Use of Individual Components and Advances in Topical Formulation Technology: Focus on Corticosteroids

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Perceptions regarding the clinical impact of specific vehicles may warrant reconsideration based on improvements in vehicle technology. For example, although ointments used in the treatment of body psoriasis have been perceived as achieving the greatest efficacy because of enhanced cutaneous penetration of a given drug, the available literature indicates that newer formulations using optimized vehicles containing clobetasol propionate 0.05%, such as foam, lotion, and solution, produce efficacy comparable to ointment formulations.[1] Advances in formulation technology have developed methodologies that allow a drug to penetrate the skin more effectively, an illustrative example being hydroethanolic foam technology with both clobetasol propionate 0.05% and betamethasone valerate 0.12%.[2,3] Since ointments are often less popular with patients than vehicles that are more cosmetically elegant and easier to apply, the issue of patient adherence to treatment may affect the actual clinical results in real-world practice.[1,4]

This column discusses advances in topical vehicle technology and their potential impact on clinical outcomes and presents a more focused review of newer formulations of higher-potency topical corticosteroids. Some illustrative examples of advances in topical vehicle technology that appear to correlate with clinical benefit are outlined in Table 1.

A Closer Look: Recently Released Higher-Potency Topical Corticosteroids

As previously stated, the efficacy of clobetasol propionate 0.05% has been sustained using several vehicle formulations. Many of these formulations have been designed to improve cosmetic elegance, allow for ease of application, provide adaptability for application to specific body sites (eg, scalp and hair-bearing areas), and achieve a high level of patient satisfaction that should translate to greater compliance with continued use.

Over the past few years, several newer formulations of higher-potency topical corticosteroids have emerged, most of which are classified as super–high-potency (class I) agents. The formulation characteristics of several of these agents are individually reviewed in this article.

More recently, a combination formulation containing calcipotriene 0.005% and betamethasone dipropionate 0.064% (class II, high-potency topical corticosteroid) was approved by the Food and Drug Administration (FDA) for treating psoriasis vulgaris in adults. Table 2 outlines information related to some major vehicle components found in more recently approved higher-potency topical corticosteroids.

Fluocinonide 0.1% Cream

Fluocinonide 0.1% cream is a super–high-potency topical corticosteroid approved by the FDA for the treatment of corticosteroid-responsive dermatoses in adults.[11] This agent is designated as a super–high-potency topical corticosteroid based on vasoconstrictor assay results. The major vehicle component of fluocinonide 0.1% cream that appears to augment its reported potency is propylene glycol (71.4% wt/wt).[11,12]

Clobetasol Propionate 0.05% Lotion

Clobetasol propionate 0.05% lotion is a super–high-potency topical corticosteroid that has been approved by the FDA for treating the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults.[13] The super–high-potency classification of this product was confirmed by vasoconstrictor assay. Although lotion formulations of given corticosteroid compounds

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TABLE 1

Advances in Topical Vehicle Technology: Examples and Correlation With Clinical Outcomes

Formulation	Drug	Comments
Microsponge	Tretinoin[5]	Reduced skin irritation Greater stability in presence of light or benzoyl peroxide
Hydroethanolic foam	Clobetasol propionate[2]	Enhanced skin penetration Easily spread; no residue Cosmetic elegance Efficacy comparable to brand comparator Contains long-chain fatty alcohols to reduce drying effect on skin Fragrance- and preservative-free
	Betamethasone valerate[3] Clindamycin phosphate[6,7]	Same as hydroethanolic foam except efficacy superior to brand comparator
Multivesicular emulsion	Salicylic acid[8]	Cosmetic elegance Enhanced skin tolerability Stacking of multiple ingredients in concentric emulsion layers May stagger release of individual ingredients Vehicle may improve barrier integrity
Water-based gels	Metronidazole[9]	Use of HSA-3* technology containing 92% water plus betadex, niacinamide, and propylene glycol Betadex used to increase metronidazole solubility Moisturization; may improve barrier integrity Enhanced skin tolerability
	Azelaic acid[10]	Increased skin penetration of active drug despite lower concentration in gel (15%) vs cream (20%) No loss of epidermal-barrier integrity with gel

*HSA-3, hydrosolubilizing agents.

have characteristically been perceived to be less potent than other vehicles, this formulation is an exception to this common assumption. The predominant ingredient in clobetasol propionate 0.05% lotion that appears to augment the potency of this formulation is propylene glycol (48.0% wt/wt),[12,13] which is combined with other components crucial to producing a lotion vehicle, such as water (30.4%), mineral oil (20.1% wt/wt), polyoxyethylene glycol 300 isostearate (0.93% wt/wt), and hydroxypropyl methylcellulose (0.13% wt/wt).[12,13]

Clobetasol Propionate 0.05% Spray

Clobetasol propionate 0.05% spray has been approved by the FDA for treating moderate to severe plaque psoriasis.[14] The predominant components of this formulation are isopropyl myristate (51.6% wt/wt), an emulsifier,

TABLE 2

Major Components of Vehicles Used in More Recently Released Higher-Potency Topical Corticosteroids

Component	Comments
Propylene glycol[20,21]	Humectant (even at low concentrations); solvent; antimicrobial/preservative (>25% concentration); penetration enhancer Common component of topical corticosteroids found in 48 of 82 (58.5%) formulations Potential for allergic and irritant reactions appear to be concentration dependent; occasional cases occur In suspected cases of allergic contact dermatitis, if testing at 10% is negative, testing at a higher concentration would be suggested. North American Contact Dermatitis Group now tests at 30% Significant irritation uncommon with patch testing using 10%–30% concentration Important not to overinterpret testing results because of widespread use in industry, including medications, foods, and industrial products Suspect possibility of propylene glycol–induced allergy or irritation if dermatosis worsens despite use of a topical corticosteroid product
Isopropyl myristate[21]	Emulsifier-enhancing miscibility of both aqueous and lipid components Very rare cause of allergic contact dermatitis
Cocamidopropyl betaine[21]	Common surfactant in shampoos; used to replace sodium lauryl sulfate because of decreased irritation Accounts for only occasional cases of allergic contact dermatitis, especially of scalp or face
Ethanol[20,21]	Solvent; penetrant Not associated with allergic contact dermatitis May be drying, especially if vehicle does not contain counteracting excipients May cause stinging/burning if applied to fissured skin

and ethanol (46.6% wt/wt), which allows for rapid drying and may serve as a solubilizing agent and/or penetration enhancer.[12,14]

Clobetasol Propionate 0.05% Shampoo

The shampoo formulation of clobetasol propionate 0.05% has been approved by the FDA for treating scalp psoriasis in adults.[15] Approved labeling based on the pivotal clinical trials indicates that this formulation is to be applied to scalp, left in place for 15 minutes, and then lathered and rinsed. The predominant components of this formulation are water (71.7% wt/wt) and ethanol (9.7% wt/wt).[12,15] Cocamidopropyl betaine, a common component of shampoo formulations, is the predominant surfactant.

Calcipotriene 0.005% and Betamethasone Dipropionate 0.064% Ointment

More recently, a combination formulation containing calcipotriene 0.005% and betamethasone dipropionate 0.064%, a high-potency (class II) topical corticosteroid, was approved by the FDA for treating psoriasis vulgaris in adults.[16] Calcipotriene has been shown to be incompatible with several other topical medications, including salicylic acid and some topical corticosteroids.[17]

As a result, this combination ointment formulation requires dissolution of calcipotriene in an anhydrous vehicle and micronization with suspension of betamethasone dipropionate to achieve prolonged stability of components when placed in proprietary packaging such as a tube.[18] The predominant vehicle components are mineral oil and petrolatum (>90% wt/wt) and polypropylene glycol stearyl ether (5.1% wt/wt).[12,16]

Because of the high potential for incompatibility when calcipotriene is combined or applied sequentially with other topical formulations, it cannot be assumed that other products can be applied concurrently with topical calcipotriene unless compatibility has been confirmed. For example, when both clobetasol propionate 0.05% foam and betamethasone valerate 0.12% foam were tested independently with application before calcipotriene using a human skin model, no effect was demonstrated on calcipotriene stability at the skin surface 4 hours postdosing.[19]

Conclusion

Previous perceptions regarding vehicle characteristics and their impact on efficacy and tolerability warrant reconsideration since advances in formulation technology have resulted in significant changes in vehicles. More recently approved higher-potency topical corticosteroids do not always depend on older ointment or solution technologies to provide drug delivery that allows for designation in higher-potency categories. Current super–high-potency formulations include foam, cream, lotion, spray, and shampoo vehicles. Individual components of some newer topical corticosteroid-containing vehicles may be required in relatively high amounts to achieve greater potency (ie, high concentrations of propylene glycol). This may affect tolerability in selected patients.

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