SEMISOLID DOSAGE FORMS

11th week

SKIN

- ✓ The skin is the largest organ in human body with a surface area of approximately 2 m^2.
- ✓The average thickness of the skin is 1.5 mm, however it may differs by age, gender and anatomic location.
- ✓ Because of its easily accessible large surface area, it has received a great research interest as a noninvasive alternative route to conventional oral or injectable administration of drugs.
- ✓However, it acts as a principal barrier for dermal and transdermal drug delivery.

- ✓ Skin can be used as a port of entry for therapeutic substances such as drugs and vaccines if the mechanisms that confer the barrier properties are understood.

Functions of Skin

✓ Mammalian skin has multiple and complex functions.

✓ The major functions of skin are;

- Protecting of the organism against environmental factors
- Regulating body temperature
- Preventing water loss of the body

Functions of Skin

- ✓ One of its main roles is to prevent invasion of the organism by acting as a defensive barrier to threats from the external environment.

- ✓ The skin has evolved defensive mechanisms which give it physical, immunological, metabolic and UV-protective barriers to allow it to inhibit attacks by microorganisms, toxic chemicals, UV radiation and particulate matter (including nanoparticles, which may occur in the natural environment).

Functions of Skin

- ✓ The surface of the skin has been recognised to be acidic, with a pH of 4.2 – 5.6.
- ✓ The surface pH of skin is influenced by gender, anatomical site, sweat, sebum and hydration.
- ✓ This acidic skin surface is described as the acid mantle.
- ✓ The acid mantle has a number of functions, especially including antimicrobial defence.

Structure of Skin

Skin consists of three main layers;

- Epidermis
- Dermis
- Hypodermis (Subcutaneous layer)

Epidermis

The epidermis contains four or five sublayers namely;

-Stratum basale

- Stratum spinosum

- Stratum granulosum

- Stratum lucidum

(It is only in skin of palm and soles)

- Stratum corneum (Horny layer)

Epidermis

- ✓ Epidermis is composed mostly of stratified keratinocytes.
- ✓ Keratinocytes undergo a process of keratinisation, in which the cells differentiate and move upward from the basal layer (stratum basale), through stratum spinosum and stratum granulosum, to the outermost layer, stratum corneum.
- ✓ Cells become flattened and anucleated when they arrive the stratum corneum.

Beyond keratinocytes, distinct type of cells for different functions such as;

- Melanin production (melanocytes)
- Sensory perception (Merkel cells)
- Immunological function (Langerhans cells)

are also present in the viable epidermis.

Stratum corneum

- ✓ The uppermost layer, stratum corneum, is primarily responsible for the barrier function of skin.
- ✓ It consists of corneocytes which are flattened, anucleated and protein-rich cornified cells.
- ✓ Corneocytes are embedded in an extracellular lipid matrix and locked by corneodesmosomes which maintain the structural integrity of stratum corneum.
- ✓ This is often referred to as a 'bricks and mortar' arrangement.

Dermis

Dermis comprises of;

- Connective tissue components
- Nerves
- Blood vessels
- Lymphatics
- Pilo-sebaceous units (hair follicles associated with sebaceous glands)
- Ecrine and apocrine sweat glands

Hypodermis

✓ Hypodermis consists of;

- Cells which produce and store fat

- Main blood vessels

✓ Hypodermis layer provides thermal insulation

Dermal drug delivery

- ✓ Semisolid dosage forms for dermatological drug therapy are intended to produce desired therapeutic action at specific sites of the skin.
- ✓Although some drugs primarily have an impact on the skin surface, the target area for most dermatological disorders is the viable epidermis or upper dermis.

Transdermal drug delivery

Skin is a potential site for the systemic drug delivery.

By this way;

- Some therapeutically active agents can be delivered transdermally with ease
- Hepatic metabolism is avoided
- Constant drug levels in the bloodstream are maintained for longer periods of time
- Potential side effects are decreased
- Patient compliance is increased

Advantages of dermal / transdermal drug application

* The application of drug is easier.

* The active substance is not affected by liver first pass effect.

* The stability of drug which is unstable in gastrointestinal system can be provided.

* Dosage form can be easily removed from skin when a side effect is observed.

Disadvantages of dermal / transdermal drug application

* There is a risk of local allergy and irritation.
* Skin has a low permeability.
* It is not an appropriate route for all of the active substances.

Percutaneous absorption is;

Releasing of active substance from the preparation which was applied to the outer surface of skin and entering microcirculation after penetration through skin layers.

* Dermal and transdermal drug delivery requires efficient penetration of active compounds through the skin barrier basically by a passive diffusion process.

Percutaneous penetration

✓ Percutaneous penetration occurs via passive diffusion.

✓ The permeation of active molecules through the skin can take place by the diffusion;

- Through epidermis (Transepidermal route)
- Through skin appendages (Transappendageal route)

The molecules can cross the intact stratum corneum by two different ways:

- Transcellular route (Intracellular route)
- Intercellular route

Hydrophilic molecules can prefer to follow the transcellular route owing to the aqueous environment in consequence of the high amount of hydrated keratin inside cells.

The pilo-sebaceous units can have an important contribution to the topical drug delivery for water soluble and polar substances. It is also playing a role as a low resistance route for nanoparticles.

It is generally accepted that the tortuous intercellular route ensures the primary way for the permeation of most of the molecules.

The passive diffusion process follows Fick's law.

1st Fick's Law;

$$\frac{dQ}{dt} = -D.A\,\frac{dc}{dx}$$

$$J = \frac{D.K.A.C}{h}$$

dQ / dt = Diffusion rate of the molecule (mg/sn)

dc / dx = Concentration gradient (mg/cm^2)

D = Diffusion coefficient of the molecule (cm^2/sn)

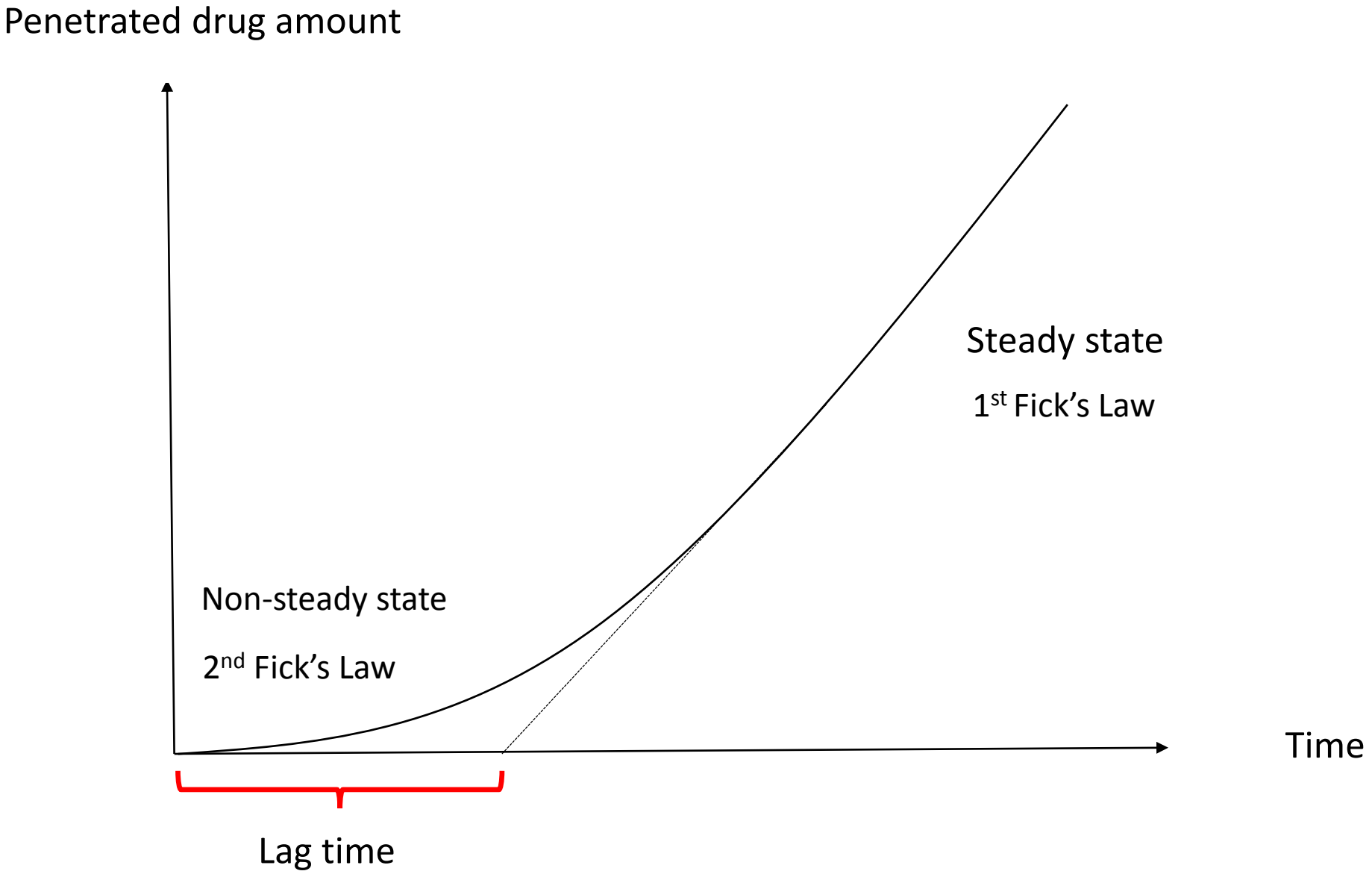
A = Diffusion surface area

J = Penetrated drug amount

K = Partition coefficient of the molecule

h = Layer thickness

Diffusion profile:



Factors which are affecting percutaneous penetration

The ability of drug to penetrate the layers of skin depends on the properties of the skin, drug and the carrier base.

- Biological factors

- Factors related to active substances

- Factors related to the formulation and excipients

Factors which are affecting percutaneous penetration;

1- Biological factors

- The health and integrity of skin
- Age
- Anatomical region
- Intensity of hair follicules
- Hydration of skin
- Skin temperature
- pH of skin
- Gender
- Application of dosage form (Friction, massage etc)

Factors which are affecting percutaneous penetration;

2- Factors related to the active substances

- Solubility
- Partition coefficient (octanol / water) of active substances
- Ionization constant (pKa)
- Molecular weight
- Particle size
- Concentration

Factors which are affecting percutaneous penetration;

3- Factors related to the formulation and excipients

- Type and properties of semisolid formulation
- Base type
- Penetration enhancers

SEMISOLID DOSAGE FORMS

They are dosage forms which are externally applied to the skin or mucosa and which have a certain viscosity.

Semisolid dosage forms according to European Pharmacopeia (EP5);

Homogeneous preparations which are used for local or transdermal administration of the active substances or for the emollient or protective effect of the formulation itself.

Classification of semisolid dosage forms according to European Pharmacopeia (EP5);

* Ointments
* Creams
* Gels
* Pastes
* Poultices
* Medicated plasters

Ointments

- USP defines ointments as semisolid preparations intended for external application to the skin or mucous membranes.

- They usually, but not always, contain medicinal substances.

- They are single-phase semi-solid preparations in which an active substance is dissolved or dispersed in an oily base.

Creams

- Creams are multi-phase semisolid preparations which are consisted of an oil phase, an aqueous phase and an emulsifier.

- They are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base.

- This term traditionally has been applied to semisolids that possess a relatively soft, spreadable consistency formulated as either water-in-oil or oil-in-water emulsions.

O/W type creams, W/O type creams

Gels

- Gels are semisolid systems consisting of either suspensions composed of small inorganic particles or large organic molecules interpenetrated by a liquid (USP 30).

- They are semi-solid preparations obtained by gelation of gelling agents with appropriate liquids.

- Gels can be either water based (hydrogels) or organic solvent based (organogels).

Pastes

- The USP defines pastes as semisolid dosage forms that contain one or more drug substances intended for topical application.

- The term paste is applied to ointments in which large amounts of solids (often ≥ 50%) have been incorporated (e.g., zinc oxide paste).

- In the past, pastes have been defined as concentrates of absorptive powders dispersed in petrolatum or hydrophilic petrolatum.

- Pastes are more viscous preparations than ointments.

- They often are used in the treatment of oozing lesions, where they act to absorb serous secretions.

Poultices

- Poultices represent one of the most ancient classes of pharmaceutical preparations.

- A poultice is a soft, moist mass of meal, herbs, seed, etc., usually applied hot in a cloth.

- The consistency is gruel-like, which is probably the origin of the word poultice.

- They were intended to localize infectious material in the body or to act as counterirritants.

- The materials tended to be absorptive, which, together with heat, accounts for their popularity.

- None is now official in the USP.

Medicated Plasters

- Plasters are substances intended for external application, made of such materials and of such consistency as to adhere to the skin and attach to a dressing.

- Plasters are intended to afford protection and support and/or to furnish an occlusive and macerating action and to bring medication into close contact with the skin.

- Medicated plasters, long used for local or regional drug delivery, are the prototypical transdermal delivery system.

- Plasters usually adhere to the skin by means of an adhesive material. The adhesive must bond to the plastic backing and to the skin (or dressing) with proper balance of cohesive strengths.

USP Classification of Semisolid Bases

1- Hydrocarbon (Oleaginous) Bases

2- Absorption Bases

a-Anhydrous absorption bases

b-W/O type absorption bases

3- Water-Removable (Water-Washable) Bases

4- Water-Soluble Bases

Hydrocarbon Bases

* They are known also as "oleaginous ointment bases" and are represented by White Petrolatum and White Ointment (USP).

* They leave a greasy feeling when they are applied to skin.

* These bases are difficult to wash off.

* Only very small amounts of an aqueous component can be incorporated into these bases.

* They have occlusive and emollient properties.

* Hydrocarbon bases serve to keep medicaments in prolonged contact with the skin and act as occlusive dressings.

* Their percutaneous penetration is low.

Hydrocarbon Bases

* Since they have occlusive effect, they increase skin hydration by reducing the rate of loss of surface water.

* Bases of this kind may be used solely for such a skin moisturizing or emollient effect.

* On the other hand, skin hydration may increase the drug activity.

Petrolatum

Plastibase

Hard paraffin

Beeswax

Cetaceum (Spermaceti)

Carnauba wax

Lard

Benzoinated lard

Olive oil, cottonseed oil, castor oil ....

Silicones

Hydrogenated cottonseed oil, peanut oil and castor oil ....

Petrolatum

- ✓Hydrocarbon bases are usually petrolatum alone or petrolatum modified by waxes or liquid petrolatum to change viscosity characteristics.
- ✓USP permits addition of waxy materials as an aid in minimizing temperature effects.
- ✓Petrolatum USP is a tasteless, odorless, oleaginous material.
- ✓Its color ranges from amber to white (when decolorized).
- ✓It has a high degree of compatibility with a variety of medicaments.
- ✓It is occlusive and nearly anhydrous; thus provide optimum stability for drugs such as antibiotics.

Plastibase

- ✓It is a gelled mineral oil vehicle represents a unique member of this class of bases.
- ✓When approximately 5% of low-density polyethylene is added to liquid petrolatum and the mixture is then heated and subsequently shock-cooled, a soft, oleaginous, colorless material resembling white petrolatum is produced.
- ✓The mass maintains unchanged consistency over a wide temperature range.
- ✓It neither hardens at low temperatures nor melts at reasonably high temperatures.
- ✓Its useful working range is between −15°C and 60°C.
- ✓Excessive heat (above 90°C) will destroy the gel structure.

White Ointment (USP 30)

White beeswax	50 g
White petrolatum	950 g