Semi- solid dosage forms

Objectives

At the end of this topic, the student will be:

Differentiate between the various types of semisolid bases on the basis of physical and chemical properties .

List the criteria for the selection of a semisolid base to treat a topical affliction. Describe the methods to incorporate (an) active ingredient(s) into a semisolid base .

Explain the difference between an ointment, a cream, and a gel.

Compare and contrast an ophthalmic ointment base and a topical ointment base for application to the skin.

Semisolid Dosage Forms

Ointments, creams, and gels are semisolid dosage forms intended for topical application .

They may be applied to the skin ,
Placed on the surface of the eye
Or used nasally, vaginally and rectally.

Most of these preparations are used for the effects of the therapeutic agents they contain.

The unmedicated ones are used for their physical effects as protectants or lubricants .

Topical preparations are used for both local and systemic effects.

A topical drug (API) dosage form would be one that is designed to deliver the drug into the skin in treating skin disorders where the skin is the target organ .

Systemic effects

Skin consists of three anatomical layers, the epidermis, the dermis and a subcutaneous fat layer.

A transdermal product is designed to deliver drugs through the skin (percutaneous absorption) to the general circulation for systemic effects, with the skin not being the target organ .

Systemic drug absorption should always be considered when using topical products if the patient is pregnant or musing, because drugs can enter the fetal blood supply and breast milk and be transferred to the fetus or nursing infant .

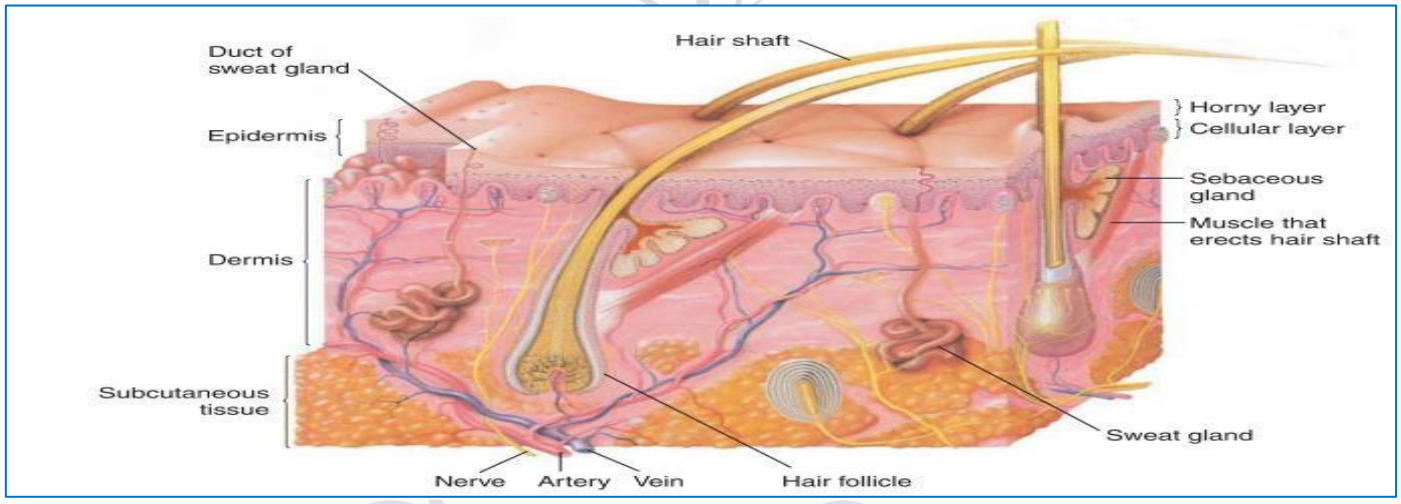
-Recently there is an increase in the number of topical ointments, creams, and gels designed to deliver a drug systemically. This is often accomplished by addition of penetration enhancers to the topical vehicle **The rate of drug movement across skin layer depends on:**

-The drug concentration in the vehicle ,

-Physicochemical properties of the drug substance such as solubility, partition coefficient, pKa, and molecular wight

-The characteristics of the base or vehicle, hydrophilic– lipophilic character and viscosity

-Conditions of the skin itself “broken, hydrated other features of the skin .



Ointments

Ointments are semisolid preparations intended for external application to the skin or mucous membranes .

Ointments may be medicated or Unmedicated .

Unmedicated ointments are used for the physical effects they provide as **protectants, emollients, or lubricants** .

Ointment bases, as described, may be used for their physical effects or as vehicles for medicated ointments .

Ointment Bases

Ointment bases are generally classified by the United States Pharmacopeia (USP) into four groups :

1.Oleaginous bases
2.Absorption bases
3.Water removable bases
4.Water soluble bases

Ideal properties of ointment bases

1.Stable
2.Neutral in reaction
3.Non-greasy
4.Not degreasing in action
5.Nonirritating
6.Non-dehydrating
7.Non-hygroscopic
8.Water-removable
9.Compatible with medications
10.Free from objectionable odor
11.Non-staining
12.Capable of serving as medium for drugs that are water and lipid soluble
13. Efficient on dry, oily or moist skin
14. Composed of readily available components of known chemical composition
15. Easily compounded by the pharmacist
16. Can melt or softened at body temperature

Oleaginous Bases (Hydrocarbon bases)

Oleaginous bases are also termed Hydrocarbon bases .

On application to the skin

1-They have an emollient effect
2-Protect against the escape of moisture
3-They are effective as occlusive dressings
4-Can remain on the skin for long periods without drying out ,

-Because of their immiscibility with water, are difficult to wash off .

-Water and aqueous preparations may be incorporated, but only in small amounts and with some difficulty .

-When powdered substances are to be incorporated into hydrocarbon bases, liquid petrolatum (mineral oil) may be used as the levigating agent **Examples:**

-Petrolatum "Vaseline,"
-White petrolatum "White Vaseline"
-Yellow ointment
-White ointment .

Petrolatum, USP, is a purified mixture of semisolid hydrocarbons obtained from petroleum. It has yellow to light amber color. it is also known as yellow petrolatum and petroleum jelly. A commercial product is Vaseline .

White petrolatum, USP, is a purified mixture of semisolid hydrocarbons obtained from petroleum that has been wholly or nearly decolorized. White petrolatum is also known as white petroleum jelly. A commercial product is White Vaseline

Yellow ointment, USP, this ointment has the following formula for the preparation of 1,000 g:

Yellow wax 50 g
Petrolatum 950 g

Yellow wax is the purified wax obtained from the honey comb of the bee **White Ointment, USP**. This ointment differs from yellow ointment by substitution of white wax (bleached and purified yellow wax) and white petrolatum in the formula .

White wax 50 g
White Petrolatum 950 g

1. Absorption Bases

These bases are of two types:

a-Those that permit the incorporation of solutions resulting in the formation of **w/o emulsion** for example, **Hydrophilic petrolatum** .

b-Those that are **w/o emulsions** that permit the incorporation of an additional quantities of aqueous solutions for example, **lanolin**

-They are used as emollients –

-They are not easily removed from the skin by water washing, because the external phase is oleaginous

-They do not provide the degree of occlusion afforded by the oleaginous bases Examples: **Hydrophilic petrolatum, lanolin and modified lanolin** .

Hydrophilic Petrolatum, USP, has the following formula for the preparation of 1,000 g :

Cholesterol	**30 g**
Stearyl alc.	**30 g**
White wax	**80 g**
White petrolatum	**860 g**

-Commercial products, **Aquaphor** and **Aquabase** variations of hydrophilic petrolatum, have the capacity to absorb up to three times their weight in water and are useful to help incorporate a water-soluble drug, for example, tobramycin sulfate, into an oleaginous ointment base

Lanolin, USP

Lanolin, USP (**anhydrous lanolin**), obtained from the wool of sheep, is a purified waxlike substance that has been cleaned, deodorized, and decolorized. It contains not more than 0.25% water.

---

2. Water-Removable Bases (Water-washable)

They are oil-in- water emulsions (o/w) resembling creams .

-Because the external phase of the emulsion is aqueous, they are easily washed from skin and are often called water-washable bases .

-They may be diluted with water or aqueous solutions .

➢ They can absorb serous discharges.

Hydrophilic Ointment, USP, is an example of this type of base.

Hydrophilic Ointment, USP, has the following formula for 1,000 g:

Methylparaben 0.25 g
Propylparaben 0.15 g

Sodium lauryl sulfate 10 g propylene glycol 120 g Stearyl alcohol. 250 g

White petrolatum 250 g
Purified water 370 g

Water-Soluble Bases (Greaseless)

-These bases do not contain oleaginous components .

-They are completely water washable.

-Because they soften greatly with the addition of water, large amounts of aqueous solutions are not effectively incorporated into these bases .

Example**: Polyethylene Glycol Ointment NF**
The general formula for preparation of 1,000 g of PEG ointment is:

PEG 335 400 g
PEG 4000 600 g

Classification and properties of USP ointment bases

Hydrocarbon base	Absorption base	Water removable base	Water soluble base
White petrolatum USP White ointment USP	Hydrophilic petrolatum USP Lanolin USP	Hydrophilic ointment USP	Polyethylene Glycol ointment NF
Hydrocarbons	Anhydrous or W/O emulsion or hydrous	O/W emulsion	Water soluble
Highly occlusive	Moderate to high	Low to moderate	Minimal
Maintain prolonged contact with application site	Allows incorporation of aqueous solutions	Water-washable; may be diluted with water	Water-washable; no water- insoluble residue
Emollient effect	Emollient effect	Allows absorption of serous discharge	

Selection of the appropriate ointment base

Selection of the base to use in the formulation of an ointment depends on careful assessment of a number of factors, including the following :

1-The release rate of the drug substance from the base .
2-Desirability of topical or systemic action.
3-Desirability of occlusion of the moisture from the skin .
4-Stability of the drug in the ointment base.
5-Effect of drug on the consistency of the base .
6-Water wash ability of the base .
7-Characteristics of the surface to which it is applied .

For example, **an ointment is generally applied to dry, scaly skin; a cream is applied to weeping or oozing surfaces**

Preparation of Ointments

Depending primarily on the nature of the ingredients, ointments are prepared by two general methods .

(a) Incorporation
(b) Fusion

Incorporation Method

In this method, the components are mixed until uniform preparation is attained .

On small scale, the pharmacist may mix the components using **mortar** and **pestle**, or a **spatula** may be used to rub the ingredients together on an **ointment slab** (a large glass or porcelain plate or pill tile) .

-If the components of an ointment react with metal (as does iodine), hard rubber or silicone spatulas may be used .

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

➢ Incorporation of solids. When preparing an ointments by spatulation, the pharmacist works the ointment with a stainless steel spatula having a long, broad blade and periodically removes the accumulation of ointment on the large spatula with a smaller one .

-For incorporating a gummy material, such as camphor, **pulverization by intervention** can be used. The material is dissolved in a solvent and spread out on the pill tile.

The solvent is allowed to evaporate, leaving a thin film of the material onto which the other ingredient or ingredients are spread .

➢ Incorporation of liquids. 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.

For example, only very small amounts of an aqueous solution may be incorporated into an oleaginous ointment, whereas hydrophilic ointment bases readily accept aqueous solutions.

◇ Levigation in ointment preparation

It often is desirable to reduce the particle size of a powder or crystalline material before incorporation into the ointment base so the final product will not be gritty.

The reduction in particle size of the powder be done by levigating, or mixing the solid material in a vehicle in which it is insoluble to make a smooth dispersion. “wet grinding. ”

-The levigating agent like mineral oil or glycerin should be physically and chemically compatible with the drug and the base .

-The levigating agent is used in an equal volume of the solid material.

-A mortar and pestle are used in levigation.

-Levigation allows both the reduction in particle size and the dispersion of the substance in the vehicle .

-Solids soluble in a common solvent that will affect neither the stability of the drug nor the efficacy of the product may first be dissolved in that solvent (e.g., water or alcohol) and the solution added to the ointment base by spatulation or in a mortar and pestle .

On large scale, Ointment or roller mills can be used to force coarsely formed ointments through stainless steel or ceramic rollers to produce ointments uniform in composition and smooth in texture

◇ Fusion Method

By this method, all or some of the components of an ointment are

combined and melted together and cooled with constant stirring until congealed .

Other components like **heat labile substances** and **volatile oils** are added after cooling the mixture to prevent their decomposition and volatilization respectively .

Substances may be added to the congealing mixture as:

Solutions

Or insoluble powders levigated with a portion of the base .

On a small scale, fusion may be done by using porcelain dish or glass beaker .

On a large scale, it is carried out in large steam-jacketed kettles.

After congealing, the ointment may be passed through an ointment mill “large scale”, or rubbed with a spatula or in a mortar “small scale” to ensure uniform texture .

-Medicated ointments containing components like beeswax, stearyl alcohol, high molecular wight PEGs are best prepared by fusion method rather than incorporation method.

-By fusion method, the materials with the highest melting points are heated to the lowest required temperature to produce a melt, then the additional substances are added with constant stirring during cooling the melt until the melt is congealed. In this way, not all components are subjected to the highest temperature .

◇ Compendial requirements for ointments

Ointments and other semisolid dosage forms must meet USP tests for :

-Microbial content
-Minimum fill
-Packaging, storage and labeling .

◇ Microbial Content

-With the exception of ophthalmic preparations, topical applications are not required to be sterile.

-Topical preparations must meet the acceptable standards for microbial contents

-Preparations that contain water tend to support microbial growth to a greater extent than water-free preparations .

-Dermatological products should be examined for the absence of Staphylococcus aureus and Pseudomonas aeruginosa.

-Other products intended for rectal, vaginal and urethral application should be tested for yeasts and molds .

-Preparations subjected to microbial growth must contain preservatives .

Among the antimicrobial preservatives used to inhibit microbial growth in topical preparations are **methylparaben, propylparaben, phenols, benzoic acid, sorbic acid, and quaternary ammonium salts** .

-Microbial limit test is conducted for both raw materials and finished products .

-The USP states certain products should be routinely tested for microorganisms because of the way they are used .

◇ Minimum fill

The USP's minimum fill test is used to determine the net weight or volume of the content of the filled containers to ensure proper content compared with the labeled amount .

Packaging, Storage, and Labeling

Ointments and other semisolid preparations are packaged either in **largemouth ointment jars** or **in metal** or **plastic tubes .**

Topical dermatologic products are packaged either in jars or in tubes, whereas ophthalmic, nasal, vaginal and rectal semisolid products are almost always packaged in tubes .

-Ointment jars are either clear or opaque glass or plastic .

-The jars and tubes should be compatible and stable with the intended product.

-Tubes are superior to jars because they are lighter in weight, relatively inexpensive, conveniently used, compatible with most formulative ingredients, and provide greater protection against external contamination and environmental conditions. They are made of aluminum or plastic sometimes equipped with applicator .

-Semisolid preparations must be stored in well-closed containers to protect against contamination and in a cool place to protect against product separation in heat .
-When required, light-sensitive preparations are packaged in opaque or lightresistant containers.

-In addition to the usual labeling requirements for pharmaceutical products, the USP directs the labeling for certain ointments and creams include the type of base used (e.g., water soluble or water insoluble) .

◇ Ophthalmic ointments

Ophthalmic ointments differ from conventional ointments in that they must be sterile.

In selecting an ointment base for an ophthalmic preparation, it must meet several qualities such as

-Must not be irritating to the eye

-Must permit the diffusion of the medicinal substance throughout the secretions bathing the eye

-Ointment bases used for ophthalmic should have a softening point close to body temperature, both for comfort and for drug release .

-Mixtures of mineral oil and white petrolatum are commonly used as the base in medicated and non-medicated (lubricating) ophthalmic ointments .

➢ Usually, the medicinal agents are added to an ointment base either as a solution or as a finely micronized powder. The ointment is made uniform and smooth by fine milling

---

Residence time

In general, ocular ophthalmic drug penetration is limited by:

1-The short residence time on the surface of the eye because of rapid removal by tearing and other natural mechanisms.

2-The small surface area of the cornea for drug absorption ,

3.The cornea's natural resistance to drug penetration .

Compared with ophthalmic solutions, ophthalmic ointments and gels provide extended residence time on the surface of the eye, increasing the duration of their surface effects and bioavailability for absorption into the ocular tissues .

Ophthalmic ointments are cleared from the eye as slowly as 0.5% per minute, compared with solutions, which can lose up to 16% of their volume per minute

---

Sterility and preservation of ophthalmic ointments

In addition to the quality standards for ointments, ophthalmic ointments must meet the USP sterility tests and the test for metal particles in ophthalmic ointment

-Rendering an ophthalmic ointment sterile requires special aseptic techniques and processing .

-Each drug, along with other components, is rendered sterile separately, aseptically weighed, and incorporated in preparing a final product that meets the sterility requirement.

This is done because of difficulty in terminal product sterilization, such as lack of penetration of steam into the ointment base and instability of components owing to high dry heating .

-Antimicrobial preservatives such as **methylparaben and propylparaben combinations, chlorobutanol and benzalkonium chloride** are used as needed.

-The USP test for metal particles is microscopic examination of a heat-melted ophthalmic ointment

---

Pastes

Pastes are semisolid preparations intended for application to the skin .

-They generally contain a larger proportion of solid material (such as 25%) than ointments and therefore are stiffer .

-Pastes can be prepared in the same manner as ointments, by direct mixing or the use of heat to soften the base prior to incorporating the solids, which have been comminuted and sieved .

-However, when a levigating agent is to be used to render the powdered component smooth, a portion of the base is often used rather than a liquid, which would soften the paste .

-Because of the stiffness of pastes, they remain in place after application and are effectively employed to absorb serous secretions .

-Because of their stiffness and impenetrability, pastes are not suited for application to hairy parts of the body .

-Among the few pastes in use today is zinc oxide paste, which is prepared by mixing 25% each of zinc oxide and starch with white petrolatum. The product is very firm and is better able to protect the skin and absorb secretions than is zinc oxide ointment .

Creams

Pharmaceutical creams are semisolid preparations containing one or more medicinal agents dissolved or dispersed in either a water-in-oil (w/o) emulsion or an oil-in-water (o/w) emulsion intended for external use .

Their consistency and rheological properties are based on whether the emulsion is o/w or w/o and on the nature of the solid in the internal phase .

-Creams are used topically, rectally and vaginally .

-Creams are preferred by many patients and physicians because they are easier to spread and remove **Example**:

Vanishing creams are oil in water emulsions (o/w) containing large percentage of water, stearic acid and other oleaginous components .

They are named so because water is evaporating leaving a thin layer of the stearic acid and other oleaginous components .

Preparation of creams

Preparation usually involves separating the formula components into two portions: lipid and aqueous. The lipid portion contains all water-insoluble components and the aqueous portion the water-soluble components.

Both phases are heated to a temperature above the melting point of the highest melting component. The phases then are mixed, and the mixture is stirred until the mixture has congealed .

-Creams usually require the addition of a preservative(s) unless they are compounded immediately prior to use and intended to be consumed in a relatively short period of time

Gels

Gels (sometimes called jellies) are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jellylike by the addition of a gelling agented ..

Among the gelling agents used are:

1-Synthetic macromolecules, such as carbomer

2-Cellulose derivatives, such CMC (Carboxymethylcellulose), HPMC (hydroxypropyl methylcellulose)

3-Natural gums, such as tragacanth

-Gels have good appearance usually translucent or transparent .

-Medicated gels may be prepared for administration by various routes, including the **skin**, and to **mucous membranes** of the **eye**, the **nose**, the **vagina**, and the **rectum**, giving high rates of release of the medicament and rapid absorption.

-Gels may thicken on standing, forming a thixotropic , and must be shaken before use to liquefy the gel and enable pouring

---

Gel preparation (Main Procedure)

Hydrophilic gelling agent is dispersed in water with continuous stirring (at the appropriate temperature for the gelling agent)

Drug is dissolved in a suitable solvent with the preservatives, and other additives.

This solution is added to the gelling agent dispersion

-In addition to the gelling agent and water, gels may be formulated to contain a drug substance, solvents, such as alcohol and/or propylene glycol; antimicrobial preservatives, such as methylparaben propyl paraben; and stabilizers, such as edetate disodium .

Examples on gels

Active Ingredient	Proprietary Product	Gelling Agent	Route and Use
Metronidazole	MetroGel Vaginal	Carbomer 934P	Vaginal: bacterial vaginosis
Clobetasol propionate	Temovate Gel	Carbomer 934P	Dermatologic: antipruritic
Cyanocobalamin	Nascobal	Methylcellulose	Nasal: hematologic
Diclofenac sodium	Voltaren emulgel		Systemic effect (transdermal)

◇ Emulgel

Emulgel is an emerging topical drug formulation which is becoming increasingly popular due to its advantages over the conventional topical preparations. The emulgel is a combination of an emulsion and a gel and thus has a dual release control system .

Its biggest and most favorable advantage has been the ability to incorporate hydrophobic drugs, thus making it emerge as a more popular choice these days.

The emulgel is also greaseless, transparent; it can be easily spread and removed, has a long shelf- life, is thixotropic and is also pleasant looking .

Voltaren emulgel contain diclofenac diethyl ammonium is an example on emulgel .