

Semisolid Dosage Forms

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Introduction

- Pharmaceutical semisolid dosage preparations include : ointments, pastes, cream, plasters and gels
- They contain one or more active ingredients dissolved or uniformly dispersed in a suitable base and any suitable excipients such as emulsifiers, viscosity increasing agents, anti microbial agents, antioxidants, or stabilizing agents etc..

Definitions

- **OINTMENT:** these are semi solid preparations meant for external application to the skin/ mucous membrane.
- **PASTE:** these are semisolid preparations intended for external application to skin.
- **CREAM:** these are viscous semisolid emulsions meant for external use.
- **GELS:** these are semisolid dispersion systems which may contain suspension of either small /large organic molecules dispersed in a suitable liquid.

Advantages of semi-solid dosage form:

- It is used externally
- Probability of side effect can be reduce
- First pass gut and hepatic metabolism is avoided.
- Local action and Site specific action of drug on affected area.
- Convenient for unconscious patient or patient having difficulty on oral administration.
- Suitable dosage form for bitter drugs.
- More stable than liquid dosage form

Disadvantages of semi-solid dosage form:

- There is no dosage accuracy in this type of dosage form
- The base which is used in the semi-solid dosage form can be easily oxidized.
- May cause staining.
- They are bulky to handle.
- Application with finger may cause contamination.
- Physico-chemically less stable than solid dosage form.
- May cause irritation or allergy to some patients

IDEAL PROPERTIES OF SEMISOLIDS

PHYSICAL PROPERTIES:

- Smooth texture
- Elegant in appearance
- Non dehydrating
- Non gritty
- Non greasy and non staining
- Non hygroscopic

PHYSIOLOGICAL PROPERTIES

- Non irritating
- Do not alter membrane / skin functioning
- Miscible with skin secretion
- Have low sensitization index

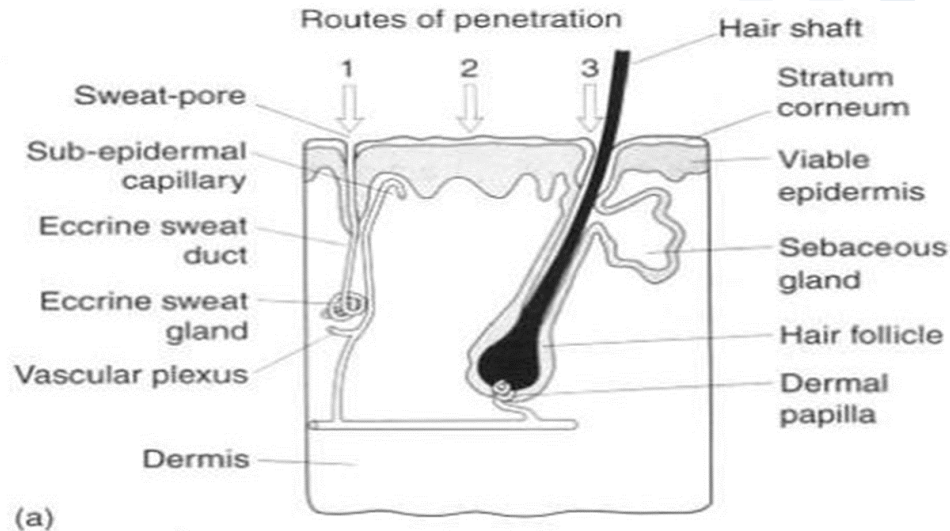
APPLICATION PROPERTIES

- Easily applicable with efficient drug release.
- High aqueous wash ability.

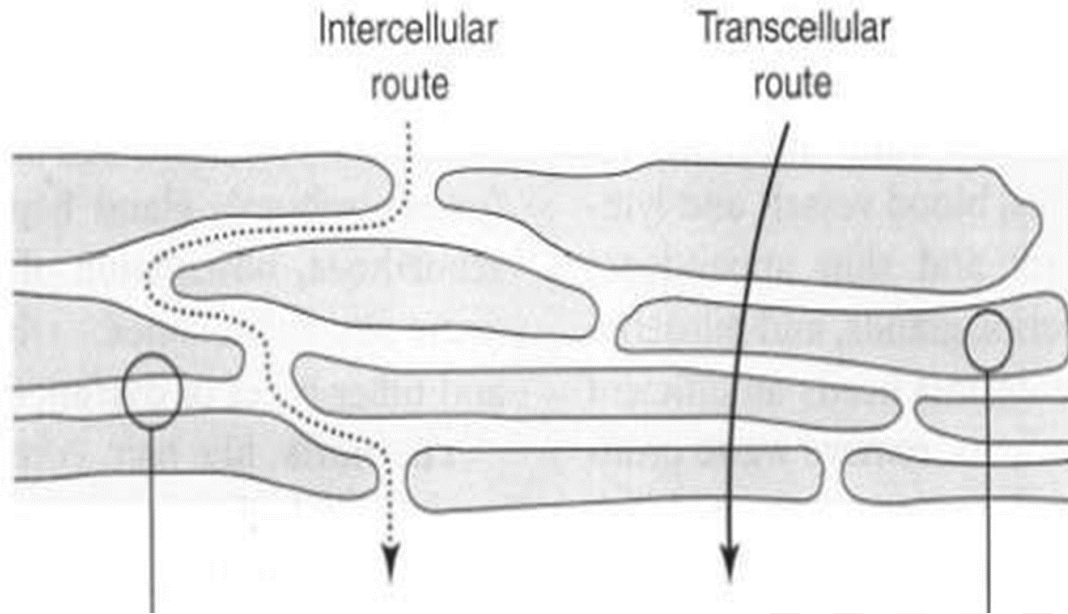
Mechanism of drug penetration through skin

Three potential entry MACRO ROUTES to the viable tissue:

- Via the sweat ducts
- Across the continuous stratum corneum
- Through the hair follicles with their associated sebaceous glands



MICRO ROUTES



- Low molecular weight molecules penetrate through stratum conium to some extent.
- Skin appendages are main route for Electrolytes, polar steroids, antibiotics and colloidal particles.
- Particles of 3-10 μ penetrate through hair follicle and particles less than 3 μ penetrate through stratum conium.
- Hair follicle route may be important for ions and large polar molecules.
- Topically applied agents such as steroids, hexachlorophane, griseofulvin, sodium fusidate and fusidic acid may form a depot or reservoir by binding within the stratum corneum.
- Once drug permeates through horny layer it readily enters living tissue and systemic circulation.
- The average residence time of drug in dermis may be 1 min before it is washed away by blood.
- NSAIDS reach far down to muscles to form depots.

FACTORS INFLUENCING DERMAL PENETRATION OF DRUGS

I. Biological factors:

- Skin condition
- Skin age
- Blood flow
- Regional skin site
- Skin metabolism
- Species difference.

II. Physicochemical factors:

- Skin hydration
- Temperature and pH
- Diffusion coefficient
- Drug concentration
- Partition coefficient
- Molecular size and shape.

BIOLOGICAL FACTORS:

1. Skin condition

- The intact, healthy skin is a tough barrier but acids and alkalis injure barrier cells and thereby promote penetration.
- Mixtures of non-polar and polar solvents, such as chloroform and methanol, remove the lipid fraction and molecules pass more easily.
- Disease alters skin condition, skin inflamed, with loss of stratum corneum thus permeability increases.
- If organ thickened, with corns, calluses and warts, drug permeation decrease.

2. Skin age

- Skin of the young and the elderly is more permeable than adult tissue.
- Children are more susceptible to the toxic effects of drugs and chemicals, because of their greater surface area per unit body weight; thus potent topical steroids, Causes severe side-effects and death.

3. Blood flow:

- An increased blood flow could reduce the amount of time a penetrant remains in the dermis, and also raise the concentration gradient across the skin.
- In clinically hyperemic disease damages the skin barrier and increase absorption.

4. Regional skin sites :

- Variations in permeability depend on the thickness and nature of the stratum corneum and the density of skin appendages.
- Absorption changes with substance, volunteer and site.
- Permeabilities depend on thickness of stratum corneum and the overall thickness of the tissue.
- Plantar and palmar callus may be 400-600 μm thick compared to 10-20 μm for other sites.
- The hyoscine Transderm system employs in postauricular skin (i.e. behind the ear) because the layers of stratum corneum are thinner
- Facial skin in general is more permeable than other body sites

5. Skin metabolism:

- The skin metabolizes steroid hormones, chemical carcinogens and some drugs.
- This is advantage to prodrugs.
- Skin can metabolize 5% of topical drugs.

6. Species differences:

- Mice, rats and rabbits are used to assess percutaneous absorption, but their skins have more hair follicles than human skin and they lack sweat glands.
- Hairless mouse, monkey and pig skins are most like that of humans.
- Hairless rat and fuzzy guinea pig may be better models for humans.
- To obtain skin penetration data it is best to use human skin

PHYSICOCHEMICAL FACTORS

1. Skin hydration:

- When water saturates the skin the tissue swells, softens and wrinkles
- and hydration of the stratum corneum increases permeability.
- Dusting powders or lotions, provide a large surface area for evaporation and therefore dry the skin

2. Temperature and pH:

- The penetration rate of material through human skin can change tenfold for a large temperature variation.
- Occlusive vehicles increase skin temperature and increase permeability.
- According to pH-partition hypothesis, only unionized molecules pass readily across lipid membranes.
- Weak acids and bases dissociate to different degrees, depending on the pH and their PKa or Pkb values.
- Stratum corneum is resistant to alterations in pH, range of 3-9.

3. Diffusion coefficient:

- The diffusional speed of a molecule depends mainly on the state of matter of the medium.
- In gases, diffusion coefficients are large than liquids
- In skin, the diffusivities reach their lowest values within the compacted stratum corneum matrix.
- The diffusion coefficient of a drug in a topical vehicle depends on the properties of the drug and the diffusion medium and on the interaction between them.

4. Drug concentration:

- Drug permeation and flux of solute is proportional to the concentration gradient across the barrier.
- Drug permeation follows Fick's law, saturated donor solution gives maximum flux.
- pH change, complex formation, or the presence of surfactants, micelles or cosolvents modify the effective partition coefficient

5. Partition coefficient(K):

- The partition coefficient is important in establishing the flux of a drug through the stratum corneum.
- Drug ($K < 1$) are water soluble, ($K > 1$) are oil soluble.
- Polar cosolvent mixtures, such as propylene glycol with water, produce saturated drug solutions and maximize the concentration gradient across the stratum corneum.
- Surfactants disruption of intercellular lipid packing in the stratum corneum, act as penetration Enhancers.
- Complex formation of drug increases the apparent partition coefficient may promote drug absorption.

6. Molecular size and shape:

- Absorption is apparently inversely related to molecular weight.
- Small molecules penetrate faster than large ones.
- It is more difficult to determine the effect of molecular shape, as it is related to partition coefficient.

Ideal Properties of Bases

They 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

1. Oleaginous/ Hydrocarbon Bases
2. Absorption/ Emulsifiable Bases
3. Emulsifying Bases
4. Water Soluble Bases

1. Oleaginous (*hydrocarbon*) bases:

- They consist of a combination of more than one oleaginous material such as water insoluble hydrophobic oils and fats

Disadvantages:

- Greasy, sticky-non washable
 - Retain body heat
 - Do not increase absorption
 - Prevent drainage on oozing area.
 - They are anhydrous, do not absorb water & insoluble in water.
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- Hydrocarbons: Paraffin wax, Soft paraffin, Liquid paraffin
 - Vegetable oils and animal fats: Peanut oil, Coconut oil, Lanolin, Bees wax
 - Hydrogenated & sulfated oils: Hydrogenated castor oil, Hydrogenated & sulfated castor oil.
 - Acids, Alcohols & Esters: Stearic acid, Stearyl alcohol, Isopropyl Myristicate.
 - Silicones: Dimethyl polysiloxanes

2. Absorption (Emulsifiable) base:

Qualities :

- Anhydrous
- Forms w/o emulsion
- Absorbs 50% water
- Due to the presence of sterol emulgent
- Easily removable by water

Classification

1) Non-emulsified bases:

- Absorb water and aqueous solutions to produce w/o emulsions Eg. wool fat, wool alcohol, beeswax, cholesterol.

2) W/O emulsions:

- Absorb more water than non-emulsified bases.
- Eg. Hydrous wool fat (lanolin)

2. Absorption (Emulsifiable) base:

Advantages of Absorption bases

- Compatible with most of the medicaments
- Absorb large quantity of water or aqueous substances
- Relatively heat stable
- Easily spreadable
- Less occlusive and good emollients
- Aqueous substances can be incorporated

Disadvantages

- Undesirable due to greasy nature
- Chances of microbial contamination.

3. Emulsion bases:

Ability to absorb water, serum discharges and forms o/w and w/o emulsions.

According to the type of emulsion these bases are classified as either W/O or O/W.

W/O- greasy, sticky. Ex: Sulfur & zinc ointments

O/W- easily removed from skin. Ex: vanishing cream.

Advantages Of Emulsion bases

- Miscible with exudates from lesions
- Does not interfere with skin function
- Good contact with skin because of surfactant content
- High cosmetic acceptability.
- Easy removable from the hair.

Disadvantages of Emulsion bases

- W/o emulsion greasy and sticky
- Its acceptance is less
- Difficult to remove from body and clothing.

4. Water soluble Bases: (Grease less Base)

As the name 'greaseless' suggests, these bases are oil free. They show complete solubility in water. They are hydrous as well as anhydrous in nature.

Carbo waxes 200,300...1500. (For viscous liquids)

Carbo waxes 1540, 3000.. 6000(For Viscous solids)

Pectin, Tragacanth & Cellulose derivatives (Form plants)

Gelatin (Animal)

Silica Gel, Bentonite (Chemical)

For low viscosity - Glycerin, Glyceryl mono stearate.

Methods of Preparation of Ointments & Creams

- Trituration
- Fusion
- Chemical reaction
- Emulsification

Methods of Preparation of Pastes

- Trituration
- Fusion

Method of Preparation of Gels

- General method

1. TRITURATION METHOD

- Widely used method
- For extemporaneous preparation of ointments.
- When the base is soft and medicament is solid insoluble Small amount of liquid to incorporated in the base

Advantage

Involves mixing as well as size reduction

Procedure:

- Reduce the solid medicament to fine powder
- Medicament is mixed with small amount of base on ointment slab with a stainless steel spatula until a homogeneous product is formed.
- Add remaining quantities of base with uniform mixing
- Incorporate any liquid ingredient if present
(mortar and pestle to be used in case of large quantity of liquid)

2. FUSION METHOD:

Suitable when ointment base contains number of solid ingredients of different melting points.

Procedure:

- Ointment base are melted in decreasing order of their melting point.
- Highest melting point should be melted first, low melting point next.
- This avoids over heating of substances of low melting point
- Incorporate medicament slowly to the melted mass
- Stir thoroughly until mass cools down and homogeneous product is formed.
- Liquid ingredients or aqueous substance should be heated to the same temperature as the melted bases before addition.
- If not, wax or solids will cool down quickly and get separated

Precautions:

- Stirring is done continuously- homogeneous mass
- Vigorous stirring should be avoided to prevent entrapment of air
- Rapid cooling should be avoided to get a uniform product.
- To remove the dust or foreign particles strain through muslin cloth

3. CHEMICAL REACTION METHOD

Preparation of some ointment involves chemical reactions

Eg – (a) Iodine ointment (iodine free form)

(b) Iodine ointment (iodine combined form with ointment base)

(a) Ointments containing free iodine

Iodine is slightly soluble in fats and vegetable oils.

Readily soluble is potassium iodide solution in water due to formation of polyiodides (KI, I₂, KI·2I₂, KI·3I₂)

Poly iodides are readily soluble in water, alcohol and glycerin.

These solutions may be incorporated with the molten absorption type ointment base.

(b) Ointments containing combined iodine

Fixed oils and many fats obtained from vegetable and animal sources contain unsaturated constituents. Iodine combines with double bonds

Free iodine is not available, So ointments appear dark, greenish black in colour

Leaves no stain when rubbed into the skin, Hence known as non-staining iodine ointment

4. EMULSIFICATION METHOD

- Fats, oils and waxes are melted together to a temperature around 70°C.
- Aqueous solution of the heat stable, water soluble compounds is also heated to the same temperature.
- Aqueous Solution is slowly added to the melted bases, with continuous stirring until cool.

Emulsifying agent is needed to make a stable emulsion

Water soluble soaps are commonly used as emulsifier for semisolid o/w emulsions.

Combination of triethanolamine stearate soap and cetyl alcohol is used in o/w emulsion

Bees wax and divalent calcium ions used in w/o emulsion.

EVALUATIONS OF OINTMENT AND CREAMS:

- Drug content
- Release rate of medicament from base
- Penetration rate of medicament
- Absorption of medicament into blood stream
- Consistency of the preparation
- Irritant effect

EVALUATION TEST

1. Drug content:--Minimum fill test

- Select any 10 filled containers
- Weigh the required amount of ointment
- Medicament is extracted in a suitable solvent
- Drug Content is determined by suitable analytical technique
- Results should be within labeled quantity.

2. Release rate of medicament from base:-

Two in vitro techniques are used

- Agar cup plate method
- Diffusion method

EVALUATION TEST

Agar cup Plate method

Used to determine the release rate of antibacterial ointment

Tested in agar medium seeded with staphylococcus aureus.

Zone of inhibition of bacterial growth is measured around circular cups



Diffusion method:

Used to find the release rate of any type of medicament from the base

A parchment membrane is tied at one end of glass tube

Ointment is filled in the tube, properly spread on the membrane

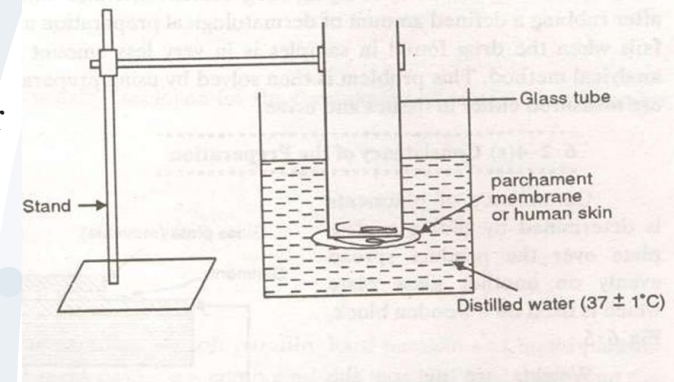
Tube is dipped in the distilled water maintained at $37 \pm 1^\circ\text{C}$

Samples are withdrawn after a specified period of time.

Samples are immediately replaced with fresh distilled water

Analyzed for the drug content

Plot a graph between drug concentration and time



EVALUATION TEST

3. Penetration rate of medicament:

Determined by rubbing weighed amount into defined areas for a fixed time

Unabsorbed material is removed completely and weighed

Difference in weight provides total base penetrated

Rate is then calculated

4. Absorption of medicament into blood stream:

Diadermic ointments are tested by in-vivo method.

Determined by assaying drug content in either blood, urine, faeces or tissues after rubbing defined amount under standard conditions

EVALUATION TEST

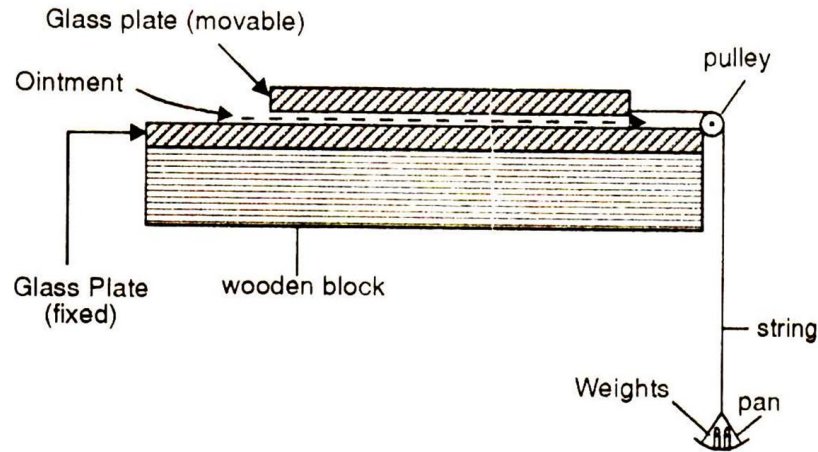
5. Consistency of the preparation:

Determined by sliding a glass plate over the product by means of a pulley.

Product is spread evenly on another glass plate fixed on a wooden block

Weights are added to the pan so that sliding of the movable glass plate is obtained

Ointment which require more weights to allow the plate to slide- over have high consistency or vice-versa



EVALUATION TEST

6. Irritant effect:--

Test is performed on skin and eyes of rabbit or human skin

Ointment is injected in to thigh muscles and under abdominal skin in rats.

Results are observed daily for a week

Irritant effect of dermatological preparation is shown as lesions on cornea, iris and conjunctiva

EVALUATION TEST

Evaluation of Pastes

- Evaluation of heat stability
- Determination of viscosity
- Compatibility with container
- Determination of safety of product
- Test for sensitization
- Determination of particle size
- Determination of gelatin behavior.

Evaluation of gels

- Rheological properties
- Determination of yield value
- Spreadability
- Stability test
- Safety evaluations.

“You Learn More From Failure Than From Success. Don’t Let It Stop You. Failure Builds Character.”

Thank You

