CHAPTER - 5

PHARMACEUTICAL FORMULATION

PART I– TABLETS

Points to be covered in this topic

5.1 TABLETS

- 5.1.1 Types of Tablets
- 5.1.2 Coated Tablets
- 5.1.3 Uncoated Tablets
- 5.1.4 Various Modified Tablets
- 5.1.5 Evaluation of Tablets

TABLET

5.1 INTRODUCTION

- **According to Indian Pharmacopoeia**, Pharmaceutical tablets are solid, flat or biconvex unit dosage form prepared by compressing a drug or a mixture of drug with or without diluents.

- They may be either **circular flat or biconvex in shape.**
- It may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characterstics.

❖ Advantages of tablets

- Tablets have the **greatest dose precision** and the least content variability.
- Its cost is lowest of all oral dosage form.
- It is lighter, compact, easiest and cheapest to package and strip.

❖ Disadvantages of tablets

- Tablets are **difficult to swallow** in case of children and unconscious patients.
- Drugs with poor wetting, slow dissolution properties, may be difficult to formulate or manufacture as tablet that will still provide adequate or full drug bioavailability.

❖ Ideal characteristics of tablets

- A tablet should have **elegant product identity** with free from defects like chips, cracks, discoloration, and contamination.
- It should have **sufficient strength to withstand mechanical shock** during its production packaging, shipping and dispensing.
- It should have the **chemical and physical stability** to maintain its physical attributes over time.

5.1.1 Types of Tablets

There are various types of tablets according to route of administration as given in Table 5.1

Table 5.1: Types of Tablets

TYPES OF TABLETS	DESCRIPTION
ORAL TABLET FOR INGESTION	
Compressed tablet	**Uncoated tablet** made by compression and intended **to provide rapid disintegration and drug release.**
Multiple compressed tablet	These are compressed tablet in which the granules of different drug **compressed into two or more layer** in the same tablet. **Two class –** Layered tablets and compression coated tablet**.**
	Multiple layered tablets - These are compressed tablets in which the granules of different drugs are compressed into two or more layers in the same tablet. **Versa press** is used for the preparation of layered tablets.
	Compression coated tablet (Tablet in tablet)- In this, one drug is compressed around previously compressed tablet of another drug, usually called as pre-compressed tablet.
Enteric coated tablet	Tablet are **coated with polymer (e.g., cellulose acetate phthalate**) that does not dissolve under acidic condition of stomach but **dissolve in alkaline condition of the small intestine.**
Chewable tablet	Intended to be **chewed in the mouth before swallowed.** Provide unit medication for infant and children and not required disintegrants. **e.g., Antacid and Vitamin tablet.**
Film coated tablet	These are the **conventional tablet coated** by the film of polymer to improve the **appearance of the formulation and mask the taste.**
Sugar coated tablet	Sugar coated tablet is done for **mask the bitter taste of drug and improve appearance.**
Controlled release tablet	They are designed to release a drug at a predetermined rate in order to **maintain a constant drug concentration drug concentration** for a specific period of time with minimum side effects

TABLET USED IN ORAL CAVITY	
Buccal tablet	Placed in the **side of cheeks**, absorbed directly into buccal cavity, by first pass metabolism
Sublingual tablet	**Placed under tongue** **e.g., Nitroglycerine, Erythrityl tetranitrate, Glyceryl trinitrate**
Troches and Lozenges	Produce local **effect in mouth or throat,** dissolve slowly in mouth. **e.g., Local anesthetic, Antiseptic, Antibacterial agent**
Dental cone	Compressed tablet placement in the **empty sockets after tooth extraction.** Dissolve in 20 to 40 minutes
TABLET ADMINISTERED BY OTHER ROUTE	
Implantation or depot tablet	**Inserted subcutaneously** by **kern injector** and must be **sterile.** Time duration - 1 month to 1 year. **e.g. Administration of hormones, Progestasert.**
Vaginal tablet	**Dissolve slowly in vaginal cavity e.g. Steroids, Antibiotics**
TABLET USED TO PREPARE SOLUTION	
Effervescent Tablet	**Active medicament + Sod. Carbamate/Citric acid/ tartaric acid.** Produce a solution rapidly with **release of CO_2**
Dispensing Tablet	Should never be dispensed as a dosage form, toxic orally. Added a **given volume of water to produce solution e.g. Silver compound, Bichloride of mercury, Quaternary ammonium compounds**
Hypodermic Tablet	Dissolve completely in **water to form injectable solution.** Administered by **parenteral route.**
Tablet Triturate	Drug mixed with **lactose, dextrose or other suitable diluents**

5.1.2 Coated Tablets

Tablet coating is the process where coating material is applied to the surface of the tablet to achieve the desired properties of dosage form over the uncoated variety.

❖ Objectives of Tablet Coating

- Improving taste, odor, and color of the drug.

- Improving ease of swallowing by the patient.
- Improving product stability.
- To protect against the gastric environment.

❖ **Tablet coating is done by using two processes**

I. **Pan Coating:** In this technique the **coating is done in a pan** made up of copper or stainless steel. The pan is rotated with the help of an electric motor. The tablets to be coated are placed in the pan. Hot air blown in it. After coating, polishing is done with a polishing pan. Pan coating technique is used for sugar coating, film coating and enteric coating.

II. **Press Coating:** In this technique the granules of coating material are prepared and a layer of coating material is placed on the preformed tablet in a **Drycota Rotary Tablet Machine**.

❖ **Types of Tablet Coating**

I. **Sugar coating**

- The process of sugar coating involves the **successive deposition of aqueous sugar solution on the tablet cores as they are rotated and tumbled in a revolving pan by spraying sugar solution** or suspensions into pans and drying off the solvent.

Example: Hyoscine butyl bromide sugar coated tablet, cefixime and ofloxacin tablets, oxandrolone tablets etc.

Steps Involved in Sugar Coating Process

There are 5 steps involved in sugar coating process

Fig 5.1: Steps of Sugar Coating

1. **Sealing:** The tablets are made water proof by depositing a thin layer of water proof materials such as arsenic free shellac, on the surface of the tablets.
2. **Sub – coating:** It involves application of large quantities of sugar-coatings (Acacia & sugar solution) to tablet core. This step round edges and build up the tablet size and increase weight by 50-100%.
3. **Smoothing:** This is done to give sugar coats; several coats of the syrup are applied. Firstly, a heavy coat of grossing syrup is given.

- Colorants are added in this step.
- This syrup contains a high concentration of sugar, dusting powder and coloring material.

4. **Color coating:** It involves the multiple application of syrup solutions (60–70% sugar solids) containing the requisite coloring materials necessary to achieve the desired shade.
5. **Polishing:** This is final step-in sugar-coating process & carried out to impart a shiny distinctive appearance to tablet.
6. **Printing:** Different tablets could be identified by manufacturer' logo, product name, dosage strength or other appropriate code.

II. Film coating

- Film Coating involves the **deposition of a thin layer of polymeric material on the tablet core**. The film/forming substance is usually a cellulose derivative, such as **Hydroxypropyl cellulose, Methyl cellulose, dissolved in a suitable aqueous or non-aqueous solvent.**

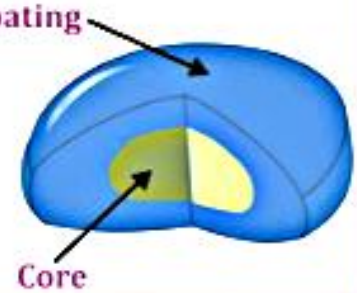
  Example: Erythromycin, Amitriptyline, Diclofenac potassium USP 100 mg, and valsartan 320 mg film-coated tablets.

Methods of Film coating

1. **Pan coating:** It is similar to sugar coating method where tablets are charged in a rotating coating pan & sprayed upon by the coating solution.
2. **Air suspension coating:** In this method, the tablets are placed in a coating chamber and hot air at sufficient velocity to cause fluidization of the tablet bed is introduced through bottom of the chamber.
3. **Dip coating:** This method involves the dipping of the tablet cores into the coating solution. The wet tablets are then dried in conventional manner in the coating pans.

III. Enteric coating

- Enteric Coating is a special type of film coating which allows the **tablet to pass intact through the stomach and to disintegrate in the small intestine this maybe desirable.**



- This method **Protect acid-labile drugs from degradation in stomach.**

Example: Rabeprazole sodium and Domperidone tablets, Dulcolax tablets, Mycophenolate sodium etc.

iv. Gelatin coated Tablets

- Gelatin coated tablets reduces the amount of acid produced by your stomach.

Example: Famotidine Gelatin coated tablet, Glucosamine Gelatin coated tablets etc.

v. Specialized coating

1. **Compressed coating:** A compression-coated tablet is a system in which the entire surface of an inner core is completely surrounded by the coat and these coats prevent drug release from the core until the polymeric coat is entirely eroded.
2. **Electrostatic coating:** Electrostatic coating is a manufacturing process that employs charged particles to more efficiently paint a work piece of a substrate.
3. **Vacuum film coating:** Vacuum film coating is a new coating procedure that employs a specially designed baffled pan. The pan is hot water-jacketed, and it can be sealed to achieve a vacuum system.

❖ Tablet Coating Defects

There are various types of tablet coating defects as shown in Table 5.2

Table 5.2: Tablet Coating Defects

DEFECTS	DESCRIPTION	CAUSES	REMEDIES
Roughness 	Rough or gritty surface	Droplets may dry too rapidly	Moving the nozzle closer to the tablet bed
Orange peel effect 	Film being rough and non-glossy	• Too rapid drying • High solution viscosity	• Use of mild drying condition • Thinning the solution

Bridging 	Coating material fills in the latter or logo	• Poor logo design • Improver atomization pressure • High viscosity of coating solution	• Increase the plasticizer content • Reduce the viscosity of solution
Filling 	Monograph or bisect is filled and become a narrow	• Solution is applied too fast • Over wetting cause filling	• Control fluid application rate • Proper mixing of tablet in the pan
Blistering 	Local detachment of film	• Too rapid evaporation of the solvent from the core • Effect of high temperature	• Uses the mild drying condition
Hazing 	Coating becomes dull immediately	• Too high processing temp. • Coating tablet are exposed to high humidity	• Decrease the plasticizer • Increase molecular weight
Cracking 	Film cracks across the crown of the tablet	• Internal stress in film exceeds then tensile strength • High viscosity of coating solution	• Uses the low molecular polymers
Flacking 	Coating material is removed as large flakes	• Excess formulation moisture • Excessive humidity in coating	• Proper drying of coating material

5.1.3 Uncoated Tablets

- Uncoated Tablets are compressed tablets, **may be a single or double layer.**
- These tablets are designed to **provide rapid disintegration** in the gastric fluid of the stomach.

- Uncoated tablets are formed by **compression of active pharmaceuticals with excipients** likes (bulking agents, disintegrates, binders, lubricants, and some coloring and sweetening agents).

Examples of compressed tablets for oral, Buccal, sublingual, or vaginal administration are Paracetamol 500 mg and Clotrimazole tablets (for vaginal insertion).

➢ Granulation Methods

- Granulation is a technique of particle enlargement by agglomeration.
- Granules prepared in the making tablets have particle size in the range of 0.2-4.0 mm.
- There are mainly three types of granulation methods
  (i) Direct Compression
  (ii) Dry Granulation
  (iii) Wet Compression as given in fig 5.2

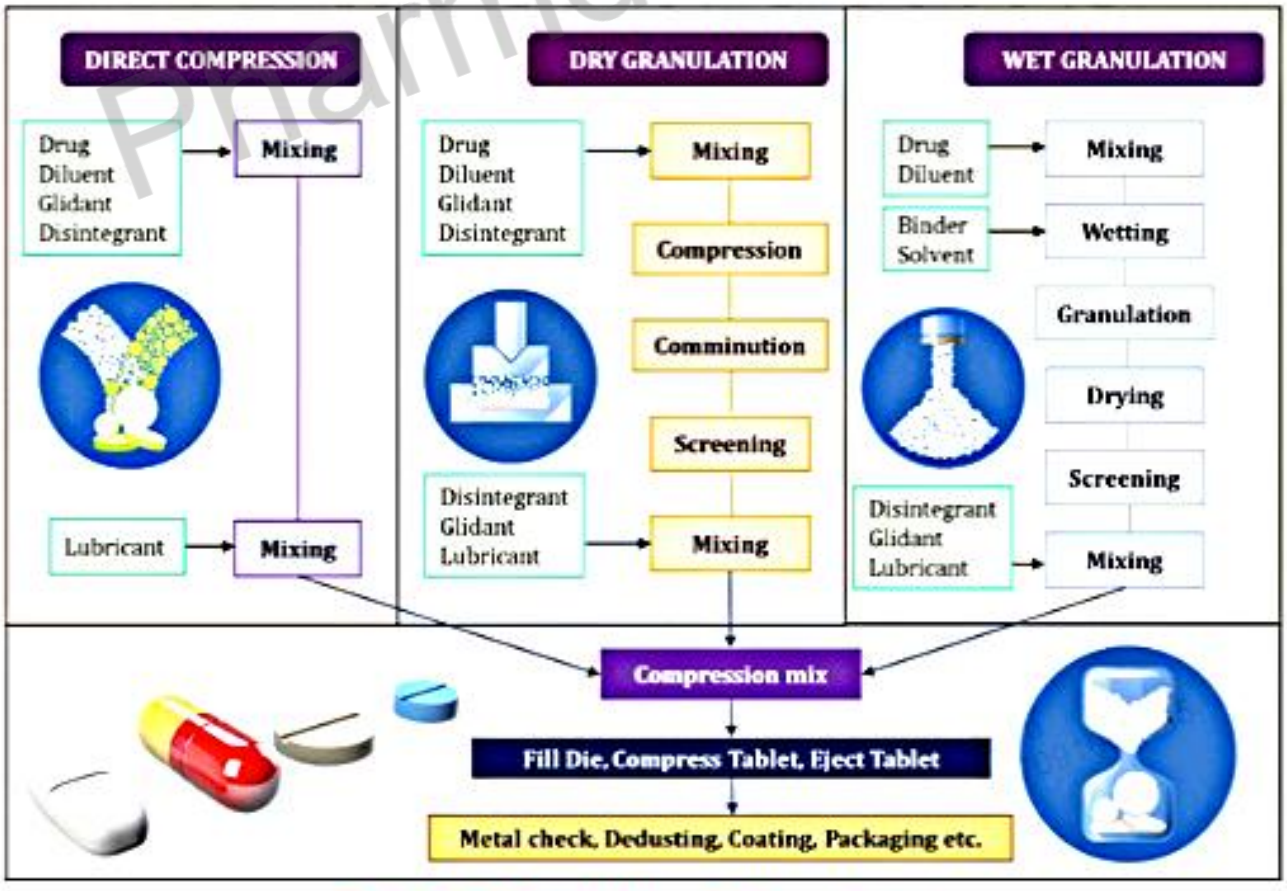


Fig 5.2: Methods of Granulation

1. Direct Compression Method

- Direct Compression Method is a dry process where in the powdered material are directly compressed into without altering its physical nature.
- Direct compression is the most straightforward manufacturing option, with the **fewest manufacturing steps**, making it the easiest to control and least expensive.

➢ **The Direct Compression uses two primary process steps**

Blending the API with excipients and compressing the finished tablets.

❖ Disadvantages

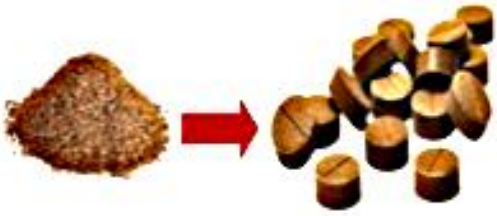
- Excipients are costly.
- Non uniform distribution of drugs in tablet.
- Large doses cannot be compressed directly.

2. DRY GRANULATION METHOD

- The dry granulation process is used to form **granules without using a liquid** solution because the product granulated may be sensitive to moisture and heat.
- This method is also called as **"Double Compression Method"**.
- Forming granules without moisture **requires compacting and densifying powders.**
- Dry granulation is a powder agglomeration process used in
- Pharmaceutical industry to **improve the flow ability of powders** by increasing particle size.

❖ Steps of dry granulation method

➢ **Step 1: Weighing formulation ingredients**



- Here, appropriate quantities of formulation ingredients are dispensed.
- The excipients and the active ingredient must be in finely divided form, otherwise, particle size reduction should be carried out.

➢ **Step 2: Mixing of formulation ingredients**

- The dispensed formulation ingredients are mixed in a powder mixer until a uniform powder mix is achieved.
- It is worth noting that half amount of lubricant in the formula is added at this stage to enhance powder flow during slugging and **to prevent sticking of compressed powder** on the die during pre -compression.

➢ **Step 3: Compression of mixed powders into slugs**

- Here, the mixed ingredients are **compressed into flat large tablets or pallets.**
- This step is **called pre compression (slugging)** and the compacts made in the process are termed slugs.

➢ **Step 4: Milling and sieving of slugs**

- Following slugging, the next stage in the manufacture of tablets by dry granulation usually **involves breaking of slugs into smaller pieces using a hammer mill** or other conventional milling equipment.
- The milled slugs are screened to produce uniform granules.

➢ **Step 5: Mixing with disintegrant and lubricant**

- After screening, the remaining lubricant and other extra granular excipients such as disintegrant, glidant etc. are added to the granulation and mixed gently to achieve a uniform blend.

➢ **Step 6: Compression of granules into tablets**

The **mixed granules are compressed into tablets** using either single or rotary tablet press fitted with appropriate punches and dies.

3. WET GRANULATION METHOD

- Wet granulation is the process in which **formation of granules is done by adding a granulating liquid.**
- Here, a granulating fluid is used for the massing of powder particles.
- However, the fluid used here is **essentially volatile and non-toxic.**

❖ **Steps involved in wet granulation method**

➢ **Step 1: Weighing and mixing of formulation ingredients (excluding the lubricant).**

- This step involves the weighing, sifting of specified quantities of drug substance.

➢ **Step 2: Preparing the damp mass**

- Here, the binder solution is mixed with the powder mixture to form an adhesive mass which can be granulated.

➢ **Step 3: Wet screening/ Screening the dampened powder into pellets or granules**

- The wet massed powder blend is screened using 6- to 12- mesh screen to prepare wet granules.

➢ **Step 4: Drying of moist granules**

- The screened moist granules are dried in an oven at a controlled temperature not exceeding 55°C.

➢ **Step 5: Sizing the granulation by dry screening**

- The dried granules are passed through a screen of smaller size than that used to prepare the moist granules.

➢ **Step 6: Lubrication of granules**

- After dry screening, the dried and screened granules are separated into coarse and fine granules by shaking them on a 250 mesh sieve.

➢ **Step 7: Compression of granules into tablets**

Here, the mixed granules are compressed in a single punch or multi-station tablet press fitted with the appropriate punches and dies.

EQUIPMENT FOR WET GRANULATION METHOD

Table 5.3: Equipment for wet granulation method

EQUIPMENT	FUNCTION
Little ford Mixer	Capable of both wet mass and blending
Diosna Mixer	Mainly works for Mixing, granulating, coating and drying

Sigma Blade mixer, Topo Mixer, FBD	Used for mixing high viscosity liquids
Gral-Mixer	Modification of planetary mixer
Oscillating granulator	Shifting of granules

❖ Stages in the development of Moist Granules

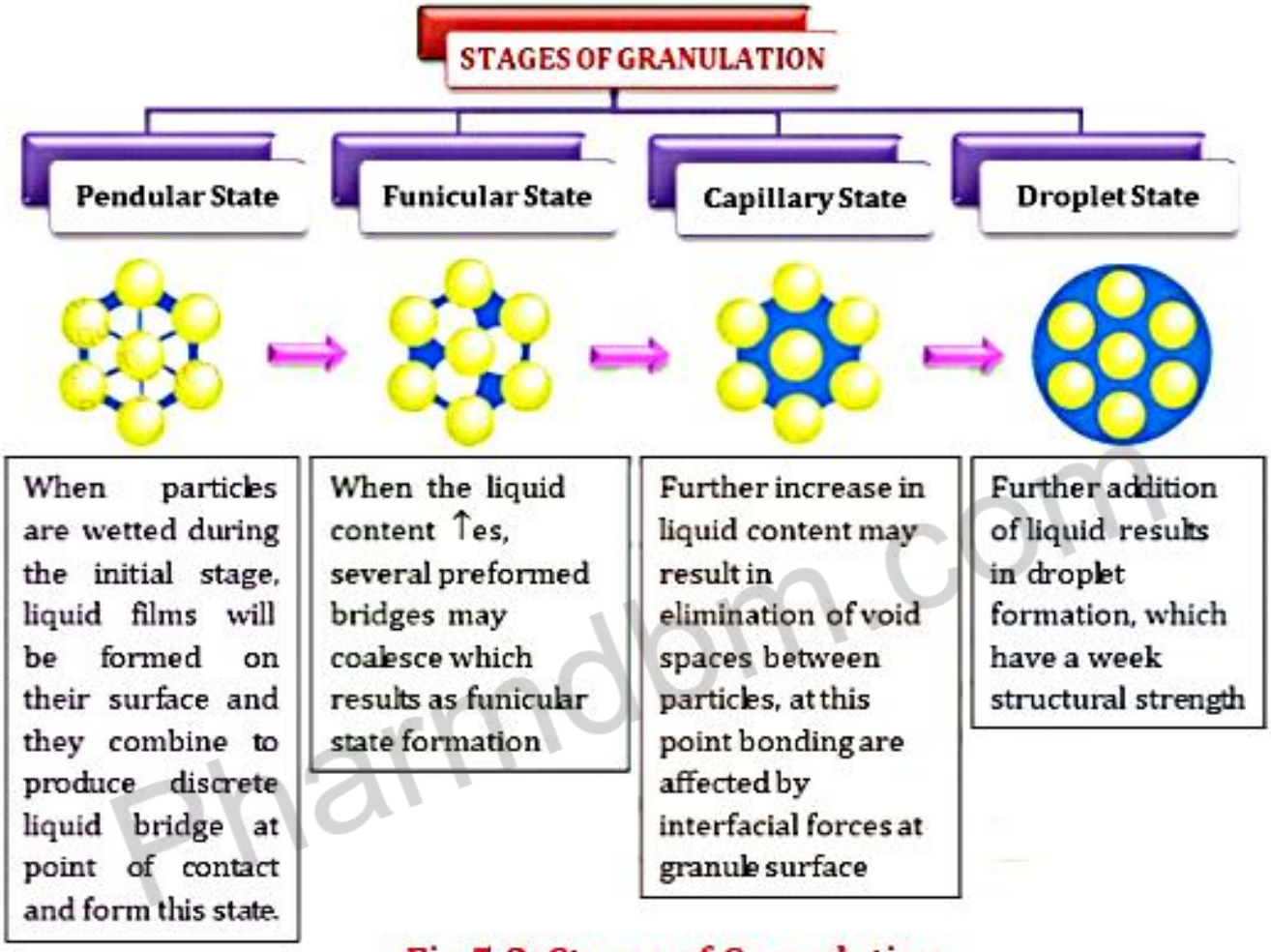


Fig 5.3: Stages of Granulation

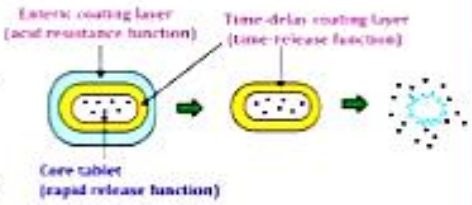
5.1.4 Various Modified Tablets

- Modified tablets are designed to release their medication in controlled manner at pre- determined rate, duration and location in the body to achieve and maintain optimum therapeutic blood level of drug.
- These are of various types as given below:

❖ Sustained-release

- Drugs maintain drug release over a **sustained period** but not at a constant rate are known as Sustained-release tablets.
- These tablets provide actual therapeutic control that would be temporal (time related), spatial (site related) or both.

Benefits of Sustained Release Tablets



- Releases more slowly into the bloodstream.
- Reduces the number of doses which lowers expenses and improves patient compliance, especially for chronic diseases.

Example: Calan SR (Verapamil ER), Alprazolam, Bupropion, Clomipramine, quetiapine etc.

Fast dissolving tablets

- A fast-dissolving drug delivery system is that which **dissolves or disintegrates quickly in the oral cavity upon the contact with saliva,** resulting in solution or suspension of the administered medicine.

- FDT dosage forms, also commonly known as **fast melt, quick melt, orally disintegrating tablets.**

Example: Benadryl Fast melt, Tizanidine HCl, Oxybutynin HCl, Rofecoxib, Ibuprofen, Promethazine Theoclate, Prednisone

Advantages

- No need of water to swallow the tablet.
- FDTs can be easily administered to pediatric, elderly and mentally disabled patients.
- Accurate dosing as compared to liquids.

Disadvantages

- Lack of mechanical strength.
- They must also stay intact during the packaging and shipping process.

Extended-release tablet

- Extended-release tablet designed **to release their medication in controlled manner.**
- These slowly release drug into the body over a period of time usually 12 hours or 24 hours.

- These are also known as controlled release (CR), sustained release (SR), delayed release (DR), Modified release (MR) etc.

Example: Alprazolam XR (Xanax), Ranolazine extended -release tablet, Metoprolol succinate, Tramadol ER etc.

➢ **Advantages**

Extended- release tablet have several advantages as given below:

- It offers less frequent dosing.
- It has less fluctuations in blood levels.
- It shows complete absorption.

➢ **Disadvantages**

- Extended- release tablet may lead to dose-dumping.
- It is expensive.
- Controlled release property may be lost, if the dosage form is broken.

❖ Multilayer tablets (2 layered or 3 layered)

- Multilayer tablets are prepared by repeated compression of powders and are made primarily to separate incompatible drugs from each other.
- It makes possible immediate release quantity in one-layer and slow-release (sustained release) portion in the second, a third layer with an intermediate release might be added.

  Example: Diclofenac and Cyclobenzaprine due to synergistic effect in pain, Metformin HCl and Atorvastatin Calcium for treatment of hyperlipidemia.

➢ **Advantages**

- It allows for multiple incompatible APIs within a single tablet.
- In this each API is compressed into a separate matrix separated by an inert barrier layer.

➢ **Disadvantages**

- It is more expensive as compared to single layer tablet.
- It may lead to layer separation, non-uniformity in weight control of individual layer.

5.1.5 Evaluation of Tablet

Fig 5.4: Evaluation of Tablet

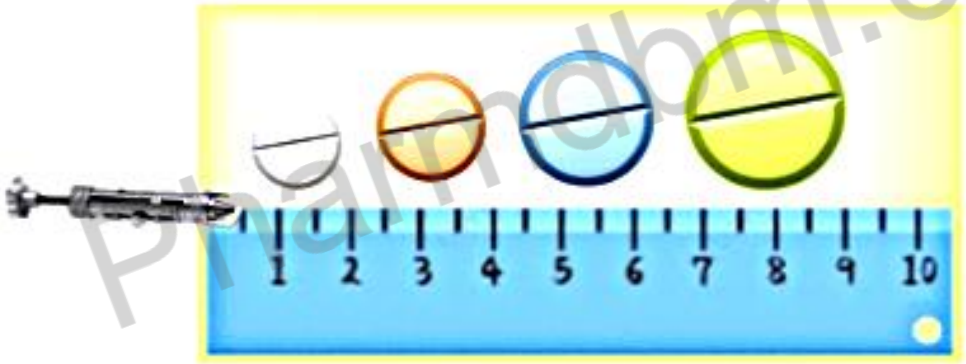
1. General appearance

➢ Color

- Non-uniformity of color over the tablet that is called as **mottling.**
- **Color quantification is determined by**
  - ✓ Reflectance spectrophotometry
  - ✓ Tristimulus colorimetry
  - ✓ Micro-reflectance photometry

➢ Size & Shape

- Compressed tablets shape and dimensions are determined by the tooling during the compression process.
  - ✓ **Crown thickness** of tablet measured by **micrometer.**
  - ✓ **Total crown thickness** is measured by **Vernier caliper.**



2. Tablet hardness

- Hardness can be tested by **placing the tablet between two jaws.**
- One of the jaws then moves towards tablet pushing it against fixed jaw until tablet breaks.

Table 5.4: Equipments used for testing Tablet Hardness

HARDNESS TESTER	COMMENTS	DIAGRAM
Monsanto Tester	Gives strength in Kgs	
Strong-cobb Tester	Force applied by hydraulic pressure & later air Pressure	

Pfizer Tester	Force applied by hydraulic pressure & later air Pressure	
Erweka Tester	Gives strength in Kgs	
Schleuniger Tester	Gives strength in Kgs & strong cobb.	
Vickers	Used to measure the surface hardness.	

3. Friability

- Tablet friability testing involves weighing the sample of tablets and then placing them into a rotating drum.
- The drum is then **rotated 100 times.**
- The sample is then reweighed **to find the % weight loss.**

➢ **Procedure**

- ✓ Pre weighed tablet sample placed in Friabilator.
- ✓ Operated 100 revolution (25 rpm for 4 minutes).
- ✓ Dropping a tablet 6 from 6-inch height.
- ✓ Maximum mean weight loss from three samples of not more than 1 %.

➢ **Friability is calculated by the following formula**

$$\% \text{ friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

4. Uniformity of weight

- The test for content uniformity is required for all dosage forms not meeting the above conditions for the weight.

➢ **Process for Uniformity of weight testing**

- E.g.-. – Say the average weight was 100 mg the sample pass the US weight variation if
  - ✓ **18 tablets remain within 90 mg to 110 mg**
  - ✓ **2 tablets remain within 80mg to 120 mg**

Table 5.5: Average weight of tablet

Average Weight of Tablet		Maximum % of difference allowed
IP	USP	
80 mg or less	130 mg or less	± 10%
More than 80mg – Less than 250 mg	130-324 mg	± 7.5 %
More than 250 mg	More than 324	± 5%

5.Uniformity of content

- Uniformity of Content is a **pharmaceutical analysis parameter for the quality control of capsules or tablets.**

6. Dissolution test

➢ **Dissolution**

- Dissolution test is done to **verify the release of drug in the solution** from the tablet because of binders, granulation, mixing and the coating may affect the release of drug from tablets.

Table 5.6: Apparatus used for Dissolution Test

USP APPRATUS	DESCRIPTION	ROTATING SPEED	DOSAGE FORM
Type 1	Basket apparatus	50-120 rpm	Conventional tablet, chewable tablet, controlled release
Type 2	Paddle apparatus	25-50 rpm	Orally disintegrating tablet, chewable tablet, controlled release, suspension
Type 3	Reciprocating cylinder	6-35 rpm	Controlled release, chewable tablet
Type 4	Flow through cell	N/A	ER, poorly soluble API, Powder, granules, micro particles, implants
Type 5	Paddle over disk	25-50 rpm	Transdermal
Type 6	Cylinder	NA	Transdermal
Type 7	Reciprocating holder	30rpm	CR

➢ Dissolution Test Apparatus

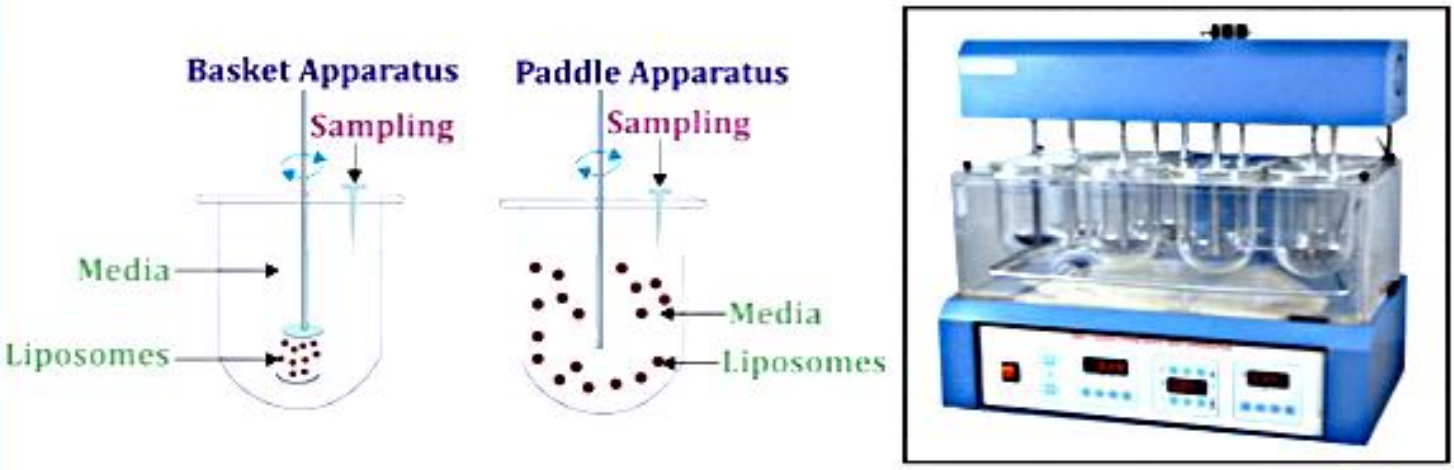


Fig 5.5: Dissolution Test Apparatus

7. Disintegration

- Disintegration is a **process of breaking down a substance into tiny fragments** to improve its solubility in a solvent.

➢ Disintegration time

- Disintegration time is the time required for a dosage form to **break up in to granules of specified size (smaller)** under carefully specified conditions.

➢ Disintegration Test Apparatus

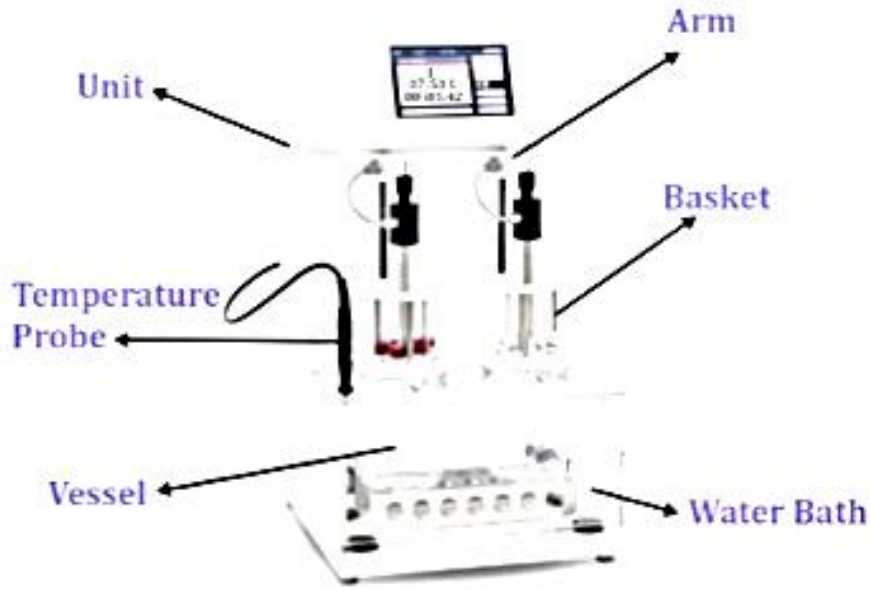


Fig 5.6: Disintegration Test Apparatus

➢ Disintegration Test Condition

Table 5.7: Condition for Disintegration Test

CONDITION	DESCRIPTION
Tablet	6 selected randomly
Glass tubes	6 glass tubes are used
Glass tube length	3 inches
Mesh Screen size	✓ 10 mesh = 1.7 mm (USP) ✓ 08 mesh = 2 mm (IP)
Beaker contains	One liter of water simulated gastric fluid or simulated intestinal fluid.
Temperature	37± 2 °C
Speed	28-32 RPM
Tablets up and down through a distance **5 to 6 cm.**	
Note: Tablet remains 2.5 cm below the surface of liquid on the upward movement and descent not closer than 2.5 cm from the bottom of the beaker.	

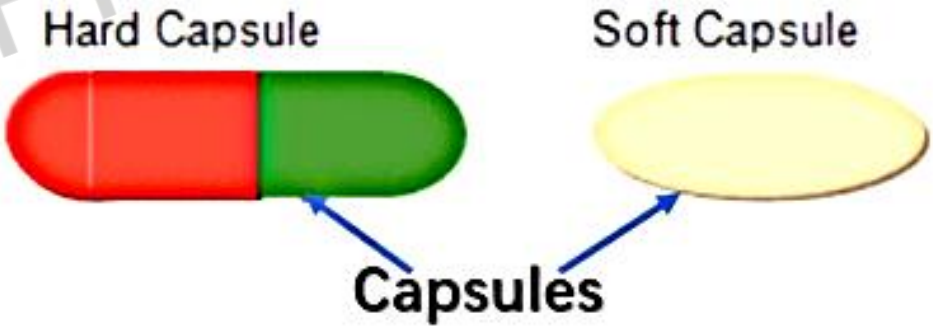
CHAPTER - 5

PHARMACEUTICAL FORMULATION

PART II– CAPSULES

Points to be covered in this topic

- **5.2 CAPSULES**
  - **5.2.1 Hard Gelatin Capsule**
  - **5.2.2 Soft Gelatin Capsule**
  - **5.2.3 Evaluation Test of Capsule**



CAPSULES

5.2 INTRODUCTION

- **Capsules"** are the solid dosage forms consisting of **single dose of drug enclosed in a water-soluble shell** of a suitable form of gelatin.
- **According to USP** capsules are "solid dosage form in which the active ingredients are sealed in a hard or soft container shell".

❖ Advantages of capsules

- Capsule can **mask the odor and unpleasant taste** of the medicine by enclosing them into the tasteless shell.
- They are easy to swallow with water.
- Its appearance is attractive as compare to other dosage form.

❖ Disadvantages of capsules

- Capsules **are not suitable for hygroscopic drugs** as they absorb water present in the capsule.
- It requires special condition for storage.
- Its production speed is slower as compared to tablets.

❖ Condition required in capsule formulation

There are certain condition required for formulation of Capsule as shown in Table 5.9

Table 5.8: Condition required in capsule formulation

S.NO.	CHARACTERISTIC	SPECIFICATION
1.	**Storage condition**	100°F (35°C)
2.	**Processing area temperature**	22° C
3.	**Humidity (handling of empty capsule)**	35-45% (In operating area)
4.	**Bloom strength**	150 – 250 gm
5.	**Viscosity for gelatin**	25 – 45 millipoise
6.	**MOISTURE CONTENT**	
	Hard gelatin capsule	12-16 %
	Soft gelatin capsule	6-10 %

❑ TYPES OF CAPSULES

Capsule is of two types as given below

Fig 5.7: Types of Capsule

5.2.1 Hard Gelatin Capsule

- James Murdock of London patented the two -piece telescoping gelatin capsule in 1847.
- A hard gelatin capsule is a type of capsule that is usually used to contain medicine in the form of dry powder or very small pellets.
- These are suitable for administration of solid medicaments.
- It consists of two parts
  - (a) Body
  - (b) Cap
- The body is first filled with the mixture of active ingredients and suitable excipients and then the cap is placed over it.

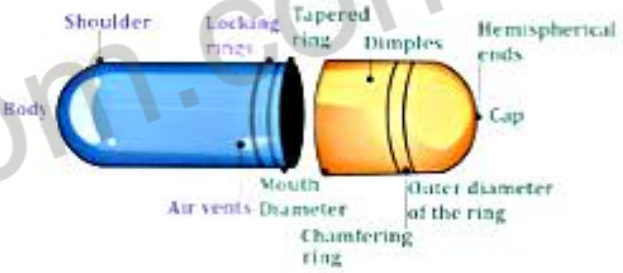


Fig 5.8: Parts of Hard Gelatin Capsule

- The diameter of the body is slightly smaller than the diameter of the cap but larger in length and the cap is slightly larger in diameter and smaller in length.

❖ PRIMARY INGREDIENTS

Hard gelatin capsule mainly consists of Gelatin, Plasticizers and other components.

i. Gelatin

- Gelatin derived from hydrolytic extraction of animal collagen.
- Common source of gelatin is skin, bones, white connective tissue frozen, pork skin.

- It **melts upon heating but solidifies once cooled** and with water it forms a semi-solid colloid gel.

✓ **Types of gelatins**

There are mainly two types of gelatins as given in Table 5.10

TYPE A	TYPE B
Pharma gel A (cationic)	Pharma gel B (anionic)
By acid treatment	By alkali treatment
Isoelectric point (pH-9)	Isoelectric (pH-4.7)
Processing of an acid bone gelatin, isoelectric point pH – 5.5 -6	From green bones

Table 5.9: Types of Gelatins

ii. Plasticizers

- Plasticizers are added to the polymers **used as film forming agents** in order to make the polymer pliable and soft, enhancing the flexibility and plasticity of the films.
- Commonly used **plasticizers in hard gelatin capsules** are glycerol, sorbitol, or polyethylene glycol.

iii. Other Components

- Hard gelatin capsules **consist of coloring agents** such as soluble synthetic dyes, preservatives such as methyl paraben, and lubricants such as stearic acid.
- It also includes insoluble pigments that are used to increase patient compliance. For example, White for analgesia, lavender for hallucinogenic effects.

❖ **FILLING CAPACITY OF HARD GELATIN CAPSULE**

- The ones most commonly employed for human use range from **size 0, the largest, to size 5**, the smallest.
- Size 00 capsules may occasionally be required because of the volume of material to be filled, but this size is not used commercially in large volume.
- Hard gelatin capsules are available in various size ranges on the basis of capsule size and volume to be filled as given in Table 5.10

Table 5.10: Size of Capsule

CAPSULE SIZE	APPROX VOL. IN ML	APPROX. WT IN M FILL WEIGHT (g) AT POWDER DENSITY IF 0.8 g/cm^{3}G
000	1.35	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.104

❖ PRODUCTION OF EMPTY HARD GELATIN CAPSULE

The basis process involved in the production of empty hard gelatin capsule

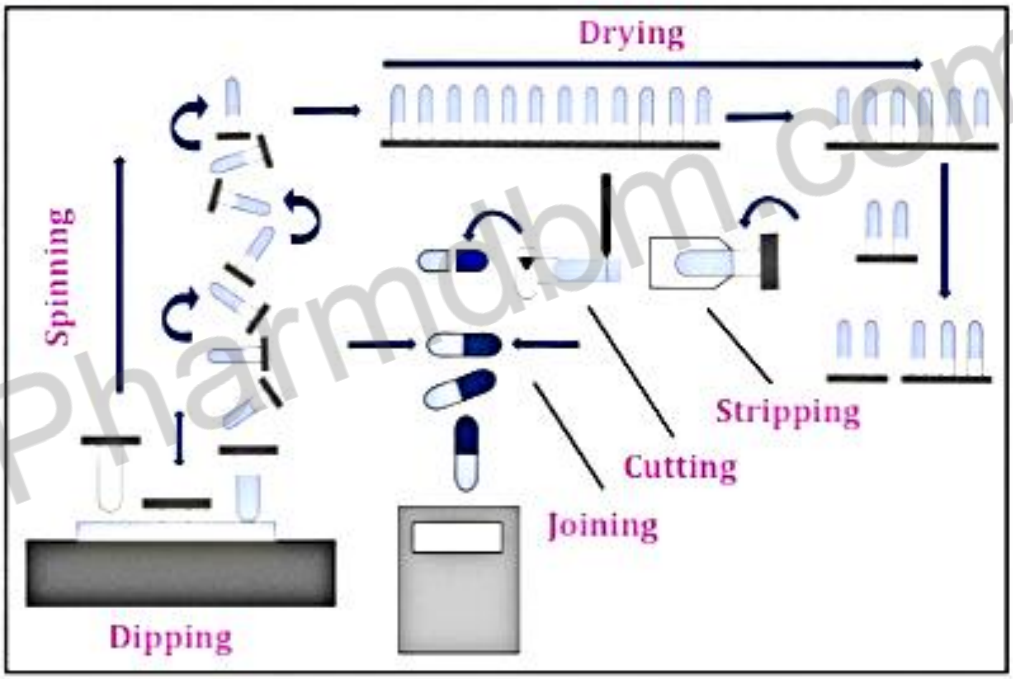
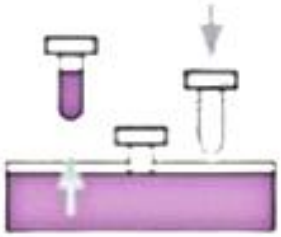


Fig 5.9: Process involved in the production of empty hard gelatin capsule

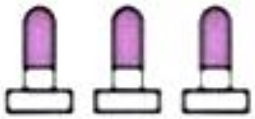
1. **Dipping:** One hundred and fifty pairs of stainless- steel pins are dipped, into a gelatin solution of controlled viscosity to form caps and bodies simultaneously.

   - Temperature of pins =22°C
   - Solution temperature = 50°C.
   - Time = 12 second

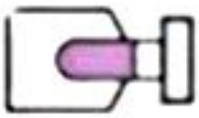


2. **Spinning:** The pins are usually rotated to distribute the gelatin uniformly during which time gelatin may be set or gelled by a blast of cool air.

3. **Drying:** The pins are moved through a series of blast air-drying kilns for the gradual and precisely controlled removal of water.



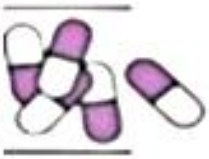
4. **Stripping:** The capsules are stripped from the pins by bronze jaws.



5. **Trimming:** The stripped body and cap are trimmed to length by stationary knives while capsule halves are being spun in chucks or collets. The entire cycle of the machine lasts for approximately 45 min.

6. **Joining:** After trimming the empty capsule shell, the cap and body are joined together by pushing slowly. Then it is ejected from the machine.

7. **Polishing:** Polishing of capsule shell is done by polymer. **Acela-cota** pan is used as a polishing pan.



❖ FILLING OF HARD GELATIN CAPSULE

➢ Hand Operated Capsule Filling Machine

- Place empty capsules onto the loading tray and place tray onto machine. Pull locking lever forward.
- Place powder tray on filler keeps powder from spilling.
- Pour & spread the **pre-measured powder.**
- This allows you to fill more powder in each capsule.
- Turn front knob to the left & lower locking plate.
- Engage lock for locking plate.
- Hold tamper handle & push down on long handle.
- Bodies are pushed up into caps.
- **Lift locking plate** and turn front knob to the right.
- Push down long handle and remove tray of completed capsules.

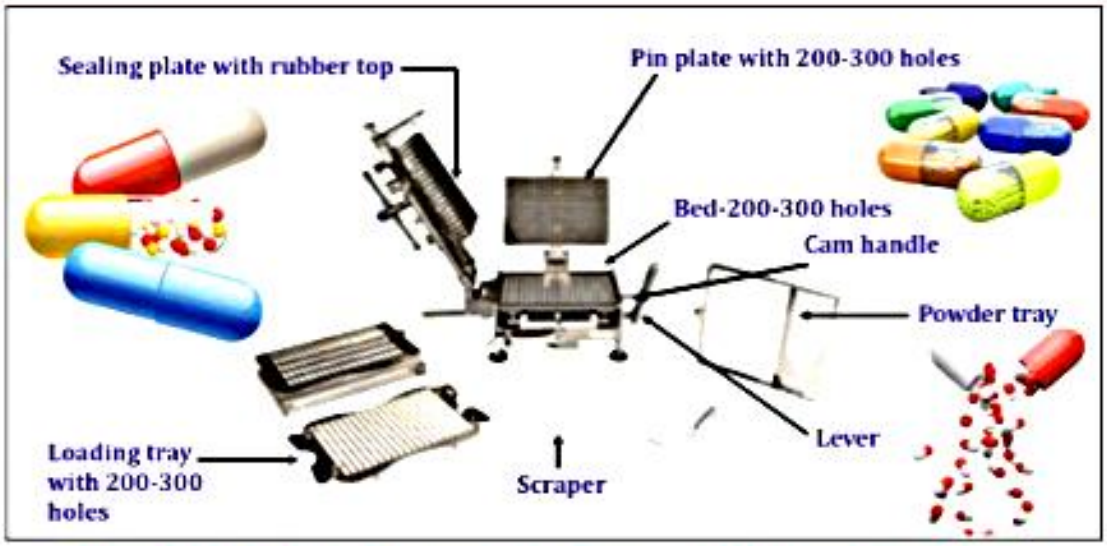


Fig 5.10: Hand Operated Capsule Filling Machine

❖ MACHINE IN CAPSULE PREPARATION

There are various types of machines used in filling of capsule as given in Table 5.12

Table 5.11: Various Capsule filling machine

MACHINE NAME	USE	SPEED (CAPSULE)
Hofliger & Karg	Bulk Powder	300-2500/mint.
Osaka	Based on vibration principle	70000-165000/hr.
Perry	Bulk powder	60000/ hour
Eli Lilly/ parke Davis	For palletized or granular material	1200/mint.
Zanasi	Powder, pellet, granules & tablet	30000-150000/hr.
Farmatic	Bulk powder	16000/hr.
Macofar	Bulk powder	3500-5000 /hr.
MG2	Continuous motion filling of powder	150-1000/mint.

➢ DEFECTS OF HARD GELATIN CAPSULES

Color deviation: It is caused by relative bad stability of selected dyes and pigments.

Short body/cap: It occurs due to insufficient entry of the body/cap into the Collet prior to cutting operation.

Long body/cap: It is caused by a missing knife/broken knife during cutting operation.

Dots/specks: In this, small fragments of shell walls generated during the trimming process getting into the dipping area.

Double cap: In this, loose cap fits over the body of another capsule after one of the caps is loose due to insufficient pre-lock position in joining block.

Damaged edge: It is caused by a blunt knife during cutting operation.

Star ends: It is caused due to uneven distribution of gelatin on dip-coated pins or an excessive amount of gelatin solution on end of the pin.

Damaged print: It occurs due to improper ink viscosity and applying pressure, uneven flow of the ink.

❖ **STORAGE CONDITION OF HARD GELATIN CAPSULE**

- Hard gelatin capsule should be protected from sunlight, excessive heat and humidity.
- It should be stored at **temperature ranges between 15-25°C** and relative **humidity of 35-65%.**
- During transportation, it should have moisture content of 13-16% and relative humidity of 50% at 21°C.

5.2.2 Soft Gelatin Capsules

- Soft gelatin capsule is also known as soft gels as it contains one-piece hermetically sealed soft shells.
- A soft gelatin capsule (Soft gel) is usually used to contain medicine in the form of liquid or powder.
- This capsule dissolved quickly in stomach acid, and the liquid inside is immediately released into the bloodstream.

❖ **NATURE AND CONTENTS OF SOFT GELATIN CAPSULE**

✓ **Soft gelatin capsule**

Soft gelatin capsule consists of following agents

Preservative: Prevent the growth of bacteria and mould in the gelatin solution during storage.

Example: Methyl paraben: Propyl Paraben (4: 1)

Opacifier: An opacifier is added in order to make the ensuing system opaque.

Example: TiO_2 (0.2-1.2%)

Sugar: To produce chewable shell and taste.

Essential Oil: Essential oils are also known as volatile oils, ethereal oils, Aetheroleum, or simply as the oil of the plant from which they were extracted, such as oil of clove, 2% for odor & taste usually referred to as the substrate. The purpose of applying coating may be decorative, functional, or both.

Example: Salol, CAP, Shellac

Formaldehyde: Cross-linked gelatin capsule bodies were prepared by treating the separated capsule bodies with formaldehyde to make them water insoluble.

1% Fumaric acid: To increase acid solubility & reduce the aldehyde tanning of gelatin.

✓ **Soft starch capsule**

- Soft starch capsules are prepared from hydroxypropyl starch.
- Moisture content in **starch ranges between 12-14% w/w** and 50% is bound to starch.

❖ **SIZE AND SHAPE**

- Soft gelatin capsules are available in different size and shape such as cylindrical, oval, elliptical, oblong and special tube shapes.
- The contents in soft gelatin capsules varies from 0.1-30 ml.

❖ **PHYSIOCHEMICAL PROPERTY**

✓ **Bloom or Gel Strength** – It measure cohesive strength of capsule between gelatin molecule and molecular weight of gelatin.

✓ **Gelatin** used for making soft gelatin capsule is obtained from the bone and skin of animals that has **bloom strength of 150-175 g**

Cohesive strength α Molecular weight of gelatin

- ✓ **Viscosity** - Determined by using 6.66% w/w of gelatin solution in water at 60°C using capillary pipette. Range must be in 25-45 milli poise.
- ✓ **Base adsorption –** Base adsorption is defined as the minimum amount of base or vehicle in grams required per gm of solid drug to form a mixture when easily can be encapsulated in SGC.

$$\text{Base Adsorption} = \frac{\text{Weight of base}}{\text{Weight of Solid}}$$

- ✓ **Minim per gram factor- M/G** is volume in minimum that is occupied by one gram of solid plus weight of liquid base required to produce a capsule mixture.

$$(M/G) = (BA+S) \times V/w$$

Soft gelatin capsules are prepared by mainly by 5 processes

i. Plate process

- The plate process is the oldest commercial method of manufacture, involves the pressing two sheets of wet gelatin together between two molds provided with depression.

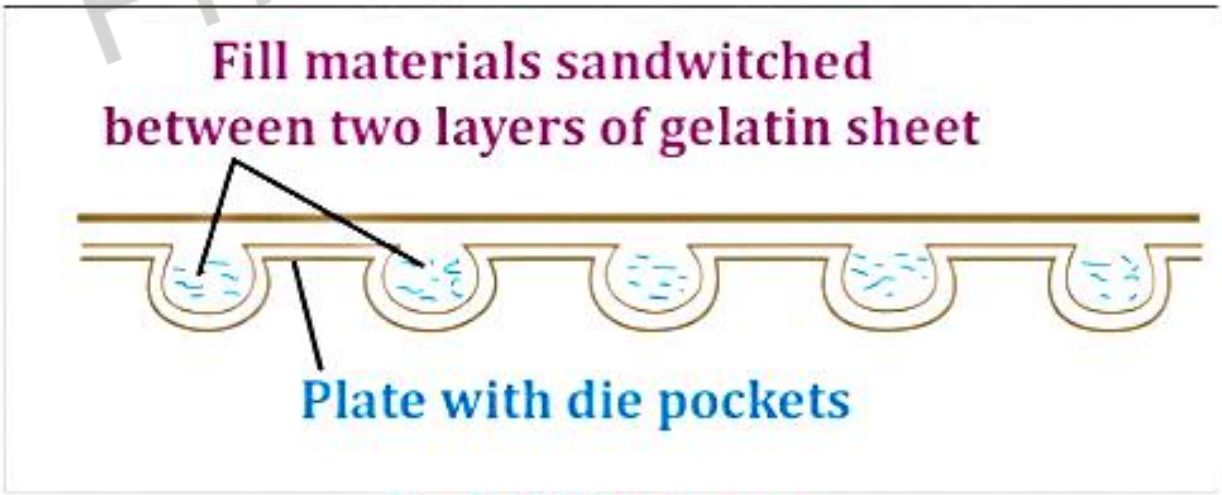
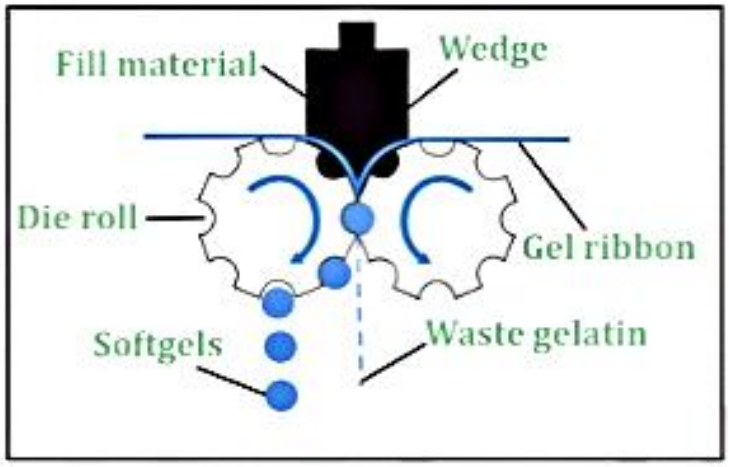


Fig. 5.11 Plate Process

ii. Rotary Process

- In this process, two plasticized gelatin ribbons (prepared in the rotary-die machine) are continuously and simultaneously fed with the liquid, semiliquid or paste fill between the rollers of the rotary die mechanism.

- The forced injection of the feed material between the two ribbons causes the gelatin to swell into the left- and right-hand die pockets which govern the size and shape of the soft gels as they converge.
- As the die rolls rotate, the convergence of the matching dies pockets hermetically seals and cuts out the filled capsules.



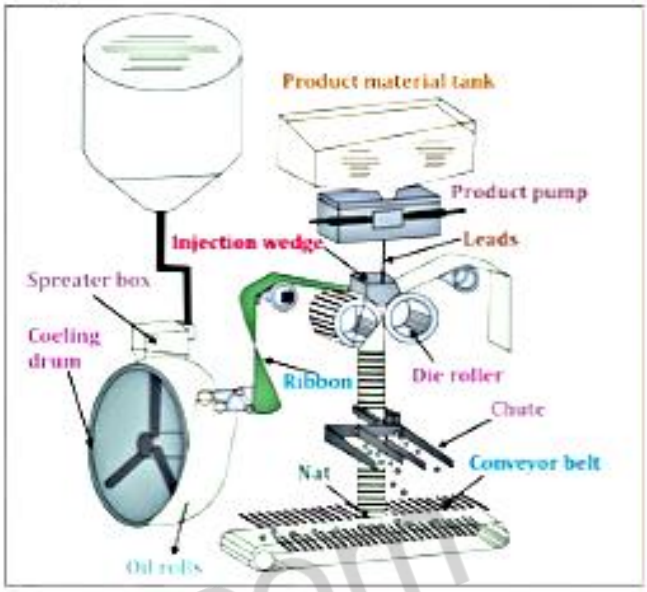


Fig 5.12: Rotary Process

iii. Reciprocating die process

- This process is similar to rotary process in that **ribbons of gelatin are formed** and used to encapsulate the fill, but it differs in the actual encapsulating process.
- The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons.
- As the capsules are cut from the ribbons, they fall into a cooled solvent bath that **prevents the capsules from adhering to one another**.

iv. Accogel Process

- The **Accogel capsule machine** is the only machine that can fill powder inner fill materials into the capsule shells.
- It involves a measuring roll, a die roll and a sealing roll. The **measuring roll rotates directly over the die roll**, and the pockets in the two rolls are aligned with each other.
- The powder or granular fill material is held in the pockets of measuring roll under vacuum.

- A **plasticized gelatin sheet** is drawn into the die pockets of the die roll under vacuum.
- As the measuring roll and die roll rotates, the measured dose are transferred to the gelatin lined pockets of the die roll.

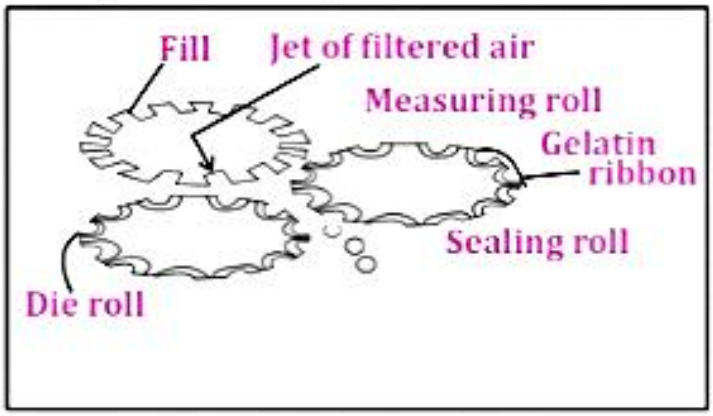


Fig 5.13: Accogel Process

v. Seamless process (Bubble Method)

- In this process, a molten gelatin stream flows though the outer nozzle of a concentric tube at a **constant rate**, and the medicated liquid formulation is dispensed through the inner orifice by means of a precision metering pump.
- The emerging stream is broken up into an intermittent but steady flow of **uniform-sized** by a pulsating mechanism, leading to the formation of droplets enveloped in molten gelatin.
- The formed capsules are quickly removed from the nozzle, slowly congealed, and automatically ejected from the system.

❖ PACKAGING AND STORAGE

- The main aim of packaging of filled capsule is to **prevent contamination & loss or gain of moisture** during long term storage.
- Storage of hard gelatin capsule shell for long time period requires proper maintenance of temperature with minimum 15^0C & humidity of minimum 35%.

5.2.3 Evaluation Test For Capsules

❖ Content of active ingredient

- It is determined on a sample of 20 capsules.
- The result of assay gives average drug content of 20 capsules which must lie within the range for content of active ingredient stated in monograph (Which is usually 90 to 110 % of the label claim).

❖ **Size and shape**

- In this, capsules are tested for **uniformity of size** and **shape** as compared to standard

❖ **Uniformity of Weight**

- 20 intact capsules are first weighed individually, then weighed after removing their contents. Difference between two weights gives weight of contents

❖ **Uniformity of content**

- In this test, ten capsules are assayed individually by the method specified in the individual monograph.
- It is applicable to capsules which have a drug content of less than 10 mg.

❖ **Disintegration test**

- The disintegration test for capsules is similar to that used for testing of tablets.
- Test is not applicable to **modified release capsules**
- The hard gelatin capsules are expected to disintegrate **within 30 minutes.**

CHAPTER - 5

PHARMACEUTICAL FORMULATION

PART III– LIQUID ORAL PREPARATION

Points to be covered in this topic

- **5.3 LIQUID ORAL PREPARATION**
  - **5.3.1 Solution**
  - **5.3.2 Syrup**
  - **5.3.3 Elixir**
  - **5.3.4 Emulsion**
  - **5.3.5 Suspension**
  - **5.3.6 Dry powder for Reconstitution**

LIQUID ORAL PREPARATIONS

5.3 INTRODUCTION

- Oral liquids are **homogenous liquid preparation** that are prepared for oral administration.
- They may contain various types of emulsifying agents, suspending agents, flavoring agents, and coloring agents.

❖ Advantages of liquid oral preparation

- These are better for children and old age patients.
- These are palatable.
- These can absorb more fast than solid.

❖ Disadvantages of liquid oral preparation

- These are **bulky and hence are inconvenient** to transport and store.
- They are **more susceptible to chemical degradation** as compared to solid dosage form.
- Dosage form such as solution can easily be contaminated with microbial growth and required suitable preservatives.

Classification of Liquid Dosage Preparation

1. **Monophasic Liquid Preparation:** Monophasic Liquid Preparation is having only one phase.
   Internal Use: Solution, syrup, mixture, linctus, parenteral preparation.
   External Use: Gargle, mouthwash, nasal drops, ear drops.
2. **Biphasic Liquid Preparation:** Biphasic Liquid Preparation is having two phases.
   Internal Use: Suspension
   External Use: Emulsion

5.3.1 Solution

Pharmaceutical solutions may be defined as liquid preparations in which the therapeutic agent and the various excipients are dissolved in the chosen solvent system.

❖ Advantages of solution

- Easy to swallow, especially for pediatric and geriatric patients.

- Uniform distribution of the drug in the dosage form.

❖ Disadvantages of solution

- Bulky, inconvenient for transport and storage and glass is breakable.
- Stability is poor due to hydrolysis.

❖ Classification of solution

The solution is classified as

1. Based on route of administration

i. **Oral solution-** It is administered through oral cavity. **Example:** Methylphenidate

ii. **Otic solution-** These are made to instilled into ear. **Example:** Glycerin and Butylene Glycol

iii. **Ophthalmic solution-** These are made to instilled into eye. **Example:** Tobramycin

iv. **Topical solution-** These are made to applied over the skin. **Example:** Clindamycin

2. Based on composition and uses

i. **Syrup-** Syrup is an aqueous solution containing sugar.

ii. **Elixir-** Elixir is a sweeten hydro-alcoholic solution.

iii. **Spirit-** Spirit is a solution of aromatic materials in alcohol.

iv. **Aromatic water-** Aromatic water is a solution of aromatic materials in water.

v. **Tincture-** Tincture is a solution prepared by extracting constituents **from** crude drugs.

3. Based on vehicle used

i. **Aqueous solution:** This type of solution is prepared by using purified water or aromatic water as a vehicle. **Example:** Salt solution

ii. **Non-aqueous solution:** This type of solution is prepared by using other solvent other than water like ethanol and ethyl ether.

iii. **Saturated solution:** These are solution in which no more solute can be dissolved at given temperature. **Example:** Simple syrup IP.

iv. **Unsaturated solution:** These are solution in which more solute can be dissolved at given temperature. **Example:** Aqueous Iodine solution.

❖ Drug Solubility Expressions

Table 5.12: Drug Solubility Expressions

S.NO.	DESCRIPTIVE TERMS	PARTS OF SOLVENT FOR 1 PART OF SOLUTE
1.	**Very Soluble**	Less than 1 part
2.	**Freely Soluble**	From 1 to 10
3.	**Soluble**	From 10 to 30
4.	**Sparingly Soluble**	From 30 to 100
5.	**Slightly Soluble**	From 100 to 1000
6.	**Very Slightly Soluble**	From 1000 to 10000
7.	**Insoluble or practically insoluble**	More than 10000

❖ Formulation of Solution

Talc mixture B.P.C Formula

Peppermint oil 20 ml
90% ethanol 600 ml
Purified talc 50 g
Purified water q.s to make it 1000 ml

Method of preparation

This method is prepared by dissolving talc powder in water and then peppermint oil and ethanol are added in it. The solution is then filtered and volume is adjusted by using purified water.

Use

This solution is used as vehicle for aqueous flavoring agent.

❖ Storage and label of solution

- Solution should be stored in **plain amber colored bottles** with a re-closable child resistant closure.
- Solution should be stored in a well closed container and **temperature below 30^{0}C.**
- Special label should be used like 'For internal use' or 'For external use'.

❖ Quality control test for Solution

1. **General test:** It includes visual appearance, color, taste, odor, labeling and homogeneity.

2. **Identification test:** It is done to identify the physiochemical test of the solution.
3. **Assay:** Assay is done to check the purity of the solution according to the standard. It can be done by titrimetry, colorimetry etc.

5.3.2 Syrup

- A liquid preparation of medicinal or flavoring substances in a concentrated aqueous solution of a sugar, usually sucrose is known as **Syrup.**
- The concentration of sugar in syrup is **66.7% w/w.**

❖ Advantages of syrup

- Exert **high osmotic pressure** and thus prevents the growth of macrobacteria's.
- Palatable sweet and used as a vehicle for bitter/nauseous substances.
- Appropriate for any patient, whatever the age is.

❖ Disadvantages of syrup

- Delayed onset of action because absorption takes time compared to some other dosage forms like solutions.
- Not suitable in emergency and for unconscious patients.

❖ Classification of syrup

1. Simple Syrup

- Simple Syrup contains sucrose that is dissolved in water or in other substances. In this USP sucrose at a **concentration of 85% w/v is added with water.**
- It exerts high osmotic pressure and thus no microbial growth occurs i.e., glycerine.

2. Medicated Syrup

- Medicated Syrup are those with **contains medicated ingredients** in it along with some therapeutic purpose.
- These are used as cholinergic, decongestant, cathartic or expectorant.
  Example: Dicyclomine HCl syrup, Ephedrine hydrochloride syrup etc.

3. Flavoured Syrup

- Flavoured Syrup contains some amount of flavoured in it.
- These do not contain any drug in it.

Example: Cherry syrup, orange syrup etc.

❖ Methods of syrup preparation

Syrups are prepared using one of four techniques:

- Solution with heat, solution by agitation, addition of sucrose to a liquid medication or flavored liquid, and percolation.
- The method of choice depends on the physical and chemical characteristics of the substances entering into the preparation.

1. Hot Process (Solution with heat)

- This method is suitable for mixture that are heat stable.

The required quantity of sucrose is weighed and added to sufficient quantity of water and heated till the solution is dissolved at **80-85^{0}C.**

- **At excessive heat,** sucrose, a disaccharide may be hydrolyzed into monosaccharides, dextrose (glucose), and fructose (levulose).
- This hydrolytic reaction is referred to as "inversion," and the combination of the two monosaccharide products is **"invert sugar."**
- The relative sweetness of fructose, sucrose, and dextrose is in the ratio of **173:100:74.**

2. Solution by agitation

- This method is suitable for those mixture that are **degraded by heat.**
- The required quantity of sucrose is added to purified water in a suitable vessel and agitated till the solution is dissolves.
- Final volume or weight is made up by **addition of more quantity of purified water.**
- This process is more **time consuming** than Solution with heat, but the product has greater stability.

3. Addition of sucrose to a liquid medication or flavored liquid

- This method is often used with fluid extracts or tinctures.

- Syrups made in this way develop precipitates, because alcohol is often an ingredient of the liquids used, and the resinous and oily substances solubilized by the alcohol precipitate when water is added.

4. Percolation Process

- The required quantity of sucrose is weighed, placed in a suitable percolator.
- Purified water is then allowed to pass through the bed of sucrose in order to effect solution.
- In this method, two main criteria are necessary that is

  i) The percolator used should be cylindrical or semi-cylindrical and cone-shaped as it nears the lower orifice.

  ii) A coarse granular sugar must be used, otherwise it will coalesce into a compact mass, which the liquid cannot permeate.

❖ Formulation of syrups

Ferrous sulphate syrup

Ferrous sulphate	40 g
Citric acid	2 g
Peppermint spirit	2 ml
Sucrose	825 gm
Purified water	1000 ml

Method of preparation

Dissolve the Ferrous Sulfate, the Citric Acid, the Peppermint Spirit, and 200 g of the Sucrose in 450 mL of Purified Water, and filter the solution until it is clear. Dissolve the remainder of the Sucrose in the clear filtrate, and add Purified Water to make 1000 mL. Mix, and filter, if necessary, through a pledge of cotton.

❖ Storage of syrup

- Syrup should be stored in tight, light resistant containers and should be kept in refrigerator till complete consumption.
- Syrups that contain stable drugs are stored at **25-27^{0}C** and those which are thermolabile should be stored at **4-5^{0}C** in refrigerator.

5.3.3 ELIXIR

- Elixirs are **sweetened hydro-alcoholic** (water and alcohol) liquids for oral use.
- When used as a pharmaceutical preparation, an elixir contains at least one active ingredient designed to be taken orally.
- Expectorant are the type of elixir, contains polyhydric alcohol and ethanol (96%).

❖ Advantages of elixir

- Elixirs are more fluid than syrups.
- It is more effective in masking tastes.
- Rapidly absorbed, because of heaving alcohol.

❖ Disadvantages of elixir

- Alcohol is not good for children's patients on antidepressant medication.
- Because they contain volatile materials, it must be stored in a water.
- Tight screw-top jar and away from sources of ignition.

❖ Classification of elixir

1. Non - Medicated Elixirs

- These are used as solvents or vehicles for preparation of medicated elixirs.
- Active ingredients are **dissolved in a 15–50%** by volume solution of Ethyl alcohol.

Example: Aromatic Elixirs (USP), Iso-alcoholic Elixirs (NF), Compound Benzaldehyde Elixirs (NF)

2. Medicated Elixirs

- Medicated elxirs are solution of active ingredients dissolved in water and alcohol and an **alcohol along with other excipients** such as preservatives.

3. Aromatic Elixir

An aromatic elixir is a pharmaceutical preparation which contains volatile compounds.

❖ **Formulation of elixir**

Formula

Phenobarbital	4.00 g
Propylene glycol	50 ml
Alcohol	200 ml
Sorbitol solution	600 ml
Saccharin sodium	5.0 g
Flavor	q.s.
Purified water	1000 ml

❖ **Storage of elixir**

- Elixir should be stored in tight, light resistant containers and should be kept in refrigerator till complete consumption.
- Elixir preparations under use must be properly closed after withdrawal of dose and should kept away from children.

5.3.4 EMULSION

- An emulsion is a **biphasic system** in which one phase is intimately dispersed in the other phase in the form of minute droplets.
- Diameter of emulsion ranging from **0.1µm to 100 µm.**
- The dispersed phase is also known as internal phase or discontinuous phase while the outer phase is called dispersion medium, external phase / continuous phase.

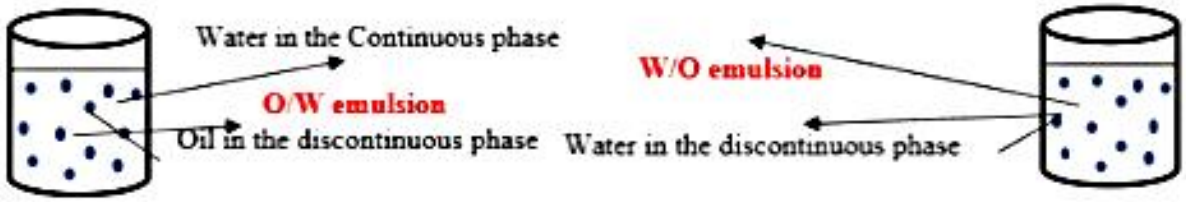


Fig 5.14: Emulsion

❖ Advantages of Emulsion

- Poorly water-soluble drugs may be easily incorporated with improved dissolution rates and bioavailability.
- The unpleasant taste or odor of oils can be masked partially or wholly, by emulsification.
- The absorption rate and permeation of medicaments can be controlled.

❖ Disadvantages of Emulsion

- Emulsions are thermodynamically unstable.
- These are bulky and hence difficult to transport.
- It needs to be shake well before use for uniform and accurate dosing.

❖ Types of emulsion

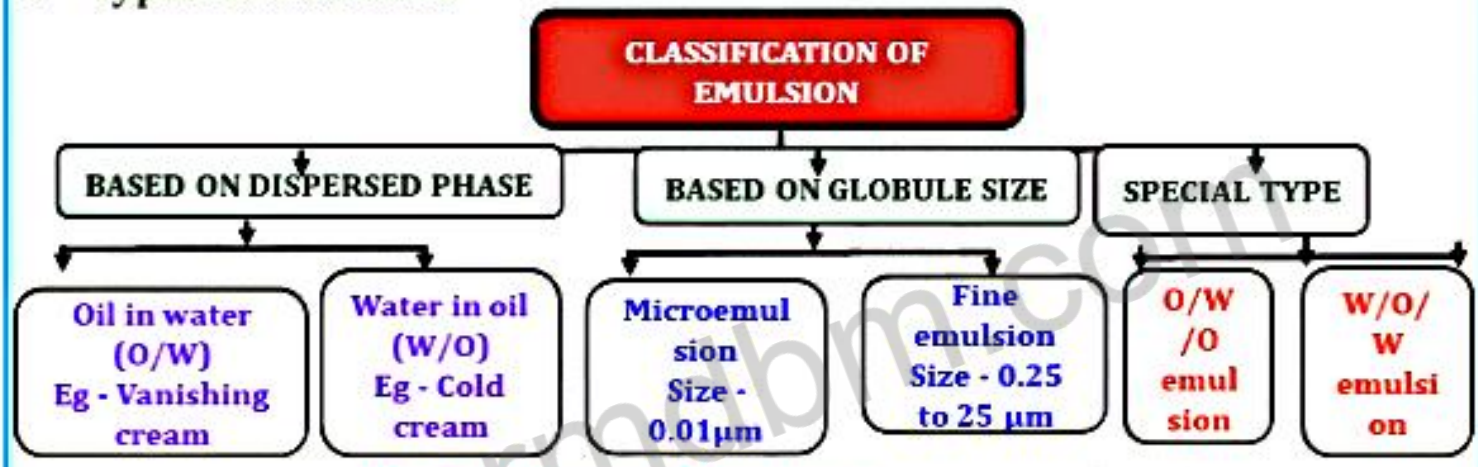


Fig 5.15: Types of Emulsion

1. Based On Dispersed Phase

Table 5.13: Difference between o/w and w/o emulsion

For O/W emulsion-water is the continuous phase and oil is the dispersed phase	For O/W emulsion-water is the continuous phase and oil is the dispersed phase
Less viscous and easily washable from the skin by water	More Viscous than O/W and not easily washable from the skin by water
Example- Vanishing cream	Example- Cold cream

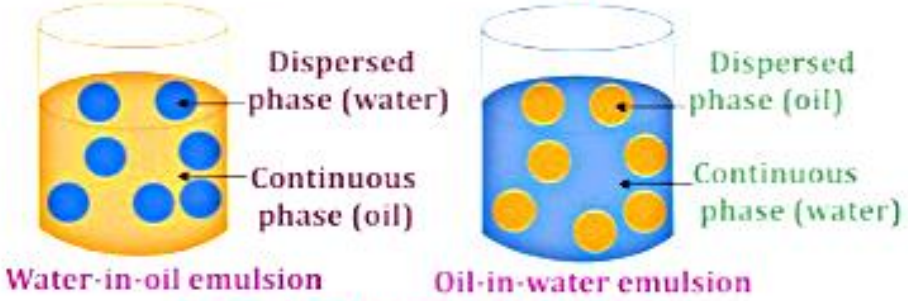


Fig 5.16: Types of Emulsion

2. Based on Globule size

a) Microemulsion

A microemulsion is a **thermodynamically stable transparent**, isotropic dispersion of two immiscible liquids such as water and oil stabilized by surfactant molecules at the water/oil interface.

Example: Cyclosporin A, Saquinavir

b) Fine emulsion

The size of the fine emulsion is **0.2 µm to 100 µm in diameter.**

3. Special Type

a) O/W/O: Oil-in-water-oil is a **multiple type of emulsion** having three phases in which water droplets are dispersed in an external oily phase.
Example- Milk, mayonnaise, cake batter

b) W/O/W: Water-in-oil-in-water is a multiple type of emulsion having three phases in which oil droplets are dispersed in an external aqueous phase.

❖ Preparation methods of emulsion

1. 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.

2. 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 thick white cream is formed.
- Once the primary emulsion is formed, the remaining quantity of water is slowly added to form the final emulsion.

3. Bottle method

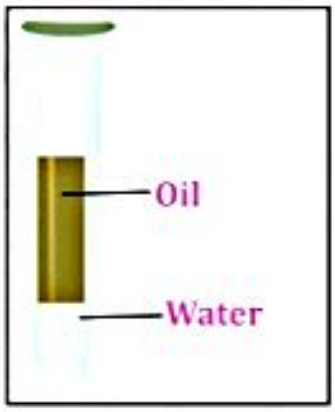
- In this method, oil or water is first shaken thoroughly and vigorously with the calculated amount of gum.
- Once this has emulsified completely, the second liquid (either oil or water) is then added all at once and the bottle is again shaken vigorously to form the primary emulsion.
- More water is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

4. In-situ method

- In this method, **emulsion is formed by chemical reaction** between the components without use of any emulsifying agents.
- These are useful in preparation of olive oil and lime water emulsion.
- Equal amount of olive oil and lime water are added in bottle and shaken. The olive oil interacts with lime water to form calcium oleate that acts as an emulsifying agent.

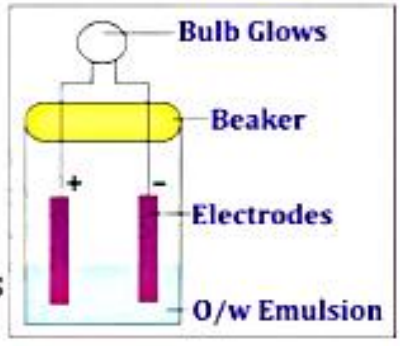
❖ Identification test for emulsion

1. Dilution test



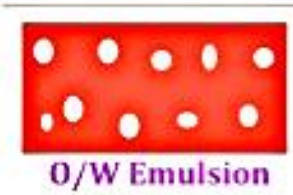
- In this test, either **oil or water is used to dilute the emulsion.**
- **Water in oil emulsion** can be diluted by adding an aqueous solvent.
- While **oil in water emulsions** can be diluted through an oily liquid.

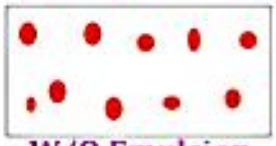
2. Conductivity test



- Since **water conducts electricity well**, it can be used as a test medium.
- Since water is the external phase in the case of ohm emulsion, this will be a positive result.
- An electric bulb is connected to a pair of electrodes that are dipped into the emulsion a pair of electrodes are dipped into an emulsion.
- **A glowing electric bulb** occurs when the emulsion is of the of **O/W type.**

3. Dye Test





- ✓ **O/W emulsion**

  A **water-soluble dye (Amaranth)** is added in emulsion, then it develops a red continuous phase in the emulsion which confirms that the emulsion is of o/w type.

- ✓ **W/O emulsion**

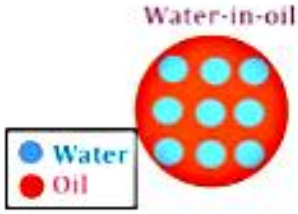
  An **oil soluble dye (Scarlet red C or Sudan III)** added to an oil emulsion causes a red continuous phase, which indicates that the emulsion is of w/o type.

4. Cobalt chloride test

- To carry out this test, a **Whatman filter strip** is impregnated with cobalt chloride solution for 10 minutes, and when the strip dries, it becomes blue.
- Blue strips are soaked in sample emulsion for 5 minutes, then dried and the results are observed.

- ✓ **Observation**
  - **The blue cobalt chloride** strip should become **completely pink**, it indicates **O/W emulsion**.
  - In these cases, pink spots appear against a blue background, which indicates the type of emulsion.

5. Florescence test



- When an emulsion shows **continuous fluorescence** under a microscope after exposure to ultraviolet radiation, it is a **w/o type.**
- It is an **o/w type** if it shows only **spotty fluorescence.**

❖ **Instability in emulsion**

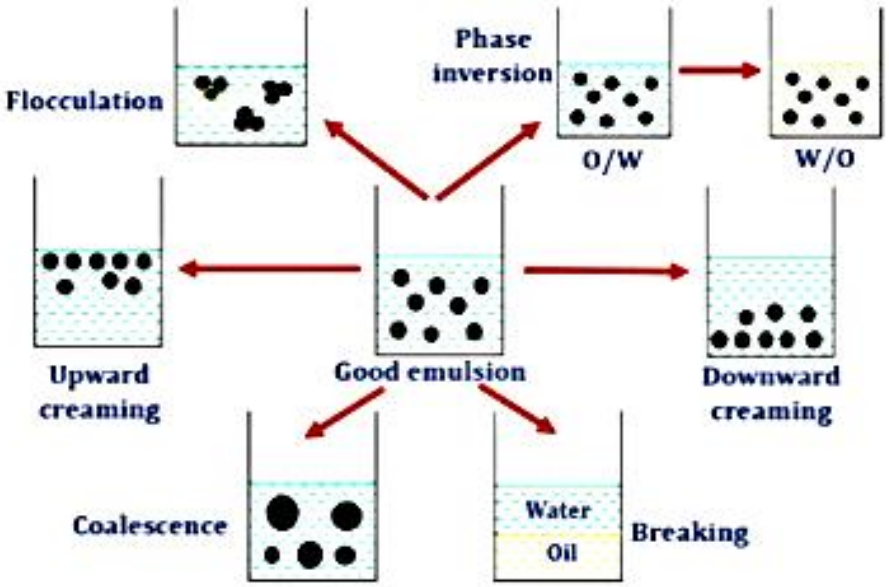
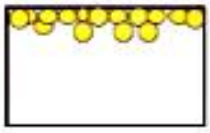


Fig 5.17: Instability of Emulsion

1. Flocculation

- Flocculation is when the **emulsion droplets aggregate** and thereby **form larger units.**
- Eventually the **phase separation will happen.**

2. Creaming



- The rise of dispersed particles to the surface of an emulsion is referred to as **creaming**

3. Coalescence or aggregation

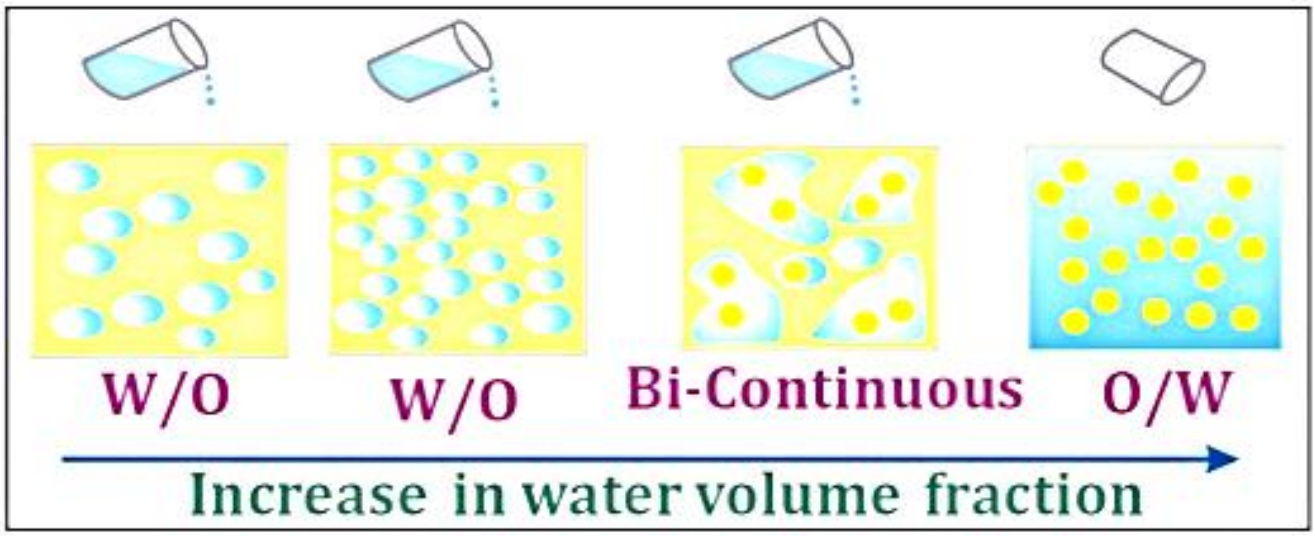
- It is characterized by **merging or aggregation of globules** of dispersed phase.

4. Cracking / Breaking

- Cracking of an emulsion refers to separation of the dispersed phase as a layer.
- Whereas a creamed emulsion may be reconstituted by shaking or agitation.
- Cracking represents **permanent instability.**

5. Phase inversion

- Phase inversion refers to a phenomenon that occurs when agitated **o/w emulsion, reverts to w/o & vice versa.** Emulsification via phase inversion is widely used in fabrication of cosmetic product, pharmaceutical products.



6. Oxidation

- **Lipid oxidation** is a major cause of quality deterioration in food emulsions.
- The design of foods with improved quality depends on a better understanding of the physicochemical mechanisms of lipid oxidation in these systems.

❖ Formulation of Emulsion

Mineral Oil Emulsion, USP

Mineral oil	500 ml
Acacia, in very fine powder	125 g
Syrup	100 ml
Vanillin	40 mg
Alcohol	60 ml
Purified water	1000 ml

Method of preparation

- The mineral oil and acacia are mixed in a dry Wedgwood mortar.
- Purified water (250 mL) is added, and the mixture is triturated vigorously, until an emulsion is formed.
- A mixture of the syrup, 50 mL of purified water, and the vanillin dissolved in alcohol is added in divided portions with trituration; sufficient purified water is then added to the proper volume; the mixture is mixed well and homogenized.

❖ Storage of Emulsion

- Emulsion should be stored in cool place avoiding refrigeration.
- It should be kept in well filled bottle with tight closures.

❖ **Quality control test for emulsion**

i. Phase separation

The rate and degree of phase separation in an emulsion can be easily determined by keeping a certain amount in a graduated cylinder and measuring the volume of separated phase after definite time intervals.

ii. Globule size

Growth in the globule size after the preparation of an emulsion is an indication of its physical instability. Hence, size of globules and their size distribution is generally ascertained in an emulsion over a certain time span.

iii. Flow properties

The rheological characteristics of an emulsion system depend upon globule size, emulsifier and its concentration, phase volume ratio etc., and hence determination of its flow characteristics could serve as an index of its stability.

iv. Effect of thermal stresses

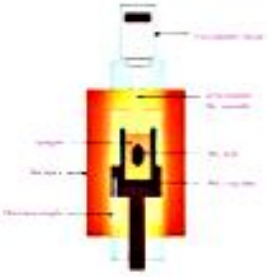
It is usual to evaluate the stability of an emulsion by subjecting it to high and low temperature in alternating cycles. The samples are first exposed to **60°C** for a w hours and then **to 0 to 4°C**.

v. Microbial test

This test is performed to check the presence of microbes or any contamination in the emulsion.

vi. Viscosity

It can be measured by **cup and bob viscometer**, cone and plate viscometer or standard capillary tube



5.3.5 SUSPENSION

- Suspensions are the **biphasic liquid dosage form** of medicament in which the finely divided solid particles ranging **from 0.5 to 5.0 micron** are dispersed in a liquid or semisolid vehicle.
- The solid particles act as disperse phase whereas liquid vehicle acts as the continuous phase.
- Suspensions are generally taken orally or by parenteral route.

❖ Advantages

1. Stability

Most of the drugs are not stable in solution form so it is necessary to prepare an insoluble form of that drug.

Example: - Procaine penicillin G.

2. Taste masking

- Drugs having unpleasant taste can be masked by adding suitable flavour and sweetener to make it palatable.
- Chloramphenicol palmitate is preferred over chloramphenicol which has bitter taste.

3. Prolonged action dosage forms

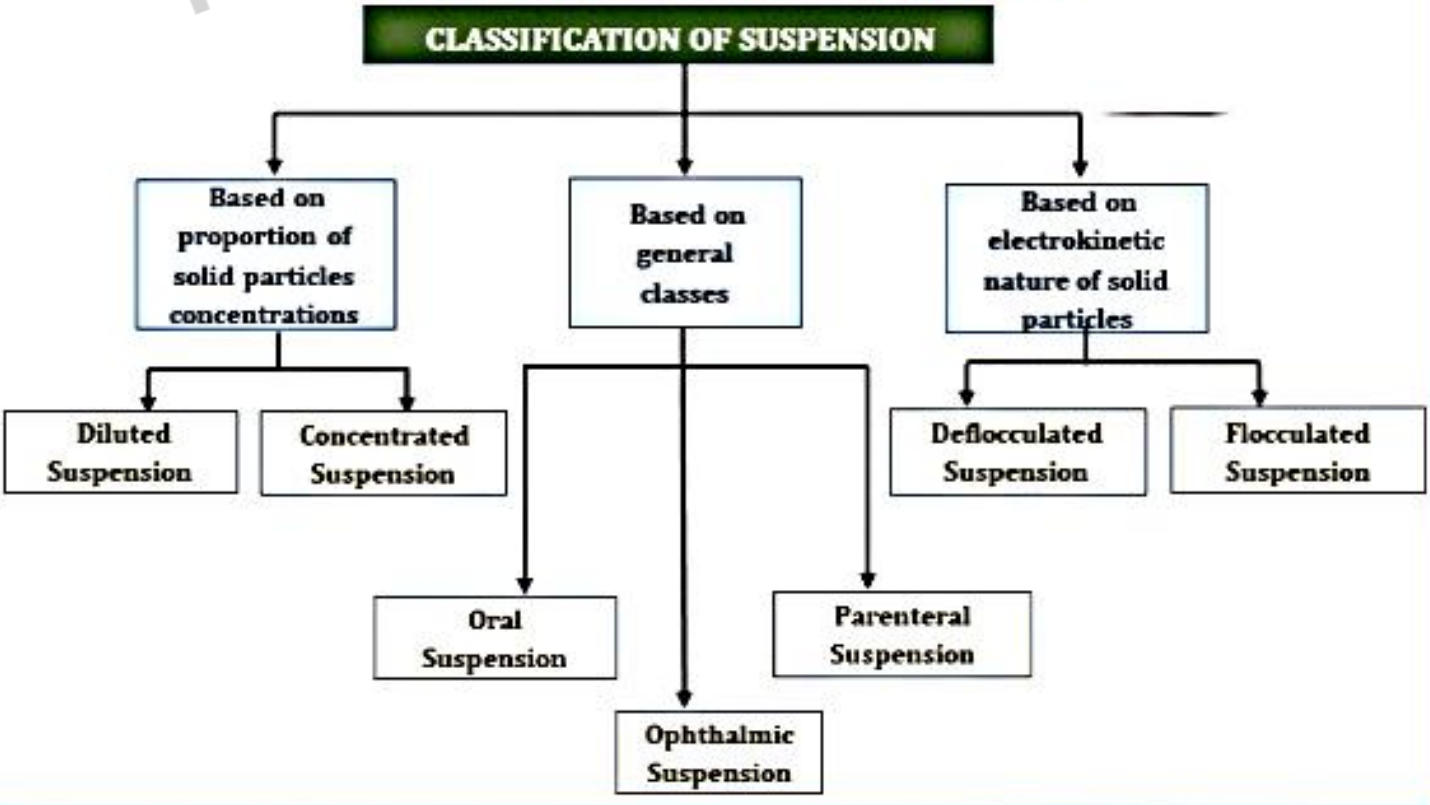
Example: - Protamine Zinc-Insulin suspension, procaine penicillin G being insoluble

❖ Disadvantages

- Sedimentation of the particle is one of the disadvantages of this dosage form.
- The formulation is quite difficult than other dosage forms.
- 100% uniform and accurate dose are not possible.

❖ Classification of suspension

Fig 5.18: Classification of Suspension



1. **Based on Proportion of Solid Particles Concentrations**

✓ **Diluted Suspension**

This suspension contains solid weights that range between 2% to 10% per volume.

Example: Cortisone acetate suspension.

✓ **Concentrated Suspension**

The solid weight per volume in these solutions is 50%.

Example: Zinc oxide suspension.

2. **Based on General Classes**

✓ **Oral Suspension**

- These suspensions are to be consumed by the patients by oral route.
- Oral suspensions generally contain flavoring agent and sweetening agent to mask the bitter taste of the drug.

Example: Paracetamol suspension antacids, Tetracycline HCl.

✓ **Ophthalmic Suspension**

- Ophthalmic suspensions are sterile liquid preparations that contain solid particles in a vehicle suitable for instillation into the eye.
- They have an ointment base and may or may not include an active drug.

✓ **Parenteral Suspension**

- Parenteral suspensions are dosage forms containing drugs having low solubility.
- Parenteral suspensions provide onset of action for prolonged time as compared to solution.

Example: Potassium / sodium chloride, Potassium / sodium citrate, Potassium / sodium acetate

3. **Based On Electrokinetic Nature of Solid Particles**

✓ **Flocculated & Deflocculated Suspension**

Table 5.14: Flocculated & Deflocculated Suspension

Flocculated suspension	Deflocculated suspension
Particles exist as loose aggregates	Particles exist as separate entities
Rate of sedimentation is high	Rate of sedimentation is low
Sedimentation formed rapidly	Sedimentation formed slowly
Sediment can easily be redispersed	Sediment can't easily be redispersed

❖ Formulation of suspension

Trisulfapyrimidines oral Suspension

Veegum	1.00 g
Syrup USP	90.60 g
Sodium Citrate	0.78 g
Sulfadiazine	2.54 g
Sulfamerazine	2.54 g

Method of preparation

- Add the Veegum slowly and with continuous stirring to the syrup.
- Incorporate the sodium citrate into the Veegum–syrup mixture.
- Premix the sulfa drugs, add to the syrup, stir, and homogenize.
- Add sufficient 5% citric acid to adjust the pH of the product to 5.6.
- A preservative and a flavoring agent may be added to the product.

❖ Storage

- Suspension should be stored in tight containers protected from heat, light and freezing.
- Suspension for oral use is packed in wide mouth soda lime or borosilicate glass with sufficient air space above the liquid for proper mixing.

❖ Quality control test for Suspension

1. **Sedimentation volume:** The sedimentation volume is the simple ratio of the height of sediment to initial height of the initial suspension. The larger the value better is the suspendability.
2. **Particle size and size distribution:** It is of importance to study the changes for absolute particle size and particle size distribution. It is performed by optical microscopy, sedimentation by using Andreasen apparatus and Coulter counter apparatus.

3. **Rheological studies:** Rheologic methods can help in determining the settling behaviour of the suspension.
   - Brookfield viscometer with variable shear stress control can be used for evaluating viscosity of suspensions.
   - It consists of T-bar spindle which is lowered into the suspension and the dial reading is noted which is a measure of resistance the spindle meets at various levels in the suspension.
4. **Stability testing:** In this physical form, the preparation would exhibit parameters that could not be extrapolated to those that would exist in the normal system.
   - The valid temperature data could be obtained that will be useful in the estimation of the physical stability of a product at normal storage conditions.
5. **Uniformity of volume:** In this test, sample of 10 filled containers are selected and the weight of content of each container is determined.
   - The weight per ml is obtained to calculate the net volume of content in each container.

5.3.6 DRY POWDER

- Powders are the mixture of **finely divided drug** or chemicals in dry form.
- They are available in crystalline or amorphous form.
- There is a relationship between particle size of powder & dissolution, absorption & therapeutic effect of drug.

❖ Advantages

- It is used both internally and externally.
- It is more stable than liquid dosage form.
- It is convenient for the physician to prescribe a specific amount of powder.
- On set of action is faster as compared to tablet, capsules because it is easily in dissolved in body fluids.

❖ Disadvantages

- Drugs have bitter taste, nausea and unpleasant taste cannot be administered in powder form.
- Deliquescent and hygroscopic drugs cannot be dispensed and powder form they are packed in double wrapping.
- Quantity less than 100 mg cannot be weighed conveniently.

❖ Types of Dry powder

1. Divided powders

➢ Oral divided powder may contain **one or more active ingredients** together with an inert diluent to produce a minimum quantity of 120 mg.

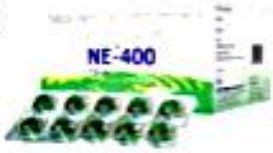
➢ Oral undivided powder is usually a simple mixture of the prescribed medication without additional ingredients.

(a) Packets

- These are dispensed in the form **of individual doses** and generally are dispensed in papers, properly folded.

(b) Cachets

- Cachets are the **solid unit dosage forms** of medicament in which drug is enclosed in tasteless sheet made by pouring mixture of rice flour and wat between two hot, polished, revolving cylinders.
- Water is evaporated and sheet of wafer formed is known **is Cachet.**



1. Bulk (Undivided) powders

(a) Dusting powder

- These are meant for external application to the skin.
- Powders passed through **sieve no 85(180µm)** to get a fine powder.
- They are two types- Medical dusting powder and surgical dusting powder

(b) Effervescent powder

- Mixture of organic acid and alkali effervesces when subjected to water due to reaction between the acid and the base with evolution of CO_2.

(C)) Antacids, laxatives

- **As an antacid,** it is used for the temporary relief of heartburn, upset stomach, sour stomach or acid indigestion.
- **As a laxative,** it is used for the relief of occasional constipation by promoting bowel movements for 30 minutes and up to 6 hours

❖ **Storage**

- Dry powder should be packaged in wide mouth container having adequate air space above the powder.
- It should be stored in **room temperature** in tight container protected from excessive heat and light.

❖ **Quality control test for Dry powders**

1. **Particle size:** Particle size is calculated by using standard microscope. Average and standard deviation of 100 particles is estimated.
2. **Drug content:** The required weight of powder is extracted with 100 ml solvent and the solution is filtered by nylon filter membrane.
   - Accurately 0.1 ml of solution is diluted to 10 ml. Its absorbance is measured by UV spectrophotometer.
3. **Drug stability:** The sample is tested for purity, stability and presence of any contamination and zeta potential.

CHAPTER - 5

PHARMACEUTICAL FORMULATION

PART IV– TOPICAL PREPARATIONS

Points to be covered in this topic

5.4 TOPICAL PREPARATIONS

- 5.4.1 Semisolid
- 5.4.2 Ointment
- 5.4.3 Creams
- 5.4.4 Pastes
- 5.4.5 Topical Gels
- 5.4.6 Liniments
- 5.4.7 Lotions
- 5.4.8 Suppositories
- 5.4.9 Pessaries

5.4 TOPICAL PREPARATIONS

5.4.1 Semisolids

- Semi solids are the **topical dosage forms** used for the therapeutic, protective or cosmetic function. They may be applied to the skin, or used nasally, vaginally, or rectally.
- They contain **one or more active ingredients** dissolved or uniformly dispersed in a suitable base.

❑ TYPES OF SEMISOLID

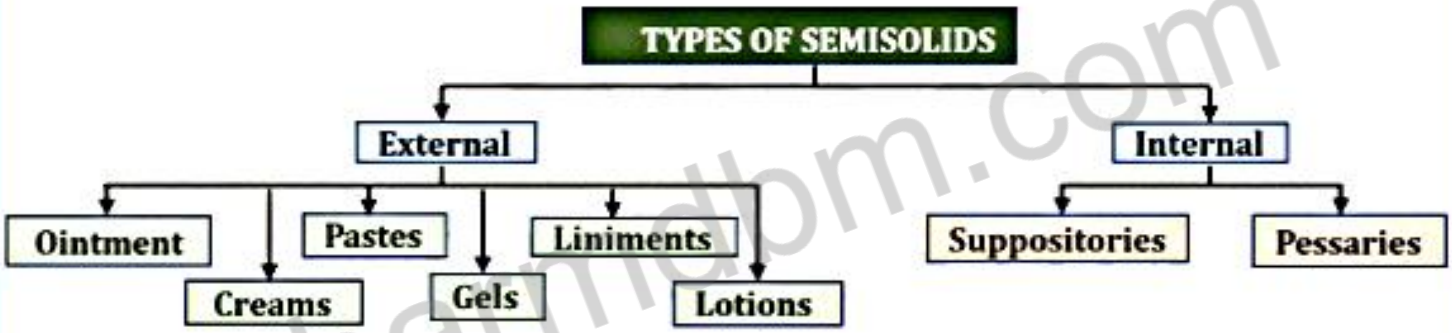


Fig 5.19: Types of Semisolid

Table 5.15: Types of Semisolid Dosage Form

SEMISOLID DOSAGE FORM	DESCRIPTION
Ointments	They usually contain a medicament or medicaments dissolves, suspended or emulsified in the base.
Creams	Creams are viscous emulsions of semisolid consistency intended for application to the skin or mucous membrane o/w type w/o type.
Pastes	Pastes are the semi-solid preparations contain a large amount of finely powdered solids such as coal tar and zinc oxide paste. These are generally very thick and stiff.

Gels	These are jelly-like semisolid dispersions of drug meant to be applied on the skin.
Liniments	Liniment is a liquid that you rub into the skin in order to reduce pain or relieve stiffness. e.g. Calamine and Camphor liniment.
Lotion	A lotion is a liquid or semisolid preparation, applied to the skin with bare hands or cotton wool, with the intent to moisturize and/or treat the skin. e.g., Calamine lotion white lotion.
Suppositories	These are meant for insertion in to the body cavities other than mouth. They may be inserted in to rectum, vagina or urethra.
Pessaries	A pessary is a silicone device that is inserted into the vagina, which is most often used to treat prolapse of the uterus, but also can help relieve urinary incontinence.

❑ TOPICAL PREPARATIONS

- Topical Preparation are type of formulations that are optimized to **applied on the skin** at a particular site.

❖ Advantages

- Avoidance of first pass metabolism.
- Avoidance of risk and inconvenience of administration.

❖ Disadvantages

- There may be chances of allergic reactions.
- These are suitable for the drugs which needs low plasma concentration.

5.4.2 Ointment

❖ Introduction

- Ointment is a **greasy or oily semi-solid preparation**, usually medicated, that can be applied externally to the skin in order to heal, soothe or protect it.
- It is a **viscous semisolid preparation** used topically on a variety of body surfaces.
- Ointments are used topically for several purposes (antiseptics) emollients, antipruritic, keratolytic, and astringents.

❖ Properties of an ideal ointment

1. Does not retard wound healing.

- Low sensitization index.
- Pharmaceutical elegance.
- A low index of irritation.

❖ Advantages of ointments

- Ointment can be **easily handled** as compared to other liquid dosage form.
- It is **more dose flexibility**.
- It is **suitable for those patients** who can not swallow the drug i.e children or elderly patients.

❖ Disadvantages of ointments

- **Hard to use** on hairy skin
- **Have a greasy appearance** and texture
- **Sometimes not preferred** due to cosmetic concerns
- Hard to spread on skin

❖ Classification of ointment

1. On the basis of penetration

- ✓ **Epidermis Ointment** These types of ointment are intended to use in the **epidermic region** of the skin and hence not get absorbed.
- ✓ **Endodermic Ointment** These types of ointment release the medicament **into the skin** after penetration and are partially absorbed.
- ✓ **Diadermic Ointment** These types of ointments release the medicaments that **pass through the skin to produce the systemic effects.**

2. On the basis of therapeutic use

Table 5.16: Classification of ointment based on therapeutic use

S. No.	Type Of Ointments	Description	Examples
1.	Antibiotic Ointment	Kill micro-organism	Neomycin, bacitracin
2.	Antifungal Ointment	Inhibit or kill fungi	Benzoic acid
3.	Anti-inflammatory Ointment	Relive from inflammation and allergic condition	Fluocinolone acetonide, hydrocortisone

4	Antipruritic Ointment	Relieve from itching	Benzocaine, coal tar
5.	Astringent Ointment	Causes contraction of skin and decreases discharges	Zinc oxide, acetic acid
6.	Antieczematous Ointment	Prevent oozing and excretion from vesicles on the skin	Salicylic acid
7.	Keratolytic Ointment	Remove or softens the horny layer of skin	Resorcinol, Sulphur
8.	Counter-irritant Ointment	Reduce the irritation on the skin	Methyl salicylate
9.	Anti-dandruff Ointment	Provides relief from dandruff	Salicylic acid, cetrimide
10.	Ointment for psoriasis	Provides relief from itching	Corticosteroid, coal-tar
11.	Parasiticide Ointment	Destroy or inhibit living infestation	Benzyl benzoate, Sulphur
12.	Protectant Ointment	Protect the skin from moisture, air, sunrays etc.	Calamine zinc oxide

❖ Ointment bases

An ointment base is useful for preparing topically applied medicament formulations. It serves as a **carrier** or **vehicle** for ointments.

➢ Types of ointment bases

1. Oleaginous Ointment Bases

- These bases are fats, fixed oils, hydrocarbon or silicones.
- It forms a film on skin so it increases the skin hydration by reducing the rate of loss of surface water.

Example: White Petrolatum, White Ointment Oleaginous

2. Absorption Bases

- Anhydrous but **hydrophilic ointment** bases, they can absorb several times their weight of water to form water-in-oil emulsion.

- They are used as protectants, emollients (+/-) vehicles for aqueous solutions, solids, and non-hydrolysable drugs

Example: Hydrophilic Petrolatum, Anhydrous Lanolin

3. Water in Oil Ointment Bases

- These are anhydrous, hydrophilic, absorbs water and non - water removable, with **low thermal conductivity** and occlusive.
- They are used as emollients, cleansing creams, vehicles for solid, liquid, or non-hydrolysable drugs.

4. Oil in Water Ointment Bases

- These bases are anhydrous, water soluble, absorb water and water washable.
- They are either carbowaxes Polyethylene Glycols (PEGS) or hydrated gums (Bentonite, Gelatin, Cellulose derivatives).

Example: PEG Ointment

❖ Method of Preparation of ointments

- Ointments are prepared either by **incorporating the active ingredients into the base** or by **melting the base** and active ingredient together.
- It can by prepared by following three methods:

➢ Fusion method

- When an ointment base contains **several solid ingredients** such as white beeswax, acetyl alcohol, Stearyl alcohol, stearic acid, hard paraffin, etc. a component of the base, it is required to melt them. **The melting can be done in two methods-**

1. Method 1

- The components are melted in the decreasing order of their melting point i.e., the higher melting point substance should be melted first, the substances with next melting point and so on.

2. Method 2

- All the components are taken in a subdivided state and melted together.
- The maximum temperature reached is **lower than Method-I, and less time** was taken possibly due to the solvent action of the lower melting point substances on the rest of the ingredients.

➢ Trituration

- Trituration in which **finely-subdivided insoluble medicaments** are evenly distributed by grinding with a small amount of the base or one of its ingredients followed by dilution with gradually increasing amounts of the base.
- Solids are finely powdered are passed through a sieve (# 250, # 180, #125).

➢ Ointment Preparation by Chemical Reaction

- Chemical reactions are involved in the preparation of several famous ointments. **Example-** Strong Mercuric Nitrate Ointment, of the 1959 B.P.C.
- **Example-** iodine, arachis oil, yellow soft paraffin.

➢ Preparation of Ointments by Emulsification

✓ **For o/w emulsion systems the following emulsifying agents**

- Water soluble soap, Cetyl alcohol, glyceryl monostearate.
- Combination of emulsifiers - triethanolamine stearate + Cetyl alcohol
- Non-ionic emulsifiers: glyceryl monostearate, glyceryl monooleate, propylene glycol stearate.

✓ **For w/o emulsion creams the following emulsifiers**

- Polyvalent ions e.g. magnesium, calcium and aluminium.Combination of emulsifiers: bees wax + divalent calcium ion

❖ Quality Control Test

1. Weight variation

- A total of 10 filled ointment container are taken, label it, clean the outer surface and each unit is weight.
- If required container is cut to remove their content by washing, dried and again weighed along with its parts.

2. Sterility

This test is applicable for ophthalmic ointment and is performed according to official monograph by membrane filtration method.

3. In vitro drug release

- This test is done in Franz diffusion cell using Whatman filter paper (No.41).
- Filter paper is soaked in phosphate **buffer (pH 6.0) for 24 h at 37^0 C.**
- A thin layer of ointment is applied to filter paper and amount of drug permeated is determined using a UV- Spectrophotometer.

4. Non-irritancy

- It is performed by patch test.
- Ointment is applied daily on specific area of skin in 24 human volunteers for specific duration and observed it carefully.
- A good ointment shows no visible reactions or erythema.

❖ Storage of Ointments

Ointment should be stored in tightly closed container in plastic or glass jars at **25^0 C.** Sterile ointments should be dispensed in tubes or single dose units to protect the product against contamination during use.

5.4.3 Creams

- Creams are **homogenous, viscous semi-solid preparation** which are meant for external use.

- The creams are of two types, aqueous and oily creams.
- In case of aqueous creams, the emulsions are oil-in-water type and in case of oily n aqueous creams, the emulsifying anionic, cationic and non-ionic waxes, Polysorbate and triethanolamine soaps are used as emulsifying agents.
- The oily creams are generally prepared with emulsifying agents, such as, wool fat, wool alcohols, bees wax and calcium soaps.

❖ Advantages of creams

- These are non-irritating when applied to the skin..

- They interfere less with skin function.
- O/W type of cream causes cooling sensation

❖ Disadvantages of creams

- Since, it is a semisolid preparation and containing oil in large amount, some of which are inedible, hence creams are not used for internal use. Basically, creams are meant for application onto the skin.
- The aqueous phase is prone to the **growth of molds and bacteria** hence preservatives should be used.

❖ Types of creams

➢ Oil-in-water (O/W) creams

- O/W creams composed of **small droplets of oil dispersed in a continuous phase.**
- These are less greasy and more easily washed off using water.
- It contains emulsifying agents of natural origins (bees wax, wool alcohols, polysorbates) emollient and creamy, white or translucent and stiff.
  Example: Vanishing Cream.

➢ Water-in-oil (W/O) creams

- W/O composed of **small droplets of water dispersed in a continuous oily phase.**
- These are more moisturizing as they provide an oily barrier which reduces water loss from the stratum corneum, the outermost layer of the skin.
  Example: Cold Cream.

➢ Cosmetic creams

- A "cosmetic" is any substance used to clean, improve or change the complexion, skin, hair, nails or teeth.
- It is of both o/w and w/o type of creams.
  Example: Cleansing cream, foundation etc.

➢ Medicated creams

Medicated creams can be both o/w or w/o type and is used to carry the medicaments.

❖ Preparation of creams

- Creams may be formulated from a variety of oils (both mineral and vegetable) and from fatty alcohols, fatty acids and fatty esters.
- Emulsifying agents include **non-ionic surfactants** and soaps.
- Preparation involves separating the formula components into two portions: lipid and aqueous. The lipid portion contains all water-insoluble components and the aqueous portion the water-soluble components.
- Both phases are heated to a **temperature above the melting point of the highest melting component**. The phases then are mixed, and the mixture is stirred until reaching ambient temperature or the mixture has congealed.

❖ Quality control test for creams

1. Type of emulsion

- Scarlet dye is mixed with the cream and drop of this mixture is placed in the slide and covered with cover slip.
- If dispersed globule appears red and ground is colorless then it is o/w type and the reverse indicates the w/o type of emulsion.

2. Patch test or sensitivity test

- The sensitivity test for the final formulated cream should be done after application to the different parts of skin surfaces. It should be observed for any skin rashes, itching, irritation, or redness for a period of 7–14 days.

3. Biological testing

- This test is mainly performed for products containing hormones, vitamin preparations, and antiseptics.

4. Removal from skin

- It can be tested by washing the applied part with the tap water.

5. Peroxide stability test in creams

- In this test, 1 g of cream is taken in a test tube and subjected to heating at a constant temperature of 95°C for 24 h.

- Care should be taken to ensure that the water level in the bath meets the upper surface of the cream in the test tube.
- Then, the contents in the test tube are emptied into 250 ml volumetric flask and subjected to peroxide content determination by using the formula

Percentage stability = (Final H_2O_2 concentration/Initial H_2O_2 concentration) × 100
The stability of the peroxide cream should be more than 95%.

❖ Storage

- Cream should be stored in a well-closed glass or plastic container with wide mouth and temperature below **15-25^{0}C** away from sun light and UV light.

5.4.4 Paste

- Pastes are the **homogenous, semisolid preparations** containing high concentration of insoluble powdered substances, not less than 20%, intended for external application to the skin.

- It consists of fatty base (e.g., petroleum jelly) and at least 25% solid substance (e.g., zinc oxide).
- Usually, they are thick and do not melt at normal temperature.
- It remains on the area for longer duration.

❖ Different bases of pastes

1. Hydrocarbon base
2. Water miscible base
3. Water soluble bases

1. Hydrocarbon base

Soft paraffin and liquid paraffin are commonly used bases for the preparation of paste.

Table 5.17: Hydrocarbon Base

PREPARATION	ACTIVE INGREDIENTS	BASE	USE
Compound Zinc Paste B.P.	Zinc oxide	Soft paraffin	Eczema, Psoriasis
Compound Zinc & Salicylic acid Paste B.P. scar's Paste)	Zinc oxide & salicylic acid	Soft paraffin	Eczema, Psoriasis
Coal tar paste	Coal tar	Soft paraffin	Eczema, Psoriasis, Ring worm
Dithranol paste compound	Dithranol	Soft paraffin	

2. Water miscible bases

These include emulsifying ointments and emulsifying wax for pastes.

Table 5.18: Water Miscible Base

PREPARATION	BASE	USE
Resorcinol & sulfur Paste B.P.C.	Emulsifying ointment	Dandruff, and are easily removable from the hair
Zinc & Coal tar Paste Magnesium sulfate paste B.P.C. Morison's paste	• Emulsifying wax • Magnesium sulfate -45%	• Eczema • Used to treat boils, because of their Phenol in glycerol powerful osmotic effect of the salt and the glycerol.
Titanium dioxide paste B.P.C.	• Suspension of • TiO_2, ZnO, light kaolin and red Fe_2O_3 in glycerol+ water.	Absorbs exudates from weeping skin conditions.

3. Water soluble base

- They consist of mixture of high and low molecular weight polyethylene glycols.
- They are either carbowaxes Polyethylene Glycols (PEGS) or hydrated gums (Bentonite, Gelatin, Cellulose derivatives).

Example: Triamcinolone Dental Paste B.P.C.

❖ Methods of preparation

- Like ointment, pastes are prepared by trituration and fusion methods.
- Trituration method is used when the base is liquid or semisolid.
- Fusion method is used when base is semisolid and/or solid in nature.

❖ Quality control test for paste

1. **Impurities**: Impurities associated with the ingredients of the paste should be tested using suitable analytical methods.
2. **Water content**: It is tested by using **Karl Fischer titrator**.
   In this, the percentage of moisture is determined by automated potentiometric titration with an iodine and sulphur dioxide reagent. Liquid is extracted into an appropriate solvent and is titrated volumetrically.
3. **Preservative content**: It should be tested by using suitable analytical method.

❖ Storage

- Paste should be stored in well closed container and in a cool place to prevent evaporation of moisture present in paste.
- It should be stored in the container which do not allow absorption of the paste.

5.4.5 Topical Gels

- Gels are **transparent or translucent, homogeneous, non-greasy**, semisolid preparation with physical and sometimes chemical cross linkage by suitable gelling agents generally applied externally.
- Gels are also formed with celluloses such as hydroxypropylcellulose and hydroxy-propyl-methylcellulose.

❖ Advantages of gels

- Gels are easy to formulate as compared to other semisolid dosage forms.
- A gel is an **elegant non-greasy** formulation.
- It can be used as **controlled release formulation** by entwining the polymer more than once.

❖ Disadvantages of gels

- Some drugs aren't absorbed easily through the skin.
- There's a possibility of an allergic reaction.
- The effect of gels initiates slower (but lasts longer).

❖ Classification of gels

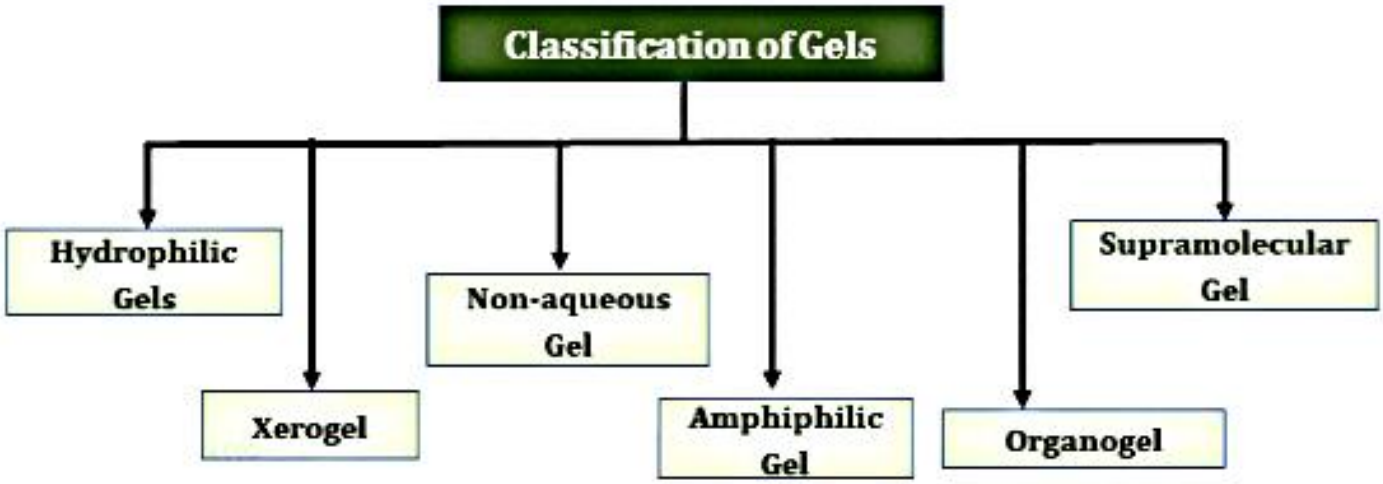


Fig 5.20: Classification of gels

1. **Hydrophilic Gel:** Hydrophilic gels that are usually referred to as **hydrogels** are networks of polymer chains that are sometimes found as colloidal gels in which water is the dispersion medium.
   Example: Collagen, Agarose, Hyaluronic acid
2. **Xerogel:** Xerogels are solid materials derived from gels which consist of interconnected particles or polymers dispersed in a liquid.
   Example: Silica gel and dried out, Compact macromolecular structures such as gelatin or rubber
3. **Non-aqueous Gel:** Non-aqueous gels are gels that do not contain water as a solvent. They are usually formulated with hydrophilic non-aqueous solvents, such as glycerin, propylene glycol, ethanol, or polyethylene glycol, and gelling agents.
   Example: Minocycline Hydrochloride
4. **Amphiphilic Gels:** Amphiphilic gels are a type of gels that consist of crosslinked polymers with both hydrophilic and hydrophobic segments.
   Example: L-Ascorbic Acid 22% Topical Serum Gel
5. **Organogel:**

   These are non-crystalline, non-glassy, thermo-reversible (thermoplastic) solid materials composed of a liquid organic phase entrapped in a three-dimensionally cross-linked network.

Example: Lanolin-based Organogel, Cholesteryl anthraquinone Organogel

6. **Supramolecular Gel:** Supramolecular hydrogels are produced when gelator molecules (or macromolecules) spontaneously self-assemble to form a 3D solid-like network via dynamic intermolecular non-covalent bonds.

   Example: Agar

❖ Formulation of Gels

Carbomer 940	0.75%
Purified water	34.25%
Solulan 98	3.00%
SD alcohol #40	50.00%
Diisopropanolamine, 10% in water	12.00

Method of preparation

Prepare a Carbomer slurry in water with gentle agitation, and add mixture of SDA #40 and Solulan mixture, mixing until no particles are visible. Neutralize carefully with Diisopropanolamine solution to avoid incorporating air.

❖ Quality control test for gels

1. **Measurement of pH:** The pH of various gel formulations can be determined by using **digital pH meter**. One gram of gel is dissolved in 100 ml distilled water and stored for two hours.
2. **Drug content:** In this method, 1 g of prepared gel is mixed with 100 ml of drug soluble or extractable suitable solvent. Aliquots of different concentrations are prepared by suitable dilutions after **filtering the stock solution and the absorbance is measured.**
3. **Viscosity: Brookfield viscometer** is used for the measurement of viscosity of the prepared gel. The gel is rotated at different values of rpm.
4. **Extrudability study:** The formulations are filled in the collapsible tubes after the gels are set in the container. The extrudability of the formulation is determined in **terms of weight in grams required to extrude a 0.5 cm ribbon of gel in 10 seconds.**

5. **In vivo studies:** The **pharmacokinetic** and **pharmacodynamic studies** on suitable animal models can be studied after obtaining permission from institutional animal ethical clearance committee.

6. **Stability:** The stability studies are carried out for all gel formulations by freeze–thaw cycling. In this, syneresis is observed by subjecting the product to a temperature of **4°C** for one month, at **25°C** for one month, and at **40°C** for one month. After this, the gel is exposed to ambient room temperature and liquid exudates separation is noted.

❖ Storage of Gels

- Gels should be stored in a cool, dry, and dark place, away from direct sunlight, heat, and moisture, to prevent degradation, contamination, or alteration of their properties.
- It should also be protected from **temperature exceeding 30°C**.

5.4.6 Liniments

- Liniment is a medicated topical preparation for application to the skin.
- Sometimes **called balms or heat rubs**, liniments are of a similar or lesser viscosity than lotion & are rubbed to create friction, unlike lotion, ointment or creams, but patches, sticks and sprays are also available.

❖ Advantages of liniments

- Liniments are very moisturizing and good for dry skin.
- They have a low risk of sensation due to having few ingredients beyond the bases oil or fat and low irritation risk.
- These are used as rubefacient, counter-irritant and penetrating action on skin.

❖ Disadvantages of liniments

- Alcoholic or hydroalcoholic solution may produce irritation to the skin.
- Avoid getting this medication in your eyes, nose, or mouth.
- It does not apply to serious burns or deep wounds.

❖ Classification of Liniments

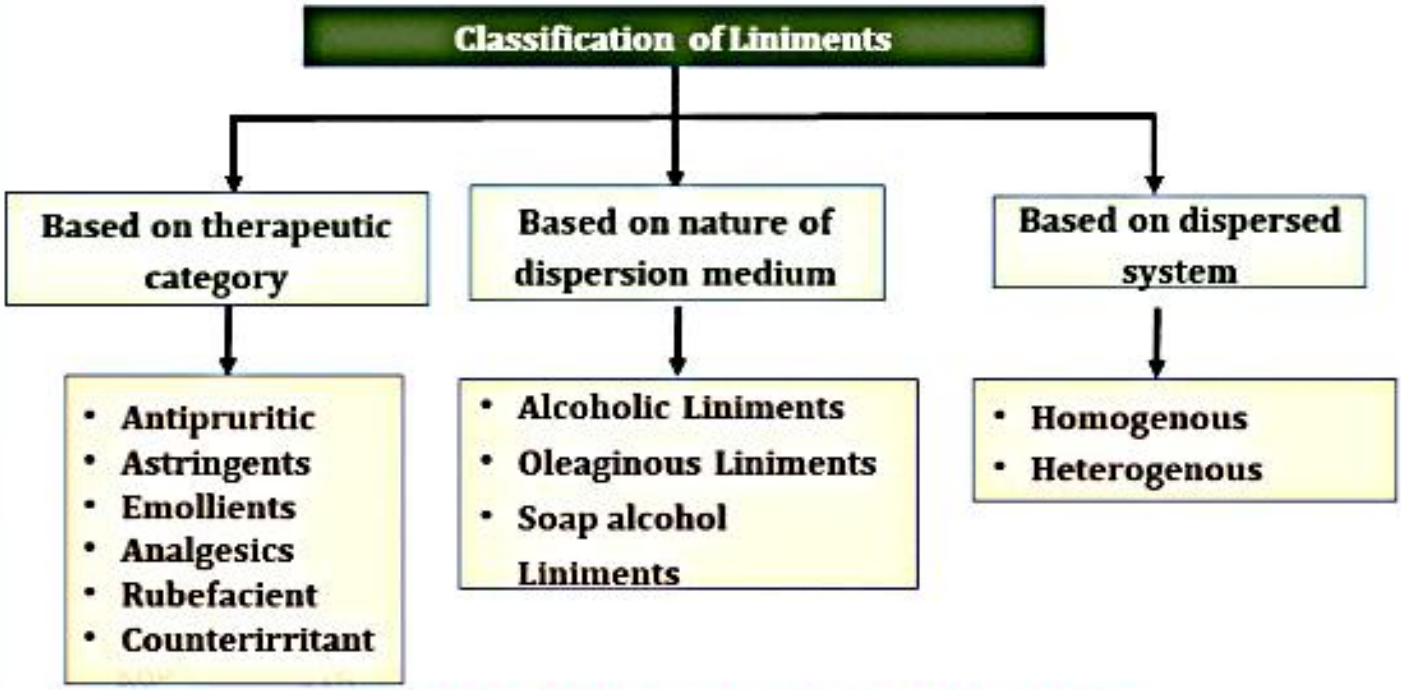


Fig 5.21: Classification of Liniments

1. Based on therapeutic category

Antipruritic: Antipruritic liniments are used to relieve itching.

Example: Diphenhydramine (Benadryl) and hydroxyzine liniments

Astringents: Astringents causes biological tissue to contract.

Example: Isopropyl alcohol liniments

Emollients: Emollients are the products that soften skin or treat dry skin.

Example: Aconite liniments

Analgesics: Analgesics are the group of drugs used to achieve relief from pain.

Example: Sloan's Liniment

Rubefacient: Rubefacient liniments are substance that causes redness (Rubar).

Example: Capsicum Liniment

Counterirritant: An agent applied locally to produce superficial inflammation with the object of reducing inflammation in deeper adjacent structures.

Example: Methyl Salicylate Liniment

2. Based on nature of dispersion medium

- **Alcoholic liniments:** Alcoholic liniments used generally for their rubefacient, counter irritant mildly astringent, and penetrating effects. Penetrate the skin more readily than do those with an oil base.

- **Oleaginous liniments:** For oleaginous liniments, the solvent may be a fixed oil such as almond oil, peanut oil, sesame oil, or cottonseed oil or a volatile substance such as wintergreen oil or turpentine, or it may be a combination of fixed and volatile oils
- **Soap alcohol liniments:** It contains alcoholic solutions of soap as a dispersion medium.

3. Based on dispersed system

- **Homogenous:** Homogenous liniments contain drugs extracted in solvents distributed homogenously in dispersion medium.
- **Heterogenous:** Heterogenous liniments contain drugs in suspension, emulsion or in combined form, dispersed in medium.

❖ Formulation of Liniments

Soft soap	2.7gm
Camphor	1.5gm
Turpentine oil	20 ml
Purified water	30 ml (q.s)

Method of preparation

Mix the soft soap with small quantity of purified water. Prepare a solution of the camphor in the freshly rectified turpentine oil. Gradually add the camphor solution to the soap mixture with trituration till a thick creamy emulsion is formed. Add sufficient purified water to produce the required volume. Mix thoroughly. Transfer the preparation to a bottle, label and dispense.

❖ Storage

- Liniments should be stored in an air-tight containers in a cool place.
- Liniments should be stored in a tightly closed container and labeled as **"FOR EXTERNAL USE ONLY"**

5.4.7 Lotion

- Lotions are liquid dosage forms for external use.
- They are generally meant for application to the skin and are applied directly without friction, with the help of some absorbent material such as

cotton wool or are charged on to cotton wool or gauze and kept on the needed part of the body.

❖ Advantages of Lotion

- Lotions can easily penetrate through the skin.
- These are thin as compared to creams hence it can cover larger area of skin.
- These are more stable and less viscous.

❖ Disadvantages of Lotion

- Lotion may lead to allergic reactions as it contains chemicals and cause skin aging.
- It may clog skin pores and cause acne.
- It shows systemic side effects like glycosuria.

❖ Classification of Lotions

- **Astringent:** It helps in cleansing and moisturizing the face.
  Example: Calamine lotion
- **Face lotion:** It helps in altering the color of the skin. It is also called as bleaching lotion.
  Example: Neutrogena Hydro boost hyaluronic acid
- **Humectant lotion:** It draws water to the skin cells to keep the skin hydrated.
  Example: Oilatum lotion
- **Emollient lotion:** It fill any space or gaps between skin cells that are missing moisturizing lipids.
  Example: Balneum lotion
- **Ceramide lotion:** It replenishes the skin with lost ceramides and are better able to retain moisture.
  Example: Ceramedx lotion

❖ Step for production of lotions

A typical oil-in-water manufacturing process might go like this:

- **Step 1**: Add flake/powder ingredients to the oil being used to prepare the oil phase.
- **Step 2:** Disperse active ingredients.
- **Step 3:** Prepare the water phase containing emulsifiers and stabilizers.

- **Step 4:** Mix the oil and water to form an emulsion.
  (Note: This is aided by heating to between 110-185°F (45-85°C) depending on the formulation and viscosity desired.)
- **Step 5**: Continue mixing until the end product is completed.

❖ Formulation of Lotion

Calamine	15 g
Zinc oxide	5 g
Bentonite	3 g
Sodium citrate	0.5 g
Liquefied phenol	0.5 ml
Glycerin	5 ml
Rose water (q.s)	100 ml

Method of preparation

- Pass zinc oxide, bentonite, and calamine in the 40, 60 no. sieves separately.
- Mix all the three in mortar and pestle.
- Add glycerin dropwise and stir continuously in one direction.
- Add sodium citrate and stir well.
- Pour the required drops of liquified phenol.
- Add some quantity of distilled water and stir well.
- Make up the volume up to 100 ml with rose water or distilled water.

❖ Storage

- Lotion should be stored in a well filled, well closed in an air tight container in a cool place.
- The container should be labelled **"FOR EXTERNAL USE ONLY"** and **"SHAKE WELL BEFORE USE".**

5.4.8 Suppositories

Suppositories are **solid dosage form of various size & shape**, usually medicated for insertion into body cavity like rectum, vagina,

& urethra. They are designated to melt, soften or dissolve at body temperature.

❖ Advantages of Suppositories

- Suppositories are introduced into the body cavity to produce local effects.
- These are unit dosage form.
- These can be easily administered to children, old person and unconscious patients.

❖ Disadvantages of Suppositories

- Suppositories causes embarrassment to patients.
- They required to be stored at **low temperature (10-20°C).**
- There may be difficulty in drug absorption as it **promotes bowel evacuation.**

❖ Classification of Suppositories

Suppositories are classified as

1. **Rectal suppositories:** These are the preparations meant for **introduction into the rectum** for their local or systemic effect. They are tapered at one or both ends and usually weigh about 2g. The rectal suppositories meant for children are smaller in size with a weight of 1 g. It is in torpedo shape.
2. **Vaginal suppositories (Pessaries):** They are semisolid bodies meant for **introduction into vagina**. They are larger than rectal suppositories and vary in weight from 3 g to 6 g or more. They may be conical, rod shaped or wedge shaped and are exclusively used for their local action. It is in globular or oviform shape.
3. **Urethral suppositories (Urethral bougies):** They are meant for **introduction into the urethra.**

   They weigh between 2 g and 4 g with length 2–5 inch. They are very rarely used and should be sterile Suppositories. It is in pencil shaped.

4. **Nasal suppositories (Nasal bougies):** They are **meant for introduction into nasal cavity.** They are similar in shape to urethral bougies and are prepared with Glycero-gelatin base. It is in cylindrical shape

5. **Ear cones (Aurinaria):** They are miniature bodies meant for **introduction into the ear.** Theobroma oil is used as a base; these are prepared in a urethral bougies mold and cut according to the required size. It is in cylindrical shape

❖ Suppository Base

Suppositories Base are used in the preparation of suppositories so that they can retain proper shape and firmness during storage and administration.

➢ Ideal suppository base

- It should melt at body temperature.
- It should be inert, non-irritating & non sensitizing.
- It shrinks sufficiently on cooling to release itself from mould.
- If the base is fatty then

✓ **Acid value - Below 0.2**
✓ **Saponification value - 200 to 245**
✓ **Iodine Value - Less than 7**

➢ Types of suppository base

1. **Oleaginous (Fatty) Base**
   - It is obtained from whole and roasted seeds of cocoa bean.
   - It occurs as a yellowish-white solid with chocolate-like odor.
   - It is solid at normal room temperature but melts in the body as the melting point range is 30–36°C.

   Example: Cocoa Butter (Theobroma oil), Synthetic Fats, Hydrogenated palm kernel oil
2. **Aqueous Base**
   - The base consists of a mixture of glycerol and water made into a stiff jelly by adding gelatin.
   - It is hydrophilic in nature and is a tailor-made base for suppositories containing belladonna extract, boric acid, chloral hydrate, iodoform or opium.

   Example: Glycerinated gelatin (14 % Gelatin + 70% glycerin + Water), Soap glycerin, Polyethylene glycol (Macrogol)

3. Emulsifying Base

- These are synthetic bases and a number of proprietary bases of very good quality are available as desired.

  Example: Massa estarinum, Witepsol, Massuppol

❖ Formulation of Suppositories

Glycerin	91 g
Sodium stearate	9 g
Purified water	5 g

Method of preparation

The glycerin is heated in a suitable container to about **120°C**. The sodium stearate is dissolved, with gentle stirring, in the heated glycerin, after which the purified water is added and mixed, and the hot mixture is immediately poured into a suitable mold.

❖ Quality control Test for suppositories

1. Visual Inspection

- The suppositories are visually inspected for its physical appearance, size, shape and texture.
- Individual suppositories should be examined for cracks and pits due to entrapment of air in the molten mass.

2. Disintegration Test

- The disintegration test can be determined by using the tablet disintegration test apparatus with necessary modification in the test media.
- According to BP, the disintegration test determines whether the suppositories or pessaries soften or disintegrate within the prescribed time when placed in a liquid medium in the experimental conditions.

3. Uniformity of Mass

- When 20 suppositories and the suppositories are weighed singly, the deviation of individual mass from the average mass should not exceed the limits of 5% with 18 number of suppositories.

4. **Melting Point Determination Test**
   - The temperature at which the partially melted substance begins to rise in the tube is regarded as the melting point.
   - Capillary tube of 10 cm in length is sealed at one end is filled with formulation to about 1 cm height.
   - The tube is then heated in electrothermal thermometer from which melting point can be determined.

5. **In vitro drug release**
   - In vitro drug release can be determined by USP rotating basket dissolution test apparatus in 900 ml **Sorenson's phosphate buffer** (pH 7.4).

6. **Fragile or Breaking Test**
   - This test is performed to determine the tensile strength of the suppository to withstand mechanical shocks during handling, transit and storage.
   - The **breaking test apparatus** is used for this purpose.
   - Water is pumped through the walls of the chamber.
   - The inner chamber consists of a disk, which holds the suppositories.
   - A rod is attached to this disk. The other end of the rod consists of another disk on which weights are placed gradually and increased at one-minute intervals.
   - The weights are added until the suppository crumbles.

7. **Test of dissolution rate**
   - It is the amount of dosage form that gets dissolved in body fluid in unit time. It is a measure of the rate of drug release from the suppository.
   - Two types of apparatus are available for testing the dissolution rate.
     - ✓ **Suppository dialysis cell:** Lipophilic suppositories are tested using suppository dialysis cell, which is also called as modified flow-through cell.
     - ✓ **Stationary basket:** Rotating paddle apparatus (USP dissolution test apparatus). Hydrophilic suppositories are tested using stationary basket - rotating paddle apparatus.

❖ **Storage**
   - Suppositories should be stored in the **refrigerator or another cool place**, so they do not melt.

- Oleaginous suppositories are stored in 30^0C and glycerinated suppositories in 20-25^0C.

5.4.9 Pessaries

- A pessary is a **prosthetic device that can be inserted into the vagina** to support its internal structure.
- It's often used in the case of urinary incontinence and a vaginal or pelvic organ prolapse. A prolapse occurs when the vagina or another organ in the pelvis slips out of its usual place.
- A collapsed pessary is inserted into the vagina and put in place just under the cervix. Depending on the type of pessary used, it may be inflated using a bulb.

❖ Advantages

- Pessaries **avoid first pass metabolism**. It does not cause nausea and vomiting due to gastric irritation in case of oral therapy.
- It is used before surgery since oral therapy is restricted.

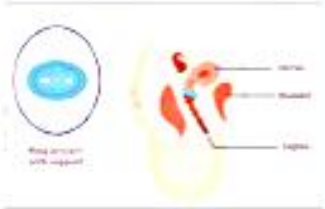
❖ Disadvantages

- Pessaries may **cause mucosal irritation** and leads to erratic and undesired absorption.
- There are sometimes **mild side effects** from pessary use, such as vaginal irritation, foul-smelling discharge, and urinary tract infections.

❖ Types of Pessaries

- There are two main types of pessaries

1. Support



- The pessary is a device that is placed into the vagina to **support the uterus or bladder and rectum**. It is a firm ring that presses against the wall of the vagina and urethra to help decrease urine leakage.

2. Space-filling

- They come in many different shapes and sies to fit a woman's individual anatomy.
- They are all usually made from **medical-grade silicone**, which makes durable and resistant to absorption.
- The most commonly used support pessary is the ring pessary with support.
- This is because it fits a large majority of women and can be used at **all stages of pelvic organ prolapse**.
- The most commonly used space-filling pessary is the Gellhorn pessary.
- This has a broad base with a stem that comes in **different lengths** so that it will also be able to fit most women.

❖ Storage

- Stored in a cool place preferably in refrigerator to avoid melting.

CHAPTER - 5

PHARMACEUTICAL FORMULATION

PART V– NASAL AND EAR PREPARATIONS

Points to be covered in this topic

- 5.5 NASAL PREPARATION
  - 5.5.1 Nasal Powder
  - 5.5.2 Nasal Gels
  - 5.5.3 Nasal Sprays
  - 5.5.4 Nasal Drops
- 5.6 EAR PREPARATIONS

NASAL PREPARATIONS

5.5 NASAL PREPARATIONS

- **Nasal preparations are products** applied in the nose to treat conditions of the nose or nasal symptoms.
- They **include medicines** such as nasal steroids, lubricants, antihistamines and decongestants and anti-infective, used to treat hay fever symptoms, congestion and infections.

❖ Advantages of nasal route of drug administration

- Nasal delivery **offers a number of advantages** for certain classes of drug compounds and vaccines. The advantages include:
- Fast onset of action **(rapid absorption).**
- Potential for local, systemic and CNS delivery

❖ Disadvantages of nasal route of drug administration

- Nasal drug administration is limited, however, to very small volumes, and thus only applicable to potent drugs with high water solubility.
- The active ingredient must have a **molecular weight <1 kDa** be absorbed.
- Nasal route of drug administration is not suitable for drugs that are irritating or injurious to the nasal mucosa.

5.5.1 Nasal Powders

- Nasal Powders are **multidose preparation** consisting of one or more powders of solid active substance(s) intended for nasal use by insufflation into the nasal cavity.
- These are produced by **spray drying** and **freeze drying.**
- It is based on mucoadhesive, swellable polymers like starch, dextran, chitosan etc.

❖ Advantages

- Nasal powders are safe and cost effective.
- These are stable and does not require preservative.
- It can be used as an alternative when liquid dosage form cannot be used.

❖ Disadvantages

- Snorting powder of any kind can **lead to inflammation** of the nasal lining, infection in the lungs and blockages of respiratory tracts and nasal airways.
- Its **bioavailability can be decreased** due to repeated administration.
- There may be rapid removal of therapeutic agent from site of absorption.

❖ Classification of Nasal Powders devices

a) Insufflators

- Insufflators consists of **extremely small fine solid particles** of the pharmaceutical powder used to inject into the nasal cavity.
- It consists of a tube that contains drug substance and sometimes syringe also.

b) Dry powder inhaler

- These are used to deliver the dry powder for local or systemic effect in the nasal route.
- These are used to treat the disease like asthma, bronchitis, COPD and also in diabetes mellitus.

Example: Levosalbutamol Dry powder inhaler, Budesonide inhaler etc.

C) Pressurized Metered Dose Inhalers

- Pressurised MDIs are widely used for treatment of asthma, chronic obstructive pulmonary diseases (COPD) and other respiratory tract disorders.
- It helps deliver a certain amount of medicine through your mouth and into your lungs.

Example: Salbutamol Pressurized MDIs, Ipratropium bromide

❖ Formulation of Nasal Powder

Menthol and Eucalyptus Inhalation B.P.C

Ingredients	Quantity
Light magnesium carbonate	70 g
Menthol	20 g
Eucalyptus Oil	100 ml
Water to produce	1000 ml

❖ Storage

- Nasal powder should be stored at controlled room **temperature 20-25^{0}C** and **relative humidity between 40-50%.**

5.5.2 Nasal Gels

- Nasal gels are high viscous thickened solution or suspension that is used for repeated administration of drug into the nasal cavity.
- It is mainly used in winters for individual having nasal sinusitis or nasal allergies.

❖ Advantages

- Nasal gel is **easy to administered** and has less systemic side effects.
- It reduces the anterior leakage of the formulation.
- It reduces irritation due to presence of soothing/emollient excipients.

❖ Disadvantages

- Nasal gel has low bioavailability.
- It may lead to irreversible damage to nasal cavity.
- Delivery volume in nasal cavity is restricted to **25-200 µL.**

❖ Classification of Nasal gels

- Nasal gel is classified as

1. **Inorganic gel:** Inorganic gel is a two -phase system. **Example:** Bentonite magma
2. **Organic gels:** Organic gel is a single -phase system. **Example:** Carbopol
3. **Hydrogel:** Hydrogel is either natural or synthetic gums inorganic gel. **Example:** Methyl cellulose, Pluronic etc.
4. **Organogel:** Organogel is hydrocarbon type animal, vegetable fats soap base greases hydrophilic gel. **Example:** Petrolatum, polyethylene gel etc.

❖ Formulation of Nasal gels

Otrivin Nasal gel

Ingredients	Quantity
Oxymetazoline HCl	0.05% w/v
Benzalkonium Chloride	0.01% w/

❖ Storage

- Nasal gel should be stored in cool place in refrigerator.
- It should be prevented from getting 'ice up' during storage in refrigeration.

5.5.3 Nasal Sprays

- Sprays are the liquid preparations of medicaments in aqueous, alcoholic, or glycerin-containing vehicle and are meant for application to the nose or throat by means of an atomizer or nebulizer.
- Coarse droplets of the medicaments will be administered to the upper respiratory tract, whereas very fine droplets penetrate into the respiratory tract.
- It can deliver an exact dose from **25-200 µL**.

❖ Advantages

- Nasal sprays can also be used daily without rebound nasal congestion or harm to the nasal tissue.
- It shows rapid onset of action.
- Bioavailability of drugs can be improved by using nasal sprays.

❖ Disadvantages

- Nasal sprays are administered at limited dose due to small absorption site.
- Sometime the bitter taste of the spray can reach to mouth.
- It is not suitable for patient suffering of nose diseases.

❖ Classification of Nasal Sprays

Fig 5.22: Classification of Nasal Sprays

1. **Nasal antihistamine Sprays:** This type of spray acts by blocking histamine. It is used to treat runny nose allergies.
   Example: Triamcinolone acetonide, Mometasone furoate etc.
2. **Nasal anticholinergic Sprays:** These types of sprays act by blocking acetylcholine that decreases secretions from glands in nasal cavities. It is used for treating both allergic and non-allergic rhinitis.

   Example: Ipratropium Bromide

3. **Combination of steroid and antihistamine sprays:** These contains both nasal steroid and antihistamine properties.
   Example: Levocabastine, Azelastine
4. **Nasal cromolyn sodium Sprays:** These types of sprays act by blocking mast cells. It helps in treatment of nasal decongestion, sneezing and runny nose in patients.
   Example: Cromolyn sodium nasal spray
5. **Nasal steroid sprays:** These types of sprays act by decreasing inflammation within nasal passages. It is available as OTC. It is used in treatment of nasal congestion, sneezing, watery eyes and runny eyes.

   Example: Fluticasone, Budesonide etc.
6. **Nasal irrigation:** This type of spray is used to rinse out the mucus out of the nose. It is used before using a nasal spray.
   Example: Ocean irrigation, Bulb syring
7. **Nasal saline spray:** This type of spray used to keep nose moist for patient who are suffering from epistaxis.
   Example: Nasal saline spray
8. **Nasal Decongestant Spray:** This type of spray used to provide relief from nasal congestion. It is suitable for short period of time.

   Example: Neo-Synephrine, Oxymetazoline HCl, Naphazoline

❖ Formulation of Nasal Spray

Phenylephrine Nasal spray

Ingredients	Quantity
Phenylephrine HCl	500 mg

Naphazoline HCl	50 mg
Thiomersal 0.05%	5 ml
Pyrilamine maleate	200 mg
Sodium chloride	556 mg
Edetate sodium	150 mg
Sodium metabisulphite	100 mg
Sterile water	100 ml

Method of preparation

- Accurately weigh and/or measure each ingredient.
- In a 250-mL beaker, dissolve the phenylephrine hydrochloride (HCl), naphazoline HCl, and pyrilamine maleate in 40 mL of Sterile Water for Irrigation.
- In a separate beaker, dissolve the edetate disodium in warm Sterile Water for Irrigation (48 mL).
- Allow to cool and then dissolve the sodium metabisulfite and sodium chloride in the solution. Mix together the two solutions.
- Add the thimerosal solution and bring to volume with Sterile Water for Irrigation.
- Package in nasal-spray bottles and label.

❖ Storage of Nasal Spray

- Nasal spray should be stored in tight, light-resistant nasal-spray containers.
- It should keep upright as directed either in room temperature **(20-25^{0}C)** or stored in refrigerator **(4-8^{0}C).**

5.5.4 Nasal Drops

- Nasal drops are aqueous solutions of drops that are instilled into the nose with a dropper.
- This can be achieved by using 0.9% sodium chloride and **0.5% methyl cellulose**.
- Nasal drops are made to instilled into the nasal cavity in which it is in contact with mucus membrane, it should be pass through sintered glass funnel before making to final volume with water.

Example: Rifampin nasal drop, Ephedrine nasal drops etc.

❖ Advantages

- Nasal drop is used for temporary relief of congestion in the nose caused by various conditions including the common cold, sinusitis, hay fever, and allergies.
- It works by **narrowing the blood vessels** in the nose area, reducing swelling and congestion.
- These are inexpensive.

❖ Disadvantages

- Temporary burning, stinging, dryness in the nose, runny nose, and sneezing may occur.
- It lacks dose precision.
- It may cause nose bleeding and rhinitis medicamentosa on regular use.

❖ Classification of Nasal drops

1. **Antibacterial nasal drops:** Antibacterial nasal drops are the preparations that are used to treat bacterial infections.
   Example: Chloramphenicol 0.5% and Dexamethasone 0.1%, Ciprofloxacin 0.3%w/v, Rifampin nasal drop etc.
2. **Nasal steroid:** Nasal steroid is used to relieve mucus production, sinus congestion. It is also used to reduce inflammation caused due to allergies.
   Example: Fluticasone nasal drop, Ciclesonide nasal drop etc.
3. **Nasal lubricants, moisturizers and irrigation:** Nasal lubricants and irrigations are saline solutions or gel form. These products are used to treat irritated or dry nasal passages that may be caused by hay fever, cold and other conditions. They are also used after nasal surgery to clean out the inner part of the nostrils.
   Example: Saline nasal drop, Rhinaris nasal drops etc.
4. **Nasal antihistamine:** Nasal antihistamine used to treat allergic condition such as sneezing, runny nose etc.
   Example: Azelastine nasal drop, Phenylephrine nasal drop etc.
5. **Nasal decongestant:** These preparations are used in treatment of nasal congestion caused due to cold, fever and allergy. It acts by constricting the blood vessel and allow air to flow more freely.
   Example: Otrivin nasal drop, Bresol nasal drop etc.

❖ Formulation of Nasal drop

Rifampin 1% Nasal drops

Rifampin	1 g
Hydroxypropyl methylcellulose	1.25g
Polysorbate 80	300 mg
Ascorbic acid	100 mg
Sodium sulfite	400 mg
Purified water q.s	100 ml

Method of preparation

- Accurately weigh or measure each ingredient.
- Heat about 90 mL of the purified water to about 70°C and sprinkle on the hydroxypropyl methylcellulose K4M while stirring.
- After dissolution, cool the mixture to room temperature, add the remaining ingredients, and stir until uniformly dispersed.
- Add sufficient purified water to final volume and mix well. Package and label.

❖ Storage

Nasal drop should be store in a cool and dry place. Keep the medicine out of the reach of children. Do not keep expired medicines or medicines that are no longer needed. Discard your nose drop 30 days after opening.

EAR PREPARATIONS

5.6 EAR PREPARATIONS

- Ear Preparations are solutions that are **instilled into the ear** with a dropper.
- The solution is generally prepared in water, glycerin or propylene glycol.
- Ear drops are generally used for cleaning the ear, softening the wax and treating mild infections.

Example: Sodium bicarbonate ear drop

❖ Advantages

- Drug degradation is absent that is observed in the gastrointestinal tract.
- Hepatic first pass metabolism can be avoided.
- The bioavailability of smaller drug is good.

❖ Disadvantages

- Dose is measured in number of drops.
- Person must retain with treated ear for 3-5 minutes.
- It may cause redness or swelling around the ears.

❖ Types of Ear Preparation

1. Ear Drop

- Ear drops are liquid medications that you put inside your ear canal. Ear drops can help treat pain, inflammation, infection and earwax blockage.
- It includes glycerine, mineral oil, and saline solutions.
- These ear drops may also contain other substances, such as carbamide peroxide, baking soda, and acetic acid.

Examples: AL-EARTONE®, Ciproxin HC®, Sofradex®

➢ Formulation of Ear drop

Antipyrine and Benzocaine Ear Drops

Ingredients	Quantity
Antipyrine	54 mg (5.4%)
Benzocaine	14 mg (1.4%)
Glycerin	Q.S
Oxyquinoline Sulfate	Q.S

➢ Uses of Ear drop

- Ear drops help relieve the pain, swelling, and congestion of some ear infections.
- This medicine is also used to soften earwax so that the earwax can be washed away more easily.

➢ Storage

Ear drop should be packed in colored, fluted glass bottle and supplied with dropper.

➢ Labelling

- "For external use only"
- "Not for injection"
- "Discontinue the use if irritations persist

2. Ear Spray

- Ear spray is the formulation that is made to instilled into the ear for treatment of various ear related diseases.
- Ear Spray has a special composition with the active ingredient Polysorbate 80 and chamomile.

➢ **Method to use Ear Spray**

- Shake the bottle or spray. Remove the top of the bottle or spray and throw away the plastic seal. Gently pull your child's earlobe backwards to open up the ear canal. Put the prescribed number of drops or spray into the ear canal.

➢ **Uses of Ear Spray**

- Ear Spray is used in the treatment of inflammation and infections of the outer part of the ear.

➢ **Storage**

- The spray has an expiry of four weeks once opened. So, it should not be stored than the expiry weeks.

3. Ear Ointment and Gels

- Ear ointment stops the growth of bacteria and fungus.
- Wetness in the ear canal can help bacteria and fungus to grow. This medication may also contain drying ingredients such as glycerin or alcohol.

  Example: Otomax Otic ointment for animals, ointment for dogs and cats
- It treats the infection and reduces pain and swelling in the ear.

➢ **Storage**

- Ear ointments can only be used for 28 days after opening but always check the PIL as some may be less, for example, preservative free.
- Most ointments and gels should be stored at room temperature and away from heat, moisture, and direct light.

CHAPTER - 5

PHARMACEUTICAL FORMULATION

PART VI– POWDER AND GRANULES

Points to be covered in this topic

- 5.7 POWDER AND GRANULES
  - 5.7.1 Insufflations
  - 5.7.2 Dusting Powders
  - 5.7.3 Effervescent Powders
  - 5.7.4 Effervescent Granules
  - 5.7.5 Quality Control Test for Powder and Granules

5.7 POWDERS AND GRANULES

- Powder is a mixture of **finely divided drugs** and/or chemicals in dry form.
- Powders can be used **internally** and **externally** (e.g., external applications to the skin).
- Powdered drugs are frequently added to other ingredient to make ointments, pastes, suppositories, and others.

❖ Advantages of the powder dosage form

- Drugs are **more stable** in solid form. For example, dry Antibiotic Syrups.
- Many pharmaceutical dosage forms can be formulated by using **pharmaceutical powders** (Tablets, capsules, powders for reconstitution, dusting powders, bulk powders for inhalation, etc.)
- Each dose can contain a different amount of active drug.

❖ Disadvantages of the powder dosage form

- Patient may **misunderstand the correct method of use**. Without clear instruction, patients may inhale through the nose a drug intended for oral administration.
- It is difficult to **protect powders containing hygroscopic**, deliquescent (tending to melt or dissolve in humid environment), or aromatic materials from decomposition.
- Uniform, individually wrapped doses of powders (sachets) are required and this may increase the manufacturing expense.

❖ Classification of Powders

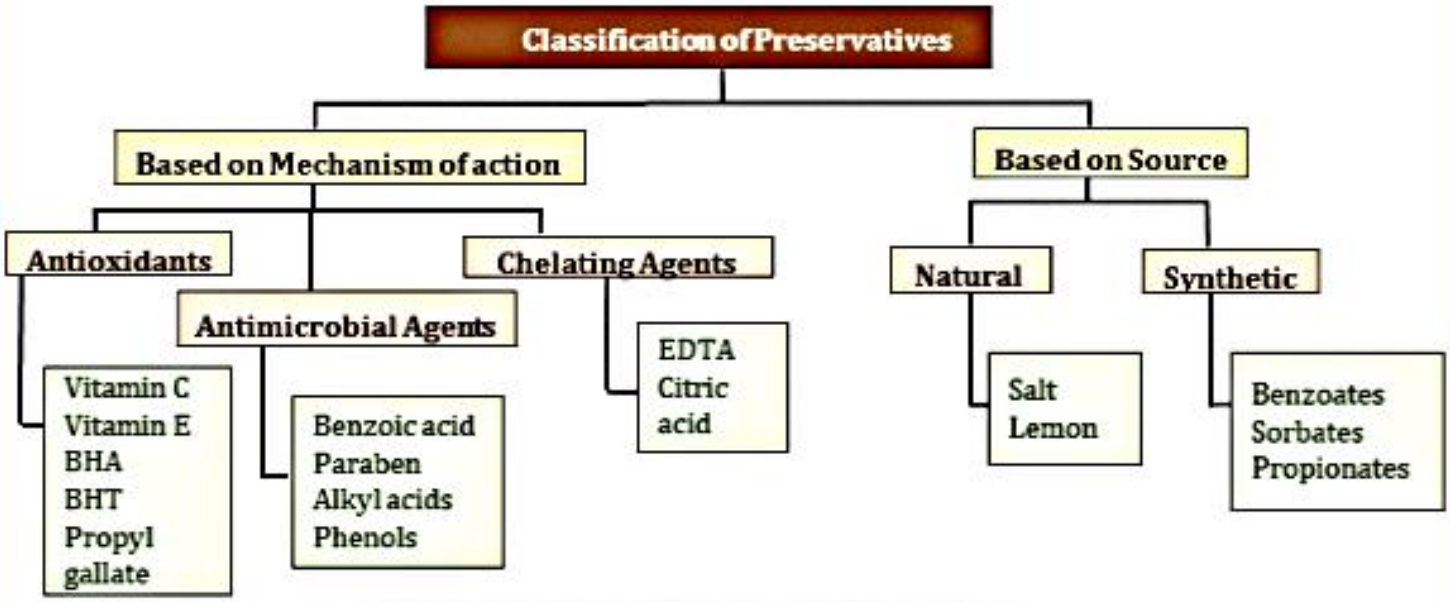


Fig 5.23: Classification of Powders

5.7.1 Insufflations

- Insufflations are **medicated dusting powders** meant for introduction into the body cavities such as nose, throat, ears and vagina with the help of an apparatus known as **"Insufflator"**.

- It sprays the powder into a stream of **finely divided particles** all over the site of application.
- Nowadays the insufflations are available in the form of pressure aerosols. These are used for the administration of potent drugs.

✓ **Advantages**

- Insufflations has **excellent control of dose** through metered valves.
- It also **protects the product** from external environment.
- The insufflations are used to produce a local effect, as in the treatment of ear, nose and throat infection with antibiotics or to produce a **systemic effect** from a drug that is destroyed in the gut.

✓ **Disadvantages**

- Insufflation may cause serious peritoneal injury, which may increase the risk of peritoneal metastasis and port site metastasis.
- It is not able to assist or control ventilation.

✓ **Uses**

- Insufflated gases and vapors are used to **ventilate and oxygenate patients** (oxygen, air, helium), It is used to induce, assist in or maintain general anaesthesia (nitrous oxide, xenon, volatile anesthetic agents).

- Positive airway pressure is a mode of mechanical or artificial ventilation based on insufflation.

5.7.2 Dusting Powders

- These are meant for external application to the skin and are generally applied in a very fine state of subdivision to avoid local irritation.
- Hence, dusting powders should be passed through an 80 sieve to enhance their effectiveness.
- Dusting powders are generally prepared by mixing two or more ingredients one of which must be either starch, kaolin or talc as one of the ingredients of the formulation.

- **The desired characteristics of powders includes**
  - ✓ Homogeneity
  - ✓ Non-irritability
  - ✓ Good Spreadibility and covering capability
  - ✓ Adsorption and absorption capacity

✓ **Advantages**

- Dusting powder protect against skin irritation.
- It is chemically stable as compared to other powders.

✓ **Disadvantages**

- Dusting Powder cannot be applied to broken skin.
- It requires special storage condition.

✓ **Classification of Dusting Powder**

Dusting Powder is classified as

i. **Medicated Dusting Powder:** Medicated Dusting Powder are pharmaceutical powders that contain single medicinal agents applied as dusting agents.

- These powders are frequently used as medicinal powder drugs and protect against skin irritation.
- The base for the dusting powder is clay, kaolin, magnesium carbonate, talc and starch.

Medicated Dusting Powder

Ingredients	Quantity
Purified talc	50

Starch powder	25 g
Zinc oxide powder	20 g
Salicylic acid	5 g

Method: Weigh the required quantity of all the ingredients.

- Mix them in ascending order of their weight. Pass the mixed powder through sieve no. 85.
- After sifting again mix lightly, transfer it in sifter top container to protect it from environmental contamination.

ii. **Surgical Dusting Powder:** Surgical dusting powders are used in body cavities and also on major wounds as a result of burns and umbilical cords of infants.

- Surgical dusting powders must be sterilized before their use.

Neosporin Dusting Powder

Ingredients	Quantity
Bacitracin	0.125 g
Neomycin	0.12 g
Polymyxin B	268 mg

iii. **Cosmetic Dusting Powder:** Cosmetic Dusting Powders are a mixture of several powders that are applied to the body to help absorb oils and moisture from the skin to leave it soft, smooth and lightly scented.

- Various ingredients present in the dusting powders absorb perspiration and excess sebum and result in cooling of the skin.

Cosmetic Dusting Powder

Ingredients	Quantity
Kaolin Clay	1 part
Arrowroot powder	2 parts
Essential oils	q.s

✓ **Storage**

- Powders should be protected from excessive heat, humidity and water.
- Within the storage vicinity, powders should be protected from contamination with foreign materials such as powder, dust, dirt, etc.

5.7.3 Effervescent Powders

- Effervescent Powders are mixture of organic acid and alkali effervesces when subjected to water due to reaction between the acid and the base with evolution of co_2.

  Example: Citric or tartaric acids with sodium carbonate or bicarbonate

✓ **Advantages**

- It masks the bitter and nauseous taste.
- It promotes gastric secretions.
- It acts as a carminative.

✓ **Disadvantages**

- It cannot be given to children due to gas toxicity.
- It has shorter shelf life.
- It is expensive as compared to solid dosage form.

5.7.4 Effervescent Granules

- The effervescent granules are the specially prepared solid dosage form of medicament, meant for internal use
- They contain a medicament mixed with citric acid, tartaric acid and sodium bicarbonate.
- Sometimes saccharin or sucrose may be added as a sweetening agent.

- Before administration, the desired quantity is dissolved in water, the acid and bicarbonate react together producing effervescence.
- The carbonated water produced from the release of carbon dioxide serves to mask the bitter and saline taste of drugs.

✓ **Advantages**

- Effervescent granules are having high solubility and high stability.
- It has fast dissolving property and are also convenient dosage forms.
- It provides alkaline solution upon neutralization of acidic drugs.

✓ **Disadvantages**

- The masking of bitter taste is not possible with this type of granules.
- Potent drug cannot be administered through this dosage form.
- It becomes unstable in presence of moisture.

✓ **Method of Preparation**

- Effervescent Granules can be prepared by two methods

i. Dry or Fusion Method

- A large porcelain or stainless -steel evaporating dish is placed over the boiling water bath.
- The dish must be hot before transferring the powder into it.
- If heating is delayed, the powder which is added to it will heat up slowly and liberated water of crystallization will go on evaporating.

ii. Wet Method

- In this method, the mixed ingredients are moistened with a non-aqueous liquid to prepare a coherent mass which is passed through sieve number 8.
- It should be dried in an oven at a temperature not exceeding 60^0C.
- It is then passed through sieve to break the lumps.

5.7.5 Quality Control test for Powders and Granules

1. Particle size and shape: Particle size and shape depends upon the processing requirement during granulation.

- The methods for determining size and shape are Sieving, sedimentation rate, microscopy.

2. Surface area: This method is not used for granules but used for powders.

- Surface area can be determined by gas absorption and air permeability method.
- In gas absorption method, gas is absorbed as monolayer in particles.
- In air permeability method, the rate of air permeates a bed of powder is used to calculate the surface area of powders.

3. Bulk and Tapped Density

- This test is used for both powders and granules.
- It is used for determination of bulk volume, flow characterstics and compressibility
- Bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the inter-particulate void volume.

$$\text{Bulk density} = \frac{Bulk\ mass}{Bulk\ Volume}$$

- Tapped density of a powder is the ratio of the mass of the powder to the.

volume occupied by the powder after it has been tapped for a defined period of time

$$\text{Tapped density} = \frac{Mass\ of\ granules}{Volume\ of\ granules}$$

4. Flow property

- This indicates the flowability of the powders and granules.
- It can be determined by two ways

i. **Angle of repose -** The angle of the heaped cone of a free-standing powder is the angle of repose.

$$\tan\theta = h/r$$

Where,

tan θ = Angle of repose

h = Maximum height

r = Horizontal range

Angle of Repose	Flowability
Less than 25	Excellent
25-30	Good
30-40	Passable
More than 40	Very poor

ii. **Hausner ratio -** This is the ratio of the tapped density to the poured/ bulk density.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

5. Moisture content

- The amount of moisture present in granules is called moisture content.
- It can be estimated by using moisture balance or IR balance.
- It can be determined by using the following formula

$$\%\ \text{Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

6. Antimicrobial activity

- This test is used for dusting powder.
- It is done by using cup plate method against Staphylococcus aureus and Escherichia coli.

CHAPTER - 5

PHARMACEUTICAL FORMULATION

PART VII– STERILE FORMULATIONS

Points to be covered in this topic

- **5.8 STERILE FORMULATIONS**
  - **5.8.1 Injectables**
  - **5.8.2 Eye Drops**
  - **5.8.3 Eye Ointments**

STERILE FORMULATION

5.8 STERILE FORMULATIONS

- Sterile dosage forms are pharmaceutical drug preparations that must be free of contamination because they **bypass the body's usual defences** against infection.
- **Example:** Injections, ophthalmic preparation etc.

5.8.1 Injectables (Parenteral Products)

- The word Parenteral is derived from the **Greek Word Para= Outside, enteron = intestine.**
- Parenteral products are dosage form that are free from microorganism and can be solutions, suspensions, emulsions of drug in aqueous or oily vehicles by means of injection into various layers of the skin and mucus membrane.

❖ **Advantages of Injectables**

- They enable the **delivery of drugs** to targeted areas such as the knee, eye, ear, and others.
- It avoids **first pass metabolism** of drugs.
- Low concentration of drug requires for administration with minimum wastage.

❖ **Disadvantages of Injectables**

- Injectables drugs are costly as compared to other dosage form.
- The drug from injectable dosage form cannot be removed if any mistake happens after administration.
- It requires trained personnel for the administration.

❖ **Formulation of parenteral products**

1. Therapeutic agents

These are the agents responsible for therapeutic activities.

2. Vehicle / Solvents

Aqueous vehicle (Water): Sodium chloride injection, Ringer solution, dextrose solution, lactated – ringer solution

Non – aqueous: Fixed oils – ethyl oleate, isopropyl myristate, peanut oil, sesame oil, corn oil, cotton seed oil, soybean oil

✓ **Water –** Most commonly used vehicle for drug solution. Test for the quality of water is the total solid content

- A gravimetric method
- Electrolytic measurement of conductivity

3. Additives

✓ **Preservatives -** A preservative is a substance or a chemical that is added to products to prevent decomposition by microbial growth or by undesirable chemical changes.

- **Quaternary ammonium:** Benzalkonium chloride, Benzethonium chloride
- **Alcohol:** Benzyl alcohol, Chlorobutanol, Cresol, Phenol
- **Esters:** Parabens (Methyl paraben Propyl paraben)
- **Mercurial:** Phenyl mercuric nitrate /acetate Thiomersal

✓ **Antioxidants -** Antioxidants are compounds that inhibit oxidation, a chemical reaction that can produce free radicals and chain reactions that may damage the cells of organisms.

Example: Ascorbic acid, Sodium bisulphide

❖ Classification of Injectables

Injectables are classified as following

1. BASED ON VOLUME

i. **Small volume parenteral (SVP):** Small volume parenteral (SVP) solutions are usually 100 ml or less and are packaged in different ways depending on the intended use.

ii. **Large volume parenteral (LVP):** Large volume parenteral (LVPs or large volume injections) are aqueous solutions usually supplied in volumes of 100 ml to 5 000 ml. LVPs are typically used to provide fluid replacement therapy.

2. BASED ON TYPE OF PACKAGING

- **Single dose:** A single dose parenteral is a type of dosage form that is meant for single use in single patient by single procedure.

Example: Ampoules, vials etc.

- **Multidose:** A multi-dose vial is a vial of liquid medication intended for parenteral administration (injection or infusion) that contains more than one dose of medication.

- Multi-dose vials are labeled as such by the manufacturer and typically contain an antimicrobial preservative to help prevent the growth of bacteria.

Example: Multidose vial

3. BASED ON PHYSICAL STATE

i. **Injectable Solution:** These are the preparation that contains drug along with aqueous or oily vehicles.

Example: Calcium solutions, Sodium chloride solution

ii. **Injectable Suspension:** These are the liquid preparations of solids suspended in a suitable liquid medium.

Example: Methyl prednisolone acetate (MPA), Amoxicillin suspension for injection

iii. **Injectable Emulsion**: These types of emulsions consist of an oil, an emulsifier and a balanced blend of amino acids in a continuous phase of distilled water.

Example: Etomidate emulsion, Diazepam emulsion etc

iv. **Injectable Powder:** Powders for injection (PIs) are a popular parenteral dosage form for drugs that cannot be marketed as ready-to-use injectables because of their instability in an aqueous environment.

Example: Amoxicillin Sodium + Clavulanate Potassium Powder, Cefoxitin sodium powder for injection

4. BASED ON ROUTES OF ADMINISTRATION

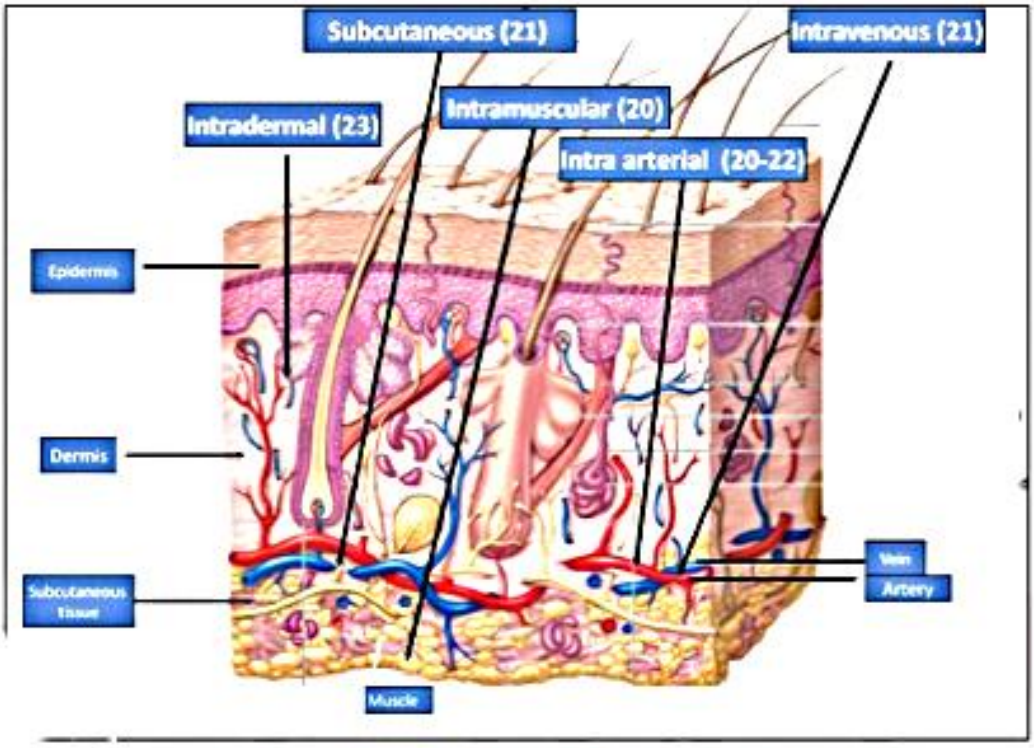


Fig 5.24: Routes of Administration

Table 5.19: Classification of Parenteral based on routes of administration

ROUTES OF ADMINISTRATION	DESCRIPTION
Subcutaneous Injection	These are made under the skin, into the Subcutaneous tissues.
Intrathecal Injection	These are given into the subarachnoid space that surrounds the spinal cord.
Intradermal /Intracutaneous Injection	These are given in between dermis and epidermis to the Skin of left forearm is usually selected for giving the injection 0.1 to 0.2 ml of parenteral solution is injected by this route.
Intra-articular Injection	These injections are given into the liquid that lubricate the articulating end of bones in joints.
Intracardial Injection	These are given into heart muscle or ventricle in an emergency only.
Intramuscular Injection	These injections are given into the muscular tissues. The muscles of the shoulder, thigh or buttock are usually selected.

❖ Quality control Tests for Injectables

1. **Leaker test (Packaging integrity test):** The leaker test is intended to detect **incompletely sealed ampoules**, so that they may be discarded.
   - To conduct a test, a container is placed in a tightly fitted chamber containing 0.5-1% methylene blue solution which is evacuated to a predetermined level of vacuum.
   - It is then applied with negative pressure making the dye to penetrate through any opening.

2. **Clarity test (Particulate matter test):** Clarity test is done by taking parenteral solution and observe it at strong beam of light and the product will be observed for any foreign particle.

   - It is done by using instrument called **Nephelometer.**

3. **Sterility test:** Sterility testing is performed for detecting microorganism in parenteral product.

It can be done by the following methods

i. **Direct transfer method**
   - **Thioglycolate culture** media is used for this method.
   - It is used for identification of aerobic and anaerobic bacteria

ii. **Membrane filtration technique**
   - It is suitable for liquids, soluble powder with bacteriostatic or fungi static oils, creams, and ointment.
   - It is done by passing the products from membrane filter with porosity of **0.45µm**, diameter 50mm.

4. **Pyrogen test:** Pyrogen testing determines the presence or absence of pyrogens in parenteral pharmaceutical products.
   - It is regulated by several standards from organizations such as the Food and Drug Administration (FDA), United States Pharmacopeia (USP), or European Pharmacopeia (EP).
   - The presence of pyrogen can be tested by Sham Test and Rabbit Test.

5. **Assay:** Assay is method to test the clarity, acidity, alkalinity purity, of known, and unknown sample according to the standards given in the monographs.

6. **Content uniformity and weight:** Content uniformity is one in a **series of tests** in a therapeutic product specification that assesses the quality of a batch.

   This can be performed by following steps:

   - 30 sterile units are selected from each batch. The weigh of 10 randomly sterile units is noted.
   - The net weight is calculated by subtracting the empty unit weight from gross weight.
   - The dose uniformity is met if the amount of active ingredient is within the range of 85-115 % of the average value.

7. **Stability Test:** Stability Test is done to **study the shelf life** of the product.
   - It is carried out by subjecting the product to forced degradation usually by heat, acid, alkali, light and peroxide.
   - Condition must be controlled so that only 20-30% degradation occurs.

8. **Isotonicity Test:** A solution is to be termed isotonic (equal tone) it must have the same osmotic pressure as a specific body fluid.
   - The isotonicity of the parenteral solution can be determined by hemolytic method or **cryoscopic method**.

9. **pH:** The pH of the parenteral solution can be determined by using pH meter.

10. **Osmolality:** Osmolality is the concentration of osmoles in a mass of solvent.
    - It can be measured using osmometer.
    - The normal osmolality of extracellular fluid is **280-295 mOsmol/kg**.

❖ Storage of Parenteral Products

- Temperature, light, moisture, pH, composition of the container, type of infusion fluid, and exposure to other chemical substances are the major determinants of the stability of parenteral medication.
- It should be stored in temperature ranges between **25^{0}C to 30^{0}C**.
- Emulsion injectables should be stored in cool place, air tight container, away from light and freezing.
- Lyophilized injectables should be stored in **4-8^{0}C** and should be protected from heat and light.

❖ Packaging and labelling

- After evaluation of the parenteral preparation, the ampoules, vials and transfusion bottles are properly labelled and packed.
- **It should contain the following information**
  - ✓ Name of the preparation
  - ✓ Quantity of the preparation
  - ✓ Mfg. Lic. no.
  - ✓ Batch no.
  - ✓ Date of manufacture
  - ✓ Date of expiry
  - ✓ Storage condition
  - ✓ Retail price
  - ✓ Manufacturer's address

❑ OPHTHALMIC PREPARATION

Ophthalmic preparations (eye preparations) are sterile, liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredient intended for application to the conjunctiva, the conjunctival sac or the eyelids.

❖ Characteristic of preparation

- Ophthalmic preparation must be sterile.
- Product must be isotonic with lachrymal secretion to avoid discomfort and irritation.
- pH should **be 7.4** to avoid irritation.
- Viscosity should be **25 – 50 cps**.

❖ Classification of Ophthalmic Products

Ophthalmic products are classified into various types as given in fig 5.25

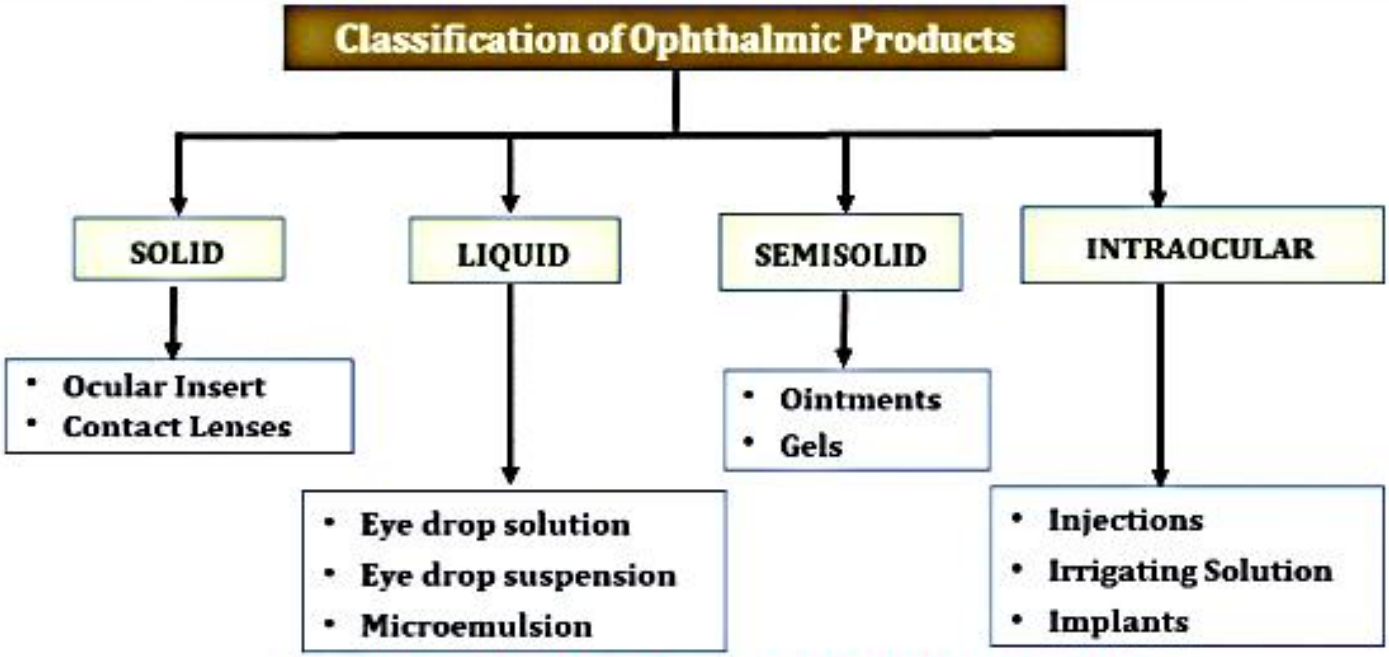


Fig 5.25: Classification of Ophthalmic Products

❖ Additives use in ophthalmic products

1. Water for Injection

- Water for Injection (WFI) is **sterile water** intended for injection into the body and for the manufacture of ophthalmic products.
- It is the **purest quality water** used by the pharmaceutical and biopharmaceutical industries.

2. Preservative

Table 5.20: Concentration of Preservative

PRESERVATIVES	CONCENTRATION (%)
Benzalkonium Chloride	0.1
Chlorohexidine acetate	0.1
Chlorobutol	0.5
Phenyl mercuric salt	0.001 – 0.004
Methyl Paraben + Propyl Paraben	4:1

3. Surfactant

Vehicle used in ophthalmic preparation must have **good wetting ability** to penetrate cornea and other tissue **e.g.,** Polysorbate 20 and 80, Dioctyl sodium sulpho-succinate etc.

4. Antioxidants

These are used to prevent oxidation of active ingredients.

Table 5.21: Concentration of Antioxidants

ANTIOXIDANT	CONCENTRATION (%)
Ascorbic acid	0.1
Acetyl cysteine	0.1
Disodium edetate	0.1
Sodium Metabisulphide	0.1
Sodium Sulphite	0.1

5. Viscosity modifier

- They are mainly used to **increase ocular contact time**; thereby decrease the drainage rate and increase drug availability and produce lubricant effect.
- Viscosity is adjusted within the range of **15-25 centipoise.**

Example: Hydrophilic polymer: Cellulose derivatives (MC, HPMC, HEC), Polysaccharides (Xanthum gum), Polyvinyl alcohol, Polyacrylic acid and Carbomers

6. Buffering agent

- Buffering is included to **minimize any changes in pH** during storage life of drugs.

Table 5.22: Buffering Agents

BUFFER	pH	CONCENTRATION
Acetic acid and salt	1.5 – 5.7	1 – 2
Citric acid	1.5 – 6	1 – 5
Glutamic acid	1.2 – 10.2	1 – 2
Phosphoric acid	6 – 8.2	0.8 - 2

5.8.2 Eye Drops

Eye drops are sterile, isotonic, and pyrogen-free preparations meant for instillation into the **cul-de-sac (the space between the eyeball and eyelid)** of the eye for irrigatory, lubricative, diagnostic, or therapeutic activity.

✓ Advantages of Eye drop

- Eye drops relieve dryness and irritation, promoting comfort.
- These are convenient to use for the patient.
- Eye drop suspensions are best for drug with slow dissolution.

✓ **Disadvantages of Eye drop**

- Stinging/redness in the eye, widened pupils, or blurred vision may occur.
- It does not show sustained action.

Types of Eye drop

i. **Eye drop solution:** These are saline containing solution to match the salinity of the eye.

- Sometimes eye drops do not contain medicaments, it is only used for cleansing and replacing the tear fluid.
- It is having neutral pH of 6.8

Example: Tobramycin eye drop, Lifitegrast solution

Ingredients	Quantity
Tobramycin 0.3%	3 mg
Benzalkonium chloride 0.01%	0.1 mg
Inactives:	

Boric acid, Sodium sulphate, Sodium chloride, Tyloxapol Sodium hydroxide and/or sulfuric acid Purified water

- **Use:** Eye drop solution is used in treatment of bacterial conjunctivitis and also in refractive surgeries.

ii. **Eye drop suspension**: These are used to treat eye inflammation by reducing swelling, redness and irritation.

- These can be symptoms of eye injuries, surgery, or damage caused by severe allergies or chemicals.
- These are used to deliver poorly soluble compounds and are sterile liquid preparations containing solid particles dispersed in a liquid carrier.

Example: Dexamethasone, Fluoromethalone, Prednisolone and Difluprednate eye drop etc.

Ingredients	Quantity
Active: Dexamethasone	0.1%
Preservative: Benzalkonium chloride	0.01%
Vehicle: Hypromellose	0.5%

Inactives: Sodium chloride, Dibasic sodium phosphate, Polysorbate 80, Edetate disodium

iii. **Microemulsion:** Microemulsions are thermodynamically stable-phase transition systems, which possess low surface tension and small droplet size (5–200 nm).

- These are useful to improve the precorneal residence time, drug corneal permeation and increase bioavailability.

Example: Cyclosporin eye drop, Chloramphenicol eye drop etc.

Ingredients	Quantity
Active: Cyclosporine	0.05%

Inactives: Glycerin; Castor oil; Polysorbate 80; Carbomer copolymer type A; Purified water; and Sodium hydroxide

✓ **Formulation of Eye Drops**

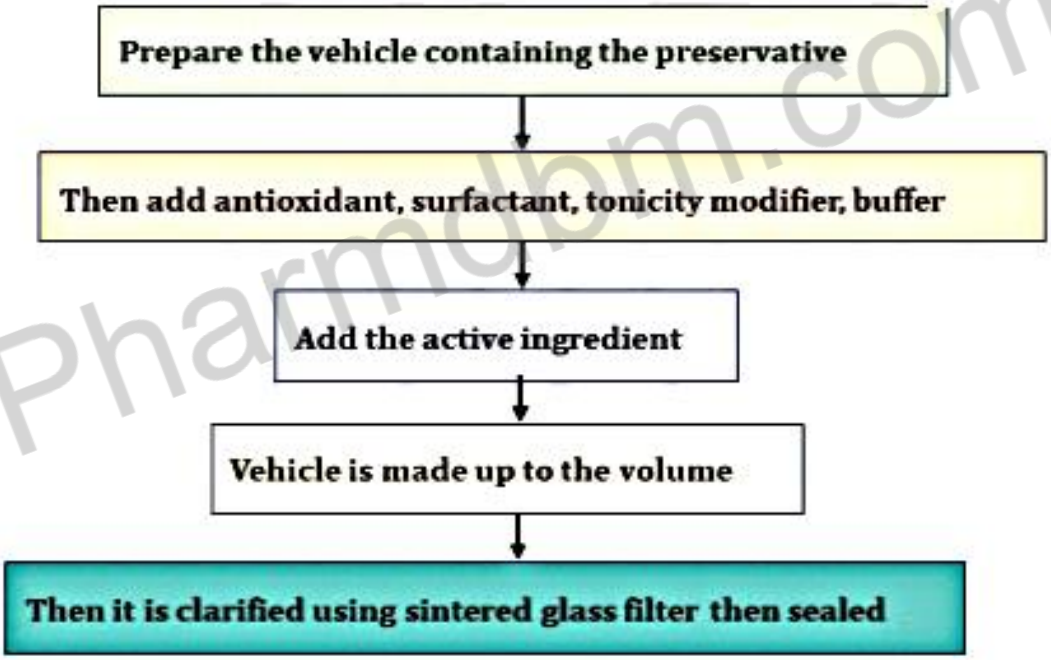


Fig 5.26: Formulation of Eye Drops

✓ **Storage**

- Eye drops should be packed in collapsible tubes to maintained sterility, capacity of 1 mg to 5 mg.
- The container should be fitted with tamper evident device.
- Dropper should be supply separately and comply with test of sterility.
- It should be labelled 'For External Use Only' and should be kept away from children.

5.8.3 Eye Ointments

- Eye Ointment is an ophthalmic ointment is a **semi-solid, greasy or creamy topical treatment** for certain eye conditions, whether mild or severe.
- Ophthalmic ointments are often recommended for eye infections, dry eyes and blepharitis (eyelid inflammation), among many other issues of the eye.

✓ Advantages of Eye Ointment

- Eye ointments are used to treat conditions such as dry eyes or eye infections (such as conjunctivitis).
- Ointments are thicker than drops and that means they can stay in your eye longer.
- It has **greater bioavailability** as compared to liquid.

✓ Disadvantages of Eye Ointment

- It may **temporarily** interfere with eye vision.
- It takes longer time to **reach peak absorption**.
- It may stick to the eyelids hence has poor patient compliance.

✓ Formulation of Eye Ointment

Ingredients	Quantity
Atropine sulphate	1 g
Sterile base	100 g

Sterile base can be prepared by using following ointment base

Liquid paraffin	10 g
Wool fat	10 g
Yellow soft paraffin	80 g

Method of preparation:

- Heat all the above given ingredients in a suitable vessel.
- Filter through a coarse filter paper in heated funnel in container with temperature 16^0C for 2 hrs.
- Atropine sulphate is added with minimum quantity of water for injection into it.
- Stir gently until it is cold.
- Transfer the eye ointment in suitable container.

✓ **Storage**

- Eye ointment should be kept in **cool place.**
- It should be supplied in metal or plastic collapsible tubes, capacity not exceeding 5 g.
- The tube should contain **nozzle of suitable shape.**

CHAPTER - 5

PHARMACEUTICAL FORMULATION

PART VIII– IMMUNOLOGICAL PRODUCTS

Points to be covered in this topic

- **5.9 IMMUNOLOGICAL PRODUCTS**
  - **5.9.1 Sera**
  - **5.9.2 Vaccines**
  - **5.9.3 Toxoids**
  - **5.9.4 Quality Control Test for Immunological Products**

5.9 IMMUNOLOGICAL PRODUCTS

- Immunology is the study of the immune system.
- The immune system is a host defence system comprising many biological structures and processes within an organism that protects us from infection and disease causes bacteria.
- Immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine.

❑ CLASSIFICATION OF IMMUNITY

Table 5.23: Classification of Immunity

TYPES OF IMMUNITY	DESCRIPTION
Innate Immunity (Natural)	Innate, or nonspecific, immunity is the defense system with which you were born. Innate immunity involves barriers that keep harmful materials from entering your body. These barriers form the first line of defense in the immune response.
Adaptive Immunity (Acquired)	These are required when innate immunity is insufficient to protect the body against microbial infections. It is of two types: **Active immunity:** Active immunity can be acquired through natural immunity or vaccine-induced immunity. Example: BCG Vaccine, Hepatitis B Vaccine **Passive immunity:** Passive immunity is provided when a person is given antibodies to a disease rather than producing them through his or her own immune system. Example: Newborn baby acquires passive immunity from its mother through the placenta.

Artificial immunity	Artificial immunity is a mean by which the body is given immunity to a disease by intentional exposure to small quantities of it.
Humoral immunity	Humoral immunity is the process of adaptive immunity manifested by the production of antibodies by B lymphocytes. It develops in bone marrow.

❑ IMMUNOLOGICAL PRODUCTS

- Immunological products contain a group of pharmaceutical preparations of varied composition but with a common pharmacological purpose, which is the modification of the immune status of the recipient, either to provide immunity to infectious disease.
- They can be used to **prevent or treat infectious diseases**, autoimmune disorders, cancer, and other conditions. They can also be used for diagnostic purposes.
- These are **administered through parenteral route** as it become inactive if given through oral route.

5.9.1 SERA

- Sera is the **colorless watery fluid** of blood and lymph containing no cells and in which erythrocytes, leukocytes and platelets are suspended.
- These are also called as **blood serum**.
- It is obtained from separating the whole human blood into its solid and liquid components after clotting.
- It is formed in animal. Animal blood is collected and separated by centrifugation.
- It may contain **antitoxic antibacterial and antiviral antibodies.**

❖ Types of antitoxin

1. Diphtheria Antitoxin

- Diphtheria antitoxin is made from equine(horse) blood.
- It is used as a treatment for diphtheria disease caused by *Cornebacterium diphtheriae* bacteria.
  diphtheria toxin.
- It is not recommended for prophylaxis use as it lasts only for 1-2 weeks

➢ **Preparation:** The method of preparation of diphtheria antitoxin is divided into following stages-

i. **Preparation of toxin for active immunization of horse -**
Cornebacterium diphtheriae is grown in a suitable culture media at 37°C for 4-7 days.
- Then it is treated with 0.5% phenol and filtered through bacteria proof filters.
- The filtrate is the crude toxin.

ii. **Selection of the horse –** Horses are selected because:
Horses produce antitoxin as it resembles man in having a natural immunity. Horse RBCs settles quickly and packs tightly. It helps in separation of the serum.

iii. **Active immunization of horse –** This toxin is given through IM route in gradually increasing dose.
- The first dose is 5 ml.
- Then it is given in interval of 2-3 days by doubling volume of injection.

iv. **Separation of serum from horses –** After 10 days of final dose, the blood is collected and observed for the adequate antitoxin is obtained or not.
- After 2 weeks, next dose is given to stimulate production of antibodies.
- The process is again repeated but not more than 4-5 times.

v. **Concentration and refinement –** Horse serum contain other types of protein which may cause undesirable reaction.
- Hence it needs to be separated by fractional precipitation or fractional proteolytic digestion.

➢ **Dose:** 10,000-30,000 IU of diphtheria antitoxin is injected intramuscularly.

➢ **Side Effect:** Itching urticarial rash, pains in joints, skin reactions etc.

➢ **Packing:** Diphtheria antitoxin -10,000 IU in 10 ml vials in temperature between 2-8°C.

2. Tetanus Antitoxin
- Tetanus antitoxin is prepared from the blood of healthy horses that have been specifically hyperimmunized.
- It is caused by a neurotoxin produced by growth of *Clostridium tetani* in narcotic tissue.
- It is colorless or a very faintly yellow liquid.

- **Preparation:** The method of preparation of Tetanus antitoxin is same as that of Diphtheria antitoxin.
- **Use:** Tetanus antitoxin has potency of 1000 IU for prophylaxis use and not less than 3000 IU for therapeutic use.
- **Storage:** It should be stored in temperature varies from 2-8^{0}C and not allowed to freeze.

3. Botulinum Antitoxin

- Botulinum Antitoxin is also called as botulism antitoxin.
- It contains antibodies or antibody antigen binding fragments.
- It helps in blocking the neurotoxin produced by the bacterial species *Clostridium botulinum*

- **Preparation:** It is produced from a culture of the Hall strain of C. botulinum and purified by a series of acid precipitations to a crystalline complex containing the toxin and other proteins.
- **Administration:** Before administration of this antitoxin, the patient is observed for hypersensitivity by skin test.
  - Patient having hypersensitivity should given this antitoxin at less than 0.01ml/min.
- **Storage:** It is placed in refrigerator at **2-8^{0}C for 14 hrs.**

4. Gan Gangrene antitoxin

- Gan Gangrene is a bacterial infection that produces tissue foul smelling gas in gangrene.
- It is characterised by necrosis of muscles and soft tissue destruction.
- Antitoxin produced by Clostridium species known as α-toxin and is present in antigen used for immunizing the horse.
- It is polymicrobial in nature.

- **Preparation:** This is prepared by specific antitoxic globulin obtained by purification from native serum and having specific power of neutralizing the toxin formed by *Clostridium oedematiens.*

- **Symptoms:** Skin discoloration, "Foul, sweet" smelling discharge from lesions formed on skin, Distinctive black, bubble lesions on skin, Necrosis, Fever.
- **Dose:** It is given IV or IM.

5.9.2 VACCINES

- Vaccines are preparations of antigenic materials, which are administered with the objective of inducing in the recipient specific and active immunity against infectious microorganisms or toxins produced by them.
- The first vaccine was developed by **Edward Jenner.**
- They contain living or killed microorganisms, bacterial toxoids or antigenic material from the particular parts of bacterium, rickettsia, or virus.

❖ Classification of vaccines

Table 5.24: Classification of vaccines

CLASS		VACCINES
Killed (inactivated) Vaccines	**Bacterial**	Typhoid – paratyphoid (TAB), Vi Typhoid polysaccharide cholera, whooping cough (pertussis) meningococcal, *haemophilus influenzae* type B, plague
	Viral	Poliomyelitis inactivated (IPV: Salk vaccine), Rabies (chick embryo cell; PCEV), Rabies (Human diploid cell; HDCV), Rabies (Vero cell; PVRV), Influenza, Hepatitis B Hepatitis A
Live attenuated Vaccines	**Bacterial**	Bacillus Calmette- Guerin (BCG), Typhoid Ty 21a (oral)
	Viral	Poliomyelitis oral vaccine (OPV, Sabin), Mumps (Live attenuated), Measles (Live attenuated), Rubella (Live attenuated), Varicella (Live attenuated)
Combined vaccines		Double antigen: Diphtheria toxoid + tetanus toxoid (DT-DA) Triple antigen: Diphtheria toxoid + tetanus toxoid + pertussis vaccine (DPT) Pentavalent vaccine: DPT+ Hepatitis B + H. *influenzae* type B vaccines Measles + mumps + rubella vaccine (MMR)

Killed (Inactivated) vaccines

- The term 'inactivated' is used for viral vaccines.
  hese vaccines are prepared by treating the whole cell or virus with chemicals that cause inactivation.

- This preserves their antigenicity (ability to trigger an immune response), but also reduces their infectivity and virulence (ability to cause disease).
- Therefore, inactivated vaccines may require fewer doses than killed vaccines to induce a sufficient immune response, but may still need adjuvants or boosters to maintain protection. Inactivated vaccines are usually preferred for people who have a healthy immune system or want a more natural-like immunity.

Example: Hepatitis A, Some influenza vaccines

1. Bacterial Vaccine

- Bacterial vaccines contain killed or attenuated bacteria that activate the immune system. Antibodies are built against that particular bacterium, and prevents bacterial infection.

➢ **Typhoid paratyphoid (TAB) or Typhoid-paratyphoid cholera (TABC)**

- Typhoid-paratyphoid cholera (TABC) vaccine is a hypothetical vaccine that aims to prevent three different types of bacterial infections: typhoid fever, paratyphoid fever, and cholera.
- These infections are caused by different strains of Salmonella bacteria that can cause serious illness.
- TAB Vaccine is mixture of ***Salmonella typhi, S. paratyphi A and S. paratyphi B.***
- TABC is mixture of TAB vaccine and S. paratyphi C.

➢ **Cholera:** Cholera is a serious bacterial infection caused by ***Vibrio cholerae.***

- It causes severe diarrhea and dehydration.
- It can be fatal if not treated promptly. Cholera is spread by contaminated water or food, or by contact with infected people or animals.
- The most common type of cholera vaccine is an oral vaccine that you take by mouth. It contains killed bacteria weakened form of the bacteria that cause cholera.
- Cholera vaccines are not 100% effective.

➢ **Pertussis:** Pertussis vaccine is a vaccine that protects against whooping cough, a serious respiratory disease caused by ***Bordetella pertussis*** bacteria.

- There are two main types of pertussis vaccine: **Whole-cell vaccines and acellular vaccines**.
- The whole-cell vaccine contains killed bacteria or a weakened form of the bacteria, while the acellular vaccine contains only parts of the bacteria.
- Both types of vaccines also protect against diphtheria and tetanus, which are other diseases that can be prevented by vaccination.

2. Viral Vaccine

- A viral vaccine is a type of vaccine that protects against viral infections.
- These components can stimulate the immune system to produce antibodies and memory cells that can recognize and fight the virus if it enters the body later.

Example: Smallpox vaccine, Rabies vaccine

➢ Rabies Vaccine

- Rabies is a **fatal but preventable** viral disease. It can spread to people and pets if they are bitten or scratched by a rabid animal.
- The vaccine should be given before exposure to the virus, preferably within 1 to 2 days of contact with an infected animal or person.
- The rabies vaccine may cause some mild side effects, such as pain, redness, swelling, fever, headache, nausea, or dizziness at the injection site or throughout your body. These are usually temporary and go away within a few days.

- **Rabies vaccine used today are**
  - (a) Vaccine for human prepared in human diploid cells
  - (b) Purified Vero cell vaccine for humans
  - (c) Purified chick embryo cell vaccine for humans

➢ Smallpox Vaccine

- Smallpox is caused by the variola virus.
- The vaccine was developed by Edward Jenner in 1796, who observed that people who had cowpox, a mild infection, were immune to smallpox, a much more severe infection.

- The smallpox vaccine works by **stimulating the immune system** to produce antibodies that can fight off the smallpox virus.
- The vaccine contains live vaccinia virus, which is a type of poxvirus that is closely related to variola major, the virus that causes smallpox.

Influenza vaccine

Influenza (the flu) is an acute respiratory infection caused by influenza viruses.

- It is given with a needle in the arm.
- Influenza (flu) vaccines (often called "flu shots") are vaccines that protect against the four influenza viruses that research indicates will be most common during the upcoming season.

Live attenuated vaccines

- Live attenuated vaccines are a type of vaccine that contain a weakened or **modified form of a virus** or bacteria.
- They are designed to stimulate the immune system to produce antibodies and memory cells that can protect the person from future infections by the same or similar pathogen.
- The virulence properties of the virus are reduced so that it does not cause disease in healthy individuals.
- Live vaccines are generally very effective and induce long-lived immunity.

Example: Measles, Mumps, Rubella, Varicella, Rotavirus, Tuberculosis (BCG)

1. Bacterial Vaccine

CG Vaccine - The BCG vaccine is a vaccine that is used to prevent tuberculosis (TB), a serious infectious disease caused by bacteria called ***Mycobacterium tuberculosis.***

- The BCG vaccine is named after its inventors, Albert Calmette and Camille Guérin, who developed it from a strain of bacteria found in cattle.
- The BCG vaccine is given by injection into the skin, usually on the upper arm.

Preparation: The BCG vaccine is prepared from culture by growing the bacilli in an artificial medium, harvesting, concentrating, homogenizing, and lyophilizing them.

- Lyophilization is a process of **freezing and drying the vaccine** to preserve its potency and stability.
- The freeze-dried BCG preparation is delivered in vials, each containing 1 to **8×10^8 colony forming units** (CFU) of BCG which is equivalent to approximately 50 mg wet weight.
- These are separated by filtration to form a cake. Cake is homogenized in a grinding flask and suspended in suitable sterile liquid medium designed to preserve it.
- Then it is transferred into sterile vials and freeze dried.

Storage: BCG vaccine should be stored refrigerated at 2–8°C (36–46°F).

2. Viral Vaccine

Yellow fever vaccine

- Yellow fever is a viral disease that is transmitted to humans by the bites of infected mosquitoes.
- A single dose of yellow fever vaccine provides long-lasting protection and a booster dose of the vaccine is not needed.
- However, some people may need two doses of the vaccine if they are traveling to certain countries or regions where yellow fever is endemic or epidemic.

Oral Polio Vaccine

- The oral polio vaccine (OPV) is a type of vaccine that helps prevent polio, a disease caused by a virus that can damage the brain and spinal cord and lead to paralysis or death.

- The OPV is given as drops in the mouth and stimulates the immune system to produce antibodies against the virus.
- The OPV is administered orally and does not require health professionals or sterile needle syringes.
- This makes it easy to use in mass vaccination campaigns.

Measles Vaccine

- Measles is a highly contagious disease caused by a virus that spreads easily through the air when an infected person coughs or sneezes.

- It can cause symptoms such as high fever, cough, runny nose, red eyes, and a rash all over the body.
- The measles vaccine is part of the MMR vaccine, which also protects against mumps and rubella.
- The MMR vaccine is recommended for children at 12 to 15 months of age, and again at 4 to 6 years of age.

5.9.3 TOXOIDS

- Toxoids are inactivated toxins and vaccine that is produced by harvesting a toxin and altering it chemically with formaldehyde to convert to a toxoid.
- It targets into a specific toxin instead of whole organism.
- It requires a series of injections for full immunity followed by boosters every 10 years.
- It neutralizes harmful exotoxins released from these bacteria.
- It cannot be used for immunization purposes due to their toxicity.

1. Diphtheria Toxoid: Diphtheria toxoid is a modified form of *Corynbacterium diphtheriae.*

It is a purified preparation of inactivated diphtheria toxin.

It is highly effective in inducing antibodies that will prevent disease.

Preparation: It is prepared by following methods.

A. Formal toxoid (FT)

- In the diphtheria toxin 0.5% of formalin is added and the mixture is incubated at 37^0C for 3-4 weeks to remove the toxicity.

b. Toxin-antitoxin floccules (TAF)

- In this, suitable quantity of toxoids and antitoxins are mixed to form the floccules which contain the good antigenic activity.
- Floccules are separated and washed to remove the contaminations and are resuspended in saline solution containing a bactericide.

C. Alum precipitated toxoid (APT)

- It produces more antibodies than formal toxoid and TAF.
- Slow absorption of precipitated toxoids from the site of injection and slow excretion from the body increased its antigenicity.
- This reacts with bicarbonate, phosphate and proteins in the toxoid to produce a precipitate of aluminum hydroxide and phosphate.

D. Purified toxoid aluminum phosphate (PTAP)

- Different purification steps are involved using magnesium hydroxide precipitate color, ammonium sulphate, cadmium chloride, and some proteins.

2. Tetanus Toxoid: Tetanus toxoid is a type of immunological product that protects against tetanus, a serious and potentially fatal disease caused by a bacterium called *Clostridium tetani.*

- Tetanus toxoid is made from tetanus toxin that has been inactivated by formaldehyde. It does not contain any live bacteria and cannot cause tetanus.
- It stimulates the immune system to produce antibodies that can neutralize the tetanus toxin in case of exposure.

Preparation: Toxigenic strains of *C. tetani* are grown in liquid media, the toxin is purified, and then inactivated by treatment with formaldehyde to produce the toxoid antigen.

- After purification and sterilization, tetanus toxoid is formulated with Aluminum or calcium salts and administered by intramuscular injection.

Side Effects: It may cause some mild side effects, such as pain, redness, and swelling at the injection site, fever, headache, and fatigue.

3. Staphylococcus Toxoid

- Staphylococcus toxoid is a type of immunological product that protects against staphylococcal infections, especially those caused by the toxin produced by *Staphylococcus aureus.*
- This bacterium can cause various diseases, such as skin infections, pneumonia, sepsis, and toxic shock syndrome.

Preparation: This method involves treating the toxin made with the Wood strain of staphylococcus aureus with formalin for 2 days.

- Add ammonium sulphate to precipitate the toxin, washing and dialyzing the solution, adding Merthiolate to preserve the antigenicity, and filtering the solution through paper.
- The average antigenic value of this method is 56.5% of that of the original toxin.

Dose: The doses range from 0.1 ml to 1.0 ml per injection, followed by booster doses given 4-weekly until endpoint.

5.9.4 QUALITY CONTROL TEST FOR IMMUNOLOGICAL PRODUCTS

1. **Stability test:** Stability study is done to **test the shelf life and validity** of the expiry date of the product.
2. **Batch purity test:** Batch purity is done to test the product for contamination in the entire batch.

    - Batch safety test is done if local and systemic reaction to vaccination with the batch to be released.
    - Batch potency test is required for each batch prior to release.

3. **Interference test:** This test is done to check the interference between individual components.
4. **Increase in virulence test:** Live vaccines are tested for the presence of viruses. It can be done by determining lethal dose of the drug.