UNIT 5

Semisolid Dosage Forms

Semisolid dosage forms are pharmaceutical preparations intended for **external application to skin or mucous membranes**, which have a **consistency between solids and liquids**. They retain their **shape** to a certain extent at room temperature but can be easily spread or applied.

They may act:

- **Locally** (e.g., for skin conditions like eczema or burns)
- **Systemically** (e.g., nitroglycerin ointment through transdermal absorption)

Ideal Characteristics of Semisolid Dosage Forms

- Should be **physically and chemically stable**
- Must **not irritate** the skin or mucosa
- Should have **good spreadability and adherence**
- Must release the **active drug** at a **desired rate**
- Should be **non-greasy, non-staining**, and easily washable (if required)

Classification of Semisolid Dosage Forms

Semisolid dosage forms are primarily classified based on their **intended site of application** and **consistency**:

A. Based on Application Site

Type	**Site of Application**	**Example**
Topical	Applied to skin surface	Ointments, creams, gels
Ophthalmic	Applied to conjunctival sac	Eye ointments
Rectal	Inserted into rectum	Rectal creams
Vaginal	Applied inside vagina	Vaginal creams, gels
Nasal	Applied to nasal cavity	Nasal gels

B. Based on Physical Consistency and Base Type

Dosage Form	Definition	Example
Ointments	Homogeneous, semisolid preparations with **greasy or non-greasy bases**	Zinc oxide ointment
Creams	Semisolid emulsions (oil-in-water or water-in-oil)	Cold cream, hydrocortisone cream
Gels	Semisolid systems with **gelling agents** in water or alcohol base	Diclofenac gel, metronidazole gel
Pastes	Contain high proportion (≥25%) of **insoluble solids** in a fatty base	Toothpaste, zinc oxide paste
Plasters	Solid or semisolid mass spread on backing material	Salicylic acid plaster
Poultices	Soft, moist masses applied hot to skin to reduce inflammation	Kaolin poultice

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C. Based on Type of Base Used

Base Type	Nature	Examples
Oleaginous (hydrocarbon)	Greasy, occlusive	White petrolatum, paraffin
Absorption bases	Absorb water to form w/o emulsion	Lanolin, hydrophilic petrolatum
Water-soluble bases	Non-greasy, washable	PEG ointment base
Water-removable bases	o/w emulsions, easy to wash	Vanishing cream base

Mechanism and Factors Influencing Dermal Penetration of Drugs

Dermal (or percutaneous) drug delivery involves the **application of a drug to the skin** for **local or systemic action**. In most semisolid dosage forms (ointments, gels, creams), **drug absorption through skin layers** is essential for therapeutic effect.

A. Mechanism of Dermal Penetration

The **skin** acts as a **barrier and a route** for drug transport. It has three primary layers:

1. **Stratum corneum** (outermost layer) – principal barrier
2. **Epidermis** – viable cells, no blood vessels

3. **Dermis** – vascularized, drug enters systemic circulation here

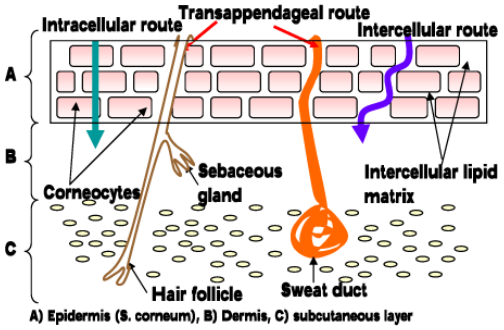
Pathways of Drug Penetration

Route	Description
1. Transcellular (Intracellular)	Drug passes **through** cells of stratum corneum (lipid-poor pathway)
2. Intercellular	Drug diffuses **between** skin cells via lipid domains (main route)
3. Appendageal (shunt route)	Drug enters through **hair follicles, sebaceous glands, or sweat ducts**

Note: The intercellular route is the **most dominant** path for most drugs.

B. Factors Influencing Dermal Penetration

Several **physiological**, **formulation-related**, and **environmental** factors affect the extent and rate of drug penetration through the skin.



1. Physiological (Skin-Related) Factors

Factor	Effect
Stratum corneum thickness	Thicker → less penetration (e.g., palms); thinner → more (e.g., face)
Hydration of skin	Moist skin enhances permeability
Skin temperature	Higher temp increases diffusion and blood flow
Skin pH	pH ~5.5 may affect ionization and solubility of drug
Age	Infants and elderly have more permeable skin
Skin integrity	Damaged or diseased skin allows more penetration
Site of application	Permeability: Scrotum > Face > Chest > Abdomen > Palm > Sole

Skin metabolism	Enzymes may degrade some drugs before they reach systemic circulation

2. Drug-Related Factors

Property	**Effect**
Molecular size	Small molecules (<500 Da) penetrate more easily
Lipophilicity	Moderate lipophilic drugs cross lipid-rich stratum corneum better
Ionization	Unionized form penetrates faster than ionized
Concentration gradient	Higher concentration = greater diffusion rate (Fick's Law)
Drug stability	Must be stable in semisolid base and at skin pH

3. Formulation-Related Factors

Formulation Element	**Influence**
Base type	Oleaginous bases occlude skin → more hydration and absorption
Use of penetration enhancers	Alcohols, DMSO, urea disrupt barrier to enhance penetration
Viscosity	Lower viscosity improves diffusion rate
Vehicle-drug interaction	Solubility and partitioning in the base affect release and availability
pH and buffer capacity	Should favor unionized drug at skin's pH (~5.5)

4. Environmental and Application Factors

Factor	**Effect**
Application duration	Longer contact time allows more penetration
Surface area covered	Larger area → higher total absorption
Use of occlusive dressings	Occlusion (e.g., plastic wrap) increases skin hydration and drug penetration
Rubbing/Massage	Improves absorption by increasing blood flow and contact

Preparation of Ointments, Pastes, Creams and Gels

Semisolid dosage forms are prepared using **specific techniques** depending on the **type of base**, **nature of the drug**, and **intended use**. The main methods used include **fusion**, **incorporation**, and **emulsification**. Below is the detailed explanation of preparation of each semisolid type:

A. Preparation of Ointments

Definition

Ointments are **semisolid greasy preparations**, usually anhydrous, intended for **external application** to the skin or mucous membrane.

Methods of Preparation

1. **Incorporation Method**
   Used when the drug is insoluble in the base.

Steps:

- Finely powder the drug and **levigate** it with a small amount of base or levigating agent (like liquid paraffin or glycerin).
- Incorporate the mixture into the remaining base using a **mortar-pestle** or **ointment slab** with **geometric dilution** technique.
- Mix until uniform.

2. **Fusion Method**
   Used when the drug is soluble in the base or base is composed of multiple ingredients with different melting points.

Steps:

- Melt the solid components in **descending order of melting point**.
- Add the drug (if heat-stable) or add later during cooling if heat-sensitive.
- Stir continuously and allow it to cool and solidify while mixing for uniformity.

Example:

Zinc oxide ointment

- Base: Simple ointment (white soft paraffin + hard paraffin + liquid paraffin)
- Drug: Zinc oxide is incorporated by levigation.

B. Preparation of Pastes

Definition

Pastes are **semisolid preparations** containing **a high percentage (≥25%) of solid particles** dispersed in a suitable base.

Method

Prepared using **incorporation technique** only.

Steps:

- Powdered solids are sieved and **levigated** with a portion of base to form a smooth mixture.
- Gradually add remaining base and mix thoroughly.
- Care should be taken to avoid air entrapment.

Characteristics:

- **Stiffer and less greasy** than ointments
- **Stay longer** on skin due to higher viscosity
- Suitable for **protective and absorbent** effects

Example:

Zinc oxide paste

- Contains zinc oxide and starch in a base of white soft paraffin.

C. Preparation of Creams

Definition

Creams are **semisolid emulsions** that may be either **oil-in-water (O/W)** or **water-in-oil (W/O)** emulsions.

Method: Emulsification (Fusion method)

Steps:

1. **Oil-soluble ingredients** (like stearic acid, cetyl alcohol) are melted in one beaker.
2. **Water-soluble ingredients** (like glycerin, preservatives) are heated separately to the same temperature (around 70°C).
3. Aqueous phase is added **to the oil phase slowly with constant stirring**.
4. Stirring is continued until the cream cools and thickens.

Notes:

- Temperature should be monitored to avoid **phase separation**.
- Perfume or volatile substances are added after cooling below 40°C.

Example:

Cold cream

- W/O emulsion containing beeswax, mineral oil, and borax (which acts as emulsifier).

D. Preparation of Gels

Definition

Gels are **semisolid systems** in which either **small inorganic particles** or **large organic molecules** are dispersed in a liquid vehicle with a **gelling agent**.

Method: Gelling (Hydration and Dispersion)

Steps:

1. Select a suitable **gelling agent** (e.g., Carbopol, tragacanth, methylcellulose).
2. Disperse it in **cold or hot water** depending on the agent used.
3. Allow the dispersion to **hydrate or swell** (can take several hours).
4. Neutralize (if needed) using **triethanolamine** or similar to form gel structure.
5. Add drug or other excipients either before or after gel formation depending on compatibility.

Notes:

- Use preservatives (e.g., parabens) in aqueous gels to prevent microbial growth.
- Avoid air entrapment during mixing.

Example:

Diclofenac gel

- Contains diclofenac diethylamine in a hydroalcoholic gel base of Carbopol.

Excipients Used in Semisolid Dosage Forms

Excipients are the **inactive components** of semisolid formulations that help to deliver the **active pharmaceutical ingredient (API)** effectively. In semisolid dosage forms like **ointments, creams, gels, and pastes**, excipients play a vital role in determining **consistency, stability, spreadability, drug release, and patient acceptability**.

Classification of Excipients Used in Semisolid Dosage Forms

Semisolid formulations typically include the following categories of excipients:

1. Bases

These are the **primary vehicles** that determine the **type of semisolid**, whether ointment, cream, or gel. Bases influence **drug release, occlusiveness, greasiness**, and **hydration**.

Type of Base	Example	Properties
Oleaginous bases	White soft paraffin, liquid paraffin	Greasy, water-insoluble, occlusive, long retention
Absorption bases	Anhydrous lanolin, wool fat	Absorb water to form W/O emulsion; greasy and occlusive

Water-removable bases	Vanishing cream base	O/W emulsions, washable, non-greasy
Water-soluble bases	Polyethylene glycol (PEG)	Greaseless, non-occlusive, completely water-soluble

2. Emulsifying Agents

Used in **creams** to stabilize **emulsions (O/W or W/O)** by reducing interfacial tension.

Type	**Examples**
Natural	Beeswax, wool fat (lanolin)
Synthetic	Cetomacrogol, polysorbates (Tween), sodium lauryl sulfate
Amphiphilic	Stearic acid + triethanolamine

3. Gelling Agents

Used in **gel formulations** to provide structure and semisolid consistency.

Type	**Examples**
Synthetic polymers	Carbopol (carbomer), HPMC
Natural polymers	Tragacanth, xanthan gum, guar gum
Inorganic agents	Bentonite, colloidal silica

4. Humectants

Prevent drying or hardening of formulation by **retaining moisture**.

Common Humectants

Glycerin

Propylene glycol

Sorbitol

5. Preservatives

Prevent microbial contamination, especially in **aqueous or emulsion-based semisolids**.

Examples	**Activity**
Methyl paraben, propyl paraben	Antifungal and antibacterial

Benzyl alcohol, phenol	Used in ophthalmic semisolid forms
Chlorocresol, sorbic acid	Broad-spectrum preservation

Note: Not needed for **anhydrous oleaginous bases**, which resist microbial growth.

6. Antioxidants

Prevent **oxidation** of sensitive drugs or excipients (e.g., oils and fats).

Examples	**Use**
Butylated hydroxytoluene (BHT)	Stabilizes fatty components
Butylated hydroxyanisole (BHA)	Prevents rancidity of oils
Sodium metabisulfite	Protects oxidation-prone drugs (like adrenaline)

7. Buffers and pH Adjusters

Maintain appropriate **pH for drug stability and skin compatibility**.

Examples

Sodium phosphate buffer

Citric acid / Sodium citrate

Triethanolamine (also used to neutralize Carbopol gel)

8. Penetration Enhancers

Improve **drug permeability** through the skin by altering **stratum corneum** structure.

Examples	**Mechanism**
Propylene glycol	Solubilizes lipids in stratum corneum
Dimethyl sulfoxide (DMSO)	Disrupts skin barrier
Urea, oleic acid	Enhance hydration and lipid fluidity

9. Coloring, Perfuming and Flavoring Agents

Added to improve **aesthetic appeal**, **odor masking**, and **patient compliance**.

Examples	**Use**
Titanium dioxide	Opacifier and white pigment
Menthol, rose oil	Fragrance and cooling effect

Vanillin	Flavor for oral semisolids (e.g., gels)

Used in **non-medicinal topical products** or pediatric formulations to enhance acceptability.

Evaluation of Semisolid Dosage Forms

Evaluation of semisolid dosage forms is essential to ensure:

- **Quality**
- **Safety**
- **Therapeutic efficacy**
- **Patient compliance**

Semisolid formulations (ointments, creams, pastes, gels) are evaluated for their **physical, chemical, microbiological**, and **performance-related** characteristics.

I. Physical Evaluation

These tests assess the **organoleptic and mechanical** properties of the formulation.

1. Appearance

- **Purpose**: To check color, odor, and uniformity.
- **Requirement**: Should be **smooth**, **homogeneous**, and **free from lumps, air bubbles, or crystals**.

2. Consistency and Texture

- Evaluated by **visual inspection and touch**.
- Should be **smooth**, **non-gritty**, and have **suitable viscosity** for spreading.

3. Spreadability

- Indicates **ease of application** to skin or mucous membrane.
- Measured by:

$$\text{Spreadability} = M \times LT$$

    - M = weight tied to upper glass slide
    - L = distance moved
    - T = time taken

- **Ideal**: Higher value indicates **better spreadability**.

4. Extrudability

- Determines the **force required** to expel the product from a tube.

- The formulation should **extrude uniformly and smoothly**.
- **Method**: Apply weight on tube and measure quantity extruded in 10 seconds.

5. Washability

- Tested by washing from skin with water.
- **Water-soluble bases** should be **easily washable**.

6. Phase Separation or Syneresis

- Mainly in **gels and creams**.
- Indicates **instability** due to water separation.
- **No separation** should be observed over time.

II. Chemical Evaluation

These tests ensure the **chemical integrity** of the formulation.

1. pH Determination

- Measured using **pH meter** after dispersing a sample in distilled water.
- Skin-compatible pH: **5.0 – 6.5**

2. Drug Content Uniformity

- Ensures each unit (dose or area) contains **uniform amount of drug**.
- A sample is analyzed using **UV spectrophotometry or HPLC**.
- Acceptance: 90–110% of label claim (as per pharmacopeial standards).

3. Assay of Active Ingredient

- Determines actual **drug quantity** present.
- Compared with **labeled amount** to ensure accuracy.

4. Stability Studies

- Performed under ICH guidelines:
    - Accelerated (40°C ± 2°C / 75% RH ± 5%)
    - Long-term (25°C ± 2°C / 60% RH ± 5%)
- Checks for **color change, pH shift, consistency**, and **drug degradation**.

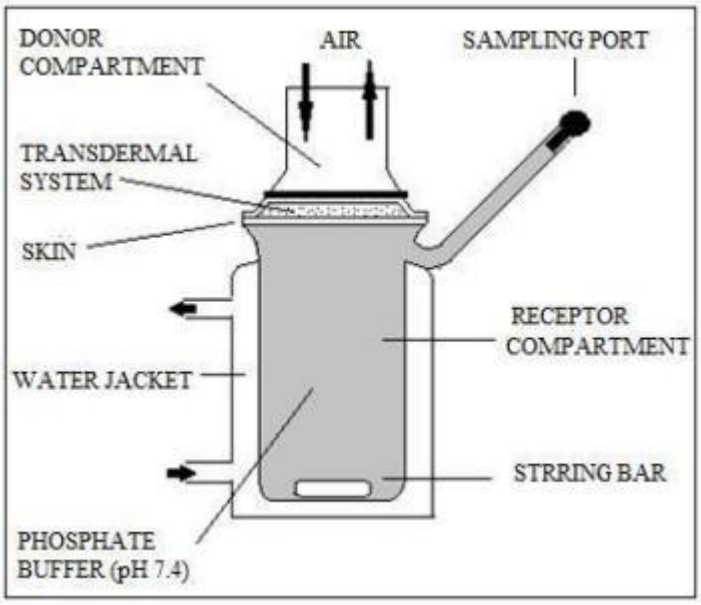
III. Rheological Properties (Viscosity Tests)

- Measured using **Brookfield viscometer**.
- Assesses **flow behavior**: Newtonian or non-Newtonian.
- Essential for predicting **spreadability, extrusion**, and **storage stability**.

IV. In Vitro Drug Release / Diffusion Study

Franz Diffusion Cell Method

- Simulates **drug permeation through skin or synthetic membrane**.
- Drug release rate is calculated over time.
- Used to **predict bioavailability** and compare **formulation batches**.



V. Microbiological Testing

- Particularly important for **aqueous formulations** (e.g., creams and gels).
- **Tests**:
    - **Total microbial count**
    - **Pathogen absence** (Pseudomonas, Staphylococcus)
- Must comply with **pharmacopoeial limits**.
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VI. Skin Irritation Test / Patch Test (optional)

- Applied to a small area of human/animal skin to assess **irritation or allergy**.
- Helps ensure **patient safety**, especially for **cosmetic or chronic-use products**.