Foam for Enhanced Topical Delivery: An Overview
Hanafi Tanojo  Xinfan Huang  Howard I. Maibach

ABSTRACT
Foam dosage form is excellent for topical application of active compounds into skin because it can increase compound partition and penetration rate. Due to unique film forming and breaking characteristics, foam can be easily transferred from the container to the intended skin application site. This advantage can particularly be enhanced using thermo-sensitive materials in the formulations. Foams can be formulated to provide moisturizing effects to the skin. Studies demonstrate that foams can deliver the active compounds at a higher rate compared with other vehicles. The observations suggest that foams may provide a rapid-permeation pathway for the delivery of drugs without undergoing rate-limiting interaction with skin cells. Some components within the foam (such as liquid alcohols) can function as additional penetration enhancers, by reversibly changing the outer stratum corneum barrier properties, and by providing extra driving force for the penetration of active compounds into skin. This contrasts with other topical delivery systems, which may first rely on hydration of the stratum corneum to enhance drug delivery. Foams also increase the effectiveness of therapy by increasing compliance by consumers, who find foams more convenient to use. (Dermatol Sinica 25: 10-15, 2007)

Key words: Foam, Aerosol, Drug delivery, Topical dosage form

INTRODUCTION
Foams, a special dosage form consisting of an emulsion in a pressurised pack containing propellant gas dissolved in the dispersed phase, have been used as topical preparations for cosmetic and dermatological uses. Cosmetic use of foams includes the mousse preparations for hair treatment and shaving creams. It is generally not intended to deliver active compounds into deeper layers of skin, although studies showed penetration may occur. Foam in shaving creams provides a mechanical lift for tiny hairs which makes the shaving process easier. Dermatological foam preparations are intended to deliver active compounds. Generally dermatological foams contain antiseptics, insecticides, skin-protectant or anti-inflammatory. Compared to other topical dosage form, foam may provide unique properties and advantages. This paper explores the characteristics of topical foam in delivering active compounds into skin.

TOPICAL DRUG DELIVERY
Skin provides the body with an effective protection and barrier to the entry of many compounds. In particular, the first skin barrier func-
The basic idea of using the foam is to trap the propellant gas inside an emulsion, so the resulting entity has the characteristics of semi-solid preparations that can easily be transferred to skin. The pressurized propellant is dissolved into the mixture containing surface active agents, water phase and organic phase inside a sealed container. Upon the release of an actuator, the mixture is dispersed out. However, the dispersion of gas to the atmosphere is hindered by an impermeable film built by either organic or water phase with the surface active agents, to form a “foam lattice”. The film stability is determined primarily by its thinning rate, which is governed by the hydrodynamic and thermodynamic interactions between the two film surfaces. During the period of film forming, the resulting foam lattice retains its shape and thus can be transferred from the container to the application area with ease.

When the foam is in contact with the skin surface, the surface interaction changes the film forming system, and breaks the film. The gas is released and the residue is deposited on the skin surface. The gas release is usually accompanied by the evaporation of volatile entities in the formulation, which result in an increase in absolute concentration of the active compounds in the formulation. The higher concentration will establish a greater concentration gradient between the inner and outer surface of the formulation, translating into a higher partition rate of the active compounds into the skin surface. Some formulations can further control the film stability using thermo-sensitive surface active agents or surfactants. While some surfactants can form a stable foam lattice at a low temperature for a long time, increasing the ambient temperature can weaken the film-forming ability and accelerate the collapse of the foam. The increase of temperature can originate from the skin surface temperature which is generally higher than the standard room temperature (25°C). This type of formulations gives additional control to the consumer, because it provides sufficient time to guide the application but then the foam will quickly disappear once it

**FOAM DOSAGE FORM**

The basic idea of using the foam is to trap the propellant gas inside an emulsion, so the resulting entity has the characteristics of semi-solid preparations that can easily be transferred to skin. The pressurized propellant is dissolved into the mixture containing surface active agents, water phase and organic phase inside a sealed container. Upon the release of an actuator, the mixture is dispersed out. However, the dispersion of gas to the atmosphere is hindered by an impermeable film built by either organic or water phase with the surface active agents, to form a “foam lattice”. The film stability is determined primarily by its thinning rate, which is governed by the hydrodynamic and thermodynamic interactions between the two film surfaces. During the period of film forming, the resulting foam lattice retains its shape and thus can be transferred from the container to the application area with ease.

When the foam is in contact with the skin surface, the surface interaction changes the film forming system, and breaks the film. The gas is released and the residue is deposited on the skin surface. The gas release is usually accompanied by the evaporation of volatile entities in the formulation, which result in an increase in absolute concentration of the active compounds in the formulation. The higher concentration will establish a greater concentration gradient between the inner and outer surface of the formulation, translating into a higher partition rate of the active compounds into the skin surface. Some formulations can further control the film stability using thermo-sensitive surface active agents or surfactants. While some surfactants can form a stable foam lattice at a low temperature for a long time, increasing the ambient temperature can weaken the film-forming ability and accelerate the collapse of the foam. The increase of temperature can originate from the skin surface temperature which is generally higher than the standard room temperature (25°C). This type of formulations gives additional control to the consumer, because it provides sufficient time to guide the application but then the foam will quickly disappear once it

**FOAM DOSAGE FORM**
Table 1. Some active compounds in marketed foam formulations

<table>
<thead>
<tr>
<th>Active compounds</th>
<th>Manufacturer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone valerate</td>
<td>Stiefel; Mipharm</td>
<td>Anti-inflammatory and antipruritus</td>
</tr>
<tr>
<td>Clindamycin phosphate</td>
<td>Stiefel</td>
<td>Treatment of acne</td>
</tr>
<tr>
<td>Clobetasol propionate</td>
<td>Stiefel</td>
<td>Anti-inflammatory and antipruritus</td>
</tr>
<tr>
<td>Felbinac</td>
<td>Lederle</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Hexachlorophene</td>
<td>Calgon Vestal</td>
<td>Surgical scrub and bacteriostatic skin cleanser</td>
</tr>
<tr>
<td>Hydrocortisone and Pramoxine</td>
<td>Schwartz Pharma; Reed and Carnick</td>
<td>Anti-inflammatory and anti-pruritus</td>
</tr>
<tr>
<td>Permethrin</td>
<td>Foamix</td>
<td>Treatment of lice</td>
</tr>
<tr>
<td>Phenothrin</td>
<td>Sutton Healthcare</td>
<td>Treatment of lice</td>
</tr>
<tr>
<td>Povidone iodine</td>
<td>Purdue Frederick; Redi-Products</td>
<td>Relief of scaling and itching due to dandruff</td>
</tr>
<tr>
<td>Pyrethrins and piperonil butoxide</td>
<td>Mipharm</td>
<td>Treatment of lice</td>
</tr>
<tr>
<td>Zinc Pyrithione</td>
<td>Quiver Pharmaceutical</td>
<td>Relief of scaling and itching due to dandruff</td>
</tr>
</tbody>
</table>

Emollient foam is another form of foam which is based on oil-in-water or water-in-oil emulsions, therefore possessing vehicle properties similar to traditional creams. The emulsions are formulated to provide soothing and moisturizing effect when applied to the skin. It may not exhibit drug delivery at the rate of hydroalcoholic foam, but it doesn’t have the side effects of alcohol, such as fast drying or defatting of the skin.7

**DRUG RELEASE PROFILES**

Hydroalcoholic foams demonstrate faster release of active compound than from other dosage forms for a short period.6 The main action of delivery usually occurred early, with the foam providing a higher rate of delivery in the first 6-8 hours post application. This translates into a rapid increase in concentration of the drug in the skin, which then is released gradually, resulting in a prolonged higher gradual rate of delivery by the foam. The faster initial permeation of active compounds from foam also means higher bioavailability in the earliest possible time post application at the targeted skin site. Among the comparable dosage forms are creams, ointments, lotions, solutions and gels.8,9

The unique skin penetration profile of foams from in vitro study as shown in Figure 1 suggests a lower penetration rate beyond 12-hour post application, whereas other dosage forms generally maintain the rate or show increasing rate. This may translate into less accumulative effects after multiple doses, which can provide a better safety profile for drugs that tends to reside longer in the skin. The higher penetration rate in the initial period of time has delivered the highest drug amount in the site, but allowing time to wash out between the applications.

This initial higher penetration rate is observed in different anatomical regions. In the excised skin from elbow, thigh, scalp, abdomen, and back area investigated in vitro, foam has yielded more active compound (clobetasol propionate) accumulated in the dermis at the 8-hour time point post application compared with creams. The palm and sole regions showed comparable penetration for foam and creams. The stratum corneum in these regions is much thicker and exerts greater resistance to penetra-
tion, which may neutralize the initial advantage of foam. Similar results were observed when foam was compared to ointment. These findings (see table 2) indicate that foam vehicle needs the least time to overcome anatomic region variations that can be correlated to stratum corneum thickness, whereas cream and ointment take longer time for the onset of delivery.

The advantage of foam application has also been reported in combination with other topical application. As combination therapy for dermatoses becomes increasingly common, the co-application of foam with other dosage form often results in acceleration of the onset of action, enhancing penetration through thicker skin. This will make possible to reduce the amount of each medication applied, due to potential additive or synergistic effects. An example of this is the co-application of betamethasone valerate foam with tacrolimus ointment and pimecrolimus cream preparations. In both cases, concomitant application with these products resulted in higher cumulative penetrated amount in the skin than when the products were applied alone or with other cream or ointment.

Clinical studies indicated that foams often produce faster effects for the treatment of some dermatoses. Most commonly reported is the use of foam corticosteroid for the treatment of psoriasis and other scalp dermatoses. This is not surprising because the scalp region is notoriously difficult to treat by other widely used dosage forms, like creams or ointments. Subsequently, the application of antifungal ketoconazole in foam dosage form is also reported to be more efficient than the current treatment with gels.

MECHANISM OF ACTION

Foam dosage form is capable to deliver more active compound in comparison to other vehicles, especially in the early phase after application. In order to produce such a unique effect, foam vehicle must have a different pathway or mechanism. It is reported that foam shows higher penetration rate across a synthetic lipophilic barrier membrane, such as Silastic film, than gel. This may suggest that the enhanced delivery of active compound by foams bypasses the rate-limiting interaction between the formulation and skin cells. Some components within the foam (for instance, the liquid alcohols) can act as short-term penetration enhancers that reversibly alter the barrier properties of the outer stratum corneum, thus

Table 2. Comparison of foam with cream or ointment to affect the in vitro skin penetration of clobetasol propionate across human excised skin from different anatomical region

<table>
<thead>
<tr>
<th>Foam &gt; Cream</th>
<th>Foam = Cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td>Palm</td>
</tr>
<tr>
<td>Elbow</td>
<td>Sole</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Abdomen</td>
</tr>
<tr>
<td>Back</td>
<td>Back</td>
</tr>
<tr>
<td>Thigh</td>
<td>Thigh</td>
</tr>
</tbody>
</table>

Fig. 1
Percutaneous flux profile of clobetasol propionate from hydroalcoholic foam, in comparison to solution, creams and lotion. (Modified from Huang et al.)
driving the delivered drug across the skin membrane via the intracellular route.

The enhancement can also happen due to the gradual increase of concentration gradient as the foam propellant drives the volatile solvents out of the formulation.\textsuperscript{19} After the release from the container and during the breaking of foam, the gaseous component evaporates together with liquid alcohol or water. This will result in higher concentration of active compound on the skin surface with time and increase drug transfer into the skin as the condition nearing saturated at the vehicle-skin interface. Once the evaporation depletes the foam of its high mobility components, the driving force is reduced, but the established concentration gradient will still be able to deliver the active compound to a certain extent due to the reservoir effect. This phenomenon actually exists in solution and liquid semi-solid formulations, as the evaporation also occurs, but not as dramatic as in foams. Therefore, the penetration enhancement effects contribute uniquely to foam dosage form.

Foam can take advantage of the extensive hydration in the intercellular spaces in the stratum corneum to enhance the penetration, as the formulations usually contain a significant amount of water phase. This effect can further be improved by the addition of moisturizers.\textsuperscript{7} Some hydrophilic compounds may take advantage of the condition. However, the effects may be overwhelmed by the above-mentioned phenomenon.

**FOAM APPLICATION**

Beside the unique property to deliver active compounds, clinicians and patients may find another advantage of using foam in terms of its application. Several studies reported that patient gives higher preference to foam than other traditional dosage form like cream or ointment due to ease of application, uniform spreading, less stickiness, less greasy feeling, less dense and therefore generally easier to spread on the skin surface, and leave relatively less residue of skin surface.\textsuperscript{7, 20} After the release from container, foam expands and allows easy spreading on the skin. Relative low density contributes to ease of distribution on the scalp or other hairy area. Other than cosmetically attractive compared with lotion or solution, the quick absorption of the foam with less residue is found to be more acceptable because it doesn’t interact with clothing or other material in contact with the applied site. The greasy feeling of many creams and ointments is less reported with foam, although the hydrating effect (especially from emollient foam) is comparable. In one survey of psoriasis patients, respondents indicated a high preference for foam over cream, gel, and ointment vehicles among topical psoriasis medications.\textsuperscript{20} Not only in scalp psoriasis patients, the preference of foam was also reported in nonscalp psoriasis patients.\textsuperscript{21} Alcohol component of foams (as in hydroalcoholic foams) may promote fast drying and defatting, which may not be comfortable for consumer with dry skin, but is found to be useful in oily application sites.

**CONCLUSION**

Among topical dosage forms and delivery systems, foams have several distinctive properties that have been proven beneficial to use:

1. Unique skin penetration profile of active compounds. In particular, hydroalcoholic foam can deliver active compound at higher rate in shorter time after application, than other dosage form.

2. Ease of application. The low density foam allows better and uniform spreading on skin.

3. Patient preference. Low residue and lack of greasy feeling can help patient compliance and therefore result in optimum efficacy of active compound.

**REFERENCES**

3. George YA, Ravis SM, Gottlieb J, et al.: Betamethasone valerate 0.12% in foam vehicle for...
1. scalp seborheic dermatitis in African Americans.
4. Wasan DT: Foam and emulsion stability: 
Interfacial rheology and thin liquid film pheno-
mena. In: Emulsions, Foams and Thin Films (Mittal 
KL, Kumar P, eds). New York: Marcel Dekker: 1-
5. Woodford R, Barry BW: Bioavailability and activ-
ity of topical corticosteroids from a novel drug 
delivery system, the aerosol quick-break foam. J 
7. Tanojo H, Lenn J, Sykes J, et al.: Effects of co-
application of betamethasone 17-valerate and tacrolimus on skin penetration and distribution of 
skin study of combined application of pime-
crolimus cream and betamethasone 17-valerate.
In: American Academy of Dermatology Annual 
Betamethasone valerate foam 0.12%, a novel 
vehicle with enhanced delivery and efficacy. Int J 
propionate foam 0.05%, a novel vehicle with 
15. Andreassi L, Giannetti A, Milani M: Efficacy of 
betamethasone valerate mousse in comparison with 
standard therapies on scalp psoriasis: an open, multi-
centre, randomized, controlled, cross-over study on 
16. Bates B: Not just for the scalp anymore betametha-
sone valerate foam battles body psoriasis. Skin & 
17. Rekacewicz I, Guillaume JC, Benkhraba F, et al.: [A 
double-blind placebo-controlled study of a 2 per-
cent foaming lotion of ketoconazole in a single 
lation on ketoconazole skin penetration and 
of Dermatology Annual Meeting. San Francisco: 
drug delivery in dermatology: Beyond the scalp. 
Patients with psoriasis prefer solution and foam 
vehicles: a quantitative assessment of vehicle pref-
21. Gottlieb AB, Ford RO, Spellman MC: The effica-
cy and tolerability of clobetasol propionate foam 
0.05% in the treatment of mild to moderate 