Foam Drug Delivery in Dermatology
Beyond the Scalp

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Abstract

Consumers of topical formulations apply a wide spectrum of preparations, both cosmetic and dermatological, to their healthy or diseased skin. These formulations range in physicochemical nature from solid through semisolid to liquid.

Pharmaceutical foams are pressurized dosage forms containing one or more active ingredients that, upon valve actuation, emit a fine dispersion of liquid and/or solid materials in a gaseous medium. They differ from most other dosage forms in their de-
pended on the function of the container, its valve assembly and the pressurized propellant, for the physical delivery of the drug in proper vehicle form.\textsuperscript{[1,2]} This is perceived to be the major disadvantage of foam formulations in that the propellant technology is relatively complex and expensive to manufacture, thereby increasing the overall cost of the product. The production expense of this type of formulation is probably the major factor that has limited the number of dermatological foam formulations available to the clinician to date, in spite of several advantages that this dosage form offers in terms of drug delivery and patient acceptance.

Foam formulations are generally easier to apply, are less dense, and spread more easily compared with other topical dosage forms. When assessed, particularly in terms of ointments, or even creams and lotions, foams require negligible mechanical shearing force in order to spread the formulation on the skin. This is a major advantage when applying a medicament to highly inflamed skin; for example, in cases of sunburn where rubbing the formulation on to the skin to effect spreading may be painful or cause further inflammation. Hydrocortisone-containing formulations have been used in Europe for some time to successfully treat moderate to severe sunburn, the rationale for product selection based on this ‘minimal-touch’ delivery convenience. Furthermore, even when applied to hirsute areas such as the scalp, these formulations break down relatively rapidly, and easily reach the stratum corneum through the hair shafts. In this respect, they behave much like lotions and scalp application solutions, therefore resulting in enhanced patient compliance.

There are several other properties that distinguish foams from other, more conventional, topical dosage forms. In clinical and experimental situations, foam vehicles (structural matrix and ingredients) undergo considerable changes after removal from the primary container and application to the skin. The initial structural matrix of the foam vehicle will undoubtedly change during and after the mechanical agitation and physico-chemical changes (e.g. evaporation of volatiles) associated with application of the foam product. This inunction and/or evaporation of ingredients (often causing phase inversion) will influence the rate of drug transfer from the foam vehicle into the skin in a time-dependent manner. The maximum drug transfer into the skin takes place when the drug is in saturated solution at the vehicle-skin interface.\textsuperscript{[3,4]} If this is not the case, the rate of drug transfer across the interface is proportional to its degree of saturation (concentration/solubility).\textsuperscript{[1,4]} Rapid evaporation of the volatile components of foam vehicles results in an appreciable increase in drug concentration in the vehicle. Evaporative concentration first leads to saturation and then to supersaturation, which, although generally a transient condition, results in a drug delivery rate exceeding that achievable with a saturated solution.\textsuperscript{[3,4]}

The thermodynamic activity or leaving potential of a permeant molecule in a foam delivery vehicle formulation has an important influence on the rate of drug transfer from the vehicle into the skin. As a drug molecule dissolves and enters into the matrix of solvent molecules in the foam delivery vehicle, there are a number of weak bonding interactions that take place between substituent groups on the solute and solvent species. This attractive interaction stabilizes the dissolved molecule in solution and prevents its precipitation. As the concentration of the solution increases, so the total number of solvent molecules that are theoretically available to interact with each solute species decreases. Therefore, there is a proportionally greater tendency for the solute molecules to be lost by partitioning to a membrane in contact with the formulation; the solute molecules have a greater thermodynamic activity or leaving potential. Thermodynamic activity is maximal in saturated solutions since there is minimal potential for the partitioning to be retarded by bonding between the solute and solvent molecules. A saturated solution is, therefore, preferable as a topical drug delivery system as the maximum concentration gradient and maximum thermodynamic activity are achieved with such a system.\textsuperscript{[3]}

### 2. Review of Data on Foam Formulations

Foam formulations, although not commonly available commercially, have been in use for several years.\textsuperscript{[5]} A comprehensive search of the published literature was performed (including Medline, International Pharmaceutical Abstracts, and Embase), which yielded a surprisingly small number of references for the use of foam dosage forms in dermatology. Table I lists representative products that are currently available on the market. The active ingredients that have been incorporated into these formulations have mainly been topical corticosteroids (e.g. betamethasone valerate) that have been used effectively in the treatment of corticosteroid-responsive dermatoses of the skin and scalp, such as eczema, seborrhea and psoriasis. Foam formulations are particularly useful for diseases of the scalp due to the nature of the formulation. A novel foam formulation with enhanced betamethasone valerate bioavailability has been shown to be superior in efficacy when compared with a lotion in the treatment of scalp psoriasis, without an associated increase in toxicity.\textsuperscript{[6-9]} Psoriasis is a chronic relapsing skin disorder that affects about 2% of the US population, approximately half of these occurrences involving the scalp. Therefore, one can gauge the usefulness of this type of dosage form in clinical practice.
A study has been performed comparing the ability of a foam formulation to release the active ingredient (betamethasone benzoate) with ointment, gel, and cream formulations. It was found that the release of betamethasone benzoate from the ointment, gel, and foam formulations was similar, but better than the release from the cream. This was one of the first investigations into the use of foams in dermatology and illustrates the usefulness of this type of formulation. A foam formulation of the superpotent corticosteroid, clobetasol propionate, has demonstrated anti-inflammatory, antipruritic, and vasoconstrictive properties. In patients with moderate to severe scalp psoriasis, topical application of clobetasol propionate foam (0.05%) twice daily for 2 weeks resulted in significant improvement of all signs and symptoms of the disease compared with placebo and clobetasol propionate solution (0.05%). Furthermore, patients who received clobetasol propionate foam demonstrated greater improvement of scaling after 2 weeks of treatment, and after 2 weeks of follow-up.

There are only a limited number of reports in the literature concerning the use of foam formulations in other fields of dermatology or nondermatological fields. Nonsteroidal anti-inflammatory and antifungal agents are among the other drug families that have been formulated into foam products, while nonoxynol-9 foam has been used vaginally as a contraceptive, and chlorhexidine gluconate foam has been used as a preoperative application. If one considers that drug delivery to the alimentary canal and mucosae may be classified as ‘topical’ delivery in the classical sense, then one may include rectal foam products in this discussion of dermatological foams.

Prednisolone, hydrocortisone, beclomethasone dipropionate, and mesalazine foams have been applied rectally in ulcerative colitis and the treatment of postepisiotomy pain and erythema. A report on a 28-day trial evaluated the efficacy and tolerability of beclomethasone dipropionate in a rectal foam formulation during the treatment of patients with ulcerative colitis, evaluating endoscopic, histologic, clinical, and tolerability parameters. Sixty male and female patients aged between 20 and 81 years, with proctosigmoiditis (47%) and ulcerative rectocolitis (53%) were evaluated in the study. Endoscopic parameters showed an improvement in 75% of patients after 28 days of treatment, and clinical improvement was achieved in 65% of patients. Eighty-two percent of patients judged the treatment to be good/excellent with regard to tolerability, emphasizing the validity of the use of foam formulations in the treatment of ulcerative colitis and proctosigmoiditis.

Similarly, a comparison of the efficacy, tolerability, and overall acceptability of a new mesalazine rectal foam with mesalazine enema in the treatment of active distal ulcerative colitis has been reported. A multicenter study was carried out in patients with active proctitis, proctosigmoiditis, and left-sided ulcerative colitis. Patients were randomly assigned to receive either mesalazine foam (2g twice daily) or mesalazine enema (2g/60ml twice daily) for 3 weeks. The mesalazine foam and enema were found to be equally effective for the treatment of proctitis, proctosigmoiditis and left-sided ulcerative colitis, and the new foam preparation was well tolerated and accepted as a therapeutic alternative to conventional mesalazine enema formulations.

Eczematous contact dermatitis is a serious work-related skin disease. Reimbursement by insurance companies for the treatment of skin diseases has become a significant cost source in some countries. An aerosol foam skin protectant has been evaluated in the prevention of contact dermatitis caused by sodium lauryl sulfate and urushiol, the resinous sap of poison ivy and poison oak.

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**Table I. A representative list of foam products that are currently commercially available**

<table>
<thead>
<tr>
<th>Tradenamea</th>
<th>Manufacturer</th>
<th>Active drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bactoshield™</td>
<td>Amsca</td>
<td>4% chlorhexidine gluconate</td>
<td>Surgical scrub, skin cleanser, skin wound cleanser</td>
</tr>
<tr>
<td>Betadine™</td>
<td>Purdue Federick</td>
<td>Povidone iodine</td>
<td>Shampoo for temporary relief of scaling and itching due to dandruff</td>
</tr>
<tr>
<td>Desenex™</td>
<td>Ciba Consumer</td>
<td>1% undecylenate</td>
<td>Antifungal and antibacterial agent for tinea pedis</td>
</tr>
<tr>
<td>Epifoam™ aerosol foam</td>
<td>Schwarz Pharma</td>
<td>1% hydrocortisone; 1% pramoxine</td>
<td>Relief of inflammation and pruritic manifestations of corticosteroid-responsive dermatoses</td>
</tr>
<tr>
<td>Luxiq™</td>
<td>Connetics</td>
<td>Betamethasone valerate</td>
<td>Relief of inflammation and pruritic manifestations of corticosteroid-responsive dermatoses</td>
</tr>
<tr>
<td>Operand™</td>
<td>Redi-Products</td>
<td>Povidone iodine</td>
<td>Shampoo for temporary relief of scaling and itching due to dandruff</td>
</tr>
<tr>
<td>ProctoFoam-HC™ aerosol foam</td>
<td>Reed and Carnick</td>
<td>1% hydrocortisone; 1% pramoxine</td>
<td>Relief of inflammation and pruritic manifestations of corticosteroid-responsive dermatoses</td>
</tr>
<tr>
<td>Sarna™ anti-itch</td>
<td>Stiefel</td>
<td>0.5% camphor; 0.5% menthol</td>
<td>Antipruritics, mild local anesthetics and counter-irritants</td>
</tr>
<tr>
<td>Septisol™</td>
<td>Calgon Vestal</td>
<td>0.23% hexachlorophene</td>
<td>Surgical scrub and bacteriostatic skin cleanser</td>
</tr>
</tbody>
</table>

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a The use of tradenames is for product identification purposes only and does not imply endorsement.
This evaluation demonstrated that the foam product was effective in reducing the irritation from sodium lauryl sulfate, but did not prevent the allergic reaction to urushiol.

A study in 25 children and infants was conducted to assess the efficacy of a chlorhexidine, prednisolone, and nystatin-containing antifungal foam formulation on candida skin infections of the diaper region.\(^{[17]}\) It was found that all infections, even the most severe, were cured within a maximum of 13 days. Similarly, 61 patients with pityriasis versicolor were treated with a single application of ketoconazole foam in a clinical trial conducted in France.\(^{[18]}\) The trial was double-blind and placebo-controlled, with 28 patients in the ketoconazole group. Of the patients who received ketoconazole, 21 demonstrated a negative mycologic examination 30 days after the single application.

Ibuprofen, ketoprofen, and diclofenac foams have been applied topically as anti-inflammatory and analgesic agents.\(^{[19-21]}\) A recently published report examined the in vitro permeation of ibuprofen from commercially available formulations, purchased in the UK, through a silastic silicone membrane monitored over a period of 72 hours using modified Franz cell apparatus.\(^{[22]}\) Individual and mean apparent release constants were obtained by linear regression analysis of plots of cumulative amount of released drug versus square root of time. The release constants and linear correlation coefficients for ibuprofen-containing topical formulations using the Franz diffusion cell apparatus are shown in table II.

The plot of cumulative amount of released drug versus time for ibuprofen-containing topical formulations is depicted in figure 1.\(^{[22]}\) The profiles obtained for the three formulations are similar between 0 and 8 hours, but diverge markedly thereafter. The initial release rates of the formulations were shown to steadily increase from 0–8 hours, with a further increase from 8–48 hours. This is indicative of a biphasic release pattern, and is possibly an example of metamorphosis of the delivery vehicle with time. Drug penetration is dependent upon the influence of the vehicle on the thermodynamic activity of the active ingredient. The cream and gel appeared to present an ideal combination of solubility and physical diffusivity through the vehicle, yielding higher ibuprofen release rates and apparent release constants than the mousse formulation. This data exemplifies the observation that nonstandard drug release kinetics may be obtained in conventional in vitro drug diffusion studies, especially those where foam vehicles are evaluated. Metamorphosis of the delivery vehicle may change drug delivery potential markedly with time, a factor that topical formulation developers need to take into account at the preformulation stage of development.

### 3. Conclusions

It is evident that there are only a small number of reports in the literature concerning the use of foam formulations in dermatology and nondermatological fields. Most of the foam dosage forms used in dermatology to date have incorporated corticosteroids, although the literature does describe products used to deliver antiseptics, antifungal agents, anti-inflammatory agents, local anesthetic agents, skin emollients, and protectants.

The type of delivery vehicle or the formulation excipients can markedly affect the percutaneous absorption of a drug. Pharmaceutical and cosmetic products are developed in terms of stability and compatibility of excipients and active agents, cosmetic acceptability, usage criteria of the vehicle, and bioavailability of the incorporated drug. Thus, the ideal topical delivery vehicle should be easy to apply and remove, nontoxic, nonirritant, nonallergenic, chemically stable, homogeneous, bacteriostatic, cosmetically acceptable, pharmacologically inert, and should readily release the drug to the stratum corneum. Foam formulations are commonplace in the cosmetic industry; in that sphere manufacturers are prepared to produce the higher cost formulations, and consumers are prepared to pay the premium for the convenience and elegance of the specialized product. The same cannot be said for the dermatologic sphere. Presumably, cost-containment to the

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**Table II.** Release constants and correlation coefficients (\(r^2\)) for ibuprofen-containing topical formulations (reproduced from Purdon,\(^{[22]}\) with permission)

<table>
<thead>
<tr>
<th>Tradename</th>
<th>Apparent release constant (\left(\mu g/cm^2/h_1/2\right))</th>
<th>(r^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Relief™ gel</td>
<td>155.81</td>
<td>0.9627</td>
</tr>
<tr>
<td>Ibuleve™ gel</td>
<td>241.87</td>
<td>0.9794</td>
</tr>
<tr>
<td>Ibuleve™ mousse</td>
<td>114.46</td>
<td>0.9931</td>
</tr>
<tr>
<td>Proflex™ cream</td>
<td>312.91</td>
<td>0.9803</td>
</tr>
</tbody>
</table>
patient has caused pharmaceutical manufacturers to shy away from foam delivery systems.

It would appear that foam products may be an extremely useful addition to the range of formulations available for topical use, but as yet only a few are available. In addition to the cost factor, this may well be due to the fact that studies have shown that there is generally little improvement in drug release from a foam dosage form when compared with cream, lotion, ointment, and gel formulations. Even for use on the scalp, it has been shown that there is no significant clinical advantage (and considerable container and manufacturing disadvantage) gained by the use of a foam formulation compared with a lotion or scalp application solution. Probably the most convincing argument for the use of foams is ease of use by the patient and the low-shear spreading and application that is possible with these products — the latter being the most significant physical property of this formulation type. However, advances are constantly being made in drug delivery technology, e.g. the employment of penetration enhancers and supersaturation delivery techniques. The use of a foam formulation appears to be an ideal medium for using delivery vehicle metamorphosis technology in the future to improve drug delivery profiles for the patient.

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