Clinical Implications of Delivery and Application Systems

Part 2 of 2

Leon H. Kircik, MD, Chair
Joseph B. Bikowski, MD
David E. Cohen, MPH, MD
Zoe Diana Draelos, MD
Adelaide Hebert, MD

June 2010

Photos courtesy of Joseph Bikowski, MD/DermEdOnline.com
Welcome to Vehicles Matter, Part II. This final edition of Vehicles Matter reviews the clinical implications of many of the technical aspects of vehicle formulation addressed in Part I (to view Part I online or to order a copy, visit VehiclesMatter.com).

The insights you’ll find in this supplement represent the combined knowledge of a panel of specialists with expertise in pediatrics, allergic contact dermatitis, clinical practice, and research. This panel convened for a lively and informative dialogue in November 2009.

Hopefully this innovative supplement series to Practical Dermatology will be a true resource for therapeutic decision-making and will enable you to support your prescribing decisions in discussions with patients, colleagues, and others involved in patient care.

— Leon H. Kircik, MD
Program Chair

Table of Contents

| Vehicles and Adherence | 3 |
| Gels                      | 5 |
| Sprays                    | 8 |
| Foams                     | 9 |
| Shampoos/Washes           | 11 |
| Medicated Pads            | 12 |
| Ointments                 | 12 |
| Creams                    | 13 |

Support for this educational initiative was provided by:

- Allergan, Inc.
- Coria Laboratories (A Division of Valeant Pharmaceuticals, NA)
- Ferndale Laboratories
- Galderma S.A.
- Intendis
- Obagi Medical Products, Inc.
- Ortho Dermatologics
- Triax Pharmaceuticals

Roundtable Panelists

- Leon H. Kircik, MD, Chair
  Clinical Associate Professor of Dermatology
  Mount Sinai Medical Center
  Indiana University School of Medicine Physicians Skin Care, PLLC
  DermResearch, PLLC
  Louisville, KY

- Joseph B. Bikowski, MD
  Clinical Assistant Professor of Dermatology
  Ohio State University
  Bikowski Skin Care Center
  Sewickley, PA

- Zoe Diana Draelos, MD
  Consulting Professor
  Department of Dermatology
  Duke University School of Medicine
  Durham, NC

- Adelaide Hebert, MD
  Professor of Dermatology and Pediatrics, Director, Division of Pulmonary, Critical Care and Allergy-Immunology Medicine
  University of Texas-Houston Medical School
  Houston, TX

- David E. Cohen, MPH, MD
  Vice Chairman for Clinical Affairs
  Director of Allergic, Occupational, and Environmental Dermatology
  New York University School of Medicine
  Department of Dermatology
  New York, NY

- Dennis P. West, PhD, FCCP, CIP
  Vincent W. Foglia Family Research Professor of Dermatology
  Professor in Dermatology, Pediatrics
  Feinberg School of Medicine
  Northwestern University
  Chicago, IL

The following conflict disclosures have been provided by panelists: Dr. Bikowski has served on the speaker’s bureau or advisory board or is a shareholder or consultant to Allergan, Coria, Galderma, Stiefel/GlaxoSmithKline, Intendis, Medicis, Promius, Quinova, Ranbaxy, and Warner-Chilcott. • Dr. Cohen has served on the speaker’s bureau, as a consultant, or on an advisory board for Abbott, Amgen-Wyeth, Stiefel/GlaxoSmithKline, Coria Laboratories, Galderma, Johnson & Johnson, Triax, Peplin, and Topica. • Dr. Draelos has served as a researcher for Allergan, Coria Laboratories, Galderma, Stiefel/GlaxoSmithKline, Intendis, Medicis, Obagi Medical Products, Inc., OrthoDermatologics, and Triax. • Dr. Kircik has served as a researcher, consultant, of speaker for Allergan, Coria, Dermik, Ferndale, Galderma, Stiefel/GlaxoSmithKline, Intendis, Medicis, Obagi Medical Products, Inc., OrthoDermatologics, and Triax. • Dr. West has relationships with Astellas, Novartis, Leo, Genentech, Celgene, Ortho, Stiefel/GlaxoSmithKline, and Sage Products.
Topical drug delivery is the most common method of dermatologic therapy, given its historic association with enhanced overall safety and minimal if any risk of systemic exposure and associated side effects. However, just as the field of topical drug formulation has evolved in recent years (see Vehicles Matter, Part I, available online at VehiclesMatter.com), yielding more tolerable and more effective treatments, so has the field of systemic drug development. In fact, the specialty of dermatology has been influenced over the past decade by the emergence of biologic therapies for psoriasis. These treatments are associated with a high level of efficacy and an overall favorable safety profile. Still, systemic therapies for psoriasis have not overtaken topical therapies, nor are they expected to. Only a small proportion of eligible patients are currently undergoing biologic therapy for psoriasis: 15 percent of patients with severe psoriasis and 11 percent of patients with moderate disease. Although biologic therapies offer notable efficacy, their onset of action may be slow, and access to treatment may be delayed by insurance pre-qualification processes. Therefore, many candidates for biologic therapy are concomitantly treated with topical agents.

Psoriasis is just one of a host of diseases that dermatologists diagnose and treat with great frequency. Although it may not in any sense be a prototypical dermatological disease, psoriasis is illustrative of the prominence of topical therapies in dermatology. Topical therapies continue to be a mainstay of patient management. Prescribers are challenged to select the proper topical treatment to meet the therapeutic needs of the patient and optimize therapeutic adherence. Selection of an appropriate vehicle and application system are key to meeting these clinical goals.

The Relationship of Vehicles to Adherence

No matter how well a formulation may perform in clinical trials, it is useless if patients do not apply it. Therefore, as noted in Part I of Vehicles Matter, cosmetic elegance is an important consideration in the evaluation of a formulation. Specifically, a patient-friendly formulation will be: non-irritating or minimally irritating; easy to dispense and apply; free of lingering odors, colored residues, or tackiness; non-interfering with clothing or other activities; fit the patient’s activities of daily living/lifestyle and be portable; and require minimal daily applications. In fact, studies show that patients’ preferences are affected by significant vehicle characteristics such as ease or difficulty of use, messiness, odors, and staining. A survey of more than 3,000 acne patients world-wide revealed that, among other factors, young age (under 15 years), occurrence of side effects, and lack of improvement as rated by a dermatologist were among primary reasons for non-adherence (See Sidebar: “Adherence or Compliance,” next page) with therapy.
Adherence or Compliance?

Although the terms "adherence" and "compliance" are often used interchangeably, they have distinct meanings. Compliance has a passive connotation and is used to signify that the patient has accepted the prescriber's treatment instructions. Some have argued that the term compliance can be associated with a degree of coercion.³

Adherence, by contrast, connotes a willing and active participation in the treatment regimen by the patient.¹ The adherent patient is dedicated to the long-term therapeutic goal and follows the medication and other associated recommendations of the physician. As such, dermatologists should strive to promote therapeutic adherence by patients who are partners in their own care.

Please note that the distinction between adherence and compliance has been somewhat vague historically; throughout this supplement, efforts are made to preserve the language of study authors with regard to assessments of compliance or adherence in trials and studies.

Table 1. Examples of Therapeutic Kits

<table>
<thead>
<tr>
<th>Kit Name</th>
<th>Contents</th>
<th>Marketed by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretin-X Kit</td>
<td>tretinoin cream; cleanser and moisturizer</td>
<td>Triax</td>
</tr>
<tr>
<td>Finacea Plus</td>
<td>azelaic acid gel, 15%; CeraVe moisturizer</td>
<td>Intendis</td>
</tr>
<tr>
<td>ClenziDerm</td>
<td>benzoyl peroxide 5% plus skincare</td>
<td>Obagi Medical Products</td>
</tr>
<tr>
<td>NuDerm</td>
<td>tretinoin plus skin care</td>
<td>Obagi Medical Products</td>
</tr>
</tbody>
</table>

Clinicians recognize that the dosage form (cream, gel, foam, etc.) as well as the application system can influence therapeutic adherence. The well-known case of SkinCap may be illustrative. SkinCap was an aerosol formulation sold over-the-counter for management of psoriasis. The marketer attributed the efficacy, reported anecdotally and in the literature⁴ of the formulation to zinc pyrithione. Subsequent investigation revealed that the spray contained clobetasol, which was not disclosed, and the product was removed from the market. Some patients had dramatic responses to SkinCap that were often characterized as better than those typically seen with then-available clobetasol formulations alone, leading some clinicians to speculate that zinc pyrithione may have had some synergistic effect with clobetasol. Study findings with regard to zinc pyrithione were negative.⁷ Many clinicians have now come to believe that the convenience of the aerosol spray enticed patients to use the product with regularity, accounting for the dramatic results seen.

Since the withdrawal of SkinCap, new corticosteroid dosage forms have come to market, including sprays and foams, and these have been endorsed by patients. For example, during studies of desonide foam for atopic dermatitis, investigators report that parents were pleased with the ease of application of the foam and the minimal time required for application.

Another recent advancement that has the potential to enhance compliance and tolerability is pump dispenser technology. In studies of the tretinoin microsphere 0.04% pump dispenser (Retin-A Micro Pump, Ortho-Dermtologics), 95 percent of patients were found to be compliant (defined as administering 75 to 100 percent of doses).⁸ Patients reported high levels of satisfaction with the tretinoin pump.⁹ A benefit of pump dispensers is controlled dosing of product so that patients do not apply too much or too little. It is anticipated that controlling the amount of topical tretinoin a patient applies may help to minimize rates of irritation associated with excessive application of the drug. Another prescription agent now available in a metered dose pump is clocortolone pivalate cream 0.1% (Cloderm, Coria Laboratories).

Finally, prescribers and the skin care recommendations that they make can play an integral role in optimizing skincare to enhance patient comfort and maximize efficacy. Data confirm that
cleansers and moisturizers can detrimentally or positively influence therapeutic outcomes depending on their composition. Properly selected moisturizers provide hydration and help preserve or promote skin barrier function. 10, 11

One study of subjects with atopic dermatitis (AD) found that those who used a topical corticosteroid in conjunction with a ceramide-rich moisturizer (CeraVe, Coria Laboratories) and used a mild cleanser (Dove bar) had more significant improvement in AD than those who used only the steroid and mild cleanser. 12

In the previously mentioned survey of adherence among acne patients, proper skin care was found to have a positive impact on adherence. 9 Optimizing skin care with a systematic approach to product selection and education is integral to successful overall patient management. Recognizing this fact, some drug developers and marketers have introduced therapeutic kits; a given drug formulation is dispensed by the pharmacy with optimized skincare products at no additional cost to the patient (Table 1). There is some evidence of improved clinical outcomes associated with the use of kits. In the case of ClenziDerm, a study found that the three-step system including salicylic acid wash 2%, salicylic acid toner 2%, and solubilized benzoyl peroxide (BPO) 5% used twice daily was at least as effective as clindamycin 1%/BPO 5% fixed combination plus control cleanser twice daily. 13 The three-step kit system was associated with improved patient compliance compared to other treatments. 13

Gels

Desonate gel (desonide 0.05%, Intendis) is an aqueous gel that does not contain alcohol or surfactants. 14 Non-solubilized desonide is suspended in the hydrogel. Upon application to the skin, water in the vehicle evaporates, leaving on the skin a micro-suspension of desonide and a small amount of propylene glycol (PG); PG then dissolves desonide and delivers it into the skin. Desonide hydrogel was studied in patients as young as three months of age in two phase III clinical trials that established its efficacy and good tolerability. 15, 16

Aczone gel (dapsone 5%, Allergan) is formulated with diethylene glycol monooethyl ether (DGME), which dissolves a fraction of the dapsone and facilitates the deposition of remaining undissolved dapsone in the pilosebaceous unit. 17 DGME helps topical dapsone to remain in the pilosebaceous unit and minimizes systemic exposure. In clinical trials, twice-daily topical application of dapsone as directed for the treatment of acne did not induce significant changes in hemoglobin or other hematologic indicators, even in G6PD-deficient patients. 18-21 Continuous use of dapsone 5% gel is not associated with an increase in plasma concentrations of the drug. 21

In clinical trials of patients with acne, topical dapsone gel treatment was well tolerated with similar reports of adverse events in the active and control groups (58.2 per-
cent and 58.6 percent, respectively). Most events were of mild to moderate intensity, resolved during treatment, and did not result in treatment discontinuation. In two randomized, controlled trials of topical dapsone gel, 44.2 percent (Trial A) and 36.9 percent (Trial B) of treated patients achieved treatment success, defined as Global Acne Severity Score of “none” or “minimal,” at week 12. This compares to success rates of 35.9 percent and 29.8 percent, respectively, for controls in those same trials. Combined analysis shows an overall success rate of 40.5 percent for aczone gel, compared to 32.8 per-

### Encapsulation Technology

**Microsponges.** Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Microsponge Delivery systems consist of macroporous beads, typically 10-25 microns in diameter, loaded with active agent. The polymeric sponge-like spherical particles can entrap a wide range of active ingredients; release of active ingredients is activated by a trigger, such as mechanical manipulation (rubbing), increased heat (body temperature), or vehicle solvents and/or perspiration. In addition to facilitating controlled release, entrapment of active drug in microsponges can preserve stability. Entrapped in microsponges, the non-photostable tretinoin molecule, for example, remains stable with UV, fluorescent, and incandescent light exposure.

The first application of microsponge technology in dermatology was for topical tretinoin, now available in the Retin-A Micro Pump 0.1% and 0.04% (Ortho Dermatologics). Microspheres are impregnated with tretinoin, which is suspended in the hydrogel vehicle. In a 12-week study of 544 patients treated with the 0.1% or 0.04% pump, tretinoin microsphere gel was found to be effective, well-tolerated, and associated with high compliance.

Recent data suggest that the micropump appears to facilitate the combined use of topical benzoyl peroxide 5% wash along with application of topical tretinoin gel microsphere 0.04% once-daily versus sequential therapy with the BPO wash each morning and topical tretinoin each evening. In a multicenter, randomized, investigator-blind, 12-week, Phase 4 trial comparing the regimens, there was a similar reduction in inflammatory and non-inflammatory lesions in the two treatment groups.

Benzoyl peroxide microsponges are also available. Due to the availability of OTC BPO formulations—many of which are high concentration and not optimized for tolerability, many patients present to the dermatologist having used topical BPO, often with significant irritation. The ability to counsel patients that microsponge formulations were specially formulated with the goal to minimize irritation may help the clinician persuade patients to adhere to therapy. NeoBenz Micro cream (benzoyl peroxide 3.5%, 5.5%, 8.5%, Intendis) utilizes microsponge delivery technology to encapsulate BPO in a cream vehicle, which has been shown to reduce the rate of release of benzoyl peroxide, potentially reducing drug-induced irritation, and appears to decrease skin oiliness.

The term microsphere is sometimes used interchangeably with the term microsponge, although the two are technically distinct. Although under investigation, microspheres have not yet been employed to deliver active agents in dermatology.

**Multi-vesicular Emulsions.** Multi-vesicular emulsions or MVEs are liposome-like concentric lipid shells that in the case of CeraVe (Coria Laboratories) release ceramides, cholesterol and fatty acids over time as they wear, break, or lyse. Due to the emulsion process by which they are formed, there is more variability in the size and shape of MVE vesicles than in traditional liposomes, although there is some variability in those, as well.

**Chemical Encapsulation.** An alternative mode of encapsulating an active agent is chemically. For example, MetroGel 1 (Metronidazole 1%, Galderma) features hydrosolubilizing agent (HSA), a cyclodextran ring in which the drug resides. Metronidazole has low solubility, however, HSA is readily dissolved in the aqueous gel vehicle, permitting an even dispersion of the highest available concentration of topical metronidazole. (Fig. 2, Next page)
Vehicles Matter

Treatment of acne with dapsone 5% gel resulted in a reduction in oiliness from 18.6 percent at baseline to 5.6 percent at week 12 and reduction in erythema from 14.8 percent at baseline to 6.2 percent at week 12.20

Another relatively new acne treatment gel, Atralin gel (tretinoin 0.05%, Coria Laboratories) was formulated in efforts to combat the well-known irritancy associated with topical tretinoin. Moisturizing agents, including soluble collagen, hyaluronic acid, and glycerin are incorporated into the gel, which is indicated for once-daily application. In randomized, controlled, clinical trials, tretinoin 0.05% gel was found to be only about 12 percent less effective than tretinoin gel microsphere 0.1%, but the incidence of skin-related adverse events at 31 percent was significantly lower for the 0.05% gel versus 52 percent for the 0.1% gel.22

Finacea (azelaic acid gel 15%, Intendis) has been shown effective and well-tolerated in the management of rosacea;23 a two-week trial showed that women with rosacea who applied the gel twice-daily had no evidence of barrier damage on TEWL or corneometry tests.24 Data show that the 15% gel provides an eight-fold increase in the delivery of azelaic acid compared to azelaic acid cream 20%.25 This enhanced delivery is likely a result of two factors. The cream formulation contains azelaic acid in suspension only; there is no solubilized active. The gel contains some solubilized active. Furthermore, milling processes have been refined so that drugs can be milled virtually down to nanoparticles. The smaller particle size of azelaic acid in the gel formulation creates a greater surface area and thus enhanced opportunity for penetration. These advancements in the size and uniformity of milled particles account for much of the improvement in formulations of particulate actives.

Epiduo (adapalene 0.1%/BPO 2.5% fixed combination gel, Galderma) is at least as well tolerated as BPO 2.5% gel alone or adapalene 0.1% gel alone in terms of cumulative irritancy.26 In a multicenter, randomized, double-blind, parallel-group, active- and vehicle-controlled study assessing the efficacy and safety of adapalene-BPO combination gel in comparison with adapalene alone, BPO alone, or vehicle, adapalene-BPO combination gel showed a significantly higher success rate and a greater percentage reduction in all acne lesion counts compared with the other treatment groups. The safety of adapalene-BPO combination gel was comparable with adapalene and BPO monotherapies and vehicle.27

Fig. 2. HSA-3 molecule: 92% water, Propylene glycol (bright green), Niacinamide (yellow), Betadex (orange) around 1% metronidazole.

A novel broad-spectrum antimicrobial gel formulation, Aloquin gel (iodoquinol 1.25%, aloe polysaccharides 1%; marketed by Ferndale Laboratories) features a patented aloe polysaccharide that is delivered via a water- and lipid-soluble biopeptide complex (Biopeptide Aloe Complex or BAC) consisting of Palmitoyl linked with amino acids Gly-Hys-Lis. The penetration enhancing effects of the biopeptide complex were demonstrated in studies using radiolabeled carnosine, an amino acid. At all time points from 0.5 to six hours, biopeptide/carnosine demonstrated significantly greater penetration into the stratum corneum and epidermis compared to carnosine alone. At three hours, peptide delivery achieved 12-times the penetration of carnosine to the stratum corneum and more than eight-times the penetration of carnosine to the epidermis compared to non-peptide delivery. The aqueous gel vehicle of Aloquin is suitable for application to numerous anatomic sites, including the axillae and face, hair-bearing areas, and larger surface areas.
Sprays

In the case of currently available spritz sprays, the dosage form (see Table: Topical Dosage Forms, below) is a solution provided in a unique application container: the spritz pump. Through simple physics, when the plunger is depressed volume displacement expels the solution out of the bottle through the nozzle as a mist. Spritz sprays contain no propellants.

An aerosol spray, by contrast, is not classified as a solution; Rather the dosage form falls into the “Other” category (See Table 2, Below). An aerosol may be used to deliver either solids or liquids in suspension. In most cases, the propellant(s) becomes incorporated into the material that is expelled from the container and, in fact, may actually help to solubilize the active drug. Upon application, the propellant evaporates, theoretically leaving on the skin a super-saturated solution that will drive the active drug into the skin.

This distinction between spritz sprays and aerosols is not to suggest that spray application is a simple matter of pouring any solution into a spray applicator system. Indeed, from the initial phases of product development, formulators must recognize that the product is intended for spray application and formulate it to maximize therapeutic benefit.

---

<table>
<thead>
<tr>
<th>Is it Pourable?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-liquid, Non-semi-solid</td>
<td>“Other”: Formulations that are not liquid or semisolid fall into this category, which includes aerosols, powders, etc.</td>
<td></td>
</tr>
<tr>
<td>Liquids</td>
<td>Solutions: Clear and homogeneous</td>
<td>&gt;50% water and other volatiles</td>
</tr>
<tr>
<td></td>
<td>Suspensions: Solids dispersed in liquids</td>
<td>Gel: Solution or colloidal dispersion stiffened with a gelling agent</td>
</tr>
<tr>
<td></td>
<td>Lotions: Emulsions</td>
<td>&lt;50% water and other volatiles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ointments: More than 50% of hydrocarbons, waxes or PEG and less than 20% water and volatiles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pastes: Contain 20-50% dispersed solids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creams: One or both does not apply:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• More than 50% of hydrocarbons, waxes or PEG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Less than 20% water and volatiles</td>
</tr>
</tbody>
</table>

Table 2. Topical Dosage Forms for Dermatological Applications

Clobex spray (Clobetasol propionate 0.05%, Galderma) is illustrative. This topical steroid preparation contains as excipients isopropyl myristate (IPM) more than 50 percent by volume and alcohol. IPM is an oily, nonvolatile solubilizing agent and penetration enhancer. Although isopropyl myristate produces a “greasy” feel on normal skin that some patients would otherwise not find cosmetically acceptable, that same lubricating effect may be beneficial for the formulation’s psoriasis indication. IPM is a lipid-based emollient that helps to reduce evaporation of moisture from the stratum corneum and helps hydrate the stratum corneum to facilitate percutaneous absorption of corticosteroid.

Clobex spray also has ethyl alcohol as a penetration enhancer that temporarily increases permeability of the epidermis to allow the corticosteroid to go through. It also has sodium laurel sulfate, which is an anionic surfactant that helps the formulation dissolve quickly. In a clinical trial of patients with moderate to severe plaque psoriasis, subjects using clobetasol spray had a median 64 percent reduction in affected body surface area (BSA), and 22 percent achieved complete clearance at two weeks. New to the market is a nozzle spray applicator for Clobex that is intended to help deposit clobetasol solution directly to treatment sites.

Foams

The original hydroethanolic foam formulations to reach the market represented the culmination of many years of research. In fact, studies on corticosteroid foam formulations date back to the 1970s, but foam formulations did not reach the market until 2000. Like aerosol sprays, aerosol foams fit the “Other” category of topical dosage forms.

Foam formulations tend to be user-friendly and elegant for use in treating scalp dermatoses. Compared to traditional clobetasol propionate solution, Olux (clobetasol propionate 0.05%, Stiefel/GlaxoSmithKline) was shown to provide enhanced absorption of clobetasol propionate in cadaver skin. Enhanced absorption may be attributable to the fact that the foam creates a super-saturated solution when applied to the skin. When the propellants and alcohols—constituting a significant proportion of the formulation—evaporate, the resulting solution left on the skin may have up to a 10-fold higher concentration of active drug compared to the initially dispensed foam. The tremendous resulting gradient creates a driving force that delivers the drug through the stratum corneum.

The rapid absorption of active drug from the foam vehicles is demonstrated through comparison of pharmacodynamic profiles of hydroethanolic foams compared to other vehicles. In trials comparing absorption of betamethasone valerate from Luxiq (betamethasone valerate 0.12%, Stiefel/GlaxoSmithKline) foam to betamethasone 0.1 lotion, foam provided nearly six-times the rate of absorption of betamethasone as the lotion. The peak rate of absorption for the lotion at 35 hours was similar to the rate of absorption for the foam at 2.5 hours. This rapid absorption may be of clinical benefit. In actual use, very little of any topically applied formulation would be expected to remain on the skin at four or six hours, thus reducing the total amount of drug actually delivered to the site of treatment. Foams appear to obviate those concerns.

The hydroethanolic foam was originally designed and proposed...
Vehicles Matter

for use on hair bearing areas, and engineered so as not to leave any residue on hairy areas; the non-volatile components left on the skin are quickly absorbed and do not crystallize.

Although patients rated their experience with hydroethanolic foams favorably in clinical trials, and the incidence of adverse events was low, these formulations were associated with potential application site stinging and burning.³⁹ To address these issues, triphasic emollient foams—consisting of oil, water, and organic solvent—were developed (VersaFoam EF).

As the name suggests, emollient foams contain petrolatum and long-chain fatty acids that lay on the skin to create physical barriers to transepidermal water loss. The foams are thermolabile. The alcohols maintain the structure of the foam at room temperature, but at about 88 or 90 degrees, the lattice collapses and the alcohol evaporates. The active drug is solubilized along with the emollient components in the residue of the vehicle. Evidence suggests that components of the formulation, likely alcohol, serve as penetration enhancers to facilitate rapid drug delivery across the skin membrane via the intracellular route.⁴⁰

Verdeso foam (desonide 0.05%, Stiefel/GlaxoSmithKline) has a similar emollient foam formulation that spreads easily and, as indicated in the package insert, is associated with minimal local application site burning and stinging.

The newest foam vehicle formulation to come to market, Extina (ketoconazole 2%, Stiefel/GlaxoSmithKline), was designed to facilitate treatment of seborrheic dermatitis, which frequently occurs in hair-bearing areas. In trials comparing ketoconazole 2% foam to vehicle foam, ketoconazole 2% cream, or cream vehicle, ketoconazole 2% foam provided a more rapid onset of action compared to active cream, as demonstrated by two-week pruritus and 2-grade+ improvement from baseline scores. With the exception of stinging, likely attributable to ethanol in the foam vehicle, ketoconazole foam had similar rates of other adverse events compared to ketoconazole cream or vehicle cream.⁴¹

Gender and Therapeutic Response Differences

Whereas patient age, skin type, or ethnicity may influence a prescriber’s selection of a particular formulation, gender is not often a consideration. However, there are cases of different responses to therapy based on sex. Consider the case of imiquimod cream 5% (Aldara, Graceway) for external genital warts. Application three times a week up to 16 weeks produced complete clearance in about two-thirds of women but only one-third of men. ⁴² The difference in response was attributed to the absorption of the drug on partially keratinized skin of the female genitalia versus keratinized skin of the male.

There are concerns, also, about adherence to a regimen of application three times a week for 16 weeks. Certainly dermatologists approach treatment of mucosa with caution, given the higher potential for drug absorption by minimally- or non-epithelialized skin.

The treatment of external genital warts has opened a new avenue for topical drug formulation: prescription botanicals. Sinecatechins, a defined green tea extract, is approved for treatment of external genital warts (Veregen 15%, PharmaDerm). In clinical trials, 54.9 percent of all treated patients achieved complete clearance following three-times-a-day application for up to 16 weeks, versus 35.4 percent of controls. However, sex-related differences in response were evident. The complete clearance rate among men was 47.3 percent, according to the prescribing information, versus 60.4 percent among women.
Although short-contact therapy seems counterintuitive, medicated shampoos and washes have been used in dermatology for many years. Traditional medicated shampoos and washes featured insoluble, particulate drugs—such as benzoyl peroxide, salicylic acid, or ketoconazole—in suspension. Upon application, particles deposit in the follicular osteum where at least some proportion remains after water rinsing.

As evidence of this depositing action, consider that when researchers compared the benefits of five-minute application/residence time of ketoconazole shampoo to no residence time, they noted some additional clinical benefit with the five-minute application. However, application with no residence time (lathered and immediately rinsed) produced a significant improvement in dandruff.\(^43\)

As Capex is mixed at the pharmacy, a failure to adequately blend the formulation can result in uneven distribution of drug with suboptimal clinical response.

Data demonstrate the efficacy of benzoyl peroxide and salicylic acid washes used as monotherapy to reduce acne lesions and \(P.\) acnes colonization.\(^44,45\) Ketoconazole shampoo has been shown effective for treatment of dandruff, seborrheic dermatitis, and tinea versicolor.\(^46,47\)

Newer technologies, which have been widely used in commercially available non-medicated body washes, permit the deposition of oil-soluble substances on the skin surface during the rinse phase, allowing the formulation of medicated washes and shampoos with non-particulate drugs.

Capex shampoo (fluocinolone acetonide 0.01%, Galderma; a predecessor of Clobex, discussed below), is a first generation medicated shampoo. As Capex is mixed at the pharmacy, a failure to adequately blend the formulation can result in uneven distribution of drug with suboptimal clinical response.

To address these and other concerns, a second-generation corticosteroid-shampoo has been developed. Clobex shampoo (Clobetasol propionate 0.5%, Galderma) is designed for prolonged contact therapy. It is meant to be applied to the scalp and left in place for 15 minutes, during which time penetration of the active drug is achieved. Once a limited amount of water is added to the formulation in the shower, a low concentration of water and a high concentration of shampoo (wash phase) allows cleansing to occur. Addition of more water (high concentration of water and low concentration of shampoo or rinse phase) washes the amphoteric chain linked to all the dirt down the drain, and leaves behind some residue.

Given the thinner skin of the face and in particular the potential for corticosteroids to influence intraocular pressure, application of a corticosteroid to the head and face area, and especially application of a product that may wash down the face, is associated with theoretical concerns of increased incidence of corticosteroid side effects.

A recently published study showed that when patients used Clobex shampoo twice a week for six months, there was no greater incidence of skin atrophy, telangiectasia, or hypothalamic-pituitary-adrenal (HPA) axis suppression in the treated group compared with vehicle controls.\(^48\) This study did not examine possible effects of the corticosteroid shampoo on intraocular pressure.

Depositing body wash technology exists in the OTC sphere and has theoretical applications in dermatology. While a corticosteroid-containing wash would probably not perform as well as a traditional leave-on formulation for most anatomic sites, it might optimize adherence for certain patients.
Vehicles Matter

Medicated Pads

Like sprays, pads represent an application system for use with a solution dosage form. Pads have been developed for topical acne medications and are associated with potentially increased convenience and adherence. Patients seem to favor pads, as one study indicated that non-prescription pads are among the most popular OTC products used by patients.

As an application system, single-use pads may have a practical benefit in a specific setting. Single use pads in foil pouches may be preferred by individuals who travel, as they bypass any restrictions on liquids or creams in carry-on baggage. Pads may be a suitable option for adolescents with dual residences, as a box can be opened with half the contents left at one parent’s home and half at the other.

The manufacture of prescription benzoyl peroxide pads highlights another potential challenge for drug formulators. Benzoyl peroxide (BPO) is a relatively unstable molecule that can be rapidly degraded by exposure to light, oxygen, and certain solvents. This medication is itself an oxidant and is potentially corrosive. As such, benzoyl peroxide disintegrates certain pads comprised of glued fibers, presenting a formulation challenge for developers.

Ointments

From the time that topical calcipotriol (Dovonex, Leo Pharma) reached the market, clinicians identified the potential synergy between it and topical corticosteroids: calcipotriol had none of the side-effects associated with steroids and was shown to thicken the skin, while topical corticosteroids suppress inflammation associated with the vitamin D3 analog. The combined use of high-potency topical corticosteroids along with topical calcipotriol has been shown to provide benefits over either agent alone, however, data also show that calcipotriol and certain corticosteroids, including betamethasone dipropionate, degrade when mixed.

Betamethasone propionate is stable at low pH, while calcipotriene is stable at a higher pH.

Taclonex (calcipotriene 0.05%, betamethasone dipropionate 0.064%, Leo Pharma) represents a breakthrough in formulation developments, as it combines two incompatible ingredients in one ointment formulation by dissolving calcipotriene in an anhydrous vehicle and suspending micronized betamethasone dipropionate within that vehicle. The active components remain stable with equal distribution of each throughout the product.

The bioavailability of betamethasone dipropionate within the fixed combination was established by an analysis of vasoconstrictor scores for the fixed combination compared to betamethasone dipropionate ointment. Scores showed equivalent bioactivity. Clinical trial results show that the fixed combination was superior to either agent alone with an adverse event profile similar to betamethasone alone and superior to cal-
In addition to the challenges of formulating a fixed combination in order to preserve the bioavailability and potency of the individual components (they do not degrade each other) while ensuring tolerability and cosmetic acceptability, the developer must then show that the final product is significantly more effective than vehicle alone and that combination is at least as effective as each of the constituents alone. This sets a high bar for demonstrated efficacy, and the costs associated with these multi-arm studies can be significant.

Nonetheless, fixed combinations have represented a substantial area of recent development and may continue to do so. Given the paucity of new chemicals coming to market, combining old chemicals to make new moieties is an attractive option for formulators.

Fixed combinations may present significant clinical benefits, notably decreased costs (since there is one product, patients have one copay) increased compliance (and potentially adherence). This holds true as long as the combination matches accepted clinical usage patterns for the constituent parts and is cosmetically acceptable to patients.

**Fixed Combinations**

In addition to the challenges of formulating a fixed combination in order to preserve the bioavailability and potency of the individual components (they do not degrade each other) while ensuring tolerability and cosmetic acceptability, the developer must then show that the final product is significantly more effective than vehicle alone and that combination is at least as effective as each of the constituents alone. This sets a high bar for demonstrated efficacy, and the costs associated with these multi-arm studies can be significant.

Nonetheless, fixed combinations have represented a substantial area of recent development and may continue to do so. Given the paucity of new chemicals coming to market, combining old chemicals to make new moieties is an attractive option for formulators.

Fixed combinations may present significant clinical benefits, notably decreased costs (since there is one product, patients have one copay) increased compliance (and potentially adherence). This holds true as long as the combination matches accepted clinical usage patterns for the constituent parts and is cosmetically acceptable to patients.

**Creams**

Locioid Lipocream (hydrocortisone butyrate 0.1%, Triax) features a type of vehicle that is somewhat common in the realm of OTC cosmetics but is rare among prescription medications. Sometimes termed a reverse emulsion, the Lipocream contains 70 percent lipids dispersed in 30 percent water, providing a more ointment-like texture, because the external phase that comes in contact with the skin initially is oily.

This oily component provides a warm skin feel as opposed to the cooling skin feel that results from the evaporation of water in traditional water-in-oil emulsions.

While Locoid functions much like an ointment clinically, patients seem more compliant with the cream. Studies have documented patient preference for the lipocream compared to traditional cream vehicles or ointments. The cream is indicated for use in pediatric patients as young as three months of age; it was not associated with any adrenal suppression or local side effects following use for up to four weeks in pediatric patients age five to 12 years.

Eletone cream (Ferndale; See Sidebar: “Device Clearance,” next page) and Pramosone E (Hydrocortisone Acetate 2.5% and Pramoxine HCl 1%, Ferndale) both also feature a 70 percent lipid/30 water emulsion, termed Hydrolipid Technology. Pramoxine is a well-known topical intervention for itch, which in combination with topical hydrocortisone may be helpful in the management of pruritic, steroid-responsive dermatoses like atopic dermatitis and mild psorias.

Renova (tretinoin 0.02%, OrthoDermatologics) also features an oil-in-water emulsion vehicle. In an initial 24-week, controlled trial of daily application of tretinoin 0.05% cream, 78 percent of subjects had an improvement in Investigators Global Assessment, compared to 55 percent of controls. In the open-label extension, the emulsion was shown to be well tolerated with 91
FDA’s Center for Devices and Radiological Health (CDRH) oversees the marketing of devices in the US. A device is any instrument, apparatus, machine, implant, in vitro reagent, or component part or accessory that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. Like a drug, a device is intended to affect the structure or any function of the body, but it does not achieve any of its primary intended purposes through chemical action within or on the body and need not be metabolized to achieve any of its primary intended purposes.

A sponsor may pursue 510(k) clearance for Class I or II devices (those associated with minimal or moderate risk of harm or unintended use) when the applicant device is “substantially equivalent” to a currently marketed device—it must have the same intended use as the predicate and either the same technological characteristics as the predicate or, if technological characteristics differ, information submitted does not raise new questions of safety and effectiveness and demonstrates that the device is at least as safe and effective as the predicate. The applicant provides data relating to 1) safety or biocompatibility and 2) stability. FDA may request clinical information that is not strictly required within a 510(k), such as human trials data.

Devices receive clearance for specific applications, and they may be marketed only for those approved uses. However, companies that wish to receive approval for a new use may submit a new 501(k) requesting clearance.

### Topical Agents with 510(k) Clearance in Dermatology

<table>
<thead>
<tr>
<th>Device</th>
<th>Marketed by</th>
<th>Intended Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mimyx</td>
<td>Stiefel/GSK</td>
<td>To manage and relieve the burning and itching experienced with various types of dermatoses, including atopic dermatitis, allergic contact dermatitis and radiation dermatitis.</td>
</tr>
<tr>
<td>Atopiclair</td>
<td>Graceway</td>
<td>To manage and relieve the itching, burning and pain experienced with various types of dermatoses, including atopic dermatitis and allergic contact dermatitis.</td>
</tr>
<tr>
<td>EpiCeram</td>
<td>Promius</td>
<td>To treat dry skin conditions and to manage and relieve the burning and itching associated with various types of dermatoses, including atopic dermatitis, irritant contact dermatitis, and radiation dermatitis.</td>
</tr>
<tr>
<td>Eletone Cream</td>
<td>Ferndale</td>
<td>To manage and relieve the burning and itching experienced with various types of dermatoses, including atopic dermatitis, allergic contact dermatitis and radiation dermatitis.</td>
</tr>
<tr>
<td>PromiSeb</td>
<td>Promius</td>
<td>To manage and relieve the signs and symptoms of seborrhea and seborrheic dermatitis such as itching, erythema, scaling and pain.</td>
</tr>
<tr>
<td>Biafine</td>
<td>OrthoDermatologics</td>
<td>For use in: Full Thickness Wounds, Pressure Sores, Dermal Ulcers including Lower Leg Ulcers, Superficial Wounds, 1st and 2nd Degree Burns, including Sunburns, Dermal Donor and Graft Site Management, Radiation Dermatitis, Minor Abrasions.</td>
</tr>
</tbody>
</table>