Pharmaceutics- (Semi-solid dosage forms)

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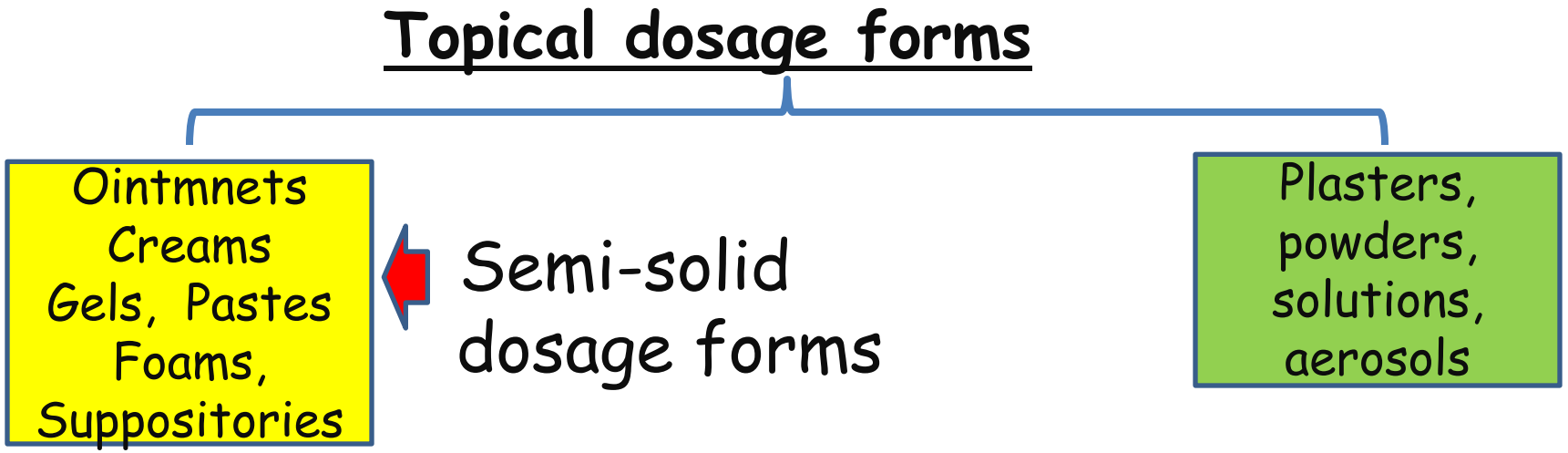
Semi-solid dosage forms

- Semisolid dosage forms: are products of semi-solid consistency and applied to skin or mucous membranes for a therapeutic or protective action or cosmetic function.



- They may be medicated (containing therapeutic agents) or non-mediacated (used for their physical effects as protectants , lubriants and emollients).

Semi-solid dosage forms

- Site of application: they are intended for topical application (non-invasive delivery), being applied as follows:

  - To the skin
  - Placed on the eye surface
  - Used nasally
  - Introduced into body cavities, such as vaginally, rectally.

  } Mucous membranes

- Intended use:

  - Local effects: treatment of dermal disorders (dermal absorption).
  - Systemic effects: e.g., transdermal products delivering drugs through the skin to the general circulation (percutaneous absorption).

Ideal properties of semi-solid dosage forms

❑ Physical properties:

a)Smooth texture
b) Elegant in appearance
c) Non dehydrating
d) Non gritty
e) Non greasy and non staining
f) Non hygroscopic

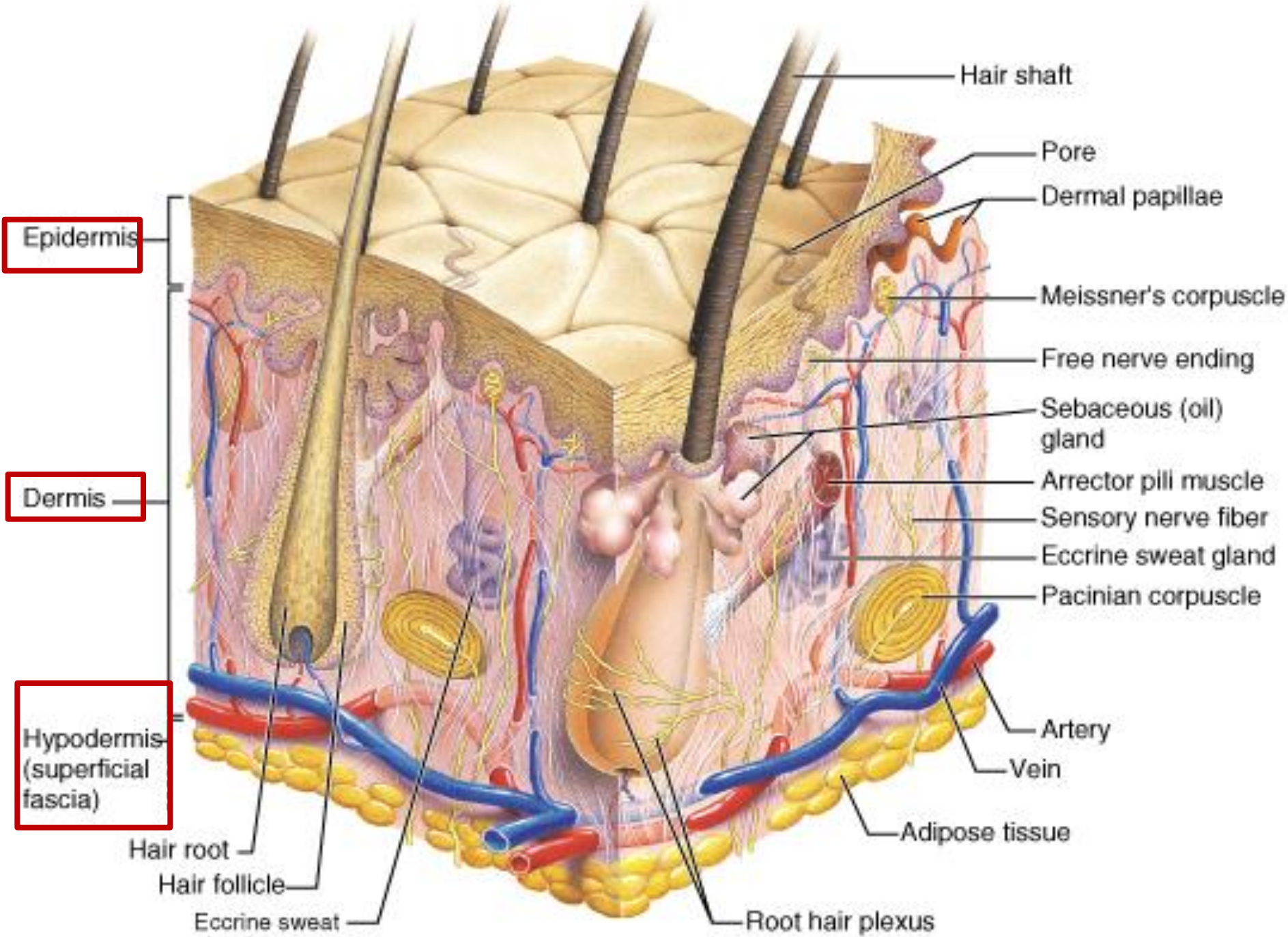
❑ Physiological properties

a) Non irritating
c) Miscible with skin secretion
d) Have low sensitization effect

❑ Application properties:

a) Easily applicable with efficient drug release

b) High aqueous washability


Epidermis
Dermis
Hypodermis (superficial fascia)
Hair shaft
Pore
Dermal papillae
Meissner's corpuscle
Free nerve ending
Sebaceous (oil) gland
Arrector pili muscle
Sensory nerve fiber
Eccrine sweat gland
Pacinian corpuscle
Artery
Vein
Adipose tissue
Hair root
Hair follicle
Eccrine sweat
Root hair plexus

Drug permeability through skin

- ✓ The stratum corneum (outermost epidermal layer of skin) is the major permeability barrier to external substances, and is regarded as the rate-limiting factor in the penetration of therapeutic agents through the skin.
- ✓ Thus, the ability of a drug to interact with the constituents of this skin layer dictates the degree to which it can penetrate.
- ✓ The ability of a drug to penetrate the skin epidermis, dermis, and subcutaneous fat layers will lead to transdermal (percutaneous) drug delivery giving rise to systemic action .
- ✓ Therefore, the extent the drug can travel through the different skin layers determines the delivery system.

Drug permeability through skin

Transdermal drug delivery

- ✓ Transdermal preparations are designed to deliver drugs systemically. This is often accomlished by adding permeation enahncers to the topical vehicle.
- ✓ Permeation enhancers include dimethyl sulfoxide, ethanol, propylene glycol, glycerin, urea, terpenes, surfactants (e.g., sodium lauryl sulphate, spans, tweens, lecithins, poloxamers,.....).

Advantages of transdermal delivery

- Avoiding hepatic first pass effect
- Continuous drug delivery
- Fewer side effect
- Therapy can be terminated at any time.
- Improved patient compliance.

Disadvantages:

- Cosmetically non-appealing
- May display erratic (irregular) absorption.

Drug permeability through skin

Possible routes of skin penetration:

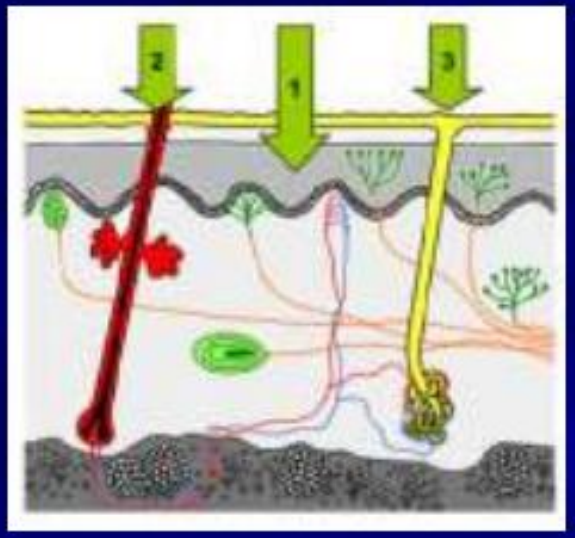
- ✓ **Drugs can penetrate skin barrier by three routes:**

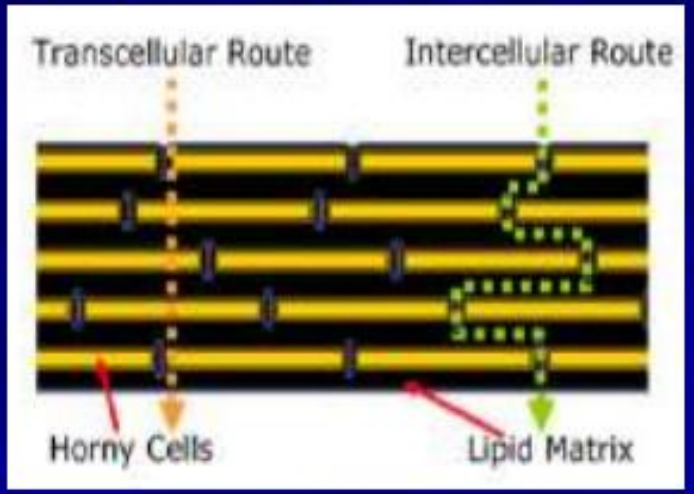
- Transcellular (across cells)
- Intercellular (between cells)
- Transappendageal (via hair follicles, sweat and sebum glands).

- ✓ Percutaneous drug absorption results from direct penetration through the stratum corneum, followed by passing through the epidermal tissues and into the dermis.

Drug permeability through skin

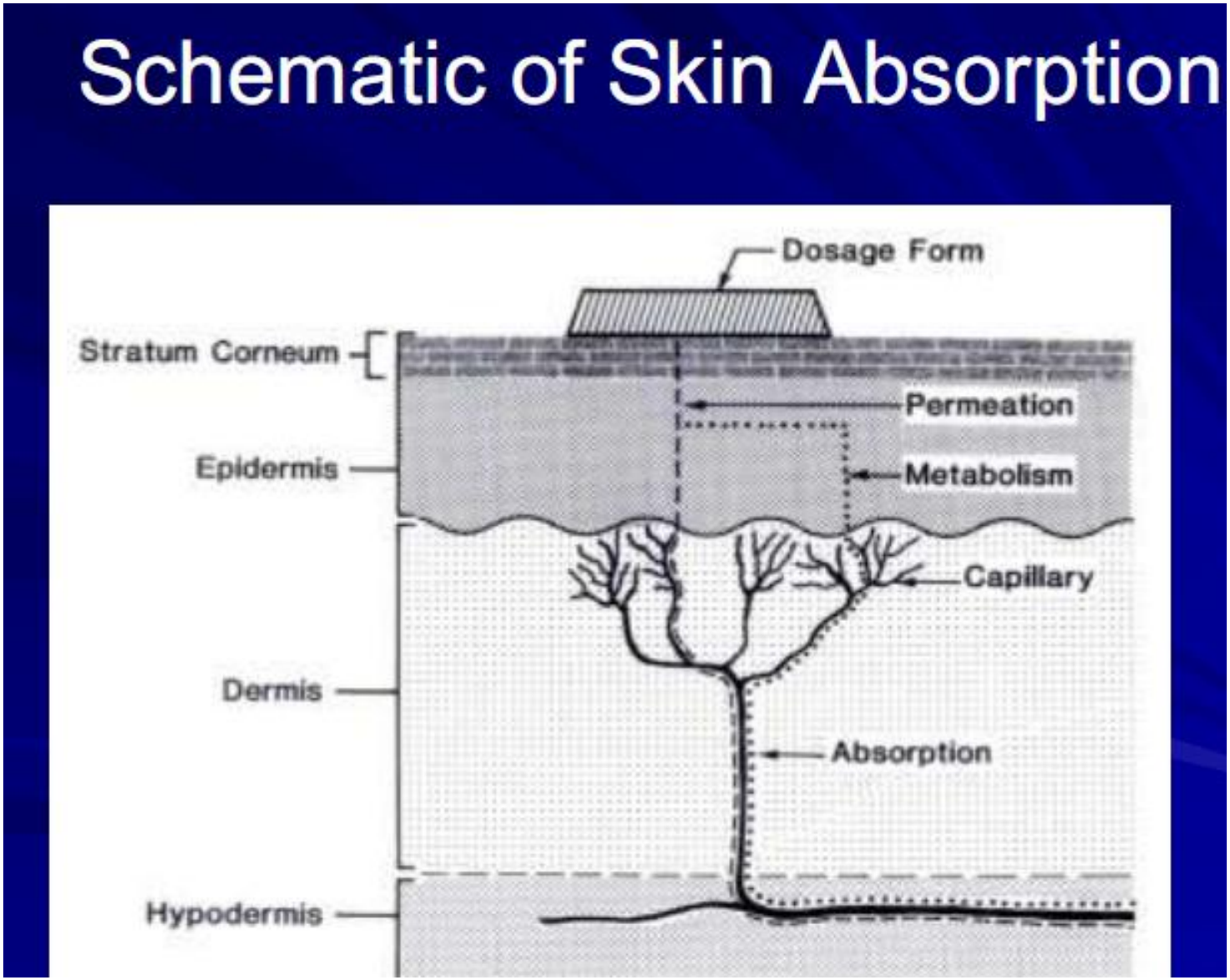
Pathways of drug penetration through ***skin***



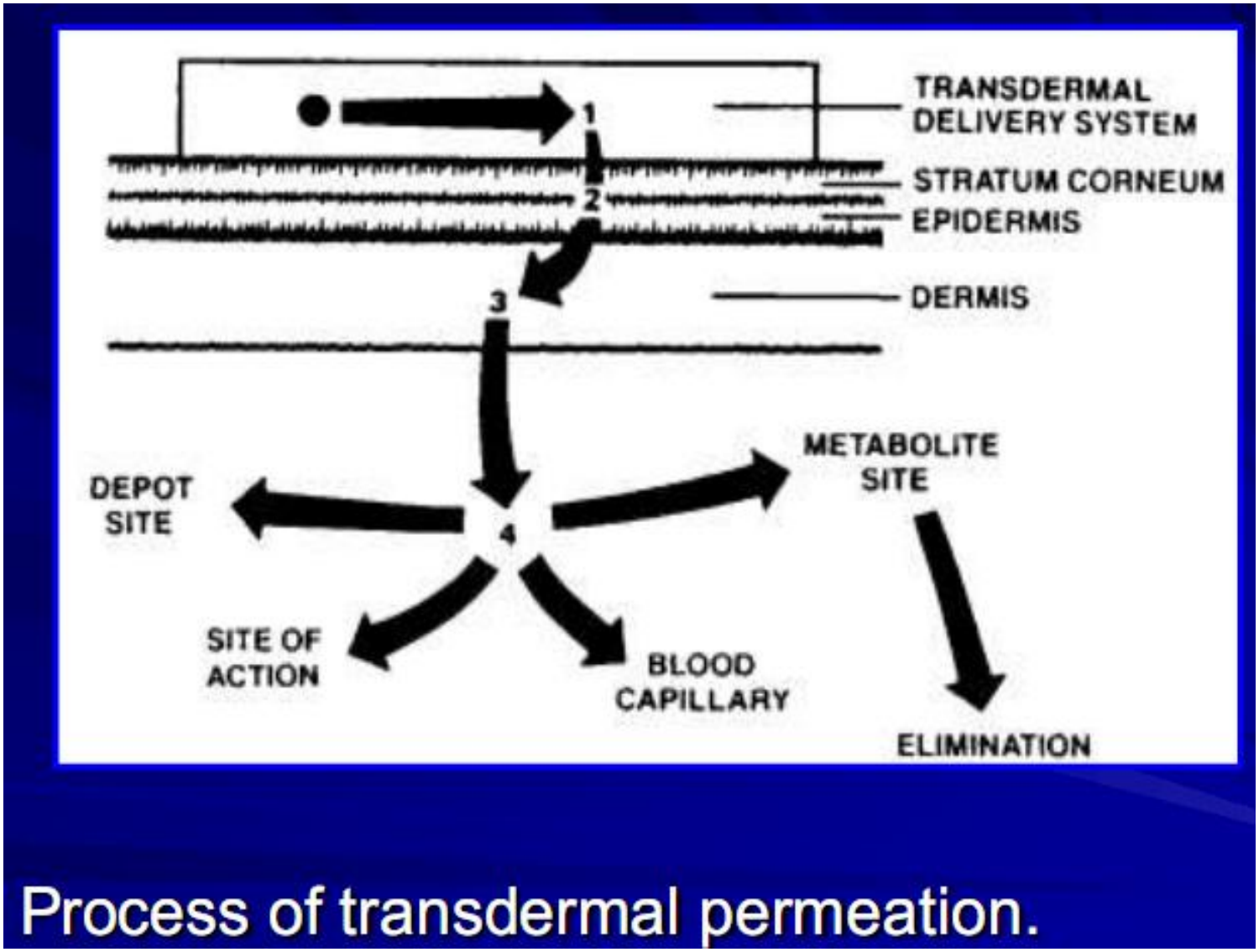


•Simplified diagrams showing routes of drug penetration.
(a) Macroroutes of drug penetration (1) across the continuous stratum corneum; (2) through the hair follicles with their associated sebaceous glands or (3) via the sweat duct.
(b) Representation of the stratum corneum membrane, illustrating two possible microroutes for permeation. (1) Intercellular (2) transcellular

Drug permeability through skin



Drug permeability through skin



Process of transdermal permeation.

Drug permeability through skin

The fraction of the drug that penetrate the skin via any route depends on:

- The physicochemical nature of the drug, specially its size, solubility and partition coefficient.
- The site and condition of the skin.
- The formulation and drug concentration in the vehicle.
- How vehicle component temporarily change the properties of the stratum corneum.

❖ **Substances with both aqueous and lipid solubility chacteristics are good candidates of diffusion through the stratum corneum.**

Formulation of semi-solid dosage forms:

Ingredients used for formulating semisolids include :

-Active pharmaceutical ingredient API ,
-Bases,
-Antimicrobial preservative ,
-Humectants ,
-Fragrances,
-Emulsifier
-Gelling agent,
-Permeation enhancer

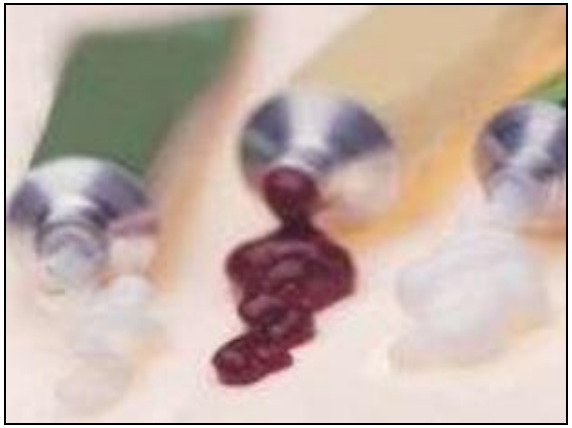
❖ Examples on APIs used in semi-solid formulations

Disease treated	API
Warts (Keratolytic)	Salicylic acid
Acne	Sulphur, resorcinol
Antipruritic	Benzocain, menthol
Emollient	lanolin
Anti-inflammatory	corticosteroid
Antifungal	Benzoic acid

❖ Ointments-Diffinition

- ✓ An ointment is a viscous semisolid preparation used topically on a variety of body surfaces. These include the skin and the mucus membranes of the eye (an eye ointment), vagina, anus, and nose.
- ✓ Since they are of greasy nature, so they stain cloths, are generally poor solvent for most drugs, and usually decrease the drug delivery capabilities of the system.

- ✓ An ointment may or may not be medicated. Typically used as:
  - Emollients to make skin more pliable
  - Protective barriers
  - Vehicles in which to incorporate medication.



❖ Ointments-Diffinition

✓ Medicated ointments primarily consist of a drug and a vehicle called **a base**.

✓ Examples on medicated ointments:

- Ophthalmic ointments
- Rectal Ointment: it is used for the symptomatic relief against anal and peri-anal pruritus, pain and inflammation associated with hemorrhoids, anal fissure, fistulas and proctitis .

For intrarectal use, apply the ointment with the help of special applicator .

❖ Ointments-Bases

- ✓ Semisolid bases do not only act as the carriers of the medicaments, but they also control the extent of absorption of medicaments incorporated therin .

- ✓ An ointment base should be compatible with skin, stable, smooth, non-irritating, non-sensitizing, inert, capable of absorbing water or other liquid preparations, and of releasing the incorporated medicament, readily .

- ✓ A base for ophthalmic semisolids must be non-irritating to the eye, and it should also be sterilizable conveniently .

❖ Ointments-Bases

❑ Appropriate Selection of Ointment Base:

Selection of ointment base depends on the following :

1-Desired release rate of the drug substance from the ointment base .
2-Rate and extent of topical or percutaneous drug absorption .
3-Desirability of occlusion of moisture from skin .
4-Stability of the drug in the ointment base .
5-Effect of drug on the consistency of base .
6-Easy removal of base on washing .
7-Characteristic of the surface to which it is applied .

Examples:

a) An ointment is usually applied to a dry scaly skin.
b) A cream is applied to weeping or oozing surfaces.
d) A lotion is applied to intertriginous areas or where friction may occur a between thighs or under armpits.

❖ Ointments-Bases

- Ointment bases may be classified in several ways but the following classification based on composition is generally used which are as follow:

A) **Oleaginous (hydrocarbon) bases .**
B) **Absorption bases .**
C) **Emulsion bases (water-removable bases).**
D) **Water soluble bases .**

❖ Ointments-Bases

A) Oleaginous (hydrocarbon) bases:

- ✓ This is a purified mixture of liquid, semi-solid or solid hydrocarbons from petroleum.
- ✓ Water and aqueous preprations may be incorporated but in small amounts with difficulty.
- ✓ Most of the early ointment bases used to be exclusively oleaginous in nature, but nowadays the materials obtained from plant, animal, as well as synthetic origin are employed as oleaginous ointment bases.
- ✓ Combinations of these materials can produce a wide range of melting points and viscosities .

❖ Ointments-Bases

A) Oleaginous (hydrocarbon) bases:

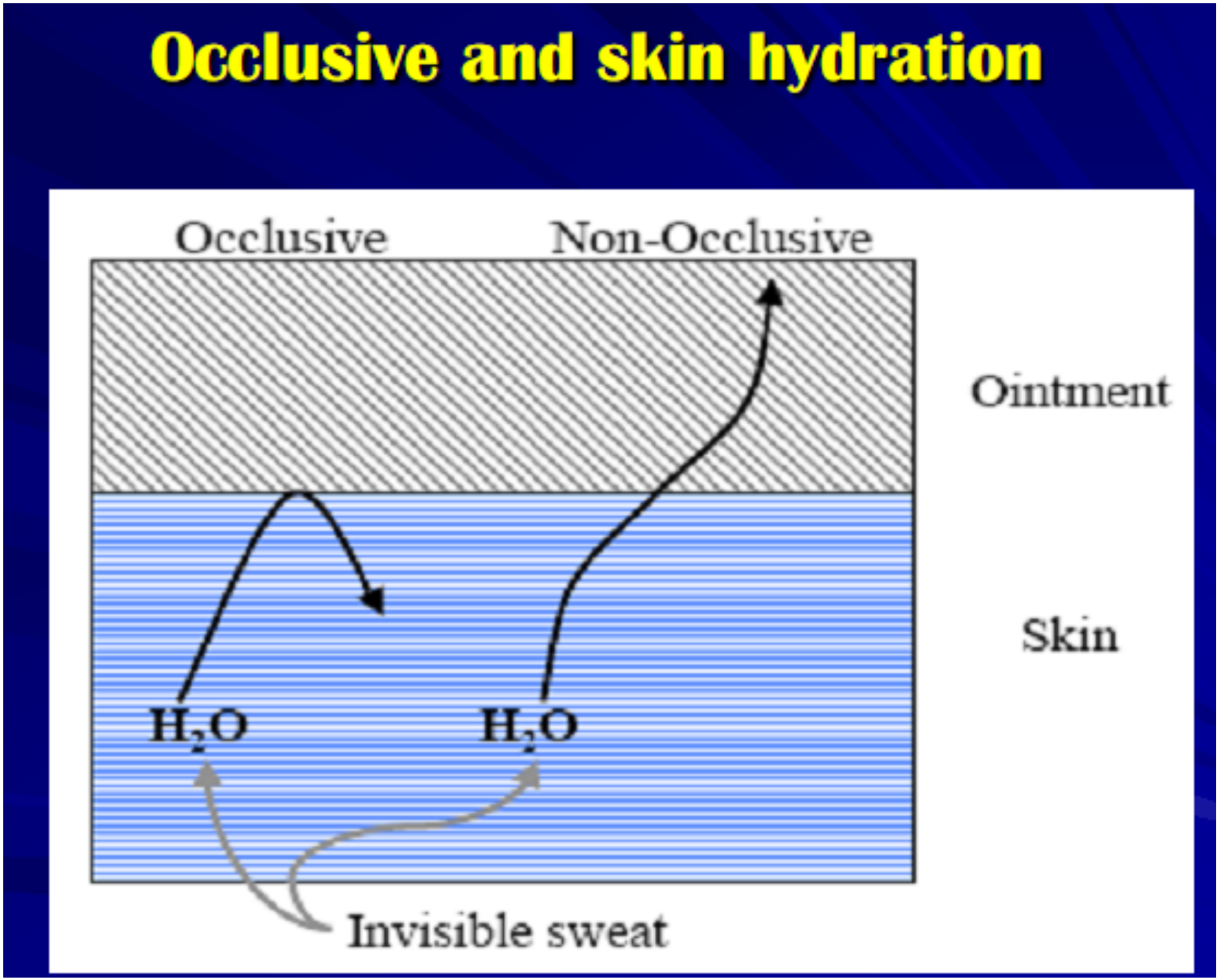
<u>These bases are:</u>

- Immiscible with water (they are difficult to wash off)
- Not absorbed by the skin, remain on the skin for prolonged period of time without "drying out"
- Absorb very little water from formulation or from skin exudates.
- Inhibit water loss from the skin by forming a water-proof film (act as an occlussive dressing).
- Improving hydration, may encourage penetration of the medication through skin.

Examples: petrolatum, white petrolatum, white ointment, yellow ointment.

Uses: protectants, emollient, and vehicle for solid drugs

❖ Ointments-Bases



❖ Ointments-Bases

B) Absorption (Emulsifiable) bases:

- ✓ They are called as emulsifiable bases because they initially contain no water but are capable of taking it up to yield W/O and O/W emulsions .

- ✓ Absorption bases are mostly W/O type emulsions and have capacity to absorb considerable quantities of water or aqueous solution without marked changes in consistency .

❖ Ointments-Bases

B) Absorption bases:

- Less occlusive than the hydrocarbon bases.
- Incorporation of aqueous solution is possible.
- Easier to spread.
- Good emollients (though not as much as oleaginous)
- They hydrate the stratum corneum.
- Difficult to wash from the skin.
- Mostly W/O

- **Uses**: protectants, emollient, and vehicle for aqueous solutions and solid drugs

❖ Ointments-Bases

B) Absorption bases –Examples:

- **Lanolin USP**: anhydrous lanolin, obtained from the sheep wool. It is a purified wax-like substance that has been cleaned, deodorized and decolorized. It can absorb about 50% of its weight of water and is used in ointments in which the proportion of aqueous fluid is too large for incorporation into a hydrocarbon base.

- **Hydrophilic petrolatum USP**:

1.	Cholestrol	30g
2.	Stearyl alcohol	30g
3.	White wax	80 g
4.	White petrolatum	860g

It is prepared by melting stearyl aLcohol and white wax on a water bath, adding cholestrol with stirring until dissolved. Then, white petrolatum is added, allowing the mixture to cool while stirring until congealed (such substances are added to some ointment bases to increase their water-absorbing power).

❖ Ointments-Bases

(C) Emulsion Bases (water-removable bases):

- ✓ They are either O/W or W/O emulsions, resembling creams.
- ✓ <u>Examples:</u>
  - **Hydrophilic Ointment USP**

1.	SLS	10g
2.	Proylene glucol	120g
3.	Stearyl alcohol	250g
4.	White petrolatum	250g
5.	Purified water	370g
6.	Methylparaben	0.25g
7.	Propylparaben	0.15g

- **Cold cream:** W/O emulsions, emollient, cleansing, not water washable, non occlusive, shiny appearance, not need glycerin.
- **Vanishing cream:** O/W emulsion contains large % of water and humectant. An excess of stearic acid in the formula helps to form a thin film when the water evaporates.

❖ Ointments-Bases

(C) Emulsion Bases (water-removable bases)

Properties of Emulsion bases:

- ✓ Water-washable, easier to remove
- ✓ Non/less greasy
- ✓ Can be diluted with water or aqueous solutions.
- ✓ Non/less occlusive
- ✓ More acceptable for cosmetic reasons
- ✓ Better compliance; Patients prefer cream to an ointment because the cream spreads more readily, less greasy, evaporating water soothes the inflamed tissue.

- ✓ **Uses:** Cleansing creams, emollients and vehicle for solid and liquid drugs.

❖ Ointments-Bases

D) Water-soluble bases (greaseless ointment bases):

- As they do not contain any oleaginous component, they are water soluble and completely water-washable.
- ✓ Because they soften with the addition of water, large amounts of aqueous solutions are not effectively incorporated into these bases.
- ✓ Uses: drug vehicle.

<u>The water-soluble bases have the advantages of being:</u>

- Water soluble and washable
- Non-greasy, non-staining.
- Non/less occlusive
- Mostly used for the incorporation of solid substances.
- Does not support mold growth
- Little hydrolysis, stable

-<u>Disadvantages</u>: May dehydrate skin and hinder percutaneous absorption.

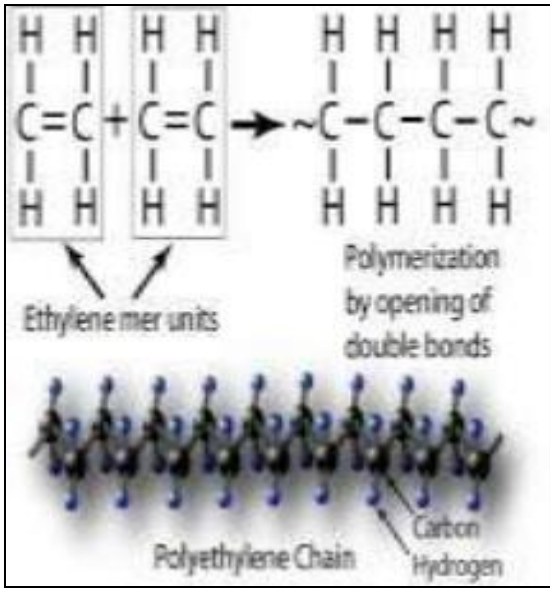
❖ Ointments-Bases

D) Water-soluble bases:

- ✓ The macrogols (carbowax) are mixtures of poly-condensation products of ethylene oxide and water and they are described by their average molecular weights (viscous liquids to waxy solids).
- ✓ Different grades of carbowaxes are available which are designated by a number roughly representing their average molecular weights e.g.- PEG 200, PEG 400, PEG1000, PEG1540 and PEG 6000.

- ✓ **Propylene glycol (PEG) ointment NF**:
  It is the prototype of these bases.

1. PEG 3350 400g
2. PEG 400 600g
The two PEGs are combined with the aid of temperature & stirring



	Oleaginous Ointment Bases	Absorption Ointment Bases	Water/Oil Emulsion Ointment Bases	Oil/Water Emulsion Ointment Bases	Water-miscible Ointment Bases
Composition	oleaginous compounds	oleaginous base + w/o surfactant	oleaginous base + water (< 45% w/w) + w/o surfactant (HLB ≤8)	oleaginous base + water (> 45% w/w) + o/w surfactant (HLB ≥9)	Polyethylene Glycols (PEGs)
Water Content	anhydrous	anhydrous	hydrous	hydrous	anhydrous, hydrous
Solubility in water	insoluble	insoluble	insoluble	insoluble	soluble
Spreadability	difficult	difficult	moderate to easy	easy	moderate to easy
Washability	nonwashable	nonwashable	non- or poorly washable	washable	washable
Stability	oils poor; hydrocarbons better	oils poor; hydrocarbons better	unstable, especially alkali soaps and natural colloids	unstable, especially alkali soaps and natural colloids; nonionics better	stable
Drug Incorporation Potential	solids or oils (oil solubles only)	solids, oils, and aqueous solutions (small amounts)	solids, oils, and aqueous solutions (small amounts)	solid and aqueous solutions (small amounts)	solid and aqueous solutions
Drug Release Potential*	poor	poor, but > oleaginous	fair to good	fair to good	good
Occlusiveness	yes	yes	sometimes	no	no
Uses	protectants, emollients (+/-), vehicles for hydrolyzable drugs	protectants, emollients (+/-), vehicles for aqueous solutions, solids, and non-hydrolyzable drugs	emollients, cleansing creams, vehicles for solid, liquid, or non-hydrolyzable drugs	emollients, vehicles for solid, liquid, or non-hydrolyzable drugs	drug vehicles
Examples	White Petrolatum, White Ointment	Hydrophilic Petrolatum, Anhydrous Lanolin, Aquabase™, Aquaphor®, Polysorb®	Cold Cream type, Hydrous Lanolin, Rose Water Ointment, Hydrocream™, Eucerin®, Nivea®	Hydrophilic Ointment, Dermabase™, Velvachol®, Unibase®	PEG Ointment, Polybase™

❖ Ointments

❑ ANTIMICROBIAL PRESERVATIVES:

- ✓ Some bases, although, resist microbial attack but because of their high water content, it require an antimicrobial preservative.

- ✓ Commonly used preservatives include Methyl hydroxybenzoate, Propyl- hydroxybenzoate, Chlorocresol, Benzoic acid, Phenyl mercuric nitrate, Phenols, Sorbic acid, Benzalkonium chloride, Chlorhexidine acetate, Benzyl alcohol and Quaternary ammonium salts.
- ✓

❖ Ointments

Other ingredients:

❑ ANTIOXIDANTS:

Example of commonly used antioxidants include: butylated hydroxy anisole, butylated hydroxy toluene .

❑ HUMECTANTS:

Example of commonly used humectants include: poly ethylene glycol, glycerol or sorbitol is added as humectants .

❑ FRAGRANCES:

Examples of widely use fragrances are lavender oil, rose oil, lemon oil, almond oil .

❖ Ointments-Methods of preparation

1- BY TRITURATION:(incorporation):When base contain soft fats and oils or medicament is insoluble or liquid, then this method is use with spatula or mortar and pestle.

A. The ointment base components are mixed until a uniform preparation is attained, by mixing or stirring depending on the base. At a small scale (usage of mortar and pestle and spatula to rub the ingredients together; usage of ointment mill or planetary mixer).

B. Incorporation of insoluble solids: with the aid of a stainless steel spatula or a hard rubber spatula, the ointment componetns are prepared by throughly rubbing and working the components together on a hard surface until the product is smooth and uniform.

C. The powdered components previously reduced to fine particles (sieving) to prevent grittiness of the ointment. The powder is then mixed with a portion of the base (volume/volume) until being uniform. Dilution is continued until all proportions of the powder and the base are combined thouroughly blended.

❖ Ointments-Methods of preparation

1- BY TRITURATION:(incorporation).

D. By **levigating**, or mixing the solid material in a liquid vehicle in which it is insoluble to make a smooth dispersion into the base. The **levigating agent** (mineral oil for bases in which oils are the external phase, or glycerin for bases in which water is the external phase) should be physically and chemically compatible with both the drug and base. Also, the levigating agent should be equal in volume to the solid material.

E. The incorporation of soluble solids: Solids are dissolved in appropriate solvents that will neither affect the stability of the drug nor the efficacy of the product (water or alcohol). The solution in added to the ointment base using a mortar and pestle.

F. For incorporating a gummy material

❖ Ointments-Methods of preparation

1- BY TRITURATION:(incorporation).

G. Incorporation of liquids: Liquid substances or solutions of drugs are added to an ointment only after knowing that the base has the capacity to accept the volume required. Only very small amount of an aqueous solution may be incorporated in an oleaginous ointment, whereas, hydrophilic ointment bases readily accept aqueous solutions. When it is necessary to add an aqueous preparation to a hydrophobic base, the solution may be first incorpoarted into a minimum amount of the hydrophilic base and, then the mixture is added to the hydrophobic base.

H. Alcoholic solutions of small volume may be added easily to oleaginous bases or emulsion bases. Natural balsams are usually mixed with an equal portion of caster oil before incorporation into the base.

I. Ointment mills can be used to force coarsely formed ointments through stainless steel or ceramic rollers to produce uniform and smooth ointments (e.g., lip stiks)

❖ Ointments-Methods of preparation

2- BY FUSION:

- ✓ Used for large quantities or for ointments in which waxes or solids of high melting points are to be mixed with semisolid or oils. Constituents are melted successively and cooled with constant stirring until congealed..
- Heat-labile substances and volatile components are added at last, when the temperature of the mixture is low enough.

- ✓ Medicated ointments and ointment bases containing components of high melting points (beewax, paraffin, high MW PEG) are prepared by fusion. Materials with the highest melting point are first heated, to the lowest required temperature to produce a melt. The additional materials are added with constant stirring during cooling of the melt until the mixture is congealed.

❖ Ointments-Methods of preparation

2- BY FUSION:

✓ Alternatively, materials can be simply melted all together under slowly increasing temperature.

- By this method, a lower tempearure is usually sufficient to achieve fusion because of the solvent action exerted by the fist melted component on the others.

✓ Incorporation of ointments having an emulsifying base, the method of manufacture often involves melting and emulsification:

- The water-immiscible components such as oil and waxe are melted together in a steam bath up to 70-75°C.
- Meanwhile, an aqueous solution of the heat-stable, water-soluble components is prepared and heated to the same temperature as the oleaginous components.
- Then, the aqueous solution is slowly added, under mechanical stirring, to the melted oleaginous mixture; while the temperature is manitained for 5-10 min, and the mixture is slowly cooled and stirred until congealed.

❖ Ointments-Methods of preparation

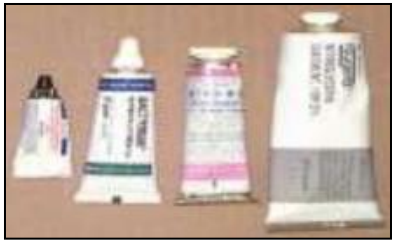
3- BY OINTMENT MILLS:

It is used for large scale production where triple roller mill is utilized which is faster then others .

❖ Ointments-Requirements & USP standards

✓ Microbial content: With the exception of ophthalmic ointments, topical preparations do not need to be sterile, but must meet the FDA requirement of the test for absence of bacteria such as S. areus and P. aeruginosa for dermatological products. For those preparations intended for urethral, rectal and vaginal use, they should be tested for the presence of molds and yeasts which are common offenders of such areas.

✓ Packaging, storage, labeling:



- Packaging: Large mouth ointment **jars**, and metal or plastic **tubes**.
- Labelling: label should include the type of base used i.e. water soluble or water insoluble
- Storage: Stored in well-closed containers to protect against contamination and light, in a cool place to protect against product separation by heat.

✓ Additional standards: viscosity, in vitro release.

❖ Creams

- ✓ Semisolid preparations containing one or more medicinal agents dissolved in either an o/w or w/o emulsion or in another type of water-washable base.
- ✓ Typically of low viscosity, two phase system (w/o or o/w).
- ✓ Appears "creamy white" due to the scattering of light.
- ✓ Traditionally, it is the w/o cold cream.
- ✓ Currently and most commonly, it is the o/w emulsion.

❖ Creams

Creams as drug delivery systems

- Good patient acceptance
- Water evaporation concentrates drug on skin surface

Examples;
Vanishing cream: o/w with high % of water and stearic acid.

Cold cream (an emulsion for softening and cleansing the skin): w/o, white wax, spermaceti, almond oil, sodium borate.

❖ As an emulsion system, creams must contain an **emulsifier**, and ideal properties of emulsifier includes:

a) Reducing surface tension for proper emulsification .
b) Preventing coalescence .
c) Being effective at low concentration .

❖ Gels (jellies)

- A semisolid dispersion systems containing a gelling agent in sufficient quantities to impart a 3-dimensional polymeric matrix
- Provides a cooling sensation when applied to the skin
- Usually translucent and non-greasy.
- They are used for medication and lubrication.
- They are based on the use of gelling agents and such agents may include:

Material	%
Carbomer 941resin NF	0.15
Carbomer 941resin NF	0.25
Carbomer 941resin NF	0.50
Carbomer 941resin NF	1.00
Sodium carboxymethyl cellulose	1.50
Guar gum	1.50
Methyl cellulose	2.00
Locust bean gum	2.50
Sodium alginate	2.50

❖ Pastes

- ✓ Pastes are basically ointments into which a high percentage of insoluble solid (granular material in a background fluid) dispersed in an aqueous or fatty vehicle.
- ✓ They are usually prepared by incorporating solids (i.e 25-50%) directly into a congealed system by levigation with a portion of the base to form a paste like mass. The remainders of the base are added with continued levigation until the solids are uniformly dispersed in the vehicle.
- ✓ Pastes are less greasy and less penetrating than ointments and do not flow at body temperature.
- ✓ Like ointments, pastes forms an unbroken, relatively water-impermeable film, but unlike ointments the film is opaque and therefore, an effective sun block accordingly. Skiers apply pastes around the nose and lips to gain a dual protection.

- ✓ Examples:
- Fatty pastes: e.g, zinc oxide paste
- toothpaste, mustard.

❖ Plasters

- They are solid or semisolid masses that adhere to the skin, being applied in the form of pieces of fabric that contains a layer of medication covered by a layer of adhesive. They are mainly used to:

- Afford protection and mechanical support.
- Furnish an occlusive and macerating action.
- Bring medication into close contact with the surface of the skin.
- Examples: medicated pain relief plasters.

❖ Rigid foams

- Foams are system in which air or some other gas is emulsified in liquid phase to the point of stiffening.
- E.g. shaving creams, whipped creams, aerosolized shaving creams.

Suppositories

- **Definition:** Suppositories are semi-solid dosage forms intended for insertion into body orifices (rectum, vagina, urethra) where they melt, soften, or dissolve and exert a local or systemic effect.

Local action: Rectal suppositories intended for localized action are most frequently used to relieve constipation or pain, irritation, itching, and inflammation associated with hemorrhoids.

Systemic action: e.g., Antiasthmatic, antirheumatic & analgesic drugs).

Suppositories

The suppository may be ideally used in:

1- Babies or old people who cannot swallow oral medication.

2- Post operative people who cannot be administered oral medication.

3- People suffering from severe nausea or vomiting.

4- Drugs inactivated by the pH or enzymatic activity of the stomach or intestine.

5- Drugs irritating to the stomach.

6- Drugs destroyed by portal circulation.

Suppositories

- ✓ The modern rectal suppository is a conical or torpedo shaped item which is about 2 - 3 centimeters in length. Suppositories for adults weigh 2 grams each and children suppositories weigh 1 gram each.

- ✓ Urethral suppositories for males weigh 4 grams each and for females they weigh 2 grams each.

- ✓ Vaginal suppositories, also called pessaries, are usually globular (ball), oviform or cone-shaped and weigh about 5 grams.

Suppositories

- ✓ The modern rectal suppository is a conical or torpedo shaped item which is about 2 - 3 centimeters in length. Suppositories for adults weigh 2 grams each and children suppositories weigh 1 gram each.

- ✓ Urethral suppositories for males weigh 4 grams each and for females they weigh 2 grams each.

- ✓ Vaginal suppositories, also called pessaries, are usually globular (ball), oviform or cone-shaped and weigh about 5 grams.

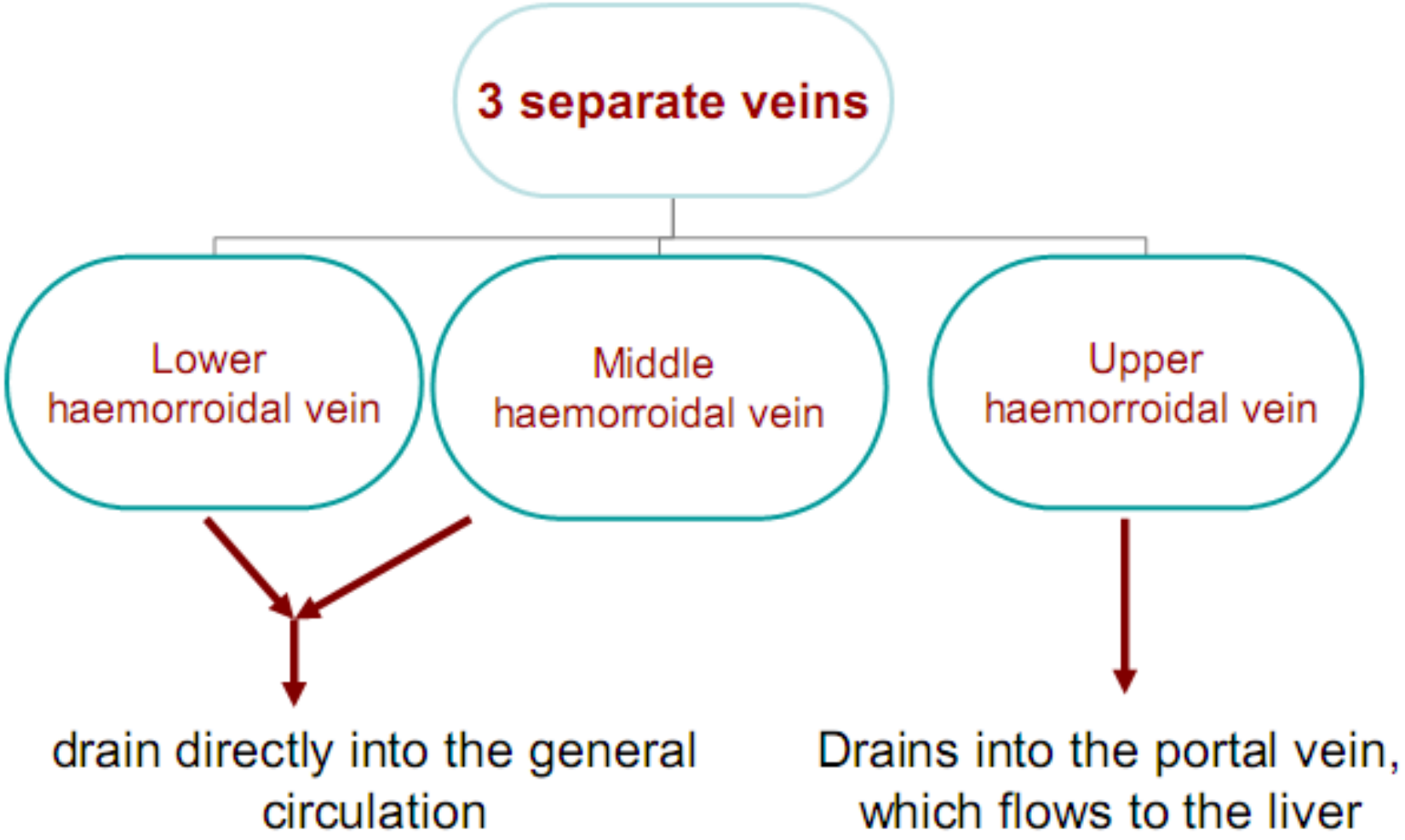
Suppositories

Anatomy and of the rectum:

- ✓ The rectum is part of the colon, forming the last 15 – 20 cm of the GI tract.
- ✓ The rectum can be considered as a hollow organ with a relatively flat wall surface, without villi.
- ✓ It contains only **2 – 3 ml** of inert mucous fluid with pH of 7.5 .

Suppositories

Absorption of drugs from the rectum:



Absorption of drugs from the rectum

I. Physiological factors affecting absorption

1- **Quantity of fluid available**: The quantity of fluid available for drug dissolution is very small (approximately 3 ml). Thus the dissolution of slightly soluble substances is the slowest step in the absorptive process.

2- **The properties of rectal fluid**: The rectal fluid is neutral in pH (7 – 8) and has no buffer capacity.

3- **Contents of the rectum**: When systemic effects are desired, greater absorption may be expected from an empty rectum as the drug will be in good contact with the absorbing surface of the rectum.

4- **Circulation route**: The lower hemorrhoidal veins surrounding the colon receive the absorbed drug and initiate its circulation throughout the body, bypassing the liver. Lymphatic circulation also assists in the absorption.

Absorption of drugs from the rectum

II. Physico-chemical factors of the drug and suppository base affecting absorption

1- Drug solubility in vehicle:

- The rate at which a drug is released from a suppository and absorbed by the rectal mucous membrane is directly related to its solubility in the vehicle or, in other words, to the partition coefficient of the drug between the vehicle and the rectal liquids.
- When drugs are highly soluble in the vehicle → the tendency to leave the vehicle will be small and so the release rate into the rectal fluid will be low.

Drug solubility and suppository formulation

Solubility in		Choice of base
Fat	Water	
low	high	Fatty base
high	low	Aqueous base
low	low	Indeterminate

Absorption of drugs from the rectum

II. Physico-chemical factors of the drug and suppository base affecting absorption

2- Particle Size:

- For drugs present in a suppository in the undissolved state, the size of the drug particle will influence its rate of dissolution and its availability for absorption.
- The smaller the particle size ⟹ the more readily the dissolution of the particle ⟹ the greater chance for rapid absorption.

3- Nature of the base:

- The base must be capable of melting, softening, or dissolving to release its drug components for absorption.
- If the base interacts with the drug inhibiting its release, drug absorption will be impaired or even prevented.
- Also, if the base is irritating to the mucous membranes of the rectum, it may initiate a colonic response and a bowel movement and, then incomplete drug release and absorption.

Absorption of drugs from the rectum
II. Physico-chemical factors of the drug and suppository base affecting absorption

4- Spreading Capacity:

- The rapidity and intensity of the therapeutic effects of suppositories are related to the surface area of the rectal mucous membrane covered by the melted base : drug mixture (the spreading capacity of the suppositories). This spreading capacity may be related to the presence of surfactants in the base.

Suppository base:

The properties of an ideal suppository base:

1- Melts at body temperature or dissolves in body fluids.
2- Non-toxic and non-irritant.
3- Compatible with any medicament.
4- Releases any medicament readily.
5- Easily moulded and removed from the mould.
6- Stable to heating above the melting point.
7- Easy to handle.
8- Stable on storage.

Suppository bases

Fatty base: Theobroma oil (cocoa butter), Synthetic hard fat.

Water soluble & water miscible base: Glycero-gelatine, Macrogols, Soap glycerin

Suppository base:

I. Fatty bases: designed to melt at body temperature.

A- Theobroma oil (Cocoa butter):

It is a yellowish-white solid with an odour of chocolate and is a mixture of glyceryl esters of different unsaturated fatty acids.

**** Advantages:**

a- A melting range of 30 - 36°C (solid at room temperature but melts in the body).

b- c- Miscible with many ingredients.

d- Non-irritating.

Suppository base:

I. Fatty bases: designed to melt at body temperature.

A- Theobroma oil (Cocoa butter):

**** Disadvantages:**

1. Polymorphism:

- When melted and cooled, it solidifies in different crystalline forms, depending on the **temperature of melting**, **rate of cooling** and the **size of the mass**.
- If melted at not more than 36°C and slowly cooled, it forms stable beta crystals with normal melting point.
- If over-heated then cooled, it produces unstable gamma crystals which melt at about 15°C or alpha crystals melting at 20°C.
- These unstable forms return to the stable condition after several days.
- Cocoa butter must be slowly melted over a warm water bath to avoid the formation of the unstable crystalline form.

Suppository base:

I. Fatty bases: designed to melt at body temperature.

A- Theobroma oil (Cocoa butter):

**** Disadvantages:**

2. Adherence to the mould:

- Cocoa butter does not contract sufficiently on cooling to loosen the suppositories in the mould.
- Sticking may be overcome by adequate lubrication.

3. Melting point reduced by soluble ingredients:

- Phenol and chloral hydrate have a tendency to lower the melting point of cocoa butter.
- So, solidifying agents like beeswax (4%) may be incorporated to compensate for the softening effect of the added substance.

Suppository base:

I. Fatty bases: designed to melt at body temperature.

A- Theobroma oil (Cocoa butter):

**** Disadvantages:**

4. Rancidity on storage: Due to the oxidation of unsaturated glycerides.

5. Poor water-absorbing ability: Improved by the addition of emulsifying agents.

6. Leakage from the body: Sometimes the melted base escapes from the rectum or vagina, so it is rarely used as a pessary base.

7. Expensive

Suppository base:

I. Fatty bases: designed to melt at body temperature.

B- Synthetic hard fat: e.g., Suppocire, witepsol.

**** Advantages:**

a-They have good resistance to oxidation because of the lower content of unsaturated fatty acids.

c- They are marketed in a series of grades with different melting point ranges, which can be chosen to suit particular products and climatic condition.

d- They contain a proportion of w/o emulsifying agents, and therefore their water-absorbing capacities are good.

e- No mould lubricant is necessary because they contract significantly on cooling.

Suppository base:

I. Fatty bases: designed to melt at body temperature.

B- Synthetic hard fat: e.g., Suppocire, witepsol.

**** Disadvantages:**

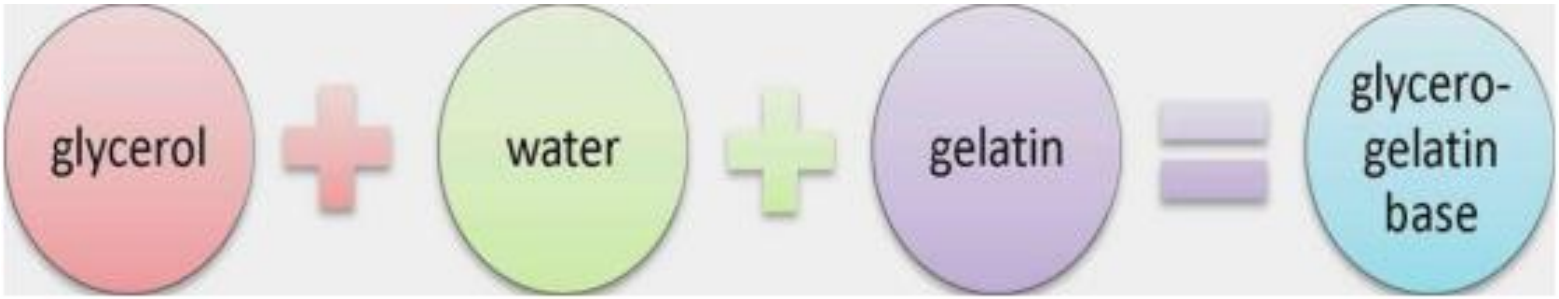
a- Brittle if cooled rapidly, avoid refrigeration during preparation.

b- The melted fats are less viscous than theobroma oil. As a result greater risk of drug particles to sediment during preparation and lack of uniform drug distribution gives localized irritancy.

Suppository base:

I. Water soluble and water miscible bases.

A- Gylcero-gelatin.



-The commonest is Glycerol Suppositories Base B.P., which has 14% w/w gelatin, and 70% w/w glycerol & water to 100%.

- The glycerol-gelatin base U.S.P. consisted of 20% w/w gelatin, and 70% w/w glycerol & water to 100%.

Suppository base:

I. Water soluble and water miscible bases.

A- Gylcero-gelatin.

**** Disadvantages:**

a- A physiological effect: osmosis occurs during dissolving in the mucous secretions of the rectum, producing a **laxative effect**.
b- Can cause rectal irritation due to small amount of liquid present.
c- Unpredictable dissolution time.
d- Hygroscopic:
So, they should be packaged in tight containers and also have dehydrating effects on the rectal and vaginal mucosa leading to irritation.
e- Microbial contamination.
f- Long preparation time.
g- Lubrication of the mould is essential.

Suppository base:

I. Water soluble and water miscible bases.

B- Macrogols (polyethylene glycols).

- Polyethylene glycols are polymers of ethylene oxide and water, prepared to various chain lengths, molecular weights, and physical states.

- The numerical designations refer to the average molecular weights of each of the polymers.

- Polyethylene glycols (PEGs) having average molecular weights of 300, 400, and 600 are clear, colorless liquids, while those with molecular weights of 600-1000 are semisolids.

- Those having average molecular weights of greater than 1000 are wax-like, white solids with the hardness increasing with an increase in the molecular weight.

Suppository base:

I. Water soluble and water miscible bases.

B- Macrogols (polyethylene glycols).

- These polyethylene glycols can be blended together to produce suppository bases with varying: melting points, dissolution rates and physical characteristics.
- Drug release depends on the base dissolving rather than melting.
- The melting point is often around 50°C.
- Higher proportions of high molecular weight polymers produce preparations which release the drug slowly and are also brittle.
- Less brittle products which release the drug more readily can be prepared by mixing high polymers with medium and low polymers.

Suppository base:

I. Water soluble and water miscible bases.

B- Macrogols (polyethylene glycols).

**** Advantages:**

a- No laxative effect.
b- Less microbial contamination.
c- The base contract on cooling and no lubricant is necessary.

d- Melting point above body temperature:
- Cool storage is not so critical.
- Suitable for hot climates
- The base dissolve in the body and disperse the medication slowly, providing a sustained effect.

e- Produce high-viscosity solutions, so leakage is less likely.
f- Good solvent properties.

Suppository base:

I. Water soluble and water miscible bases.

B- Macrogols (polyethylene glycols).

**** Disadvantages:**

a- Hygroscopic:
Thus may cause irritation to the mucosa. This can be overcome by instructing the patient to dip the preparation in water prior to insertion.

b- Poor bioavailability of medicaments: The good solvent properties may result in retention of the drug in the liquefied base with consequent reduction in therapeutic effect.

c- Incompatibilities: Incompatibility with several drugs and packaging materials, e.g. benzocaine, penicillin and plastic, may limit their use.

d- Brittleness: if cooled too quickly and also on storage.

Suppository base:

I. Water soluble and water miscible bases.

C- Soap gylcerin: Obtained by : stearic acid + sodium carbonate in glycerin solution stearin soap (i.e. curd soap, sodium stearate) (used as suppository base).

Advantages over gelatin:

- It makes glycerin sufficiently hard for suppositories.
- It allows the incorporation of large quantity of glycerin up to 90-95% of the mass.
- Soap assists the laxative action of glycerin, whereas gelatin does not.

Disadvantages:

- Very hygroscopic & require to be wrapped in waxed paper or pure tin foil & protected from the atmosphere.

Preparation of suppositories:

Suppositories are prepared by four methods:

I. ***Hand moulding:***

-Hand molding is useful when we are preparing a small number of suppositories.

✓ Steps:

1. The drug is made into a fine powder.
2. It is incorporated into the suppository base by kneading with it or by trituration in a mortar.

3. The kneaded mass is rolled between fingers into rod shaped units.

4. The rods are cut into pieces and then one end is pointed.

Preparation of suppositories:

II. Compression molding:

- The cold mass of the base containing the drug is compressed into suppositories using a hand operated machine.

**Advantages:

1. It is a simple method, giving suppositories that are more elegant than hand moulded suppositories.
2. In this method, sedimentation of solids in the base is prevented.
3. Suitable for heat labile medicaments.

**Disadvantages:

1. Air entrapment may take place, causing weight variation.
3. The drug and/or the base may be oxidized by this air.

Preparation of suppositories:

III. Pour moulding:

- Using a suppository mould which is made of metal or plastic. Traditional metal moulds are in two halves which are clamped together with a screw.

Steps:

1. The base is melted and precautions are taken not to overheat it.
2. The drug is incorporated in it.
3. The molten liquid mass is poured into chilled (lubricated if cocoa butter or glycrogelatin is the base) molds.
4. After solidification, the cone shaped suppositories are removed.

Lubricants for use with suppository bases:

- Lubricating the cavities of the mould is helpful in producing elegant suppositories and free from surface depression.
- The lubricant must be different in nature from the suppository base, otherwise it will be become absorbed and will fail to provide a buffer film between the mass & the metal.
- The water soluble lubricant is useful for fatty bases, while the oily lubricant is useful for water soluble bases.
- The lubricant should be applied on a pledget of gauze or with fairly stiff brush.

Base	Lubricant
Theobroma oil	Soap spirit
Glycerol-gelatin base	liquid paraffin
Synthetic fats	No lubricant required
Macrogols	No lubricant required

Preparation of suppositories:

IV. Automatic moulding machine:

- All the operations in pour moulding are done by automatic machines. Using this machine, up to about 10,000 suppositories per hour can be produced.

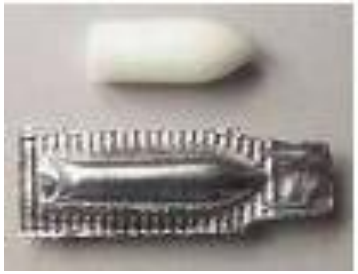
Suppositories package & storage:

- Suppositories are usually packed in tin or aluminium, or plastic.

- Poorly packed suppositories may give rise to staining, breakage or deformation by melting.

- Both cocoa butter and glycerinated gelatin suppositories stored preferably in a refrigerator.

- Polyethylene glycol suppositories stored at usual room temperature without the requirement of refrigeration.



Problems in suppositories formulation:

1- Water in suppositories:

Formulators do not like to use water for dissolving drugs in suppositories for the following reasons :

a. Water causes oxidation of fats.
b. If suppositories are manufactured at a high temperature, the water evaporates and, then drugs crystallize out.
c. Absorption of water-soluble drugs is enhanced only if the base is an o/w emulsion with more than 50% of the water in the external phase.
d. Drug excipient interactions are more likely to happen in the presence of water.
e. Bacterial contamination may be a problem, so a preservative must be added.

Problems in suppositories formulation:

2- Hygroscopicity:

- Glycerogelatin suppositories lose moisture in dry climates and absorb moisture in humid conditions.
- The hygroscopicity of polyethylene glycol bases depends on the chain length of the molecule. As the molecular weight of these ethylene oxide polymers increases, the hygroscopicity decreases.

3- Drug-excipient interactions:

- Incompatibilities exist between polyethylene glycol base and some drugs.
- Sodium barbital and salicylic acid crystallize out of polyethylene glycol.
- High concentrations of salicylic acid soften polyethylene glycol to an ointment like consistency.
- Penicillin G is stable in cocoa butter and other fatty bases. It decomposes in polyethylene glycol bases.

Problems in suppositories formulation:

4- Viscosity:

- When the base has low viscosity, sedimentation of the drug is a problem.
- 2% aluminium monostearate may be added to increase the viscosity of the base.
- Cetyl and stearyl alcohols or stearic acid are added to improve the consistency of suppositories.

5- Brittleness:

-Cocoa butter suppositories are elastic, not brittle.
- Synthetic fat bases are brittle.
- This problem can be overcome by keeping the temperature difference between the melted base and the mold as small as possible.
- Materials that impart plasticity to a fat and make them less brittle are small amounts of Tween 80, castor oil, glycerin or propylene glycol.

Problems in suppositories formulation:

6- Lubrication of moulds:

- ✓ Some widely used lubricating agents are mineral oil, aqueous solution of SLS and alcohol. These are applied by wiping, brushing or spraying.

7- Rancidity:

- ✓ The unsaturated fatty acids in the suppository bases undergo auto-oxidation and decompose into aldehydes, ketones and acids. These products have strong, unpleasant odours.
- ✓ The lower the content of unsaturated fatty acids in a base, the higher is its resistance to rancidity.

Problems in suppositories formulation:

8- Volume contraction:

- ✓ On solidification, the volume of the suppository decreases. The mass of the suppository pulls away from the sides of the mould. This contraction helps the suppository to easily slip away from the mould, preventing the need for a lubricating agent.

- ✓ Sometimes when the suppository mass is contracting, a hole forms at the open end. This gives an inelegant appearance to the suppository. Weight variation among suppositories is also likely to occur.

- ✓ This contraction can be minimized by pouring the suppository mass slightly above its congealing temperature into a mould warmed to about the same temperature. Another way to overcome this problem is to overfill the molds, and scrape off the excess mass which contains the contraction hole.

Problems in suppositories formulation:

9- Weight and volume control:

- ✓ Various factors influence the weight of the suppository, the volume of the suppository and the amount of active ingredient in each suppository. These factors include :

1. Concentration of the drug in the mass.
2. Volume of the mould cavity.
3. The specific gravity of the base
4. Volume variation between moulds.
5. Weight variation between suppositories due to the inconsistencies in the manufacturing process.

- The upper limit for the weight variation in suppositories is 5%.