SEMISOLID DOSAGE FORMS

12th week

Absorption Bases

- ✓ The word absorption in this context refers only to the ability of the base to absorb water.
- ✓ Absorption bases also are useful as emollients.
- ✓ Absorption bases are greasy when applied and are difficult to remove. However, both of these properties are less pronounced than with hydrocarbon bases.

a- Anhydrous absorption bases

- ✓ They are anhydrous bases which absorb water to become water-in-oil (W/O) emulsions.
- ✓ The anhydrous types can be used when the presence of water would cause stability problems with specific drug substances (e.g., antibiotics).

Hydrophilic Petrolatum, Anhydrous Lanolin

Anhydrous Lanolin

- It is an fatty substance obtained from sheep's wool.

- It has a light yellow color, semi-solid consistency and a specific odor.

- It can hold water twice of its own weight without losing its consistency.

- Water absorption feature is result from the aliphatic alcohols, triterpenic alcohols, cholesterol and cholesterol derivatives.

Hydrophilic petrolatum (USP)

* It is an anhydrous absorption base.

* Its W/O emulsifying property is conferred by the inclusion of cholesterol.

* Inclusion of stearyl alcohol and wax adds to the physical characteristics, particularly firmness and heat stability.

%3	Cholesterol
%3	Stearyl alcohol
%8	White beeswax
%86	White petrolatum

Simple Ointment (BP 1999)

Anhydrous lanolin	50 g
Hard paraffin	50 g
Cetostearyl alcohol	50 g
Petrolatum	850 g

b- W/O type absorption bases

- ✓ They are W/O type emulsions which have the ability to absorb additional water.

  Cold cream (USP)

Cold Cream (USP 21 – NF 16)

Cetaceum	125 g
White beeswax	120 g
Liquid paraffin	560 g
Borax	5 g
Purified water	190 ml

Water-removable bases

- ✓Water-removable bases are oil-in-water (O/W) emulsions.
- ✓They also are described as "water-washable bases" because they may be readily washed from the skin or clothing with water, an attribute that makes them more acceptable for cosmetic purposes.
- ✓Some drugs may be more effective in these bases than in hydrocarbon bases.
- ✓They can be diluted with water.

- ✓ They do not leave a greasy feeling on the skin.
- ✓ They do not have occlusive effect.
- ✓ They can easily loose their water, since their outer phase is water.
- ✓ They are susceptible to mould growth. It is absolutely necessary to add an antimicrobial preservative into the formulation.

Hydrophilic Ointment (USP 30)

White petrolatum	25 g
Stearyl alcohol	25 g
Propylene glycol	12 g
Sodium lauryl sulphate	1 g
Methyl paraben	0.025 g
Propyl paraben	0.015 g
Purified water	37 g

Water-soluble bases

- ✓ This group of bases are called "greaseless ointment bases" since they comprise of water-soluble constituents.
- ✓ They are more correctly called as Gels.
- ✓ They contain no water-insoluble substances such as petrolatum, anhydrous lanolin or waxes.
- ✓ They are completely soluble in water.
- ✓ They do not leave a greasy feeling on skin.
- ✓ They do not have an occlusive effect.

- ✓ Main components, and in some instances the only components, of water-soluble bases are the polyethylene glycols (PEGs).
- ✓ PEGs are relatively inert, nonvolatile, water-soluble or water-miscible liquids or waxy solids identified by numbers that are an approximate indication of their molecular weight.
- ✓ Polyethylene glycol 400 is a liquid while polyethylene glycol 6000 is a waxy solid.
- ✓ Polyethylene glycol 1500 is similar to petrolatum.

- ✓ Polyethylene glycols, particularly 1500, can be used as a vehicle alone; however, better results often are obtained by using blends of high- and low-molecular-weight glycols, as in polyethylene glycol ointment NF.
- ✓ Polyethylene Glycol Ointment (NF) is the only pharmacopeial preparation in this group.

Polyethylene glycol Ointment (USP 30)

Polyethylene glycol 3350	400 g
Polyethylene glycol 400	600 g

Glycerin Ointment

Wheat starch	7 g
Glycerin	93 g
Purified water	7 g

Choice of Base

The choice of an semisolid base depends on many factors such as;

- The action desired
- The nature of the drug to be incorporated and its bioavailability and stability
- The required shelf life of the finished product

* In some cases, it is necessary to use a base that is less than ideal in order to achieve the stability required.

* For example, drugs that hydrolyze rapidly are more stable in hydrocarbon bases than in bases that contain water, even though they may be more effective in the latter.

Enhancement of percutaneous penetration

1- Physical methods

2- Chemical methods

3- Drug delivery systems

Enhancement of percutaneous penetration

1- Physical methods

- Sonophoresis / Phonophoresis
- Iontophoresis
- Electroporation
- Microneedles

Iontophoresis

- ✓It is a technique which requires application of a small electrical current across the skin, has been used to deliver ionized drug molecules and peptides at a faster rate than normal.
- ✓Essentially, the charged molecule is forced into the stratum corneum as it is repelled from the electrode of similar polarity.
- ✓A particular advantage of iontophoretic delivery is that the flux of the permeant can be effectively controlled by alteration of the applied current.

Iontophoresis

- ✓The alteration of skin permeability following iontophoretic delivery is maintained for a brief period after termination of current application, after which normal barrier function is restored.
- ✓This would suggest that physical changes of the skin or stratum corneum rather than electrostatic forces alone are responsible for improved penetrability of the skin barrier.

Ultrasound / Phonophoresis / Sonophoresis

- ✓It is defined as the transport of drugs through the skin and into the soft tissue during or following the influence of an ultrasonic perturbation.
- ✓Ultrasound frequencies used in medicine can vary from 20 kHz to 16 MHz.
- ✓Lower and medium range ultrasound frequencies (20–200 kHz and 0.2–1 MHz, respectively) are predominantly used for sonophoresis due to their relatively higher cavitational effects.
- ✓Higher ultrasound frequencies are generally used for imaging, physiotherapy and for gallstone and kidney stone pulverization.

Ultrasound / Phonophoresis / Sonophoresis

✓Although sonophoresis is known to increase skin permeability, the fundamental mechanism is still not clearly understood or characterized.

✓Several proposed mechanisms of sonophoresis include;

- Thermal effects by absorption of ultrasound energy

- Cavitation effects caused by collapse and oscillation of cavitation bubbles in the ultrasound field.

✓Between these two effects, cavitation is believed to be the predominant mechanism responsible for sonophoresis.

Electroporation

- ✓ Electroporation (or electropermeabilization) involves the creation of transient aqueous pathways across lipid bilayer membranes by applying a short, high-voltage pulses.
- ✓Electroporation, originally used to transfect cells with macromolecules such as DNA, involves the application of a pulsating electrical field at high voltage (>50 V, typically 1–100 ms) to the skin.
- ✓This causes the formation of transient aqueous pores in the stratum corneum, through which molecular transport is attainable.

Electroporation

- ✓Electroporation leads to enhanced skin permeability, mainly attributed to electrophoretic movement and diffusion through the newly created aqueous pathways.
- ✓Although electroporation involves the application of an electric field similar to that of iontophoresis, the enhanced transports in these procedures are based on different principles.
- ✓While iontophoresis directly acts on the drug molecule to propel it into the skin, electroporation acts mainly on the skin to increase its permeability.

Microneedles

- ✓Microneedles are designed to create a physical pathway through the upper epidermis to increase the skin permeability.
- ✓They are applied to the skin surface and pierce the outer epidermis layer (which contains no nerves) deep enough to increase skin permeability and allow drug delivery, but superficially enough not to cause any pain through the sensory receptors of the dermis.

Microneedles

- ✓Microneedles are a technology developed from transdermal patches and hypodermic needles, attempting to gain advantages and eliminate disadvantages from both.
- ✓Compared to hypodermic needle, microneedles are painless and can significantly reduce the pain depending on the length of the needle.

Microneedles

- ✓It was found out that the needle length below 750 μm is painless and bloodless. However, the microneedles that are less than 300 μm long have been shown not able to penetrate the skin.
- ✓The main development of the microneedles technology which makes it distinct from other transdermal drug delivery methods is that it has greatly extended the range of drug molecular weight that can be delivered.

Enhancement of percutaneous penetration

2- Chemical methods

Penetration enhancers

- ✓Substances that help promote drug diffusion through the stratum corneum and epidermis are referred to as penetration enhancers, accelerants, adjuvants or sorption promoters.
- ✓Penetration enhancers improve drug transport by reducing the resistance of the stratum corneum to drug permeation.

General effects of various enhancers on the skin, formulation, and the drug are;

- increasing the diffusivity of the drug in the skin
- causing stratum corneum lipid-fluidization, which leads to decreased barrier function (it is a reversible action)
- increasing and optimizing the thermodynamic activity of the drug in the vehicle (base) and the skin
- resulting in a reservoir of drug within the skin
- affecting the partition coefficient of the drug, increasing its release from the formulation into the upper layers of the skin

✓ The outcome of enhancer action is usually a result of one or more of this mechanisms.

* To date, none of the existing chemical penetration enhancers has proven to be ideal.

* In particular, the efficacy of penetration enhancers towards the delivery of high molecular weight drugs remains limited.

Some of the more desirable properties of penetration enhancers acting within skin;

- They should be nontoxic, nonirritating and nonallergenic.
- They would ideally work rapidly.
- The activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body.
- The penetration enhancers should work unidirectionally. It means that they should allow therapeutic agents into the body while preventing the loss of endogenous material from the body.

Some of the more desirable properties of penetration enhancers acting within skin;

- When they removed from the skin, barrier properties of skin should return both rapidly and totally.
- The penetration enhancers should be appropriate for formulation into various topical preparations
- They should be compatible with both excipients and drugs.
- They should be chemically stable.
- They should be cosmetically acceptable with an appropriate skin 'feel'.

Water

- One long-standing approach to improve transdermal and topical delivery of drugs is to use water.
- In general, increased tissue hydration appears to increase transdermal delivery of active agents.
- The water content of human stratum corneum is typically around 15–20% of the tissue dry weight, although this varies depending on the external environment such as humidity. 25–35% of the water present in stratum corneum can be assessed as 'bound water'; it is associated with some structural elements within the tissue. The remaining water within the tissue is 'free water' and is available to act as a solvent within the membrane for polar permeants.

Water

- Despite extensive research in the area, the mechanisms of action by which water increases transdermal drug delivery are unclear.
- Free water within the tissue could alter the solubility of a permeant in the stratum corneum and hence could modify partitioning of it.
- Such a mechanism could partially explain elevated hydrophilic drug fluxes under occlusive conditions but it would fail to explain hydration-enhanced delivery for lipophilic permeants such as steroids.

Sulfoxides

- Dimethylsulphoxide (DMSO) is one of the earliest and most widely studied penetration enhancers.
- It is an effective penetration enhancer that promotes permeation by reducing skin resistance to drug molecules or by promotion of drug partitioning from the dosage form.
- It has been postulated that DMSO denatures the structural proteins of the stratum corneum or promotes lipid fluidity by disruption of the ordered structure of the lipid chains.
- Dimethylacetamide (DMAC) and dimethylformamide (DMF) are also powerful aprotic solvents with structures similar to that of DMSO.

Alcohols

- Ethanol is commonly used in many transdermal formulations.
- It can exert its permeation enhancing activity through various mechanisms.
- Firstly, as a solvent, it can increase the solubility of the drug in the vehicle.
- Further, permeation of ethanol into the stratum corneum can alter the solubility properties of the tissue with a consequent improvement for drug partitioning into the membrane.
- In addition, ethanol as a volatile solvent may extract some of the lipid fraction within the stratum corneum when used at high concentrations for prolonged times; such a mechanism would clearly improve drug flux through skin.

Glycols

- Propylene glycol is widely used as a penetration enhancer.
- Permeation of the propylene glycol through the tissue could alter thermodynamic activity of the drug in the vehicle which would in turn modify the driving force for diffusion.

Fatty acids

- Percutaneous drug absorption has been increased by a wide variety of long chain fatty acids, the most popular of which is oleic acid.
- Considerable efforts have been directed at investigating the mechanisms of action of oleic acid as a penetration enhancer in human skin.
- It is clear from numerous literature reports that the enhancer interacts with and modifies the lipid domains of the stratum corneum.
- Lauric acid, linoleic acid and linolenic acid are also used and evaluated as penetration enhancers.

Azone (Laurocapram)

- Azone was the first molecule specifically designed as a skin penetration enhancer.
- It is a colourless, odourless liquid and possesses a smooth, oily but yet non-greasy feel.
- Azone is a highly lipophilic material and it is soluble in and is compatible with most organic solvents including alcohols and propylene glycol.
- It has low irritancy, very low toxicity and little pharmacological activity.
- The literature contains reports describing activity in promoting flux of both hydrophilic and lipophilic permeants.
- Azone probably exerts its penetration enhancing effects through interactions with the lipid domains of the stratum corneum.

Pyrrolidones

- N-methyl-2-pyrrolidone and 2-pyrrolidone are the most widely studied enhancers of this group.
- In terms of mechanisms of action, the pyrrolidones partition well into human corneum stratum. Within the tissue they may act by altering the solvent nature of the membrane and pyrrolidones have been used to generate 'reservoirs' within skin membranes. Such a reservoir effect offers potential for sustained release of a permeant from the stratum corneum over extended time periods.
- However, clinical use of pyrrolidones is precluded due to adverse reactions. They can cause erythema, although this effect was relatively short lived.

Urea

- Urea is a hydrating agent used in the treatment of scaling conditions such as psoriasis, ichthyosis and other hyperkeratotic skin conditions.
- The penetration enhancing activity of urea probably results from a combination of increasing stratum corneum water content and through its keratolytic activity.

Surfactants

- Surfactants are usually added to formulations in order to solubilise lipophilic drugs, so they have potential to solubilise lipids within the stratum corneum.
- Anionic and cationic surfactants have potential to damage human skin. Sodium lauryl sulphate (SLS) is a powerful irritant.
- Non-ionic surfactants tend to be widely regarded as safe.
- Surfactants generally have low chronic toxicity and most have been shown to enhance the flux of materials permeating through biological membranes.

Terpenes

- Terpenes are found in essential oils.
- Both the mono- and sesquiterpenes are known to increase percutaneous absorption of compounds by increasing diffusivity of the drug in stratum corneum and/or by disruption of the intercellular lipid barrier.
- A further mechanism of activity that has been postulated is that the terpenoids increase electrical conductivity of tissues thereby opening polar pathways within the stratum corneum.