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Review

Foams for pharmaceutical and cosmetic application

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ABSTRACT

Foaming of cleaning agents in the household is an effect which is not connected with the quality of cleaning process. Foam development of some cosmetic formulations such as hair mousse or shaving foam has its functionality. Foam formation during application of a foam bath or shampoo is only a cosmetic attribute. In the pharmacy, foams represent new vehicles for drug delivery. The European Pharmacopoeia comprises a monograph called "Medicated Foams" and the interest for the development of these alternative vehicles is steadily growing. Depending on the way of pharmaceutical application we can define between rectal, vaginal and topical foams. Foams for dermal drug delivery have some advantages compared to the traditional vehicles for treatment of topical disorders such as ointment, creams, lotions, gels or solutions. Vaginal and rectal foam vehicles also feature some application benefits compared to the standard vehicles such as suppositories, creams and ointments. There are only a few foam formulations commercially available so far. Moreover, only few publications describing these vehicles have appeared in the recent years, predominantly patents. It is the intention of this article to review available literature, to summarize recent development and to highlight the potential of foam vehicles.

Contents

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1. Introduction

Foams, in common with emulsions, are colloids and are composed of two or three distinct phases: normally a hydrophilic liquid continuous phase with a foaming agent, throughout which a gaseous dispersion phase is distributed. There may be a third hydrophobic dispersed phase (Wilson, 1989).

Foaming of cosmetic formulations is a well-established operation. Foam characteristics may be used by manufacturers to achieve customers' attention. Voluminous and stable foams generally are desired for "sale appeal" of "psychological effect" (Bikerman, 1973). But foams are also used in other different fields such as *e.g.* in fire-fighting. In food industry, terms "static" and "dynamic" foams are clearly defined. Examples of static foams are marshmallows, filling creams, ice cream, *etc.* Dynamic foams are cakes, bread and soufflés (Russo, 1976). Moreover, a glass of beer is unthinkable without foam. Nowadays, foams attract more attention in the pharmacy as a carrier for active substances.

2. Definition

Commonly foam is defined as a dispersion of gas in a liquid or a solid, whereas the volume fraction of gas in the foam is mostly between 0.5 and 0.9. The bubble size is mostly between 0.1 and 3 mm (Wilson, 1989). Foams can be classified into 2 types: liquid and solid foams. In this review the authors will concentrate their attention on liquid foams. Solid foams can be generated when the liquid phase is changed into gel or solid phase after foam formation. These systems are also known under the definition of dry foam, xerogel or sponge and often used as sore cover materials. They may contain disinfecting agents, antibiotics or steroids. Mostly, collagen or gelatine sponges which can absorb a lot of ichor because of their high capillarity are used. These materials also are available for a temporary skin replacement after burn or in cosmetic surgery (Bauer et al., 1999). Furthermore, solid foams such as foam rubber and polyurethane foams have great commercial importance (Bikerman, 1973). Foams are thermodynamically and mechanically unstable systems (Wilson, 1989). They are characterized by a vast interface, which tends to reduce itself. Foams are elastic systems as the gas phase trapped in the foam bubbles can be compressed. There are two fundamental parameters determining the structure and behaviour of foams as disperse systems: the volume fraction of gas which is known as the phase volume and the diameter of the bubbles.

The European Pharmacopeia, in press European Pharmacopoeia comprises a monograph called "Medicated Foams" (*Musci medicati*) which defines foam as "formulation, consisting of a large amount of gas dispersed in a liquid phase". The US Pharmacopoeia simply lists "foam aerosol" as a sub-part of the aerosol section. Nevertheless, one should consider pharmaceutical foams as a "transition state" between device for foam generation *e.g.* aerosol can and the skin of a patient. For example, if a foamable formulation in the aerosol can is an emulsion, it would evolve into foam upon release from the can. After being administered to the skin as a foam, it would return to an emulsion state at the skin surface.

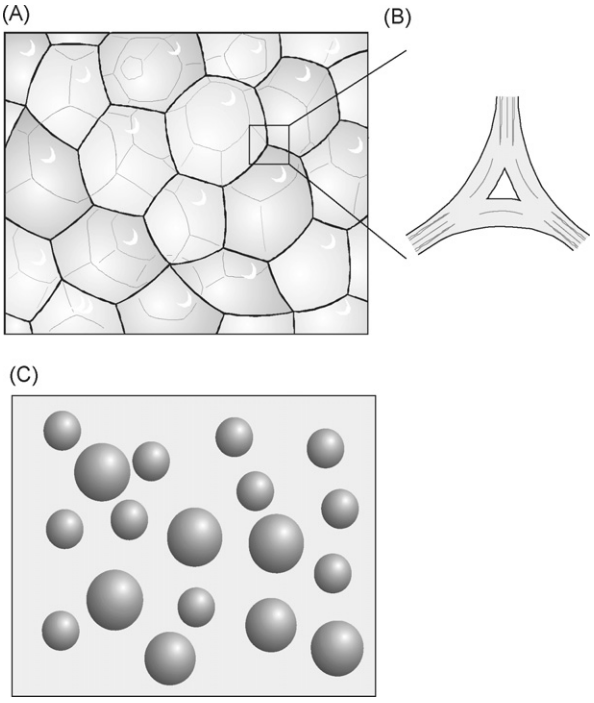

Fig. 1. Schematic illustration of foam structures: A. polyhedral foam, phase volume >0.7, B. plateau border region, C. foam, phase volume <0.7.

3. Foam structure

Foam structure is described, *e.g.* by Bikerman (1973). The bubbles in the foam can be more or less homogeneous, they can vary in size and shape ranging from almost spherical to irregular polyhedral depending on how the foam was generated and on the excipients employed. Different parameters such as nature and concentration of foaming agent, viscosity of liquid phase, temperature and pH of the system can affect the foam structure. Foam generation conditions also affect foam appearance and, therefore, stability of foam bubbles. At moderate gas phase volumes the bubbles dispersed in liquid phase are uniform and packed as spheres. But at higher phase volumes, typically higher than 0.7, the air bubbles deposited near each other start to deform themselves (Yoshimura, 1988) (Fig. 1A and C). A polyhedral bubble shape with partly plane faces is a result of this deformation. The thin layer of the continuous liquid phase (film) separating the faces of two adjacent polyhedral bubbles are called lamellae, while the thicker channels where three lamellae meet are known as plateau borders (Fig. 1B), (Hansen and Derderian, 1976). Plateau, the blind physicist, was the first one, who investigated these films (Bikerman, 1973). The thickness of lamellae can vary between 10 nm and 1 μm (List, 1985). The

size of air bubbles is proportional to the length of plateau borders. As the bubbles have the same size, their boundaries or lamellae meet at an angle of 120° (Wilson, 1989). The curvature of lamellae results in the occurrence of a region of a low pressure at plateau region (Hansen and Derderian, 1976). The liquid in lamellae is fixed by the molecules of a foaming agent which is fixed at both surfaces of lamellae. This fixation is very critical; otherwise the liquid in vertical lamellae would drain immediately. It was shown that the presence of a liquid crystalline phase in equilibrium with an aqueous micellar solution of surfactant improves the stability of the foams formed from surfactant solution. Addition of a reversed micellar solution (*e.g.* an organic solution) capable to solubilize the liquid crystalline phase of such foam causes foam breaking (Friberg and Saito, 1976). In spite of the firm fixation, liquid tends to drain into plateau border region from lamellae as the pressure within this region is lower than in air bubbles and in lamellae. This process causes the lamellae to become thinner. Thin lamellae are unstable and rupture because their surface area is too large for their volume (Bikerman, 1973). The most obvious cause of foam stability was pointed out by Plateau; he called it surface viscosity. The essential idea is that each film is stratified and has a sandwich-like structure. The inner layer of such a film has the viscosity of the liquid in bulk solution but the two exterior layers (adjacent to the gas phase) are much more viscous (Bikerman, 1973). Foams have unique rheological properties. The bulk flow of foam is very different from that of either Newtonian (laminar or turbulent) fluid or "conventional" two-phase fluids (Wilson, 1989). Presence of a significant yield stress is required to cause the flow (analogous to semisolids) and there is a strongly shear thinning behaviour. These properties derive largely from the unique microscopic structure of foams (Yoshimura, 1988).

4. Foaming agents and surface activity

Pure liquids do not foam (Bikerman, 1973). The presence of a foaming agent is essential for foam generation and stabilisation. Foaming agents are amphiphilic substances: the hydrophilic part of a molecule is responsible for their solubility in water. When a foaming agent is added to water the hydrophobic parts of the molecule arrange themselves in a way to minimize the area of contact with water. This leads to their orientation at the air–water interface and to formation of micelles in the bulk of liquid phase. When a foaming agent is adsorbed into the air–water interface, the surface tension of water is lowered and the surface pressure is increased. The surface pressure is defined as the difference between the initial surface tension of the system and the surface tension after addition of a foaming agent. Therefore, this parameter indicates the activity of a foaming agent. Nevertheless, higher values for surface pressure and low values for surface tension do not always lead to an increase of foam stability. For foam stability, the concentration of foaming agent in an adsorbed layer is more important (surface concentration of a foaming agent). The relation between surface tension and adsorption of molecules into the air–liquid interface is given by the Gibbs equation (Eq. (1)) (Wilson, 1989).

$$\tau = -\frac{1}{2.303 \cdot R \cdot T} \cdot \frac{\mathrm{d}\gamma}{\mathrm{d}\log c} \quad (1)$$

with R gas constant 8.31 (Joule/mol K); T temperature (K); γ surface tension of the liquid (mN/m); c molar concentration of the foaming agent, (mol/L); $\mathrm{d}\gamma/\mathrm{d}\log c$ decrease in surface tension caused by increasing the concentration of foaming agent.

Adsorption in this case is defined as the amount of foaming agent per unit surface area compared to the amount of foaming agent molecules that would be present at the surface if this foaming agent would not have any preference to adsorb onto the surface. The Gibbs equation is based on a dynamic equilibrium between the adsorbed and dissolved amount of foaming agent molecules. Adsorption of foaming agent is, therefore, reversible. But due to their extremely high surface activity, the molecules of the foaming agent are very hard to desorb by lowering for example their bulk concentration. Moreover, desorption of foaming agent molecules is slower, the higher the molecular weight and the lower the surface tension is.

During foam formation a rapid adsorption of the foaming agent is desirable. The rate of foaming agent adsorption depends on its diffusion rate. The diffusion rate of a foaming agent is given by the Fick's law of diffusion (Eq. (2)) and the Einstein-Sutherland equation (Eq. (3)), respectively.

$$\frac{\mathrm{d}m}{\mathrm{d}t} = -D \cdot A \cdot \frac{\mathrm{d}c}{\mathrm{d}x} \quad (2)$$

$$D = \frac{R \cdot T}{6 \cdot \pi \cdot \eta \cdot r \cdot N} \quad (3)$$

with $\mathrm{d}m/\mathrm{d}t$ diffusion rate (m/t); D diffusion coefficient (cm^2/s); A diffusion area (m^2); $\mathrm{d}c/\mathrm{d}x$ concentration gradient (Joule/mol K); R gas constant 8.31 (Joule/mol K); T absolute temperature (K); η dynamic viscosity of the solvent (mPa s); r hydrodynamic radius of molecule (m); N Avogadro number ($6.02 \times 10^{23}\ \mathrm{mol}^{-1}$).

The thickness of solution layer that can provide the surfactant to adsorb to a surface and the concentration of foaming agent in the bulk of the liquid determine the diffusion rate of molecules towards the interface. Foaming agents may also be transported from one site of the surface to another one by spreading, if it is unevenly distributed. The spreading rate is much slower than the mixing speed. The rate of foaming agent adsorption depends on its concentration and agitation in the bulk of liquid and is critical for foam formation. During foam formation, concentration of foaming agent in the bulk phase will decrease with the increase of the created surface area. The higher the volume fraction and the smaller the air bubbles, the larger the surface area will be. Reduction of foaming agent concentration in the bulk solution leads to the decrease of the concentration gradient and, therefore, diffusion rate. Therefore, to assure a rapid diffusion of a foaming agent to the surface, high foaming agent concentrations and a low viscosity of the liquid phase are needed. The ratio between the free energy of adsorption of foaming agent to the surface of the solution and the free energy of micellisation of it in the solution is a convenient criterion for estimation foaming power of a foaming agent (Skrylev and Streltsova, 1985).

There are three stages of foam generation:

- solution of foaming agent (without incorporated air),
- emulsion of gas (solution starts to incorporate air, at the lower volume fractions air bubbles do not have contact to each other; no influence on bubble geometry),
- foam (polyhedral foam, air bubbles have contact to each other through lamellae, their spherical geometry is disturbed).

In some homologous series of foaming agents the maximum of foaming ability is observed at a concentration equal to, or near to, the critical micelle concentration (Bikerman, 1973).

A combination of two foaming agents can either lead to a faster foam generation and increased foam stability or to a decreased foam stability. The salt concentration of the solution also influences the process of foam generation (Jellinek, 1959).

Foam boosters are substances which enhance foam formation. The majority of these substances is from the chemical group of fatty acid alcohol amides, *e.g.* oleic acid diethanol amide, coco fatty acid diethanol amide, polycarboxylic acid poly diethanol amide. They are normally used at the concentration of 5%; otherwise irritation of mucosa can happen (Nowak, 1969).

Table 1
Excipients for foam production/foam destruction.

Foaming agents	Foam stabilisers	Foam destroyers	Foam inhibitors
Surfactants, *e.g.* sodium stearate, sodium oleate, sodium dodecyl sulphate, dioctyl sulfosuccinate. Proteins, *e.g.* collagen	Hydrocolloids, *e.g.* xanthan gum, hydroxypropylmethylcellulose, methylcellulose, alginates, agar-agar	Oils, alcohols, solvents, *e.g.* acetone	Silicon oils, glycerides, polyamide

Addition of some polymers to foamable formulations can lead to an increase of foam stability. So it was shown that addition of polyacrylic acid to non-ionic surfactants leads to the formation of a surfactant-polymer complex through interactions between polymer and surfactant, which contributes to the foam stability (Zhukov et al., 1987). Polymers such as cellulose derivatives or xanthan gum can also be used to increase foam stability.

It is known, however, that addition of small quantities of specific agents to foaming systems can cause a reduction of the stability of formed foams (Table 1). These agents can be divided into two types. The first, foam destroyers, are added to existing foams, and they are generally considered to act in the form of small droplets, which spread on the foam lamellae. By this, a lamella is thinned and the foam breaks. These substances (*e.g.* oils, alcohols or organic solvents) are normally poorly soluble in water; they orientate themselves at the surface, leading to an increase of the surface pressure and a reduction of the elasticity of the surface film, formed by a foaming agent. The presence of oil droplets in the system leads to a change of the surface tension and to an increased liquid drainage causing the rupture of lamella. Foam inhibitors, on the other hand, are generally believed to have a good affinity to the air–water interface. They adsorb at the interface in preference to the foaming agents and in this way prevent foam generation (Roberts et al., 1976). Addition of some electrolytes to the foaming solution can lead to changes in the foam strength (Nakagaki, 1950). Presence of poorly wettable solid particles can also lead to the rupture of lamellae. If a film has thinned sufficiently for a particle in it to bridge the film, and if the material of the particle is sufficiently hydrophobic, the Laplace pressure in the film next to the particle may become positive (depending also on the shape of the particle), causing liquid to flow to a region of lower pressure, and, thus, leading to film rupture (Wilson, 1989).

5. Production of foams

Foams can be produced by mechanical means or by supersaturation of the liquid phase with gas (Wilson, 1989). Liquids can be supersaturated with gas either by dissolving gas under pressure or by gas formation in situ. Nucleation of gas bubbles in this case is the critical process.

5.1. Whipping

Whipping or beating can be carried out with different devices that agitate a liquid in order to form an interface with gas phase. This method is a standard method of gas introduction to the liquid. The volume of the air incorporated into the foam usually increases with an increase of beating intensity, whereas beating of a high viscous liquids leads to generation of unstable foams. Every air bubble undergoes severe mechanical stresses throughout whipping, therefore, a more rapid coalescence happens during foam generation than in a standing foam. Final foam volume during this mechanism of foam generation reflects a dynamic equilibrium between mechanical air bubble formation and destruction of the bubbles. The mechanical stress also leads to the destruction of the bigger air bubbles into the smaller ones. Foam generation by whipping is used in food industry for production of cream, instant desserts and toppings.

5.2. Shaking

This method is used rarely. The rate at which air bubbles are introduced to a solution depends on the frequency and amplitude of shaking, the volume and shape of container and the volume and viscosity of liquid. Only low foam volumes at long generation time can be produced by this method.

5.3. Bubbling

By bubbling foams are generated by injection of gas through narrow openings. This method is reproducible and gives uniform bubble sizes. Foam volume produced by this method depends on the total amount of foaming agent in the solution being bubbled.

5.4. Pressurized aerosol foams

Aerosol foam formulations represent a range of dosage forms that have achieved international commercial success in the recent years as innovative vehicles.

There are two types of aerosol foams: two-phase and three-phase aerosol foams (Jellinek, 1959).

In two-phase (Fig. 2A) systems the liquefied propellant is solved in the solution of a foaming agent under pressure. The aerosol can contains in this case a continuous liquid and a gas phase. The liq-

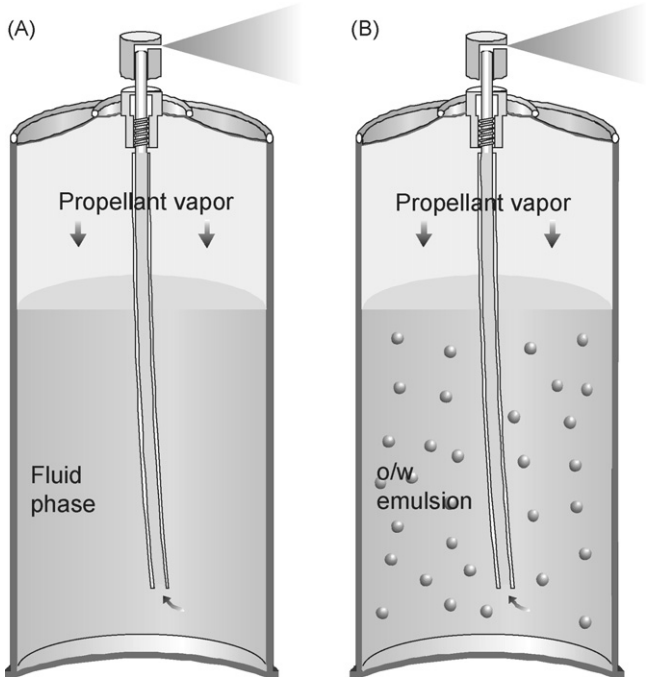

Fig. 2. Aerosol foam products: A. two-phase aerosol foam, B. three-phase aerosol foam (adopted from Jellinek, 1958).

uid phase consists of a solvent, foaming agent and foam stabiliser, whereas the gas phase is composed of propellant vapor. The gas phase practices a pressure on the aerosol can and the fluid phase in it, which is always higher than the atmospheric pressure. This pressure is dependent on the composition and the concentration of the propellant in the system and typically is in the range of 2–4 bar. When the nozzle of the spray head is opened so that there is a connection with the external air; the fluid phase will be pressed out of the aerosol can through a tube. At atmospheric pressure the dissolved propellant evaporates instantaneous, generating the foam (Müller, 1998). Foam formation is supported through specific foam actuators placed to the outlet of the can.

Three-phase systems (Fig. 2B) represent an o/w emulsion (Voigt, 2006). The propellant is solved in a lipid phase, which is emulsified with a water phase through addition of an emulsifier. The foaming agent can also in this case act as an emulsifier. The third phase is the vapor phase of the propellant over the emulsion. Both two-phase and three-phase systems should be shaken before application. The velocity of foam generation is dependent on the rate of propellant evaporation. Propellants with low boiling points evaporate rapidly leading to immediate foam generation. If the propellant blend also contains a component with a higher boiling point, this will lead to a delayed foam generation. Water is the most frequently used solvent in foam aerosols. Besides water, ethanol and isopropanol are occasionally used as solvents. Many foam aerosols can be mixed in cold state. But more often the oil phase should be warmed to 70 to 80 °C and brought to the liquid state. The aqueous phase, with water soluble ingredients has also to be brought up to the same temperature and subsequently mixed into the oil phase. Temperature sensitive ingredients such as extracts and vitamins can be introduced after cooling back down to 40 °C. Finally the product has to be homogenised. The production is carried out under vacuum where foaming can be avoided (Hoffbauer, 1996). Examples for this type of systems are shaving foam, hair styling mousse, aerosol shampoo, aerosol hand cream and aerosol mask (Jellinek, 1959; Raab and Kindl, 1999).

The formulation is filled into an aerosol package, comprising a can, valve and an actuator. The materials of aerosol cans can be aluminium or tin. Both of the metals can be incompatible with some solvents, therefore, the inside of the can is oft coated with epoxide resins. A foam valve is crimped onto the aerosol can. Special foam valves are used for foam generation. Foam valves comprise a stem which is usually made of polyethylene and a valve seat made of aluminium. Foam valves can be with or without a metering chamber. These valves should have a special valve support, which should be corrosion-resistant due to the presence of the water phase in the system (Voigt, 2006). The valve seal should be compatible with solvents, surface active substances and propellants used in the formulation, and detection of possible "leachables" and "extractables" in the system is of a great importance. Foam valves are available, *e.g.* from Lindal and Precision Valve (Kuplien, 1994). The foam actuator is fixed to the valve and has the function to dispense the aerosol foam. Foam actuators with upright orifice, two-piece actuators with a membrane or one-piece actuators to produce an improved foam quality can be used (Hoffbauer, 1996). Using a spray actuator, spray foams may be produced. The nozzle geometry of an actuator has a significant effect on the quality of generated foams.

After the valve has been crimped onto the aerosol can, the propellant is added to the aerosol container, either through the valve or during the crimping process.

The most often used propellants are hydrocarbon propellants, *e.g.* n-butane, isobutane, n-propane or mixtures thereof. These propellants are liquefied under pressure and their blends have a wide interval of boiling points. The concentration of the propellant in the aerosol can is typically in the range of 3–12% (Voigt, 2006). This amount of propellant is sufficient to produce a suitable quality of foam. There are also systems containing primary propellants, in the meaning of "immediately" evaporating propellants (*e.g.* compressed air) and secondary propellants (*e.g.* n-pentane, isopentane, isobutane) which evaporate with a delay, causing a cooling effect on the skin surface (Kroepke et al., 2004). Nitrogen, oxygen, helium, argon, dinitrogen oxide and carbon dioxide can also be used as propellants. Hydrofluoroalkane propellants are also described for this application (Hirsh et al., 2005). The use of propellants is considered to be the major disadvantage of aerosol foam formulations as the propellant technology is relatively complex and expensive to manufacture, therefore, increasing the overall cost of the product. The production expense of this type of formulations is a major factor that limits the number of foam formulations available on the market nowadays (Prudon et al., 2003). Also, toxicological concerns are more and more raised by regulatory bodies with respect to propellant toxicology, extractables and leachables.

5.5. "Bag-in-can" system

It is also possible to formulate a semi-solid gel system that foams when it is rubbed on the body. These products usually contain a low-boiling hydrocarbon such as isopentane which has a boiling point of about 28 °C. Application and agitation of such a product at body temperature causes the isopentane to vaporize and generates a foam with similar properties than a pressurized aerosol foam system. Because of the low boiling point of isopentane, these formulations are also packaged in pressurized containers but a barrier system separates the product with solubilized isopentane from the pressurizing gas. The external pressure is needed to dispense the product and also to keep the isopentane in the product. The formulation is added to the bag and the system is pressurized from the bottom of the can and then sealed with a plug (Schlesinger, 2000). Such systems are available from *e.g.* CCL Container (PA, USA).

5.6. In situ gas generation

The gas which is needed for foam production can as well be generated *in situ* as *e.g.* in vaginal and rectal foams and tablets by means of an effervescent formulation composition. Through the contact with mucosal secretions the gas is generated, leading to a foam production (Friess et al., 1999).

5.7. Airspray® foam pump line

Airspray® pump foam dispensers create foam without the use of gas propellants. This patented technology (Van Der Heijden and Maria, 2008) allows mixing of liquid and air, resulting in foam generation. In the stationary position the liquid dosing chamber (a) is filled with the formulation. The ball valve (b) of the chamber is closed and the steel spring (c) is released. In the operating position the air in the air dosing chamber is compressed by a piston (d). At the same time the bore holes of the piston in the air dosing chamber are closed by a diaphragm valve (e). The steel spring is compressed and the ball valve of the liquid dosing chamber is closed. The formulation from the formulation dosing chamber and air from the air dosing chamber are transferred through an uptake tube (f) and pressed through a foam generator with a double sieve (g). In the discharge position the compressed steel spring moves the piston of the air dosing chamber in the stationary position. The diaphragm valve of the air dosing chamber opens and lets the chamber to be filled with air. The ball valve of the liquid dosing chamber opens and the empty dosing chamber can be filled with formulation (Fig. 3A and B). There are also foam dispensers including two separated chambers with two pumps that are coupled. One chamber can contain the cosmetically and dermatological active substances, the other chamber contains surfactants (Doerschner et al., 2005).

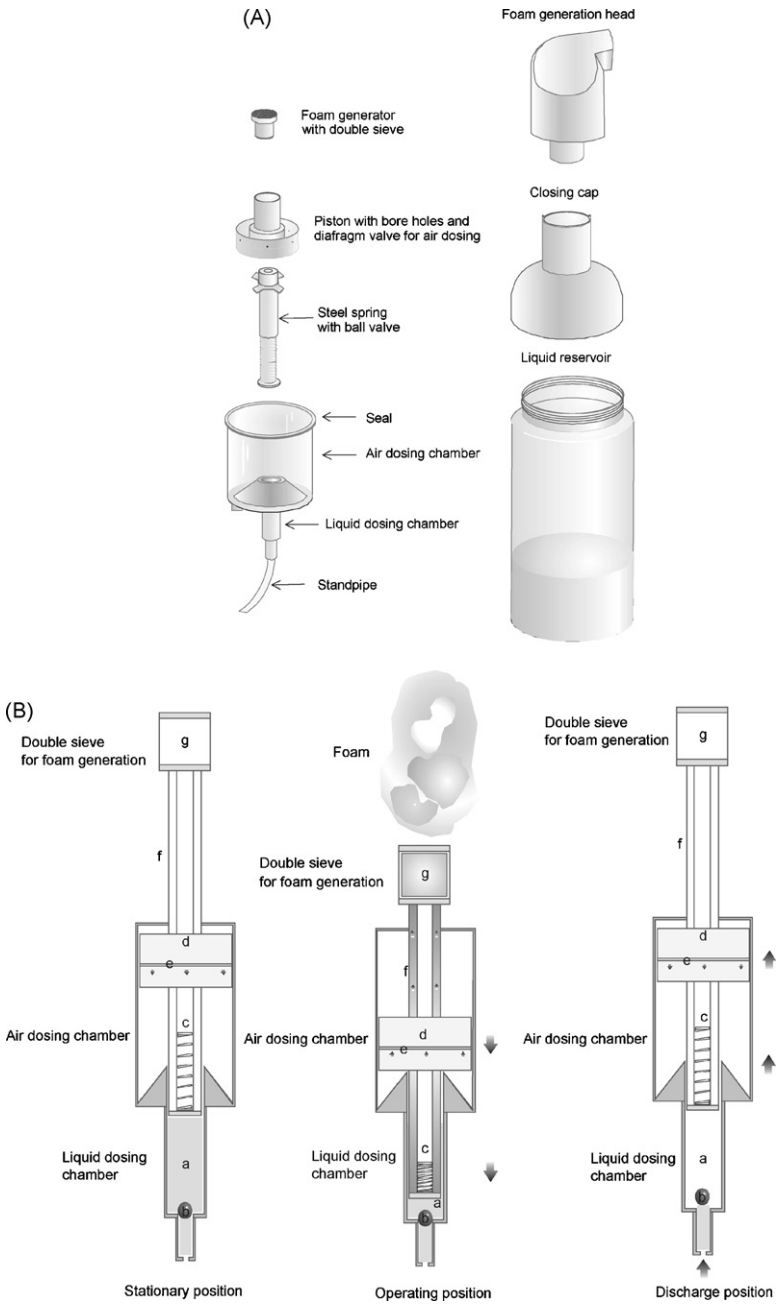

Fig. 3. A. Illustration of the Airspray® foam dispenser, B. mechanism of foam generation by the Airspray® foam dispenser.

Foam quality generated by Airspray® foam dispensers differs from that generated by the means of a propellant (aerosol foam). Aerosol foams are finer pored and more viscous than those generated in a propellant-free way (Fig. 4).

6. Foam stability

"It is perhaps surprising to find in 1958 that no thoroughly satisfactory explanations have been given to why certain liquids foam strongly, others feebly, and many not at all (Exerova et al., 1976). Nowadays it is almost true to use the same sentence. In spite of many investigations it is very difficult to develop a general theory of foam stability as many different, both dynamic and static factors determine it.

If the film between two bubbles ruptures, the bubbles will coalesce. The stability of foams has been, therefore, related to the colloid stability of the thin films by which the distance relations of the independent Van der Waals' attraction and the electric double-layer repulsion potential are dominant factors (Friberg and Saito, 1976).

Several different processes can be identified in the breakdown of foams. These are: disproportionation (Ostwald ripening), gravitational separation (creaming, bubble rise and drainage) and encounter mechanism (Brownian motion) (Fig. 5). These processes do not happen separately but to a considerable extent simultaneously, enhance each other and lead to many possible intermediate stages between a uniform dispersion and two completely separated phases. As soon as bubbles are formed, several changes start to occur. The pressure inside the air bubbles is higher than that in

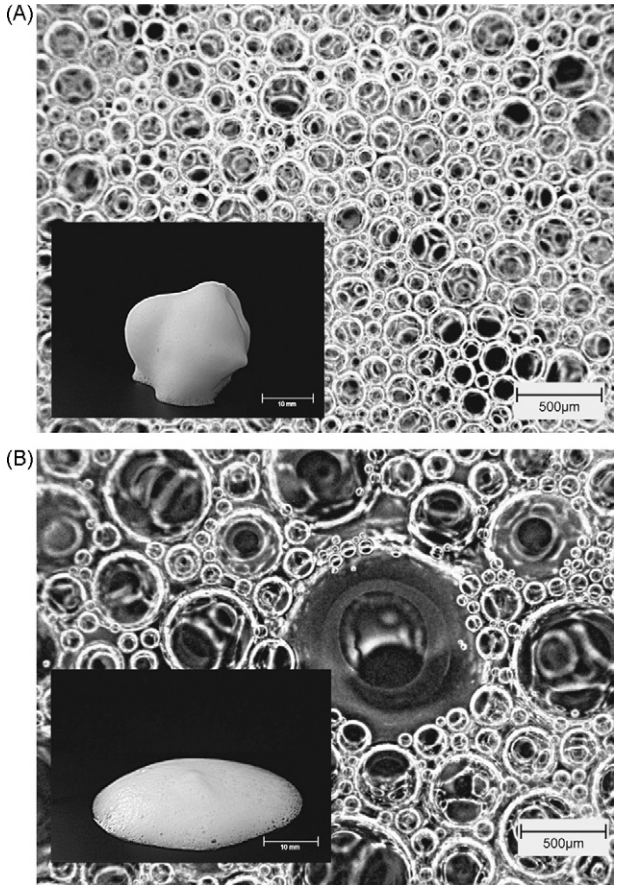

Fig. 4. Microscopic and macroscopic comparison: A. aerosol foam, B. Airspray® foam.

the solution or air. This pressure increase can be described by the Laplace equation (Eq. (4)) (Bikerman, 1973).

$$\Delta P = \frac{4\gamma}{d} \tag{4}$$

with ΔP pressure difference (Pa); γ surface tension (mN/m); d droplet diameter (m).

Moreover, the pressure and the solubility of the dispersed air phase is greater for smaller bubbles. This defines a driving force for diffusion from small air bubbles to larger ones or to bulk liquid phase. The rate of diffusion depends on the solubility of the dispersed air phase in the continuous liquid phase. That is why it comes to Ostwald ripening of foam bubbles (Wilson, 1989). As a result of this destabilisation mechanism, the smaller air bubbles dissolve while bigger bubbles grow in size by gas diffusion through the liquid phase (Hansen and Derderian, 1976).

Because of the density difference between the phases, gravitational and capillary forces cause the flow of the continuous liquid phase around the dispersed air bubbles. The air bubbles move towards the top, while the gravitation forces lead the liquid to drain within the foam lamellae. At low gas volume fractions the creaming mechanism of foam destabilisation predominates, whereas, at higher gas volume fractions the liquid drainage prevails (Wilson, 1989). The liquid drainage leads to the generation of a foaming agent concentration gradient within the lamellae and, therefore, a surface tension gradient. This gradient can be stabilised through the adsorption of foaming agent from bulk solution. Nevertheless, both of these processes causes segregation of the foam into the foam layer on the top and drained liquid layer on the bottom. Foam drainage is a complicated process that is not fully understood. The flow through individual channels depends on the type of surfactant used to create a foam (Koehler et al., 2004).

The drainage is principally independent from bubble rupture, although bubble rupture may contribute to this phenomenon (Bikerman, 1973). The reason for rupture of lamellae is the insufficient elasticity of the surface film. Under elasticity, in this case, the ability of lamellae to stabilise themselves is understood when through the liquid drainage the concentration of the foaming agent at the surface becomes inhomogeneous. Liquid drainage can also cause the increase of air bubbles size without a collapse. When the film is elastic, it means that the liquid with the foaming agent is transported to the place of the possible rupture ("closing the wound"). This effect is called Marangoni effect (Ross and Nishioka, 1976). The Marangoni effect is generally believed to be the main cause of film stability (Bikerman, 1973).

7. Foam stabilisation

The objective of stabilisation measures is to stop the destabilising mechanisms. Foams with a higher gas volume fraction are more stable. In this case the liquid drainage as well as creaming is delayed. Higher concentrations of foaming agent are also advantageous, leading to a higher elasticity of a surface film. Creaming and foam drainage depend on the solution viscosity. Therefore, higher viscosities could lead to the delay of the phase break-up. In this case, the application of thixotropic substances is beneficial. Arabic gum, methyl cellulose and similar hydrophilic materials of high molecular weight raise the stability of foams due to increase in viscosity (Bikerman, 1973). Temperature also affects the rate of drainage by altering the liquid bulk viscosity. The DLVO-theory also can be used to explain foam stabilisation. When a substance is added to foam leading to the charge of the surface film, this can result in the repulsion of the air bubbles coming near to each other. Electrostatic or steric stabilisation can be achieved through the use of macromolecules in the formulation. The macromolecules orientate themselves at the surface and, therefore, can provide a steric stabilisation, hindering the air bubbles to coalesce.

8. Characterisation of foams

Macroscopic processes of foam destabilisation and the observed changes in foam appearance correspond directly to the microscopic processes described above. Collapse of the foam column leads to the decrease of the foam volume, essentially through the loss of gas. The problems of measuring foam stability depend first of all on the insufficient characterisation of these processes. Whereas the increased volume of drained liquid is easy to measure, the coalescence, *e.g.* of the air bubbles cannot be measured easily. Applicable development methods to measure bubble coalescence include *e.g.* microscopy or freeze-fracture TEM measurements after different time-points post-actuation.

The European Pharmacopoeia describes two characterisation methods in the Monograph "Medicated foams". These are, firstly, estimation of the relative foam density as an indication of the foam firmness and, secondly, the foam expansion time as a parameter for the foamability of the formulation. Density of produced foams is determined by weighing a predefined volume of foam compared to the weight of the same volume of water (Eq. (5)).

$$\mathrm{FD} = \frac{m(\mathrm{foam})}{m(\mathrm{water})} \tag{5}$$

with m(foam) mass of foam per volume unit (g); m(water) mass of water per volume unit (g).

For determination of foam expansion time, a foam volume is released into a burette and foam expansion is followed within a defined time. Specifically, the latter method is inapplicable

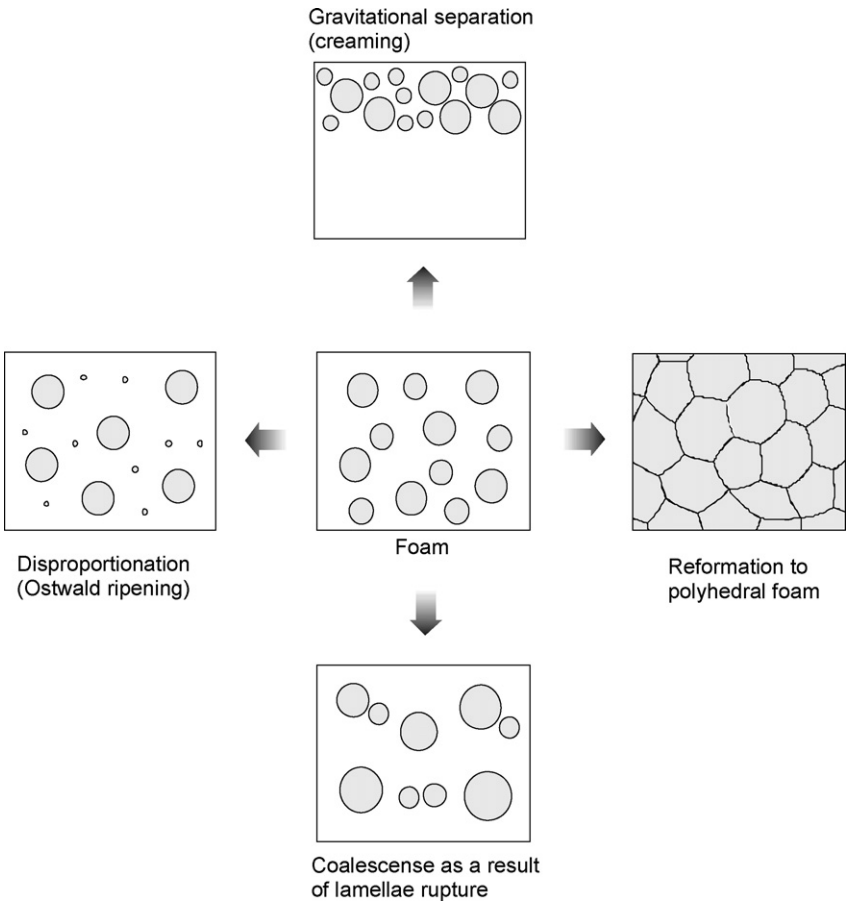

Fig. 5. Mechanism of foam destabilisation (adopted from Oungbho, 1997).

for foams generated via mechanical pump systems or *in situ* mechanisms. The determination of foam stability is not considered in this monograph. Independent from the foam generation mechanism, knowledge of such foam parameters as well as the assessment of the "before-application" stability is crucial for the pre-formulation development stage. Moreover, an assessment of the general appearance as well as the stability and the intensity of expansion are important factors for the cosmetic acceptability.

Another important foam quality which has a high significance is the so-called foam "breakability". According to this property, foams can be classified into several categories having very different application properties.

- "Quick breaking" foams are thermally unstable and collapse upon exposure to skin temperature. Hydro-ethanolic foams are typically thermally unstable and, therefore, their application to large skin areas is cumbersome.
- Lathers are soapy foams that remain stable as they are formed or increase in volume when rubbed (like shaving foam).
- "Breakable" foams are stable at skin temperature, but collapse and spread easily upon application of mild shear forces. The thermal stability of the "breakable" foams coupled with their fast collapse and high spreading properties make them ideal for use in dermatological and mucosal tissue application.

Some additional methods for foam characterisation are described in the literature. For example one method to measure foam consistency is described by Exerova et al. (1976). The foam in this case is produced in a vertical cylinder vessel provided with a small indentation in the centre of its base. The rounded end of a glass rod is placed in this indentation and the rod is held vertically by an upper support. Withdrawal of the support allows the rod to fall against a wall of the vessel. The time of fall is used empirically as a measure of foam consistency. Further methods to measure foam consistency such as determinations with mobilometer, foam consistometer and Brookfield viscosimeter are described, *e.g.* by Scott and Thompson (1952).

8.1. Macroscopic evaluation

Foams can be characterised macroscopically, with the determination of such characteristics as being fine pored or coarsely porous, viscous or runny.

8.2. Foam bubble size/microscopic evaluation and image analysis system

Bubble size and structure of generated foams can be observed and measured with a stereo microscope connected with a digital ocular. Foam uniformity can also be determined with this method as homogeneity of air bubbles. The major disadvantage of this method is, however, that the resolution of these observations is severely limited by the wavelength of visible part of the spectrum. Because of the large semi-aperture angle, they have a small depth of field which reduces the potential for stereo observations of the highly three-dimensional foamed materials (Wilson, 1989).

Produced foams can also be analysed by means of an Image Analysis System (*e.g.* Sympatec GmbH, Germany). The size (Ferret diameter), roundness and the aspect ratio of incorporated air bubbles as well as bubble amount in a predefined area are the parameters of interest in foam characterisation. Measurements can

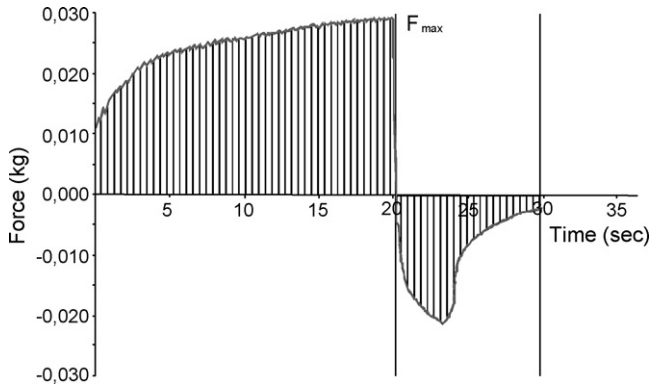

Fig. 6. Force-time plot to measure foam firmness as derived from a Texture Analyser.

be carried out direct after foam generation and after defined time intervals to follow foam destabilisation mechanisms which allows for a foam stability assessment.

8.3. Foam texture (texture analyser)

The properties which principally influence foam firmness are surface viscosity, bulk liquid viscosity, bubble size distribution and foam geometry.

Foams can be characterised using a Texture Analyser (*e.g.* Texture Analyser TA.XT.plus, Stable Micro Systems, England). The foam should be dispensed into a container and the sample is then stressed with a disk which is pressed through the foam to a specified depth. The required force is recorded. During penetration the force is shown to gradually increase until the point of maximum penetration depth. The sample then proceeds to withdraw from the disk. The maximum positive peak indicates the firmness of the foam (Fig. 6).

8.4. Cylinder method (determination of foamability and foam stability)

Foam stability is usually reflected by the initial foam volume and subsequent measurements of the volume as a foam ages. A cylinder method can be used as an easy method for routine evaluations (Patel et al., 1988; Poole, 1989).

This test can be carried out to determine the following parameters: foam expansion (FE, %, Eq. (6)), foam liquid stability (FLS, %, Eq. (7)), foam volume stability (FVS, %, Eq. (8)) and foam gas fraction (GF, ml, Eq. (9)).

The foam is discharged into a glass cylinder. Initial volume of foam, the volume of aged foam and the volume of drained liquid after defined time intervals are recorded. By this, the separation of the liquid due to liquid drainage can be observed, *e.g.* after 30 min, to describe the foam stability over this time period.

$$\mathrm{FE}(\%) = \frac{V(\mathrm{foam}) - V(\mathrm{formulation})}{V(\mathrm{formulation})} \cdot 100\% \quad (6)$$

with V(foam) volume of produced foam (mL); V(formulation) volume of formulation to produce V(foam) (mL).

The higher the FE the more foamable is the formulation.

$$\mathrm{FLS}(\%) = \frac{V(\mathrm{liquid}_{30\,\mathrm{min}})}{V(\mathrm{formulation})} \cdot 100\% \quad (7)$$

with $V(\mathrm{liquid}_{30\,\mathrm{min}})$ volume of liquid drained after 30 min.

The lower the FLS the more stable is the produced foam.

$$\mathrm{FVS}(\%) = \frac{V(\mathrm{foam}_{30\,\mathrm{min}})}{V(\mathrm{foam})} \cdot 100\% \quad (8)$$

with $V(\mathrm{foam}_{30\,\mathrm{min}})$ volume of foam after 30 min.

The higher the FVS the more stable is the produced foam.

Foam gas fraction can be determined as a difference between foam volume and volume of the expanded formulation.

$$\mathrm{GF(mL)} = V(\mathrm{foam}) - V(\mathrm{formulation}) \quad (9)$$

8.5. Foam stability/Turbiscan method

Tyndall light scattering can be used to measure foam stability. This method is based on the Faraday-Tindall effect which postulates that colloidal solutions can scatter light. The method is based on differences in refractive indices between solution of foaming agent and air resulting in different intensities of transmission and backscattering. Intensities of transmitted and backscattered light are dependent on the amount of air in foam. During the process of foam destabilisation, the amount of air changes in different depths of the measuring cell as a result of air bubble growth (foam ripening) and liquid drainage. Therefore, transmission and backscattering signals also change.

Because of the different refractive indices of both phases, interactions of photons (diffusion and diffraction) happen. The backscattering signal is inversely proportional to the square root of the mean free distance covered by a photon being backscattered (Eq. (10)).

$$\mathrm{BS} \approx \frac{1}{\sqrt{l^*}} \quad (10)$$

with l^* mean free distance of a photon (m).

The higher the phase volume of gas in foam, the shorter is the free distance covered by a photon and, therefore, the more intense is backscattering and the less intensive is transmission.

For measurements, the foam is dispensed into a measuring cell and scanned through with infrared light (λ = 850 nm). A light source and two detectors move along the measuring cell and backscattering and transmission signals are detected every 40 μm from the bottom of the cell till the height of 55 mm. Therefore, such physical processes as liquid drainage at the bottom and air bubble growth in the bulk of the foam can be detected. Intensity of the backscattered light is detected under the under the angle of 45° (nephelometry). Intensity of the transmitted light is detected under the angle of 180° (turbidimetry). Under this angle only the photons that do not change their orientation are registered.

Transmission and backscattering intensities are given as measurements results over the whole height of the measurement cell.

A clear transmission signal can be detected at the bottom (approximately at the height of 15 mm) of the measurement cell (Fig. 7A). At this height the light can be transmitted through a phase of separated (drained) liquid. This signal is also called a drainage peak.

At the central part of the measurement cell (20–35 mm) no transmission signal can be observed. The light cannot be transmitted because of the high concentration of dispersed air bubbles.

At the upper part of the measurement cell (35–55 mm) where growth of air bubbles takes place, the transmission signal can be observed again. This signal should, nevertheless, only be treated as a shift of the foam meniscus and not as a development of a new phase.

When a transmission signal is detected, there will be also a backscattering signal at the same zone (Fig. 7B). This signal should, nevertheless, not be evaluated, as the reason for this signal is a secondary light reflection at the wall of the measurement cell.

Foam ripening in the bulk of foam (central part of the measurement cell, 20–35 mm) illustrates the growth of air bubbles in foam and can be detected as a parallel shift of the backscattering intensity curve to lower values.

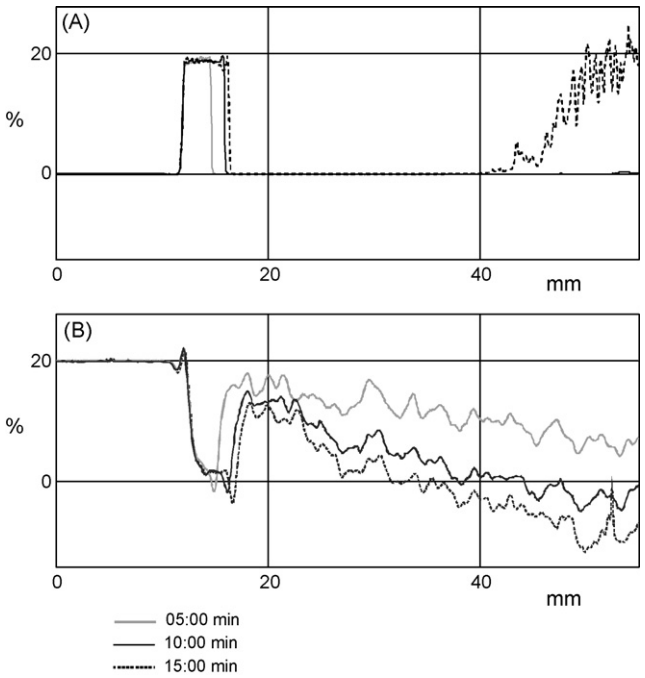

Fig. 7. Backscattering and transmission profiles from a Turbiscan analysis.

For foam sample analysis the change of transmission intensity is evaluated over time as a change in the thickness of the liquid drainage peak. A delta $H(t)$ kinetic curve is obtained. A slop of this curve reproduces the development of the liquid phase in mm/min.

Change of backscattering intensity is analyzed as a mean value kinetic curve or delta BS(t) curve at the central part of the measurement cell. Interference factors, such as negative backscattering peaks at the bottom or the shift of the foam meniscus at the top, should be avoided. The slope of this curve represents the increase of air bubble size over the time (%/min).

These tests are typically carried out in the reference-mode where all obtained curves are compared to the chosen initial curve. In this mode, changes in the intensities can be better estimated.

In the non-reference mode it is possible to detect the initial and the final value for backscattering. The difference of these two values shows the change in air bubble size over measurement time.

Light (back)-scattering techniques (*e.g.* Turbiscan, Malvern Instruments) provide a fast and practical approach to characterize the foam stability. Foamability of a formulation, can, nevertheless, not be detected with this method.

8.6. Rheological properties

Rheological properties of foams are very difficult to measure, especially for weak foams. First of all, foams are unstable because of liquid drainage and Ostwald ripening. Additionally, the generation of a liquid film slip layer at the wall during the measurement will affect its accuracy (Mleko et al., 2007). However, rheological methods may be used in oscillatory mode to learn about foam film elasticity and, therefore, foam stability.

8.7. Foamability measurements in cosmetic formulations

The most often test used to measure the foaming capacity of cosmetic formulation is the test of Ross and Miles (Jellinek, 1959). This test is based on the fact that the volume of foam is an approximately linear function of the height of fall and that the various materials differ in the stability of their foams and not in their capacity to foam (Nowak, 1969). The test liquid with a foaming agent is filled into a pipette of a defined geometry and dropped through a pipette aperture into container which also contains the test solution. The volume of the foam, generated under these conditions is measured direct after generation and after 5 min to evaluate the stability of the foam column.

A faster screening method to compare the foam generation characteristics of different foaming agents is to fill the solutions into a graduated cylinder and to measure the height of the foam column after shaking and after 5 min (Jellinek, 1959).

A rotor-test can also be used for a quick and reliable assessment of the foam kinetics of test solutions with and without addition of defoaming agents. The solution of the foaming agent is thermostated in a cylindrical vessel with a water jacket. A stirrer with a rotating disk at the bottom end of the stirrer rod is immersed into the solution, whereas the revolutions per minute of the stirrer are set. During foam generation the foam height is recorded every 10 s within 3 min (Engels et al., 1998).

The Schlachter-Dierkes and Colson tests are based on the fact that presence of fat leads to a worsening of the foaming capacity. During these tests, the height of a foam column generated from a test formulation without fat contamination by beating is compared to a height of a foam column after addition of a defined amount of a defined fat blend to the same formulation. During the Wilmsmann test the rate of foam generation (foam "boost"), foam stability and foam drainage are tested in a special device with and without fat contamination (Nowak, 1969). Wehle (1957) has proposed a method to measure the foam strength of tooth care products by determination of a foam strength number by means of the foam height before and after shaking.

With the SST-test (stress-stability test) the mechanical stability of foams can be measured. The foam of the test solution is generated in a cylindrical vessel with a thermostated water jacket by means of nitrogen gas passing through a very fine metal sieve. After 2 min the gas flow is stopped and an aluminium plate with a definite weight is placed on top of the foam column. The plate compresses the foam and passes down to the bottom of the vessel destroying the foam. The height of the plate as a function of time is a measure of the foam stability (Engels et al., 1998).

Half-head-test is a one-to-one comparison under realistic conditions for hair shampoos. In this case, the two products are applied on each of the two hemispheres of the head of a test person. Parameters such as feel of the foam as well as feel of the wet and dry hair, the visual appearance and the rinse-off characteristics of the foam are evaluated by a group of five experts (Engels et al., 1998).

9. Pharmaceutical foams

The interest in the development of new vehicles for topical delivery is steadily growing nowadays. Foams represent one portion of such new pharmaceutical vehicles. Depending on the way of pharmaceutical application rectal, vaginal and dermal foams can be defined.

Foams for dermal drug delivery have some advantages compared to the traditional vehicles for treatment of topical disorders such as ointment, creams, lotions, gels or solutions. These conventional vehicles often have drawbacks that are dictated by the excipients. Ointments comprise a high viscous, non-volatile vehicle which can be unpleasant to apply and often difficult to remove from skin and clothing. Creams, ointments and gels can leave residues after application and stain clothing. Solutions often flow away from the site of application because of their low viscosity.

Negative sensory attributes such as greasiness, oiliness or tackiness can be to some degree avoided using foams as a vehicle for drug delivery. There is no sticky feeling and shiny look after application.

Moreover, foams absorb and penetrate quickly without leaving any greasy residue (Prudon et al., 2003). That is why these vehicles can be used on hair bearing skin; the vehicle breaks down rapidly and reaches the *St. corneum* through the hair shafts. Foam density is approximately one tenth of the density of conventional vehicles. Therefore, foams as more gentle products can be applied and spread more easily onto large areas with negligible mechanical shearing required than during application of traditional vehicles. Foams can be easily applied to mucosal areas, to sensitive or to highly inflamed skin, when rubbing the formulation onto the skin may be painful or causes further inflammation.

Although there is no clinical evidence that foamed formulations are superior to the un-foamed formulation, foams have a clear application advantage for patients resulting in increased compliance. The study of Housman et al. (2002) showed that patients prefer foam and solution vehicles over creams, gels and ointments.

Moreover, rapid evaporation of foam ingredients can influence the rate of drug transfer from the vehicle into the skin, as the rate of drug transfer is proportional to its degree of saturation in the vehicle at the vehicle-skin interface (Prudon et al., 2003). Also, because of evaporation of the solvent, foams are likely to be cooler than the ambient air, offering a cooling effect to an inflamed skin (Bikerman, 1973).

Feldman et al. (2000) showed with fingertip units test that topical foam vehicles offer comparable coverage compared to traditional vehicles.

There are not yet a lot of foam formulations that are commercially available, but they have been used for several years in the treatment, predominantly, of some topical diseases.

Vaginal and rectal foam vehicles also feature some application advantages compared to the standard vehicles such as suppositories, creams and ointments. Foam vehicles offer both, convenient application and one-step administration, within one product. No leak of the vehicle takes place during application. Moreover, the residence time of the active pharmaceutical ingredients can be controlled through the use of bio-adhesive polymers.

There are also nasal compositions containing foaming agents such as saponin and lecithin under development which should moisturise the nasal cavity in treatment of rhinitis. Nasal foams containing non-steroidal anti-inflammatory and analgesic agents for treatment of low back pain, arthralgia, distorsion and tendosynovitis (Nakagawa et al., 1991) are also described.

9.1. Classes of foams

Not all foams are the same. While in the past there were few types of medicated foams, *i.e.* aqueous foams and hydro-ethanolic foams, today there are several classes of foam formulations being marketed and further classes under development, which are distinct from each other by their composition and functionality. It is important for pharmaceutical scientist as well as for the practicing physicians to understand the difference between different classes of foam formulations to be able to select the right type of formulation for a given clinical condition. The parallels between various classes of foams and traditional topical dosage forms are given in Table 2. For example, an emulsion based foam is a parallel of a cream (Tamarkin et al., 2006a).

9.2. Dermal foams

Dermal foams can be used in the treatment of different skin conditions, as for example seborrheic dermatitis (SD). SD is a chronic, recurrent skin condition that affects three to five percent of the population. This condition is characterised by flaking, itching and redness and most often affects the scalp (dandruff), but also can affect skin on other parts of the body, including the face, chest and the creases of the legs, arms and groin.

Extina® foam developed by Connetics Corporation (USA) is a foam containing 2% of ketoconazole for the treatment of mycoses and other dermatological indications, particularly SD which was approved by FDA in 2007. This product utilises Connetics' proprietary foam drug delivery technology - Versa Foam HF (hydroethanolic formulation) technology (Popp and Yuhas, 2004). This foam was proved to be an effective and safe topical therapy for mild to severe SD, significantly relieving symptoms after 4 weeks of therapy (Rolz-Cruz and Kimball, 2008). Extina® foam was also proved to be superior to placebo foam in Phase III clinical trials and equivalent to ketoconazole cream in the treatment of SD. Moreover, patients reported to prefer foam formulations because they were easier to use and were absorbed faster than other vehicles (Elewski et al., 2007). The most frequently reported adverse experiences in the ketoconazole foam group were application site reactions which were generally mild and transient (Koller et al., 2004). In the treatment of dandruff, the foam containing ketoconazole was shown to be as effective as ketoconazole 2% lotion (Milani and Quadri, 2004).

As combination therapy of ketoconazole and betamethasone valerate sometimes becomes necessary in the treatment of SD, there are studies which have investigated synergistic effects between these two substances when applied from a foam vehicle (Tanojo et al., 2004).

More foam products from Connectics Corporation and Stiefel Laboratories are available on the US dermatology market such as Evoclin® clindamycin phosphate foam, 1%; Olux® and Clarelux® (since 2006 also on the German market from Pierre Fabre Dermo-Kosmetik) clobetasol propionate (CP) foams, 0.05% and Luxiq® betamethason valerate (BMV) foam, 0.12%.

Evoclin® foam is indicated for topical application in the treatment of acne vulgaris. Olux® and Clarelux® foams are used for short-term topical treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatosis of the scalp, and for short-term topical treatment of mild to moderate plaque-type psoriasis of non-scalp regions excluding face and intertriginous areas. Luxiq® foam is used for relief of the inflammatory conditions of corticosteroid-responsive dermatoses of the scalp including eczema, SD, psoriasis and contact dermatitis. BMV foam and CP foam were shown to be absorbed more rapidly and demonstrated greater total absorption than their respective comparator formulations, namely BMV lotion and CP solution (Melian et al., 2001; Stein, 2005). It is likely that components within the foam (alcohols) act as penetration enhancers, and reversibly alter the barrier properties of the *St. corneum*, thus driving the delivered drug across the skin membrane. This is in contrast to traditional topical vehicles, which rely on hydratation of the intercellular spaces in the *St. corneum* to achieve drug delivery (Huang et al., 2005). BMV bioavailability from the foam vehicle and, therefore, scalp psoriasis treatment efficacy was shown to be increased, without an associated increase in toxicity (Franz et al., 1999). BMV treatment from the foam vehicle was shown to be more effective than standard therapy (corticosteroid and calcipotriol lotions) commonly used in the treatment of scalp psoriasis. This vehicle was considered to be better than lotions in terms of usage, with superior patient acceptability and positive effect on the Psoriasis Disability Index (Andreassi et al., 2003). Moreover, BMV foam was effective for scalp psoriasis with both once-a-day and twice-a-day use (Feldman et al., 2001). The study of Stein et al. (2001) showed that BMV foam is also effective against nonscalp psoriasis. Another study showed that twice-daily application of BMV foam was well tolerated and compliance exceeds 90%. BMV foam was also was shown to be effective in the short-term treatment of seborrhoeic dermatitis (Massimo et al., 2003). In the treatment of mild-to-moderate *Alopecia areata*, BMV foam was also shown to be

Table 2
Different classes of foams.

Foam		Traditional topical dosage form designation (USP and PhEur, combined)	Attributes
Class	Main formulation characteristics		
Foam hydrophilic emulsion	Oil in water emulsion	Emulsion, Cream, Hydrophilic cream	-Emollient formulation
Foam lipophilic emulsion	Water in oil emulsion	Emulsion, Cream, Lipophilic cream	-Can carry lipophilic and hydrophilic APIs
Foam ointment	Single phase	Ointment, white ointment, hydrophobic ointment	-Occlusive
	Petrolatum is a main ingredient		-Serves to keep medicaments in prolonged contact with the skin -In the absence of water, protects water sensitive actives -Does not require preservatives
Foam hydrophilic ointment	Single phase	Polyethylene glycol ointment, hydrophilic ointment	-Greaseless ointment base
	Main ingredient is PEG or other hydrophilic solvents		-Serves to solubilize medicaments, thus rendering them more bioavailable -In the absence of water, protects water sensitive actives -Does not require preservatives
Foam oil	Single phase Liquid oil is main component	Oil solution, oil suspension	-Partially occlusive -Nourishes and lubricates the skin -Serves to keep medicaments in prolonged contact with the skin -In the absence of water, protects water sensitive actives -Does not require preservatives
Hydro-ethanolic foam	Lower alcohols and water are main ingredients	Solution, tincture	-Serves to solubilize medicaments, thus rendering them more bioavailable -Adequate for oily skin areas -Does not require preservatives
Aqueous foam	Main ingredients are water, gelling agents and surfactants	Gel	-Non-greasy
Foam suspension	Suspended API in a foam formulation	Topical suspension	-Non-greasy -Desiccative

effective and well-tolerated (Mancuso et al., 2003). The study of Weiss et al. (2005) showed that betamethasone valerate foam was effective and well-tolerated in the treatment of stasis dermatitis. A combination of BMV foam (in the morning) with tazarotene cream (in the evening) was shown to be an effective approach to treat localized plaque-type psoriasis (Dhawan et al., 2005). Deflatop® from Astellas Pharma is a foam formulation on the German market containing BMV, 0.1%. It is used in treatment of head skin diseases which are responsive to corticosteroid therapy such as psoriasis or *Alopezia areata* for example. The same formulation is launched on the UK market by Mipharm under the trade name Bettamousse™.

CP foam was shown to be safe and effective for the treatment of plaque-type psoriasis on scalp and nonscalp areas, when applied twice daily for two weeks (Lebwohl et al., 2002; Gottlieb et al., 2003; Reid and Kimball, 2005). The study of Franz et al. (2000) showed that CP foam was superior to a currently marketed solution product. The study of Bergstrom et al. (2003) showed, that compared to CP cream and lotion, the foam vehicle performed better considering the absolute improvement of psoriasis severity. The patient also noted to spend less time applying foam vehicle compared to solution and cream. CP foam therapy was also recommended for patient with Hailey-Hailey disease (familial benigh chronic pemphigus) who breaks through suppressive therapy with tacrolimus a few times per year (Umar et al., 2004). CP foam and BMV foam were shown to be effective in improving acne keloidales in an open label study (Callender et al., 2005).

There are also products from Connetics Corporation which are still under development such as Actina™, a foam formulation with clindamycin phosphate; Desilux™ desonide foam, 0.05%—a low potency topic steroid formulated to treat atopic dermatitis and Primolux™ clobetasol propionate foam, 0.05%. Clindamycin phosphate foam was shown to be at least as safe and effective as clindamycin phosphate gel (Shalita et al., 2005).

Epifoam® a combination of topic corticosteroid (hydrocortisone acetate, 1.0%) and local anaesthetic (pramoxine hydrochloride, 1.0%) for treating inflammation and itching of the skin due to certain conditions is available on the US market.

There are also other drugs under development in a foam vehicle. For example, thiocolchicoside, which is a semi-synthetic derivate of colchicoside and used in topical formulations for its anti-inflammatory and muscle-relaxant properties, has been formulated as a foam formulation (Miotens®, Bonita et al., 2002). Ibuleve® Mousse with ibuprofen, 5.0% is launched in the UK pharmaceutical market. It should be applied for fast pain relief such as backache, rheumatic and muscular pain, sprains and strains and for pain relief in common arthritic conditions.

Mipharm has also brought a new synergised pyretrine foam for the treatment of scabies onto the UK market (Milice®). Pimecrolimus aerosol foam can be used for treatment of various skin, nail and mucosal diseases (Eini et al., 2005). There also some foam products for disinfection. For example Soft'N Sure™ antiseptic hand foam from STERIS is used for hand disinfection and contains 62% ethyl alcohol and vitamin E as skin moisturizer. Desenex™ foam with 10% of undecylenate from Ciba Consumer is used as an antifungal and antibacterial product for *Tinea pedis*. Septisol™ foam with 0.23% hexachlorophene from Calgon Vesal is used as bacteriostatic skin cleanser. Betadine™ foam from MundiPharma and Operand™ foam from Redi-Products containing povidone iodine are used as a shampoo to relief itching due to dandruff.

Emollient Foam™, Ointment Foam™, Waterless Hydrophilic Foam™, OleoFoamix™, Potent Solvent Foam™, Hydro-ethanolic Foam™, Suspension Foam™ and Saccharide Foam™ are plat-

form foam technologies offered by Foamix Ltd. (Israel). Emollient Foam™ is a patented alcohol free foam vehicle which is based on o/w or w/o emulsions with oil content from 6 to 75%. Ointment Foam™ is a petrolatum based foamable formulation. Waterless Hydrophilic Foam™ is a vehicle based of hydrophilic solvents such as PEG, propylene glycol and glycerine, providing hight solubilization power and penetration enhancement. OleoFoamix™ is a foam vehicle containing up to 90% of liquid oil phase. Potent Solvent Foam™ contains high concentrations of strong solvents, *e.g.* dimethyl isosorbide ans DMSO for high solubility and enhanced drug delivery. Hydro-ethanolic Foam™ is a foamable formulation containing high amounts of ethanol but still being thermally stable. Suspension Foam™ is a foam vehicle containing non soluble components such as zink oxide, titane oxide or acyclovir. This vehicle is also alcohol-free and shows no sedimentation and caking despite of the presence of insoluble components. Saccharide Foam™ contains high amounts of saccharides and honey and is used for wound and burn therapy. These platforms have been used to develop a large amount of foam products containing a variety of APIs, including antibiotic agents, anti-fungals, antiviral agents, immunomodulators, corticosteroids, steroid hormones, anti-acne agents, anti-psoriasis agents and skin barrier-building agents for the treatment of atopic dermatitis. Two products are currently marketed. Scytera®, a foam against psoriais comprising cla tar as active agent is marketed in the US by Promius Inc. FannyFoam®, which contains zinc oxide for diaper rash is also marketed in the US by NextWave Pharmaceutical. Some other products are in advanced clinical trials.

Foamix Ltd. has also patented a foamable vehicle containing liquid or solid waxes to solubilize and stabilise active ingredients (Tamarkin et al., 2009) and a foamable vehicle prepared from a nanoemulsion (Tamarkin et al., 2008a). Moreover, a special device to deliver foams into the body cavities was patented by Foamix Ltd. (Eini et al., 2009). Most of the products using one of the platform technologies are under development, some of them are in phase I or II clinical studies (see Table 3).

Derma Foamix™ represents a patented alcohol free foam vehicle with lowered irritation potential. The stability of the foam is provided by inclusion of a gelling agent into the foam composition (Friedman et al., 2005). The vehicle contains hydrophobic solvents such as mineral, vegetable, silicone or emollient oils to control the skin conditioning (Tamarkin et al., 2008d). The vehicle contains non-ionic surfactants which are less irritative than anionic surfactants. This vehicle can be used as a carrier for hydrophilic and hydrophobic dermatological drugs as well as for particulate compounds. Corticosteroids (Friedman et al., 2006b), antibiotics (Friedman et al., 2006a), antifungal drugs, antiviral drugs, local anaesthetics, vitamin A, B, E and D derivatives, antiallergic agent, hair growth agents, repellent agents and insecticide agents [for example permethrin (Tamarkin et al., 2007b)] could be used as candidate drugs for this topical vehicle. Foamable compositions containing a channel agent (for example nifedipine), cholinergic agent or a nitric oxide (Tamarkin et al., 2008b); substances for treatment of hyperhidrosis (Tamarkin et al., 2007a) are also patented.

GyneFoamix™ is a foam vehicle patented for vaginal application. This vehicle can have advantages being used for a variety of female disorders such as candidal vaginitis, bacterial vaginosis, vaginal dryness, acute and chronic vulvitis, *Herpes simplex*, genital ulcers, human papillome virus, genital warts and hormonal therapy. Candidate drugs can, therefore, be antifungals [miconzole, clotrimazole (Tamarkin et al., 2005b)], antibiotics (metronidazole, clindamycin), steroids, hormones, local anaesthetics and antihistamines.

Baby Foamix™ are vehicles applied against diaper rush. Most of these vehicles are water based and occasionally contain alcohol and glycols but no oils.

CosmetoFoamix™ are patented foam vehicles which can contain retinol and retinoids (Tamarkin et al., 2005a); vitamin B and C and their derivatives such as ascorbic acid, niacinamide (Tamarkin et al., 2008f), panthenol, panthotenic acid and magnesium ascorbyl phosphate; arbutin, kojic acid and other whitening agents; α- and β-hydroxy acids or herbal extracts. These foam formulations can be used for facial and body moisturization, whitening, sunless tanning, anti-aging, sun protection and body firming treatment. Moreover, a cooling agent (for example menthol) or a warming agent can be comprised in such a composition (Tamarkin et al., 2008c). Cosmetic foam vehicles can also contain a coloured excipient or colouring agent (Tamarkin et al., 2008e).

9.3. Rectal foams

Rectal foams are mostly aerosol foams (Sachetto, 1996). Procto Foam® HC is a mucoadhesive and anti-inflammatory foam on the US market used against anorectal inflammation and swelling associated with haemorrhoids, anal fissures and other anal discomfort. It contains hydrocortisone acetate, 1% and pramoxine hydrochloride, 1%. On the German market two rectal aerosol foams are presented: Colifoam® with hydrocortisone acetate, 1% and Claversal® with mesalazine, 20%. Mesalazine foam is patented by Falk Pharma (Kuehn, 2003). Both are used for the treatment of the large intestine inflammation diseases *Morbus Crohn* or *Colitis ulcerosa*. Local therapy with Colifoam® can be considered an additional treatment of radiation-induced colitis (Szepesi et al., 1990). Colifoam® can be also used in the treatment of distal proctocolitis, where the ease of retention and apparent nonabsorption of active component is the specific advantage of this vehicle (Neumann et al., 1989). Hydrocortisone acetate foam was shown to be as effective as hydrocortisone acetate enema in the treatment of distal ulcerative colitis, but subjective improvement was shown to be greater with the foam preparation, and several patients expressed a preference to this vehicle (Ruddell et al., 1980).

Mesalazine foam was shown to be well-tolerated and more effective than placebo foam, accepted and effective as mesalazine enema in the treatment of patients with distal ulcerative colitis (Ardizzone et al., 1999; Pokrotnieks et al., 2000; Rufle et al., 2000). In the study of Lee et al. (1996) mesalazine foam was superior to prednisolone foam with regards to clinical remission in patients with acute distal ulcerative colitis. Both treatments were well-tolerated. Budesonide foam was shown to be as effective as budesonide enema in the treatment of active ulcerative proctitis or proctosigmoiditis (distal ulcerative colitis, left-side colon). In this trial the patient prefered foam vehicle to an enema (Gross et al., 2006). Budesonide foam and hydrocortisone foam showed a similar efficacy and safety in patients with proctosigmoiditis (Bar-Meir et al., 2003). Study of Arcidiacono et al. (1999) confirmed the efficacy and tolerability of beclometasone dipropionate foam in the treatment of ulcerative colitis and proctosigmoiditis. It was shown that budesonide foam and mesalazine foam effectively spread up to the colon and distribute uniformly at the site of action (Campieri et al., 1992; Wilding et al., 1995; Brunner et al., 2005). The studies have shown that the quality of life is not significantly different in patients during treatment with budesonide foam or betamethasone enema for active distal ulcerative colitis. However, while having comparable clinical efficacy budesonide foam had less effect on the plasma cortisol level thus potentially minimizing steroid size effects (Hammond et al., 2004). Azathioprine delivered to colon by a rectal foam formulation considerably reduces systemic 6-mercaptopurine bioavailability by the patients with inflammatory bowel disease compared to oral delivery (Van Os et al., 1996). There are also patented foam formulations that comprise means of *in situ* foam generation (Friess et al., 1999).

Table 3
Examples of foams under development.

Products	Pipeline	Active ingredient	Indications
MupiFoam™		Mupirocin (bactroban)	Impetigo Infections caused by *St. aureus* and β-hemolytic Streptococci
BetMetFoam ™ Emollient	Dermatological	Betamethasone valerate 0.12%	Psoriasis Atopic dermatitis
BetMetFoam ™ Oily	Dermatological	Betamethasone valerate 0.12%	Psoriasis Atopic dermatitis
TerbiFoam™ Emollient	Dermatological	Terbinafine 2.0%	Dermal mycoses Dermatophite infections
TerbiFoam™ Watterless	Dermatological	Terbinafine 2.0%	Dermal mycoses Dermatophite infections
AcycloFoam™	Dermatological	Acyclovir 5.0%	Genital herpes Labial herpes
DicloFoam™	Dermatological	Diclofenac 1.0%	Osteoarthritis joints pain Back pain
DicloFoam™	Dermatological	Diclofenac 3.0%	Actinic keratoses
PerFoam™	Dermatological	Permethrin 1.0%	Head lice Public lice Scabies
DEETFoam™	Dermatological	Diethyl toluamide 25.0%	Protection from insect bite
LactiFoam™	Dermatological	Ammonium lactate 12.0%	Dry, scaly skin *Ichtyosis vulgaris*
UreaFoam™	Dermatological	Urea 10%, 20% and 40%	Dry, scaly skin *Ichtyosis vulgaris*
AtopiFoam™	Dermatological	Non-steroidal agent	Topical dermatitis
BabyFoamix Zinc™	Cosmetic	Zinc oxide	Diaper rush
BabyFoamix Oil™	Cosmetic		Baby skin care
BabyFoamix™ Emollient	Cosmetic		Baby skin care
Emollient Day Mousse	Cosmetic		Skin care moisturizing
Intensive Night Mousse	Cosmetic		Skin care moisturizing
FoamixWhite™	Cosmetic		Hyperpigmentation age spots
Foot Foam™	Cosmetic		Dry, scaly skin of the foot

9.4. Vaginal foams

These are formulations containing spermicide substances and are used for local contraception. Foam in this case is generated *in situ* from a tablet containing an alkaline and an acidic component, *e.g.* sodium hydrogen carbonate and tartaric acid, by the contact with the cervical secretion. Foam generation on the other hand has a mechanical barrier function as well. Contraception with vaginal foaming tablets with menfegol has resulted in low pregnancy rates, few complications and complains because of the messiness and burning sensation (Youssef et al., 1987). Patentex® Oval vaginal suppository from Merz Consumer Care with p-nonylphenoxypolyethoxyethanol represents for example such a formulation on the German market. This method of contraception combines the advantages of high contraceptive efficiency, good tolerance and no contraindications (Brehm and Haase, 1975). Aerosol foam containing nonylphenoxpolyethoxyethanol 80% and benzethonium chloride 0.2% showed a contraception rate of 1.75 pregnancies/100 woman year of exposure (Bushnell, 1965). There are also patents for a vaginal foam containing rifaximin for treatment of vaginal infections (Marchi et al., 1993).

10. Antifoaming agents in the medicine

The two most often occurring problems in the upper gastrointestinal tract for which patients seek medical advice are hyperacidity and gas. The cheapest way to treat dyspepsia is by way of antacids. But it is commonly accepted that this condition is caused by a combination of both hyperacidity and flatulence, treatment with antacids is frequently not possible since the antacid is prevented from making contact with the excess acid by the gas bubbles (Burton, 1976). Thus, there is a range of pharmaceutical products which contain polydimethylsiloxane as an antifoaming agent in combination with a suitable antacid mixture (Hevert®-Enzym comp., Pankreoflat®). Polydimethylsiloxane activated by silica is the antifoaming agent of choice since it spreads very easily to form a surface film which is immiscible with water, although the enhancement of the antifoaming properties of the silicone by silica is less apparent when the oil is formulated into tablets (Enzym Lefax®, Imodium® acut complex). There are also products containing only an antifoaming agent as polydimethylsiloxane (sab simplex®, Ceolat® LF, Ilio-Funkton®) or silica activated polydimethylsiloxane (Elugan®, Endo-Paractol®, Espumisan®).

11. Cosmetic foams

Over years foams have their claimed role in the cosmetic scene. Customers want to see a good foam generation while using a foam bath or a hair shampoo (Tamarkin et al., 2006b).

Foam generation happening during the use of the cleaning and washing agents can critically be seen as a nonessential side effect, which is not connected to the quality of the washing or cleaning process. Nevertheless, the customers are used to associate an exuberant foam formation with good washing or cleaning properties. A washing agent that does not foam seems to be not effective. This attitude leads the cosmetic manufacturer to give their products a good foaming quality, in spite of the fact that the newly developed synthetic detergents create a good washing quality without foam generation. Some authors consider the addition of a foaming agent in *e.g.* tooth paste as controversial as it leads to the development of a wrong psychical conjunction from the customers' side between

washing activity and the amount of the generated foam (Charlet, 1989).

In some cosmetic formulations foam has also functionality, *e.g.*, hard fine pored shaving foam helps to uphold the hair during the shaving process. Hair mousse helps to give the hair desirable shape and volume (Umbach, 1988). Foam formation during the application of a foam bath or foam bath powder is only a cosmetic attribute. For foam baths some foam characteristics such as fast foam generation ("flash foam"), big foam volume, good stability of foam and slow foam drainage are especially important. For shampoos, a good foamability of a formulation even under a strong fat contamination is of specific importance (Nowak, 1969). There are also aerosol hair dyeing foams on the market. Cosmetic foaming compositions can contain keratolytics, lubricating agents, germicide agents (*e.g.* triclosan (Paul, 2006) or sunscreens. Dry aerosol foams containing zeolite can be used as dry aftershave talc foam, dry deodorant foam, dry makeup foundation foam or dry body talc foam (Gupte and Bogardus, 1987).

There are also foam compositions for application to the skin as a barrier to skin irritants in the prevention of contact dermatitis caused for example by sodium lauryl sulfate. Such formulations, as *e.g.* a protective foam containing dimethicone and glycerine was shown to improve chronic hand dermatitis in individuals with previously uncontrolled dermatitis despite continuing their regular occupation (Fowler, 2000).

Bepanthen® is a foam formulation marketed in Germany by Roche Consumer Health Ltd containing dexpanthenol which is used to improve the healing process of the skin (Neubeck and Weber, 2004). Allpresan® is a trade name for different foam formulations used to treat dry skin conditions which contain urea in different concentrations (5%, 10%, 15% and 18%).

12. Summary

Foaming of some cosmetic, cleaning and washing formulations is a well-established application since many years. Moreover, nowadays foams attract more attention in the pharmaceutical research as new alternative carriers for active substances, which comprise several advantages in comparison to the traditionally used vehicles for rectal, vaginal and rectal drug delivery. European Pharmacopoeia defines foam as "formulation, consisting of a large amount of gas dispersed in a liquid phase". The presence of a foaming agent and hydrocolloids is essential for foam generation and stabilisation. The problem of foam stabilisation is still an actual topic nowadays. Foams can be produced by mechanical means or by supersaturation of the liquid phase with gas. Most formulations on the pharmaceutical market are aerosol foams. These formulations achieved international commercial success in the recent years as innovative vehicles. Airspray® Pump foam dispensers create propellant-free foams. Foams as a vehicle for drug delivery have some advantages compared to the traditional vehicles. For example, negative sensory attributes connected with the use of typical excipients in the conventional vehicles can be to some degree avoided. Moreover, there is evidence that patients prefer foams over other vehicles leading to an increase in compliance.

References

Andreassi, L., Giannetti, A., Dilani, M., 2003. Efficacy of betamethasone valerate mousse in comparison with standard therapies on scalp psoriasis: an open, multicentre, randomized, controlled, cross-over study on 241 patients. Brit. J. Derm. 148, 134–138.

Arcidiacono, R., Zanasi, G., Giannelli, C., Gioiemi, A., Ruscello, D., Di Blasi, M., Di Stefano, A., Russo, A., Aprile, G., Braghi, M., 1999. The topical therapy of ulcerative colitis. A multicenter study with beclomethasone dipropionate foam. Minerva Chir. 54, 635–644.

Ardizzone, S., Doldo, P., Ranzi, T., Sturniolo, G.C., Giglio, L.A., Annese, V., D'Arienzo, A., Gaia, E., Rullini, S., Riegler, G., Valentini, M., Massa, P., Del Piano, M., Rossigni, F., Guidetti, C.S., Pera, A., Greinwald, R., Porro, G.B., 1999. Mesalazine foam (Salofalk foam) in the treatment of active distal ulcerative colitis. A comparative trial vs Salofalk enema. The SAF-3 study group. Ital. J. Gastroenterol. Hepatol. 31, 685–687.

Bar-Meir, S., Fidder, H.H., Faszczyk, M., Bianchi Porro, G., Sturniolo, G.C., Mickisch, O., Muller, R., Greinwald, R., Chowers, Y., Grobeta, V., 2003. Budosonide foam vs hydrocortisone acetate foam in the treatment of active ucerative proctosigmoiditis. Dis. Colon. Rectum. 46, 929–936.

Bauer, K.H., Frömming, K.H., Führer, C., 1999. Lehrbuch der pharmazeutischen Technologie, sixth ed. Wissenschaftliche Verlagsgesellschaft Stuttgart, p. 414.

Bergstrom, K.G., Arambula, K., Kimball, A.B., 2003. Medication formulation affects quality of life: a randomized single-blind study of clobetasol propionate foam 0.05% compared with a combined program of clobetasol cream 0.05% and solution 0.05% for the treatment of psoriasis. Cutis 72, 407–411.

Bikerman, J.J., 1973. Foams. Springer-Verlag, New York.

Bonita, F., Puglia, C., Trombetta, D., Dragani, M.C., Gentile, M.M., Clavenna, G., 2002. Vehicle effects on in vitro skin permeation of thiocolchicoside. Pharmazie 57, 750–752.

Brehm, H., Haase, W., 1975. Alternative to hormonal contraception? Significance and reliability of a contraceptive foam ovulum applied vaginally. Med. Welt. 26, 1610–1617.

Brunner, M., Vogelsang, H., Greinwald, R., Kletter, K., Kvaternik, H., Schrolnberger, C., Eichler, H.G., Brunner, H., Dudczak, R., Muller, M., 2005. Colonic spread and serum pharmacokonetics of budesonide foam in patients with mildly to moderate active ulcerative colitis. Aliment. Pharmacol. Ther. 22, 463–470.

Burton, J.S., 1976. Foams and their clinical implications. In: Akers, R.J. (Ed.), Foams, Proceedings of a Symposium organized by the Society of Chemical Industry, Colloid and Surface Chemistry Group, and held at Brunel University, Academic Press, London, pp. 127–147.

Bushnell, L.F., 1965. Aerosol foam: a practical and effective method of contraception. Pac. Med. Surg. 73, 353–355.

Callender, V.D., Young, C.M., Haverstock, C.L., Carroll, C.L., Feldman, S.R., 2005. An open label study of clobetasol propionate 0.05% and betamethasone valerate 0.12% foams in the treatment of mild to moderate acne keloidalis. Cutis 75, 317–321.

Campieri, M., Corbelli, C., Gionchetti, P., Brignola, C., Belluzzi, A., Di Febo, G., Zagni, P., Brunetti, G., Miglioli, M., Barbara, L., 1992. Spread and distribution of 5-ASA colonic foam and 5-ASA enema in patients with ulcerative colitis. Dig. Dis. Sci. 37, 1890–1897.

Charlet, E., 1989. Kosmetik für Apotheker. Wissenschaftliche Verlagsgesellschaft, Stuttgart.

Dhawan, S.S., Blyumin, M.L., Pearce, D.J., Feldman, S.R., 2005. Tazarotene cream (0.1%) in combination with betamethasone valerate foam (0.12%) for plaque-type psoriasis. J. Drugs Dermatol. 4, 228–230.

Doerschner, A., Argembeaux, H., Detert, M., Ruppert, S., Albrecht, H., Kuether, J., Speiser, F., 2005. Foaming cosmetics and dual chamber foam dispenser for cosmetic cleansing compositions. DE Patent 102 004 002 168 A1, 4 Aug.

Eini, M., Friedman, D., Hirsch, S., Meyenburg, S., Sekkat, N., Tamarkin, D., 2005. Pimecrolimus foam compositions containing hexylene glycol, optionally oleyl alcohol, dimethylisosorbide and/or medium-chain triglycerides. PCT Int. Appl., Patent WO 2005097068 A1, 20 Oct.

Eini, M., Schuz, D., Shifrin, H., Hazot, Y., Tamarkin, D., 2009. Device for delivery of a foamable composition. US Pat. Appl., Patent US 20090068118 A1, 12 March.

Elewski, B.E., Abramovits, W., Kempers, S., Schlessinger, J., Rosen, T., Gupta, A.K., Abraham, S., Rowell, R., 2007. A novel foam formulation of ketoconazole 2% for the treatment of seborrheic dermatitis on multiple body regions. J. Drugs Dermatol. 6, 1001–1008.

Engels, T., von Rybinski, W., Schmiedel, P., 1998. Structure and dynamics of surfactant-based foams. Prog. Colloid. Polym. Sci. 111, 117–126.

European Pharmacopeia, 6.0, Deutscher Apotheker Verlag, Stuttgart.

Exerova, D., Khristov, K.H.R., Penev, I., 1976. Some techniques for the investigation of foam stability. In: Akers, R.J. (Ed.), Foams, Proceedings of a Symposium organized by the Society of Chemical Industry, Colloid and Surface Chemistry Group, and held at Brunel University, Academic Press, London, pp. 109–127.

Feldman, S.R., Sangha, N., Setaluri, V., 2000. Topical corticosteroid in foam vehicle offers comparable coverage compared with traditional vehicles. J. Am. Acad. Dermatol. 42, 1017–1020.

Feldman, S.R., Ravis, S.M., Fleischer, A.B., McMichael, A., Jones, E., Kaplan, R., Shavin, J., Weiss, J., Bartruff, J.K., Levin, D.L., Del Rosso, J., Kpea, N., 2001. Betamethasone valerate in foam vehicle is effective with both daily and twice a day dosing: a single-blind, open-lable study in the treatment of scalp psoriasis. J. Cutan. Med. Surg. 5, 386–389.

Fowler, J.F., 2000. Efficacy of a skin-protective foam in the treatment of chronic hand dermatitis. Am. J. Contact. Dermat. 11, 165–169.

Franz, T.J., Parsell, D.A., Myers, J.A., Hannigan, J.F., 1999. Betamethasone valerate foam 0.12%: a novel vehicle with enhanced delivery and efficacy. Int. J. Dermatol. 38, 8.

Franz, T.J., Parcell, D.A., Halualani, R.M., Hannigan, J.F., Kalbach, J.P., Harkonen, W.S., 2000. Clobetasol propinate foam 0.05%: a novel vehicle with enhanced delivery. Int. J. Dermatol. 39, 535.

Friberg, S., Saito, H., 1976. Foam stability and association of surfactants, In: Akers, R.J. (Ed.), Foams, Proceedings of a Symposium organized by the Society of Chemical Industry, Colloid and Surface Chemistry Group, and held at Brunel University, Academic Press, London, pp. 33–39.

Friedman, D., Besonov, A., Tamarkin, D., Eini, M., 2005. Pharmaceutical foams comprising surfactants and gelling agents. US Pat. Appl., Patent US 2005271598 A1, 8 Dec.
Friedman, D., Besonov, A., Tamarkin, D., Eini, M., 2006a. Antibiotic kit and compositions. US Patent US 2006269485 A1, 30 Nov.
Friedman, D., Besonov, A., Tamarkin, D., Eini, M., 2006b. Steroid kit and foamable compositions. US Pat. Appl., Patent US 2006018937 A1, 26 Jan.
Friess, S., Heckenmuller, H., Kublik, H., Szambien, O., 1999. New foam-forming pharmaceutical composition for rectal or vaginal administration. PCT Int. Appl., Patent WO 9912521 A1, 18 March.
Gottlieb, A.B., Ford, R.O., Spellman, M.C., 2003. The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plague-type psoriasis of nonscalp regions. J. Cutan. Med. Surg. 3, 185–192.
Gross, V., Bar-Meir, S., Lavy, A., Mickisch, O., Tulassay, Z., Pronai, L., Kupcinskas, L., Kiudelis, G., Pokrotnieks, J., Kovacs, A., Faszczyk, M., Razbadauskas, A., Margus, B., Stolte, M., Muller, R., Greinwald, R., 2006. Budosonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. Aliment. Pharmacol. Ther. 23, 303–312.
Gupte, A.J., Bogardus, R.E., 1987. Dry aerosol foam containing zeolite, for use in cosmetics and pharmaceuticals. Eur. Pat. Appl., Patent EP 247608 A2, 2 December.
Hammond, A., Andus, T., Gierend, M., Ecker, K.W., Scholmerich, J., Herfarth, H., 2004. Controlled, open, randomized multicenter trial comparing the effects of treatment on quality of life, safety and efficacy of budesonide foam and budesonide enemas in patients with active distal ulcerative colitis. Hepatogastroenterology 1, 1345–1349.
Hansen, R.S., Derderian, E.J., 1976. Problems in foam origin, drainage and rupture. In: Akers, R.J. (Ed.), Foams, Proceedings of a Symposium organized by the Society of Chemical Industry, Colloid and Surface Chemistry Group, and held at Brunel University, Academic Press, London, pp. 1–17.
Hirsh, J., Willis, J.C., Hirsh, M., 2005. Topical aerosol foams comprising an HFA propellant, PCT Int. Appl., Patent WO 2004-US32714 4 October.
Hoffbauer, B., 1996. Foam aerosols. Aerosol Spray Rep. 35, 508–515.
Housman, T.S., Mellen, B.G., Rapp, S.R., Fleischer, A.B., Feldman, S.R., 2002. Patients with psoriasis prefer solutions and foam vehicles: a quantitative assessment of vehicle performance. Cutis 70, 327–332.
Huang, X., Tanojo, H., Lenn, J., Deng, C.H., Krochmal, L., 2005. A novel foam vehicle for delivery of topical corticosteroids. J. Am. Acad. Dermatol. 53, 26–38.
Jellinek, J.S., 1959. Kosmetologie. Dr. Alfred Hüthig Verlag, Heidelberg.
Koehler, S.A., Hilgenfeldt, S., Weeks, E.R., Stone, H.A., 2004. Foam drainage on the microscale II. Imaging flow through single Plateau borders. J. Colloid Interf. Sci. 276, 439–449.
Koller, T., Spellman, M., Yaroshinsky, A., Elewski, B., 2004. A randomized, double-blind, double-dummy, placebo-controlled study of the safety and efficacy of ketoconazole foam, 2%, versus ketoconazole 2% cream in the treatment of seborrheic dermatitis. J. Am. Acad. Dermatol. 50, 103.
Kroepke, R., Bleckmann, A., Riedel, H., Rohde, O., Trau, J., 2004. Cosmetic post-foaming preparations with secondary propellant to achieve cooling effect. Eur. Pat. Appl., Patent EP 1391192 A1, 25 February.
Kuehn, R., 2003. Foaming rectal mesalazine composition for the treatment of inflammatory bowel diseases. Eur. Pat. Appl., Patent EP 1312368 A1, 21 Mai.
Kuplien, R., 1994. New ways to a better foam. Aerosol Spray Rep. 33, 132–133.
Lebwohl, M., Sherer, D., Washenik, K., Krueger, G.G., Menter, A., Koo, J., Feldman, S.R., 2002. A ranomized, double-blind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis. Int. J. Dermatol. 41, 269–274.
Lee, F.I., Jewell, D.P., Mani, V., Keighley, M.R., Kingston, R.D., Record, C.O., Grace, R.H., Daniels, S., Patterson, J., Smith, K., 1996. A randomized trial comparing mesalzine and prednisolone foam enemas in patients with acute distal ulcerative colitis. Gut 38, 229–233.
List, P.H., 1985. Arzneiformenlehre. Wissenschaftliche Verlagsgesellschaft Stuttgart, Stuttgart, pp. 177–182.
Mancuso, G., Balducci, A., Casadio, C., Farina, P., Staffa, M., Valenti, L., Milani, M., 2003. Efficacy of betamethasone valerate foam formulation in comparison with betamethasone dipropionate lotion in the treatment of mild-to-moderate alopecia areata: a multicenter, prospective, randomized, controlled, investigator-blinded trial. Int. J. Dermatol. 42, 572–575.
Marchi, E., Rotini, L.G., Desai, S., Grilli, M., 1993. Pharmaceutical compositions containing rifaximin for treatment of vaginal infections, Eur. Pat. Appl, Patent EP 547294 A1, 23 June.
Massimo, M., Molfetta, S.A.Di, Gramazio, R., Fiorella, C., Frisario, C., Fuzio, E., Marzocca, V., Zurilli, M., Turi, G.Di, 2003. Efficacy of betamethasone valerate 0.1% thermophobic foam in seborrhoeic dermatitis of the scalp: An open-label, multicentre, prospective trial on 180 patients. Curr. Med. Res. Opin. 4, 342–345.
Melian, E.B., Spenser, C.M., Jarvis, B., 2001. Clobetasol propionate foam, 0.05%. Am. J. Clin. Dermatol. 2, 89–92.
Milani, M., Quadri, G., 2004. Efficacy of a new antidandruff thermophobic foam: a ramdomised, investigator-blinded trial vs. ketoconazole 2% lotion. J. Am. Acad. Dermatol. 50, 93.
Mleko, S., Kristinsson, H.G., Liang, Y., Gustaw, W., 2007. Rheological properties of foams generated from egg albumin after pH treatment. Food Sci. Technol. 5, 908–914.
Müller, R.H., 1998. Pharmazeutische Technologie: moderne Arzneiformen. Wissenschaftliche Verlagsgesellschaft, Stuttgart, p. 302.
Nakagaki, M., 1950. Studies on Foams. IV. The effect of electrolyte on the foam formation of congo red solution. Bull. Chem. Soc. Jpn. 23, 47–49.
Nakagawa, A., Myata, S., Masuda, K., 1991. Foaming aerosol preparations of non-steroidal anti-inflammatory and analgesic agents. Patent JP 03072433 A, 27 March.
Neubeck, W., Weber, K., 2004. Pharmaceutical foam aerosol comprising dexapanthenol. Eur. Pat. Appl., Patent EP 1468678 A1, 20 October.
Neumann, G., Niv, Y., Bat, L., Abramowich, D., Shemesh, E., 1989. Effectiveness and absorption of rectal hydrocortisione acetate foam in nonspecific proctocolitis. Isr. J. Med. Sci. 25, 189–192.
Nowak, G.A., 1969. Die kosmetische Präparate. Verlag für chemische Industrie H. Ziolkowsky, Augsburg.
Oungbho, K., 1997. Biodegradable Sponges from Hydrocolloids as sustained release drug carrier systems, Ph.D Thesis, Christian Albrecht University, Kiel, Germany.
Patel, P.D., Stripp, A.M., Fry, J.C., 1988. Whipping test for the determination of foaming capacity of protein: a collaborative study. Int. J. Food Sci. Tech. 23, 57–63.
Paul, L., 2006. Antimicrobial liquid foam producing compositions and dispensing system therefore. US Pat. Appl., Patent US 2006122082 A1, 8 June.
Pokrotnieks, J., Marlicz, K., Paradowski, L., Margus, B., Zaborowski, P., Greinwald, R., 2000. Efficacy and tolerability of mesalazine foam enema (Salofalk foam) for distal ulcerative colitis: a double-blind, randomized, placebo-controlled study. Aliment Pharmacol. Ther. 14, 1191–1198.
Poole, S., 1989. The foam-enhancing properties of basic biopolymers. Int. J. Food Sci. Tech. 24, 121–137.
Popp, K.F., Yuhas, E.R., 2004. Foamable pharmaceutical compositions for the dermatological administration of corticosteroids and antifungal agents. US Pat. Appl., Patent US 2004241099 A1, 2 December.
Prudon, C.H., Haigh, J.M., Surber, C., Smith, E., 2003. Foam drug delivery in dermatology. Beyond the scalp. Am. J. Drug Deliv. 1, 71–75.
Raab, W., Kindl, U., 1999. Pflegekosmetik. Wissenschaftliche Verlagsgesellschaft, Stuttgart.
Reid, D.C., Kimball, A.B., 2005. Clobetasol propionate foam in the treatment of psoriasis. Expert Opin. Pharmacother. 6, 1735–1740.
Roberts, K., Axberg, C., Österlund, R., 1976. Emulsion foam killers in foams containing fatty and rosin acids. In: Akers, R.J. (Ed.), Foams, Proceedings of a Symposium organized by the Society of Chemical Industry, Colloid and Surface Chemistry Group, and held at Brunel University, Academic Press, London, pp. 39–51.
Rolz-Cruz, G., Kimball, A.B., 2008. Ketoconazole 2% foam for treatment of seborrheic dermatitis. Expert Rev. Dermatol. 3, 15–21.
Ross, S., Nishioka, G., 1976. Foaming behaviour of partially miscible liquids as related to their phase diagrams. In: Akers, R.J. (Ed.), Foams, Proceedings of a Symposium organized by the Society of Chemical Industry, Colloid and Surface Chemistry Group, and held at Brunel University, Academic Press, London, pp. 17–33.
Ruddell, W.S., Dickinson, R.J., Dixon, M.F., Axon, A.T., 1980. Treatement of distal ulcerative colitis (proctosigmoiditid) in relapse: comparison of hydrocortisone enemas and rectal hydrocortisone foam. Gut 21, 885–889.
Rufle, W., Fruhmorgen, P., Huber, W., Kimmig, J.M., 2000. Budesonide foam as a new therapeutic principle in distal ulcerative colitis in comparison with mesalazine enema. An open, controlled, randomized and prospective multicenter pilot study. Z. Gastroenterol. 38, 287–293.
Russo, J.V., 1976. Food foams-static and dynamic. In: Akers, R.J. (Ed.), Foams, Proceedings of a Symposium organized by the Society of Chemical Industry, Colloid and Surface Chemistry Group, and held at Brunel University, Academic Press, London, pp. 273–283.
Sachetto, J., 1996. Aqueous foamable compositions for rectal or vaginal administration of drugs. PCT Int. Appl., Patent WO 9603115 A1, 8 February.
Schlesinger, M., 2000. Topical aerosol foam formulations. Cosmetics Toiletries 115, 67–72.
Scott, G.V., Thompson, W.E., 1952. Measurements of foam consistency. J. Am. Oil Chem. Soc. 9, 386–391.
Shalita, A.R., Myers, J.A., Krochmal, L., Yaroshinsky, A., 2005. The safety and efficacy of clindamycin phosphate foam 1% versus clindamycin phosphate topical gel 1% fort the treatment of acne vulgaris. J. Drugs Dermatol. 4, 48–56.
Skrylev, L.D., Streltsova, E.A., 1985. Adsorption-micellar energy ratio of surfactants as a criterion of their foaming capacity. Khim. Khim. Tek. 28, 62–66.
Stein, L., 2005. Clinical studies of a new vehicle formulation for topical corticosteroids. J. Am. Acad. Dermatol. 53, 39–49.
Stein, L., Sherr, A., Solodkina, G., Gottlieb, A.B., Chaudhari, U., 2001. Betamethasone valerate foam for treatment of nonscalp psoriasis. J. Cut. Med. Surg. 5, 303–307.
Szepesi, S., Jacobi, V., Vercsei, P., Bottcher, H.D., 1990. Treatemnt of radiogenic colitis with a rectal foam containing cortisol. Clinical and pharmacological data. Strahlenther. Onkol. 166, 271–274.
Tamarkin, D., Besonov, A., Eini, M., Dnziger, J., 2008a. Foam prepared from nanoemulsions for administration to the skin. US Pat. Appl., Patent US 2008138296 A1, 12 June.
Tamarkin, D., Eini, M., Friedman, D., 2005a. Retonoid immunomodulating kit. US Pat. Appl., Patent US 2005205086 A1, 22 September.
Tamarkin, D., Eini, M., Friedman, D., Berman, T., Besonov, A., 2008b. Foamable compositions and kits comprising one or more of a channel agent, a cholinergic agent, a nitric oxide donor. US Pat. Appl., Patent US 2008317679 A1, 25 December.
Tamarkin, D., Eini, M., Friedman, D., 2006b. Foam: The future of effective cosmeceuticals. Cosmetics Toiletries 121 (11), 75–84.
Tamarkin, D., Eini, M., Friedman, D., Zlatkis, E., Schuz, D., Berman, T, 2008c. Sensation-modifying topical composition foam. US Pat. Appl., Patent US 2008253973 A1, 16 November.

Tamarkin, D., Eini, M., Zlatkis, E., 2007a. Foamable compositions, kits and drug delivery methods for treating hyperhidrosis. US Pat. Appl., Patent US 2007253911 A1, 1 November.

Tamarkin, D., Friedman, D., Eini, M., 2008d. Alcohol-free cosmetic and pharmaceutical foam carrier comprising hydrophobic solvent such as mineral/silicone/vegetable oil, triglycerides, isopropyl myristate, octyl dodecanol, foam adjuvant agent, surfactant and gelling agent. US Pat. Appl., Patent US 2008031907 A1, 7 February.

Tamarkin, D., Friedman, D., Eini, M. 2008e. Coloured or colourable foamable topical composition and foam. PCT Int. Appl., Patent WO 2008032212 A2, 20 March.

Tamarkin, D., Friedman, D., Eini, M., 2005b. Kit and composition of imidazole with enhanced bioavailability and therapeutic uses thereof. US Pat. Appl., Patent US 2005186142 A1, 25 August.

Tamarkin, D., Friedman, D., Eini, M., 2007b. Nonflammable insecticidal foams for treating parasite infestations. US Pat. Appl., Patent US 2007020304 A1, 25 January.

Tamarkin, D., Friedman, D., Eini, M., Berman, T., Schuz, D., 2008f. Foamable vihicle and vitamin and flavonoid pharmaceutical compositions thereof for treatment of skin and other disorders. US Pat. Appl., Patent US 2008069779 A1, 20 March.

Tamarkin, D., Friedman, D., Shemer, A., 2006a. Emollient foam in topical drug delivery. Expert Opin. Drug Deliv. 3 (6), 799–807.

Tamarkin, D., Keynan, R., Schuz, D., Berman, T., 2009. Wax foamable vehicles and pharmaceutical compositions thereof. US Pat. Appl., Patent US 20090041680 A1, 12 February.

Tanojo, H., Lenn, J., Huang, X., 2004. Compatibility of betamethasone 17-valerate and ketoconazole foam formulations in combination topical therapy. J. Am. Acad. Dermatol. 50, 173.

Umar, S.A., Bhattacharjee, P., Brodell, R.T., 2004. Treatment of Hailey-Hailey disease with tacrolimus ointment and clobetasol propionate foam. J. Drug Dermatol. 3, 200–203.

Umbach, W., 1988. Kosmetik. Entwicklung. Herstellung und Anwendung kosmetischer Mittel. Georg Thieme Verlag, Stuttgart, pp. 162–164.

Van Der Heijden, Edgar Ivo Maria, 2008, Foam Dispenser WO patent application WO2008007943A1.

Van Os, E.C., Zins, B.J., Sandborn, W.J., Mays, D.C., Tremaine, W.J., Mahoney, D.W., Zinsmeister, A.R., Lipsky, J.J., 1996. Azathioprine pharmacokinetics after intravenous, oral, delayed release oral and rectal foam administration. Gut 39, 63–68.

Voigt, R., 2006. Pharmazeutische Technologie, tenth ed. Deutscher Apotheker Verlag, Stuttgart.

Wehle, H., 1957. A method for the measurement of foam strength of toothpastes and tooth soaps (powders) and establishment of a foam strength number. Pharmazie 11, 135–138.

Weiss, S.C., Nguyen, J., Chon, S., Kimball, A.B., 2005. A randomized controlled clinical trial assessing the effect of betamethasone valerate 0.12% foam on the short-term treatment of static dermatitis. J. Drugs Dermatol. 4, 339–345.

Wilding, I.R., Kenyon, C.J., Chauhan, S., Hooper, G., Marshall, S., McCracken, J.S., Staab, H.J., Armbrecht, J., 1995. Colonic spreading of a non-chlorofluorocarbon mesalazine rectal foam enema in patients with quiescent ulcerative colitis. Aliment Pharmacol. Ther. 9, 161–166.

Wilson, A.J., 1989. Foams: Physics, Chemistry and Structure. Springer-Verlag, Berlin/Heidelberg.

Yoshimura, A.S., 1988. Foam and emulsion rheology, Ph. D Thesis, Princeton University, USA.

Youssef, H., Crofton, V.A., Smith, S.C., Siemens, A.J., 1987. A clinical trial of Neo Sampoon vaginal tablets and Emko foam in Alexandria, Egypt. Contaception 35, 101–110.

Zhukov, I.N., Polozova, T.I., Shatava, O.S., 1987. Study of surfactant foam-forming capasity in the presence of polyacrylic acid. Kolloid. Z. 49, 758–762.