Topical Skin Preparations

Dermatological products are products designed to be applied onto the skin to achieve either a local or systemic effects.

Dermal Products : Localized effects
Transdermal Products: Systemic effects

Examples

Ointments, creams, lotions, pastes, gels, aerosols, transdermal drug delivery systems like transdermal patches

Uses

1 Physically as skin protectants, lubricants, emollients...

2 Medical applications

1 Locally: for skin infections, itching, burns, diaper rash, insect stings and bites, athlete's foot, calluses, warts, dandruff, acne, psoriasis, eczema.

2 Systemically: hypertension, psychosis….

FUNCTIONS OF THE SKIN

1 Protective functions:

the skin is to act as a barrier. The skin provides protection from: mechanical impacts and pressure, variations in temperature, micro-organisms, radiation and chemicals.

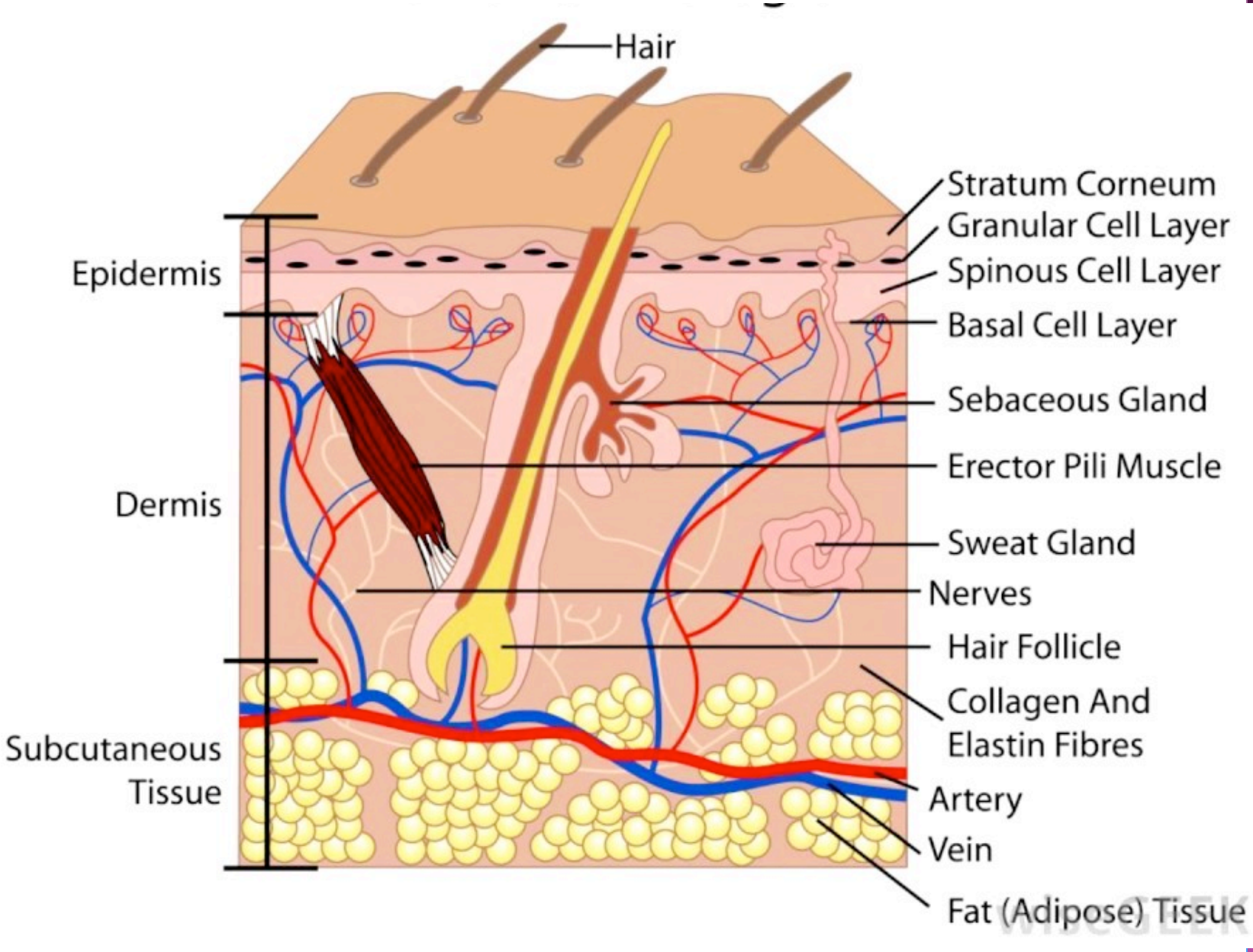
2 Regulatory functions:

The skin regulates several aspects of physiology, including: body temperature via sweat and hair, and changes in fluid balance via sweat. It also acts as a reservoir for the synthesis of Vitamin D.

3 Sensory Functions:

The skin contains an extensive network of nerve cells and separate receptors for heat, cold, touch, and pain. Damage to these nerve cells is known as neuropathy, which results in a loss of sensation in the affected areas.

STRUCTURE OF THE SKIN



STRUCTURE OF THE SKIN

Skin is composed of two main layers in addition to the underlying hypodermis or subcutaneous fatty layer:

I. Epidermis

1-stratum corneum

It is the outermost layer of the skin and constitute the major barrier for any drug diffusion process.

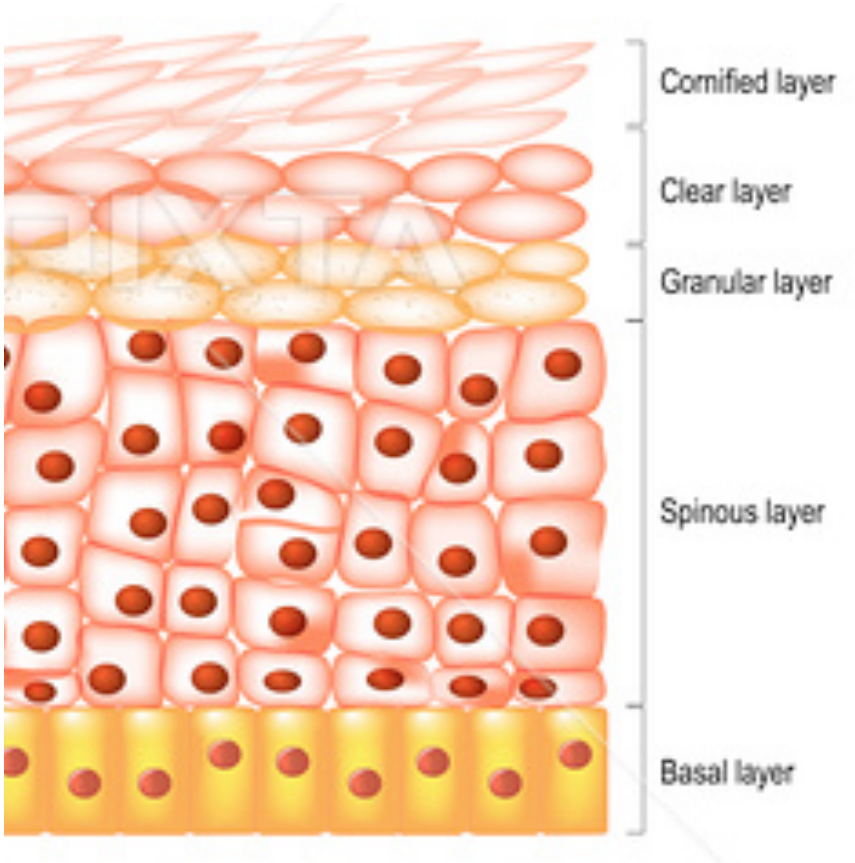
- composed of protein rich corneocytes impeded in lipid rich matrix, free fatty acids, cholesterol & phospholipids.
- The lipid content is concentrated in the extracellular phase of the stratum corneum & forms a large extent to the membrane surrounding the cells

2nd layer (stratum granulosum)

composed of granular keratin cells

3rd layer (stratum spinosum) composed of flattened polygonal cells.

4- The deep layer (stratum basale) composed of columnar cells which surrounding the melanocytes cells which produce melanin pigment



II- The dermis

1-fibroblasts, collagen & elastin

2- mast cells

3-blood supply

4-hair follicles & sebaceous glands (Skin appendages)

5- sweat glands

The hypodermis

The deepest layer is called subcutaneous tissue, the hypodermis, or subcutis.

It is not technically part of the skin but helps attach the skin to underlying bone and muscle.

The hypodermis is mostly made of fat, connective tissue, and elastin (an elastic protein that helps tissues return to their normal shape after stretching).The high levels of fat help insulate the body and prevent us from losing too much heat. The fat layer also acts as protection, padding our bones and muscles.

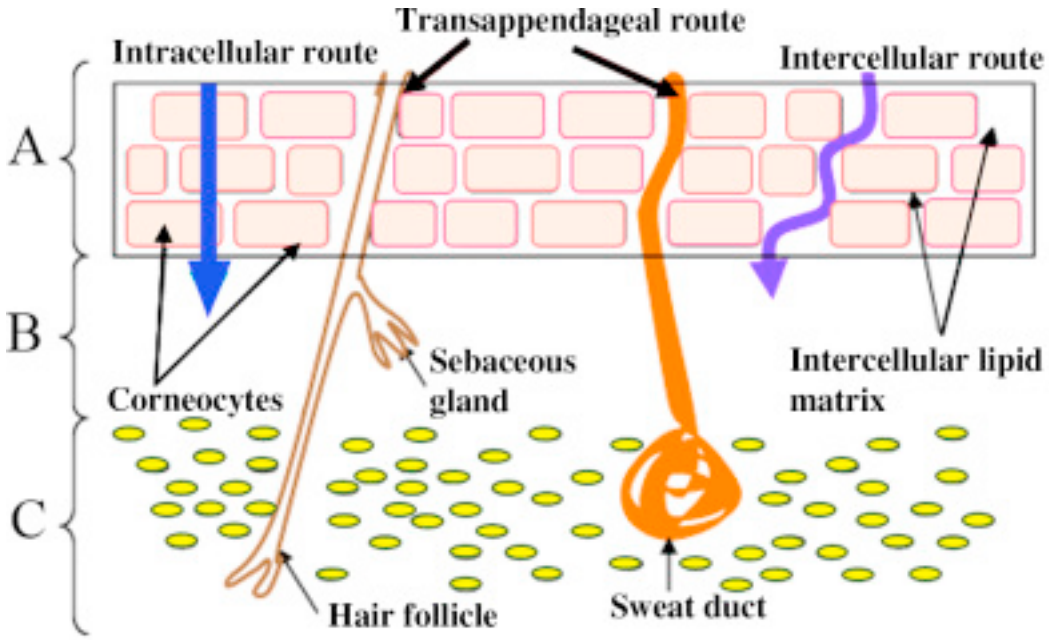
PENETRATION OF THE SKIN BY DRUGS

Permeation through skin can occur by diffusion via:

1. Transcellular (Intracellular) penetration (across the cells)

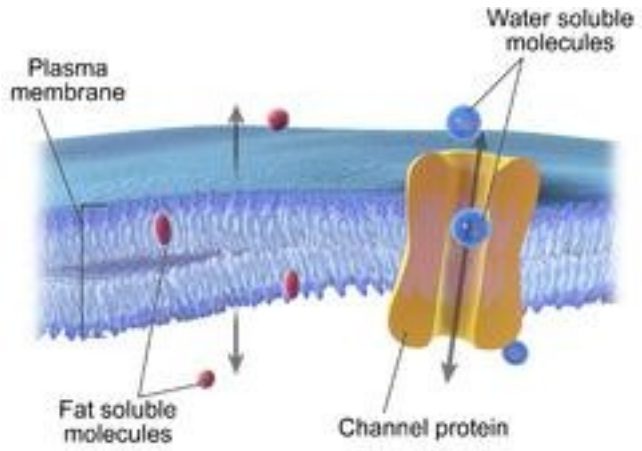
2. Intercellular penetration (between the cells)

3.Transappendageal penetration (via hair follicles, sweat and sebaceous glands)



Membrane permeability

1. For drug to produce a biologic response; the drug must first cross a biologic membrane.
2. This membrane acts as a lipid barrier to most drugs & permits the absorption of lipid soluble drugs by passive diffusion
3. The lipid insoluble drugs can diffuse across the barrier only with considerable difficulty



Diffusion Across the Plasma Membrane

- The stratum corneum behaves as a semipermeable membrane
- Drug molecules can penetrate membrane by passive diffusion
- The rate of drug penetration & movement across skin layer depends on :

1. drug concentration, physicochemical properties (i.e. pKa , lipid solubility, absorption) & aqueous solubility in the vehicle
2. partition coefficient of the drug between the stratum corneum and drug vehicle.
3. the properties of the pharmaceutical vehicle
4. the condition of the skin

THE DIFFUSION PROCESS

In passive diffusion, material moves from high concentration region of a system to lower concentration with no need of energy , a pump or a catalyst.

The equation that describes the steady state diffusion using Fick`s law :

$$dm/dt = AKDC_0/h$$

where, $P = DK/h$

P is the permeability

dm/dt is the diffusion rate of the drug

- m is the mass diffused at time t,
- A is the surface area,
- K is the partition coefficient,
- D is the diffusion coefficient,
- C_0 is the drug concentration (diffusant),
- h is the membrane thickness.

INFLUENCE OF MATERIAL PROPERTIES ON DIFFUSION

- The physicochemical properties of the medicinal substances and barrier phase affect diffusion are:

1)Diffusant solubility

2)Partition coefficient

3)Diffusivity

4)Effective concentrations

1) Diffusant solubility

- The diffusion of the medicinal substances through a membrane is directly proportional to its lipid solubility
- Generally, drug penetrates the skin better in their unionized form
- Nonpolar drugs tend to **cross** the cell barrier through the lipid rich regions (transcellular route)
- The polar drugs favour intercellular route

2)Partition coefficient

- This is when drug distributes itself between its vehicle & skin
- The partition coefficient is important in establishing the diffusion of a drug through a membrane.

3)Effective concentrations

- The concentration gradient is usually considered to be the driving force for diffusion.

- Generally, the amount of drug absorbed /unit surface area/ time interval increases with an increase in the concentration of the drug .

4)Diffusivity (diffusion coefficient)

- In gases and air, diffusion coefficients are large because the void space available to the molecules is great compared to their size, and the mean free path between molecular collisions is big.

- In liquids, the free volume is much smaller, mean free paths are decreased, and diffusivities are much reduced.

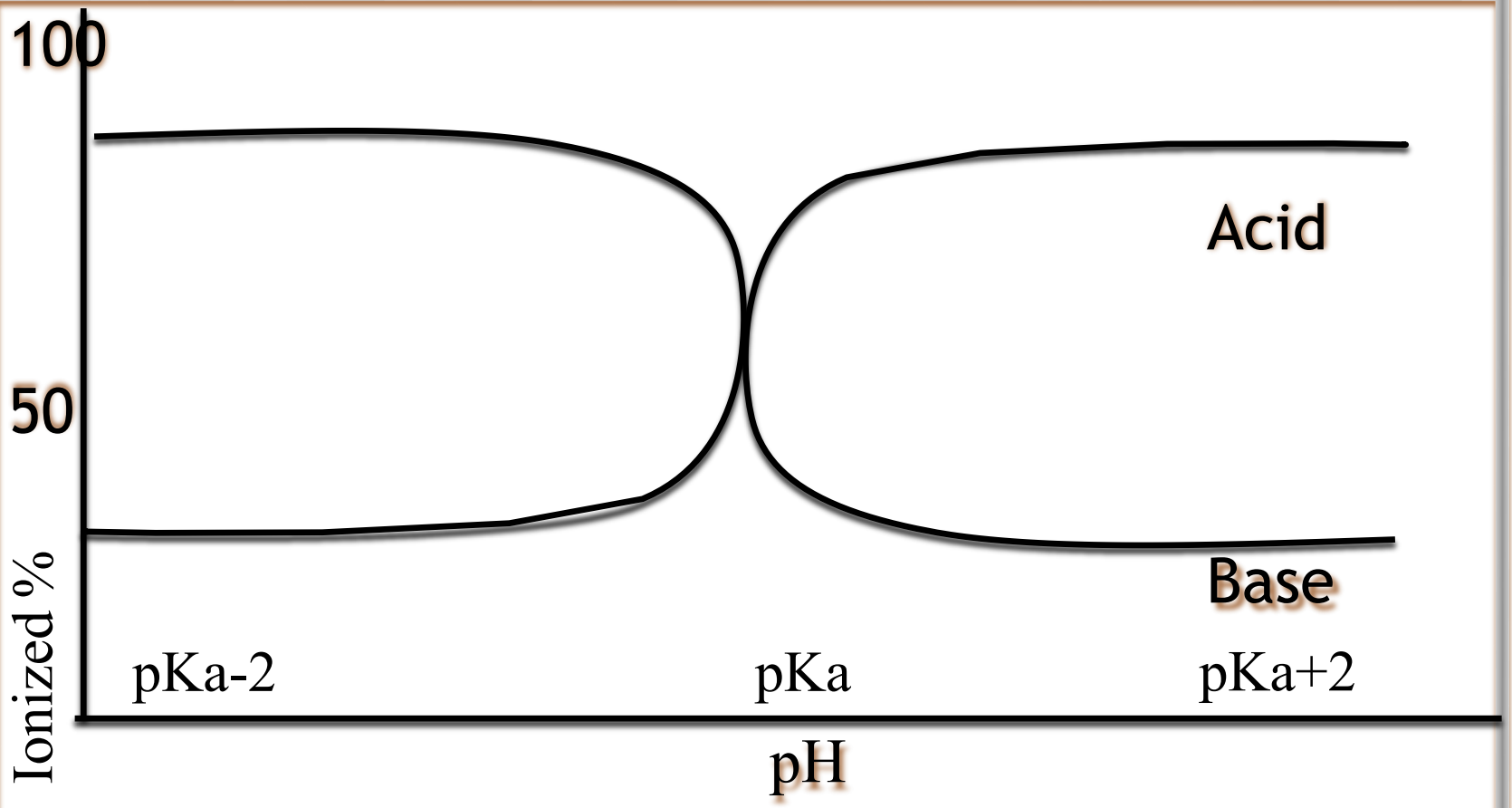
- In skin, the diffusivities drop progressively and reach their lowest values within the compacted stratum corneum matrix.

Thus, the activity of a penetrate through the membrane may be altered by,

1. pH change,
2. co-solvents

pH variation :

- Only the unionized molecules pass readily across lipid membranes.
- weak acids and bases dissociate to different degrees depending on the pH and their *pKa* or *pKb*.



Ionized % of weak acid and base as a function of pH

- The previous figure shows that:

1 The basic drug is completely ionized at pH below its pka by 2 units (pka-2)

2 While it is completely unionized at pH above its pka by 2 units (pka+2)

3 The acidic drug is completely ionized at pH above its pka by 2 units

4 While it is completely unionized at pH below its pka by 2 units

5 Both acidic and basic drugs are exactly 50% ionized at their pka values

Co-solvents

Polar cosolvent mixtures such propylene glycol with water may produce saturated drug solutions and so maximize the concentration gradient across the stratum corneum.

However, the partition coefficient of a drug between the membrane and the solvent mixture generally decreases as the solubility in the solvent system rises.

Thus, these two factors, may oppose each other in promoting diffusion through the membrane.

Hence, it is important not to over solubilize a drug if the aim is to promote penetration.

5- Particle size:

- Reducing the particle size of a poorly soluble drug in suspension improves the therapeutic activity by increasing dissolution rate and therefore, release from the vehicle.

6- Drug structure:

- Changes of drug structures should be prevented , as changing structures leads to the formation of many forms of one drug with different physical properties, such as low solubility, that are unfavourable to penetration.

7- Molecular weight:

- Drugs with molecular weights between 100 and 800 Da with adequate lipid and aqueous solubility can permeate skin.
- The ideal molecular weight for TDD is believed to be 400 Da or less.

8- Surface area:

- More drugs are absorbed through percutaneous absorption when the drug substance is applied to large surface area

9- Drug skin interaction:

- The drug substance should have a greater physicochemical attraction to the skin than to the vehicle in which it is presented in order for the drug to leave the vehicle in favour of the skin.

Topical Semisolid preparations

1- Ointments

Definition

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

Classification

1 unmedicated :

They are used for their physical effects as protectants, emollients ,lubricants and vehicles for medicated ointments.

2 medicated :

They are ointments that contain active constituents so used for their therapeutic effects.

- **Ointments Bases**

An ointment base functioning as a drug vehicle should be optimized for a specific drug and, as possible, for specific disease states, or skin conditions**.**

- **The physicochemical properties of an ideal ointment base are :**

1 non irritating.
2 easily removable.
3 non staining.
4 stable.
5 pH independent.
6 widely compatible with a variety of medicament.
7 melting or softening at body temperature.
8- should release the medicament easily.

Classification of ointment bases

- Ointment bases can be classified into four groups: I- Fatty **Oleaginous** bases,

II- Absorption bases

III- Water removable bases

IV- Water-soluble bases.

I. Fatty (Oleaginous) Bases:

- **They are also called hydrocarbon bases**
- **Properties :**

1. they are water free ...
2. they have emollient effect to the skin
3. they prevent the escape of moisture of the skin
4. remain on the skin for long time without drying out
5. are difficult to wash off …..
6. they act as occlusive dressing ....

- **Incorporation with different substances :**

7. water & aqueous preparations may be incorporated but only in small amounts & with difficulty.
8. some powdered substances are incorporated after levigation with mineral oil.

- **Types:**

I-i) Paraffins

I-i-A) Semisolid:

I-i-A-1) Petrolatum (soft paraffin):

- **Properties :**

1- it is purified mixture of semisolid hydrocarbons obtained from petroleum.

2- m.p. 38 ^{0}C to 56 ^{0}C.

3 it varies from yellow to light amber colour.

4 it is also known as yellow petrolatum & petroleum jelly.

5- the commercial product is Vaseline.

I-i-A-2) White petrolatum

- **Properties :**

1- it is petrolatum that has been decolorized

2- used for the same purpose of petrolatum

3 because of its non water-washable characteristics ; it is useful to treat diaper rash & dry skin

4 it is also known as white petroleum jelly & white Vaseline

I-i-B)Mineral oil (liquid paraffin):

- **Properties :**

1 it is purified mixture of liquid hydrocarbons obtained from petroleum.

2 used as levigating substance to wet and incorporate solid substances , e.g. Salicylic acid , zinc oxide.

3 colourless, odourless, tasteless, oily liquid.

4 insoluble in water and alcohol but soluble in ether and chloroform.

1-i-C)-Hard paraffin:

1 this is a mixture of solid hydrocarbons obtained from petroleum.

2 colourless, odourless, tasteless, translucent, wax-like substances.

3 it is used to stiffen the ointment base. Congealed between 47 ^{0}C and 65 ^{0}C.

I-ii)Plastibase (Jelene):

- **Properties**

1 this is a mixture of hydrocarbons in the liquid form and wax (i.e.Plastibase consists of mineral oil jelled with high molecular weight hydrocarbon wax.

2 has a jelly like consistency.

3 it maintains its consistency over a wide range of temperature i.e. (15 to 60 ^{0}C).

4it releases medications more rapidly than petrolatum.

5- provides a better appearing ointment.

6- it is compatible with most of medicaments.

Disadvantages:

1 Menthol, salicylates and camphor are dissolved by plastibase producing ointments that are too soft. This probably due to interaction with the high molecular wax used to gel the mineral oil.

2 Prescriptions using plastibase as the vehicle cannot be prepared by fusion because it is difficult to cool the resultant mixture to smooth consistency.

Note: preparation of plastibase commercially is carried out with a shock cooling procedure (very rapid cooling to a low temperature).

I-iii)Lard

1- similar to butter **&** has a suitable ointment consistency.

2- it has a poor water- absorbing power.

3 it is liable to oxidation (Rancidity).

I-iv)Vegetable Oils

- They are liquid oils that are used to give the ointment a smooth and creamy consistency. (e.g. Olive oil, cottonseed oil and almond oil).

I-v)Silicones

- they are polymers of silicon with carbon, Hydrogen & Oxygen , . Some common forms include silicon oil , silicon grease, silicon rubber, silicon resin make good ointments for protecting the skin from moisture.

II) Absorption Bases:

- General characteristics are:

1. anhydrous.
2. absorb water but insoluble in it.
3. not water− removable.
4. used as emollients
5. they do not provide the degree of occlusion afforded by the oleaginous bases
6. useful to incorporate aqueous solutions of drugs into oleaginous bases ; e.g. sodium sulfacetamide & gentamicin sulfate….

- **Types of absorption bases :**

A. Those that permit the incorporation of aqueous solutions resulting in the formation of water in oil emulsions

B. Those that are already water in oil emulsions that permit the incorporation of small , additional quantities of aqueous solutions

II-A-1)Anhydrous refined wool fat (anhydrous lanolin):

1. purified anhydrous fat−like substance obtained from wool of sheep.
2. it consists of esters of higher alcohols with different fatty acids.
3. may contain no more than 0.25% of water
4. insoluble in water but can be mixed with twice its weight of it without separation.

5. it is too sticky and have an offensive odour.

6. it is an important base of simple ointment base and eye ointment base.

7. Used as vehicle to protect against

bed sores

II-A-2)Hydrophilic Petrolatum

1- composed of a mixture of cholesterol, stearyl alcohol, white wax and white petrolatum

2- absorb water to form W/O emulsion

3- aquaphor is an example of a highly

refined type of Hydrophilic Petrolatum ;

it can absorb up to 3 times its weight in wat

II- B-1) Hydrous wool fat (Lanolin):

1. it is prepared from wool fat. It is a w/o emulsion that contains between 25% to 30% water.
2. it is used alone as emollient and vehicle of several other ointments.

II-B-2) Cold cream

1. it is w/o emulsion of cetyl esters wax, white wax, mineral oil and sodium borate ….
2. acts as emollient & ointment base
3. e.g. w/o emulsion of petrolatum, mineral oil, mineral wax, wool wax, alcohol & bronopol ; that acts as a vehicle for lactic acid & glycerol to treat dry skin
4. Used as make-up remover, cleanser and moisturizer (Why cold?)

(III) Water removable bases:

- General characteristics are:

1. they are o/w emulsion
2. hydrous.
3. absorb water.
4. water removable or washable.
5. they have the ability to absorb discharges in dermatologic conditions
6. offer better absorption of its incorporated medicinal agents by skin than other bases
7. may support microbial growth.

- e.g. Hydrophilic ointment

1. water loving
2. composed of stearyl alcohol and white petrolatum with propylene glycol and water
3. contains sod. lauryl sulphate as emulsifying agents & parabens.

IV) Water Soluble bases:

- General characteristics are:

1. absorb water.
2. soluble in water.
3. water removable or washable .
4. contain only water soluble components
5. they are greaseless due to the absence of any oleaginous materials
6. they soften greatly with the addition of water
7. better to incorporate nonaqueous or solid substances …..

Disadvantages :

1. they are liable to dehydration.
2. they need the addition of a preservative.
3. examples Polyethylene glycols (macrogols) :

a) the lower molecular weight compounds, e.g. 400 and 600 (average molecular weights) are liquids resembling glycerol

b) PEG 1000 has the consistency of ointment,

c) and 3000 and 6000 are solids.

d) the most satisfactory ointment consistency is obtained with a mixture of solid and liquid polyethylene glycol.

e) these ointments have a dehydrating effect on the skin.

Water number:

1. it is the maximum amount of water (in grams) that 100 g of an ointment base or fat will hold at 20ºC.

2. it is advisable to add water in quantities of 10 to 15% less than is indicated by water number: this will preclude the possibility of water bleeding from the base because of temperature variation. e.g. **Water number of some bases**

Example	**W a t e r n u m b e r**
Petrolatum	9.3-15.6
Petrolatum + 4% cetyl alcohol	38.8-51.1

- **Selection of the appropriate base**
- it depends on number of important factors including the following:

1) desired release rate of the drug from the ointment base
2) desired target site of the drug…..
3) occlusion of moisture from the skin
4) stability of the drug in the ointment base
5) the effect of the drug on the physical properties of the ointment base
6) characteristics of the surface to which ointment base is applied
7) if Water removable properties is required

- **Preparation of ointments:**
- A well−made ointment must be:

1. smooth (free from grittiness as gritty preparation may injure the skin further and impede the healing process.
2. more finely divided powders increase the medication surface area thereby increasing the potential availability for therapeutic activity.