Semisolids

5th stage
Industrial pharmacy –II
Course number 512
College of pharmacy
University of Basrah

1. Semisolids
2. Percutaneous absorption;
3. types of bases
4. Formulation and processing
5. (vehicles) preservation;
6. evaluation.

Semisolids:

Semisolid dosage form :

- Pharmaceutical semisolid preparations include ointments, pastes, cream emulsions, gels, and rigid foams.
- The vast majority of ***topically*** applied formulations are semi-solids…….. WHY?
  - ✓They offer good residence time on the skin; due to their plastic rheologic behavior.
  - ✓There are numerous options available to the formulator.
  - ✓semi-solids are generally well accepted by patients.

✓**The bulk** of these products are applied to the skin (acting as vehicles for medication, emollients or as protective or occlusive dressings), and **a lesser portion** is applied to mucous membranes (buccal, rectal, vaginal, urethral, nasal, otic and cornea).

Percutaneous absorption;

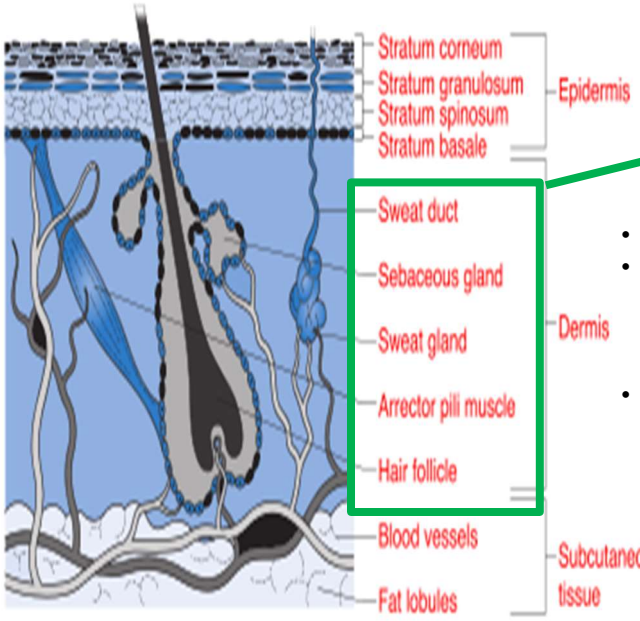
Target site for topical formulations

- certain topical formulations; such as, emollients, antimicrobials, and deodorants act primarily on the surface of the skin,
- however, the target area for most dermatologic disorders lies in the viable epidermis or upper dermis. This requires diffusive penetration of the skin or percutaneous absorption.

Skin structure and function

- skin 'keeps the outside out and the insides in'.
- -represents 10% of the body mass; circa 1.8 m2.
- the intact skin presents a formidable barrier and a difficult challenge to formulation scientists.

skin structure

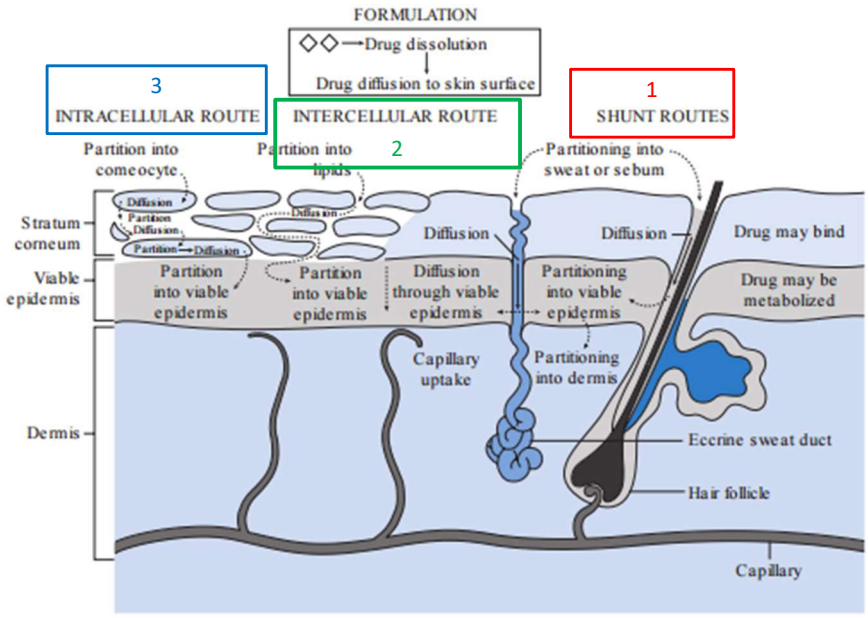


St.cor. responsible for the barrier properties of human skin and limits drug delivery into and across the skin.

Appendages or absorption shunt route

- **Dermis:**3–5 mm ;major component of skin.
- is composed of(collagen;elastin; mucopolysaccharide gel, **appendages**; [nerve endings, pilosebaceous units (hair follicles and sebaceous glands) ,and sweat glands]
- blood supply near the dermis provides continuous drainage of absorbed medication.

- (several millimeters' thick)
- is seldom an important barrier for drug delivery



Factors affecting permeation and absorption of permeant(drug)

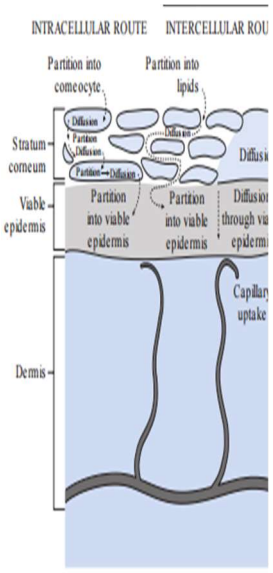
- ***A. The physicochemical properties of the permeant(drug)***
- ***B. factorts related to Formulation***
- ***C. factors related to Skin***

Factors affecting permeation and absorption of permeant(drug)

- ***A. The physicochemical properties of the permeant(drug)***

1. Partitioning (log P):
   - For both the transcellular and intercellular routes, the drug molecule has to cross the multiple lipid bilayers between the corneocytes and hence partitioning into, and diffusion through these lipid environments is essential.
   - However, to reach the systemic circulation the molecule must also pass through the more aqueous environment of the viable epidermal cells and enter the blood.

- ➔Thus, molecules which are lipophilic are usually seen as better candidates for transdermal delivery than hydrophilic compounds, but high lipophilicity is problematic for clearance…….????



2. The molecular weight of the permeant:
   - The skin is designed to act as a barrier to external chemicals and so prevents the entry of large molecules, such as larger peptides and proteins.
3. Chemical structure:
   1. molecular structure (in particular hydrogen-bonding potential) can control the extent of binding to skin constituents and hence affect bioavailability.
4. Solubility and drug release:
   - Naturally, the drug must have some solubility in the formulation and whilst transport through the stratum corneum is usually **the rate limiting step in transdermal delivery,** poor drug release from a formulation can occasionally limit drug transport.

B. Formulation factors:

- pH, type of vehicle is used, viscosity of formulation , the release rate form formulation, Concentration of drug….etc

C. Skin conditions:

- Hydration of skin
- Skin condition (intact or injured)

types of bases

Ointments:

- Ointments are fatty preparations that are usually self-occlusive and are generally used on dry lesions.
- Unmedicated ointments are used as emollients to soothe, smooth and hydrate dry skin conditions.
- ***Types of ointments bases:***
  1. **Hydrocarbon bases:**
  2. **Absorption bases.**
  3. **Emulsifying bases.**
  4. **Water-soluble bases.**

1. Hydrocarbon bases (oleaginous):

- hydrocarbon base ointments are produced from **soft, hard and liquid** paraffins (or similar excipients)
- **ADVANTAGES:**
- The bases are highly occlusive and so prevent transepidermal water loss; this, in turn, causes the skin to hydrate and hence they are useful in dry skin disorders.
- Provide prolonged drug delivery because of :
  1. Hydration of the stratum corneum that tends to increase transdermal drug flux
  2. the excellent residence time of these formulations on the skin,
- **DISADVANTAGES**
- thick greasy ointments can be difficult to spread, particularly on broken skin where they are commonly applied,
- these formulations to be messy to use.

2. Absorption bases.

- contain a hydrocarbon, such as a **paraffin**, together with a miscible substance that is polar, such as **sorbitan monooleate**. This combined system can absorb up to 15% water.
- These contain an emulsifying agent that allows the formulation to soak up water or aqueous secretions whilst remaining semi-solid.
- E.g. of added materials; wool fats and lanolin,
- **ADVANTAGES:**
  - provide some occlusion of the skin,
  - hydrate the stratum corneum
  - Prolonged contact with skin.
- **DISADVANTAGES:**
  - Allergic reaction to added substance→ using purified lanolin reduces allergic reaction

3. Emulsifying bases.

- These are similar to absorption bases but can form an oil-in-water system, for example by using a mixture of paraffins with cetostearyl alcohol and a surface active agent such as sodium lauryl sulphate (SLS) or cetrimide.
- **ADVANTAGES:**
  - These emulsifying agents generate a water-miscible ointment which can be easily washed from the skin surface, in contrast to greasy hydrocarbon bases.
  - Anionic (e.g. SLS), cationic (e.g. cetrimide) or nonionic (e.g. cetomacrogol) emulsifying ointments can be formulated, to ensure compatibility with any incorporated drug such that, for example, a cationic or non-ionic base would be selected for a cationic drug.

4. Water-soluble bases.

- These are usually prepared from a mixture of water-soluble polyethylene glycols of varying molecular weights which can be blended to generate bases which soften or melt when applied to the skin surface.
- **ADVANTAGES:**
  - Water-soluble bases mix easily with skin secretions,
  - spread well on the skin surface
  - and can be readily washed off.
- **DISADVANTAGES:**
  - However, they lose their semi-solid consistency if around 10% water is taken into the ointment
  - and they may be incompatible with several classes of compounds including phenols and penicillin.

Gels

- Gels are typically formed from a liquid phase that has been thickened with other components and may contain dissolved (single phase) or dispersed (two-phase) drug in a semi-solid system.
- The liquid in the gel essentially forms a continuous phase with the thickening agent enhancing viscosity by providing the porous scaffold of the gel.
- As with solutions or suspensions, the liquid phase may be ***aqueous, alcoholic, miscible blends or a non-polar solvent*****,**

- **ADVANTAGES:**
  - the solvent may evaporate, cooling the skin and increasing drug flux by enhancing thermodynamic activity of the drug in the evaporating vehicle.
  - the continuous phase allows unhindered diffusion of dissolved molecules throughout the polymer scaffold and hence drug release should be equivalent to that from a simple solution, unless the drug binds to the polymer in the gel or polymer loading generates a highly viscous gel.

- the selection of thickening agents is influenced by:
  - the physicochemical properties of the drug
  - and compatibility with the solvent.
- Natural polymers such as carageenans ; tragacanth, pectin, agar, and alginic acid
- or refined/synthetic polymers such as hydroxypropyl methylcellulose or Carbopols are commonly employed gelling agents.

Creams

- Creams are the most common semi-solid topical dosage form and are typically two phase emulsions, either: (water-in-oil) or (oil-in-water).

Disadvantages of creams

- **The processes occurring during delivery from a cream are complex and difficult to define; …….. WHY?**

1. the cream changes as it is **applied**, **rubbed in, the continuous phase evaporates** (or if oily may penetrate the skin) **and the emulsion cracks.**
2. the active ingredient may be loaded in one phase but will partition between the continuous and dispersed phases or may become incorporated into micelles as the formulation collapses.
3. creams usually include an antimicrobial preservative which may have surface activity,
4. a buffer, an antioxidant and fragrance materials. All these additives makes prediction of release is difficult.

Oily creams (w/ o semi-solid emulsions)

- **ADVANTAGES:**
  - are less greasy than ointments,
  - are easier to apply
  - and can usually be simply washed off the skin surface,
  - ➔And hence are well accepted by patients.
- **DISADVANTAGES** :
  - However, whilst a water-in-oil cream can deposit a protective oily layer on the surface, they tend to be less occlusive than an ointment and so may not be as beneficial in dry skin conditions.

Oil-in-water creams

- (also called ‘washable’ or ‘vanishing’ creams) with a continuous aqueous phase are often rubbed into skin and again can provide a cooling sensation.

Pastes

- Pastes (either two- or multi-phase) are stiff preparations containing up to 50% solids, commonly in a fatty base.
- These preparations are useful for treating localized skin sites, as with Lassar's paste (zinc and salicylic acid) or dithranol paste.
- Pastes tend to be less greasy than ointments as the powder may absorb some of the more mobile hydrocarbons from the fatty base.

Formulation and processing;

Formulation options

- skin type:
  - for normal to oily skin types, gels are often preferred
  - for normal to dry skin types, lotions are often preferred
  - for dry skin, creams are often preferred.
- the skin site:
  - for hairy areas, lotions, gels or sprays are usually preferable
  - for intertriginous areas (sites where skin may touch or rub such as the axilla of the arm),creams or lotions are usually preferred.
- the lesion type then:
  - for a wet, vesicular or weeping lesion, a 'wet' usually aqueous based formulation is generally preferred (cream, lotion, gel)
  - for a dry, thickened scaly lesion, a 'dry' usually fatty formulation is preferred (ointments, pastes).

Methods of preparation

- Primarily depend on the nature of ingredients, and quantities (small or large scale).
  - ➢ Incorporation (cold method).
  - ➢ Trituration (mixing principle with milling).
  - ➢ Levigation (use of levigating agent).
  - ➢ Fusion (Hot method).

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Equipment involved

- Mixers : Kettle and tank fitted with agitator (high shear mixers) , tumbler, Blade mixers and kneaders
- Homogenizers, colloid mills, roller mills, hammer mill, ball mill, micronizer
- Filling and packaging machines

vehicles preservation;

Preservation from Microbial Spoilage

- The preservatives are added to semisolids to prevent contamination, deterioration, and spoilage by bacteria and fungi, since many of the components in these preparations serve as substrates for these microorganisms.
- Should be compatible with all ingredients (active and excipient)
- Plastic containers may adsorb the preservative and thereby decrease the quantity available for inhibiting or destroying the microorganisms responsible for spoilage.
- Some preservatives may sting or irritate the mucous tissues of the eye or nasal passages
  - ; such as Methylparabens and propylparabens tend to be more irritating when applied in the nose than quaternary ammonium compounds (e.g. benzalkonium chloride) or the phenylmercuric salts.

- Perfumes, high concentrations of glycerin, and electrolytes make the environment less favorable to microbial growth, thus enhancing the effectiveness of the preservatives.
- Preservative action appears to depend on the concentration of the free preservative in the aqueous phase.
- Surfactant solubilized preservative may be bound within the micelles and there inactivated, or on the contrary, the micelles may act as reservoirs of preservative in an actively preserved system.
- The solid parabens may be difficult to incorporate into some formulations because of their low water solubility

Evaluation.

Evaluation

- In process monitoring of:
  - Particle size, Viscosity (Rheological properties), Irritancy, Preservative effectiveness
- Microbial content
- Minimum fill
- Content uniformity
- Dissolution test
- Leakage test
- Sterility (for sterile semisolid products), as in liquids.

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Consistency type	Approximate viscosity in cps at 25°C	Pharmaceutical example
Soft, spreadable	100,000-300,000	W/O, O/W CREAM
Plastic flow, spreadable	300,000-1,000,000	Ointment

Microbial content

- Microbial limits are stated for each preparation in the USP
- 10 gm or 10 ml of the products is tested after suitable dilution and added to a specific media and incubate between 30-35 °C for 24-48 h
- For purpose of confirming a doubtful result, retesting on 25 gm specimen of the product may be conducted.

Minimum Fill

- Select 10 filled containers, remove any labeling.
- Clean and dry the outside of the containers, and weigh individually.
- Quantitatively remove the contents from each container, cutting the latter open and wash with a solvent.
- Dry and weigh again each empty container.
- The difference between the two weights is the net weight of the contents:

- The average net content of the 10 containers is not less than the labeled amount, and the net content of any single container is not less than 90% of the labeled amount where the labeled amount is 60 g or 60 ml or less .
- Or not less than 95% of the labeled amount where the content is 60 g/or ml – 150 g /or ml.
- If this requirement is not met, determine the content of 20 additional containers.

- The average content of the 30 containers is not less than the labeled amount, and the content of not more than 1 of the 30 containers is less than 90 % of the labeled amount where the labeled amount is 60 g or 60 ml or less .
- or not less than 95% of the labeled amount where the content is 60 g/or ml – 150 g /or ml.

Content Uniformity

Monitoring Output	Acceptance Criteria (n = 10)	Sampling Plan
Content Uniformity	90- 110%	3 – 4 units from beginning, middle and end of filling cycle; total = 10 units
	SD ≤ 4.2%	
● The average result of 10 individual results must meet the release limit for assay. ● The usual sample size for testing ranges between 0.5 and 1.5 g per sample assay.		

- Dissolution Testing:
- It is primary used as a quality control procedure to determine product uniformity.
- secondary as a means of assessing the in vivo absorption of the drug in terms of a possible in vitro/vivo correlation.

- For cream/ointments, the Franz in vitro flow through diffusion cell or microdialysis has been modified by using silicon rubber membrane barrier to stimulate percutaneous dissolution unit for testing purpose.

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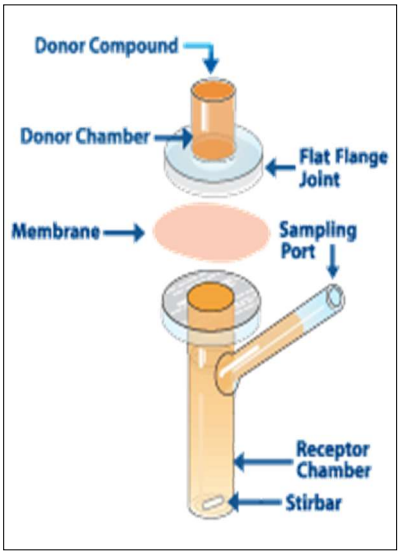

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Leakage test

- Select 10 sealed tubes of the ointment
- Clean and dry the exterior surfaces
- Place the tubes with an absorbent sheet in oven at 60°C ± 3 for 8 hours
- If leakage is observed from one, but not more than one, of the tubes, repeat the test with 20 additional tubes
- The requirement is met if no leakage is observed from the first 10 tubes, or if leakage is observed from not more than 1 of 30 tubes tested.