

## SEMISOLID DOSAGE FORMS

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### INTRODUCTION

Pharmaceutical semisolid dosage preparations include ointments, pastes, cream, emulsions, gels and rigid foams.

**Ointments** are soft semisolid preparations meant for external application to the skin or mucous membrane. They usually contain medicament, which is either dissolved or suspended in the base.

They have emollient and protective action.

**Creams** are semisolid emulsions for external application and are generally of softer consistency and lighter than ointments.

They are less greasy and are easy to apply.

**Pastes** are semisolid preparations for external application that differs from similar products in containing a high proportion of finely powdered medicaments. They are stiffer and are usually employed for their protective action and for their ability to absorb serous discharges from skin lesions.

Thus when protective, rather than therapeutic action is desired, the formulation pharmacists will favor a paste, but when therapeutic action is required, he will prefer ointments and creams.

**Jellies** are transparent or translucent, non-greasy, semisolid preparation mainly used externally.

In these systems the liquid phase is entrapped within a three-dimensional polymeric matrix in which a high degree of physical cross-linking has been introduced.

The polymers (gelling agents) used include:

*Natural Polymers :*

Tragacanth, pectin, carageenan, agar, alginic acid and gelatin.

*Synthetic and Semisynthetic polymers:*

Methyl cellulose, hydroxymethyl cellulose, carboxymethyl cellulose and Carbopols.

### STRUCTURE OF SKIN

The skin has three main layers: the epidermis, dermis and hypodermis.

**Epidermis** is the outermost layer. It consists of:

- The *basal layer* (innermost) is one cell thick layer. Its cells divide constantly and the daughter cells are steadily pushed towards the surface.
- The *prickle cell layer*: The cells in this region are linked by tiny bridges or prickles.
- The *granular layer*: When they reach this region, the upwardly moving cells become granules and begin to synthesize the inert protein keratin.
- The *horny layer* (stratum corneum). This is the outermost layer and the cells are heavily keratinized and dead. The dead cells slough off gradually.

**Dermis** is the middle and the main part of the skin. The dermis is made up of protein collagen and elastin. The collagen is in the form of gel that is reinforced by a framework of elastin.

Dermis contains the following structures:

- Blood vessels, lymphatics and nerves.
- Epidermal appendages e.g. hair follicles, sebaceous glands and sweat glands.

**Hypodermis**, the innermost layer, consists of adipose tissues. It gives physical protection and thermal insulation to underlying structures.

N.B.

Epidermis is non-granular but is penetrated by hair follicles, sebaceous glands and sweat glands.

Sebum is the secretion of sebaceous glands. Sebum is a mixture of fatty substances and emulsifiers; it mixes with water producing a fluid of pH 5.5 that covers the skin surface and permeates the upper layer of keratinized cells – this is called the “acid-mantle” of skin.

Keratin is hydrophilic, the stratum corneum normally contains about 20% w/w of water, the amount varying with atmospheric humidity. This moisture keeps the skin supple and if its level falls below about 12% the cells become dry and brittle and then shrink and curl at the edges, making the skin feel rough.

Cracking may follow, causing discomfort. Loss of water may be the result of excessive evaporation, over-usage of detergents (which removes sebum) and cold weather (which inhibits sebum production).

### PERMEABILITY OF DRUG THROUGH EPIDERMIS

Most dermatological preparations belong to one of two classes:

- Preparation intended to remain on the surface*  
e.g. products for penetration or for emollient action.
- Preparations intended to penetrate the skin but will not enter into blood stream*

Drugs penetrate the epidermis by two main routes:

(a) Through the keratinized cells of the stratum corneum.

The keratinized cells are fused together so drug molecules directly diffuse through them. These cells contain keratin which is hydrophilic and phospholipids which is hydrophobic, so drug molecules having solubility in both water and oil have good permeability through this route.

(b) Via hair follicles

Although the hair follicles occupy only a small area of the total epidermis, they provide a very important route of penetration. The fat soluble drugs dissolve in sebum, diffuse in to the sebum-filled follicles and passes to dermis.

#### FACTOR AFFECTING PERMEABILITY OF A DRUG THROUGH SKIN

##### A. Factor associated with the skin

(a) *Hydration of the horny layer*

The hydration of keratinized cells is raised by covering the area with a moisture-proof plastic film to prevent evaporation of perspiration. Hydration increases the drug penetration.

(b) *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.

(c) *Skin condition*

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

##### B. Factors associated with the medicament

(a) *Solubility of the drug*

Highly lipid soluble molecules enters through hair follicles. Moderately lipid soluble molecules penetrates directly across the horny layer.

(b) *Dissociation constant (pKa)*

If a drug is ionized in the surrounding pH of the dermis then the penetration of the ionic species are restricted by electrostatic interactions. Degree of ionization depends on the pKa of the drug.

e.g. Methyl salicylate and methyl nicotinate penetrate much faster than salicylic acid and nicotinic acid respectively.

(c) *Particle size*

Reducing the particle size increases the dissolution of a poorly soluble drug in suspension and thus increases the release rate from the vehicle.

(d) *Crystal structure*

The metastable polymorph is much more soluble than its stable form, so the release of drug in metastable state is much more faster than stable form.

##### C. Factors associated with vehicles

The rate of release of a drug from a vehicle to stratum corneum is governed by *vehicle-to-stratum corneum partition coefficient*. The thermodynamic activity of the drug in the vehicle is the product of the concentration of the drug and the activity coefficient ( $\gamma$ ) of the drug in the vehicle. Drugs held firmly by the vehicle exhibit low activity coefficient, hence slow rate of release from that drug-vehicle combination. Drug held loosely by the vehicle shows higher activity coefficient, hence shows faster rate of release.

The vehicles may enhance the penetration of a drug in one or more of the following ways:-

- a) By ensuring good contact with the surface of the body
- b) By increasing the degree of hydration of the stratum corneum
- c) By penetrating the epidermis
- d) By directly altering the permeability of the skin

(a) Contact with body surface

Sticky bases such as soft paraffin, Paraffin ointment B.P.C., Simple ointment B.P. etc. adheres well to the skin but are difficult to apply evenly and remove completely.

Creams are easier to apply and remove. Oil in water (o/w) creams mix with sebum and are more suitable for weeping or wounded surface.

(b) Hydration of stratum corneum

An occlusive layer reduces evaporation of water from skin, increasing hydration of the horny layer and, therefore, promotes penetration of medicament.

e.g. hydrocarbons, wool fat and isopropyl myristate containing ointments produce occlusive films on the skin. Water in oil (o/w) type creams have some occlusive effects.

Humectants like glycerols are not good for retaining water because at low atmospheric humidities, because they tend to increase loss of water by absorbing it from the skin.

(c) Penetration of the epidermis

Bases miscible with the sebum penetrate into the regions of the skin in which sebum is found.

e.g. Woolfat (originating from sebaceous glands of sheep) penetrates into the skin.

Vegetable oils penetrate more slowly and liquid paraffin does not penetrate at all.

(d) Alteration of skin permeability

Penetration can be improved by dissolving the medicament in an organic liquid such as ethanol, dimethylformamide(DMF), dimethyl acetamide, dimethylsulfoxide (DMSO) and propylene glycol. They increases the hydration of skin.