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.

Official requirements for semisolids

Ointments and other semisolid dosage forms must meet the USP tests for microbial content, minimum fill, packaging, storage and labelling.

Ophthalmic ointments must meet tests for sterility and metal particle content.

Microbial content

With the exception of ophthalmic preparations, topical applications are not required to be sterile, they must however meet acceptable standards for microbial content and preparations which are prone to microbial growth must be preserved with antimicrobial preservatives. e.g. methyl and propyl parabens and quaternary ammonium salts.

- For example, Betamethasone valerate ointment USP, must meet the requirements of the tests for the absence of staphylococcus aureus and Pseudomonas aeruginosa.

These microbes are of special importance in dermatological preparations because of their capacity to infect the skin. Semisolids intended for rectal and vaginal use should be tested for the presence of yeasts and moulds.

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

Minimum fill

The USP minimum fill test involves the determination of the net weight or volume of the contents of the filled containers to assure proper contents compared with the labelled amount.

Packaging and storage

Ointments and other semisolid preparations are packaged in metal or plastic tubes. The tubes are first tested for compatibility and stability for the intended product.

Tubes used to package topical products are light in weight, relatively inexpensive, convenient for use by the patient, compatible with most formulative components and provide greater protection against external contamination and environmental conditions than jars.

Ointment tubes are made of aluminium or plastic. Tubes of aluminium generally are coated with epoxy resin to eliminate any interactions between the contents and the tube.

Plastic tubes are made of high or low density polyethylene (HDPE or LDPE) or blend of them, polypropylene (PP) and plastic-foil paper laminates. Laminates provide an excellent moisture barrier due to foil content, high durability and product compatibility.

These qualities and flexibility make plastic and plastic laminate tubes preferred over metal tubes for the packaging of pharmaceuticals.

Topical dermatological preparations most frequently are packaged in 5, 15 and 30 g tubes.

Ophthalmic ointments are packaged in small aluminium or collapsible plastic tubes holding 3.5 g. The tubes are sterilised before being filled.

Semisolids must be stored in well-closed containers to protect against contamination and in a cool place to protect against product separation due to heat. When required, light-sensitive preparations are packaged in light-resistant containers.
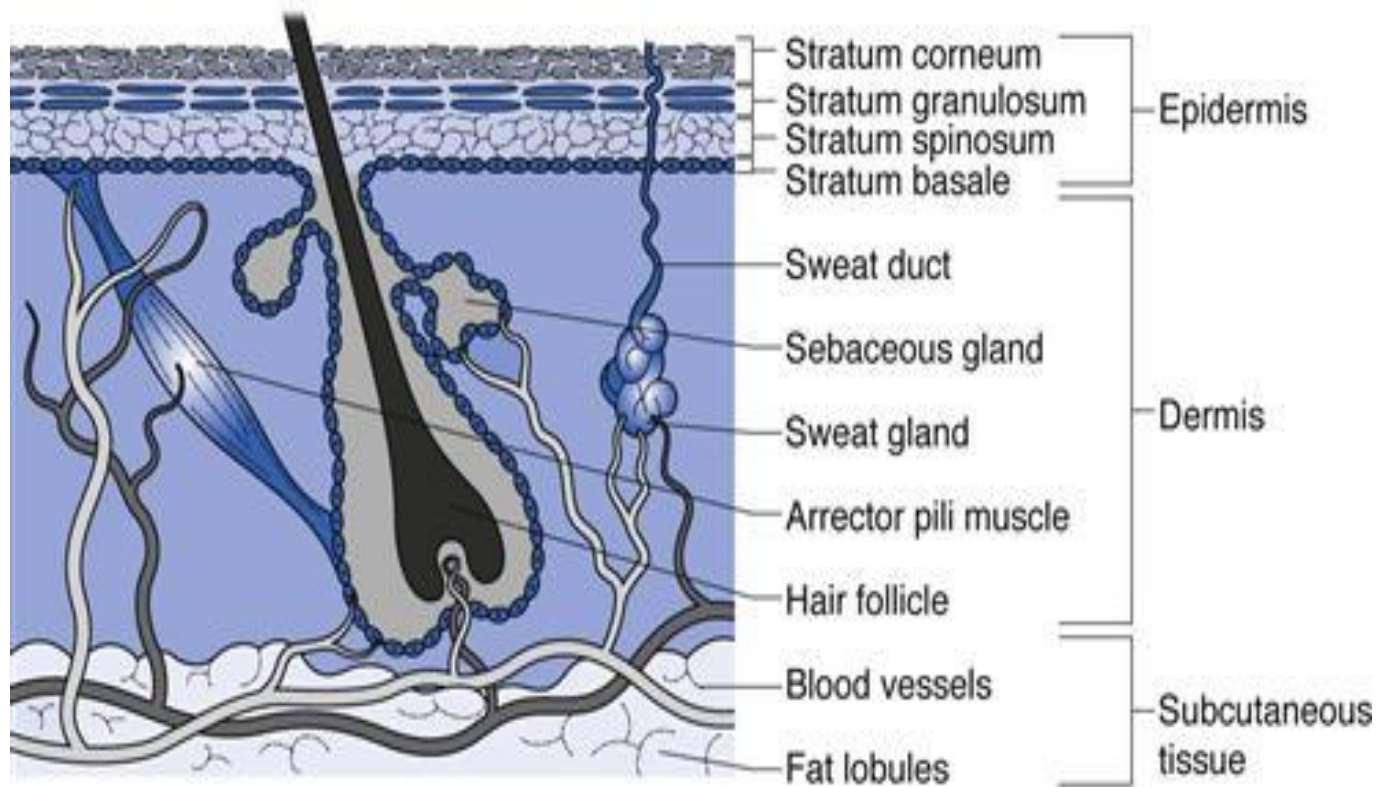
Skin structure and function

Human skin is a highly complex multi-layered structure and it represents the largest organ of the body, comprising around 10% of the body mass.

The main function of the skin is to act as a barrier between the body and the outside environment. This barrier prevents the entry of chemicals, microorganisms, UV radiation and the loss of water and body fluids. In addition, the skin plays a role in the regulation of body temperature and it also acts as a sensory organ.

Skin layers

1. The Epidermis
2. The Dermis
3. The Subcutaneous Fatty layer

Stratum corneum
Stratum granulosum — Epidermis
Stratum spinosum
Stratum basale

Sweat duct

Sebaceous gland — Dermis

Sweat gland

Arrector pili muscle

Hair follicle

Blood vessels

Fat lobules — Subcutaneous tissue

1. The Epidermis

The epidermis is the outer avascular layer of the skin. It is a multi-layered region that varies in thickness from 0.8 mm on the palms of the hands and soles of the feet to 0.06 mm on the eyelids.

The *stratum corneum* (or 'horny' layer) is predominantly responsible for the barrier properties of human skin which limits the permeation of chemical substances and microorganisms from the skin surface. The *stratum corneum* is around 10-20 µm thick when dry (although it can swell to several times this when wet). It is composed of anucleated flattened corneocytes packed with keratin filaments and surrounded by a lipid bilayer. The *stratum corneum* is composed of approximately 80% protein and 20% lipid.

2. The Dermis

The dermis is the second layer below the epidermis and it is about 3-5 mm thick and composed of a network of connective tissue, mainly of collagen and elastin embedded in a mucopolysaccharide gel. This provides an aqueous environment similar to a hydrogel. Nerves, blood vessels and lymphatics traverse the matrix and skin appendages such as hair follicles, sebaceous glands, and sweat glands penetrate through it .

**3.   Subcutaneous fatty layer**

The thickness of this inner layer of the skin is several millimetres and it is composed mainly from adipose tissue which insulates the body, acts as thermal barrier and provides mechanical protection against physical shock.

Drug transport and permeation through the skin

When a drug is applied topically, the drug diffuses out of its vehicle onto the surface of the skin.

The drug molecules have three routes to traverse the intact *stratum corneum* depending on their physicochemical properties, these being:

- Intracellular (across corneocytes)

- Intercellular (across lipids) considered the major route of penetration

- Appendageal (via skin appendages)
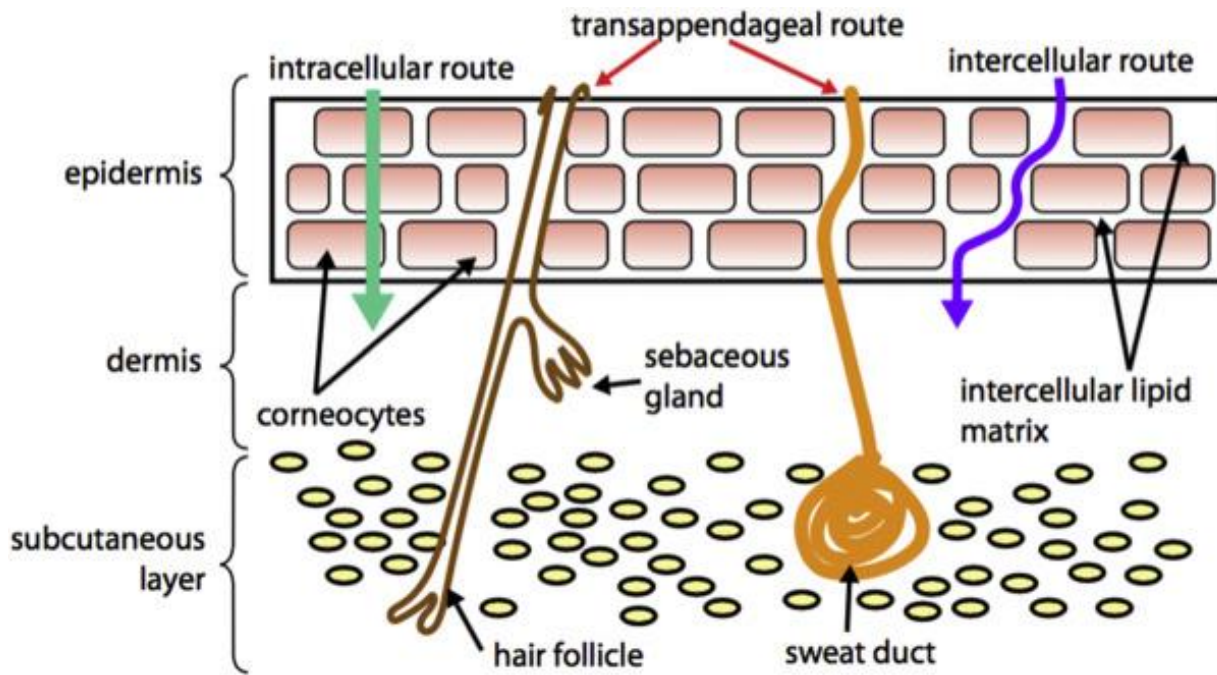
- The intracellular pathway provides a polar route for the diffusion of hydrophilic molecules. However, the corneocytes are bound to a lipid envelope that connects to the lipid bilayers which need to be crossed.

- The intercellular route represents the major pathway for drug molecules to cross the *stratum corneum*, since the intercellular transport occurs through the lipid domains and also the intracellular transport needs the lipid bilayers between the corneocytes to be crossed.

- The appendages (hair follicles, sebaceous and sweat glands ducts) provide pores that overcome the *stratum corneum* barrier. This route represents a shunt route or shortcut through which the drug molecules can move across the *stratum corneum.*

- For a permeant with an intermediate partition coefficient (log *P* 1-3), the intercellular route probably predominates.

- For more hydrophilic molecules (log *P* <1), the intracellular route increasingly predominates.

- The transport of a highly hydrophilic and charged permeant is predominantly through the appendageal route.

Factors affecting skin penetration

The rate and extent of a drug that penetrate the skin depends on:

1. Physicochemical properties of the drug (molecular weight, partition coefficient "lipid solubility" and aqueous solubility).

2. Type of vehicle used and concentration of the drug in a vehicle.

3. Skin condition

Ophthalmic ointments

The major route by which drugs enter the eye is by simple diffusion via the cornea.

The cornea is a lipophilic epithelial layer and lipophilic drugs are more capable of penetration than hydrophilic compounds.

In general, ocular drug penetration is limited due to the short residence time that the ophthalmic preparations have on the surface of the eye because of their rapid removal by tearing, the small surface area of the cornea available for drug absorption and 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. Therefore, increasing the duration of their effects and bioavailability for absorption into ocular tissue.

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.

The ointment base selected for an ophthalmic ointment must be:

- Non-irritating to the eye.

- Permit the diffusion of the medicinal substance into the eye.

- Have a softening point close to body temperature both for patient comfort and for drug release.

Mixture of white petrolatum and liquid petrolatum (mineral oil) are utilised as the base in medicated and non-medicated ophthalmic ointments. A gel-base of polyethylene glycol and mineral oil is also used.

Medicinal agents are added to an ointment base either as a solution or as a finely micronized powder. The ointment made uniform by fine milling.

Ophthalmic ointments must meet the USP sterility test and the test of metal particles.

Rendering an ophthalmic ointments sterile requires special techniques and processing. The terminal sterilisation of a finished ointment by standard methods may have some limitations.

Steam sterilisation or ethylene oxide methods are ineffective because neither is capable of penetrating the ointment base.

Although dry heat can penetrate the ointment base, the high heat required may affect the stability of the drug substance and can separate the ointment base from other components.

Because of these difficulties, terminal sterilisation is not undertaken, rather strict methods of aseptic processing are employed as each drug and non-drug component is sterilised and then aseptically weighed and incorporated in a final product, also preservative can be added.

Among the antimicrobial preservatives used are combination of methylparaben 0.05% and propylparaben 0.01%, chlorobutanol and benzalkonium chloride.

The USP test for metal particles involves the microscopic examination of a heat-melted ophthalmic ointment. The detected metal particles are counted and measured.

The requirement met if the total number of particles 50 µm or larger from 10 tubes does not exceed 50.

Pastes, Plasters and Glycerogelatins

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 they 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. 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 the paste, they remain in place after application and they are effectively employed to absorb serous secretions. In addition, because of their stiffness and impermeability, pastes are not suitable for application to hairy parts of the body.

e.g. zinc oxide paste, prepared by mixing 25% each of zinc oxide and starch with white petrolatum. The product is very firm and is able to protect the skin and absorb secretions than is zinc oxide ointment.

Plasters: are solid or semisolid adhesive masses spread on a backing of paper or plastic, the adhesive material is a rubber base or a synthetic resin.
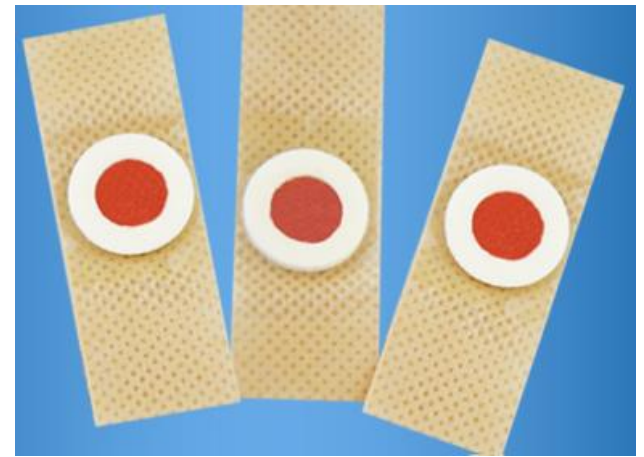
Plasters are applied to the skin to provide prolonged contact at the site. Unmedicated plasters provide protection or mechanical support at the site of application.

Medicated plasters provide effects at the site of application. e.g. salicylic acid plaster used on the toes for the removal of corns. The horny layers of skin are removed by the keratolytic action of salicylic acid. The concentration of salicylic acid used ranges from 10-40%.

Glycerogelatins: are plastic masses containing gelatine 15%, glycerine 40%, water 35% and an added medicinal substances 10% such as zinc oxide.

They are prepared by first softening the gelatine in water for 10 minutes, then heating on a steam bath until gelatine is dissolved, followed by the addition of the medicinal substance mixed with glycerine and allowing the mixture to cool with stirring until congealed.

Glycerogelatins are applied to the skin for the long term. They are melted before application, cooled to slightly above body temperature and applied to the affected area with a fine brush.

Following application, the glycerogelatin hardens and is usually covered with a bandage and is allowed to remain in place for weeks.

e.g. zinc glycerogelatin used in the treatment of varicose ulcer, it was also known as zinc gelatine boot because of its ability to form a pressure bandage.

Transdermal Drug Delivery Systems (TDDS)

TDDS facilitate the passage of therapeutic quantities of drug substances through the skin into the general circulation for their systemic effects, with the skin not being the target organ.

Advantages of TDDS

- They can avoid gastrointestinal drug absorption problems caused by GIT pH, enzymes and drug interaction with food, drink or with other orally administered drugs.

- They avoid the first-pass effect responsible for metabolism and deactivation of drug by liver enzymes.

- They can substitute for oral administration of drugs when that route is unsuitable as in cases of vomiting and or diarrhoea.

- They provide extended therapy with a single application, thereby improving patient compliance over other dosage forms requiring more frequent dose administration.

- TDDS are non-invasive, avoiding the inconvenience of parenteral therapy.

- Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

- Ease of rapid identification of the medication in emergencies e.g. unconscious or comatose patient due to the identifying-markings on the TDDS.

Disadvantages

- Not all drugs are suitable candidates for TDDS due to the natural limit of drug entry imposed by the skin impermeability.

- Some patients may develop contact dermatitis at the application site, requiring the discontinuation of therapy.

There are certain parameters that can be used to predict the feasibility of an active drug ingredient for transdermal administration. These include:

1. Log P, ideally the log partition coefficient of the drug should be in the range of 1-3.

2. Molecular weight (MW), ideally the molecular weight of the drug should be less than 500 Dalton.

3. Aqueous solubility, ideally the aqueous solubility of the drug should be equal or greater than 1 mg/mL.

4. Melting point of the permeant should be less than 200 °C.

5. The effective daily dose of the drug should be in the range of 10-40 mg/day.

Transdermal delivery patches

Are designed to deliver a constant and controlled dosage over extended periods of time for systemic therapy.

Due to the barrier properties of the skin, relatively few drug molecules have the appropriate physicochemical and therapeutic properties for sustained transdermal delivery. However some successful products have reached the market such as scopolamine, nicotine, estradiol, fentanyl, testosterone and glyceryl trinitrate transdermal patches.

Design of transdermal patches

Numerous patch design exist. The simplest systems contain the drug in an adhesive, with more complexity introduced in matrix type patches and reservoir systems.

1. Drug-in-adhesive patches are the simplest and most common patch design and are widely used to deliver nicotine and glyceryl trinitrate.

| Backing layer |
| --- |
| Drug in adhesive layer |
| Removable release liner |
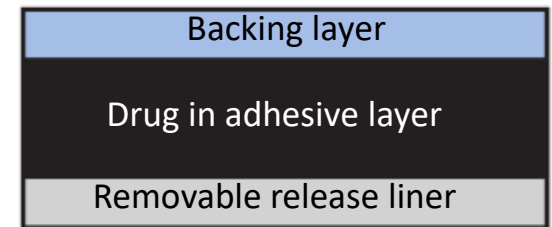
Simple drug-in-adhesive patch

These patches are formed by dissolving or dispersing drug within an adhesive which is then coated onto a backing layer before a release liner is applied. Drug-in-adhesive patches tend to be thinner and more flexible than other systems, but drug loading constraints can reduce the period of delivery. For example, nicotine patches are designed for less than one day use.

2. Drugs can be included in a separate matrix which can be formulated to increase the drug content in the system, allowing longer term delivery. The drug containing matrix or reservoir is often a polymeric mixture, for example polyvinylpyrrolidone and polyvinylacetate, potentially with the addition of a plasticizer such as glycerol. Hydrogels may also be used as the matrix. Drug released from the matrix will partition into and diffuse through the adhesive layer.

| Backing layer |
| Drug in matrix/reservoir |
| Adhesive layer |
| Removable release liner |
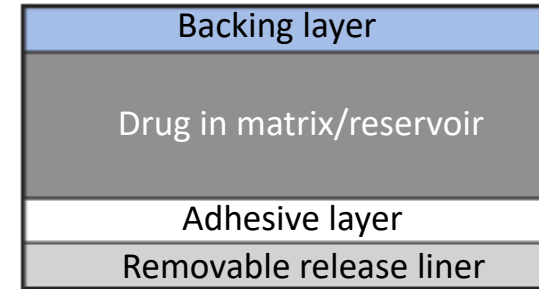
Drug-in-matrix patch

3. More complex rate limiting membrane systems typically contain the drug in a reservoir but with release controlled through a semi-permeable membrane. The reservoir may be liquid or more often a gel and can be designed to contain higher drug loadings than a simple drug-in-adhesive system for prolonged delivery.

| Backing layer |
| Drug in matrix/reservoir |
| Rate-limiting membrane |
| Adhesive layer |
| Removable release liner |
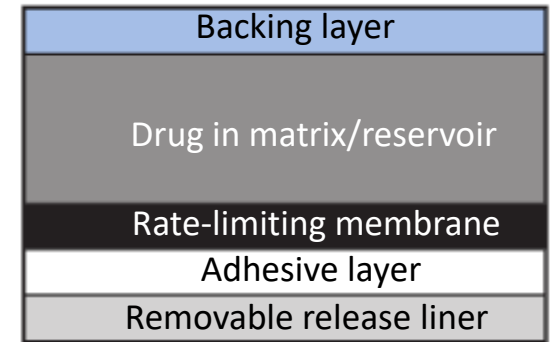
Rate-limiting membrane-type patch

For all the above configurations, patches have some common components:

- **Removable release liner:** A liner temporarily covers the adhesive and is the layer that is removed to allow the patch to be applied to the skin. Liners are often made from polymers such as ethylene vinyl acetate or aluminium foil dependent on the nature of the adhesive that it covers.

The liner must be easily peel away from the adhesive but must be bonded firmly enough to prevent accidental removal. Liners are usually occlusive to prevent the loss of volatile patch components such as ethanol prior to use.

- **Adhesive:** The adhesive is a crucial component of all transdermal delivery patches and pressure sensitive adhesives (PSAs) such as acrylates, polysiloxane adhesives are usually used. The adhesive must:

➢ Stick to the skin for the patch's lifetime.

➢ It must be non-irritating and non-allergenic as it may be in place for up to 7 days.

➢ It must be compatible with the drug and other excipients.

➢ It should allow the patch to be removed painlessly without leaving adhesive residue on the skin surface.

- **Backing layer:** Numerous materials can be used for patch backing layers, depending on the patch design, size and length of intended use. For relatively short use small patches, an occlusive backing layer may be selected and this will hydrate the underlying skin which can improve delivery. Example materials include polyethylene or polyester films. For larger and longer term use patches, backing layers that permit some vapour transmission are preferred such as polyvinylchloride films. In addition, the backing layer should allow multidirectional stretch and be pliable to allow the patch to move as the skin moves.

- **Matrix/reservoir:** A drug matrix or reservoir is usually prepared by dissolving the drug and polymers in a common solvent before adding in other excipients such as plasticizers.

The viscosity of the matrix can be modified by the amounts of polymers incorporated in the matrix and can consequently be used to control diffusion of the active ingredient through the matrix to the adhesive and then on to the skin surface.

- **Rate-limiting membrane:** semi-permeable membranes are used to separate reservoir from the underlying adhesive layer and designed to control the rate of delivery of the active ingredient to the skin surface. Membranes can be prepared from co-polymers of ethylene acetate with vinyl acetate with or without plasticizers. As with other patch components, the rate limiting membrane must be compatible with the drug, non-toxic, stable and pliable.

General clinical consideration in the use of TDDS

1. Percutaneous absorption may vary according to the site of application, there is a preferred application site stated in the literature of each product.

    The patient should be advised of the importance of using the recommended site and rotating locations within that site in the application of replacement patches. Rotating locations is important to allow the skin beneath a patch to regain its normal permeability characteristics after being occluded and also prevent the possibility of skin irritation. Skin sites may be re-used after a week.

2. TDDS should be applied to clean and dry skin areas that are relatively free of hair and not oily or irritated, inflamed broken area.

3. TDDS should not be physically altered by cutting (as in attempt to reduce the dose) since this would destroy the integrity of the system.

4. The protective removable release liner should be removed to expose the adhesive layer while being careful not to touch the adhesive surface which may contains drug to the finger tips. The patch should be pressed firmly against the skin site with the hand for 10 seconds to assure uniform contact and adhesion.

5. TDDS should be worn for the full period of time stated in the product's instructions and care should be taken not to touch the eyes or the mouth during handling of the system.

Examples of TDDS

1. **Transdermal Scopolamine:** used to prevent travel-related motion sickness, nausea and vomiting. The TDDS contains 1.5mg of scopolamine and is designed to deliver the drug at constant rate to the systemic circulation over 3 days. The patch is worn in a hairless area behind the ear.

2. **Transdermal Nitroglycerin:** designed to provide controlled release of nitroglycerin for the treatment of angina. Each patch delivers nitroglycerin over 24 hrs (Daily application) to the chest, shoulder and upper arm.

Nitroglycerin is rapidly metabolised by the liver when taken orally and therefore this effect can be prevented by the transdermal route. Nitroglycerin patch is available in two strengths 5mg and 10mg.

Transdermal Nicotine: are used in smoking cessation programmes. They have been shown to be an effective aid in quitting the smoking habit when used according to product-recommended strategies.

They provide sustained blood levels of nicotine as nicotine replacement therapy. The available patches contain from 7-22mg of nicotine for daily application for 6-12 weeks applied to the arm.