SHAMBHUNATH INSTITUTE OF PHARMACY, JHALWA, ALLAHABAD

LECTURE NOTES
ON

PHARMACEUTICS -I

UNIT -V

(BP-103T)

B. PHARM. 1st Year 1st Sem

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UNIT V

SEMISOLID DOSAGE FORMS

Definition: Semi solid pharmaceutical system comprises of products, which when applied to skin or accessible mucous membranes tends to alleviate or treat a pathological condition or other protection against harmful environment.

TYPES OF SEMI-SOLID DOSAGE FORMS

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.

STRUCTURE OF SKIN

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

Epidermis is the outermost layer. It consists of:

(a) The *basal layer* (innermost) is one cell thick layer. Its cells divide constantly and the daughter cells are steadily pushed towards the surface.
(b) The *prickle cell layer*: The cells in this region are linked by tiny bridges or prickles.

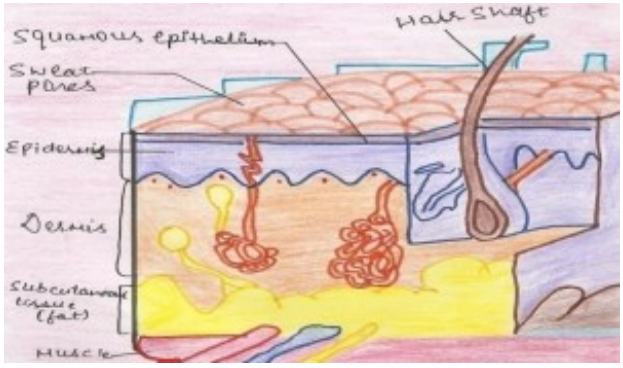
(c) The *granular layer*: When they reach this region, the upwardly moving cells become granules and begin to synthesize the inert protein keratin.
(d) The *horny layer* (stratum corneum). This is the outermost layer and the cells are heavily keratinized and dead. The dead cells sloughs off gradually.

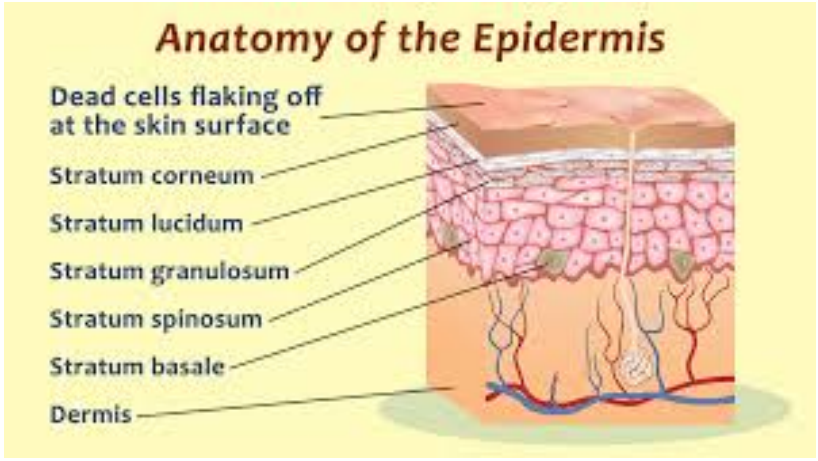
Dermis is the middle and the main part of the skin. The dermis is made up of protein collagen and elastin. The collagen is in the form of gel that is reinforced by a framework of elastin.

Dermis contains the following structures:

(a) Blood vessels, lymphatics and nerves.
(b) 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.





The structure of Skin

PENETRATION OF DRUG THROUGH EPIDERMIS:

Most dermatological preparations belong to one of two classes:

1. ***Preparation intended to remain on the surface***

e.g. products for penetration or for emollient action.

2. *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 contains 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) <u>Via hair follicles</u>

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 of epidermis

The hydration of keratinized cells in epidermis 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 example, 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 enter through hair follicles. Moderately lipid soluble molecules penetrate 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 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 (γ) 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.

METHOD OF PREPARATION OF OINTMENTS

According to their therapeutic properties based on penetration of skin.

(a) Epidermic, (b) Endodermic, (c) Diadermic

(a) Epidermic ointments

- These ointments are intended to produce their action on the surface of the skin and produce local effect.
- They are not absorbed.
- They acts as protectives, antiseptics and parasiticides.

(b) Endodermic ointments

- These ointments are intended to release the medicaments that penetrate into the skin.
- They are partially absorbed and acts as emollients, stimulants and local irritants.

(c) Diadermic ointments

- These ointments are intended to release the medicaments that pass through the skin and produce systemic effects.

PREPARATION OF OINTMENTS

A well-made ointment is –

(a) Uniform throughout i.e. it contains no lumps of separated high melting point ingredients of the base, there is no tendency for liquid constituents to separate and insoluble powders are evenly dispersed.

(b) Free from grittiness, i.e. insoluble powders are finely subdivided and large lumps of particles are absent. Methods of preparation must satisfy these criteria.

Two mixing techniques are frequently used in making ointments:

1. **Fusion**, in which ingredients are melted together and stirred to ensure homogeneity.

2. **Trituration**, in which finely-subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base or one of its ingredients followed by dilution with gradually increasing amounts of the base.

1. **Ointments prepared by Fusion method**:

When an ointment base contain a number of solid ingredients such as white beeswax, cetyl alcohol, stearyl alcohol, stearic acid, hard paraffin, etc. as components of the base, it is required to melted them. The melting can be done in two methods:

Method-I

The components are melted in the decreasing order of their melting point i.e. the higher m.p. substance should be melted first, the substances with next melting point and so on. The medicament is added slowly in the melted ingredients and stirred thoroughly until the mass cools down and homogeneous product is formed.

Advantages: This will avoid over-heating of substances having low melting point.

Method-II

All the components are taken in subdivided state and melted together.

Advantages:

The maximum temperature reached is lower than Method-I, and less time was taken possibly due to the solvent action of the lower melting point substances on the rest of the ingredients.

Example:

Simple ointment B.P. contains

Wool fat	50g
Hard paraffin	50g
Cetostearyl alcohol	50g
White soft paraffin	q.s. upto 1000gm

Type of preparation: Absorption ointment base

Procedure:

Hard paraffin and cetostearyl alcohol on water-bath. Wool fat and white soft paraffin are mixed and stirred until all the ingredients are melted. If required decanted or strained and stirred until cold and packed in suitable container.

2. Ointment prepared by trituration:

This method is applicable if the base is in the form of a semisolid and some medicament in powder form.

(i) Solids are finely powdered are passed through a sieve (# 250, # 180, #125).

(ii) The powder is taken on an ointment-slab and triturated with a small amount of the base. A steel spatula with long, broad blade is used. To this additional quantities of the base are incorporated and triturated until the medicament is mixed with the base.

(iii) Finally liquid ingredients are incorporated. To avoid loss from splashing, a small volume of liquid is poured into a depression in the ointment and thoroughly incorporated before more is added in the same way. Splashing is more easily controlled in a mortar than on a tile.

Example:

Whitfield ointment (Compound benzoic acid ointment B.P.C.)

Formula:	Benzoic acid, in fine powder	6gm
	Salicylic acid, in fine powder	6 gm
	Emulsifying ointment	q.s. upto 100gm

Method: Benzoic acid and salicylic acid are sieved through No. 180 sieves. They are mixed on the tile with small amount of base and levigated until smooth and dilute gradually.

METHOD OF PREPARATION OF PASTES:

Like ointment, pastes are prepared by trituration and fusion methods. Trituration method is used when the base is liquid or semisolid.

Fusion method is used when the base is semisolid and/or solid in nature.

E.g.

Name: **Compound Zinc Paste**

Formula	Zinc oxide, finely sifted	25 g
	Starch, finely sifted	50 g
	White soft paraffin	q.s. upto 100 gm

Type of preparation: Paste with semi-solid base prepared by fusion and trituration.
Procedure;

(a) Zinc oxide and starch powder are passed through No. 180 sieve.
(b) Soft paraffin is melted on a water bath.
(c) The required amount of powder is taken in a warm mortar, triturated with little melted base until smooth. Gradually rest of the base is added and mixed until cold.

METHOD OF PREPARATION OF CREAMS:

A cream is an emulsion system containing an oil phase, an aqueous phase and an emulsifying agent.

For o/w emulsion systems the following emulsifying agents are used:

(i) water soluble soap

(ii) cetyl alcohol

(iii)glyceryl monostearate

(iv) combination of emulsifiers: triethanolamine stearate + cetyl alcohol

(v) non-ionic emulsifiers: glyceryl monostearate, glyceryl monooelate, propylene glycol stearate

For w/o emulsion creams the following emulsifiers are used:

(i) polyvalent ions e.g *magnesium, calcium and aluminium* are used.

(ii) combination of emulsifiers: *beeswax + divalent calcium ion*

The viscosity of this type of creams prevent coalescence of the emulsified phases and helps in stabilizing the emulsion.

Example:

Cold cream:

White bees wax	7.5 gm
Stearic acid	15 gm
Wool fat	9.0 gm
Liquid paraffin	15.0 gm
Terpineol	1.5 gm
Triethanolamine	1.25 gm
Propylene glycol	7.5 gm
Water	q.s. upto 100 gm
Perfume	q.s.

Vanishing Cream:

Stearic acid	1.2 gm
Potassium Crabonate	0.25 gm
Borax	1.0 gm
Beeswax	1.0 gm
Water	q.s. upto 25 gm
Perfume	q.s.

Procedure:

(i) Water immiscible components e.g. oils, fats, waxes are melted together over water bath (70^0C).

(ii) Aqueous solution of all heat stable, water soluble components is heated (70^0C).

(iii) Aqueous solution is slowly added to the melted bases with continuous stirring until the product cools down and a semi-solid mass is obtained. The perfume is added at the end when the formulation is about to solidify.

Note: The aqueous phase is heated otherwise high melting point fats and waxes will immediately solidify on addition of cold aqueous solution.

METHOD OF PREPARATION OF GELS/JELLIES:

Pharmaceutical jellies are usually prepared by adding a thickening agent such as tragacanth or carboxy methylcellulose (CMC) to an aqueous solution in which drug has been dissolved.

The mass is triturated in a mortar until a uniform product is obtained.

For the preparation of jellies whole gum is preferred rather than powdered gum because the former gives a clear preparation of uniform consistency.

The gelling agents used for the preparation of jellies and gels include tragacanth, gelatin, methyl cellulose, starch, pectin, sodium alginate, etc…..

Example:

Formula	Drug	q.s.
	Gelatin	1.5 g
	Alcohol 95%	5.0 g
	Glycerin	1.0 g
	Purified water q.s.	q.s. upto 50 gm

Procedure:

(i) Alcohol is taken in a 100 ml, wide mouthed jar; and then gelatin is added to it. (The reverse order may lead to lump formation). Mixed well.

(ii) Water is added as quickly as possible and mixed.

(iii) Separately drug, glycerin and 10 ml water is mixed. Final weight is adjusted by adding more of water.

INGREDIENTS FOR SEMI SOLID DOSAGE FORMS:

- ✓ Active pharmaceutical ingredients
- ✓ Bases
- ✓ Preservatives
- ✓ Humectants
- ✓ Anti oxidants
- ✓ Organoleptic Agents

Bases:

- ✓ It is one of the most important ingredient used in the formulation of semisolid dosage form
- ✓ Ointments and suppository base do not merely acts as the carrier of the medicaments, but they also control the extent of absorption of medicaments incorporated with them

Base should be:

- ✓ Compatible with skin ph and drug
- ✓ Inert ,non irritating and non sensitizing

- ✓ Good solvent and/or emulsifying agent
- ✓ Emollient , protective , non greasy and easily removable
- ✓ Release medicaments easily at the site of administration
- ✓ Pharmaceutical elegant and possess good stability.

Types of bases:

A. Oleaginous bases

B. Absorption bases

C. Water miscible or emulsion bases

D. Water soluble bases

A. <u>Oleaginous bases:</u>

- These bases consists of oils and fats.
- The most important are the hydrocarbons i.e. petrolatum, paraffins and mineral oils.
- The animal fat includes lard.
- The combination of these materials can produce a product of desired melting point and viscosity.

E.g. **Petrolatum (Soft paraffin), White soft paraffin (White petroleum jelly, White petrolatum), Hard paraffin (Paraffin), Liquid paraffin (Liquid petrolatum; White mineral oil), etc..**

B. Absorption base:

- The term absorption base is used to denote the water absorbing or emulsifying property of these bases and not to describe their action on the skin.
- These bases (sometimes called emulsifiable ointment bases) are generally anhydrous substances which have the property of absorbing (emulsifying) considerable quantity of water yet retaining its ointment-like consistency.
- Preparations of this type do not contain water as a component of their basic formula but if water is incorporated a W/O emulsion results.

  E.g. **Wool Fat (anhydrous lanolin), Hydrous Wool Fat (Lanolin), Wool Alcohol, Beeswax, Cholesterol, etc…**

C. Water miscible bases:

- They are miscible with an excess of water.
- Ointments made from water-miscible bases are easily removed after use.

- There are three official anhydrous water-miscible ointment bases:-

Example:-

Emulsifying ointment B.P. – contains anionic emulsifier.

Cetrimide emulsifying ointment B.P. – contains cationic emulsifier

Cetomacrogol emulsifying ointment B.P. – contains non-ionic emulsifier

D. Water soluble bases:

- Water soluble bases contain only the water soluble ingredients and not the fats or other greasy substances, hence they are known as grease-less bases.
- Water soluble bases consists of water soluble ingredients such as polyethylene glycol polymers (PEG) which are popularly known as "carbowaxes" and commercially known as "macrogols".
- They are a range of compounds with the general formula:

$$CH_2OH . (CH_2OCH_2)_n CH_2OH$$

- The PEGs are mixtures of polycondensation products of ethylene and water and they are described by numbers representing their average molecular weights. Like the paraffin hydrocarbons they vary in consistency from viscous liquids to waxy solids.

Example:-

Macrogols 200, 300, 400 – viscous liquids

Macrogols 1500 – greasy semi-solids

Macrogols 1540, 3000, 4000, 6000 – waxy solids.

<u>Preservatives</u>:

Some bases, although, resist microbial attack but because of their high water content, it require an anti microbial preservative.

- Commonly used preservative include: **Methyl hydroxy benzoate, Propyl hydroxy benzoate**, **Chorocresol, Benzoic acid, Phenyl mercuric nitrate**

<u>Antioxidants</u>:

- Oxygen is highly reactive atom that is capable of becoming of potentially damaging molecules commonly called "free radicals".
- Free radicals are capable of attacking the healthy cells of the body, causing them to loose their structure and functions
- To prevent this an anti oxidant is added.

- Example : **Butylated hydroxy anisole , Butylated hydroxy toluene**

Humectants:

A humectant is a hygroscopic substance . It is often a molecule with several hydrophilic groups, most often hydroxl group.

Humectants are used to:

- ✓ **Increase the solubility of active ingredients**
- ✓ **To elevate its skin preparation**
- ✓ **Elevate the hydration of the skin.**

Evaluation of semisolid dosage forms:

- **Drug Content**
- **Uniformity of Drug Content**
- **pH measurement**
- **Penetration**
- **Rate of release of medicaments**
- **Absorption of medicaments into blood stream**
- **Irritant effect**
- **Spreadability**
- **Extrudability**

Drug content –Fixed Quantity of dosage form was accurately weighed in a 50ml of volumetric flask to which 20ml purified water was added with continuous shaking. Volume was adjusted. The drug quantity was assayed.

Uniformity of drug content -For uniformity of drug contents, six tubes were taken randomly and assayed for the drug content as stated above.

Measurement of pH -The pH of dosage form was determined by digital pH meter. One gram of dosage form was dissolved in 100ml of distilled water and stored at 4°C for two hours.

Penetration- A weighed quantity of dosage form is rubbed over skin for a given period of time and unabsorbed dosage form is collected and weighed. The differences in weights represent the amount absorbed.

Rate of release of medicaments- These tests can be done in-vivo (using animals) or in-vitro (using diffusion cell or dialysis membrane or other suitable equipment), the samples are withdrawn at regular time intervals and then analyzed for drug content.

Absorption of medicament into blood stream

The dosage form should be evaluated for the rate of absorption of drug into the blood stream. This test can be run in-vivo only.

Definite amount of dosage form should be rubbed through the skin. Under standard conditions and medicaments are estimated in the blood plasma or urine.

Irritant Effect

The irritant effect can be judged to a certain extent by injecting the dosage form into thigh muscles and under the abdominal skin of rats. Reactions are noted at intervals of 24, 48, 72 and 96 hours. Lesions on cornea, iris, and conjunctiva are used for judging the irritancy to the eyes. Presence of patches on the skin within 2 weeks indicates irritancy to pressing skin.

Spreadability- A modified apparatus consisting of two glass slides containing dosage form in between with the lower slide fixed to a wooden plate and the upper one attached to a balance by a hook was used to determine spreadability.

Extrudability - A simple method was adopted for determination of extrudability in terms of weight in grams required to extrude a 0.5cm ribbon of dosage form in 10 seconds from the collapsible tube.