

Review Article

Towards sustainable pharmaceutical foams: A comparative review of propellant-containing, propellant-aided and propellant-free foams

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ABSTRACT

Pharmaceutical and personal care foams used for active pharmaceutical/cosmetic ingredient delivery are attractive formulations because of their ease of application, high spreadability including over hair-bearing skin, and ability to coat body cavity surfaces. Currently developed pharmaceutical foams for topical uses are propellant-containing whereas personal care foams may be propellant-containing or propellant-free, depending on their use. The use of propellants produces an elegant dosage form and provides benefits for topical drug delivery, however they are also associated with adverse environmental impact, safety challenges and more complex formulation development and manufacturing processes. To maintain the advantages of foams as topical dosage forms, whilst improving their environmental sustainability, propellant-aided foams based on Bag-on-Valve technology and propellant-free foams, including those using novel technologies such as EcoDrive™, may potentially be developed. Foams produced using propellants and propellant-free foams differ in their design and development in terms of formulation, method of foam generation and packaging requirements. These differences affect the quality of the final foam structure and its performance. This review, firstly, describes pharmaceutical liquid foams used for topical drug delivery and then compares them with propellant-aided and propellant-free foams in terms of their method of foam generation and formulation. This comparison identifies the potential and drawbacks of these formulations for pharmaceutical applications. Through this comparative study, the potential of eliminating environmentally hazardous propellants from these pharmaceutical formulations using ecofriendly technologies such as Bag-on-Valve and EcoDrive™ for topical drug delivery applications is discussed.

1. Introduction

Foams are dispersions of gas bubbles in a continuous phase such as a solid, liquid, or gel. This continuous phase with a thickness of 10nm–1µm creates a large surface area and the high content of gas in the foam structure results in their low specific density [1]. Foams, where the continuous phase is liquid are regularly developed for topical uses in pharmaceutical, cosmetic, and personal care products and are sometimes referred to as liquid foams to distinguish them from other types of foam [2,3]. Their low density and high surface area characteristics make foams relatively easy to apply and spread over large surface areas of the skin, including hair-bearing areas. They can be formulated to have improved aesthetic properties compared to other semi-solid products such as creams, ointments, or gels used for topical delivery [4]. Compared to liquid formulations, which flow easily, foams are easier to control on the site of application and can cover mucous membrane

surfaces when applied to body cavities [1,3]. Moreover, formulation of a product as a foam may provide improved drug/active delivery [5] which make foams an advantageous dosage form for patients and pharmaceutical or cosmetic formulators [6,7].

Pharmaceutical or medicated foams which are intended to be applied on the skin or mucous membranes are formed at the time of the administration through a specific device consisting of a container, valve and actuator. Once actuated, the surfactant-containing foam exhibits a light, semisolid structure and can be formulated to collapse rapidly into a liquid for quick absorption or to maintain the foam integrity for extended contact with the application site [8,9].

Pharmaceutical foam products have been used for various types of skin conditions such as rosacea [10], acne vulgaris [11,12], plaque psoriasis [13], and dermatitis [14]. One notable example is minocycline foam, which has demonstrated clinical efficacy for both rosacea and acne vulgaris. In two large phase 3 clinical trials, a 1.5 % minocycline

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foam significantly reduced inflammatory lesions in patients with moderate to severe papulopustular rosacea, whilst maintaining a favourable safety profile [15]. For acne vulgaris, a 4 % minocycline foam formulation has been extensively evaluated in multiple clinical studies [16–20]. These trials consistently reported significant reductions in both inflammatory and non-inflammatory lesion counts, along with high tolerability and minimal systemic absorption as an important advantage over oral antibiotics [16–20]. Foam formulations have also shown promise in managing truncal acne, a condition often challenging to treat due to the large surface area involved. A case series involving adult female patients reported successful outcomes using a combination of azelaic acid 15 % foam and tretinoin lotion 0.05 %, offering a topical alternative to systemic antibiotics with improved patient adherence [21]. Beyond acne, foam-based therapies have demonstrated effectiveness in treating inflammatory skin disorders such as plaque psoriasis and seborrheic dermatitis. A novel halobetasol propionate 0.05 % foam was shown to significantly improve clinical signs of psoriasis including plaque elevation, erythema, and scaling as well as pruritus, with a safety profile comparable to its vehicle and convenience of application over hairy or large areas [22]. Similarly, roflumilast foam 0.3 %, a nonsteroidal phosphodiesterase-4 inhibitor, has shown strong efficacy and tolerability in both phase 2 and phase 3 clinical trials for seborrheic dermatitis, with improvements in erythema, itch, and scaling [23,24].

Foam formulations have also been successfully applied beyond dermatological inflammation, particularly in hair regrowth therapies [25] and gastrointestinal conditions [26]. Minoxidil 5 % foam, available in both men's and women's formulations, is widely used for the treatment of androgenetic alopecia [25]. Its unscented, thermolabile foam format enhances ease of application and patient adherence [27,28]. Clinical studies have confirmed its effectiveness in increasing hair density over a 24-week period, with significant improvements observed in hair counts. Importantly, the treatment was well tolerated, and a high proportion of patients, i.e., over 90 %, reported satisfaction with the foam dosage form and its usability [29]. This high level of satisfaction highlights the importance of formulation design in promoting adherence and perceived treatment success.

Similarly, in the context of plaque psoriasis, real-world evidence from a multicentre observational study demonstrated that patients treated with a combination of calcipotriol and betamethasone dipropionate foam reported high satisfaction scores for both effectiveness and convenience [30]. These findings align with broader clinical data showing that foam formulations can offer enhanced efficacy compared to ointments and creams [31,32]. Moreover, patient preference studies consistently show a strong inclination toward foams over other topical vehicles ($P < 0.01$) [33], which contributes to improved-patient adherence [34–36].

This combination of clinical effectiveness, patient satisfaction, and better adherence has important implications for healthcare systems. By improving treatment outcomes and reducing the likelihood of non-compliance, foam formulations may help lower the overall burden on healthcare resources, minimising the need for additional interventions or specialist referrals [37]. A comparative study on the foam versus ointment formulation of betamethasone dipropionate and calcipotriol showed that the enhanced efficacy of foam resulted in fewer consultation visits, a lower risk of progressing to second-line therapy, and a more cost-effective treatment approach [38].

Pharmaceutical foaming formulations currently available are traditional propellant-containing foams in which the liquid is combined with a propellant or a mixture of propellants in a pressurised spray can. Although these pharmaceutical propellant-containing foams which contain surfactant(s), and aqueous or non-aqueous liquid [8] have shown good drug delivery features and foaming properties, there are some drawbacks associated with the propellants required for their formulation. Propellants used in pharmaceutical foams are mainly hydrocarbons or dimethyl ether (DME). The emission of these propellants into the atmosphere and their contribution to tropospheric ozone

pollution has a negative impact on the environment. Moreover, these flammable and explosive propellants cause safety challenges during their manufacturing, handling, transport, and upon application of product [13,39–41].

Despite these negative aspects, propellant-containing foams are highly desirable because of their advantages as topical drug delivery systems. Eliminating hazardous propellants from the formulation through developing non-hazardous propellant-aided foams and propellant-free foams are attractive alternatives.

Propellant-aided foams in which non-hazardous propellants such as compressed air or nitrogen are used apply a technology called Bag-on-Valve (abbreviated as BOV from here on) which has been available for some time but recently has seen a resurgence in interest. With this technology, environmentally friendly propellants are utilised with minimal pressure loss occurring within the packaging during use.

Currently, most topical propellant-free foam products on the market are for personal care uses which highlights their potential for translation into the pharmaceutical space and some academic studies have been performed to examine their merits. However, realising their potential for drug delivery applications requires appreciation of the characteristics of these foams in comparison to their propellant-containing counterparts, their capabilities as a drug delivery system and a critical understanding of challenges associated with developing these types of foams.

This review, which focuses on foams for pharmaceutical applications, provides an overview of foam formulation and describes the key components of their formulation, their stability, and their behaviour with particular reference to skin drug delivery, which is their commonest application. Propellant-containing, propellant-aided, and propellant-free systems are compared and discussed along with their recent promising development to produce foams. The devices required for generating foams upon application, environmental impact, manufacturing process complexities and cost are also discussed for each type of these foams.

2. Liquid foams and their stability

Liquid foams are two-phase systems in which the gas phase is distributed in a liquid phase [42]. The dispersed gas is in the form of bubbles with a variable size from micrometres to millimetres [43]. To create the gas-liquid interface in the foaming process, energy is required. This energy is the product of surface tension and total area created. However, the system of bubbles in the foam tends to reach the minimum surface area and energy. This results in the complete separation of gas and liquid phases causing foam destruction. Therefore, surface-active agents or surfactants are added to the liquid formulation intended to foam. These are adsorbed at the gas-liquid interface reducing the surface tension and the amount of energy required to create the bubble interfaces in the foam structure, facilitating foam formation and improving its stability (Fig. 1) [42,44]. Foams remain thermodynamically unstable however and will collapse with time. They are destabilised through three dynamic destabilisation processes; coalescence, coarsening, and drainage [45]. Coalescence refers to the rupture of the thin liquid film separating bubbles in the foam structure. Coarsening or disproportionation happens as a result of gas diffusion from high pressure areas to lower pressure areas amongst the bubbles. During coarsening, the size of smaller bubbles decreases until they disappear, whereas larger bubbles grow, and the total number of bubbles is reduced. Drainage refers to the flow of liquid through the Plateau borders, which are the liquid microchannels in which three thin liquid films meet. When a fresh liquid foam is applied on a surface, under the influence of gravity, the liquid starts to drain out through the Plateau border network. This results in a dry foam with a lower liquid volume fraction at the top and a wet foam with a higher liquid volume fraction at the bottom of the foam structure. The shape of the bubbles and structure of the liquid foam depends on liquid volume fraction (ϕ_l) which is

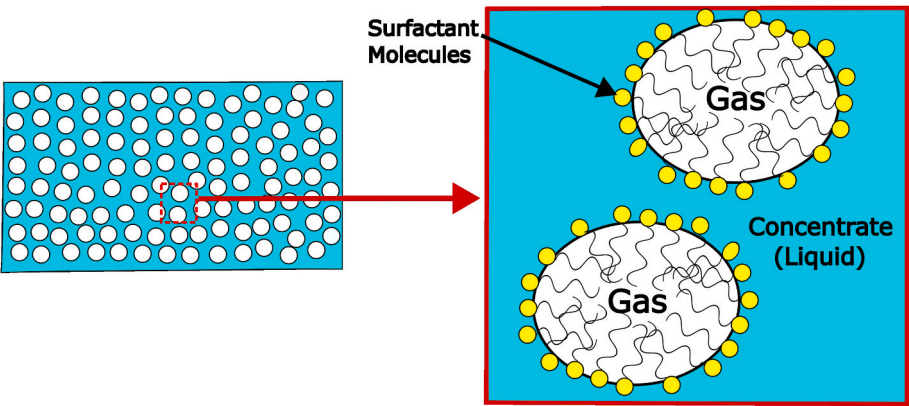


Fig. 1. Gas-liquid interface covered by surfactant molecules in the foam structure.

defined in Equation (1).

$$\varphi_l = \frac{V_l}{V_f}$$

Equation 1

In this equation, V_l and V_f are the volumes of liquid and foam, respectively. At high liquid volume fractions (wet foams), the bubbles in a foam structure are spherical whereas smaller liquid volume fractions (dry foams) result in the deformation of bubbles to a polyhedral shape (Fig. 2) [42,46–48]. Analysis of the microgeometry of bubbles and liquid films is important in the study of foam stability and destabilisation

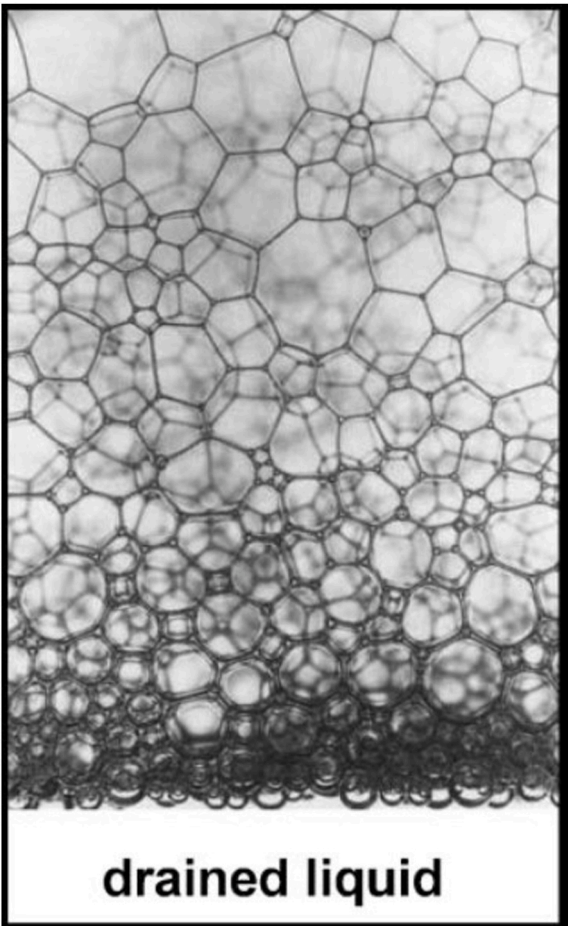


Fig. 2. A foam after drainage. Dry foam with low liquid volume fraction at the top shows polyhedral bubbles. Wet foam with high liquid volume fraction at the bottom shows spherical bubbles [47].

which must be tailored for specific applications such as drug delivery [49].

Surfactants which are considered as foaming agents slow down the dynamic destabilisation processes, i.e. drainage, coarsening, and coalescence [42]. However, in many cases, foam bubbles break easily due to the destabilisation mechanisms. Therefore, foam stabilisers can also be added to the foam formulation to boost foam formation and the stability of the foam. Foam stabilisers increase the viscosity of the foaming solution and extend the foam life [50].

3. Topical Foam formulations

Different active pharmaceutical ingredients (APIs) such as anti-acne agents, steroids, anti-inflammatory agents, vitamins, antibiotics, and antifungals have been incorporated into liquid foam formulations [51]. Prior to the addition of propellant, the API and rest of the foam formulation which is in liquid state and is known as the concentrate is formulated [52,53]. Typical components of the concentrate of topical foams include: the API, solvents, surfactants and foam stabilisers [54]. Other formulation ingredients such as antioxidants or preservatives may also be added as required.

The concentrate could be aqueous, oil-based, an emulsion, micro/nano-emulsion, suspension, hydroethanolic, or based on an alternative solvent (Table 1) [3,51,54]. For example, the concentrate in Finacea® foam used for topical treatment of rosacea is a suspension of azelaic acid in an oil-in-water emulsion [10]. In contrast, the concentrate could be a non-aqueous oil-based suspension as in the case with AMZEEQ®, a minocycline containing foam, used for the treatment of acne [55].

A wide variety of solvents are suitable for inclusion in foam formulations and may be selected for their suitability based on the solubility and stability of active ingredients as well as the clinical application.

Table 1
Classification of foams [3,51,54].

Class	Formulation Base	Topical Dosage Form
Aqueous foam	Water, surfactants, and gelling agent	Gel
Oil foam	Oil	Oil solution, oil suspension
Lipophilic emulsion foam	Water-in-oil emulsion	Cream, emulsion
Hydrophilic emulsion foam	Oil-in-water emulsion	Cream, emulsion
Nano-emulsion foam	Oil-in-water nano-emulsion	–
Suspension foam	Suspension of non-soluble components	Topical suspension
Hydroethanolic foam	Ethanol in high amount and water	Solution, tincture
Potent solvent foam	High concentrations of strong solvents	Solution, gel

They may also have a further functionality beyond that of a solvent, for example, hydrophobic/oil-based solvents may be used as emollients whilst others can act as chemical penetration enhancers, increasing the penetration of APIs through the skin barrier [54].

Choosing a suitable combination of surfactants and foam stabilisers with non-irritant behaviour on the skin is crucial during formulation [56,57]. Concentrates can contain any type of surfactant; anionic, cationic, zwitterionic, or nonionic surfactants. In formulations where ionic surfactants may be a source of skin irritation, nonionic surfactants can be used as surface-active agents [58]. In combination with surfactants, cosurfactants are also used to cooperate with surfactants to improve the foaming properties. Fatty acids are a category of cosurfactants which are sometimes called foam boosters [59]. Foam stabilisers such as polymers can be combined with surfactants to delay foam collapse after it has been formed [54].

Additional excipients such as preservatives and chemical penetration enhancers may also be added to the concentrate formulation [51,54]. To develop an ideal foam formulation, all excipients should be non-toxic, non-allergenic, and non-irritating on the skin [60,61].

The type and concentration of surfactant, cosurfactant, foam stabilisers, and interactions between various ingredients in the formulation affect the surface tension and thickness of the inter-bubble film of liquid in the foam structure. Therefore, foam formulation directly impacts foam stability [59,62].

4. Foam-based topical drug delivery

When topical foams are applied onto the skin surface, a network of bubbles with low density and large surface area is formed on the skin. This foam structure should be stable enough that it resists the liquid phase flowing off the skin, yet it should eventually break down on the skin, including in response to being rubbed (shear forces), releasing the gas in the foam structure and depositing a residual layer on the skin surface (Fig. 3) [63].

Drug delivery to the skin will be controlled by the properties of this residual layer [63]. A high local concentration/saturation of the active ingredient in the residual layer will provide a thermodynamic driving force for drug delivery to the skin [5,63]. The use of volatile propellants or solvents which evaporate upon the application can improve saturation and drug delivery which may also be influenced by formulation excipients such as chemical penetration enhancers [3,40]. Drug delivery to the skin from a foam vehicle may potentially also be influenced by the foam characteristics through bubble motion or coalescence in which the size of the bubbles becomes bigger causing rapid liquid film drainage [64]. This liquid film increases the local hydrodynamic pressure which may result in enhanced treatment penetration [64,65], although there is a scarcity of research relating foam characteristics and topical drug delivery.

Topical foams may exhibit different behaviours in terms of stability/breakability on the skin which affecting the formation of the residual layer from which drug delivery occurs. Based on their breakability,

topical foams can be classified into three groups [3]:

1. Quick-breaking foams: These thermally unstable foams such as hydroethanolic foams collapse once they make contact with the skin. An example of a thermolabile hydroethanolic foam is Evoclin® Foam which is indicated for acne vulgaris [11].
2. Breakable foams: These foams remain stable at skin temperature though they easily collapse and spread when mild shear forces are applied. Some dermatological foams products use such foams which possess both thermal stability and convenient spreadability.
3. Lathers or soapy foams: These foams will remain stable upon application on the skin or their volume increases when they are rubbed onto the skin. Foaming cleansers are an example of such foams which normally need removal by washing with water after application [3].

In the design process of a topical foam product, the desired qualities of the final foam including stability, breakability, and consistency which depend on the application and/or indication for which the foam is used are considered [66]. For pharmaceutical applications, which are typically 'leave-on' applications, quick-breaking and breakable foams are used because these types of foams are not washed off the skin after application. Upon application of these pharmaceutical foams onto the skin, the foam lattice will break down due to either thermal instability or shear forces.

5. Topical propellant-containing foams

Currently available pharmaceutical foam products in the market contain propellants in contact with the formulation [3]. In pharmaceutical propellant-containing foams, a liquid foam concentrate containing the API is placed in a pressurised spray can along with single- or multi-component gases [63]. The containers can be made of tin-plated steel or aluminium and must be able to withstand the required pressure [52,53]. The method of foam production from this spray can is known as sudden pressure reduction (Fig. 4, a). The propellant gas is dissolved in the liquid concentrate under pressure and thus is in direct contact with the concentrate formulation [67]. By increasing the pressure in a closed system of gas and liquid, the liquid becomes supersaturated with gas and most of the propellant in the container is dissolved in the concentrate, with some being present in the form of vapor in the head space [63]. Upon actuation of the valve on the pressurised spray can, the pressure is released, and the propellant-containing formulation is ejected from the can. With the sudden pressure reduction, bubbles are formed within the foam that is generated (Fig. 5) [3,68–70]. Upon evaporation of the propellants which can act as solvents for the API, high saturation of the API in the foam and residual formulation may be produced, providing the driving force for drug delivery.

For pharmaceutical products, propellants such as hydrocarbons (such as n-butane, n-propane, isobutane, n-pentane, isopentane, or a mixture of them), DME, or hydrofluoroalkanes (HFAs) are typically used (Table 2). The boiling point of the propellant which affects its rate of

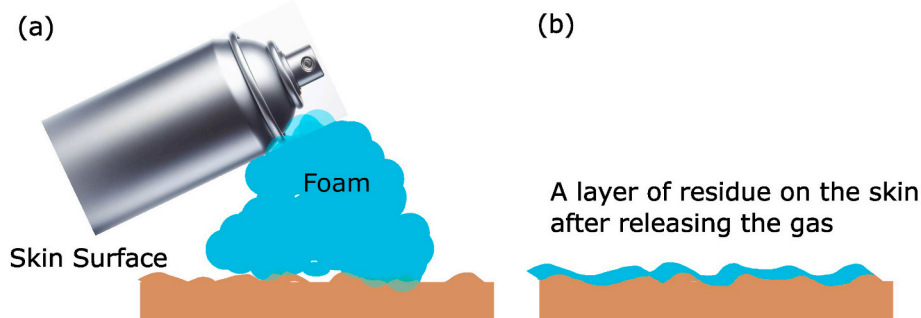


Fig. 3. (a) Foam on the skin surface, and (b) formation of a residual layer on the skin surface after releasing the gas.

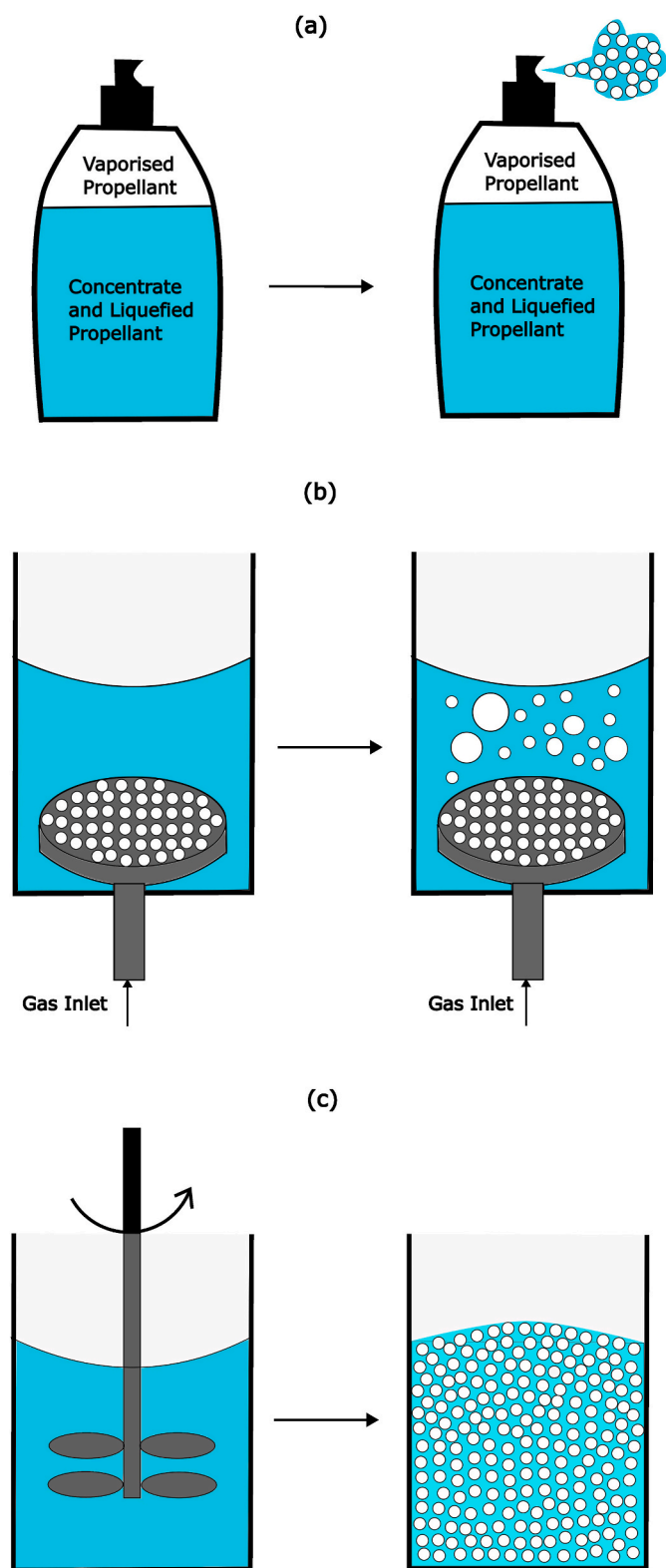


Fig. 4. Foam production methods: (a) sudden pressure reduction, (b) injection or gas bubbling, and (c) agitation.

evaporation and formation of residual layer is a key point in choosing the propellant or mixture of propellants in the propellant-containing system [71,72]. Moreover, the propellants must provide suitable pressure inside the container as well as compatibility with the product and packaging [67,73]. Some products such as ecoza® antifungal foam contain only one hydrocarbon propellant [74] whereas most

propellant-containing foam products usually use a blend of various components such as n-butane, propane, isobutane, n-pentane, and isopentane to achieve an acceptable internal pressure and compatibility with formulation and the container [67,73]. An example of a foam using a mixture of hydrocarbon propellants is SORILUX™ used for the topical treatment of plaque psoriasis of the scalp [75].

Other propellants that have been used in foams more generally include compressed gases (such as carbon dioxide, nitrogen, and nitrous oxide) [63], which are more popular for food applications [5,69,76,77]. Because of the low boiling point of these compressed gases, accurate dosing of a pharmaceutical foam product is likely to be challenging when these gases are used as propellants in direct contact with the liquid concentrate [40]. However, there are literature reports of nitrous oxide (N_2O) being used as a propellant to produce temperature-responsive foam formulations to study their potential for nanoparticle delivery [78].

Propellant-containing foams using a spray can dispense a drug dose without introducing environmental contamination including oxygen and moisture to the formulation, helping to maintain product stability. These foams are viscous and have fine porosity (Fig. 6, a) [3]. Moreover, they can be formulated as both quick-breaking, i.e., thermolabile, and breakable foams requiring a shear force upon the application. The full range of pharmaceutically acceptable solvent systems can be incorporated in propellant-containing foams. Oil-in-water emulsion propellant-containing foams for pharmaceutical and cosmetic purposes have been used in traditional devices in which hydrophobic solvent(s), water, foam stabiliser, surfactant, and water gelling agent are used in combination with a liquified gas propellant [79]. There are also propellant-containing foams of water-in-oil emulsions or lipophilic emulsion foams in which both hydrophilic and lipophilic drugs can be carried. Hydroethanolic propellant-containing foams have also been used to increase drug bioavailability [51]. There are also some oil-based propellant-containing foam formulations in which no water has been used. In these waterless formulations, an oil and a surfactant are used as the carrier for the propellant-containing pharmaceutical composition [54,80]. Non-aqueous foam delivery systems have shown benefits for the delivery of APIs that have limited stability in aqueous media. Enstilar® Foam used for topical treatment of plaque psoriasis is an example of such a non-aqueous foam [13]. In this product, calcipotriene and betamethasone dipropionate, which are individually stable in alkaline and acidic environments respectively, have been combined in a paraffin based foam system [72]. Other solvents such as propylene glycol may also be used in non-aqueous foams [81]. In some formulations, excipients such as ethanol are specifically avoided. For example, alcohol-free foams for the treatment of mild-to-moderate psoriasis have shown a high rate of acceptability and rapid effectiveness [36]. Gelling foams and nanosuspension foams are other examples of foam formulations that have been developed in which propellants have been used [82–85].

In addition to propellant-containing foams used for skin drug delivery, rectal foams such as Salofalk® containing mesalamine (mesalazine) and propellants have been developed for treating inflammatory bowel disease [26]. More examples of dermatological and rectal foams using propellants are listed in Table 2.

As shown in Table 2, most of pharmaceutical foam products use volatile organic compounds (VOCs) including hydrocarbons and DME as the propellant. Due to the contribution of VOCs to tropospheric ozone pollution, using them as the propellants is not ideal from an environmental perspective [41]. Moreover, VOCs affect human health through direct inhalation or through contribution to degraded air quality [41]. Although propellants such as chlorofluorocarbons (CFCs) which contribute to ozone layer depletion and global warming have been phased out [40,54,101], some medical propellant-containing foams such as Enzoclear™ Foam for acne treatment still use HFA-134a [1,100]. This hydrofluorocarbon is a greenhouse gas with approximately 1500 times greater global warming potential than CO_2 [102,103].

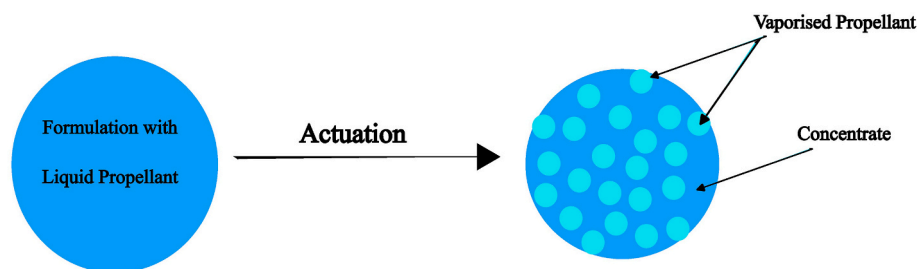


Fig. 5. Formation of propellant-containing foams due to the presence of propellant in the concentrate.

In addition to the adverse environmental impact of propellants used in propellant-containing foams, the manufacturing process requirements can be challenging. For pharmaceutical propellant-containing foams, cold-filling and pressure-filling processes are the two main techniques used [70]. In the cold-filling process, the propellant gas is first liquified by decreasing its temperature to -34°C to -40°C . The concentrate is also chilled to be added to the propellant in the container. The formulation must not be negatively impacted by the cold temperatures which could for example affect the solubility of the drug or excipients in the formulation [70,104]. To overcome these challenges the pressure filling process is now more common where the concentrate and propellant are mixed inside the container under pressure [70]. This process also has the benefits of less loss of propellant and reduced risk of moisture contamination [70,105].

The environmental challenges, along with the time consuming and costly development and manufacturing processes of propellant-containing foams are of significant drawbacks. Therefore, consideration of technologies using less hazardous propellants and also propellant-free methods to generate foams for pharmaceutical applications may be promising solutions which will be discussed in the following sections.

6. Topical propellant-aided foams

For propellant-containing foams, hazardous substances with significant environmental impacts and stringent safety requirements are often utilised. This issue can be mitigated by employing less harmful propellants. However, because of the low boiling points of these less harmful alternatives, such as air and nitrogen, achieving precise dosing in pharmaceutical foam products presents a considerable challenge if these are used similarly to current pharmaceutical products, where the propellant forms part of the pharmaceutical formulation.

BOV technology might be a suitable solution for these challenges [106]. This technology is based on an airtight container in which propellants are usually outside the bag containing pharmaceutical formulation. In this system shown in Fig. 7, a valve has been sealed with a laminated multilayer airless bag in which the concentrate is filled. The BOV containing the concentrate is placed inside a can filled with a non-hazardous environmentally friendly propellant (air or nitrogen) in either its liquid or compressed gas state. In this propellant-aided technology, the role of the propellant is to squeeze the foaming content out of the bag.

Despite using compressed air or nitrogen, the pressure loss in BOV systems is similar to conventional propellant-containing cans [106]. Therefore, provision of accurate dosing is comparable with propellant-containing foams. BOV technology is suitable for oxygen-sensitive products and those where maintaining product integrity and preventing environmental contamination are crucial. The design of this technology provides a high range of product emptying. It also enables 360-degree actuation and can be used in any position, unlike conventional propellant-containing containers that should be held vertically for optimal performance. This feature is particularly significant for the application of pharmaceutical products in areas of the body

where maintaining the canister in a vertical position may be challenging, such as with rectal administration. Additionally, BOV technology can be used for both viscous and liquid concentrates [107]. This technology has been used to produce pharmaceutical and medical device products such as eyewash sprays, nasal sprays, ear sprays, burn gels, and skin disinfection sprays [108].

For foam formulations, BOV technology may be modified so that, the formulation also contains some propellant. This may be a conventional propellant, e.g. VOC or environmentally friendly propellant, but typically would be included at a lower level than propellant containing formulations [109,110]. This alongside suitably developed valves enable the production of foams using BOV technology and has been used for shaving and depilatory foaming gels, creating a post-foaming effect after the product is applied to the skin [107,111]. Similar to the foam formation mechanism in propellant-containing foams, the foam produced by the modified BOV technology is also created through the evaporation of the propellant [109,111,112]. Consequently, this may affect drug saturation in the residual formulation left on the skin surface and could improve drug delivery in a similar way to propellant-containing foams.

Foam formulations utilising BOV technology, where some propellant or dissolved gas [65] is contained within the formulation bag, benefit from the advantages of BOV, including the use of environmentally friendly propellants to provide adequate pressure provision. The manufacturing process of propellant-aided products using the BOV technology however can be as complex and expensive as conventional propellant-containing products. Although there are currently no foam products employing BOV technology without propellants inside the formulation bag, this technology has demonstrated significant potential for further development and innovation [111,113].

7. Topical propellant-free foams

A wide variety of personal care propellant-free foam products such as cleansing foams and foaming soaps can be found in the market (Table 3). Propellant-free foams can be produced using various methods including gas bubbling (injection) and agitation. With the bubbling method, gas is sparged through a surface with narrow capillaries into the liquid. At the end of each capillary, the injected gas is detached from the surface and bubbles are formed directly (Fig. 4, b). The bubble size is controlled by the diameter of the capillaries or small pores. The foam volume and properties depend on the size and layout of the capillaries, the amount of surface-active agent, and the gas flow rate through the capillaries. Gas bubbling which is sometimes also known as Bikerman's method reproducibly generates foams with uniform bubble size [3,68,69,114].

Agitation is another propellant-free mechanical method that can be used to obtain a foam. Stirring, pouring, shaking, and whipping are different types of agitation. With the agitation method, the liquid concentrate containing surface-active agents is agitated so that the gas is incorporated into the liquid continuous phase and a gas-liquid interface is formed (Fig. 4, c). Several process parameters affect the foam microstructure obtained from a device used for agitation. The power input, residence time in the agitation geometry, rotational velocity,

Table 2

Examples of dermatological/rectal propellant-containing foams based on the propellants used in their composition.

Active Ingredient (s)	Indication(s)	Trade Name	Propellant
Hydrocarbon-based Propellants			
Azelaic Acid	Topical treatment of inflammatory papules and pustules of mild to moderate rosacea	Finacea®	Isobutane, butane, and propane [10]
Betamethasone Valerate	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp.	Luxiq®	Propane and butane [86]
Budesonide	Remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.	Uceris®	Isobutane, n-butane, and propane [87]
Calcipotriene	Topical treatment of plaque psoriasis of the scalp and body in patients 12 years and older.	SORILUX®	Isobutane, n-butane, and propane [75]
Clindamycin	Treatment of acne vulgaris in patients 12 years and older.	EVOCLIN®	Propane and butane [11]
Clobetasol Propionate	Treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients aged 12 years and older.	Olux-E®	Propane and butane [88]
Coal Tar	Relief of the symptoms of psoriasis.	Scytera™	Propane and butane [89]
Desonide	Topical treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.	Verdeso®	Propane and butane [14]
Econazole Nitrate	Treatment of interdigital tinea pedis caused by Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum in patients 12 years of age and older.	ecoza®	Butane [74]
Halobetasol Propionate	Topical treatment of plaque psoriasis in patients 18 years of age and older.	LEXETTE™	Isobutane and propane [90]
Hydrocortisone Acetate and Pramoxine Hydrochloride	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.	epifoam®	Isobutane and propane [91]
Hydrocortisone Acetate	As adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.	cortifoam®	Isobutane and propane [92]
Hydrocortisone Acetate and Pramocaine Hydrochloride	Relief of the inflammatory and pruritic manifestations of corticosteroid-	Proctofoam HC	Isobutane and propane [93]

Table 2 (continued)

Active Ingredient (s)	Indication(s)	Trade Name	Propellant
Ketoconazole	responsive dermatoses of the anal region. Treatment of seborrheic dermatitis in immunocompetent patients 12 years of age and older.	extina® & Ketodan®	Propane and butane [94,95]
Mesalazine	Treatment of active, mild ulcerative colitis of the sigmoid colon and rectum.	Salofalk	Isobutane, n-butane, and propane [26]
Minocycline	Treatment of inflammatory lesions of rosacea in adults.	zilxi™	Isobutane, n-butane, and propane [96]
Minocycline	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.	AMZEEQ®	Butane, isobutane, and propane [55]
Minoxidil	Hair regrowth treatment.	Rogaine	Propane and butane [27,28]
Roflumilast	Treatment of seborrheic dermatitis in adult and pediatric patients 9 years of age and older.	ZORYVE®	Isobutane, butane, and propane [97]
Selenium sulfide	Treatment of seborrheic dermatitis and tinea versicolor of the skin.	TERSI FOAM	Butane, propane [98]
Tazarotene	Topical treatment of acne vulgaris in patients 12 years of age or older.	Fabior™	Isobutane, n-butane, and propane [99]
Dimethyl Ether-based Propellants			
Betamethasone Dipropionate and Calcipotriene	Topical treatment of plaque psoriasis in patients 18 years of age and older.	Enstilar®	Dimethyl ether and butane [13]
HFA-based Propellants			
Benzoyl Peroxide	Topical treatment of mild to moderate acne vulgaris.	Enzoclear™ Foam	1,1,1,2-tetrafluoroethane (HFA-134a) [100]

static pressure, and temperature are some of the parameters affecting the structure of such foams [3,69,115,116]. Some academic studies have considered the gas bubbling method and agitation techniques in the development of pharmaceutical foams in the laboratory [101,117–121].

The main component of a commercial device used for propellant-free foam production is a foaming pump which is a foam-forming assembly comprising of a valve and a housing with liquid passage, air passage, dispensing passage, and dispensing opening. By compressing the pump, the pressure in the container, liquid passage, and air passage is increased. A stream of air and a stream of liquid come in contact in the dispensing passage. In this passage, the mixture is passed through a number of sieves or porous matrix to generate the foam. This foam is dispensed through the dispensing opening [125,126]. Airspray® foam dispenser is an example of a foaming pump [125,126]. The design of the foaming pump can be altered, although the mechanism of operation is usually similar [127]. Because of their design, there is the possibility of environmental exposure of the unused portion of the content due to ingress of air into the container and suction of the small amount of liquid present in the pump head into the pump system following actuation [39,128]. Using a propellant-free foaming pump device, various classes of foams such as aqueous, hydroethanolic, and alcohol-free foams can be formulated [121,128,129].

Propellant-free foams have shown increasing potential in pharmaceutical applications, particularly for topical drug delivery. For instance,

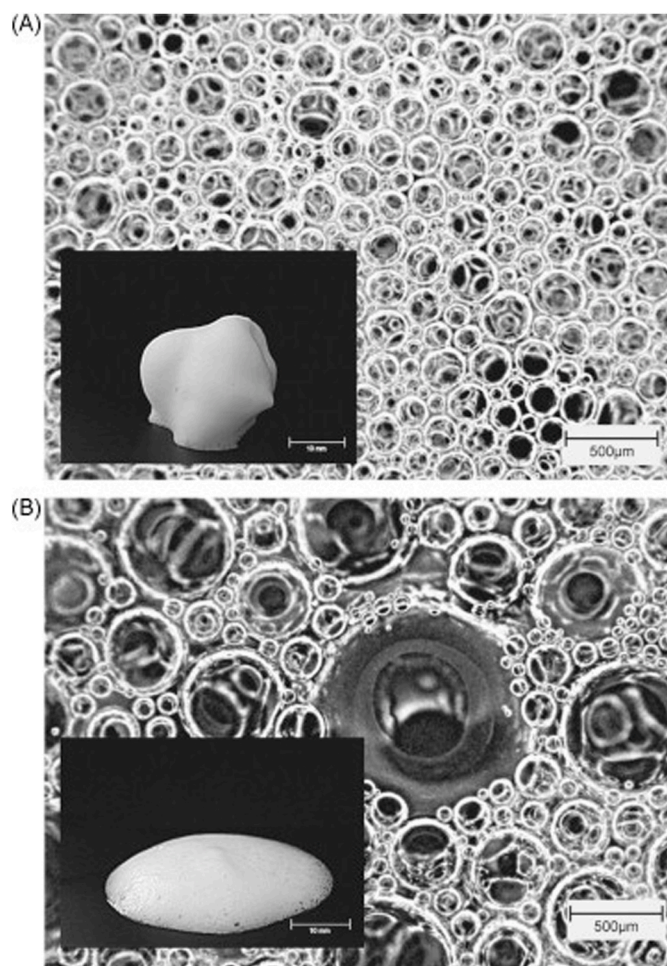


Fig. 6. Macroscopic and microscopic comparison between a (a) propellant-containing foam, and a (b) propellant-free foam [3].

atorvastatin has been successfully incorporated into lipoidal nanovesicles called emulsomes and formulated into an aqueous-based propellant-free foam, demonstrating good foam stability (Fig. 8) [118]. Similarly, a rapid release of diclofenac sodium from a propellant-free foam carrier has been observed in both *in vitro* and *ex vivo* studies, suggesting promising performance for topical drug delivery [4]. These systems also offer the flexibility to combine multiple APIs in a single formulation. For example, propellant-free foams with an oil-in-water emulsion base, combining hydrophilic salicylic acid and lipophilic cholecalciferol, have been developed for psoriasis treatment, showing favourable spreadability and physicochemical stability [119].

Propellant-free foam formulations can be optimised, for example by using emollients to maintain or increase the moisture content of stratum corneum (SC) [129,130]. Studies have shown that these formulations can also be combined with chemical penetration enhancers such as oleic acid, oleyl alcohol, and isopropyl myristate to achieve an optimised propellant-free alcoholic and hydroalcoholic foam formulations [7, 131].

Although the number of patents and academic studies on propellant-free formulations for pharmaceutical and drug delivery applications is limited, the existing research suggests that propellant-free foams have potential to work alongside propellant-containing foams as effective drug delivery systems. However, the differences between propellant-containing foams and propellant-free foams need to be considered during the development process. Propellant-free foams are less viscous

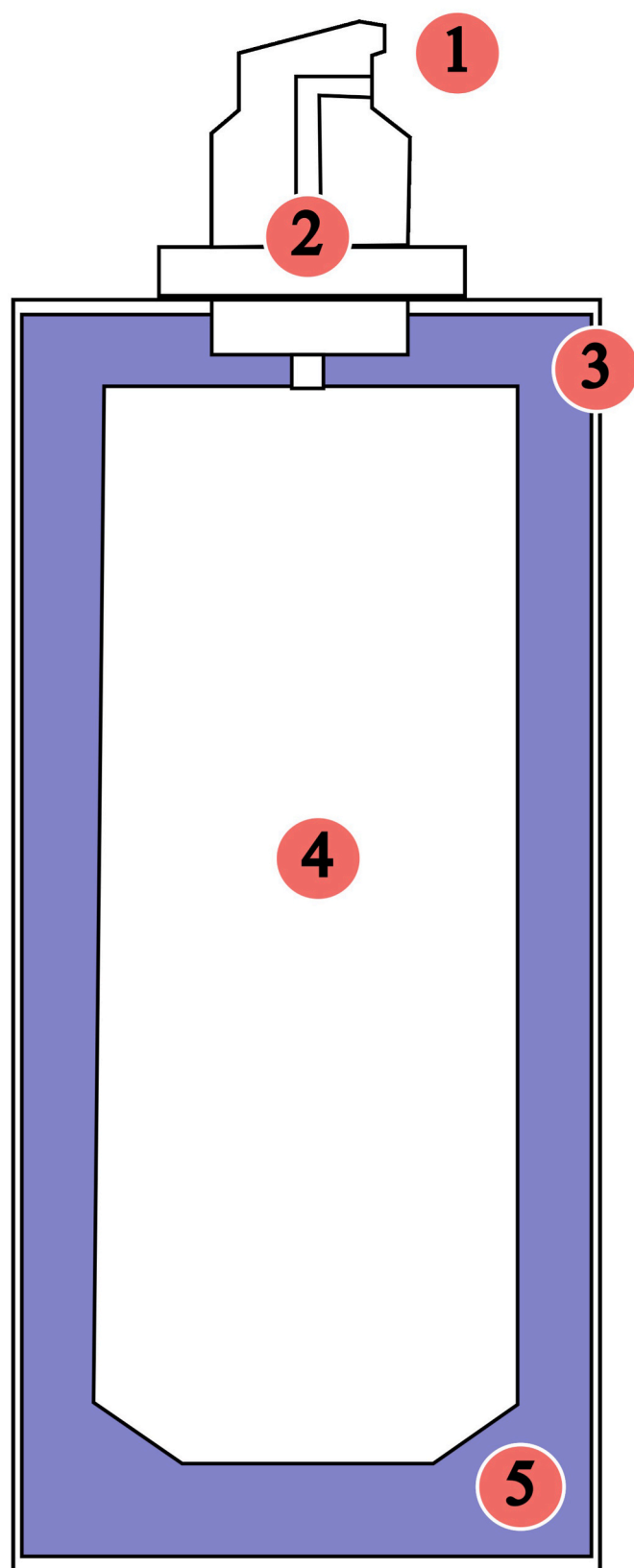


Fig. 7. Components of the spray device using BOV technology: (1) actuator, (2) valve, (3) can, (4) concentrate inside the bag, and (5) propellant.

Table 3

Some examples of propellant-free foams currently on the market [122–124].

Active Ingredient(s)	Indication(s)	Trade Name	Remarks
2QR-Complex, a Patented Bio-active Bacterial Blocker	Rapid relief from irritation, itching and sensitivity associated with chickenpox in children.	PoxClin Cool Mousse	Intended for larger areas. No rub is required for being absorbed.
Aloe Vera, Tea Tree Oil, Allantoin, and Oil Control Complex	Cleansing the skin of impurities and makeup.	novaclear ACNE Facial Foam	Rinsing with lukewarm water is required.
Camomile Extract	Cleansing agent with soothing effects.	B. CLEANSE INSTANT FOAMING CLEANSER	Rinsing is required.
Coconut Yogurt	Cleanser with minimising signs of irritation and blemishes.	Naturally Radiant GLOW	Rinsing is required. For richer foam, the bottle should be shaken before use.
Hyaluronic Acid and Amino Acids	Cleanser of dirt and makeup.	CeraVe Hydrating Cream-to-Foam Cleanser	Rinsing is required.
Hyaluronic acid, Niacinamide, and 3 Essential Ceramides	Cleanser to help maintain the skin's barrier, attract hydration and calm the skin.	CeraVe Foaming Cleanser	Rinsing is required.
Tea Tree Oil	Anti-Blemish cleanser with purifying and antibacterial properties.	tea tree FOAMING FACIAL WASH	Rinsing is required.
Tea Tree Oil, Chamomile Extract, D-Panthenol, Allantoin and Boric Acid	Ocular cleansing to remove secretions from eyelashes and eyelids, caused by inflammatory conditions due to blepharitis and blepharo-conjunctivitis or after surgery. Daily hygiene and removal of the ocular secretions from the eyelids of contact lens wearers.	naviblef	Rinsing is required.
Vitamin E, Pro-vitamin B5, and Glycerin	Daily cleanser and softener.	Cetaphil Gentle Foaming Cleanser	Rinsing is required.

than propellant-containing foams which have finer porosity (Fig. 6) [3]. The viscosity of such propellant-free formulations can be tailored though, using foam stabilisers such as polymers which improve the foam properties by increasing the viscosity and stabilising the foam structure. Xanthan gum, hydroxyethyl cellulose (HEC) and hyaluronic acids are the examples of such polymers that can be used in propellant-free foams [120]. As there are no hazardous propellants in propellant-free foams, the *in situ* analysis of these foams is more convenient than that of propellant-containing foams, simplifying their development [39]. In addition to the wide range of possibilities in modifying the formulation, propellant-free foams are convenient to use for patients and end users. In some cases, such as in the treatment of burns, propellants may cause irritation and damage of the skin tissue, and propellant-free foams may be preferred [121].

In addition to the demonstrated benefits and patient-friendliness of these propellant-free foam delivery systems shown in *in-vitro*, *ex-vivo*, and *in-vivo* academic studies [118,119,121], they are convenient in terms of manufacturing and quality control. In the manufacturing

process of propellant-free foams, the liquid reservoir is filled with the pharmaceutical propellant-free formulation. Then, a suitable foam dispenser or foaming pump is inserted on the reservoir [3].

Despite these advantages, potential environmental contamination of propellant-free foams using foaming pump devices following their first use remains a concern. With propellant-free foam pump devices, the container is not airtight. Therefore, oxidation and moisture contamination of the pharmaceutical concentrate inside the liquid reservoir may occur. Therefore, this critical packaging point must be considered when propellant-free foams are being considered as a potentially commercial alternative for propellant-containing and propellant-aided pharmaceutical foam products.

To overcome this issue, EcoDrive™ technology has been developed by GreenSpense. EcoDrive™ is a dispensing system which combines the principles of BOV technology and propellant-free dispensing systems [132,133]. With the EcoDrive™ technology, which is refillable and does not use any gas propellant [134], an elastic sleeve fitted over bag imparts the pressure to the bag to dispense the concentrate through the valve and actuator. As a propellant-free variant of BOV technology, EcoDrive™ offers reduced costs and simplified manufacturing and supply chain processes compared to propellant-aided BOV technology in the production of dispensable pharmaceutical products. Therefore, EcoDrive™ propellant-free technology holds significant potential to facilitate the development of efficient pharmaceutical foaming products with a reduced carbon footprint and lower costs, provided that foam formation is achievable, compared to propellant-containing and propellant-aided foam products.

In this context, packaging innovation such as the use of advanced dispensing systems like EcoDrive™ can serve as a valuable complement to formulation development. While formulation strategies aim to optimise foam stability, drug delivery, and patient acceptability, packaging solutions help maintain product integrity, prevent contamination, and ensure consistent application performance. A synergistic approach that integrates both formulation and packaging considerations is therefore essential for the successful development and commercialisation of propellant-free pharmaceutical foams.

A summary of the comparison between propellant-containing, propellant-aided, and propellant-free foams has been provided in Fig. 9.

8. Conclusion

Pharmaceutical and personal care foams including dermatological and rectal foams for topical drug and cosmetics delivery can be produced using propellant-containing foam dispensing systems, propellant-aided BOV technology dispensing systems, and propellant-free foam pumps. Currently, the available pharmaceutical foam products on the market are all propellant-containing which can provide ideal foam characteristics and protect the formulation from environmental exposure during usage. However, they have a negative environmental impact because of the hazardous propellants they contain and their development and manufacturing process can be lengthy and expensive. In contrast, propellant-free foams are easier to manufacture and do not have these environmental concerns. Various classes of foams can be incorporated into propellant-free formulations and the devices are simple, cost-effective, and convenient-to-use. However, the lower viscosity of foams they produce may not be suitable for some pharmaceutical applications. Moreover, the formulation may be at risk of contamination or stability issues following its first use as it is not sealed from the environment. To provide the advantages of both propellant-containing and propellant-free foams and eliminate/reduce their disadvantages, propellant-aided foams have considerable potential. BOV technology provides a more environmentally friendly alternative to traditional propellant-containing foams, utilising compressed gases such as nitrogen as a propellant, which is kept separate from the formulation. The airtight packaging in the BOV system protects the formulation from the environment once in use. BOV technology can be modified to include

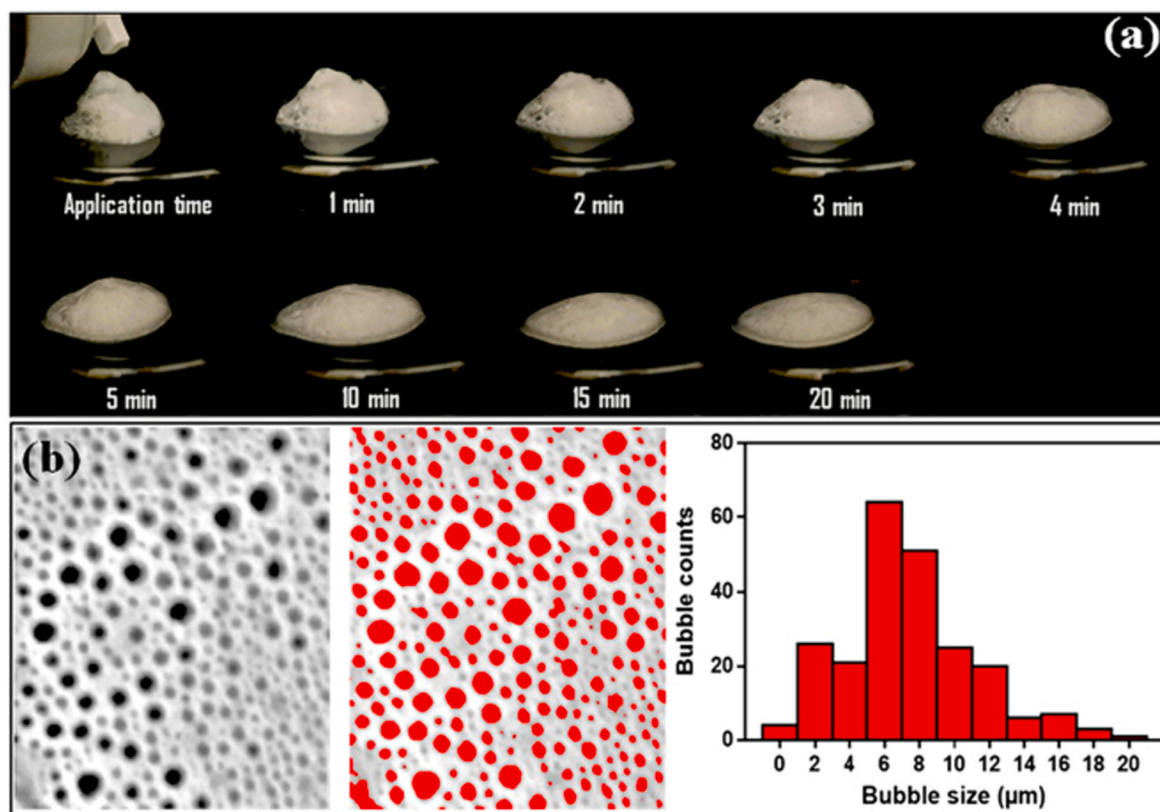


Fig. 8. (a) Foam collapse time after actuating from the side view and (b) bubble size distribution analysis [118].

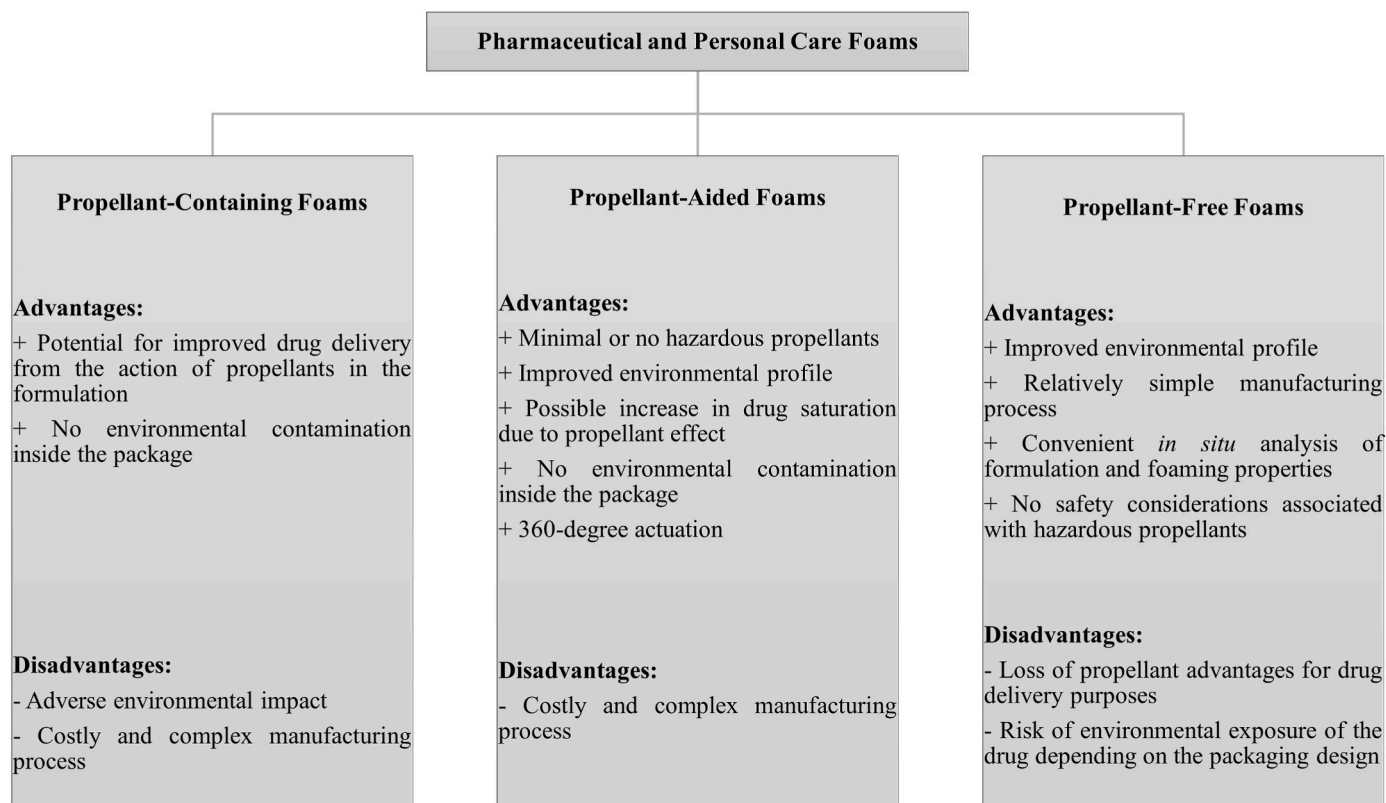


Fig. 9. Comparison between propellant-containing, propellant-aided, and propellant-free foams.

some propellant withing the formulation to act as a foaming aid, that may improve drug delivery as is seen with propellant containing foams. To reduce the costs of BOV technology and retain its benefits, this technology has been modified as a propellant-free technology known as EcoDrive™. The design of this technology, along with other BOV-based technologies, presents a potentially promising solution for developing more sustainable pharmaceutical foam formulations that can achieve the same level of patient satisfaction as propellant-containing foam products.

Looking ahead, future research could consider not only the sustainability of propellant systems but also the environmental impact of other formulation components, such as excipients. The use of biodegradable [135] or bio-based materials, including surfactants, polymers, and packaging, could be explored as part of a broader effort to reduce the ecological footprint of foam-based drug delivery systems. Foam formulations also offer flexibility that could support the incorporation of additional technologies, such as nanocarrier platforms (e.g., liposomes, emulsomes, or polymeric nanoparticles), depending on formulation goals. Similarly, stimuli-responsive systems that adapt to physiological conditions (e.g., pH or temperature) may be investigated for specific therapeutic applications.

Overall, a multidisciplinary approach that integrates formulation science, device engineering, and sustainability principles will be essential in guiding the responsible development of next-generation pharmaceutical foams.

CRediT authorship contribution statement

Farzaneh Hajirasouliha: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **William J. McAuley:** Writing – review & editing, Supervision, Resources, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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