Recent Advances in Semisolid Dosage Forms for Dermatological Application

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This article discusses some of the recent advances in semisolid dosage forms for dermatological application. Several studies have demonstrated the utility of semisolid bases for systemic drug delivery by dermatological application. Studies about the effect of formulation excipients on the rheology of semisolids have contributed significantly toward their characterization. The development of computer-assisted instruments also has contributed substantially to their characterization and thereby to improving their quality. Moreover, some of the guidelines established by regulatory agencies, especially by FDA, are major steps toward the standardization of these dosage forms.

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Semisolids constitute a significant proportion of pharmaceutical dosage forms. They serve as carriers for drugs that are topically delivered by way of the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining (1). Because of their peculiar rheological behavior, semisolids can adhere to the application surface for sufficiently long periods before they are washed off. This property helps prolong drug delivery at the application site. A semisolid dosage form is advantageous in terms of its easy application, rapid formulation, and ability to topically deliver a wide variety of drug molecules.

Semisolids are available as a wide range of dosage forms, each having unique characteristics (2–4). *Ointments* are semisolid preparations for external application to skin or mucous membranes. Their composition softens but does not melt upon application to the skin. Therapeutically, ointments function as skin protectives and emollients, but they are used primarily as vehicles for the topical application of drug substances. *Creams* are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base, usually an oil-in-water emulsion or aqueous microcrystalline dispersion of long-chain fatty acids or alcohols that are water-washable and are cosmetically and aesthetically acceptable. *Gels* are semisolid systems that consist of either suspensions of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels can be either water based (aqueous gels) or organic solvent based (organogels) (5). *Pastes* are semisolid dosage forms that contain one or more drug substances incorporated in a base with large proportions of finely dispersed solids.

A wide range of raw materials is available for the preparation of a semisolid dosage form. Apart from the usual pharmaceutical ingredients such as preservatives, antioxidants, and solubilizers, the basic constituents of a semisolid dosage form are unique to its composition. Figure 1 shows the basic raw materials used in the development of various semisolid dosage forms. The choice of suitable raw materials for a formulation development is made on the basis of the drug delivery requirements and the particular need to impart sufficient emolliency or other quasi-medicinal qualities in the formulation.

Semisolid dosage forms usually are intended for localized drug delivery. In the past few years, however, these forms also have been explored for the systemic delivery of various drug

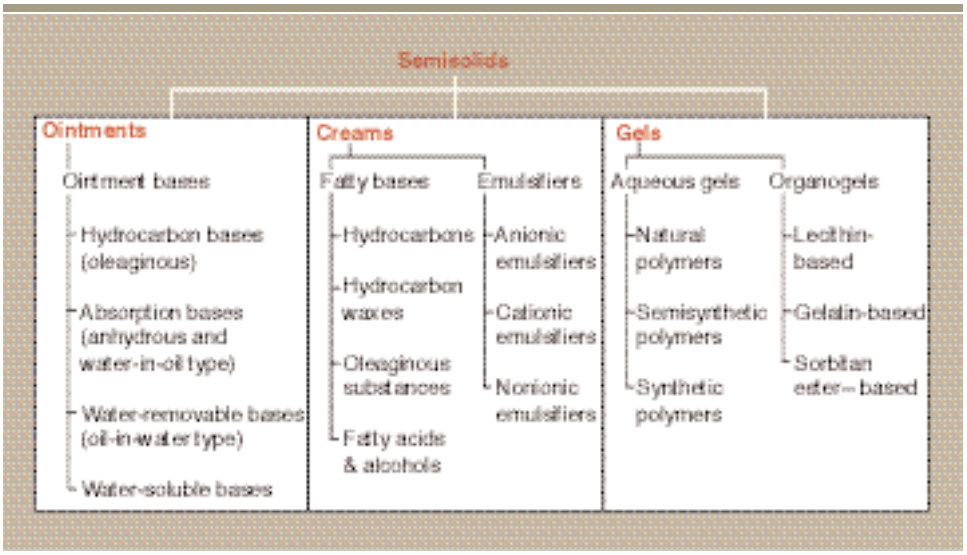

Figure 1: The basic constituents of various semisolid dosage forms.

Table I: Penetration enhancers for transdermal drug delivery.

Penetration Enhancer	Drug Tested	Reference
Menthol, carvacrol, linalool	Propranolol hydrochloride	64
Limonene	Indomethacin, ketoprofen	64
Geraniol, nerolidol	Diclofenac sodium	65
Oleic acid	Piroxicam	66
Lecithin	Hydrocortisone acetate, heparin	67,68
Propylene-glycol-dipelargonate	Heparin	68
Cyclodextrins	Hydrocortisone	69

Table II: Combinations of penetration enhancers and cosolvents for transdermal drug delivery.

Penetration Enhancer	Cosolvent	Drug Tested	Reference
Isopropyl myristate	Propylene glycol	Diclofenac sodium	70
Cineole	Ethanol	TRH analogue *p*-Glu-3-methyl-His-Pro amide	71
Ethanol	Propylene glycol	Aspirin	72

candidates whose peroral bioavailability is questionable. Several novel drug-carrier systems have been examined that offer enhanced release, controlled release, or a stable environment for the incorporated drug. Even greater interest has been shown in the advancement of methods with which to characterize semisolid dosage forms.

Skin, which is the most easily accessible organ of the human body, continues to be the preferred site for the application of topical drug delivery systems. This article examines the major advancements in the formulation and characterization of semisolid dosage forms for application to the skin. The authors have compiled information from literature published in the past six to seven years and herein present the latest developments in semisolid dosage forms as well as project new directions for research in this fast-evolving field.

Percutaneous drug absorption

Semisolid dosage forms for dermatological drug therapy are intended to produce desired therapeutic action at specific sites in the epidermal tissue. A drug's ability to penetrate the skin's epidermis, dermis, and subcutaneous fat layers depends on the properties of the drug and the carrier base. Although some drugs are meant primarily for surface action on the skin, the target area for most dermatological disorders lies in the viable epidermis or upper dermis. Hence, a drug's diffusive penetration of the skin — percutaneous absorption — is an important aspect of drug therapy.

The main portals of drug entry into the skin (see Figure 2) are the follicular region, the sweat ducts, or the unbroken stratum corneum between these appendages (6,7). A substance's particular route mainly depends on the physicochemical properties of the drug and the condition of the skin.

Advances in the formulation of semisolid dosage forms

The formulation of a suitable semisolid dosage form involves the selection of an appropriate drug-carrier system, with a special emphasis on the drug's physicochemical properties and required therapeutic application. Drug delivery by means of semisolid dosage forms has seen new challenges in the past few years in terms of altered drug-release profiles as well as the enhanced stability of active pharmaceutical ingredients (APIs).

Systemic drug delivery. The skin's large surface area, ~1.73 m^2, facilitates its use as a potential site for the application of topical dosage forms (8). With this method, not only can some therapeutically active agents be delivered transdermally with ease, but first-pass gut and hepatic metabolism is avoided, constant drug levels in the bloodstream are maintained for longer periods of time, potential side effects are decreased, bioavailability is improved, the dosage is smaller, patient compliance is increased, and drug termination in problematic cases is facilitated as compared with other routes of drug administration (9). Semisolid dosage forms have proven to be ideal carriers for this purpose, and several novel developments in their formulation technologies have emerged in recent years.

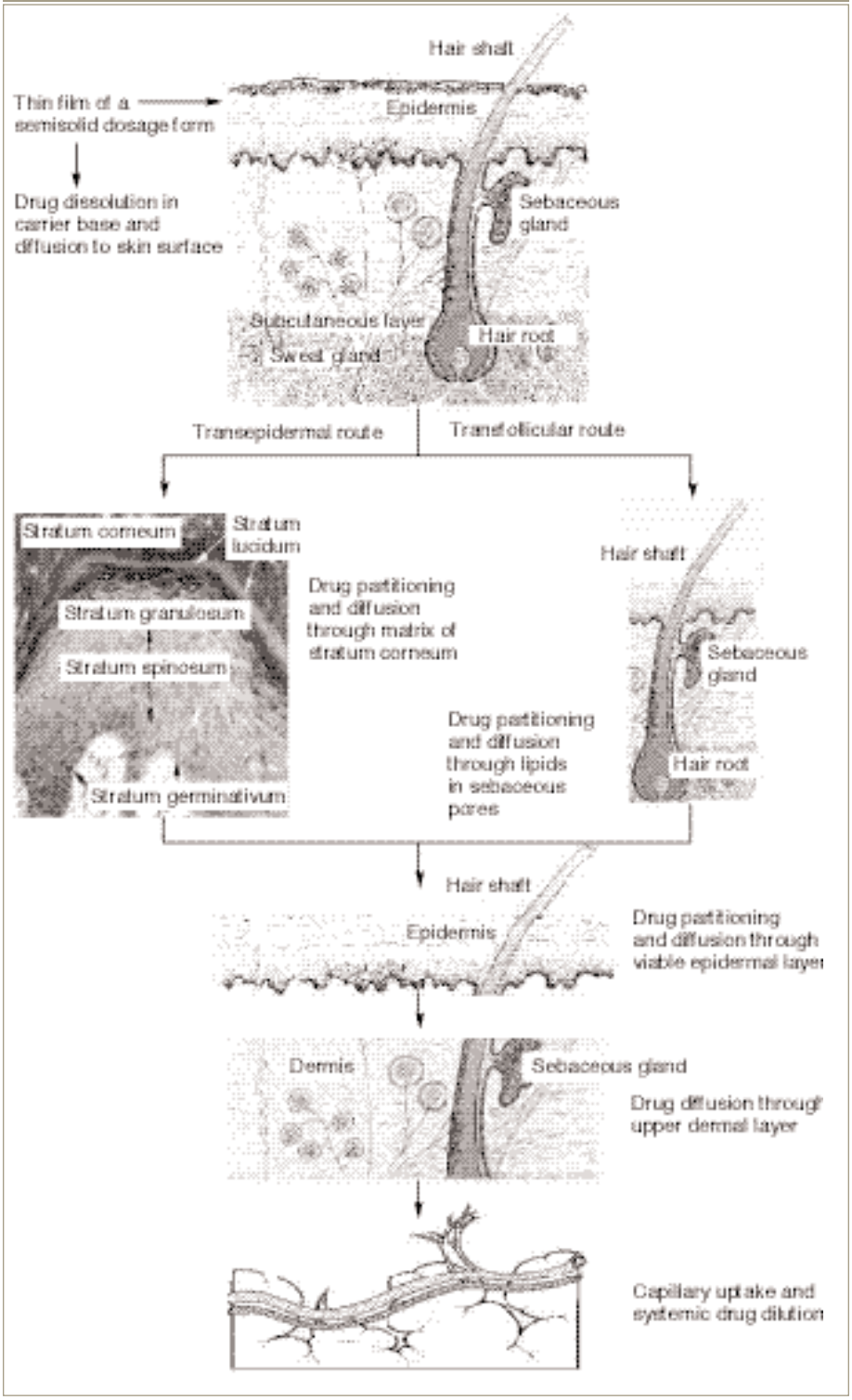

Figure 2: Schematic representation of percutaneous absorption of a topically applied drug.

Gels with permeation enhancers. Skin can act as a barrier to the deeper penetration of drug molecules. With the introduction of various penetration enhancers, however, systemic drug delivery through the transdermal route has gained major footing. These chemicals, incorporated in a suitable drug-carrying semisolid vehicle, enhance the amount of drug permeation through skin either by reversibly disordering the lamellar packing of stratum corneum or by increasing the thermodynamic activity of the drug (10). Another class of penetration enhancers acts by increasing the amount of drug in solubilized form at the skin surface, resulting in the enhanced permeability of lipophilic drug molecules. A large number of chemicals have been studied for penetration-enhancement activity (11,12). The search continues for new chemicals with desirable activity at low concentrations and with minimal cutaneous irritation potential. Table I lists some of the chemicals studied in the past few years for penetration-enhancing activity and those that meet this criterion.

In addition to the use of penetration enhancers alone, their combination with cosolvents that deliver a drug in solubilized form has led to the achievement of higher drug permeability. Table II lists some of the combinations that recently have been studied.

Submicron emulsion vehicle system. Conventional creams have a mean droplet size ranging from 10 to 100 μm. Such formulations have demonstrated poor penetration of drug-loaded oil droplets into deep skin layers. It has been reported that microparticles with diameters ranging from 3 to 10 μm selectively penetrate follicular ducts, whereas particles >10 μm remain on the skin surface, and those <3 μm are distributed randomly into hair follicles and stratum corneum (13,14). Taking these constraints into consideration, researchers have developed the submicron emulsion vehicle system (SMEVS) for improving drug permeation. The submicron lipid particles of an SMEVS penetrate the layers of the stratum corneum, increasing its fluidity and leading to the disruption of barrier continuity. Significant hydration of the stratum corneum, assisted by gap formation, permits the penetration of submicron emulsion particles by forming a drug depot in the skin. The result is slow, continuous, and controlled systemic delivery of the drug. An SMEVS can be formulated by processing a medium-chain triglyceride emulsion with a high-pressure homogenizer. In addition, the presence of lecithin, an efficient dispersing agent, causes a drastic reduction in droplet size, usually to between 100 and 300 nm. Such a system is highly valuable for the transport of hydrophobic drugs, which are incorporated into the oil

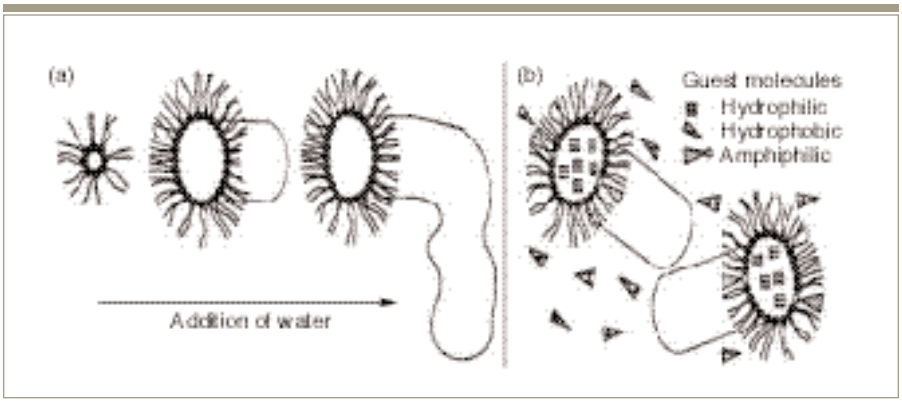

Figure 3: Microemulsion-based gels: (a) schematic representation of the formation of lecithin gels upon addition of water to small phosphatidyl choline reverse micelles in apolar solvents; (b) localization of solubilized guest molecules within lecithin gels (36). Reprinted courtesy of Elsevier Science.

phase of submicron emulsions and thereby improve penetration of the stratum corneum. Studies of SMEVSs have shown effective transdermal delivery of diazepam (15) and various steroidal and nonsteroidal anti-inflammatory agents (16).

Volatile vehicle–antinucleant polymer systems. Studies have investigated various techniques to enhance the transdermal permeation of topically applied drug molecules. Increasing the thermodynamic activity of drug molecules was found to be the most efficient approach. This increase can be achieved by the volatile vehicle–antinucleant polymer system (17). Enhanced permeation of sodium nonivamide acetate (an antinociceptive agent) was observed with ethanol–buffer solutions (pH 4.2) containing antinucleant polymers. The system used supersaturation (achieved by evaporation of the vehicle) for penetration enhancement. In supersaturated solutions the drug is in a high state of activity and has a great leaving tendency, resulting in increased flux. However, supersaturated solutions are physically unstable and can result in the crystallization of a drug upon preparation of the solution. This effect can be controlled by antinucleant polymers such as methylcellulose and hydroxypropyl cellulose. These polymers are adsorbed on the hydrophobic surface of crystals, thus stabilizing the precipitates and increasing the thermodynamic activity of the drug. A higher permeation of sodium nonivamide was observed when ethanol was replaced with *n*-propanol because of the higher drug solubility in an *n*-propanol–buffer solution (pH 4.2). This method also resulted in a greater reduction of diffusional barriers by the extraction of stratum corneum lipids and proteins.

Lecithin microemulsion gel. Lecithin microemulsion gel is a promising matrix system for transdermal drug delivery (18). Microemulsion gels are obtained by dispersing soybean lecithin (a mixture of phosphatidyl cholines) in a nonpolar organic solvent, thereby forming an entangled network of long and flexible multimolecular aggregates (see Figure 3). Fatty-acid esters such as isopropyl palmitate are preferred organic solvents because of their relatively high viscosity and complete optical transparency. Lecithin microemulsion gels are of particular interest because of their ability to solubilize drug molecules of various physicochemical properties, their low potential for acute and cumulative skin irritation, and the action of lecithin and isopropyl palmitate as possible skin-penetration modifiers.

The high diffusion rates of indomethacin and diclofenac show that lecithin microemulsion gel is a suitable matrix for transdermal drug delivery. However, the partition coefficient of the drugs from the gel into the stratum corneum was found to be unfavorable (18). Hence, relatively large amounts of the drug had to be used to obtain the required penetration rates.

Localized drug delivery. Localized drug delivery by semisolid dosage forms continues to be a major area of research. Advances in formulation approaches have led to increased drug stability as well as improvement in the aesthetic appeal of semisolid dosage forms.

Oleo-hydrogel systems. Oleo-hydrogel systems for localized skin action have been explored successfully. Rhee et al. examined transdermal permeation using various vehicle systems to avoid systemic side effects and gastrointestinal irritation from ketoprofen upon oral administration (19). When compared with conventional gel or plaster formulations, the oleo-hydrogel system was found to be the optimal formulation because it decreased systemic circulation of the drug and increased localized action. The researchers examined an oleo-hydrogel system that consisted of ketoprofen incorporated into an emulsion of oil and carbomer hydrogel mixture, with *N*-methylpyrrolidone as a permeation enhancer. The greater bioavailability of ketoprofen in the oleo-hydrogel system was ascribed to good drug-release properties, higher emulsion droplet stability of the carbomer gel, and the penetration-enhancing effect of *N*-methylpyrrolidone. A high degree of correlation was observed between in vitro permeation and in vivo percutaneous absorption parameters. The formulation of ketoprofen oleo-hydrogel that showed maximum percutaneous absorption was one that contained 3% ketoprofen, 1% carbomer, 10% *N*-methylpyrrolidone, 10% oils, 8% surfactant, and water adjusted to pH 4.6 using triethanolamine.

Deoxycholate hydrogels. Sodium deoxycholate (a low molecular weight drug carrier) was found to be a better alternative to high molecular weight polymers as a gelling agent (20). It also acts as a penetration enhancer for topically administered drug molecules. Sodium deoxycholate offers advantages such as low melt viscosity, potential biocompatibility and biodegradability, and absence of toxic impurities from synthesis residues such as organic solvents, catalysts, and initiators. When it comes in contact with excess buffer systems, it forms a viscous thixotropic gel with enhanced membrane permeability. Sodium deoxycholate gels leave no residue after application, and because of their thixotropic behavior, they are easy to apply on large skin areas. The surfactant action of sodium deoxycholate facilitates the solubilization of several drugs by forming mixed micelles. This system has been studied for its enhanced absorption of progesterone and prednisolone through hairless mouse

skin by producing structural changes in the stratum corneum.

Cream containing lipid nanoparticles. For enhanced penetration of topical drugs, occlusion of skin is the prime criterion. This requirement can be achieved easily by the incorporation of large quantities of fats and oils, especially liquid and semisolid paraffin. However, such formulations have the limitations of poor cosmetic properties characterized by a greasy feel and glossy appearance. The development of a water-in-oil cream containing small particles of solid paraffin was studied as an alternative (21). A high degree of occlusivity was obtained with smooth, flexible films prepared by drying aqueous dispersions of solid-paraffin particles with a mean size of ~200 nm (nanoparticle dispersion). However, this nanodispersion revealed a rough texture when applied. The development of a water-in-oil cream wherein the aqueous phase was divided into small droplets solved this problem. Nanoparticles were incorporated in the aqueous phase. Hence, the oil phase in which the water droplets were dispersed served as a lubricant for nanoparticles, thereby preventing a rough feel during application.

Solid lipid nanoparticles. Solid lipid nanoparticles of glyceryl behenate have been investigated as efficient carrier systems for topical use (22). They provide both burst and sustained drug release. Burst release improves the penetration of drug into the skin. Because of the presence of a solid matrix, sustained drug release is exhibited. This effect helps prolong drug delivery and minimizes the irritation potential of certain drug candidates. Solid lipid nanoparticles possess the advantages of better drug penetration because the small particle size of their drug-carrier system ensures close contact to the stratum corneum and increases the amount of encapsulated drug penetrating the skin. Solid lipid nanoparticles can be incorporated in topical dosage forms such as aqueous gels or creams in which stability is maintained. Because a film forms when the gel or cream is applied, occlusive properties on the skin also are obtained.

Localized and systemic drug delivery. **Liposomes as drug carriers.** Liposomes have shown great potential as novel drug carriers for dermal and transdermal systems. Liposomes are microscopic vesicles composed of membrane-like lipid layers surrounding an aqueous compartment (23). Phospholipids most often are used in the preparation of liposomes. Because of the amphiphilic nature of phospholipids, when they are dispersed in aqueous solutions they arrange in bilayers, with the fatty-acid tails (nonpolar) located in the membrane's interior and the polar heads pointing outward. One of the advantages of using liposomes as drug carriers is that both lipophilic as well as hydrophilic drugs can be incorporated within the lipid bilayers and aqueous compartment, respectively. They also serve as a reservoir for the prolonged release of drugs within various skin layers (23–28), thereby reducing the rapid elimination of drug into the blood or lymphatic circulation (29). This quality makes the liposome delivery system useful for treating various skin disorders. Because they are nongreasy and nontacky, liposomal preparations are cosmetically acceptable.

Various mechanisms have been proposed for the delivery of drugs through the skin using liposomes as a drug carrier. In these systems, liposomes carry a drug in dissolved form to the skin surface, and their lipid bilayer ruptures as a result of both their interaction with surface lipids and the action of bacterial flora that are present. Thus the encapsulated drug is freed, allowing it to penetrate (23). Small liposomes disintegrate quickly on the skin surface and may form a lipid layer that prevents the hydrophilic substance from reaching the skin (30). However, this action enhances the absorption of lipophilic substances. Liposomes may penetrate the stratum corneum and epidermis, either intact by means of intercellular channels or appendageal shunt routes (29,31–33) or as fragments of lipid bilayers (23,32,34), thus delivering the lipophilic drug entrapped in the lipid bilayer.

A study of the liposomal form of triamcinolone acetonide (TRMA) showed that because of the affinity of their cell surface (with a net negative charge at physiological pH), positive multilamellar vesicles (MLVs) had a significantly higher skin retention of the drug than did neutral small unilamellar vesicles (35). In addition, TRMA skin permeation was enhanced to a significantly higher degree by liposomes consisting of skin lipid composition (ceramide, cholesterol, palmitic acid, and cholesteryl sulfate) as compared with other liposomes. The enhanced permeation was attributed to the optimum solubility of these constituents with lipid layers of skin, which can facilitate the release and transport of TRMA from the formulation to deeper layers of skin.

A study that proposed the use of topical retinoids (e.g., vitamin A acid [isotretinoin]) in liposome form found that nonliposomal forms are susceptible to oxidation and show irritant action as a result of the large dose of drug in the formulation (23). Liposomal encapsulation allowed a large portion of the applied dose in enclosed form to be released in small amounts for prolonged periods, thus reducing local irritation. In addition, the enclosed drug was found to be less susceptible to the risk of deactivation by oxidation. Other drugs that yielded better results with liposomal formulations include methyl nicotinate (36), hydrocortisone, betamethasone valerate, econazole base and its nitrate, minoxidil, tetracaine, lidocaine, dibucaine, interferons, methotrexate, tobramycin, and silver sulphadiazine (23,29).

Solutions and aqueous gels are two of the most common forms in which liposomes are applied to skin. The choice of hydrophilic polymers that minimally influence the stability as well as the rate of penetration of liposome-entrapped substances into the skin is a crucial factor in their efficient functioning. Aqueous gels of carboxymethylcellulose were found not to influence the stability of the hydrogenated soya lecithin-cholesterol liposomes for several weeks and appeared to be convenient vehicles for liposome formulations as compared with xanthan gum (37).

Classical liposomal formulations for skin application present two significant limitations: they are inefficient in terms of deep penetration of skin layers, and they compromise the quality of the drug being delivered. Ethanol has been used widely as a skin permeation enhancer, but only in small concentrations. In addition, the amount of ethanol incorporated into the liposomal vesicles is limited. A novel system, ethosomes, is composed of phospholipids, ethanol, and water, with sufficiently high concentrations of ethanol (38). With these systems, increased mi-

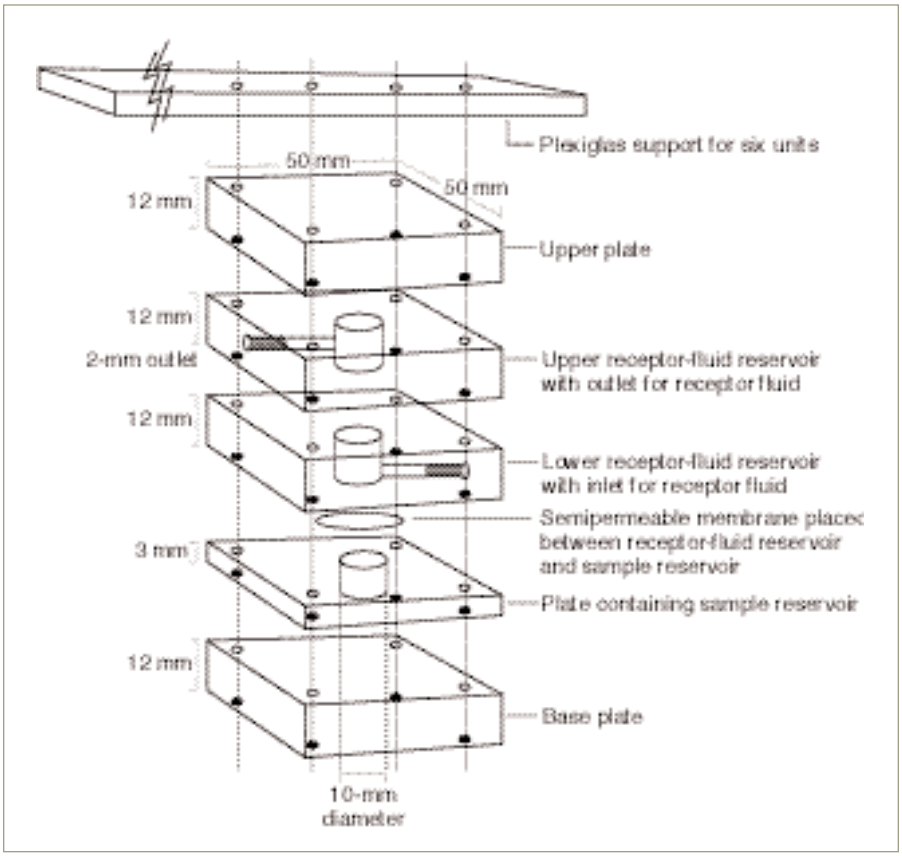

Figure 4: A Plexiglas flow-through cell (59). Reprinted courtesy of Elsevier Science.

noxidil penetration into deeper skin layers was observed as compared with that of ethanolic, hydroethanolic, or phospholipid ethanolic micellar solutions. An optimized formulation was obtained with 2% soy phosphatidyl choline, 30% ethanol, and water to 100% w/w. Electron microscopy was used to confirm the multilamellar-vesicle form of the formulation, and the bilayer configuration of the lipids was confirmed by ^{31}P nuclear magnetic resonance. Calorimetry and fluorescence measurements confirmed the flexibility of vesicular bilayers. Differential light-scattering measurements showed the ethosomes to be stable for at least two years at room temperature with respect to their average size and size distribution. A high entrapment capacity for molecules of various lyophilicities was observed with experiments involving fluorescent probes and ultracentrifugation. In conventional liposomes, both highly lipophilic molecules and amphiphilic molecules usually are confined to the bilayer and do not enter the aqueous core. In contrast, these molecules were found to fill the entire volume of the vesicle. Ethosomal systems have been characterized and tested clinically for dermal delivery of acyclovir (39).

Characterization of semisolid dosage forms

Characterization of semisolid dosage forms is another area that is gaining wide attention. Because of the complex nature of a semisolid network, several mechanisms interplay in their in vitro release, rheology, structural integrity, and so forth. New methods have been suggested for precise quantitative measurements of these parameters and correlation with clinical applications.

Rheological behavior. Gels as semisolid systems exhibit both liquid- and solid-like properties, called *viscoelastic behavior.* The relative contributions of elastic and viscous elements within a polymer solution are governed by the extent of intermolecular association–aggregation and chain entanglement, respectively. Characterization has been conducted using conventional rheometers and other devices to determine the spreadability, pourability, and processability of gel formulations. Modification of rheological behavior using various additives is another research-intensive area of study. A rheological study with hydroxypropyl cellulose gels reported an increase in apparent viscosity and decrease in non-Newtonian index with an increase in polymer concentration and molecular weight (40).

Observations about the consistency of hydroxyethyl cellulose (HEC), carboxymethyl cellulose, and hydroxypropyl methylcellulose gels showed that an increase in cosolvent (ethanol, propylene glycol, or glycerol) content produced an increase in gel consistency as high as the maximum, after which a further increase reduced the consistency or, in some cases, completely destroyed the gel (41). This behavior was attributed to the swelling of polymers in the cosolvents, leading to an increase in consistency. When the proportion of cosolvent was increased, the hydration of polymers was reduced, resulting in loss of structure.

Carbopol (Noveon, Inc., Cleveland, OH) forms a low-viscosity acidic solution in water that transforms into gel as the solution pH is increased. The effect of HEC used as a viscosity-enhancing polymer in Carbopol gel was studied (42). It was found that a network is formed between Carbopol and HEC during the process of neutralization and swelling of adjacent chains of Carbopol.

A study of gels of Carbomer-940 (Acofarma, Tarrasa, Spain) with tretinoin (43) and α-tocopherol (44,45) as drugs and ascorbic acid as an antioxidant showed the change in rheological behavior of the formulation during storage. The pH of the formulation was adjusted to ~5.4, considering the stability of ascorbic acid and Carbomer as well as the nonirritability of the formulation to human skin. When stored, the gel decreased in pH as the result of oxidation of ascorbic acid to dehydroascorbic acid, a process that also decreased the apparent viscosity. The change resulted from the coiling of polymer molecules at a lower pH, which increased the spreading area with time.

Few reports exist about the combination of polymers and their synergistic behavior. Xanthan and locust bean gums do not gel individually but form thermoreversible elastic gel in

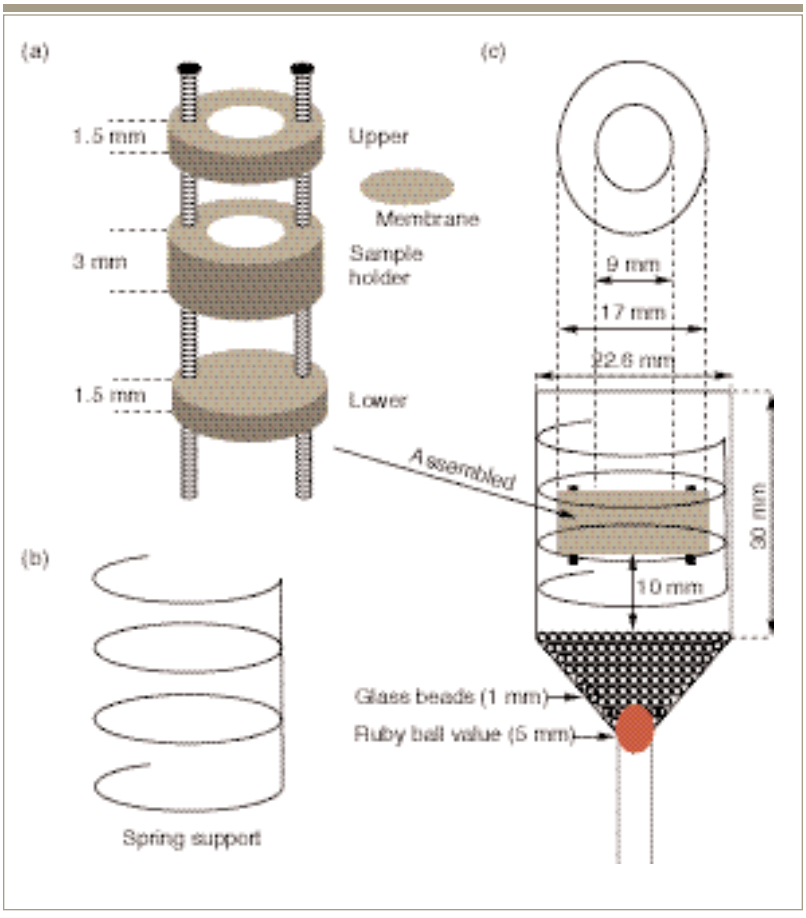

Figure 5: Insertion cell in a compendial flow-through cell: (a) insertion cell; (b) spring support used during turbulent-flow studies; (c) insertion cell inside compendial flow-through cell (60). Reprinted courtesy of Elsevier Science.

combination, exhibiting greater synergy at a 1:1 ratio (46). Xanthan gum existed in equilibrium between its two conformational states. Its helix-to-coil transition at a temperature range of 50–70 °C suggested that the disordered form of xanthan gum might be necessary for interaction with locust bean gum.

Gel-strength measurement. Gels have gained wide acceptance as semisolid dosage forms. It has been postulated that the strength rather than the viscosity of a gel layer plays a major role in determining the amount of drug release from hydrophilic matrices. Recent advances have occurred in the development of an optimal apparatus to characterize gel strength. One proposed apparatus consists of a sample holder placed on an electronic microbalance connected to a computer (47). A probe is lowered into the sample by means of a motor equipped with a speed transformer, and the force required to penetrate the gel is measured. The increase in force with time is a function of the mechanical resistance of the sample to the penetration of the probe. Because the lowering speed is known, the displacement covered by the probe as a function of time is calculated and used to compute the gel-strength parameter or mechanical resistance of the gel system.

In vitro release study. The release of an API from semisolid dosage forms is an important quality control tool. The drug released from a semisolid dosage form in which the drug is completely dissolved is described by the Higuchi diffusion equation in which Q is the amount of drug released into the receptor phase per unit area of exposure (mg/cm^2),

$$Q = 2C_0\sqrt{\frac{Dt}{\pi}}$$

C_0 is the initial drug concentration in the dosage form (mg/mL), D is the apparent diffusion coefficient of the drug (cm^2/s), t is time after application (s), and π is a constant (48). To date, no single device has been universally accepted for measuring in vitro drug release from semisolid dosage forms. Several reviews have cited the important considerations to be made when designing such devices (49,50). Various approaches, described in the literature, include custom-designed assemblies (51–53), Bronaugh diffusion cells (54,55), Franz diffusion cells (51), and modified Franz diffusion cells (56–58). The current trend is toward the development of systems with automated operations, better instrument controls, and minimal instrument-related variables.

Plexiglas flow-through cells. Plexiglas cells have been developed for studies of in vitro drug release from semisolid dosage forms (see Figure 4) (59). The system consists of a base plate supporting a plate containing a sample reservoir. A receptor-fluid reservoir is placed above it, and a semipermeable membrane is supported between the receptor-fluid reservoir and sample reservoir. The receptor-fluid reservoir is divided into two equal sections, one carrying the inlet and the other carrying the outlet for the receptor fluid. A solid Plexiglas block seals the top of the receptor-fluid reservoir. The entire cell is immersed in a constant-temperature water bath. The system is automated and computer controlled by connecting it to a pump for the receptor fluid, a medium splitter, and a fraction collector. This instrument is especially useful for measuring the effect of variables such as membrane type, flow rate of a receptor fluid, and temperature upon release rates.

Insertion cell. An insertion cell, whose dimensions permit the cell to be used with the compendial flow-through cell, has been devised (see Figure 5) (60). It is easier to use and does not require the removal of air bubbles from the membrane–liquid interface, a common problem with the use of Franz-diffusion cells. The upper section of the insertion cell consists of an oblong Plexiglas block with a 9-mm circle cut out of it. The middle section consists of a matching oblong Plexiglas block with a similar 9-mm circle cut out of it, which acts as the sample holder. The lower component is a solid Plexiglas block. All three sections are screwed together. A membrane is placed between the upper section and the sample-holder section. A stainless steel spring supports the insertion cell (for the turbulent-flow mode), and a layer of glass beads in the conical section of the flow-through cell supports the insertion cell (for the laminar-flow mode). The insertion cell is positioned 10 mm from the

conical section of the flow-through cell when it is used with the spring support. The entire assembly is automated in the same way as for the Plexiglas flow-through cell. To study the effect of the flow of receptor fluid on drug release, it is recommended that the insertion cell be used in a downward orientation.

Modified USP Type II dissolution apparatus. A USP Type II dissolution apparatus was modified for studying the in vitro release of phenol from ointment (61). It comprised a 200-mL vessel, 2.5 × 1.5 cm paddle, and an Enhancer diffusion cell (VanKel, Cary, NC) composed entirely of PTFE. The cell contained an adjustable-capacity sample reservoir, a washer for controlling the exposure of the surface area, and an open screw-on cap to secure the washer and membrane over the sample reservoir. The water bath was maintained at 37 °C. Filled cells were placed in the bottom of the vessels, and the paddles were lowered to 1 cm above the sample surface. Fifty milliliters of high-performance liquid chromatography–grade filtered water, degassed and prewarmed to 37 °C, was used as the dissolution medium. The system was found to yield reproducible results with good reliability in the data generated.

FDA guidance

FDA has established guidelines for semisolid dosage forms. These guidelines cover various aspects such as in vivo bioavailability, bioequivalence, in vitro release, scale-up and postapproval changes, and skin irritation and skin sensitization tests of generic transdermal drug products (62). FDA guidance serves as the primary reference for the development of dosage forms so as to facilitate their regulatory approval (63).

Future prospects

Increasing attention has been focused on achieving systemic delivery of drugs by means of dermatological application of semisolid dosage forms. This method provides great opportunities for future research about skin-barrier function and how to calculate correct dosages and determine dosage forms. Much more inclination has been shown toward the study of gel systems as compared with the study of ointments because of the former's better performance and aesthetic appeal. Controlled release of an incorporated drug by means of semisolid dosage forms as well as the development of instruments and methods for characterization of these dosage forms also continue to be the focus of recent interest and development. Thus, because semisolid dosage forms provide the most suitable systems for topical drug delivery, this area of study has marked potential for advancement.

Conclusion

Semisolid dosage forms have been the subject of extensive research in the past few years. Attempts have been made to improve the performance of these systems, be it the therapeutic efficacy of the incorporated drug or the cosmetic acceptability of the formulation. Various drug-carrier systems have been proposed that result not only in stable formulations but also in a favorable capacity for desired drug release. Greater emphasis has been placed on achieving comparable drug release with new drug-carrier systems, eliminating the cosmetically unfavorable qualities of the conventional semisolid dosage forms. Significant attention has been placed on the exploitation of semisolid dosage forms for systemic delivery of a topically applied drug on the skin. Incorporation of drug-in-emulsion droplets of submicron size has eliminated the need for a drug's physicochemical properties to be responsible for successful drug permeation. New systems have been proposed that function on the principle of occlusivity but are devoid of the drawbacks of conventional ointments. Liposomes have been introduced as suitable drug carriers for topical use, although with variable results.

Major efforts are being made to study characteristics such as the rheological behavior of dosage forms and the effect of various excipients on the rheology of formulation as well as the need for establishing in vitro release profiles of dosage forms. Various instruments have been proposed for this purpose and have generated reproducible and reliable results. Great opportunities for the development of semisolid dosage forms exist because of the diverse class of drugs, with unique characteristics, that are proposed for topical delivery.

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