Integrated Physical Pharmacy and Pharmaceutics II (Phar 2092)

Semisolid dosage forms

JOHN M.

OUTLINE

- Introduction to semisolids
- Classification of semisolid
- Rheological properties of semisolids
- Rational approach to drug delivery to the skin
- Factors influencing percutaneous absorption
- Maximizing the bioavailability of drug to skin:
  - ✓ Ointments
  - ✓ Pastes
  - ✓ Jellies
  - ✓ Creams

Introduction to semisolids

- **Definition**: products of semisolid consistency and applied to skin for therapeutic or protective action or cosmetic function.

- Tend to alleviate or treat a pathological condition

- Protection against a harmful environment.
  - They have the property to cling to the skin or mucous membrane for a protracted period of time
    - ✓ exert their therapeutic effect through **protection and occlusion**

Introduction, cont'd

- Intended for **localized drug delivery**.
  - applied topically to the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, external ear lining ,etc

- explored for the **systemic delivery** of various drugs.

Introduction, cont'd

Ideal Properties Of Semisolid Dosage Forms

Physical Properties: -

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

Introduction, cont'd

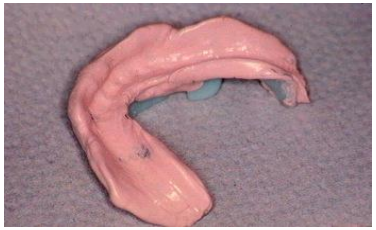
- **Physiological Properties: -**
  - Non irritating
  - Do not alter membrane / skin functioning
  - Miscible with skin secretion
  - Have low sensitization index

Introduction, cont'd

Classification of Semisolid dosage forms

- Semisolid dosage forms include

ointments pastes creams gels

- **Ointments:** semisolid preparations intended for external application to the skin or mucous membranes

- The semisolid **vehicle** into which drug substances may be incorporated in preparing medicated ointments…**Bases**

- Ointment bases recognized for use as vehicles fall into four general classes:
  - the hydrocarbon bases
  - the absorption bases
  - the water-removable bases
  - the water-soluble bases.
- Each therapeutic ointment possesses as its base a representative of one of these four general classes

Classification, cont'd

Cream:

- are semisolid preparations containing **one or more medicinal agents** dissolved or dispersed in either **a W/O emulsion or an oil-in-water emulsion** or in another type of water-washable base

- more recently the term has been restricted to products consisting of oil-in-water emulsions
  - or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically acceptable.

Classification, Cont'd

Gels: – are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jellylike by the addition of a **gelling agent**

- are transparent or translucent, non-greasy, semisolid systems generally applied externally for their medication, lubrication and miscellaneous purposes.

Pastes: – semisolid dispersion system, where a solid particles (> 20%, e.g. ZnO) are dispersed in ointment bases - mostly oleaginous (Petrolatum)

Rheological properties of semisolids

- Semisolid dosage forms exhibit different rheological properties

- Semisolids do not flow at **low shear stresses** but undergo reversible deformation like elastic solids.

- When a characteristic shear stress, called the yield value or yield stress, is exceeded, they flow like liquids.

Rheological properties, cont'd

- At a stress below yield value no flow will be formed but only elastic deformation.
- When the yield stress is exceeded, the network is partly ruptured and flow occurs.
- Gels or jellies are characterized by a comparatively high degree of elasticity.

Rheological properties, cont'd

- Pastes - Pastes have little elasticity

- Cannot recover their shape except from very small deformations.

- At stresses above their yield values, pastes turns into free-flowing liquids (**plasticity**).

- Brownian motion builds up the networks in gels and pastes and restores them when they have been ruptured by stress higher than yield stress.

Rheological properties, cont'd

- Plastic materials:- ointments and pastes, creams, butter , margarine…
- Semisolids with high yield values are described as "hard".
- When their plastic viscosity is high, they are described as "stiff".
- Instrument for determining the rheological properties of pharmaceutical semisolid are:
  - Rotational viscometer.
  - Cone-plate viscometer

Rational approach to drug delivery to & via the skin

1. **Manipulate the barrier function of the skin**:

- Topical antibiotics and anti bacterials help a damaged barrier to ward off infection
- **Sunscreen agents** protect the viable tissues from ultraviolet radiation;
- **Emollient preparations** restore pliability to a desiccated horny layer

Rational approach, Cont'd

2. Directing drugs to the viable skin tissues

3. Delivering drugs skin for systemic treatment.

- E.g., transdermal therapeutic systems provide systemic therapy for conditions such as motion sickness, angina and pain.

Skin structure

Skin also known as cutaneous membrane or integument

- external membranous covering of an animal body

- The largest organ of the body, it is thin at some places (eye lids thickness =0.5 mm) where as thick at other places (sole of foot, palm of hand thickness=5mm).

- Average thickness of skin is 1-2mm (0.04-0.08in).

Skin structure, cont'd

- Skin consists of three layers: **Epidermis, dermis and subcutaneous**

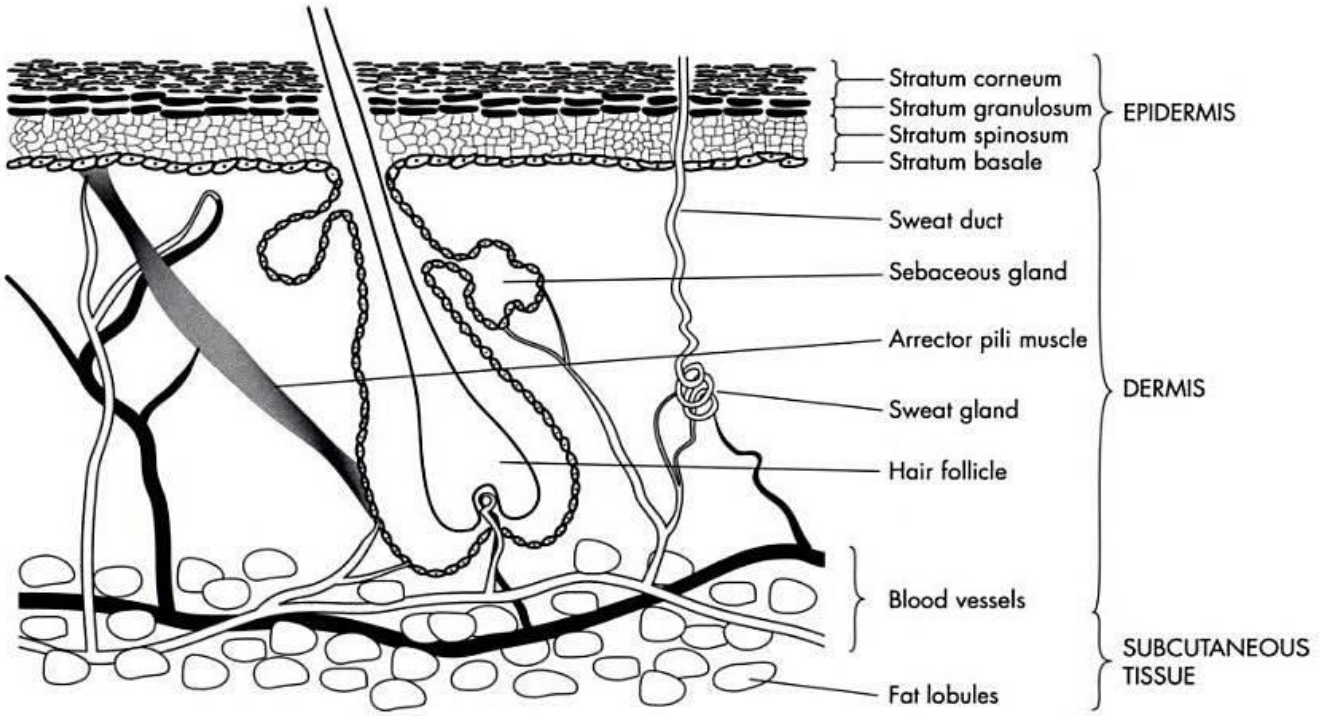


Figure 1.1 A diagrammatical cross-section through human skin.

Skin structure, cont'd

Epidermis

- The superficial , thinner portion composed of keratinized stratified squamous epithelial tissue

- it is nourished by diffusion of nutrients from a vascular network of dermis

- Composed of 4 type of cells

1. keratinocytes
2. melanocyets
3. langerhans cell
4. merkel cell

Skin structure, cont'd

Keratinocytes :(keratino= horny like, cytes=cell)

- 90 % of epidermal cells are keratinocytes.
- Responsible for production of **keratin**…a tough fibrous protein
  - protect the skin and underlying tissues from **heat, microbes and chemical.**

Melanocytes: (*Melano*=black, *cytes*=cell)

- 8% of epidermal cells are melanocytes.
- Produces a pigment ***melanin*** (a yellow red or black brown pigment) contribute in skin color
  - absorbs damaging uv light

Skin structure, cont'd

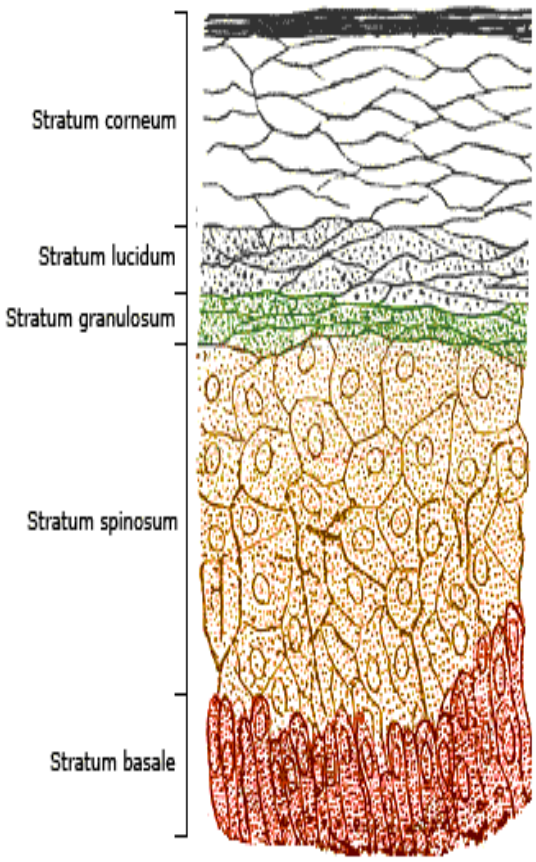
Langerhans cells

- Participate in immune responses against microbes that invade the skin
- Helps other cells of immune system to recognize an invading microbe and destroy it.

Merkel cell

- Participate in detection of touch sensation.

Skin structure, cont'd



- Epidermis consists of different layers
  - a) Stratum corneum (Horney layer)
    - Barrier to Percutaneous absorption
  - b) Stratum lucidum (Barrier zone)
    - ✓ Barrier to transfer of water across skin,
    - ✓ damage resulted in increased permeability.
  - c) Stratum granulosum (Granular layer)
    - ✓ Participate in keratinisation
  - d) Stratum spinosum (Prickle cell layer)
  - e) Stratum basale (Stratum germinativum)
    - ✓ Melanocytes the pigment-producing cells of the epidermis,

Skin structure, cont'd

Dermis :

- The sensitive connective tissue layer of the skin located below the epidermis, containing nerve endings, sweat and sebaceous glands, and blood vessels, hair follicles, fibroblast, histocytes and lymph vessels.

- Composed of strong connective tissue containing collagen (for strength) and elastin (for stretch)

Skin structure, cont'd

Hypodermis :

- Below the dermis is hypodermis also known as subcutaneous layer **(** Sub mean under and cutaneous mean skin).

- Loose layer of connective tissue which is anchored to the underlined tissue (muscle and bones).

- Most fat cells are present in hypodermis (adipose tissues)
  - acts as insulator to protect the body from excessive heat and cold environment

Skin appendages

1.Sweat glands

- The sweat glands are coiled tubules in the dermis which open on to the skin surface; they can be sub-divided in to two classes;

- **Eccrine glands:**
  - involved in the regulation of body temperature by water elimination.
  - About two million eccrine sweat glands on the average human body.

Skin structure, cont'd

- **Apocrine sweat glands**:
  - Are larger than eccrine sweat but few in number.
  - mainly located in the hairier regions of the maxillae and around the nipples.
  - Apocrine sweat differs in composition from eccrine and may be cloudy and colored

Skin structure, cont'd

2.Hair follicles

- Hair follicles are sebum-filled openings from which keratinous hair filaments protrude.

- Follicles occupy about 0.1% of the skin surface area; but are absent from plantar and palmar surfaces, the red areas of the lips, and parts of the genitalia.

Functions of skin

- Containment of body fluid and tissue
- Protection from external stimuli
  - Microbial barrier
  - Chemical barrier
  - radiation barrier
  - Thermal barrier

Percutaneous absorption (Transdermal drug delivery)

- **Percutaneous absorption :** the absorption of substances from outside the skin to positions beneath the skin, including entrance into the blood stream.

- Drugs may penetrate intact skin after topical application through
  - the walls of the hair follicles,
  - the sweat glands
  - the sebaceous glands,
  - Trough the cells of the horny layer

Percutaneous absorption, cont'd

- The main route for the penetration of drug is generally through the epidermal layers (b/c of surface area).

- The stratum corneum is the outermost 'horny' layer of skin, comprising about partially desiccated, dead, keratinized epidermal cells.

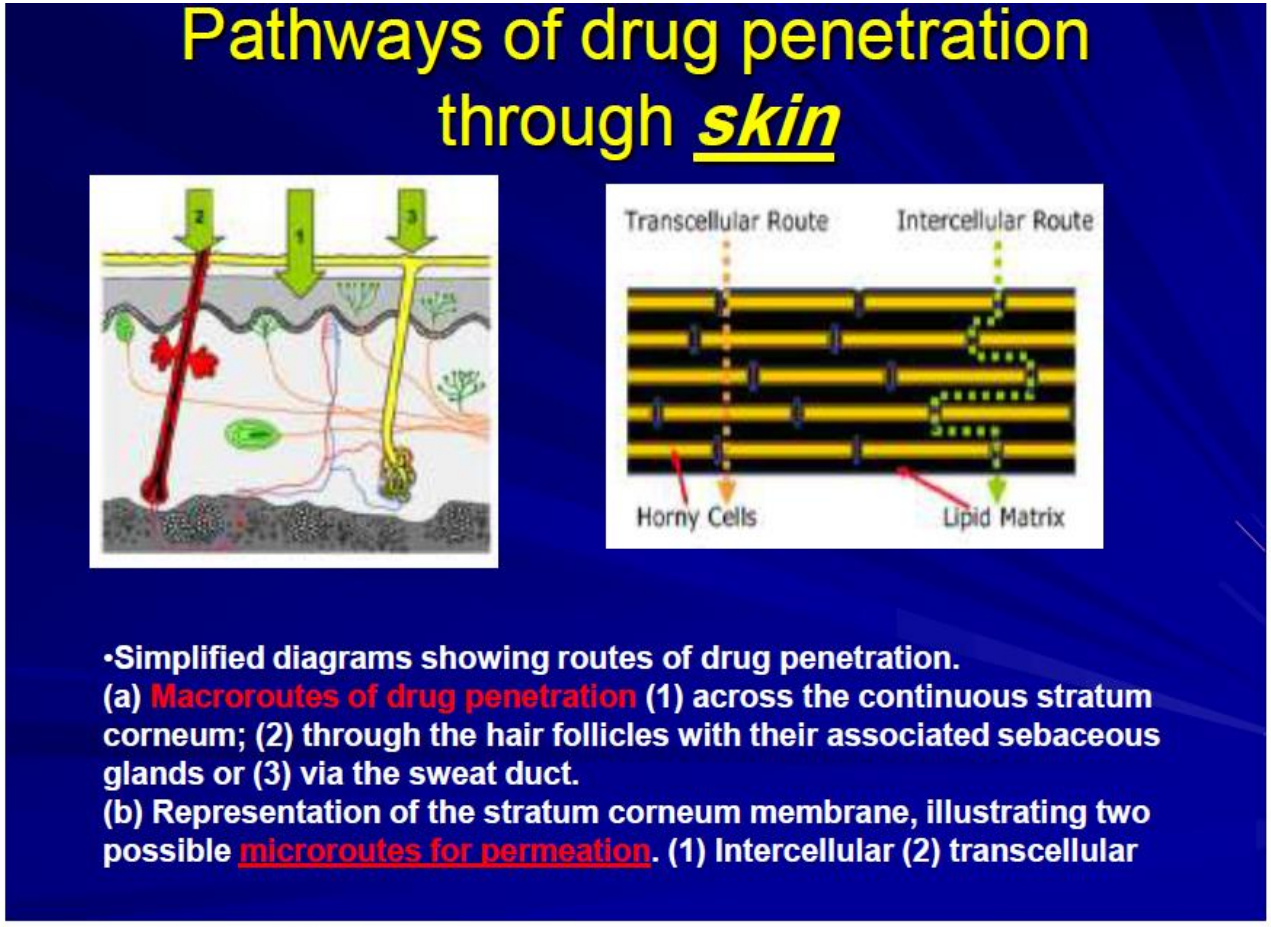
- It is the rate-limiting barrier to percutaneous drug transport

Percutaneous absorption, cont'd

- Transport of lipophilic drug molecules is facilitated
  - ❖ by their dissolution into intercellular lipids
- Absorption of hydrophilic molecules into skin can occur through 'pores' or openings of the hair follicles and sebaceous glands
- But, the relative surface area of these openings is barely 1% of the total skin surface.
  - ❖ limits the amount of drug absorption

Percutaneous absorption, cont'd

- Permeation of the substances can occur by diffusion via:
  - Transcellular penetration
  - Intercellular penetration



Factors Affecting Percutaneous Absorption: Nature of Skin

1. ↓ The thickness stratum corneum

→ ↑ Percutaneous absorption

2. Multiple application dosing

→ ↑ Percutaneous absorption than single Application

3. ↑ Time of contact with the skin

→ ↑ Percutaneous absorption

4. Broken skin permit (remove of the stratum corneum)

→ ↑ Percutaneous absorption

Factors Affecting Percutaneous Absorption: Nature of the drug

1. ↑ Drug concentration → ↑ Percutaneous absorption

2. ↑ Drug partition coefficient (greater attraction to the skin than to the vehicle) → ↑ Percutaneous absorption

3. ↓ Molecular weight below 800 → ↑ Percutaneous absorption

4. ↓ Particle Size → ↑ Percutaneous absorption

5. ↑ Solubility in mineral oil and water → ↑ Percutaneous absorption

Factors Affecting Percutaneous Absorption: Nature of Vehicle

1. ↑ Spread ability of the vehicle → ↑ Percutaneous absorption

2. ↑ Mixing with the sebum → ↑ Percutaneous absorption

3. ↑ Hydration of the skin → ↑ Percutaneous absorption

Oleaginous vehicles act as moisture barriers through which the sweat from the skin cannot pass, thus increased hydration of the skin beneath the vehicle and increase Percutaneous absorption.

Factors influencing, cont'd

Miscellaneous Factors

- Site of application
- Time of contact
- Amount of preparation employed
- State of ionization
- pH of applied preparation
- pH of Skin
- Molecular structure etc.

Maximizing the bioavailability of drug to skin

- Drug or prodrug selection
- Hydration
- Ultrasounds(phonophoresis)
- Iontophoresis
- Stratum corneum removal
- Chemical penetration enhancers

Chemical penetration enhancers

Materials used to enhance absorption:

- surfactants, dimethylsulfoxide (DMSO), dimethylacetamide, dimethylformamide, alcohol, acetone, propylene glycol, and polyethylene glycol.

Mechanism of action for percutaneous absorption enhancers

- Reduction of the resistance of the stratum corneum
- Alteration of the hydration of the stratum corneum
- Effecting a change in the structure of the lipids and lipoproteins in the cellular channels, through denaturation
- Carrier mechanism in the transport of ionizable drugs

Iontophoresis and Sonophoresis

- Iontophoresis: the delivery of charged chemical compounds across the skin membrane using an applied electrical field.

  Eg: lidocaine, amino acids/peptides/insulin, verapamil, and propanolol

- Sonophoresis : high-frequency ultrasound, is also being studied as a means to enhance transdermal drug delivery

  Eg.: hydrocortisone, lidocaine, and salicylic acid in such formulations as gels, creams and lotions

Advantage of TDD

- Avoids gastrointestinal drug absorption difficulties
- Substitutes for oral administration of medication when that routes is unsuitable.
- Avoids first-pass effect
- Provides the capacity for multiday therapy with a single application

Advantage of TDD, cont'd

- Provides sustained and controlled administration(for chronic diseases).
- Provides capacity to terminate drug effect rapidly.
- Permit self administration
- Extends the activity of drugs having short half-life through the reservoir of drug present in the therapeutic delivery system

Disadvantage of TDD

- unsuitable for drugs that irritate or sensitize the skin.
- Only relative potent drugs are suitable candidates
- Technical difficulties are associated with the adhesion of the systems to different skin types and under various environment conditions
- Poor diffusion of large molecules

OINTMENTS & PASTES

- Pharmaceutical ointments are semisolid systems that are applied externally
  - ✓ primarily to the skin
  - ✓ mucous membranes e.g. the rectum, the vagina, the eye.
- Medicated ointments: for the tt of infection, inflammation …
- Non-medicated ointments are commonly used as emollient/ lubricating properties.

Advantages of pharmaceutical ointments, pastes, and gels

- Ointments easily spread on skin, being retained at the site of application as an occlusive layer
  - thereby preventing moisture loss from the skin.
  - useful in restoration of the physical characteristics of the skin (e.g. due to inflammation)

- Ointments are associated with lubricating properties that may be employed to reduce trauma of an affected site upon spreading.

- Pharmaceutical pastes are generally composed of ointment bases that contain a high concentration of dispersed drug.
  - The viscosity of pharmaceutical pastes is greater than that of pharmaceutical ointments
- The increased viscosity of pharmaceutical pastes ensures that a thick film of the dosage form is applied to the site of action
  - shows excellent persistence

Advantages, Cont'd

- Due to the high solids content, Paste
  - act to absorb moisture and chemicals within the exudates.
  - enables to be used as a sun block.

- The chemical stability of therapeutic agents that are prone to **hydrolysis** will be dramatically enhanced by formulation within pharmaceutical ointments and pastes.

- Pharmaceutical gels may be formulated to provide excellent spreading properties and will provide a cooling effect due to solvent evaporation.

Disadvantage

- Ointments are generally greasy and difficult to remove (cosmetically unacceptable).
- Pharmaceutical pastes are generally applied as a thick layer at the required site (cosmetically unacceptable).
- Staining of clothes is the problem
- Problematic in ensuring spreading of the dosage form over the affected site.
  - The viscosity of pharmaceutical ointments, and in particularly pastes

Disadvantage

- Pharmaceutical ointments may not be applied to exuding sites
- Problems concerning drug release from pharmaceutical ointments may occur if the drug has limited solubility in the ointment base
- Pharmaceutical pastes are generally not applied to the hair
  - due to difficulties associated with removal.
- Drugs that are prone to hydrolysis should not be formulated into aqueous gels.

Ointments

Classification of Ointments

- According to their therapeutic properties based on penetration
- According to their therapeutic uses.

Ointments, cont'd

According to their therapeutic properties based on penetration

1. Epidermic ointments
   - Act on epidermis & produce local effect.
   - Used as protectives, antiseptic, local anti-infectives & parasiticides.
2. Endodermic ointments
   - Act on deeper layers of cutaneous tissues.
   - Partially absorbed & act as a emollients, stimulants & local irritants.
3. Diadermic ointments
   - Meant for deep penetration and release the medicaments and produce systemic effects.

Ointments, cont'd

ii) **According to their therapeutic uses.** :

1. Antibiotic ointments:
   - Used to kill micro-organisms.

   Eg- bacitracin, Neomycin, Chlortetracylclines, etc.

2. Antifungal ointments- Inhibit or kill the fungi.

   Eg- Benzoic acid, salicylic acid, nystatin etc.

3. Anti-inflammatory ointments: Relieve inflammatory, allergic & pruritic conditions.

   Eg- Betamethasone valerate, Hydrocortisone & its acetates.

Ointments, cont'd

4. Anti-pruritic ointments: Relieve itching

Eg- Benzocaine & coal tar

5. Astringent ointments:

-Causes contraction of skin & decreases discharge.

Ex- Calamine, ZnO, Acetic acid, Tannic acid

6. Anti eczematous Ointments:

-Prevent oozing & excretion from vesicles on the skin.

Ex- Hydrocortisones, ichthamol, coal tar & salicylic acid

Ointments, cont'd

7. Keratolytic Ointments:
   - Used to remove or soften the horny layer of the skin.

   E.g- Resorcinol, salicylic acid & sulphur

8. Counter-irritant Ointments:
   - Applied locally to irritate skin, thus reducing or relieving another irritation or deep seated pain.

   E.g- methyl salicylate, iodine, oleoresin

9. Protectant Ointments:
   - Protect skin from moisture, air, sun rays, chemicals.

   E.g-Calamine, ZnO, silicones, titanium dioxide etc.

Ointments, cont'd

10. Antidandruff ointments:

    Eg- Salicylic acid, cetrimide.

11. Ointment For Psoriasis treatment:

    E.g.- coal tar, coticosteroid, & salicylic acid mixed with suitable ointment base.

12. Parasiticide ointments:

- Destroy or inhibit living infestation like ticks & lice.

E.g.- Benzyl benzoate, hexachloride, sulphur etc.

Ointments, cont'd

- The formulation of ointments and pastes involves the dispersal or dissolution of the selected therapeutic agent into an ointment base

- The physicochemical properties of the ointment base are fundamental to:
  - the clinical
  - non-clinical performance of this type of dosage form.

Ointments, cont'd

The choice of ointment base is dependent on several factors, including:

1.Dermatological factors

- Absorption and penetration
- Effect on the skin
- Miscibility with skin secretion
- Compatibility with skin secretion
- Non-irritant (eye ointments)
- Emollient property
- Patient skin condition (old, baby and young)
- the site of application;

2. Pharmaceutical factors

- the required rate of drug release;
- the chemical stability of the drug; and
- the effect of the therapeutic agent on formulation viscosity

Types of base for ointments and pastes

- There are four types of base that are used to formulate pharmaceutical ointments and pastes:

(1) hydrocarbon;

(2) absorption;

(3) water-miscible/removable; and

(4) water-soluble.

Types of base, Cont'd

Hydrocarbon bases (Oleaginous bases):

- non-aqueous formulations, emollient
- restrict water loss from the site of application
  - Due to the formation of an occlusive film
- Excellent retention on the skin
- Predominantly hydrophobic
  - Difficult to remove from the skin by washing
  - difficult to apply to (spread over) wet surfaces (e.g. mucous membranes, wet skin)

Hydrocarbon bases, Cont'd

- Small amount of water (5%) can be incorporated into it with difficulty
- Can be protective to water labile drugs such as tetracycline and bacitracin.
- Greasy and can stain clothing.
- Chemically inert

Hydrocarbon bases, Cont'd

E.g. of hydrocarbon bases:

1. Petrolatum, USP
   - Yellow petrolatum/petrolatum jelly /Vaseline
   - Melts at 38-60°C
2. White petrolatum, USP
   - Decolored petrolatum,
   - White petroleum jelly/white vaseline

Hydrocarbon bases, Cont'd

3. Yellow ointment, USP

Yellow beeswax (5% w/w) + petrolatum (95% w/w)

4. White ointment, USP

White beeswax + white petrolatum

- Hydrocarbon bases frequently contain the following components:
  (1) hard paraffin;
  (2) white/yellow soft paraffin; and
  (3) liquid paraffin (mineral oil)

Hydrocarbon bases, Cont'd

Hard paraffin

- A mixture of solid saturated hydrocarbons that are derived from petroleum or shale oil.

- a colourless or white wax-like material that is physically composed of a mixture of microcrystal.

- The melting temperature of hard paraffin is between

  47 and 65^{o}c and,

  - used to enhance the rheological properties of ointment bases.

Hydrocarbon bases, Cont'd

White/yellow soft paraffin

- A purified mixture of semisolid hydrocarbons that are derived from petroleum.
- Consists of microcrystals embedded in a gel composed of liquid and amorphous hydrocarbons.
- The melting range of the soft paraffins is between 38 and 60°c.

Hydrocarbon bases, Cont'd

- White soft paraffin and yellow soft paraffin (the former being a bleached form of yellow soft paraffin)
  - used as an ointment base without the need for additional components, although it may be combined with liquid paraffin

Hydrocarbon bases, cont'd

Liquid paraffin (mineral oil, Liquid petrolatum)

- mixture of refined liquid saturated hydrocarbons obtained from petroleum
- Levigating agent to incorporate lipophilic solids
- An excipient in topical formulations where its emollient properties are exploited

Hydrocarbon bases, cont'd

- usually formulated with white/yellow soft paraffin to achieve the required viscosity for application to the required site.

- Formulations containing liquid paraffin require the incorporation of an antioxidant
  - due to the ability of this material to undergo oxidation

Absorption bases

- Absorption bases, unlike the hydrocarbon types, are hydrophilic and, therefore, can absorb considerable amounts of water or aqueous solutions.

I. Non-emulsified bases

- These bases absorb water and aqueous solutions to produce water-in- oil (W/O) emulsions.
  - Compared with the hydrocarbon bases:-
    - They are less occlusive, nevertheless, are good emollients
    - They assist oil-insoluble medicaments to penetrate the skin
    - They are easier to spread.

Absorption bases, cont'd

- Typically non-emulsified bases are commonly composed of:

  (1) one/more paraffins, and

  (2) a sterol-based emulsifying agent.

- Examples: (1) lanolin (wool fat);
  (2) wool alcohols; and
  (3) beeswax (white or yellow).

Absorption bases, cont'd

Lanolin (wool fat)

- Lanolin is a wax-like material that is derived from sheep's wool.

- It is available in two forms, termed

  Anhydrous lanolin (wool fat) and hydrous lanolin.

  Anhydrous lanolin:

  - called **wool wax**, **wool fat**, or **wool grease**,
  - a greasy yellow substance
  - contains < 0.25% of water

Absorption bases, cont'd

- Typically mixed with paraffins to produce an ointment base
  - Can absorb approximately twice its own weight of water to produce water in oil emulsions.
  - The usual concentrations of lanolin used in ointments (e.g. Simple Ointment BP) range from 5 to 10% w/w.

Absorption bases, cont'd

- Wool fat is a major constituent of **Simple Ointment B.P** and **Eye Ointment**

Simple ointment B.P

- Hard paraffin 50g
- Cetosteryl alcohol....50g
- Wool fat.....50g
- Soft paraffin.....850g

Eye Ointment B.P

Liquid paraffin.....100g

Wool fat.....100g

Yellow soft paraffin.....850g

Absorption bases, cont'd

Wool alcohols

- A crude mixture of sterols and triterpene alcohols

- Added to mixtures of paraffins (hard, so white/yellow soft or liquid) to produce the required consistency.

- The inclusion of wool alcohols (5% w/w) results in a 300% increase in the concentration of water

  e.g. wool alcohol ointment B.P

Absorption bases, cont'd

Beeswax (white or yellow)

- A wax that consists of esters of aliphatic alcohols (C_{24}–C_{36}) and linear aliphatic fatty acids (up to C36) that is combined with paraffins to produce non-emulsified bases.

- White beeswax is the bleached form of yellow beeswax.

- included in some ointment bases to increase water-absorbing power.

Absorption bases, cont'd

II. Water in oil emulsions

- These are similar in properties to the previous group and are capable of absorbing water.

- Absorption bases are less occlusive than the hydrocarbon bases and easier to spread.

- They are good emollients.

Eg. hydrous lanolin, which is a mixture of lanolin and 25–30% water.

Absorption bases, cont'd

- It is used alone as an emollient and is an ingredient of several B.P. ointment bases, i,e

  Hydrous wool fat ointment

  Calamine and coal tar ointment

  Methyl salicylate ointment

Absorption bases, cont'd

Properties of absorption bases

- Non-emulsified absorption bases (anhydrous)
  - Emollient
  - Occlusive
  - Absorbs water
  - Greasy
- W/O emulsion
  - Emollient
  - Occlusive
  - Contains water, absorbs additional water
  - Greasy

Water-washable/removable bases

- Water-miscible bases that are used to form O/W emulsions.

- They can be applied to **scalp** and other **hairy regions.**

- There are 3 official anhydrous water-miscible bases.
  - Emulsifying ointment B.P – anionic
  - Cetrimide emulsifying ointment B.P – cationic
  - Cetomacrogol emulsifying B.P- non-ionic

Water-washable/removable bases

- **Advantages of water-miscible bases**
  - ✓ able to accommodate large volumes of water
  - ✓ able to accommodate excess moisture

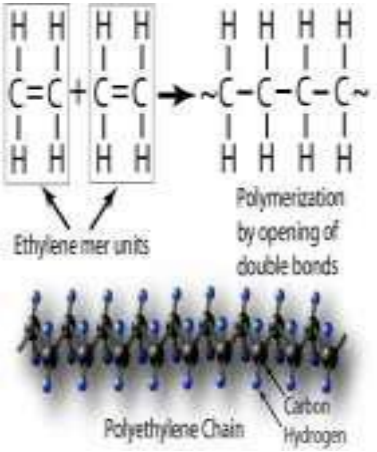
    e.g. exudate from abrasions & wounds.
  - ✓ Reduced interference with skin function
  - ✓ easily washed from the skin and from clothing.
  - ✓ readily applied to (and removed from) hair, skin. Hence High cosmetic acceptability
    - ✓ **N.B.** Ointments with **hydrocarbon** or **absorption** bases are not very suitable for **scalp** conditions because their removal is unpleasant and difficult.

Water removable bases, cont'd

Characteristics of water removable bases

- Resemble creams in their appearance
- May be diluted with water or with aqueous solution
- Certain medicinal agents may be better absorbed in the skin
- Water washable
- Contains water
- Can absorb water
- Non-occlusive
- Non-greasy

Water-soluble bases



- Completely water-soluble bases have been developed from the Macrogols (Polyethylene glycols), a range of compounds with the general formula:-

$$CH_2OH.(CH_2OCH_2)n.CH_2OH$$

Water-soluble bases, cont'd

- Polyethylene glycols are polymers of ethylene oxide and water Polycondensation

$$C_2H_4O + H_2O \longrightarrow \text{Poyethylene glycol (Macrogol)}$$

- The chain length may be varied to achieve polymers having desired viscosity and physical form
  - Macrogols 200,300 ,400 - Viscous liquids, Macrogol 1500 - Semi-solids, Macrogols 6000 - waxy solids

Example:

- PEG ointment, NF

  - PEG 3350 .....400 g

  -PEG 400 ..... 600 g

water-soluble bases, cont'd

Advantages of water- soluble bases

- Water solubility
  - Easily removal from the skin
  - Readily miscible with tissue exudates
- Good absorption by the skin
  - valuable when drugs are required to penetrate the skin
- Good solvent properties
  - For some water soluble dermatological e.g. Hydrocortisone

water-soluble bases, Advantages, cont'd

- Freedom from greasiness

- Satisfactory ageing properties
  - They don't hydrolyze, rancidity or support microbial growth

- Compatibility with many dermatological medicaments

  e.g. - Ammoniated mercury

  - Yellow mercuric oxide

water-soluble bases, cont'd

Disadvantages of water-soluble bases

- Less bland than paraffins, possibly due to their hygroscopic nature.

- Reduction in activity of certain antimicrobial agents, due to hydrolysis

- Solvent action on polythene and bakelite; these plastics should not be used in containers or closures for macrogol ointments

water-soluble bases, disadvantage, cont'd

- Inability to incorporate large volumes of aqueous solutions b/c
  - Ointments will soften or
  - dissolve the ointment base if the concentration of water is large enough.

  ❖Its use is usually reserved for the incorporation of solid therapeutic agents.

- It may incorporate up to 25% of an aqueous solution if a portion of the lower-molecular-weight polyethylene glycol is replaced with stearyl alcohol.
  - This enhance the mechanical properties of the ointment.

Properties of water-soluble bases

- Water soluble and washable
- Non-greasy
- Non/less occlusive
- Lipid free
- Synthetic base
- Relatively inert
- Does not support mold growth
- Little hydrolysis, stable

	OLEAGINOUS OINTMENT HC BASES	ABSORPTION OINTMENT BASES	WATER-REMOVABLE OINTMENT BASES	WATER-SOLUBLE OINTMENT BASES
Composition	Oleaginous compounds	Oleaginous bases + w/o surfactant	Oleaginous base + Water (> 45%) + O/W surfac. (HLB ≥9)	Polyethylene Glycols (PEGs)
Water Content	Anhydrous	anhydrous	hydrous	anhydrous, hydrous
Affinity for Water	Hydrophobic	hydrophilic	hydrophilic	hydrophilic
Spreadability	difficult	difficult	easy	moderate to easy
Washability	non-washable	non-washable	washable	washable
Stability	oils poor; hydrocarbons better	oils poor; hydrocarbons better	unstable	stable
Drug Incorporation Potential	•Solids •Oils (oil soluble drugs)	•Solids •Oils •Aqueous solutions	• Solid • Aqueous solutions (small amounts)	•Solid •Aqueous solutions •Non-aqueous solutions

Continue	OLEAGINOUS OINTMENT BASES	ABSORPTION OINTMENT BASES	WATER-REMOVABLE OINTMENT BASES	WATER-SOLUBLE OINTMENT BASES
Drug Release	poor	poor but > oleaginous	fair to good	good
Occlusiveness	yes	yes	no	no
Uses	•Protectants (occlusive dressings, diaper rash) •Emollients • Vehicles for hydrolysable drugs	•Protectants •Emollients •Vehicles for aqueous solutions, solids, and non hydrolyzable drugs	•Emollients • Vehicles for solid, liquid, or non-hydrolyzable drugs	Drug vehicles
Examples	•Yellow Petrolatum • White Petrolatum • Yellow Ointment • White Ointment	• Hydrophilic Petrolatum (Aquaphor®), • Anhydrous Lanolin • Lanolin	Hydrophilic Ointment Vanishing cream,	PEG Ointment

Miscellaneous excipients

Miscellaneous excipients: of ointments and pastes

- the therapeutic agent may be added as a solid component

- In absorption and water-miscible bases, the addition may be in the form of a solution.

  - aqueous, alcoholic (e.g. propylene glycol, glycerol) or hydroalcoholic

    - must not adversely affect the physical stability and/or the appearance

Miscellaneous excipients, cont'd

- Other excipients may be included in ointments and pastes, including:

  (1) additional/alternative solvents;

  (2) preservatives; and

  (3) antioxidants.

Miscellaneous excipients, cont'd

Additional/alternative solvents

- Are hydrophobic liquid components that may be added to ointment bases (predominantly hydrophobic or absorption bases).

- Examples include:

  (1) liquid silicone;

  (2) vegetable oils; and

  (3) organic esters

Miscellaneous excipients, cont'd

❖ **Antioxidants**

➢ The antioxidants that are used in ointment bases are similar to those listed for emulsion

- Butylated hydroxyanisole BHA))
- ,Butylated hydroxytolnene (BHT),
- ethyl,propyl or dodecyl gallates.

➢ Chelating agents such as ethylendiaminetetra-acetic acid (EDTA) may also be used.

Miscellaneous excipients, cont'd

- **Preservatives**
  - Preservative may not be required in anhydrous ointments because the substrate is generally unfavorable to the multiplication of any contaminating micro-organisms.
  - Ointment with an aqueous component requires effective antimicrobial agents to prevent the growth of organisms that may cause spoilage and pathogenecity.

Miscellaneous excipients, cont'd

- The preservative for emulsions are also suitable for hydrous ointment bases.

- Those used most commonly are mixtures of hydroxybenzoate esters, sorbic acid, phenethyl alcohol, organic mercurials and quaternary ammonium compounds.

- The effectiveness of the preservative system should be established by challenge tests with appropriate organisms

Method of preparation

- A well-made ointment is:-

  a). Uniform throughout, i.e. it contains no lumps of separated high melting pt ingredient of the base.

  b). Free from grittiness, insoluble powders are finely subdivided and large clumps of particles are absent.

- Methods of preparation must try to satisfy these criteria.

Method of preparation, cont'd

- Both in large and a small scale, ointments are prepared by two general methods.
  - Incorporation
  - Fusion

- The method for particular preparation depends primarily up on the nature of ingredients.

Method of preparation, cont'd

I. Incorporation method

- In the incorporation method the component of the ointment are mixed together by various means until a uniform preparation has been attained.

- Before incorporation the ingredient should have the finest state.
- On a small scale, as in the extemporaneous cpding of Rx:
  - **Mortar and pestle**
  - **Ointment tile (Slab) and spatula** : are a large glass or porcelain plate may be used to rub the ingredients together.

Method of preparation, Incorporation method…

- **Mortar and Pestle**

  - Used:

  1. when large quantities of liquids are to be incorporated.

  2. when large quantity of ointment is to be prepared

Method of preparation, Incorporation method…

- Otherwise, tile and spatula is satisfactory due to its large surface area.

- On a large scale manufactured in stainless steel tank.

Method of preparation, Incorporation method…

1. **Incorporation of solids**

- When preparing an ointment by spatulation, the pharmacist generally works the ointment with a stainless steel spatula with a long, broad blade and periodically removes the accumulation of ointment on the larger spatula with a smaller spatula.

- If the component of an ointment are reactive with the metal of the spatula (e.g., phenol), hard rubber spatula may be used.

Method of preparation, Incorporation of solids…

- The ointment is prepared by thoroughly rubbing and working the component together on the hard surface with the spatula until the product is smooth and uniform.

- Generally the ointment base is placed on one side of the working surface, and the powdered components, previously reduced to fine powders and thoroughly blended in the mortar, area placed on the other.

Method of preparation, Incorporation of solids…

- Then a portion of powder is mixed with a portion of the base until uniform, and the process is repeated until all portions of the powder and base are combined.

- The portions of prepared ointment are then combined and thoroughly blended by continuous & movement of the spatula and through the combined portions of ointment.

Method of preparation, Incorporation of solids…

- When only a small portion of powder is to be added, it may be added in its entirely to a small portion of ointment base.

- If the quantity of active ingredient is very small you have to use levigating agent (mineral oil, and glycerin).

- After levigation, the dispersion is incorporated with the remainder of the base by spatulation or by using the mortar and pestle

Method of preparation…

2. Incorporation of liquids

- Any liquids ingredients should be incorporated at the end of levigation.

- Generally, mortar and pestle is preferred when large volumes of liquid are added than an ointment slab.

- Liquid substances or solutions of drugs are added to an ointment only after due consideration of an ointment base's capacity to accept the volume required.

- When it is necessary to add an aqueous preparation to a hydrophobic base,
  - the solution first may be incorporated into a minimum amount of a hydrophilic base and then that mixture added to the hydrophobic base.
- However, all bases, even if hydrophilic, have their limits to retain liquids, beyond which they become too soft or semi liquid

Fusion method of preparation

- All or some of the components of an ointment are combined by being melted together and cooled with constant stirring until congealed.

- When ointment base contains several ingredients of different melting point; first add constituent of high melting point and then adding in descending order of melting point.

Fusion method…

- **Advantages** of melting in descending order of melting point:
  - Quicker
  - Require less heat
  - Avoid over heating of easily melted constituent.

Fusion method…

- Those components not melted are generally added to the congealing mixture as its is being cooled and stirred.

- Naturally, heat-labile substances and any volatile components are added last when the temperature of the mixture is low enough not to cause decomposition and volatilization of the component.

Fusion method…

- Many substances are added to the congealing mixture in solution, others are added as insoluble powders generally levigated with a portion of the base.

- On a small scale; the fusion process may be conducted in a porcelain dish or glass beaker.

- On a large scale; it is generally carried out in large steam-jacketed kittles.

Fusion method…

- Once congealed, the ointment may be passed through:
  - ✓ an ointment mill (in large-scale manufacture)
  - ✓ rubbed with a spatula or in a mortar (in small scale ppn) to ensure a uniform texture.
- Many medicated ointments and ointment bases containing such components as beeswax, hard paraffin, stearyl alcohol, and high molecular weight polyethylene glycols, which do not tend themselves well to mixture by incorporation, are prepared by **fusion**.

Fusion method…

- After melting; the melted ointment base should be stirred taking care, not to cause localized cooling of high melting ointment constituents .

- Localized cooling can be occurred due to:-
  - Cold spatula or stirrer
  - Putting the dish on cold surface
  - Transferring melted base to cold dish

Fusion method…

- If the product is granular after cooling, it has to be remelted with minimum amount of heat and stirred gently until it sets fully.

- We use fusion method when:-
  - Constituents are with hard consistency (high melting point components).
  - The medicaments is soluble in melted base.

Difficulties encountered in preparation of ointment

- Danger of chemical reaction between steel spatula and some reactive ingredients.

  Ex. I_2 , salicylic acid, Benzoic acid.....

  Solution :- to minimize this problem, use bone spatula, wooden spatula or hard rubber spatula.

- Incorporation of aqueous solution in to hydrocarbon base.

  Solution: addition of wool fat.

- Incorporation of antibiotics sensitive to hydrolysis

  Solution:- use hydrocarbon base.

Packaging and storage of ointment

- Ointments are usually packaged either:-
  - Jars
  - Tubes

Jars : - May be made of glass, uncolored, dark green, amber, or blue

- Or made of plastic, or porcelain.

Packaging and storage of ointment…

- Tubes:- are made of tin or of plastic (collapsible tube)

Packaging and storage of ointment…

- Ointment jars may be filled on a small scale by packaging the weighed amount of ointment in to the jar by means of a flexible spatula and forcing the ointment down and along the sides of the jar to avoid the entrapment of air.

- Ointments prepared **by fusion** may be poured directly in to the ointment jars for congealing with in the jar. These oints. normally assume a finished look

Packaging and storage of ointment…

- In the large-scale manufacture of ointments, pressure fillers force a specified amount of an oint in to a jar.

- Tubes are generally filled by pressure fillers from the open back and (opposite and from the cap end) of the tube which is then closed and sealed.

Packaging and storage of ointment…

- Tube-filled ointment predominate over jar-filled ointments primarily b/s they are more convenient for the patient.

- Ointments in tubes are less exposed to air and to potential contaminants and are therefore likely to be more stable
  - ✓ remain efficacious for longer periods of time

- Most ointments must be stored at temperature below 30^0c to prevent the softening and liquefying.

PASTES

- Pastes, like ointments, are intended for external application to the skin.

- They differ from ointments primarily in that they containing large proportion of solid materials
  - as a consequence are thicker and stiffer than ointment.

- Pastes are used principally as
  - absorbents,
  - antiseptics
  - protective, or to soothe broken skin surfaces

Pastes…

- They are emollient but, because of the powder content, porous, hence, perspiration can escape.

- The powder absorb exudates, less macerating than ointments with similar base.

- Are less greasy than ointments because of the absorption of the fluid hydrocarbon fraction to the insoluble particles.

Pastes…

- Most are **unsuitable for treating scalp** conditions because they are **difficult** to remove from the hair.

- Because of the stiffness and absorptive qualities of pastes, they remain in place after application with little tendency to softer and flow
  - therefore effectively employed to absorb secretion from the site of application.

Pastes…

- Pastes are therefore preferred for acute lesions that have a tendency toward crusting, or oozing.

- The film formed on application is opaque and thus can often serve as a sun-block.

- Pastes are prepared similarly to ointments.
  - However, when a levigating agents is to be used to render the powdered component smooth, a portion of the base is often used rather than a liquid like mineral oil

Pastes…

- Among the few pastes in use today is zinc oxide paste (Lassar's Plain Zinc Paste),
  - prepared by levigating and then mixing 25% each of zinc oxide and starch and calamine with white petrolatum.

- The product is very firm and is better able to protect the skin and absorb secretions than is zinc oxide ointment

Zinc oxide paste, USP

- Zinc oxide 25.0%
- Starch 25.0%
- Calamine 5.0%
- White petrolatum q.s. 100%

Procedure:

- Triturate the calamine with the zinc oxide and starch and incorporate uniformly in the petrolatum by levigation in a mortar or on a glass slab with a spatula.
- Mineral oil should not be used as a levigating agent,
- A portion of petrolatum can be melted and used as a levigating agent if so desired.

Creams

- The term 'cream' in pharmacy and medicine is applied to viscous emulsion or semi-solid emulsion preparation consisting of solutions or dispersions of one or more medicaments in suitable base and intended for application to the skin or mucous membrane.

- The term cream is widely used in pharmaceutical and cosmetic industry.

Creams…

- Many patients and physicians prefer creams to ointments.
  - they are generally easier to spread, and, in the case of cream of the oil-in-water emulsion.
  - Easier to remove than many ointments

- They are applied to the skin for:-
  - Protective
  - Beautifying
  - Therapeutic or prophylactic purposes

Creams…

- Creams may contain suitable antimicrobial or preservatives unless the medicaments or bases have sufficient intrinsic bactericidal and fungicidal activity
- Creams are mainly two types:-

  1). Water- in –oil (W/O) - oily cream

  2). Oil –in-water (O/W) - aqueous cream

- O/W emulsions are most useful as water-washable bases, whereas w/o emulsions are emollient and cleansing.

Creams…

- Patients often prefer O/W b/s
  - Cream spreads more readily.
  - Is less greasy
  - Evaporating water soothes the inflamed tissue.

Creams…

- **O/W (vanishing cream)** After application of the cream the water evaporates leaving behind a thin residue film of the stearic acid.
  - For oozing or weeping surface (wound that release exudates from skin) = b/s O/W mix oozing surface.

- **Vanishing cream** is prepared by incorporation of significant amount of stearic acid in an oil-in-water emulsion.

- **Humectants** (glycerin, PEG, 7% sorbitol) are frequently added to vanishing creams and O/W emulsions to decrease evaporation of water from the surface of the base.

General compounding procedure for creams

- Emulsified creams are prepared by heating the components of the oily phase until molten and then cooled .

- The component of the aqueous phase are mixed in a separate vessel and also heated to 60^0c.

- The aqueous phase is then added to the oily phase at the same temperature.

General compounding of creams…

- This is important and a thermometer should be used.
  - ✓ The resulting emulsion should be stirred until cool .
- Rapid cooling may result in separation of high melting point components.
- Excessive aeration caused by vigorous stirring may also lead to a granular product.

General compounding of creams…

- If necessary the product may be homogenized after cooling.
- Creams may contain one or more medicaments in solution in one or other of the phases.
- Finally powdered insoluble medicaments may be dispensed in a cream base

Container of Creams

- Wide-mounthed squat jars may be used for creams where the risk of contamination in use is considered to be minimal, e.g. Oils creams.

- The container must be well closed and prevent water evaporation.

- The mouth of the jar should be covered with a disc of grease proof paper.

Container of Creams…

- **Collapsible metal or flexible plastic tubes** are to be preferred since these reduce the risk of contamination in use and most proprietary products are packed in tubes.

Gels (Jellies)

- Gels are transparent or translucent semi-solid or solid preparations, consisting of solutions or dispersions of one or more active ingredients in suitable hydrophilic or hydrophobic bases.

- Semisolid preparations that contain small inorganic particles or large organic molecules interpenetrated by a liquid.

Gels (Jellies)…

- Gels made of inorganic materials are usually two - phase systems where small discrete particles are dispersed throughout the dispersion medium.
  - E.g. Aluminum hydroxide gel, bentonite magma
- When the particle size of the dispersed phase is larger, they are referred to as magmas.

- Gels made of organic molecules are single - phase systems, where no apparent physical boundary is seen between the dispersed phase and the dispersion medium.
  - E.g. Carbomer and tragacanth

Gels (Jellies)…

The dispersion medium:

- aqueous
- Hydroalcoholic or oleaginous base

- Gels are attractive delivery systems:
  - simple to manufacture
  - suitable for administering drugs through skin, oral, buccal, ophthalmic, nasal, otic, and vaginal routes
  - provide intimate contact between the drug and the site of action or absorption.

Gels (Jellies)…

- Gels exhibit different physical properties, namely, imbibition, swelling, syneresis, and thixotropy

- **Thixotropy**: *non* -Newtonian flow nature of gels, which is characterized by a reversible gel - to – sol formation with no change in volume or temperature

- **Imbibition-** is the taking up of a certain amount of liquid by a gel without a measurable increase in volume.

Gels (Jellies)…

- **Swelling-**is the taking up of a liquid by a gel with an increase in volume.

- **Syneresis-**Syneresis refers to the contraction or shrinkage of gels as a result of squeezing out of dispersion medium from the gel matrix.

- Syneresis is a form of instability in aqueous and non aqueous gels

Classification and Types of Gels

Classification based on the chemical nature

1. **Inorganic hydrogels -**are usually two phase systems such as aluminum hydroxide gel

2. **Organic Gels** -are usually single phase systems and may include such gelling agents as Carbomer and Tragacanth and those that contain an organic liquid, such Plastibase.

Classification and Types of Gels

- Gels are also classified as hydrogels and organogels based on the physical properties of the gelling agent in the dispersion.

- Hydrogels: prepared with water - soluble materials or water - dispersible colloids.
  - E. g. Natural and synthetic gums such as tragacanth, sodium alginate, and pectin
    - inorganic materials: alumina, bentonite, silica, and veegum
    - organic materials such as cellulose polymers

Classification and Types of Gels

- Organogels (oleaginous gels): prepared using water - insoluble oleaginous materials

  - Prepared using water - insoluble lipids such as glycerol esters of fatty acids, which swell in water
  - Eg. Glycerol monooleate, glycerol monopalmito stearete, and glycerol monolinoleate

Allows incorporation of both hydrophilic and lipophilic drugs.

Components in gel formulation

Gelling agent

- Gelling agent causes thickening
  - are either organic hydrocolloids or hydrophilic inorganic substance.

- They are water dispersible, possess swelling properties, and improve the viscosity of dispersions

Components in gel formulation …

An ideal gelling agent

- Not interact with other formulation components
- Be free from microbial attack.
- Changes in the temperature and pH during pps and preservation should not alter its rheological properties.
- Economic
- Readily available
- Colorless gels,
- provide cooling sensation on the site of application, and possess a pleasant odor.

Examples of Gelling Agents

1. Acacia
2. Bentonite
3. Carboxymethylcellulose Na
4. Colloidal silicon dioxide
5. Gelatin
6. Hydroxyethylcellulose
7. Hydroxyproprylmethylcelluose
8. Maltodextrin
9. Polyvinyl alcohol
10. Propylene carbonate
11. Alginic acid
12. Carbomer
13. Cetostearyl Alcohol
14. Ethylcellulose
15. Guar gum
16. Hydroxypropryl cellulose
17. Magnesium Al silicate
18. Methylcellulose
19. Povidone
20. Sodium alginate
21. Sodium starch glycolate
22. Starch
23. Tragacanth
24. Xanthan gum

Components in gel formulation …

- **Preservatives**
  - Methylhydroxybenzoate
  - Propylhydroxybenzoate
- **Hygroscopic agents (Humectant)**
  - Eg. Glycerol, propylene glycol or sorbitol solution.
- **Chelating agents**
  - For ingredients which are sensitive to heavy metals. eg. EDTA.

Components in gel formulation

Flavours/sweetening agents

- Included in pharmaceutical gels that are designed for administration into the oral cavity

  e.g. for the treatment of infection, inflammation or ulceration.

Buffers

- As in other pharmaceutical formulations, buffers (e.g. phosphate, citrate) may be included in aqueous & hydroalcoholic-based gels

Colorants??

Magmas

- Are aqueous suspensions of insoluble, inorganic drugs and differ from gels mainly in that the suspended particles are larger.

- When prepared, they are thick and viscous, so no need of a suspending agent.

Preparation of Gels and Magmas

- Generally, the water soluble components are initially dissolved in the vehicle in a mixing vessel with stirring.

- The hydrophilic polymer must be added to the stirred mixture slowly to prevent aggregation then continuing stirring until dissolution of the polymer
  - ❖ excessive stirring of pharmaceutical gels results in entrapment of air.

Therefore, to prevent this the mixing rate must not be excessive

Preparation of Magmas and Gels

- By freshly precipitating the disperse phase (chemical rxn)
  - ✓ The desired gelatinous precipitate results when solutions of inorganic agents react to form an insoluble chemical having a high attraction for water.

- Eg: Milk of magnesia is a preparation containing 7 to 8.5% magnesium hydroxide.

Preparation of Magmas and Gels…

- It may be prepared by a reaction between sodium hydroxide and magnesium sulfate.

$$2NaOH + MgSO_4 \longrightarrow Mg(OH)_2 + Na_2SO_4$$

- By direct hydration of inorganic chemical in water.

Example**:** Hydration of Magnesium oxide

$$MgO + H_2O \longrightarrow Mg(OH)_2$$

Gels (Jellies)….

- Use: for **medication**, **lubrication** and some **miscellaneous** application
- Medicated Jellies
  - Jellies contain a considerable amount of water and are particularly suitable as vehicle for water–soluble medicaments such as local anesthetics, spermicides, and antiseptics.
- Lubricants Jellies
  - Lubricants for - glove
- Miscellaneous jellies
  - Patch testing : As a vehicle for allergens applied to the skin to detect sensitivity

Examples of Magmas and Gels

Bentonite Magma	NF	suspending agent
Sodium Fluoride and Phosphoric Acid Gel	USP	dental care prophylactic
Fluocinonide Gel	USP	Anti-inflammatory corticosteroid
Tretinoin Gel	USP	treatment for acne
Erythromycin and Benzoyl peroxide Gel		
Clindamycin Topical Gel		
Hydroquinone Gel		Hyperpigmented skin
Salicylic acid Gel		keratolytic
Desoximethasone Gel		anti-inflammatory and antipruritic
Aluminum Phosphate Gel (Amphogel)	USP	antacid
Aluminum hydroxide Gel	USP	antacid
Dihydroxyaluminum Aminoacetate Magma	USP	antacid
Milk of Magnesia (Magnesia Magma)	USP	Antacid; laxative

Containers

- Containers should be well-filled,
  - to minimize evaporation of water into the air space,
- well closed and stored in a cool place,
  - to prevent drying out.