A novel foam vehicle for delivery of topical corticosteroids

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Skin, particularly the uppermost layer—the stratum corneum—presents a formidable, largely impassable barrier to the entry of most compounds. Recently, a novel thermolabile, low-residue foam vehicle, VersaFoam (Connetics Corp, Palo Alto, Calif), has emerged that offers a number of clinical and cosmetic advantages for the delivery of therapeutic agents through the skin. Two corticosteroids—mid-potency betamethasone valerate and ultra-high-potency clobetasol propionate—are now available in this formulation, and other products are in development to deliver clindamycin and ketoconazole in the foam vehicle. A series of in vitro studies have demonstrated that the new foam has the ability to deliver the active drug at an increased rate compared with other vehicles. These findings suggest that the new foam utilizes a nontraditional "rapid-permeation" pathway for the delivery of drugs. It is likely that components within the foam (probably the alcohols) act as penetration enhancers, and reversibly alter the barrier properties of the outer stratum corneum, thus driving the delivered drug across the skin membrane via the intracellular route. This is in contrast to traditional topical delivery vehicles, which must first rely on hydration of the intercellular spaces in the stratum corneum to achieve drug delivery. The latter mechanism reflects a hydration-dependent process, which may result in comparatively slower drug permeation. (J Am Acad Dermatol 2005;53:S26-38.)

PRINCIPLES OF TOPICAL DRUG USE

To be effective, topically applied agents, such as corticosteroids, must gain entry to the skin and pass from one layer of tissue to the next.* Most topical drugs cannot achieve this if administered alone, but only if part of a formulation, that is, as a solute in a vehicle or solvent that carries the active agent or at least enhances its delivery. In this setting, penetration refers to the entry of the solvent (vehicle) and solute (active agent) into a particular skin layer, and permeation describes the penetration of a compound from one skin layer to another functionally and structurally different skin layer.[1] Absorption refers to the situation in which the topically applied drug is taken up by the blood vessels within the skin to enter the systemic circulation. When dealing with topical drugs for skin conditions, clinicians wish to minimize absorption so as to keep the drug restricted to the diseased area; in fact, this is often a reason for giving the drug topically as opposed to systemically. Topical administration also offers the advantage of avoiding potential side effects associated with systemic exposure.

Abbreviations used:

BMV:	betamethasone valerate
CP:	clobetasol propionate
HPLC:	high-performance liquid chromatography
PEG:	polyethylene glycol
TCI:	topical calcineurin inhibitor

However, skin, particularly the uppermost layer—the stratum corneum—presents a formidable, largely impassable barrier to the entry of most compounds. All 3 processes—penetration, permeation, and absorption—therefore are affected by (1) the structure of the skin, (2) the physiochemical characteristics of the penetrant, (3) the physiochemical characteristics

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*To enhance the understanding of the concepts discussed herein, a glossary of terminology is presented at the end of the article, as certain terms may convey different meanings in other contexts.

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of the vehicle in which the drug penetrant is carried, and (4) the applied dose and other issues related to the dosing regimen. Recently, a novel thermolabile, low-residue foam vehicle, VersaFoam (Connetics Corp, Palo Alto, Calif), has been developed that offers a number of clinical and cosmetic advantages for the delivery of therapeutic agents, including the potential to bypass this barrier function. Two corticosteroids—mid-potency betamethasone valerate (BMV) and ultra-high-potency clobetasol propionate (CP)—are now available in this formulation, and other products are now in development to deliver clindamycin and ketoconazole in the foam vehicle. A series of in vitro studies have elucidated the impact of this novel vehicle on the distribution and permeation of the two corticosteroids in skin structure. To better understand the implications of these data, a brief review of skin structures and the mechanisms of skin barrier function and permeation may prove helpful.

SKIN STRUCTURE AND FUNCTION

Skin, the largest organ of the body, is a complex biologic structure, the functions of which are to protect the body, maintain homeostasis, and sense the external environment.[2] It serves as a barrier against chemicals, microbes, allergens, fungi, and radiation.

Skin is typically divided into 3 layers: the epidermis, dermis, and hypodermis.[3] The epidermis, the top layer of skin, is a continuously renewing, stratified, squamous epithelium that keratinizes and gives rise to derivative structures or appendages, such as pilosebaceous units, nails, and sweat glands. It is composed predominantly of keratinocytes—cells that produce keratins (sulfur-containing proteins) and various lipids while differentiating from live to dead, fully keratinized cells, or corneocytes. An important function of the epidermis is the generation of the heterogeneous, 10- to 20-μm thick, outermost protective layer, the stratum corneum, which plays a crucial role in the permeation of most compounds into the body. The stratum corneum consists of the nonliving, nonnucleated, fully keratinized epithelial corneocytes about to be lost by desquamation. As keratinocytes, these cells originate in the stratum basale preprogrammed for self-destruction and undergo many morphologic changes in their 21-day progression through the various layers of the epidermis to the stratum corneum.[2] The remaining 5% of the cells of the epidermis include Langerhans cells, melanocytes, and Merkel cells. A basement membrane joins the innermost portion of the epidermis to the underlying dermis and allows cells, nutrients, and other substances to move back and forth between the two skin layers.[3]

Thicker than the epidermis, the dermis is an integrated system of fibrous, filamentous, and amorphous connective tissue that contains nerve and vascular networks, as well as epidermally derived appendages.[3] Its major cell type is the fibroblast, which synthesizes the various fibers making up the acellular portion of the dermis and the soluble mediators that are involved in interactions between the epidermis and dermis. Other dermis cell types include neurons and various cells involved in defense, such as mast cells, mononuclear phagocytes, T lymphocytes, and dendritic cells.

The third major layer of skin, the hypodermis, is the deepest layer of the skin. It acts as a heat insulator, shock absorber, and energy storage region; anchors the skin to underlying muscle; and molds body contours.[2,3] The region's primary cell type is mesenchymally derived adipocytes. These cells are organized into lobules separated by septa of fibrous connective tissue that are richly networked with nerves, vessels, and lymphatics.[3] Fibroblast and macrophages are also present.[2]

STRATUM CORNEUM AND DRUG DELIVERY

The field of cutaneous drug delivery has centered on the stratum corneum, as this layer offers the major resistance to drug penetration and permeation.[4] The structure of the stratum corneum is thought to be analogous to a brick wall—with the corneocytes forming the bricks and the extracellular lipid, organized into lamellar lipid bilayers to form continuous lipid phases, as the mortar.[2,5] Impenetrability of the stratum corneum appears to stem from the largely insoluble nature of the corneocytes to most diffusing solutes, a state produced by keratinization,[6] which is characterized by extensive cross-linking of both the cell envelope and intracellular proteins. However, the lipid lamellae, composed of ceramides, cholesterol, and free fatty acids, likely also play a role.[4,7]

The transport that does occur across the stratum corneum is largely passive diffusion and depends on the physiochemical properties of the permeating agent.[4] Two routes exist for this diffusion across the skin: transappendageal and epidermal (Fig 1).[8] In the transappendageal route, hair follicles, sebaceous glands, and sweat glands represent sites of discontinuities in the integrity of the skin barrier, potentially permitting permeants to bypass the low diffusivity of the stratum corneum.[9] However, the contribution of this pathway remains controversial; these appendages cover only approximately 0.1% of the total skin surface area and, therefore, many investigators have thought their contribution insignificant.[4,8] On the other hand, the transappendageal route may be

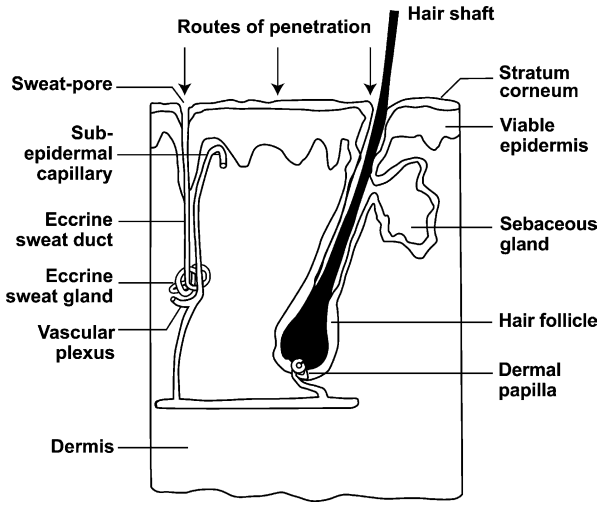

Fig 1. Possible macro routes for drug penetration across human skin via intact stratum corneum or hair follicles or sweat glands. (Adapted from Williams AC, Barry BW. Crit Rev Ther Drug Carrier Syst 1992;9:305-53; with permission from Begell House, Inc.)

important for ions and for large polar molecules that slowly permeate through the stratum corneum. The choice of vehicle or solvents to carry the penetrant may affect its ability to utilize transfollicular penetration.

The epidermal route offers two potential micropathways through the stratum corneum: transcellular (or intracellular) and intercellular (Fig 2).[8] Polar or hydrophilic compounds may move through the transcellular route, while lipophilic penetrants travel along the rather tortuous intercellular route. This latter pathway is probably the principal means of entry for and the major barrier to most drug permeation.[8] Some data suggest extremely polar solutes also utilize the intercellular route.[10]

The hydrophobic barrier of the stratum corneum, with its intercalating mix of proteinaceous dead corneocytes and lipids, places special demands on compounds intended for use as topical drugs.[11]

TOPICAL DRUG ADMINISTRATION AND CORTICOSTEROID DRUG FORMULATIONS

Vehicles

Topical drug products or formulations typically consist of the active ingredient(s) plus one or more relatively inert, nonmedical substances, or excipients that serve a variety of purposes. Together these other substances can be considered the vehicle, which must allow adequate release of the active compound and be nonallergenic, nonirritating, and cosmetically acceptable. In the case of topical corticosteroids, the type of delivery vehicle or formulation of excipients can markedly affect the penetrant properties and absorption of the active agent, and thereby affect drug potency or effectiveness.[12]

Vehicles for topical corticosteroids traditionally have included ointments, creams, lotions, gels, aerosol sprays, and powders. However, distinguishing between some of these vehicles can be problematic (eg, lotion vs cream, gel vs cream/lotion, and ointment vs cream)[13]; vehicles that traditionally have been perceived as belonging to different categories are often structurally similar. For example, ointments are semisolid preparations that spread easily and are often protective, hydrating, and lubricating.[14] Their bases can be hydrocarbons; absorption or hydrophilic substances (allowing for the absorption of water-soluble drugs), such as lanolin or cholesterol; emulsions of water in oil (<24% water); emulsions of oil in water (>31% water); and water soluble, which contain various polyethylene glycols (PEGs). However, the water-in-oil and oil-in-water emulsion bases are called creams by convention. Gels, which are lattices of organic macromolecules and are made from water-soluble bases by formulating water, propylene glycol, or PEGs with a cellulose derivative or Carbopol (Noveon, Inc, Cleveland, Ohio), are also ointments. Solutions are composed of two or more solutes dissolved into a liquid vehicle that may be aqueous, hydroalcoholic, or nonaqueous to homogenous clarity. A lotion consists of a finely divided, insoluble drug that is dispersed in a liquid. Aerosols are formulations of drugs in solution within propellants that are typically blends of nonpolar hydrocarbons. Foam falls into this category.

Recently, the Food and Drug Administration proposed new definitions that include the appearance and feel of a vehicle as well as a decision tree to pinpoint the category into which a particular formulation falls.[13] For example, a vehicle will be considered a lotion if it is pourable with viscosity less than 30,000 cp (at 5 rpm and 25°C) and a greater than 50% loss upon drying and an ointment if upon drying it loses less than 20% of content and possesses greater than 50% hydrocarbon or PEG content. Such clarifications may resolve some of the controversy.

Certain body areas lend themselves better to one vehicle type than another.[15] For example, clinicians traditionally prefer ointments for glabrous areas, such as the palms and soles, or on skin with short or sparse hair, because of the difficulty in washing off the preparation. Creams are frequently applied to infected and exudative psoriatic plaques as well as flexural and genital areas. Lotions, gels, and, obviously, shampoos are used in the treatment of scalp psoriasis.

Once the formulation—the corticosteroid in its vehicle—is applied to the skin, it does not remain

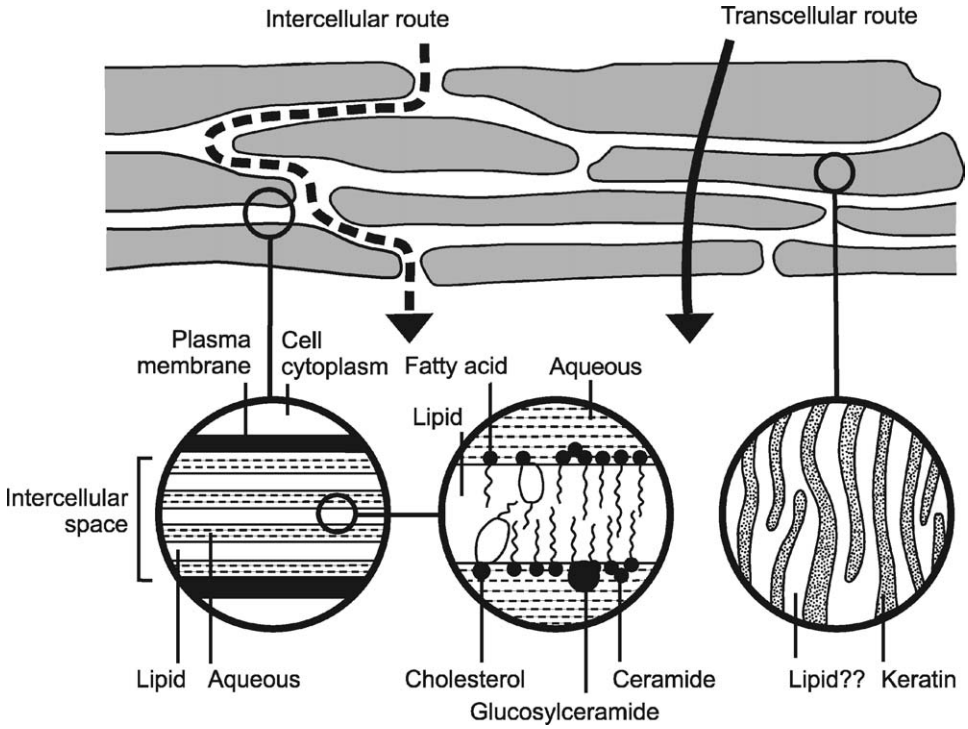

Fig 2. Potential micropathways through brick and mortar model of the stratum corneum. (Reprinted from Williams AC, Barry BW. Crit Rev Ther Drug Carrier Syst 1992;9:305-53; with permission from Begell House, Inc.)

homogenous.[9] Volatile ingredients of the vehicle, such as alcohol, will be lost to evaporation while lipid or polar compounds may undergo changes in composition during interactions with skin-surface lipids. This may result in a heightened concentration or supersaturated "solution" of the corticosteroid on the skin surface or in the upper layers of the stratum corneum.[4,16] There, the vasoconstrictive effects of the corticosteroid can cause it to be maintained in place for extended periods. This phenomenon, called the reservoir effect, means that the stratum corneum can act as a depot for the agent.

The new foam offers several benefits to both the clinician and the patient. Its unique properties warrant a separate discussion from the other delivery formulations previously mentioned.

Thermolabile, triphasic foam: A new vehicle for delivery of topical corticosteroids

The new foam exists as a liquid pressurized in an aluminum can with a hydrocarbon propellant (propane/butane), which upon valve actuation forms a foam lattice. This matrix is thermolabile; although stable at room temperature, it breaks down rapidly and melts at about approximately 32°C (or 90°F, close to body temperature). At that point, the volatile constituents (alcohol), evaporate, and within 20 to 30 seconds, little or no residue remains on the skin. The new foam vehicle consists of 3 phases—oil, water, and organic solvent—making it the first triphasic topical delivery system on the market. More specifically, the foam's constituents include ethanol, purified water, cetyl and stearyl alcohol, polysorbate 60, citric acid, and potassium citrate, with no fragrances or formaldehyde or nonformaldehyde preservatives. Cetyl alcohol is used as an emulsifier and emollient in many cosmetic and pharmaceutical products; allergic reactions to it are rare. Stearyl alcohol is a lubricant and foam control agent in many cosmetics, pharmaceuticals, and other products; it, too, rarely causes allergic reactions.

As previously stated, two corticosteroids—mid-potency BMV and ultra-high-potency CP—are now available in this vehicle. Several unpublished in vitro studies, described in this article, have been conducted using these two formulations to better understand the impact of the new foam on drug delivery and penetration and permeation through the stratum corneum.

Preclinical studies of VersaFoam

Most of the following studies used skin from live human donors that was harvested at the time of elective surgery, defatted manually with a scalpel, and sectioned with a dermatome to a thickness of 0.25 mm, producing split-thickness skin, which

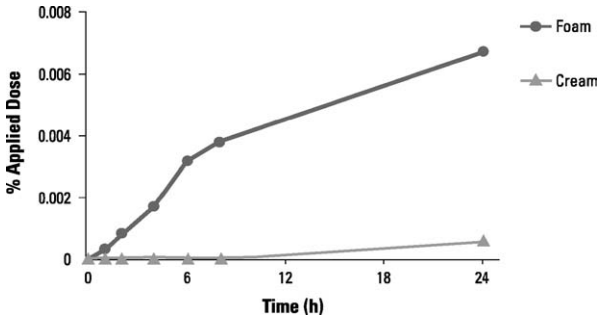

Fig 3. Cumulative amount of ketoconazole in the receptor fluid after penetrating through Silastic membrane (study A).

included both the epidermis and superficial papillary dermis layers. The skin samples were then stored in vapor-impermeable plastic bags at −70°C for up to 1 month and thawed in a room-temperature water bath on the same day of the experiment. For each experiment, all skin samples used were derived from a single donor and were cut into multiple smaller sections large enough to fit into diffusion cells. Formulations were applied to the skin sample with a positive displacement pipette and then spread over the entire surface with the pipette's Teflon (Dupont, Wilmington, Del) tip. For certain studies, Silastic (Dow Corning Corporation, Midland, Mich) membrane was used in place of skin. These studies examined the impact of foam on delivery and permeation of the active agent through the stratum corneum. In addition, in vitro studies have investigated the effect on delivery, permeation, and chemical stability when the two foam formulations are combined with other commonly used topical agents.

Permeation/penetration studies

Study A—Mechanisms of enhanced skin penetration. This study investigated mechanisms underlying enhanced skin penetration with foam through a Silastic membrane, although it utilized the antifungal ketoconazole, rather than a corticosteroid. Silastic membrane, rather than skin sections, was used to model the effect of the vehicle on percutaneous absorption and understand physiochemical relationships without introducing some of the complexities that occur within the stratum corneum.[17]

Penetration of 2% ketoconazole in foam and cream through 1.05-mm thick Silastic membranes was measured using a static Franz cell.[18] A target dose of 5 to 10 μL/0.64 cm^2 of all formulations was applied, and receptor fluid was sampled for ketoconazole content at 1, 2, 4, 6, 8, and 24 hours. Results showed increased penetration of ketoconazole from the foam formulation as measured by flux compared with cream (Fig 3). Total absorption of ketoconazole through the Silastic membranes was 11-fold higher from the foam than the cream formulations.

Study B—Skin permeation profile of clindamycin foam and gel formulations. In this study, penetration and distribution of clindamycin in foam and gel vehicles in split skin samples were compared. Permeation (ie, through the stratum corneum, epidermis, and dermis) was measured through split-thickness (~0.25 mm) human skin using flow-through diffusion cells. Receptor fluid was collected at 4-hour intervals for 24 hours, and the amount of clindamycin was measured. At 24 hours after dosing, following the last receptor solution sample collection, the skin surface was washed, wiped, and tape-stripped twice consecutively. The epidermis was then carefully peeled off the dermis. The drug was extracted from the surface washing materials, epidermis, and dermis by using acetonitrile. Quantification of drug content was performed by high-performance liquid chromatography (HPLC) mass spectrometry.

Fig 4 demonstrates that clindamycin foam had a higher rate of delivery of active drug into the skin than clindamycin gel. The difference was apparent soon after application and continued over the 24-hour experiment. At 24 hours (data not shown), HPLC showed comparable amounts of drug (expressed as a percentage of applied dose) in the epidermis for both vehicles and slightly more drug in the dermis for the gel compared with the foam. The main action of delivery occurred early, with the foam providing a higher rate of delivery than the gel. This translates into a rapid increase in concentration of the drug into the skin, which then is released gradually, resulting in a prolonged higher rate of delivery by the foam.

Study C—Impact of vehicle on CP skin permeation and drug distribution in vitro. In this study, drug permeation through split-thickness human skin was measured using flow-through diffusion cells (PermeGear, Bethlehem, Pa).[19] To assure the integrity of each skin section, its permeability to tritiated water was determined before the application of test products. All formulations were radiolabeled before application to the skin samples. Five drug formulations (CP foam, cream, emollient cream, lotion, and solution) then were applied individually to the skin samples, and receptor fluid was sampled for CP content at 4-hour intervals for 24 hours. At 24 hours after dosing, after the last receptor solution sample collection, the skin surface was washed, wiped, and tape-stripped twice consecutively. The epidermis was then carefully peeled off the dermis. The drug was extracted from the surface washing materials, epidermis, and dermis by using

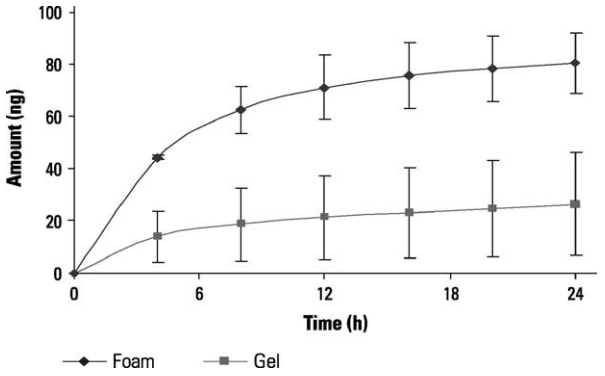

Fig 4. A greater accumulation of clindamycin was found in receptor fluid after penetrating through skin membrane in the 24 hours after application when delivered in a foam compared with a gel vehicle (study B).

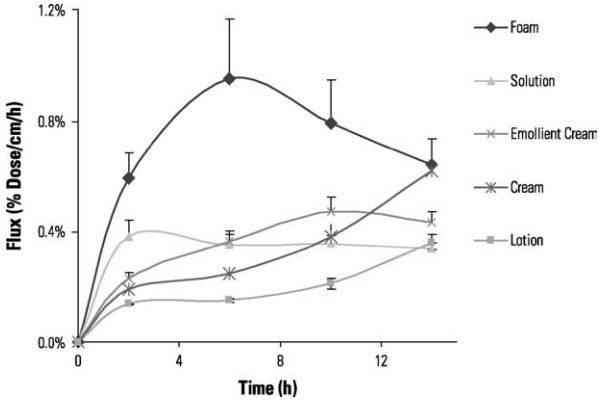

Fig 5. Cumulative amount of CP in the receptor is shown after topical application of CP in 5 different vehicles through 14 hours (study C).

acetonitrile. Quantification of drug content was performed by liquid scintillation.

The results (Fig 5) demonstrate that the foam formulation resulted in a faster initial permeation of CP compared with the other vehicles. In the first 14 hours after application, foam delivered a similar amount of drug (measured by flux and represented by the area under the curve) compared with the emollient cream and a greater amount of drug compared with the solution, cream, and lotion.

Results showed that the foam vehicle delivered more CP than the other formulations (Fig 6 and Table I). The distribution profile results demonstrated that, compared with other commercially available CP vehicles, foam delivers CP more efficiently.

Study D—Vehicle impact on permeation capability in various anatomic regions. Because earlier work[20] demonstrated a marked variation in drug permeability at different anatomic sites, reflecting differences in the thickness of the stratum corneum in various anatomic regions, this in vitro

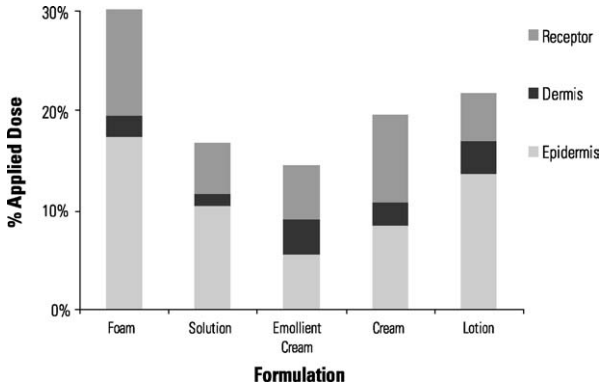

Fig 6. Skin distribution profile of CP at 24 hours after application of different formulations (study C).

Table I. Percentage of applied drug accumulated in collection fluid at 12 hours (study C)

Vehicle	Mean (standard error)
Foam	5.9% (1.1%)
Solution	2.8% (0.3%)
Emollient cream	2.7% (0.3%)
Cream	2.1% (0.2%)
Lotion	1.3% (0.1%)

study examined permeation of CP in foam, cream, and emollient cream applied to different anatomic regions. Skin samples from the elbow, thigh, scalp, abdomen, back, palm, and sole were prepared from several human donors cut with a dermatome to a thickness of 0.5 mm. Samples from each donor were kept separate. Receptor fluid was collected at 4-hour intervals for 24 hours.

The permeation profile of CP foam (Fig 7, *A*) indicates that the CP foam achieved a consistently faster onset of delivery compared with both cream and emollient cream. The cumulative amount of drug at the 8-hour time point after application, shown by the difference in drug content collected in the receptor fluid, was more pronounced for foam in the elbow, thigh, scalp, abdomen, and back compared with both creams. The amount delivered to the palm and sole was comparable for all 3 vehicles—not surprising, as the stratum corneum in these regions is much thicker and exerts greater resistance to penetration.[14] Similar results were observed when penetration was compared between foam and ointment (Fig 7, *B*). Together, these findings show that foam vehicle needs the least time to overcome anatomic region variations that can be correlated to the thickness of stratum corneum, whereas cream and ointment take a longer time for the onset of delivery.

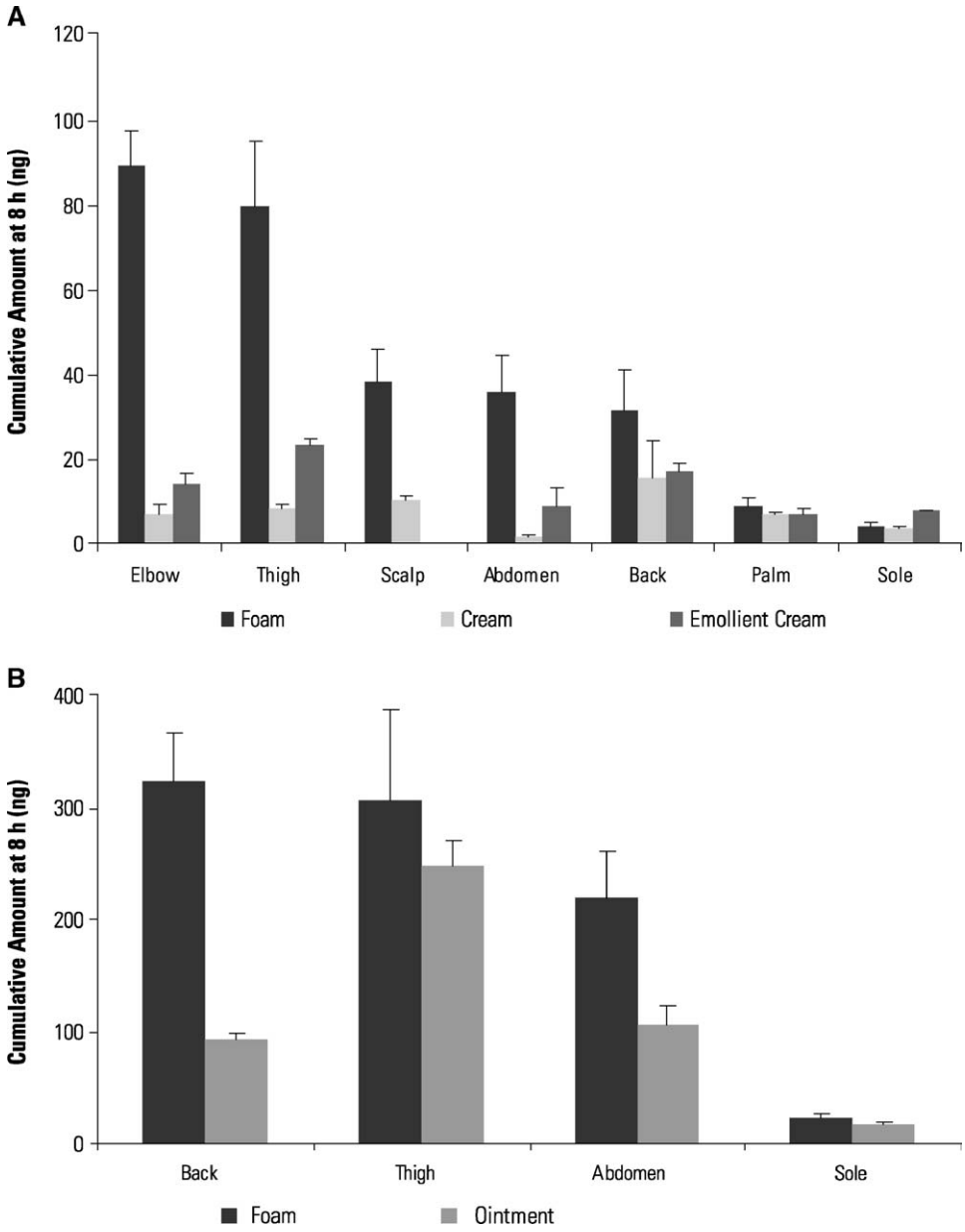

Fig 7. Cumulative amounts of CP in receptor fluid at 8 hours after applied to skin membrane samples (study D). Foam is compared with cream (**A**) and ointment (**B**).

Compatibility studies

Study E—Calcipotriene stability in the presence of CP or BMV foam. In this study, the stability of calcipotriene in the presence of foam was investigated using the human cadaver skin model. Split-thickness (~0.25 mm) skin was divided into multiple sections and mounted on 0.8-cm^2 Franz cells maintained at 37°C. The epidermal surface was left open to ambient laboratory conditions, and the dermal surface was bathed with isotonic saline. It was then dosed first with 5 μL of CP foam (5 mg) or BMV foam (5 mg) and, after 2 to 3 minutes, with 5 μL of calcipotriene solution. For comparison, separate skin sections were dosed with calcipotriene solution only. Four hours after dosing, the skin surface of all sections was washed 3 times with isopropyl alcohol, and the combined washes were analyzed for calcipotriene content by HPLC. Results showed that more than 64% of the applied calcipotriene was recovered from the surface wash of the sections dosed with calcipotriene alone as well as the sections dosed with both calcipotriene and one of the foam agents (Fig 8). No reduction in calcipotriene recovery was found with previous application of foam. These findings

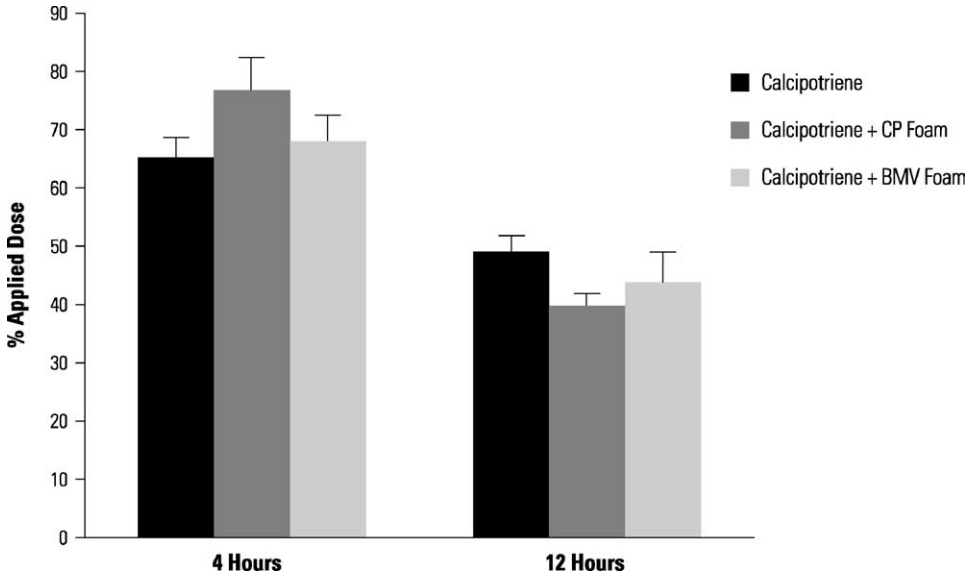

Fig 8. Calcipotriene recovery from skin surface when applied in combination with corticosteroid foams (study E).

indicate that application of the corticosteroid foam, either BMV or CP, before application of calcipotriene solution had no effect on calcipotriene stability at the surface of the skin 4 hours after dosing.

Study F—Co-application of BMV in various vehicles and pimecrolimus. The topical calcineurin inhibitors (TCIs) pimecrolimus and tacrolimus are becoming increasingly common therapies for various dermatoses. Combining topical corticosteroids with TCIs could potentially accelerate the onset of action, enhance permeation through thicker skin, and reduce the amount of each medication applied because of the potential additive or synergistic effects of topical steroids and TCIs. This study investigated the feasibility of coapplication of BMV in various vehicles with pimecrolimus.

Pimecrolimus cream 1% was applied to 3 replicate skin samples from 3 different donors, followed 5 minutes later by application of BMV 0.12%, in foam, ointment, or cream vehicle. BMV and pimecrolimus were also applied individually to serve as controls. Receptor fluid was collected at 4-hour intervals; 24 hours after application, the skin was washed and split into epidermis and dermis to measure drug content within these layers. Drug content in samples was measured by HPLC. Results showed that pimecrolimus and BMV content was stable over a 24-hour period when applied in combination (Fig 9; stability for BMV shown only). Interestingly, the BMV foam, when coapplied with pimecrolimus, delivered more BMV compared with BMV foam alone and compared with any other BMV formulation, whether applied with pimecrolimus or alone (Fig 10, *A*). An increased amount of pimecrolimus was delivered when coapplied with BMV foam (Fig. 10, *B*) than with the other BMV formulations, and BMV ointment seemed to have a negative impact on pimecrolimus delivery, as it is unlikely that a 1% delivered dose at 24 hours would be desired. Although the amount of delivered pimecrolimus was increased when coapplied with BMV foam, this relatively modest increase in skin concentration would most likely not be sufficient to lead to a significant increase in the rate of systemic absorption or to an increase in adverse event rates to the level seen with systemic administration of pimecrolimus.

Study G—Effect of coapplication of BMV in various vehicles with tacrolimus. In this study, BMV 0.12% (foam, cream, or ointment) and tacrolimus ointment 0.1% were applied sequentially at 5-minute intervals to 3 replicate skin samples from at least 3 different donors. In addition, tacrolimus was applied and followed 5 minutes later by application of BMV foam (ie, the order of application was reversed). All products were also applied alone to serve as controls. Again, receptor fluid was collected at 4-hour intervals for 24 hours, and drug content in samples was quantified by HPLC. Fig 11 shows that coapplication of BMV foam and tacrolimus ointment on the same skin site resulted in enhanced permeation of BMV (Fig 11, *A*) and tacrolimus (Fig 11, *B*) compared with the individual application or coapplication of BMV ointment or cream with tacrolimus ointment. When tacrolimus was applied first, the

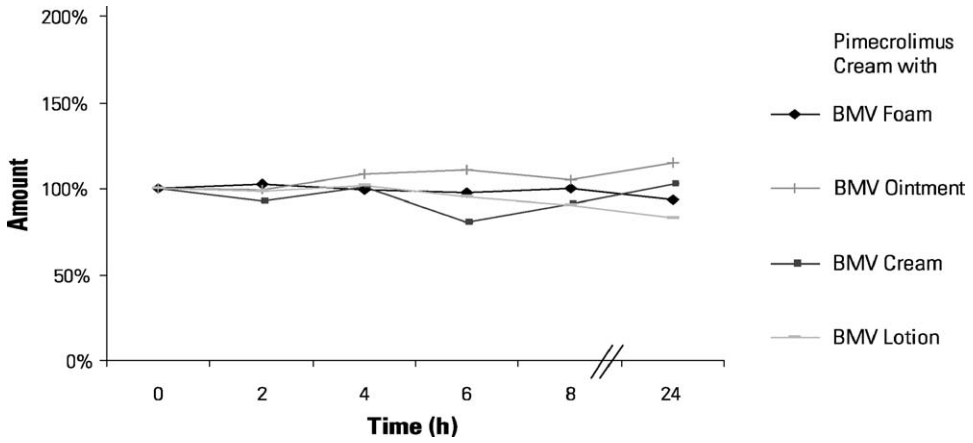

Fig 9. Stability of BMV in the presence of pimecrolimus cream when incubated for 24 hours at 37°C (study F).

cumulative amount of BMV was slightly elevated compared with application of BMV foam alone (Fig 11, *C*). In addition, the cumulative amount of tacrolimus was elevated compared with BMV foam alone or if the order of application was reversed (ie, BMV foam then tacrolimus). In all cases, the increased permeation was not sufficiently dramatic to predict that significant change would occur in the systemic safety profile of either BMV or tacrolimus after topical application.

DISCUSSION

The studies presented herein demonstrated that the new foam has the ability to deliver a greater amount of the active drug at an increased rate compared with other vehicles. This was true whether entry occurred into a synthetic lipophilic barrier (Silastic membrane) or into split-thickness skin samples (from live human donors). These findings also suggest that the new foam utilizes a nontraditional "rapid-permeation" pathway for the delivery of drugs. It is likely that components within the foam (probably the alcohols) act as penetration enhancers[8] and reversibly alter the barrier properties of the outer stratum corneum, thereby driving the delivered drug across the skin membrane via the intracellular route. This is in contrast to traditional topical delivery vehicles, which must first rely on hydration of the intercellular spaces in the stratum corneum to effect drug delivery. The latter mechanism reflects a hydration-dependent process, which may result in comparatively slower drug permeation.

Researchers have speculated that the physical changes that a foam vehicle such as this new foam undergoes after release from the container has important implications for the rate of penetration and permeation of an agent through the stratum corneum.[12] It is well known that maximum drug transfer into the skin takes place when the drug is in a saturated solution at the vehicle-skin interface.[12,21] The evaporation of volatiles from the foam, which leaves behind little if any residue from the vehicle, may cause the active ingredient to concentrate at the interface, leading to the aforementioned saturation and then to supersaturation. This supersaturation, although generally a transient condition, results in a drug delivery rate exceeding that of a saturated solution that may occur with other vehicles, further contributing to the enhanced rate of delivery seen with the new foam. In addition, supersaturation may permit the formation of a drug reservoir within the stratum corneum.

In addition to enhanced penetration and permeation, the new foam may offer several other advantages for both clinicians and patients. Patients find foams less dense and therefore generally easier to apply to and spread on the skin surface.[12] This may have important clinical implications, especially if the diseased area is inflamed and overly sensitive to mechanical shearing forces. In addition, because the new foam leaves little or no residue after application, patients find the vehicle cosmetically attractive compared with the "greasy" sensation often experienced after the use of ointments. Patient responses to questionnaires on vehicle preference support this. In one survey of 20 patients with psoriasis who sampled different topical psoriasis medications, respondents indicated a significant preference for foam and solution vehicles over cream, gel, and ointment vehicles.[22] In a separate study of 241 patients with moderate to severe scalp psoriasis, patients indicated a significantly greater preference

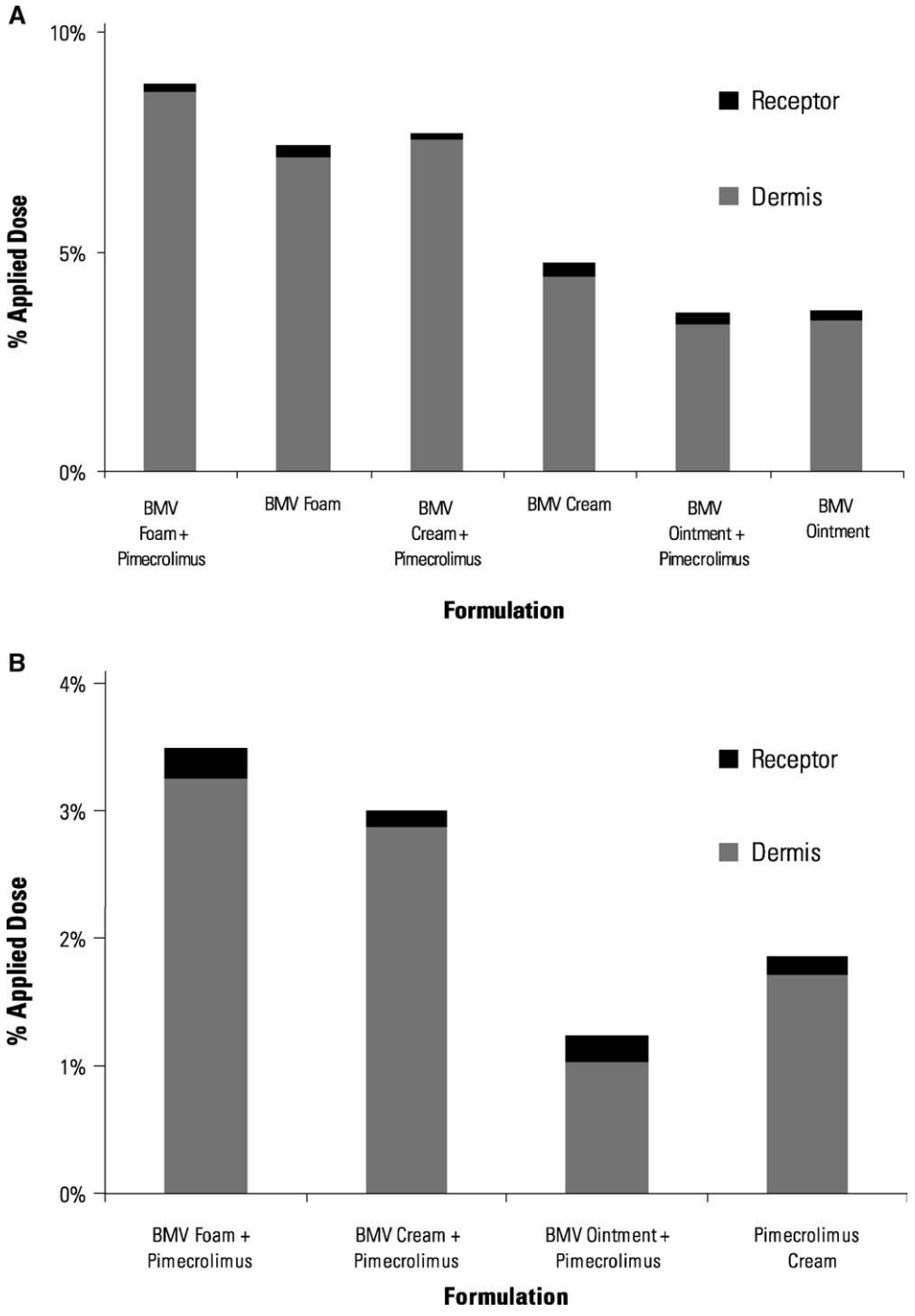

Fig 10. Skin permeation profiles when BMV formulations are coapplied with pimecrolimus (study F). Measurements at 24 hours show the amount of BMV (**A**) and pimecrolimus (**B**).

for BMV foam over other treatments, including corticosteroids in different vehicles and calcipotriene lotion.[23] Not only was the vehicle's use appreciated by patients with scalp psoriasis, but its efficacy and preference by patients were also demonstrated in a study of patients with non-scalp psoriasis.[24] In this trial, of 279 patients who were treated with CP foam, 95% rated the foam characteristics of no residue, stain-free, quick-drying, and fragrance-free as excellent or good and found the foam vehicle to be superior to other formulations in ease of use, ability to continue daily tasks, feeling free of medication, and ability to apply to any body area (see Stein, pages S39-49, for a more detailed discussion of these

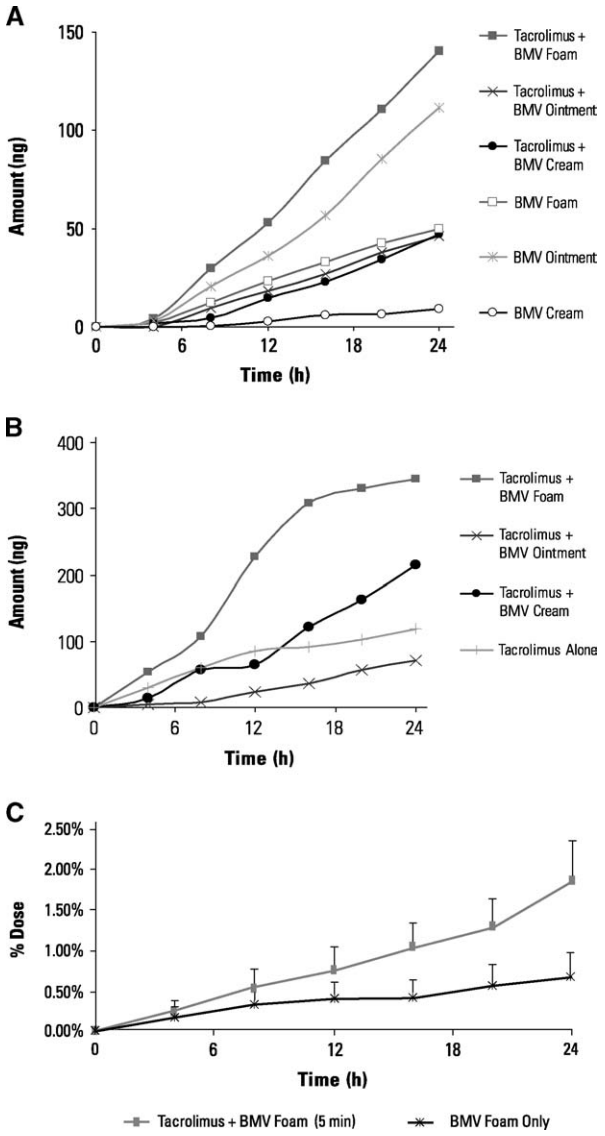

Fig 11. Skin permeation profiles when BMV formulations are coapplied with tacrolimus are shown (study G). **A**, Cumulative amount of BMV in the receptor fluid when BMV is applied first and tacrolimus second. **B**, Cumulative amount of tacrolimus in the receptor fluid when BMV is applied first and tacrolimus second. **C**, Cumulative amount of BMV in the receptor fluid when tacrolimus is applied first and BMV foam second.

studies). Such findings suggest that an increased preference for the formulations in the foam vehicle may lead to greater compliance with treatment and, ultimately, improved outcomes.

The new foam has not been associated with increases in the incidence of adverse events; any reported have been found to be generally low and transient in nature, which, in fact, may further contribute to greater compliance relative to other formulations. However, it should be noted that adverse events, particularly at the site of application, may be difficult to assess accurately because of the pre-existing injury inflicted by the disease itself. In studies of CP and BMV foam, the most common adverse events were burning, itching, and dryness at the site of application, which occurred, depending on the study, at rates similar to the active comparator (ie, corticosteroid in lotion) or to placebo, and possibly were the result of the alcohol normally present in foam and lotion formulations.[24-31] Furthermore, in at least one study, reports of application site reactions diminished in active treatment groups versus placebo groups; the investigators speculated that this may have been the result of the healing of damaged skin.[28] Finally, the new foam may offer some advantages in ethnic groups in which unique traits in skin or hair have been identified. For example, the hair of African Americans has a greater tendency to be brittle and dry, so the daily application of medicated shampoo or tar preparations and agents in vehicles such as ointments, which will require regular cleansing, are not options. Thus these persons may benefit from treatment with a foam corticosteroid that disappears on application.[32,33] Furthermore, the benefits offered by an active agent in a foam vehicle in scalp and nonscalp areas may outweigh any potential increase in initial discomfort experienced by darker pigmented persons; however, the literature is far from clear on differences in irritant reactions resulting from skin pigmentation and their implications for treatment.[33] Clinical studies of delivered by this new foam agents that examine differences among ethnic or racial groups may be warranted.

Another potential benefit of the new foam may be its use in combination therapy with other topical treatments. The current findings showing stability of calcipotriene solution (which can degrade in the presence of certain corticosteroids[34]), tacrolimus ointment, and pimecrolimus cream with either CP or BMV foam support this approach. In addition, results of the BMV foam/TCI combination studies (F and G) suggest that the coapplication of BMV foam and a TCI enhances skin penetration and permeation of each agent. Furthermore, the increased permeation of BMV when applied before tacrolimus implies that the TCI ointment acts by occluding the BMV in the foam. Treatment paradigms for psoriasis and, increasingly, atopic dermatitis frequently call for combination therapy, as it allows clinicians greater flexibility or more options in treatment.[35,36] The new foam offers physicians an attractive and versatile addition to their armamentarium and represents an advance in the science of topical drug delivery.

GLOSSARY

Absorption: Uptake of a substance into systemic circulation

Flux: The amount of solute passing through a unit area of membrane in a unit time.

Intercellular pathway: Pathway along lipid lamellae between corneocytes

Lipophilicity: The mass flux of a molecule at the interface of 2 immiscible solvents is governed by its lipophilicity. The more lipophilic a molecule, the more soluble in a lipophilic organic phase.

Passive diffusion: Process by which a diffusant will move down a concentration gradient (chemical potential difference) by random molecular motion to form a homogenous state

Penetration: Entry of a compound into a layer of skin

Percutaneous absorption: Penetration of substances into various layers of skin and then into systemic circulation

Permeation: Penetration of a compound from one skin layer to another functionally and structurally different skin layer

Rapid-permeation pathway: A nontraditional permeation pathway through the stratum corneum that is accomplished via reversible alteration of the stratum corneum's barrier properties

Reservoir: High concentration of a drug on the skin surface or upper layers of the stratum corneum; in the case of corticosteroids, their vasoconstrictive effects cause further retention.

Transcellular pathway: Pathway across the corneocytes

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