Semisolid Dosage Forms

Ointments, creams and gels

Ointments, creams and gels are semisolid dosage forms intended for topical application. They may be applied to the skin, placed onto the surface of the eye or used nasally, vaginally or rectally.

The majority of these preparations are used for the effects of the therapeutic agents they contain. Those which are non-medicated are used for their physical effects as protectants or lubricants.

Topical preparations are used for the localised effects produced at the site of their application, although some unintended systemic drug absorption may occur, it is usually in sub-therapeutic quantities. However, systemic drug absorption can be an important consideration in certain instances, as when the patient is pregnant or nursing because drugs can enter the fetal blood supply and breast milk and be transferred to the fetus or nursing infant.

Transdermal drug delivery systems are designed for the systemic absorption of drug substances in therapeutic quantities.

The following distinction is an important one with regard to dermatologic applications, a topical product is designed to deliver drug into the skin to treat dermal disorders with the skin as the target organ.

A transdermal drug delivery system 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.

Ointments

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

Ointments may be medicated or non-medicated, non-medicated ointments are used for the physical effects that they provide as protectants, emollients or lubricants.

Ointment Bases

Ointment bases may be used for their physical effects or as vehicles in the preparation of medicated ointments. Ointment bases are classified into four general groups:

1. Hydrocarbon bases (oleaginous bases)
2. Absorption bases
3. Water-removable bases
4. Water-soluble bases

Hydrocarbon Bases

Hydrocarbon bases are also termed oleaginous bases, on application to the skin they have an emollient effect, protect against the escape of moisture, effective as occlusive dressing and can remain on the skin for prolonged periods of time without drying out and because of their immiscibility with water are difficult to wash off.

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

Petrolatum, white petrolatum, white ointment and yellow ointment are examples of hydrocarbon ointment bases.

When powdered substances are to be incorporated into hydrocarbon bases, liquid petrolatum (mineral oil) may be used as levigating agent.

Petrolatum, USP:

Petrolatum, USP is a purified mixture of semisolid hydrocarbons obtained from petroleum. It is an oily mass, varying in colour from yellowish to light amber. It melts at temperature between (38-60 °C) and may be used alone or in combination with other agents as an ointment base.

Petrolatum is also known as 'Yellow Petrolatum' and 'Petroleum Jelly'. A commercial product is 'Vaseline'.

Yellow ointment, USP:

This ointment has the following formula for the preparation of 1000 g:

Yellow wax	50 g
Petrolatum	950 g

Yellow wax is the purified wax obtained from the honey comb of the bee. The ointment is prepared by melting the yellow wax on a water bath, adding the petrolatum until the mixture is uniform, then cooling with stirring until congealed.

White ointment, USP:

This ointment differs from yellow ointment by substituting white wax (bleached and purified yellow wax) and white petrolatum in the formula.

Absorption Bases

Absorption bases are of two types:

1. Those that permit the incorporation of aqueous solutions resulting in the formation of w/o emulsions e.g. Hydrophilic petrolatum.
2. Those that are w/o emulsions (emulsion bases) permit the incorporation of additional quantities of aqueous solutions. e.g. Lanolin

These bases may be used as emollients although they don't provide the degree of occlusion afforded by the hydrocarbon bases. Absorption bases are not easily removed from the skin, since the external phase of the emulsion is oleaginous.

Absorption bases are useful as pharmaceutical adjuncts to incorporate small volumes of aqueous solutions into hydrocarbon bases. This is accomplished by incorporating the aqueous solution into the absorption base and then incorporating this mixture into the hydrocarbon base.

Hydrophilic Petrolatum, USP:

Hydrophilic petrolatum, USP has the following formula for the preparation of 1000 g:

Cholesterol	30 g
Stearyl alcohol	30 g
White wax	80 g
White petrolatum	860 g

It is prepared by melting stearyl alcohol and the white wax on a steam bath, adding the cholesterol with stirring until dissolved, then adding the white petrolatum and allowing the mixture to cool while being stirred until congealed.

Lanolin, USP:

Lanolin, USP obtained from the wool of sheep. It is a purified wax like substance that has been cleaned, deodorised and decolourised. It contains not more than 0.25% water. Additional water may be incorporated into lanolin by mixing.

Water-removable Bases

Water-removable bases are o/w emulsions resembling creams in appearance and because the external phase of the emulsion is aqueous, they are easily washed from the skin and are often called 'water-washable bases'. They may be diluted with water or aqueous solutions. They have the ability to absorb serous discharge.

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

Hydrophilic ointment, USP:

Hydrophilic ointment has the following formula for the preparation of about 1000 g:

Methyl paraben	0.25 g
Propyl paraben	0.15 g
Sodium lauryl sulfate	10 g
Propylene glycol	120 g
Stearyl alcohol	250 g
White petrolatum	250 g
Purified water	370 g

In preparing this ointment, the stearyl alcohol and white petrolatum are melted together at about 75 °C.

The other agents are dissolved in the purified water and then added with stirring until the mixture congeals.

- Sodium lauryl sulphate (SLS) is the emulsifying agent.
- Stearyl alcohol and white petrolatum comprising the oleaginous phase of the emulsion and the other ingredients form the aqueous phase.
- Methyl paraben and propyl paraben are antimicrobial preservatives.

Water-soluble Bases

Water-soluble bases don't contain oleaginous components, they are completely water-washable and often referred to as 'greaseless'.

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

Polyethylene glycol ointment, NF is an example of water-soluble base.

Polyethylene Glycol ointment, NF:

Polyethylene glycol (PEG) is a polymer of ethylene oxide and water represented by the formula $H(OCH_2CH_2)_nOH$ in which (n) represents the average number of oxyethylene groups. The numerical designations associated with PEG refer to the average molecular weight of the polymer.

PEG having average molecular weights below 600 are clear, colourless liquids and those with molecular weights above 1000 are wax-like materials and those with molecular weights in between are semisolids. The greater the molecular weight, the greater the viscosity.

The general formula for the preparation of 1000 g of PEG ointment is:

Polyethylene Glycol 3350	400 g
Polyethylene Glycol 400	600 g

The combining of PEG 3350, a solid, with PEG 400, a liquid, results in a very pliable (flexible) semisolid ointment.

If a firmer ointment is desired, the formula may be altered to contain up to equal parts of the two ingredients.

When aqueous solutions are to be incorporated into the base, the substitution of 50 g of PEG 3350 with an equal amount of stearyl alcohol is advantageous in rendering the final product more firm.

Selection of appropriate base

The selection of the base to be used in the formula of an ointment depends on a number of factors:

1. Desired release rate of the drug substance from the ointment base.
2. Desirability of occlusion of moisture from the skin.

3. Stability of the drug in the ointment base.
4. Effect of the drug on the consistency of the ointment base.
5. The desire for a base that is easily removed by washing with water.
6. Characteristics of the skin surface to which it is applied.

Preparation of ointments

Ointments are prepared by two general methods:

1. Incorporation
2. Fusion

The method used depends primarily on the nature of the ingredients.

Incorporation

By the incorporation method, the components are mixed until a uniform preparation is attained, on a small scale the pharmacist may mix the components using a mortar and pestle or a spatula and slab (a glass or porcelain plate).

Incorporation of solids

When preparing an ointment by spatulation, the pharmacist works the ointment with a stainless steel spatula having a long, broad blade. If the components of an ointment are reactive with the metal of the spatula (e.g. as in the case of phenol), hard rubber spatula may be used.

The ointment base is placed on one side and the powdered components previously reduced to fine powders on the other side. A small portion of the powder is mixed with a portion of the base until uniform mixture is obtained. The process is continued until all portions of the powder and the base are combined and thoroughly and uniformly blended.

It is often desirable to reduce the particle size of a powder or crystalline material before incorporation into the ointment base, so that the final product will not be gritty. This may be done by levigation process (i.e. mixing the solid material in a vehicle to make a smooth dispersion).

The levigating agent used should be physically and chemically compatible with the drug and base.

The levigating agent for example is mineral oil for oleaginous bases or the bases where oils are the external phase and glycerine for bases where water is the external phase.

The amount of levigating agent used should be about equal in volume to the solid material. A mortar and pestle is used for levigation, this allows both reduction of particle size and the dispersion of the substance in the vehicle. After levigation, the dispersion is incorporated into the ointment base by spatulation or with the mortar and pestle until the product is uniform.

Incorporation of liquids

Liquid substances or solutions of drugs are added to an ointment according to 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.

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 limit to retain liquids beyond which they become too soft or semiliquid. Alcoholic solutions of small volume may be added well to oleaginous vehicles or emulsion bases.

- On large scale, roller mills force ointments through stainless steel rollers to produce ointments that are uniform in composition and smooth in texture.

Fusion

By the fusion method, all or some of the components of an ointment are combined by being melted together and cooled with constant stirring until congealed. Components not melted are added to the congealing mixture as it 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 or volatilization of the components.

Substances may be added to the congealing mixture as solutions or as insoluble powders levigated with a portion of the base. On a small scale, the fusion process may be conducted in a porcelain dish or glass container.

Medicated ointments and ointment bases containing components as bees wax, paraffin, stearyl alcohol and high molecular weight PEG which do not lend themselves well to mixture by incorporation are prepared by fusion.

In the preparation of ointments having an emulsion base, the method of manufacture involves both a melting and an emulsification process.

The water-immiscible components such as the oil and waxes are melted together in a steam bath to about 70-75 °C, and an aqueous solution of the heat-stable water soluble components is prepared and heated to the same temperature as the oleaginous components, then the aqueous solution is slowly added with mechanical stirring to the melted oleaginous mixture. The temperature is maintained for 5-10 minutes and the mixture is slowly cooled with the stirring continued until congealed.

If the aqueous solution were not the same temperature as the oleaginous melt, there would be solidification of some of the waxes upon the addition of the colder aqueous solution to the melted mixture.

Creams

Pharmaceutical creams are semisolid preparations containing one or more medicinal agents dissolved in either an o/w or w/o emulsion.

Creams have a relatively soft, spreadable consistency. An example of an o/w cream is hydrophilic ointment and an example of a w/o cream is cold cream. When the term “cream” is used without further qualification, a water-washable formulation is generally inferred.

Creams find primary application in topical skin products and also in products used rectally and vaginally.

Many patients and physicians prefer creams to ointments because they are easier to spread and remove than ointments. Pharmaceutical manufacturers frequently manufacture topical preparations of a drug in both ointment and cream bases to satisfy the preference of the patient and physician.

Preparation of creams

Creams may be formulated from a variety of oils (both mineral and vegetable) and from fatty alcohols, fatty acids and fatty esters. Emulsifying agents include non-ionic surfactants and soaps.

Preparation 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 reaching ambient temperature or the mixture has congealed. Mixing is continued during the cooling process to promote uniformity. High-shear homogenisers may be employed to reduce particle or droplet size and improve the physical stability of the resultant dosage form.

- Vanishing creams are o/w emulsions containing large percentage of water and stearic acid. After application of the cream, the water evaporates leaving behind a thin residue film of stearic acid or other oleaginous components.

Gels

Gels are usually clear, transparent non-greasy semisolids containing solubilised active substances in an aqueous liquid vehicle rendered jelly-like by the addition of a gelling agent.

Among the gelling agents used are synthetic macromolecules such as carbomer, cellulose derivatives as carboxymethyl cellulose or hydroxypropyl cellulose and natural gums as tragacanth.

Carbomers are high molecular weight water-soluble polymers of acrylic acid cross-linked with allyl ethers of sucrose and depending on their polymeric composition different viscosities result, for example carbomer 910, 934 and 940. They are used as gelling agents at concentrations of 0.5-2% in water. Carbomer 940 yields the highest viscosity (40,000 – 60,000 centipoises) as a 0.5% aqueous dispersion.

Gels may be used as lubricants or medicated gels administered by various routes including the skin, the eye, the nose, the vagina and the rectum.

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 methyl and propyl parabens and stabilisers such as edetate disodium.

Gels are easy to apply and the evaporation of the water produces a pleasant cooling effect and it is easily removed by washing when treatment is complete.

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

Single-phase gels are gels in which the macromolecules are uniformly distributed throughout a liquid with no apparent boundaries between the dispersed macromolecules and the liquid. A gel mass consisting of floccules of small distinct particles is termed a two-phase system often referred to as a magma.