evading the host immune response and decreasing phagocytic activities.
- Simple formulation and manufacturing so less investment and cost.

5.12 IMPORTANCE OF IN-SITU GELLING SYSTEM

- The major importance is the possibilities of administrating accurate and reproducible quantities compared to already formed gel.
- In-situ forming polymeric delivery system such as ease of administration and reduced frequency of administration improved patient compliance and comfort.

- Poor bioavailability and therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are instilled as drops into eye and undergoes a sol-gel transition from instilled dose.
- Liquid dosage form that can sustain drug release and remain in contact with cornea of eye for extended period of time is ideal.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.

Note

- The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation from which the drug gets released in a sustained and controlled manner.
- Various biodegradable polymers that are used for the formation of in-situ gels include pectin, guar gum, carbopol, xyloglucan, gellan gum, alginic acid, xanthum gum, chitosan, hydroxy propyl methyl cellulose (HPMC), poloxamer etc. Mainly in-situ gel administered by oral ocular, rectal, vaginal, injectable and intaperitoneal routes.

Ideal characteristics of polymers for preparation of in-situ gels

1. It should be biocompatible.
2. It is capable of adhering to the mucous membrane.
3. Preferred pseudo plastic behaviour of polymer.
4. Good tolerance and optical clarity is more preferred.
5. It should influence the tear behaviour.
6. The polymer should be capable of decreasing the viscosity with increasing shear rate.

Mechanism of in-situ gels

In-situ formation based on physical mechanism:

1. **Swelling:** In-situ formation may also occur when material absorbs water from surrounding environment and expand to desired space. One such substance is myverol (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in-vivo by enzymatic action.
2. **Diffusion:** This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system. In-situ formation based on chemical reactions mechanism Chemical reactions that results in-situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes

Applicability of in-situ polymeric drug delivery system

- Used in oral drug delivery system.
- Used in ocular drug delivery.
- Used in nasal drug delivery.
- Used in rectal drug delivery system.
- Used in injectable drug delivery system for dermal and transdermal drug.

Evaluation of in-situ gel:

- **Test for Clarity test:** The clarity of formulated solution is determined by visual inspection under black and white background.
- **Texture analysis:** The consistency, firmness and cohesiveness of in-situ gel are assessed by using texture profile analyzer which mainly indicated gel strength and easiness in administration in-vivo. Higher values of adhesiveness of gels are needed to maintain an intimate contact with mucous surface.
- **Determination of pH:** pH can be determined formulation is taken in beaker and 1 ml sodium hydroxide is added drop wise with continuous stirring. pH is checked by using pH meter.
- **Gelling capacity:** In-situ gel is mix with simulated tear fluid (in the proportion of 25 : 7 i.e. application volume 25 µl and normal volume of tear fluid in eye is 7 µl) to find out gelling capacity of ophthalmic product. The gelation assessed visually by noting the time for and time taken for dissolution of the formed gel.
- **Rheological studies:** The viscosity measured by using Brookfield viscometer, cone & plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity 5-1000 mPas, before gelling and after ion gel activation by eye will have viscosity of from about 50-50,000 mPas.
- **In-vitro drug release studies:** In-vitro release study of insitu gel solution is carried out by using Franz diffusion cell. The best fit model is check for Krosmeyers Peppas and Fickinian diffusion mechanism for their kinetics.
- **Sterility testing:** Sterility testing is carried out as per the IP 1996. The formulation is incubated for not less than 14 days at 300- 350°C in the fluid thioglycolate medium to find the growth of bacteria and at 200-250°C in Soya bean casein digest medium to find the growth of fungi in formulation.
- **Isotonicity evaluation:** Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity.

QUESTIONS

Short Answer Questions

1. Define paste.
2. Define ointment.
3. Define clear gels.
4. Define oleaginous base.
5. What are emollient?
6. What are humectants?
7. What are preservatives? Give examples.
8. What is the difference between aqueous cream and oily cream?
9. What are surfactants?
10. Name various methods used for preparation of ointments.
11. Give a list of marketed preparation covered under semi-solid dosage forms.

Long Answer Questions

1. What are semi-solid dosage forms? Classify them.
2. Classify different semi-solid dosage form bases with examples.
3. Discuss the factors which affect the skin permeation.
4. Write in brief about the ideal properties of semi-solid base.
5. What are the various factors which help in the selection of an ideal base.
6. Differentiate between paste and ointment.
7. Differentiate between cream and paste.
8. What are the excipients used in semisolid dosage forms?
9. Discuss the formulation and evaluation of semisolid dosage form.
10. Define the term gel. What are different types of gels?
11. Define cream and various types of creams.
12. What are the various bases used for pastes?
13. What are the various methods to prepare ointments?
14. Give the characteristics and examples of oleaginous bases.

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