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Review

Dynamic foams in topical drug delivery

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Abstract

Objectives Pharmaceutical foams are not new inventions and their application in topical therapy can be traced back three decades. However, foam formulations have been gaining in popularity with over 100 patents published globally in the last 10 years alone. The aim of this paper is to review the current status and explore the future potential of dynamic foam vehicles in the field of topical drug delivery.

Key findings The use of foam technology to deliver a range of topical active agents has been claimed, including sun-screening compounds, corticosteroids, and antibacterial, antifungal and antiviral agents. Although foams present distinct application advantages and improved patient compliance, the real reason for the rapid growth of topical foam technology is that foams as elegant, aesthetic and cosmetically appealing vehicles provide an alternative, promising formulation strategy in the highly competitive dermatological market. Although there is a plethora of published data proving the safety profiles of topical foams there is a lack of sufficient clinical evidence to demonstrate any superiority of foams over other traditional topical vehicles such as creams and ointments for drug delivery.

Summary Recent literature suggests that when foams are properly engineered using the advances of *in situ* analysis techniques, the enhancement of topical drug delivery via engineering this type of vehicle can be achieved.

Keywords drug delivery; dynamic; foam; topical; vehicle

Introduction

The current markets of topical/dermatological products are almost exclusively dominated by conventional vehicles including lotions, creams, ointments and gels. Analysis of the patent literature shows that more and more interest is being shown in another type of topical vehicle, foam, despite the lack of comparison to traditional vehicles (Figure 1). The growing interest of the pharmaceutical industry in foam vehicles is not only due to their marketing potential, but also thanks to their apparent application advantage, improved cosmetic appeal and thus consumer acceptance and preference compared to the more conventional gels, creams and ointments. For example, when treating inflamed skin conditions such as sunburn and eczema, topical foams are preferred as they can spread more easily and minimise the rubbing that is often required in traditional topical dosage forms to disperse the formulations.[1] In a survey of 20 psoriasis patients by Housman *et al*. patients indicated a significant preference for foam vehicles over creams, ointments and gels.[2] Tamarkin *et al*. evaluated the usability profile of foams against a cream control based on 120 panelists' opinions and concluded that the foam was significantly better than a cream control with regard to ease of application, uniform spreading, stickiness, greasy feeling and appearance.[3] Recent work by Cash and Quigley found that foam vehicles were preferred by patients (n = 139) with mild to severe seborrhoeatic dermatitis over traditional vehicles, regardless of gender, age or ethnicity.[4] Another trial with a larger group (279 patients) treated with a clobetasol propionate foam suggested an increased preference for foam vehicles.[5] The work of Kahanek *et al*. also revealed that desonide foams showed increased patient compliance in the treatment of steroid-responsive dermatoses.[6]

Published investigations on topical foams have demonstrated an acceptable safety profile. For instance, in a phase II open-label study of a desonide foam involving 81 patients aged from 3 months to 17 years, the foam was shown to be safe and well-tolerated in those participants with mild to severe atopic dermatitis and the safety profile of this vehicle was consistent with more than 30 years of use of desonide in other vehicles

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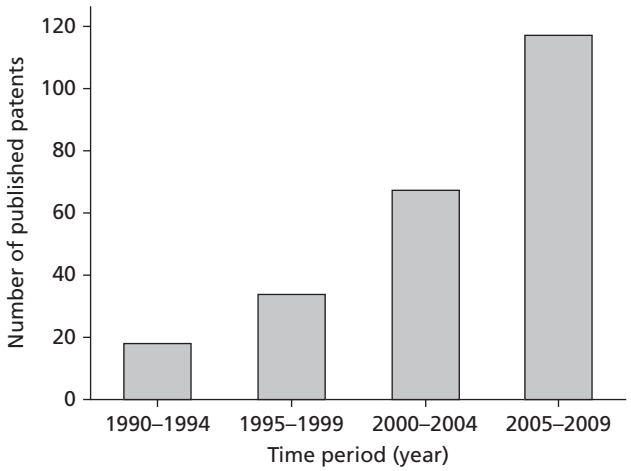

Figure 1 The numbers of patent publications describing topical foam vehicles over the past 20 years. Data were obtained using the terms 'topical' and 'foam' via the FreePatentsOnline search engine which covers US Patents, US Patent Applications, EP documents, Abstract of Japan and WIPO (PCT)

(cream, ointment, lotion).[7] Phase II open-label and phase III randomised controlled studies of clobetasol foams demonstrated that this formulation is safe for the treatment of atopic dermatitis and plaque-type psoriasis.[8] The safety of topical foams has also been proven in other studies.[9–11]

The efficacy of topical foams has been described in a range of studies. A randomised, double-blind study of a clobetasol propionate foam demonstrated that the foam is more effective than a control in the treatment of psoriasis.[12] Another independent study also showed that a foam vehicle delivers more clobetasol than other formulations (cream, solution and lotion) using an in-vitro human skin permeation model.[13] Studies by other groups concurred with these results.[14,15] The work of Franz *et al*. revealed that a betamethasone valerate (BMV) foam shows greater improvement in the primary signs of psoriasis compared with a lotion.[16] Andreassi *et al*. compared a BMV foam with a lotion control in 241 patients with psoriasis from 28 European centres and concluded that the foam vehicle was more effective than the lotion.[17] The effective treatment of psoriasis by the BMV foam was also reported in another study.[18] In addition, a BMV foam was shown to improve the treatment of seborrheoic dermatitis in a multicentre trial on 180 patients.[19] However, the success of topical foams is not only limited to corticosteroids. The penetration of ketoconazole from foam vehicles across a silicone membrane was found to be 11-fold higher than that from creams.[13] Meanwhile, a clindamycin foam was proven to have a higher rate of delivery of active drug into human skin and showed stronger efficacy compare to gel vehicles.[10] In addition, a minoxidil foam was shown to be able to increase hair growth in significantly more subjects than a solution vehicle.[20] The effective treatment of hyperkeratosis with urea foam has also been reported previously.[21]

The most significant difference of topical foams compared to creams, ointments and gels is their dynamic characteristics, i.e. on dose application to the skin the foam vehicle undergoes considerable changes, including evaporation of propellants and volatile solvents, collapse and drainage of foam bubbles, and concentration of excipients. Unfortunately the majority of previous investigations of topical foams have not realised this feature and its potential impact on topical delivery enhancement. As such, the objectives of this review are to clarify the definitions and properties of dynamic topical foams, to summarise the characterisation techniques which can be used for evaluating dynamic foams, and to assess the capability of dynamic foam vehicles to enhance topical drug delivery.

What are topical foams?

Definition

Despite the wide use of the term 'foam(s)', its definition is ambiguous in terms of topical application. Weaire and Hutzler defined a foam as a two-phase system in which gas cells are enclosed by liquid.[22] The work of Purdon *et al*. described pharmaceutical foams as pressurised dosage forms, containing one or more active ingredients that, on valve actuation, emit a fine dispersion of liquid and/or solid materials in a gaseous medium.[23] In the *European Pharmacopoeia* (Monograph: 1105), the definition of a medicated foam is 'a preparation consisting of large volumes of gas dispersed in a liquid generally containing one or more active substances, a surfactant ensuring their formation and various other excipients'. In the *United States Pharmacopeia 32* (General Chapters: 1151), a foam aerosol is defined as an emulsion containing one or more active ingredients, surfactants, aqueous or non-aqueous liquids, and the propellants. Sanders stated that an aerosol foam is normally packed in the container as an emulsion, in which the liquefied gas propellant is dispersed as droplets throughout the aqueous phase; when the emulsion is discharged, the propellant vaporises into a gas that is trapped by the aqueous solution and this forms a foam.[24] By summarising the above information, topical foams can be defined as: dynamic dosage forms intended for application to the skin; usually containing active agents, propellant, surface active agents, solvents and other excipients; prior to dose application they are sealed in a pressurised canister in the form of emulsion or suspension or solution; post dose or valve actuation, the propellant evaporates from the pressurised system producing a liquid or semi-solid foam product that is expanded with air. A schematic representation of the dynamic topical foam application process is shown in Figure 2.

Excipients

Topical foams contain active agents, propellant, surface active agents, solvents, cosolvents and viscosity-modifying agents. Although most of the commercial topical foams incorporate corticosteroids, the active agents can also be selected from antibacterial, antifungal and antiviral agents, anti-inflammatory agents, local anesthetic agents, skin emollients and protectants, depending on the skin conditions to be treated.

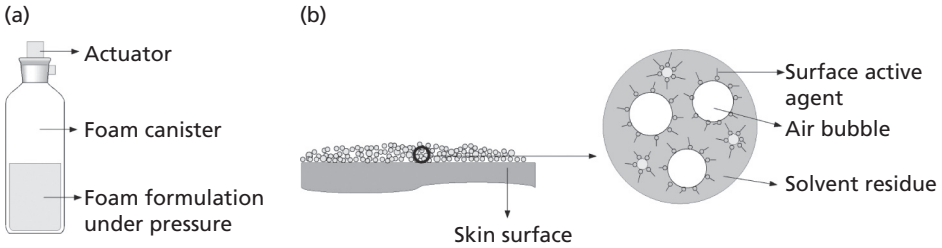

Figure 2 The schematic illustration of topical foam application. (a) Prior to dose application, topical foams are sealed in a pressurised canister in the form of emulsion or suspension or solution. (b) On dose application to the skin surface, volatile propellants and solvents evaporate and the foam bubbles are stabilised by surface active agents and dispersed in the solvent residue

As a pressurised dosage form, propellants are a key component of topical foams and make foams unique, as they can be self-generating under the loss of propellants on valve actuation. However, the selection of an 'ideal' propellant is not easy despite the availability of various types such as compressed gases, hydrocarbons, chlorofluorocarbons, hydrochlorofluorocarbons, dimethyl ether and hydrofluroalkanes (HFAs). Nitrogen, nitrous oxide and carbon dioxide are typical compressed gas propellants; they are cheap, but their low boiling point (< –50°C) may be a concern for consistent accurate dosing since a pressure decrease inside the pressurised foam canister is possible during use. Butane, isobutene and propane are hydrocarbons that are relatively inexpensive and have a high boiling point (> –42°C) without the metering problem of compressed gases. However, the biggest concern with a hydrocarbon propellant is the potential safety hazard due to the high flammability and explosivity. Therefore, extensive precautions are essential during their manufacture, storage and disposal. Dimethyl ether propellant, which has a boiling point of –24.8°C, is another alternative for generating topical foams, but is still flammable. Chlorofluorocarbons and hydrochlorofluorocarbons do not have the problem of flammability, despite their higher boiling points compared to hydrocarbons, and have been widely employed as pharmaceutical propellants. Nevertheless, these types of propellants have an ozone layer depletion effect and thus there are legislative restrictions on their use. For example, The Montreal Protocol, 7th edn dictates that production and consumption of chlorofluorocarbons and hydrochlorofluorocarbons should be phased out (with possible essential-use exemptions for chlorofluorocarbons) globally by 2010 and 2030, respectively.[25] Thus, during the past decade, HFA propellants such as difluoroethane (HFA 134a) and heptafluoropropane (HFA 227) have been gaining more attention for pharmaceutical application.[26–29] HFAs are ideal for topical foam generation since they display a high vapour pressure (572 and 390 kPa for HFA 134a and HFA 227, respectively).[30] Furthermore, HFAs are non-explosive, non-flammable and non-chlorinated, with no concerns regarding ozone depletion.

The second critical component for the successful production of topical foams is the foaming agents which are usually surface active agents (surfactants). Exceptions include certain proteins and particles that are also capable of generating foams.[31] On valve actuation and the rapid evaporation of propellants, the foaming agents can adjust their orientation and adsorb at the air–water (or other solvent) interface, trying to lower the interfacial tension. However, in terms of pharmaceutical application, surfactants are the most common foaming agents. Both ionic and non-ionic surfactants can be used but the former are known for their skin irritancy and thus non-ionic surfactants are preferred, particularly when the target area of treatment is infected or inflamed.[3]

Solvents and sometimes cosolvents are the primary constituents of topical foams. Depending on the solvent(s) employed, topical foams can be either aqueous or non-aqueous, i.e. containing no or little water. In most cases topical foams are water-based since the generation of non-aqueous foams is more difficult. For instance, Tamarkin *et al*. claimed a type of oleaginous foam for pharmaceutical or cosmetic use containing a high percentage (>70%, w/w) of non-aqueous solvents selected from polyethylene glycol, polyethylene glycol derivatives or mixtures thereof.[32]

Another essential ingredient of topical foams is a viscosity-modifying agent (gelling agent), which can facilitate the creation of a foam with desirable texture and optimum spreading properties.[3] Gelling agents are often selected from naturally occurring polymers (e.g. xanthan gum), semi-synthetic polymers (e.g. cellulose ethers) and synthetic polymers (e.g. polyvinylpyrrolidone).

Besides the above elemental components, other excipients can also be incorporated, depending on the active agent and the required foam characteristics. For example, when formulating a foam containing the ionisable drug minoxidil, used for hair loss treatment, an acid can be employed to enhance the drug's solubility and/or to maintain the pH of the formulation at a most favourable range to enable the maximum amount of drug to be formulated.[33] When foam compositions are used to administer chemically unstable topical therapeutic agents, e.g. ascorbic acid, a stabiliser (e.g. flavonoids) can be added to the formulation to ensure that the active agent is not degraded before dose application.[34] In addition, topical foams can also incorporate a cooling agent (e.g. menthol), a warming agent (e.g. polyhydric alcohols) or a soothing agent (e.g. aloe vera) to generate a unique sensation or sensation modifying effect on application.[35]

Preparation

Foams can be generated by various approaches. Typical methods include (1) whipping, i.e. mechanical agitation of a liquid or a solution, (2) bubbling, i.e. injecting a stream of gas or liquid or the mixture into a liquid, and (3) sudden pressure

reduction, i.e. rapidly actuating the valve of pressurised systems (a solution or emulsion or suspension).[36,37]. For pharmaceutical or topical use, foams are often generated *in situ* using the method of sudden pressure reduction. The inclusion of foam excipients in the pressurised canister usually employs a method called 'pressure-fill'.[38] First, all other foam ingredients except propellants, i.e. active agents, solvents, foaming agents, etc. are measured into open containers in a premix, then the canisters are sealed and the propellant is forced under pressure into the containers to make the final foam products. Depending on the miscibility of the propellant with the solvents/cosolvents, and the solubility of active agents, gelling agents and other ingredients in the mixture, a solution, suspension or emulsion, sealed under pressure in the canister, can be produced. However, such formulations are multiple-phase systems irrespective of their form inside the container as these pressurised systems contain a vapour phase; that is, even if they exist as a solution there are still two phases (gas phase and liquid phase).

Stability

The stability of topical foams involves consideration of two factors: prior to dose application (i.e. inside the canister) and post-dose application (i.e. outside the canister). However, the evaluation of topical foam stability inside the canister is often neglected. This may be partly because of the explosiveness and flammability of certain propellants such as hydrocarbons, which makes the in-situ analyses of these pressurised systems difficult. In addition, there may be a lack of awareness of the link between foam structure inside the canister and foam stability on application. For example, when the propellant is in the internal (disperse) phase (i.e. of the propellant-in-water type), a stable foam will be discharged, and if the propellant is in the external (continuous) phase (i.e. of the water-in-propellant type), a quick-breaking foam will be generated.[39]

The foam stability outside the canister is well understood and is associated with three main factors: Ostwald ripening (disproportionation), drainage and film rupture. These processes are not independent actions and often happen concurrently. Ostwald ripening involves the transport of gas between foam bubbles of different sizes, which causes the growth of bubbles and can be explained by the Laplace equation (1).[40]

$$P = P_a + 2\gamma/R \quad (1)$$

where P is the pressure in a gas bubble, P_a is the atmospheric pressure, γ is the surface tension and R is the bubble radius. From equation (1) it can be concluded that the pressure in the foam bubbles is greater than atmospheric pressure. It is also clear that the smaller the radius of the foam bubbles, the greater the pressure in the bubbles, i.e. the smaller bubbles have a higher internal pressure compared to larger bubbles. This is therefore the driving force of Ostwald ripening, i.e. the air diffuses from small bubbles through the liquid film into larger ones. Foam drainage is the flow of liquid through channels between the bubbles, which is usually driven by capillary (surface tension) forces and is resisted by viscous forces.[41] The thickness of the channels that separate the foam bubbles can be reduced by foam drainage, a phenomenon that can expedite Ostwald ripening and film rupture.[42] Rupture of the liquid films separating the bubbles leads to the coalescence of the bubbles and complete collapse of the foam structure. Nevertheless, the presence of surfactants at the interfaces can form a strong interfacial film around the foam bubbles and thus retard coalescence when the bubbles do come into contact. Such interfacial surfactant films may form a diffusion barrier, leading to a low permeability to gas molecules, and thus can decrease the effect of Ostwald ripening on foam stability.[24]

Topical foam evaluation

As a transient structure, the characterisation of topical foams is not easy, but they can be assessed both qualitatively and quantitatively. For example, the method described by Sanders suggested that foam stability and viscosity can be obtained by simply discharging foams onto a paper towel and observing the extent to which a foam wets the paper towel, retains its shape and peaks when a glass rod is placed within and then raised vertically.[24] Similarly, Abram and Hunt designed a rating scale from 0 to 5 to assess pharmaceutical foams; the lower the value the more stable the foam, e.g. a rating of 0 means a full, fine and stable foam that holds structure or undergoes a very slow, small collapse over 30–60 s and a rating of 5 represents a foam comprising large bubbles or those that immediately break to large bubbles.[43]

The density of a foam can be obtained via filling a container of known volume with the foam and determining its weight.[24] Alternatively, using the method described in the *European Pharmacopoeia* (Monograph: 1105), the relative foam density can be determined by weighing a predefined volume of foam compared to the weight of the same volume of water. Another parameter, foam expansion time, is an indicator of the foamability of the pressurised formulations and can be tested, according to Monograph 1105, by introducing *ca.* 30 ml of the formulation into a 50 ml burette with 0.1 ml graduations (15 mm in internal diameter) and reading the volume of foam in the burette until the maximum volume is reached.

Foam stability is an important parameter for foam evaluation that can be assessed by the semi-quantitative determination of foam drainage rate, wetting time and collapse time by discharging foams into a measuring cylinder or onto a paper towel.[24] Foam stability together with foam bubble size and distribution can also be assessed using various approaches, including optical microscopy, light scattering, fluorescence and magnetic resonance imaging.[44] Due to the friable structure of topical foams, rheological measurements of such systems have been problematic. Recently, Kealy *et al.* developed a novel vane sensor with four blades (diameter 21 mm and height 16 mm) that can minimise the disruption to the sample compared to traditional sensors. This made it possible to determine foam rheological parameters, such as yield stress, elastic modulus and complex viscosity. Using such a method the viscoelastic flow properties of a variety of topical foams (hydroethanolic, emulsion and aqueous based) were assessed and provided an insight into the macrostructure of dynamic foam systems differing in composition.[45]

Another recently developed means for quantitative foam analysis is cryogenic scanning electron microscopy (cryo-SEM).[39] In this method, foam samples upon release from the container are rapidly frozen using liquid nitrogen, fractured using a precision rotary knife and then sputter-coated with chromium before obtaining SEM images. Quantitative analysis of such images can give both morphological and stability information of foam samples such as bubble size and size distribution. Two typical cryo-SEM images of topical foams (one is quick-breaking and the other is relatively stable) are shown in Figure 3. The advantage of such a technique is its capability for assessing quick-breaking foams that are often hard to characterise via other methods.

Recent investigations have showed that in-situ characterisation of topical foams containing a non-flammable HFA propellant is possible using a specifically designed pressurised cell for measuring the conductivity/pH of the system and/or via constructing phase diagrams.[39] In addition, the temperature, pressure and surface tension of HFA/water emulsions can also be determined via the development of a high-pressure tensiometer.[46,47] Likewise, a 'spectroscopic cell' held under pressure can be coupled either with small angle neutron scattering or UV-vis spectroscopy to screen surfactants that can be used to stabilise HFA/water emulsions.[48] The characterisation of topical foams inside the canister can provide essential information on the state of the ingredients prior to dosing and formulation structure under pressure, which would dictate foam properties on application. Since HFA-containing foams can be relatively easily analysed *in situ* under pressure, the future development of topical foams may well be focused in this area.

Engineering foam vehicles to enhance topical drug delivery

As most of the previous investigations on topical foams have focused on their application advantages, the extent to which topical drug delivery can be enhanced by such dynamic vehicles has often been ambiguous.[23,49,50] In fact, topical foams are not only comparable to other traditional vehicles in terms of delivery efficiency, but also can perform better when they are properly engineered. One good example is the thermolabile (temperature-sensitive) foams developed by Stiefel Laboratories, Inc. (now GSK).[43,51] Such dynamic foams contain large amounts of alcohol, which is believed to function as a skin penetration enhancer. They have been marketed as Olux (0.05% clobetasol propionate) and Evoclin (1% clindamycin phosphate).[3,50] Likewise, other penetration enhancers such as fatty acids and fatty alcohols can also be included in dynamic foams to improve topical delivery.[52] Another way of engineering topical foams is to incorporate occlusive agents such as petrolatum in the vehicle to form an occlusive layer on the skin on application. It has been shown that the occlusive layer can reduce the evaporation of moisture from the skin, leading to increased hydration of the stratum comeum (SC) and thus enhanced delivery.[53,54] Such technology has been employed in products including Olux-E (0.05% clobetasol) and Verdeso (0.05% desonide). Furthermore, dynamic foams containing water-insoluble film-forming polymers can produce a water-resistant film on application.[55] Such film-forming foams are attractive as most of the active agents are often washed away from the skin when they are exposed to water, e.g. after swimming or bathing, resulting in reduced effectiveness. Furthermore, this foam engineering technique is especially desirable for sun-screening agents since these can eliminate the need for reapplication after exposure of the applied area to water.

Engineered topical foams can also be combined with other skin delivery enhancement strategies. For example, it is known that drug-loaded submicron particles can protect the degradation of topical active agents that are chemically unstable. Recent work has demonstrated that such drug-loaded submicron particles incorporated in dynamic foams can be 'broken open' on dose application to enable drug release from the particles.[56] However, the influence of particle properties such as size on foam stability and consistency of dosing is still not clear and needs further investigation.

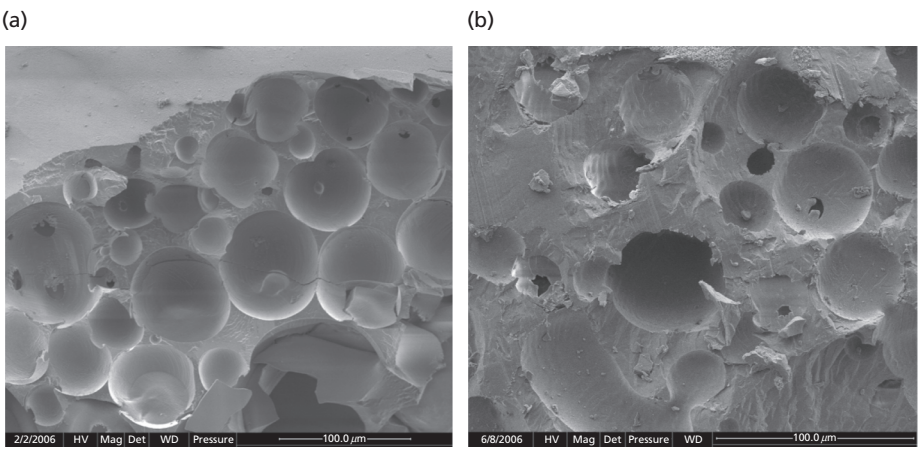

Figure 3 Typical scanning electron microscope images of two topical foam systems. (a) Hydrofluoroalkane-in-water system, which generates relatively stable foams. (b) A water-in-hydrofluoroalkane system, which produces quick-breaking foams on application

Another promising approach to engineering topical foams is to bring together the foam vehicles with supersaturation, a popular means for skin penetration enhancement. Due to the dynamic nature of topical foams, the evaporation of propellants and volatile solvents (if present) would cause a change of drug solubility in the foam residue solvents. Theoretically, when the active agents, solvents, co-solvents and propellants are carefully selected and matched, a supersaturated foam system could be generated on application. Despite the current absence of published literature about this system, a similar pressurised topical spray formulation that could generate supersaturation on delivery has been produced recently.[57]

The future of novel topical foams

Dynamic topical foams have already been a useful addition to conventional topical formulation approaches, as can be seen from the growing number of topical foam products on the market and the increasing number of foam patents filed in recent years. The attractiveness of elegant topical foams currently lies in their application advantage and aesthetics, which patients prefer. However, consideration of their potential ability to enhance and/or assist drug delivery to the skin when engineered properly should not be neglected. As such, it is expected that the interest in the development of novel topical dynamic foams will continue, with the aid of the various foam evaluation tools described herein and their combination with other drug delivery technologies such as supersaturation and penetration enhancers.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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References

1. Ricciatti-Sibbald D, Sibbald RG. Dermatologic vehicles. *Clin Dermatol* 1989; 7: 11–24.
2. Housman TS *et al*. Patients with psoriasis prefer solution and foam vehicles: a quantitative assessment of vehicle preference. *Cutis* 2002; 70: 327–332.
3. Tamarkin D *et al*. Emollient foam in topical drug delivery. *Expert Opin Drug Deliv* 2006; 3: 799–807.
4. Cash K, Quigley MO. The vehicle found in ketoconazole foam 2% is preferred by patients with mild to severe seborrheic dermatitis over other vehicles, regardless of gender, age, or ethnicity. *J Am Acad Dermatol* 2008; 58: AB92.
5. Gottlieb AB *et al*. The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. *J Cutan Med Surg* 2003; 7: 185–192.
6. Kahanek N *et al*. Desonide: a review of formulations, efficacy and safety. *Expert Opin Investig Drugs* 2008; 17: 1097–1104.
7. Hebert AA. Desonide foam 0.05%: safety in children as young as 3 months. *J Am Acad Dermatol* 2008; 59: 334–340.
8. Kimball AB *et al*. Clobetasol propionate emulsion formulation foam 0.05%: review of phase II open-label and phase III randomized controlled trials in steroid-responsive dermatoses in adults and adolescents. *J Am Acad Dermatol* 2008; 59: 448–454.
9. Stein LF *et al*. Betamethasone valerate foam for treatment of nonscalp psoriasis. *J Cutan Med Surg* 2001; 5: 303–307.
10. Shalita AR *et al*. The safety and efficacy of clindamycin phosphate foam 1% versus clindamycin phosphate topical gel 1% for the treatment of acne vulgaris. *J Drugs Dermatol* 2005; 4: 48–56.
11. Frangos JE, Kimball AB. Clobetasol propionate emollient formulation foam in the treatment of corticosteroid-responsive dermatoses. *Expert Opin Pharmacother* 2008; 9: 2001–2007.
12. Lebwohl M *et al*. A randomized, double-blind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis. *Int J Dermatol* 2002; 41: 269–274.
13. Huang X *et al*. A novel foam vehicle for delivery of topical corticosteroids. *J Am Acad Dermatol* 2005; 53: S26–S38.
14. Stein L. Clinical studies of a new vehicle formulation for topical corticosteroids in the treatment of psoriasis. *J Am Acad Dermatol* 2005; 53: S39–S49.
15. Mazzotta A *et al*. Clobetasol propionate foam 0.05% as a novel topical formulation for plaque-type and scalp psoriasis. *J Dermatol Treat* 2007; 18: 84–87.
16. Franz TJ *et al*. Betamethasone valerate foam 0.12%: a novel vehicle with enhanced delivery and efficacy. *Int J Dermatol* 1999; 38: 628–632.
17. Andreassi L *et al*. Efficacy of betamethasone valerate mousse in comparison with standard therapies on scalp psoriasis: an open, multicentre, randomized, controlled, cross-over study on 241 patients. *Br J Dermatol* 2003; 148: 134–138.
18. Mancuso G *et al*. Efficacy of betamethasone valerate foam formulation in comparison with betamethasone dipropionate lotion in the treatment of mild-to-moderate alopecia areata: a multicenter, prospective, randomized, controlled, investigator-blinded trial. *Int J Dermatol* 2003; 42: 572–575.
19. Milani M *et al*. Efficacy of betamethasone valerate 0.1% thermophobic foam in seborrhoeic dermatitis of the scalp: an open-label, multicentre, prospective trial on 180 patients. *Curr Med Res Opin* 2003; 19: 342–345.
20. Olsen EA *et al*. A multicenter, randomized, placebo-controlled, double-blind clinical trial of a novel formulation of 5% minoxidil topical foam versus placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol* 2007; 57: 767–774.
21. Goldstein J, Gurge R. The treatment of hyperkeratosis with a new, 30% urea emollient foam: a series of case studies. *J Am Acad Dermatol* 2008; 58: AB41.
22. Weaire D, Hutzler S, eds. *The Physics of Foams*. Oxford: Oxford University Press, 2001: 1–18.
23. Purdon CH *et al*. Foam drug delivery in dermatology: beyond the scalp. *Am J Drug Deliv* 2003; 1: 71–75.
24. Sanders PA eds. *Handbook of Aerosol Technology*, 2nd edn. New York: Van Nostrand Reinhold Company, 1979: 299–309.
25. Anon. Summary of control measures under the Montreal Protocol. In: *Handbook for the Montreal Protocol on Substances That Deplete the Ozone Layer*, 7th edn. 2006: 27–40.
26. Vervaet C, Byron PR. Drug-surfactant-propellant interactions in HFA-formulations. *Int J Pharm* 1999; 186: 13–30.
27. McDonald KJ, Martin GP. Transition to CFC-free metered dose inhalers – into the new millennium. *Int J Pharm* 2000; 201: 89–107.
28. Wright P. Polymers for the colloidal stabilization of drugs in HFAs. *RDD IV* 2006; 1: 243–248.
29. Ridder KB *et al*. Surfactant solubility and aggregate orientation in hydrofluoroalkanes. *Int J Pharm* 2005; 295: 57–65.

30. Solvay Fluor. Solkane® 227 pharma and 134a pharma – properties. 2006.
31. Murray BS, Ettelaie R. Foam stability: proteins and nanoparticles. *Curr Opin Colloid Interface Sci* 2004; 9: 314–320.
32. Tamarkin D *et al.* Oleaginous pharmaceutical and cosmetic foam. US Patent Appl 20070292461 (2007).
33. Wai-Chiu S *et al.* Pharmaceutical composition. US Patent 6946120 (2005).
34. Tamarkin D *et al.* Foamable vehicle and vitamin and flavonoid pharmaceutical compositions thereof. US Patent Appl 20080069779 (2008).
35. Tamarkin D *et al.* Sensation modifying topical composition foam. US Patent Appl 20080253973 (2008).
36. Pilpel N. Foams in pharmacy. *Endeavour* 1985; 9: 87–91.
37. Schramm LL eds. *Emulsions, Foams, and Suspensions: Fundamentals and Applications*, 1st edn. Weinheim: Wiley-VCH. 2005: 201–223.
38. Purewal TS, Grant DJW. *Metered Dose Inhaler Technology.* Buffalo Grove: Interpharm Press. 1998: 97–99.
39. Zhao Y *et al*. Engineering novel topical foams using hydrofluroalkane emulsions stabilised with pluronic surfactants. *Eur J Pharm Sci* 2009; 37: 370–377.
40. Wilson AJ. Experimental techniques for the characterization of foams. In Prud'homme RK, Khan SA, eds. *Foams: Theory, Measurement and Applications*, 1st edn. New York: CRC Press. 1995: 243–274.
41. Stone HA *et al*. Perspectives on foam drainage and the influence of interfacial rheology. *J Phys Condens Matter* 2003; 15: S283–S290.
42. Langevin D. Aqueous foams: A field of investigation at the frontier between chemistry and physics. *Chemphyschem* 2008; 9: 510–522.
43. Abram AZ, Hunt BT. Pharmaceutical foam. US Patent 7374747 (2008).
44. Weaire D, Hutzler S eds. *The Physics of Foams.* Oxford: Oxford University Press. 2001: 56–75.
45. Kealy T *et al*. The rheological properties of pharmaceutical foam: implications for use. *Int J Pharm* 2008; 355: 67–80.
46. Peguin RPS *et al*. Microscopic and thermodynamic properties of the HFA134a-water interface: atomistic computer simulations and tensiometry under pressure. *Langmuir* 2006; 22: 8826–8830.
47. Selvam P *et al*. Surfactant design for the 1,1,1,2-tetrafluoroethane-water interface: ab initio calculations and in situ high-pressure tensiometry. *Langmuir* 2006; 22: 8675–8683.
48. Chokshi U *et al*. Reverse aqueous emulsions and microemulsions in HFA227 propellant stabilized by non-ionic ethoxylated amphiphiles. *Int J Pharm* 2009; 369: 176–184.
49. Feldman SR *et al*. Topical corticosteroid in foam vehicle offers comparable coverage compared with traditional vehicles. *J Am Acad Dermatol* 2000; 42: 1017–1020.
50. Huang X *et al*. A novel foam vehicle for delivery of topical corticosteroids. *J Am Acad Dermatol* 2005; 53: S26–S38.
51. Jones JI *et al.* Method of treating a skin disease with a corticosteroid-containing pharmaceutical composition. US Patent 6126920 (2000).
52. Abram AZ, Goldstein L. Fatty acid pharmaceutical foam. US Patent Appl 20080015271 (2008).
53. Abram AZ. Mousse composition. US Patent 7029659 (2006).
54. Abram AZ. Mousse composition. USA Patent 6730288 (2004).
55. Huggins JK, Houlden RJ. Film foaming hydroalcoholic foam. US Patent Appl 20060233727 (2006).
56. Zhao Y *et al*. A dynamic topical hydrofluoroalkane foam to induce nanoparticle modification and drug release in situ. *Eur J Pharm Biopharm* 2009; 72: 521–528.
57. Brown MA, Jones SA. Topical formulations. US Patent Appl 20090191271 (2009).