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Emollient foam in topical drug delivery

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Foams offer an innovative and more convenient means of topical drug delivery. The successful introduction of hydroalcoholic foams paved the way for the development of a new generation of foam products that provide skin barrier build-up and hydration. Such foams, designated as emollient foams consist of oil-in-water or water-in-oil emulsions with necessary excipients, such as non-ionic surfactants, gelling agents and foam adjuvants. Emollient foams can carry a broad variety of topical drugs, including water-soluble, oil-soluble and suspended active agents. This paper reviews emollient foam compositions and their physicochemical properties. It further accounts for the usability and functional advantages of emollient foam as a vehicle of topical drugs, including: i) improved usability, which affects treatment, compliance and, consequently, improves therapeutic results; ii) safety; iii) controllable drug delivery; iv) skin barrier build-up and hydration; and v) enhanced clinical efficacy.

Keywords: emollient foam, skin penetration, topical therapy, usability

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1. Introduction

Topical therapy is one of the foundations of a dermatologist's therapeutic tools for symptomatic relief, control or cure of the underlying disease.

The vehicles that are used to deliver topical therapy can considerably influence drug performance: they can affect the delivery of the active agent, and its physical appearance and sensory properties affect compliance. Although semisolid compositions, such as creams, lotions, gels and ointments, are commonly used by consumers, new forms are desirable, in order to achieve better control of the application, improve skin absorption and maintain or achieve the therapeutic benefit of such products.

Foam is becoming a prominent delivery system for topical drugs. This platform provides an innovative, easy to apply, modern alternative to creams and ointments. A significant advantage of the foam formulation is that it spreads easily on large skin areas, and does not leave a greasy or oily film on the skin after application.

The use of foam in dermatology was first reported in 1977 by Woodward and Berry, who studied the therapeutic benefit of betamethasone benzoate in a hydroalcoholic 'quick-break' foam in comparison to a corresponding semisolid dosage form [1]. The activity of the foam, as determined by a vasoconstriction test, was similar to the corresponding ointment and was better than cream. The later studies by Parrini *et al.* and Daffonchio *et al.* investigated the anti-inflammatory and analgesic profile of a topical foam formulation of ketoprofen lysine salt, which exhibited anti-inflammatory and analgesic effectiveness [2,3]. A comprehensive review on foam drug delivery in dermatology was written by Purdon *et al.* in 2003 [4].

2. Overview of the market: current foam technologies

Only a few prescription dermatological foam products are commercially available. Olux Foam® and Luxiq Foam® (Connetics), which contain 0.05% clobetasol propionate and 0.12% betamethasone valerate, respectively, are both thermolabile steroid foams,

consisting of ethanol (~ 60%), purified water, propylene glycol, cetyl alcohol, stearyl alcohol, polysorbate 60, citric acid, and potassium citrate and a hydrocarbon propellant [5]. Evoclin® (Connetics) is another hydroalcoholic foam, comprising of clindamycin 1%, and is indicated for acne [6].

Alcohol induces the skin penetration of drugs, as has been broadly reported in the literature. Recent *in vitro* studies have demonstrated that drugs formulated in hydroalcoholic foam exhibit drug delivery at an increased rate compared with other vehicles. These findings suggest that components within the foam (probably the alcohol) act as penetration enhancers, and reversibly alter the barrier properties of the outer stratum corneum, thus driving the delivered drug across the skin membrane via the intracellular route [1].

Alcohol also promotes fast drying and, thereby, attempts to address the sticky feeling that is left by many topical formulations after application. However, alcohol is a defatting agent and may cause skin to become dry and cracked. Due to this undesirable property, hydroalcoholic foams have not been proposed for the treatment of atopic dermatitis: a childhood inflammatory skin disorder that involves dry, itchy skin and rashes on various body areas.

In addition, because the hydroalcoholic foams are thermolabile (temperature sensitive), their use is hindered by the recommendation not to dispense them directly onto the hands or to the target skin area, as the foam melts on contact with warm skin.

Hydroalcoholic foams are also available in Europe. These include BettaMousse® (betamethasone valerate 0.1%; Mipharm), MILICE® (pyrethrins and piperonil butoxide; Mipharm), Full Marks (phenothrin; Sutton Healthcare Group) and Traxam® foam (felbinac; Lederle). EpiFoam® (pramoxine and hydrocortisone; Schwartz) and Proctofoam® (pramoxine and hydrocortisone; Reed and Carnrick), are both based on aqueous vehicles.

3. Emollient foam

The term emollient foam relates to a foam that has a soothing and moisturising effect when applied to the skin. Emollient foams are emulsions comprised of water and oil, and, as such, they possess vehicle properties that are similar to traditional creams. They act by refatting the skin; thereby reducing the loss of water from the skin. They further increase the moisture content of the stratum corneum by generating a humectant effect, which increases the water-holding capacity of the stratum corneum. Emollients are used to correct dryness, wrinkles and scaling of the skin; they also provide symptomatic relief in xerotic skin diseases such as ichthyoses, xeroderma, disorders of keratinisation and atopic dermatitis [7,8].

Foams and, in particular, foam emulsions are complicated systems that do not form under all circumstances. Even slight shifts in the emulsion foam composition, such as with the addition of active ingredients, may destabilise the foam. Furthermore, many emulsions do not provide the high foam capacity, foam stability and/or fast-breaking action under stress or temperatures that are desired in a topical foam composition.

3.1 Emollient foam composition

The primary components of emollient foams are water and oil, which are present in the formulation as an emulsion. The oil component can be selected from all pharmaceutically acceptable oils, including mineral oil; triglycerides, such as plant oils and capric/caprylic triglyceride; fatty acid esters (e.g., isopropyl myristate, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate); and essential oils. In certain cases, the oil may be selected for its therapeutic benefits. For example, omega-3 and omega-6 polyunsaturated oils could be included, which have been reported to exert a therapeutic effect on inflamed skin disorders, as part of the oil phase. Silicon oils also may be used and are desirable due to their known skin protective properties.

Petrolatum is less desirable, due to its greasy nature. Formulations that include high petrolatum concentrations leave a greasy and sticky feeling after application and occasionally stain clothes.

The choice of a surfactant system for stabilising the emulsion involves the following considerations:

- The surfactant's hydrophilic/lipophilic balance (HLB) should be selected taking into account the desired type of emulsion. Typically, an oil-in-water emulsion requires an emulsifier system with a HLB of 9 – 14. If a foam composition is required, consisting of a water-in-oil emulsion, an emulsifier system with an HLB of 4 – 9 should be selected.
- The type of surfactant should be carefully considered. Ionic surfactants are effective as foaming agents; however, they are known for their skin and mucosal irritancy. Therefore, non-ionic surfactants are preferred, especially when the target area of treatment is infected or inflamed.

A gelling agent is an essential component for the creation of a foam with desirable texture and spreading properties. Gelling agents or other polymeric additives may be present in a range of ~ 0.05 – 2.0% in the formulation. Exemplary gelling agents include naturally occurring polymeric materials (such as locust bean gum and xanthan gum), semisynthetic polymerics (such as cellulose ethers [e.g., hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose and hydroxypropylmethyl cellulose]), polyvinylpyrrolidone, polyvinylalcohol, guar gum, hydroxypropyl guar gum, soluble starch, cationic celluloses, cationic guars and synthetic polymeric materials, such as carboxyvinyl polymers and polyvinylpyrrolidone. Mixtures of the above compounds are often used to attain optimal foam properties. Some of the gelling agents also possess film-forming properties, which serve to maintain drugs at the site of application. In certain cases, they promote the penetration of active agents into the skin (intradermal penetration) and through the skin (transdermal penetration), as they create an occlusive or semiocclusive layer at the treatment site.

The gelling agent has a stabilising effect on the emulsion, which is particularly important, as the composition has low viscosity, as mentioned above. The gelling agent further contributes to the smoothness of the foam when applied to the skin.

Another group of components that contribute to the stability and sensory properties of the foam are foam adjuvants. Adjuvants are selected from the variety of fatty alcohols and fatty acids, such as cetyl alcohol, stearyl alcohol, behenyl alcohol, stearic acid and behenic acid.

Optionally, a polar solvent (i.e., organic solvents that are soluble in both water and oil) is added to the foam composition, in order to increase the solubility of the active agents or to enhance skin penetration. Examples of polar solvents include polyols, such as glycerol, propylene glycol, hexylene glycol, dimethyl isosorbide, dimethyl sulfoxide and diethylene glycol monoethyl ether (transcutol). PEGs or PEG derivatives that are liquid at ambient temperature, such as PEG_{200}, PEG_{400} and PEG_{600}, can also be used as polar solvents. Preferably, the emollient foam should not contain ethanol or other short-chain alcohols.

Finally, there is an indispensable role of the propellant. Aerosol propellants that are used at present in the pharmaceutical industry include volatile hydrocarbons, such as butane, propane, isobutane and fluorocarbon gases. Combinations of these propellant gasses can be used.

A pharmaceutical emollient foam product may consist of a single drug or a combination of drugs, which can be dissolved in the water phase or the hydrophobic phase of the carrier composition. Yet, in certain cases, when the drug is not fully soluble in either the water or oil phase of the composition, it can still be dispersed in the emulsion. Small molecules, as well as macromolecules, can be incorporated in the composition. Examples of drugs that have been successfully incorporated in emollient foam formulations include antibiotics, antifungals, antivirals, corticosteroids, NSAIDs, retinoids, keratolytic agents, immunomodulators, anaesthetics, antiallergic agents and antiproliferative drugs. The concentration of drugs may be adopted to exert a therapeutic effect on a disease when applied to an afflicted area.

3.2 Emollient foam properties

Pharmaceutical emollient foams should be designed to be very easy to use. When released from the aerosol canister, they should be in a foam state, allowing free application without spillage. Yet, once applied gently onto the skin, they should freely spread on the surface and be rapidly absorbed.

The composition must maintain shelf-life chemical and physical stability. Oils and propellants tend to impair the stability of emulsions and to interfere with the formation of a stable foam on release from a pressurised container. However, by designing the foam composition, as described above, stable compositions are attained that do not exhibit phase separation for long periods of time and form fine bubble structures that do not break immediately on contact with a surface. They also spread easily on the treated area and absorb quickly.

Importantly, the composition should also be free flowing, to allow it to flow through the aperture of the aerosol container and create foam. Typically, the viscosity of the composition should not exceed 10,000 cps.

Foam quality can be graded as follows:

- Grade E (excellent): very rich and creamy in appearance; does not show any bubble structure or shows a very fine (small) bubble structure; does not rapidly become dull; on spreading on the skin, the foam retains the creaminess property, spreads easily and does not appear watery.
- Grade G (good): rich and creamy in appearance; very small bubble size; 'dulls' more rapidly than an excellent foam; retains creaminess on spreading on the skin; spreads easily and does not become watery.
- Grade FG (fairly good): a moderate amount of creaminess noticeable; bubble structure is noticeable; on spreading on the skin the product dulls rapidly and becomes somewhat lower in apparent viscosity.
- Grade F (fair): very little creaminess noticeable; larger bubble structure than a 'fairly good' foam; on spreading on the skin it becomes thin in appearance and watery.
- Grade P (poor): no creaminess noticeable; large bubble structure; and when spread on the skin it becomes very thin and watery in appearance.
- Grade VP (very poor): dry foam; large, very dull bubbles; difficult to spread on the skin.

Topical foams must have a quality grade of E or G when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously on discharge from the container. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

Emollient foams possess several advantages, when compared with hydroalcoholic foam compositions:

- Breakability. The emollient foam is thermally stable. Unlike hydroalcoholic foam compositions, the emollient foam is not 'quick breaking' (i.e., it does not readily collapse on exposure to body temperature). Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability, as it allows comfortable application and well-directed administration to the target area.
- Skin hydration and skin barrier function. Alcohol is known to dry the skin and impair the integrity of the skin barrier. By contrast, including oils in the foam composition helps build-up the desirable skin barrier function, thereby improving the condition of damaged skin.
- Irritability. Due to the lack of alcohol and improvement in skin barrier function, skin irritability is eliminated.

In terms of usability, the foamable composition provides significant advantages, as revealed by clinical trials (**Box 1**).

Another property of the foam is its density, as measured on release from the aerosol canister [9]. Typically, emollient foams

Box 1. Advantages of the foamable composition.

Ease of application

- When the foam is released, it expands and allows easy spreading on the target area. This feature is particularly meaningful with regard to the treatment of large skin surfaces.
- On application, the foam readily spreads and absorbs into the skin.

The foam is drip free

- The foam is not liquid and, therefore, does not leak when applied.
- This allows precise application of the product to the target area, which is less likely to get on clothes or other parts of the body.

have densities in the range of 0.03 and 0.1 g/ml, depending on their composition and on the propellant concentration.

3.3 Emollient Foam™: usability profile and exemplary products

Although there are no commercially available pharmaceutical emollient foams, several of them are in development, as demonstrated in the recent stream of granted patents and patent applications [101-106]. Several emollient foam products are in advanced development in different parts of the world and are likely to become available in the market in the near future.

The purpose of this section is to illustrate the features and properties of the Emollient Foam™ (Foamix) platform, using examples of studies that were carried out on products under development.

3.3.1 The usability profile of emollient foams

Usability is a paramount feature of foam products, which affects treatment, compliance and therapeutic results. A series of controlled usability studies have been conducted to compare the usability of foam in comparison with cream.

The degree of importance of each usability parameter is highly important in the evaluation of a product. Based on 120 panelists, the following hierarchy of the parameters, in order of decreasing importance, was identified:

- Skin absorption;
- Ease of application;
- Uniform spreading;
- Stickiness (shortly after application);
- Odour;
- Greasy feeling;
- Shiny look.

As shown in **Figure 1**, foam was rated as superior to cream in all of the above evaluation parameters.

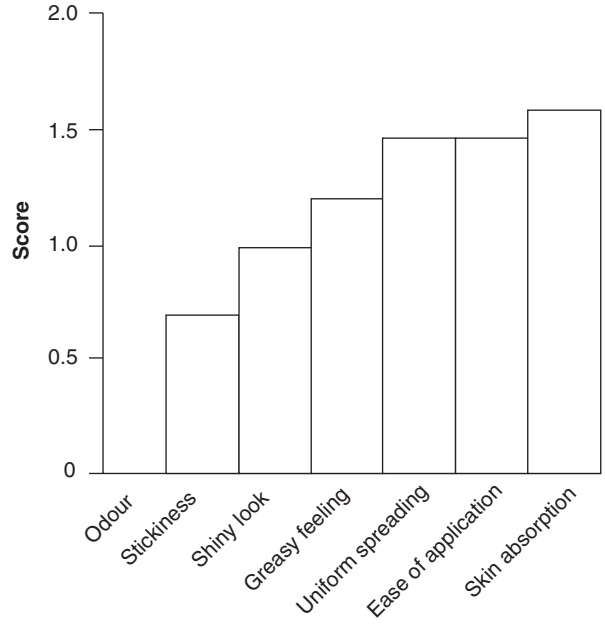

Figure 1. Mean score (foam versus cream) for each usability evaluation parameters. Illustrates the results of comparison between a representative emollient foam and cream, for each of the above parameters. The results are presented as mean values in a bar chart, where 0 stands for 'foam equal to cream'; and 3 means 'foam is much better than cream'.

Additional observations from this study are highlighted:

- Most panellists thought that the foam was better than the comparator cream and ointment, in most parameters of the evaluation.
- The majority of panellists (66%) rated the foam as 'better than the comparator cream or ointment'; 24% rated the foam as equal to the cream or ointment, and only 10% thought that the cream or ointment was better than the foam (**Figure 2**).
- The panelists emphasised the distinct advantage of foam, which spreads easily and the absorption of the foam immediately on application.

Further usability studies were carried out in the context of facial treatment, revealing a statistically significant preference of foam over cream and lotion.

3.3.2 AtopiFoam™: the emollient effect in action

AtopiFoam™ (Foamix) is a steroid-free, skin-hydrating foam that was designed to provide extensive skin hydration and to alleviate the itch and inflammation associated with atopic dermatitis. Clearly, the use of an easily spreadable emollient foam (rather than cream) in atopic dermatitis patients, who are mostly infants and children, with very itchy skin, is

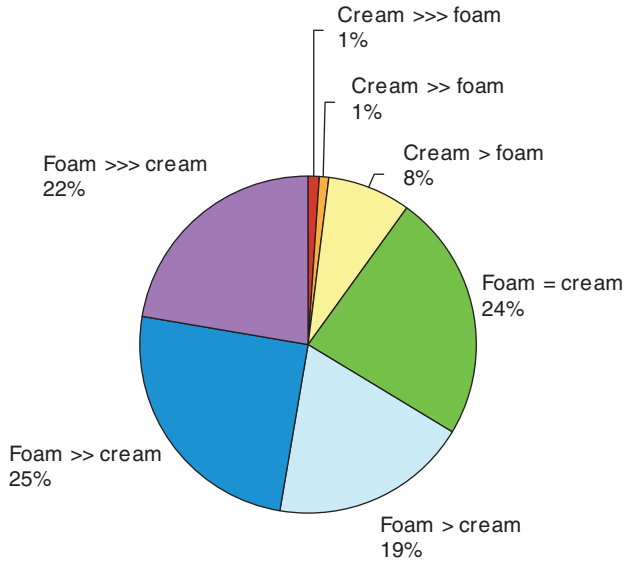

Figure 2. Overall score of the foam versus the comparator cream.

advantageous. The AtopiFoam composition contains glycerin, avocado oil, shea butter and mineral oil as refatting and humectant substances; silicons, advanced hydrophilic copolymers and sodium hyaluronate to build-up the skin barrier; and extracts of liquorice and aloe vera, as well as tocopheryl acetate, α-bisabolol and allantoin, which are known for their anti-inflammatory properties.

The skin hydration capacity of AtopiFoam was tested on 13 human volunteers, in comparison with a commercially available prescription moisturising cream for atopic dermatitis (active ingredients: hyaluronic acid, telmesteine, vitis vinifera and glycyrrhetinic acid; Atopiclair). Skin hydration levels were determined using a Corneometer® CM 825 instrument (Courage and Khazaka). As shown in **Figure 3**, non-treated areas maintained with practically constant hydration values throughout the study. AtopiFoam afforded elevated skin hydration of 40 – 50% during the 6-h follow up, and Atopiclair was effective for 1 h only. Notably, the change from baseline was statistically significant for AtopiFoam throughout the 6-h assessment, whilst Atopiclair was effective for 1 h. The difference between AtopiFoam to Atopiclair was statistically evident at the 3- and 6-h measurements. No skin irritation was noted following treatment.

3.3.3 Emollient betamethasone valerate foam: delicate mid-potency corticosteroid emollient foam

Psoriasis is a chronic skin disorder that most commonly appears as inflamed swollen skin lesions covered with silvery white scales. It may appear on any skin surface, although the knees, elbows, scalp and trunk are the most common locations. Psoriasis affects 3% of the population. Atopic dermatitis is another very common chronic condition that begins in infancy and childhood. The most common symptoms are dry, itchy skin and rashes on the face, inside the elbows, behind the knees, and on the hands and feet. An estimated 20% of infants and young children experience symptoms of the disease.

An emollient foam composition, containing 0.12% of the mid-potency steroid betamethasone valerate, is being developed with the aim of treating patients with mild-to-moderate psoriasis and atopic dermatitis. The composition was specifically designed to contain delicate oils and non-ionic surfactants, in order to minimise skin irritation. A Phase II, randomised, single-centre, blinded, right-left comparison within patient clinical trial was carried out including 30 patients with mild-to-moderate psoriasis. Two similar plaque areas of psoriasis (i.e., both knees or both elbows), were selected for treatment for each patient. Patients received topical administration of the foam preparation on one affected side and Betnovate cream (betamethasone valerate 0.12%; GlaxoSmithKline) on the other side, both for 6 weeks.

Both treatments were effective in the treatment of the psoriatic lesions. After 3 weeks of treatment, there was a statistically significant improvement from baseline in all efficacy parameters, including thickness (42 – 43% improvement), redness (36 – 44%), scaling (49 – 56%), itch (77 – 78%) and global score (42 – 44%). The difference between treatments was not statistically significant. These clinical improvements persisted following an additional three weeks of treatment.

Notably, the mean global assessment of change after the 3-week treatment, on a scale between 0 (no change) and 3 (marked improvement) was 1.35 for the foam and 1.07 for the cream. The investigator identified six 'marked improvement' responses for the foam, versus three such cases for the comparator cream. No drug-related adverse effects were recorded.

Patients rated the foam as better than the respective cream, in the following usability parameters: skin absorption, oily residue, shiny look after treatment, stickiness and odour, both in visit 2 and visit 3, as shown in **Figure 4**.

In conclusion, this study revealed that the betamethasone valerate emollient offers an attractive alternative to exisiting mid-potency creams. It also has a preferred usability profile. As such, it is more likely that psoriasis patients will use their medication as frequently as prescribed and will gain the desirable therapeutic benefits.

Being an emollient foam, which contributes to skin barrier build-up and hydration, while delivering the drug, the betamethasone valerate foam emollient can also be prescribed for atopic dermatitis patients whose skin is sensitive and itchy. This is particularly important, as most of these patients are primarily infants and children who generally resist being treated with creams or ointments that require lengthy rubbing in order to reach full absorption. The use of hydroalcoholic steroid foams in atopic dermatitis patients is unacceptable because of the irritability and skin drying adverse effects of such foams.

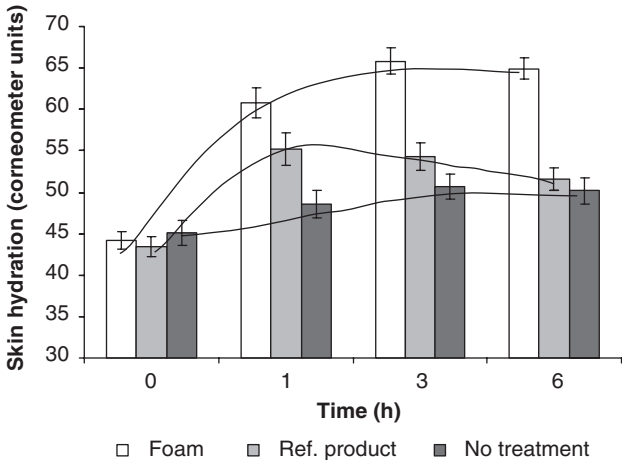

Figure 3. Skin hydration: AtopiFoam™ versus commercially available prescription moisturising cream (Atopiclair™ was the ref. product).

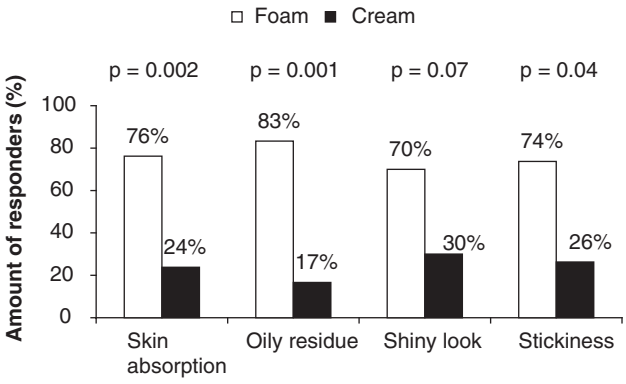

Figure 4. Usability preference: product nature characteristics foam versus cream: visit 2.

3.3.4 *PerFoam™ 1%: an effective vehicle of an anti-lice product*

PerFoam™ 1% (Foamix), an alcohol-free, permethrin 1% foam, was developed for the treatment of head lice (*Pediculosis capitis*). In order to overcome the commonly known resistance of lice to permethrin, two dedicated excipients were added to the composition: an essential oil that influences the susceptibility of lice to drug absorption and a polar solvent, which also contributed to the penetration of the drug through the cuticle.

A clinical study was conducted in order to i) assess the efficacy and safety of PerFoam 1%, in the treatment of head lice in paediatric patients; ii) detect any side effects of the product; and iii) assess the usability of the foam product [10].

The study was performed as a single-centre, open study, including 56 healthy male and female paediatric patients, 3 – 15 years of age, diagnosed as having *Pediculosis capitis*. All of the patients' parents gave written informed consent for their child to participate in the study. The test product, PerFoam 1%, was applied by the investigator, using an average quantity of 20 g per patient, according to hair type (length, thickness, curliness) on wet hair. The product was administered under the hair via an applicator connected to the foam canister (**Figure 5**). The foam was spread throughout the hair via gentle massaging. The foam remained in contact with the hair for 10 min. It was then washed off with water and a regular shampoo. The same procedure was repeated 10 days later. After 24 h from the first treatment, patients were examined for lice (visually and by combing for 2 – 3 min). Lice and nits found were counted and recorded. Dermal side effects (itching, pain, irritation), along with any other adverse events, were recorded throughout the study period.

Figure 5. PerFoam™ is administered under the hair via applicator connected to the foam canister. The foam is spread throughout the hair with gentle massaging and remains in contact with the hair for 10 min.

The product was found to be effective in lice killing in 96.4% of the patients, and the product further eradicated viable nits in 60% of the patients. No drug-related adverse effects were recorded. The usability results are reported in **Box 2**.

In conclusion, the study provides evidence that PerFoam 1% is safe and effective and is highly usable in the treatment of head lice in paediatric patients.

3.3.5 *Metronidazole 1% emollient foam: demonstration of efficient drug solubilisation and favourable skin bioavailability*

Rosacea is a chronic skin disorder of the face, which afflicts ~ 13 million Americans. Skin involvement in rosacea is

Box 2. The usability of PerFoam™.

Ease of application

- Due to the foam texture of the product, PerFoam 1% was found to be easier to use in comparison with other products available in the market.
- When the foam is released, it expands in the hair and effectively coats all surfaces. This advantage is particularly meaningful with regard to areas of difficult access, such as the neck and behind the ears.
- Using the product with the applicator attached to the foam container enables direct administration under the hair, enhancing convenience.

The foam is drip free

- The foam is not liquid and, therefore, does not leak when applied.
- The foam does not run and, therefore, allows precise application. The product does not get on clothes or other parts of the body.
- Not a single case of contact with eyes was recorded throughout the study. It should be noted that the issue of contact with eyes is a common problem when treating with shampoo, lotion or a spray, which frequently cause eye irritation and burning.

Patient response

- Throughout the study it was evident that children enjoyed being treated with foam and, therefore, did not resist the therapy.

characterised by erythema, telangiectasias, papules, pustules and sebaceous gland hypertrophy. The lesions are distributed across the blush areas of the face, involving the nose, cheeks, chin and central area of the forehead.

The current leading topical drug for rosacea is metronidazole, which is available in gel, cream and lotion at 0.75 and 1% concentrations. As the solubility threshold of metronidazole in water is relatively low (≤ 0.75), 1% metronidazole is not expected to be fully dissolved in an aqueous vehicle.

Emollient foam compositions were designed with the aim of dissolving ≥ 1% of metronidazole. These compositions were further constructed to provide efficient skin moisturisation and low irritancy, by including delicate emollient oils (such as isopropyl myristate, isopropyl palmitate and capric/caprylic triglycerides), and non-ionic surfactants at low concentrations. Surprisingly, compositions containing metronidazole 1 – 2% demonstrated improved solubility over aqueous metronidazole solutions. When the compositions were released from the aerosol can, the number of metronidazole crystals, as visually observed under magnification (e.g., × 100) was negligible, as shown in **Figure 6**.

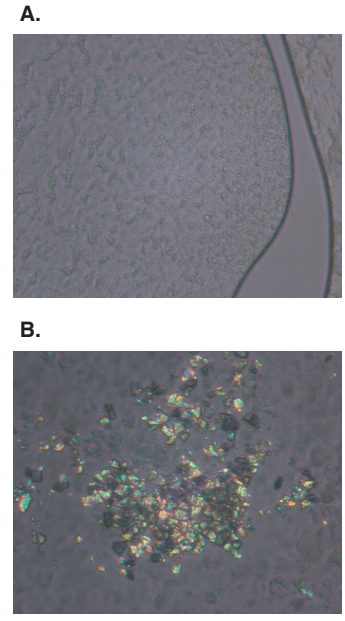

Figure 6. Metronidazole 1% emollient foam versus Noritate® cream. A. No crystals in the 1% emollient foam. **B.** Metronidazole crystals in Noritate.

An *in vitro* skin penetration study was conducted using excised human skin mounted in a flow-through diffusion cell over a 16-h period, aiming to compare the intradermal penetration and the absorbed dose profile of metronidazole 1% emollient foam. Two foam compositions were tested: one with propylene glycol 2.5% as a penetration enhancer and the other without propylene glycol – in comparison with Noritate® cream (metronidazole 1%; Dermik). A total of 10 mg of each formulation (metronidazole 100 µg) were applied to a skin surface of 1 cm^2. Metronidazole concentrations were assessed in the receptor fluid fractions over time, and the remaining metronidazole in the skin at the end of the study was assayed by HPLC. **Table 1** summarises the amounts of metronidazole in the stratum corneum and epidermis, and dermis, as well as the amount of metronidazole that was absorbed.

In conclusion, the *in vitro* total cutaneous penetration of metronidazole was shown to be significantly higher (two- to threefold) with the two foams than with Noritate cream. The presence of propylene glycol as a skin enhancer in the foam significantly increased the delivery of metronidazole in the receptor fluid (i.e., absorbed dose; **Figure 7**).

Thus, it was concluded that the enhanced solubility, as provided by the emollient foam, is potentially useful in enhancing the effectiveness of topical metronidazole.

Table 1. *In vitro* skin penetration of two metronidazole 1% emollient foams, versus metronidazole 1% cream: metronidazole concentrations found in the stratum corneum, epidermis, dermis and the receiving compartment.

	MZ	MZPG	Noritate®
Metronidazole concentration (w/w)	1%	1%	1%
Real metronidazole applied amount (µg)	94.00 ± 2.90	87.60 ± 1.70	96.80 ± 4.76
SC + E (µg)	4.87 ± 0.52	4.26 ± 0.69	1.99 ± 0.24
% of the applied dose	5.2%	4.9%	2.1%
D (µg)	1.72 ± 0.18	1.87 ± 0.25	0.65 ± 0.08
% of the applied dose	1.9%	2.1%	0.69%
Total skin (SC + E + D; in µg)	6.59 ± 1.00	6.13 ± 0.77	2.64 ± 0.27
% of the applied dose	7.0%	7.00%	2.8%
Absorbed dose (A; in µg)*	3.54 ± 0.69	5.85 ± 1.03	2.04 ± 0.18
% of the applied dose	3.9%	6.7%	2.2%
Total penetrated amount (SC + E + D + A; in µg)	10.13 ± 0.66	11.98 ± 1.29	4.68 ± 0.34
% of the applied dose	11%	14%	5.0%

*Absorbed dose: sum of cumulative receptor fluid (0 – 16 h) + receptor rinse.
A: Absorbed dose; E: Epidermis; MZ: Metronidazole; MZPG: Metronidazole propylene glycol; SC: Stratum corneum.

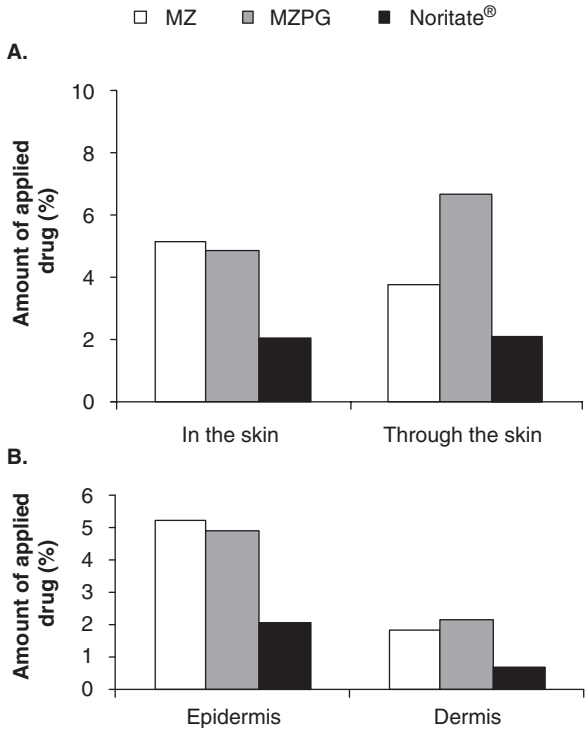

Figure 7. Metronidazole 1% emollient foam versus cream. **A.** Enhanced intradermal delivery (stratum corneum plus epidermis) and absorbed dose. **B.** Delivery to all skin layers stratum corneum/epidermis and dermis.

4. Conclusion

Creams and ointments have historically been used in skin care and dermatology. Foams offer an innovative and more convenient means of topical drug delivery. The recent successful introduction of hydroalcoholic foams has paved the way for the development of a new generation of foam products that provide skin barrier build-up and hydration. These emollient foams can deliver a variety of topical drugs, including antibiotics, antifungals, antivirals, corticosteroids, NSAIDs agents, retinoids, keratolytic agents, immunomodulators, anaesthetics, antiallergy agents and antiproliferative drugs.

As demonstrated in a series of laboratory and human trials, emollient foams offer several advantages:

- Usability: emollient foams are convenient to use. They can easily be applied on large areas, without the need of extensive rubbing. This is especially important in the treatment of infants and children. Emollient foams readily absorb into the skin, thereby allowing users to get back to routine activity immediately after treatment. These usability features are expected to enhance patient compliance and consequently, improve the therapeutic results.
- Safety: by selecting delicate oils and low concentrations of mild non-ionic surfactants, safe and non-irritating foams are obtained, which are suitable for the treatment of sensitive and itchy skin. In this respect, emollient foams are better than hydroalcoholic foam, which exert a high incidence of irritation.
- Controllable drug delivery: emollient foam formulations can include skin penetration enhancers, which can modify the intradermal and/or transdermal delivery of active agents.
- Emollience: skin barrier build-up and hydration are

important attributes of emollient foams, which are able to correct dryness and scaling of the skin, and provide symptomatic relief in xerotic skin diseases, such as ichthyoses, xeroderma, disorders of keratinisation, and atopic dermatitis.

- Clinical efficacy. As shown in clinical trials that have been reviewed in this article and other studies described in the literature, emollient foams are suitable for delivering high clinical efficacy of their active agents.

5. Expert opinion

The foam story has just begun. Foams offer an innovative and more convenient means of topical drug delivery. Hydro-alcoholic foams have recently been successfully introduced, and their acceptance is still growing. However, alcohol is a defatting agent and may cause skin to become dry and cracked. This makes products with alcohol unsuitable for treating dry-skin disorders, such as atopic dermatitis. Newly developed emollient foams, consisting of oil-in-water or water-in-oil emulsions, offer a combination effect of skin barrier build-up, hydration and an efficient delivery of drugs. The favourable usability profile of emollient foams, which are easily applied and instantly absorbed into the skin, will improve patient compliance and, hence, enable more patients to use their drugs as prescribed. These properties are bound to broaden the spectrum of topical drugs that are delivered in emollient foam. Medicated emollient foams will enter the market in the near future. It is highly likely that these treatments will become the preferred choice over creams and ointments.

Is emollient foam the final word in foam drug delivery? The answer is probably no, as new generations of foam are concurrently being developed. These include oil-based foams to accommodate the need for a convenient ointment-like vehicle, and foams without water (waterless foam) as vehicles for water-sensitive drugs.

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101. CONNETICS AUSTRALIA PTY LTD: US6730288 (2004)

•• **Basic patent that covers emollient foams; their specifications exemplify emollient foam compositions, drugs that can be included in foam and uses of emollient foams as topical delivery system**

102. FOAMIX LTD: WO037225 (2004)

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