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Semisolids

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Pharmaceutical semisolid preparations include ointments, pastes, cream emulsions, gels, and rigid foams. Their common property is the ability to cling to the surface of application for reasonable duration before they are washed or worn off. This adhesion is due to their plastic rheologic behavior, which allows the semisolids to retain their shape and cling as a film until acted upon by an outside force, in which case they deform and flow.[1]

Ointments, in general, are composed of fluid hydrocarbons meshed in a matrix of higher-melting solid hydrocarbons. While most ointments are based on mineral oil and petrolatum, there are alternative types. Polyethylene can be incorporated into mineral oil to yield a plastic matrix (e.g., Plastibase, manufactured by Squibb). Mixtures of polyethylene glycols can yield products of ointment consistency that are water-soluble. Most ointments are prepared by melting the components together. Drugs or other components are added in the fluidized state. If the solids are insoluble and to be suspended, the system is put through a milling process (a colloid mill, homogenizer, or ultrasonic mixer) so that the solids are fully dispersed.

Pastes are basically ointments into which a high percentage of insoluble solids has been added. They are valuable as protective barriers on the skin, such as for treating diaper rash or protecting the face and lips from the sun. Pastes are usually prepared by incorporating a solid directly into a congealed system by levigation with a portion of the base to form a paste-like mass. The remainder of the base is added with continued levigation until the solids are uniformly dispersed in the vehicle.

Creams are semisolid emulsion systems with opaque appearances, as contrasted with translucent ointments. Their consistency and rheologic character depend on whether the emulsion is a water-in-oil or oil-in-water type and on the nature of the solids in the internal phase. The subject of emulsions is treated in Chapter 17.

Gels are semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix (consisting of natural or synthetic gums) in which a high degree of physical (or sometimes chemical) cross-linking has been introduced. The polymers used to prepare pharmaceutical gels include the natural gums tragacanth, pectin, carrageen, agar, and alginic acid and such synthetic and semisynthetic materials as methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, and the Carbopols, which are synthetic vinyl polymers with ionizable carboxyl groups. Gels are prepared by either a fusion process or a special procedure necessitated by the gelling characteristics of the gellant.

The bulk of these semisolid preparations are applied to the skin, where they usually serve as vehicles for topically applied drugs, as emollients, or as protective or occlusive dressings. A lesser portion of topical semisolid dosage forms are applied to mucous membranes, such as rectal tissue, buccal tissue, vaginal mucosa, urethral membrane, external ear lining, nasal mucosa, and cornea. The mucous membranes permit more ready access to the systemic circulation, whereas normal skin is relatively impenetrable. The emphasis of this chapter is on the skin and on dermatologicals, but the general concepts and rationale apply to all semisolid topical therapy.

*Deceased.

Skin

The skin is a large multilayered organ that in the average adult weighs about eight pounds, excluding fat. It covers a surface exceeding 20,000 cm^2 and has varied functions and properties. The skin serves as a barrier against physical and chemical attack. Some materials, such as nickel ions, mustard gas, and the oleoresins from Rhus toxicodendron, commonly known as poison ivy, can penetrate the barrier, but most substances cannot. The skin acts as a thermostat in maintaining body temperature, shields the body from invasion by micro-organisms, protects against ultraviolet rays, and plays a role in the regulation of blood pressure.

Anatomically, the skin has many histologic layers, but in general, it is described in terms of three tissue layers: the epidermis, the dermis, and the subcutaneous fat layer. Figure 18-1 represents an idealized section of the skin, showing the glands, hair follicles, nerves, blood vessels, and other skin accessories. The outermost layer is the stratum corneum, or horny layer, which consists of compacted, dead, keratinized cells in stratified layers with a density of 1.55. Because of the dense nature of the stratum corneum, values of diffusion coefficients in this tissue are a thousand or more times smaller than in any other skin tissue, which results in higher resistance and general impenetrability.[2]

The stratum corneum is the rate-limiting barrier that restricts the inward and outward movement of chemical substances. Structurally, the stratum corneum is a heterogeneous tissue composed of flattened keratinized cells, the outer

FIG. 18-1. *Stratified organization of the skin. (From Pillsbury, D. M.: A Manual of Dermatology. W. B. Saunders, Philadelphia, 1971).*

layers of which are less densely packed than those adjacent to the underlying granular layer. The stratum corneum exhibits regional differences in thickness over the body. It is as thick as several hundred micrometers on the palms of the hand and soles of the feet in an adult, but over most of the body it is about 10 μm thick when dry, increasing to about 40 to 50 μm when fully hydrated.[3]

There is limited knowledge of the chemical composition of the barrier. The main cellular components are the proteins, lipid, and water, combined into an ordered structure. The approximate composition in the dry state is 75 to 85% protein, 15 to 20% lipid, and 15% water. Although the surface lipids offer little resistance to the passage of compounds, studies of the removal of lipids from the cutaneous surface indicate that they participate in epidermal water function.[4–10] Barrier function is restored when the extracted lipids are returned to the skin, which suggests variations in biologic membrane permeability, depending largely on the specific nature or distribution of the lipid contained in the cell membrane.

Beneath the stratum corneum are the metabolically active layers of the epidermis. The basal or germinal layer lies right above the dermis. Epidermal cells start their mitotic journey upward to the surface; the cells flatten and shrink as they slowly die from lack of oxygen and nutrition.

The next distinctive histologic layer shown in Figure 18-1 is the dermis, or corium, which is approximately one eighth of an inch thick and constitutes the main mass of the skin. The dermis essentially consists of about 80% of protein in a matrix of mucopolysaccharide "ground substance."[11]

Contained and supported within the dermis are numerous blood vessels, lymphatics, and nerves, as well as the epidermal appendages such as the hair follicles, sebaceous glands, and sweat glands. Hair follicles are distributed over the entire skin surface with the exception of the soles of the feet, the palms of the hand, the red portion of the lips, and select portions of the sex organs. Each hair follicle is associated with one or more sebaceous glands, which are outgrowths of epithelial cells. The fractional area of the skin surface occupied by the hair follicles has been estimated to be roughly 1/1000 of the total surface.[12] The sweat glands are divided into the eccrine and apocrine types. They are widely distributed over the surfaces of the body. The eccrine glands are particularly concentrated in the palms and soles. The principal function of the glands is for heat control, as they secrete a dilute salt solution. The apocrine glands are found in the axillae (armpits), in anogenital regions, and around nipples. They are coiled tubular glands about ten times larger than eccrine glands and extend entirely through the dermis and well into the subcutaneous layer.[11]

Percutaneous Absorption

The usual object of dermatologic drug therapy is to produce a desired therapeutic action at specific sites on the epidermal tissue. While certain topical drugs such as emollients, antimicrobials, and deodorants act primarily on the surface of the skin, the target area for most dermatologic disorders lies in the viable epidermis or upper dermis. This requires diffusive penetration of the skin or percutaneous absorption.

Routes of Penetration

When a drug system is applied topically, the drug diffuses out of its vehicle onto the surface tissues of the skin. There are three potential portals of entry: through the follicular region, through the sweat ducts, or through the unbroken stratum corneum between these appendages. There is little convincing evidence that eccrine sweat glands play any significant role in cutaneous permeability. Material may enter the ducts, and even the glands, but there appears to be no penetration from these areas to the dermis.

For substances absorbed by the transepidermal route, penetration is fairly rapid, although slower than intestinal tract absorption, and is almost always accompanied by some degree of pilosebaceous penetration as well. For substances that are absorbed through both pathways, the transepidermal route is the principal portal of entry because of the total, relatively small, absorbing surface offered by the pilosebaceous units. The epidermis presents a surface area 100 to 1000 times greater than the other routes of absorption. The appendages, sweat glands, and hair follicles are scattered throughout the skin in varying numbers, but are comparatively sparse; their total cross-sectional area is probably between 0.1 and 1.0% of the skin area.

The particular route a substance may take and the relative importance of one in contrast with the other, depend almost entirely on the physicochemical properties of the drug and the condition of the skin. Under the appropriate conditions, each of the contending routes of permeability may change and be the overwhelmingly dominant one. In particular, the transient

diffusion that occurs shortly after the application of a substance to the surface of the skin is shown to be potentially far greater through the appendages than through the matrix of the stratum corneum. After steady-state diffusion has been established, the dominant diffusion mode is probably no longer intra-appendageal, but occurs through the matrix of the stratum corneum. Flux through shunts is difficult to measure experimentally, except possibly through hair. The recognition of transient diffusion, occurring primarily via follicles and ducts, and steady-state diffusion, occurring primarily through the intact stratum corneum, results in a considerably more self-consistent and orderly treatment of the process of percutaneous absorption.

Once a substance passes through the stratum corneum, there is apparently no significant further hindrance to penetration of the remaining epidermal layers and corium; there is then a ready entry into the circulation via the capillaries. The concentration gradient essentially ends in the dermal layer at the beginning of the circulation. The systemic circulation acts as a reservoir or "sink" for the drug. Once in the general circulation, the drug is diluted and distributed rapidly with little systemic buildup.[1]

Diffusion through the horny layer is a passive process. There is little evidence to support specialized active transport systems for cells of the stratum corneum. The passive process is affected only by the substance being absorbed, by the medium in which the substance is dispersed, and by ambient conditions. On the other hand, percutaneous absorption is a more complicated process, of which epidermal diffusion is the first phase, and clearance from the dermis the second. The latter depends on effective blood flow, interstitial fluid movement, lymphatics, and perhaps other factors that combine with dermal constituents.[5]

Study Methods

In Vitro Technique. The principal in vitro technique for studying skin penetration involves use of some variety of a diffusion cell in which animal or human skin is fastened to a holder and the passage of compounds from the epidermal surface to a fluid bath is measured. The simplicity of methods and equipment ranges from just stretching human skin over the mouth of a funnel to using special glass chambers. The penetration rates can be quantitated, particularly by radioactive measurements. The area of spread of radioactive agent on the surface is detected with autoradiographs, allowing expression in terms of quantity per unit area per unit time. Radioactive agents have not taken over completely. Many chemical agents penetrate in sufficient concentration to be determined by one or the other techniques of physical or chemical analysis.

More recently, model systems have been used that do not use membranes. Solvents such as alcohol-water have been utilized as models chosen to have negligible solubility in the phase representing the skin, but in which the drug is fairly soluble.[13–17] A receptor phase or "sink" is used to receive the penetrant. Chloroform and isopropyl myristate have served as sinks. Since they are immiscible with the alcohol-water, it is not necessary to introduce an artificial membrane to separate these sinks from the vehicles. The important factors influencing the release into the receptor phase are the solubility in the vehicle and the partition coefficient of the drug between the vehicle and the receptor phase. Optimal release is obtained from vehicles containing the minimum concentration of solvent required for complete solubilization of the drug.[13]

In Vivo Technique. The major in vivo methods are histologic techniques, use of tracers, analysis of body tissues and fluids, and elicitation of a biologic response. Tissue changes in skin following the application of various substances to the cutaneous surface can yield information about the specific tissue affected, so that not only absorption, per se, is revealed, but also the route of penetration. The method is limited to dyes and to a small number of other substances that yield perceivable colored end products with specific chemical reactions. Following the movements of penetrants through dyes, fluorescence and radioactive labeling represent the most widespread tracer methods. The studies are always combined with other techniques such as histologic or chemical analysis of tissues or fluids. While radioactive methods give information on the amount of the compound that moves across the skin, they yield little or no information on the route of penetration or on the localization of the penetrant within the structure of the skin.

Urine analysis is by far the most frequently used method. Although the urinary method is extremely valuable, caution is indicated since the recovered agent will not necessarily be the original material or the amount needed to penetrate the skin. Some of the applied agent may have gone elsewhere than into the urine; some may have been metabolized and therefore may be no longer detectable. A steady state between absorption and excretion needs to be reached before measurements can be accepted. The use

of topical agents that elicit a physiologic reaction when they reach the dermis makes it possible to demonstrate not only penetration, but also the time required for a reaction to occur. The method is intriguing because it is simple and has practical applications. For example, responses such as sweat secretion, vasoconstriction, vasodilation, pigmentation, and vascular permeability can be recorded with reasonable accuracy by visual observation.

Various methods have been used for studying in vitro and in vivo percutaneous absorption. There are three variables in all the methods: application of the medicament, apparatus, and measurement of the medicament. The combinations of these variables lead to numerous methods, and comparisons between investigations is difficult.[18]

Factors in Skin Penetration. The factors that influence skin penetration are essentially the same as those for gastrointestinal absorption, with the rate of diffusion depending primarily on the physicochemical properties of the drug and only secondarily on the vehicle, pH, and concentration. Differing physiologic variables involve the condition of the skin, i.e., whether it is intact or injured, the skin age, the area of skin treated, the thickness of the skin barrier phase, the species variation, and the skin moisture content.

The principal physicochemical factor in skin penetration is the hydration state of the stratum corneum, which affects the rate of passage of all substances that penetrate the skin. Hydration results from water diffusing from underlying epidermal layers or from perspiration that accumulates after application of an occlusive vehicle or covering on the surface. Under occlusive conditions, the stratum corneum is changed from a tissue that normally contains little water (5 to 15%) to one that contains as much as 50% water. The clinical importance of hydration can be found in the use of occlusive plastic film in steroid therapy. Here, the prevention of water loss from the stratum corneum and the subsequent increased water concentration in this skin layer apparently enhances the penetration of the steroid. The temperature of the skin and the concentration of drug play significant roles, but they are secondary to that of hydration.

The solubility of a drug determines the concentration presented to the absorption site, and the water/lipid partition coefficient influences the rate of transport. An inverse relationship appears to exist between the absorption rate and the molecular weight. Small molecules penetrate more rapidly than large molecules, but within a narrow range of molecular size, there is little correlation between the size and the penetration rate. Materials of higher molecular weight also show variable penetration. Very large molecules, such as proteins and polysaccharides, go through poorly, if at all.[19,20]

Vehicles and Skin Penetration. The efficiency of various types of vehicles in aiding penetration can be reasonably predicted by the way in which the vehicle alters the activity of water in the stratum corneum and influences the *stratum corneum/vehicle* partition coefficient. Greases and oils are the most occlusive vehicles and induce the greatest hydration through sweat accumulation at the skin-vehicle interface. This is accentuated if the skin is covered with occlusive bandages or plastic. Emulsions of the water-in-oil type are somewhat less occlusive than greases. Substances in the vehicle, such as humectants, which have a high affinity for water, may under certain circumstances dehydrate the stratum corneum and decrease penetration. Similarly, powders increase the surface area and increase the rate of evaporation of water, and so decrease the extent of hydration. Conversely, vehicles may also affect penetration by their ability to reduce loss of water vapor on the skin surface. Paraffin bases suppress transepidermal water diffusion, whereas a number of other standard vehicles cause a lesser degree of transepidermal water loss suppression.

The role of vehicles on skin penetration is often confusing and contradictory, since the emphasis has generally been placed on the compatibility, stability, and appearance of the product. Only in recent years has attention been given to the influence of components in the vehicle on the movement of the drug through the skin. The release of a substance is favored by the selection of vehicles that have a low affinity for the penetrant or in which the drug is least soluble. This is consistent with the view that the rate of release is governed by the vehicle-to-receptor phase (stratum corneum) partition coefficient. For a given concentration of drug in certain vehicles, the activity coefficient of the drug at that concentration may vary by as much as 1000-fold from one vehicle to the other. The thermodynamic activity of the drug in the vehicle is the product of the concentration of the drug and the activity coefficient of the drug in the vehicle. Solutes held firmly by the vehicle, such as those occurring when the drug forms a soluble complex with the vehicle, exhibit low activity coefficients; hence, the rate of release from such drug-vehicle combinations is slow. Solutes held "loosely" by the vehicle (with less affinity of the vehicle for the drug or solute) exhibit high activity coefficients; therefore, the rate of release

from such drug-vehicle combinations is fast. Varied materials require individual formulation based on solubility characteristics, and the formulation may also need modification for different concentrations of the agent to obtain maximal release rates.

Materials have been experimentally studied in attempts to increase the rate of absorption of topically applied drugs. These agents are often called "accelerants." They appear to swell the stratum corneum and leach out essential structural material, thus reducing the diffusional resistance and increasing the permeability. The most effective is dimethylsulfoxide (DMSO) followed by dimethylformamide (DMF), dimethylacetamide (DMA), urea, propylene glycol, and surface-active agents. DMSO, DMF, and DMA are all strongly hygroscopic and it is likely that the presence of these substances in the stratum corneum increases the hydration of the tissue and therefore its permeability. These agents are currently restricted to experimental use. Surface-active agents appear to increase the permeability of the skin to water by altering the physical state of water in the skin in such a way as to permit greater freedom to the passage of charged hydrophilic substances. When penetration occurs, anionics penetrate best, followed by cationics and nonionic surfactants. Among anionic substances, the laurate ion is reported to have the greatest penetration and the greatest effect on the penetration of other solutes. Soaps of different fatty acids have this property in varying degrees, with penetration more significant for salts of fatty acids having a carbon length of 10 or less. The penetration of fatty acid soaps varies inversely with pH. At higher pH (approximately 11), the action of the anionic surfactant appears to be attenuated or overshadowed by the influence of the more alkaline pH itself.

Raw Materials

More raw materials are available for use on the skin than for oral use, and in turn, more are available for oral use than for parenteral use. The difference in the number of materials available for each route of administration is due to the type of absorption barrier and physicochemical environment surrounding the absorption sites. Substances such as isopropyl myristate and butyl stearate may be used topically without toxic effects, yet these esters may not be used orally, because hydrolysis of the esters by digestive enzymes yields poorly tolerated alcohols. The absence of comparable hydrolytic enzymes on the skin surface makes these compounds satisfactory for dermatologic medication.

The Federal Food and Drug Administration (FDA) approves chemical substances and states the maximum concentration that is considered to be safe for use in a particular food or cosmetic. The information is published in the "Federal Register," and a compilation of all such substances is available.[21] All raw materials should be checked against this list if there is any doubt regarding the current status of a particular substance; however, each new pharmaceutical dosage form must receive individual approval. The supplier of a chemical substance usually indicates in his brochure, or upon request, the safety tests that have been performed and whether approval from the FDA has been received for its use in a particular form. The tests should be thorough and well designed; they should include human patch tests, eye irritation studies, determination of minimum lethal dose on at least two animal species, and chronic toxicity studies.

Names of suppliers of various raw materials for semisolids, manufacturing equipment, and other pertinent information can be obtained from trade and scientific journals. Consultation with representatives of suppliers frequently reduces the development time required for a new pharmaceutical semisolid, but independent critical judgment is needed.

The suppliers of raw materials such as emollients, emulsifiers, fats, oils, waxes, cellulose derivatives, humectants, lanolin derivatives, and water absorption bases have detailed knowledge of their specific products. Many of the suppliers have well-equipped laboratories in which workers are constantly developing new uses for their materials in the pharmaceutical, cosmetic, toiletries, and chemical specialties fields. The formulator must be cautious, however, in accepting a supplier's claims about the utility of a raw material. It is necessary to ascertain the biologic properties as well as the significant physical and chemical parameters of the substance and its stability on storage at different temperatures.

It is a fundamental concept in formulating any dosage form that chemical and physical incompatibilities that affect the therapeutic efficacy of a drug must be avoided. In advance of any formulation, the physicochemical properties of the drug must be evaluated. The stability of the active substance under alkaline or acidic conditions can be established from its pH profile. The sensitivity of the drug to oxidation and reduction, moisture, and light, and its solubility in various materials, indicate the type of base most suitable for the stability of the drug and for its absorption. Compatibility with the container is of equal importance, and it is necessary to

conduct stability studies of the product in the finished container.

Perfumes generally are not included in the semisolid formulations because in the past many dermatologists have objected to their use for the treatment of a skin condition in view of the danger of sensitization. Many manufacturers of fragrances have run toxicity, sensitization, and irritation tests on the various perfume materials and can supply fragrances that have successfully passed critical testing in animals. However, such animal tests do not obviate the need for testing on humans.

The industrial pharmacist who develops the dosage form must be aware of the chemical composition of the materials at his disposal and their physical properties, so that he can set or have specifications set for the raw materials. Broad specification limits may lower the cost of a raw material, but represent false economy if the quality of the product is affected. New raw materials suitable for use in semisolids are continually being introduced. Flynn has published an excellent compilation of these materials that includes their functions in formulations.[1]

Hydrocarbons

Except for water, petrolatum and mineral oil are perhaps the most widely used substances in semisolids. Petrolatum is a complex mixture of semisolid hydrocarbons, containing aliphatic, cyclic, saturated, unsaturated, branched, and unbranched substances in varying proportions. Although extensively used for more than 85 years, petrolatum still has broad physical and chemical specifications in the USP. Wide density and melting point ranges, as well as variation in chemical composition, are permitted in the official compendia throughout the world.

Petrolatum is available in the form of a short or long "fiber." The type of fiber possessed by the petrolatum is usually determined by dipping the index finger into the petrolatum sample and then withdrawing it slowly. The long fiber type tends to form a transparent continuous film or thread joining the finger and the sample. The short fiber variety ruptures easily and does not exhibit this film. The long fiber petrolatum is preferred for an occlusive dressing because of the continuous film it forms over the surface of the skin.

Mineral oil is obtained from petroleum, as is petrolatum, by collection of a particular viscosity-controlled fraction. It is produced in many viscosity and specific gravity ranges. The lower viscosity oils are preferred for semisolids, since they are less tacky and greasy. An excellent review of the chemistry and the properties of petrolatum and mineral oil has been published.[22]

Hydrocarbon Waxes

Hydrocarbon waxes frequently are employed in the manufacture of creams and ointments to increase the viscosity of mineral oil in order to prevent its separation from an ointment. *Ozokerite* is a mined wax with a melting point range of 65 to 75°C and consists of a mixture of saturated hydrocarbons ranging in carbon content from C_{35} to C_{55}. *Paraffin wax* is obtained from petroleum and is available in a variety of melting points ranging from 35 to 75°C. Another wax that is often used is *ceresin*, which is a mixture of ozokerite and paraffin wax. Its melting point varies, depending on the paraffin wax content. Ozokerite and ceresin possess the property of retaining oils within a matrix-like structure without the sweating or oozing of the oils.

Synthetic waxes have been developed from vegetable oils and naturally occurring waxes by a process of hydrogenation and catalytic splitting that involves long C_{18}–C_{36} hydrocarbon chains. Like all true waxes, the synthetic waxes exhibit thermoplastic, crystalline properties and are not pure chemical compounds but complex mixtures of mainly long chain saturated aliphatic chemical entities. The synthetic waxes are chemically closely related to the naturally occurring waxes in that they contain long chain wax fatty acids, but are not considered to be direct replacements for them. However, they may be used in conjunction with or can replace the natural waxes in some formulations to achieve certain desired properties. Synchrowaxes,* the brand name of a series of such waxes, have unique gelling characteristics that may be used in formulating synthetic petrolatums with occlusive properties to help moisturize the skin without the inelegant properties of natural petrolatum.

Oleaginous Substances

Vegetable oils such as peanut oil, almond oil, sesame oil, and olive oil are mono-, di-, and triglycerides of mixtures of unsaturated and saturated fatty acids. Trace metal contaminants in the oils may catalyze oxidation reactions that can be prevented by the addition of antioxidants, such as butylated hydroxyanisole, butylated

*Synchrowaxes are available from Croda, Inc., New York, NY.

hydroxy toluene or propyl-gallate, and by the addition of metal chelating agents such as salts of ethylenediamine tetraacetic acid.

Antioxidants may produce problems of drug compatibility or dermal sensitivity in some patients. The exact chemical composition of a particular vegetable oil varies from lot to lot because of its natural origins. Its composition depends on the climatic conditions, the soil, the amount of rainfall during the growth of the vegetable crop, and the storage conditions of the harvested crop and the oil.

The trend toward the isolation and synthesis of pure chemical entities present in the vegetable oils is evident in the literature and supplier's catalogs. Perhaps when these chemically pure substances are available in quantity, the influence of a homologous series of compounds, either individually or in combination, on the quality of an emulsion and the release of a drug from such a base can be more rigidly controlled.

Fatty Acids and Alcohols

The commercially available fatty acids are really mixtures of related fatty acids. Stearic and palmitic acids are present in the greatest proportion in triple pressed stearic acid along with varying quantities of other fatty acids. Various fixed ratios of stearic/palmitic acids can be obtained from the suppliers. A slight change in the ratio of the saturated fatty acids changes the structure and size of the fatty acid crystal, the x-ray diffraction pattern, and the solubility. For this reason, stearic acid of rigidly controlled purity is used in many topical preparations.

Similar variations in chemical structure exist in almost all materials of natural origin, in polymeric substances having a long chain length, and in combinations of polymers with fatty acids or alcohols. The number of moles of ethylene oxide, for example, in a polyethylene reaction product such as $ROCH_2CH_2[OC_2H_4]_nOH$ merely represents an average rather than an exact amount. Rigid purchasing and quality control specifications must be established for such materials if variations in the quality and consistency of semisolid emulsions are to be avoided.

Stearic acid is used in water-removable creams as an emulsifier to develop a certain consistency in the cream and to give a matt effect on the skin. When a stearate soap is used as an emulsifier, enough potassium hydroxide or triethanolamine usually is added to react with about 8 to 20% of the stearic acid. The unreacted fatty acid increases the consistency of the cream. These creams are soft and develop a sheen or luster upon aging, owing to the formation of stearic acid crystals. Creams formed with sodium stearate are much firmer in consistency.

Stearyl alcohol and *cetyl alcohol* (palmityl alcohol) are used in creams as auxiliary emulsifiers and emollients. In sufficient quantity, stearyl alcohol produces a firm cream that may be softened with cetyl alcohol.

For a description of waxes of animals, insect, and vegetable origin such as lanolin, beeswax, carnauba wax, candelila wax, silicones, branched chain compounds, isopropylesters, polyols, cellulose ethers, and other raw materials suitable for creams and ointments, the reader is advised to check sources such as the CTFA Cosmetic Ingredient Dictionary,[23] as well as suppliers' catalogs.

A list of the various raw materials and their functions has recently been published.[1] Another listing of cosmetic raw materials appeared in the FD&C Reports ("The Rose Sheet")[24] which was reproduced from the Japan Cosmetic Ingredient Dictionary of 148 government-approved raw materials. The dictionary is the result of a collaborative effort between the Cosmetic, Toiletry and Fragrance Association (CTFA), the U.S. Commerce Department, the Japanese Government, and the Japan Cosmetic Industry Association (JCIA). The second supplement to the dictionary lists 173 raw materials and is reproduced in a later issue of the same trade periodical.[24] The dictionary will eventually list approximately 2,000 to 3,000 raw materials. According to the CTFA, inclusion of the raw materials in the dictionary is based on "(1) chemical (not brand name), (2) whether the substance is free from patent and/or 'technical know-how problems,' (3) whether it is free of safety problems, and (4) a specified alkyl group." The interest and purpose of CTFA is "to eliminate testing, certification, and standards activities that act as barriers to trade with Japan."

Emulsifiers

The water-soluble soaps were among the first emulsifiers used for semisolid oil-in-water emulsions. The viscosity of the cream or ointment prevents coalescence of the emulsified phases and helps to stabilize the emulsion. The addition of fatty polar substances, such as cetyl alcohol and glyceryl monostearate, tends to stabilize the semisolid oil-in-water emulsion. The interfacial film formed around the dispersed phase globules in such a system is generally solid, thereby making the emulsified preparation more rigid. Polyvalent ions, such as magnesium, calcium, and aluminum, tend to stabilize water-in-oil emulsions by cross-linking with the polar groups of

the fatty materials. Nearly all semisolid creams and emulsified ointments require more than one emulsifier. The combination of a surface active agent with an oil-soluble auxiliary emulsifier is referred to as a *mixed emulsifier system*. Triethanolamine stearate soap combined with cetyl alcohol is an example of an oil-in-water mixed emulsifier; beeswax and divalent calcium ions or small quantities of a water-soluble surface active agent exemplify mixed emulsifiers for a water-in-oil emulsion. Maximum stability of an emulsion occurs when a complex interfacial film is formed. Such a film forms when an oil-soluble substance is added and reacts at the interface with the water-soluble surfactant. Soft water-in-oil cream bases can be made with calcium ions as an auxiliary emulsifier. The bases can be made firmer by decreasing the mineral oil content. Formula #1 is used to make a soft water-in-oil cream base employing divalent calcium ions in the form of water-soluble saccharated lime.

Formula #1	%
A Mineral oil, 65 to 75 viscosity	30.00
Lantrol*	3.00
Microcrystalline wax†	2.00
Acidlan 20*	4.00
Propylparaben	0.20
B Borax	0.20
Methylparaben	0.20
Water	49.75
C Saccharated lime	0.65
Purified water	10.00

*Available from Emery Industries, Cincinnati, OH.
†Should have a melting point of 75 to 79°C and should be tested for safety on animal and human skin, since petroleum residues may be present in the wax.
Procedure: Heat parts A, B, C separately to 78°C. Add B to A. After the emulsion has formed, add C. Cool and pass through a homogenizer.

The clay, magnesium aluminum silicate, has been used as a thickener, suspending agent, and oil-in-water emulsion stabilizer because of the colloidal structure of its aqueous dispersions. It also contributes to the stability of water-in-oil emulsions when used with suitable emulsifiers, probably owing to its thickening action on the internal phase whereby it inhibits coalescence. The magnesium aluminum silicate may migrate to the interfacial area, resulting in a stronger film.[25]

Formula #2	%(w/w)
A Magnesium aluminum silicate (MAS)*	2.0
Purified water	37.0
B Mineral oil, light	20.0
Petrolatum	9.0
Isopropyl myristate	5.0
Lantrol (lanolin oil)†	3.0
70% sorbitol solution	20.0
Arlacel 186 (glyceryl oleate and propylene glycol)‡	1.0
Polysorbate 80	1.0
Preservative	q.s.

*Available from Veegum, R.T. Vanderbilt Co., Norwalk, CT.
†Available from Emery Industries, Cincinnati, OH.
‡Available from ICI Americas, Inc., Wilmington, DE.
Procedure: Add the MAS to the water slowly, agitating continually until smooth. Heat A to 70 to 75°C. Heat B with stirring to 70 to 75°C. Add A to B, and mix until cooled.

The soap-type emulsion may be unstable in the presence of acidic substances. Cationic or nonionic emulsifiers are preferable for drugs requiring an acid pH. Quaternary ammonium compounds like cetyl trimethyl ammonium chloride help to stabilize these emulsions in combination with such fatty alcohols as cetyl alcohol.

The nonionic emulsifiers are employed for both oil-in-water and water-in-oil emulsified pharmaceutical semisolids because they are compatible with many drug substances. The nonionic emulsifiers are versatile and may be used with strongly acidic salts or with strong electrolytes.

Formula #3 *Tripelennamine Hydrochloride Cream**	%(w/w)
Oil Phase	
Cetyl alcohol	5.0
Glyceryl monostearate	15.0
Sorbitan monooleate	0.3
Polysorbate 80, USP	0.3
Aqueous Phase	
Tripelennamine HCl	2.0
Methylcellulose 100 cps	1.0
Purified water, q.s. ad	100.0
Preservative	q.s.

*Available from ICI Americas, Inc., Wilmington, DE.
Procedure: Disperse the methylcellulose in hot water in which the preservative has been dissolved, and then chill at 6°C until dissolved. Heat the oil phase to 70°C. Heat the methylcellulose solution to 72°C, and add to the oil phase, stirring continuously. Add the tripelennamine HCl at 35°C, and stir continuously until dissolved.

Recently, a series of emulsifiers have been marketed that contain chemically bonded lactic acid with fatty acids. These acyl lactylates are claimed to be mild and nonirritating to the skin and eyes,* to produce an emollient feel to the skin, and to serve as oil-in-water or water-in-oil emulsifiers. The sodium salts are suggested for use in oil-in-water. The particular fatty acid lactylate that is selected should be based on the desired application of the final product as well as on the most compatible fatty acid derivative. Some of the available lactylates and the calculated HLB values are as follows:

Types of Fatty Acid	*Calculated HLB*
1. Stearic	6.5
2. Stearic/Palmitic	8.3
3. Lauric/Myristic	14.4
4. Capric/Lauric	11.3
5. Isostearic	5.9

Items 3 and 4 are foamers. Item 4 shows good bacteriostatic properties, owing to the presence of the moderately short chain capric acid.

An example of an oil-in-water cream utilizing one of the emulsifiers that can serve as a vehicle for a compatible active substance follows:

Formula #4	%(w/w)
A *Oil Phase*	
Cetearyl alcohol	5.0
Silicone oil, 200 fluid	1.0
Isopropyl myristate	2.0
Sodium stearoyl-2-lactylate	2.0
B *Aqueous Phase*	
Propylene glycol	5.0
Sodium citrate	0.2
Preservative	q.s.
Purified water, q.s. ad	100

Procedure: Mix A and heat to 65°C. Combine B and heat to 70°C. Add B to A with suitable agitation. Mix with moderate agitation while cooling.

To achieve adequate stability in creams in which the oil content exceeds 10%, the supplier recommends the use of a co-emulsifier to achieve adequate stability. The HLB system should be utilized to calculate the ratio between the two emulsifiers for the lipid(s) being used. Several ratios should be checked to either side of the calculated HLB value to optimize the emulsion.

Formula #5 *Antiperspirant Cream*	%(w/w)
A *Oil Phase*	
Mineral oil	23.0
Calcium stearoyl-2-lactylate	3.2
PEG 400 dioleate	0.8
B *Aqueous Phase*	
Glycerine	3.0
Sodium lactate (60%)	10.0
Purified water	20.0
C Aluminum chlorohydrate (50%)	40.0

Procedure: Heat A, B, and C to 70°C in separate vessels. Add B to C immediately before adding to A. Mix with moderate agitation while cooling.

The Promulgens* are a series of nonionic emulsifiers composed of a mixture of fatty alcohols and their ethoxylates. Two types, D and G, are available and are described in the boxed area below.

The two types differ in melting point and in consistency of the emulsions that they form. According to the supplier, the emulsions formed with type D are usually thicker in consistency. Since there are no ester linkages, these emulsifiers are not subject to hydrolysis. In addition, they are compatible with anionic surfactants of the sodium lauryl sulfate type or with cationics such as quaternary ammonium compounds. Type D tends to form creams, and type G tends to form liquid emulsions. It is suggested that they be used in combination to achieve a desired viscosity level.

	Promulgen D	*Promulgen G*
CTFA adopted name—	Cetearyl alcohol and Ceteareth-20	Stearyl alcohol and Ceteareth-20
Chemical description—	Cetearyl alcohol and ethoxylated cetearyl alcohol	Stearyl alcohol and ethoxylated cetearyl alcohol
Melting point—	47 to 55°C	55 to 63°C

*Available from Patco Products, Kansas City, MO.

*Available from Amerchol Corporation, Edison, NJ.

Polyols

Glycerine, propylene glycol, sorbitol 70%, and the lower molecular weight polyethylene glycols are used as humectants in creams. The choice of a humectant is based not only on its rate of moisture exchange, but also on its effect on the texture and viscosity of the preparation. These materials prevent the cream from drying out and prevent the formation of a crust when the cream is packaged in a jar. They also improve the consistency and rub-out qualities of the cream when it is applied to the skin, permitting the cream to be spread without rolling. Increasing the humectant content tends to cause tackiness.

Sorbitol 70% is more hygroscopic than glycerine and is used at a lower concentration, usually 3% as compared to 10% for glycerine. Propylene glycol and the polyethylene glycols occasionally are used in combination with glycerine, since their ability to absorb moisture is less than that of glycerine.

Insoluble Powders

Insoluble drugs must be uniformly dispersed throughout the vehicle to ensure homogeneity of the product. The solid must be impalpable to the touch; otherwise, grittiness results. Particles less than 74 microns in size, equivalent to the mesh openings in a 200-mesh sieve in the U.S. Standard Sieve series, are impalpable to most people. Milling to a finely divided state provides more surface area for contact with the dermal site and increases the rate of dissolution of poorly soluble substances.

Some powders do not disperse uniformly, but tend to aggregate in the base, whereas others present no difficulties even though the particle size is the same. The difference may be due to the electrically charged surface condition of the particles after milling. Aggregation of particles becomes a problem for those that are 5 microns or smaller in size. For particles below 0.5 microns in size, the dispersion problems increase exponentially. Different powdered substances show similar problems of aggregation in the submicron size.

Many drug substances used in topical preparations (e.g., prednisolone; fluorocortisone acetate) exist in several polymorphic states. Compounds that exist in different crystalline forms at room temperature possess varying amounts of free energy or thermodynamic activity. The physiologic activity and availability of a drug substance often are directly related to its thermodynamic activity[26] and the choice of the proper crystalline form for use in the semisolid is vitally important. Following its incorporation into the semisolid, the maintenance of the selected polymorphic form in the semisolid is of equal concern. The components of the vehicle and the method of preparation of the semisolid dosage form affect the stability of the polymorphic form.

Types of Vehicles

The vehicle used for a pharmaceutical differs from that used for a cosmetic because with a cosmetic, penetration into the skin is not desired. Penetration or protection is desired in a pharmaceutical semisolid, and its cosmetic effect or appearance on the skin is less important. A well-formulated pharmaceutical semisolid should be both therapeutically effective and cosmetically appealing, with the major effort in the medical direction.

The therapeutic preparations included in the semisolids classification are products intended for application to the skin, scalp, and certain body orifices. These preparations include ophthalmic ointments, nasal jellies, gels, and sterile lubricants for surgical use. In this chapter, however, attention is given to those dosage forms that are used in the prevention or treatment of skin disease.

The solubility and stability of the drug in the base, as well as the nature of the skin lesion, determine the choice of the semisolid vehicle. The United States Pharmacopeia (USP) XX recognizes four classes of semisolids under the general classification of ointments: hydrocarbon bases, absorption bases, (anhydrous form and emulsion form), water-removable bases, and water-soluble bases.[27]

Hydrocarbon Bases

Petrolatum and white ointment, which is petrolatum with 5% beeswax, are typical of this class of lipophilic vehicles. The most commonly used raw material in ointment vehicles is petrolatum because of its consistency, its bland and neutral characteristics, and its ability to spread easily on the skin. These bases are difficult to wash off the skin and may be used as occlusive coverings to inhibit the normal evaporation of moisture from the skin. A thin film of petrolatum produces a sensation of warmth on the skin because the insensible moisture does not evaporate. Very little water can be incorporated into these greasy bases without the addition of other substances.

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Absorption Bases

The absorption bases are formed by the addition of substances miscible with hydrocarbons and possessing polar groupings, such as the sulfate, sulfonate, carboxyl, hydroxyl, or an ether linkage. Lanolin, lanolin isolates, cholesterol, lanosterol and other sterols, acetylated sterols, or partial esters of polyhydric alcohols (e.g., sorbitan monosterate or monooleate) may be added to make the hydrocarbon bases hydrophilic. Such hydrophilic mixtures have been known as "absorption bases," although the term "absorption" is a misnomer. The bases do not absorb water on contact, but with sufficient agitation, they do absorb aqueous solutions and can be considered water-in-oil emulsions. (The notations o/w for oil-in-water and w/o for water-in-oil are convenient abbreviations for the respective emulsion types.)

The absorption bases are of two types: the anhydrous form and the emulsion form. Anhydrous lanolin and hydrophilic petrolatum are examples of anhydrous vehicles that absorb water to form water-in-oil emulsions.

Formula #6
Hydrophilic Petrolatum (USP XX)

	g
Cholesterol	30.0
Stearyl alcohol	30.0
White wax	80.0
White petrolatum	860.0
	1000.0

The maximum amount of water that can be added to 100 g of such a base at a given temperature is known as the *water number*. To determine the water number, the base is stirred continuously as the water is being added. Distilled or deionized water should be used. The end point is reached when no more water can be "absorbed" into the base, as evidenced by droplets of water remaining in the container.

In a study involving the separate addition of a series of surfactants to a semisolid base, it was found that the water-absorbing capacity of the base increased as the HLB number (hydrophilic-lipophilic number) of the surfactant decreased[28] (see Table 18-1).

Hydrous lanolin was the prototype or forerunner of the absorption bases because of its ability to absorb water. Various absorption bases were developed as various lanolin isolates and derivatives became commercially available. Many of these lanolin fractions aid in the formation of water-in-oil emulsions. A typical example of a lanolin absorption base follows:

Formula #7
Lanolin Absorption Base

	%
Lanolin alcohols	10
Lanolin	25
Mineral oil, low viscosity	30
Purified water	35

Mineral oil is added to reduce the tackiness of the base. Nonionic water-in-oil emulsifiers, such as glyceryl monostearate, cholesterol, cetyl alcohol, and the sorbitan fatty acid derivatives, may be added for improved stability and water-absorbing capacity. These vehicles have "emollient" properties and deposit an oily film upon the skin. Examples of water-in-oil emulsion vehicles that utilize the absorption base principle are given in Formulas #8 and #9.

Formulas	#8* %	#9† %
Oil Phase		
Lanolin, anhydrous USP	3.1	15.0
Petrolatum, white, USP	25.0	—
Mineral oil, heavy	25.0	8.0
Beeswax (white wax, USP)	10.0	7.0
Sorbitan sesquioleate	1.0	—
Propylparaben	0.05	0.05
Amerchol CAB	—	20.0
Aqueous Phase		
Sodium borate, USP	0.7	—
Polyethylene glycol 1500	—	5
Methylparaben	0.15	0.15
Purified water	35.0	49.8

*Available from Hans Schott, Temple University, Philadelphia, PA.

†Available from Amerchol, a Unit of CPC International, Inc., Edison, NJ.

Procedure: Heat the oil phase to 70°C, and add the aqueous solution at 72°C to the oil phase, stirring continuously.

Cold cream base, which reportedly dates back to Galen, was the forerunner of these water-in-oil emulsion vehicles.

The cold cream type of emulsion frequently utilizes a borax-beeswax combination as the emulsifier, with mineral oil or a vegetable oil as the continuous phase. A protective oil film remains on the skin following the evaporation of the water. The slow evaporation of water gives the skin a cooling effect.

TABLE 18-1. *Determination of Water Numbers Using 10-g Samples*

Surfactant	*HLB*	*Grams Water Absorbed*		*Water Number*
		Sample 1	*Sample 2*	
(Control: White petrolatum)		0.40	0.40	4.0
Sorbitan monolaurate	8.6	5.21	5.41	53.1
Sorbitan monopalmitate	6.7	8.20	8.52	83.6
Sorbitan monostearate	4.7	10.59	10.17	103.8
Sorbitan monooleate	4.3	24.75	25.25	250.0
Sorbitan sesquioleate	3.7	29.84	31.04	304.4
Sorbitan trioleate	1.8	41.95	40.31	411.3

From Mendes, R.W., et al.: Drug Cosm. Ind., 95:34, 1964.

Semisolid water-in-oil emulsions of the borax-beeswax type frequently exhibit poor long-term physical stability. The development and large-scale commercial manufacture of water-in-oil emulsifiers have made it possible to prepare stable semisolids that are oily to the touch. Also, relatively nongreasy water-in-oil emulsions may be prepared by a judicious combination of raw materials.

Synthetic substances are replacing natural raw materials as the latter become restricted in availability. As an example, the supplies of natural beeswax have declined with the steady price rises that result from both supply and inflation. A number of synthetic beeswaxes have appeared with properties quite similar to the natural. Synthetic spermaceti types have replaced the natural grade since the latter was banned as a result of endangering the whale. Formula #10 illustrates the use of synthetic beeswax in a relatively nongreasy cold cream.

Formula #10 *Cold Cream*[29]	%
A Purified water	34.60
Borax	1.00
Methylparaben	0.25
B Light mineral oil	50.00
Synthetic beeswax flakes	13.00
Glyceryl monostearate, pure	1.00
Propylparaben	0.15

Procedure: Dissolve the methylparaben and borax in water at 75 to 80°C. Dissolve the propylparaben in a well-mixed mixture of phase B heated to 75 to 80°C. Add phase A to phase B while stirring rapidly.

Hydrophilic ointment is an example of a water-in-oil absorption base type vehicle that does not have any lanolin or its derivatives in the formula.

Formula #11 *Hydrophilic Ointment (USP XX)*	%
Methylparaben	0.25
Propylparaben	0.15
Sodium lauryl sulfate	10.00
Propylene glycol	120.00
Stearyl alcohol	250.00
White petrolatum	250.00
Purified water	370.00

This ointment can be used as a vehicle for many drug substances, but is not a cosmetically elegant preparation. The high petrolatum content leaves an unctuous residue upon the skin that may be uncomfortable. Modification of the formulation by reducing the petrolatum content, and the addition of other emollients such as cetyl alcohol, hexadecyl alcohol, and fatty acid esters (isopropyl myristate or palmitate), can add cosmetic appeal to the preparation. The effect of such modifications on the activity of a drug substance incorporated in the base must be determined.

Formulas #12 and #13 represent different types of hydrophilic ointment bases.

Formula #12 *Hydrophilic Ointment Base**	%
Oil Phase	
Amerchol CAB*	50.0
Cetyl alcohol	2.0
Stearyl alcohol	2.0
Aqueous Phase	
Sodium lauryl sulfate	2.0
Water	34.0
Methyl gluceth-20	10.0
Preservative	q.s.

*Available from Amerchol, a Unit of CPC International, Inc., Edison, NJ.

Procedure: Add the water phase at 80°C to the oil phase at 80°C. Cool while mixing to just above congealing temperature.

Variations: For greater firmness, increase ratio of stearyl to cetyl alcohol.

Formula #13 *Hydrophilic Ointment Base**	%
Oil Phase	
Acetylated lanolin*	5.0
Mineral oil 70 vis.	5.0
Amerchol L-500*	10.0
Amerchol CAB*	15.0
Microcrystalline wax, 195°C	5.0
Cetyl alcohol	5.0
Brij 52†	6.0
Brij 58†	4.0
Aqueous Phase	
Water	40.0
Methyl Gluceth-20	5.0
Preservative	q.s.

*Available from Amerchol, a Unit of CPC International, Inc., Edison, NJ.

†Available from ICI Americas, Inc., Wilmington, DE.

Procedure: Add the water phase at 80°C to the oil phase at 80°C. Cool while mixing to just above congealing temperature.

Water-Removable Bases

The water-removable bases are oil-in-water emulsions and are referred to as "creams." The vanishing cream bases fall into this category. The vanishing creams are so termed because upon application and rubbing into the skin, there is little or no visible evidence of their former presence. Formulas for some typical vanishing cream bases in which different types of emulsifiers are used are given in Table 18-2.

Removal of these creams from skin or clothing is facilitated by the oil-in-water emulsifiers they contain. Creams may be applied to moist skin lesions, since the oil-in-water vehicle tends to absorb any serous discharge. The water removable bases form a semipermeable film on the site of application following the evaporation of water. The semisolid water-in-oil emulsions, however, tend to form a hydrophobic layer on the skin.

Semisolid emulsions are intimate, relatively stable mixtures or dispersions of a hydrophilic phase with a lipophilic phase. The phase that is dispersed in the form of fine microscopic globules is referred to as the discontinuous or internal phase; the other is the continuous or external phase. The vanishing cream type vehicles are representative of the oil-in-water emulsions, whereas the absorption bases are generally water-in-oil emulsions.

Water-Soluble Bases

Water-soluble vehicles are prepared from mixtures of high- and low-molecular-weight polyethylene glycols, which have the general formula: $HOCH_2[CH_2OCH_2]_nCH_2OH$. The low-molecular-weight glycols in this category are liquids; those with a moderately higher molecular weight are somewhat unctuous; and the higher molecular weight polyethylene glycols are solids. Suitable combinations of high- and low-molecular-weight polyethylene glycols yield products having an ointment-like consistency, which soften or melt when applied to the skin. No water is required for their preparation. They are water-soluble because of the presence of many polar groups and ether linkages.

If the polyethylene glycol ointment has a high percentage of crystalline material, the softening and melting of the ointment rubbed onto the skin will not be as gradual as with petrolatum, since the crystalline material melts sharply with an increase in temperature. The polyethylene glycol ointments are much less occlusive than in water-in-oil emulsions of the absorption base type; they mix with skin exudates and are readily washed from the skin. The polyethylene glycol vehicles are softened by the addition of water, owing to solution of the glycols. The USP states that 5% of the polyethylene glycol 4000 may be replaced with an equal amount of stearyl alcohol when 6 to 25% of aqueous solution is to be added to the vehicle.

The "water-soluble" bases are also known as greaseless ointment bases. The compatibility of these bases with drug substances and their release rate must be evaluated for each class of drugs.

Pastes, Gels, and Jellies

Pastes are dispersions of high concentrations of insoluble powdered substances (20 to 50%) in a fatty or aqueous base. The fatty bases are less greasy as well as stiffer in consistency than ointments because of the large amount of powdered material present. These pastes adhere well to the skin and are of benefit in the treatment of chronic or lichenified lesions. Zinc gelatin paste, USP XX, for example, is used when a protective film on the skin is desired following the evaporation of water. Pastes provide a protective layer, and when covered with suitable dressings, prevent excoriation of the patient's skin by scratching.

Jellies are water-soluble bases prepared from natural gums such as tragacanth, pectin, alginates, and boroglycerin, or from synthetic derivatives of natural substances such as methylcellulose and sodium carboxymethylcellulose.

Gels are usually clear transparent semisolids containing the solubilized active substance. Carbomer 940 swells when dispersed in water in the presence of such alkaline substances as triethanolamine or diisopropanolamine to form a semisolid.

Formula #18	
	%
A Carbomer 940*	0.5
Water	42.5
Sorbitol 70% solution	2.0
B Ameroxol OE 20†	10.0
Solulan 98†	3.0
Polyvinylpyrrolidone (PVP) K-30	1.0
Triethanolamine	1.0
S.D. alcohol #40	40.0

*Available from B.F. Goodrich Company, Cleveland, OH.
†Available from Amerchol, a unit of CPC International, Inc., Edison, NJ.
Procedure: Phase A—Disperse Carbomer 940 thoroughly in water with good stirring. Add sorbitol solution. Phase B—Add the Ameroxol OE 20 to the alcohol, warm to 35°C, and stir until uniform. Add Solulan 98, PVP, and triethanolamine consecutively, mixing after each addition. Add phase B to phase A with gentle mechanical mixing until gel forms.

Formula #19	
	%
Carbomer 940	0.75
Purified water	34.25
Solulan 98*	3.00
S.D. alcohol #40	50.00
Diisopropanolamine, 10% in water	12.00

*Available from Amerchol, a unit of CPC International, Inc., Edison, NJ.
Procedure: Prepare a Carbomer slurry in water with gentle agitation, and add mixture of SDA #40 and Solulan mixture, mixing until no particles are visible. Neutralize carefully with diisopropanolamine solution to avoid incorporating air.
For greater firmness, increase the concentration of the Carbomer and diisopropanolamine.

Gels are also formed with celluloses such as hydroxypropylcellulose and hydroxypropylmethylcellulose. A popular over-the-counter benzoyl peroxide gel contains 6% polyoxyethylene lauryl ether, 40% ethyl alcohol, colloidal magnesium aluminum silicate, hydroxypropylmethylcellulose, citric acid, and purified water.

Ophthalmic Ointments

Semisolid ophthalmic vehicles frequently contain soft petrolatum, a bland absorption base, or a water-soluble base. The water-soluble base may be prepared with polyethylene glycols or with a water-soluble gum. Mineral oil is frequently added to petrolatum to lower its fusion point, but its addition introduces a problem of separation upon storage. Such oil separation may be prevented by the addition of small quantities of natural waxes such as ozokerite, ceresin, or microcrystalline wax. The amount of wax added should not appreciably raise the melting point of the base.

All materials used in the ophthalmic ointment should be impalpable to avoid eye discomfort and possible irritation. Ophthalmic ointments, especially when used on injured eyes, should be sterile.

Numerous variations of the aforementioned basic vehicles are possible because of the availability of new raw materials, which permit the pharmacist to vary his formulation to obtain the desired therapeutic effect and to make a semisolid that is both convenient and comfortable for the patient to apply. A minimal number of materials should be used in a semisolid dosage form, since fewer constituents reduce inventory, decrease the possibility of chemical interference with the analytic procedure, and decrease the

TABLE 18-2. *Formulas for Vanishing Cream Bases*

	#14 Anionic Stearate Emulsifier % *By Weight*	*#15 Anionic Emulsifier* % *By Weight*	*#16 Nonionic Emulsifier* % *By Weight*	*#17 Cationic Emulsifier* % *By Weight*[30]
Stearic acid	13.0	7.0	14.0	
Stearyl alcohol	1.0	5.0		
Cetyl alcohol	1.0	2.0	1.0	
Glyceryl monostearate				10.0
Isopropyl palmitate			1.0	
Lanolin				2.0
Methylparaben	0.10	0.10	0.10	0.1
Propylparaben	0.05	0.05	0.05	
Sorbitan monostearate			2.0	
Glycerin	10.0	10.0		15.0
Sorbitol solution [70%]			3.0	
Potassium hydroxide	0.90			
Sodium lauryl sulfate		1.0		
Polysorbate 60			1.5	
Stearyl colamino formyl methyl pyridinium chloride				1.5
Purified water, q.s. ad	100	100	100	100

danger of allergic reactions in unusually sensitive patients.

Many formulas for creams and ointments can be found in the scientific literature, formularies, and catalogs of chemical suppliers of emulsifiers and other raw materials. These formulas should only serve as a guide for developmental work, because many of them have not been checked for stability, ease of application, or ability to release the drug to the absorption site. The requirements of the drug should determine what materials are used. Only by subsequent experimentation can the typical problems regarding consistency, application, and stability be overcome.

In the past, many pharmaceutical semisolids used to treat skin disease lacked the elegance and aesthetic appeal of the better cosmetics and toiletries. However, the availability of a host of new and safe raw materials suitable for use as dermatologic semisolids has made it possible for the patient to apply to his skin a preparation that is therapeutically effective and cosmetically acceptable. For cosmetic appeal, the semisolid should be easy to apply and feel comfortable on the skin. It should not feel clammy, excessively moist, or too dry. When a protective film is formed or deposited on the skin, the film should not be tacky or excessively adhesive. All these properties may be summed up under the expression "pharmaceutical elegance."

Preservation from Microbial Spoilage

Chemical preservatives for semisolids must be carefully evaluated for their stability with regard to the other components of the formulation as well as to the container. Plastic containers may absorb the preservative and thereby decrease the quantity available for inhibiting or destroying the microorganisms responsible for spoilage. Some preservatives may sting or irritate the mucous tissues of the eye or nasal passages. Methylparabens and propylparabens tend to be more irritating when applied in the nose than quaternary ammonium compounds (e.g. benzalkonium chloride) or the phenylmercuric salts. Boric acid may be used in the ophthalmic preparations, but is omitted from products to be used in the nose because of possible toxic effects if absorbed in large quantities.

The preservatives are added to semisolids to prevent contamination, deterioration, and spoilage by bacteria and fungi, since many of the components in these preparations serve as substrates for these microorganisms. Several terms are used to describe microbial organisms associated with pharmaceutical and cosmetic products: "harmful," "objectionable," and "opportunistic."

The USP XX uses the term "harmful" to refer to microbial organisms or their toxins that are

responsible for human disease or infection. Examples of organisms that must not be present in a product are given, namely, Salmonella species, Escherichia coli, certain species of Pseudomonas, including P. aeruginosa, and Staphylococcus aureus. An "objectionable" organism can cause disease, or its presence may interrupt the function of the drug or lead to the deterioration of the product. Organisms are defined as "opportunistic" pathogens if they produce disease or infection under special environmental situations, as in the newborn or the debilitated person. Included in the latter group are the aged, those undergoing extensive surgical or accidental trauma, and the compromised host, defined as those who are on antibiotic, anticancer, or immunosuppressive therapy. The newborn has increased susceptibility to gram-negative infections, while the other individuals have various forms of immunologic deficiency, which increase the susceptibility to infections. Recognized opportunistic pathogens are "objectionable."[31] The following objectionable organisms should not be present in a pharmaceutical or cosmetic product: P. putida, P. multivorans, P. maltophilia, Proteus mirabilis, Serratia marcescens, Klebsiella sp., Acinetobacter anitratus (Bacterium anitratum), and Candida sp.[32]

The success or failure of a preservative in protecting a formulation against microbial spoilage depends upon many factors. The interaction of the preservative with surfactants, active substances, other components of the vehicle, sorption by polymeric packaging materials, and product storage temperature may change the concentration of the unbound or free preservative in the aqueous phase.

Perfumes, high concentrations of glycerine, and electrolytes make the environment less favorable to microbial growth, thus enhancing the effectiveness of the preservatives. Preservative action appears to depend on the concentration of the free preservative in the aqueous phase. Surfactant solubilized preservative may be bound within the micelles and there inactivated, or on the contrary, the micelles may act as reservoirs of preservative in an actively preserved system.

The minimum inhibitory concentration of preservative necessary to prevent microbial spoilage may be estimated by (1) the use of experimentally determined physicochemical parameters such as the oil/water partition coefficient, concentration of surfactant, the number of independent binding sites on the surfactant, oil/water phase ratio, and concentration of free preservative in the aqueous phase;[33] (2) an ultracentrifuge technique;[34] and (3) direct dialysis.[33]

These techniques provide an approximate value for the minimum preservative concentration required for a formulation, but to ensure quality, the product must be tested for its ability to withstand accidental and deliberate microbial contamination.[35]

Preservative efficacy in a formulation is determined by the addition of pure or mixed cultures of microbial organisms to the finished preparation. The number of microorganisms initially present in the inoculated material is determined by plating aliquots of suitable dilutions. Table 18-3 gives the USP XX procedure and the investigational FDA procedure for topicals, including the organisms used, the levels of inoculum, sampling periods, and the measure of effectiveness. Various neutralizers for the preservative are added to the culture media to recover a maximum number of organisms. A TAT broth consisting of tryptone (2%), azolectin (0.5%), and polysorbate 20 (4%) has been found to be a suitable medium for topical products. Azolectin is a neutralizing agent for quaternary ammonium compounds and polysorbate 20 inactivates parabens. The samples should be tested at intervals for both slow-growing and rapidly proliferating organisms.

The USP XX has procedures for determining the microbial content of raw materials and finished products. Suitable limits on the number

TABLE 18-3. *Preservative Efficacy (High-Level Inocula Challenge) Tests*

A. USP XX Procedure
1. Organisms used: C. albicans, A. niger, E. coli, S. aureus, P. aeruginosa.
2. Inoculum: 0.1ml/20 ml; 100,000 to 1,000,000 cells/ml.
3. Sampling at 7, 14, 21, and 28 days following inoculation.
4. Effectiveness: vegetative cells not more than of 0.1% of initial concentrations by 14th day; concentration of viable yeasts and molds at or below initial concentration after 14 days; concentration of each test organism remains at or below these levels after 28 days.

B. Investigational FDA Procedure for Topicals
1. Organisms used: same as USP XX plus P. putida, P. multivorans, Klebsiella sp., S. marcescens.
2. Inoculum: 0.2 ml/20 ml; $0.8–1.2 \times 10^6$ cells/ml.
3. Sampling: weekly observations.
4. Effectiveness: vegetative cells <0.01% survival by 28 days; C. albicans <1% survival; A. niger <10% survival.
5. Re-inoculate: vegetative cells: $1–2 \times 10^5$ cells/ml; 0.1% survival in 28 days.

Modified from Bruch: Drug and Cosm. Ind., *110*:32, 1972.

and types of microorganisms have not been officially specified, however. All materials must be free of the harmful microorganisms listed in the USP XX. Manufacturers have set up their own microbiologic specifications suitable to their raw materials and finished products. A typical manufacturer's microbiologic specification may read as follows: (1) The material must be free of viable organisms restricted by the USP XX. (2) The total aerobic count must not be more than 5000 microorganisms per gram; (3) not more than 100 molds per gram; (4) not more than 100 yeasts per gram; and (5) not more than 90 coliforms per gram.

Microbiologic quality guidelines have been established by The Cosmetic, Toiletry and Fragrance Association, Inc.[36] These have been grouped according to product type:

1. Baby products—not more than (nmt) 500 microorganisms per gram or milliliter;
2. Products used about the eye—nmt 500 microorganisms per gram or milliliter;
3. Oral products—nmt 1000 microorganisms per gram or milliliter;
4. All other products—nmt 1000 microorganisms per gram or milliliter.

There is a further specification that the products must be free from microorganisms recognized "as harmful to the user as determined by standard plate count procedures."[36]

Limits on the maximal microbial content of potable and purified water are stated in the United States Public Health Service regulations.[37] The test is made for the presence of the coliform group of bacteria, since experience has shown that this group is a significant indicator of pollution. The membrane filter technique, as well as the fermentation tube method, is used for detecting and estimating the number of coliform bacteria present.

Raw materials of botanical or animal origin that contain high levels of microorganisms must be treated before use to remove these contaminants. The greatest source of contamination in nasal jellies, for example, are the natural gums, but treatment of the thickener with ethylene oxide vapor destroys the bacterial and fungal contaminants. Tests for ethylene oxide residues should be made before using the material. The amount of allowable ethylene oxide residues have not been established. The residues are ethylene oxide (ETO), ethylene chlorohydrin (ETC), and the various monomeric forms of ethylene glycol (ETG). Bruch has stated: "Recent studies have shown the LD_{50} (Gm./Kg.) by different routes for different animal species to approximate the following: ETC > ETO > ETG (least toxic). Acute topical irritation studies show on Gm./Kg. basis that the activity is ETO > ETC > ETG."

The FDA has proposed the following:[38] "Each drug product of a type listed in this paragraph for which ethylene oxide is used as a sterilant in the manufacture of the finished product, its components, or its market container shall not, when tested as packaged in its market container, exceed the following residue levels . . . ." (See Table 18-4.)

The manufacturer cannot depend on the preservative or a type of sterilizing process, such as radiation sterilization or a liquid chemical sterilant, to eliminate organisms introduced during the manufacturing process or by contaminated raw materials. Though the microbiologic quality of a product may be high as a result of the sterilization process, endotoxins may be present as a result of lysing of the bacterial cells. Some endotoxins have been shown to be allergens. These substances should be absent from semisolids just as sterile products should be free of pyrogens. Methods for detection of endotoxins are being investigated.[39]

A manufacturer can lessen the microbial hazards in his products by following the Good Manufacturing Practices (GMPs) recommended by

TABLE 18-4. *Residue Limits of Ethylene Oxide and Derivatives (Parts per million)*

Drug product	*Ethylene oxide*	*Ethylene chlorohydrin*	*Ethylene glycol*
Ophthalmics (for topical use)	10	20	60
Injectables (including veterinary intramammary infusions)	10	10	20
Intrauterine device (containing a drug)	5	10	10
Surgical scrub sponges (containing a drug)	25	250	500
Hard gelatin capsule shells	35	10	35

From Federal Register, 43(122), June 23, 1978, part 221, p. 27482.

the FDA.[40] These procedures do not spell out the specific details that a manufacturer should follow to avoid contamination with microbial or foreign matter in pharmaceutical products. An interesting sanitary guideline was developed with the food industry in mind, but it is applicable to any industry in which sanitary procedures must be followed. The Sanitary Design Principles are in the form of a checklist covering many details, such as the construction of the manufacturing plant, processing and packaging equipment, floors, walls and ceilings, plant services, and the relative ease of cleaning both equipment and the environment.[41]

If the bacterial count in the finished product is high despite precautions taken to prevent contamination in the raw materials, including the water supply, then the pipelines, filling equipment, and containers must be checked for sources of contamination or interference with the activity of the preservatives. For example, some filling equipment may still contain some of the semisolid after rinsing or flushing of the equipment during the cleaning operation. In such cases, complete disassembly and thorough cleaning are mandatory.

The container may contribute to contamination by harboring bacterial spores, or by sorption or chemical interaction with the preservative, which thereby lowers its concentration in the preparation. Plastic containers, rubber seals, and closures have been shown to react with some preservatives.[42] Reduced preservative concentration also can occur through chemical complexation with the surfactant or gum as shown in Table 18-5.

In the presence of 5% polysorbate 80, 80% of the total methylparaben present in the aqueous phase is inactive.[44] Such inactivation also occurs with benzalkonium chloride, benzoic acid, cetylpyridinium chloride, dehydroacetic acid, and sorbic acid. The partial inactivation of the preservative can be overcome by an excess of the same preservative, by the substitution of a noncomplexing preservative, or by the substitution of a noncomplexing emulsifier system.

TABLE 18-5. *Degree of Binding of p-Hydroxybenzoate Esters by Various Macromolecules*

Macromolecule 2% w/v	*Unbound Methylparaben %*	*Unbound Propylparaben %*
Gelatin	92	89
Methylcellulose	91	87
Carbowax 4000	84	81
PVP	78	64
Myrj 52	55	16
Tween 20	43	14
Tween 80	43	10

From Barkley, E. L.: Am. Perf. Aromat., 73:33, 1959.

The antibacterial or bacteriostatic activity of the preservative depends also on its partition coefficient. The preservative may partition between the oil and the aqueous phase, and if the preservative is more soluble in one phase than another, an additional quantity of the preservative must be added so that both phases are protected from microbial spoilage. Hence, methylparaben and propylparaben are frequently used in semisolids because of their better solubility in aqueous and oil phases, respectively.

Many of the preservative studies reported in the literature are performed in simple aqueous systems. It is comforting to know that the preservatives appear to be more effective in the finished formulations than indicated in the complexation studies. The interactions occurring in a complex emulsion system in a semisolid apparently do not apply.[45] However, in view of the fact that interaction of preservatives with macromolecules does occur, the finished formulation should be tested microbiologically for preservative adequacy.

The p-hydroxybenzoate esters are used in combination with one another because of their synergistic action. In general, they are employed at a concentration level approaching their maximum solubility in water. The solubilities of some commonly used preservatives are given in Table 18-6. The propyl or butyl ester is usually dissolved in the fat phase and should be increased for vehicles with a high fat content. Satisfactory protection of the emulsion against microbial growth may possibly be attained with sorbic acid, in which the p-hydroxybenzoate esters prove to be ineffective.[45]

The paraben esters of p-hydroxybenzoic acid are still popular as preservatives because their toxicity is low, they are odorless, they do not discolor, and they are nonirritating to the skin. On the negative side, the parabens have a low solubility in water and are less effective against gram-negative bacteria than molds and yeasts. Combining the parabens with phenoxyethanol,[47] or with imidazolidinyl urea (Germall II),[48] improves their activity against bacteria, yeast, and molds. The supplier* claims that the combination system retains activity against yeast and mold even when paraben activity has been diminished by interaction with nonionics or other substances in the formulation, or has migrated into the oil phase. Germall II is used in concentrations of 0.1 to 0.5% alone or in combination with the parabens. It should be added to the product below 60°C.

*Sutton Laboratories, Inc., Chatham, NJ

TABLE 18-6. *Solubilities of Some Preservatives in g/100 ml Solvent at 25°C*

	Water	*Mineral Oil*	*Propylene Glycol*
Bithional	0.0004	1.0	0.5
Butyl-p hydroxybenzoate	0.02	S	110
p-Chloro-m-xylenol	0.0025	SS	1.5*
Dehydroacetic acid	0.10	0.01	1.7
Ethyl paraben	0.075		
Methyl-p-hydroxybenzoate	0.25	0.03	22
Propyl-p-hydroxybenzoate	0.06		26
Sorbic acid	0.2		5.5

S = soluble; SS = slightly soluble; * = in glycerin. These descriptive terms are approximate solubilities as defined in USP XX.

The solid parabens may be difficult to incorporate into some formulations because of their low water solubility. A 50% by weight oil-in-water emulsion (Liqua Par*) has been marketed. The oil phase is a mixture of p-hydroxybenzoic acid esters: n-butyl, isobutyl and isopropyl. The aqueous portion contains water with emulsion stabilizers. The solubility of the active ingredients in water at 25°C is 0.06 g/100 g and is freely miscible with propylene glycol. The preservative should be added to the aqueous phase at a temperature not exceeding 70 to 75°C and stirred until thoroughly dissolved before the preparation of the emulsion. Paraben hydrolysis may occur if the temperatures exceed 80°C. The supplier recommends the use of a concentration ranging from 0.05 to 0.3% active ingredient.

Another preservative that is available is Dowicil 200†, which is described as a broad-spectrum antimicrobial effective against bacteria, yeast, and molds at concentrations of 0.02 to 0.3% weight. It is not inactivated by nonionic, anionic, or cationic formulation ingredients. The substance is extremely soluble in water but is virtually insoluble in oils and organic solvents. Chemically, it is the cis isomer 1-(3-chloroallyl)-3,5,7-triaza-l-azoniaadamantane chloride. The preservative should not be heated above 50°C and is unstable in solution below pH 4 and above pH 10. Discoloring of this material may occur, but can be prevented by the addition of sodium sulfite. Strong oxidizing or reducing agents should be avoided since these may adversely affect the antimicrobial efficacy.

Newer preservatives are being marketed, but all of these substances must be thoroughly evaluated for their effectiveness in the product, and their effect on the physicochemical stability of the product. As with all new dermatologicals under development, patch testing must be conducted to eliminate any possibility of skin irritation or sensitivity with the products containing these substances.

Rapid determination of preservative efficacy in semisolids can be done in 48 hours for bacteria and 7 days for molds.[49] The method utilizes the so-called D-value, or decimal reduction time, which is calculated from a plot of the log number of surviving organisms per gram against time of inoculation of the product with specific organisms. The D-value is a numerical value of rate of destruction of a particular organism in a specific product. Since it is a quantitative expression, it can be used to compare the rate of inactivation of different organisms in one or more products. The D-value permits the calculation of the time required for the complete destruction of any size population of organisms.

The method consists of inoculating the product with known amounts of the test organisms. The products are then sampled periodically to record the population of each test organism, and the log of the surviving organisms at each sample time is plotted. The slope of the line is determined by linear regression, and the negative reciprocal of the slope represents the D-value. The time predicted for complete destruction of the test organism in a product is calculated by linear estimate of the x-intercept. Figure 18-2 shows the effect of different concentrations of parabens on the death rate of Staphylococcus aureus in a cream.

The D-values for the control, the cream with the lower, and the cream with the higher concentrations of parabens were 18, 4, and 0.6 hr, respectively. The times predicted for the complete destruction of S. aureus in these samples were 63, 19, and 3 hr for the control, low-paraben-content cream, and high-paraben-

*Mallinckrodt, Inc., St. Louis, MO.
†Dow Chemical, U.S.A., Midland, MI.

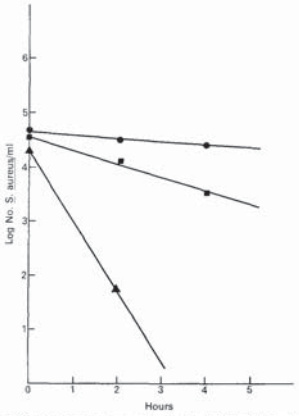

FIG. 18-2. *Survivor curves showing the effects of different concentrations of parabens on the rate of death of Staphylococcus aureus* (in a cream. Symbols: ●—●, *cream with no parabens (control);* ■—■, *cream with 0.12% methyl- and 0.08% propyl-paraben; and* ▲—▲, *cream with 0.2% methyl- and 0.1% propyl-paraben. (From Orth, D. S.: J. Soc. Cosm. Chem.,* 30:321, 1979.)

content cream, respectively. The time required for the complete destruction of a specific organism of known population in a particular product may be predicted from the D-value. If the mean D-value for S. aureus in a product is 2.5 hr, the time for 10^6 S. aureus per milliliter to be totally inactivated is given by the product of the log number of the organisms per milliliter multiplied by the D-value, or 6×2.5 hr = 15 hr.

Table 18-7 shows the composition of the vehicles of several corticosteroid creams. It is designed to show how currently marketed semisolids utilize the principles described in the previous sections, namely, the different physiologically innocuous fatty materials used in the fat phase, the emulsifier systems, and the humectants, preservatives, antioxidants, and chelating agents.

Antioxidants

Antioxidants are added to semisolids whenever oxidative deterioration is anticipated. The antioxidant system is determined by the components of the formulation, and the selection depends on several factors, such as toxicity, irritancy, potency, compatibility, odor, discoloration, solubility, and stability. Often, two antioxidants are used, since the combination is often synergistic. Listed in Table 18-8 are some physical and chemical properties of antioxidants in common use. Acids such as citric, maleic, phosphoric, or tartaric may be added to the combination to chelate trace quantities of metals.

Industrial Processing

Pilot plant or small-scale production equipment is essential in developing a manufacturing procedure for a production-size batch. The preparation of many batches, ranging in size from 2.5 to 25.0 or more kilograms, for product evaluation and clinical testing provides opportunity to observe, correct, or improve the effects of minor but important variations in the manufacturing technique or formula. Mixing and stirring operations are critical in the preparation of emulsions, and in the laboratory these operations can be carefully controlled in 0.5- or 1.0-kg batches of finished product.

The electrically operated propeller-type mixer can be manually adjusted and positioned in the laboratory mixing vessel to achieve maximum turbulence. The angle of entry of the propeller shaft and the depth of the propeller can be easily varied in the laboratory to prevent aeration. A metal spatula can be held or positioned in the beaker during mixing to serve as a baffle to increase turbulence without entrainment of air. Similar maneuverability and control of the mixing action is more limited with larger stationary equipment used for the manufacture of semisolids. High-speed agitation may introduce air into the product, and slow mixing may not form a satisfactory emulsion.

Such problems occur in large-scale manufacture, but would not be apparent in small 1- or 2-kg batches for which a beaker and a laboratory mixer are used. Small-scale equipment similar to the production models can approximate production conditions. It may not be possible to predict the exact mixing time and rotational speed of the agitator, but the overall processing characteristics can be ascertained if identical mixers are used.

Aeration of the semisolid should be avoided,