SEMI-SOLID DOSAGE FORMS

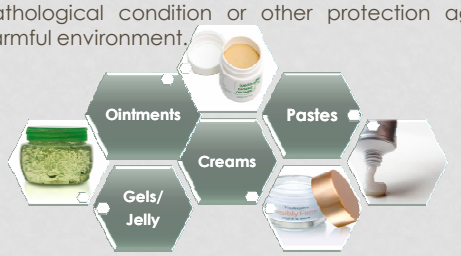
OINTMENTS, CREAMS, PASTES & GELS

INDUSTRIAL PROCESSING

INTRO, PROPERTIES, EXAMPLES

SEMI-SOLID DOSAGE FORMS

- Semi solid pharmaceutical system comprise a body of product ,which when applied to skin or accessible mucous membranes tends to alleviate or treat a pathological condition or other protection against harmful environment.



BASIC INTRODUCTION

Transdermal formulation are designed to applied on skin for the purpose of delivery of drug through the skin into the systemic circulation for their effect.

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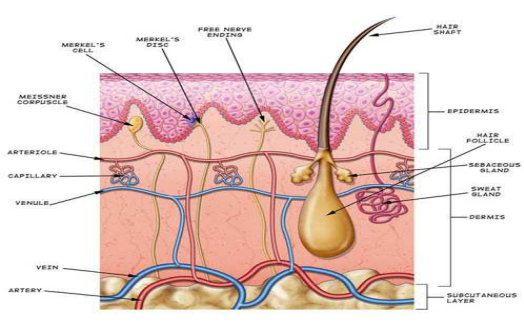
STRUCTURE OF SKIN



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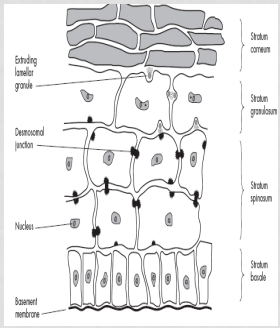
- Subcutaneous fat layer
- Dermis
- Epidermis

1. Stratum Corneum
2. Stratum Granulosum
3. Stratum Spinosum
4. Stratum Germinativum



A representation of human epidermal cell differentiation

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PERCUTANEOUS ABSORPTION

- ***Absorption–***

The act of taking up or in by specific chemical or molecular action; especially the passage of liquids or other substances through a surface of the body into body fluids and tissues.

-Chemical Absorption

-Digestive Absorption

-Radiation Absorption

-**Percutaneous Absorption**

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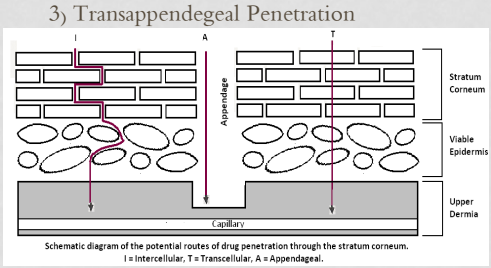
PENETRATION OF DRUG

1) Intra cellular penetration
2) Inter cellular penetration
3) Transappendegeal Penetration



Schematic diagram of the potential routes of drug penetration through the stratum corneum. I = Intercellular, T = Transcellular, A = Appendageal.

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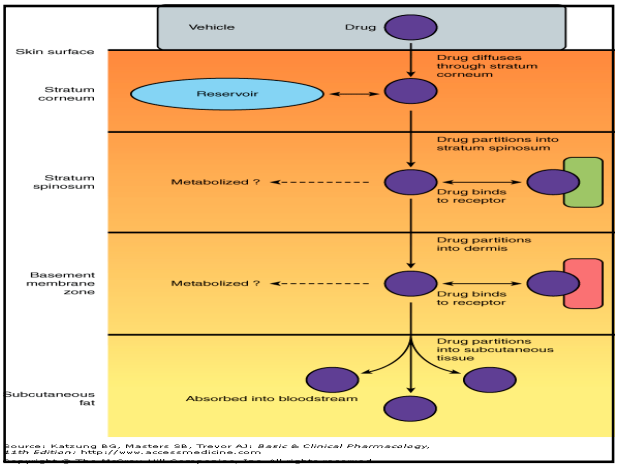


IDEAL PROPERTIES OF SEMI SOLID DOSAGE FORM

Physical properties

a) Smooth texture
b) Elegant in appearance
c) Non dehydrating
d) Non gritty
e) Non greasy and non staining
f) Non hygroscopic

Physiological properties

a) Non irritating
b) Do not alter membrane function
c) Miscible with skin secretion

Application properties

a. Easy applicable with efficient drug release
b. High aqueous washibility

OINTMENTS

- Ointments are homogenous, translucent, viscous, semi solid preparation intended for external application to skin or mucous membranes. Ointment may be medicated or not.

❖Applied to mucous membrane or skin

❖**Uses**

- Emollient
- Application for active ingredients to the skin
- Occlusive

OINTMENTS (CONT.)

Ointment Bases

- Oleaginous Bases
- Absorption Bases
- Water-Removable Bases
- Water-Soluble Bases

Preparation of Ointments

- Incorporation
- Fusion

Compendial Requirements for Ointments

- Microbial Content
- Minimum Fill
- Packaging, Storage, and Labeling
- Additional Standards

CREAMS

- Viscous semi solid emulsion with opaque appearance as
- Contrasted with translucent ointments
- Consistency depends on whether the cream is W/O or O/W

W/O Creams	O/W Creams
Contain lipophyllic emulsifying agent	*Contains O/W emulsifying agent*
Used as emollient or as cleansing agent	*O/W creams are elegant drug delivery system*

PASTES

❖Contains high percentage of insoluble solid(usually 50% or more)

❖Pastes are usually prepared by incorporating solids directly into a congealed system by levigation with a portion of base to form paste like mass.

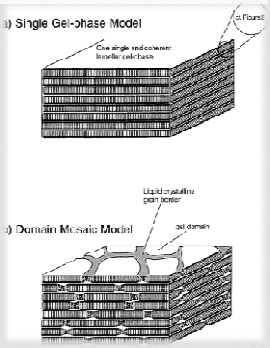
❖They have good adhesion on skin and less greasy.

GELS/JELLY

- Gels are semi solid system in which liquid phase is constrained with a **3-D** polymeric matrix having a high degree of physical or chemical cross linking
- Gels are aqueous colloidal system of hydrated forms of insoluble medicaments.
- Jellies are transparent or translucent non greasy semisolid and contain more water than gels.
- Used for medication, lubrication and carrier for spermicidal agents to be used intra vaginally with diaphragm.

TYPES OF GEL-PHASE

- **Single Phase**
  - ✓ **Gels in which the macromolecules are uniformly distributed throughout a liquid with no apparent boundaries between the dispersed macromolecules and the liquid**
  - ✓ **Usually involve organics**
- **Two Phase(Domain)**
  - ✓ **When the gel mass consists of floccules of small distinct particles**
  - ✓ **Usually involve inorganics**



Gel Composition

- Gelling agent
- Water
- Cosolvents
- Preservatives
- Stabilizers

Gelation

- As a hot, colloidal dispersion of gelatin cools, the gelatin macromolecules lose kinetic energy.
- With a reduction of kinetic energy or thermal agitation.
- Gelatin, agar, pectin, Irish moss, pectin, tragacanth form gels by this mechanism.

Kinds of Gels

- Hydrogels
  - ✓Silica, bentonite, pectin, sodium alginate, methylcellulose, alumina
- Organic Gels
  - ✓Contain an organic liquid (e.g., Plastibase)
- Carbomer Gels
  - ✓Aqueous dispersion neutralized with sodium hydroxide or triethanolamine
- Methylcellulose Gels
- Starch Glycerite
- Aluminum Hydroxide Gel

FORMULATION OF SEMI-SOLIDS

Ingredients used in preparation of semi solid dosage form:

- ✓ *Active pharmaceutical ingredients*
- ✓ *Bases*
- ✓ *Preservatives*
- ✓ *Humectants*
- ✓ *Anti oxidants*
- ✓ *Emulsifier*
- ✓ *Gelling agent*
- ✓ *Buffers*

BASES

❖It is one of the most important ingredient used in the formulation of semisolid dosage form

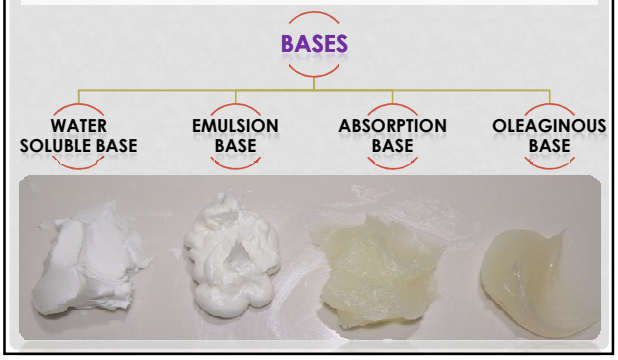
❖Ointments and suppository base do not merely acts as the carrier of the medicaments, but they also control the extent of absorption of medicaments incorporated with them

IDEAL PROPERTIES

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.

CLASSIFICATION OF BASES



EXAMPLES OF BASES

Oleaginous Bases
Hydrocarbons (mineral oils, petrolatums, paraffins, waxes)
Animal fats/vegetable oils (castor oil, cottonseed oil, olive
Synthetic esters (glyceryl monostearate, butyl stearate, isopropyl lanolate, stearyl alcohol)

Absorption Bases
Hydrophilic petrolatum
Aquaphor
Aquabase

Emulsion Bases
Water-in-oil:
Cold Cream (Petrolatum-Rose Water Ointment)
Lanolin
Oil-in-water:
Hydrophilic Ointment
Velvachol

Water Soluble Bases
Polyethylene Glycol Ointment
Biozyme Ointment, Desenex Ointment, Whitfields Ointment
Veegum 10% Dermatological base
Veegum 5% Thixotropic lotion

PRESERVATIVES

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**

ANTI-OXIDANTS

(WITH CLASSIFICATION)

- 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 are added.
- Example : **Butylated hydroxy anisole , Butylated hydroxy toluene**

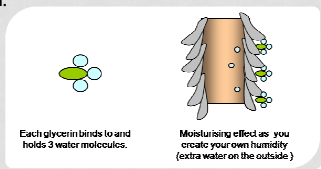
ANTIOXIGENS	REDUCING AGENT	ANTIOXIDANT SYNERGIST
Acts by reacting with the free radicals. e.g. •Butylated hydroxy anisole (BHA) •Butylated hydroxy tocopherols (BHT) (used for oil system)	Have lower redox potential than drug,hence gets oxidized first. e.g. •Ascorbic acid •Potassium and sodium metabisulfite •Thiosulfite (used for aqueous system)	Chelating or sequestering agents, enhance the effect of anti oxidants. e.g. •Citric acid •Tartaric acid •Lacithin

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.**



GELLING AGENTS

- Gelling agent forms a gel dissolves in a liquid phase as a colloid mixture that forms a weakly cohesive internal structure.
- These are organic hydro colloids or hydro phillic inorganic substances.

Example : **tragacanth, sodium alginate, pectin, gelatin, cellulose derivatives.**

Material	%	Brook field viscosity
Carbomer 94 1 resin NF	0.15	2900
Carbomer 94 1 resin NF	0.25	6300
Guar gum	1.50	8040
Methyl cellulose	2.00	5200
Sodium alginate	2.50	10400

EMULFISIERS

Anionic	Cationic	Non ionic
•Alkyl sulphates •Soaps •D odecyl benzene •Sulfonates •Lactylates •Sulfosuccinates •Monoglycerides •Sulfonates •Phosphate esters •Silicones •Taurates	•Quaternary ammonium compounds •alkoxyalkylamines	•Polyoxyethylene •Alkyl-aryl ethers •Polyoxy ethylene •Sorbitan esters •Sorbitan fatty acid esters •Glyceryl fatty acid esters

BUFFERS

Buffers are added to various purpose such as:

✓ Compatibility with skin

✓ Drug solubility

✓ Drug Stability

✓ Influence on ionization of drug

Example: **Sodium acetate , Sodium Citrate , Potassium meta phosphate**

PENETRATION ENHANCERS

- Substance exist which temporarily diminish the impermeability of the skin, known also as accelerants or sorption promoters
- Example of Penetration enhancers
  - Sulphoxides (dimethylsulphoxide)
  - Pyrrolidones
  - Fatty acids and alcohols
  - Azone and its derivatives
  - Surfactants – anonic,cationic and non-ionic
  - Urea and its derivatives
  - Alcohols and glycols

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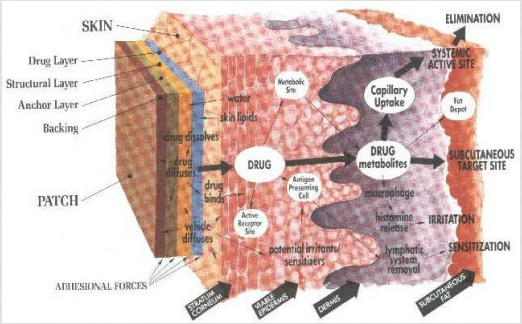
TRANSDERMAL DRUG DELIVERY SYSTEMS

Factors Affecting Percutaneous Absorption

1. Nature of the drug itself
2. Nature of the vehicle
3. The nature of the skin
4. Presence of moisture

Many Factors to Consider



Ideal Drug Properties Needed for Passive Transdermal Delivery

Aqueous solubility	>1 mg ml^{-1}
Lipophilicity (oil-water partition)	$10<K_{o/w}<1000$
Molecular weight	<500 Da
Melting point	<200° C
pH (saturated aqueous solution)	pH 5-9
Dose deliverable	<10 mg day^{-1}

Mechanism Of Action For Percutaneous Absorption Enhancers

Mechanism Of Action

- Reduction of the resistance of the stratum corneum by altering its physicochemical properties
- Alteration of the hydration of the stratum corneum
- Effecting a change in the structure of the lipids and lipoproteins in the cellular channels, through solvent action or denaturation
- Carrier mechanism in the transport of ionizable drugs.

METHODS OF PREPARATION

PREPARATION OF SEMI SOLIDS

(OINTMENTS, CREAMS, PASTES)

- Trituration method — Ex. Ointments creams pastes
- Chemical reaction method — Ex. Ointments creams
- Fusion method — Ex. Ointments creams pastes
- Emulsification method — Ex. Ointments creams

Trituration Method

Fusion Method

PREPARATION OF OIL AND AQUEOUS PHASES

- ✓ The components of the oil mixtures are placed into a stainless steel steam jacketed kettle, melted and mixed.
- ✓ Some of the solid components e.g. stearic acid, cetyl alchol are available in many different forms like cakes, flakes or powder. The flakes are more preferable because of the convenience of handling.
- ✓ Petrolatum is inconvenient to handle unless it is melted and transferred by pumping or pouring from its drum.
- ✓ The oil phase is then strained through several layers of cheese cloth to remove any foreign matter.
- ✓ If petrolatum is used as oil phase then it should be passed through filter medium particularly in ophthalmic preparations.
- ✓ The oil phase is transferred by gravity or pump to the emulsion mixing kettle.
- ✓ The components of the aqueous phase are dissolved in the purified water and filtered, A soluble drug may be added to this aqueous phase.

MIXING OF PHASES

- The phases are usually mixed at a temperature of 70 to 72^{0}C,because at this temperature intimate mixing of the liquid phases can occur.
- The properties of some emulsions depend on the temperature at which the phases are mixed. The initial mixing temperature must be raised above 70 to 72 ^{0}C.

Ways of Mixing the Phase

1. Simultaneous blending of the phases
2. Addition of the discontinuous phase to the continuous phase
3. Addition of the continuous phase to the discontinuous phase

MIXING OF PHASES (CONT.)

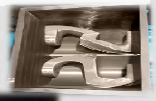
- ❑The simultaneous blending of the phases requires the use of a proportioning pump and a continuous mixer.
- ❑This method is used for continuous or large batch operation.
- ❑The second method is used for emulsion systems that have a low volume of dispersed phase.
- ❑The third process is preferred for many emulsion systems.

EQUIPMENTS USED FOR MIXING OF PHASES

- **Agitator mixers** – Sigma mixer and planetary mixer
- **Shear mixers** – Triple roller mill and Colloidal mill

Sigma blade mixer:

The mechanism of mixing is shearing. The sigma shaped blades creates high shear.



Advantages:

1.It creates a minimum dead space during mixing.

2.It is used for wet granulation process.

Disadvantages:

1.It works at a fixed speed.

Colloidal mill:

It consists of two steel discs. Here one disc rotates and another one is stationary. When the material is passed through these discs they get sheared. Thus coarse particles are break down to small particles due to shear.

Advantages:

1.It can be used in the production of sterile products.

Disadvantages:

1.It is not used for dry milling.

2.Heat is generated during milling.

STORAGE CONDITIONS OF SEMISOLIDS

STORAGE OF SEMI-SOLIDS

- Unless rapid in process methods of analysis are developed, it is the usual practice to store the semisolid until the specified quality control tests have been completed before packaging into appropriate.
  containers: **tubes, jars, or single dose packets.**
- A product is considered to be in process until it has been packaged.
- The active substance in the cream or ointment may react with the storage container unless a Highly resistant, stainless steel, is used for bulk storage.
- Evaporation of water from a cream must be retarded; this can be effectively accomplished by placing non-reactive plastic sheeting in direct contact with the cream, as well as covering the storage container with a tight-fitting stainless steel lid.

TRANSFER OF MATERIAL FOR PACKAGING

- ***The semi-solid may be gravity fed, if it is a two-Level operation or pumped to the filling equipment.***
- ***It must be able to resist the shear stress developed in the transfer of the product, as well as that due to the mechanical action of the filling equipment.***
- ***Once a formal manufacturing procedure has been established, there should be no deviation from it.***
- ***The manufacturing and packaging equipment should be sanitized following thorough cleaning with detergents.***
- ***They should be flushed with chlorinated water, formalin, or other suitable sterilant followed by a bacteria-free water rinse.***
- ***Water and swab samples should be taken to verify microbial elimination.***

EVALUATION OF OINTMENTS & CREAMS

Evaluation Parameters

1- PHYSICAL APPEARANCE
2-PARTICLE SIZE DETERMINATION
3-WEIGHT VARIATION TEST
4-SOLUBILITY TEST
5-VISCOSITY DETERMINATION
6-ACTIVE INGREDIENTS
7-MICROBIAL CONTAMINATION
8-METAL PARTICLE IN OPHTHALMIC OINTMENTS

1- PHYSICAL APPEARANCE

- The main characteristics need to be checked are
  - Cracking of creams (separation of oil and water)
  - Development of granular and lumpy appearance
  - Marked change in viscosity
  - Crystal growth
  - Microbial contamination

2-PARTICLE SIZE DETERMINATION

- Dilute a suitable qty of preparation with equal volume of glycerol or liquid paraffin, as specified
- Mount on a glass slide and examine under light microscope
- Count the number of particles with daimeter above or below than that specified in monograph
- Compare the percentage with official limits

3-WEIGHT VARIATION TEST

- Applies to those products in which labeled net weight is not more than 150g
- Select 10 filled containers, remove the label, clean and weigh individually
- Remove the contents by cutting the containers and wash with suitable solvent

- Dry and again weigh each empty container together with its corresponding part, take difference as weight of contents.
- The average net weight of contents of 10 containers should not be less than the labeled amount
- The net weight of contents of any single container should not be less than 90% of the labeled amount (for ≤ 60g)

- And not less than 95% of the labeled amount (60-150g)
- If this requirement is not met repeat this procedures taking additional 20 containers
- The average net weight of contents of 30 containers should not be less than labeled amount

- Contents of not more than 1 of the 30 units should be less than 90% of the stated amount (for ≤ 60g)
- And not less than 95% of the labeled amount (60-150g)

4-SOLUBILITY TEST

- The preparation should be soluble in 9 parts of water and 1.7 parts of hot water
- The preparation should be miscible with alcohol, ether and chloroform

5-VISCOSITY DETERMINATION

- Viscosity is determined using a method specified in official monograph

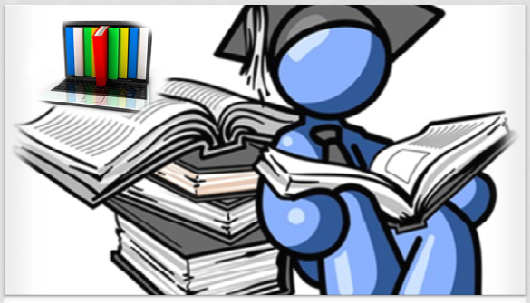
6-ACTIVE INGREDIENTS

- Assay of active ingredients should be performed according to monograph
- Percentage contents should be within the official limits

7-MICROBIAL CONTAMINATION

- Microorganisms can grow, if no preservative is added, or even if added, its efficiency is reduced due to interaction with other ingredients
- Microorganisms may get into the preparation during handling and storage
- Therefore, aseptic techniques of handling are needed

- Antimicrobial assay should be performed according to official monograph, usually
  - Direct inoculation method
  - Membrane filtration method



REFRENCES

REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY
PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN BY AULTON
ANSEL'S PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS


Thank you
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