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Semisolid Dosage Forms

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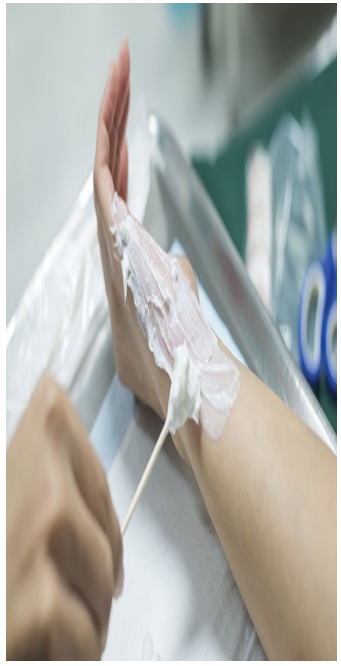
Semisolids

- Ointments, creams, pastes, and gels are semisolid dosage forms intended for **topical** application on **skin** and **mucous membranes**.
- Their **common** property is the ability to **cling** to the surface of the application for a reasonable duration before they are washed or worn off.

Applications:

1. Most of these preparations are used as a vehicle for applying a **therapeutic** for local and systemic effects (**medicated ointments**).
2. To promote hydration of the skin such as **emollients**.
3. **Protect skin** and mucous membranes from chemical and physical irritants.



Action:

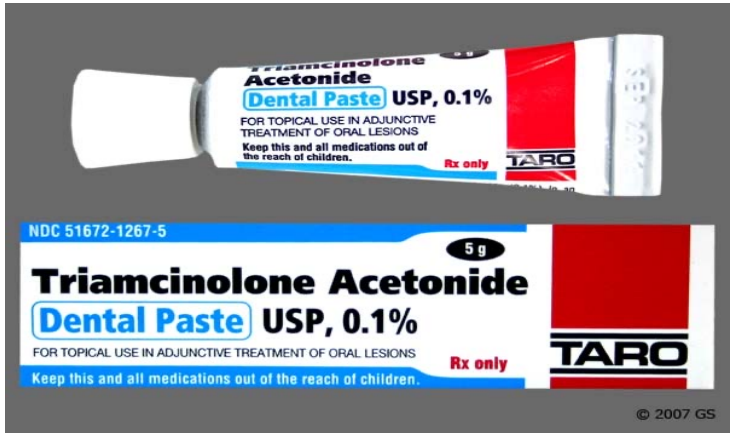
1. A product can target skin as an organ and these products are called **topical or dermatological** products.
2. A product can be designed for a **systemic effect** where the drug can pass skin and reach other organs. This type is called a **transdermal** product.

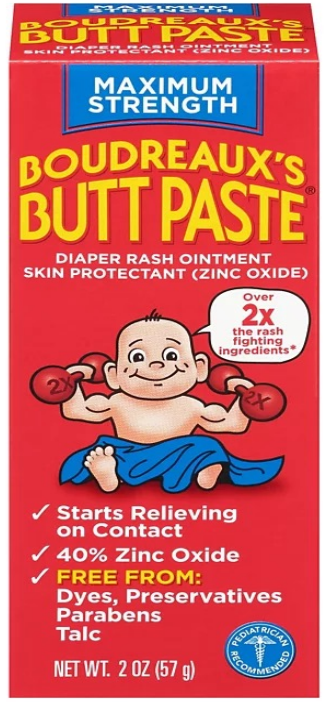
Ointments

- **Ointments** are semisolid preparations intended for external uses to the skin or mucous membranes (**USP definition**).
- It has a **translucent** appearance and is composed of fluid hydrocarbons meshed in a matrix of higher-melting solid hydrocarbons.
- Most ointments are based on mineral oil and petrolatum (more than 50%).
- Most ointments are prepared by **melting** the components together and the drug and other components are **added in a fluidized state**.

Paste

- Ointment but with a **higher** percentage of **insoluble** solids.
- Remain **more adherent than ointment** to the location they are applied
- They can form **protective barriers** on the skin such as some products to treat diaper rash or protect the face from the sun.
- They prepared by adding the drug in a **solid form** into a congealed system using **levigation**.





Creams

- **Creams** are semisolid preparations containing a medicinal agent **dissolved** or **dispersed in an emulsion**.
- It does contain **more water** than in ointments and **less hydrocarbons**.
- After application of the cream, the water **evaporates**, leaving behind a thin film of the oleaginous component.
- Creams have applications in **topical** skin products and products used **rectally** and **vaginally**.
- Many patients and physicians **prefer** creams to ointments because they are easier to spread and remove.

Creams

- Creams are prepared as an emulsion
- Either W/O (**non-washable** cream) or
- O/W (**washable** because of the external phase is water)
- Pharmaceutical manufacturers frequently manufacture topical preparations of a drug in both cream and ointment bases to satisfy the preferences of the patient and physician.

Gels

- **Gels**: are semisolid preparations consisting of medicinal agents **dispersed** in aqueous liquid rendered jelly-like by the addition of a *gelling agent*.
- Gels are clear and transparent
- Among the gelling agents used are **carbomer**, CMC, or HPMC.
  - Gels may thicken on standing and must be shaken before use to liquefy the gel and enable pouring.
- Medicated gels may be prepared for administration by various routes, including the skin, the eye, the nose, the vagina, and the rectum.

Types of Semisolid Bases

- The base is the vehicle used for pharmaceutical semisolids.
- **Types of Bases**
- Semisolid bases are generally classified into **four groups**:

1. Oleaginous bases (hydrocarbon base).
2. Absorption bases.
3. Water-removable bases.
4. Water-soluble bases.

- The solubility and stability of the drug in the base, as well as the nature of the skin lesion, determine the choice of the semisolid vehicle.

Oleaginous Bases

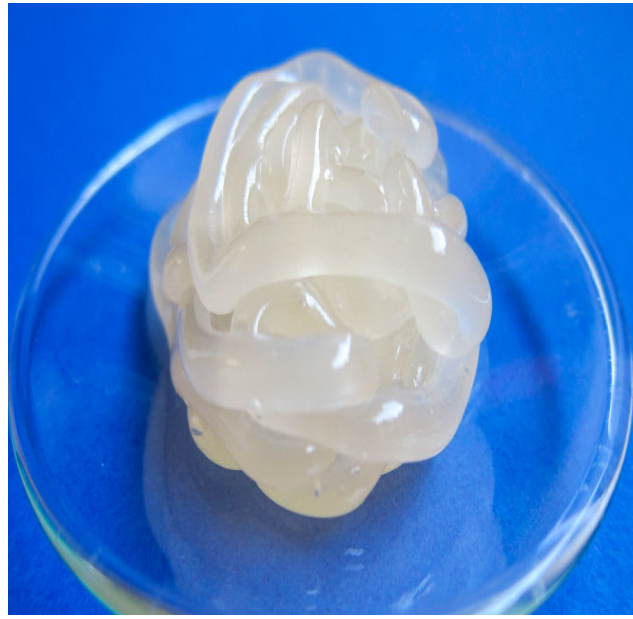
- Oleaginous bases are also termed hydrocarbon bases.
- Properties (**advantages**):

1. **Low** capacity to absorb water (➔keep water on skin or act as **emollient** effect).
2. Exert high **occlusiveness** by forming water impermeable layer on the skin.
3. **Difficult to wash off** and they can **remain** on the skin for relatively long periods without drying.
4. Act as a **vehicle** that provides an advantage for water-sensitive drugs such as antibiotics.

Oleaginous Bases

Disadvantages:

1. Relatively low **patient acceptability** because of greasy nature.
2. It can **stain** clothes.
3. Poor aesthetic appeal.
4. **Very little** water can be incorporated into this type (5% or less)



- **Examples:**
- Petrolatum (Vaseline), White petrolatum (purified Vaseline).
- When powdered substances are to be incorporated into hydrocarbon bases, liquid petrolatum (**mineral oil**) may be used as the levigating agent.

Absorption Bases

- **Absorption bases**: they are **hydrophilic** anhydrous materials.
- **Advantages:**
- **Absorb** water or permit the incorporation of aqueous solutions resulting in the formation of W/O emulsions.
- They have the capacity to absorb water up to three times their weight.
  - They do **not** absorb water by contact but with sufficient agitation.
- Absorption bases are not easily removed from the skin by washing, because the external phase of the emulsion is oleaginous.
- Absorption bases are useful to incorporate **small** volumes of aqueous solutions and are used mostly in the preparation of **ophthalmic** ointments.
- Act as emollient and occlusive **but less** than oleaginous bases

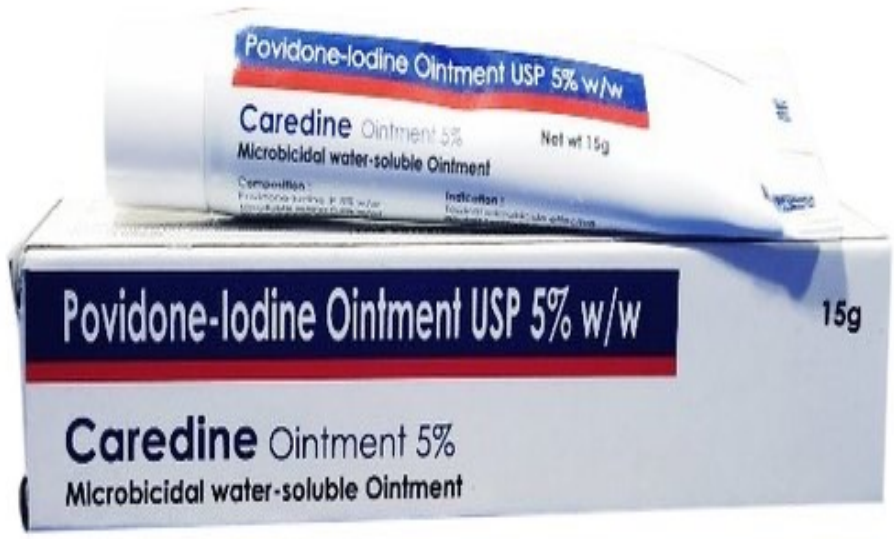
Water-Removable Bases

- Water-removable bases are **O/W** emulsions resembling creams **in appearance**.
- Because the external phase of the emulsion is **aqueous**, they are **easily** washed from the skin. They may be diluted with water or aqueous solutions.
- Non-occlusive, non-greasy

Water, Glycerin, **Petrolatum,** Dicaprylyl Ether, Dimethicone, Glyceryl Stearate, Cetyl Alcohol, Helianthus Annuus (Sunflower) Seed Oil, Peg-30 Stearate, Panthenol, Niacinamide, Prunus Amygdalus Dulcis (Sweet Almond) Oil, Tocopheryl Acetate, Pantolactone, Dimethiconol, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Carbomer, Propylene Glycol, Disodium Edta, Benzyl Alcohol, Phenoxyethanol, Sodium Hydroxide, Citric Acid

Water-Soluble Bases

- Water-**soluble** bases do **not** contain oleaginous parts (non-greasy, non-occlusive).
- They are **completely** water washable.
- They absorb water to the **point of solubility**. So they may **dehydrate** the skin.
- Water soluble materials can be incorporated with a small amount of water
- Insoluble powders can be levigated with a small quantity of glycerin, propylene glycol, or PEG 400.



Selection of Appropriate Base

Condition (dry or 'weeping').

1. **Desired consistency** (for protection, hydration, …).
   - Oily bases are preferred for dry or scaly conditions. They help with softening and moisturizing the skin.
2. The site of application (for example -unbroken skin vs mucous membrane.
   - Water miscible bases (**cream**) are preferred for moist or 'weeping' conditions.

Stability

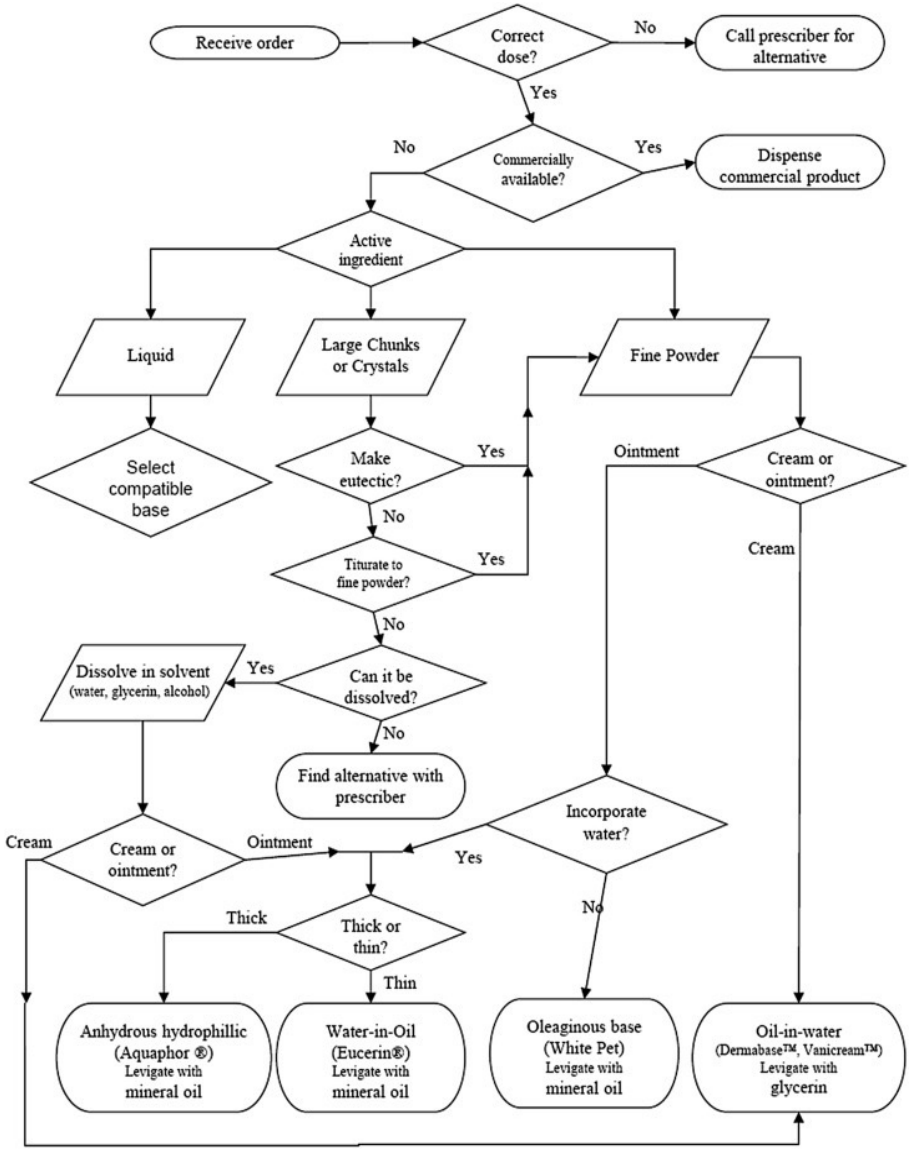
1. Stability of the individual components (ex. oils)
2. Physical and chemical stability of base with added ingredients
3. **Compatibility** of the drug with the base composition

Drug release from the preparation

1. Drugs solubility in the vehicle and drug concentration.
2. The partition coefficient of the drug between the vehicle and the skin
3. Whether the drug is intended for topical or systemic applications.

Incorporation of Active Substances into Ointment Bases

- **Main Objective**: Semisolid Must be **smooth non-gritty** product.
- Solids should therefore be either be **dissolved** or **incorporated as fine particles.**
- The solubility of the drug in the base will dictate whether the drug will be in solution or suspended in the base.
- For emulsion bases, the dissolved drug will be partitioned between the two phases.
- For suspended solids in the formulation, **particle size distribution** of the solids and homogeneous distribution in the final preparation is critical.



Ointment Preparation

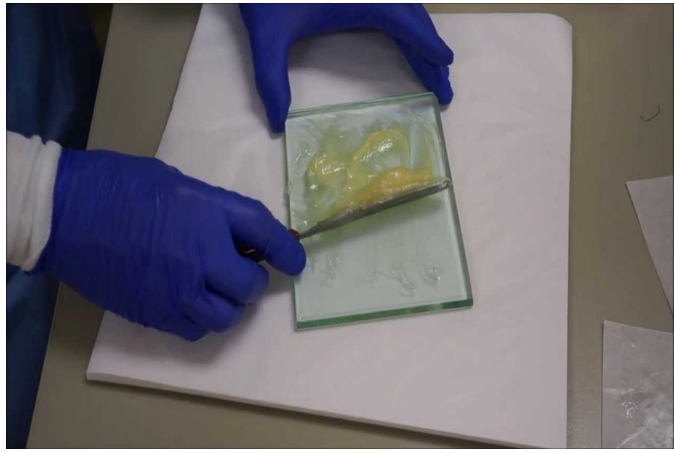
- Ointments are prepared by two methods, **depending** on the nature of the ingredients:

First: Incorporation method: in this method

- The active ingredient and the ointment base are mixed together until a uniform preparation is obtained.
- Before the incorporation of the active ingredient, it is often desirable to **reduce the particle** size of any powder (if any) so the final product will not be gritty.
  - This can be done by **levigation.**
- Alternatively, solids may first be **dissolved** in a small amount of a solvent (e.g., water or alcohol) and the solution is then mixed with the ointment base.
- On a small scale, the pharmacist may mix the components using a mortar and pestle, or a slab and spatula. On large scale (up to 1500 kg), ointments are manufactured in stainless steel tank which has a built-in mixer.

Levigation

- **Levigation** involves the mixing of a drug with a small amount of **base material** itself or **with a liquid** in which it is insoluble.
- It also involves the **reduction** in the particle size of a solid by triturating it in a mortar
- **Advantage**: appropriate particle size reduction, wetting, and dispersion of the drug substance.
- The '**levigated mixture**' can then be incorporated into the selected ointment base.
- **Levigating agents** should be compatible, inert, non-toxic, and not affect the preparations' target physical or therapeutic properties.
- https://youtu.be/G4vzxzk7Cqg



Types of Levigating Agents

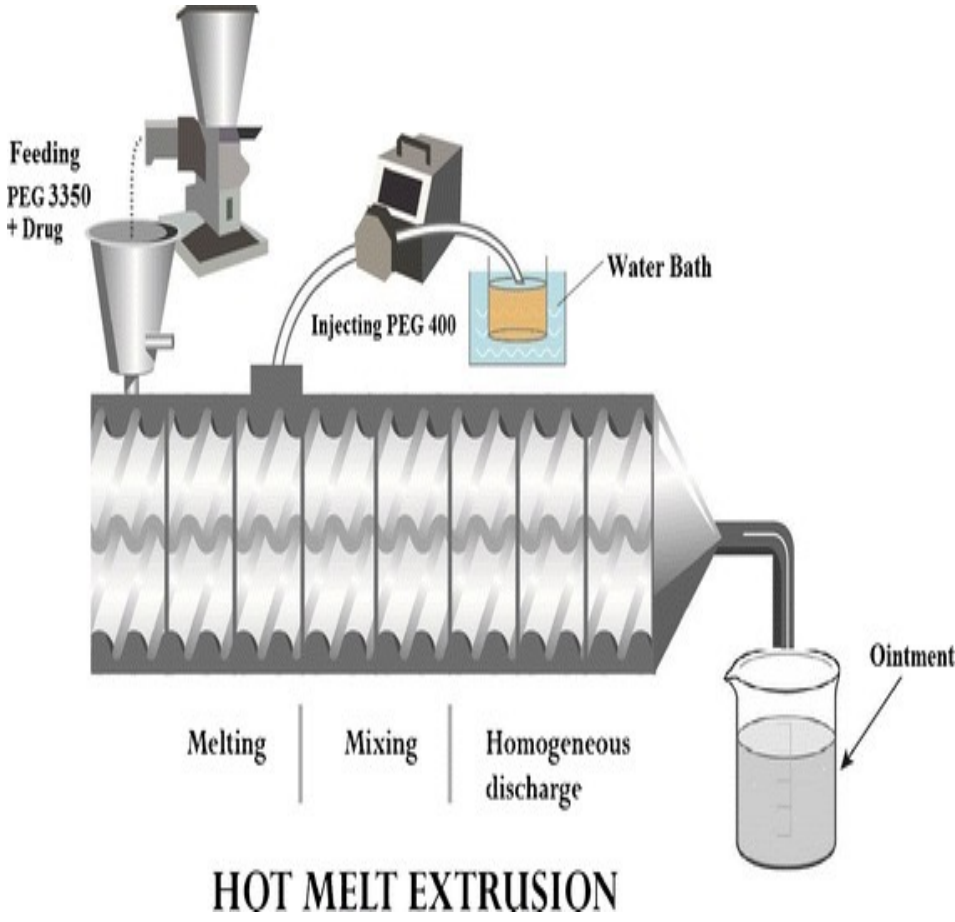
1. **Water miscible**: Glycerin, propylene glycol, polyethylene glycol 400 -used for water-washable and water-soluble bases
2. **Oil miscible**: Mineral oil, castor oil, cottonseed oil -used for hydrocarbon bases and absorption bases
3. A small quantity of the **molten ointment base** can be used as a levigating agent **if suitable**.
4. If the formulation contains an **ingredient** that is suitable as a levigating agent, **we should use it**. For example, if the formula contains glycerin, then we use it.

- **Note:**
  - The levigating agent should be about **equal in volume** to the solid material.
  - Solid drugs may be dissolved in **appropriate solvents** prior to incorporation into bases. The solvent used should not affect the stability and efficacy of the drug and the product.

Ointment Preparation

Second: Fusion method:

- By the fusion method, **all or some** of the components of an ointment are **melted** together and cooled with constant stirring until congealed.
- Components that are not melted at the beginning (e.g. heat sensitive and volatile substances) are added last to the congealing mixture as it is being cooled and stirred.
- Ointments containing components such as beeswax, paraffin, stearyl alcohol, and high molecular weight PEGs, which cannot be mixed well by incorporation method, are prepared by fusion.



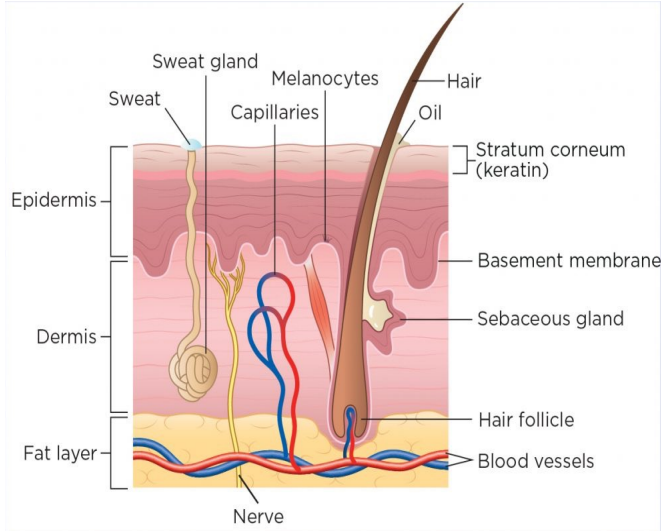
Preservation

- Except for ophthalmic preparations, topical preparations usually are **not** required to be sterile.
- However, preparations that **contain water** tend to support microbial growth to a greater extent than water-free preparations and may, therefore, require preservation.

Transdermal Delivery: Human Skin

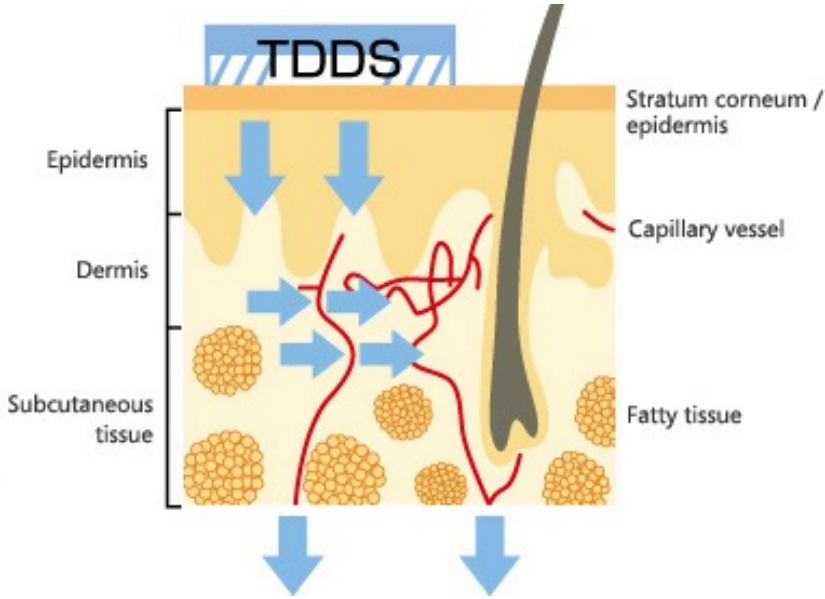
- Skin is a multilayer organ that an average adult has about 3.6 kg excluding fat.
  - Skin serves as a **barrier** against physical and chemical attacks.
  - It acts as a **thermal barrier** to keep body temperature. It also protects against microorganisms.
- **Skin Anatomy**: consists of three layers:

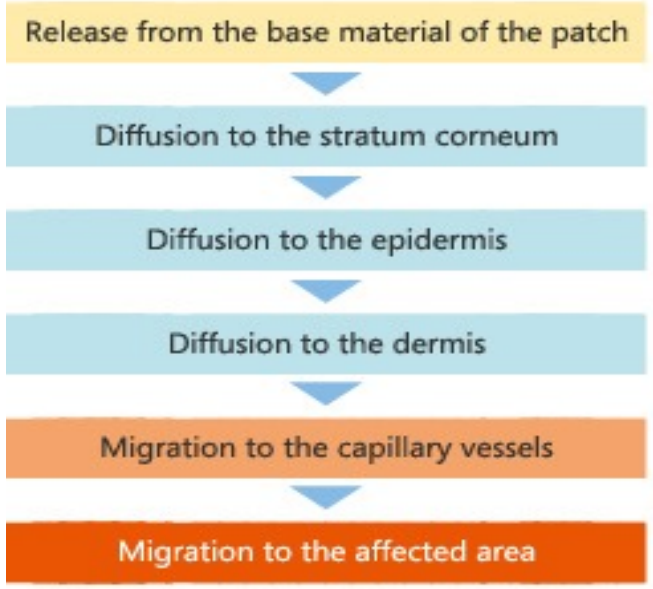
1. **Epidermis**: thin outer layer of skin that consists of an **outer** layer of dead keratinized cells (stratum corneum). It represents the **rate-limiting** step for drug penetration into the skin. And the **inner** living and metabolically active part of the epidermis.
2. **Dermis**: consists of the larger part of the skin and consists mainly of protein and **contains** hair follicles and sweat glands that originated here and penetrate the epidermis to the skin surface.
3. **Hypodermis or fat layer:** inner layer that consists of loose fatty connective tissues.



Transdermal Drug Delivery Systems

- Transdermal drug delivery systems (TDDS) are designed for the passage of drugs **through** the skin into the general circulation for their **systemic** effects.
- TDDS may be an ointment, cream, gel, or **patch**.
- **Percutaneous absorption** of a drug generally results from penetration (passive diffusion) of the drug through the stratum corneum. After the stratum corneum, drug molecules may pass through the deeper epidermal tissues and into the dermis. When the drug reaches the vascularized dermal layer, it becomes available for absorption into the general circulation.





Percutaneous Absorption

- Three entry pathways:

1. Follicular region (trans-follicular).
2. Sweat duct.
3. Through intact stratum corneum (trans-epidermal or diffusion)

Note: Hair follicles and gland ducts can provide rapid entry for drugs, **but** because their relative surface area is so small compared to the total epidermis, they have little effect on drug absorption.

- **Not all** drug substances are **suitable** for transdermal delivery.
- Among the factors playing a part in percutaneous absorption are the physical and chemical **properties** of the drug, and the **condition** of the skin.

Factors affecting Percutaneous Absorption

1. **Drug concentration**: the drug absorption **increases** with an increase in the concentration of the drug.
2. Drug affinity for water and lipid (**partition coefficient**). The **aqueous** solubility determines the drug concentration that is **ready for absorption** while the **lipid** solubility influences the **rate of transport** across the skin. Accordingly, drugs penetrate better in their unionized form.
3. Drugs with **molecular weights** of (100 to 800 Da) can penetrate the skin. The **ideal** molecular weight of a drug for transdermal drug delivery is believed to be 400Da or less.
4. **The hydration state** of the skin generally increases percutaneous absorption. Therefore, TDDS that utilizes an **occlusive base** may have more absorption than non-occlusive types.
5. **Application site**: Percutaneous absorption is greater when the TDDS is applied to a site with a **thin** horny layer than with a thick one.

Absorption Enhancers: Chemical Enhancers

- These are **chemical** permeation enhancers and **physical** methods that can increase the percutaneous absorption of therapeutic agents.
- **Chemical Enhancers**
- A chemical penetration enhancer increases skin permeability by **reversibly** altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance.
- Among the alterations are:
  - **Increasing** hydration of the stratum corneum,
  - A **change** in the structure of the lipids and
  - **Proteins denaturation**.
- Examples are acetone, dimethyl sulfoxide, ethanol, and polyethylene glycol.
- The selection of a permeation enhancer should be based not only on its efficacy in enhancing skin permeation but also on its dermal toxicity and its compatibility with the other components in the dosage form.

Absorption Enhancers: Physical Enhancers

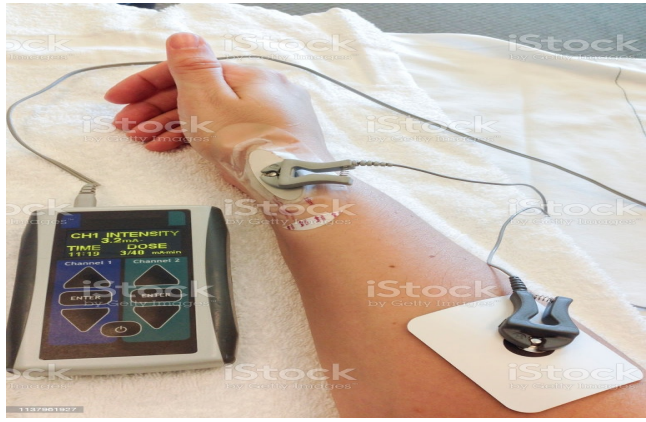
- **Physical Methods**

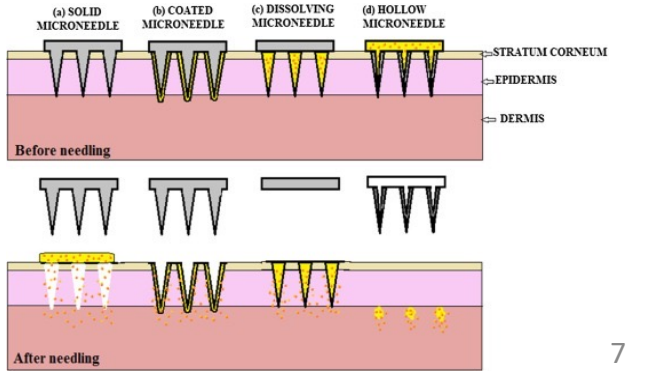
1. **Iontophoresis** is the delivery of a **charged compound** across the skin membrane by using an electrical field.

- Several drugs have been the subject of iontophoretic studies; e.g., dexamethasone, propranolol, peptides, and insulin. It shows some success in peptide and protein administration.

2. **Transdermal microneedle:** involves the disruption of the skin layer thus creating micron size pathways that lead the drug directly to the epidermis or upper dermis region from where the drug can directly go near blood vessels without facing the barrier.

- This can be in the form of **microneedle patches** or a **device** that is used to make holes in the skin prior to the application of the transdermal patch.





Microneedles

Evaluation of Semisolids
Release Study and In vitro permeation

- To study the release of drugs from TDDs, the following methods are used:

1. **In vivo** method: by taking blood samples and finding the amount of drug absorbed.
2. **In vitro** method: skin permeation may be tested using various skin tissues (human skin, animal skin, or artificial skin) in a diffusion cell. In these systems, skin membranes may be employed as barriers to simulate the biological system.

- The diffusion cell has two chambers, one on each side of the membrane.
- A temperature-controlled solution of the drug is placed in one chamber and a receptor solution is in the other chamber. Drug diffusion through the skin may be determined by **periodic sampling** and assay of the drug content in the receptor solution.
- The skin may also be analyzed for drug content to show permeation rates and/or retention in the skin.