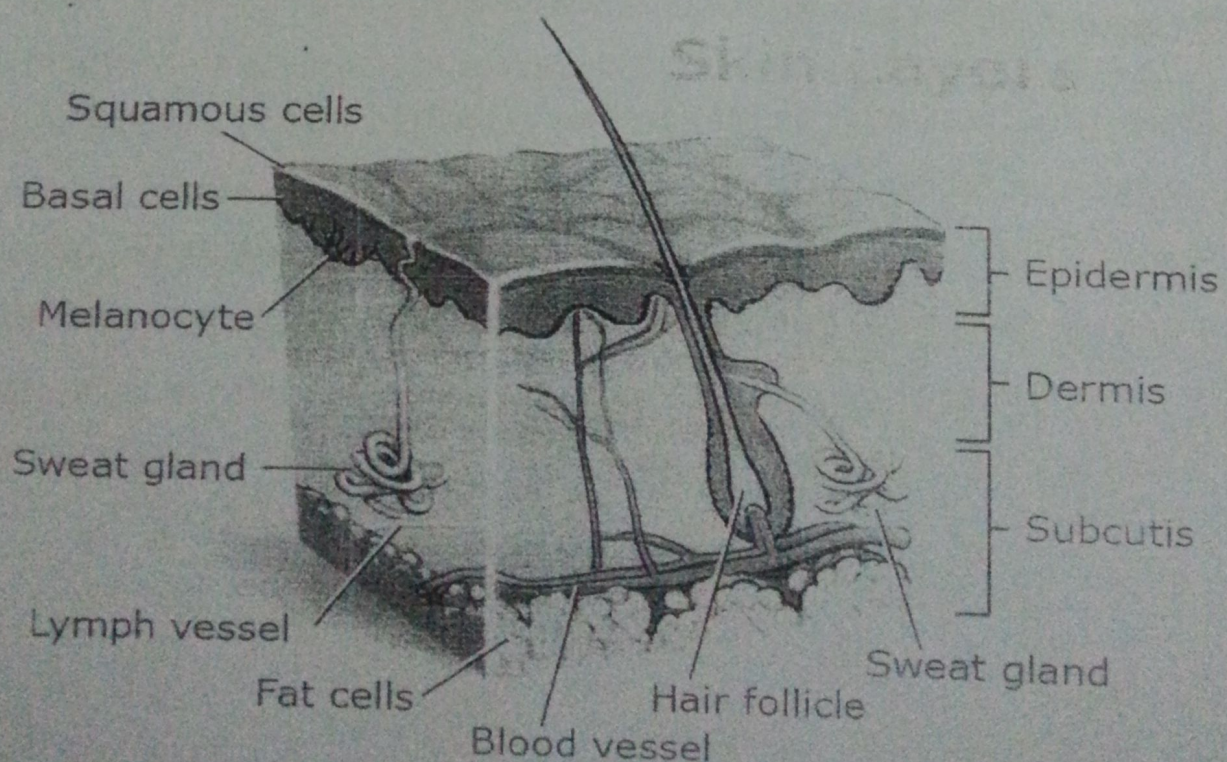
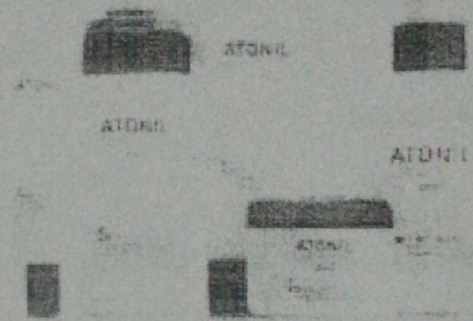


SEMISOLID PREPARATIONS ١٣/٤/٢٠١٤

تقنيات صيدلانية
A

Introduction:

The skin combines with the mucosal linings of the urogenital, digestive and respiratory tracts to protect the internal body structure from a hostile external environment of varying pollution, temperature, humidity and radiation. The skin safeguards the internal organs, limits the passage of chemicals in to and out of the body, stabilizes blood pressure and temperature, and mediates the sensations of heat, cold, touch and pain. It expresses emotions (such as the pallor of fear, the redness of embarrassment and anger, and the sweating of anxiety). The integument identifies individuals through the characteristics particular to humans, e.g. color, hair, odor and texture.



Skin damages easily: mechanically, chemically, biologically and by radiation. Thus the tissue suffers cuts, bruises, burns, bites and stings; detergents, chemical residues, organic solvents and pollutants attack and penetrate the surface; and microorganisms and plants deliver contact allergens. The human skin comprises three tissue layers:

1- The epidermis: the multilayered epidermis varies in thickness, ranging from about 0.8 mm on the palms and soles to 0.006 mm on the eyelids. The epidermis is made of two layers, basal layer (viable) and outer layer (non-viable). The outer layer is called the stratum corneum (S.C.), it is a thick layer of dead epidermal cell and composed of 40% protein (keratin), water and lipids. The high content of keratin in S.C. makes it an efficient barrier for percutaneous absorption.

2- The dermis: the dermis, (or corium), at 3-5 mm thick, consists of a matrix of connective tissue woven from fibrous proteins (collagen, elastin and reticulin) that are embedded in an amorphous ground substance of mucopolysaccharide. Nerves, blood vessels and lymphatic vessels traverse the matrix and skin appendages (eccrine sweat glands, apocrine glands, and pilosebaceous units) pierce it.

3- The subcutaneous tissue: the subcutaneous fat (*subcutis*, *hypoderm*) provides a mechanical cushion and a thermal barrier; it synthesizes and stores readily available high-energy chemicals.

The skin appendages

The *eccrine sweat glands* (2-5 million) produce sweat (pH 4.0-6.8) and may also secrete drugs, proteins, antibodies and antigens. The *apocrine sweat glands* develop at the pilosebaceous follicle to provide the characteristic duct distribution in the armpit (axilla), the breast areola and the perianal region. *Hair follicles* develop over all skin except the red part of the lips, the palms and soles, and parts of the sex organs. One or more *sebaceous glands*, and in some body regions an apocrine gland, open into the follicle above the muscle that

attaches the follicle to the dermoepidermal junction. The *nails*, like hair, consist of 'hard' keratin with relatively high sulphur content, mainly as cysteine.

Routes of Drug Penetration:

Drug may penetrate intact skin after topical application through:

a- S.Co. b- Skin appendages.

Drug could penetrate through the S.C. either by:

1- Transcellular (through the keratinized cells of S.Co.).

2- Intercellular (between the keratinized cells of S.Co.).

After the drug molecules pass the S.Co., these 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.

On the other hand, drug could bypass S.Co. and penetrate the skin appendages which include hair follicles, sebaceous and sweat glands and pass into the general circulation.

In general, if the skin is intact, the main route for the penetration of the drug is through the epidermis layers (S.Co.), rather than the skin appendages where the effect of the appendageal diffusion is usually minimized due to the relatively small fractional area on the skin.

Percutaneous Absorption: is the passage of the drug through the skin into the blood circulation that involves dissolution of a drug in its vehicle, diffusion of solubilized drug from the vehicle to the surface of the skin and penetration of the drug through the layers of the skin principally the S.Co.

Generally, drug absorption into the skin occurs by passive diffusion. The rate of drug transport across the S.Co. follows Fick's law of diffusion which states that:

$$\frac{dm}{dt} = \frac{DC_0K}{h}$$

Where $\frac{dm}{dt}$ is the steady state flux across the S.Co.

D: diffusion coefficient of drug molecules.

C₀: constant concentration of drug in the donor solution.

K: partition coefficient of the drug between the skin and the formulation medium.

h: thickness of the S.Co.

Factors affecting the percutaneous absorption

They can be classified into:

Factors related to the skin:

- 1- *Skin age*: the skin of the fetus, young and elderly are more permeable than adult.
- 2- *Skin condition*: diseases commonly alter the skin condition e.g. inflamed skin with the loss of the S.Co. increase the skin permeability.
- 3- *Skin site*: variation in cutaneous permeability depends on the thickness and nature of the S.Co. and the density of skin appendages

e.g. Hyoscine Transderm system employs at the post auricular skin (i.e. behind the ear) to insert the drug into the blood stream where the layer of the S.Co. are thinner and less dense and there are more sweat and sebaceous glands.

4- *Skin metabolism*: the skin metabolizes some drugs e.g. steroid hormones.

5- Circulatory effect (Blood flow).

6- Species differences.

🍏 Factors related to the drug:

1- *Drug concentration*: the amount of the drug absorbed increased as the concentration of the drug in the vehicle is increased.

2- *Surface area*: more drugs are absorbed when they applied to a large surface area.

3- *Partition coefficient*: the drug substances should have a greater physicochemical attraction to the skin than to the vehicles in which it is presented (high p.c.) in order for the drug to leave the vehicle in favor of the skin.

4- *Diffusion coefficient of the drug*.

🍏 Factors related to the vehicles:

- Drug absorption appears to be enhanced from vehicles that easily cover the skin surface, mix readily with the sebum and bring the drug into contact with the tissue cell for absorption.

- Vehicles that increase the hydration of the skin generally favor the percutaneous absorption of drugs.

- Vehicles that increase the temperature of the skin like occlusive vehicles may effect on the absorption.

Pharmaceutical semisolid preparations may be defined as topical products intended for



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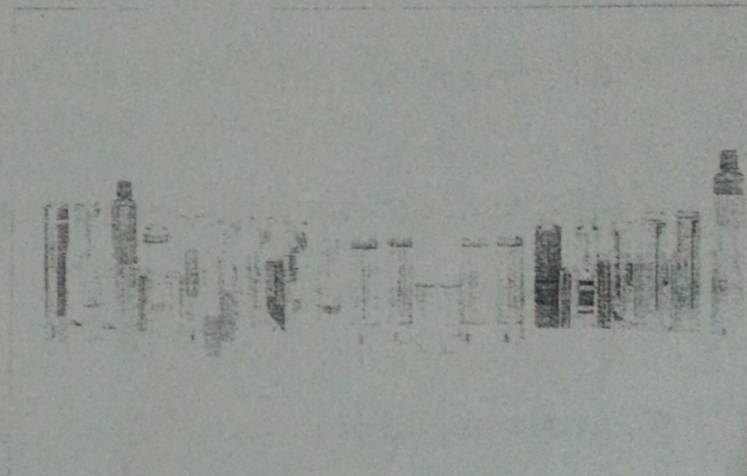
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application on the skin or accessible mucous membranes to provide localized and sometimes systemic effects at the site of application. Ointments, creams, and gels are semisolid dosage forms intended for topical application. They may be applied to the skin, placed onto the surface of the eye, or used nasally, vaginally or rectally. The majority of these preparations are used for the effects of the therapeutic agents they contain. Those which are nonmedicated are used for their physical effects as protectants or lubricants.

Ideal Properties of Semisolid Dosage Forms

Physical Properties:

1. Smooth texture.
2. Elegant in appearance.
3. Non- dehydrating.
4. Non- gritty.
5. Non greasy and non-staining.
6. Non hygroscopic.



Physiological Properties:

1. Non- irritating.
2. Do not alter membrane / skin functioning.
3. Miscible with skin secretion.
4. Have low sensitization effect.

Application Properties

1. Easily applicable with efficient drug release.
2. High aqueous washability.

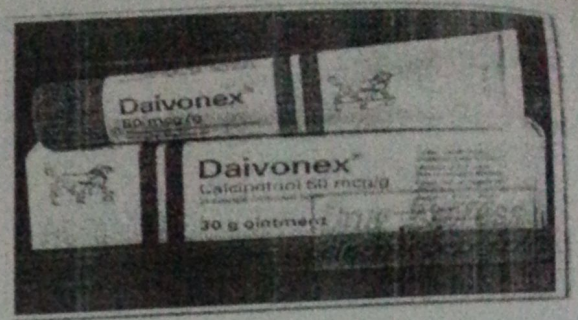
Ointments

Ointments are semisolid preparations intended for external application to the skin or mucous membranes.

Ointments may be medicated or nonmedicated.

Nonmedicated ointments are used for the physical

effects that they provide as protectants, emollients or lubricants. Ointment bases may be used for their physical effects or as vehicles in the preparation of medicated ointments. Properties of ointments may vary from product to product depending on their specific use, ease, and extent of application.



In general, ointment bases may be classified into four general groups:

- ✓ Hydrocarbon bases.
- ✓ Absorption bases.
- ✓ Water-removable bases.
- ✓ Water-soluble bases.

Hydrocarbon Bases

Hydrocarbon bases are also termed *oleaginous bases*. On application to the skin, they have an emollient effect, protect against the escape of moisture from the skin to the atmosphere, can remain on the skin for prolonged periods of time without "drying out", and because of their immiscibility with water are difficult to wash off. They act as occlusive dressings, thus increasing skin hydration by reducing the rate of loss of surface water.

Water & aqueous preparations may be incorporated into them, but only in small amounts and with some difficulty.

Common examples of these bases include: *Petrolatum*, *White petrolatum*, *White & Yellow ointment*. When powdered substances are to be incorporated into hydrocarbon bases, liquid petrolatum (mineral oil) may be used as the levigating agent.

1. Petrolatum, USP, is a purified mixture of semisolid hydrocarbons obtained from petroleum. It is an unctuous mass, varying in color from yellowish to light amber. It melts at temperatures between 38 and 60°C and may be used alone or in combination with other agents as an ointment base.

2. White petrolatum, USP, is a purified mixture of semisolid hydrocarbons from petroleum that has been decolorized, either partially or wholly. It is used for the same purpose as petrolatum, but due to its lighter color it is considered more esthetic by some pharmacists and patients. White petrolatum is particularly useful to treat diaper rash and dry skin.

3. Yellow ointment, USP, this ointment has the following formula for the preparation of 1000g:

Yellow Wax	50g
Petrolatum	950g

Thus, it contains 5% yellow wax and 95% petrolatum in the formulation.

Yellow wax is the purified wax obtained from the honeycomb of the bee. The ointment is prepared by melting the yellow wax on a water bath, adding the petrolatum until the mixture is uniform, then cooling with stirring until congealed. The ointment also has been called "Simple Ointment".

4. White ointment, USP, this ointment differs from Yellow Ointment by substituting White Wax (bleached & purified Yellow Wax) and White Petrolatum in the formula.

5. **Mineral oil**, it is a mixture of liquid hydrocarbons obtained from petroleum. These are useful as levigating agents to wet and incorporate solid substances (e.g., salicylic acid, zinc oxide) into the preparation of ointments that consist of oleaginous bases as their vehicle.

Absorption bases

Absorption bases are of two types:

1. Those that permit the incorporation of aqueous solutions resulting in the formation of water-in-oil (w/o) emulsions (e.g., Hydrophilic Petrolatum).
2. Those that are water-in-oil (w/o) emulsions (emulsion bases) and permit the incorporation of additional quantities of aqueous solutions (e.g., Lanoline).

These bases are useful as emollients, although they do not provide the degree of occlusion as oleaginous bases. They are also used pharmaceutically to incorporate aqueous solutions of drugs (e.g., sodium sulfacetamide solution) into oleaginous bases. This is accomplished by incorporating the aqueous solution into the absorption base and then incorporating this mixture into the hydrocarbon base.

Absorption bases are not easily removed from the skin with water washing since the external phase of the emulsion is oleaginous.

A typical example of an anhydrous absorption base is **hydrophilic petrolatum, USP**, which has the following formula for the preparation of 1000g:

White Petrolatum	860g
Cholesterol	30g
Stearyl alcohol	30g
White wax	80g

It is prepared by melting the stearyl alcohol and the white wax together on a steam bath. then add the cholesterol and stir until it completely dissolves. Add the white petrolatum and mix then allowing the mixture to cool and stir until mixture congeals.

A commercially available absorption base includes Aquaphor, is a variation of Hydrophilic Petrolatum and has the capacity to absorb up to three times its weight in water.

Anhydrous lanolin, USP, obtained from the wool of sheep, is a purified, wax-like substance that has been cleaned, deodorized, and decolorized. It contains not more than 0.25% water. Additional water may be incorporated into lanoline by mixing. Its water-absorbing capacity is improved to 50% by the addition of cholesterol.

Among the absorption bases, lanolin is the oldest and best known. However, because of its tackiness and viscous nature and reports of allergic reactions, the use of lanolin is very limited.

Absorption bases, either hydrous or anhydrous, are seldom used as vehicles for commercial drug products because the w/o emulsion is more difficult to handle than the more conventional o/w system, and also there is reduced patient acceptance because of greasiness.

Cold Cream, it is a semisolid, white, w/o emulsion prepared with cetyl esters wax, white wax, mineral oil, sodium borate, and purified water. Cold cream is employed as an emollient and ointment base.

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 skin or clothing with water and are often called "water-washable" bases. They may contain water-soluble and -insoluble components. From a therapeutic viewpoint, they have the ability to absorb serous discharges in dermatologic conditions. The water-removable bases form a semipermeable

film on the site of application after the evaporation of water. As such, the base consists of three component parts: the oil phase, the emulsifier, and the aqueous phase. The oil phase, also called the internal phase, is typically made up of the petrolatum and/or liquid petrolatum. Other ingredients such as cetyl and stearyl alcohol may be added to make up the oil phase.

A typical water-removable emulsion base is **hydrophilic ointment, USP** which has the following formula for the preparation of 1000g:

Stearyl alcohol	250g
White petrolatum	250g
Methylparaben	0.25g
Propylparaben	0.15g
Sodium lauryl sulfate	10g
Propylene glycol	120g
Purified water	370g

In the preparing the ointment, the stearyl alcohol and white petrolatum are melted together at about 75°C. Add the other ingredients previously dissolved in purified water and warmed to 75°C, and stir mixture until it congeals.

Sodium lauryl sulfate used as the emulsifying agent, with stearyl alcohol & white petrolatum representing the oleaginous of the emulsion while propylene glycol and water representing the aqueous phase. Methylparaben and Propylparaben are used to preserve the ointment against microbial growth.