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UNIT-5

Semisolid dosage forms: Definitions, classification,
mechanisms and factors influencing dermal penetration of drugs.
Preparation of ointments, pastes, creams and gels.
Excipients used in semi solid dosage forms.
Evaluation of semi solid dosages forms

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(Used Externally & Internally.)

SEMI SOLID DOSAGE FORMS

(Blw Solid & Liquid).

(API + Excipient).

Adhere to application Surface long lasting before they Washed off.

★ Novel Semi-Solid Must be Non-Greasy, They are Made up of Water Washable Bases. & they Cause low Irritation to Skin.

Semi-Solid Dosage form.

→ Dermatological Preparation.

→ Apply Externally to produce Local or Systemic Effect.

→ Contain One or More Active Ingredient dissolve/Uniformly dispersed in Suitable base. Or Excipient Such as Emulsifier, Viscosity Enhancing Agent, Antimicrobial, Antioxidant.

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INTRODUCTION

- Semi-solid dosage forms are dermatological preparations intended to apply externally on the skin to produce local or systemic effect e.g. ointments, creams, gels and pastes.

- 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 , antimicrobial agents, antioxidants, or stabilizing agents.

- Semisolids can adhere to the application surface for sufficiently long periods before they are washed off. This property helps prolong drug delivery at the application site.

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- Novel semisolids are non-greasy since they are made up of water washable bases. Hence, they cause less irritation to skin and are superior to conventional semisolid dosage form.

- **SEMI-SOLID** forms are made up of active ingredient & excipients [to maintain stability] {they contain antimicrobial, anti- oxidant & viscosity enhancing properties}

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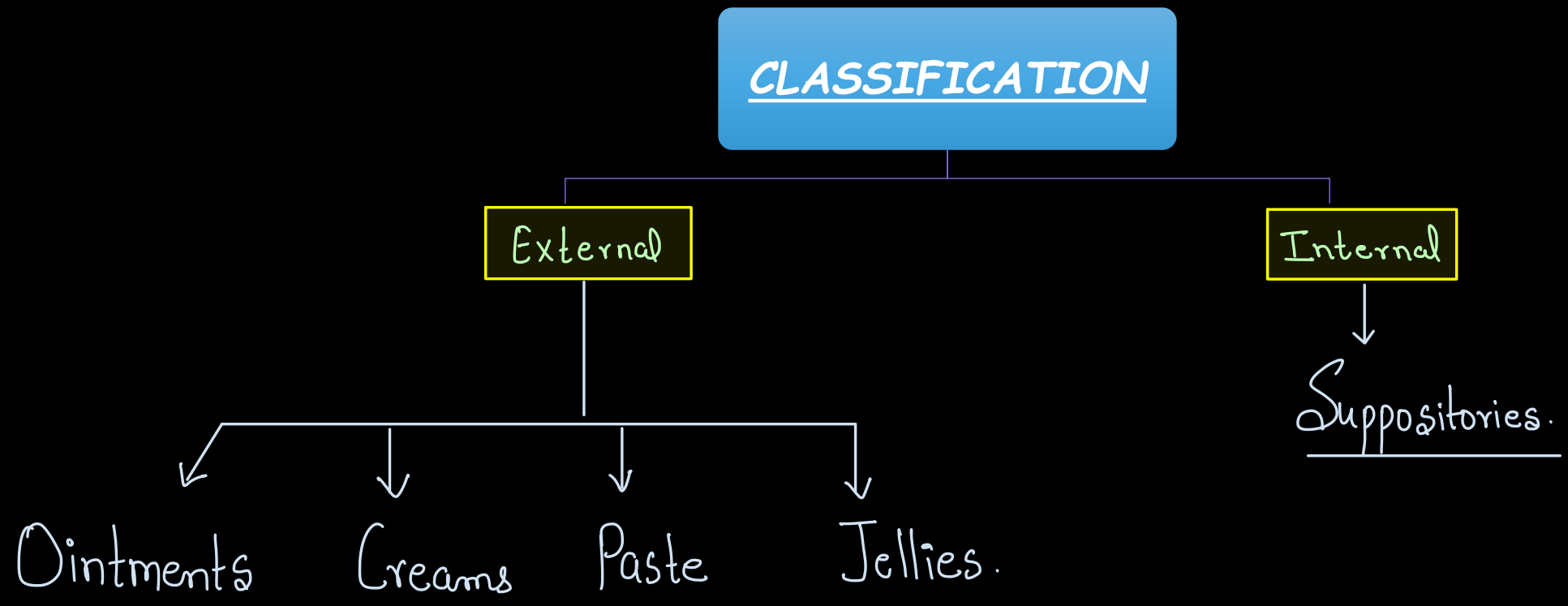

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TYPES OF CONVENTIONAL SEMISOLID DOSAGE FORMS

Ointments

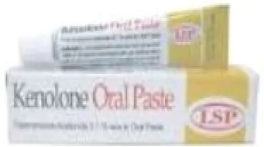
An ointment is usually applied to a dry scaly skin.

Creams

A cream is applied to weeping or oozing surfaces

Gels

Paste



Suppositories

Advantages

(i) Easy to apply Topically.

(ii) Provide Localized Action & reduce the risk of Systemic Side Effect.

(iii) Versatile option (contain wide range of drug).

(iv) Improved Patient Compliance.

(v) Provide protection to Sensitive A.P.I.

Disadvantages

(i) Limited Bioavailability.

(ii) Variability in Absorbtion.

(iii) Skin Irritation.

(iv) Stability Issue (API degradation / Physical Property Change).

(v) Difficulty in Scalling Up (Low → High).

(vi) May get Contaminated when we applied by using fingers.

(vii) May Cause Allergy in Some patient.

(viii) Less Stable then Solid Dosage forms.

(v) Regulatory Challenges (Complex regulatory requirement).

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ADVANTAGES

1. **Ease of administration:** Semi-solid dosage forms, such as ointments and creams, are easy to apply topically, making them a convenient option for patients.
2. **Localized action:** Semi-solid dosage forms can provide localized action, reducing the risk of systemic side effects.
3. **Flexibility in formulation:** Semi-solid dosage forms can be formulated to contain a wide range of active ingredients, making them a versatile option.
4. **Improved patient compliance:** Semi-solid dosage forms can be more appealing to patients than other dosage forms, improving patient compliance.
5. **Protection of sensitive APIs:** Semi-solid dosage forms can provide a protective environment for sensitive active pharmaceutical ingredients (APIs).

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DISADVANTAGES

1. **Limited bioavailability:** Semi-solid dosage forms can have limited bioavailability, reducing their effectiveness.
2. **Variability in absorption:** The absorption of semi-solid dosage forms can be variable, making it challenging to achieve consistent therapeutic effects.
3. **Skin irritation:** Some semi-solid dosage forms can cause skin irritation, reducing patient compliance.
4. **Stability issues:** Semi-solid dosage forms can be prone to stability issues, such as degradation of the API or changes in the physical properties of the formulation.
5. **Difficulty in scaling up**: Semi-solid dosage forms can be challenging to scale up from small-scale batches to large-scale commercial production.
6. **Regulatory challenges:** Semi-solid dosage forms can be subject to complex regulatory requirements, making it challenging to bring new products to market.

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TYPES OF SEMI-SOLID DOSAGE FORM

- **Ointments:** Ointments are semisolid preparations meant for external application to the skin or mucous membrane. They usually contain a medicament or medicaments dissolves, suspended or emulsified in the base.
- **Creams**: Creams are viscous emulsions of semisolid consistency intended for application to the skin or mucous membrane and o/w type and w/o type.
- **Pastes:** Pastes are the preparations which contains a large amount of finely powdered solids such as starch and zinc oxide. These are generally very thick and stiff.
- **Gels:** These are jelly-like semisolid dispersions of drug meant to be applied on the skin.

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Semi-Transparent

- **Jellies:** These are thin transparent or translucent, non-greasy preparations. They are similar to mucilage because they are prepared by using gums but they differ from mucilages in having jelly like consistency.
- **Suppositories:** These are meant for insertion in to the body cavities other than mouth. They may be inserted in to rectum, vagina or urethra.

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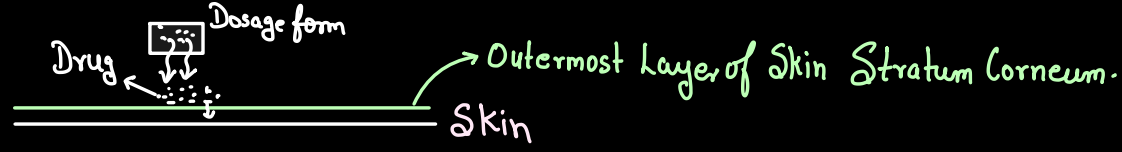
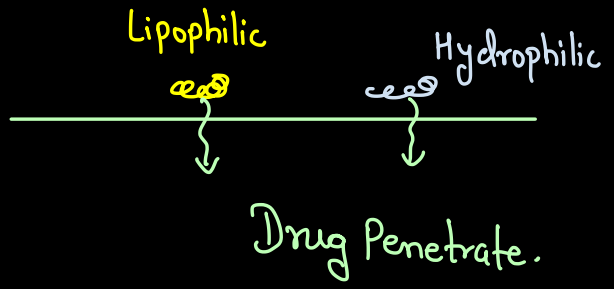
MECHANISM OF DRUG PERMEATION IN SKIN SEMI-SOLIDS



- **Step 1: DIFFUSION**
- The drug diffuses from the semi-solid formulation (e.g., cream, ointment, gel) into the skin's outermost layer, the stratum corneum.

- **Step 2: PARTITIONING**
- The drug partitions into the skin's lipophilic (fatty) or hydrophilic (aqueous) pathways, depending on its physicochemical properties .



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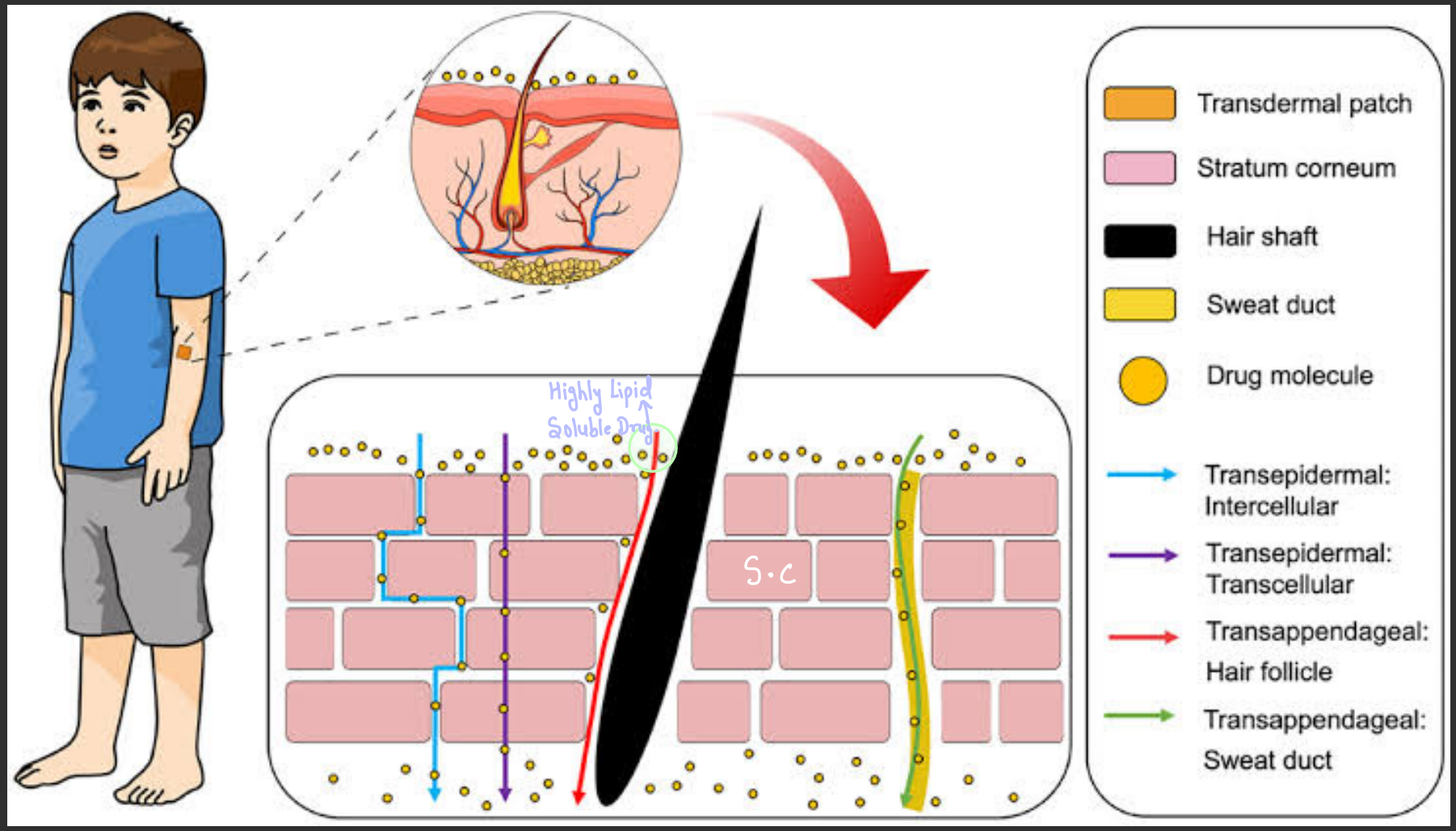

Drug

↓

Stratum Corneum → Deeper Epidermis → Dermis → Dermal Layer → Dermal Circulation से Distribute

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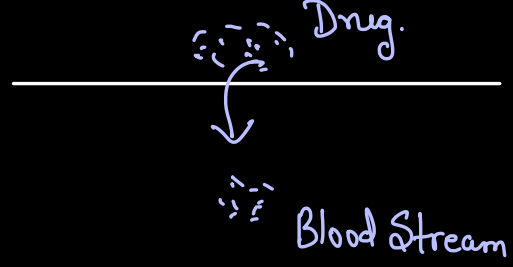
- **Step 3: PERMEATION**
- The drug permeates through the skin's layers, including the stratum corneum, epidermis, and dermis, via:
  1. **Inter-cellular** (between skin cells)
  2. **Trans-cellular** (through skin cells)
  3. **Appendageal** (through hair follicles, sweat glands)

- **Step 4: ABSORPTION**
- The drug is absorbed into the bloodstream, where it can be distributed to the target site.



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FACTORS INFLUENCING DERMAL PENETRATION OF DRUG

- **Skin condition:** The permeability of the skin is affected by age, disease, climate and injury.

- **Skin hydration:** 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.

→ More Hydrate Skin = More permeability of drug. [Hydration the Stratum Corneum Enhance the Absorbtion or Penetration of Drug]

- **Skin age:** The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug.

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- **Blood flow:** Changes in peripheral circulation can affect transdermal absorption.

T ↑ = Absorp. of drug ↑ & Lipophilic & Unionized drug Absorb faster.

- **Skin temperature:** The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

- **Regional skin site:** Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

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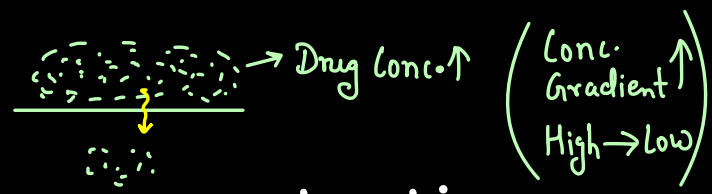
- **Skin metabolism:** Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin. (Metabolise about 5% of drug).

- **Molecular characteristic of drug:** Molecular weight upto 400 Daltons can easily penetrate through the skin surface.



- **Drug concentration:** The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

- **Solubility and partition coefficient:** Highly lipid soluble molecules enters through hair follicles. Moderately lipid soluble molecules penetrates directly across the horny layer.

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- Molecular size and shape→ Size of drug ↓ → Absorbtion ↑

  Molecular weight ↓ → Absorbtion ↑

Percutaneous Enhancer-

Use to Enhance the Absorbtion of Drug.

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Lipophilicity ~~too high~~ ~~too low~~

- **Partition coefficient:** The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

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1. PREPARATION OF OINTMENT → Drug + Base + other Excipient.

Equipment

1. Mixing vessel
2. Heat source (e.g., water bath, steam jacket)
3. Stirrer (e.g., spatula, paddle)
4. Grinding equipment (optional)
5. Weighing scale

Ingredients

1. Active pharmaceutical ingredient (API)
2. Ointment base (e.g., petrolatum, lanolin)
3. Excipients (e.g., preservatives, antioxidants)

A smooth substance that you put on sore skin or on an injury to help it get better

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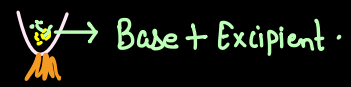
• STEPS

1. **Weighing:** Accurately weigh the API, ointment base and excipients.
2. **Mixing:** Combine the ointment base and excipients in a mixing vessel.


3. **Heating:** Heat the mixture to a suitable temperature (e.g., 50-70°C) to melt the base.
4. **Adding API:** Gradually add the API to the melted base, stirring constantly.
5. **Mixing:** Continue stirring until the API is uniformly distributed.
6. **Cooling:** Allow the mixture to cool to room temperature.


7. **Grinding (optional):** Grind the mixture to a smooth consistency.
8. **Filling:** Fill the ointment into suitable containers (e.g., jars, tubes)
9. **Packaging:** Label and package the ointment.

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METHODS OF PREPARATION OF OINTMENT

- ***Fusion Method:*** Melt the ointment base, add the active ingredient, and stir until uniform.
- ***Mixing Method:*** Combine the ointment base and active ingredient at room temperature, mixing until uniform.
- ***Grinding Method:*** Grind the active ingredient into a fine powder, then mix with the ointment base.
- ***Levigation Method:*** Reduce particle size of active ingredient using a mortar and pestle.
- ***Homogenization Method:*** Use high-speed mixing to create a uniform dispersion.
- ***Emulsification Method:*** Combine oil and water-soluble ingredients using an emulsifying agent.

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2. PREPARATION OF PASTES

Pastes are a type of semi-solid dosage form that consists of a mixture of a drug and a suitable vehicle, typically a mixture of oils, waxes, and solvents.

MATERIALS NEEDED:

- Active pharmaceutical ingredient (API)
- Vehicle (or Base.) (e.g., mineral oil, petrolatum, beeswax)
- Solvents (e.g., ethanol, isopropanol)
- Preservatives (e.g., parabens, phenol)
- Flavoring agents (optional)

EQUIPMENT NEEDED:

- Mixing vessel (e.g., stainless steel or glass bowl)
- Heat source (e.g., water bath, heating mantle)
- Stirring device (e.g., spatula, mechanical stirrer)
- Mill or grinder (optional)

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• METHOD OF PREPARATION:

1. **Weighing and measuring:** Weigh the API and vehicle components accurately, and measure the solvents and preservatives volumetrically.
2. **Mixing the vehicle:** Mix the vehicle components (e.g., mineral oil, petrolatum, beeswax) in a suitable mixing vessel until a uniform blend is obtained.
(Mix).
3. **Adding the API:** Add the API to the vehicle mixture and mix until the API is uniformly distributed.
4. **Adding solvents and preservatives:** Add the solvents and preservatives to the mixture and mix until a uniform paste is obtained.

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5. Heating and mixing: Heat the mixture to a suitable temperature (e.g., 50°C to 70°C) and mix until the paste is smooth and uniform.

6. Cooling and milling: Allow the paste to cool to room temperature, and then mill or grind the paste to a suitable consistency, if necessary.

7. Packaging and labeling: Package the paste in suitable containers (e.g., tubes, jars) and label them with the necessary information (e.g., product name, ingredients, instructions for use).

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PREPARATION OF CREAMS

Equipment

1. Mixing vessel
2. Heat source (e.g., water bath, steam jacket)
3. Stirrer (e.g., spatula, paddle)
4. Homogenizer (optional)
5. Weighing scale

Creams are semi-solid emulsions of oil and water. They are divided into two types: oil-in-water (O/W) creams which are composed of small droplets of oil dispersed in a continuous water phase, and water-in-oil (W/O) creams which are composed of small droplets of water dispersed in a continuous oily phase.

Ingredients

1. Active pharmaceutical ingredient (API)
2. Oil phase (e.g., mineral oil, petrolatum)
3. Water phase (e.g., purified water, glycerin)
4. Emulsifier (e.g., Tween 80, Span 20)
5. Preservatives (e.g., parabens, phenoxyethanol)
6. Excipients (e.g., antioxidants, pH adjusters)

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• STEPS

1. **Weighing:** Accurately weigh the API, oil phase, water phase, emulsifier, preservatives and excipients.
2. **Preparing Oil Phase:** Combine the oil phase ingredients in a mixing vessel and heat to a suitable temperature (around 70-80°C).
3. **Preparing Water Phase:** Combine the water phase ingredients in a separate mixing vessel and heat to a suitable temperature (around 70-80°C).
4. **Emulsification:** Slowly add the oil phase to the water phase, mixing constantly.
5. **Homogenization:** Use a homogenizer or high-speed mixer to create a uniform dispersion.

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6. **Cooling:** Allow the mixture to cool to around 30-40°C.

7. **Additives:** Add preservatives, antioxidants and other excipients.

8. **pH Adjustment:** Adjust the pH to a suitable range.

9. **Filling:** Fill the cream into suitable containers.

10. **Packaging:** Label and package the cream.

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PREPARATION OF GELS

Equipment

1. Mixing vessel
2. Heat source (e.g., water bath, steam jacket)
3. Stirrer (e.g., spatula, paddle)
4. Homogenizer (optional)
5. Weighing scale

A gel is a semi-solid substance that exhibits both liquid and solid properties. It consists of a network of molecules, often polymers, that trap liquid within their structure, giving it a jelly-like consistency. Gels are typically soft, flexible, and can hold their shape while allowing some flow, depending on their formulation. They are commonly used in products like cosmetics, medicines, foods, and industrial applications.

Ingredients

1. Active pharmaceutical ingredient (API)
2. Oil phase (e.g., mineral oil, petrolatum)
3. Water phase (e.g., purified water, glycerin)
4. Emulsifier (e.g., Tween 80, Span 20)
5. Preservatives (e.g., parabens, phenoxyethanol)
6. Excipients (e.g., antioxidants, pH adjusters)

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• STEPS

1. **Weighing:** Accurately weigh the API, gelling agent, solvent, preservatives and excipients.

2. **Preparing Gel Base:** Combine the gelling agent and solvent in a mixing vessel. Heat to dissolve the gelling agent.

3. **Adding API:** Add the API to the gel base and mix until uniform.

4. **Homogenization:** Use a homogenizer or high-speed mixer to create a uniform dispersion.

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5. **Cooling:** Allow the mixture to cool to room temperature.

6. **Additives:** Add preservatives, antioxidants and other excipients.

7. **pH Adjustment:** Adjust the pH to a suitable range.

8. **Filling:** Fill the gel into suitable containers.

9. **Packaging:** Label and package the gel.

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EXCIPIENTS USED

- Semi-solid bases
- Anti oxidant
- Chelating agents
- Vehicles
- Micellar solubilizers
- Buffers
- Preservative
- Humectants
- Gelling agents
- Emulsifiers
- Permeation enhancer

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• SEMI-SOLID BASES-

- Bases used in ointment & suppositories
- They have-
  - Smooth texture
  - Elegant appearance
  - No irritation
  - Not affect skin function
  - Applied with ease & should be washed with water
  - Free from gritty particle
  - Not be hygroscopic

CLASSIFICATION-

- Hydrocarbon bases
- Emulsifiable base [O/W or W/O]

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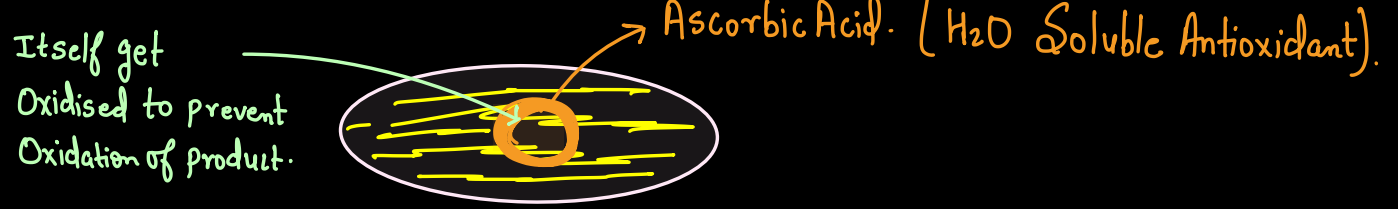
• ANTI-OXIDANT

- Add in foods, cosmetic & drug to prevent oxidation
- Anti-oxidants:
- butylated hydroxy toluene [B.H.T.]
- Butylated hydroxy anisole. [B.H.A]

- Ascorbic acid is an water soluble antioxidant , it itself gets oxidised & prevent from oxidation



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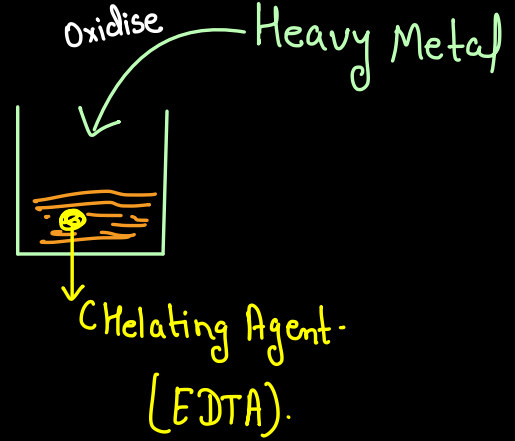
• CHELATING AGENT



- Prevent oxidation of product
- Like EDTA- forms complex with heavy metal
- Unavailability of metal ion to catalyze the oxidation

• VEHICLES

- Water is universal solvent
- Solvent instead of water is given to stabilize the drugs

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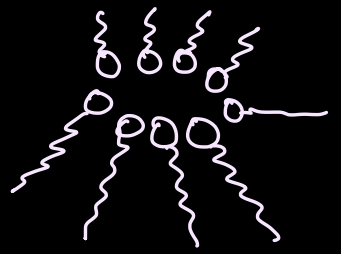
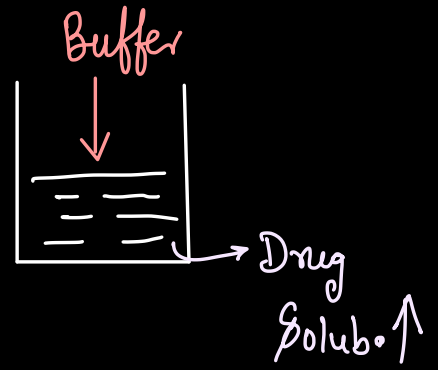
• SURFACTANT / Surface Active Agent -



- Possessing both – hydrophilic & hydrophobic group
- Due to hydrophilic functional group it enhance the solubility of poor water soluble drugs

• BUFFER

- E.g – sodium citrate
- Drug solubility is aided by buffer system
- Buffer of suitable pH maintain max stability of drug



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• PRESERVATIVE

Base + Drug + Excipient

- Bases have high water content but capable for tolerating microbial attack due to presence of preservative
- E.g- methyl hydroxyl benzoate

• HUMECTANTS

- Hygroscopic in nature- used in creams (to prevent) from getting dried

• GELLING AGENT

- E.g- tragacanth, pectin: used to produce a gel like consistency

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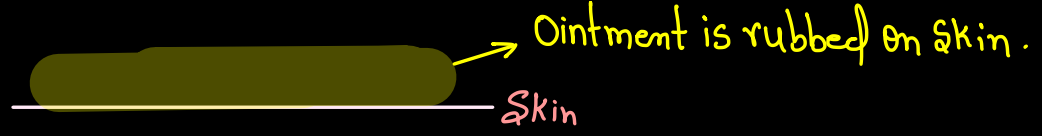
EVALUATION OF SEMI- SOLID DOSAGE FORM

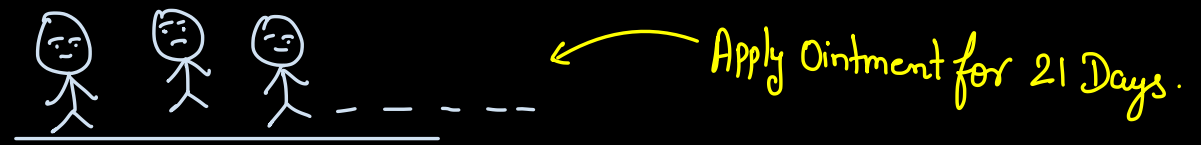
1. PHYSICAL METHOD-



a. Test of rate of absorption

- In this test ointment is rubbed on skin & at regular time interval we collect serum & urine sample & then estimate the amount of drug absorbed

b. Test on non- irritancy



- Select 24 human volunteers: apply ointment for 21 days & check pharmacological action.
- If oedema, skin redness & itching is not there then the ointment can be marked as good ointment base

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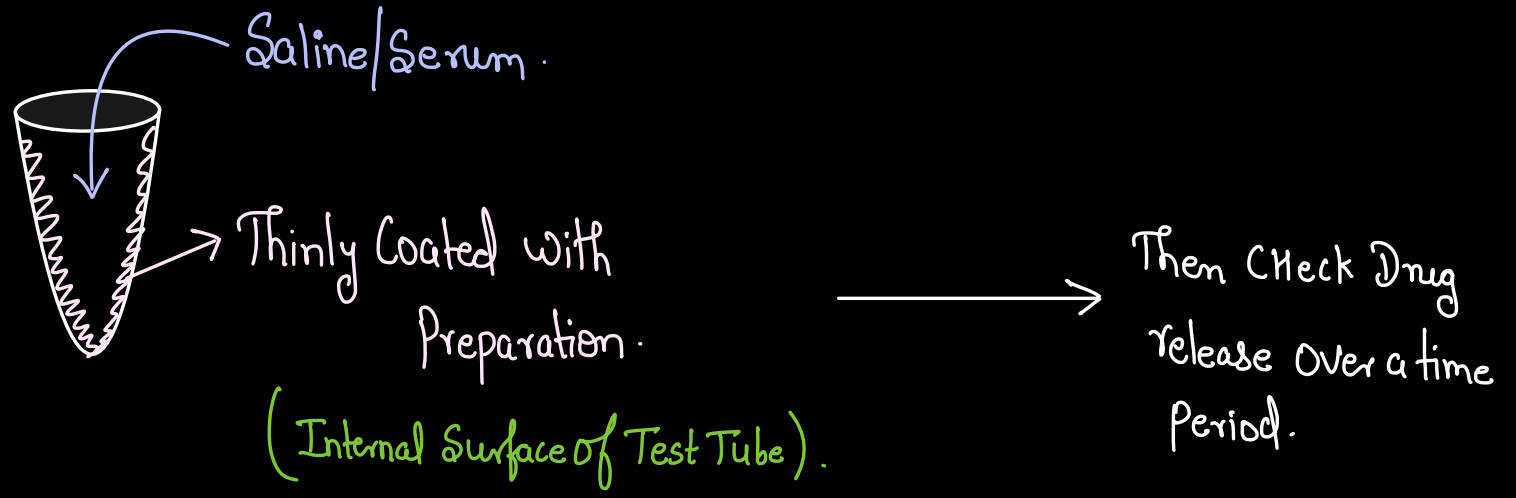
c. Test of rate of penetration

- When more penetration is there more absorption will take place leading to more action
- Check diffusion [from high concentration to low concentration]

b. Test of rate of drug releaase



Internal surface of test tube is coated with preparation and the saline/serum is added then check the drug releases over a time period (Drug release rate)

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e. Test of rheological properties [flow properties]

- Easy withdrawal from container
- Ease in application for skin
- Test of viscosity done by cone & plate viscometer

f. Test of content uniformity

- Weigh 10 filled ointment container
- Result obtained must be match with labelled quantity

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g. Microbiological method-

a) Test of microbial content -

Microbiological testing is important for patient safety in the pharmaceutical industry and for ensuring consumer safety in food production.

b) Test of preservative efficacy-

A preservative efficacy test (PET) is a laboratory test that evaluates how well a product's preservatives prevent microbial contamination. It's also known as an Antimicrobial Effectiveness Test (AET).

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Packaging- Must be non reactive, non toxic, non irritant, must be stable inert

Glass or Plastic used → Prepared for Cream, Ointment.

↓ For Medium bulk quantities (2kg).

→ Effectively protect the Ingredient.

Metal Used → (Stainless Steel).

↓ for bulk (25-50kg)

↓ Chemical resistance.

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