



# **A TEXT BOOK OF PHARMACEUTICS-1<sup>ST</sup>**

**PRACHI PANDEY  
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# **“A Textbook of Pharmaceutics - I”**

**By**

**Prachi Pandey, Rahul Pal and Shiva Kant Thakur**



# JEC PUBLICATION

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# Acknowledgement

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We are grateful to the almighty, the most beneficent and merciful, the owing on the gift of forbearance. Self-control and patience that carried us through our endeavor and finally made this text book a grand success.

The satisfaction, which accomplish a successful completion of any task, are incomplete without the mentioning of the names of those people who makes it possible.

We are pleased to express our deep sense of gratitude towards our parents for their creative suggestions, unfailing advice and constant encouragement to transform teaching in the form of a user-friendly book for the students helping.

We shall remain thankful to all teaching and non-teaching staff members of NIMS Institute of Pharmacy, NIMS University, Jaipur Rajasthan India for encouraging me to writhe this text book.

We thanks to our all known and unknown persons for their comments, suggestions and encouragement.

We hope this text book will leave the desired impression and look forward to receive the comments from the readers.

## **Authors**

*Prachi Pandey*

*Rahul Pal*

*Shiva Kant Thakur*

# Preface

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This book having entitles “**A Text Book of Pharmaceutics-I**” (As Per Pharmacy Council of India, PCI Regulations).

This text book is designed to impart a fundamental and theoretical knowledge on the art and sciences of various pharmaceutical dosage forms used in pharmaceutical industry as well as marketed level.

This Pharmaceutics subjects deals with the various physical and physicochemical properties and their formulations/evaluations. The practice of the subject helps the students to get a better insight into the various areas of formulations research, development and stability studies of pharmaceutical dosage forms.

The main objectives of the completion of this course students shall be able to:

01. Known the complete history of pharmacy profession since lastly.
02. Understand the basics of different dosage forms, pharmaceutical incompatibilities and pharmaceutical calculation involving in it.
03. Understand the professional ways to handling the prescriptions.

This text book consists the various chapter in the form of units such as: Historical background and development of profession of pharmacy, Dosage forms, prescriptions, posology, pharmaceutical calculations, powders, liquid dosage forms, monophasic and Biphasic liquids, emulsions, suspensions, suppositories, pharmaceutical incompatibilities and semi-solid dosage forms.

This book is designed according to the pharmacy council of India (PCI) curriculum of undergraduate courses in pharmacy specially for B. Pharm students, which mainly useful all over India.

We sincerely request reader to send their valuable suggestions and constructive comments for making improvement in the text edition of the book. We extend out good wishes to the students and professor and sincerely hope to have the continued support from them and to our other books in future.

## **Authors**

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***Rahul Pal***

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# Syllabus

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## BP103T. PHARMACEUTICS-I (Theory)

### UNIT-I

**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.

### UNIT-II

**Pharmaceutical calculations:** Weights and measures – Imperial & 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 & 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

**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 & stability problems and methods to overcome.
- **Emulsions:** Definition, classification, emulsifying agent, test for the identification of type of Emulsion, Methods of preparation & stability problems and methods to overcome.

### UNIT-IV

**Suppositories:** Definition, types, advantages and disadvantages, types of bases, methods of preparations. Displacement value & its calculations, evaluation of suppositories.

**Pharmaceutical incompatibilities:** Definition, classification, physical, chemical and therapeutic incompatibilities with examples.

### UNIT-V

**Semi-solid 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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**UNIT : 1**

# Chapter: 01

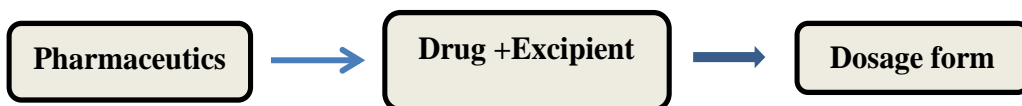
## HISTORICAL BACKGROUND AND DEVELOPMENT OF PROFESSION OF PHARMACY

### **Pharmaceutics:**

The word pharmaceutics is used in pharmacy and pharmaceutical sciences to encompass many subject areas, which are all associates with the steps to which a drug is subjected towards the end of its development i.e.

It is the stages that follow its discovery or synthesis, its isolation and purification and testing for advantageous pharmacological effect and the absence of serious toxicological problems. Put at its most simplistic, pharmaceutics converts a drug into a medicine.

Pharmaceutics is concerned with the scientific and technological aspects of the design and manufacture of dosage forms.



**Drug:** According to WHO A Drug is defined as an any substance intended for use in the **diagnosis cure, mitigation, treatment**, or prevention of disease in human or animals.

**Dosage form:**

Dosage form is defined as the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption. Common dosage forms include **pill, tablet or capsule, drink or syrup, aerosol or inhaler, liquid injection**, and **natural or herbal** form such as plant or food of sorts. The route of administration for drug delivery is dependent on the dosage form of the substance.

**Pharmaceutics** is the discipline of pharmacy that deals with the process of turning a new chemical entity (NCE) or old drugs into a medication to be used safely and effectively by patients. It is also called the science of dosage form design. There are many chemicals with pharmacological properties, but need special measures to help them achieve therapeutically relevant amounts at their sites of action. Pharmaceutics helps relate the formulation of drugs to their delivery and disposition in the body. Pharmaceutics deals with the formulation of a pure drug substance into a dosage form.

**Note:** - Medicines are drug delivery system that is they are a means of administering drugs to the body in a safe, efficient, reproducible and convenient manner.

**History of profession of pharmacy in India in relation to pharmacy education:**

- The allopathic system of medicine was introduced in India during the British rule. It was mainly meant for ruling class. By the 19<sup>th</sup> century it became popular and was used for the common people also. In the beginning the medicines were imported from Europe, later they were manufactured in India.
- The Bengal chemical and pharmaceutical works was setup by Acharya P. C. Ray in 1901 in Calcutta. Prof. T.K. Gujjar set up a small factory in Bombay at part 1930 and the Alembic Chemical works in 1907 at Baroda.

- The import of drugs was stopped during the first world war. It was resumed after the war. There was no restriction on the quality of the imported drug so there were inferior quality drugs in the markets. Therefore a number of acts were passed to regulate the quality of drugs.
- In 1903 a committee was appointed under the leadership of Pro. R.N. Chopra to look into the issue related to the pharmacy in India. It reported that pharmacy did not exist as a specialized profession.
- After this prof. Mahadeva Lal Schroff started the pharmaceutical education in the Banaras Hindu University.
- The united province pharmaceutical association was set up in 1935 which later became the Indian pharmaceutical association. In 1939 Prof. Mahadeva Lal Schroff started the Indian journal of pharmacy.
- The all-India pharmaceutical congress association was set up in 1940 which held its session at various places and tried to publicize the idea of pharmacy. To regulate the manufacture, import, distribution and sale of drug, the drugs act of 1950 was adopted.

### **INDUSTRY AND ORGANISATION:**

- It is well known fact that because of the British rule, pharmaceutical industry could not be developed significantly in India.
- After independence, the government declared its industrial policy in the year 1950.
- The government gave importance to the development of the pharmaceutical industry.
- During 1950, there were 65 domestic pharmaceutical units in india, while foreign units where 28 in numbers.

- In 1952 about 1643 licenses were issued under the drug act.
- In 1989, the number has increased to 1200. There only 1554 were manufacturing units.
- In 1952, total investment in the pharmaceutical industry was only Rs. 24cr which increased to Rs.1175cr in 1984-85, and in 2000-05, it has reached over Rs.15000 crores.
- Due to development of the pharmaceutical industry, the average life expectancy of Indian increased from 32-60 years. In fact, India has also made adequate research in the field.
- However, the multi-nationals have already entered the Indian market. These companies are competing with the Indian pharmaceutical companies.

### **PHARMACOPOEIA:**

- Pharmacopoeia is accepted as a book of standards.
- The word pharmacopoeia derived from Greek words Pharmacon (Drug) and poiea (to make).
- Pharmacopoeia contains-
  - List of drugs and formula for medicinal substances and preparations.
  - Description
  - Tests
  - Standards
- **It is** issued under the authority of the government of country.
- The countries don't have own pharmacopoeia can use pharmacopoeia of other countries.

- Pharmacopoeia is an official compendium condoning list of established drugs with its nomenclature, molecular and structural formula, category/ use, test for it identify, purity and potency along with assay.

### **INDIAN PHARMACOPOEIA:**

- It is an autonomous institution of the university of Health and family welfare which sets standards for all drugs that are manufactured, sold and unsummed in India.
- The set of standards are published under the title Indian Pharmacopeia (IP).

### **HISTORY**

- The history of IP is as old as BP.
- The Bengal Pharmacopoeia was published in 1844 (Nearly 20 before first BP).
- As on record, first pharmacopoeia of India published in 1868 under the authority of Her Majesty's, secretary of state for India in council.
- **It contains -**
  - Vegetable
  - Inorganic material & medica.
  - Animal.
  - Products of fermentation.
  - Distillation.
- **Its** supplement was published in 1869.
- **It was** the BP which was considered as the book of standards during the pre-independence.



- In 1902 Bose published –official indigenous Drugs of India. It was published as enlarge edition in 1932 as pharmacopoeia India.

## **AFTER INDEPENDENCE**

- Indian pharmacopeia committee was appointed in 1948 to prepare National pharmacopoeia.
- The first edition of IP was published in 1955. Followed by supplement in 1960.
- IP 1966-second edition, followed by supplement in 1975.
- IP 1985-third edition, followed by its addendum in 1989 and 1991
- Indian Pharmacopoeia- 1996 Fourth edition, followed by its addendum 2000, supplement 2000 for veterinary products, addendum 2002 and addendum 2005.
- Indian pharmacopoeia 2007- Fifth edition, followed by addendum 2008.
- Indian pharmacopoeia 2010- six edition, followed by its addendum 2012
- Indian pharmacopoeia 2014 with DVD- seventh edition.
- Indian pharmacopoeia 2018 with DVD - eighth edition.

## **Number of volumes in each edition of IP:**

- IP 1955, 1965 and 1985 was published in 1 volumes.
- IP 1996 was published in 2 volumes.
- IP 2007 and 2010 was published in 3 volumes.
- IP 2014 was published in 4 volumes.
- IP 2018 was published in 4 volumes.

## **BRITISH PHARMACOPOEIA**

- First edition of **BP** was published in 1864.

- It consists of two sections, **Part I:** Materia Medica & **Part II:** preparation & compounds.
- Second edition of BP was published in 1867.
- Fourth edition of BP was published in 1898.
- Fifth edition of BP was published in 1914.
- Eighth edition titles of BP were published in 1953.
- In this edition titles of drugs & 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.
- Term ‘prolonged release’ has been replaced the term ‘slow’ and the term ‘gastro-resistant’ has been replaced with ‘enteric coated’ in number of monographs.
- BP 2008 contains approximately 3100 monographs for substances, preparation and articles used in practice.
- It has been made effective from 1<sup>st</sup> January 2008.
- BP 2007-2009 were given in i.e., **Volume I** to **Volume VI**.
- Volume I & II contains medicinal substances.
- Volume III contains formulated preparations, blood related products, immunological products, radiopharmaceutical preparations, surgical materials & homoeopathic preparations.
- Volume IV contains supplementary chapters, IR spectra etc.
- Volume V contains veterinary.
- Volume VI contains CD ROM version.

- Current edition of BP edition of BP 2010 is in process.

## **UNITED STATES PHARMACOPOEIA**

- First edition of united state pharmacopeia was published on 15<sup>th</sup> December 1820 in both Latin & English.
- From 1820 to 1942 it was published at Ten years intervals.
- From 1942 to 2000 it was published at Five years intervals.
- First National formulary of the united state appeared in 1888.
- USP21-NF17, 1990 is the third revision that consolidates USP &NF into a single volume.
- Electronic version of USP-NF on floppy disks was introduced in 1992.
- USP23-NF18, was published in Mumbai as an Asian edition at the end of 1994.
- USP23 has ten supplements.
- First supplement was published in January & last in May 1999.
- USP24-NF19, appeared from first January 2000.
- USP30-NF25, appeared from May 2007.
- It contains scientific standards for drugs, dietary substance, biological products & Excipients used in dosage forms.
- It contains 4,100 monograph and 200 general chapters.
- It has been printed in three volume set.
- Volume I contain general chapters & Volume II & III contains monographs.
- First supplement to USP30-NF250, appeared from AUGUST 2007 & second supplement from November 2007 which will be considered official from May 2008.
- From 2006, Spanish edition of USP is also being published.
- Current edition of USP 2014 is in process.

## **EXTRA PHARMACOPEIA**

- William Martindale (1840-1902), he was a pharmacy proprietor and an analyst in his pharmacy. He published the first edition under the title 'Martindale' the 'Extra' in the title was used in the sense of "outside", since the book aimed to describe drugs and medicines were not include in the current British Pharmacopoeia (BP) that time.

### **History and editions:**

- The book was successful start from a slim pocket volume of 313 pages. The 'EP' has grown to its current 4160 pages.
- In 1883, 1<sup>st</sup> edition of Martindale: The Extra Pharmacopoeia (EP) was published.
- In 1885, a 4<sup>th</sup> edition was published.
- In 1901 a 10<sup>th</sup> edition was published.
- William Meartindate was in poor health and he committed suicide in February 1902. After death of William Harrison Mertindate had taken over the responsibility of publication of Martndale extra pharmacopoeia in association with Dr, Wynn Westcott at intervals of 2 to 3 years until Westcott's death in 1925.
- After Harri's death in 1933, the Martindale businesses were split and the copyright of the EP was acquired by the Pharmaceutical Society of Great Britain.
- Last edition is 37<sup>th</sup> in 2011.

- Martindale contains information on drugs in clinical use worldwide, as well as selected investigational & veterinary drugs, herbal & complementary medicines, pharmaceutical excipients, vitamins & nutritional agents, vaccines, radiopharmaceuticals, disinfectant & pesticides.

# **Chapter: 02**

## **DOSAGE FORMS**

- ❖ Dosage Form Drugs are rarely delivered as pure chemical entities but are approximately usually provided as prepared formulations i.e., dosage form. After converting them into an appropriate dose formulation, they are delivered in several dosage forms.
- ❖ To create an alternative dosage form, non-medicinal chemicals (also known as pharmaceutical ingredients or excipients) are added. By adding pharmaceutical ingredients that solubilize or suspend or thicken or dilute or emulsify or stabilize or preserve them, drug dosage forms can be made more effective and appealing.
- ❖ **Definition of Dosage Form**

*Dosage forms are the mechanism by which drug molecules / APIs are administered to areas of action inside the body to generate maximum intended benefits and the lowest unwanted effects.*

OR

*The Dosage form is the combination of Active Pharmaceutical Ingredients (API) and Excipients in the formulation.*

### **Need Of Dosage**

Forms Mainly depend on Patient Safety and Drug Safety/ Benefits.

- Deliver precise dosages in a safe and easy manner. Example – Tablets, capsules, syrups

- Cover bitter taste or odor of drug substances. Example – Capsules, coated tablets, flavored syrups.
- Insoluble or unstable in the selected vehicle, provide a liquid formulation of the insoluble or unstable medication. Example – Suspension.
- Controlled-release methods prolong the duration of medication effect. Example – Controlled release tablets, capsules, suspensions.
- After oral delivery, a drug substance is protected from stomach acid. Example – Enteric-coated tablets.
- Provide optional drug action from topical administration sites. Example – Ointment, cream, ear and nasal preparations
- Drugs can be injected into the body's tissues. Example – Implants.
- Inhalation treatment is the most effective way to get optimum medication activity. Example – Inhalants.
- Liquid dosage forms of chemicals soluble in the vehicle of your choice. Example – Solution
- Provide for the introduction of medication into the body's orifice. Example – Rectal and vaginal suppositories.
- Protection of a drug substance from atmospheric oxygen or moisture. Example – Coated capsules, sealed ampules.

#### ❖ **Definition of Drug (Active Pharmaceutical Ingredients)**

- Drogue is an old French term that means "dry herb" and is sometimes used interchangeably with the word "drug".
- Chemical compounds intended for use in the diagnosis, prevention, treatment, and management of disease(s) in humans and other animals are referred to as "pharmaceutical products" or "pharmaceuticals". Chemical/organic synthesis,

molecular modification, and biotechnology have all been used to produce medicines in recent years.

**OR**

- The Active Pharmaceutical Ingredient (API) is the component of a medication that creates its action. Definition of Excipients Do not increase or affect the therapeutic action of the active components. They are also known as inactive components or excipients and have no pharmacological action in general. Examples of inactive components are dyes, preservatives, sweetening agents, binding materials, coloring agents and flavoring agents, etc.

### **Classification of Dosage Form**

#### **Based on different state of dosage form**

1. **Liquid Droughts:** Liquid oral formulations comprising single or several doses of medication. Elixirs: Excipients and medicaments in a liquid formulation for oral administration.

**Emulsions:** Water-based suspension of oils and fats using an emulsifying agent. Emulsifying agent coats oil particles so they do not coalesce when the interfacial tension between oil and water decreases.

**Suspensions:** One or more active components dispersed in a suitable medium are used in biphasic liquid formulations for oral administration. When shaken, it disperses into a uniform suspension that is stable enough to deliver the precise dosage.

**Gargles:** Externally applied aqueous solutions that are concentrated for treating throat infections.



**Gels:** Dispersions of medicaments in water used as antacids. **Lotions:** External liquid preparations are generally administered without friction.

**Liniments:** The application of external liquid preparations is generally done via friction.

**Mixtures:** One or more medications are included in liquid oral preparations.

**Mouthwashes:** In a similar manner to gargles, these mouthwashes are used for oral cleanliness and to treat oral infections.

**Nasal drops:** Dropper-instilled liquid solutions used to treat nose infections and blockages.

**Solutions:** Liquid medicine that can be used for internal or exterior applications.

- 2. Solid Powders:** Solid dose formulations comprising micron-sized, finely fragmented particles.

**Tablets:** Medication in solid dose form, either with or without excipients.

**Granules:** Particles in a group.

**Capsules:** Gelatin capsules are used to encapsulate drugs. **Pills:** Excipients are contained in this small pill.

**Lozenges:** Sugar and gum-based solid formulations used to treat mouth and throat disorders.

**Suppositories:** Solid dosage form carrying medication that is put into bodily cavities other than the mouth, such as the rectum, nose, or ear.

- 3. Semisolid Ointments:** Ointment-based semisolid dose forms for external application that include or do not contain medications.

**Creams:** With or without medicaments, semisolid external dose forms with an appropriate fatty basis are available.

**Paste:** With an appropriate fat basis, semisolid external dosage forms include a significant proportion of finely powdered medicaments.

**Gels:** Contains hydrophilic or hydrophobic base and gelling agents. Transparent semisolid dose forms for external usage.

- 4. Gaseous Aerosols:** Dispersion of solid or liquid particles in gas for application to the respiratory tract, using an atomizer.

**Inhalations:** It consists of pharmaceutical liquid preparations for internal consumption, which are either dispersed or suspended in the propellant.

**Sprays:** Application of alcohol-containing medication aerosols to the nose or throat using an atomizer or nebulizer.

# **Chapter: 03**

## **PRESCRIPTION**

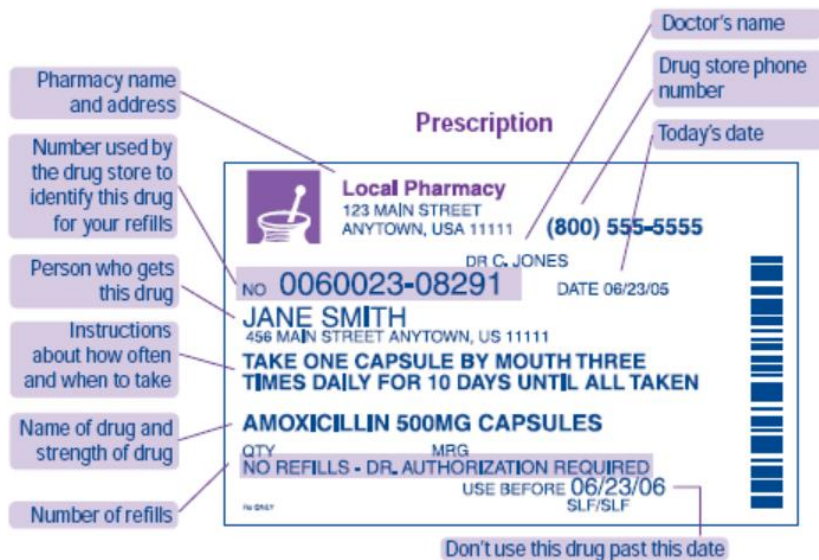
A prescription is a written instruction for medicine from a physician or a registered medical practitioner. There is a link between the physician and the pharmacist when it comes to prescribing. Doctors, dentists, and pharmacists are examples of medical practitioners.

**Physician (RMP) → Pharmacist → Patient**

Praescriptus, which means "*before writing*", is the Latin phrase that gives rise to the English word "prescription." Prior to compounding and administering a medication, it was necessary to write a prescription.

**Parts of Prescription:** As an example, a common prescription might include:

1. Prescriber office information
2. Date
3. Patient data (Name, Age, Sex, and Address of the Patient)
4. Superscription (Symbol  $\mathcal{R}$  )
5. Inscription (Medication prescribed)- Main part of a prescription
6. Subscription (Direction to Pharmacist/ Dispenser)
7. Signatura or Transcription (Direction for Patient)
8. Renewal instructions
9. Prescriber's signature and registration number



## 1. Physician (Prescriber) office Information

When a patient becomes ill, having information on their physician is vital to being able to reach them in an urgent situation. The prescription contains the following information.

- Name of the doctor or office;
- Address with phone number and e-mail;
- Prescription no. (required when calling the pharmacy for a refill)

## 2. Date of the Prescription

The top of the prescription should have the date. As a result, a pharmacist can quickly determine the date of the prescription. If the prescription is being refilled, knowing when the last time the drug was dispensed is also helpful. The date protects the patient from abusing a medication that is habit-forming.

### 3. Patient Data

This section should contain the patient's name, age, weight, gender, and address. This is a very necessary feature since it is used to identify the person.

Identifying information such as the patient's name and address is required. Child patients must provide their age, weight, and gender in order to determine the necessary dose.

### 4. Superscription

This is the section of the prescription that contains the sign "Rx", which stands for "Take Thou". It's a Latin term, and it's a good one. You take is a common expression in English. In the past, the sign was thought to have come from the Jupiter sign. God of healing Jupiter is a Greek deity. The patient's fast recovery was requested by using this sign.

### 5. Inscription (Medication Prescribed)

The inscription, which is the most important portion of the prescription, contains information about the drug's composition and dose. The medication may be either an official or non-official formulation of some kind.

**a) Official Preparation (i.e., from pharmacopoeia):** The name of the preparation is the only thing written. E.g., Piperazine Citrate Elixir IP.

**b) Non-official Preparation:** Each ingredient's quantity and preparation type will be specified.

### 6. Subscription

In the prescription, the subscription contains instructions for the pharmacist on how to produce a dose. This section of the prescription specifies the number of dosage units

and the amount to be administered. E.g., 10 Tabs of Paracetamol, for instance (that means 10 pieces paracetamol tablet).

## **7. Signature**

To be printed on the label. "Signature" is the most common way to refer to it. The prescription is completed by signing the prescription. t.i.d (three times a day), b.i.d (two times a day), and o.d (one day) are used in the signature (once a day). Signed and stamped prescriptions are issued by a licensed medical professional.

## **Handling of Prescription**

The handling of the prescription is crucial. The pharmacist should follow the following steps when processing a prescription for compounding and dispensing:

- a. Receiving.
- b. Reading and checking.
- c. Collecting and weighing the materials.
- d. Compounding, packaging and labelling.

### **1. Receiving**

The pharmacist must get the prescription. While accepting a prescription, a pharmacist should not alter his/her facial expression in any way. It creates the appearance that the patient is puzzled or stunned after seeing the prescription.

### **2. Reading and Checking**

Behind the counter, the prescription should be checked after it is received. The validity of the prescription should be verified. Verify the prescriber's signature and the date of the prescription. In order to properly fill up a prescription, the pharmacist must read all

of the lines and words. He/she must not make any guesses about the words. As soon as he or she has any doubts, a pharmacist should call another pharmacist or a prescriber.

### **3. Collecting and Weighing the Material**

Materials should be retrieved from shelves or drawers prior to compounding a script. On the left-hand side of the balance, all of the materials are maintained. Each material should be placed on the correct side of the balance once it has been measured. After the prescription components have been compounded, they are returned to the shelves or drawers. Three times each container of material should be inspected during compounding.

- (i) As soon as they are removed from the shelves/drawers.
- (ii) Measurement of materials.
- (iii) When the containers are placed back on the shelves or drawers, the process is complete.

### **4. Compounding, Packaging and Labelling**

It is recommended that just one prescription be prepared at one time. Clean surfaces should be used during compounding. Each piece of equipment must be thoroughly cleaned and dried before use. It should be created under the supervision of the doctor or in accordance with pharmacopoeia or formulary instructions. It is important to fill the containers with the prepared compounds. The container should be clearly marked with a label.

**Source of Errors in Prescription:** Medication or prescription mistakes can occur for a variety of reasons.

**1. Legibility:**

- The handwritten prescription might be difficult to read in some cases.
- Medicines are often misspelled. Metrix and Metriz are two examples. It's easy to confuse these two brands. Metriz, on the other hand, includes metronidazole, and Metrix, glucosamine.

**2. Checking:**

To recheck the entire medicine, no one is accessible to do so.

**3. Too Many Customers:**

The dispenser needs additional time to adequately manage a large number of clients. As a result, mistakes arise when consumers are pressed for time.

**4. Lack of Concentrations:**

If they do not, every dispenser should focus on prescriptions. There is a problem.

**5. Too many phone calls and social media:**

The use of a mobile phone during business hours should be avoided or turned off.

**6. Lack of Experience:** In this area, experience is crucial.



# **Chapter: 04**

## **POSODOLOGY**

From the Greek "posos" and "logos" comes "posology." As a field of medicine, the study of posology focuses on the dosages or quantities of medicines that can be provided to achieve the desired pharmacological effects. Age, climate, weight, gender, and time of administration are all factors that affect the outcome.

For each indication, use the recommended dosage and mode of administration. How much to take? Amount of medication to be taken per day, such as 1 or 2 milligrams per kilogram or mg/m<sup>2</sup>, or every 6 hours.

**Dose:** Amount administered or consumed by a patient in order to get the desired medical result. A patient's therapeutic benefit should be maximized with the least amount of medication.

**Factors Affecting Posology:** There are some factors that affect posology:

1. Age
2. Sex
3. Body Weight
4. Time of Administration
5. Body Surface Area
6. Route of Administration
7. Emotional factors
8. Accumulation
9. Environmental Factors

10. Presence of Disease
11. Additive effect
12. Idiosyncrasy
13. Synergism
14. Tachyphylaxis
15. Antagonism
16. Tolerance
17. Metabolic Disturbances
18. Drug Dependence/ Addiction

### **1. Age**

As a result of their underdeveloped hepatic and renal functions, newborn infants (pediatrics) are particularly susceptible to some medications. Drugs accumulate in the body's tissues if they are not detoxified and eliminated.

Drug clearance may be slowed in the elderly (geriatric) due to a loss in renal and hepatic function, increasing the risk of drug build-up and eventual toxicity. Age-related changes in target tissues and organs may also lead elderly persons to respond inappropriately to the typical dose of a medication.

### **2. Sex**

It is possible that women do not react to medicines in the same manner as males. The use of medicine at these times requires special caution for pregnant and nursing women.

It takes longer for women to get sedated after taking morphine or barbiturate. During menstruation, pregnancy, and nursing, it is necessary to take extra measures while giving medicines.

Serious purgatives, antimalarials, and ergot alkaloids are prohibited during pregnancy. The fetus is affected by alcohol, barbiturates and opioids when pregnant.

### **3. Body Weight**

It is always given in milligrams per kilogram of body weight (mg/kg) in any situation.

This technique is also used for individuals weighing 50-100kg.

It is possible that obese adults, small children, and malnourished individuals will not receive this dosage. It should be dependent on the individual's body weight.

As a result, medication concentrations at the site of action depend on the amount of medicine administered in proportion to body size. Thin or obese adults may require a dose adjustment.

Based on body weight, determine the dosage of a medication for children.

Children's medication dose should be determined based on body weight rather than age.

### **4. Time of Administration**

Drug absorption is slowed down by food in the stomach.

Unfilled stomachs allow for faster absorption of medicines.

When taken on an empty stomach, the drug's effectiveness may be diminished.

Iron, arsenic, and cod liver oil should always be taken after meals.

### **5. Body Surface Area**

Many physiological systems and body surface area are closely related (BSA).

It is possible to calculate the surface area of a human using a nomogram comprised of scales for height, weight, and surface area.

Adult and child-specific nomograms are provided.

A person's height and weight are connected by a straight line, which intersects the surface area column.

## **6. Route of Administration**

The therapeutic effectiveness of the medication is affected by its route of delivery.

Intravenously given drugs enter the bloodstream directly, resulting in the presence of the whole quantity provided in the bloodstream.

As a result of multiple physical, chemical and biological obstacles to their absorption, including interactions with stomach and intestinal contents, oral medications are seldom entirely absorbed.

Through the intravenous method, the medication's effect is rapid, and the risk of drug toxicity is higher.

## **7. Emotional Factor**

Females are more emotional than males, therefore certain medicines require less dosage in order to get the desired effect.

Angina pectoris and bronchial asthma have been successfully treated with placebos, which are inert dose forms that physically mimic the genuine medication.

## **8. Accumulation**

After repeated administration, medications that are slowly eliminated can build up to hazardous levels in the body, resulting in toxic symptoms. E.g., digitalis, emetine and heavy metals.

## **9. Environmental Factors**

Stimulating medicines are more effective when taken in the daylight, whereas hypnotic drugs are less effective when used in the daytime. This is due to the fact that darkness is a sedative. At night, hypnotics are more effective than during the daytime. During the day, the amount of barbiturate necessary to induce sleep is significantly higher than that needed at night.

## **10. Presence of Disease**

Patients with liver cirrhosis may experience exceptionally long-lasting effects from drugs such as barbiturates and chlorpromazine.

Because streptomycin is mostly eliminated via the kidney, people with renal failure may be at risk of toxicity.

## **11. Additive Effect**

Additive impact occurs when the combined pharmacological activity of two or more medicines is equal to the total of their separate actions.

The treatment of asthma can involve the use of substances such as ephedrine and aminophylline.

## **12. Idiosyncrasy**

Allergy is another name for idiosyncrasy. It is termed idiosyncrasy when a patient's response to a medication is distinct from its typical pharmacological effect.

Aspirin, for example, may induce gastrointestinal hemorrhage at modest doses.

Penicillin with sulphonamide, for example, can induce severe toxic effects in certain people.

### **13. Synergism**

When two or more medicines are used together, their effects are enhanced as a result. As a result, a phenomenon known as synergism has developed.

Examples include a mixture of procaine and adrenaline that extends procaine's effect.

### **14. Tachyphylaxis**

If a medication is delivered repeatedly, the cell receptors get blocked and the drug's pharmacological effect is reduced. Tachyphylaxis or acute tolerance is the term used to describe the occurrence of a reduced reaction that cannot be reversed by increasing the dose.

Due to tachyphylaxis, repeated doses of Ephedrine in the treatment of bronchial asthma, for example, may generate very little response.

### **15. Antagonism**

Drug antagonism occurs when one drug's activity is countered by another drug's action on the same pharmacological system. When acid poisoning is treated with milk of magnesia, the alkaline action of milk of magnesia neutralizes the effects of acid poisoning.

**1. Competitive/Reversible antagonism:** Both agonists and antagonists attach to the same location on the cell membranes. Acetylcholine and atropine are two examples.

**2. Non- competitive/ Irreversible antagonism:** Antagonists inactivate receptors, preventing the formation of an effector complex with an agonist. A combination of phenoxybenzamine and adrenaline acts on the  $\alpha$ -receptor in the brain.

**3. Physiological antagonism:** Two receptors are occupied by an agonist and an antagonist, but their actions are opposing. Hepatotoxic substances include adrenaline (bronchodilation) and histamine (bronchoconstriction).

## **16. Tolerance**

The capacity to withstand the effects of a drug, especially if it is developed via repeated usage.

It is typical for medicines, such as antihistaminic and narcotic analgesics, to cause tolerance. Normal sensitivity can be restored by temporarily stopping the drug's administration. When starting therapy, use the lowest effective dosage and avoid extended administration to limit the development of tolerability.

## **17. Metabolic Disturbances**

It is possible that changes in water-electrolyte balance, acid-base equilibrium and body temperature may alter the effects of medicines.

Salicylates only lower the body temperature if the individual's body temperature has increased. They do not have antipyretic properties at all.

## **18. Drug Dependence/ Addiction**

Euphoria; Tolerance; Dependence/Habituation

**i) Physical Dependence:** Tea, Nicotine

Rely on drugs in order to function.

Withdrawal syndrome can occur.

When a drug is abruptly stopped.

1. Drug classes differ from one another.
2. Unbalance is created by compensating processes.

**ii) Psychological Dependence:** LSD, Marijuana, Opiates

In addition, there is a behavioral dependency.

High incidence of drug use, drug desire, and tendency to relapse after ceasing usage.

Properties of drugs that enhance their effectiveness

### Measurement Conversions for Liquids:

1 cc	1 ml
5 ml	1 tsp
15 ml	1 tbsp
30 ml	1 oz
480 ml	1 pt
3785 ml	1 gal
3 tsp	1 tbsp
2 tbsp	1 oz
16 oz	1 pt
2 pt	1 pt



<b>4 qt</b>	<b>1 gal</b>
<b>1 L</b>	<b>1000 ml</b>
Pt= pint, Gal= gallon, Tsp= Tea Spoon , Tbsp= Table Spoon , Oz= Ounce, Qt= quarter	

### **Measurement Conversions for Solids:**

<b>1 kg</b>	<b>2.2 lbs</b>
<b>1 lbs</b>	<b>454 gm</b>
<b>1 oz</b>	<b>30 gm</b>
<b>16 oz</b>	<b>1 lb</b>

### **Pediatric Dose Calculation Based on Age, Body Weight and body Surface Area**

Throughout childhood and adolescence, pediatrics refers to diseases that affect children. New-borns are defined as newborns to 1 month old; infants 1 month to 1 year of age; early childhood is defined as 1 up to 5 years; late childhood is defined as 6 through 12 years, and adolescents are classified as 13-17 years of age 1.

During the first month after birth, infants are considered neonates. One who is between one month and one year old.

The adolescent stage encompasses the ages of 13 and 17.

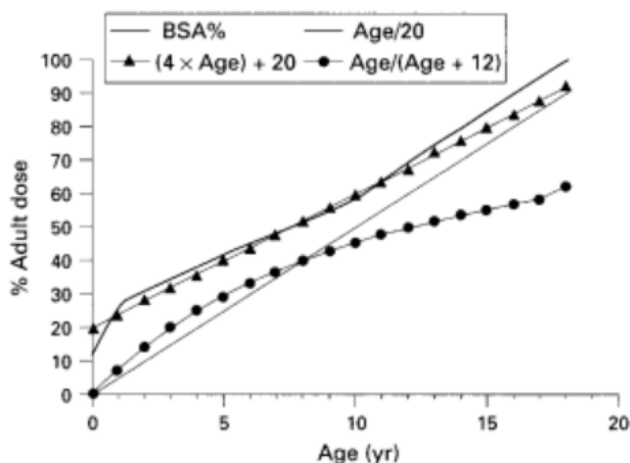
Children's dosage depends on factors such as their age and weight, their health status, their respiratory system, and the stage of development of their body systems for drugs

metabolism (e.g., liver enzymes) and elimination (e.g., kidneys). Newborns are not capable of fully developing these biological functions and systems. It begins during the second year of life that the nervous and renal systems are developed. Antimicrobial agents are frequently introduced to newborns, infants, and young children, who mainly excrete them through their kidneys. Because antibiotics are the most commonly prescribed drugs in these populations, this is especially relevant in this case. Drugs can accumulate in the body and cause overdose and toxicity if the rate of drug elimination is not considered properly.

When dealing with pediatric patients as well as adults, body weight plays a key role in dose calculation. The safe pediatric dose is calculated by two different methods. The calculation is measured in milligrams or micrograms per kilogram based on body weight or in square meters and based on body surface area (BSA). Chemotherapeutic agents are often measured by the BSA method since it is more accurate. Milligrams per kilogram is what it is called in most other places. A microgram per kilogram dose may be used for medications given in small amounts.

### **Rules-based on age**

Age was used as the foundation of the first rules. Augustsberger pointed out that Dilling's rule ( $\text{age}/20$ ) dates back to the 8th century.  $\text{Age}/20$ ,  $(4\text{age})/20$ , and  $\text{age}/(\text{age}+12)$  is the most commonly used in figure 1, plotted using ages weighted by the standard tables. Age determines weight considerably (between the 3rd and 97th percentiles); it was 25 percent to 20 percent at 10 kg at 1 year, and it was 45 to 26 percent at 40 kg at 13 years. This leads to a very unreliable set of rules. The BSA curve for normal-sized children is best fitted to the  $\text{weight (age)}/20$  estimate if weight is unavailable.



### Young's Formula

$$\text{Dose for child} = \frac{\text{Age in years}}{\text{Age in years} + 12} \times \text{Adult dose}$$

### Dilling's Formula

$$\text{Dose for child} = \frac{\text{Age in years}}{20} \times \text{Adult dose}$$

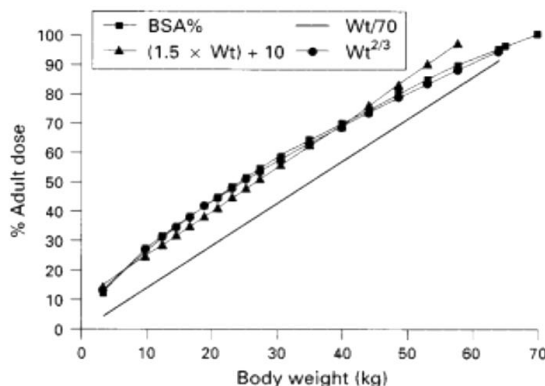
### Fried's Formula

$$\text{Dose for child} = \frac{\text{Age in months}}{150} \times \text{Adult dose}$$

### Rules-based on weight

The first weight proportional regimen for drug therapy, according to Professor A.J. Clark of Edinburgh, was established in 1861. His first rule was: the fraction of an adult dose equal to the weight (lb) per 150 grams.

Augsberger made this method more accurate by substituting multiplication for division and adding ten, resulting in:  $((1.5 \text{ wt (kg)})10)$  percent of an adult dose. In practice, this rule is not quoted widely because it is difficult to calculate. At 60 kg, it reaches 100%, which is the best fit to the BSA curve that can be made.



Despite its disadvantages, mg kg dosages have been very popular due to their attractive simplicity.

1. Using it effectively requires knowledge of diverse dosages of drugs (n mg kg), as well as different doses for different ages.
2. The mathematics in the bedside rule may not be as straightforward, adding tenths, hundredths, or thousandths of an mg kg may result in the decimal point being misplaced.
3. Since it does not relate immediately to adult doses, it is not obvious when maligned prescriptions are written.
4. As that varies between approximately 45% at 15 kg to 20% at 40 kg when compared with the BSA graph, assays of drug concentrations show that its use "under doses" for much of its range.

**Clark Formula:**

$$\text{Child dose} = \frac{\text{Weight in Pounds}}{150} \times \text{Adult dose}$$

$$\text{Child dose} = \frac{\text{Weight in Kg}}{70} \times \text{Adult dose}$$

$$\text{Child dose} = \frac{\text{Weight in lbs}}{150} \times \text{Adult dose}$$

**Rules-based on body surface area**

A device's surface area is strongly recommended for drug dosage calculations because the rate of metabolism or redistribution of drugs is proportional to its metabolic rate, which in turn reflects the amount of heat that is lost, which in turn correlates with warm objects' surface area. Assays of blood concentrations of drugs and measurements of organ dimensions and volumes correlate well with BSA.

$$\text{Child dose} = \frac{\text{Child body surface Area m}^2}{1.73 \text{ m}^2} \times \text{Adult dose}$$

# **UNIT : 2**

# **Chapter: 01**

## **PHARMACEUTICAL CALCULATIONS**

### **INTRODUCTION:**

#### **Scope of Pharmaceutical Calculations:**

The use of calculations in pharmacy is varied and broad-based. It encompasses calculations performed by pharmacists in traditional as well as in specialized practice settings and within operational and research areas in industry, academia, and government. In the broad context, the scope of pharmaceutical calculations includes computations related to:

- Chemical and physical properties of drug substances and pharmaceutical ingredients;
- Biological activity and rates of drug absorption, bodily distribution, metabolism and excretion (Pharmacokinetics);
- Statistical data from basic research and clinical drug studies;
- Pharmaceutical product development and formulation;
- Prescriptions and medication orders including drug dosage, dosage regimens, and patient compliance;
- Pharmacoeconomics; and other areas,

To have a complete understanding of various types of calculations, which are involved in dispensing. It is desirable that the pharmacist should have a thorough knowledge regarding weights and measures which are used in calculation.

Pharmaceutical preparations have a wide range and their several forms are dispensed as mixtures, solution, emulsions, suspensions, powders, tablets, capsules, lotions, liniments, creams/pastes and suppositories etc.

Pharmaceutical calculations involve the use of mathematical principles to determine the appropriate dosage of medication for a patient. One essential aspect of these calculations is the use of weights and measures, both in the imperial and metric system. Pharmaceutical calculations are the area of study that applies the basic principles of mathematics to the preparation and safe and effective use of pharmaceuticals. It is the application of mathematics that require the study.

To have a complete understanding of various types of calculations which are involved in dispensing, it is desirable that the pharmacist should have a thorough knowledge regarding weights and measures which are used in calculations. They are two systems of weights and measures:

- 1) The Imperial System
- 2) The metric System (or) International System

#### **Imperial system:**

- **Weight:** The basic unit of weight in the imperial system is the pound (lb). One pound is equal to 16 ounces (oz).
- **Volume:** The basic unit of volume in the imperial system is the gallon (gal). One gallon is equal to 4 quarts (qt) or 128 fluid ounces (fl oz).

#### **Measurement of Weight in Imperial System:**

Weight is a measure of the gravitational force acting on a body and is directly proportional to its mass. The imperial system is divided into two parts for the purpose of measurement of weight. These are



(a) Avoirdupois System

(b) Apothecaries System

**(a) Avoirdupois System:** “In this system the “pound” is the standard unit for weighing, and all measures are derived from the Imperial Standard Pound (Lb)”, thus

**1Lb =16 oz (avoir)**

**1Lb =7000 grains**

**1oz =437.5 grains**

**(b) Apothecaries System:** This system is also known as the Troy system. The grain is the standard unit in this system and all other units are derived from it.

**20 grains = 1 scruple**

**60 grains = 1 drachm**

**480 grains = 1 ounce**

**8 drachms = 1 ounce**

**12 ounces = 1 pound (Lb) and 5760 grains = 1 pound**

**Measurement of Capacity in Imperial System:** The standard units for capacity are same in both the Avoirdupois and Apothecaries systems. The “gallon” is the standard unit and all other measures of capacity are derived from it.

**1 gallon = 160 fluid ounces**

**$\frac{1}{4}$  gallon = 1 quart**

**$\frac{1}{8}$  gallon = 1 pint**

**$\frac{1}{160}$  gallon = 1 fluid ounce**

**1/8 fluid ounce = 1 fluid drachm**

**1/60 fluid drachm = 1 minim**

**1 quart = 40 fluid ounces**

**1 pint = 20 fluid ounces**

**1 fluid ounce = 480 minims**

**1 fluid drachm = 60 minims**

**Metric system:** The International System of Units (SI), formerly called the metric system, is the internationally recognized decimal system of weights and measures. This system was formulated at France in the late eighteenth century. Today, the pharmaceutical research and manufacturing industry, the official compendia, the United States Pharmacopeia—National Formulary, and the practice of pharmacy reflect conversion to the SI system. The reasons for the transition include the simplicity of the decimal system, the clarity provided by the base units and prefixes of the SI, and the ease of scientific and professional communications through the use of a standardized and internationally accepted system of weights and measures. The base units of the SI are the meter and the kilogram. Each table of the SI contains a definitive, or primary, unit. For length, the primary unit is the meter; for volume, the liter; and for weight, the gram (although technically the kilogram is considered the historic base unit).

- **Weight:** The basic unit of weight in the metric system is the gram (g). One kilogram (kg) is equal to 1,000 grams.
- **Volume:** The basic unit of volume in the metric system is the liter (L). One liter is equal to 1,000 milliliters (mL) or 1,000 cubic centimeters (cc).

It is also crucial to use the appropriate units of measure for the medication being administered. For example, liquid medications may be measured in milliliters, while solid medications may be measured in grams or milligrams. The correct unit of measure must be used to ensure that the correct dose of medication is given to the patient.

**Measure of Length:** The meter is the primary unit of length in the SI:

<b>1 kilometer (km)</b>	<b>1000.000 meters</b>
<b>1 hectometer (hm)</b>	<b>100.000 meters</b>
<b>1 decameter (dam)</b>	<b>10.000 meters</b>
<b>1 decimeter (dm)</b>	<b>0.100 meters</b>

<b>1 centimeter (cm)</b>	<b>0.010 meter</b>
<b>1 millimeter (mm)</b>	<b>0.001 meter</b>
<b>1 micrometer (μm)</b>	<b>0.000,001 meter</b>
<b>1 nanometer (nm)</b>	<b>0.000,000,001 meter</b>

**Measure of Volume:** The liter is the primary unit of volume. It represents the volume of the cube of one tenth of a Meter, that is, of 1 dm<sup>3</sup>.

<b>1 kiloliter (kl)</b>	<b>1000.000 liters</b>
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<b>1 hectoliter (hl)</b>	<b>100.000 liters</b>
<b>1 decaliter (da)</b>	<b>10.000 liters</b>
<b>1 liter (l)</b>	<b>1.000 liter</b>
<b>1 deciliter (dl)</b>	<b>0.100 liter</b>
<b>1 centiliter (cl)</b>	<b>0.010 liter</b>
<b>1 milliliter (ml)</b>	<b>0.001 liter</b>
<b>1 micoliter (μl)</b>	<b>0.000001 liter</b>

**Measure of Weight:** The primary unit of weight in the SI is the gram, which is the weight of 1 cm<sup>3</sup> of water at 40C, its temperature of greatest density.

<b>1 kilogram (kg)</b>	<b>1000.000 grams</b>
<b>1 hectogram (hg)</b>	<b>100.000 grams</b>
<b>1 decagram (dag)</b>	<b>10.000 grams</b>
<b>1 gram (g)</b>	<b>1.000 gram</b>
<b>1 decigram (dg)</b>	<b>0.1000 gram</b>
<b>1 centigram (cg)</b>	<b>0.010 gram</b>
<b>1 milligram (mg)</b>	<b>0.001 gram</b>
<b>1 microgram (μg or mcg)</b>	<b>0.000, 001 gram</b>

<b>1 nanogram (ng)</b>	<b>0.000,000,001 gram</b>
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## **WEIGHTS AND MEASURES:**

The ingredients required for compounding pharmaceutical products must be calculated and measured accurately.

Weight is a measure of the gravitational force, acting on a body and is directly proportional to its mass. Volume is the measurements of any liquid substance.

### **Measurements Systems:**

The systems usually followed for weight and measurements are:

01. Imperial system
02. Metric system
03. A voirduposi system
04. Apothecaries' system
05. Household measurements

**Matric system:** Metric system is used in the Indian Pharmacopeia for the measurement of weights and capacity.

It was implemented in India from 1st April, 1964 in pharmacy profession.

**Avoirdupois system:** In this system the pound is the standard unit for weighing and all measures of mass are derived from the imperial standard pound (lb).

**Apothecaries system:** This system is also known as troy system. The grain is the standard unit in this system and all other weight are derived from it.

## CALCULATIONS INVOLVING PERCENTAGE SOLUTIONS:

Percentage means “*parts per hundred*” or fractions having denominators of 100. Thus, the terms 10 percent solutions can be expressed as 10%, 10/100, 0.10 or 10 parts per 100 parts.

It is the duty of a pharmacist to compound solution of desired percentage strength. Percentage in that respect means parts of active ingredients per 100 parts of the total preparation.

Percentage concentration of the solution are usually expressed in any one of the three common forms:

$$\text{Weight in volume percent (w/v)} = \frac{\text{Weight of solute (gm)}}{\text{volume of solution (ml)}} \times 100\%$$

$$\text{Weight percent (w/v)} = \frac{\text{Weight of solute}}{\text{volume of solutio}} \times 100\%$$

$$\text{Volume percent (v/v)} = \frac{\text{Volume of solute}}{\text{volume of solutio}} \times 100\%$$

## WEIGHT IN VOLUME SOLUTION (%W/V):

In this case, the solute is weighed and the solvent is measured the general formula for 1% w/v solution is:

Solid	1 part by weight
Solvent to produce	100 parts by volume

Either 1gm of solute is dissolved in sufficient amount of water to produce 100m or 10mg of solute is dissolved in 1ml of water to make 1% w/v solution unless and until any specific instructions are mentioned in the pharmacy.

The resulting solution is supplied as w/v solution.

**WEIGHT IN WEIGHT SOLUTION (%W/W):** In this special case, the solute and the solvent are measured by weight, the general formula for 1% w/w solution is:

Solid	1 part by weight
Solvent to produce	100 part by weight

Percentage solutions of solids are not made w/w unless especially requested.

**VOLUME BY VOLUME SOLUTIONS (%V/V):**

In this case, the solute and the solvent are measured by volume. The general formula for 1% v/v solution is:

Solute	1 part by volume
Solvent to produce	100m parts by volume

**ALLIGATION METHODS:** When the calculation involves mixing of two similar preparations of different strength, to produce a preparation of intermediate strength, the alligation method is used. The method is recommended for the purpose of checking the calculations.

At the end of this lecture, student will be able to:

- Calculate the amount of diluent required to make a desired lower strength.
- Calculate the amount of API which must be added to make a higher strength.
- Calculate the amount of higher and lower strength preparation that must be combined to make a desired amount of an intermediate strength.

### **Pharmaceutical Calculations Alligation Methods:**

When the calculation involves mixing of the two similar preparations of different strengths, to produce a preparation of intermediate strength, the Alligation method is used in this condition.

### **PROOF SPRIT:**

The strength of alcoholic preparations is indicated by degrees, “over proof” or “under proof”. Proof spirit is that mixture of alcohol and water which at 51oF 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 any alcoholic solution which contains 57 % v/v alcohol is a proof spirit which is said to be 100 proofs. 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.).

The strength of alcohol is calculated in proof degrees. The Indian standard of 100% proof spirit is equal to 57% v/v of ethyl alcohol.

$$\text{i.e., } 100\% \text{ p.s.} = 57\% \text{ v/v ethyl alcohol}$$

If the value is more than 57% then it is said to be as over proof spirit.

If the value is less than 57% then it is said to be as under proof spirit.

### **ISOTONIC SOLUTIONS:**

Solution that to be used as an ophthalmic and injectable should be isotonic, e.g., if a ophthalmic solution with tear secretion, irritation and pain is prevented. Tonicity of isotonic solution is adjusted by employing osmotic pressure as these solutions are usually iso-osmotic.



Most ophthalmic preparations are formulated to be isotonic, or approximately isotonic, to duplicate ophthalmic tears for the comfort of the patient.

A pharmacist does not usually receive the prescription for paratonic solution which may be either hypertonic or hypotonic. The quantity of solute in hypertonic solutions is more than the quantity is required for making them isotonic, while the quantity is less in hypotonic solution.

Tonicity can be adjusted by introducing an inert material into the solution. This material should also be compatible with the drug:

The methods by which the isotonicity can be calculates are:

01. Freezing point method

02. Molecular weight method.

**01. Freezing Point Method:** Since a number of solutes which freeze at  $-0.52^{\circ}\text{C}$  are present in lachrymal fluid, all the solutions with freezing point  $-0.52^{\circ}\text{C}$  will be isotonic with the lachrymal fluid. Similarly, human blood plasma also exhibits the same freezing point, thus, the solutions freezing at  $-0.52^{\circ}\text{C}$  will be isotonic with it.

Tonicity adjustment can be eased if the freezing point of the drug and the inert salt is known for various strength of their solutions. Tables providing this information's are maintained by the pharmacists and the same information can also be obtained from the standard tests. Freezing points in this case are expressed in terms of 1% solutions and the quantity can be determined by multiplying the freezing points with the factor. The equations given below section such as:

**Freezing Point of the tear secretion**

**or**

**Human Blood Plasma**

**=**

**Freezing point of the drug**

**+**

**Freezing point of the adjusting  
substance**

The calculations based on freezing point method are exemplified as follows:

Example: **200ml** of an eye wash containing 1% of boric acid is to be dispensed.

On applying the above equation:

$$-0.52 = -0.29 + (-X)$$

Therefore,  $X = 0.52 - 0.29$ , i.e., sodium chloride sufficient to produce a freezing point lowering of  $0.23^{\circ}\text{C}$  is required.

It is given that 1% sodium chloride lowers the freezing point by  $0.58^{\circ}\text{C}$ , thus, sodium chloride required to produce lowering of  $0.23^{\circ}\text{C}$  will be:

$$\frac{1 \times 0.23}{0.58} = \frac{0.39\text{gm}}{100\text{ml}} \text{ or } 0.39\%.$$

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

Boric acid (1%, for 200ml) =  $1\text{gm} \times 2 = 2\text{gm}$

Sodium chloride (0.39% for 200ml) =  $0.39\text{ gm} \times 2 = 0.78\text{gm}$ .

Purified water sufficient to produce 200ml

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

Lowering of  $0.29^{\circ}\text{C}$  in F.P. is produced by 1gm of boric acid

Lowering of  $0.52^{\circ}\text{C}$  in F.P. is produced by  $\frac{1 \times 0.52}{0.29} = 1.8\text{gm}$

Therefore 1.8gm of boric acid is required for making the 100ml of an eye wash and the working formula will be:

Boric acid (1.8% for 200ml) =  $1.8 \times 2 = 3.6\text{gm}$

Purified water sufficient to produce 200ml.

**02. MOLECULAR WEIGHT METHOD:** A solution freezing point inversely depends on the concentration of the solutes dissolved in it. Thus, greater solute concentration lowers the freezing point of the solution. This indicates that freezing point is a function of the concentration of gram moles of the solutes.

- It can also be said that freezing point depends on the numbers of ions (numbers of effective ions), the drug weight, and its molecular weight. For a 0.9% solution of sodium chloride the concentration can be expressed as:

$$\frac{\text{Numbers of grams of sodium chloride} \times \text{Number of effective ions}}{\text{molecular weight of sodium chloride}} = \text{Isotonic factor or ilotonicity}$$

In other words;  $\frac{g \times n}{m} = \text{Isotonic factor or, } \frac{0.9 \times 2}{58.5} = \text{Isotonic factor}$

i.e., isotonicity factors for sodium chloride is 0.03.

Isotonicity of 0.9% sodium chloride solution (normal saline) is similar to those of body fluids. Thus, 0.03 will be the isotonicity or tonicity factors for tear secretion and blood serum. The quantities for making the eye solution can be calculated by equating the 0.03 value with the tonicity factors of the drug and additives.

The equation which can be used for calculating the additives quantity is given below:

$$0.03 = \frac{g \times n}{m} + \frac{g_1 \times n_1}{m_1} + \frac{g_2 \times n_2}{m_2}$$

Where; g = weight in gram, n = effective ion concentration and m = molecular weight of the medicament.

The generalizations given below helps in determining the effective ionic concentration:

- The value of **n is 1** for non-ionizable substances (dextrose)
- The value of **n is 1.5** for partially ionizable solutes in two ions (silver nitrate).
- The value of **n is 2** for highly ionizable solutes in two ions (sodium chloride)
- The value of **n is 2** for partially ionizable solutes in three ions (sodium sulphates)

**Example:** Prepare 100ml of eye drops of silver nitrate.

$$0.03 = \frac{g \times n}{m}, g = \frac{0.03 \times m}{n} + \frac{0.03 \times 169.8}{1.5} = 3.4\text{gm}/100\text{ml}$$

Let us assume that 100ml of 1% eye drops of silver nitrate is to be prepared:

$$0.03 = \frac{g \times m}{m} + \frac{g_1 \times n_1}{m_1}$$

$$0.03 = \frac{1 \times 1.5}{169.8} + \frac{g_1 \times 1.5}{85} \quad (g_1 = 1.26\text{g}/100\text{ml})$$

Sodium nitrate is the substance which is used to make solution isotonic because of its compatibility with silver nitrate. If sodium chloride is added, silver chloride will precipitate out. Thus, 100ml of eye drop containing 1% silver nitrate can be prepared using the following formula:

Silver nitrate	1 gm
Sodium nitrate	1.26gm
Purified water q.s. add	100ml

If making solution with isotonicity similar to lachrymal secretion is desirable. It should be known paratonic solution within the range of 0.7-1.5% of sodium chloride or its equivalent in relation to other substances are easily tolerated by the eye.

# **Chapter: 02**

## **POWDER**

### **Definition:**

Powders are solid forms of dosage containing finely divided medications and other substances intended for ingestion or external application. In its finely divided state, it is a solid substance (varying between 10nm and 1000µm), typically sorted through crushing, grinding, or comminuting. In addition to the pharmaceutical industry, powder has applications in many more fundamental fields, such as foods, cosmetics, and chemicals. In general, APIs are marketed as powdered dosage forms, which are processed and mixed into small amounts.

Even though tablets and capsules have largely replaced the use of powder in modern medicine, they still represent one of the oldest forms of dosage and continue to hold some advantages that make them valuable for pharmaceutical applications. The point of this article is to present both the advantages and disadvantages of powder formulations.

### **Classification of powders:**

- 1) **Bulk powders:** As bulk powders are non-potent and can be dosed accurately and safely with measuring devices such as teaspoons, cups, and insufflators, they are non-potent. The limited prescriptions of bulk powders in the oral form are antacids, dietary supplements, laxatives, and pain relievers. The vast majority of bulk powders are topical.

**2) Dusting powders:** Powders for dusting are fine medicinal (bulk), dry powders that are intended to be dusted onto the skin using a sifter-topped container. Powders containing single medicinal agents can be applied as dusting powders; however, bases are frequently used to apply medicinal agents and protect skin against irritation. Among the inert dusting, powder bases are the clay, kaolin, kieselguhr, magnesium carbonate, talc, starch, and starch. Powder bases are effective for absorbing secretions and draining congestion, and they impart a cooling sensation. It is recommended that extemporaneous dusting powders be filtered through a 100-200 mesh sieve to remove any grit that will further inflame traumatized areas.

**3) Douche powders:** Douche powders, also called douches, are used to prepare vaginal cleansing solutions. The majority of douche powders will be used for their hygienic effects. However, some will contain antibiotics. In general, patients have prescribed powders as a matter of convenience, since a powder is easier to transport compared to a bulky solution.

A certain volume of water is used to dissolve a teaspoonful or tablespoonful of powder so that the specified concentration is achieved. A pH of 3.5 to 5 is usually appropriate for the preparation of the solution. A feminine bulb syringe or a fountain syringe is used to irrigate the vaginal area.

The ingredients in douche powder may contain volatile substances (e.g., menthol, thymol, and volatile oils). The containers need to be made of glass, large enough to hold the food. Several commercial douche powder packets come in metal foil bags. Each bag contains the appropriate amount of powder for one douche. Numerous douches are also available in disposable applicators that have already been prepared for use.

- 4) **Insufflations:** As the name implies, insufflations are extremely fine powders that are used to be injected into the body. A powder is placed in the insufflator, and the medicine is inhaled by the air current when the bulb is squeezed. When the air current travels directly to the patient's skin, the particles are inhaled. An insufflation resulting from extemporaneous compounding must be passed through a size 100 mesh sieve before being administered. As an elegant solution for administering insufflations, pressured packages provide an excellent solution.
- 5) **Powder sprays:** Dispensing powders under pressure will provide a uniform and targeted application, as opposed to simply dusting powders. A sterile environment can be maintained in an aerosol container for powdered medicines. To prevent clogging of the valve orifice and to maintain the uniform application of powder, the particles must be of a specific size range. For powder to be sprayed effectively, it must contain particles smaller than 50 microns if it is to be packaged as a powder spray.
- 6) **Divided powders:** A divided powder or chart is a single dose of powdered medicines in one or more individual packages, such as cellophane, metallic foil, or paper. The patient does not participate in the measurement process of powder divided into smaller dosage units, which makes them a more accurate dosage form than bulk powder. Divided powders are available in foil, cellophane, or paper packs, each providing better protection from the external environment due to their sealed nature. Cellophane, foil, and paper are all commercially available powders that protect themselves from external factors.



**Advantages of powders:** The powder must initial stage of dosage form formulation, it should contain the various merits which are such as:

- The ingredients are available in a wide range, and the dose can be easily established for the patient.
- Liquid dosage forms have a shorter shelf life and less physicochemical stability than powder dosage forms. For example, powders for antibiotic syrups are shelf-stable for two to three years, but they lose their shelf life once they are reconstituted with water.
- In adults and children who find tablets or capsules difficult to swallow, powders may be a better choice.
- The powder form allows for the effective administration of a very large dose that would be impossible to administer in any other way. Sometimes it is not feasible to produce tablets if the dose of a drug is between 1 and 5 grams.
- Taking pills in powder form rather than in compressed form causes the medication to disperse rapidly in the stomach.
- A water-soluble drug contained in an oral powder dissolve much more rapidly than a similar drug contained in a tablet or capsule, in which the tablet or capsule shell must be disintegrated before dissolution.
- Water or another liquid can be dissolved in a powder, making it easier to swallow.
- Mixing the oral powder with a beverage or applesauce immediately before taking the supplement is highly recommended.
- Powder dosage forms are relatively inexpensive to manufacture, so the product price is quite low as compared to other forms.
- Mixing powders allow for a great deal of versatility.
-

## **Disadvantages of powders:**

- If you take a drug that has an unpleasant taste, powders are not the best dosage forms. A taste that is masking an unpleasant quality may be problematic.
- As much as possible, powders should not be dispensing drugs that deteriorate rapidly in terms of exposure to the atmosphere or acidic pH. Salts of ferrous iron, for instance, oxidize easily and should not be administered as powders.
- Carrying powder is a hassle since it is bulky and heavy.
- It is not appropriate to use the powder dosage form for administering medications, such as pills and pills, that inactivate in the stomach or that can harm the stomach.
- The use of powders for potent drugs requiring small doses may not be an appropriate method of delivering them (e.g., bulk powders). Due to variations in spoon fill (e.g., heaped or level Spoonfuls) when individual doses are extracted from bulk, individual doses typically are extracted from the bulk using a 5 ml spoon.
- The dispensing of deliquescent or hygroscopic drugs is not suitable for powders.

## **Simple And Compound Powder:**

The powdered form of a drug or chemical consists of finely divided components in dry form. Powders can be applied internally and externally. The powdered form of a drug or chemical consists of finely divided components in dry form. Powders can be applied internally and externally. Powders can be either crystalline-like or amorphous. It is believed that the particle size of powder and dissolution, absorption, and therapeutic effect of drugs are correlated.

**Advantages:**

The stability of powder dosage forms is greater than that of liquid dosage forms. Liquid dosage form has a lower chance of incompatibility compared to liquid medication. Powdered forms of the drug are more rapidly acting as compared to other solid forms of the drug, such as tablets and capsules. In body fluids, powder dissolves easily because of its smaller particle size. Dissolving or mixing powdered drugs in appropriate liquids enables the patient to consume a greater quantity of the medicine orally. Whether dispersed in water or any other liquid, powdered drugs are easy to take my small children or elderly patients. A powder dosage form is more economical than other forms of dosage because no specialized machines or techniques are needed. Liquid dosage forms are heavier and more difficult to transport than powders.

**Disadvantage:**

It is impossible to dispense powdered medications that have bitter, nauseous, or unpleasant tastes. The powder form of deliquescent and hygroscopic drugs is not permitted. The powder form of some drugs is not suitable for dispensing because they are affected by atmospheric conditions. The process of dispensing powder is very lengthy.

**Internally administered powders, simple & compound**

Individual doses of powder are enclosed in a paper in this form. A compound powder has more than one ingredient, such as simple powder but less than one is simple powder. To make powders easily handled by patients and weighed accurately, the minimum quantity of each powder should not be less than 100 mg.

**Simple powders:** There are generally only one or two ingredients in a powder, either crystallized or amorphous. The powder may be present in crystalline form, in which

case it is crushed to a fine powder, measured, divided into portions, and packaged individually.

**Example:** Dispatched six aspirin powders, each containing 300 mg of aspirin.

Rx, aspirin 300mg

**Procedure** - Prepare the aspirin by powdering it & weighing the required amount. Individually wrapped powder paper is used to weigh and package aspirin powder. There is 300 mg of aspirin in each packet.

**Direction** - You need to take one powder after every eight hours.

**Compound powders:** Powders mixed from two or more substances constitute compound powders. Afterward, divide it into the desired number of doses. Each powder paper is then dispensed with the solution.

**Example** - Dispense 8 powders of A.P.C, each powder containing 500mg of A.P.C

Rx, Aspirin 300mg

Paracetamol 150mg

Caffeine 50mg

**Procedure** - Make sure that each powder is accurately weighed and mixed in ascending order by weight. Each dose should be wrapped in powder paper after weighing 500 mg of the mixed powder.

## **Preparation of powders:**

**1) Step 1. particle size reduction:** The powder is created by grinding each ingredient into fine particles; thus, to prepare powder, different procedures and equipment need to be used to reduce the particle size of powder ingredients. This is called comminution.

- As a powder formulation method, the most common way to reduce particle size is to triturate. This is done by placing the chemical in a mortar and grinding it between the mortar and pestle throughout the process using a strong, downward press.
- Making sure that all powder particles are evenly reduced and mixed requires frequent scraping of the sides of the mortar.
- In addition to the levigating agent, the solid is manipulated with a triturating machine to further reduce the particle size, or with a spatula to wet the mixture for further reduction in particle size after it has been triturated.

In the laboratory, certain methods can be used:

- a. Levigation
- b. Pulverization
- c. Trituration

In industrial methods, certain methods can be adopted:

- a. Hammermill
- b. Roller mill
- c. Microfluidics particle reduction
- d. Bowl chopper
- e. Colloid mill
- f. Attrition mill

g. Ball mill

Advance size reduction technologies

**2) Step 2 – preparing the homogenous mixture:** One of the following methods may be used to mix the powders:

- a. Geometric dilution
- b. Trituration
- c. Sifting and tumbling
- d. Speculation

**a. Geometric dilution:** If a large amount of diluent has been mixed with potent substances, the method is used to separate the substances. A mortar is used to place the potent drug on the dilute and mix the substances, which is done by triturating the mixture.

An equal volume of diluent is added to the powder mixture in the mortar, and it is triturated again. As diluents are added in equal volume to the mortar mixture at each step, the process is repeated until all the diluents have been incorporated.

**b. Trituration:** In addition to reducing particle size, it is also used to mix powders.

The glass mortar with a smooth working surface is preferred for particle reduction along with powder mixing. Using a porcelain mortar with a rough inner surface is the best method for blending powder and reducing particle size.

**c. Sifting:** In the mixing process, powders are passed through sifters. Processes like this produce an extremely light, fluffy product and are not suitable for the inclusion of potent drugs into diluent solutions.

**d. Tumbling:** An electric motor rotates a large container while powders are mixed inside. Industrial blenders are used widely for mixing powders in large volumes.

e. **Speculation:** Mixing powders using this method involves moving the spatula over the piece of paper or porcelain tile on which they are to be mixed. When mixing powder or liquid substances that liquefy (eutectic mixtures) the method is very useful.

3) **Step 3 – packaging of powders:** A lot of powdered bulk products are packaged in shaker top containers so that topical application is easier and more convenient. In addition to dispensers with wide mouth jars or flip-top lids, wide mouth jars with a flip-top are also available. It is recommended that the jar or plastic container be tightly sealed, especially when compounds with volatile ingredients are present. This will enhance the stability of the compound and offer protection from moisture and light. "For external only use" should be clearly labeled on the packaging.

**Double wrapping:** Menthol, thymol, citric acid, Pepsin, and other volatile or hygroscopic drugs need double-wrapping to maintain their effectiveness. Drugs with volatile properties should also be double wrapped to prevent the drug from being ruined by the atmosphere.

Drugs with volatile properties should also be double wrapped to prevent the drug from being ruined by the atmosphere. Individual powders should be dissolved in a little water or placed on the tongue before being swallowed by the patient.

**Dusting powders:** Generally, dusting powders fall into two categories:

1. Surgical
2. Medical Surgical

Dusting powders are used mainly in body cavities and on burns and umbilical cords of infants as a result of major wounds, whereas medical dusting powders are used on superficial skin conditions. In contrast, medical dusting powders must be free of

pathogenic microorganisms while surgical dusting powders must be sterilized before use. It is generally possible to prepare dusting powders by mixing two or more ingredients, of which starch, talc, or kaolin must be one element. The most common materials used are talc and kaolin because they are chemically inert. These ingredients are prone to contamination by pathogenic bacteria, however, so before using them they must be sterilized by dry heat method (160 degrees for 2 hours).

Among their many uses, dusting powders serve as antiseptics, astringents, absorbents, antiperspirants and antipruritic. Alternatively, dusting powder is delivered in aerosol containers with a sifter top. Although pressure aerosol containers are more expensive than sifter-top containers, they provide for easier application of the preparation. In addition to powder puffs and sterilized gauze pads, dusting powder can be applied using dusting powder puffs.

Powdered dusting powders are generally considered non-toxic, but exposure to fine powdered ingredients by infants might cause irritation to the lungs. When handling these preparations, proper care should be taken.

**Example - Rx,** starch (powdered form) - 25gm

Zinc oxide (powdered form) - 20 gm

Purified talc (sterilized) - 50 gm

Salicylic acid (Powdered form) - 5 gm

**Direction -** Apply two or three times a day on the affected parts.



**Method** - All ingredients should be ground into powder. The components talc, starch, zinc oxide, and salicylic acid should be weighed out. Combine in ascending order of their weights. After mixing again, pass the powder through a No.85 sieve. Sift again after mixing lightly. To protect powder from atmospheric contamination, transfer it into sifter-top containers.

**Effervescent powders:** In effervescent powders, acids and carbonates or hydrogen carbonates are generally combined with water to release carbon dioxide when exposed to it. The powders may be single-dose or multi-dose prepared. Water is usually used to dissolve or disperse these drugs before administration.

**Storage** - Powder effervescent should be stored tightly closed in a container.

It is possible to take a large dose of ingredients in one serving via an effervescent tablet or powder. Upon combining organic food acid with carbonate, it forms potassium, sodium, calcium or magnesium salts of the acid, which buffer the pH of the solution to make it easier on the stomach. Studies have demonstrated that ingredients in a variety of effervescent products can penetrate the bloodstream as quickly as 15 minutes after application.

**Absorption:** Effervescent tablets make a pleasant tasting solution in soda, water, and fruit juice. The acid in the tablets comes from organic fruit. The stomach cannot break down solid compounds quickly, which delays or reduces absorption in conventional solid tablets. A liquid solution dissolves effervescent tablets, allowing the ingredients to be absorbed quickly, completely, and uniformly.

**Compatibility:** Conventional solid tablets or capsules dissolve slowly as they travel to the stomach after swallowing. Anatomical and physiological factors have an effect on the passage time in different people. Solid dosage forms can partially dissolve if they

are passed through the body after a longer period of time, causing irritation to the mucous membranes. The ingredients of an effervescent tablet are evenly distributed in the solution, preventing concentrations that are high in one area. Acids and carbonates are present in a balanced ratio in the solution of the effervescent tablet. A buffer is formed by this balance.

### **Sudden increase in liquid intake:**

In adults, 1.5 - 2 litres the effervescent tablets also provide additional liquid intake, in addition to the nutritional value intended. As dissolved effervescent tablets support the daily liquid supply during times of excessive fluid loss from events such as intense physical activity, diarrhoea, or high temperatures, they are especially useful during events such as intense physical activity, diarrhoea, or summertime high temperatures. of liquid should be consumed daily.

**Efflorescent powders:** In the chemical world, efflorescent powders are crystallized powders containing water of hydration or crystallization, such as alums, atropine sulphate, citric acid, caffeine, and codeine. When exposed to a low-humidity environment, this water can be liberated either through manipulation or when exposed to manipulation. Powders will become pasty and sticky if this happens, or may even liquefy. In an anhydrous salt form of the drug, it is possible to keep in mind the differences between its potency during its anhydrous form and during its hydrated form. It is also possible to use a bulky powder when mixing the powders, as well as a light, non-compacting method for drying it.

- Solids with efflorescent properties can spontaneously lose water when exposed to hydrated salts.

- Solids that spontaneously lose water from salt hydrates are called efflorescent substances.

Hydrated salts are inorganic salts that contain a definite ratio of molecules of water. The molecules of water in these salts can evaporate outside the container. In the presence of moisture in the air, the hydrate's aqueous vapor pressure is greater than that of the water vapor. Hydrated salts are among the most efflorescent substances. For example,  $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ ,  $\text{Na}_2\text{CO}_3$ , and  $\text{FeSO}_4$  are among the examples. Drying of cement is another reason for efflorescence. Due to the loss of water, the hydrated salt becomes powdery, as it loses these water molecules. This will eventually cause the salt to solidify. Water becomes gaseous when this occurs.

**Hygroscopic powders:** The term hygroscopic means that these substances can absorb or adsorb water from their surroundings. Those substances that adsorb or absorb water from the surroundings are known as hygroscopic substances. The water molecules in hygroscopic substances are absorbed into the crystal structure when water vapor is absorbed.

As a consequence, the size of the substance increases. A change in hygroscopic properties can be seen in colour, boiling point, viscosity and others due to hygroscopic nature.

A salt is an example of a hygroscopic substance.  $\text{ZnCl}_2$ ,  $\text{NaCl}$ , and  $\text{NaOH}$  are among the many examples of zinc chloride. Additionally, there are some other commonly hygroscopic substances. Honey, silicone gel, germinating seeds, etc., are among these compounds.

**Eutectic mixtures:**

The term eutectic was first used by physicist and chemist Frederick Guthrie in 1884. When a homogeneous mixture of substances melts or solidifies at a single temperature, it means that the melting point of each component is lower than the temperature of the entire system.

The eutectic state can also be defined as a state when a mixture of substances is melted or frozen at a temperature that was smaller than the melting point of each of the individual components or a mixture of them. As such, it is known as the eutectic temperature, as it is the lowest melting temperature that can be reached by mixing all component species.

After cooling a mixture of random liquid substances, one part begins to detach in solid form as the temperature is lowered, and continues to do so as lower temperatures are reached. Upon dividing this portion, the resulting liquid becomes increasingly rich in one constituent, until the structure of the liquid approaches a point where all elements dissolve into an intimate mixture of solids. A eutectic structure solidifies at a temperature, and the temperature is the eutectic temperature. Since the melting temperatures of their constituents are different for components with different lattices, no eutectic ratios would have different melting temperatures for their constituents. However, a non-eutectic aggregate would solidify as it cooled, solidifying at various temperatures until it solidified completely.

In chemical chemistry, eutectic mixtures are defined as mixtures of derivatives that, rather than reacting and creating new compounds, inhibit their crystallization at certain ratios, producing melting points lower than those of the constituents individually. There are multiple ways to create eutectic mixtures within the pharmaceutical industry,

including combining APIs, APIs, and excipients, or excipients, allowing for a variety of pharmaceutical applications.

**Eutectic mixtures are usually created by the following factors:**

1. Liquid components must be miscible with liquid components and solid components must be miscible with solid components.
2. The contact-induced melting point depression requires close contact between the eutectic forming materials.
3. An interaction between two chemical groups that results in a physical bond, such as intermolecular hydrogen bonds and modified version of VantHoff's law.

**Eutectic temperature:** The eutectic temperature remains the lowest melting temperature irrespective of the compositional ratios present in a eutectoid. When a superlattice reaches this temperature, all of the components will evaporate, and the entire eutectic structure will melt into a jelly. As opposed to a eutectic mixture, in a non-eutectic mixture, each portion solidifies into a lattice at its temperature before the whole mix solidifies.

**Eutectic composition:**

Eutectics are melt-and-freeze compositions made up of at least two elements of the same melting and freezing properties. The crystallization process creates a mixture of all the components, allowing the product to behave as a unit. (Lane, 1989) The materials form a dense crystal network and melt together simultaneously, with no distinction. Eutectics are chemical mixtures of organic and/or inorganic substances. The result is that organic-organic blends, inorganic-organic blends, and organic-inorganic blends can be made.

**Geometric Dilutions:** In the pharmaceutical industry, geometric dilution involves thoroughly mixing a small amount of drug with the appropriate amount of a solvent,

which thins or binds it. By doing so, the resultant compound is evenly distributed with the drug.

As with any compound, the method of preparation varies with the compound, its form (such as an ointment or tablet), and the substances used. The UNC Eshelman School of Pharmacy explains that geometric dilution methods include triturating powders and mixing powders into ointments, as well as the liquid aliquot method, which combines fluids to produce a solution.

When a substance is triturated, it is reduced to particle size by grinding equal parts of both substances in small batches and then adding the same amount of each substance to the other and re-mixing until both substances have been thoroughly mixed. An aliquot is a method for dissolving a drug in an appropriate solvent to obtain the desired volume. Most commonly, it is water or alcohol.

# **Chapter: 03**

## **LIQUID DOSAGE FORMS**

Dosage forms are essentially pharmaceutical products in the form which involves a mixture of active drug components and nondrug components (excipients). Liquid form of a dose of a drug used as a drug or medication intended for administration or consumption.

### **Liquid dosage forms are prepared:**

- a. By dissolving the active drug substance in an aqueous or nonaqueous (e.g., alcohol, ether, glycerin) solvent,
- b. By suspending the drug in appropriate medium, or
- c. By incorporating the drug substance into an oil or water phases.

### **ADVANTAGES OF LDF:**

- a. Better for patients who have trouble swallowing expiration than other.
- b. Faster absorption than solids.
- c. More flexibility in achieving the proper dosage of medication.
- d. Palatable.



**Representation of Liquid dosage forms**

#### **DISADVANTAGES OF LDF:**

- a. Shorter life than other dosage form,
- b. Harder to measure accuracy,
- c. Need special storage condition.
- d. Less stable,
- e. Easily affected by microorganisms,
- f. Bulky to carry around.
- g. Easy to loss by the breakage of the container.
- h. Measuring dose is required.

**VARIOUS ADMINISTRATION ROUTES OF LDF:** Liquid dosage forms can be administered:

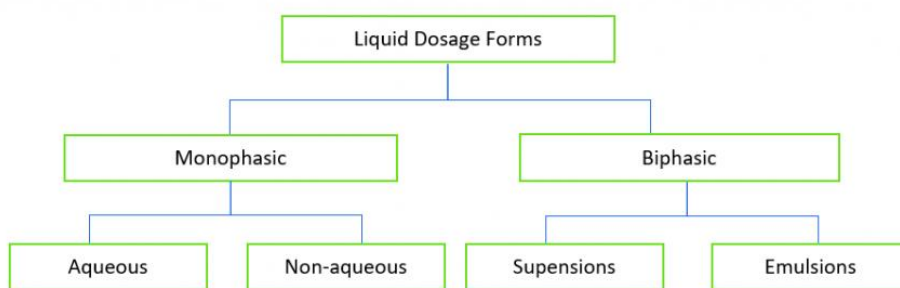
- a. **Topically** – Lotions or suspension applied to the skin, nasal drops, ear drops, eye solutions.
- b. **Orally**: oral suspension, emulsion & solution.



### c. Parenterally:

- Subcutaneous Injection (S.C.)
- Intramuscular Injection (I.M.)
- Intravenous Administration (I.V.)

**CLASSIFICATION OF LDF:** The liquid dosage form mainly, classified into the monophasic, biphasic formulation which are shown in the given below section:



### The different classification of liquid dosage form chart flow

#### MONOPHASIC:

Monophasic liquid dosage forms are liquid preparations containing only one base. These are also known as true solutions. A true solution is a clear homogenous mixture, prepared by dissolving a solid, liquid, or gas in a liquid phase. Monophasic liquid dosage forms are made for internal as well as external use. Syrups, mixtures, elixirs, and linctuses are meant for internal use, while gargles, mouthwashes, lotions, liniments, eye drops, ear drops, nasal drops, douches, and throat pains are **meant for external use**.

## 01. SYRUPS:

Syrups are sweet viscous liquid formulations, intended for oral use. They are also termed as the concentrated or saturated solution of sucrose, as they contain 66.7 w/w amount of sugar in them. The presence of sugar in syrups makes them a valuable vehicle for the administration of nauseous substances.

Purified water is preferred over potable water as potable water contains volatile and non-volatile impurities. Additives such as chemical stabilizers, coloring agents, flavoring agents, and preservatives are added to enhance the stability and shelf life of syrups. Syrups are mainly stored in colorless or amber-colored (light resistance container) bottles. Syrups are divided into two categories, medicinal and flavored syrups.

Ex- **Dexorange syrup.**



## 02. MIXTURES:

Mixtures are liquid dosage forms in which medicaments are dissolved in a suitable vehicle. These are manufactured for oral use and are usually supplied in three different-sized bottles (60ml, 120ml, and 240ml). Bottles containing a single dose are termed as draught. Ingredients of mixtures involve, water, aromatic water, and medicated vehicle, which acts as a vehicle for mixtures, and chemical stabilizers, coloring agents, flavoring agents, and preservatives are added as adjuncts (additives).

Mixtures are not prepared to be stored for a longer period, as they are used to treat acute conditions like cough, diarrhea, constipation, and indigestion.

### **03. LINCTUSES:**

Linctuses are liquid oral doses, in form of syrups, developed to cure dry coughs and sore throats. Linctuses are viscous in comparison to syrups and contain medicaments such as demulcent, sedatives, and expectorants. Sucrose and glycerin are used as vehicles for linctuses. Additives, such as chemical stabilizers, coloring agents, flavoring agents, and preservatives are also used in the formation of linctuses. Codeine linctus, a syrup-like linctus, is widely used by pharmacists. They are supplied in air-tight glass bottles containing screw caps.



### **04. ELIXIRS:**

Elixirs are clear hydroalcoholic liquids intended for oral use. Ethyl alcohol, water, glycerin or propylene glycol, flavoring agents, preservatives, and coloring agents are the main ingredients of elixirs. Elixirs are of two types, medicated and flavored. Medicated elixirs are used to induce therapeutic effects, while flavored ones are used as flavors and vehicles.



## 05. GARGLES:

Gargles are defined as liquid dosage forms of medicaments, intended for external use. These aqueous solutions are used to treat throat infections. These are diluted with warm water before their use, as per the directions given by the medical practitioner. The medication needs to be kept in contact with the mucous membrane of the throat for a few seconds before they are thrown out of the mouth. Phenol is present in small concentrations for its anti-bacterial activity, whereas potassium chlorate is added in some gargles for its weak astringent effects. Phenol gargles and potassium gargles are widely recommended by physicians for mild-throat infections. Ex: **Betadine sore throat infection**



## 06. MOUTHWASHES:

Mouthwashes are aqueous solutions having a pleasant taste and odour to clean and deodorize the buccal cavity. They are often used for dental hygiene, but an antibacterial mouthwash can also be used to treat gum infections. The formulation of mouthwashes includes antibacterial agents, sweeteners, flavoring agents, alcohol, glycerine, and coloring agents. Ex- **Listerine**.



## 07. LOTIONS:

Lotions are defined as preparations meant for external use without friction. These are applied directly to the skin for cooling and protective purposes. They are also used for their anti-septic actions, for example, calamine lotions. Alcohol is also added in some formulations to enhance the cooling and soothing effect. e.g., **salicylic acid lotion**. **Colored fluted bottles** are used for dispensing lotions.



## 08. LINIMENTS:

Liniments are liquid or semi-solid dosage forms, which are intended for external use. These are applied on the skin surface to provide analgesic, rubefacient, anti-irritant, and soothing effects. They are generally applied with rubbing or friction. Liniments should not be applied to the broken skin to avoid excess irritation. Liniments are available as alcoholic, oily solutions or as emulsions. They are dispensed in colored fluted bottles to differentiate them from preparations meant for internal use. Ex- botanical liniments sore joints or analgesic activity.



## 09. EYE DROPS:

These are sterile dosage forms, which are intended for introduction in the eyes. Eye drops are used in small amounts and are administered on the surface of the eyes to treat mild infections. Eye drops contain saline in order to match the salinity of the eyes. Eye drops are commonly used to treat dry eyes or simple eye irritation, such as itching or redness. Ex- **Cipla Ciprofloxacin**, Patanjali Dristi.



## 10. EAR DROPS:

Ear drops are liquid dosage medications, used for short-term treatments of the ear. These drops are meant to be instilled into the ear with the help of a dropper to induce therapeutic effects. These topical medications are useful in treating mild infections, reducing inflammation, and clearing ear wax. Ex- **Otex ear drops**.



## 11. NASAL DROPS:

Nasal drops, as the name suggests, are aqueous solutions that are meant to be instilled in nose cavities with the help of a dropper. These drops are used to provide temporary relief from congestion caused in the nose by common cold, allergies, and hay fever.

Ex- **Otrivine Nasal spray**



## 12. DOUCHES:

A douche is a liquid dosage form of medication intended to be instilled in body cavities. The word, 'douche' is generally used for vaginal solutions, but these douches are also used to irrigate other body cavities, such as eyes, ears, and nasal cavities. Their significant role is to remove the foreign particles present in the body. Apart from cleansing properties, douches also possess antiseptic and astringent properties. They are directed to be diluted with warm water before their use. Ex- **SheNeed Feminine Intimate Douche-Extra Protection.**



## 13. THROAT-PAINTS:

Throat paints are viscous liquid formulations used to treat mouth and throat infections. Glycerin is used as a base and due to its viscous nature, the medication clings to the mucous membrane for a longer time. Glycerin also provides a sweet taste to the formulation. The most commonly used throat paints are boro glycerin, phenol glycerin, and tannic acid glycerin. Ex- **Betadine providone iodine**



## **BIPHASIC:**

### **1) Suspensions:**

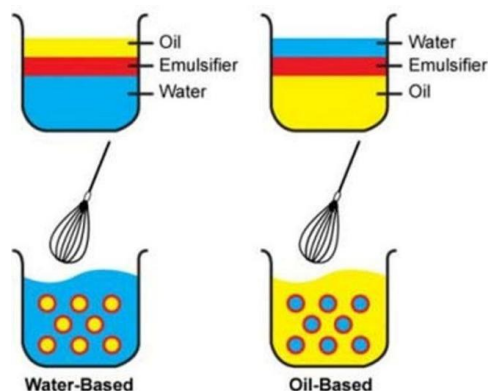
Suspensions are heterogeneous mixtures that are composed of finely divided solid particles, 0.5-5.0 in size, completely dispersed in a liquid or a semi-solid medium. The solid particles act as the dispersed phase, while the liquid phase act as the continuous phase. These mixtures can be easily separated through filtration. The particle size of the dispersed phase is kept smaller and fine, as it increases the rate of dissolution. These particles are apparent through the naked eye.

Suspensions are administered mainly through oral and parenteral routes. They are also used for external as well as ophthalmic use. Ophthalmic suspensions are rarely used as compared to eye drops. Additives added in the formulation of suspension are, flocculating agents, thickening agents (polysaccharides, inorganic agents), wetting agents, preservatives, and organoleptic additives. Suspending agents are also required in the formulation of suspensions to avoid aggregation of particles.

<b>Drug</b>	<b>Brand Name</b>	<b>Manufacturer</b>
Aurothioglucose	Solganl <sup>®</sup>	Schering
Betamethasone sodium phosphate and Betamethasone acetate	Celestor <sup>®</sup>	Schering
Penicillin G Procaine	Bicillin <sup>®</sup>	CR Wyeth
Medroxyprogesterone acetate	DepoMedrol <sup>®</sup>	Upjohn

## 2) Emulsions:

Emulsions are the heterogenous mixtures of two immiscible liquids, one of which is dispersed as minute globules into another. The globule size in emulsion varies from 0.25 to 25  $\mu\text{m}$ . The minute globules phase is the dispersed phase, and the other in which minute globules are dispersed is termed as the continuous phase. Generally, two immiscible liquids cannot be dispersed for an extended period, therefore, emulsifying agents are added to the mixture for the formation of a stable emulsion. Emulsions cannot be separated through filtration. Emulsions are of two types, oil in water (o/w) and water in oil (w/o)



Various excipients including emulsifying agents are added to form a stable emulsion:

- a) **Oil in water (o/w) type:** Oil in water emulsions is generally meant for internal use, where oil act as the dispersed phase and water is the continuous phase. Emulsifying agents used in the preparation of such emulsions are, gum, acacia, tragacanth, methylcellulose, saponins, synthetic substances, and soaps formed + from monovalent bases ( $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{NH}^{+4}$ ) are used.



- b) Water in oil (w/o) type:** Water in oil type emulsions is generally meant for external use, such as lotions and creams. In these types of emulsions, water is the dispersed phase and oil is the continuous phase. Emulsifying agents used for such emulsions are, wool fat, resins, beeswax, and soaps from divalent bases ( $Ca^{++}$ ,  $Mg^{++}$  and  $Zn^{++}$ ) are used.



### EXCIPIENTS INVOLVING IN LDF:

Along with the active drug substance, liquid dosage forms contain excipients. Vehicle/solvent, Co-solvents, Surfactants, Viscosity/suspending agents. Along with the active drug substance, liquid dosage forms contain excipients. These serve a variety of pharmaceutical purposes.

The amount of these excipients is usually greater than the amount of the drug substance since the drug substance comprises the bulk of the formulation. To ensure that liquid

dosage forms are made of chemically and physically compatible components, all of the excipients that are used in the preparation should be compatible with every other component.

These excipients are included in the formulation of liquid dosage forms for pharmaceuticals:

- a) Vehicle/solvent:** The vehicle is an important component of liquid pharmaceutical formulations, as it is a platform in which excipients and drugs are dissolved or dispersed. Hence, when bonds break, effective charges on ions decrease, which increases forces of attraction between solutes and solvents, which are ultimately greater than that between solutes and solvents;

There are several ways to formulate liquid dosage forms using water, polyhydric alcohols, hydro-alcoholic solutions, and buffers, as well as oils or organic oily bases. Examples of vessels include vegetable oils or mineral oils, organic oily bases, and emulsified bases. Physicochemical properties of the active pharmaceutical ingredient (API) determine what kind of vehicle is used and the formulation's intended use.

- Water can be used as solvents
- Alcohol can also be used as solvents
- Glycerin, USP (glycerol) can be used as solvents
- Propyl glycol is also an option for being used as solvents
- Polyethylene glycol is also a good vehicle for liquid dosage forms

- b) Co-solvents:** Essentially, co-solvents are designed to increase the water solubility of drugs that do not contain ionic groups and their water solubility

cannot be increased by adjusting the pH. It is possible for them to function because aqueous solutions and hydrophobic solutes have decreasing pressures. Hydrogen bond donors and acceptors present in co-solvents enable them to bind to water and be miscible with it. It is important to consider several factors when choosing a co-solvent, such as a solubility and stability of the drug substance in the vehicle, as well as the vehicle's toxic properties. Water-miscible organic liquids however tend to be toxic and are rarely found in pharmaceutical solutions.

Co-solvents have a specified range of acceptable concentrations that cannot be exceeded without causing biological damage. When co-solvents are used in parenteral formulations, they can generally cause embolism and necrosis at the injection site due to the uncontrolled precipitation of drug substances after dilution in aqueous or biological media. In addition to in vitro and in vivo models, in vitro and in vivo studies have been conducted to evaluate excipients and co-solvents. The low molecular weight PEGs, glycerol, and propylene glycol are examples of excipients used as cosolvents.

- c) **Surfactants:** Microparticles in aqueous media can be described as dynamic aggregates with defined polar (hydrophilic) and nonpolar (hydrophobic) regions, called surfactants or surface-active agents. It's possible for drugs that are non-polar to partition into soluble micelles. Surfactants vary considerably with the nature of the polar area, especially sodium dodecyl sulfate, cationic (trialkyl ammonium), zwitterionic (glycine and proteins), and non-ionic (polyethylene glycol).

Surfactants come in many different types in addition to anionic and non-ionic types. Non-ionic surfactants are generally considered to be more suitable in pharmaceutical applications due to their lower toxicity as well as because their shells exhibit stealth properties without absorbing through the reticular endothelial system (RES). Therefore, their lifetime in the bloodstream is prolonged.

A higher concentration of surfactants is generally necessary when enhancing drug solubility due to micelles, which cause solubilization. A critical micelle concentration is a concentration that causes microcapsules to form. A normal micelle will either be spherical, cylindrical, or lamellar in shape, depending on the surfactant concentration.

**d) Preservatives:** Formulations are protected from microbial contamination with preservatives, chemical compounds added to them. The best preservatives are those that do not contain harmful substances.

- a. Microorganisms of all types can be killed at low concentrations
- b. API, other excipients, and the container system soluble, non-sensitizing, and non-toxic
- c. that prevents the substance from oxidizing.

When liquid dosage forms are manufactured in an aqueous environment, there is a significant risk of contamination by microorganisms. As such, the use of preservatives as a method of prevention upon production and storage becomes necessary in such cases. There is a rising concern about the bioactivity and adverse effects of these excipients, so it would be ideal if no preservatives were

used in formulations. Unfortunately, most formulations must include preservatives to ensure no microbial growth occurs.

The majority of preservatives are acidic or non-acidic and act bacteriostatically rather than bactericidal. The acidic types include phenol, benzoic acid, boric acid, chlorocresol, 9-phenyl phenol, alkyl esters of para hydroxybenzoic acid, and sorbic acid, as well as their salts. In addition to chlorobutanol and benzyl alcohol, beta-phenylethyl alcohol can also be used as preservatives.

The need for preservatives is generally not recommended at alkaline pH values since it is believed that microbial growth will be minimal. The need for preservatives is generally not recommended at alkaline pH values since it is believed that microbial growth will be minimal. Additionally, several parameters should be evaluated during the formulation development process in connection with the API, other excipients, and container system, as well as the antimicrobial potential of the excipient.

- e) **Viscosity/suspending agents:** Excipients such as viscosity modifiers and suspending agents, which act as energy barriers and minimize particle attachment and aggregation are known as viscosity modifiers and suspending agents, respectively. When making a pharmaceutical suspension, selecting a suitable suspending agent is one of the most critical steps. Choosing a suspension agent, for instance, involves taking into account several factors, such as rheological properties, suspension ability, pH stability, chemical compatibility with the drug, and hydration time.

In addition to polymers synthesized (such as carbomers, polyvinyl pyrrolidone, polyvinyl alcohol, and poloxamers), other compounds are reported (such as colloidal silicon dioxide and silicates). Combining these excipients is common in many cases.

### **Solubility Enhancer Technique:**

As the pharmaceutical industry trends show, many manufacturers of drugs are creating materials with higher degrees of lipophilicity, molecular weight, and complexity of physical form, and lower aqueous solubility. Due to these characteristics, poorly soluble drugs are often produced, which necessitates the addition of excipients or processes that improve the dissolution and bioavailability of the drug.

To achieve desired pharmacological responses in the systemic circulation, solubility is one of the most important parameters, which gives rise to homogeneous (anticipated) reactions between a solute and solvent. In both the generic drug development as well as formulation development of new chemical entities, low aqueous solubility is the major obstacle.

The majority of new chemical entities (NCEs) developed within the pharmaceutical industry cannot be dissolved in water. The challenge of ensuring water solubility for formulations is enormous. An absorbed drug must be present in the solution at the absorption site to be absorbed. The solubility of poorly soluble drugs can be increased through a variety of methods, including modifying the physical and chemical properties and use of particle size reduction, crystal engineering, salt development, solid dispersion, and surfactants.

An oral formulation's oral bioavailability is greatly influenced by the solubility of the drug, which determines its liberation and absorption. Drug solubility directly affects



how fast it dissolves. Drugs in the new generation are low in water solubility; therefore, they are difficult to formulate into delivery systems for drug administration. In the formulation phase of pharmaceutical product development research, therefore, solubility enhancement is an essential element of poorly water-soluble drugs. This method is uniquely suitable for improving dissolution characteristics, oral bioavailability, and dissolution characteristics of poorly water-soluble drugs.

### **Particle size reduction**

As one of the most widely used and crucial unit operations within the pharmaceutical manufacturing industry, size reduction is a highly valued unit operation. Reducing the size of large masses of solids into smaller masses, coarse particles, or fine particles is known as size reduction. Comminution, diminution, or pulverization are also known as processes for reducing size. In most cases, it is a hardness that determines the characteristics of size reduction because nearly all size reduction methods create new surface areas, and increasing that area requires adding pressure proportional to the strength of the bonds holding the feed particles together. Many pharmaceutical applications require size reduction. Besides simplifying handling and increasing surface area per unit volume, size reduction is important to separate components that are entrapped in the unit volume.

**Crystal engineering:** Drug molecule properties and structures are altered through crystal engineering by utilizing intermolecular interactions. The knowledge of this kind has been applied by pharmaceutical scientists to modify the structure of crystalline drugs to remedy the problems of a large number of new drugs developed which suffer from low solubility and, consequently, poor bioavailability, thus limiting their application.

**Salt formation:** Most acidic and basic drugs dissolve more readily when they are dissolved in salt, which is the most common and effective method for increasing solubility and dissolution rates. Increasing the solubility of drugs may be accomplished through the formation of salts. Besides its effectiveness, this technique offers many other benefits.

The method is also fairly affordable. Salt is produced by the protonation of active pharmaceutical ingredients or by protons functional group structures that can be ionizable.

**Solid dispersion:** A solid dispersion approach can greatly enhance the solubility of an aqueous solution. Dispersions or suspensions are solid products that have at least two components, such as a hydrophilic matrix and a hydrophobic drug. Both crystallized and amorphous matrixes can be used.

**Use of surfactant:** Lipophilic drugs are better dispersed in aqueous media when surfactants are added. In addition, they stabilize liquid medicaments. Additionally, surfactants improve wetting and increase the rate at which solids are disintegrated into smaller particles.

# **UNIT : 3**

# Chapter: 01

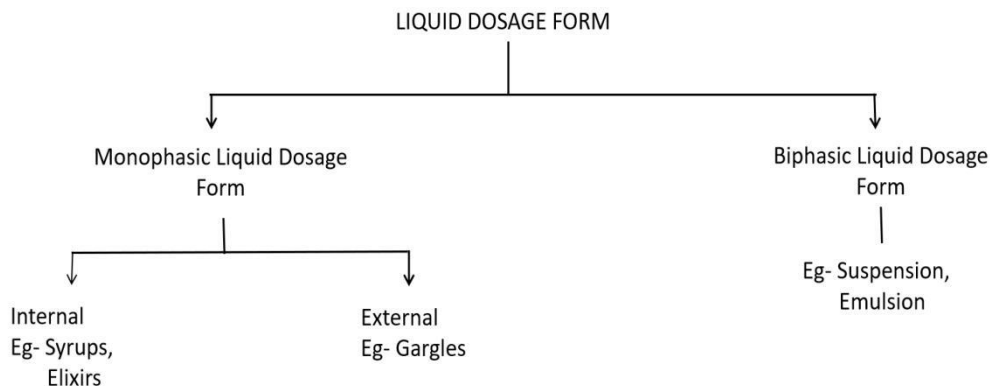
## MONOPHASIC LIQUID DOSAGE FORM

Pharmaceutical dosage forms are often categorised as solid, liquid, or gas. Monophasic and biphasic liquid dosage forms are the most common types of liquid dosage forms. The classification of liquids dosage form is mentioned in the given below description.

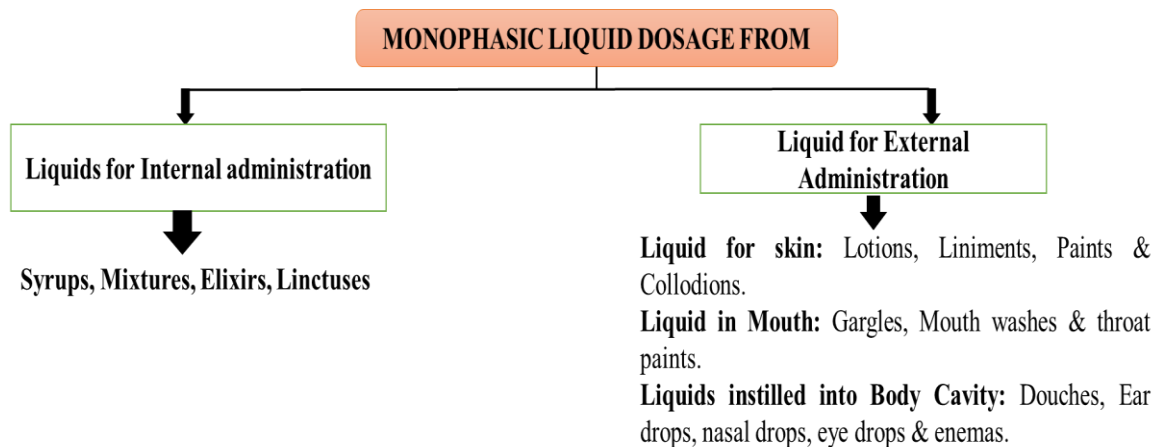
Liquid dosage forms are primarily divided into two primary groups, as defined below:

**01. MONOPHASIC LIQUIDS DOSAGE FORM:** *A liquid preparation containing two or more components in a single-phase system is known as a monophasic liquid dosage form. Monophasic is a single-phase system for liquid dosage forms that includes the solution's solute and solvent.*

**02. BIPHASIC LIQUID DOSAGE FORM:** These dosage forms typically have two distinct phases, like emulsions and suspension. Which are depicted in the figure below (Figure 01):



**CLASSIFICATION:** The monophasic liquid dosage forms are mainly classified which represented as below section:



### **Different Classification of Monophasic Dosage Form**

**In the** above description the monophasic liquid dosage forms are classified into the two-category including *internally applied and externally applied*.

### **LIQUIDS APPLIED FOR INTERNAL ADMINISTRATION**

It mainly includes as syrups, elixirs and mixtures other more, such as described as following;

#### **01. SYRUPS:**

**DEFINITION:** “Synthetic sucrose syrups are concentrated solutions of sucrose in water that are sweet and viscous.

Sucrose is 66.7% by weight when mixed with water (100 ml) in simple syrup I.P.”

Syrups are concentrated aqueous solutions of sucrose or other sugars that are sweet and viscous. Medicated syrups are syrups that contain therapeutic or medicinal agents.

While syrups with flavours but no medicinal agents are flavouring or flavoured or non-medicated syrups.

**CLASSIFICATION OF SYRUPS:** syrups are mainly classified into the following classes such as:

**01. Simple Syrup** – These syrups are made up of simple solutions or are admixture of solution. 85% of the syrup is sucrose (w/v). The syrup is prepared in 100 ml of purified water.

**Example** of simple syrups (I.P.) are ginger syrup, orange syrup and lemon syrup.

Simple Syrup I.P.	
Sucrose	667gm
Purified water, sufficient to produce	1000gm

**02. Medicated Syrup** - A medicinal or therapeutic syrup that contains active ingredients. Example – cough syrup and chlorpheniramine maleate syrup.

**03. Flavored Syrup** - Syrup flavored with flavorings, but not medicinal substances. Example – mango syrup, cherry syrup, tolu balsam syrup etc.

The formulae for tolu syrup according **I.P.** below;

Tolu Balsam	12.5gm
Sucrose	660.0gm
Purified water sufficient to produce	1000.0gm

**Tolu Balsam Syrup I.P.**

**PREPARATION:** There are lots of specific methods which are adopted for the preparation of any depends on the physicochemical properties of the substance to be

used in the formulation. Physical characteristics and chemical composition of the substance determine which method to use.

**01. Hot process:** Active constituents that are neither volatile nor heat-labile are subjected to this method.

**Procedure:** In a beaker, we weigh out the sucrose. It is combined with pure water. The bath is heated in water (less than 70°C) until a solution is obtained. The impurities are then removed with a filter. The product volume is made to the standard - q.s. Excessive heat may be the cause of sucrose inversion. Syrup prepared by this method include syrup I.P. acacia syrup NF, Cocoa syrup NF and tolu syrup I.P. etc.

**02. Percolation:** Percolator is filled with sucrose. As water passes through sucrose, the sucrose dissolves. A thick cotton cloth is placed at the front of the percolator. Cotton governs percolation rate, and dissolution rate governs dissolution rate. When complete dissolution has occurred, q.s. is made up of the residual solution.

**03. Agitation without heat:** Components with adjustable heat lability. All ingredients, including sucrose, are accurately weighed. The ingredients are dissolved in pure water. The syrup should be stored in a bottle twice as large as the syrup followed by constant stirring. Approximately equal volumes of syrup are prepared. An example of syrups prepared by this method included *ferrous sulphate syrup U.S.P.*

**04. Addition of medicating or Flavouring Liquid to Syrup:** This method is used for preparing syrups containing fluids extracts, tinctures, or other liquids. These liquids contain alcohol to facilitate the dissolution or resinous and oleo resinous substances; but when added to the syrup, these liquids may precipitate the

substances soluble in alcohols as they get diluted with water. Alcohol used as a preservative in these syrups.

**Example:** Citric acid syrup and **Codeine phosphate syrups I.P., B.P.C.**

Codeine phosphate	5gm
Chloroform spirit	25ml
Purified water	15ml
Syrups (q.s.)	1000ml

**Procedure:** This type of syrups is mainly used as an analgesic and anti-tussive. It is prepared by dissolving codeine phosphate (0.46-0.54% w/v) in purified water, followed by addition of chloroform spirit (as preservative). The final volume is made up using syrups. The syrup be stored in a loosely corked bottle in a moderately cool place and protected from the light.

**Differences Between IP And USP Syrups:** Some of difference as follows:

**List of Difference in simple syrup I.P. and U.S.P.**

Basis of Difference	Simple Syrup I.P.	Simple Syrup U.S.P.
<b>Formulation</b>	66.7%w/w sucrose solution in purified water.	66.74%w/w or 85% w/v sucrose solution in purified water.
<b>Preparation methods</b>	Mainly prepared by hot process.	Mainly of prepared by cold process
<b>Stability</b>	More stable	Less stable
<b>Ingredients</b>	Invert sugar	Sucrose
<b>Sweetness</b>	Sweeter	Less sweet



## 02. ELIXERS

Elixirs are mainly defined as a clear, sweetened, aromatic, hydroalcoholic liquids intended for oral use. They provide a palatable means of administering potent or nauseous drugs. Elixirs are less sweet and less viscous than syrups and may contain less or no sucrose.

In simple language elixirs are clear preparation and drugs in liquid form to be administered orally.

The elixirs may also include flavoring and coloring agents for flavoring and coloring purposes. In elixirs, preservatives are not needed because the alcohol content contains enough preservatives.

### DEFINITION

Generally speaking, liquid elixirs are considered clear, aromatic, sweetened, hydroalcoholic beverages that are designed to be consumed orally. Their sweetness and viscosity are less than syrups as they contain less or no sucrose.

Elixirs have greater stability than syrups, so are preferred over syrups. Elixirs contain between 4 and 40% alcohol (ethanol).

**CLASSIFICATION:** The elixirs are generally, classified into the two major categories such as:

01. **Non-medicated Elixirs-** The flavoring agent is non-medicated and does not contain any medicament. Example; Aromatic elixir U.S.P. and compound benzaldehyde elixirs NF etc.
02. **Medicated Elixirs-** Medicine containing antibiotics, antihistamines, sedatives, and other potent drugs. Example; Chlorphenhydramine hydrochloride elixirs U.S.P. and Terpin hydrate elixirs etc.

## METHOD OF PREPARATION

The preparation methods for elixirs are the **simple dissolution method** involving the following steps;

01. In this method, either an admixture of two or more liquids components is used or the components are dissolved in agitation.
02. **Always the aqueous solution** is added to the alcoholic solution for maintaining the ideal alcoholic strength and preventing the separation of alcohol-soluble ingredients.
03. The desired volume is adjusted using the vehicle or solvent specified in the formulation.
04. In case, the elixirs preparation is kept aside for some time so that the hydro-alcoholic solvents saturate resulting in the cluster of globules.
05. Filtration facilitates the removal of these globules.
06. To absorb the excess oil and removing from the elixir's solution, up to 3% of talc is used.
07. Filtration yields a bright and clear product.

**Example:** Aromatic elixir NF, phenobarbital elixirs etc.

## LIQUIDS APPLIED FOR EXTERNAL ADMINISTRATION

### 01. GARGLES

Gargles contain potassium chloride, which helps to restore the tone of a relaxed throat due to its mild astringent impact. It mainly increased the flow of the saliva for relieving the dryness of throat.

In terms of formulation, gargles differ from mouthwashes since they include more therapeutically effective ingredients and must be diluted before use.

When gargles are employed, the mucous membrane of the throat is permitted to remain in close contact with them.

**DEFINITION:**

“These are aqueous hydroalcoholic solutions used to treat or prevent throat infections and contain *phenol & thymol, potassium chlorate* which are known as ***gargles***.” They are typically used to treat sore throat infections and should have a deodorant effect.

**METHOD OF PREPARATION**

Gargles are prepared by adding amaranth solution (1% w/v in chloroform water) to a comparatively less quantity of water and then mix phenol glycerin (16% w/w phenol & 84% w/w glycerin) to it. Then stir the solution to make up to the volume with purified water. Dilute with an equal quantity of water before use.

**Container:** Strong damp-proof and water-proof with a leak-proof plastic cap.

**Labeling:** The label should clearly indicate:

1. Proper Prescription for diluting the Gargle.
2. Secondary label- "FOR EXTERNAL USE ONLY"
3. Auxiliary label- "NOT TO BE SWALLOWED"

**Direction:** Dilute 1-20 ml or as per directions by the physician with water, gargle for 30 seconds, repeat 3 to 4 times a day. Dispensed in concentrated form with warm water. Make contact with the mucous membrane of the throat and let it sit there for few moments.

**Warning:** Read the instructions on the label carefully. Avoid contact with eyes, nose etc.

**Storage:** Store at room temperature Keep out of the reach of children. Store away from direct sunlight, heat and moisture.

**Ex:** Potassium chlorate, Alum Gargles, Aspirin Gargles and phenol gargle etc.

### **Method of Preparation of Phenol Gargle:**

#### **Formula**

Rx,

1. Phenol Glycerin – 5 ml
2. Amaranth solution – 1 ml
3. Purified water - q.s. To 100 ml

#### **02. MOUTHWASH:**

“Medicated liquid with pleasant taste and odor used to clean and deodorize the buccal cavity, contain antibacterial agents, glycerol, and sweetening agent, flavoring agent, coloring agent and astringent.”

Different types of mouthwashes, such as antiseptic and anti-plaque mouthwashes, anti-cavity mouth rinse, etc. are available. The antiseptic mouthwashes remove the bacterial plaques which may give rise to foul breath, caries and gingivitis, while the latter adds fluoride to provide protection against tooth decay.

#### **DEFINITION:**

“In order to deodorise and clean the buccal cavity and maintain oral hygiene, mouthwashes, sometimes referred to as mouth rinse, use hydro-alcoholic solutions.”

**CLASSIFICATION:** They are generally, categorized in the two types:

01. **Cosmetic/Non-Medicated Mouthwashes:** They are almost all the commercial over-the-counter mouthwashes. They typically include essential oils like thymol, eugenol, and others. Cosmetic mouthwashes additionally lessen bad breath (Bad breath).
02. **Therapeutic/Medicated Mouthwashes:** They primarily aid in the prevention and treatment of specific oral health conditions, such as the prescription of fluoride-containing anti-plaque mouthwashes for the treatment of dental plaque. The mouthwashes containing the fluoride prevent tooth decay and also provide strength to the teeth.

**Example;**

1. Analgesics such as lidocaine hydrochloride and antiseptics like phenolic mouthwash.
2. Bactericidal such as Fluoride Mouthwash and Anticavity such as Fluoride Rinse.

**METHODS OF PREPARATIONS OF MOUTHWASH:**

The preparation and formulae for two straightforward mouthwashes are provided in the section below, essentially in the form of the two formulae. The following guidelines are provided for making mouthwashes:

**Formula I**

Formula I	
Boric acid	1.5
Thymol	0.1
Eucalyptol	0.5
Methyl salicylate	0.1
Oil of thyme	0.03
Menthol	0.1
Alcohol	30.0
water	67.67

**Procedure:** Boric acid is dissolved in 60% of water and the other ingredients are dissolved in 60% of alcohol separately. The resultant aqueous solution is added to the resultant alcoholic solution. The combination contains 2% pure talc, which is added, combined with the remaining water, and alcohol.

## Formula II

Formula II	
<b>Benzoic Acid</b>	<b>1.0</b>
<b>Boric acid</b>	<b>2.0</b>
<b>Alcohol</b>	<b>8.5</b>
<b>Eucalyptol</b>	<b>0.05</b>
<b>Oil of thyme</b>	<b>0.1</b>
<b>Oil of wintergreen</b>	<b>0.3</b>
<b>Water</b>	<b>88.0</b>
<b>Caramel colouring</b>	<b>0.05</b>
	<b>Total: 100.0</b>

**Procedure:** Boric acid is dissolved in water by boiling. The obtained solution is diluted with the remaining water and allowed to cool. Benzoic acid is dissolved in sufficient quantity of alcohol and oils in the remaining alcohol. These solutions are mixed into the aqueous solution quickly, and caramel colouring is added. The treatment has been filtered and refrigerated.

Other examples of mouthwashes: It mainly included Benzydamine hydrochloride mouthwashes, cetylpyridium chloride mouthwashes, sodium benzoate mouthwashes, povidone-iodine containing mouthwashes etc.

**Container:** Clear fluted plastic bottles with a narrow neck with a leak-proof plastic cap.

**Storage:** Stored at room temperature away from children and not to be exposed to sunlight.

**Labeling:** The label should clearly indicate: Proper prescription for diluting the mouthwash use. Secondary label- “FOR EXTERNAL USE ONLY” Auxiliary label - “NOT TO BE SWALLOWED IN LARGE AMOUNT”

**Directions:** Brush the teeth before use. Measure the amount to use and add water to it. Use it for 30 seconds. Avoid eating, smoking, rinsing etc. for at least 30 minutes.

### **03. THROAT PAINT**

Throat paints are viscous and non-aqueous solution applied on the mucous membrane of the throat. They exert local action and are used for treating ulcerative stomatitis, pharyngitis and tonsillitis.

When applied to the skin, the solvent evaporates, leaving a drug-resinous coating that sticks to the skin intact.

#### **DEFINITION:**

“Solutions that contain multiple active ingredients are used to treat mucosa throat or mouth. These are vicious because the high content of glycerin, which is thick in nature sticks to the surface, affects the site, and prolongs the action.”

Paints are collodion base and viscous solution which are applied over the skin or oral mucosa.

## **PREPARATION OF THROAT PAINT:**

- Compound Iodine Paint (Mandl's Paint) - Used for pharyngitis, laryngitis and sore throat.
- Crystal Violet Paint - Used for Thrush.
- Phenol Glycerin - Used for Ulcerative Stomatitis as it has analgesic effects.
- Tannic Acid Glycerin - helps in the sore throat as it has astringent actions

### **Compound Iodine Paint (Mandl's Paint):**

Needed experiments are as follows:

Potassium Iodide - 25g

Iodine - 12.5g

Alcohol (90% v/v) - 40ml

Water - 25ml

Peppermint Oil - 4ml

Glycerol - up to 1000ml

**METHOD OF PREPARATION:** Dissolved potassium iodide in water. Add iodine to concentrated potassium iodide solution to form  $KI_3$ . Dissolve peppermint oil in alcohol (90% v/v). Iodine solution is added to alcohol solution. The necessary amount of glycerin should be added to it.

**Packaging:** Glass bottles with a wide opening, fluted design, and leak-proof screw caps ought to be utilized. Waxed card liners should be placed on caps to protect the material



from an iodine attack. Bottles should be ambered coloured. As preservatives, use sodium citrate or sodium acetate.

**Storage:** These paints is stored in a cool and dark place.

**Directions:**

Avoid food and water both before and after applying, should be applied by soft brush or cotton swabs.

**Labeling:**

Only for local applications.

Store in a cool place.

Shake to mix the solution inside the bottle.

Avoid swallowing in large amounts.

**Example:** Here are a few more examples of throat paints to consider:

01. Compound iodine paints.
02. Compound podophyllin paints.
03. Crystal violet paints.
04. Phenol glycerine paint.
05. Tannic acid glycerine paint.

#### **04. EAR DROPS**

Production of liquid medication that treats infections of the external ear canal or loosens ear wax, when there is excessive cerumen (ear wax), or when there is an ear infection, inflammation, or pain. Ear preparations are usually applied in minute amounts by drops into the ear canal. It is an opening to the ear, that is enclosed by the ear lobe. Starting of ear is at the auricle and ending is at the tympanic membrane.

In the external auditory canal, the cerumen contains sweat and sebaceous gland secretions. The secretions get sticky semisolid when allowed to dry, hold shed fallen hairs, dust, epithelial cells and other foreign objects that travel into the ear canal. Pain, itching and hearing loss may be caused by excessive cerumen in the ear. If earwax is not regularly removed, it can become impacted and become harder and more painful to remove.

To facilitate the removal, vegetable oil, light mineral oil, and hydrogen peroxide were commonly used as softeners. Synthetic surfactant solutions have allowed them in effectively remove of earwax. A typical cerumen removal method involves placing an eardrop or a cotton plug in the ear canal while the head is tilted at an angle of 45 °, followed by a lukewarm water flushing using a rubber syringe.

Rarely, treatments are prescribed for the pruritus and inflammation associated with ear infections and occurring allergic symptoms, such as liquid dexamethasone sodium phosphate and hydrocortisone. Physicians may prefer and prescribe corticosteroids as ointments as eye tubes. As an alternative to steroids and antibiotics for treating otitis externa, boric acid 2.75% in isopropyl alcohol is also preferred. Both are 2% acetic acid in aluminum acetate solution.

Along with the drugs, the vehicles also contribute to reacidifying the ear canal. Maintaining the ear canal dry reduce the growth of microorganisms, usually *P. aeruginosa*.

In-house solutions containing acetic acid 2% to 2.5%, as needed, with rubbing alcohol (70% ethanol or isopropyl alcohol), propylene glycol, or anhydrous glycerin.

Ear drops are dispensed in coloured fluted bottles (eye dropper bottles can also be used) with a dropper and plastic screw-cap closure. In addition to any special direction, ear drops should be labelled "For External Use Only".

Some of the commercially available products are formulated in a manner that they serve both as eye and ear drops.

## **05. NASAL DROPS**

Nasal drops are aqueous or oily solutions that are instilled into the nostrils with the help of a dropper. This solution contains antiseptics, analgesics, and a vasoconstrictor. Medicine droppers are used to insert nasal drops into the nostrils with medicated liquid formulations.

Some examples of these are nasal steroids, nasal lubricants, antihistamines, decongestants, as well as antibiotics, which treat symptoms of hay fever, congestion, and infection. The preparations available for nasal irrigation include sprays, drops, ointments, creams, and creams. Nasal antihistamines and decongestants

A nasal antihistamine or decongestant is a medicine that contains an antihistamine or decongestant in a device designed to be used under the nose.

Nasal drops are packaged in coloured fluted glass bottles with a plastic screw cap and a glass dropper tube with a rubber teat. They must also be available in a plastic squeeze bottle with a plastic cap and a dropper.

**DEFINITION:** Nasal drops are drugs in solution that are instilled into the nose using a dropper or a plastic squeeze bottle, known as *nasal drops*.

Neither nasal lubricants nor irrigations are in the form of fluids. Products like these are used to treat irritating or drying nasal passages, such as those associated with hay fever, colds, and other conditions.

**PREPARATION:**

The ingredients which are required to prepare the nasal drops are given bottle table form such as:

Ingredients Types	Example Included
Vehicle	Purified water.
For tonicity adjustment	Sodium chloride, dextrose
Buffer	Phosphate buffer (pH-6.5)
preservatives	Chlorobutanol, benzalkonium chloride and aromatic alcohols.

**Storage:** The nasal drops are store at cool place is required for the storing it.

**Example:**

- **Ephedrine hydrochloride nasal drops**
- **Phenylephrine hydrochloride nasal drops**

### **Ephedrine Hydrochloride Nasal Drops:**

**Rx,**

Ephedrine Hydrochloride                      0.5gm

Chlorbutol    0.5gm

Sodium chloride                                      0.5gm

**Procedure:** All of the ingredients are dissolved in purified water, filtered, and packaged in a clear bottle. The ephedrine hydrochloride nasal drops should be kept in a tightly sealed vial with a dropper. Ephedrine hydrochloride is used as an anti-asthmatic and nasal decongestant in this preparation. As a preservative and antiseptic, chlorbutol is added. Sodium chloride is used to adjust the tonicity of the preparation. As a vehicle, purified water is used.

### **06. NASAL STEROIDS**

Nasal steroids (also known as nasal corticosteroids) are medications that contain glucocorticoids such as beclomethasone, budesonide, fluticasone, or triamcinolone in nasal preparations. Corticosteroids, among other things, can reduce inflammation, particularly allergy-induced inflammation. Symptoms such as nasal congestion, blocked nasal passages, mucus production, and swelling in the nasal passage are improved by nasal steroids used in conditions such as hay fever.

Nasal corticosteroids have been shown to reduce pollen, animal dander, and dust mite sensitivities.

## 07. ENEMAS

Most commonly, enemas are used to cleanse the bowels before a medical exam or to treat constipation (**soapsuds enemas**). Enemas can also be used lower gastrointestinal as a vehicle for food, water and medicine for treating diarrhoea.

Certain alternative health therapies include enemas. They also aid in the administration of some medicinal or recreational medications by cleaning the bowels and removing any food particles or constipation issues.

To clean the rectum, empty the bowels, or medicate, an enema is injected into the abdominal region as a liquid. Rectal injection is used to administer evacuation enemas, which empty the colon. Depending on the severity of the obstruction, laxatives and enemas may need to be administered.

### DEFINITION:

Enemas, commonly referred to as clysters, are liquid treatments for constipation that are injected into the lower abdomen via the rectum.

**TYPES:** There are mainly many types of preparations in enema which are stated below:

- 01. Cleansing enema:** A cleansing enema is water-based and held for a short time in the rectum to flush out the colon. Upon injection, the drug is kept for a few minutes as your body removes the fluid along with loose materials in your intestinal tract. Here are a few commonly used cleansings enemas.
- 02. Oil-retention enemas:** These enemas used for the lubricating the rectum and colon. The faeces become soft by absorbing the oil of these enemas, thus, can be easily passed.

For the best result patients are recommended to retain the enemas for 30-560 min. the amount of solution instilled into adults is 150-200ml and children is 75-100ml.

**03. Medicated Enema:** These enemas exert local action on the rectal mucosa.

For example, a neomycin (antibiotic)-containing enema reduces colon bacteria before bowel surgery. This enema has a systemic effect as well.

*Sodium polystyrene sulphonate* containing enema treat patients with high level of potassium in their serum.

## 08. LINIMENTS

Liquid or semisolid preparations meant to be applied to unbroken skin *by friction*, and placed on the affected part. Soap solutions or emulsions can be used. The oil or soap base makes application and massage easier. Liniments typically contain anti-irritants such as methyl salicylate or turpentine. Alcohol has a rubefacient effect and aids in the absorption of medications. Camphor produces local action. The contents, such as aconite and belladonna, act as pain-relieving liniments. Liniments are no longer considered official in IP.

The procedure of preparation for liniments is determined by their individual ingredients. Thus, they are prepared by methods used for preparing solutions, suspensions or emulsions, as the case may be. Liniments should be stored in well-closed containers, and in a cool place.

Liniments are not to be applied to skin areas that are bruised or broken. Liniments should be dispensed in fluted bottles carrying a 'For External Use Only' label. In addition, a 'Shake Well' label is also necessary if the liniment is an emulsion or a suspension.

## **PREPARATIONS:** Examples of some of the formulations

### **1. Camphor Liniment**

*Other names* - Camphorated oil

*Formula* -

Camphor - 200gm

Arachis oil - 800 gm

Camphor has a 20%w/w content and is dissolved in arachis oil in a closed and dry vessel. Dissolution is time-consuming because the vessel is in warm (not hot) water with constant agitation.

***Storage*** - In well-closed containers in a cool place.

***Uses*** - Counter-irritation

### **2. Turpentine Liniment -**

*Formula* -

<b>Formula</b>	<b>Quantity</b>
Soft Soap	75 gm
Turpentine oil	650 ml
Camphor	50 gm
Purified Water	225 ml

Turpentine oil has a 65% v/v content. By triturating the camphor solution into the soap mixture, a thick creamy emulsion is formed. To make up the volume, purified water is added.

***Uses*** - Rubefacient and Counter- irritant.



### 3. Soap Liniment

#### *Ingredients-*

Soft soap (8% w/v)

Camphor

Lemongrass oil

Purified Water

Alcohol (90%) (61 to 65% v/v)

In alcohol, soft soap, camphor and lemon grass oil is dissolved. Alcohol and purified water are added to make up the volume, set it aside for a week and filter.

***Storage:*** In well- closed container

***Use:*** Detergent and mild local irritants

## 09. LOTIONS

### **Definition and Introduction**

Lotions are dilute aqueous suspensions or solution meant for external application to the body. That can be applied to the skin or hair or eyes *without friction*. Alcohol as an evaporating vehicle can be used when a cooling effect is desired on application to the skin. The majority of lotions are perfumed. There are soluble tablets on the market that can be dissolved in a specific amount of water to provide the required strength to lotions. Fluidity of lotions must permit rapid and uniform spreading over a large surface area. Lotions are no longer office in IP.

Lotions can be made by triturating the ingredients to form a smooth paste and then carefully diluting them with liquid phase as needed. Lotions should be dispensed in bottles, which can be distinguished by touch from those used for internal use

e.g., fluted bottles. The bottles should bear the label 'For External Use Only', and 'Shake Well', if the product is a suspension.

## METHOD OF PREPARATION

The preparation majorly included as example - **Calamine lotion**, another name is – **Lotion calamine**.

Formula	Quantity
Calamine	80g
Zinc oxide	80g
Glycerine	20ml
Bentonite magma	20ml
Calcium hydroxide solution q.s.	q.s. to make 1000ml

The bentonite magma should be diluted with calcium hydroxide solution in an equal volume. Using about 100mL of dilute magma, thoroughly mix the powders with the glycerin, tribulation until a smooth, uniform paste is obtained. It is not possible to completely define the powders. Add enough calcium hydroxide solution to make 1000ml of solution.

Although Calamine Lotion is not sterile, it must be free of microbial contamination for external use, as specified in IP 2014.

**Uses** - The use of this product is to astringent and protect.

**Note** - Before dispensing lotions, shake them thoroughly. Adding more bentonite magma to the mixture will give it a viscous consistency, but not more than 400ml.

# **Chapter: 02**

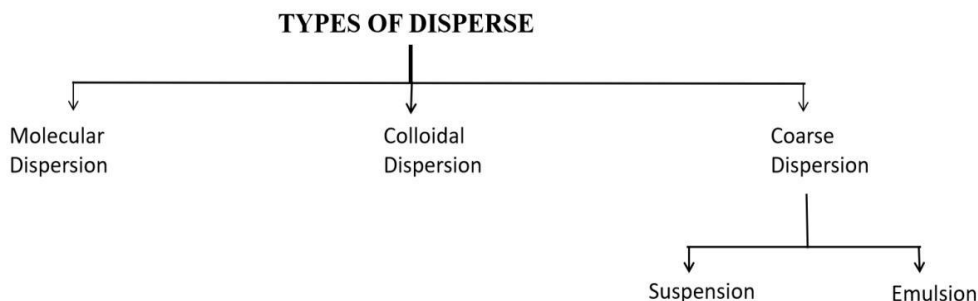
## **BIPHASIC LIQUIDS**

Generally liquid preparation having the two phases are known as Biphasic liquids. To dissolve numerous insoluble solids and liquid medications that are either insoluble in or immiscible with water, these preparations fundamentally need a dispersed phase and a dispersion medium.

Biphasic liquids tend to be stiffer and more complex than the previous parameter.

### **COARSE DISPERSION: “EMULSIONS”**

The coarse emulsions have large-sized globules, whereas fine emulsions have mean diameter below 5 $\mu$ m. The micro-emulsions are milky and clear, with globules as small as 10 nm in diameter. The dispersion system is majorly classified into the two portion one is suspension another is emulsions. This can show is the given below



### **Type of dispersion system**

There are mainly of two types of biphasic liquid dosage forms; such as:

- 01. Emulsion:** These are biphasic liquid preparations of two immiscible liquids, with one liquid dispersed in the other liquid (continuous phase) in the form of globules.
- 02. Suspension:** These are biphasic liquid preparation in which the finely divided drug particle (with minimum solubility) is uniformly dispersed throughout the vehicle.

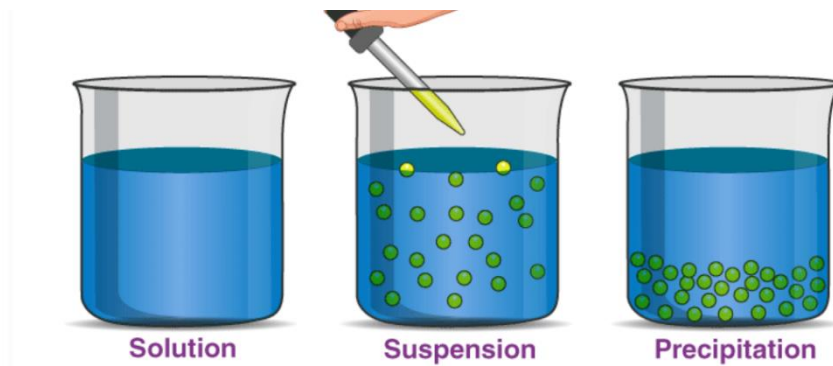
## **Chapter: 02 (A)**

### **Suspension**

Suspension is biphasic liquid preparation containing finely divided 0.5-5.0-micron solid drug particles dispersed or suspended throughout a liquid or semi-liquid vehicle. The suspension is intended for oral administration, external application or parenteral use.

***Definition:*** “A suspension is defined as a heterogeneous mixture in which the solid particles are spread throughout the liquid without dissolving in it.”

A suspension is defined as a heterogeneous mixture of particles with a diameter greater than 1000 nm such that the particles are visible to naked eyes. In this type of mixture, all the components are completely mixed and all the particles can be seen under a microscope. A suspension is a heterogeneous mixture containing solid particles that are sufficiently large for sedimentation.



**Figure. 01 The difference between the solution, suspension and precipitation**

If we take a glass full of water and mix mud in it, it will form a heterogeneous mixture. We can easily identify the components of these mixtures. After some time, we will observe that particles of mud settle down due to gravity. The particles in suspension are larger than the particles in a solution.

The term "*Disperse System*" refers to a system in which one substance (The Dispersed Phase) is distributed, in discrete units, throughout a second substance (the continuous Phase).

**IDEAL PROPERTIES OF SUSPENSION:** An ideal suspension should possess the following properties such as:

- A suspension is a heterogeneous mixture.
- The size of solute particles in a suspension is quite large.
- The particles of a suspension can be seen easily.
- The particles of a suspension do not pass through a filter paper. So, a suspension can be separated by filtration.
- The suspension is unstable. The particles of a suspension settle down after some time.

- A suspension scatters a beam of light passing through it because of its large particle size.

**Examples of Suspension;** Some common examples of suspension are;

1. Muddy water.
2. Milk of magnesia.
3. Sand particles suspended in water and Flour in water.
4. Slaked lime for whitewashing.
5. Paints in which dyes are suspended in turpentine oil.

### **SOLUTION:**

A solution is a homogeneous mixture of substances. For example, when salt dissolves in water, a homogeneous mixture, or solution, forms. The component of a mixture that is present in the greatest quantity or that determines the state of matter of the solution is called the solvent and the other component is called the solute.

### **COLLOID:**

A Colloid is an intermediate between solution and suspension. It has particles with sizes between 2 and 1000 nanometers. A colloid is easily visible to the naked eye. Colloids can be distinguished from solutions using the Tyndall effect. Tyndall effect is defined as the scattering of light (light beam) through a colloidal solution. The particles are termed as colloidal particles and the mixture formed is known as colloidal dispersion. Liquid, solid and gases all mix together to form a colloidal dispersion.

The different types of colloidal solution are:

- **Aerosols:** Solid or liquid mixed with gas; Example: fog (liquid in gas)
- **Sols:** Solid mixed with liquid; Example: Paint
- **Emulsion:** Liquid with liquid; Example: oil and water Difference between Colloid and Suspension.

## THE DIFFERENCE BETWEEN SUSPENSION AND COLLOIDS:

The difference between the suspension and colloids are describing such as:

Suspension	Colloid
It is a form of the heterogeneous solution	It is a form of a homogeneous solution
Particle size greater than 1000 nm	Particle size range from 1 and 1000 nm
Particles settle down well	Particles do not separate
Can be separated by filtration	Cannot be separated by filtration
May scatter light	Shows Tyndall effect (scatters light)
Opaque	Translucent
Easily visible through the naked eye	Not visible through the naked eye

### **The reasons for the formulation of a pharmaceutical suspension: -**

- When the drug is insoluble in the delivery vehicle.
- To mask the bitter taste of the drug.
- To increase drug stability.
- To achieve controlled/sustained drug release.

### **SOME PHARMACEUTICAL SUSPENSION:**

1. Antacid oral suspensions
2. Antibacterial oral suspension
3. Dry powders for oral suspension (antibiotic)
4. Analgesic oral suspension
5. Anthelmintic oral suspension
6. Anticonvulsant oral suspension and Antifungal oral suspension

**CLASSIFICATION OF SUSPENSION:** Suspension are classified such as following:

#### **01. On the Basis of their General Classes**

- **Oral suspension:** This type of suspension which are for administration in which one or more insoluble medicaments are dispersed in the liquid vehicle. eg: Paracetamol suspension antacids, Tetracycline HCl.
- **Externally Applied Suspension:** These are meant for topical application. eg: Calamine lotion.
- **Parenteral suspension:** These are heterogenous systems in which the solid phase is dispersed within a liquid phase. eg: Procaine penicillin G Insulin Zinc Suspension.

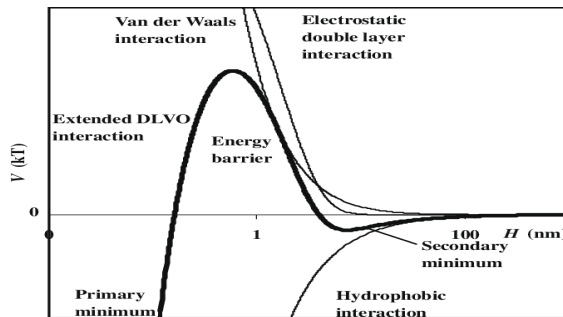


## 02. Based on Proportion of Solid Particles:

- **Dilute suspension:** The mainly these types of suspension which are mainly of consists such as (2 to 10% w/v solid). Eg: cortisone acetate, prednisolone acetate.
- **Concentrated suspension:** The another these types of suspension which as composites of solid concentration such as in the form of (50% w/v solid). Eg: zinc oxide suspension.

## 03. Based on Electrokinetic Nature of Solid Particles:

- ✓ **Flocculated suspension:** These types of suspension which are involved in chemical bridging between the particles to form aggregates. The weak Vander wall forces attraction forces which are present in the between light and fluffy aggregates or flocs formation will occurs.  
**Example:** It mainly attained by adding extra anions to a positive charged deflocculated suspension.
- ✓ **Deflocculated suspension:** This system contains the free solid particles. In comparison to the flocculated suspension, the deflocculated suspension also undergo aggregation but at a much slower rate. These types of system have relatively greater bioavailability than flocculated systems.



## Potential energy curves for particle interaction in suspension

### 04. Based on Size of Solid Particles:

- ✓ **Colloidal suspensions (<1 micron):** Suspensions having particle sizes of suspended solid less than about 1 micron in size are called as colloidal suspensions.
- ✓ **Coarse suspensions (>1 micron):** Suspensions having particle sizes of greater than about 1 micron in diameter are called as coarse suspensions.
- ✓ **Nanosuspension (10 micron):** Suspensions are the biphasic colloidal dispersions of nanosized drug particles stabilized by surfactants. Size of the drug particles is less than 1mm.

### ADVANTAGES OF SUSPENSION:

- Suspension can improve chemical stability of certain drug. E.g. Procaine penicillin G.
- Drug in suspension exhibits higher rate of bioavailability than other dosage forms.
  - *Solution > Suspension > Capsule > Compressed Tablet > Coated tablet*

- Duration and onset of action can be controlled. E.g. Protamine Zinc-Insulin suspension. Suspension can mask the unpleasant/ bitter taste of drug. E.g. Chloramphenicol
- **Choice of Solvent:** Drugs can be dispensed as suspension if they are water insoluble and if only water and no other solvents can be used as vehicles.
- **Bioavailability:** Drug particles dispersed in suspension are known to possess greater surface area and higher dissolution rate. However, bioavailability of suspension is not greater than solution forms.

#### **DISADVANTAGES OF SUSPENSION:**

- ✓ Physical stability, sedimentation and compaction can cause problems. It is bulky sufficient care must be taken during handling and transport.
- ✓ It is difficult to formulate.
- ✓ Uniform and accurate dose cannot be achieved unless suspension is packed in unit dosage form.
- ✓ The sedimentation of solids often given a false impression about the appropriateness of the suspension.
- ✓ Oxidation and hydrolysis may affect the chemical stability of suspension.

#### **APPLICATIONS OF SUSPENSION:**

- ✓ Suspension is usually applicable for drug which is insoluble (or) poorly soluble. E.g. Prednisolone suspension
- ✓ To prevent degradation of drug or to improve stability of drug. E.g. Oxy tetracycline suspension

- ✓ To mask the taste of bitter of unpleasant drug. E.g. Chloramphenicol palmitate suspension
- ✓ Suspension of drug can be formulated for topical application e.g. Calamine lotion.
- ✓ Suspension can be formulated for parenteral application in order to control rate of drug absorption. E.g. penicillin procaine
- ✓ Vaccines as a immunizing agent are often formulated as suspension. E.g. Cholera vaccine
- ✓ X-ray contrast agent are also formulated as suspension. eg: Barium sulphate for examination of alimentary tract.

### **FEATURES DESIRED IN PHARMACEUTICAL SUSPENSIONS**

- ✓ The suspended particles should not settle rapidly and sediment produced, must be easily re-suspended by the use of moderate amount of shaking.
- ✓ It should be easy to pour yet not watery and no grittiness.
- ✓ It should have pleasing odour, colour and palatability.
- ✓ Good syringeability.
- ✓ It should be physically, chemically and microbiologically stable.
- ✓ Parenteral /Ophthalmic suspension should be sterilizable.

### **Some theoretic considerations are:**

- ✓ Particle size control.
- ✓ Wetting
- ✓ Sedimentation
- ✓ Brownian movement
- ✓ Electrokinetic
- ✓ Aggregation

## **THEORIES OF SEDIMENTATION:**

Sedimentation means settling of particle (or) floccules occur under gravitational force in liquid dosage form.

Velocity of sedimentation expressed by Stoke's equation

$$v_{sed} = \frac{d^2(\rho_s - \rho_o)}{18 \eta_o}$$

Where, d = Diameter of particle, r = radius of particle,  $v_{sed}$ . = sedimentation velocity in cm / sec

$\rho_s$  = density of disperse phase

$\rho_o$  = density of disperse media

g = acceleration due to gravity

$\eta_o$  = viscosity of disperse medium in poise

### **Limitation of Stoke's Equation:**

- Stoke's equation applies only to: Spherical particles in a very dilute suspension (0.5 to 2 gm per 100 ml).
- Particles which freely settle without collision.
- Particles with no physical or chemical attraction.

## **SEDIMENTATION PARAMETERS**

Sedimentation volume (F) or height (H) for flocculated suspensions: Definition: Sedimentation volume is a ratio of the ultimate volume of sediment ( $V_u$ ) to the original volume of sediment ( $V_o$ ) before settling:

$$F = V_u / V_o$$

Where,  $V_u$  = final or ultimate volume of sediment,  $V_o$  = original volume of suspension before settling

F has values ranging from less than one to greater than one.

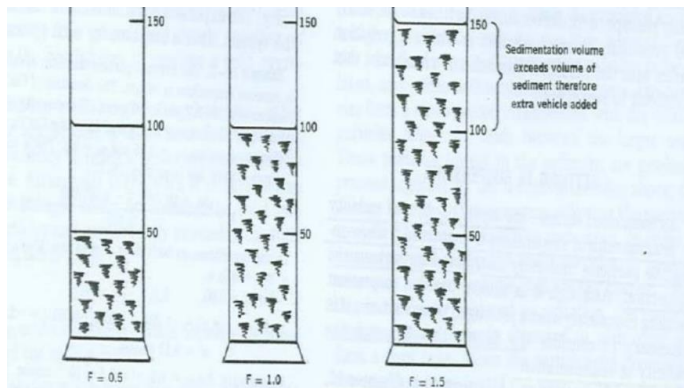
$$\text{When } F < 1 \quad V_u < V_o$$

$$\text{When } F = 1 \quad V_u = V_o$$

The system is in flocculated equilibrium and show no clear supernatant on standing.

$$\text{When } F > 1 \quad V_u > V_o$$

Sediment volume is greater than the original volume due to the network of flocs formed in the suspension and so loose and fluffy sediment. The sedimentation volume gives only a qualitative account of flocculation.



### Suspensions quantified by sedimentation volume (f)

**01. DEGREE OF FLOCCULATION (B):** It is the ratio of the sedimentation volume of the flocculated suspension, F, to the sedimentation volume of the deflocculated suspension:

$$F \propto$$

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

$$\beta = \frac{V_U / V_0 \text{ Flocculated}}{V_U / V_0 \text{ Deflocculated}}$$

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

**02. Brownian Movement (Drunken walk):** Brownian movement of particle prevents sedimentation by keeping the dispersed material in random motion.

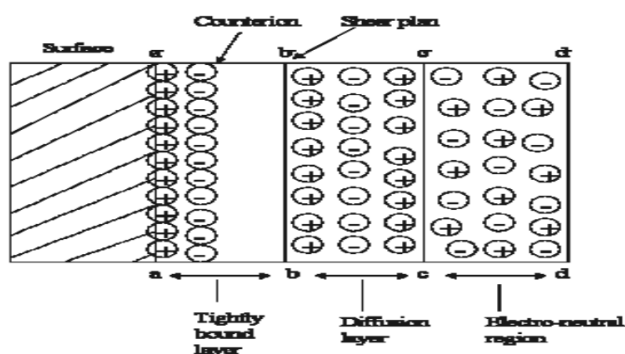
- ✓ Brownian movement depends on the density of dispersed phase and the density and viscosity of the disperse medium.

- ✓ The kinetic bombardment of the particles by the molecules of the suspending medium will keep the particles suspending, provided that their size is below critical radius ( $r$ ). Brownian movement can be observed.
- ✓ If particle size is about 2 to 5mm,
- ✓ When the density of particle & viscosity of medium are favorable.

## 2. Electro kinetic Properties

### ZETA POTENTIAL:

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



### Representation of zeta potential

As the potential drops off rapidly at b first, followed more gradual decrease as the distance from the surface increases.

This is because the counter ions close to the surface acts as a screen that reduce the electrostatic attraction between the charged surface and those counter ions further away from the surface. Zeta potential has practical application in stability of systems containing dispersed particles.



Since this potential, rather than the Nernst potential, governs the degree of repulsion between the adjacent, similarly charged, dispersed particles. If the zeta potential is reduced below a certain value, the attractive forces exceed the repulsive forces, and the particles come together. This phenomenon is known as “*flocculation*”.

The flocculated suspension is one in which zeta potential of particle is -20 to +20 mV. <sup>3</sup>/<sub>4</sub> Thus the phenomenon of flocculation and de flocculation depends on zeta potential carried by particles.

### **DEFLOCCULATION AND FLOCCULATION:**

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

**Deflocculated suspensions:** In deflocculated suspension, individual particles are settling. Rate of sedimentation is slow, which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation. This phenomenon called ‘caking’ or ‘claying’.

In deflocculated suspension larger particles settle fast and smaller remain in supernatant liquid so supernatant appears cloudy.

### **Ingredients in formulation of suspension**

**Wetting agents-** They are added to disperse solids in continuous liquid phase.

**Flocculating agents-** They are added to floc the drug particles

**Thickeners-** They are added to increase the viscosity of suspension.

**Buffers and pH adjusting agents-** They are added to stabilize the suspension to a desired pH range. Ex - carbonates, citrates.

**Osmotic agents-** They are added to adjust osmotic pressure comparable to biological fluid. Ex- mannitol, sorbitol.

**Coloring agents-** They are added to impart desired color to suspension and improve elegance. Ex- Titanium dioxide (white), Amaranth (red).

**Preservatives-** They are added to prevent microbial growth. Ex- Disodium EDTA 0.1%, Benzalkonium chloride 0.01-0.02%

**External liquid vehicle-** They are added to construct structure of the final suspension.

## **LIST OF SUSPENDING AGENTS**

- Methylcellulose, Alginates.
- Hydroxyethyl cellulose (HEC) and Carboxymethylcellulose
- Sodium Carboxymethylcellulose and Microcrystalline cellulose
- Acacia and Tragacanth

## **EVALUATIONS OF SUSPENSION:**

- Sedimentation method
- Rheological method

- Electro kinetic method
- Micromeritic method

**01. Sedimentation method:** Two parameters are studied for determination of sedimentation.

1. Sedimentation volume.
2. Degree of flocculation.

**Sedimentation volume:** The suspension formulation (50 mL) was poured separately into 100 mL measuring cylinders and sedimentation volume was read after 1, 2, 3 and 7 days, and thereafter at weekly intervals for 12 weeks.

Triplicate results were obtained for each formulation. Sedimentation volume was calculated according to the equation:

$$F = V_u/V_o$$

Where, F = sedimentation volume,  $V_u$  = ultimate height of sediment and  $V_o$  = initial height of total suspension.

**02. Rheological method:** It provide information about Settling behaviour. The arrangement of the vehicle and the particle structural features. Brookfield viscometer is used to study the viscosity of the suspension. It is mounted on Heli path stand and using T-bar spindle. bar spindle is made to descend slowly into the suspension and the dial reading on the viscometer is then a measure of the resistance the spindle meets at various level. This technique also indicates at which level of the suspension the structure is greater owing to particle agglomeration.

The dial reading is plotted against the number of turns of the spindle. The better suspension shows a lesser rate of increase of dial reading with spindle turns, i.e. the curve is horizontal for long period.

**03. Electro kinetic method:** Measurement of Zeta-potential using Micro electrophoresis apparatus & ZetaPlus (Brookhaven Instruments Corporation, USA). It shows the stability of a disperse system.

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 measurement. Parameters set to a temperature of 25°C and refractive index (1.33)

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

**04. Micromeritic method:** The stability of suspension depends on the particle size of the dispersed phase. Change in the particle size with reference to time will provide useful information regarding the stability of a suspension. A change in particle size distribution and crystal habit studied by microscopy coulter counter method.

#### **PHOTOMICROSCOPIC TECHNIQUE:**

The microscope can be used estimate and detect changes in particle size distribution and crystal form.

Rapid processing of photo micrographs is enhanced by attaching Polaroid camera to the piece of monomolecular microscope. By using this photo micrographs, we can determine the changes in physical properties and stability of suspensions.

Freeze-Thaw test conducted by placing the sample in a freezer for 18 hours followed by thawing at room temperature for 4 to 6 hours. Repeat the Freeze-Thaw cycle for up to 10 times. This test is conducted to determine the tendency to crystallize or cloud.

## **pH MEASUREMENT**

The measurement and maintenance pH are also very important step in the Quality control testing. Generally, there are 2 different types of methods used in the measurement of pH.

### **METHODS FOR pH MEASUREMENT:**

The simplest and cheapest is to dip a piece of pH paper into the sample. The paper is impregnated with chemicals that change color and the color may be compared to a chart supplied with the paper to give the pH of the sample. If greater accuracy is required a pH meter should be used. A typical pH meter consists of a special measuring glass electrode connected to an electronic meter that measures and displays the pH reading.

### **VISUAL INSPECTION:**

With visual inspection, the ingredients and the final products are carefully examined for purity and for appearance. Physical appearance of products for patient adherence and compliance is critical so it should be: good looking, Elegance in appearance.

## **INNOVATIONS OF SUSPENSIONS**

1. Nano suspensions
2. Taste masked pharmaceutical suspensions
3. Sustained release suspensions

## **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.

### **STORAGE:**

Suspensions should be stored in cool place but should not be kept in a refrigerator

Freezing at very low temperatures should be avoided which may lead to aggregation of suspended particles Stored at controlled temperature from 20-25<sup>0</sup>C

- Bentonite and Carbomer.
- Carrageen, Powdered cellulose and Gelatin.

## **Chapter: 02 (B)**

### **Emulsion**

“An emulsion is a mixture of two or more liquids that are normally immiscible (unmixable or unbendable) owing to liquid-liquid phase separation.”

An emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules (the dispersed phase) in the other liquid phase (the continuous phase), stabilized by the presence of an emulsifying agent.

The particle diameter of the dispersed phase generally extends from about *0.1 to 10  $\mu\text{m}$* , although particle diameters as small as  $0.01 \mu\text{m}$  and as large as  $100 \mu\text{m}$ .

#### **Examples:**

Emulsions basically consist of a dispersion of two liquids that are immiscible with each other. One of the liquids act as the dispersion medium and the other will act as the dispersed phase. In simple words, emulsions are colloids in which both the dispersed phase and dispersion medium are liquids. Oil and the mixtures of water are the emulsions when are shaken together. The oil forms drop and then disperses throughout the water.

The term emulsion is also applied to a group of mixed systems called as solutions, or gels or suspensions. Take, for example, the photographic emulsion is a gelatin gel consisting of tiny crystals dispersed in it. Some other examples of emulsions include butter which is an emulsion of water in fat and egg yolk containing lecithin.

**ADVANTAGES:** The advantages of emulsions as dosage forms are:

01. The flavouring of aqueous phase of emulsion is possible.
02. They are more rapidly absorbed than the solid dosage form.
03. Two incompatible ingredients can easily be incorporated, with one in each other.
04. The objectionable taste of oils can be concealed.

**PROPERTIES OF EMULSIONS:** An ideal emulsion mainly consists of the various properties such as following which are mentioned below section of data-

- Emulsions contain both a continuous and the dispersed with the boundary coming between the phases that are called “interface”.
- Emulsions have a cloudy appearance due to many phase interfaces scattering light passing through the emulsions.
- Emulsions appear in white colour when the light is dispersed in equal proportions.

If the emulsion is dilute, then higher-frequency and the low-wavelength type of light will be scattered in more fractions, and this kind of emulsion will appear in blue in colour. This is also referred to as the *Tyndall effect*.

## **TYPES OF EMULSION**

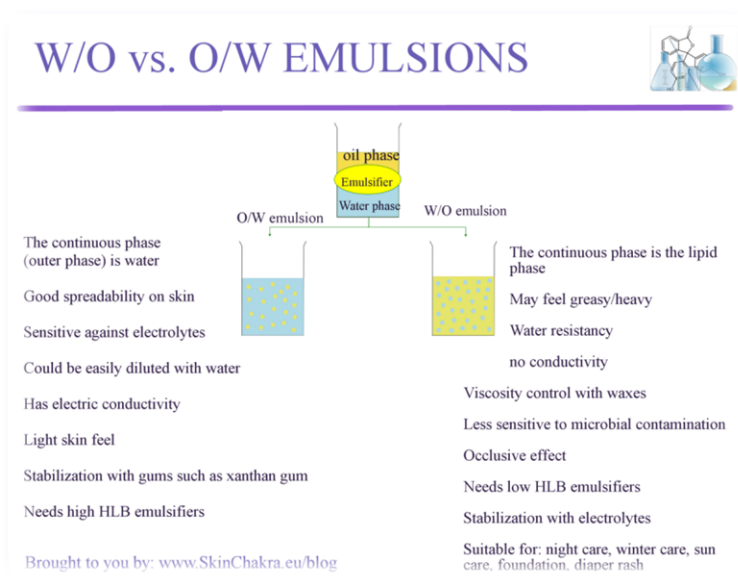
Emulsions can be classified on the basis of the properties of the dispersed phase and the dispersion medium:

- 1) **Oil in water (o/w):** In this type of emulsion, the oil will be the dispersed phase and water will be the dispersion medium.



The best example for o/w emulsion is milk. In milk, the fat globules (which act as the dispersed phase) are suspended in water (which acts as the dispersion medium).

**2) Water in oil (w/o):** In this type, water will be the dispersed phase and oil will be the dispersion medium. Margarine (a spread used for flavoring, baking and working) is an example of water in oil emulsion.



## Types of emulsion such as W/O AND O/W

### EMULSIFIER / EMULSIFYING AGENT

These are substances which are added to emulsions for stabilization purpose. The various characteristics of emulsifiers are given below:

- They are substances which have a hydrophilic end (polar) as well as a hydrophobic end (non-polar).
- They are soluble in both water and oil.

- Emulsifiers form a layer between the dispersed phase and the dispersion medium, thereby preventing the dispersed phase particles to come together to form larger particles and separate out.
- Emulsifiers can be cationic, anionic or even non-polar.
- It is not just the percentage of water and oil which decides whether it is oil-in-water or a water-in-oil emulsion. On the other hand, it depends on which among water and oil can solvate the emulsifier to a larger extent.
- If the emulsifier is more soluble in water than the water becomes the dispersion medium and oil becomes the dispersed phase and hence we get oil in water emulsion.
- On the other hand, if the emulsifier is more soluble in oil, then oil becomes the dispersion medium and water becomes the dispersed phase.

The commonly used emulsifiers for o/w emulsions are proteins, gums, soaps etc. and the commonly used emulsifiers for w/o emulsions are heavy metal salts of fatty acids, long-chain alcohols etc.

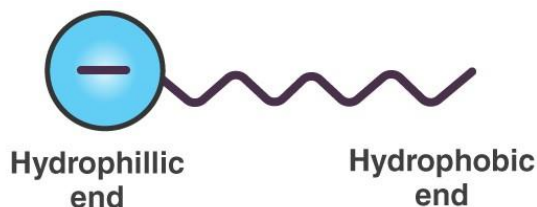
Some common examples of emulsifiers are egg yolk, mustard, sodium phosphates, DATEM, Mono- and diglycerides, cellulose, soy lecithin, etc.

## **HOW DO EMULSIFIERS WORK?**

To understand this, firstly we need to understand the process of coalescing. Coalescing is the process in which the similar particles in the emulsions come together to form larger and bulkier particles leading to the separation of the dispersed phase and dispersion medium.

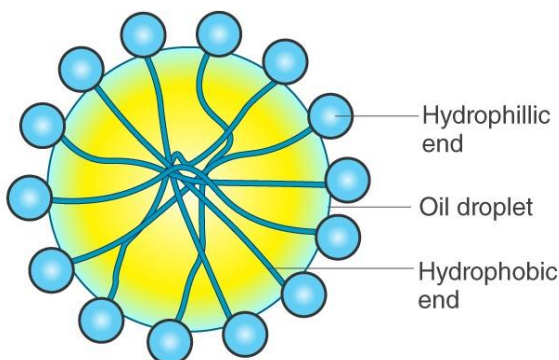
Emulsifiers help in preventing coalescing by forming a physical barrier between the dispersed phase and dispersion medium.

As we have seen before emulsifiers, like soap, has both a hydrophilic end and a hydrophobic end. Hence, they can attach to both polar and non-polar substances. Let us take the example of sodium stearate.  $C_{17}H_{35}COO-Na$  can be represented as:



### Hydrophilic and Hydrophobic End

When this is added to an o/w emulsion, molecules of  $C_{17}H_{35}COOH-$  surround the oil droplet with their non-polar tails/hydrophobic end (the hydrocarbon chain) extending into the oil & their polar heads/hydrophilic end (the carboxylate ion) facing the water as:



### Structure of the emulsion

This arrangement brings a stronger adhesive force between the oil (dispersed phase) and water (dispersion medium). This new formed adhesive force will be more than the cohesive force between oil – oil and water – water.

Hence, oil particles will not have the tendency to come together to form larger particles. This helps in preventing coalescing, thereby stabilizing the emulsion.

**NOTE:** For w/o emulsion, the orientation of the emulsifier would be the opposite as that of o/w. i.e. non-polar (hydrophobic end) tail extends outside and polar (hydrophilic end) head faces inwards.

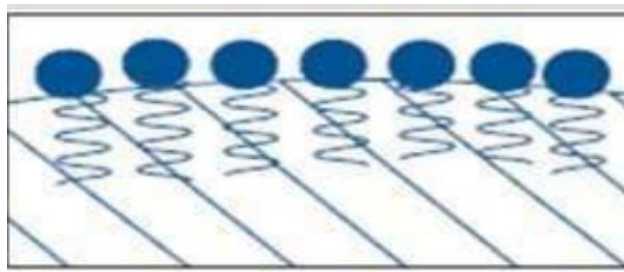
### **THEORIES OF EMULSIFICATION:**

Since there are different processes and mechanisms (both chemical and physical) involved in the process of emulsification, there are several theories-

- Monomolecular Adsorption theory
- Oriented-Wedge Theory
- Oriented adsorption theory
- Plastic or Interfacial film theory and Viscosity theory.
- Surface tension theory and Interfacial tension theory
- Fischer's theory of hydrates and solvates.

### **MONO-MOLECULAR ADSORPTION THEORY:**

Surface-active agents, or oil- water amphiphiles, reduce interfacial tension because of their adsorption at the interface to form monomolecular films as:



**Mono-Molecular Adsorption theory**

In practice, combinations of emulsifiers rather than single agents are used most frequently today in the preparations of emulsions. Hydrophilic emulsifier in the aqueous phase and a hydrophobic agent in the oil phase to form a complex film at the interface.

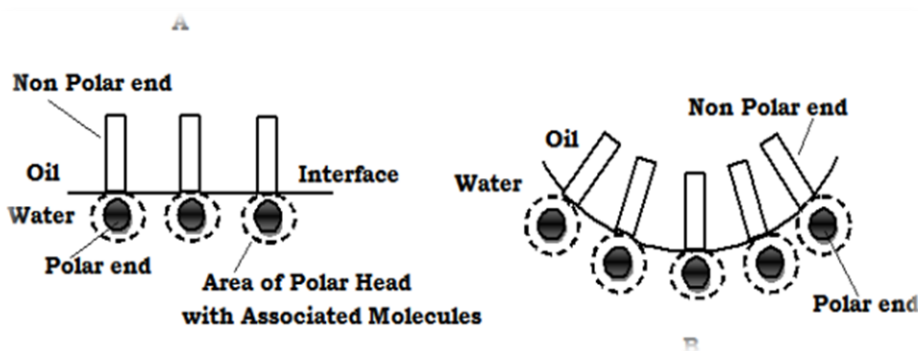
### Examples:

1- Three mixtures of emulsifying agents at the oil–water interface. The combination of Sodium cetyl sulfate and cholesterol leads to a complex film that produces an excellent emulsion.

2- Sodium cetyl sulfate and Oleyl alcohol do not form a closely packed or condensed film, consequently, their combination results in a poor emulsion.

### ORIENTED-WEDGE THEORY

This theory deals with formation of monomolecular layers of emulsifying agent curved around a droplet of the internal phase of the emulsion.



### Oriented-Wedge theory

A. Emulsifier molecules oriented at interface. Dotted lines indicate the large volume occupied by polar head due to formation of hydrated complex it shows that close packing of molecules ‘fits’ this curvature.

**Example:** In a system containing two immixible liquids, emulsifying agents would be preferentially soluble in one of the phases and would be embedded in that.

**ORIENTED ADSORPTION THEORY:** As per this theory, the added emulsifying agent forms a mechanical film by getting adsorption at the interface of the liquid and offers stability to emulsion. However, this theory could not explain the formation of type of emulsion.

### **PLASTIC OR INTERFACIAL FILM THEORY**

- The plastic or interfacial film theory places the emulsifying agent at the interface between the oil and water, surrounding the droplets of the internal phase as a thin layer of film adsorbed on the surface of the drops.
- The formation of an o/w or a w/o emulsion depends on the degree of solubility of the agent in the two phases, with water-soluble agents encouraging o/w emulsions and oil-soluble emulsifier the reverse.

### **SURFACTANT THEORY**

- According to the surface tension theory of emulsification, the emulsifying agents cause a reduction in the interfacial tension of the two immiscible liquids, reducing the repellent force between the liquids and withdrawing the attraction of liquids for their own molecules. In this way, the surfactants convert large globules into small ones and avoid small globules from coalescing into large ones.
- In this way, the surfactants convert large globules into small ones and avoid small globules from coalescing into large ones.

## **INTERFACIAL TENSION THEORY**

- When two immiscible liquids come in contact, the force causing each liquid to resist breakage is known as interfacial tension. When a high interfacial tension existed between two liquids emulsification is difficult, and if the tension could be reduced emulsification facilitated.
- The explanation that in oil in water dispersion, the interfacial tension is so great that when two globules of dispersed phase approach each other it withdraws the liquid from between them, with the result they coalesce. When the interfacial tension is greatly reduced by the addition of emulsifier the globules remain separate.

## **FISCHER'S THEORY OF HYDRATES AND SOLVATES**

- Fischer noted the application of particular emulsifying agent to continuous phase ratios and asserted that the amount of water in these ratios was completely consumed in the formation of a colloidal hydrate. Fischer's hydrates and solvates theory.
- This theory does not attempt to explain the formation of concentrated emulsions and not explains how globules in an emulsion are prevented from coalescing and separation into two layers.

## **VISCOSITY THEORY**

- As per this theory, an increase in viscosity of an emulsion will lead to an increase in the stability.
- This theory failed to explain about the milk which shows considerable stability even though its viscosity is less.

- This theory holds good for emulsions prepared with gums as emulsifying agents, but it collapses or no explanation of emulsions made which comparatively low viscosity and great stability.

## **METHODS TO IDENTIFY THE TYPE OF EMULSIONS**

### **1) Dilution test**

On adding water to an o/w emulsion, it will still remain stable as water is the dispersion medium, but on adding oil it will get destabilized as oil & water are immiscible. Similarly, w/o emulsion can be diluted with oil & would still be stable, but would get destabilized on the addition of water.

### **2) Conductivity test**

In this test the emulsion is kept between 2 electrodes and a bulb is connected in the circuit as shown in the diagram. An o/w emulsion will conduct electricity as water conducts electricity, but a w/o will not conduct electricity.

### **3) Dye test**

In this, a water-soluble dye is added to the emulsion. If it is an o/w emulsion, the dispersion medium appears red and the dispersed phase colourless and vice-versa.

## **PREPARATION OF EMULSIONS**

### **A- Trituration Method**

#### **A-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.



## **A-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.

## **Equipments- high-pressure homogenizers**

The emulsion phases are pumped together under high pressure into a small volume or through a small orifice – the interaction chamber – where pressures in the tens of thousands of PSI create very high shear forces.

Droplet size as small as 0.2  $\mu\text{m}$ .

## **Physical Stability of Emulsions**

Emulsions are thermodynamically unstable. The instability problems seen in emulsions during are given below.

- Creaming
- Flocculation
- Coalescence (agglomeration)
- Phase decomposition (Breaking)
- Phase inversion
- Ostwald Ripening (Disproportionation)

**NOTE-** A physically stable emulsion should be able to reach its initial state homogeneously with little agitation, with no separation during the shelf life, no dispersed phase, and should be able to flow easily.

### **a) CREAMING AND SEDIMENTATION**

- This process results from external forces usually gravitational or centrifugal. When such forces exceed the thermal motion of the droplets (Brownian motion), a concentration gradient builds up in the system with the larger droplets moving faster to the top (if their density is lower than that of the medium) or to the bottom (if their density is larger than that of the medium) of the container. The creaming rate is inversely proportional to viscosity. physical stability of the emulsion can be increased by increasing the viscosity of the external phase. (Viscosity enhancing agents such as methyl cellulose, gummi tragacanth, sodium alginate)

- Creaming is faster in case of the emulsions with larger droplets compared to smaller ones. So, the diameter of the droplets is the most important factor in determining the rate of creaming.

## FACTORS AFFECTING CREAMING

We can conclude the following things by analyzing **Stoke's equation**:

$$(F = 6 \pi \eta r v)$$

As we look at the equation, we come to know that when the density of the dispersed phase is less than the density of the dispersion medium, the value of  $v$  becomes negative. This is known as ***upward creaming***. This generally happens in the case of o/w emulsion where oil is less dense than water.

On the contrary, when the density of the dispersed phase is greater than that of the dispersion medium, then the value of  $v$  is positive and ***downward creaming*** occurs.

The rate of creaming increases as the difference between viscosity of the dispersed phase and dispersion medium increases. Further, the lower the **viscosity of a dispersion medium**, the greater the creaming rate.

The diameter of dispersed particles is at the nominator. So, the greater the size of the particle, the greater will be the creaming rate. So, we need to keep the **particle size** as low as possible.

When we increase the **force due to gravity** ( $g$ ) using methods like centrifugation, the rate of creaming also increases.

Theoretically, when **densities of both** dispersed phase and dispersion medium are the same, we can avoid creaming.

Stoke's equation does not mention another factor affecting creaming rates and that is the **homogenization of dispersed particles**. When we have uneven particles, the smaller particles will get attracted to the larger ones, which causes creaming.

**Solutions to overcome creaming:** The following suggestions can help improve the stability of emulsion by preventing creaming, as discussed in these considerations:

**Make dispersed particles homogenized:** For example., in homogenized milk, it is only the homogeneity of the particles that are responsible for most of its stability.

**Reduce particle size of dispersed particles:** As per Stoke's equation, the lesser the diameter lesser will be the rate of creaming. Formulators found that when the particles size was about 2 to 5  $\mu\text{m}$ , the rate of creaming was even less than what was expected by Stoke's law. This happens because, at this size range, the Brownian motion is dominant which causes repulsive forces.

**Make densities of both the phases equal:** As we saw earlier, if we keep both the densities equal, creaming should not happen. But in reality, temperature change also changes the densities. However, formulators try to keep the difference between the densities as low as possible. Generally, the oil phase has a low density in the formulation. So, adding an oil-soluble substance increases the density of the oil phase. For pharmaceutical and food emulsions, *food-grade brominated oil* is used to maintain the densities.

**Increase viscosity of the dispersion medium:** We can increase the viscosity of the dispersion medium using viscosity improvers or thickening agents such as *methylcellulose, tragacanth, sodium alginate*, etc.\

## **b) FLOCCULATION:**

- Flocculation of the dispersed phase may occur before, during, or after creaming. It is defined as the reversible aggregation of inner phase droplets. It is affected by surface charge of emulsifying globules.
- In situations where there is no protective mechanical barrier at the interface, for example, if the amount of emulsifier is not sufficient, the emulsion droplets rapidly agglomerate and coagulate.
- During flocculation, the interfacial film and particles maintain their individuality.
- Redispersibility of aggregates depends on the strength of the interaction between the particles.
- This interaction is determined by:
  - The concentration of soluble materials such as electrolytes and ionic emulsifiers.
  - The chemical properties of the emulsifiers.
  - The phase volume ratio.

## **c) COALESCENCE:**

- Coalescence is the process in which two or more droplets merge together to form a single larger droplet.
- This refers to the process of thinning and disruption of the liquid film between the droplets with the result of fusion of two or more droplets into larger ones.
- The limiting case for coalescence is the complete separation of the emulsion into two distinct liquid phases.
- The driving force for coalescence is the surface or film fluctuations which results in close approach of the droplets whereby the van der Waals forces is strong thus preventing their separation.

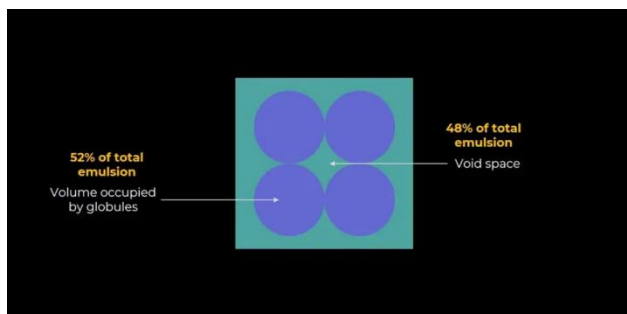
#### **d) PHASE SEPARATION-BREAKING:**

- The creaming phase should be considered different from phase separation; because phase separation is non-reversible, but the creaming is a reversible event.
- Cream flocs can be redispersed easily by agitation and a homogeneous mixture can be obtained; because the fat globules are still surrounded by a protective film formed by the emulsifier.
- Globules cannot be dispersed by mixing when the film surrounding the droplets is broken.
- The phase separation depends on
  - The droplet size.
  - The viscosity of the dispersion medium.
  - The phase volume ratio.

#### **FACTORS AFFECTING COALESCENCE AND BREAKING**

When the dispersed particles are non-uniformly distributed, the rate of coalescence increases. Whereas, when the particles are homogeneous and uniformly distributed, the emulsion becomes stable. Therefore, **uniform dispersion** affects the stability of the emulsion.

Even though the **viscosity** has little relation with the stability of the emulsion, we consider a viscous solution to improve the stability. The next factor is the **phase-volume ratio**. That means the relative volumes of oil and water phase in an emulsion. Let's see what is the phase-volume ratio using the following diagram.



As you can see in the diagram, the pores occupy 48% of the total volume of an emulsion whereas, the globules occupy the rest 52%. Typically, this 48:52 ratio gives a stable emulsion. However, owing to the different demands from the emulsion, the volume occupied by the globules can be increased to 74%. But 74% is a *critical point*. That means if we exceed the globule volume beyond 74% then the globules will coalesce and the emulsion breaks.

### **Solutions to overcome coalescence and breaking**

**Determine phase-volume ratio:** Many experiments have proven that when we keep phase-volume ratio 50:50 the emulsion is in the most stable form. That is why most of the pharmaceutical emulsions keep the phase-volume ratio 50:50.

**Increase in zeta potential:** As we know, attractive forces between the dispersed particles cause instability of emulsion. So, we can increase the zeta potential by increasing the electrostatic repulsion. For example., the addition of lecithin in perfluorocarbon emulsion. At physiological pH, lecithin has a negative charge. Lecithin adsorbs on the droplet surface giving it a negative charge and eventually increasing electrostatic repulsive forces.

**Decreasing interfacial tension using a good emulsifier:** In pharmaceutical or any industry, a good emulsifier is the one that is both tough and elastic and should form rapidly during emulsification.

**e) Phase inversion:**

- Conversion of a W/O type of emulsion to O / W type or otherwise is called phase inversion.
- This phenomenon can be seen during the preparation of the emulsion, during mixing of the two phases, heating and cooling of the emulsion.
- Phase inversion is caused by:
  - The changes on the phase volume ratio
  - The addition of an electrolyte

**f) Ostwald Ripening (Disproportionation)**

This results from the finite solubility of the liquid phases. Liquids that are referred to as being immiscible often have mutual solubilities that are not negligible. With emulsions, which are usually polydisperse, the smaller droplets will have larger solubility when compared with the larger ones (due to curvature effects). With time, the smaller droplets disappear and their molecules diffuse to the bulk and become deposited on the larger droplets. With time, the droplet size distribution shifts to larger values

**IDENTIFICATION TESTS:** The different types of tests involving in the identification of emulsions such as:

01. **Miscibility Tests with oil or water:** The liquids miscible with the continuous phase of emulsion will also be miscible with the emulsion.



02. **Conductivity Measurements:** Emulsions having aqueous continuous phases rather than oily phases will conduct electricity rapidly.

03. **Staining Tests:** In this test, a blend of water-soluble or an oil-soluble dye with the emulsion is subjected to microscopic observation to determine whether or not the continuous phase or the dispersed droplets are colored.

### **Applications and Uses of Emulsion:**

Emulsions are very much famous in various fields of science. It is utilized in the tanning and dyeing industries, used in the manufacturing process of plastics and synthetic rubber.

- Usually used in cosmetics, pharmaceuticals, personal hygiene.
- Microemulsions are used to deliver vaccines to kill various microbes.
- It is used in chemical synthesis mainly in the manufacture of polymer dispersions.
- It is used in firefighting.
- Nano-emulsion such as soybean oil are used to kill microbes.
- Mayonnaise is an oil in water emulsion with egg yolk or sodium stearyl lactylate.

# **UNIT : 4**

# **Chapter: 01**

## **PHARMACEUTICAL SUPPORISORIES**

### **1. INTRODUCTION AND DEFINITION**

**Suppositories are defined as:** “A suppository is a medicated solid/semi-solid dosage forms that is inserted into the **rectum** (rectal suppository), **vagina** (vaginal suppository), or **urethra** or **urethral tract** (urethral suppository), where they dissolve or melts and exerts local or systemic effects. Suppositories are used to deliver medications which act as both systemically and locally effects for the related disease.”

Generally, Suppositories are also as a solid body of various weights and shapes, adapted for introduction into the rectal, vaginal, or urethral orifice of the human body. A suppository may act as a local tissue protectant or palliative at the site of administration, or as a carrier of therapeutic agents for systemic or local action. **All types of suppositories are melted at normal body temperature after introducing in body cavity and produce their effect.**

**According to,** British Pharmacopoeia (BP) definition: “*Suppositories are solid, single-dose preparations. The shape, volume and consistency of suppositories are suitable for rectal administration.*”

The available suppositories vary in shapes, sizes (usually 1-4gm), and drug content (less than 0.1-40%). In most suppositories, the drug is added after it has been dissolved in the vehicle, but in some cases, the ingredients are co-formulated.

### **Comparison of orally administered dosage form and suppositories:**

The difference in the drug distribution from an orally and rectally route of administered drug into the human body is shown the below section:

#### **Orally administered dosage forms**

Drug  $\Rightarrow$  Absorption  $\Rightarrow$  Small intestine  $\Rightarrow$  Hepatic portal vein  $\Rightarrow$  Liver  $\Rightarrow$  Chemical modification in liver  $\Rightarrow$  Reduced systemic effectiveness

#### **Rectally administered dosage forms (suppositories)**

Drug in anorectal area  $\Rightarrow$  Lower hemorrhoidal vein surrounding the colon and rectum enters into the inferior's vena cava  $\Rightarrow$  Bypass the liver  $\Rightarrow$  Drug absorption into the systemic circulation occurs in 50–60% of cases.

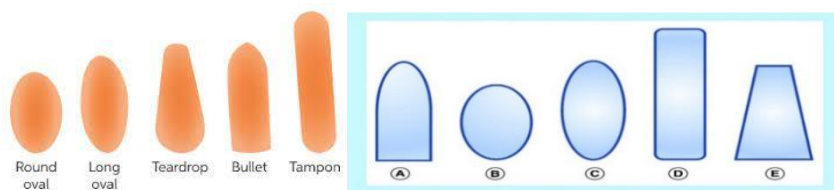
**2. TYPES OF SUPPOSITORIES:** The suppositories are inserted with the different route of drug administration so they can differently types. Suppositories are majorly classified in the various forms, shapes and sizes as:

- A. Rectal Suppositories:** These suppositories which are intended to be administered to adults are trapped either at one or both the ends and weigh about **2gm (as per U.S.P.)**. this weight is due to cocoa butter base present in it; however, the weight may vary with other bases. These suppositories can be used for delivering drugs with systemic effects (e.g., Sedatives, tranquillizers and analgesics). But the one dispensed as OTC (over the counter) is used as hemorrhoid remedy.
- B. Vaginal Suppositories:** These suppositories are globular or oviform-shaped and weigh about **5gm (as per USP)**, varying molecular weights of PEG are used as bases in these suppositories. These are used in the delivery of drug used

for treating the infections of female genitourinary tract. Contraceptive drugs can be also be administered using these suppositories.

- C. Urethral suppositories:** These suppositories are cylindrically shaped. Based on the use of cocoa butter base, the diameter, length and weight of these suppositories for females should be 5mm, 50mm and **2gm** respectively while in males it should be 5mm, 125mm and **4gm** respectively. This formulation is available in the form of a sterile micro pellet (1.4 mm in diameter and 6mm long) and consists of the drug and *polyethylene glycol 1450*. It is inserted 3cm deep into the urethra with the help of a hollow applicator.
- D. Nasal Bougies:** These bougies (Similar to urethral ones) are thinner, 8cm in size and about **1.2gm** in weight. These are prepared from gelato-glycerin base.
- E. Ear cones (Aurinaries):** These suppositories are about **1gm** in weight and are cylindrical-shaped to facilitate their insertion into the ears. These are rarely used and contains cocoa butter as the base. They are prepared in the mould of urethral bougies and cut into desired shape.

There are the lots of available suppositories used in the formulations which are usually vary with their sizes and shapes, hence the different sizes of suppositories shown in the given (**Figure.01**)



**Figure: 01 Different shapes and sizes of suppositories**

**3. ADVANTAGES OF SUPPOSITORIES:** The suppositories are generally, consisting the different numbers of merits, which are describes as following:

- It is the alternated dosage form for drugs which have less bioavailability when it is taken orally.
- Drugs having bad Odour and taste can be used in suppository form.
- It is suitable for unconscious patients which cannot taken drugs orally.
- It is suitable for drugs which produce irritating effect in GIT.
- It is suitable for infants and old people who find difficulty in swallowing of drugs.
- It is suitable for the drugs which are destroyed by portal circulation.
- It can exert local effect on rectal mucosa
- It can be used to promote evacuation of bowel.

**Higher drug load:** Suppositories can be used for the delivering two- or three-times higher drug loads, depending on the concentration of other excipients presents.

Avoidance of overdosing, oral administration of sedative drugs may give arise to accidental or intentional overdosing issues. This danger is overcome by administration drugs rectally.

**4. DISADVANTAGE OF SUPPOSITORY:** Each suppository is prepared with the different types of methods as per this the suppository having advantage and disadvantages as following:

- The manufacturing process is more difficult as compare other formulation.
- The drugs which cause irritation to mucous membrane cannot be administrated by this form.

- The most important problem is storage condition because it stored at low temp. (10-20°C). Other than the bases get liquefied.
- The problem of patient acceptability and suppositories are not suitable for patients suffering from diarrhea.

Expensive, suppositories are expensive than tablets. The drugs having *low aqueous solubility* may undergoes restricted dissolution due to small volume (3ml) of fluids in rectum. 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 and incomplete absorption may be obtained because suppository usually promotes evacuation of the bowel.

**5. EXCIPIENTS:** The ingredients in the formulation of a suppository generally, comprises of numbers of excipients which are mentioned below:

- 1) **Suppository bases.**
- 2) **Antioxidants.**
- 3) **Emulsifying agents.**
- 4) **Hardening agents.**
- 5) **Preservatives.**
- 6) **Thickening agents.**
- 7) **Plasticizers.**

**01). SUPPOSITORY BASES:** The suppository bases are composed of different available substances, depending on their composition and physical properties, these bases are classified as following:

- i. **Oleaginous (fatty) bases.**
- ii. **Aqueous (water soluble or miscible) base.**
- iii. **Emulsifying base.**

**i. Oleaginous/Fatty Bases:** It comprise in two major portion such as:

**i.1. Theobroma oil or Cocoa Butter:** Theobroma oil or butter is considered an ideal, suppository base due to its properties. It exists as a hard, amorphous solid at 15-25°C (room temperature), while it melts to a bland, non-irritating oil at 30-35 °C (body temperature). It is required to store Theobroma oil in refrigerators during warm climates.

Due to its polymeric nature, cocoa butter gets converted into a metastable form at temperature above 35°C. the finished suppositories will melt at room temperature, rendering them unfit to use.

The reduce melting point of cocoa butter due to the addition of chloral hydrate and phenol is enhanced up to the desired range by adding spermaceti or beeswax.

**Advantages:**

- It gets rapidly liquified when heated, while sets rapidly when cooled.
- Its non-irritant to mucous membrane and efficient release water soluble drugs.

**Disadvantages:**

- Require a drug and dark place for the storage as undergo rancidification.
- It requires the additional number of lubricants while pouring in a holder, leakage some case.

**i.2. Triglycerides:** These synthetic tri-glycerides are made up of hydrogenated vegetable oils. They are generally, preferred over Theobroma oil as they lack polymorphism. Bu these are much expensive than Theobroma oil. Tri-glycerides is a series are varying to give a range of melting points.



## **ii. Aqueous/Water Soluble/Water Miscible Bases:**

**01. Glycerinated gelatin:** This base is mostly used for the vaginal suppository. It can be incorporated with various drugs including alkaloids, boric acid and zinc oxide due to its compatible nature. The suppository contains base are translucent, resilient, gelatinous solids undergoes dissolution in mucous membrane secretions at a slow rate from prolonged release of drugs.

These suppositories should store in the cool place packed in well-closed containers. This is because on coming in contact with atmospheric moisture they get absorbed and dissolved. These suppositories demand the addition of a preservative (methyl paraben and propyl paraben or combination) for extending their shelf-life. These suppositories can be easily administered by dipping in water prior to use.

**Advantages:** It provides strong and translucent suppositories.

It disperses slowly in the body cavity, thus prolonging the drug release and its action.

**Disadvantages:** Preservative requirements, the gelatin present in it is incompatible with protein precipitants.

The produce a laxative effect, it dehydrates and irritates the rectal mucosa.

**02. Polyethylene glycol polymer:** These suppository bases have gained importance due to their properties. They are chemically inert or stable, non-irritant and miscible with water and mucous secretions. They can be formulated in a wide range of hardness and melting point either by moulding or compression.

They do not melt on coming in contact with body but dissolve for prolonging the drug -release (more than Theobroma oil).

PEG polymer is used along while manufacturing suppositories; mostly suppositories demand PEG polymers of two or more molecular weights combined in various proportions. They are formulated with much higher melting points. This facilitates their storage at room temperature.

**Advantages:** They are thermostable, does not undergo degradation or hydrolysis.

- It does not come out of the body cavity once inserted.
- Its chemical stability is high.

**Disadvantages:**

- It requires a drug or dark place for storage.
- It requires emulsifiers which facilitates water absorption.
- Different batches possess different physical properties.
- In certain cases, it may leak out from the body cavity after insertion.

**iii. Emulsifying Bases:** These bases are marketed under the trade name **Massa Esternium, Witepsol and Massupol**. Massa Esternium comprises of the mono, di and tri-glycerides of the fatty acids (having the formula  $C_{11}H_{23}COOH$  to  $C_{17}H_{35}COOH$ ). Witepsol, available in 9 grades comprises of hydrogenated triglycerides of lauric acid with added monoglyceride. Massupol comprises of glycerol esters of lauric acid with an additional minute quality of glyceryl monostearate. These bases lack the disadvantages of cocoa butter and also do not require a mould lubricant.

**DESIRABLE IDEAL PROPERTIES OF SUPPOSITORY BASES:** Suppositories are prepared with the numbers of excipients in their formulation's, as similar suppository base are important term or excipients in the formulation of suppositories. All the suppository bases are having its own desirable properties in the formulation such as:

- Chemically and physically stable under normal conditions of use and storage.
- Nonreactive and compatible with a wide variety of drugs and auxiliary agents.
- Free from objectionable odor and an aesthetically appealing appearance and nontoxic, no sensitizing, and nonirritating to sensitive tissues.
- Expansion–contraction characteristics such that it shrinks just enough on cooling so that it releases easily from suppository molds

They can melt or dissolves in the intended body orifice to release the drug and nonbinding of drugs and Mixes with or absorbs some water

**Specification characters for suppository bases:** Certain standard for suppository bases have been put forward based on various physical and chemical measurements such as:

- Origin and chemical composition.
- Melting range.
- Saponification values.
- Solid fats index (SFI).
- Iodine value.

- Hydroxy value.
- Solidification point.
- Water number and Acid values.

**02). Emulsifying Agents:** These agents act by enhancing the ability of fatty bases to absorb water, thus, allowing the incorporation of aqueous solution in suppositories. Polysorbates (tween 61), wool alcohol and wool fat are some of the common employed emulsifying agents.

**03). Antioxidants Agents:** These agents prevent the drug as well as the bases from getting degraded by oxidation. Ethyl or propyl gallate, ascorbic acids and its esters, hydroquinone and tocopherols are some of the common employed antioxidants.

**04). Hardening agents:** These agents normalize the melting point value of the formulation in which the melting point of the base has been reduced by the drug. High molecular weight macrogols are common employed as hardening agents.

**05). Thickening agents:** These agents are added in the formulation for enhancing the molten base viscosity and preventing the suspended insoluble solids from forming sediment. Aluminium monostearate, colloidal silica and, magnesium stearate are as thickening agents.

**06). Preservative:** These are added to prevent the growth of microbes in suppositories containing water soluble bases. Methyl paraben and propyl paraben are the agent used as preservative.

**07). Plasticizers:** These agents are making the fatty bases elastic and less brittle. Castor oil, glycerin, glycol, tween 80 and tween 85 are some of the efficient plasticizers used in the formulation of suppositories.

According to the USP, there are six general classes of suppository bases (1): 1. *Cocoa butter* 2. *Cocoa butter substitutes* 3. *Glycerinated gelatin* 4. *Polyethylene glycol base* 5. *Surfactant base* 6. *Tableted suppositories or inserts*.

## **6. METHODS OF PREPARATION OF SUPPOSITORIES:**

Suppositories can be prepared by the three main methods involving in the preparation such as:

01. Hand rolling and moulding.
02. Compression moulding.
03. Fusion moulding (hot process).

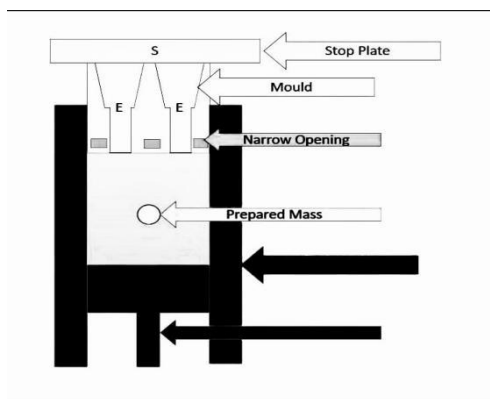
Among these, the first two methods are ancient and not in use at present time.

**6.1. Hand rolling and Moulding:** a few numbers of suppositories using butter can be prepared with this traditional and simple methods, which does not require heating of cocoa butter. These steps involved in these methods are:

01. The cocoa butter and other ingredients are grated and triturated in a mortar to form a plastic-like mass.
02. This mass is shaped into a ball by rolling between the palms of the hands.
03. This mass does not adhere on the hands and rolling surface if starch or talc is applied on them.
04. The cylindrical mass so obtained is cut into desired number of pieces.
05. These pieces are rolled on one end to form a conical shape.

This method of hand rolling can be performed by skillful workers who requires practice. The triturated mass should not be much soft otherwise on pressing, it may result in cracked and centrally hollow suppositories.

**6.2. Compression Moulding:** in this method, the mixture containing grated suppositories base and medicament are forced through a compression method. Determining the mould capacity prior to use is recommended. This involves compression a small amount of base into the dies and weighing the finished suppositories. A small part of the base is neglected based on the density of the ingredients added.



**Fig. 01 Compression Moulding Machine**

The cylinder in the equipments is filled with the suppository mass to be moulded. This mass is forced to extrude through the moulds by pushing it with a piston regulated via hand-turned wheel.

**Advantages:**

- This method involves a simplified process.
- This method prevents the solids in the base from settling at the bottom.
- The thermolabile medicaments can be moulded by this method.

**Disadvantages:** however, the disadvantages of this method are:

- In this method air entrapment may occurs.
- The entrapped air may result in weight variation and oxidation of drug and. Or the base.

**6.3. Fusion Moulding:** The suppository moulds are available commercially in variety of shapes and sizes. In dispensaries, suppository moulds (shown in fig.) having 6 or 12 cavities of desired shapes and sizes are used. On a large-scale basis, moulds having around 500 cavities are used. Metals like stainless steel, plastic, copper alloy, bras, Aluminium used for the making these moulds (Figure shown)



**Fig. 02 Fusion Moulding machine**

Fusion moulding methods involving the following steps:

01. The suppository base is melted and the drug is either dispersed or dissolved in it.
02. The resultant mixture is removed from the heat and poured into a suppository mould.
03. After the mixture solidifies in the moulds, they are termed suppositories and are removed.

For preparing suppositories the ingredients and drug are weighed, mixed, melted and poured into suppositories moulds. The volume occupied by the melted mass in the mould is termed as the **mould cavity**. Suppositories of accurate dose can be obtained

by determining the density and calibrating the moulds because the ingredients and drugs are measured by weighed but compounds by volume.

The mould cavity should be smooth from within and their inner surface mould be scratch-free, or else eleven surfaced suppositories will be obtained.

## **7. DISPLACEMENT VALUE AND ITS CALCULATIONS:**

Formation of suppositories involves dispersing or dissolving the drug in a molten base and pouring the resultant mixture into a suppository mould, available in different sizes of 1gm, 2gm, 3gm & 4gm. These values are the approximate weights of suppositories containing Theobroma oil (cocoa butter), the mould volume however remains constant. The weight of base used for preparing suppositories varies depending on the medicament used. This is because the medicament density and the base density are different from each other. For example, the volume occupied by 2gm of a medicament (with twice the density of Theobroma oil) would be same as the volume of 2gm of suppository base.

The required weight of suppositories bases for preparing medicated suppositories is calculated by the **Displacement Values (DVs)** of medicament. **The displacement value of a medicament is the number of parts by weights of a medicament that will displace one part of suppository base (normally Theobroma oil).** Pharmaceutical codex enlists the displacement value for various medicaments.

### **Calculation of displacements value of medicament:**

10 suppositories containing only the base are weighed = (A)gm



10 suppositories containing 40% of medicament are weighed = (B)gm

The amount of base present in the medicated suppositories is calculated = © gm

The amount of medicament present in the medicated suppositories is calculated = (D)g

The amount of base displaced by (D) gm of medicament is calculated = (A-C) gm

Displacement value of medicament (DV) =  $D/A-C$

**Example 01:** If a prescription requires 400mg of bismuth subgallate per suppository weighing two grams, what would be the displacement value if it is known that six suppositories with required bismuth subgallate weigh 13.6gm?

**Solution:** The theoretical weight of six cocoa butter suppositories without bismuth subgallate  $H_e = 12\text{gm}$ .

Given weight is six cocoa butter suppositories with bismuth subgallate = 13.5gm

Amount of bismuth subgallate in the suppositories =  $0.4 \times 6 = 2.4\text{gm}$

Amount of cocoa butter subgallate in the bismuth subgallate suppositories =  $13.5 - 2.4 = 11.2\text{gm}$

Cocoa butter displaced by 2.4 gm of bismuth subgallate =  $12 - 11.2 = 0.8$

**Ans;** The displacement value of bismuth subgallate  $s 2.4/0.8 = X/I$  or  $X = 3$ .

## 8. EVALUATION OF SUPPOSITORIES:

1. Uniformity of weight test.
2. Penetration test.
3. Disintegration/dissolution test.

4. Mechanical strength and crushing test.
5. Melting range test.
6. Softening time test.

**8.1. Uniformity of weight test:** The suppositories may vary in weight if the moulds are non-uniformly filled. Weight uniformity can be checked by weighing 20 suppositories to calculate their average weight. Thereafter, each suppository is weighed individually. The suppository meets the standard if not a single one deviates by more than 5% from the average weight, with the exception that two of them can deviate by not more than 7.5%.

**8.2. Melting range test:**

The physical properties and absorbing capacity of the suppositories are examined by this test. Their melting behaviour can be determined by techniques like the open capillary tube methods, the u-tube methods & the drop-point method. The suppository melting point generally is either equal to or less than 37 °C.

**8.3. Penetration test:** the temperature at which the suppository becomes so soft that a penetrating rod passes through its entire length is determined by this test. The temperature is maintained at 37°C and the suppository and penetration rod are placed in the device. This device is moved down to a constant temperature bath and a stopwatch is started. The time at which the penetration rod drops through the softened suppository is noted.

**8.4. Mechanical strength/Crushing test:** The degree of mechanical force required to break the suppository classifies them into brittle or elastic types. This test is used to determine the weight (kg) a suppository can withstand without breaking. An ideal suppository breaks under 1.8-2kg pressure. The apparatus is used for testing the

mechanical strength of a suppository in laboratories. The suppository is placed vertically in this device and increasing weights are put in it till it breaks. This test is performed to check whether or not a suppository can bear transportation conditions and administered to the patient without any difficulty.

#### **8.5. Disintegration/dissolution test:**

The disintegration or dissolution of suppositories can be performed with the apparatus used for the compressed table; although the test medium should be modifying as per the requirements. Suppositories comprising the water-soluble bases are tested for their disintegration and dissolution properties.

The suppositories may melt, deform, and disperse in the dissolution medium used, thus, posing a difficulty in determining the in-vitro rate of drug release. In the earlier times, the suppositories were put in a beaker containing a medium.

The variation in mass/medium interface can be controlled by various methods. Studies have been carried out by sealing the samples in dialysis tubing or natural membranes. Flow cell dissolution apparatus have also been used in which the sample is positioned with cotton, wire screening, or glass beads.

### **9. PACKAGING REQUIRED IN SUPPOSITORIES:**

The packaging of suppositories should be such that each is over-wrapped. If they are packed in containers, they should not be in contact with each other. If these conditions

are not maintained i.e., the poorly wrapped or packaged suppositories will undergo staining, breakage or deformation by melting caused by manhandling or adhesion.

If the suppositories are in direct contact with each other, they fuse due to changes in ambient temperature. The outer package often gets stained with suppositories which are partially melted; therefore, they require over-wrapping or are packed with a material which forms a barrier between the suppositories and the outer containers. Suppositories are wrapped using tin, aluminum, paper or plastic strips.

The suppositories are over-wrapped either manually or by using a machine. Since hand packaging is a slow process which also produces non-uniform and inelegant products, modern packaging machines are employed. These machines uniformly wrap around 8000 suppositories per hour.

There is a type of machine available in which the chill-hardened suppositories are positioned in a matched turntable and then introduced to the packaging station. Here the foil is unwound from a roll, cut to size and wrapped over each suppository. The suppository is mechanically placed in one half and the second half is sealed over it.

However, there are many suppositories which are not wrapped individually. Instead, they are placed in cardboard boxes or plastic containers having compartments for carrying 6-12 suppositories.

## **10. STABILITY PROBLEMS OF SUPPOSITORIES**

**a. BLOOMING:** During storage, cocoa butter suppositories sometimes show deposition of white powder on the surface.

This result in suppositories of disagreeable appearance.

**b. HARDENING:** During storage, the suppositories made of fatty bases become hard.

It occurs due to crystallization of bases and it is also affecting the melting and rate of absorption of drugs.

# **Chapter: 02**

## **PHARMACEUTICAL INCOMPATIBILITY**

### **Introduction and Definition:**

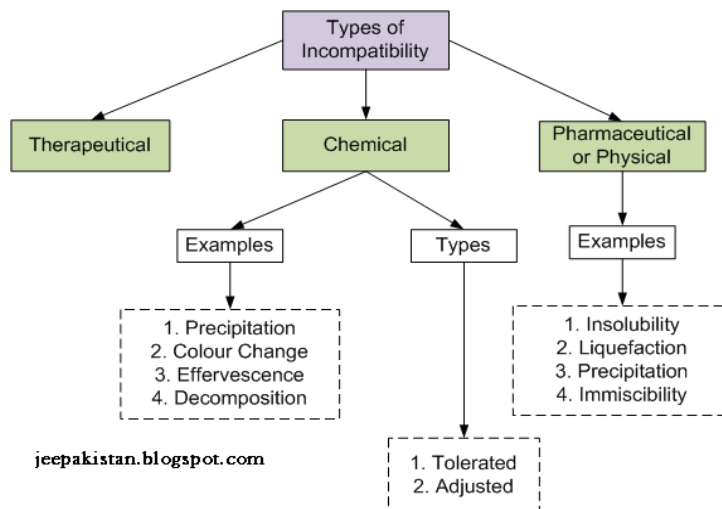
Compatibility is a term used to describe the interaction of two or more substances that results in changes to the medical, physical, or chemical properties of the pharmaceutical dosage form.

A condition in which two or more agents when brought together resulting in chemical decomposition, physical dissociation and therapeutic opposition, this condition known as “*Pharmaceutica incompatibility*”.

Formulating, manufacturing, packaging and administration drugs are the processes during which compatibilities may develop.

**Classification of Incompatibilities:** The pharmaceutical drug incompatibilities are mainly classified in the main three types such as:

1. Physical Incompatibility
2. Chemical Incompatibility
3. Therapeutic Incompatibility



**Figure. 01 Classification of pharmaceutical incompatibility**

Physico-chemical incompatibility is the combination of physical incompatibility and chemical incompatibility.

**1. Physical Incompatibilities:** Compounding of medicines give rise to this incompatibility, which is also known as **pharmaceutical incompatibility**. Changes in color, taste, texture, odor, viscosity, viscosity, and morphology are caused by the interaction of two or more substances.

The physical incompatibility can be viewed as such (though eyes) and their remedies involves the adding of suspending or emulsifying agents or changing the mixing order.

There is a visible change in the physical world of the medications. A product is formed that is unpalatable, non-uniform, and unacceptable. Measuring doses accurately is difficult. A pharmaceutical skill can correct the problem. Interaction between two or more substances which may lead to change in color, odor, taste, viscosity and morphology. It is also called as pharmaceutical incompatibility.

**Manifestations of Physical Incompatibilities:** The following list outlines the various ways incompatibility between or among drug agents may be manifested. The different ways by which physical incompatibility may rise between or among different drugs are listed below:

**01) Insolubility:** Insolubility of prescribed agents in vehicle.

It means the inability of material to dissolve in a particular solvent system. The majority of incompatibilities is due to insolubility of the inorganic as well as organic compounds in particular solvents.

The following factors affect the solubility of prescribed agent in vehicle and may render it less soluble:

- Any change in previous factors may lead to precipitation of drugs and change in their properties
- Complex formation.
- Some tinctures containing resins or chlorophyll may provide precipitation when added to the aqueous system.
- Substances like chalk, acetyl salicylic acid, succinylsulphothiazole, zinc oxide, and calamine are the common examples of in diffusible solids.
- Surfactant.
- Chemical reaction.
- Change in pH.
- Co-solvent.
- Milling.



**Example: “Mixture of prepared chalk”**

Rx,

Chalk powder –2g

Tincture catechu – 2ml

Cinnamon water – 2ml

**Causes:** Chalk powder is not soluble in water. It gets precipitated when added to aqueous medium. These precipitates are found in diffusible in nature which results in physical incompatibility.

**Remedy:** Use of suspending agents is necessary to suspend the precipitated chalk particles.

Generally, 2% W/V of compound tragacanth powder is recommended as suspending agent. The corrected prescription is Mixture of prepared chalk

Rx

Chalk powder –2g

Tragacanth – 0.4g

Tincture catechu – 2ml

Cinnamon water up to 30ml

**02) Immiscibility of Liquids:** Immiscibility of two or more liquids. This property is commonly observed in emulsions, creams lotions and some ointments as

resulting of which the two phases may separate. Which are immiscible with each other.

When two such ingredients are combined resulting in a non-homogenous product, such ingredients are called immiscible to each other and the phenomenon is called immiscibility. This manifestation appears clearly in emulsions, creams, lotions, some types of ointments. Separation in two phases is noticed in this pharmaceutical dosage form. Storage must be in room temperature to prevent separation.

**Incomplete mixing Example:** The oil drops may float on the surface of the water when aqueous preparations containing flavorings such as orange oil or lemon oil, or their alcoholic solutions, are prepared. Their presence makes the solution appear turbid and cloudy. There are lots of factors which are responsible to immiscibility:

- Improper and incomplete mixing.
- Adding of concentration of a surfactant.
- Microbial growth on constituents of mixture.
- Storing.

**Example: “Castor oil emulsion”**

Rx

Castor oil – 15ml

Water – 60ml

**Causes:** In this prescription castor oil is immiscible with water due to high interfacial tensions, which is a sign of incompatibility.

**Remedy:** To overcome this type of incompatibility emulsification is necessary with the help of an emulsifying agent. The corrected prescription is Castor oil emulsion

Rx

Castor oil – 15ml

Acacia – 2% W/V

Water– up to 60ml

**03) Precipitation:** It occurs due to solvent is insoluble when it is added to solution. Solubilized substances may precipitate from its solution if a non-solvent for the substances is added to the solution. **Example:** Resins are insoluble in water,

**Alcoholic solution of resins + Water = Precipitated resins**

Aqueous dispersions of hydrophilic colloids (Polysaccharide Mucilage + High concentration of alcohol or salts) = Precipitated Colloids.

High concentration of electrolytes causes cracking of soap emulsion by salting out the emulsifying agents. Vehicles (one or more organic liquids) use to dissolve medicaments of low solubility; water soluble adjuvant practically inorganic salts may be precipitated in such vehicles. When tinctures containing resinous matter are added in water, resin agglomerates forms in diffusible precipitates. This can be prevented by slowly adding the undiluted tincture with vigorous shake. Suspension or by adding some suitable thickening agent.

**Example: “Lotion of compound tincture of benzoin”.**

Rx

Tincture benzoin compound – 5g

Glycerin – 10ml

Rose water up to 100ml

**Causes:** Tincture benzoin compound contain resins. This change in solvent system results in an unavoidable precipitate.

**Remedy:** Addition of tincture with rapid stirring yields a fine colloidal dispersion. So, there is no need of any suspending agents.

**04) Liquefaction of solid mix in a dry state / In a state of dry mix, solids**

**liquefy:** Mixing of two solid substances results in their transformation into liquids.

When certain low melting point solids are mixed together, a liquid or soft mass known as eutectic mixture is produced. This occurs due to the lowering of the melting point of the mixture to below room temperature and liberation of hydrates. If such conditions take place, compounding such powders becomes difficult since the ultimate mixture turns to liquid.

The medicaments showing this type of behavior are camphor, menthol, phenol, thymol, chloral hydrate, aspirin, sodium salicylates, etc.....

**Example: “Insufflations”**

Rx

Menthol – 5g

Camphor – 5g

Water – 60ml

**Causes:** This mixture is a physical incompatibility because both the ingredients in the prescription are liquefiable if mixed together.

**Remedy:** These substances can be dispensed by any one of the following methods. Triturate together to form liquid and mixed with an absorbent (light kaolin, magnesium carbonate) to produce the following powder. The individual

medicaments are powdered separately and mixed with an adsorbent and then combined together tightly and filled in a suitable container.

Hence the corrected prescription is:

Rx

Menthol – 5g

Camphor – 5g

Light kaolin– 0.2g

## **2. Chemical Incompatibilities:**

When the prescription ingredients undergo chemical interactions, a harmful product may form. This gives rise to “**chemical incompatibility**”

A change in the chemical properties of pharmaceutical dosage forms as a result of a reaction between more than two substances. Reaction between two or more substances which lead to change in chemical properties of pharmaceutical dosage form. As a result of this a toxic or inactive or product may be formed.

Chemical incompatibilities occur, due to the chemical properties of drugs and additive like: *pH change, Oxidation-reduction reactions, Acid-base hydrolysis, Double decomposition and Complex formation etc.*

These reactions may be noticed by:

- Precipitation
- Effervescence
- Decomposition
- Color change
- Explosion

**Causes:**

Carbon dioxide is emitted as a result of chemical incompatibilities.

Calcium and magnesium soluble salts with soluble bicarbonate.

Sodium bicarbonate and bismuth subnitrate

Glycerin and sodium bicarbonate with borax.

### **Types of chemical Incompatibility:**

- Oxidation
- Isomerization
- Absorption of Carbon-di-oxide
- Hydrolysis
- Formation of insoluble complexes
- Polymerization
- Decarboxylation
- Combination

There are four types of chemical incompatibility:

1. Tolerated
2. Adjusted
3. Intentional
4. Unintentional

### **Classification of Chemical Incompatibility:**

**Based on chemical interactions**

- **Tolerated incompatibility:** In this type incompatibility, the chemical interactions can be changing the order of mixing the solutions in dilute forms, without or by changing the order of mixing.
- **Adjusted incompatibilities:** In adjusted incompatibility change in the formulation is needed with a compound having equal therapeutic value. E.g.: substitution of caffeine citrate with caffeine in sodium salicylate and caffeine citrate mixture.

#### **Based on nature of chemical reaction**

- **Immediate incompatibilities:** - If the chemical reaction takes place, immediately after combining the prescription ingredients, they are called immediate incompatibilities. Hence, they should be dispensed only after correction.
- **Delayed incompatibility:** - When the chemical reaction proceeds at a very slow rate and no appreciable visible change occurs which may develop on keeping the product for a long time are called delayed incompatibility.

#### **Based on the prescriber**

- **Intentional:** When the prescriber knowingly prescribes the incompatible drugs.
- **Unidirectional:** When the prescriber prescribes the drugs without knowing that there is incompatibility between the prescribed drugs.

Generally, reaction between strong solution proceed at a faster rate and the precipitates are formed are thick and do not diffuse readily.

Reaction between the dilute solutions proceeds at a slow rate and the precipitates formed are light and diffuse readily in the solution. Hence, the reacting substances should be diluted as much as possible before mixing.

### Corrections of Chemical Incompatibility:

This type of incompatibility can be corrected by the following addition:

**01. Preventing Drug Oxidation:** The measure which should be taken to prevent drug oxidation are;

- i. **Antioxidants:** Vitamin E, C and inorganic Sulphur compounds should be added.
- ii. **Chemicals forming complexes** with metals; EDTA, Benzalkonium chloride should be added.
- iii. The drug should be protected be added:
  - Storing in dark container, storing in dark places
  - Packing with light absorbing substance (e.g., oxybenzene)
- iv. Drug pH should be maintained using buffers.
- v. An appropriate solvent (instead of water) should be selected.
- vi. The drug should be protected from air by; placing in closed container and replacing oxygen with nitrogen.
- vii. The drug should be stored at low temperature.

**02. Preventing Drug Hydrolysis:** The measures which should be taken to prevent drug hydrolysis are:

The drug should be protected from moisture by packing moisture impermeable substance and adding water absorbing substance ( $\text{CaCO}_3$ )

**03.** Drug pH should be maintained using buffers, Surfactants should be used for micelle formation.

**04.** The solubility of substance (suspension instead of solution) should be reduced.

### Methods to remove Chemical Incompatibility:



The prescription involving the formation of diffusible or indiffusible precipitates are dispensed by either of the two methods discussed below:

- 1) **Method A:** This method involves dividing the vehicle in two equal portions and dissolving one reacting substance in one portion and the other in another portion. The two portions containing the reacting substances are gradually mixed vigorous stirrings. The method A of removing chemical incompatibility is applicable when very small amount of diffusible precipitate is formed.
- 2) **Method B:** This method involves dividing the vehicle in two equal portions and dissolving one reacting substance in one portion and the other portion is triturated in a mortar with tragacanth powder. This results in a smooth mucilage which is mixed with the other reacting substance. In the final step, the two portions containing the reacting substance are gradually mixed with vigorous stirrings. The method B of removing chemical incompatibility is applicable when indiffusible precipitates are formed in an appreciable portion of the mixture.

A secondary label: “**SHAKE THE BOTTLE BEFORE USE**” should be fixed on the container whenever method A or method B is followed in dispensing the prescription.

### **Therapeutic Incompatibilities:**

In simple terms, it means altering the therapeutic effects of a drug by administering it concurrently with another. Drug interactions are also called interactions between drugs. Therapeutic incompatibility is an unintentional change in pharmacodynamic or pharmacokinetic parameters resulting from the use of medicinal products.

When one or more drugs produce a response or intensity which differs from that intended in the patients, **therapeutic incompatibility** arise.

For example:

- 01.** Drugs containing amino acids cannot be taken with monothioglycerol oxidase inhibitors.
- 02.** The bacterial action of penicillin is antagonized by chloramphenicol.

**Mechanisms of Therapeutic Incompatibility:** The mechanism of therapeutics incompatibility is grouped as follows:

- 1) Pharmacokinetics:** This deals with the effect a drug produces on another drug, e.g., absorption, distribution, metabolism and excretion.
- 2) Pharmacodynamics:** This deals with the pharmacological action produced when two or more drugs are interacted, e.g., synergism, antagonism, altered cellular transport and effect on the receptor site.

**Classification of Therapeutics Incompatibility:**

Therapeutic incompatibility is of the following types;

- 01. Overdose:** In this type of incompatibility, a patient health may convert a single dose into an overdose. Including example; a dose which is normal for a 70kg adult male by an overdose for a person of lower weight. Overdose is also termed as excessive single dose.

**Example;**

Rx

Atropine sulphate 6mg

Phenobarbital 360mg

Make capsules.

**Label:** One capsule to be taken three time a day before meals.

Atropine sulphate and phenobarbital doses in this prescription are 12 times more than normal doses. The physician thought of prescribing 12 capsules but either, they wrote a faulty prescription or the prescription itself is not complete.

**02. Underdose:** In this type of incompatibility, a drug effect is either reduced or antagonized by another drug. A few examples represent the condition of undergoes by the combination different drugs;

- Combination of sympathetic stimulants (methamphetamine) with parasympathetic stimulants (pilocarpine)
- Combination of purgatives (castor oil, paraffin) with anti-diarrheal agents (bismuth carbonates)
- Combination of acidifiers (dilute hydrochloric acid) with alkalizers (sodium bicarbonate)

**03. Improper consumption by patients:** Patients requires special directions for drug administration which should be mentioned in the prescription. If the patients are not advised or they do not follow the prescribed direction, the drug will fail to produce the desired therapeutic action due to low bioavailability.

**For example;**

Rx

Tetracycline hydrochloride 250mg

Prepare capsules.

Supply 10 capsules.

**Label:** Take one capsule every six hour.

If tetracycline is consumed with milk, the calcium present in milk will inactivate tetracycline and it will fail to produce the desired effect.

**04. Contraindicated Drugs:** Some drugs either alone or in combination are contraindicated in particular diseased condition.

**Example:**

- Corticosteroids are contraindicated in peptic ulcer.
- Vasoconstrictors are contraindicated in hypertension.
- Barbiturates and morphine are contraindicated in asthma.

**Methods to removing the therapeutic Incompatibility:** The therapeutic incompatibility can be removed by the following method:

- Dosing error should be avoided.
- The drug should be given in the specific desired form wherein the drug produces the maximum effect.
- The drug contraindicated in patients with specific disease should not be used.
- The drugs producing maximum drug interactions should not be used

**UNIT : 5**

# Chapter: 01

## SEMI-SOLID DOSAGE FORM

Semi-solid dosage forms are dermatological preparations intended to apply externally on the skin to produce local or systemic effects 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 the skin and are superior to the conventional semisolid dosage form.

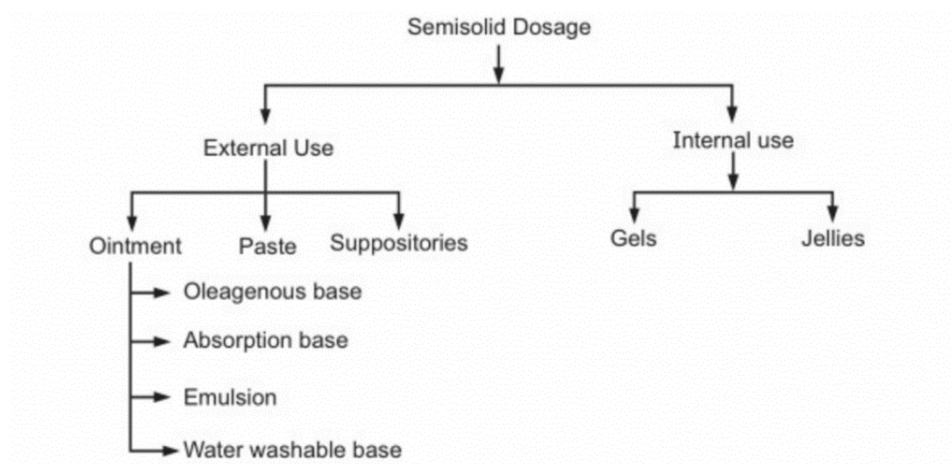
**Definitions:** The semi-solid dosage form are associated with the following important terms such as:

- 1) **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.
- 2) **PASTES:** Pastes are preparations that contain a large amount of finely powdered solids such as starch and zinc oxide. These are generally very thick and stiff.

- 3) **JELLIES:** These are thin transparent or translucent, non-greasy preparations. They are similar to mucilage because they are prepared by using gums but they differ from mucilage in having jelly-like consistency.
- 4) **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.
- 5) **GELS:** These are jelly-like semisolid dispersions of a drug meant to be applied to the skin.
- 6) **SUPPOSITORIES:** These are meant for insertion into the body cavities other than the mouth. They may be inserted into the rectum, vagina, or urethra.
- 7) **POULTICES:** These are also known as **cataplasms**. They are soft viscous wet masses of solid substances.
- 8) **PLASTERS:** These are semi-solid masses applied to the skin to enable prolonged contact of the 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.

#### **Classification of Semi-Solid Dosage Form:**

The semi-solid dosage forms can be classified as per shown below:



**Ideal Properties of semi solid dosage forms:** The various properties of physical, physiological and application of semi-solid dosage forms such as followings:

**Physical Properties:** The physical properties mainly discussed in the below section such as follows:

- They should have a smooth texture.
- They should be elegant.
- They should be non-dehydrating.
- They should be non-gritty.
- Semi-solid dosage forms possess non-greasy and non-staining property.
- They are non-hygroscopic.

**Physiological Property:** There are lots of physiological properties including in the semi-solid dosage form such as:

- They should be non-irritating.



- They should not alter skin functioning.
- They should be easily miscible with skin secretion.
- They should have a low sensitization effect.

**Application Property:** Some of them lots of application properties such as below:

- a) They should be easily applicable with efficient drug release.
- b) They should possess high aqueous washability.

**Advantages of Semi-Solid Dosage Form:** The various merits involving in the semi-solid dosage forms mentioned below section:

- It is used externally.
- The probability of side effects can be reduced.
- First, pass gut and hepatic metabolism is avoided.
- Local action and Site-specific action of the drug on the affected area.
- Convenient for unconscious patients or patients to have difficulty in oral administration.
- Suitable dosage form for bitter drugs.
- More stable than a liquid dosage form.

**Disadvantages of Semi-Solid Dosage Form:**

- The accuracy can't be measured, for the semisolid dosage form.
- May cause staining.
- They are bulky to handle.
- Application with a finger may cause contamination.
- Physico-chemical is less stable than a solid dosage form.
- May cause irritation or allergy in some patients.

## **Factor influencing penetrations of drugs:**

### **a) Factor associated with skin:**

**Hydration of the horny layer:** Increase hydration of horny layer is increase penetrations of drug.

**Thickness of the horny layer:** Horny layer thickness is increasing its decrease drug penetrations.

**Other conditions** like age, disease, injury etc. are also affected.

### **b) Factor associated with the medicament:**

**Solubility of the drug:** Lipid soluble drug are easily penetrations.

**Dissociation constants (pKa):** If the pKa value is increasing drug penetrations is decrease.

**Particle size:** Particle size is decrease it is increasing penetrations of molecules.

**Crystal structure:** Metastable form are rapidly penetrated.

### **c) Factor associated with vehicle:**

**Alterations of skin permeability:** Organic solvent is increasing hydration of penetrations.

**Penetrations of the epidermis:** Bases miscible with the sebum penetrate into the region of the skin in which sebum is found.

**Hydration of stratum corneum:** An occlusive layer reduces evaporation of water from skin. Increasing hydration of the horny layer and therefore promotes penetration of medicament.

**THE VARIOUS EXCIPIENTS IN SEMI-SOLID DOSAGE FORM:** The various excipients used in the formulations of semi-solid dosage forms as followings discussed:

- 1) Bases
- 2) Preservative
- 3) Humectants
- 4) Antioxidants
- 5) Emulsifier
- 6) Gelling agent
- 7) Permeation enhancer
- 8) Buffers

**01. Bases:** It is one of the most important ingredients used in the formulation of the semisolid dosage form. Ointment bases do not merely act as the carriers of the medicaments, but they also control the extent of absorption of medicaments incorporated in them.

The ointment base is the substance or part of an ointment preparation which serves as carrier or vehicle for the medicament.

Ideal characterization of bases used in semisolid dosage form: They should be:

- Inert, non-irritating, and non-sensitizing.
- Compatible with skin pH and the drug.
- Good solvent and/or emulsifying agent.
- Emollient, protective, non-greasy and easily removable.
- Release medicament readily at the site of application.
- Pharmaceutically elegant and possess good stability.

**Selection of semi solid bases:** The selection of semi-solid bases such as describing in the below section:

1. Desired release rate of the drug substance from the ointment base.
2. Rate and extent of topical or percutaneous drug absorption.
3. Desirability of occlusion of moisture from skin.
4. Stability of the drug in the ointment base.
5. Effect of drug on the consistency of base.
6. Easy removal of base on washing.
7. Characteristics of the surface to which it is applied.

**Classification of Bases:** According to USP ointment bases are classified into four general groups:

- *Hydrocarbon bases* (Oleaginous bases) (Petrolatum, Paraffin, Lanolin, etc.).
- *Absorption bases* (Cold cream, anhydrous lanolin, etc.).
- *Water-removable bases* (Oil in water).
- *Water-soluble bases* (Polyethylene glycol).

**02. Preservatives:** Preservatives are used to inhibit the growth of contamination of microorganisms.

**Example:** Para-hydroxybenzoate (parabens), phenols, benzoic acid and sorbic acid etc.

**03. Humectant:** The humectant is a hygroscopic substance used to increase the solubility of the active ingredient to increase skin penetration. It's also used to improve the hydration of the skin.

**04. Antioxidants:** Oxygen has the capability to become a part of potentially damaging molecules called “free radicals”. Free radicals can attack the healthy cells of the body. It can break their structure and that's why the function is also affected.

Example: Butylated hydroxyanisole, Butylated hydroxytoluene.

**05. Emulsifiers:** Emulsifiers are used to improve the stability of an emulsion by increasing its kinetic stability. It reduces surface tension and prevents coalescence. It helps to increase the viscosity at low concentration.

**Sodium lauryl sulfate:** Oil/Water emulsion - Sodium stearate and calcium stearate.

**Glyceryl Monostearate:** This is a weak Water/Oil emulsifying agent and it is used as a stabilizer and emollient in the Oil/Water emulsion.

**06. Gelling Agent:**

**07. Permeation Enhancer:** Skin can act as a barrier. There are various penetration enhancers that can help the drug to penetrate through the skin.

Example: Oleic acid.

**08. Buffers: Buffers** are added for various purposes. Such as:

- (i) Compatibility with skin.
- (ii) Drug solubility.
- (iii) Drug stability.
- (iv) Influence the ionization of drugs.

## **OINTMENTS:**

Ointments are homogenous, translucent, viscous semi-solid preparations, most commonly a greasy, thick oil (oil 80% and water 20%) intended for external application to the skin or mucous membrane. Drug ingredients can be dissolved, emulsified or suspended in the ointment base.

**Preparation of Ointment:** The Preparation of the ointment as follows:

1. All components of the base are uniform, meaning there are no lumps of high melting point constituents, liquids do not separate, and insoluble powders are evenly dispersed throughout.
2. Grittiness is absent, namely finely divided insoluble powders, and large lumps of particles are not present.

**This requires precision in preparation methods. Ointments are commonly made by mixing two techniques:**

1. Fusion is one of the methods for ensuring homogeneity, in which the ingredients are melted together.
2. Grinding together finely divided soluble substances with a small amount of a basis or one of its ingredients and then diluting with gradually increasing amounts of the basis to evenly disperse the soluble components.

**Fusion method for preparing ointments:**

All solid ingredients included in cremes or ointments, such as beeswax, cetyl alcohol, stearyl alcohol, stearic acid, paraffin, etc. should be melted before application to prevent burning. The melting can be accomplished in two ways:

**Method I:** Melting the components is done in order of decreasing melting points, which means that the substances with the highest melting points should be melted first, the substances with the next melting points, and so on. When the medicament is added to the ingredients in a liquid form, a thorough stirring is carried out until the mixture cools down and becomes homogenous.

**Advantages:** Substances with low melting points will be protected from overheating in this way.

**Method II:** Substances with low melting points will be protected from overheating in this way.

**Advantages:** There was a lower maximum temperature reached and a shorter reaction time compared to Method-I, possibly because substances with low melting points acted as solvents on the other components.

**Cautions:**

- 1) As components melt (beeswax, wool alcohols, paraffin, higher fatty alcohols, emulsifying waxes), waxy components are ground by stirring and the dish is lowered so that the highest surface area is heated.
- 2) Various ingredients may discolor as a result of oxidation, such as the fat and alcohol in wool, and these discolored surfaces need to be cleaned before use.
- 3) When ointment is cooled, stir it thoroughly until it has completely set, taking care not to cause localized cooling, for example, by using a cold spatula or transferring the dish to a cold container before it has set completely. In case these precautions are ignored, hard lumps will not separate.
- 4) In addition, vigorous stirring causes excessive aeration, so it should not be done after the ointment is thickened.
- 5) Ointment bases are greasy, so many of the constituents tend to pick up dirt while being stored, which can be observed after melting. In both cases, after allowing the melt to sediment, the supernatant is decanted, or the muslin is passed through a warm strainer with support. Once melted, the clarified liquid is collected in a second bowl hot enough to collect it.
- 6) As a result of the separation of the ingredients that compose the high M.P. of the product, it becomes granular after cooling. The product should be remelted, with the minimum amount of heat, and stirred once more.

## **PASTES:**

Pastes are homogeneous semisolid dosage form contains high conc. of insoluble powder substance (not less than 20%) dispersed in the suitable base.

The paste is usually less greasy, more absorptive & stiffer than ointments. They have good adhesion on skin & they do not melt at ordinary temperature.

### **Preparation of pastes:**

To make pastes, you must grind them and fuse them, just like ointments. Typically, liquid or semisolid bases are triturated. For bases that are semisolid or solid, the Fusion method must be used.

### **Preparation 1:**

<b>Formula</b>	<b>Quantity</b>
<b>The Zinc Oxide it is finely sifted</b>	<b>25 g taken as a sample</b>
<b>A starch finely sifted</b>	<b>25 g taken as a sample</b>
<b>The white soft paraffin</b>	<b>50 g taken as a sample</b>

This preparation consists of a semi-solid paste formed by fusion and trituration.

### **Procedure:**

- The starch powder and zinc oxide are filtered through sieve no. 180.
- A water bath is used to melt soft paraffin.
- It is required to take the required amount of powder in a cold mortar, mix with melted base, and triturate until smooth. A cooling process is then performed to mix in the remaining base.



## **Preparation 2:**

<b>Zinc Oxide fined shifted</b>
<b>Coal tar</b>
<b>Emulsifying agent</b>
<b>Starch</b>
<b>Yellow soft paraffins</b>

### **Type of preparation:**

The paste is made by fusing semi-solid components.

### **Procedure:**

#### **Method I:**

- A tared dish is used to melt emulsifying wax (70°C).
- A dish is used to weigh coal tar and Mixed.
- Melted paraffin is added to the tar-wax mixture after it has been melted in a separate dish (70 degrees.
- Mix until well combined. To make sure everything is blended well, give it one last stir.
- The mixture was allowed to cool at about 300°C, and the mixture was combined with zinc oxide (previously filtered through 180 meshes) and starch. The mixture was then cooled.

-

## **Method II:**

It was melted together with paraffin, blended well, and stirred until almost set. On a warm tile, the powder and tar are mixed. This eliminates the possibility of overheating the tar.

## **CREAMS:**

Creams are semisolid dosage forms containing more than 20% water or volatile components and typically less than 50% hydrocarbons, waxes, or polyols as vehicles. They may also contain one or more drug substances dissolved or dispersed in a suitable cream base.

### **Preparation of creams:**

- **Trituration:** When adding finely divided insoluble powders or liquids, geometric dilution is used. When adding liquids, a well is made into the center. To avoid air pockets, we used glass slabs when smaller quantities were needed. Large quantities of powder were ground with a mortar and pestle.
- **Levigation:** Adding coarse particles that are insoluble, this is also referred to as "wet grinding". A molten liquid base, a liquid base, or a semisolid base is used to rub coarse powder. The shearing force must be considered to avoid grittiness.
- **Fusion method:** In the fusion technique, drugs and other solids are dissolved in an ointment base and then combined. By melting the ingredient into the base, the soluble constituents are dissolved. After speculation or trituration, the congeal mixture is smoothed out. Fusion uses special techniques to ensure that the base and other components will not be damaged by thermal degradation.

## **JELLY:**

Jellies are transparent or translucent non-greasy semisolid dosage form. They are less greasy compare with gel. They are mainly used for mucous membrane for lubricating, antiseptic purpose. Jellies are also used for lubricating surgical gloves, catheters & rectal thermometers. Vaginal jellies & contraceptive jellies are also commonly used.

**Preparation of Gels:** Three methods can be used:

- 01. Cold method:** After cooling water to 4 to 100 degrees, it was poured into a mixing vessel. The peeling agent was added slowly and agitated until the complete solution was reached. Temperatures below 100 °C were maintained during the melting process. A solution of the drugs was slowly added while mixing gently. The liquid should be transferred to a container and allowed to warm to room temperature, where it will become a clear gel.
- 02. Dispersion method:** Stirring the gelling agent in water at 1200 rpm for 30 minutes dispersed the gelling agent. The nonaqueous solvent was used to dissolve the drug. The preservative was also added. Continuous stirring was performed while adding this solution to the gel above.
- 03. Fusion method:** This method involves the use of various waxy materials as gallant in a non-polar medium. In this method, waxy materials are melted and drugs are added. A uniform gel was formed by stirring slowly until it was dissolved.

**Following jelling agents are used:**

- Tragacanth
- Sodium alginate
- Pectin, Starch
- Gelatin, Cellulose derivatives

## EVALUATION OF SEMI SOLID DOSAGE FORM:

Pharmaceutical semi-solid dosage forms include creams, ointments, gels, and pastes. The following are some of the key factors that are evaluated for pharmaceutical semi-solid dosage forms:

- 1. Appearance:** The visual appearance of the product is assessed for uniformity in color, texture, and homogeneity.
- 2. Consistency:** The consistency of the semi-solid dosage form is evaluated using a penetrometer or a rheometer to ensure that it is suitable for use and that it can be easily applied to the skin.
- 3. pH:** The pH of the semi-solid dosage form is measured to ensure that it is within an acceptable range for the intended use.
- 4. Active ingredient content:** The amount of active ingredient present in the product is determined to ensure that the correct dosage is being delivered to the patient.
- 5. Stability:** The stability of the semi-solid dosage form is evaluated over time to ensure that the active ingredient remains effective and that the product does not degrade or lose its physical properties.
- 6. Microbial content:** The microbial content of the product is evaluated to ensure that it is free from contamination and safe for use.
- 7. In-Vitro drug release:** In vitro drug release testing is performed to assess the release rate of the active ingredient from the semi-solid dosage form.
- 8. Patient acceptance:** The ease of application and patient acceptance of the product is evaluated to ensure that it is a viable dosage form for the intended patient population.



Note:



# ABOUT THE AUTHORS



**Prachi Pandey** is the author of this book. I am pursuing my M. Pharm (Pharmaceutics) from NIMS University, Jaipur, Rajasthan, and completed my B. Pharm from Amity University, Lucknow, Uttar Pradesh. I had published a number of review articles under UGC Care list of Journal and Scopus on the topics of Pharmaceutics based on Novel Drug Delivery System (nano-particles), Computer Aided Drug Design, Polymers and many more. I am active on researchgate as well as on google scholar. I also have slideshare profile along with my linkdin profile. I published my first practical book on "Pharmaceutics Practical Ist" for M. Pharm 1st Semester which is available on amazon as e-book.



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