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.

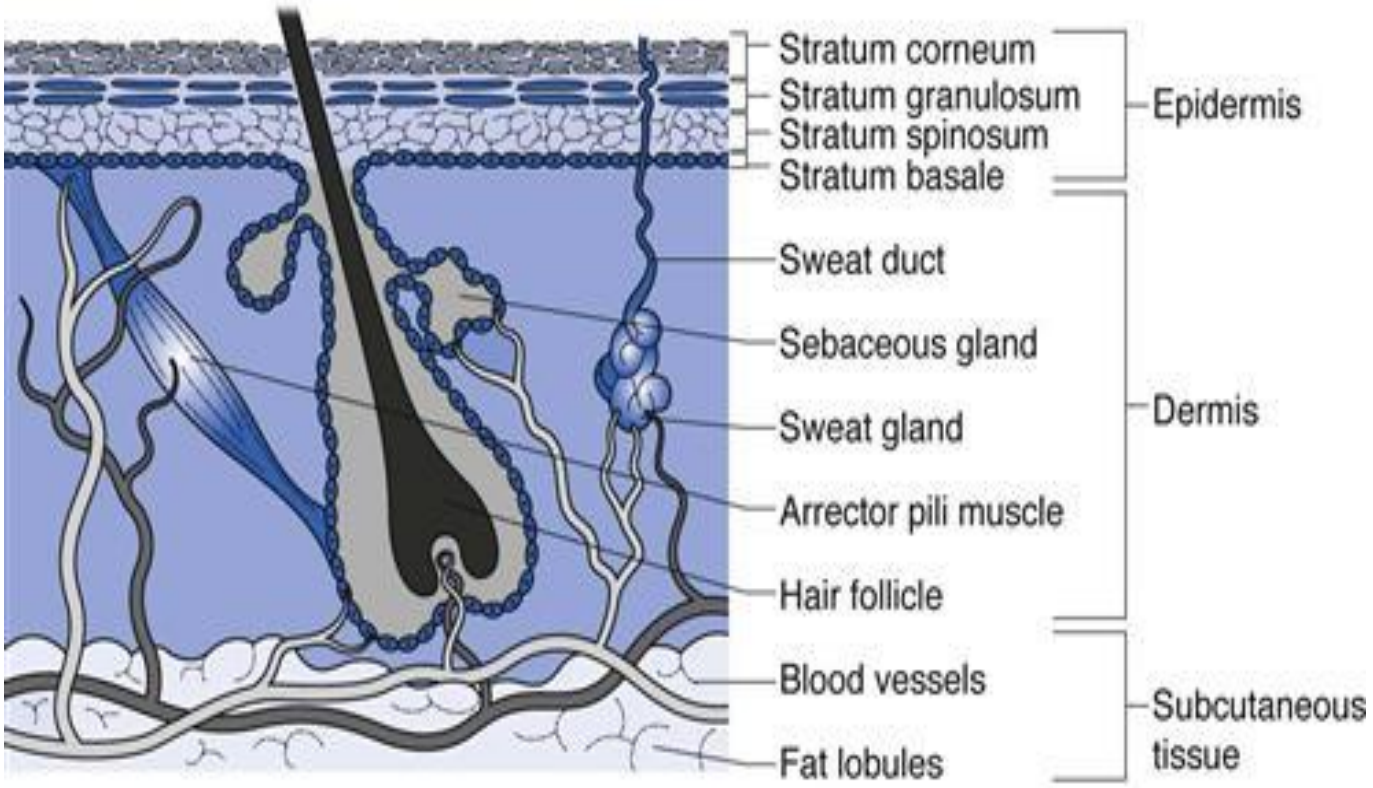
Skin structure and function

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



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

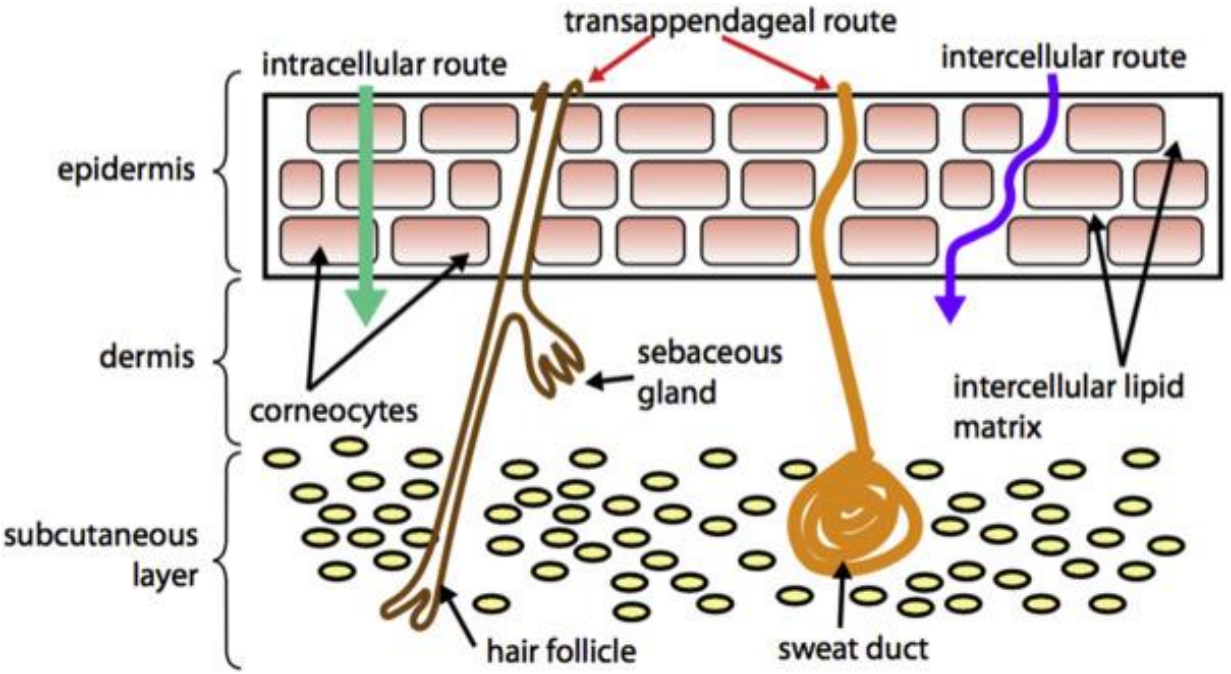
The thickness of this inner layer of the skin is several millimetres and it is composed mainly from adipose tissue which insulates the body, acts as thermal barrier and provides mechanical protection against physical shock.

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 bases 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

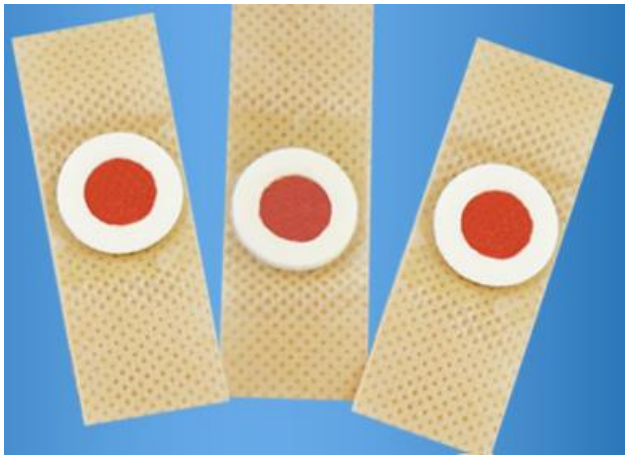
Pastes: are semisolid preparations intended for application to the skin, they generally contain a larger proportion of solid material (such as 25%) than ointments and therefore they are stiffer.

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.

Collodions

Collodions are liquid preparations composed of pyroxylin dissolved in a solvent mixture usually composed of alcohol and ether with or without added medicinal substances.

Pyroxylin (i.e., nitrocellulose, soluble gun cotton, collodion cotton), obtained by the action of a mixture of nitric and sulfuric acids on cotton, consists chiefly of cellulose tetranitrate. It has the appearance of raw cotton when dry but is harsh to the touch.

Pyroxylin, like collodions, is exceedingly flammable and must be stored away from flame in well-closed containers, protected from light.

Collodions are intended for external use. When applied to the skin with a fine brush or glass applicator, the solvent rapidly evaporates, leaving a filmy residue of pyroxylin. This provides an occlusive protective coating to the skin, and when the collodion is medicated, it leaves a thin layer of that medication firmly placed against the skin.

Naturally, collodions must be applied to dry tissues to adhere to the skin's surface. The products must be clearly labeled "for external use only" or with words of similar effect.

Collodion

Collodion is a clear or slightly opalescent viscous liquid prepared by dissolving pyroxylin (4%w/v) in a 3:1 mixture of ether and alcohol.

The resulting solution is highly volatile and flammable and should be preserved in a tight container remote from fire at a temperature not exceeding 30°C.

The product is capable of forming a protective film on application to the skin and the volatilization of the solvent. The film is useful in holding the edges of an incised wound together. However, its presence on the skin is uncomfortable because of its inflexible nature. The following product, which is flexible, has a greater appeal when a pliable film is acceptable.

Flexible Collodion

Flexible collodion is prepared by adding 2% camphor and 3% castor oil to collodion. The castor oil renders the product flexible, permitting its comfortable use over skin areas that are normally moved, such as joints, fingers, and toes. The camphor makes the product waterproof.

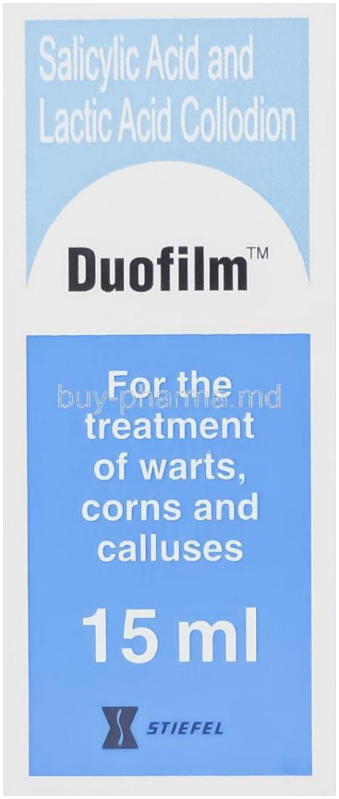
Salicylic acid collodion

Salicylic acid collodion is a 10% solution of salicylic acid in flexible collodion. It is used for its keratolytic effects, especially in the removal of corns from the toes. Patients who use such products should be advised about their proper use.

The product should be applied one drop at a time on the corn or wart, allowing time to dry before the next drop is added. Because salicylic acid can irritate normal, healthy skin, every attempt must be made to ensure application directly on the corn or wart. A useful preventive measure is to line the adjacent healthy skin with some white petrolatum prior to application of the product. Proper tightening and storage of the product after use are absolutely necessary because of the volatility of the vehicle.

Commercial products of collodions





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