

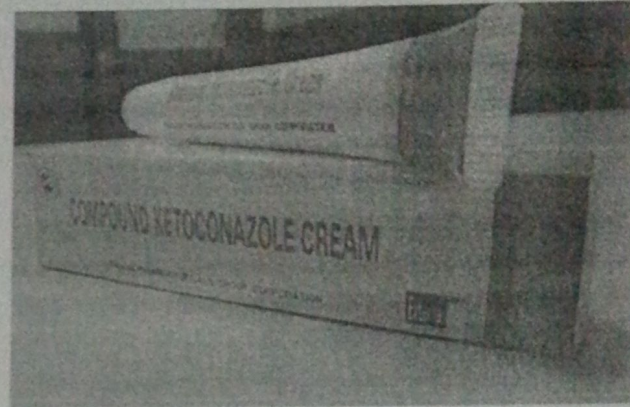
drug- release tests involve diffusion cell studies to determine the drug's release profile from the semisolid product.

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Creams

Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base. This term traditionally has been applied to semisolids that possess a relatively soft, spreadable consistency formulated as either water-in-oil or oil-in-water emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.



i.e. Pharmaceutical creams are semisolid preparations containing one or more medicinal agents dissolved or dispersed in either an o/w emulsion or in another type of water-washable base.

So-called "vanishing creams" are o/w emulsions containing large percentages of water and stearic acid. After application of the cream, the water evaporates leaving behind a thin residue film of the stearic acid.

The vanishing creams are so called because on application and rubbing into the skin, there is little or no visible evidence of their presence.



Creams find primary application in topical skin products and in products used rectally and vaginally. Many patients and physicians may prefer creams to ointments because they are easier to spread and remove than may ointments.

Pharmaceutical manufacturers frequently manufacture topical preparations of a drug in both cream and ointment bases to satisfy the preference of the patient and physician.



Gels

Gels are defined as semisolid preparations consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jelly-like through the addition of a gelling agent. Gels are an intermediate state of matter, containing both solid and liquid components and sometimes called jellies. Gelling agents commonly used are synthetic macromolecules (e.g., carbomer 934), cellulose derivatives (e.g., carboxymethylcellulose and hydroxypropylmethylcellulose), and natural gums (e.g., tragacanth). Carbomers in particular are high molecular-weight water-soluble polymers of acrylic acid cross-linked with allyl ethers of sucrose and/or pentaerythritol. Depending on their polymeric composition, different viscosities result.

The NF contains monographs for six such polymers: carbomers 910, 934, 934P, 940, 941 and 1342. They are used as gelling agents at concentrations of 0.5–2.0% in water. Carbomer 940 yields the highest viscosity; between 40,000 and 60,000 centipoises as a 0.5% aqueous dispersion.

Gels may be classified as two-phase or single-phase systems. *Single-phase gels* are gels in which the macromolecules are uniformly distributed throughout a liquid



direct interactions between the dispersed particulates and by absorption of the liquid hydrocarbons from the vehicles onto the surface of the particles.

Thus, they contain a larger proportion of solid material than ointments and therefore are stiffer. When prepared with an oleaginous base they are less greasy than ointments due to the reduced amount of base used.

Because of the stiffness of pastes, they remain in place after application and are used effectively to absorb serous secretions. Pastes as such are not suited for application to hairy parts of the body because of their stiffness and impenetrability.

Examples of insoluble ingredients serving as the dispersed phase include starch, zinc oxide, and calcium carbonate. Pastes make good protective barriers for the following reasons. In addition to forming an unbroken film, pastes also absorb and neutralize certain harmful chemicals before they reach the skin surface. This last feature is attributed to the presence of insoluble particulate matter within the paste formulations. For example, for the treatment of diaper rash, when spread over the baby's bottom, the pastes absorb irritants formed by bacterial action on urine. Pastes also provide a protective layer over skin lesions and, when covered with suitable dressings, prevent excoriation of the patient's skin by scratching. Pastes afford emollient action as do ointments. In addition, the water-impermeable film formed on application is opaque and thus can often serve as a sunblock.

A clinically distinctive feature, which is generally attributed to pastes, is the ability to absorb exudates by nature of the powder or other absorptive components. Among the few pastes in use today is zinc oxide paste which is prepared by levigating and then 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.

PLASTERS

with no apparent boundaries between the dispersed macromolecules and the liquid. Examples of such gels include tragacanth and carboxymethylcellulose.

A *two-phase gel* system consists of floccules of small distinct particles rather than large molecules, thus called a two-phase system often referred to as magma. Milk of magnesia (or magnesia magma), which comprises a gelatinous precipitate of magnesium hydroxide, is an example of such a system. The gel structure in the two-phase systems is not always stable and thus may thicken on standing, forming a thixotrope, and must be shaken before use to liquefy the gel and enable pouring.

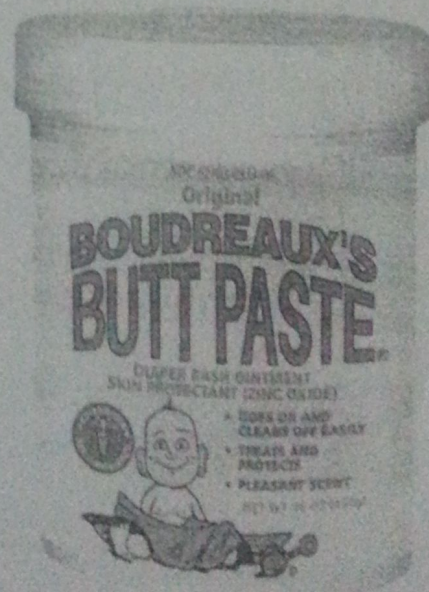
In addition to the gelling agent and water, gels may be formulated to contain a drug substance, cosolvents such as alcohol and/or propylene glycol, antimicrobial preservatives such as methylparaben and propylparaben or chlorhexidine gluconate, and stabilizers such as edetate disodium.

Medicated gels may be prepared for administration by various routes including topically to the skin, to the eye, nasally, vaginally, and rectally.

MISCELLANEOUS SEMISOLID PREPARATIONS:

PASTES

Pastes are semisolid preparations intended for application to the skin. They may be defined as ointments incorporating a high percentage of insoluble particulate solids; sometimes as much as or more than 50%. The use of this high amount of insoluble particulate matter renders stiffness to the system as a result of



Plasters are solid or semisolid adhesive masses spread upon a backing material of paper, fabric, moleskin or plastic. The adhesive material used is a rubber base or a synthetic resin. Plasters are applied to the skin to provide prolonged contact at the site.

Nonmedicated plasters provide protection or mechanical support at the site of application. Adhesive tape was formerly official under the title of "Adhesive Plaster", the use of this material being well known.

Medicated plasters provide effects at the site of application. They may be cut to size to conform to the surface to be covered. Among the few plasters in use today is Salicylic Acid Plaster used on the toe 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 in commercial corn plasters ranges from 10-40%.

Glycerogelatins

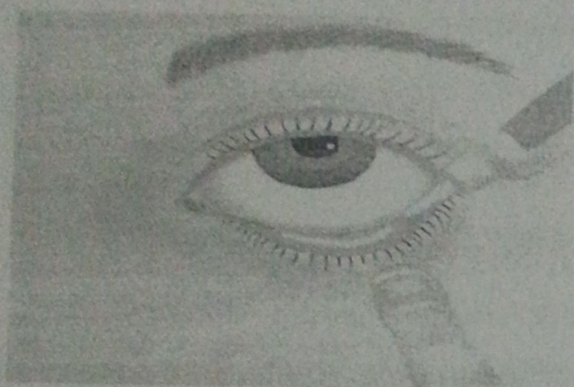
Glycerogelatins are plastic masses containing gelatin (15%), glycerin (40%), water (35%), and an added medicinal substance (10%) as zinc oxide. They are prepared by first softening the gelatin in the water for about 10 minutes, heating on a steam bath until the gelatin is dissolved, adding the medicinal substance mixed with glycerin, and allowing the mixture to cool with stirring until congealed.

Glycerogelatins are applied to the skin for long term residence. 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, is usually covered with a bandage and is allowed to remain in place for a period of weeks.



The most recently official glycerogelatin was Zinc Gelatin, used in the treatment of varicose ulcers. It was also known as "zinc gelatin boot" due to its ability to form a pressure bandage.

Features & Use of Ophthalmic Ointments and Gels

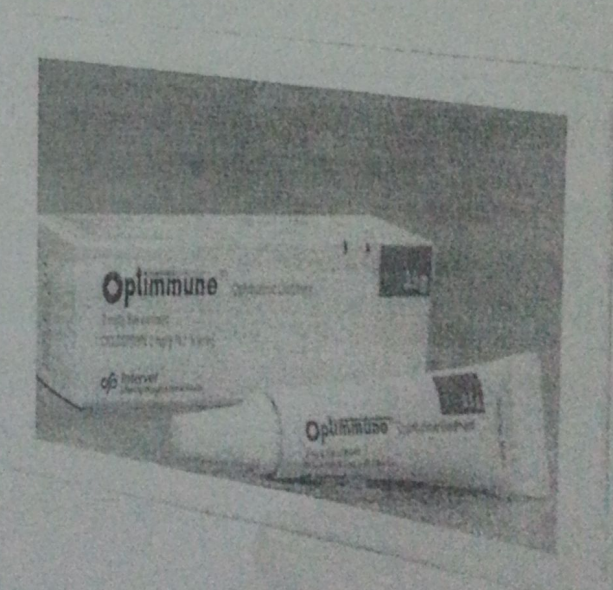


The application of medication to the eye or conjunctival sac results in effects on the surface of the eye and in underlying tissues due to drug penetration. The major route by which drugs enter the eye is by simple diffusion via the cornea. For drugs that are poorly absorbed by the cornea, the conjunctive and sclera provide an alternative route.

The cornea is a trilaminar structure with a lipophilic epithelial layer, a hydrophilic stromal layer, and a less lipophilic endothelial layer on the inside. Drug penetration is dependent on a drug's ability to traverse these three layers. Lipophilic drugs are more capable of penetration than hydrophilic compounds.

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

Ophthalmic ointments differ from conventional ointments in that they must be sterile. Although the USP does not specify any particular base in the ophthalmic drug monographs, it states that the ingredients used must be sterilized under rigid aseptic conditions and again in its final container.

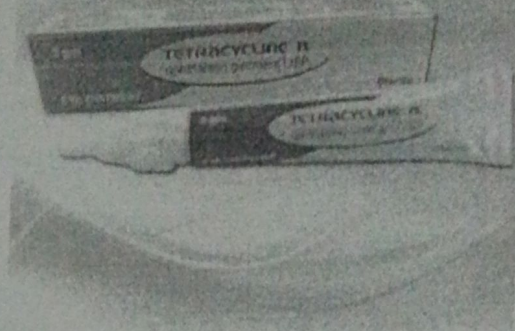
In choosing an ointment base for an ophthalmic preparation, it must meet several qualities such as having the ability to diffuse the medication throughout the secretions bathing the eye. It must also have a softening point close to body temperature, both for patient comfort and for drug release. To avoid the risk of damage to the eye, it is imperative that the ointment be free of large particles and any metal particles.

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 and are subjected to fine milling to render the preparation uniform and smooth. The ophthalmic ointments also must meet the USP sterility tests and the test for metal particles in ophthalmic ointments.

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 (0.05%) and propylparaben (0.01%) and its combinations phenylmercuric acetate (0.0008%), chlorobutanol (0.5%), and benzalkonium chloride (0.008%) are used as needed.

Features & Use of Nasal Ointments and Gels

The nose is a respiratory organ which is a passage way for air to the lung. Its surface is coated with a continuous thin layer of mucous produced by subepithelial mucous glands. Drugs introduced into the nasal passage are primarily for localized effects on the mucous membranes and underlying tissues (e.g., nasal decongestants). The nasal route of administration is used for the systemic absorption of a number of drugs including butorphanol tartrate (an analgesic), cyanocobalamin (a hematopoietic), narfaralin acetate for the treatment of endometriosis & nicotine (as an adjunct in smoking cessation).



Features & Use of Rectal Preparations

Ointments and creams are used for topical application to the perianal area and for insertion within the anal canal. They largely are used to treat local conditions of anorectal pruritus, inflammation and the pain and discomfort associated with hemorrhoids.

The drugs employed include astringents (e.g., zinc oxide), protectants and lubricants (e.g., cocoa butter, lanolin), local anesthetics (e.g., pramoxineHCl), and antipruritics and anti-inflammatory agents (e.g., hydrocortisone).

The rectal route is used for the systemic absorption of therapeutic levels of certain drugs (e.g., prochlorperazine as suppositories) when the oral route is unsatisfactory, as in conditions of vomiting. However, systemic effects from ointments/creams intended for localized action is usually limited due to the insolubility of certain agents (e.g., zinc oxide) and the subtherapeutic amounts absorbed of soluble drugs, which may be present in the formulation.

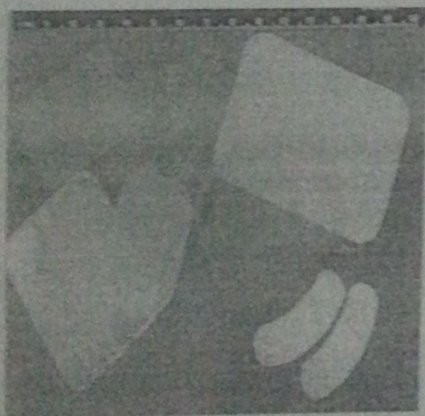
The bases used in anorectal ointments and creams include combinations of polyethylene glycol 300 & 3500, emulsion cream bases utilizing cetyl alcohol and cetyl esters wax, and white petrolatum and mineral oil.

Features & Use of Vaginal Preparations

The vaginal surface is lined with squamous epithelium cells and mucous produced from various underlying glands. Topical products are used to treat vulvovaginal infections, vaginitis, and conditions of endometrial atrophy and for contraception with spermaticidal agents.

Some preparations are applied externally to the vulva; others are intended to deliver into the vagina by means of inserter-applicator tips which accompany the products. Creams with water washable bases are preferred over oleaginous ointment.

TRANSDERMAL DRUG DELIVERY SYSTEMS



Transdermal drug delivery systems (TDDS) are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver the drug(s) through the skin to the systemic circulation. Systems typically comprise an outer covering (barrier), a drug reservoir that may have a drug release-controlling membrane, a contact adhesive applied to some or all parts of the system and the system/skin interface, and a protective liner that is removed before the patient applies the system.

The dose of these systems is defined in terms of the release rate of the drug(s) from the system and surface area of the patch and is expressed as mass per unit time for a given surface area.

With these drug products, the skin typically is the rate-controlling membrane for the drug input into the body. The total duration of drug release from the system and system surface area may also be stated.

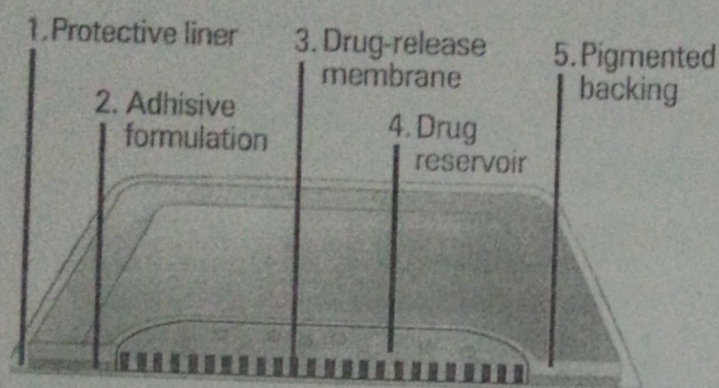


Figure 1. Schematic of a multilayer transdermal system.

TDDS work by diffusion: The drug diffuses from the drug reservoir, directly or through the rate-controlling membrane and/or contact adhesive if present, and then through the skin into the general circulation. Typically, modified-release systems are designed to provide drug delivery at a constant rate so that a

true steady-state blood concentration is achieved and maintained until the system is removed. Following removal of the system, blood concentration declines at a rate consistent with the pharmacokinetics of the drug.

Advantages of TDDS:

Transdermal drug delivery offers several important advantages over more traditional dosage forms. The steady permeation of drug across the skin allows for more consistent serum drug levels, often a goal of therapy. Intravenous infusion also achieves consistent plasma levels, but it is more invasive than transdermal drug delivery.

- 1- The lack of peaks in plasma concentration can reduce the risk of side effects. Thus, drugs that require relatively consistent plasma levels are very good candidates for transdermal drug delivery. In addition, if toxicity were to develop from a drug administered transdermally, the effects could be limited by removing the patch.
- 2- Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy. Transdermal drug delivery can be used as an alternative route of administration to

accommodate patients who cannot tolerate oral dosage forms. It is of great advantage in patients who are nauseated or unconscious. Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine. Drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets. First pass metabolism, an additional limitation to oral drug delivery, can be avoided with transdermal administration.

Disadvantages of TDDS:

- 1-One of the greatest disadvantages to transdermal drug delivery is the possibility that a local irritation will develop at the site of application. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation. For most patients, site rotation can minimize irritation. However, some patients develop severe allergic reactions to transdermal patches, and, in these cases, therapy must be discontinued.
- 2- Another significant disadvantage of transdermal drug delivery is that the skin's low permeability limits the number of drugs that can be delivered in this manner. Because the skin serves protective functions, it inhibits compounds from crossing it. Many drugs with a hydrophilic structure permeate the skin too slowly to be of therapeutic benefit. Drugs with a lipophilic character, however, are better suited for transdermal delivery. Many of the recent developments in transdermal drug delivery target the more hydrophilic compounds that were previously undeliverable via this method.
- 3- Damage to a transdermal patch, particularly a membrane or reservoir patch, can result in poor control over the release rate. The release rate from a damaged patch would more likely be controlled by the skin than the patch, resulting in a higher, perhaps toxic, rate of drug delivery. Patients should be advised to discard a patch if the outer packaging or the patch itself appears damaged or altered in any way.

Table 1: Ideal Properties of a Transdermal Drug Delivery System

Properties	Comments
Shelf life	Up to 2 years
Patch size	< 40 cm ²
Dose frequency	Once a daily to once a week
Aesthetic appeal	Clear, tan or white color
Packaging	Easy removal of release liner and minimum number of steps required to apply
Skin reaction	Non irritating and nonsensitizing
Release	Consistent pharmacokinetic and pharmacodynamic profiles over time

Selection of Drug Candidate

The transdermal route of administration cannot be employed for a large number of drugs, only a small number of drug products are currently available via transdermal delivery. In many cases, a drug's physical properties, including molecular size and polarity, have limited its capacity to be delivered transdermally. Similarly, the biological properties of drug molecules, including dermal irritation and insufficient bioavailability, have been problematic. In the product development the focus must be on the rationality of drug selection based on pharmacokinetic parameters and physicochemical properties of the drug. Physiochemical factors such as solubility, crystallinity, molecular weight <400, polarity, melting point <200, partition coefficient Log P (octanol-water) between -1.0 to 4 must be considered.

Biological factor should also be considered such as skin irritation, site of application of the patch e.g. scopolamine patch for motion sickness is applied backside of the ear and Transderm-Nitro is applied on the chest. When a pharmacologically active material has to be

presented to the skin, an occlusive or allergic response is significant, limits have to be determined for the acceptability of the undesired effect.

The pharmacokinetic information of the drug is a critical factor in deciding its suitability for delivery by the transdermal route as it is suitable only for drugs whose daily dose is in few milligrams. The resulting plasma concentration of active agent depends on the clearance; however, if one assumes a small volume of distribution and relatively long half-life, plasma level in excess of few micrograms per milliliter is very unlikely. Another important factor is the half-life, (e.g., nitroglycerin $t_{1/2}$ is 3 min) which provides information on the disposition of a drug in our body other parameters such as effective plasma level; also determine whether a transdermal delivery can be developed or not.

Table 2: Factors To Be Considered For Transdermal Dose Calculation

Physiochemical	Pharmacokinetic	Biological
Solubility	Half life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular Weight	Total body clearance	Allergic reactions
Polarity	Therapeutic plasma concentration	Skin metabolism
Melting Point	Bioavailable factor	Skin permeability

Percutaneous Absorption Enhancers:

There is great interest among pharmaceutical scientists to develop chemical permeation enhancers and physical methods that can increase the percutaneous absorption of therapeutic agents.

Chemical Enhancers:

A chemical penetration enhancer increases skin permeability by reversibly damaging or by altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance. Among alterations are increased hydration of the stratum corneum and/or a change in the structure of the lipids and lipoproteins in the intercellular channels through solvent action or denaturation. Some drugs have an inherent capacity to permeate the skin without need of chemical enhancers.

However, in instances in which this is not the case, chemical permeation enhancers may be effective in rendering an otherwise impenetrable substance useful in transdermal drug delivery. Examples of some skin penetration enhancers include acetone, azone, dimethylacetamide, dimethylformamide, dimethylsulfoxide (DMSO), ethanol, oleic acid, polyethylene glycol, propylene glycol and sodium lauryl sulfate.

The selection of a permeation enhancer in developing a TDDS should be based not only on its efficacy in enhancing skin permeation, but also on its dermal toxicity (low), and its physicochemical and biocompatibility with the system's other components.

Examples of TDDS:

Transdermal Nitroglycerin, Transdermal Scopolamine, Transdermal Clonidine, Transdermal Nicotine, Transdermal Estradiol, and Transdermal Testosterone.

For example: Transdermal Nitroglycerin, the patch delivers nitroglycerin through the skin directly into the blood stream for 24 hours, and it is used to treat and prevent angina. The system consists of a water resistant backing layer; a reservoir of nitroglycerin, followed by a semipermeable membrane to control precisely and predictably the release of medicine, and an adhesive layer to hold the system onto the skin. The adhesive layer also contains an initial priming dose of nitroglycerin to insure prompt release and absorption of the medication.

Figure 2

