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Review article

Topical foams containing natural saponins: a world of opportunities in pharmaceutical and cosmetic sciences

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ABSTRACT

The cosmetic and pharmaceutical markets are witnessing a rising number of topical foam products, particularly for cosmetic applications, alongside a significant increase in foam-related patents in recent years. What makes topical foams attractive is their superior application experience and aesthetics properties. While foam formation in products like shampoos or bath foams is largely a cosmetic feature, medicated topical foams represent an innovative drug delivery system for managing skin diseases or disorders. This review highlights the advantages of using topical foams over other topical dosage forms, as well as the ingredients used in their formulation. It also explores the growing trend of using more eco-friendly surfactants, particularly the use of saponins as surfactant. A major advantage of natural surfactants is that they are derived from naturally occurring materials, making them both economical and sustainable. Additionally, their biodegradability distinguishes them from synthetic surfactants, which are often non-biodegradable. The role of surfactants in improving drug permeation through the skin has been extensively studied, demonstrating their effectiveness as chemical penetration enhancers in dermal and transdermal drug delivery. This work examines the surface-active characteristics that determine their potential as pharmaceutical and personal care surfactants. The future perspectives for topical foams containing natural surfactants in the development of more sustainable and effective skincare products are also presented.

1. Introduction

By definition, foam is a dispersion of gas in a liquid or a solid, with liquid foams being the most common form used in cosmetics and medicines [1]. Parameters such as the gas volume fraction and the bubble size have also been defined as critical factors controlling foam structure and behaviour [2]. Solid foams, commonly referred to as dry foams or sponges, have several applications. They can serve as cover materials impregnated with anti-bacterial agents or, due to their high capillarity, can be used as absorbing structures [3,4].

Foams represent inherently unstable systems from both thermodynamic and mechanical perspectives, owing to their elevated interfacial free energy and the lifetime of a foam can pass through several different stages. The mechanism involved in each stage is diverse [5]. Moreover, foams, considered as metastable supersaturated systems, are elastic systems as long as the gas phase (bubbles) can be compressed [6]. Foams have significant practical interest across multiple industries, namely firefighting, food industry, cosmetics and pharmaceutical industry. Especially in the last case, foams have become an effective method for delivering active pharmaceutical ingredients (API) [4].

Foams are highly dependent on their packaging system. In the particular case of topical foams, the ability to transform liquid formulations into a larger volume of an easy-to-spread foam with a single press, enhances both sensorial properties and patient compliance, creating a unique opportunity for improved user experience. Several high-tech pumps empower the user to create sophisticated foams upon application to the skin [7]. These pump foam dispensers can generate foam either with or without using gas propellants [7]. The type of foam-generating device is also responsible for the quality of the foam produced. Propellant-free dispensers generate what is simply referred to as "foams", while the propellant-aerosol foam maker is responsible for the production of finer pored foams, commonly called "mousses".

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Moreover, as stated above, the European Pharmacopoeia defines foam as a "large amount of gas dispersed in a liquid phase". However, this definition does not apply to formulations packaged in containers without propellant gas. In this case, "foam" should be considered as a transition state between the foam formation apparatus and the skin [7].

Foams are stabilised by amphiphilic molecules (Fig. 1), which reside on the liquid/air interface and reduce the surface tension, thereby requiring less energy for bubble formation [8]. Proteins and colloidal particles offer alternative foam stabilization pathways similar to surfactants [9]. Fig. 1 demonstrates the typical structural configuration observed in foams. While gas bubbles in the dry foam (top) are polyhedral with distinct edges, those in the wet foam (bottom) adopt more spherical, stable morphologies [10]. Between two bubbles the liquid foam film (lamellae) is covered by surfactant monolayers.

Three different processes govern foams dynamics: coarsening, drainage, and collapse [12]. These three interdependent phenomena happen during foam aging process, being drainage the major factor contributing to foam instability. During drainage, the thin liquid films separating gas bubbles lose liquid content, leading to a reduction in film thickness [13]. As a result, gas diffusion through the films is easier, facilitating bubble coarsening. Larger bubbles continue to grow, ultimately causing thinning films rupture. Bubble size distribution also modifies, raising the rate of liquid drainage [13]. Thin films rupture by insufficient elasticity, which will decrease the number of bubbles [14].

Advantages of topical foams compared to other more conventional topical formulations rely on biopharmaceutical aspects [4]. In foams, the enhancement of drug skin permeation - typically achieved using excipients in ointments, creams or gels - is instead achieved by increasing the drug's thermodynamic activity [15].

2. Foam-skin interaction: the rationale for topical foams

Most of the studies on topical foams for skin application focus on foam structure and stability assessment rather than evaluating foam interaction with the skin and destabilisation mechanisms after application on the skin [14]. The European Pharmacopoeia describes medicated foams (*musci medicati*) as preparations consisting of a "large volume of gas dispersed in a liquid for skin or mucosal applications" [4]. Their composition includes one or several active pharmaceutical ingredients (APIs), surface-active agents for foam production, and excipients. Foams are typically generated *in situ* during administration from a pressurized liquid formulation. The delivery system comprises a specialized container fitted with an actuator valve assembly, which facilitates foam application [16]. Medicated foams are exploited to administer several APIs, with most market-available foams delivering either corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) for treating, respectively, psoriasis or muscle-skeletal disorders. In fact, as they require minimal force to spread, they are ideal for sensitive skin. Examples of their applications include their use as vehicles in psoriasis, rosacea and acne management. Calcipotriol and betamethasone, formulated as a foam presented significantly higher steady-state levels of both drugs comparatively to an ointment formulation containing the same drugs at the same concentrations [17]. The azelaic acid foam formulation showed significant therapeutic effectiveness with excellent patient tolerability in the management of rosacea symptoms [18]. In acne, systemic exposure to tazarotene was significantly reduced when delivered as a foam compared to its gel formulation [19].

The majority of topical pharmaceutical formulations are designed for localized therapeutic effects being formulated to minimize systemic drug absorption. These includes the formulation of antiseptics, antifungals, and anti-inflammatory drugs, and local anaesthetics wherein a degree of hydration or protection is frequently achieved [20].

Cosmetic industry has also explored the technology of the foams taking advantage of their sensorial and emotional benefits [21]. Cosmetic foams are not intended for delivering active molecules within the skin. They have been mainly associated to cleansing products. In the last years, cosmetic foams have been developed to promote sustainability as they reduce the amount of water and weight of a product.

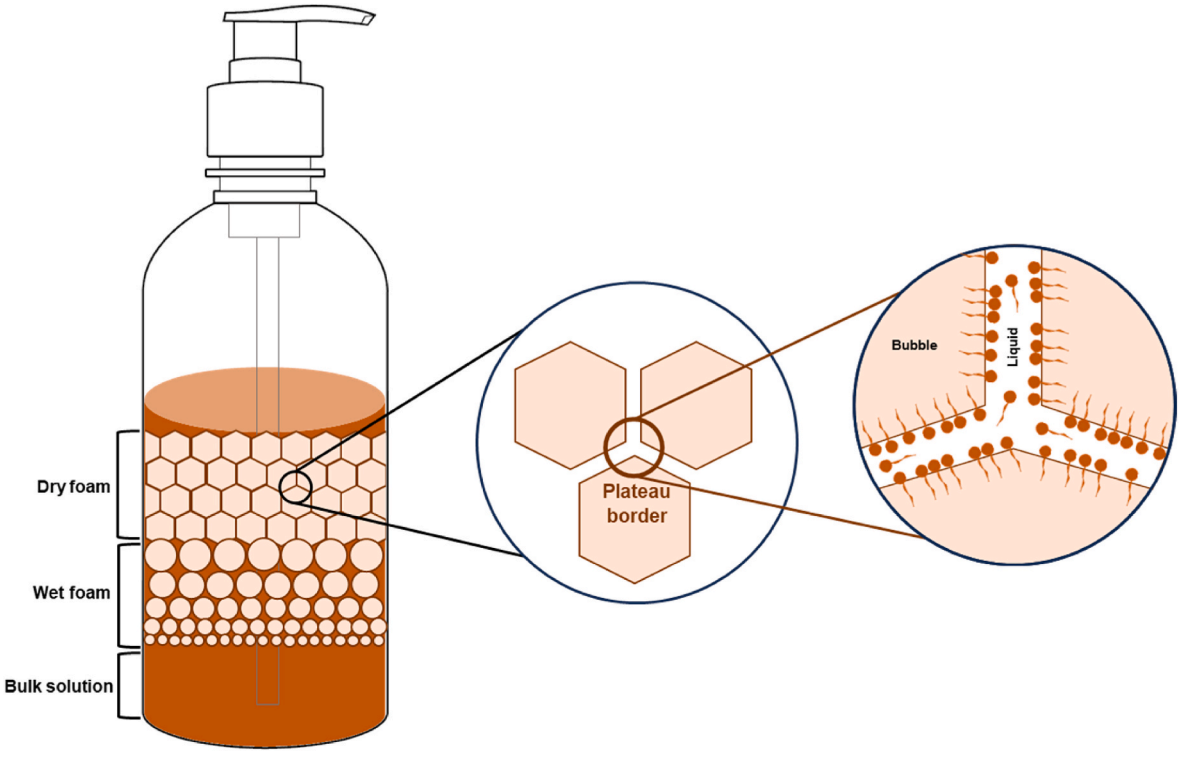

Fig. 1. Schematic representation of a dry and a wet foam. In detail, the diagram shows the thin liquid film interface, separating the polyhedral bubbles. Bubble-separating liquid films are coated with surfactant monolayers - polar heads (schematically shown as circles) oriented toward the aqueous phase and hydrophobic tails extending into the gaseous phase. Adapted from Refs. [8,11].

The structural organization of human skin comprises three principal layers: epidermis, dermis and hypodermis (Fig. 2), along with associated structures such as hair follicles, sweat glands and nails. The epidermis, forming the outermost cutaneous layer (0.1–1.5 mm thick), is mainly composed of keratinocytes at various stages of differentiation and melanocytes [22,23]. It acts as the first barrier against foreign agents and is also responsible for keratin production and the desquamation process. The most superficial layer of the epidermis, the *stratum corneum* (SC or horny layer), is particularly significant as it consists of empty, dead and completely differentiated keratinocytes (corneocytes) established in a lipidic extracellular matrix, resulting in an excellent barrier and a challenge for the dermal or transdermal drug delivery [24,25]. The dermis contains collagen and keratin fibres, which confers structural strength to the skin. Beneath the dermis lies the hypodermis, a fatty layer that helps protect the body from temperature fluctuations and mechanical stress (see Fig. 2).

Since the skin constitutes a vast portion of the human body and offers a convenient route for drug or cosmetic application, topical and transdermal drug delivery methods are highly desirable but at the same time challenging [26,27].

Foams offer several advantages over other topical formulations, including a less compact structure, superior cutaneous spreadability, and enhanced permeability due to surfactants that act as permeation enhancers. Additionally, foams also exhibit significant surface area coverage with a minimal liquid volume [4].

Foam technology has been in use for a long time, however modern formulations incorporate different ingredients and innovative dispensing mechanisms. Foams are puffy, airy and lightweight, making them easy to apply. They can be very delicate or very rich and dense. In the case of topical foams, a liquid foamable formulation, when pressurized, transforms into a foam and is released from the dispensing device. Upon cutaneous application, the foam reverts to its liquid state [28]. The same mechanism happens when the foamable formulation is an emulsion, i.e., after administration on the skin, it reverts to an emulsion.

Foam generation requires surfactant molecules. The intentional over-formulation of surfactants beyond their critical micelle concentration (CMC) in shampoos and soap systems enhances foam production, with greater concentrations leading to a stronger foaming effect. However, such products are ultimately rinsed off the hair and skin. Compared to semi-solid emulsions, foams typically contain lower amounts of surfactants, which makes them a beneficial option for acne-prone or sensitive skin [29,30].

The rationale behind topical foam development can be summarized in three key objectives: to improve patient compliance by enhancing formulation mildness; to increase drug or excipient interaction with the skin; or both. Enhanced medication adherence and improved treatment outcomes make foams advantageous over other topical dosage forms. Table 1 condenses the factors contributing to the decrease patient compliance when using topical formulations.

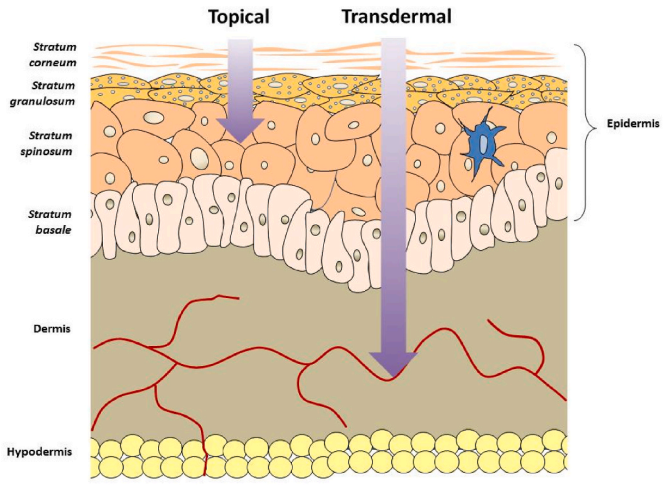

Fig. 2. Schematic representation of the human skin structure.

However, designing an effective topical drug delivery system can be a challenging task since the stratum corneum's inherent barrier functionality restricts API penetration, as explained above.

Compared to other types of vehicles, foam produces no occlusion effect and little or no hydration effect. However, the composition of the foam formulation can be optimized to improve these properties. Table 2 presents the desirable features of medicated foams from a patient standpoint. The drug permeation enhancement exerted by the foams is directly associated with their composition, mainly with the presence of surfactant molecules, recognised as effective skin permeation enhancers [32].

As represented in Fig. 1, closely packed gas bubbles are separated by lamellae, ie, foams have large gas content and low fluid volume meaning that the active ingredient is highly concentrated in the lamellae. If large skin areas can be exposed to high drug concentrations, it improves the potency of foam-based local treatment comparatively to liquid forms [33]. It is thus crucial to ensure the dissolution of the active agent in the formulation since, after application, volatile components evaporate from the applied foam. Such supersaturated layer on the skin increases the thermodynamic activity of the drug with positive impact on drug permeation rate avoiding drug crystallization at the skin surface [34]. Comparatively to gels, creams and ointments, foams are more adequate for the treatment of hirsute areas, as they possess excellent spreading capabilities on the skin, without the need for intense rubbing [34]. As an example, FDA recently approved ZORYVE® (roflumilast) topical foam for once-daily application on all affected areas of the body, including hair-bearing areas, to treat seborrheic dermatitis [35]. Another advantage over other conventional topical forms is the stability. Foams are stored in sealed containers which minimizes microbiological contamination.

3. Foam preparation

Foams can be produced by different methods, such as by "**whipping**" which means by air incorporation via mechanical agitation, by "**bubbling**", i.e., through the injection of a gas into a liquid, and by **sudden pressure reduction** of a liquid or a solution, causing gas expansion [36]. Foams intended for topical application of drugs fall under the category of aerosol foams, that are pressurized liquid or semi-solid formulations packaged in aerosol cans. More recently, propellant-free foam dispensers Fig. 3 became quite popular, especially for cosmetic purposes [37].

Aerosol foam systems can be biphasic or triphasic structural formulations, depending on whether the liquid is a solution or an emulsion/suspension. The propellant is dissolved under high pressure in the liquid, in the case of two-phase, or in the internal phase of the emulsion, in the case of three-phase foams [7]. In both cases, shaking before use is required.

Topical foams can be classified mainly as aqueous, hydroethanolic and emollient foams [38]. Hydroethanolic foams may contain high

Table 1
Factors contributing to the decrease of patient compliance when using topical formulations [31].

Form	Factors contributing to the decrease of patient compliance
Solutions, lotions	- cannot always guarantee a prolonged adhesion to skin surface
Patches	- may lack aesthetic properties (clearly visible)
Gels and creams	- cannot always guarantee a prolonged adhesion to skin surface - susceptibility to mechanical removal through textile contact
Ointments	- adhesive and oily skin feel after application - not suitable for large areas of application

Table 2
Advantageous characteristics of foams as topical drug delivery vehicles.

Advantages	References
- Effortless administration regardless of body surface area, hair density, or inflammatory status	[4,16]
- Good spreadability;	[4]
- Drug delivery ability, as permeation enhancers are easily incorporated in the composition;	[15]
- Demonstrates substantially reduced greasiness compared to traditional semisolid formulations	[7]
- Can be easily removed, in case of need;	[16]
- Propellant or solvent evaporation increases API concentration, causing supersaturation, increasing the rate of API skin absorption	[15]

ethanol concentrations (around 60 %) to achieve better penetration of APIs into the skin. The rapid ethanol evaporation from the skin surface accelerates foam drying; however, ethanol's drying effect on the skin limits its use, especially in sensitive skin conditions. Emollient foams are complex systems, as they rely on emulsified preparations. Both conventional or nanosized emulsions (micro- and nanoemulsions) offer promising approaches due to their ability to enhance insoluble APIs bioavailability and efficacy and the capability of hydrating the skin [39].

Foams are usually characterized in terms of structure by the gas volume fraction (typically ranging from 0.5 to 0.9) and the bubble diameter (generally from 0.1 to 3 mm), both influenced by formulation and preparation method [15].

4. Foam ingredients

As pure liquids do not foam, to prepare a topical foam it is necessary foaming agents to enable both foam generation and stabilization. A foaming agent is a substance, typically a surfactant, that enables foam formation by reducing liquid surface tension, thereby facilitating gas bubble entrapment and stabilization through interfacial film formation [40].

4.1. Surfactants

Surfactants are amphiphilic compounds that contribute to foam formation due to their self-assembly at the air-water interface. The polar heads face the polar aqueous phase, while the non-polar tails face the gas phase. The hydrophobic tail determines the origin of the surfactant, whereas the hydrophilic headgroup and associated counterion determine the surfactant charge [41]. Surfactants can be chemically classified into three main categories based on their polar moiety: ionic (cationic and anionic), non-ionic, and zwitterionic. Ionic surfactants generally exhibit superior foaming ability but exhibit significant skin irritant potential. Cationic surfactants exhibit antimicrobial activities but demonstrate significant toxicity, whereas anionic surfactants present lower toxicity risks. Non-ionic surfactants usually are nontoxic and less irritating to the skin and therefore favoured for sensitive skin, particularly for inflamed or infected sites [14].

For foam preparation, surfactant blends typically consist of two main components: 1) A primary foam-generating agent mixture that contains an amphoteric surfactant and a non-ionic surfactant; 2) An acyl glycine surfactant that increases foam volume and contributes to the formation of a spherical foam structure. The use of surfactant blends is advantageous because it provides a rich, stable lather and improves the viscosity and softness of the foam on the skin [42]. Depending on the Hydrophilic Lipophilic Balance (HLB) value, a non-ionic surfactant can act as a wetting agent, foaming agent, or emulsifier for dermatological applications. The ionic character of a biosurfactant for cosmetic use requires evaluation, due its influence on potential skin/eye irritation, hair absorption and antimicrobial activity.

However, the industry's strong demand for using "green" technologies has driven the development of formulation containing natural surfactants. For that reason, nowadays a classification based on its origin is more adequate, splitting the surfactants into synthetic or natural. Natural surfactants can be further divided into three subgroups: animal-based, plant-based, and microorganism-based surfactants, which are detailed below [41].

The selection of certain surfactants in cosmetics and pharmaceuticals in detriment of others is based on a balance of several characteristics: safety, efficacy, stability, environmental impact, and regulatory compliance. Mild, biodegradable, and functionally effective surfactants such as non-ionic and amphoteric surfactants are often preferred over harsh anionic surfactants for improved skin compatibility and reduced irritation [43].

The European Commission proposed in 2023 a revised Regulation on detergents and surfactants to enhance health and environmental protection while ensuring the efficient functioning of the Single Market with changes aligned with the objectives of the European Green Deal and the Chemicals Strategy for Sustainability [44]. However, the implementation of the proposal is currently under consideration by the

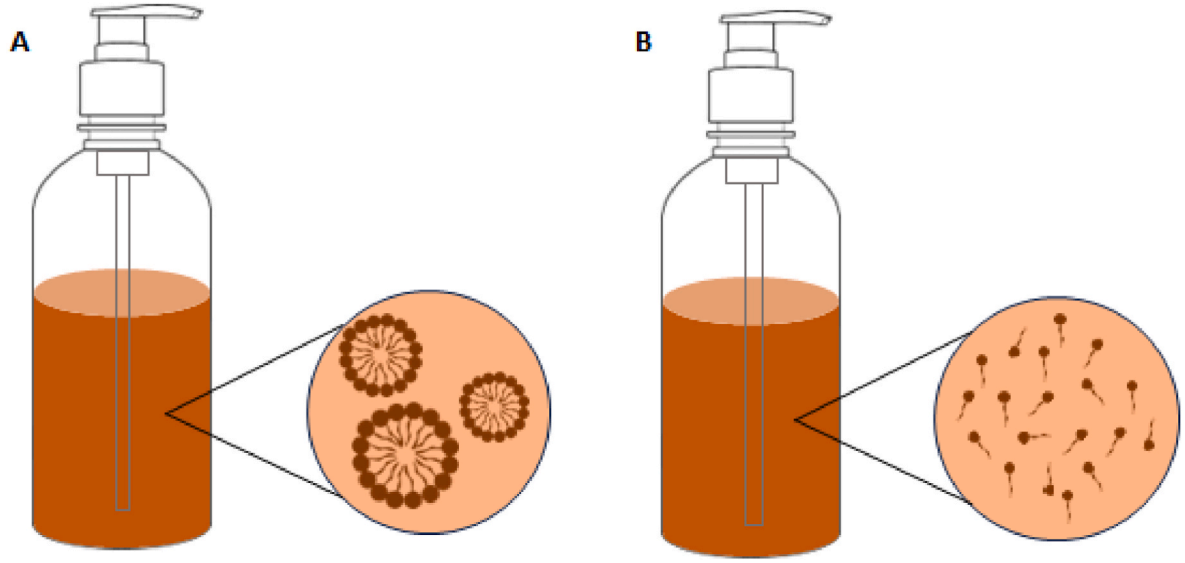

Fig. 3. Illustration of a propellant-free foam dispenser. (A) The surfactant concentration is higher than CMC, forming micelles. (B) The surfactant concentration is lower than CMC, the surfactant occurring as individual molecules. Adapted from Refs. [16,37].

European Parliament and Council as part of the ordinary legislative procedure.

The European bio-based chemicals sector reflects the EU's commitment to sustainability and reducing reliance on fossil fuels [45]. However, it faces several challenges such as the production costs and the investment risks associated with infrastructure investments and market acceptance.

4.1.1. Animal-based surfactants

This type of surfactants is obtained from animals or animals' products. Originally, surfactants were derived solely from renewable sources like plant oils or animal fat and, historically, soaps were prepared from animal fat. Although animal-based surfactants are not commonly used in pharma and food industry, the milk proteins β-Casein, β-lactoglobulin and α-lactalbumin have already been accepted for use, showing good foam ability [41]. Egg white protein, displaying foaming properties, is already used by the food industry [46]. Fish collagen, a fibrous protein derived from skin or scale of fish, also presents good foaming ability [47].

4.1.2. Microorganisms-based surfactants

Microbial surfactants or biosurfactants are surface-active compounds naturally synthesized by microorganisms such as yeast, fungi and bacteria [48]. The rationale for being classified as "bio" relates to their biological origin, biodegradability, low toxicity, bioactivity and multifunctionality (including antimicrobial, anti-inflammatory, and emulsifying properties) [49]. However, their production cost is still high [41]. Biosurfactant production involves microbial fermentation using cost-effective substrates, while purification relies on techniques such as acid precipitation, solvent extraction, membrane filtration, and chromatography to achieve high-purity products. The selection of a purification method depends on factors like required purity, intended application, and cost efficiency [50]. Microorganisms can produce biosurfactants through various fermentation methods. These include both controlled fermentation processes and spontaneous fermentation approaches [48]. The main classes of biosurfactants originated from microorganisms are glycolipids, polymer surfactants, lipopeptides, fatty acids and phospholipids. The majority of biosurfactant research focuses on glycolipids and lipopeptides, due to the presence of molecules with exceptional potential in cosmetic formulations [51].

4.1.3. Plant-based surfactants

Surfactants present in plant extracts exhibit promising characteristics be included in products as foams and emulsions for topical application [52]. Phospholipids, saponins, and proteins/protein hydrolysates comprise the major plant-derived surfactants, with saponins exhibiting particularly versatile biotechnological utility owing to their dual physicochemical and biological properties. Recently, the functional properties of a biosurfactant isolated from corn wet milling byproducts were assessed for dermal applications. The authors found that the biosurfactant extract functions as a multifunctional additive in dermal formulations, serving as a co-stabilizer with penetration-enhancing and antioxidant properties [53]. In addition to their physicochemical characteristics, biosurfactants exhibit biological properties that enable multifunctional applications; examples are represented by the antioxidant and antimicrobial activities that create new opportunities in the field of personal care.

Cocamidopropyl betaine also derives from natural sources and is produced by firstly reacting dimethylaminopropylamine with fatty acids from coconut or palm kernel oil. However, allergic effect has been described upon its use [54,55]. It has been used in many personal care and household products as a surfactant, foam enhancer, and thickening agent.

Glucoside derivatives are surfactants used in personal care products and are considered safe and nonirritating when used in cosmetics [56]. Because they are made from sustainable raw materials, these surfactants are biodegradable and can be used in products with an eco-label [57]. The synthesis method, involving glucose and anhydrous ethanol reaction under acidic conditions, qualifies as environmentally sustainable due to its renewable feedstock utilization [58]. The most common used glucosides are decyl glucoside, coco glucoside, lauryl glucoside and capryl glucoside, presenting high foaming properties and compatibility with other surfactants [59].

Fatty acids and protein can also be obtained from vegetables, flowers and nut oils presenting foaming properties [41,60,61].

Saponins are a special case within the plant-based surfactants. It is common that this type of surfactants presents other health promoting activities, such as antimicrobial, fungicide, among others [62]. Examples of saponins already used by the food or cosmetic industry include *Sapindus mukorossi* (soapnut) solution [63,64], *Acacia Concinna* extract [65], *Yucca schidigera* and *Sapindus mukurossi* extract [66]. Probably the most well-known example of saponins used as surfactant is *Quillaja Saponaria,* which is approved for use as a food additive [67,68]. Saponins will be detailed described below.

4.1.4. The special case of saponins

Saponins are botanical surfactants with great potential for foamable product development [69]. These bioactive compounds, naturally occurring in various plant species, serve as effective foaming and emulsifying agents. First discovered in the 1800's from the root of *Saponaria officinalis* [70], saponins continue to be valued for their surface-active properties. Saponin-rich plants extracts have been tested as cosmetics ingredients due to their multifunctional benefits, particularly antioxidant, regenerative, and antiaging activities, along with their established safety profile [51,71]. The growing consumer preference for cosmetics of natural origin has prompt industry to find new ingredients to replace synthetic formulation components. Saponins, as natural emulsifiers, are well-positioned to meet this new demand for biocompatible, biodegradable and stable surface-active agents [72]. The term "saponin" derives from the Latin word "*sapo*" that means soap, reflecting the foaming properties these compounds exhibit when shaken in aqueous solutions [73]. As naturally occurring non-volatile surface-active, saponins are widely distributed in nature. Approximately 100 plant families contain saponins as secondary metabolites [74] where they function as a natural defence mechanism against pathogens. It is common that plants present a mixture of different saponins [70]. Saponins exhibit structural variability featuring non-polar aglycone cores (600–2000 Da) glycosidically linked to sugar chains. The amphiphilic behaviour of saponins results thus from the existence of polar and non-polar structural elements in the same molecule. Fig. 4 illustrates the general structure of saponins and their behaviour in aqueous solution.

Saponins are categorized into two primary classes - triterpene or steroidal - based on their aglycone structure. In both cases, aglycone derives from oxidosqualene (30 carbon atoms). Triterpene aglycones have a pentacyclic nucleus (30 carbon atoms) and occur in nature as both saponins and free aglycone. Steroidal aglycones (27-carbon structures) occur in nature exclusively in the form of saponins [76]. Steroidal and triterpene sapogenins may contain various functional groups including hydroxyl, carboxyl, and methyl substituents [72].

Regarding the sugars, the most common molecules found in saponins are D-glucose, D-galactose, D-glucuronic acid, D-galacturonic acid, L-rhamnose, L-arabinose, D-xylose, and D-fructose [76]. Saponins are also classified in three different groups based on the number of attached saccharide side chains in the structure: monodesmosidic, bidesmosidic and tridesmosidic. Monodesmosidic saponins have the saccharide chain attached by an ether linkage to the C3 hydroxy group. This sugar chain can be branched and usually has 2–5 monosaccharide units. Bidesmosidic saponins have two saccharide chains. In the triterpenoid saponins, the second chain is usually attached via an ester linkage to the C28 carboxy group. The rarest group is the tridesmosidic saponins that have three saccharide chains attached at different positions of the aglycone [77]. The foaming capacity of saponins depends on their number of

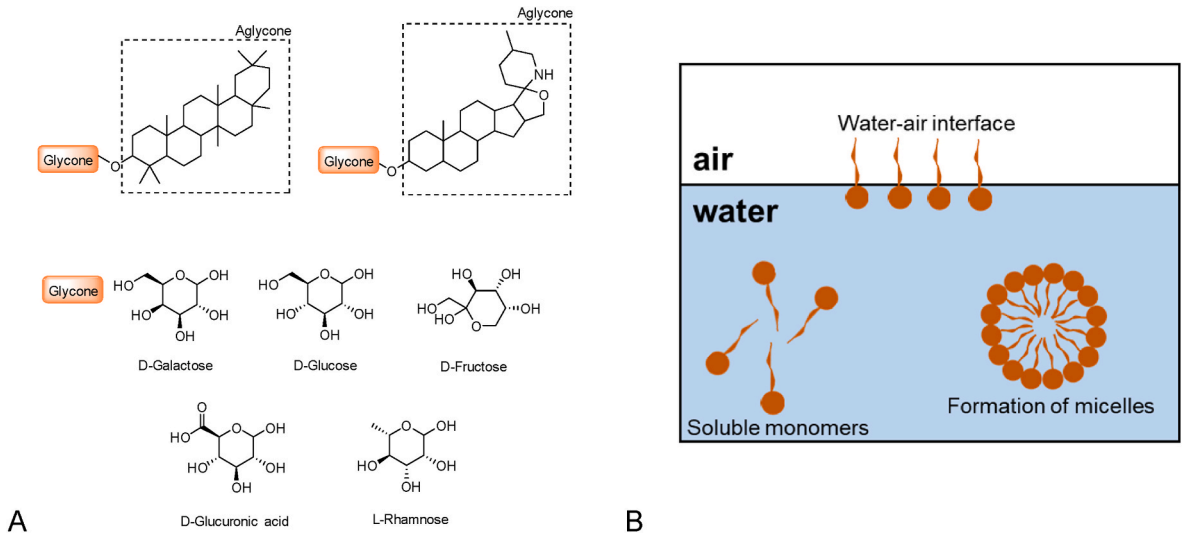

Fig. 4. A) General chemical structure of saponins with structure of some of the possible sugars in the glycone moiety. B) Schematic representation of the saponins behaviour in an aqueous solution. Adapted from Ref. [75].

sugar chains. Monodesmosidic saponins (containing one sugar chain) typically demonstrate the highest foaming ability [41].

Saponins are found in different species across the plant kingdom, with both edible and non-edible sources. Common food sources include legumes (soybeans, peas, chickpeas, peanuts, beans, lentils), grains (oats, quinoa), and vegetables (garlic, asparagus, spinach, beets, yams), as well as tea leaves [78]. Non-food sources, such as the soap bark tree (*Quillaja saponaria*), are equally abundant and serve as important industrial raw materials for health-related applications [68]. CosIng, the European Commission of Cosmetic Ingredients database, has listed certain Quillaja products for use as cosmetic ingredients with different functions (emulsifying, foaming, masking, moisturizing, surfactant) depending on the material used. However, most research on Quillaja saponin foams has focused on food application, with limited studies examining how structural differences amongst saponins affect foam-forming properties. Quillaja saponins were used to prepare foamed emulsions forms by creating a strong viscoelastic network that stabilizes the air/water-interface [79–81]. Dermatological research has also investigated their topical use for treating scalp disorders [51].

Recent studies have evaluated saponin-based foams focusing on their formation mechanisms, structural characteristics, and stability [82]. Authors discussed the importance of understanding the saponin interfacial arrangements, as these vary by plant source and molecular structure. Researchers identified critical conditions that favour the stability of saponin foams, including high viscoelasticity, high solubility, and rapid adsorption kinetics. Several reports have studied different saponin-rich plants and compared their extracts for surface activity and foaming properties [51,80,83,84]. The foaming properties of saponins derived from *Camellia oleifera* seeds have been studied [84]. A solution of the crude saponin extract from this plant showed foam stability after 5 min equivalent to that obtained with the anionic surfactant sodium lauryl sulfate. Similarly, the mesocarp of the fruit of *Balanites aegyptiaca* has been described as having surfactant properties comparable to those of commercial surfactants SDS and Triton X-100, with additional benefits including high emulsification index and high oil-displacement diameter [85].

Saponins have been shown to have similar properties to synthetic emulsifiers, obtaining comparable values of surface and interfacial tension among them, making saponins a promising alternative for various applications, particularly in the cosmetics and personal care industries [72]. Due to saponins' surface-active properties, they are widely used in various cosmetic applications, particularly in cleansing products such as shampoos, body cleansers, liquid soaps and toothpastes [86,87]. Before synthetic surfactants were developed, naturally available surfactants like saponins were frequently used in household and cosmetic applications [83]. In skincare saponins can be found in body washes and face creams. They are effective at removing impurities from skin without removing its natural oils. Flour made from dried seeds of *Vigna radiata* and transformed into a paste is used as soap, body scrub, bathing powder and hair cleanser [88]. In face creams, saponins are valued for their antiaging and antioxidant effects too [89]. In hair care they are used in shampoos for their cleansing properties. Extracts from the genus *Sapindus* are used in shampoos and natural conditioners [88]. These extracts also exhibit antifungal activity, making them effective against dandruff. Similar antimicrobial and antifungal properties have been observed in extracts from *Acacia concinna* and *Trigonella foenum--graecum* [88]. Saponins are also used in fabric care, where they are incorporated into detergents and in oral care, where they can be found in toothpaste and mouthwash. For instance, saponins from the *Quillaja* and *Yucca* trees are used as cleansing/foaming agent in toothpaste [90]. Additionally, extracts from *Sapindus* species are used in laundry detergents due to their superior emulsifying action, outperforming synthetic alternatives like sodium dodecyl sulfate [88].

Tomato plants provide a clear example of saponins' biological role - these compounds act as the plant's "immune system" or natural defence system exhibiting antimicrobial properties against bacteria and fungi [91]. Alpha-tomatine is thought to be the main triterpenoidal surfactant in tomato. However, Yamanaka et al. [92] studied different triterpenoid glycosides present in unripe tomato fruits and found that tomatoside A is more abundant than alpha-tomatine in tomatoes, presenting a similar critical micellar concentration. A green tomato extract rich in alpha-tomatine was already used as surfactant of a formulation [93]. Tomatine used as surfactant in foam formulations will stabilize the air-liquid interface and lower interfacial tension between these two phases [75]. Furthermore, as it is of natural origin it is an alternative to synthetic surfactants and meets the increasing consumers' demand for more eco-friendly and sustainable products [94]. In the specific case of tomatine, it is also known that it possesses other health-promoting activities, such as antioxidant and anti-inflammatory, being of particular interest for this possible double function in formulation [89].

However, the use of natural ingredients is affected by the environmental conditions from where they derive, namely the weather, soil, and time of harvest [72]. It is also known that the extraction process of the saponins affect its foaming ability independently from the molecular structure [41], so reproducible extraction techniques are required. Table 3 summarizes the main saponins already known and their

properties.

4.2. Solvents

The selection of solvents for topical foam formulations requires careful consideration and may include hydrophilic (e.g., water, propylene glycol) or hydrophobic solvents (e.g., emollients). These solvents can also be categorized by polarity (polar: polyols, water, alcohols; non-polar: paraffin oil, vegetable oils), origin (organic: polyols, alcohols; inorganic: water), and/or solvation strength (e.g. dimethyl sulfoxide, isosorbide derivatives).

Water is the predominant solvent in cosmetic formulations, yet certain APIs present instability or poor solubility in aqueous systems - including low-water compositions (e.g. water-in-oil emulsion) – which may impair their efficacy. To address this, hydrophobic solvents are employed to enhance APIs solubility and stability [95].

Topical foam formulations may incorporate hydrophobic solvents—including unsaturated, silicone, or mineral oils—to deliver emollient effects (e.g., softening, soothing) and/or skin conditioning properties. These solvents are useful in treating skin conditions involved with dry and flaky skin. Fatty alcohols are often used, despite their potential for skin irritation, since they are useful in vehicles for dermal drug delivery as they enhance the rate of absorption of specific actives [96]. In general, alcohols have good solubilizing potential and once applied on the skin promote quick drying of the formulation, thus preventing the feeling of stickiness after application of several topical formulations on the skin surface. Apart from this, alcohols exhibit antimicrobial activity, making them effective for skin disinfection.

Short-chain alcohols like ethanol have been combined with water, surfactants, polymers and fatty alcohols to prepare the so-called hydroalcoholic (hydroethanolic) foams [14] and the ethanol concentration in such preparations can reach 60 %. Ethanol promotes better skin penetration of the APIs than other vehicles [97]. It induces reversible modifications to the *stratum corneum*'s barrier function, improving its penetration. In the specific case of foams, the rapid evaporation of the alcohol from the skin causes the foam to dry quickly and also contributes to the heat-labile nature of hydroalcoholic foams, promoting direct application to affected areas rather than hand dispensing [16].

Substantially stable surfactant-free formulations have been patented comprising a combination of hydrophobic solvent, petrolatum, fatty alcohol, fatty acid and/or wax, and/or shea butter, and a liquefied or compressed gas propellant [98]. The disclosed invention found that the combining cellulose-based polymers (e.g. hydroxypropyl cellulose) with C14-C22 fatty alcohols generated bubbling liquids rather than stable hydroalcoholic foam.

Furthermore, substantially water-free foams are being developed to allow the use of insoluble or unstable APIs in the form of foams. The formulation would prevent the growth of microorganisms, eliminating the need for preservatives while optimizing emollient performance [99].

Table 3
Properties, sources, and uses of natural saponins.

Saponin	Source	Properties	Uses	Reference
Quillaja Saponins	*Quillaja saponaria* (Soapbark tree)	High foaming ability, emulsifying properties, surfactant	Food and beverages emulsifiers, cosmetics, pharmaceuticals	[68,72,87]
Licorice saponins	Glycyrrhiza glabra (Licorice root)	Sweet flavor, weak surfactant	Food and beverage foaming agents, natural sweeteners	[72,83,87]
Soapnuts saponins	Sapindus spp. (Soapnut tree)	High foaming ability	Natural detergents, shampoos, cleansers	[88]
Alfalfa saponins	Medicago sativa (Alfalfa plant)	High foaming ability	Animal feed, limited use in foaming applications	[83]
Tea seed saponins	Camellia oleifera (Tea seed plant)	Foam-stabilizing and emulsifying agent	Natural detergents, cosmetics	[84]
Fenugreek Saponins	Trigonella foenum-graecum (Fenugreek)	Moderate foaming	nutraceuticals, skincare	[88]
Yucca Saponins	Yucca schidigera (Yucca plant)	Moderate foaming, emulsifier agent	Cosmetics, foaming agents in beverages	[72]
Soy saponins	Glycine max (Soybean)	High foaming	Food additives, skincare products	[83]

4.3. Stabilizer agents

Topical foams are delivery systems designed for easy application, but they tend to be unstable. To address this drawback, stabilizer agents have been introduced to enhance the technological properties of these dispersed systems. As mentioned above, foam collapse occurs through three primary mechanisms: (i) liquid drainage through thin films separating gas bubbles, (ii) bubble coarsening resulting from gas diffusion from smaller bubbles to larger ones and (iii) bubble coalescence. Foam stability can be enhanced by adding various stabilizing compounds, particularly surfactants. These essential components serve dual functions: they facilitate foams generation while also stabilizing the structure by forming strong elastic films at bubble interfaces and thus retarding coalescence.

In addition to surfactants, polymers with high molecular weight enhance foam stability by increasing viscosity, thereby reducing drainage. The viscosity-modifying agent is usually required in a concentration range of 0.05 %–2.0 % [38]. Pharmaceutical and cosmetic foams may incorporate various polymers such as: acidic types (alginic acid), natural polymers (xanthan gum, arabic gum, gelatin, agar), semi-synthetic derivatives (cellulose ethers), poloxamers, and polyethylene glycol.

The addition of electrolytes can be also useful as it causes the electrostatic stabilization of the bubbles [15].

Foam adjuvants represent another critical component class that enhances both stability and sensory characteristics. These include selected fatty alcohols (e.g. cetyl, stearyl, behenyl) and fatty acids (e.g. stearic, behenic) [100].

Besides the foam structure stability, other excipients can also be incorporated to stabilize the API. For example, to formulate ionizable drugs like minoxidil, an acid can be employed to maintain the pH in the most favourable range [38].

Natural waxes have been used as a novel strategy to enhance foam stability of aerated emulsions [101]. Foamix Ltd. has developed a patented foamable vehicle that uses liquid or solid waxes to effectively solubilize and stabilize active pharmaceutical ingredients (APIs). These wax-based formulations offer several key advantages: their occlusive properties enhance skin penetration of APIs while reducing transepidermal water loss, they exhibit excellent skin compatibility, and they contribute significantly to API stability. The patented technology specifically demonstrates that mineral oil-based formulations containing 10–50 % by weight of paraffin wax with a melting point between 51 and 53 °C can generate high-quality foams with collapse times exceeding 3 min. Notably, these formulations achieve this performance without requiring traditional surfactants or foam adjuvants like fatty alcohols. The research revealed that foam quality depends exclusively on two factors: the concentration of mineral oil and the wax content in the formulation [98].

5. Current developments and future perspectives

Foams have been used for a wide range of applications, both in cosmetics and in pharmaceutic products. Cosmetic foams became popular in hair care market and medicated foams received great acceptance in dermatological treatments as APIs were successfully incorporated in foams for the treatment of skin disorders. Examples of APIs incorporated in foams are local anesthetic agents, antibiotic agents, anti-fungal and antiviral agents, immunomodulators, corticosteroids, steroid hormones, anti-acne agents and anti-psoriasis agents [7]. Currently there are several foam platforms developed by Foamix Ltd (Israel) to incorporate these different APIs [7].

Currently, foam formulations remain less common in the market compared to traditional topical products like creams, gels, and ointments. However, their popularity is expected to grow significantly in coming years with more foam formulations appearing in the market, as foams offer superior patient' compliance due easier application and better spreadability.

Medicated foams for dermal, vaginal, rectal and nasal route are currently available (Table 4) [7].

Examples of dermal foams are Extina® from Connetics Corporation containing 2 % of ketoconazole that is commercialized for mycoses. Finacea® from Bayer containing azelaic acid is another example of a dermal foam for rosacea treatment [16]. Enstilar from Leo Pharma A/S (betamethasone + calcipotriol) and Clarelux from Pierre Fabre (Clobetasol) are also commercially available [104,105]. For hand disinfection, it is commercialized for example Soft'N SureTM antiseptic hand foam from STERIS [7]. Furthermore, they can be applied to sensitive or highly inflamed skin where rubbing the formulation is painful [7].

Vaginal foams are found as for vaginal contraceptive, moisturizes, cleansing or treatment. Vaginal contraceptives contain spermicide substances (usually nonoxynol-9 or octoxynol or both in combination) and can be already in the foam form or be vaginal tablets and ovulum, that foams when in contact with cervical mucus [125]. Vaginal Contraceptive Film (VCF) vaginal foam and Delfen are examples of vaginal foam spermicides [4]. Betadine Vaginal Foam is an example of cleansing foam [102].

For rectal foams, one of the most known in market is Budenofalk® (budesonide) and Salofalk® (mesalazine) from Dr. Falk Pharma GmbH for ulcerative colitis treatment [16].

An example of a nasal foam is RAPID RHINO SINU-FOAM [126].

However, achieving uniformity and consistency in foam texture, structure and performance batch to batch requires robust manufacturing processes to ensure product quality [127]. Without a doubt, one the major challenge for foam formulations is in the development of more sustainable formulations produced by green manufacturing processes, incorporating natural ingredients. The conjugation of foam formulations with advanced drug delivery systems capable of a targeted delivery or controlled release and capable of improving skin penetration will also be present in future development of foam formulations.

Finally, natural materials have long been overlooked as potential ingredients and excipients in cosmetic and pharmaceutical products. It applies also for formulating foams for topical administration. However, there is still no specific framework for innovative products that merge traditional knowledge with modern scientific advancements.

Table 4
Foam formulation currently available in the market.

Name	API	Function	References
Betadine®	Iodopovidone	Antiseptic	[102]
Budenofalk®	Budesonide	Ulcerative colitis	[16,103]
Clarelux®	Clobetasol	Dermatoses	[104]
Delfen®	Nonoxynol-9	Contraceptive	[4]
Enstilar®	Betamethasone + calcipotriol	Plaque psoriasis	[105]
EpiFoam®	Hydrocortisone acetate + pramoxine hydrochloride	Relief of inflammatory and pruritic manifestations of dermatoses	[39,106]
Evoclin®	Clindamycin phosphate	Acne	[39,107]
Extina®	Ketoconazole	Mycoses, seborrheic dermatitis	[16,108]
Fabior®	Tazarotene	Acne	[39,109]
Finacea®	Azelaic acid	Rosacea	[16,110]
Lexette®	Halobetasol proprionate	Plaque psoriasis	[111]
Luxiq®	Betamethasone valerate	Psoriasis, eczema, dermatitis	[39,112]
Olux®	Clobetasol propionate	Psoriasis	[113]
Olux-E®	Clobetasol propionate	Inflammatory and pruritic manifestations	[114]
Rogaine®	Minoxidil	Androgenetic alopecia	[115,116]
Salofalk®	Mesalazine	Ulcerative colitis	[16,117]
Scytera™	Coal tar	Psoriasis	[39,118]
Soft'N SureTM®	Ethyl alcohol	Antiseptic hand foam	[7]
Sorilux®	Calcipotriene	Psoriasis	[39,119]
Synalar	Fluocinolone acetonide	Psoriasis, eczema, dermatitis	[120]
Tricovivax®	Minoxidil	Androgenic alopecia	[121]
Vaginal Contraceptive Film (VCF®) vaginal foam	Nonoxynol-9	Contraceptive	[4]
Verdeso®	Desonide	Dermatoses	[39,122]
ZORYVE®	(Roflumilast) topical foam, 0.3 %	Seborrheic dermatitis	[123,124]

6. Conclusions

Foams can be considered an innovative and very convenient drug delivery system for skin applications. While aqueous foams dominate the cosmetic market, recent research has advanced more complex formulations including hydroalcoholic, emulsion-based, and high oil-content foams. In fact, considering their potential to enhance drug delivery to the skin, foam formulation systems are evolving from simple solutions to more advanced systems gaining advantage of supersaturation, emulsification or the presence of penetration enhancers. The development of more hydrophilic or lipophilic foams is related to the final aim of the foam application. Aqueous foams are easy to formulate while oil containing foams offer superior skin protection and moisturization. Natural surfactants and specially saponins can determine a new concept of foam formulation considering the growing consumer demand for natural and eco-friendly products, using sustainable ingredient and green processing techniques. However, incorporating natural surfactants in dermal formulations requires further investigation. Current research is still in its initial phases with a critical need for long-term safety data, especially relevant for chronic skin conditions treatments where extended use is anticipated.

CRediT authorship contribution statement

Catarina Faria-Silva: Writing – review & editing, Writing – original draft, Investigation. **Denise Scavone:** Writing – review & editing, Methodology, Investigation. **Joana Marto:** Writing – review & editing, Validation. **Manuela Carvalheiro:** Writing – review & editing, Investigation. **Sandra Simões:** Writing – review & editing, Supervision, 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

Data will be made available on request.

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