

Semisolid dosage form

LEC 1 , LEC 2

Assistant lecturer : Hiba Sabah Sabry

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Pharmaceutical semisolid preparations

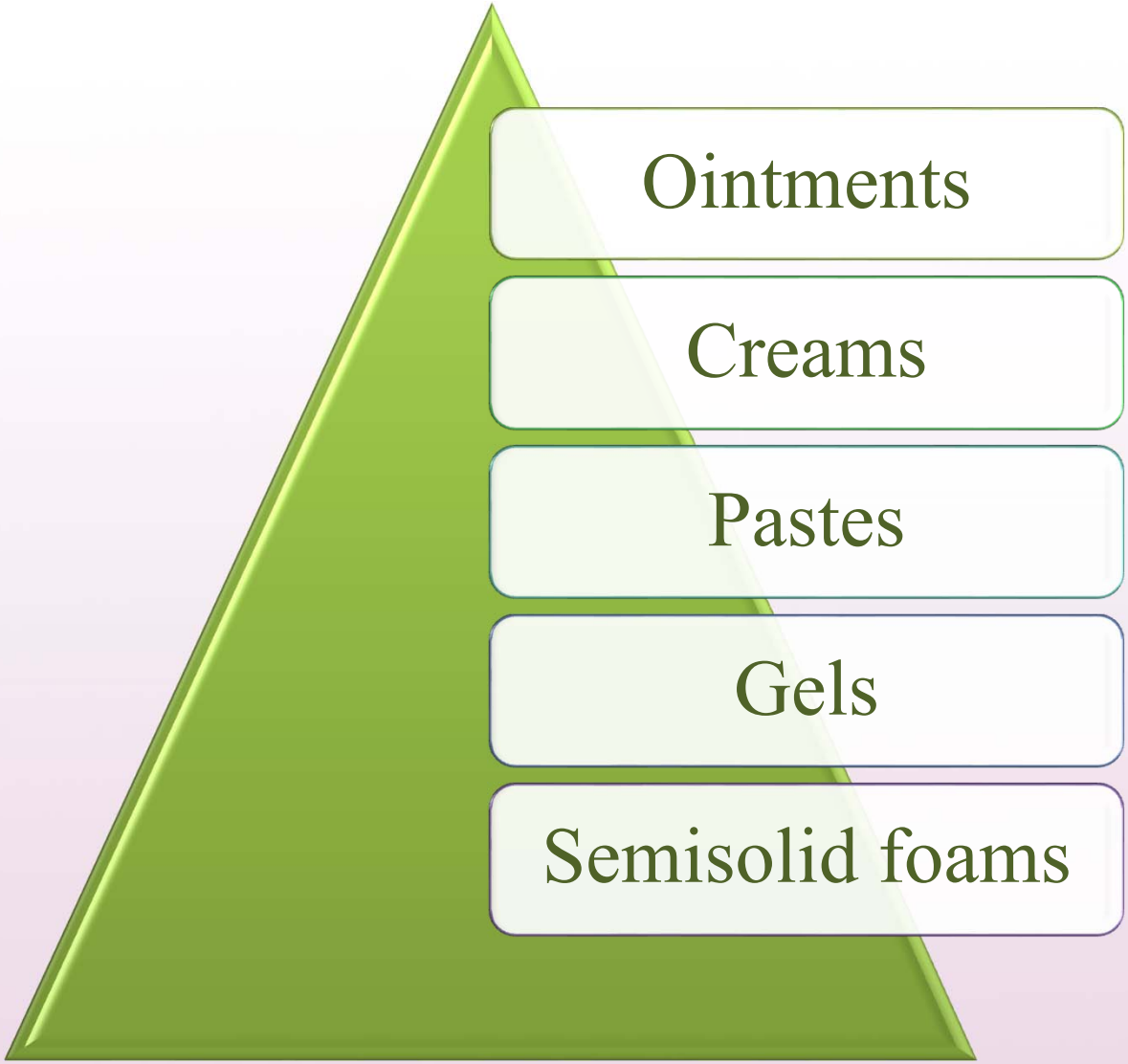
Are products of semisolid consistency that applied to the skin for therapeutic, protective action or cosmetic function.

the common property

the ability to cling to the surface of application for reasonable duration before they are washed or worn off due to **their plastic rheological behavior,** which allows the semisolids to retain their shape and cling as a film until acted upon by an outside force, in which case they deform and flow.

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Types of Semisolid Dosage Form



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Ointments

Ointments, in general, are composed of fluid hydrocarbons meshed in a matrix of higher melting solid hydrocarbons. While most ointments are based on mineral oil and petrolatum, there are alternative types:

- Polyethylene can be incorporated into mineral oil to yield a plastic matrix (e.g., Plastibase).
- Mixtures of polyethylene glycols can yield products of ointment consistency that are water-soluble.

Preparation of ointments

Most ointments are prepared by melting the components together. Drugs or other components are added in the fluidized state. If the solids are insoluble and to be suspended, the system is put through a milling process (a colloid mill, homogenizer, or ultrasonic mixer) so that the solids are fully dispersed.

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Creams

Creams are semisolid emulsion systems with opaque appearances, as contrasted with translucent ointments. Their consistency and rheologic character depend on whether the emulsion is a water-in-oil or oil-in-water type and on the nature of the solids in the internal phase.



Pastes

Pastes are basically ointments into which a high percentage of insoluble solids has been added. Pastes are usually thick and stiff. They are valuable as protective barriers on the skin, such as for treating diaper rash or protecting the face and lips from the sun.

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Preparation of pastes

Pastes are usually prepared by incorporating a solid directly into a congealed system by levigation with a portion of the base to form a paste-like mass. The remainder of the base is added with continued levigation until the solids are uniformly dispersed in the vehicle.



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Gels

are semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix (consisting of natural or synthetic gums) in which a high degree of physical (or sometimes chemical) cross-linking has been introduced.

Polymers used to prepare pharmaceutical gels

natural gums tragacanth, pectin, carrageen,

agar and alginic acid

synthetic and semisynthetic materials as methylcellulose, carboxy methyl cellulose and carbopols(which are synthetic vinyl polymers with ionizable carboxyl groups.

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Gels are prepared by either a fusion process or a special procedure necessitated by the gelling characteristics of the gellant. Gels are a relatively newer class of dosage form formed by entrapment of high amounts of aqueous or hydro alcoholic liquid inside a network of colloidal solid particles.

Within the major sets of semisolid preparations, the usage of transparent gels have extended both in cosmetics and in pharmaceutical preparations



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Semisolid foams





Foam is system made by trapping air or gas bubbles inside a solid or liquid. Typically, the volume of gas is much larger than that of the liquid or solid, with thin films separating gas pockets.

How Foam Forms?

Three requirements must be met in order for a foam to form. Mechanical work is needed to increase surface area. This can occur by agitation, dispersing a large volume of gas into a liquid, or injecting a gas into a liquid. The second requirement is that surfactant or surface active agent must be present to decrease surface tension. Finally, the foam must form more quickly than it breaks down.

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Application of semisolid preparation

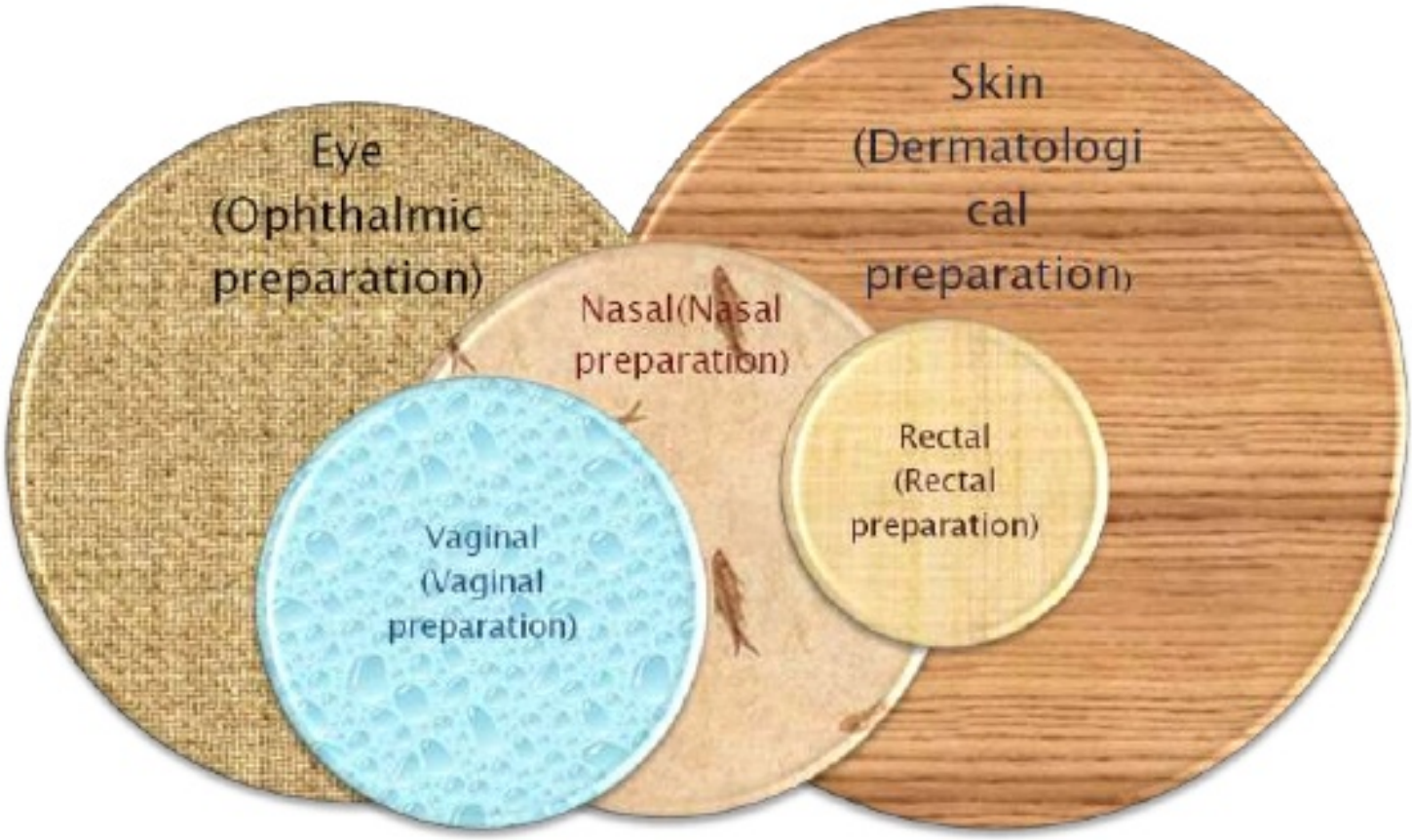
The bulk of these semisolid preparations are applied to the skin, where they usually serve as

1. **Vehicles for topically applied drugs (betamethasone topical foam vehicle)**
2. **Emollients (creams & gels)**
3. **Protective or occlusive dressing (ointments & pastes)**

- A lesser portion of topical semisolid dosage forms are applied to mucous membranes, such as rectal tissue, buccal tissue, vaginal mucosa, urethral membrane, external ear lining, nasal mucosa, and cornea. The mucous membranes permit more ready access to the systemic circulation, whereas normal skin is relatively impenetrable.

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Semisolid dosage forms intended for topical application



Skin

the skin is a large multilayered organ that covers outside of the body and it presents ideal and multiple sites for administration of therapeutic agents for both local and systemic actions.

Functions of skin

- The skin serves as a barrier against physical and chemical attack.
- The skin acts as a thermostat in maintaining body temperature.
- It shields the body from invasion by micro organisms
- It protects against ultraviolet rays
- plays a role in the regulation of blood pressure.

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Some materials, such as nickel ions and mustard gas, commonly known as poison ivy, can penetrate the barrier of skin.

Skin generally consists of three parts, namely

1) The outer epidermis (waterproof layer).

2) The inner dermis which consists of connective tissue, blood vessels, hair follicles, sweat glands.

3) Hypodermis (subcutaneous tissue) which consists of delicate connective tissue.

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Epidermis

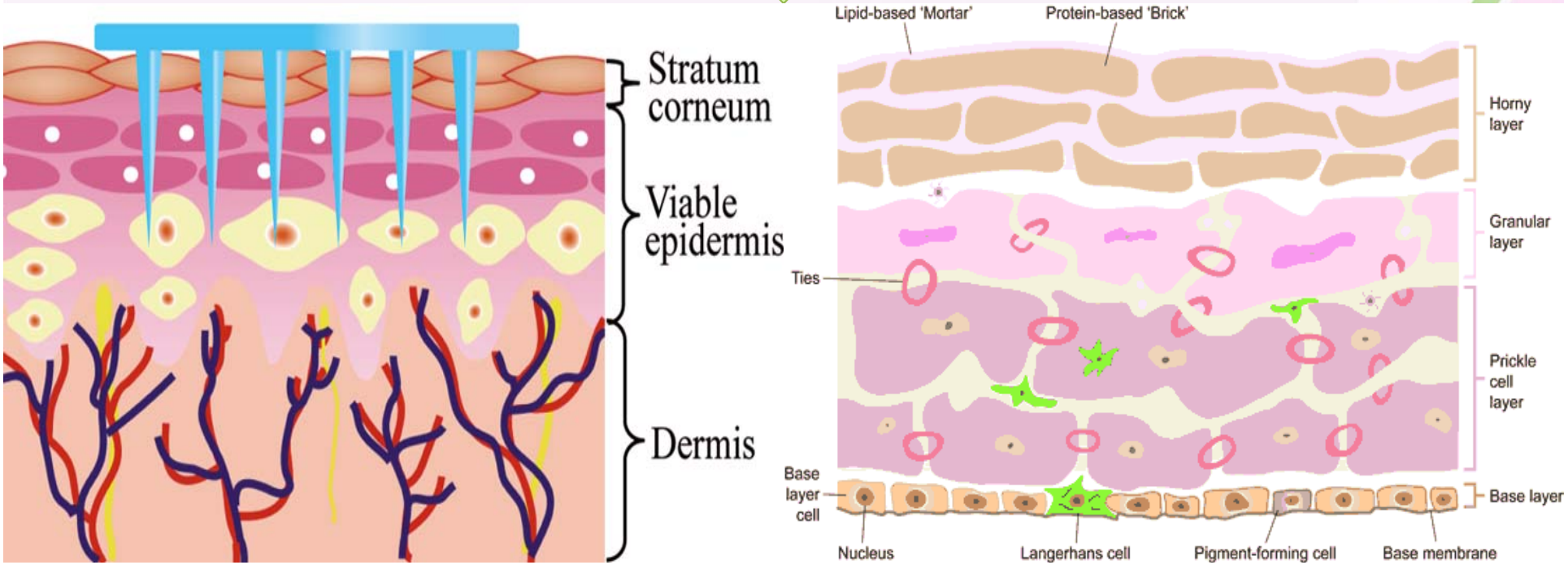
The outermost layer is the stratum corneum, or horny layer, which consists of compacted, dead, keratinized cells in stratified layers with a density of 1.55. Because of the dense nature of the stratum corneum, **values of diffusion coefficients in this tissue are a thousand or more times smaller than in any other skin tissue,** which results in higher resistance and general impenetrability.

The stratum corneum is the rate-limiting barrier that restricts the inward and outward movement of chemical substances.

The stratum corneum exhibits regional differences in thickness over the body. It is as thick as several hundred micrometers on the palms of the hand and soles of the feet in an adult.

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Beneath the stratum corneum are the metabolically active layers of the epidermis(viable epidermis), the basal or germinal layer lies right above the dermis. Epidermal cells start their mitotic journey upward to the surface; the cells flatten and shrink as they slowly die from lack of oxygen and nutrition.



dermis

Is the layer of skin beneath the epidermis that is characterized by lots of elastin fibers which provide the stretching ability as well as lots of collagen that provides the strength to the skin.

- Dermis also plays a major role in temperature regulation.
- Nerves are present and they are responsible for pressure and pain sensations.
- It also contains the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels.

The blood vessels in the dermis supply nourishment and removal of the waste from its own cells as well as for the epidermis.

- Dermis has a thickness of 3-5 mm.

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hypodermis

The hypodermis is the layer that lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle. It consists of loose connective tissue and elastin. The main cell types are fibroblasts, macrophages and adipocytes, the hypodermis contains 50% of body fat, Another name for the hypodermis is the subcutaneous tissue.

Percutaneous Absorption

The usual object of dermatologic drug therapy is to produce a desired therapeutic action at specific sites on the epidermal tissue.

Most dermatological preparation belong to one of two classes:

1. Certain topical drugs act primarily on the surface of the skin such as emollients, antimicrobials, and deodorants
2. Certain topical drugs intended to penetrate the skin to the viable epidermis or upper dermis. This requires diffusive penetration of the skin or percutaneous absorption.

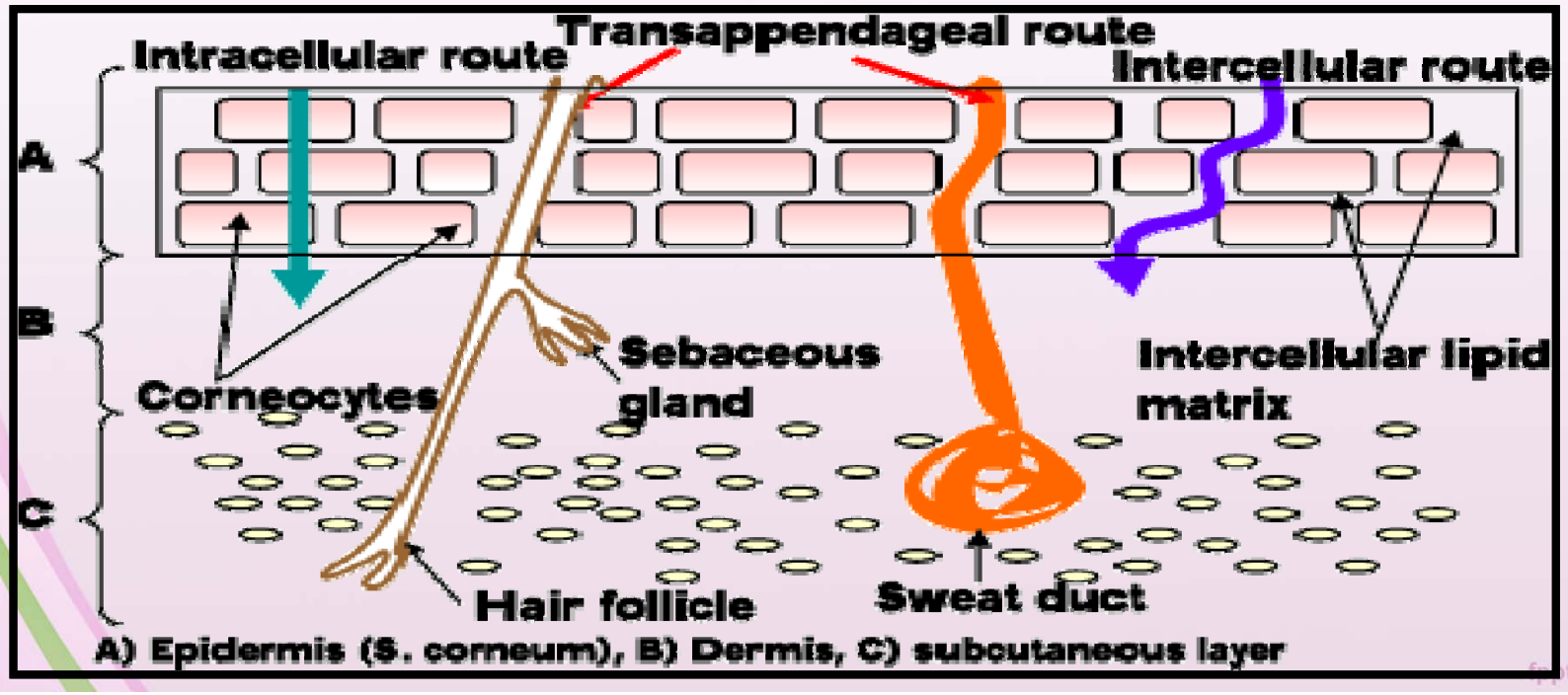
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When a drug system is applied topically (drug + vehicle) → the drug diffuses out of its vehicle → onto the surface tissues of the skin.

Mechanisms of Absorption through Skin:

Permeation can occur by diffusion via:

- A-Intracellular (Transdermal) permeation, through the stratum corneum.
- B-Intercellular permeation, between cells of the stratum corneum.
- C-Trans appendage permeation, via the hair follicle, sebaceous and sweat glands



A. Intracellular Permeation (Transcellular): The chemical is transferred by intracellular route through corneocytes cells that containing highly hydrated keratin and they are surrounded by a lipid envelope which connects the cells to the interstitial lipids. These keratinized skin cells are separated by multiple lipid bilayers; therefore the diffusion pathway for a chemical via the transcellular route requires a number of partitioning and diffusion steps. After partitioning into and diffusing through the relatively aqueous corneocytes, the drug must partition into the surrounding lipid envelope, and subsequently partition in and out of the multiple lipid bilayers separating corneocytes

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B. Intercellular permeation: The chemical is transferred around the corneocytes in the lipid-rich extracellular regions. The lipid lamellae of the intercellular spaces (each one including two or three bilayers and made mainly of ceramides, cholesterol, and free fatty acids).This yield a tortuous pathway for intercellular drug permeation, Most solute substances penetrate across intercellular lipid pathways.

C. **Follicular (Transappendageal) permeation:** The chemical bypasses the corneocytes, entering the shunts provided by the hair follicles, sweat glands, and sebaceous glands. Skin appendages impart a continuous channel directly across the stratum corneum barrier. However, their effect on drug penetration is impeded by a number of factors such as limiting the area available for direct contact of the applied drug due to small surface area that occupied by hair follicles and sweat ducts (typically 0.1% of skins surface area); therefore such pathway is limited.

The particular route that a substance may take depend almost entirely on the

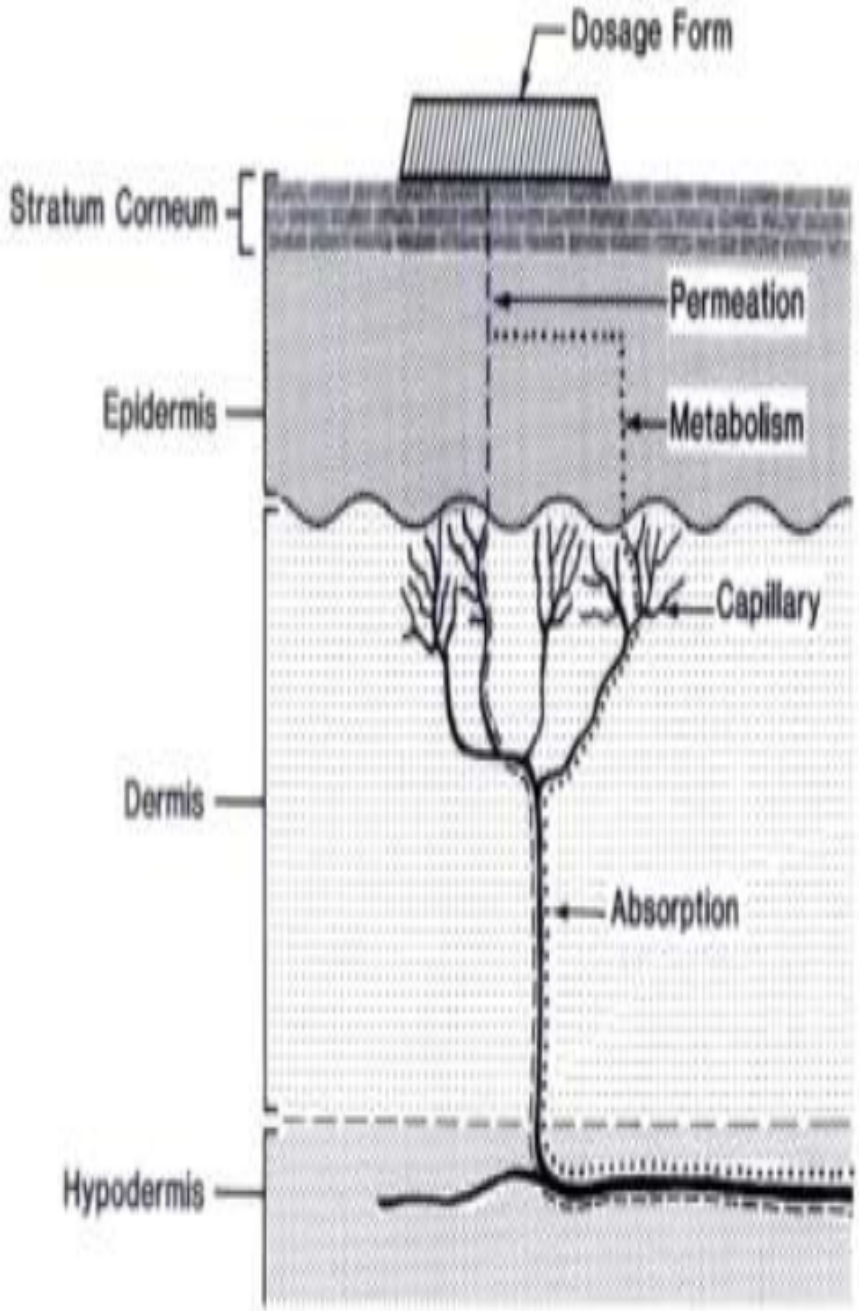
- physicochemical properties of the drug, vehicle, pH and concentration.
- The condition of the skin whether it is intact or injured and skin age.

Under the appropriate conditions, the transient diffusion that occurs shortly after the application of a substance to the surface of the skin is shown to be potentially far greater through the appendages than through the matrix of the stratum corneum. After steady-state diffusion has been established, the dominant diffusion mode is probably no longer intra-appendageal, but occurs through the matrix of the stratum corneum.

Note: The recognition of transient diffusion, occurring primarily via follicles and ducts, and steady-state diffusion, occurring primarily through the intact stratum corneum, results in a considerably more self-consistent and orderly treatment of the process of percutaneous absorption.

- Once a substance passes through the stratum corneum, there is apparently no significant further hindrance to penetration of the remaining epidermal layers and corium; there is then a ready entry into the circulation via the capillaries. The concentration gradient essentially ends in the dermal layer at the beginning of the circulation. The systemic circulation acts as a reservoir or "sink" for the drug. Once in the general circulation, the drug is diluted and distributed rapidly with little systemic buildup.
- Diffusion through the stratum corneum is a **passive process**. There is little evidence to support specialized active transport systems for cells of the stratum corneum. The passive process is affected **only**
  - by the substance being absorbed.
  - by the medium in which the substance is dispersed.
  - by ambient conditions.

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Percutaneous absorption is a more complicated process, of which epidermal diffusion is the first phase, and clearance from the dermis the second.

The latter depends on effective blood flow, interstitial fluid movement, lymphatics, and perhaps other factors that combine with dermal constituents.

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FACTORS AFFECTING PERMEABILITY OF A DRUG THROUGH SKIN

A. Factors associated with the skin

(1)Hydration of the horny layer

Hydration results from water diffusing from underlying epidermal layers or from perspiration that accumulates after application of an occlusive vehicle or covering on the surface. Under occlusive conditions, the stratum corneum is changed from a tissue that normally contains little water (5 to 15%) to one that contains as much as 50% water. The clinical importance of hydration can be found in the use of occlusive plastic film in steroid therapy. Here, the prevention of water loss from the stratum corneum and the subsequent increased water concentration in this skin layer apparently enhances the penetration of the steroid.

(2)Thickness of the horny layer

The horny layer is thickest on palms and soles and thinnest on the face; penetration rate increases with decreased thickness of horny layer.

(3)Skin condition

The permeability of the skin is affected by age, disease and injury. For example, absorption occurs rapidly in children and if the dermis is exposed by a wound or burn.

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B. Factors associated with the medicament

(1)Solubility of the drug

The solubility of a drug determines the concentration presented to the absorption site, Highly lipid soluble molecules enters through hair follicles. Moderately lipid and aquous soluble molecules penetrates directly across the horny layer.

(2)Partition coefficient

lipid/water partition coefficient influences the rate of transport.

(3) molecular weight

An inverse relationship appears to exist between the absorption rate and the molecular weight. Small molecules penetrate more rapidly than large molecules, but within a narrow range of molecular size, there is little correlation between the size and the penetration rate. Materials of higher molecular weight also show variable penetration. Very large molecules, such as proteins and ,polysaccharides, go through poorly, if at all.

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C. Factors associated with vehicles

1) The efficiency of various types of vehicles in aiding penetration can be reasonably predicted by the way in which the vehicle alters the activity of water in the stratum corneum and influences the stratum corneum/vehicle partition coefficient.

The rate of release of a drug from a vehicle to stratum corneum is governed by vehicle to *stratum corneum partition coefficient.*

- ❖ Greases and oils are the most occlusive vehicles and induce the greatest hydration through sweat accumulation at the skin-vehicle interface. This is accentuated if the skin is covered with occlusive bandages or plastic.
- ❖ Emulsions of the water in- oil type are somewhat less occlusive than greases.
- ❖ Substances in the vehicle, such as humectants, which have a high affinity for water, may under certain circumstances dehydrate the stratum corneum and decrease penetration.
- ❖ powders increase the surface area and increase the rate of evaporation of water, and so decrease the extent of hydration.

2) vehicles may also affect penetration by their ability to reduce loss of water vapor on the skin surface.

❖Paraffin bases suppress transepidermal water diffusion

3) the influence of components in the vehicle on the movement of the drug through the skin.

The thermodynamic activity of the drug in the vehicle is the product of the concentration of the drug and the activity coefficient of the drug in the vehicle.

A. Solutes that held firmly by the vehicle, such as those occurring when the drug forms a soluble. Complex with the vehicle, exhibit low activity coefficients: hence, the rate of release from such drug-vehicle combinations is slow.
B. Solutes held "loosely" by the vehicle (with less affinity of the vehicle for the drug or solute) exhibit high activity coefficients; therefort, the rate of release from such drug-vehicle combinations is fast.

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Accelerants: Materials have been experimentally used to increase the rate of absorption of topically applied drugs.

Mechanism of action

These agents appear to swell the stratum corneum and leach out essential structural material, thus reducing the diffusional resistance and increasing the permeability.

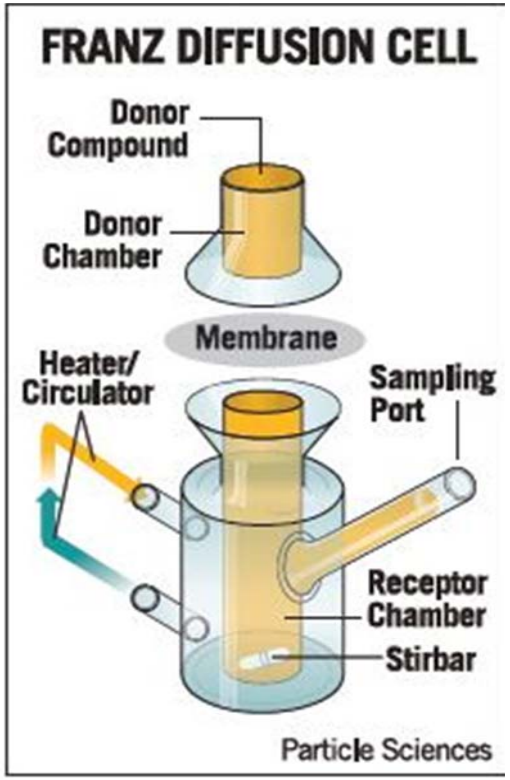
The most effective is dimethylsulfoxide (DMSO) followed by dimethylformamide (DMF), dimethylacetamide (DMA), urea, propylene glycol, and surface-active agents.

- DMSO, DMF, and DMA are all strongly hygroscopic which increases the hydration of the tissue of stratum corneum and therefore its permeability. These agents are currently restricted to experimental use.
- Surface- active agents appear to increase the permeability of the skin to water by altering the physical state of water in the skin in such a way as to permit greater freedom to the passage of charged hydrophilic substances, laurate ion (anionic surfactant) is reported to have the greatest penetration effect.

Study Methods

In Vitro Technique.

1. Studying drug skin penetration by using (FRANZ diffusion cell) in which human or animal skin is fastened to a holder and the passage of compd. form epidermal surface to a fluid path is measured. Then as the drug penetrate sufficiently, it can be determined by physical or chemical analysis.



2. Model system that do not use membranes but instead they used solvents. In donor chamber **(alcohol-water)** fairly soluble the drug. While receptor chamber **(sink phase)** contain **chloroform and isopropyl myristate** which are immiscible with alcohol-water but they act to receive penetrant after release form vehicle (affected by solubility of drug in the solvent with minimum conc. And the P.C. of drug between vehicle and receptor phase).

In vivo technique

Major histological methods (histological techniques):

1. Tracers
2. Analysis of body tissues and fluids
3. Elicitation of biologic response

1) Tracers:

Application of dyes and small no. of substances (fluorescence and radioactive labeling)

Specific tissue changes in skin (absorption and penetration)

Perceivable colored end product with specific chemical reaction

Give information about the amount of compd. moves across the skin (but not route of penetration or localization of penetrant within the skin).

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2) Analysis of body tissues and fluids

Urine analysis (will not necessarily give an indication for the original material or the amount of material penetrating the skin)

Since

some materials will not gone to urine but may be metabolized and no longer detected .

(a steady-state between absorption and excretion need to be reached before measurement).

3) Elicitation of a biologic response (simple and practical)

Use of topical agents elicit a physiologic reaction when they reach the dermis (demonstrate penetration and time required for reaction to occur)

Appear as

Sweat secretion, vasoconstriction, vasodilation, pigmentation and vascular permeability (with visual observation).

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Raw Materials

The raw materials are available for skin use> oral use > parenteral use.

The difference in the number of materials available for each route of administration is due to the type of absorption barrier and physicochemical environment surrounding the absorption sites.

Examples: isopropyl myristate and butyl stearate may be used topically without toxic effects, yet these esters may not be used orally, because hydrolysis of the esters by digestive enzymes yields poorly tolerated alcohols. The absence of comparable hydrolytic enzymes on the skin surface makes these compounds satisfactory for dermatologic medication.

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The Federal Food and Drug Administration (FDA) approves chemical substances and states the

1. maximum concentration that is considered to be used.
2. safety for using in a particular food or cosmetic.
3. Biological properties.
4. Physicochemical properties.
5. Stability on storage.

❖ All raw materials should be checked against this list if there is any doubt regarding the current status of a particular substance.

Several tests should be thorough and well designed for these substances:

1. human patch tests,.
2. eye irritation studies.
3. Determination of minimum lethal dose on at least two animal species
4. chronic toxicity studies.

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Examples of raw materials used in semisolids

emollients	water absorption bases	fats
waxes	oils	Cellulose derivatives
Humectants	Emulsifiers	lanolin derivatives

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A fundamental concept in formulating of any dosage form:

1. chemical and physical incompatibilities that affect the therapeutic efficacy of a drug must be avoided.
2. the physicochemical properties of the drug must be evaluated.
3. The stability of the active substance under alkaline or acidic conditions can be established from its pH profile.
4. The sensitivity of the drug to oxidation and reduction, moisture, and light.
5. the solubility of drug in various materials, indicate the type of base most suitable for the stability of the drug and for its absorption.
6. Compatibility with the container is of equal importance, and it is necessary to conduct stability studies of the product in the finished container.

Perfumes generally are not included in the semisolid formulations for the treatment of a skin condition in view of the danger of sensitization, irritation and toxicity.

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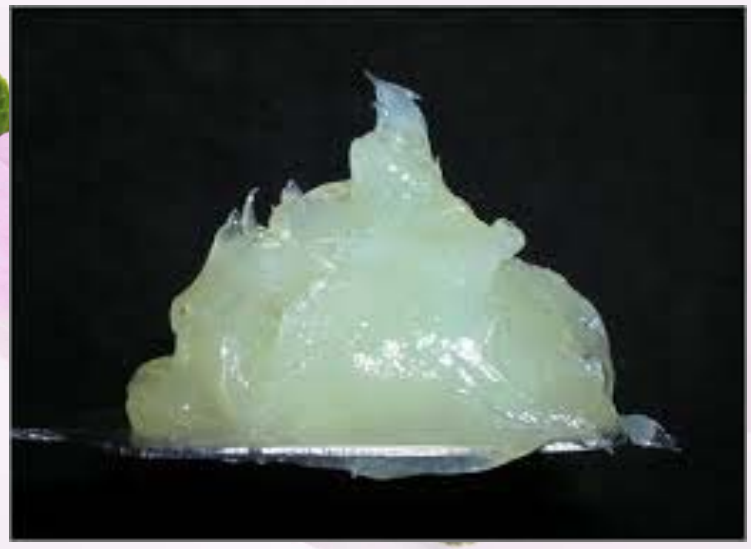
Raw materials

A) Hydrocarbons (Petrolatum and Mineral oil)

Except for water, petrolatum and mineral oil are perhaps the most widely used substances in semisolids.

1. **Petrolatum (Soft paraffin -Yellow and white)**

is a complex mixture of semisolid hydrocarbons, containing aliphatic, cyclic, saturated, unsaturated, branched, and unbranched substances in varying proportions.





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- Petrolatum is available in the form of a short or long "fiber.“
- The type of fiber possessed by the petrolatum is usually determined by dipping the index finger into the petrolatum sample and then withdrawing it slowly. The long fiber type tends to form a transparent continuous film while the short fiber variety ruptures easily and does not exhibit this film.
- The long fiber petrolatum is preferred for an occlusive dressing because of the continuous film it forms over the surface of the skin.

2. Mineral oil is obtained from petroleum, as is petrolatum, by collection of a particular viscosity- controlled fraction. It is produced in many viscosity and specific gravity ranges. The lower viscosity oils are preferred for semisolids, since they are less tacky and greasy.

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B) Hydrocarbons Waxes

Hydrocarbon waxes frequently are employed in the manufacture of creams and ointments **to increase the viscosity of mineral oil in order to prevent its separation from an ointment.**

- ❖ Ozokerite is a mined wax.
- ❖ Paraffin wax is obtained from petroleum.
- ❖ Ceresin, which is a (mixture of ozokerite and paraffin wax).

Synthetic waxes

Synthetic wax have been developed from vegetable oils and naturally occurring waxes by a process of hydrogenation and catalytic splitting that involves long C18-C36 hydrocarbon chains.

- ❖ The are chemically closely related to the naturally occurring waxes in that they contain long chain wax fatty acids, they may be used in conjunction with or can replace the natural waxes in some formulations to achieve certain desired properties.

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Synthetic waxes

- They Exhibit thermoplastic, crystalline properties.
- They can be used in formulating synthetic petrolatum with occlusive properties to help moisturize the skin without the inelegant properties of natural petrolatum. Example (synchrowaxes).



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C) Oleaginous Substances

Vegetable oils such as peanut oil, almond oil, sesame oil, and olive oil are mono-, di-, and triglycerides of mixtures of unsaturated and saturated fatty acids.

Trace metal contaminants in the oils may catalyze oxidation reactions

The oxidation reaction can be prevented by the addition of antioxidants, such as butylated hydroxyanisole, butylatedhydroxy toluene , or by the addition of metal chelating agents such as salts of EDTT

Antioxidants may produce problems of drug compatibility or dermal sensitivity in some patients

Isolation and synthesis of pure chemical entities present in vegetable oil that effect on quality of emulsion and release of a drug from a base. that is rigidly controlled


Thank
You!