

FOAMS AS NOVEL DELIVERY VEHICLE  
FOR TOPICAL APPLICATION

Dissertation

submitted in fulfilment of the requirements for the degree of

**Doctor in Natural Science**

at the

Christian Albrecht University, Kiel, Germany

by

**Alexandra Arzhavitina**

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Prof. Dr. L. Kipp

(Dean)

Never let the future disturb you.  
You will meet it, if you have to,  
with the same weapons of reason,  
which today arm you against the  
present.

Marcus A. Antonius,  
Roman Emperor

Dedicated to my father

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**List of abbreviations**

AIDS	Acquired immunodeficiency syndrome
Aqua bidest.	Double distilled water
BMV	Betamethasone-17-valerate
Ch.	Batch
CMC	Critical micelle concentration
CP	Clobetasol propionate
FD	Foam density
FE	Foam expansion
Fig.	Figure
FLS	Foam liquid stability
FSA	Foam stabilizing agent
FVS	Foam volume stability
HIV	Human immunodeficiency virus
HLB	Hydrophilic-lipophilic balance
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropyl methyl cellulose
MC	Methyl cellulose
mg	Milligram
min	Minute
n	Number of measurements
o/w	Oil in water
PCS	Photon correlation spectroscopy
PEG	Polyoxyethylene
Ph. Eur.	Pharmacopoeia Europaea
PIT	Phase inversion temperature
rpm	Rotations pro minute
SC	<i>Stratum corneum</i>

SD	Seborrheic dermatitis
sd	Standard deviation
Tab.	Table
UK	United Kingdom
US	The United States
USA	The United States of America
w/o	Water in oil
μm	Micrometer
η*	Complex viscosity
ρ	Density, $\frac{kg}{m^3}$
<i>et al.</i>	<i>Et alii</i>
<i>e.g.</i>	<i>Exempli gratia</i>
<i>i.e.</i>	<i>Id est</i>
<i>q.s.</i>	<i>Quantum satis</i>
<i>vs.</i>	<i>Versus</i>
°C	Degree Celsius

# 1 Introduction and objectives

## 1.1 Introduction

Scalp psoriasis is a frequently occurring pathological dermal condition affecting approximately 2% of the Western population (van de Kerkhof and Franssen, 2001). It affects at least 80% of patients suffering of psoriasis (Wozel, 2008). Plaque type psoriasis (*Psoriasis vulgaris*) is the most common form of it. Due to psychological and social distress, the quality of life can be seriously reduced by this disease (van de Kerkhof and Franssen, 2001; Szepietowski *et al.*, 2009). Despite of numerous available treatment options of scalp psoriasis, therapeutic experience of patients and physicians is reported to be disappointing. This fact was recently confirmed by a survey of 17.990 patients with scalp psoriasis in 7 European countries (Wozel, 2008).

Seborrheic dermatitis (SD) is a chronic, recurrent skin condition that affects 3% to 5% of the population (High *et al.*, 2006). It mostly affects the scalp (dandruff), but can also affect skin on other parts of the body.

The eventuality of scalp skin involvement and the necessity of topical corticosteroid application to the scalp skin is a common feature of these two pathological conditions.

Drug delivery to the scalp skin is a challenge for galenical formulation development, as the patient's acceptance of the vehicle should be assured in terms of cosmetical satisfactoriness and application comfort. Nevertheless, cosmetical unacceptability and application discomfort are often negative features of the vehicles on the market leading to therapy refusal. The vehicles used to deliver the topical therapeutics have been shown to have a considerable impact on patients' compliance (Chan *et al.*, 2009). Poor compliance is reported to be an important factor for reduced clinical efficacy (Feldman *et al.*, 2000).

Ointments, creams, lotions, gels and solutions represent traditional topical delivery vehicles used in the treatment of scalp psoriasis and other topical

pathological conditions of the scalp requiring topical delivery of corticosteroids. However, all these conventional vehicles have drawbacks when being applied on hairy body regions due to viscosity limitations, finally affecting cosmetic hair condition (*e.g.* oily hair, brittle hair, dryness of scalp skin, unpleasant smell) (Stein, 2005; Wozel, 2008). These drawbacks are often dictated by the excipients. Ointments comprise high viscous, non-volatile vehicles which can be unpleasant to apply and often difficult to remove from scalp and clothing. Creams, ointments and gels can leave residues after application and stain clothing. Solutions often run off from the site of application because of their low viscosity. Moreover, patients with affected hairy body regions complain the conventional topical therapy to be time-consuming to apply and remove as well as often cosmetically unacceptable (Feldman and Housman, 2003).

Another realistic problem of topical scalp treatment is the availability of the active compound on the skin surface. If a preparation is evenly distributed to the hair and the scalp, the skin exposure is between 20 and 100 times lower than that of the hair surface. Thus, any patient will carefully make an effort to avoid hair exposure with a preparation, leading to a decreased active compound exposure to the scalp skin. Moreover, a high sebum content of the scalp can lead to a decrease in the availability of lipophilic components for penetration (Wozel, 2008).

Shampoos represent another vehicle for the treatment of pathological scalp conditions. Ketoconazole shampoos are used for the treatment of seborrheic dermatitis for example. Nevertheless, the disadvantage of these vehicles is short application time only during the washing process.

Foams for dermal application represent new drug delivery vehicles to deliver drugs to the scalp. These vehicles have certain advantages compared to the traditional vehicles for treatment of scalp disorders. 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 of

the hair after the application. Moreover, foams absorb and penetrate quickly without leaving any greasy residue on the hair bearing surfaces (Prudon *et al.*, 2003).

Foams as low-residual vehicles can also be applied and spread more easily to the hair bearing skin than ointments or cream formulations. These vehicles break down rapidly during application and reach the *Stratum corneum* (SC) through the hair shafts. Foam density is approximately one tenth of the density of conventional vehicles. Therefore, foams can be applied and spread more easily onto large areas with less mechanical shearing compared to application of traditional vehicles. Feldman *et al.* (2000) showed with a "fingertip units test" that topical foam vehicles offer similar coverage compared with traditional vehicles. As low mechanical work is required, foams can be applied to sensitive or to highly inflamed skin, when it may be too painful or cause further inflammation if the formulation is rubbed onto the skin.

Moreover, these application advantages for the scalp can be transferred when using foams to other haired body regions such as abdomen and chest for the treatment of corticosteroid responsive dermatoses. 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).

In spite of the described cosmetical problems of drug delivery to the scalp and the fact that foams represent optimal delivery vehicles for this application site, there are only two foam formulations which are commercially available on the German market. These formulations have been successfully used not only in the treatment of pathological scalp conditions, but also corticosteroid responsive dermatoses of other body regions.

Clarelux<sup>®</sup> foam formulation containing 1% clobetasol propionate (CP) is available on the German market from Pierre Fabre Dermo-Kosmetik since 2006.

Deflatop<sup>®</sup> from Astellas Pharma is a second foam formulation on the German market containing betamethasone valerate (BMV) at a concentration of 0.1%. Both formulations represent pressurized foam formulations which require the use of a propellant for foam generation. 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 and, 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). Both formulations also contain ethanol as a solvent which is considered unsuitable for sensitive and inflamed skin.

Although there is few clinical evidence that foam formulations are currently superior to other conventional delivery vehicles, these formulations 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. Patients reported to prefer foam formulations because they are easier to use and are absorbed faster than other vehicles. The other study showed that twice-daily application of BMV foam was well tolerated and compliance exceeded 90% (Elewski *et al.*, 2007).

In spite of these positive facts raised from clinical experience, from the galenical point of view the formulation approach of these foams can not be considered as ideal. Both formulations contain ethanol which is used as a solvent for the active ingredients. Application of this excipient on the highly inflamed skin is not considered as harmless, leading additionally to skin dryness and irritation. Ethanol in these formulations may also affect drug penetration through the SC and may increase the corticosteroid penetration through epidermis leading to higher rates of systemic absorption. This is in contrast to traditional topical vehicles which rely on hydration of the intercellular spaces in the SC to achieve drug delivery (Huang *et al.*, 2005). Rapid evaporation of ethanol can

also 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).

*In vitro* permeation studies are an important step in the development of new topical vehicles to evaluate the absorption, penetration, bioavailability and, therefore, the potency of the drug for topical application.

The first step to study the bioavailability of a topical formulation starts with *in vitro* tests. These tests offer a prescreening for later *in vivo* release studies. For *in vitro* permeation studies, human or animal full thickness skin, dermatomized skin or excised SC as a main barrier for drug penetration can be used (Dreher *et al.*, 1996 and Dreher *et al.*, 1997). Such studies can also be carried out using artificial membranes such as cellulose acetate or cellulose nitrate membranes. These membranes may be saturated with lipophilic liquids, such as isopropyl myristate, to simulate the barrier function of the SC (Csóka *et al.*, 2001). This approach to characterize galenical formulations allows the prediction of the drug penetration depth and drug absorption.

The growing interest in the development of foams for drug delivery rises the necessity to characterize these new vehicles for *e.g.* foamability of the formulations, foam stability and firmness which is an important step in the formulation development. However, suitable *in vitro* methods for foam characterization are currently lacking.

The European Pharmacopoeia in the monograph "Medicated Foams" (*Musci medicati*) suggests two characterization methods. These are, firstly, the 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. Specifically, the latter method is inapplicable for foams generated via other generation methods than pressurized foams. Furthermore, the determination of the foam stability is not considered in this monograph.



The assessment of the “before-application” stability is crucial for the pre-formulation development stage independent from the foam generation mechanism. Moreover, an assessment of the general appearance as well as the stability and the intensity of expansion are important factors for the cosmetic acceptability of foams.

## **1.2 Objectives**

The objective of this work was to develop a comprehensive approach to foam characterization as an alternative and supplement to the methods suggested by the Ph. Eur. The methods should be also applicable for the characterization of propellant-free formulations in terms of their foamability, foam stability and foam firmness.

Further aim of this work was to develop foamable formulations applying two different foam generation mechanisms. The first approach was to use a propellant-free foam generation mechanism. The Airspray<sup>®</sup> foam dispenser should be used for foam generation and be investigated for the delivery of pharmaceutical foams for dermal application. The foamable formulations to be developed should represent an advanced vehicle for topical drug delivery in the treatment of corticosteroid responsive diseases of the haired body regions such as psoriasis or seborrheic dermatitis. Abdication of propellants leads to reduction of production cost and to reduction of production time, omitting a process of propellant fill.

The second approach was to develop a foamable formulation in pressurized containers using an alkane blend as a propellant. The target formulation should be alcohol-free to avoid enhancer properties of the formulation for drug permeation through the skin and decrease, in this way, possible side effects caused by systemic drug absorption. This foam should be applied during the day to the scalp improving cosmetic acceptability or should be used instead of a

shampoo. If the formulation is applied as a shampoo, a relative high amount of surface active substances should be present in the formulation.

Both vehicles should be used for topical delivery of *e.g.* corticosteroids, antimycotics or anti-inflammatory agents. Corticosteroids, as many other topical therapeutic agents, are poorly soluble in aqueous vehicles. Therefore, most of the vehicles containing corticosteroids contain a lipophilic compound or organic solvent as *e.g.* ethanol. The aim of this work was to develop an innovative formulation platform to facilitate incorporation of steroids into an ethanol-free vehicle, containing no or only a small amount of lipophilic components.

Two approaches were used for the formulation development: firstly, a foam on the base of an o/w emulsion with a low oil phase fraction and solubilized active ingredient and, secondly, a solution-based foam. Betamethasone valerate was used as a model substance. Solubilization of the active ingredient in the vehicle may have a positive effect on the drug release profiles in comparison to that of a dissolved or suspended drug. In case of the solution-based foam, betamethasone valerate is dissolved in the vehicle. Topical availability of betamethasone valerate from the newly developed vehicle was investigated by *in vitro* permeation studies.

Another important aspect of this work was to investigate the release of betamethasone valerate from the developed formulations using artificial membranes and permeation of betamethasone valerate across animal or human skin. Deflatop<sup>®</sup> foam (Astellas Pharma) and Betagalen<sup>®</sup> lotion (Galen Pharma) were used as benchmark for a marketed ethanol containing foam formulation and a formulation in a conventional vehicle. The developed formulation should show at least similar release and permeation profiles or be superior compared to these commercial formulations.

## 2 Theoretical background

### 2.1 Foams

#### 2.1.1 Definition

A foam is commonly 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 typically between 0.1 and 3 mm (Wilson, 1989). The European Pharmacopoeia comprises a monograph called "Medicated Foams" (*Musci medicati*) which defines a foam as "formulation consisting of a large amount of gas dispersed in a liquid phase".

Foams can be classified into 2 types: liquid and solid foams. Solid foams can be generated when the liquid phase is transformed into a gel or solid phase after foam formation. These systems are also known as dry foams, xerogels or sponges and are often used as sore cover materials. They may contain disinfecting agents, antibiotics or steroids. Mostly, collagen or gelatin sponges which can absorb a lot of ichor because of their high capillarity are used. These materials are also available for 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. There are two fundamental parameters determining the structure and behavior of foams as disperse systems: the volume fraction of gas which is known as the phase volume and the diameter of the bubbles.

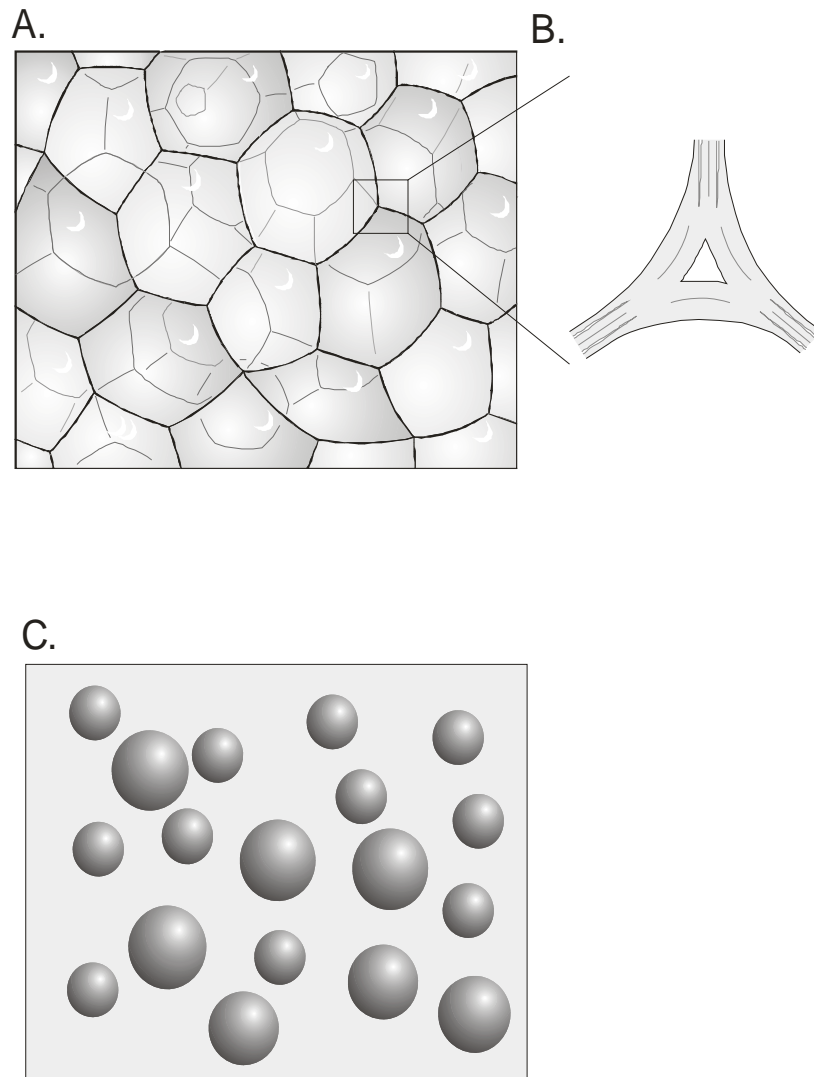
Foams, in common with emulsions, are colloids and are composed of two or three distinct phases: normally a hydrophilic liquid continuous phase with a foaming agent, throughout which a gaseous dispersion phase is distributed. There may be a third hydrophobic dispersed phase (Wijnen, 1997).

### 2.1.2 Foam structure

The foam structure is, *e.g.*, described by Bikerman (1973). The bubbles in the foam can be more or less homogeneously distributed. They can vary in size and shape ranging from almost spherical to irregular polyhedral, depending on foam generating method and on the employed excipients. Different parameters, such as nature and concentration of foaming agent, viscosity of the liquid phase, temperature and pH of the system, affect the foam structure. Foam generation conditions also affect foam appearance and, therefore, the stability of foam bubbles. At moderate gas phase volumes, the bubbles dispersed in the liquid phase are uniform and packed as spheres, whereas, at higher phase volumes, typically higher than 0.7, the air bubbles deposited close to each other start to deform themselves (Yoshimura, 1988) (Figure 1A and 1C). 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 (Figure 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  $\mu\text{m}$  (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  $120^\circ$  (Wilson, 1989). The curvature of lamellae results in the occurrence of a region of low pressure at the plateau region (Hansen and Derderian, 1976). The liquid in the lamellae is fixed to the molecules of a foaming agent which is adsorbed at both surfaces of lamellae. This fixation is very critical; otherwise the liquid in vertical lamellae would drain immediately. It was shown that presence of a liquid crystalline phase in equilibrium with an aqueous micellar solution of surfactant improves the stability of the foams formed from a surfactant solution.

Addition of a reversed micellar solution (*e.g.* an organic solution) capable to solubilize the liquid crystalline phase of such a foam causes foam breaking (Friberg and Saito, 1976). In spite of the firm fixation, liquid tends to drain into the plateau border region from the lamellae, as the pressure within this region is lower than in air bubbles and in the 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 foams is very different from that of either Newtonian (laminar or turbulent) fluids 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 strong shear thinning behavior. These properties derive largely from the unique microscopic structure of foams (Yoshimura, 1988).



**Figure 1** Schematic illustration of foam structures:  
**A. Polyhedral foam, phase volume  $> 0.7$**   
**B. Plateau border region**  
**C. Foam, phase volume  $< 0.7$**

### 2.1.3 Foaming agents and surface activity

Presence of a foaming agent is essential for foam generation and stabilization. Foaming agents are amphiphilic substances: the hydrophilic part of a molecule is responsible for water solubility. When a foaming agent is added to water, the hydrophobic parts of a 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 to 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 lower values for surface tension do not always lead to an increase of foam stability. For foam stability, the concentration of foaming agent in the 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 (Equation 1), (Stricker, 1987).

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 to the surface.

$$\Gamma = -\frac{c}{R \cdot T} \cdot \frac{d\gamma}{dc} \quad \text{Equation 1}$$

$\Gamma$  - molecules adsorbed to interface, (*mol*)

$\gamma$  - surface concentration of a foaming agent,  $\left(\frac{\text{mol}}{\text{m}^2}\right)$

$c$  - molar concentration of the foaming agent,  $\left(\frac{\text{mol}}{\text{L}}\right)$

$R$  - gas constant 8.31,  $\left(\frac{\text{Joule}}{\text{mol} \cdot \text{K}}\right)$

$T$  - temperature, (*K*)

$\gamma$  - surface tension of the liquid,  $\left(\frac{\text{mN}}{\text{m}}\right)$

$\frac{d\gamma}{dc}$  - decrease in surface tension caused by increased concentration of foaming agent,  $\left(\frac{mN \cdot m \cdot L}{mol}\right)$

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 extreme 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 more the surface tension is lowered.

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 (Equation 2) and the Einstein-Sutherland equation (Equation 3), respectively (Wilson, 1989).

$$\frac{dm}{dt} = -D \cdot A \cdot \frac{dc}{dx}$$

**Equation 2**

$$D = \frac{R \cdot T}{6 \cdot \pi \cdot \eta \cdot r \cdot N}$$

**Equation 3**

$\frac{dm}{dt}$  - diffusion rate,  $\left(\frac{mol}{s}\right)$

$D$  - diffusion coefficient,  $\left(\frac{m^2}{s}\right)$

$A$  - diffusion area,  $(m^2)$

$\frac{dc}{dx}$  - concentration gradient,  $\left(\frac{mol}{L \cdot m}\right)$

$R$  - gas constant 8.31,  $\left(\frac{Joule}{mol \cdot K}\right)$

$T$  - absolute temperature,  $(K)$

$\eta$  - dynamic viscosity of the solvent,  $(mPa \cdot s)$



$r$  - hydrodynamic radius of molecule, ( $m$ )

$N$  - Avogadro number ( $6.02 \cdot 10^{23} mol^{-1}$ )

The thickness of the 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 the other 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 the 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 created surface area will be. Reduction of the foaming agent concentration in the bulk solution leads to a decrease of the concentration gradient and diffusion rate. Therefore, to assure a rapid diffusion of a foaming agent to the surface, a 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 are convenient criteria for estimation of foaming power for a foaming agent (Skrylev *et al.*, 1985).

There are three stages of foam generation:

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

In a 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 decrease in foam stability. Also, the salt concentration of the solution may influence the process of foam generation (Jellinek, 1959).

Foam boosters are substances which enhance foam formation. The majority of these substances are 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 a concentration of 5%, otherwise skin irritation is likely to occur (Nowak, 1969).

Addition of some polymers to foamable formulations can lead to increased foam stability. For example, it was shown that the addition of polyacrylic acid to non-ionic surfactants leads to the formation of a surfactant-polymer complex through interactions between polymer and surfactant, contributing to the foam stability (Zhukov *et al.*, 1987). Polymers such as cellulose derivatives or xanthan gum are also 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, spreading on the foam lamellae. By this, lamellae are 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 surface pressure and a reduction of elasticity of the surface film formed by a foaming agent. The presence of oil droplets in the system leads to change of the surface tension and to an increased liquid drainage causing the rupture of the lamellae. Foam inhibitors, on the other hand, are generally believed to have a good affinity to the air-water interface.

**Table 1** Excipients for foam production / foam destruction

<i>Foaming agents</i>	<i>Foam stabilizers</i>	<i>Foam destroyers</i>	<i>Foam inhibitors</i>
<i>Surfactants, e.g.</i> <i>Sodium stearate</i> <i>Sodium oleate</i> <i>Sodium dodecyl sulfate</i> <i>Diocetyl sulfosuccinate</i>	<i>Hydrocolloids, e.g.</i> <i>Xanthan gum</i> <i>Hydroxypropyl methyl cellulose</i> <i>Methyl cellulose</i> <i>Alginates</i> <i>Agar-agar</i> <i>Arabic gum</i>	<i>Oils</i>  <i>Alcohols</i>  <i>Solvents, e.g.</i> <i>Acetone</i>	<i>Silicon oils</i>  <i>Glycerides</i>

They adsorb at the interface in preference to the foaming agents and, by this, prevent foam generation (Roberts *et al.*, 1975). Addition of some electrolytes to the foaming solution can lead to changes in foaming capacity (Nakagaki, 1950). Presence of poorly wettable solid particles can also lead to the rupture of lamellae. If a film is sufficiently thin for a particle to bridge it, and if the material of the particle is sufficiently hydrophobic, the Laplace pressure in the film next to the particle may become positive. This would cause liquid to flow to a region of lower pressure, and, thus, leading to film rupture (Wilson, 1989).

#### **2.1.4** 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.

#### **2.1.4.1 Whipping**

Whipping or beating can be carried out with different devices that agitate a liquid in order to form an interface with the gas phase. This method is a standard method of gas introduction to a 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 the generation of unstable foams. Every air bubble undergoes severe mechanical stresses through whipping, therefore, a more rapid coalescence happens during foam generation compared to a standing foam. Final foam volume is a result of dynamic equilibrium between mechanical air bubble formation and bubble destruction. The mechanical stress also leads to the destruction of bigger air bubbles into smaller ones. Foam generation by whipping is used in food industry for production of *e.g.* whipped cream, instant puddings or toppings (Wijnen, 1997).

#### **2.1.4.2 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 with long generation times can be produced by this method.

#### **2.1.4.3 Bubbling**

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

#### 2.1.4.4 Pressurized aerosol foams

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

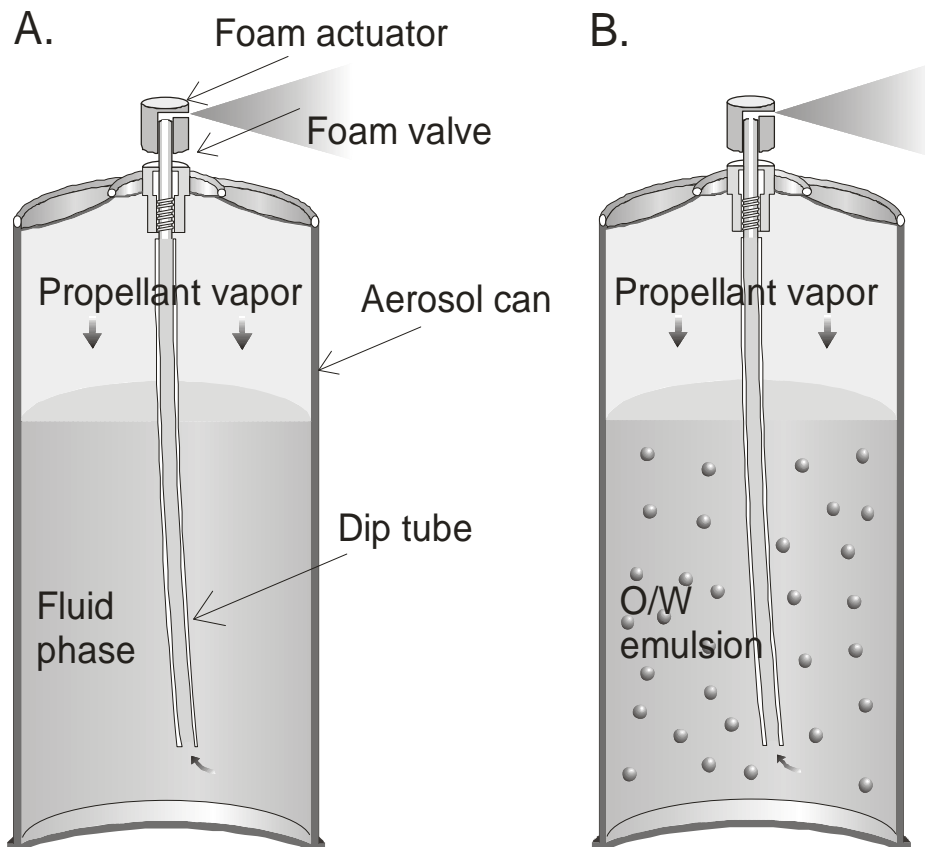
There are two types of aerosol foams: two-phase and three-phase aerosol foams (Jellinek, 1959).

In two-phase (Figure 2A) systems the liquefied propellant is solved in the solution of a foaming agent under pressure. The aerosol can contains a continuous liquid and a gas phase. The liquid phase consists of a solvent, foaming agent and foam stabilizer, whereas the gas phase is composed of propellant vapor. The gas phase practices pressure on the aerosol can containing the fluid phase which is always higher than the atmospheric pressure. This pressure is dependent on the composition of the propellant in the system and is typically in the range of 2 - 4 bar. When the nozzle of the spray head is opened connecting the interior with the external air, the fluid phase will be forced out of the aerosol can through an orifice. At atmospheric pressure, the liquefied propellant evaporates instantaneously, generating a foam (Mueller, 1998). Foam formation is supported through specific foam actuators placed to the outlet of the can.

Three-phase systems (Figure 2B) are for example o/w emulsions (Voigt, 2006). The propellant is solved in a lipid phase which is emulsified into a water phase through addition of an emulsifier. The foaming agent can also act as an emulsifier. The third phase is the vapor phase of the propellant above the emulsion. Both two-phase and three-phase systems should be shaken before actuation. 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 leads to a delayed foam generation. Water is the most frequently used solvent in foam aerosols. Beside water, ethanol and

isopropanol are occasionally used as solvents. Many pressurized aerosol foams can be mixed in cold state. But more often the oil phase should be warmed up to 70 to 80°C and brought into 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 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 system 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 aluminum or tin. Both of the metals can be incompatible with some solvents, therefore, the inside of the can is often 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 and can be produced with or without a metering chamber. These valves should have a special valve support being 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. 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).



**Figure 2** Aerosol foam products (adopted from Jellinek, 1958)

**A. Two-phase system**

**B. Three-phase system**

Using a spray actuator, spray foams may be produced. The nozzle geometry of an actuator has an effect on the appearance of the generated foam.

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 and 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 systems which contain both 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 as well be used as propellants. Hydrofluoroalkane propellants are also described for this application (Hirsh *et al.*, 2005).

#### **2.1.4.5 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 a 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 (USA).

#### **2.1.4.6 *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. Through the contact with mucosal secretions the gas is generated, leading to foam production (Friess *et al.*, 1999).



### 2.1.5 Foam stability

''It is perhaps surprising to find in 1958 that no thoroughly satisfactory explanation have been given to why certain liquids foam strongly, others feebly, and many not at all'' (Exerova *et al.*, 1975). 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 colloidal stability of these thin films. The stability of the films is dependent among others on van der Waals' attractive forces and the electric double-layer repulsion potential (Friberg and Saito, 1975).

Several different processes can be identified in the breakdown of foams (Wijnen, 1997). These are:

- disproportionation (Ostwald ripening),
- gravitational separation (creaming, bubble rise and drainage) and
- encounter mechanism (Brownian motion) (Figure 3).

These processes happen to a considerable extent simultaneously, enhancing each other. This leads 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 the solution or air. This pressure increase can be described by the Laplace equation (Equation 4) (Bikerman, 1973).

Moreover, the pressure and the solubility of the dispersed air phase are greater for smaller bubbles. This creates a driving force for diffusion from small air bubbles to larger ones or to the bulk liquid phase. The rate of diffusion depends on the solubility of the dispersed air phase in the continuous liquid phase.

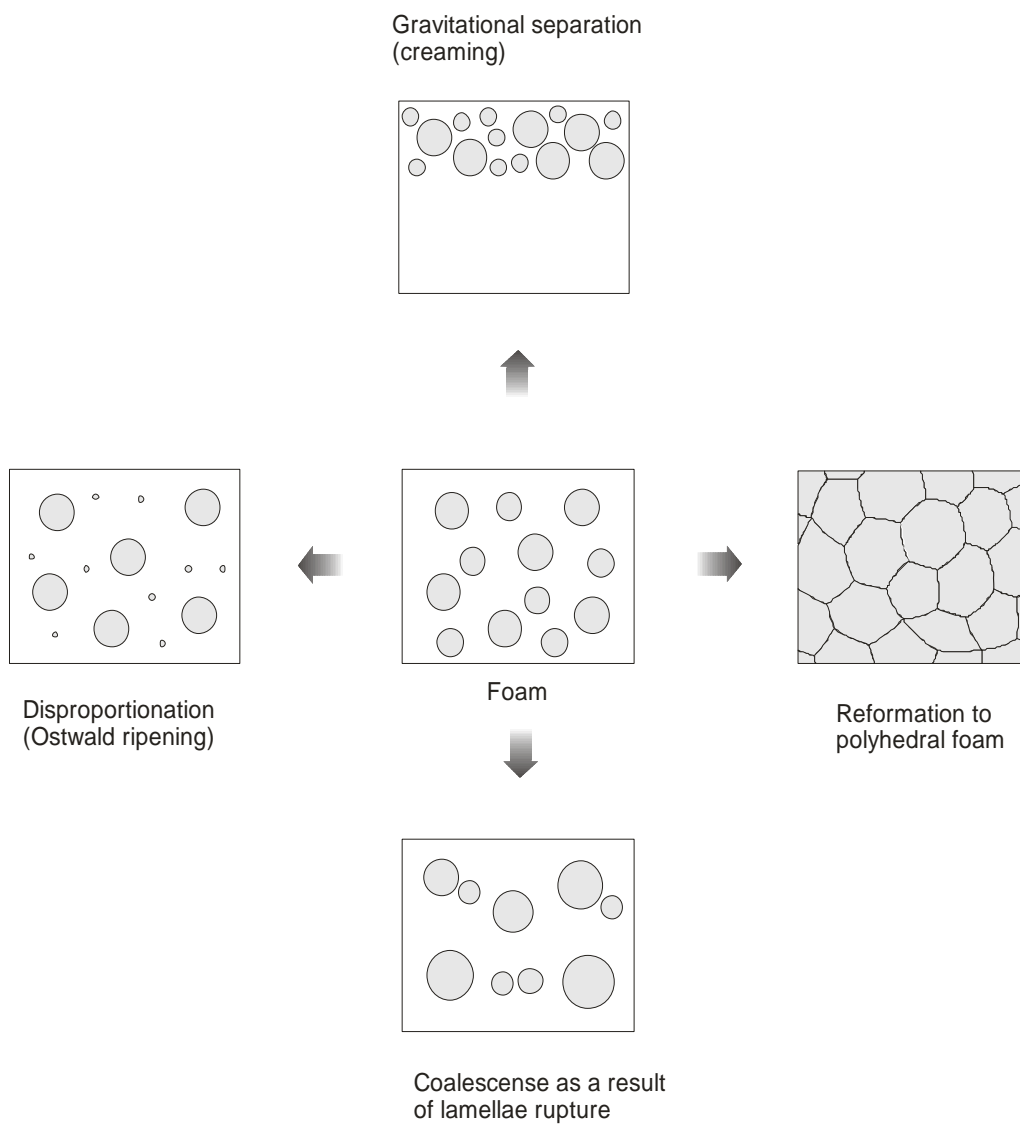
$$\Delta P = \frac{4\gamma}{d}$$

**Equation 4**

$\Delta P$  – pressure difference,  $\left(\frac{N}{m^2}\right)$

$\gamma$  – surface tension of the liquid,  $\left(\frac{mN}{m}\right)$

$d$  – diameter of the bubble,  $(m)$



**Figure 3 Mechanism of foam destabilization (adopted from Oungbho, 1997)**

That is the reason for Ostwald ripening of foam bubbles (Wilson, 1989). As a result of this destabilization 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 a density difference between the phases, gravitational and capillary forces cause a 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 destabilization predominates whereas at higher gas volume fractions the liquid drainage prevails (Wilson, 1989).

The liquid drainage leads to generation of a foaming agent concentration gradient within the lamellae and, therefore, a surface tension gradient. This gradient can be stabilized through the adsorption of foaming agent from the bulk solution. Nevertheless, both of these processes cause 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 the foam (Koehler *et al.*, 2004).

The drainage is completely independent from bubble rupture (Bikerman, 1973). The reason for a bubble rupture is an insufficient elasticity of the surface film. Under elasticity one can understand the ability of lamellae to stabilize themselves when through the liquid drainage the concentration of the foaming agent at the surface becomes inhomogeneous. Liquid drainage can also cause increase of air bubbles size without a collapse. When the film is elastic, it means that the liquid with foaming agent is transported to the place of the possible rupture (‘‘closing the wound’’). This effect is called Marangoni effect (Ross and Nishioka, 1975). The Marangoni effect is generally believed to be the main cause of film stability.

### **2.1.6 Foam stabilization**

Foams with a higher gas volume fraction are more stable. In this case, liquid drainage as well as creaming is delayed. Higher concentrations of a foaming agent are also advantageous, leading to a higher elasticity of the surface film. Creaming and foam drainage depend on the solution viscosity. Therefore, higher viscosities could lead to a delay of phase break-up. In this case, the use of thixotropic substances is beneficial. Arabic gum, methyl cellulose and similar hydrophilic materials of high molecular weight raise the stability of foams due to an 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 stabilization. When a substance is added to foam leading to a change of the surface film, this can result in repulsion of the air bubbles coming close to each other. Electrostatic or steric stabilization can be achieved through the use of macromolecules in the formulation. The macromolecules orientate themselves at the surface and, therefore, can provide a steric stabilization, hindering the air bubbles to coalesce.

### **2.1.7 Characterization of foams**

Macroscopic processes of foam destabilization correspond directly to the microscopic processes described above. Collapse of the foam column leads to a decrease of foam volume which happens essentially through loss of gas. The problems of measuring foam stability depend first of all on the insufficient characterization of these processes. Whereas the increased volume of drained liquid is easy to measure, the coalescence *e.g.* of the air bubbles can not be measured this easy.

### 2.1.7.1 Methods of the European Pharmacopoeia

The European Pharmacopoeia (Eur. Ph. 6.0) describes two characterization methods for foams in the Monograph “Medicated foams”: determination of relative foam density and foam expansion time.

Density of produced foams is determined by weighing a predefined volume of foam compared to the weight of the same volume of water (Equation 5).

$$FD = \frac{m(\text{foam})}{m(\text{water})} \quad \text{Equation 5}$$

$m(\text{foam})$  - mass of foam per volume unit, (g)

$m(\text{water})$  - mass of water per volume unit, (g)

For determination of foam expansion time, a foam volume is fed in a burette and foam expansion is followed within a defined time.

### 2.1.7.2 Additional methods

Some additional methods for foam characterization are described in literature. One method to measure foam consistency is described by Mitkevich (1952). The foam in this case is produced in a vertical cylinder vessel provided with a small indentation in the center 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 a mobilometer, foam consistometer and Brookfield viscosimeter are described by Scott and Thompson (1952).

### **2.1.7.3 Macroscopic evaluation**

Foams can be characterized macroscopically, with the determination of descriptive parameters as being fine pored or coarsely porous, viscous or runny.

### **2.1.7.4 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 analyzed 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. Measurements can be carried out directly after foam generation and after defined time intervals to follow the foam destabilization mechanisms allowing for a foam stability assessment.

### **2.1.7.5 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.

### **2.1.7.6 Foamability measurements in cosmetic formulations**

The test most often used for measurements of 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 a container which also contains the test solution. The volume of the foam, generated under these conditions is measured directly after generation and after 5 min to evaluate the stability of the foam column.

A faster screening method to compare 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 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 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 minutes (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 (Nowak, 1969).

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 aluminum 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).

The half-head-test is a clinical one-to-one comparison under realistic conditions for hair shampoos. In this case, 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, visual appearance and rinse-off characteristics of the foam are evaluated by a group of five experts (Engels *et al.*, 1998).



### 2.1.8 Pharmaceutical foams

The interest in the development of new vehicles for topical delivery is steadily growing nowadays. Foams represent one option 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. Vaginal and rectal foam vehicles also feature some application advantages compared to the standard vehicles such as suppositories, creams and ointments. Foam vehicles require a "one step" administration, they are convenient to insert, and no leakage 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 moisturize 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.

#### 2.1.8.1 Dermal foams

Dermal foams can be used in the treatment of different skin conditions, as for example seborrheic dermatitis (SD).

Extina<sup>®</sup> 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 utilizes Connetics' proprietary foam drug delivery technology - Versa Foam HF<sup>™</sup> (hydroethanolic formulation) technology (Popp *et al.*, 2004). This foam was proven 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<sup>®</sup> foam proved to be superior to placebo foam in phase III clinical trials and equivalent to ketoconazole cream. 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 events 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).

More foam products from Connectics Corporation and Stiefel Laboratories are available on the US dermatology market, such as Evoclin<sup>®</sup> clindamycin phosphate foam, 1%; Olux<sup>®</sup> and Clarelux<sup>®</sup> clobetasol propionate (CP) foams, 0.05% and Luxiq<sup>®</sup> betamethasone valerate (BMV) foam, 0.12%.

Clarelux<sup>®</sup> foam is indicated for short-term topical treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp and plaque-type psoriasis of non-scalp regions excluding face and intertriginous areas. Deflatop<sup>®</sup> foam is used in the treatment of head skin diseases which are responsive to corticosteroid therapy such as psoriasis or *Alopecia areata*.

The CP foam was shown to be safe and effective for the treatment of plaque type psoriasis of scalp and nonscalp areas when applied twice daily for two weeks (Lebwohl *et al.*, 2002; Gottlieb *et al.*, 2003; Reid and Kimball, 2005). The studies of Franz *et al.* (2000) and Bergstrom *et al.* (2003) showed that CP foam was superior to a currently marketed solution, cream and lotion vehicle in terms of improvement of psoriasis severity. Patients also indicated to spend less time applying foam vehicle compared to solution and cream. Moreover, CP foam and BMV foam were shown to be effective in improving *Acne keloidales* in an open label study (Callender *et al.*, 2005).

The foam containing BMV was shown to be more effective than the standard therapy (corticosteroid and calcipotriol lotions) commonly used in the treatment of scalp psoriasis. This vehicle was considered to be better than a lotion in terms of application convenience, leading to superior patient acceptability and a positive effect on the Psoriasis Disability Index (Andreassi *et al.*, 2003). Moreover, the BMV foam was effective in the treatment of scalp psoriasis with both once-a-day and twice-a-day application (Feldman *et al.*, 2001). BMV foam was also shown to be effective against nonscalp psoriasis (Stein *et al.*, 2001) and in the short-term treatment of seborrheic dermatitis (Massimo *et al.*, 2003). Mancuso *et al.* (2003) considered BMV foam to be effective and well-tolerated in the treatment of mild-to-moderate *Alopecia areata*. 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). The study of Melian *et al.* (2001) and Stein (2005) showed that BMV foam and CP foam were absorbed more rapidly and demonstrated greater total absorption than their respective comparison formulations, namely BMV lotion and CP solution. The other study showed that although BMV bioavailability from the foam vehicle was increased, this was not associated with an increase in toxicity (Franz *et al.*, 1999).

Evoclin<sup>®</sup> foam is indicated for topical application in the treatment of *Acne vulgaris*. Luxiq<sup>®</sup> and Olux<sup>®</sup> foams are used for symptom relief of inflammatory state of corticosteroid-responsive dermatoses of the scalp including eczema, SD, psoriasis and contact dermatitis.

A betamethasone valerate foam, 0.1% is also launched on the UK market by Mipharm under the trade name Bettamousse<sup>™</sup>.

There are also products from Connetics Corporation which are still under development, such as Actina<sup>™</sup>, a foam formulation with clindamycin phosphate; Desilux<sup>™</sup> desonide foam, 0.05% - a low potency topical steroid formulated to treat atopic dermatitis and Primolux<sup>™</sup>, a 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<sup>®</sup>, a combination of topic corticosteroid (hydrocortisone acetate, 1.0%) and local anesthetic (pramoxine hydrochloride, 1.0%) for treating inflammation and itching of the skin due to certain conditions, is available on the US market.

Thiocolchicoside, a semi-synthetic derivate of colchicoside, is used in topical formulations for its anti-inflammatory and muscle-relaxant properties, has been also formulated as a foam formulation (Miotens<sup>®</sup>, Bonita *et al.*, 2002). Ibuleve<sup>®</sup> Mousse with ibuprofen, 5.0%, is launched in the UK 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 new synergized pyretrine foam for the treatment of scabies onto the UK market (Milice<sup>®</sup>). A pimecrolimus aerosol foam can be used for treatment of various skin, nail and mucosal diseases (Eini *et al.*, 2005). There are also some foam products for disinfection. For example Soft'N Sure<sup>™</sup> antiseptic hand foam from STERIS is used for hand disinfection and contains 62% ethyl alcohol and vitamin E as skin moisturizer. Desenex<sup>™</sup> foam with 10% of undecylenate from Ciba Consumer is used as an antifungal and antibacterial product for *Tinea pedis*. Septisol<sup>™</sup> foam with 0.23% hexachlorophene from Calgon Vesal is used as bacteriostatic skin cleanser. Betadine<sup>™</sup> foam from MundiPharma and Operand<sup>™</sup> foam from Redi-Products containing povidone iodine are used as a shampoo to relief itching due to dandruff.

### 2.1.8.2 Rectal foams

Rectal foams are mostly aerosol foams (Sachetto, 1996). Two rectal aerosol foams are present on the German market: Colifoam<sup>®</sup> with hydrocortisone acetate, 1% and Claversal<sup>®</sup> with mesalazine, 20%. The 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*. The ease of retention and apparent nonabsorption of active component, leading to minimizing steroid side effects are the specific advantages of these formulations (Neumann *et al.*, 1989; Hammond *et al.*, 2004).

### 2.1.8.3 Vaginal foams

These are formulations containing spermicide substances which are used for local contraception. The 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.

Patentex<sup>®</sup> Oval vaginal suppository from Merz Consumer Care with p-nonyl phenoxy polyethoxy ethanol represents such a formulation on the German market. This method of contraception combines the advantages of high contraceptive efficiency and good tolerance with no contraindications (Brehm and Haase, 1975). The aerosol foam containing p-nonyl phenoxy polyethoxy ethanol 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 the treatment of vaginal infections (Marchi *et al.*, 1993).

### 2.1.9 Cosmetic foams

Over years foams have claimed their role in the cosmetic scene. Nevertheless, the addition of a foaming agent in *e.g.* tooth paste is discussed controversially as it leads to the development of a wrong psychical conjunction from the customers' view between washing activity and the amount of 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''), high foam volume, good stability of foam and slow foam drainage are especially desired. For shampoos, good foamability of a formulation even under 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 to prevent contact dermatitis caused for example by sodium lauryl sulfate. Such formulations, as *e.g.* a protective foam containing dimethicone and glycerine, were shown to improve chronic hand dermatitis in individuals with previously uncontrolled dermatitis despite continuing their regular occupation (Fowler, 2000).

Bepanthen<sup>®</sup> 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<sup>®</sup> 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%).

## **2.2 Human skin**

Human skin is an effective anatomical outer barrier of the body of approximately 1.5-2.0 m<sup>2</sup> that separates the human organism from the environment. The skin functions are very multifaceted and can be separated into the following groups: human skin

- plays a key role in protecting the body against external substances and pathogens,
- regulates water evaporation and presents a protection for the body against excessive water loss and, therefore, helps to regulate temperature,
- impacts to the sensation containing a variety of nerve endings that react to heat, cold, touch, pressure, vibration and tissue injury,
- synthesizes vitamin D and
- plays an aesthetic role (Braun-Falco, 2000).

### **2.2.1 Structure of the human skin**

The structure of the human skin is described in detail elsewhere (Hornstein and Nuernberg, 1985; Niedner and Ziegenmeyer, 1992).

The macroscopic structure of human skin can be divided into the following layers: epidermis, dermis and hypodermis (subcutaneous adipose layer).

The epidermis is the outermost layer of the skin which contains no blood vessels. It is made up of a stratified squamous epithelium with the underlying basal lamina. The main cell types are keratinocytes and Merkel cells; melanocytes und Langerhans cells are also present. The epidermis can be further

subdivided into the following layers: *Stratum corneum (SC)*, *Stratum lucidum*, *Stratum granulosum*, *Stratum spinosum*, *Stratum basale*. The keratinocytes are formed through mitosis in *Stratum basale*. They move up the layers changing shape and composition as they move away from the blood source; the cytoplasm is released and replaced by keratin. This process is called keratinisation and takes place within about 27 days. The structure of the SC is described by the "brick-and-mortar-model". The unique lipid matrix of it consists of ceramides, cholesterol, cholesterol ethers and fatty acids. The thickness of the SC differs between different body regions (Charlet, 1989).

The dermis is a layer of skin beneath the epidermis and connected to the epidermis by the *Stratum basale*. The dermis consists of connective tissue with collagen and contains blood and lymphatic vessels, hair follicles, sweat, sebaceous and apocrine glands. The main cells are fibroblasts which produce collagen and elastin – the main element of the connective tissue. The dermis is structurally divided into two areas: the *Stratum papillare* – a layer adjacent to the epidermis - and a deeper area called *Stratum reticulare*. The *Stratum papillare* is composed of loose areolar connective tissue. The *Stratum reticulare* is composed of dense irregular connective tissue.

The hypodermis is not a part of the skin and is located below the dermis. It consists of loose connective tissue and elastin. The main cell types are fibroblasts, macrophages and adipocytes.

### **2.2.2 Drug permeation through the skin**

Drugs which are applied onto the skin can be intended for local or systemic therapy. When the drug permeates through skin and reaches the systemic circulation, systemic effects as well as side effects are caused. The SC is a main barrier for drug penetration and absorption during topical drug administration. The drugs can penetrate through different pathways such as passive diffusion



along the transcellular route (through corneocytes) or along the concentration gradient by the intercellular route. Moreover, the glandular and transfollicular routes play a role in drug penetration (Ritschel and Hussain, 1988). Important factors which influence the way of the drug penetration are:

- molecule size,
- chemical structure of the molecule,
- molecule polarity,
- partition coefficient between the phases,
- hydration grade of the SC,
- composition of the topical vehicle and
- drug concentration (Niedner and Ziegenmeyer, 1992; Franz *et al.*, 2003).

The partition coefficient influences the drug release from the vehicle. Inverse proportionality between the drug release rate from the vehicle and vehicle lipophilicity was shown (Murakami *et al.*, 1998). Polar drugs penetrate along the transcellular pathway; drugs with low polarity use the intercellular pathway. After release from the vehicle, diffusion to the skin surface and penetration through the SC, the drug permeates through the living cell layer and can reach the blood vessels in the dermis, where a systemic absorption and the transport can take place. Nevertheless, the drug penetration rate through the SC is a main factor which defines the velocity of drug absorption. Systemic effects of the topically applicable drug are dependent on its permeation rate. Penetration enhancers can act through different mechanisms to increase the penetration rate. The SC can also be a reservoir for topical drugs (Roberts *et al.*, 2004). The drug penetration rate is, therefore, also dependent on its reservoir capacity (Rougier *et al.*, 1983).

In permeation studies, skin tissue is oversimplified to an isotropic membrane, through which a passive diffusion of the dissolved drug takes place.

The driving force of this process is a concentration gradient which defines the diffusion rate. The drug permeation profile can be defined through plotting the cumulative penetrated drug amount per area at a defined time point against the time.

For investigation of the drug reservoir capacity of the SC, the tape-stripping technique can be used. Single layers of the SC are taken away by skin biopsy which is carried out with an adhesive tape. The drug is then extracted and analytically assayed (Wiechers *et al.*, 1989).

Animal skin models (domestic pig skin, rodent guinea pig skin, rat skin) can be used for these studies as well. Pig ear skin is not completely physiologically and histologically equivalent to human skin, nevertheless, it was shown to be an *in vitro* tool for investigation of drug permeation through the skin (Dick and Scott, 1992; Sekkat *et al.*, 2002; Jacobi *et al.*, 2007; Vallet *et al.*, 2007; Barbero and Frasc, 2009). Pig ear skin disposes only few hair follicles and the follicular pathway in this case can be neglected.

Human skin for the permeation studies can be obtained as a waste product after plastic surgery.

Reconstructed human skin equivalents e.g. EpiDerm<sup>®</sup> can be also employed. It consists of normal, human-derived epidermal keratinocytes and is cultivated on microporous membranes (Wagner *et al.*, 2001; Lotte *et al.*, 2002).

### **2.3 Topical diseases affecting the scalp region**

Topical diseases with scalp involvement require a treatment adapted to the particularities of this anatomical site. Social effects are connected with pathological scalp conditions. Therapeutic complexity, on the other hand, contributes to the psychological distress (Zschocke *et al.*, 2005).

Application of topical corticosteroids is the most frequently used treatment option (van der Kerkhof *et al.*, 1999). The vehicle itself plays a significant role

in the treatment of the scalp area. The choice of the vehicle depends on its cosmetic aspect. Ideally, easy-to-use vehicles are preferred since they improve the compliance to therapy (Wauters *et al.*, 2007). Patient's compliance is reported to be better for liquid or foam formulations than for creams and lotions (Feldman and Housman, 2003; Uhoda *et al.*, 2004).

### **2.3.1 Scalp psoriasis**

Psoriasis is a chronic, inflammatory and hyperproliferative skin disease with a genetic basis. Multiple environmental factors are also afflicted to the pathogenesis of psoriasis. Psoriasis is characterized by distinct increased proliferation and incomplete differentiation of the epidermis, a marked increase in cutaneous blood flow and leukocytic infiltration of the papillary dermis and epidermis. However, the molecular reactions triggering this state of immunologic activation remain unclear (Gudjonsson and Elder, 2007).

Scalp is a well-known predilection site for psoriasis. The affected skin areas, called plaques or lesions, are inflamed or covered with silvery white scales which appear particularly along the hair line (Naldi and Gambini, 2007). Scalp psoriasis is limited to the scalp alone or can be associated with type I and type II psoriasis, pustular psoriasis, erythrodermia and psoriatic arthritis (Wozel, 2008). Many patients indicate that scalp psoriasis is both psychologically and socially distressing and the most difficult aspect of their disease. Itch and scaling are reported to be the leading symptoms in terms of frequency of occurrence as well as in terms of distress (van der Kerkhof *et al.*, 1999; Papp *et al.*, 2007).

The erythematous lesions on the scalp are mostly asymmetrical, sharply demarcated, showing a silver-white scaling and pruritus.

It was shown that responses of T-cells are abnormal in this disease. Abnormally activated T-cells elaborate cytokines inappropriately, perpetuating inflammation which, in turn, leads to skin damage manifesting clinically as psoriasis.

Tumor necrosis factor (TNF- $\alpha$ ), produced by keratinocytes, activated T-cells, macrophages and dendritic cells plays a central role in the pathogenesis of psoriasis. TNF- $\alpha$  stimulates and propagates widespread immunological activity by targeting various cells in the skin, such as endothelial cells, keratinocytes and dendritic cells (Chong and Wong, 2007). TNF- $\alpha$  induces keratinocytes to express at least 70 genes, ranging from chemokines to other cytokines. In addition, under the influence of TNF- $\alpha$ , macrophages generate cytokines and chemokines and dendritic cells undergo maturation in preparation to present antigens to T-cells.

The main therapeutic classes of current standard treatment of scalp psoriasis are dermocorticosteroids, keratolytics *e.g.* salicylic acid 5% to 10%, antimycotics, vitamin A derivatives *e.g.* tazarotene and vitamin D derivatives *e.g.* calcipotriol for topical application (Gottlieb, 2005; Bos and Spuls, 2008). A topical combination of corticosteroid and vitamin D derivative appears to provide a balanced approach to psoriasis treatment (Del Rosso, 2006). Coal tar shampoos, containing 2% to 10% coal tar solution are also effective in scalp psoriasis. Dithranol 0.1% to 3% can be also used. The management of scalp psoriasis requires long term strategies in order to reach an optimal improvement of the symptoms while avoiding adverse effects associated with long term use of medicaments. The main aim of the treatment is to reduce the burden of disease over time by controlling symptoms, helping the patient to cope with the chronic nature of the disease, limiting psychological consequences and preventing systemic complications (Naldi and Gambini, 2007).

### 2.3.2 Seborrheic dermatitis

The term seborrheic dermatitis or seborrhiasis describes an overlap with psoriasis. In this condition, psoriasis mostly predominates, with associated facial involvement showing a greasy scaling with yellowish colour (Wozel, 2008). Common manifestations include erythema and variable pruritus (High *et al.*, 2006). Sites of predilection include areas rich in sebaceous follicles: the face, ears, neck, upper trunk, creases of the legs, arms and groin and the scalp. Dandruff, which affects 5% to 10% of the population, is considered to be the mildest or perhaps initial form of seborrheic dermatitis (Gupta *et al.*, 2003). The origin of seborrheic dermatitis (SD) remains a matter of debate; *e.g.* the increased sebum production and the overgrowth of the scalp with *Malassezia* species is a well known feature of this disease (Naldi and Rebora, 2009). There is an increased incidence of SD in HIV and AIDS patients, suggesting that the immune system plays a role in the disease (Gupta *et al.*, 2003). SD is associated with depression of T-cells, increased sebum levels and activation of the alternative complement pathway.

There is an idea that not an absolute increase in sebum production but an increase of the static pool of already secreted sebum due to immobility and muscular paralysis plays a permissive role for growth of *Malassezia* yeasts and SD development. It was noted that in patients with neurologic disorders, such as Parkinson's disease, multiple sclerosis and depression, an increased incidence of SD happens (Mastrolonardo *et al.*, 2003).

The treatment involves antifungal agents *e.g.* imidazole derivatives, often in combination with shampoos containing selenium sulphide or zinc pyrithione, but topical corticosteroids are commonly used for the treatment (van de Kerkhof and Franssen, 2001; Gupta *et al.*, 2003; High *et al.*, 2006).

### 2.3.3 Topical corticosteroids for the treatment of scalp diseases

Corticosteroids for topical application are the first choice medicaments for treatment of scalp psoriasis (Chan *et al.*, 2009). Topical corticosteroids were also shown to provide clinical benefits for the treatment of seborrheic dermatitis of the scalp (Shin *et al.*, 2009). Corticosteroid therapy aims at strong anti-inflammatory and antiproliferatory action. Topical corticosteroids are categorized by numerous classification systems based on different measurements, *e.g.* vasoconstrictor assay, UV-B-induced erythema test, psoriasis plaque test, atrophogenicity potential, (Del Rosso and Friedlander, 2005).

Corticosteroids are lipophilic substances and penetrate via the intercellular pathway. A strong reservoir effect for corticosteroids takes place in the SC. Depending on the intensity of the skin inflammation state it can last from 15 min to two hours for corticosteroids to penetrate through the SC. The living epidermis is permeated within a shorter period of time. Ointments, creams, lotions are conventional vehicles for topical delivery of corticosteroids. Corticosteroids for topical administration are different in the strength of their anti-inflammatory and antiproliferatory activity. Topical corticosteroids that are used nowadays, are drugs of the 4<sup>th</sup> generation. Because of their high anti-inflammatory activity and low atrophogenic activity, they have an advanced benefit / risk ratio for the therapy of skin diseases (Wozel, 2008).

The anti-inflammatory effect is connected with inhibition of phospholipase A-2 and, therefore, inhibition of arachidonic acid synthesis as a prestage for prostaglandin synthesis. Antiproliferatory activity is due to simulation of RNA-synthesis for special proteins which influence the glucose and aminoacids transport into cells (Hornstein and Nuernberg, 1985).

The prevalent side effect of corticosteroids for topical application is a decrease of the epidermis and dermis thickness as the corticosteroids inhibit the apoptosis of keratinocytes. The degree of this skin atrophy is dependent on the activity of

corticosteroid, structure of the medicated area and duration of the treatment. Skin atrophy is rarely observed in the scalp, possibly because of its dense vascularization (Chan *et al.*, 2009). Corticosteroids inhibit the division of keratinocytes and also show antiproliferatory activity for fibroblasts. Protein synthesis of fibroblasts is inhibited as well. Interleukin IL-1 $\alpha$  is involved to inflammation within keratinocytes. Within fibroblasts, IL-1 $\alpha$  and IL-6 are involved into cell proliferation. Therefore, effective inhibition of interleukin synthesis within keratinocytes leads to an anti-inflammatory effect, but within fibroblasts, in contrast, to an antiproliferatory effect. Hindered proliferatory activity leads to reduction of the dermis and epidermis thickness. Skin becomes thinner and less elastic. The chemotaxis activity of fibroblasts is also reduced, which can lead to dysfunction of the wound healing process. Corticosteroids also decrease synthesis of collagen and mucopolysaccharides in the dermis, by reduction of the procollagen gene expression (Del Rosso and Friedlander, 2005).

### **3 Materials and Methods**

#### **3.1 Materials**

##### **3.1.1 Foaming agents**

Different surfactants from different chemical groups (Table 2) were tested, initially, to define their activity as foaming agents. The ability of these surfactants to generate a foam and foam stability characteristics were investigated by means of a foamability method after Jellinek (1959), (see 3.2.1.1). Secondly, the surfactants should have an ability to solubilize a lipophilic active component in emulsion-based foamable formulations. Based on the preliminary test, a foaming agent or a foaming agents' combination and a solubilizing agent or solubilizing agents' combination were chosen for further formulation development. Moreover, the surface activity of foaming agents as well as the critical micelle concentration was measured by means of the Wilhelmy plate method.

##### **3.1.2 W/O surfactants**

Following w/o surfactants were used for formulation development (Table 3). All used w/o surfactants were nonionic with exception of Lanette<sup>®</sup> O, which was anionic.



**Table 2**      **Foaming agents**

<b>Trade name</b>	<b>Chemical name</b>	<b>Group</b>	<b>Supplied by</b>
<i>Medialan</i> <sup>®</sup>	<i>Sodium lauryl sarcoside, 30% solution</i>	<i>Anionic</i>	<i>Clariant GmbH, Germany</i>
<i>Hostapon</i> <sup>®</sup>	<i>Sodium cocoyl glutamate</i>	<i>Anionic</i>	<i>Clariant GmbH, Germany</i>
<i>Serwet</i> <sup>®</sup> WH 172	<i>Sodium di-2-ethylhexyl sulfosuccinate 60% solution in 1,2-propylenglycol/ water</i>	<i>Anionic</i>	<i>Condea Servo, Germany</i>
<i>Rewopol</i> <sup>®</sup> SB CS 50K	<i>Disodium polyoxyethylene-5 lauryl citrate sulfosuccinate; sodium laureth sulfate</i>	<i>Anionic</i>	<i>Degussa/Goldschmidt GmbH, Germany</i>
<i>Texapon</i> <sup>®</sup> K 12	<i>Sodium lauryl sulfate</i>	<i>Anionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>TEGO Betain</i> <sup>®</sup> L7	<i>Cocamidopropyl betain</i>	<i>Amphoteric</i>	<i>Degussa/Goldschmidt GmbH, Germany</i>
<i>TEGO Betain</i> <sup>®</sup> 810	<i>Capryl/capramidopropyl betain</i>	<i>Amphoteric</i>	<i>Degussa/Goldschmidt GmbH, Germany</i>
<i>TEGO Care</i> <sup>®</sup> CG90	<i>Cetyl stearyl glucoside</i>	<i>Nonionic</i>	<i>Degussa/Goldschmidt GmbH, Germany</i>
<i>Plantaren</i> <sup>®</sup> 818 UP	<i>Coco glucoside</i>	<i>Nonionic</i>	<i>Cognis Care, Germany</i>
-	<i>Sucrose laurate</i>	<i>Nonionic</i>	<i>Harke Group, Germany</i>
<i>Imwitor</i> <sup>®</sup> 380	<i>Citric/lactic acid ester of partial glycerides</i>	<i>Nonionic</i>	<i>Nordmann, Rassmann GmbH, Germany</i>
<i>ABIL</i> <sup>®</sup> Care 85	<i>Bis- polyoxyethylene/ polyoxypropylene 16/16 polyoxyethylene/ polyoxypropylene 16/16 dimethicone; caprylic/capric triglyceride</i>	<i>Nonionic</i>	<i>Degussa/Goldschmidt GmbH, Germany</i>
<i>Teginacid</i> <sup>®</sup> C	<i>Polyoxyethylene (25) cethyl stearyl ether</i>	<i>Nonionic</i>	<i>EVONIK/Goldschmidt GmbH, Germany</i>
<i>Eumulgin</i> <sup>®</sup> B2	<i>Polyoxyethylene (20) cethyl stearyl ether</i>	<i>Nonionic</i>	<i>Cognis Care, Germany</i>
<i>TAGAT</i> <sup>®</sup> CH 40	<i>Polyoxyethylene (40) ricinoleate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>TAGAT</i> <sup>®</sup> S2	<i>Polyoxyethylene (20) glyceryl monostearate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>TAGAT</i> <sup>®</sup> 02	<i>Polyoxyethylene (20) glyceryl monooleate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>TAGAT</i> <sup>®</sup> L2	<i>Polyoxyethylene (20) glyceryl monolaurate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>TEGO</i> <sup>®</sup> SML	<i>Sorbitan monolaurate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>Brij</i> <sup>®</sup> 35	<i>Polyoxyethylene (23) lauryl ether</i>	<i>Nonionic</i>	<i>FLUKA Chemie AG, Germany</i>
<i>Brij</i> <sup>®</sup> 58	<i>Polyoxyethylene (20) cetyl ether</i>	<i>Nonionic</i>	<i>FLUKA Chemie AG, Germany</i>
<i>Brij</i> <sup>®</sup> 98	<i>Polyoxyethylene (20) oleyl ether</i>	<i>Nonionic</i>	<i>FLUKA Chemie AG, Germany</i>
<i>Tween</i> <sup>®</sup> 20	<i>Polyoxyethylene (20) sorbitan monolaurate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>Tween</i> <sup>®</sup> 40	<i>Polyoxyethylene (20) sorbitan monopalmitate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>Tween</i> <sup>®</sup> 60	<i>Polyoxyethylene (20) sorbitan monostearate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>Tween</i> <sup>®</sup> 80	<i>Polyoxyethylene (20) sorbitan monooleate</i>	<i>Nonionic</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>

**Table 3** W/O surfactants

<i>Trade name</i>	<i>HLB value</i>	<i>Chemical name</i>	<i>Supplied by</i>
<i>Brij<sup>®</sup> 72</i>	<i>4.9</i>	<i>Polyoxyethylene (2) stearyl ether</i>	<i>I. C. I. Surfactants, Belgium</i>
<i>Span<sup>®</sup> 20</i>	<i>8.6</i>	<i>Sorbitane monolaurate</i>	<i>Croda Iberica SA, Spain</i>
<i>Span<sup>®</sup> 80</i>	<i>4.3</i>	<i>Sorbitane monooleate</i>	<i>Croda Iberica SA, Spain</i>
<i>Lanette<sup>®</sup> O</i>	<i>1.5</i>	<i>Cetyl stearyl alcohol</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>

### 3.1.3 Foam stabilizing agents

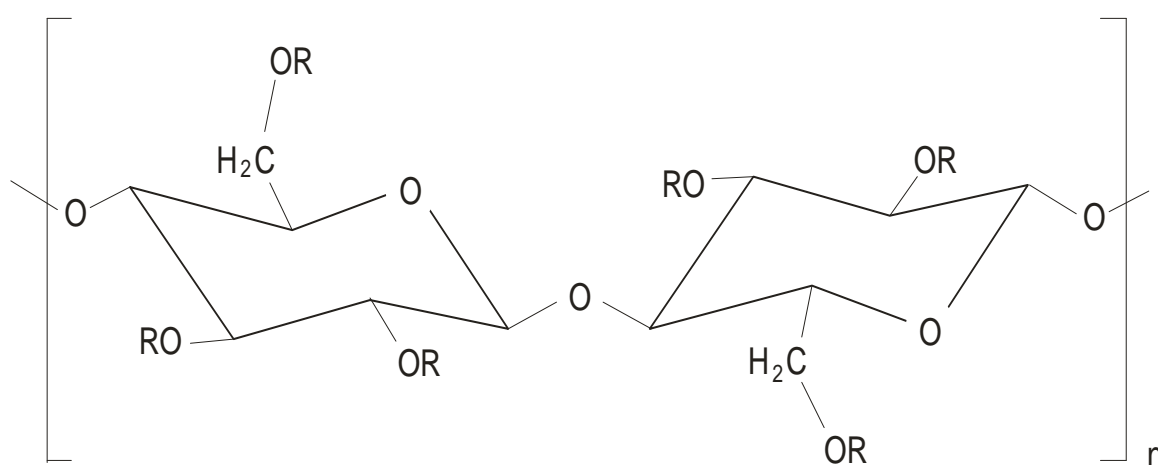
In preliminary tests, gelling agents and their combinations were used in different concentrations to increase foam stability for determination of the optimal stabilizing agent. An increase of foam stability in this case is due to the increase of solution bulk viscosity and, therefore, slowing down the process of foam drainage. Surface activity of foam stabilizing agents was measured by means of the Wihelmy plate method.

#### 3.1.3.1 Cellulose derivatives

The hydrophobic part of cellulose derivatives adsorbs at the oil-water interface. The hydrophilic part swells in water forming a gel network around the oil droplets providing on the one hand emulsion stability (Rimpler, 1996). On the other hand through increase of formulation viscosity, the foam liquid drainage is slowed down and stabilization is reached. Both effects were utilized in the formulation studies.

The viscosity of cellulose derivatives' colloidal solutions is dependent on the length of the polymer chain and the polymer concentration. Solutions with higher polymer concentration show a pseudoplastic flow behavior. But at low concentrations, deviation from the Newtonian flow can be neglected.

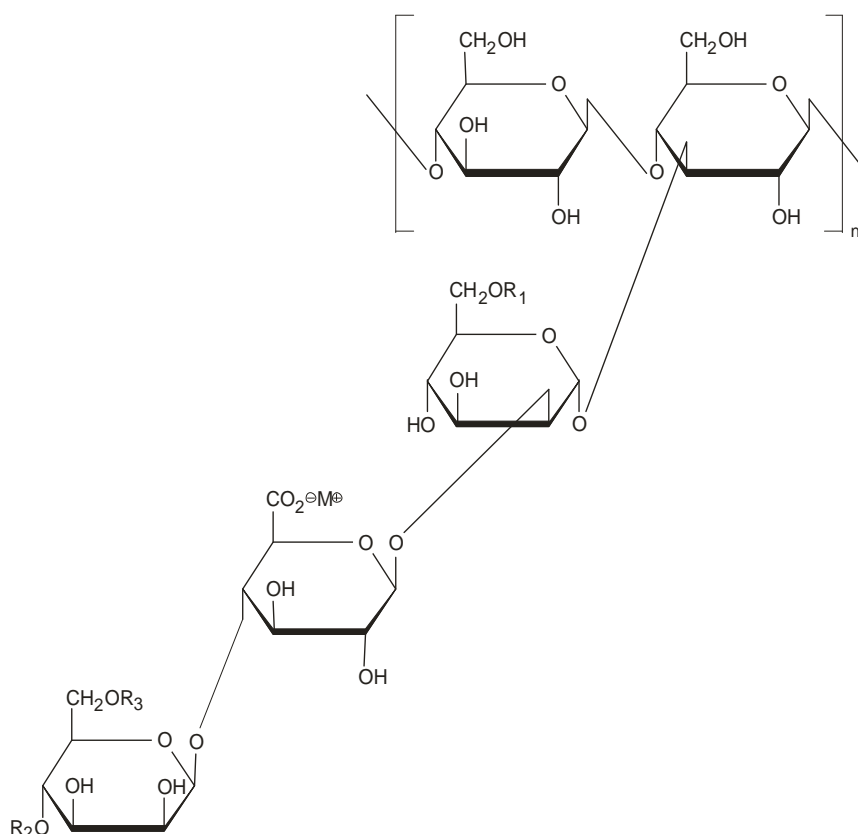
Therefore, determination of solution complex viscosity at low concentrations can be carried out as one-point measurement. These measurements were performed by means of oscillatory rheology (see 3.2.1.2). Surface tension of the solutions was determined using the Wilhelmy plate method. Methyl cellulose (MC, Tylose MH 300, Hoechst AG, Germany) and hydroxypropyl methyl cellulose (HPMC, Metolose 60 SH 50, Shin-Etsu Chemical Co. Ltd, Japan) were used for these studies (Figure 4).



**Figure 4** General structure of cellulose derivatives

### 3.1.3.2 Xanthan gum

Xanthan gum (Xanthan Gum Powder 200 Mesh, Alfred L. Wolff GmbH, Germany) is a high molecular weight polysaccharide with a backbone made up of  $\beta$ -1,4-linked D-glucose molecules (Figure 5). A trisaccharide branch containing one glucuronic acid unit between two mannose units is linked to every other glucose unit at position 3. Xanthan gum is able to produce a large increase of viscosity at a concentration as low as 0.5%. The colloidal solutions of xanthan gum have a pseudoplastic flow behavior. At low concentrations, nevertheless, the pseudoplasticity can be neglected, allowing one point measurements of viscosity (Alfred L. Wolff GmbH, User information of product).



**Figure 5** Structure of xanthan gum

### 3.1.3.3 Polymers of polyacrylic acid

#### 3.1.3.3.1 Carbopol<sup>®</sup>

Carbopol<sup>®</sup> (981 PNF, Noveon Inc., USA) polymers are acrylic acid polymers with high molecular weight. These polymers are used as a gelling agent. For viscosity increase, neutralization, *i. e.* converting the free carboxyl groups to the salt form, is essential. In the range of pH 3-6 a considerable increase of viscosity happens which remains constant to pH 10 and then decreases.

#### 3.1.3.3.2 Pemulen<sup>®</sup>

Pemulen<sup>®</sup> (TR-2 NF, Noveon Inc., USA) polymers are high molecular weight polymers of acrylic acid modified by long chain ( $\text{C}_{10}$ - $\text{C}_{30}$ ) alkyl acrylates and crosslinked with allylpentaerythritol, containing both hydrophilic and

hydrophobic parts within the molecule. They are primarily used to form stable oil-in-water emulsions. The proposed mechanism of emulsion stabilization by these emulsifiers is named *electrosteric stabilization* and represents a combined effect of electric repulsion and steric stabilization. In the presence of an oil phase, hydrophobic alkyl chains anchor to the surface of oil droplets by hydrophobic interactions. At the same time, the long hydrated and negatively charged hydrophilic chains form microgels around dispersed oil droplets and, therefore, prevent their coalescence (Simovic *et al.*, 1999). In formulation studies this excipient was used as foam stabilizing agent and emulsion stabilizing agent. The increase of viscosity happens under neutralization in the range of pH value 4 to 10 with the maximum at pH values 5 to 7.

### 3.1.4 Solvents

Different solvents (Table 4) were used to dissolve the model drug for the development of low viscous solution-based foamable formulations for foam generation by means of the Airspray<sup>®</sup> foam dispenser.

**Table 4 Solvents**

<i>Trade name</i>	<i>Chemical name</i>	<i>Supplied by</i>
-	<i>Propylene glycol</i>	<i>Caesar &amp; Loretz GmbH, German</i>
-	<i>Hexylene glycol</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>Pharmasolve<sup>®</sup></i>	<i>N-methyl-2-pyrrolidone</i>	<i>ISP Technologies, Inc., UK</i>
<i>Arlasolve<sup>®</sup></i>	<i>Dimethyl isosorbide</i>	<i>ICI Surfactants, Belgium</i>

### 3.1.5 Oil phase

Different oils (Table 5) were used in the formulation studies to develop a low viscous foamable emulsion for foam generation by means of the Airspray<sup>®</sup> foam dispenser.

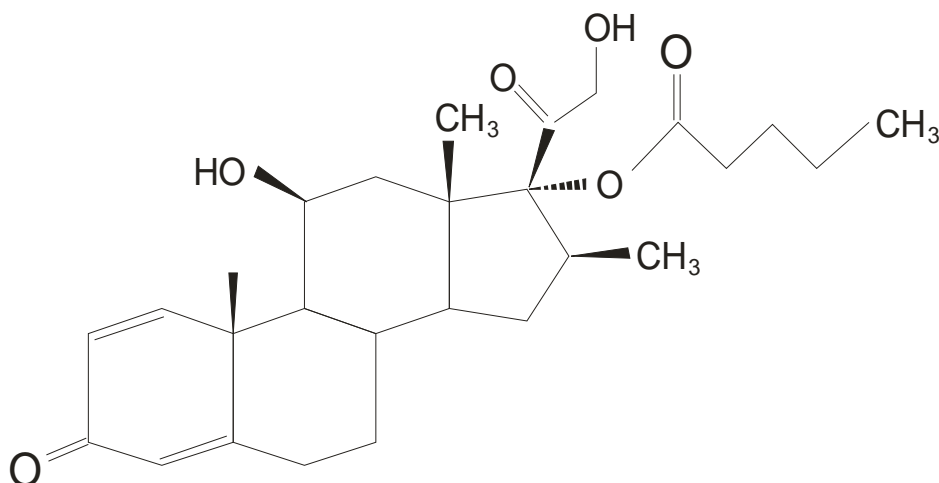
**Table 5 Oil phase**

<i>Oil</i>	<i>Chemical group</i>	<i>Density<sup>1</sup>, g·cm<sup>-3</sup></i>	<i>Supplied by</i>
<i>Medium chain triglycerides</i>	<i>Ttriglyceride</i>	<i>0.95-0.96</i>	<i>Sasol GmbH, Germany</i>
<i>Olive oil</i>	<i>Triglyceride</i>	<i>0.92</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>Soybean oil</i>	<i>Triglyceride</i>	<i>0.92-0.93</i>	<i>Caesar &amp; Loretz GmbH, Germany</i>
<i>Paraffin oil</i>	<i>Hydrocarbone</i>	<i>0.83-0.87</i>	<i>MKR &amp; Co. Ltd, UK</i>
<i>Abil 100</i>	<i>Silicone oil</i>	<i>0.93-0.97</i>	<i>Goldschmidt GmbH, Germany</i>
<i>Cyclomethicone</i>	<i>Silicone oil</i>	<i>-</i>	<i>Dow Corning, Belgium</i>
<i>Isopropyl palpitate</i>	<i>Wax</i>	<i>0.85</i>	<i>Cognis Care, Germany</i>
<i>Isopropyl myristate</i>	<i>Wax</i>	<i>0.86</i>	<i>Cognis Care, Germany</i>
<i>Oleyl oleate</i>	<i>Wax</i>	<i>-</i>	<i>Cognis Care, Germany</i>

<sup>1</sup>- literature data

### 3.1.6 Betamethasone-17-valerate

Betamethasone-17-valerate (BMV, Synopharm GmbH, Germany) is a lipophilic (logP 3.98) corticosteroid. Its high activity is caused by the F-atom in 9 $\alpha$  position (Figure 6). At basic pH values an isomerisation to betamethasone-21-valerate (BM21V) can take place. The 21-ester is less active than the 17-ester; it has approximately 15% of the biologic activity of the 17-ester. The 21-ester is metabolized through an esterase to betamethasone which is not active by topical application. The 17-ester is on the other hand stable to the activity of the cutaneous esterase which is responsible for cutaneous metabolism. This is the reason for entrapping of corticosteroid molecules within several days in SC (reservoir effect). The stability optimum for the formulation is at pH 4.5.



**Figure 6** Structure of betamethasone-17-valerate

### 3.1.7 Buffer solution

Phosphate buffer solution pH 4.5 (Ph. Eur. 6.0) was used for maintaining the pH optimum for BMV.

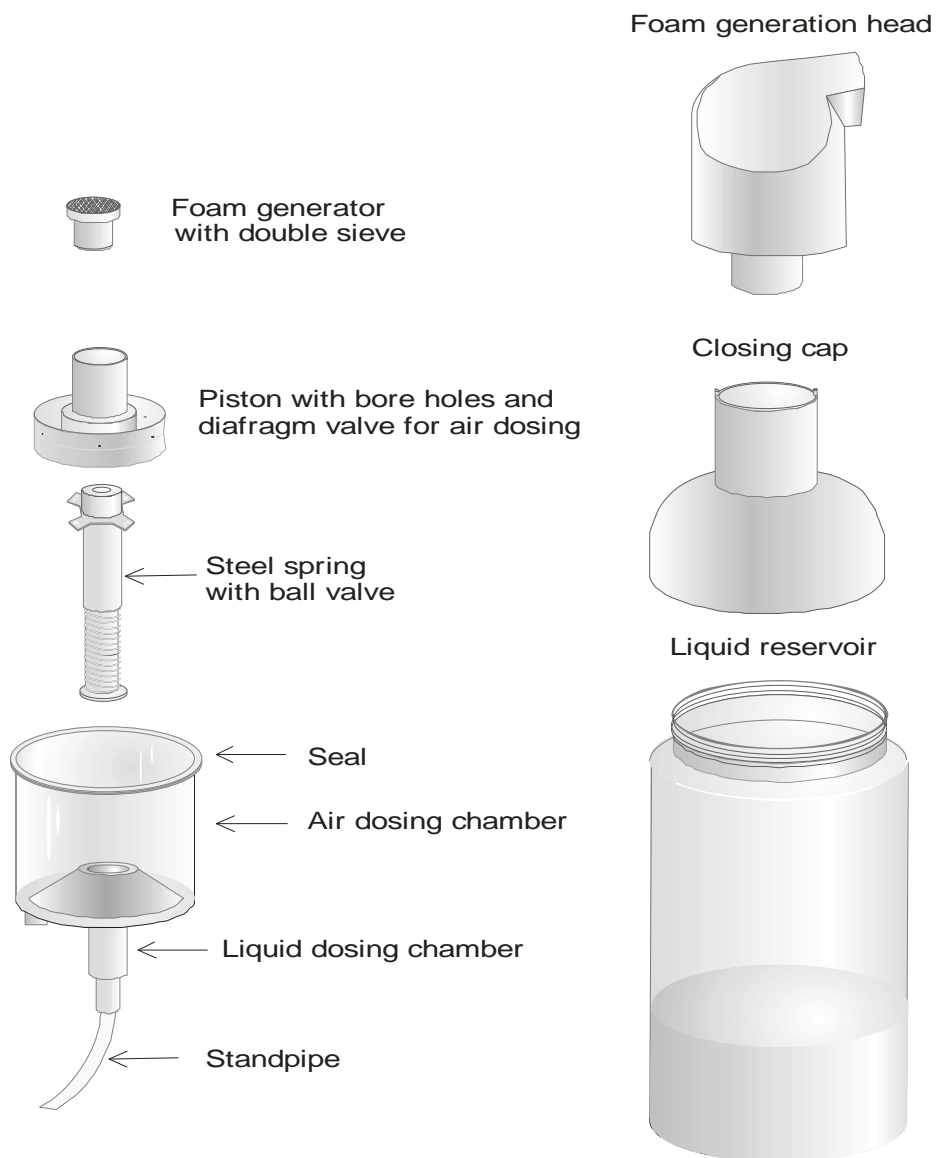
### 3.1.8 Preservative

Sodium benzoate 0.1% was used as a preservative for the BMV formulations.

### 3.1.9 Airspray<sup>®</sup> foam dispenser

The Airspray<sup>®</sup> Pump foam dispenser (Airspray International, Netherlands) was used for propellant free foam generation. The main parts of the dispenser are a liquid reservoir, air and liquid dosing chambers, a piston with bore holes and diaphragm valve, a foam generator with a double sieve and a foam generation head (Figure 7).

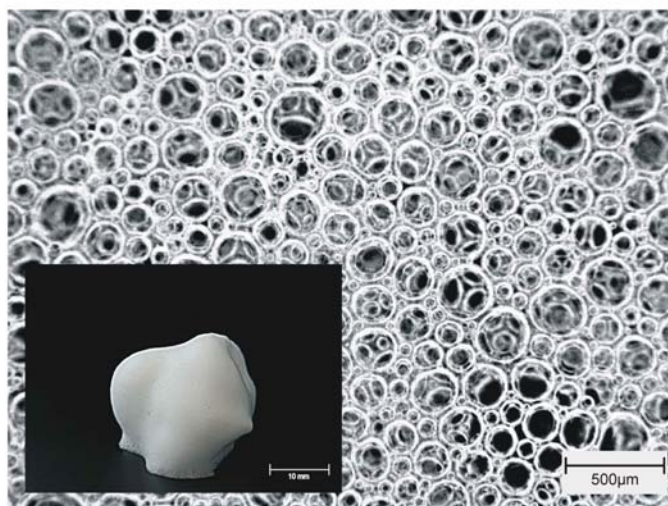
The foam quality generated by Airspray<sup>®</sup> foam dispensers differs from that generated by means of a propellant (aerosol foam). Aerosol foams are finer pored and more viscous than those generated in a propellant-free way (Figure 8).



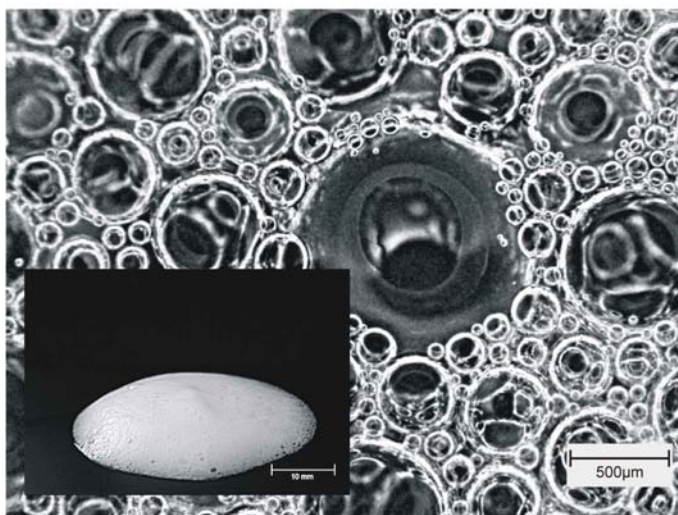
**Figure 7** Illustration of the Airspray® foam dispenser



A.



B.



**Figure 8** Microscopic and macroscopic comparison

**A. Aerosol foam**

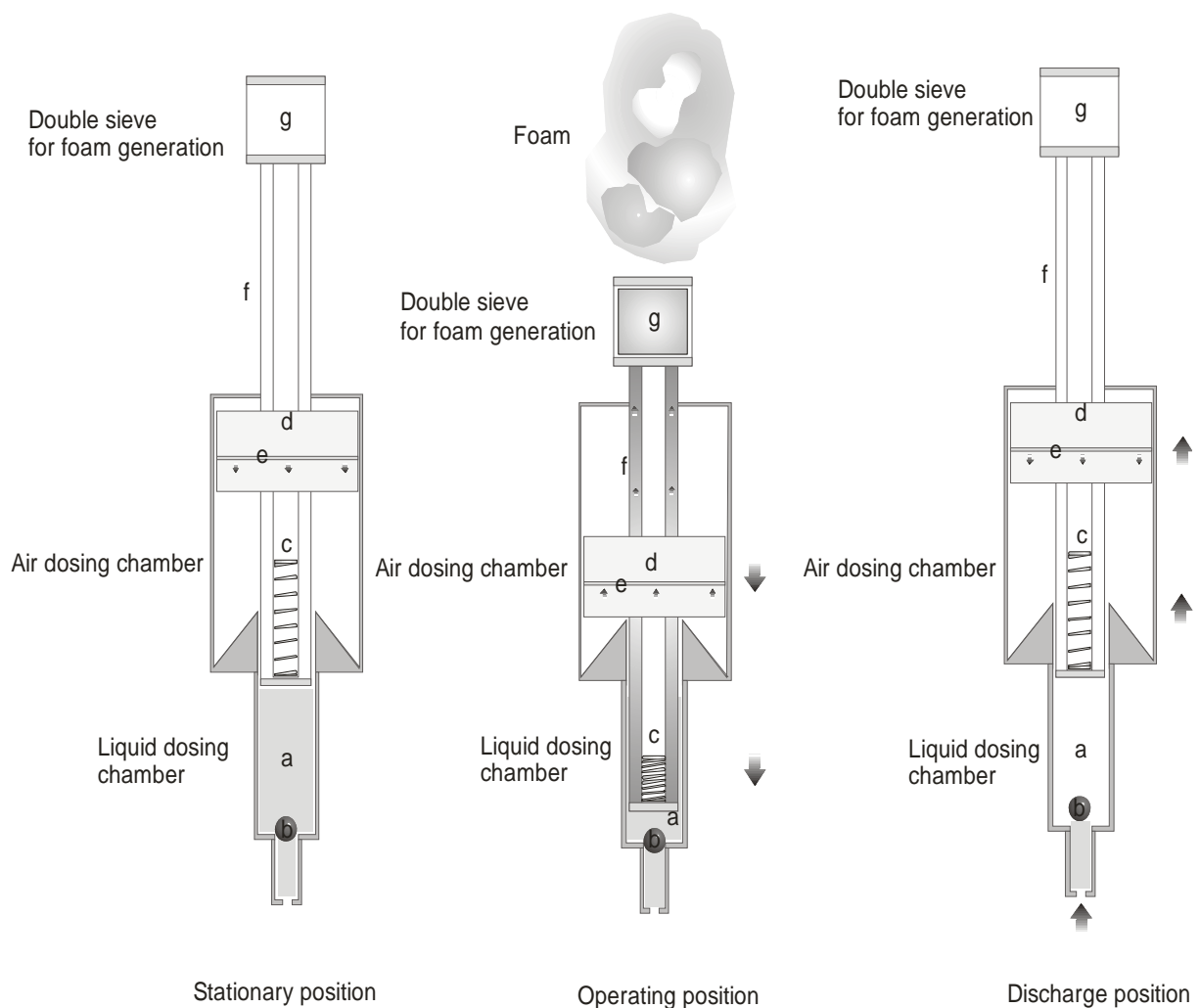
**B. Airspray<sup>®</sup> foam**

### 3.1.9.1 Principle of foam generation

Principle of foam generation by means of Airspray<sup>®</sup> foam dispenser is presented in Figure 9.

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.



**Figure 9** Mechanism of foam generation by the Airspray® foam dispenser

### **3.1.10 Pressurized aerosol foams**

Emulsion- and solution-based foamable formulations were used further for aerosol foam generation. The formulations were filled into aerosol packages which comprise a glass container, valve and an actuator.

#### **3.1.10.1 Containers, valves, actuators**

Glass containers (aerosol dome 15 mL, glass type III, transparent, Saint-Gobain-Glass AG, Germany) were used to observe instability processes in formulations. Foam valves without a metering chamber were used for foam generation (KCO 20 mm valves, Lindal Group, Germany). The valves comprise a stem made of polyethylene and a valve seat made of anodized silver aluminum. The valve seal (Buna 168S) is compatible with solvents, surface active substances and propellant used in the formulation. The foam actuator was fixed to the valve to dispense the aerosol foam (251/321 white foam actuator, Valois, Germany), (see Figure 2).

#### **3.1.10.2 Propellant mix**

An isobutane : n-butane : propane blend (14.83 mol/% : 29.75 mol/% : 55.42 mol/% respectively, Air Liquide GmbH, Germany) at a concentration of 8 % (m/m) was used as a propellant. Application of such propellant amount is described in literature (Voigt, 2006).

#### **3.1.10.3 Propellant filling process**

An aerosol container was filled with formulation and a foam valve was crimped onto the aerosol container. The propellant filling process was carried out through the valve at the Pamasol filling and sealing machine (type 2016, Pamasol Willi Mäder AG, Switzerland). Filling control was carried out gravimetrically.

## **3.2 Methods**

### **3.2.1 Preliminary methods**

Preliminary methods were used as screening methods to choose the foaming agents, foam stabilizing agents, oils for formulation studies of emulsion-based foamable formulations and solvents for formulation studies of solution-based foamable formulations.

#### **3.2.1.1 Foamability and foam stability screening test for foaming agents**

A modified test after Jellinek (1959) was performed. Solutions of different surfactants in water were prepared in concentrations of 1%, 2%, 3%, 4% and 5%. One mL of each solution was placed in a small graduated container. The solutions were shaken by hand for one minute and the height of the foam column was determined by means of a graduated scale. The stability of the generated foams was determined as a height of the foam column after 15 min and 30 min after foam generation. Tests were carried out at room temperature (25°C).

#### **3.2.1.2 Oscillation rheometry**

The determination of the viscoelastic properties of macromolecules was carried out by means of a Bohlin rheometer (Bohlin rheometer CVO 120 HR, Bohlin Instruments GmbH, Germany). The plate-plate measuring modus (plate diameter 40 mm) with automatic gap size adjustment (50  $\mu\text{m}$ ) was used. The temperature of the plates was maintained at 25°C. The oscillation measurements were carried out at constant shear stress which was determined within the linear visco-elastic interval. This linear visco-elastic interval was determined via performance of an amplitude sweep (frequency 1 Hz, 20 measurement points) before each measurement. The dependent variable of the oscillation measurements is the

complex viscosity  $\eta^*$  (Pa·s). The complex viscosity corresponds to the dynamic viscosity and can be divided into elastic and viscous parts. Determination of the complex viscosity was carried out through a 10 point measurement (Schramm, 1995).

### **3.2.1.3 Measurements of surface tension and determination of critical micelle concentration**

Critical micelle concentration (CMC) is the saturation point of a surface active substance in a water system. It is defined as the point where the surfactant molecules in solution are in equilibrium with the surfactant molecules in the air/water interface. At this point no changes in the surface tension are detectable upon further increase of the surfactant concentration.

The determination of surface tension and critical micelle concentration was carried out with a Processor tensiometer K12 using K122 software (KRÜSS GmbH, Hamburg, Germany). The Processor tensiometer was connected with a thermostated water bath to control the temperature ( $25^\circ\text{C} \pm 1^\circ\text{C}$ ).

The ring method (DuNouy ring) which is based on force measurements, was used. The ring is submerged below the solution interface (dipping distance 2.00 mm) and raised upwards. As the ring is brought upwards, it raises a lamella of liquid and the measured force starts to increase. The maximum force is reached when the lamella tears from the ring. The measurements were carried out with a 10.00 sec interval and done in triplicate. Before each measurement the ring was rinsed with demineralized water, annealed with a Bunsen burner and cooled to room temperature. The sample vessel was rinsed several times with demineralized water and the sample solution. The tensiometer was calibrated with demineralized water until the value of  $72 \text{ mN}\cdot\text{m}^{-1}$  was reached.

For the determination of critical micelle concentration a series of solutions of different concentrations (w/v) was prepared.

#### 3.2.1.4 Polarity measurements

Oils differ from each other in their polarity which is relatively difficult to determine. The oil polarity was determined through measurements of the interfacial tension between the oil phase and water phase. The oil is, thus, more polar if the interfacial tension between this oil and the water phase is lower. It was decided arbitrarily for simplification sake to describe the oils with interfacial tension to water lower than  $25 \text{ mN}\cdot\text{m}^{-1}$  as polar. Oils with interfacial tension to water higher than  $25 \text{ mN}\cdot\text{m}^{-1}$  were described as nonpolar. The interfacial tension between the oil and water phase was measured with the Processor tensiometer K12. The ring method was used. The ring was brought below the surface of the oil phase and the oil phase was covered with the water phase (thickness of the water phase approximately 1 cm). As the ring was pulled out from the oil phase into the water phase the increase of the force was measured. Measurements were carried out in triplicate at  $25^\circ\text{C}$ .

#### 3.2.1.5 Solubility of BMV in different media

Two methods were used for the determination of the BMV solubility in different media.

**HPLC method:** BMV was added in excess to the stirred medium (magnetic stirrer / heater IKA Combimag RET, Germany) until the visual saturation point was detected as presence of a sediment on the bottom of the vessel. In case of semisolid media, the temperature was increased to bring the medium to its melting point to be able to stir it. Temperature influence on the solubility was neglected for the semi-solid components. The suspensions were stirred for 24 hours and then centrifuged 15 min at  $40^\circ\text{C}$  and  $20000 \text{ min}^{-1}$  rotation speed (Heraeus Sepatech GmbH, Germany) to separate the sediment from the overlaying solution. The solution of the BMV was mixed with 2 mL of organic solvent (75% methanol : 25% water, v/v) to extract the BMV from the medium. The BMV amount was determined by means of HPLC (see Appendix).

**Visual determination:**

The solvent was added to a defined mass of BMV until no visual sediment was detected. The concentration of BMV in the medium was calculated.

**3.2.1.6 Determination of particle size / micelle size**

Particle size measurements were carried out by means of photon correlation spectroscopy (PCS, Zetasizer DTS Nano, Malvern Instruments Ltd, UK) with an automatic function for determination of measuring points per run (based on the signal strength and signal variation the program chooses the number of measuring points per single measurement, measurement duration 20 s). Measurements were carried out in triplicate approximately 24 h after preparation (storage at room temperature). Measurements were performed at 25°C and at a scattering angle of 173° at the wavelength of 633 nm. Only measurements with polydispersity index  $\leq 0.7$  were evaluated. The mean value and the standard deviation were calculated from three measurements (User guide, Zetasizer DTS Nano, Malvern Instruments Ltd).

**3.2.1.7 Determination of interfacial surfactant adsorption (velocity)**

Velocity of interfacial occupation by molecules of foaming agents was measured by means of the Contact Angle System OCA 20 (Dataphysics Instruments GmbH, Germany). The relaxing drop method was used. A water droplet was generated with a fine needle of 0.9 mm diameter (droplet volume range between 10 and 19  $\mu\text{l}$ ). Surface tension was measured and assured to be 72  $\text{mN}\cdot\text{m}^{-1}$ . Surface tension was calculated from the shape of generated droplet. 1.0% solution of foaming agent was dosed to this droplet with a second needle of smaller diameter (0.5-2.0  $\mu\text{l}$ ). This measuring facility was constructed in-house (Department of Food Technology, Christian Albrecht University, Kiel, Germany). During the dosing and after dosing, surface tension was observed

over the next minute. Single measurements of surface tension and droplet volume were performed each second, so that at the end of measurement time approximately 60 to 80 single measurement points were determined. Measurements were carried out at room temperature.

### 3.2.2 General methods

#### 3.2.2.1 Foam characterization

##### 3.2.2.1.1 Cylinder method (Detection 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 test was carried out to determine the following parameters: foam expansion (FE, %, Equation 6), foam liquid stability (FLS, %, Equation 7) and foam volume stability (FVS, %, Equation 8). Foam gas fraction was determined as the difference between the initial foam volume and volume of the nonexpanded formulation (Equation 9).

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

$V(\text{foam})$  - volume of produced foam, (mL)

$V(\text{formulation})$  - volume of formulation to produce  $V(\text{foam})$ , (mL)

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

$V(\text{liquid}_{30 \text{ min}})$  - volume of liquid drained after 30 min

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

$V(\text{foam}_{30 \text{ min}})$  - volume of foam after 30 min



$$GF(mL) = V(\text{foam}) - V(\text{formulation})$$

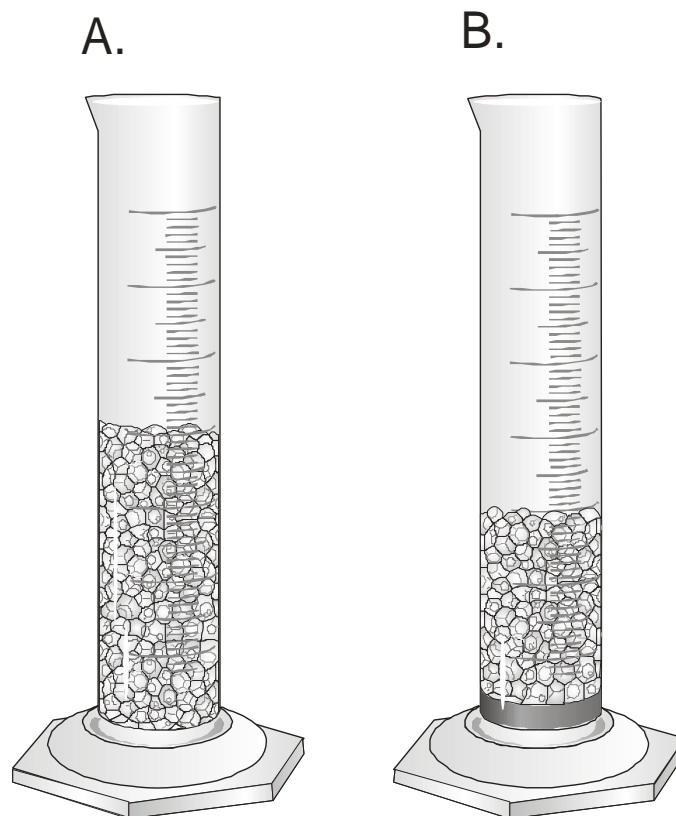
**Equation 9**

$V(\text{foam})$  - initial foam volume

$V(\text{formulation})$  - volume of nonexpanded formulation

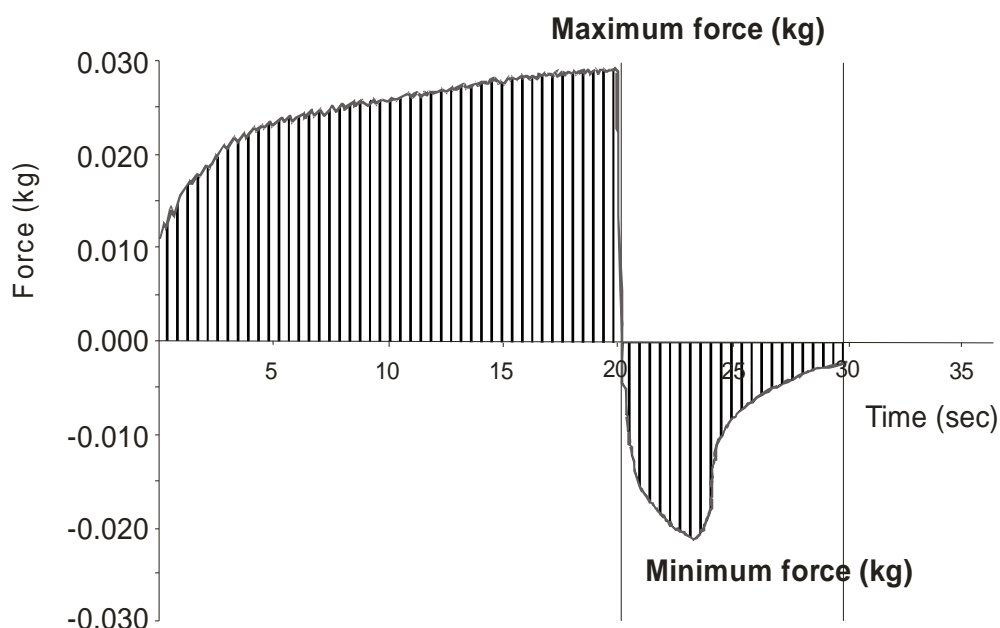
The higher the FE the more foamable is the formulation. The lower the FLS and the higher the FVS the more stable is the produced foam.

The foam was discharged into a glass cylinder. The initial volume of foam, the volume of the aged foam and the volume of drained liquid after a defined time period was measured (Figure 10). The separation of the liquid due to liquid drainage was observed after 15 min.

**Figure 10****Cylinder method****A. Foam volume direct after foam generation****B. Decreased foam volume with drained liquid after 15 min**

### 3.2.2.1.2 Foam texture (Texture Analyser)

Properties which principally influence foam firmness are surface viscosity, bulk liquid viscosity, bubble size distribution and foam geometry. Therefore, generated foams were characterized using a customized, newly developed method with a Texture Analyser (TA, Texture Analyser TA.XT.plus, Stable Micro Systems, UK). The instrument is equipped with a load cell registering the mass acting on it. Although not completely correct, the measured mass is displayed as force in (g) from the instrument which can easily be transformed into the gravitational force  $F_g$  (N) by multiplication with the gravitational acceleration of  $9.80665 \text{ m}\cdot\text{s}^{-2}$ . To simplify matters, the instrument output "force" in (g) was used for the evaluation of the results. The foam was dispensed into a container and then stressed with a disk (diameter 45 mm) which was pressed through the foam to a specified depth (10 mm). Test speed was preset to  $0.5 \text{ mm}\cdot\text{s}^{-1}$  and control force to 1.0 g. Measurements were carried out in triplicate. From the resultant force-time curve, the required forces were recorded. During penetration the force gradually increases until the point of maximum penetration depth is reached. The sample then proceeds to withdraw from the disk. A force is required to overcome the foam stickiness. The maximum positive force indicates the firmness of the sample. The maximum negative force indicates the stickiness of the sample (Figure 11).



**Figure 11** Force-time plot to measure foam firmness as derived from a Texture Analyser

### 3.2.2.1.3 Light (back-) scattering method (Foam stability)

Light (back-) scattering method is based on the Faraday-Tindall effect which postulates that colloidal solutions can scatter light. Differences in refractive indices between the solution of foaming agent and air result in different intensities of light transmission and light backscattering. Intensities of transmitted and backscattered light are dependent on the amount of air in foam. During the process of foam destabilization, 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 different refractive indices of both phases, interactions of photons (diffusion and diffraction) happen. The backscattering signal (BS) is inversely proportional to the square root of the mean free distance covered by a photon being backscattered (Equation 10).

$$BS \approx \frac{1}{\sqrt{l^*}}$$

**Equation 10**

$l^*$  - mean free distance covered by a photon, (m)

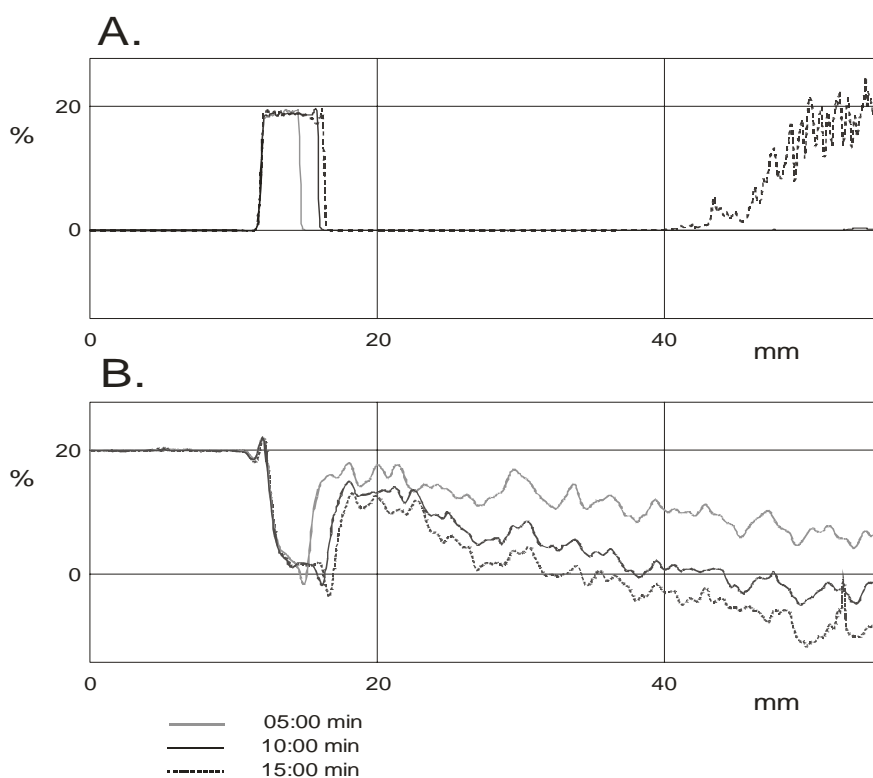
The higher the phase volume of gas in the foam, the shorter is the free distance covered by a photon and, therefore, the more intense is backscattering and the less intensive is transmission.

For the measurements, the foam was dispensed into a glass measuring cell and scanned through with infrared light ( $\lambda = 850$  nm). A light source and two detectors move along the measuring cell and backscattering and transmission signals are detected every 40  $\mu\text{m}$  from the bottom of the cell to the height of 55 mm (Turbiscan LabExpert, Formulation, l'Union, France). 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 angle of  $45^\circ$  (nephelometry). Intensity of the transmitted light is detected under the angle of  $180^\circ$  (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 sample scan is shown exemplarily in Figure 12. A clear transmission signal can be detected at the bottom (approximately at the height of 15 mm) of the measurement cell (Figure 12, top). 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 can not be transmitted because of the high concentration of dispersed air bubbles.

During foam destabilization process the foam volume would decrease, therefore, at the upper part of the measurement cell (35-55 mm) the transmission signal can be observed again. This signal should only be treated as a shift of the foam meniscus and not as a development of a new phase.



**Figure 12**    **A. Backscattering profiles from a Turbiscan analysis**  
**B. Transmission profiles**

When a transmission signal is detected, there will also be a backscattering signal at the same zone (Figure 12, bottom). This signal should 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 the foam (central part of the measurement cell, 20-35 mm) illustrates the growth of air bubbles in the foam and can be detected as a parallel shift of the backscattering intensity curve to lower values.

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. The slope of this curve reproduces the development of the liquid phase in  $\text{mm}\cdot\text{min}^{-1}$ .

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 ( $\%\cdot\text{min}^{-1}$ ).

These analyses 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.

Samples were analyzed at 25°C. Foam stability was observed for 15 min.

### 3.2.2.2 Emulsion based foamable formulations

#### 3.2.2.2.1 Production of oil-in-water (o/w) emulsions

To avoid pronounced foam generation leading to loss of foaming and emulsifying agent during production of oil-in-water emulsions, the production process was optimized according to the following process flow chart (Table 6).

**Table 6** Choice of production method / 1

<i>Method</i>	<i>Oil phase</i>	<i>Water phase</i>	<i>Incorporation</i>	<i>Foam generation</i>
1	<i>Heated up to 55°C</i>	<i>Foaming agent added, heated up to 55°C</i>	<i>Water phase into the oil phase</i>	<i>Intense foam generation</i>
2	<i>Heated up to 55°C</i>	<i>Foaming agent added, heated up to 55°C</i>	<i>Oil phase into the water phase</i>	<i>Intense foam generation</i>
3	<i>Foaming agent added, heated up to 55°C</i>	<i>Heated up to 55°C</i>	<i>Water phase into the oil phase</i>	<i>Intense foam generation</i>
<b><u>4</u></b>	<i><u>Foaming agent added, heated up to 55°C</u></i>	<i><u>Heated up to 55°C</u></i>	<i><u>Oil phase into the water phase</u></i>	<b><u>The intense foam generation is avoided</u></b>

Following the findings of this preliminary investigation the “hot-hot” emulsion inversion method (method number 4) was applied. The phase inversion temperature method is based on the changes in solubility of polyoxyethylene-type nonionic surfactants with temperature. This type of surfactants becomes more lipophilic with increasing temperature because of dehydration of the polyoxyethylene chains.

The foaming agent or foaming agent composition (acting in this case also as emulsifiers for o/w emulsion) was dissolved in the dispersed phase (oil phase)

and the oil phase was heated up to 55°C (water bath, Polzin Laborbedarf, Germany). The continuous phase (aqueous phase) was separately heated up to 55°C. The oil phase with dissolved foaming agent was gradually added to the water phase and dispersed with an ultra turrax (8000 rpm) for 5 min (T25 basic IKA Labortechnik, Germany). The formulation was cooled down at continuous stirring to room temperature for another 5 min. The duration of dispersion and the speed of the ultra turrax were also determined during preliminary investigations. The speed and duration, where no intense foam generation took place, were chosen (Table 7). When betamethasone-17-valerate was incorporated into the formulation, it was combined with the oil phase before phase merging.

**Table 7** Choice of production method / 2

<i><b>Time, min</b></i>	<i><b>Speed, rpm</b></i>	<i><b>Notes</b></i>
15	20500	<i>Intense foam generation</i>
15	13500	<i>Intense foam generation</i>
15	8000	<i>Intense foam generation</i>
10	20500	<i>Intense foam generation</i>
10	13500	<i>Intense foam generation</i>
<u>10</u>	<u>8000</u>	<u><i>Acceptable foam generation</i></u>
5	20500	<i>Intense foam generation</i>
5	13500	<i>Intense foam generation</i>
5	8000	<i>Acceptable foam generation</i>



### 3.2.2.2.2 Stability tests

Oil-in-water emulsions should be stable at least two years through storage under normal conditions. To evaluate the stability of foaming formulations within a shorter time period, accelerated thermal and physical stress tests were employed.

#### High temperature-low temperature cycles

Samples were stored under accelerated thermal conditions in a thermostated cabinet (Rumed 3501, Rubarth Apparate GmbH, Germany). Temperature was changed from - 10°C to + 40°C within one cycle of 24 hours duration (Figure 13). Samples were stored for 7 cycles, afterwards macroscopic evaluation of sample stability was carried out. Temperature change within one cycle was chosen to cover different storage conditions (Table 8).

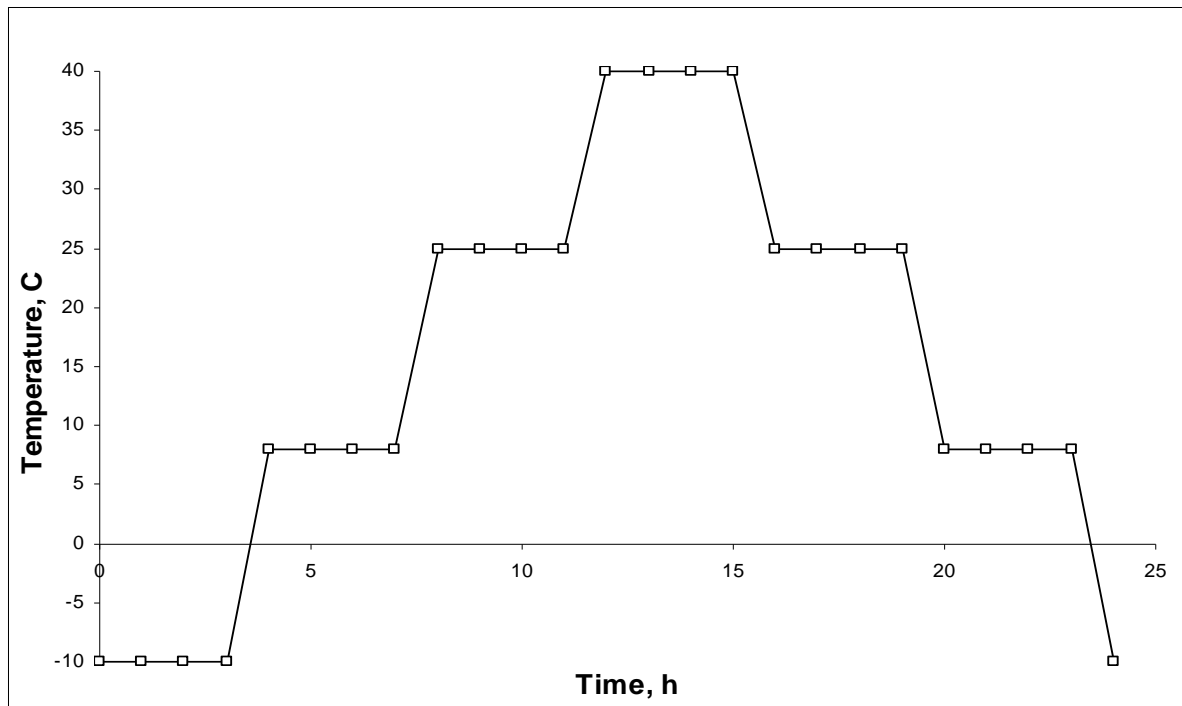
**Table 8** Temperature program

<i>Temperature</i>	<i>Condition</i>
- 10°C	<i>Cooled</i>
+8°C	<i>Refrigerated</i>
+25°C	<i>Room temperature</i>
+40°C	<i>Stress</i>

#### Centrifuge test

Samples were centrifuged (Biofuge A, Heraeus Sepatech GmbH, Germany) by increasing revolution (RPM) at room temperature for predefined time intervals (Table 9). Stability of the samples was evaluated macroscopically after each step.

After accelerated stability tests, formulations were observed macroscopically and evaluated according to the following scheme after Quack *et al.* (1975, Table 10).



**Figure 13** Temperature cycle

**Table 9** Centrifuge test

<i>Step</i>	<i>RPM</i>	<i>Duration, min</i>
<i>1</i>	<i>1000</i>	<i>10</i>
<i>2</i>	<i>3000</i>	<i>10</i>
<i>3</i>	<i>5000</i>	<i>10</i>

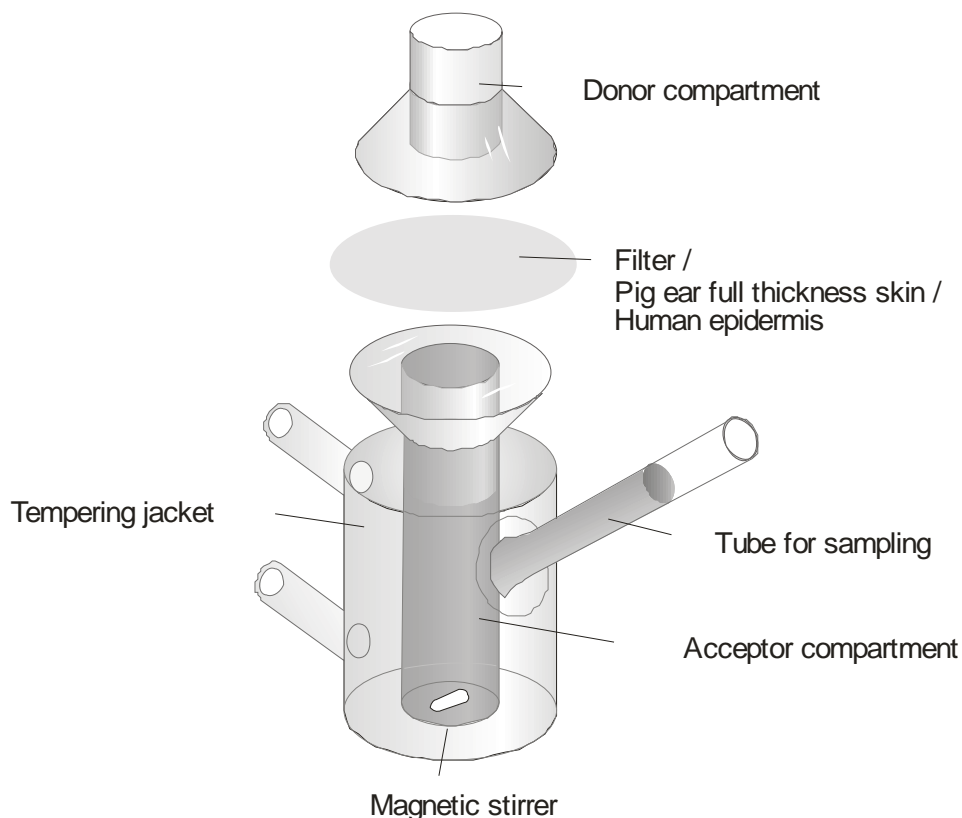
**Table 10** Stability evaluation schema for o/w emulsions<sup>1</sup>

<i>Note</i>	<i>Characteristic</i>
0	<i>Complete breakup into oil and water phase</i>
1	<i>Clear breakup Intense coalescence</i>
2	<i>Clear breakup Slight coalescence</i>
3	<i>Clear breakup Slight coalescence Definite layer at the bottom</i>
4	<i>Homogeneous upper phase Definite layer at the bottom</i>
5	<i>Clear stripline Definite layer at the bottom</i>
6	<i>Slightly noticeable stripline No definite layer at the bottom</i>
7	<i>Slightly noticeable stripline Nearly homogeneous emulsion</i>
8	<i>No noticeable stripline Completely homogeneous, unaltered emulsion</i>

<sup>1</sup>- modified after Quack *et al.*

### 3.2.2.3 BMV release (liberation) from topical formulations

The construction scheme of a Franz cell which was used for release and permeation studies is shown in the Figure 14 (Franz cell, Crown Glass Company Inc., USA). The acceptor compartment has a volume of 8 mL and the contact area between the donor and acceptor compartments is 1.00 cm<sup>2</sup>. The acceptor compartment was kept at 32°C by circulating water through a water jacket. For *in vitro* drug release tests from topical formulations different membrane systems can be used among others *e.g.* the artificial membranes saturated with *n*-octanol or oils with low polarity (Hueckstaedt, 2005).



**Figure 14** Franz cell

Untreated cellulose acetate membranes (Whatman International Ltd, England) with a pore size of  $0.2\ \mu\text{m}$  and membranes saturated with isopropyl myristate were used for the release studies. Phosphate buffer solution pH 4.5 (Ph. Eur. 6.0) with 25% (v/v) methanol was used as acceptor medium. It was ensured that perfect sink conditions were present (*i.e.* that the concentration of the drug in the acceptor medium was below 10% of the solubility of the drug in the medium).

Artificial membranes were fixed between the compartments assuring that no air bubbles from the acceptor medium are trapped under the membrane. The formulations were applied onto the membrane (0.5 g) between the upper and lower chamber of the diffusion cell after 1 h equilibrium period. Occlusive conditions were used. The formulations remained in contact with the membrane on the donor side for 24 hours. Samples were taken from the acceptor medium (500  $\mu\text{L}$  aliquots) after preset time intervals (1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h)

and the volume of the acceptor medium was substituted with fresh medium. Concentration of the drug in the acceptor medium was determined by HPLC analysis (see Appendix). Release profiles were obtained by plotting the amount of BMV assayed in the acceptor medium in  $\mu\text{g}$  per unit area against the time. Studies were carried out in triplicate.

#### **3.2.2.4 Skin permeation studies**

Excised porcine ear skin from German domestic pigs was used for skin permeation studies. The viability of the skin is not a prerequisite for permeation testing, since the process depends on passive diffusion and there is no evidence for active transport (Diembeck et al., 1999).

Pig ears were taken from the slaughterhouse (slaughterhouse Neidhardt, Holtsee, Germany). The pigs were slaughtered on the same day. Ears were cleaned with cold water and dried using soft tissue. Excessive hairs were removed through cutting and shaving. Skin from both sides from the ear was used. Skin was separated from the underlying cartilage and frozen at  $-25^{\circ}\text{C}$  until further use.

Drug permeation studies were performed in the analogical way as release studies. By plotting the amount of BMV permeated across the skin in  $\mu\text{g}$  per unit area against the time, permeation profiles were obtained.

## 4 Results and Discussions

### 4.1 Development of a comprehensive approach for foam characterization

The methods suggested by the Ph. Eur. 6.0 for foam characterization have some drawbacks. Specifically, the method for determination of foam expansion time is inapplicable for foams generated via mechanical pump systems or *in situ*. Moreover, this monograph does not consider determination of foam stability. Independent of the foam generation mechanism, evaluation of foam quality parameters in the addition to the information about foam stability is crucial for formulation development. Furthermore, an estimation of general foam appearance as well as stability and degree of expansion are essential factors for cosmetic acceptance.

Limitations of the suggested methods and lack of a method for the determination of foam stability lead to the necessity to develop a new approach which can be used for routine analysis. This method should allow a fast and comprehensive determination of foam appearance, consistency and stability as well as formulation foamability independent of the foam generation mechanism.

For simplification of data interpretation, it was decided to use simple solutions of foaming agents which showed good results in the test after Jellinek (see 4.2.1.2). Tween<sup>®</sup> 20, Brij<sup>®</sup> 35, Tagat<sup>®</sup> O2, Tagat<sup>®</sup> L2 and Tagat<sup>®</sup> S2 were used as foaming agents at concentrations ranging from 1.0% to 5.0%. All foams were produced by means of the Airspray<sup>®</sup> foam dispenser.

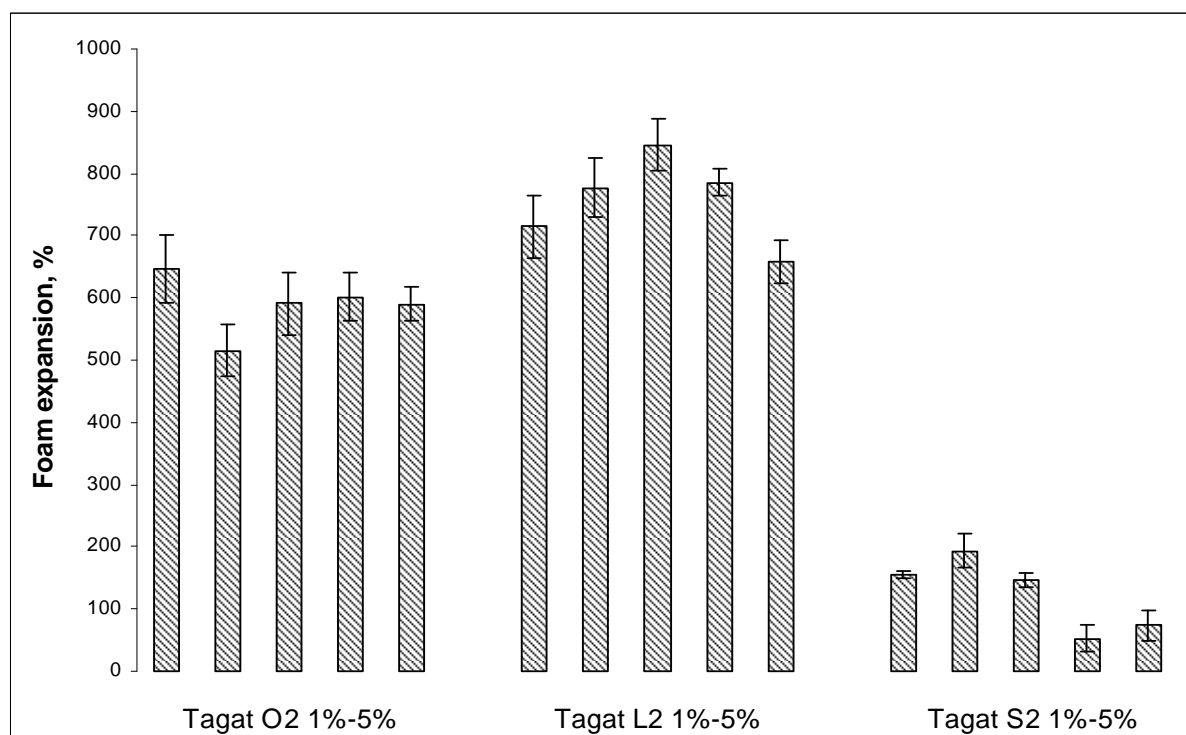
Cylinder method, Texture analyser method and light (back-) scattering method were compared to each other. These methods were evaluated in terms of significance, determination time and ease of operation.

## 4.1.1 Cylinder method

### 4.1.1.1 Foam expansion

Foam expansion is a parameter of formulation foamability. Higher foam expansion values are to strive for as it would result in higher foam volumes which can be produced from a defined volume of a foamable formulation.

In the homologue series of three foaming agents (Tagat<sup>®</sup> row, chemically presenting esters of fatty acids with glycerol, containing 20 units of polyoxyethylene in the molecule) different values for foam expansion were determined. Compared to foam expansion values of Tagat<sup>®</sup> O2 and Tagat<sup>®</sup> L2, much lower values for Tagat<sup>®</sup> S2 were detected. Tagat<sup>®</sup> L2 showed better foamability than Tagat<sup>®</sup> O2. No dependency of foam expansion values from foaming agent concentration was observed (Figure 15).



**Figure 15** Foam expansion within the Tagat<sup>®</sup> homologue series

Differences in the foaming capacity of these foaming agents from the Tagat<sup>®</sup> homologue series could be explained due to the differences in the flexibility of foaming agent molecules which are involved into stabilization of newly generated interfaces. The mobility of molecules of the foaming agent is the factor which influences the effectiveness of a surfactant as a foaming agent. The only difference in the chemical structure of the used foaming agents is the length of the fatty acid chain incorporated into the molecule and representing the lipophilic part of the molecule. The long chain (C<sub>18</sub>) of stearic acid is more rigid and less mobile than chains of oleic acid (C<sub>18</sub>, double bond) and lauric acid (C<sub>12</sub>). This leads to a less pronounced mobility of the molecules. Presence of oleic acid which has a double bond in the molecule structure seems to lead to a higher flexibility of the foaming agent molecules than that caused by the presence of stearic acid but lower than that caused by the presence of lauric acid. Presence of lauric acid in the structure of the foaming agent molecule leads to a higher flexibility of the molecules, formation of flexible lamellae and, therefore, higher values for foam expansion. Presence of the stearic acid in the structure of the foaming agent molecule leads to a formation of rigid lamellae and, therefore, low values for foam expansion. No concentration dependence was determined as all foaming agents were used above their CMC.

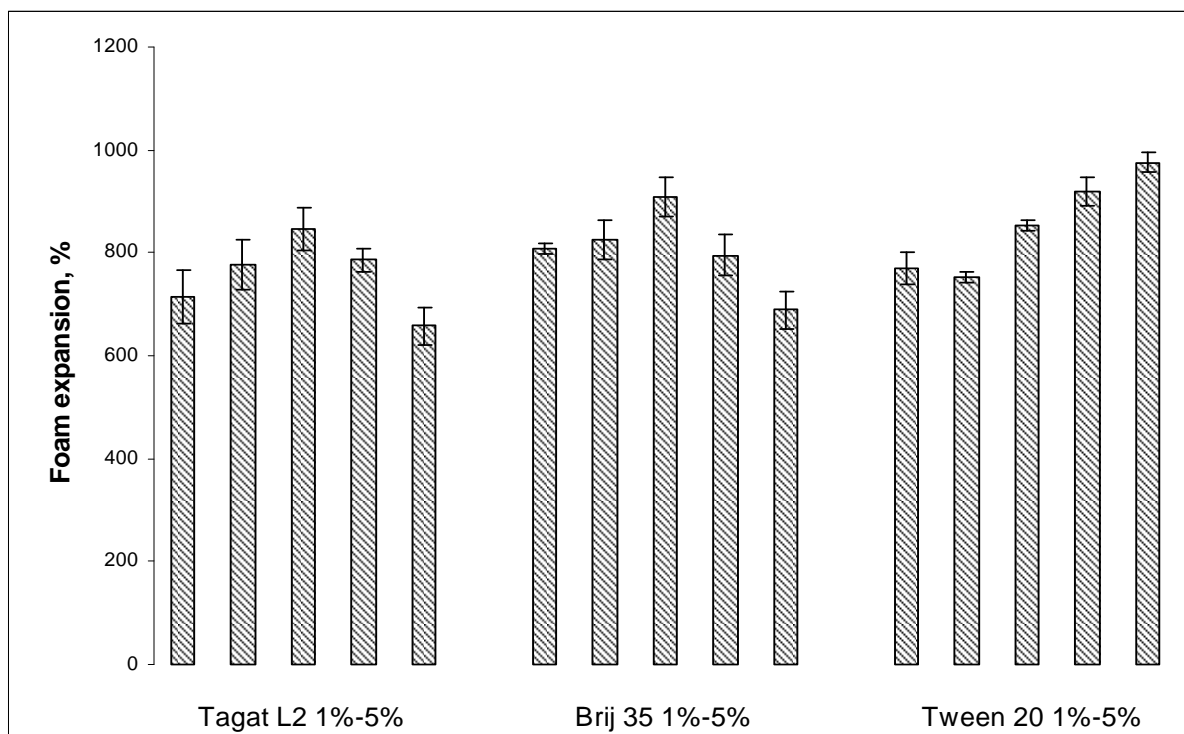
Considering the data for adsorption velocity of these three foaming agents, Tagat<sup>®</sup> L2 is thought to show a faster surface occupation than Tagat<sup>®</sup> O2 and Tagat<sup>®</sup> S2 (see 4.1.1.4).

The hypothesis about better foamability caused by low surface film rigidity due to presence of lauric acid in the structure of Tagat<sup>®</sup> L2 is supported through comparison of the foam expansion parameter of two other foaming agents also containing lauric acid in their structure. These foaming agents were Brij<sup>®</sup> 35 (ether of lauric alcohol and 23 units of polyoxyethylene) and Tween<sup>®</sup> 20 (ester of lauric acid with sorbitol, containing 20 units of polyoxyethylene).



No differences in the foaming capacity of Tagat<sup>®</sup> L2, Brij<sup>®</sup> 35 and Tween<sup>®</sup> 20 were observed (Figure 16).

This is due to the same elasticity of the foaming agent film on the interface. The size of the hydrophilic part of a molecule seems to have only a minor effect on the foamability of the formulations.



**Figure 16** Foam expansion of solutions produced with foaming agents containing lauric acid in their structure

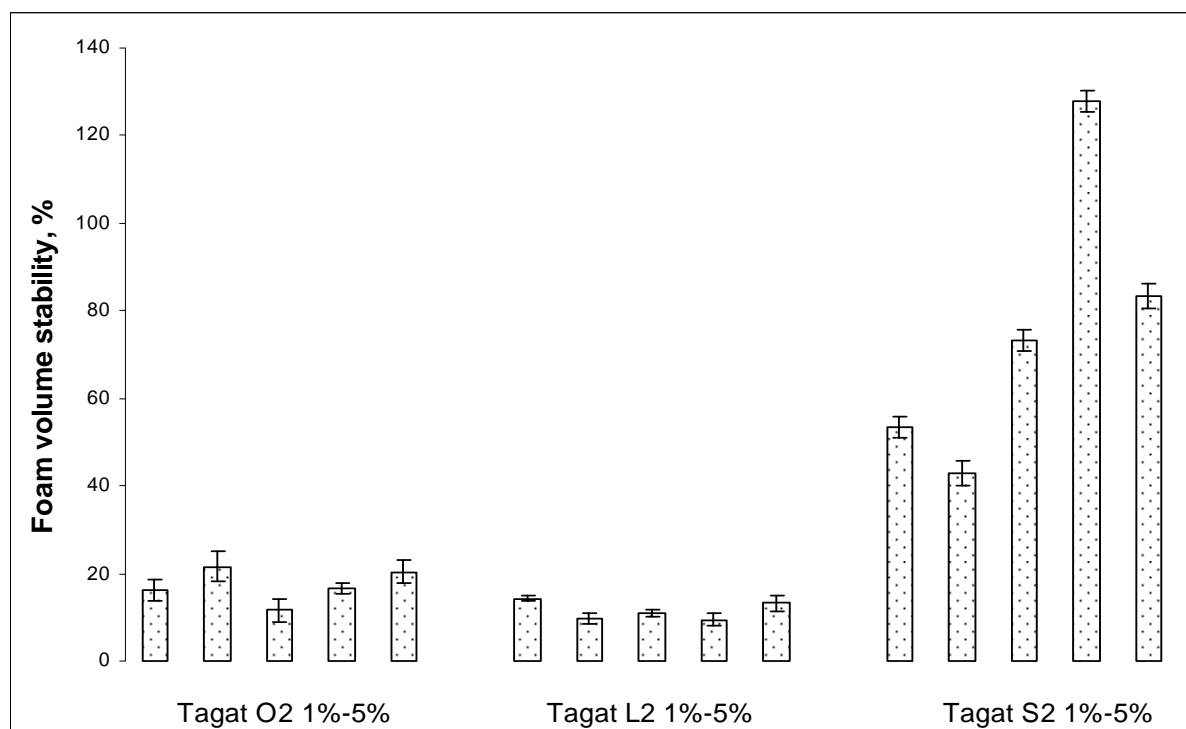
#### 4.1.1.2 Foam volume stability

Foam volume stability is a parameter indicating the stability of air bubbles incorporated into a foam structure against rupture. If the parameter of foam volume stability is high, air bubbles are more resistant to the process of bubble rupture.

Considering the parameter of foam volume stability within the homologue Tagat<sup>®</sup> series, an opposite ranking of the foaming agents than during foamability

observations was found. The highest foam volume stability values were determined for Tagat<sup>®</sup> S2, the stearic acid ester of the series.

Foam volume stability values of Tagat<sup>®</sup> O2 and Tagat<sup>®</sup> L2 were found to be much lower than that of Tagat<sup>®</sup> S2 whereas foam volume stability values of Tagat<sup>®</sup> O2 only were slightly higher than that of Tagat<sup>®</sup> L2 (Figure 17). No concentration dependence was determined.



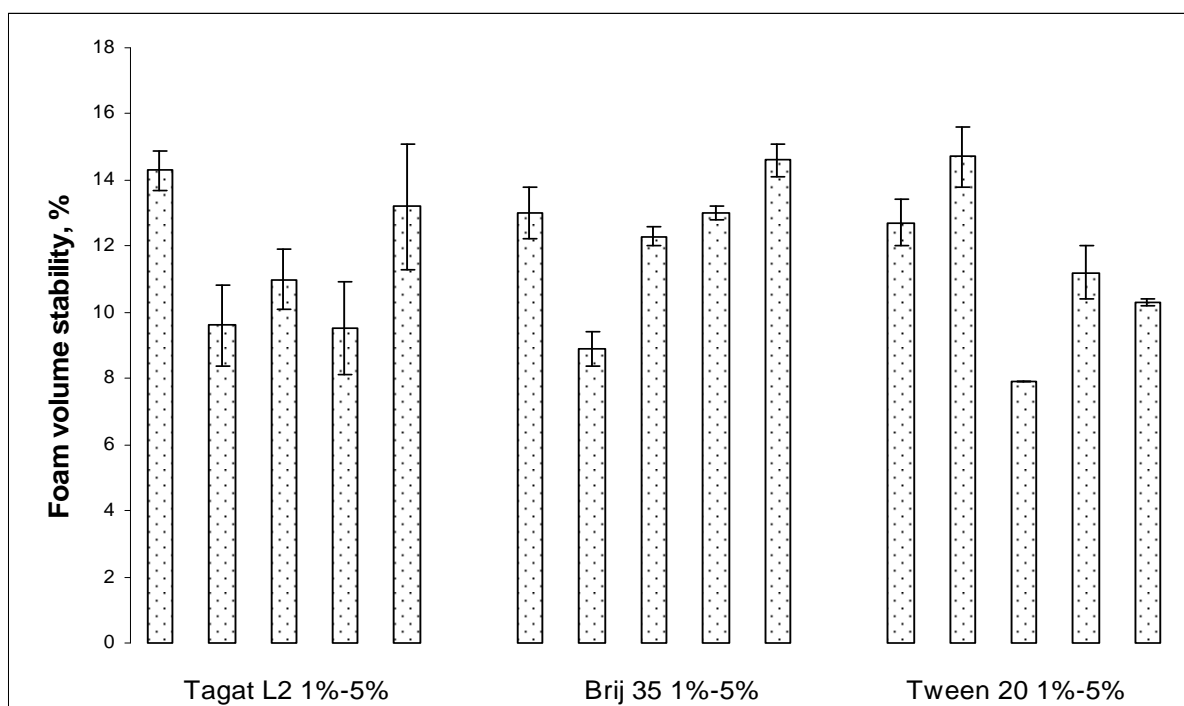
**Figure 17** Foam volume stability within the Tagat<sup>®</sup> homologue series

Bubble rupture is connected with the elasticity / rigidity of the foaming agent film formed in the interface. When molecules of Tagat<sup>®</sup> S2 which contains stearic acid in its structure are adsorbed in the new interface, a rigid, low elastic film is built. This, on one hand, is the reason for low foam expansion (see 4.1.1.1). On the other hand, the rigidity and inelasticity of the adsorbed film lead to the better stability of foam bubbles against rupture. Adsorption of the Tagat<sup>®</sup> O2 and Tagat<sup>®</sup> L2 molecules in the interface leads to the formation of a flexible, elastic films because of the low rigidity of lauric and oleic acid chains in the

structure of these foaming agents. This would lead to a more pronounced mobility of the molecules in the interface and, therefore, low stability of air bubbles against rupture.

A concentration dependence could not be observed, probably because the foaming agents were used in concentrations above their CMC.

Considering the foam volume stability of Brij<sup>®</sup> 35 and Tween<sup>®</sup> 20 against the foam volume stability of Tagat<sup>®</sup> L2, no differences in values for all three foaming agents could be seen (Figure 18). The length of the hydrophilic part of foaming agent molecules as well as presence of sorbitol or glycerol molecules in its structure seems to have no effect on the foam volume stability of the produced foams.

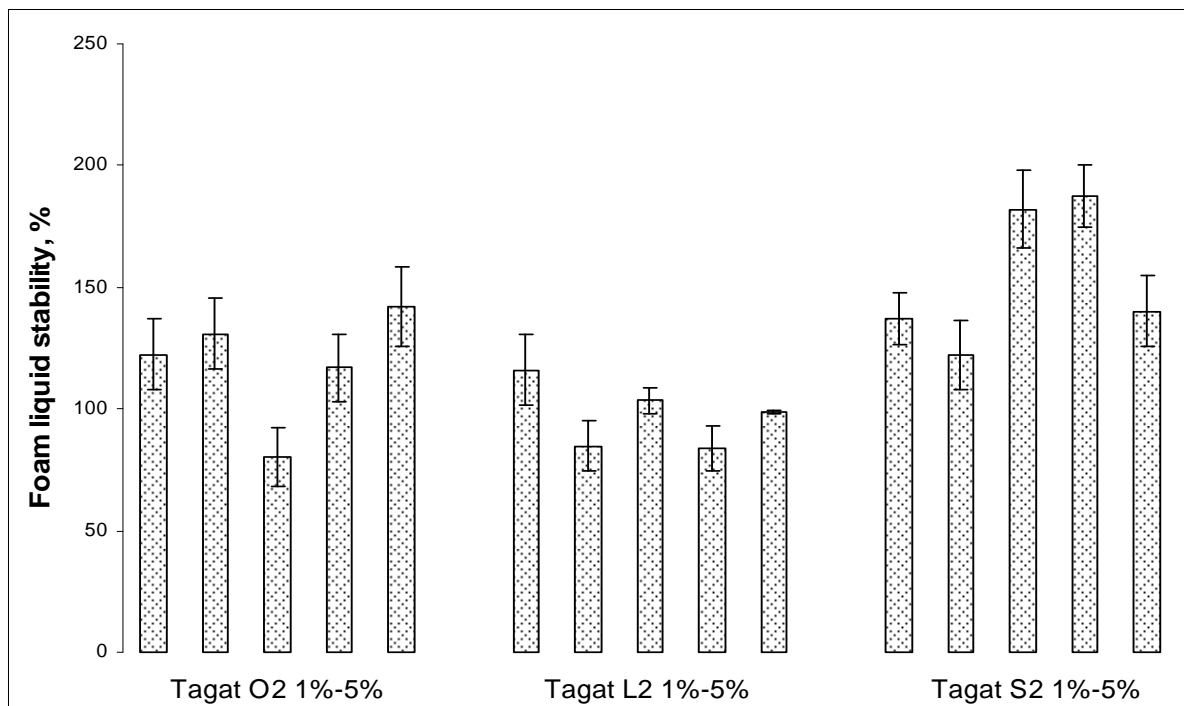


**Figure 18** Foam volume stability of foams produced with foaming agents containing lauric acid in their structure

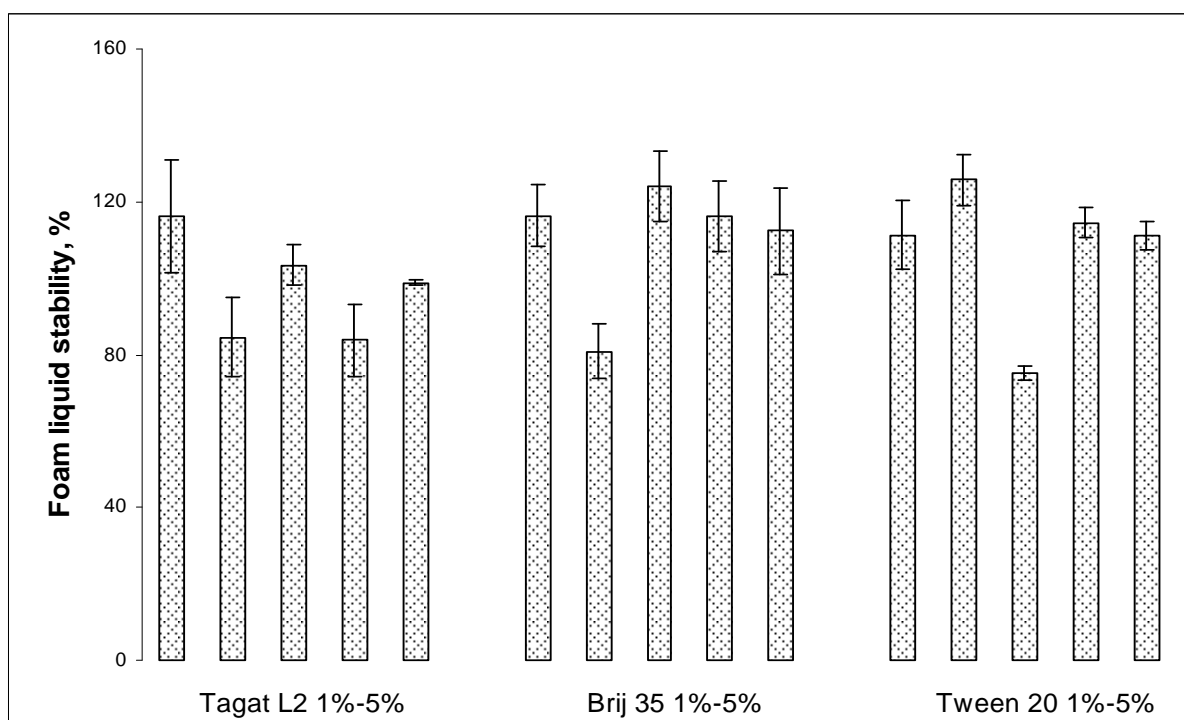
### 4.1.1.3 Foam liquid stability

Foam liquid stability is a parameter which reflects the intensity of liquid drainage. Low values for foam liquid stability indicate a low volume of liquid phase which was separated during the foam aging and, therefore, better foam stability. Foam drainage is a complicated process which is not fully understood (see 2.1.5). The drainage process is independent from bubble rupture (Bikerman, 1973). The type of foaming agent is a factor which influences the flow of the liquid through individual lamellae channels (Koehler *et al.*, 2004).

Considering the data for foam liquid stability derived from the cylinder test, a slightly higher drainage rate was determined for the foam generated with Tagat<sup>®</sup> S2 as foaming agent. Slightly lower drainage intensity was determined for foams produced by means of Tagat<sup>®</sup> O2 and Tagat<sup>®</sup> L2 (Figure 19). Foams produced from solution of Tagat<sup>®</sup> S2 were shown to have a low foam expansion but high foam volume stability (foam stability against bubble rupture), (see 4.1.1.1 and 4.1.1.2). This was explained through a high rigidity of foam lamellae. The air bubbles in the foam are stable and do not rupture, but the liquid drains, however, through the foam lamellae. This leads to higher values for foam liquid stability. Foams produced from solutions of Tagat<sup>®</sup> O2 and Tagat<sup>®</sup> L2 show high foam expansion but low foam stability against rupture because of high flexibility of molecules in the surfactant film which is adsorbed in the interface. The liquid in lamellae in this case is well bonded because of a good pronounced Marangoni effect. This leads to lower values of foam liquid stability and, therefore, lower liquid drainage. No differences for the liquid drainage rate were observed comparing the three different foaming agents containing lauric acid in their structure (Figure 20). The structure of the molecule and the length of the fatty acid chain seem to be among many other factors such as, *e.g.*, bulk solution viscosity and surface film elasticity which influence liquid drainage. The effect of the chain length on foam drainage is pronounced to a lesser extent than on foam expansion and foam volume stability parameters.



**Figure 19** Foam liquid stability within the Tagat® homologue series



**Figure 20** Foam liquid stability of foams produced with foaming agents containing lauric acid in their structure

#### 4.1.1.4 Adsorption velocity of foaming agents into the interface

This investigation was used to correlate the data of foamability and foam stability with the velocity of foaming agent molecules to adsorb into the interface (see 3.2.1.7).

The following data for the foaming agents involved into the cylinder test were obtained.

Tagat<sup>®</sup> O2, Tagat<sup>®</sup> S2 and Brij<sup>®</sup> 35 molecules showed a slow velocity of interfacial adsorption (Figures 21, 22 and 23). After volume increase, through addition of foaming agent solution, no decrease of the surface tension was observed during the measurement time. In contrast, Tagat<sup>®</sup> L2 and Tween<sup>®</sup> 20 molecules tend to a fast interfacial occupation (Figures 24 and 25). The reduction of surface tension below  $40 \text{ mN}\cdot\text{m}^{-1}$  was observed directly after dosing of foaming agent solution into the droplet of water. The data for occupation velocity could, nevertheless, not be correlated with the data for formulation foamability or foam stability parameters.

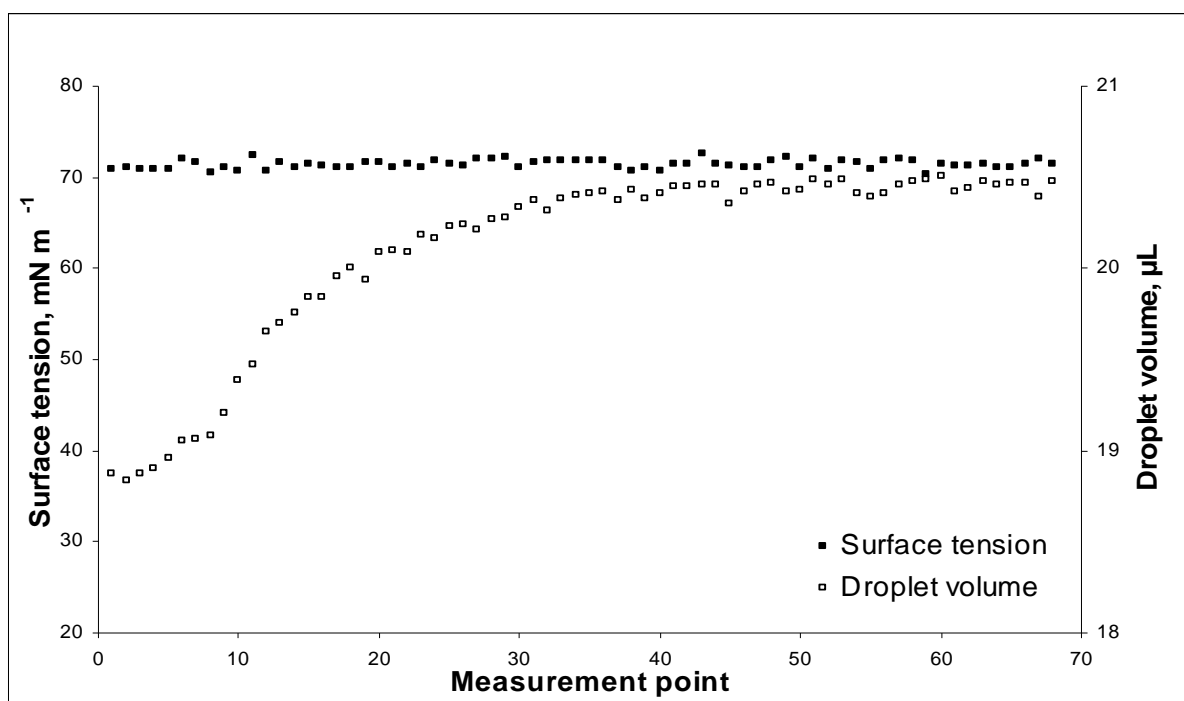


Figure 21 Adsorption velocity of Tagat<sup>®</sup> O2 into the interface

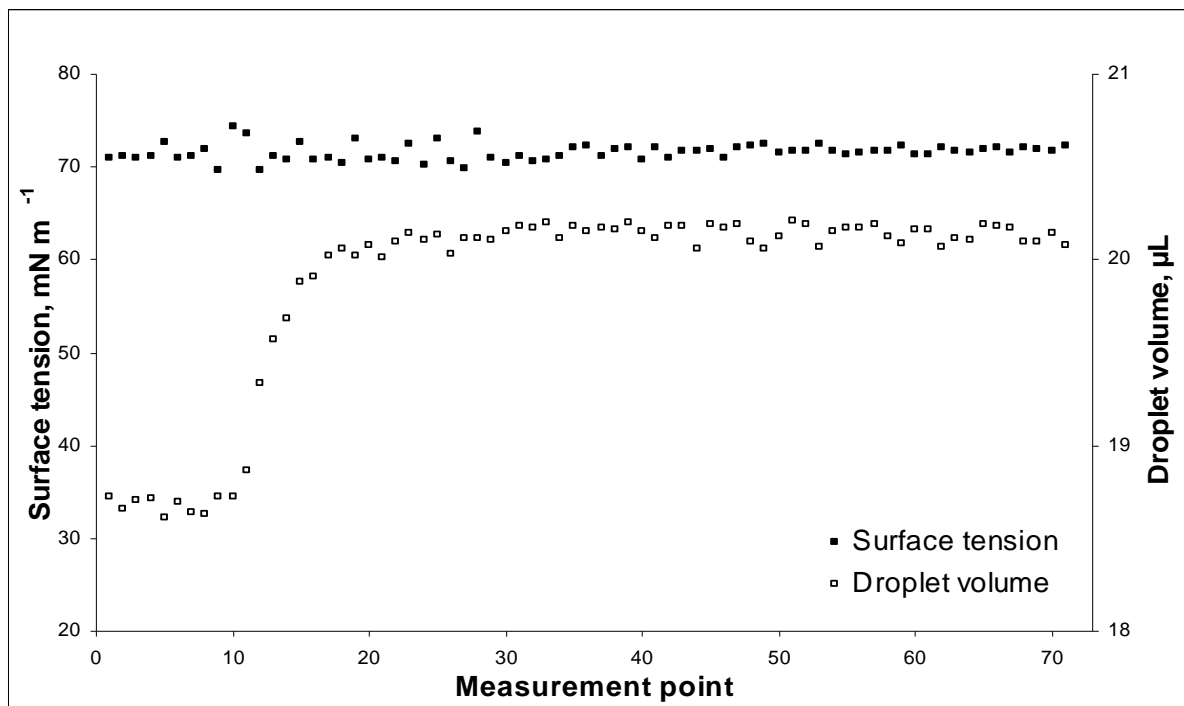


Figure 22 Adsorption velocity of Tagat<sup>®</sup> S2 into the interface

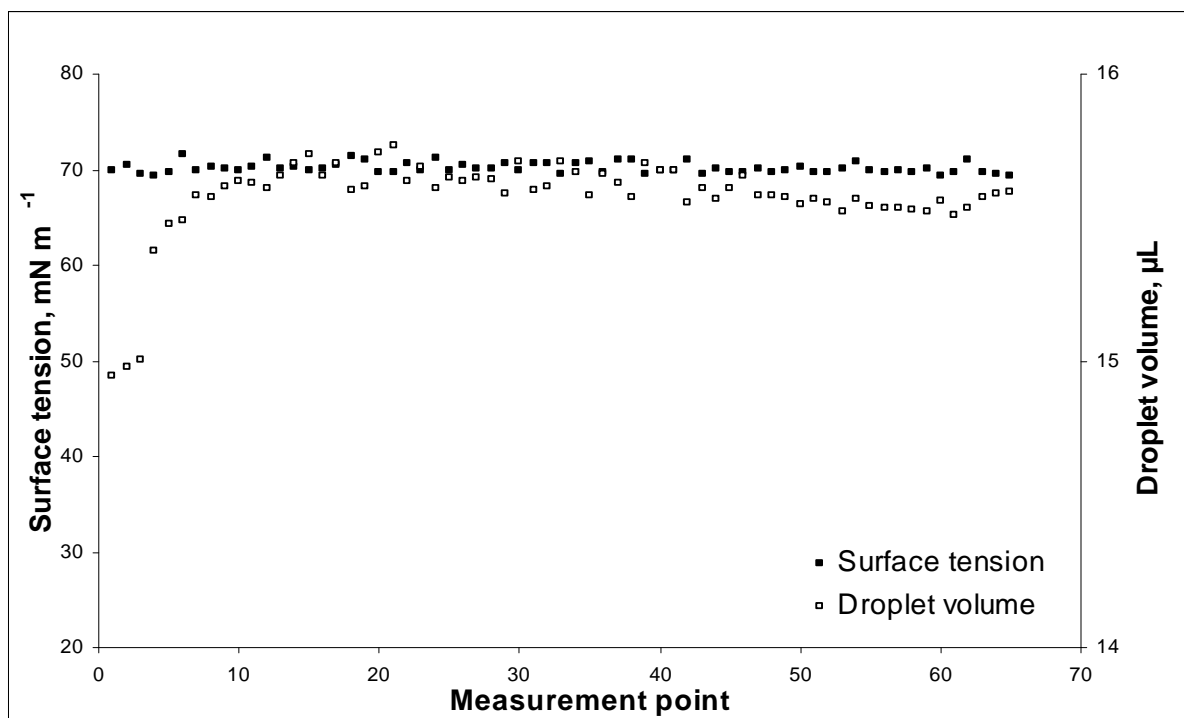


Figure 23 Adsorption velocity of Brij<sup>®</sup> 35 into the interface

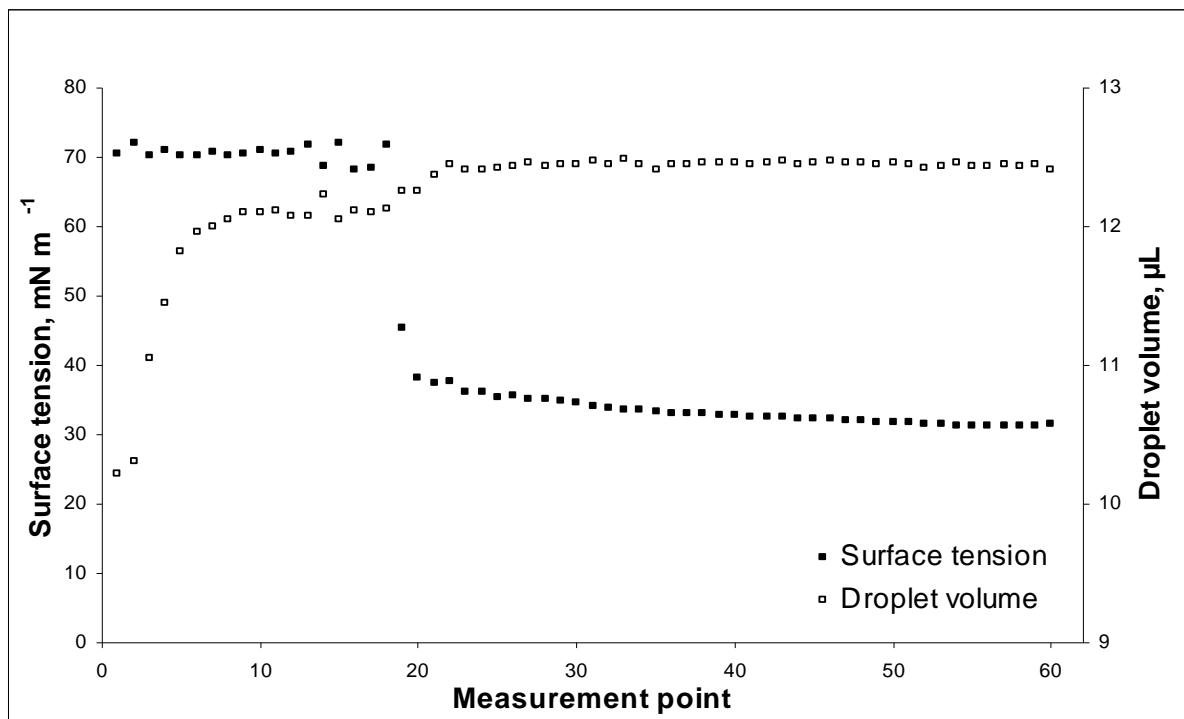


Figure 24 Adsorption velocity of Tagat<sup>®</sup> L2 into the interface

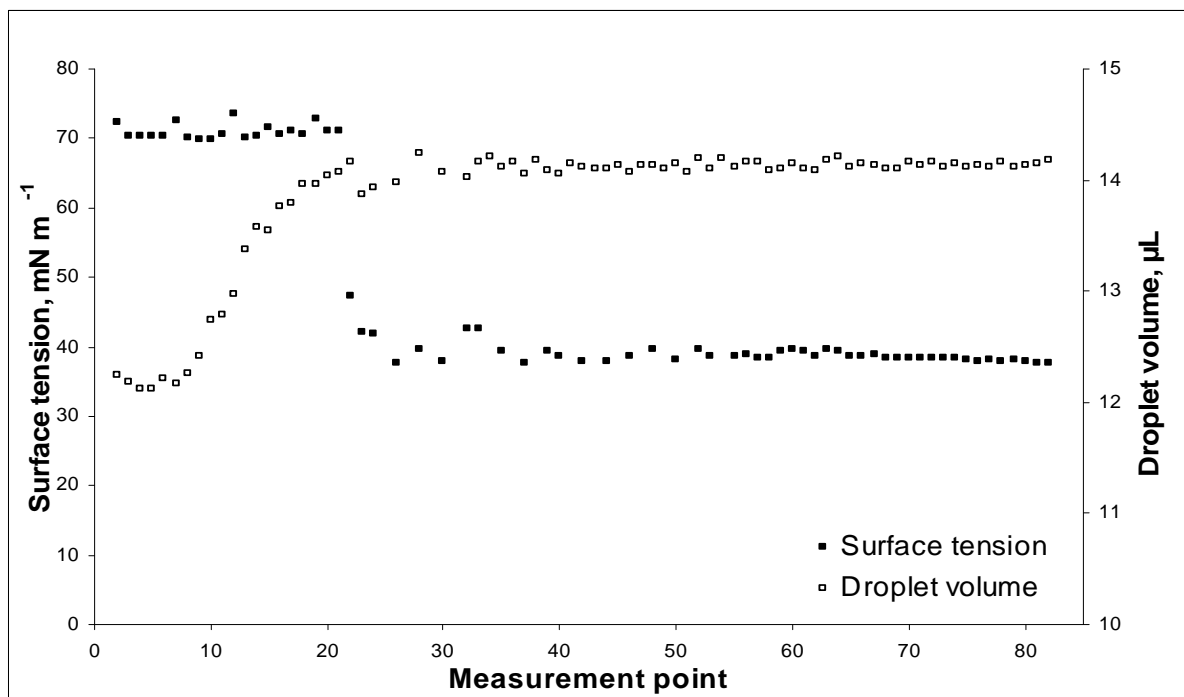


Figure 25 Adsorption velocity of Tween<sup>®</sup> 20 into the interface



#### **4.1.1.5 Summary**

The cylinder test presents a test for the determination of formulation foamability, foam volume and foam liquid stability. The test can be carried out easily. It requires no specific equipment or materials. Results for foamability show low standard deviations of the data. This is not the case during determination of foam volume and foam liquid stability.

The length of the fatty acid chain in the structure of a foaming agent seems to be a factor influencing foamability capacity of a formulation and foam volume stability. No significant differences for foaming agents were determined by evaluation of foam liquid stability. This is due to complex combination of factors influencing this process.

The cylinder test can be used for fast routine analyses of foamability and foam volume stability in formulation studies.

Droplet shape analysis was used in this study to get deeper insight into adsorption velocity and surface tension changes over time and, with this, to find a correlation to the data obtained with the cylinder test.

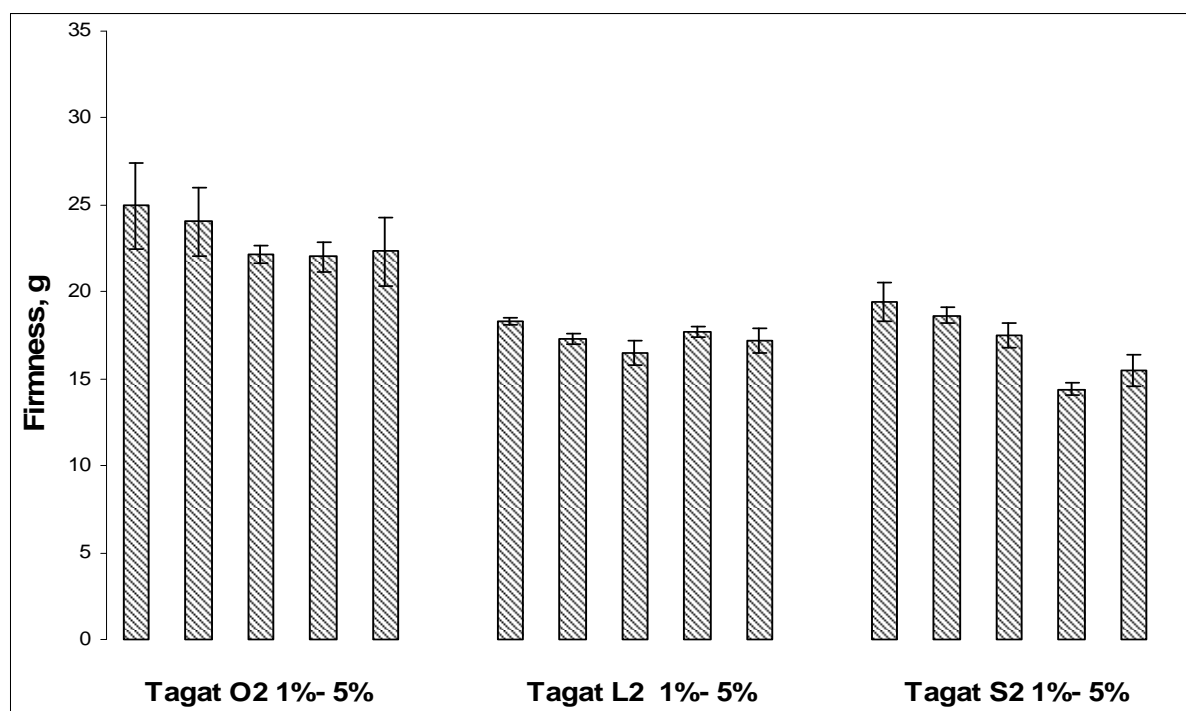
Droplet shape analysis was found to be a useful tool to investigate such parameters as adsorption velocity and surfactant film elasticity. However, a direct correlation to the stability parameters derived from the cylinder test could not be found.

#### **4.1.2 Texture analyser**

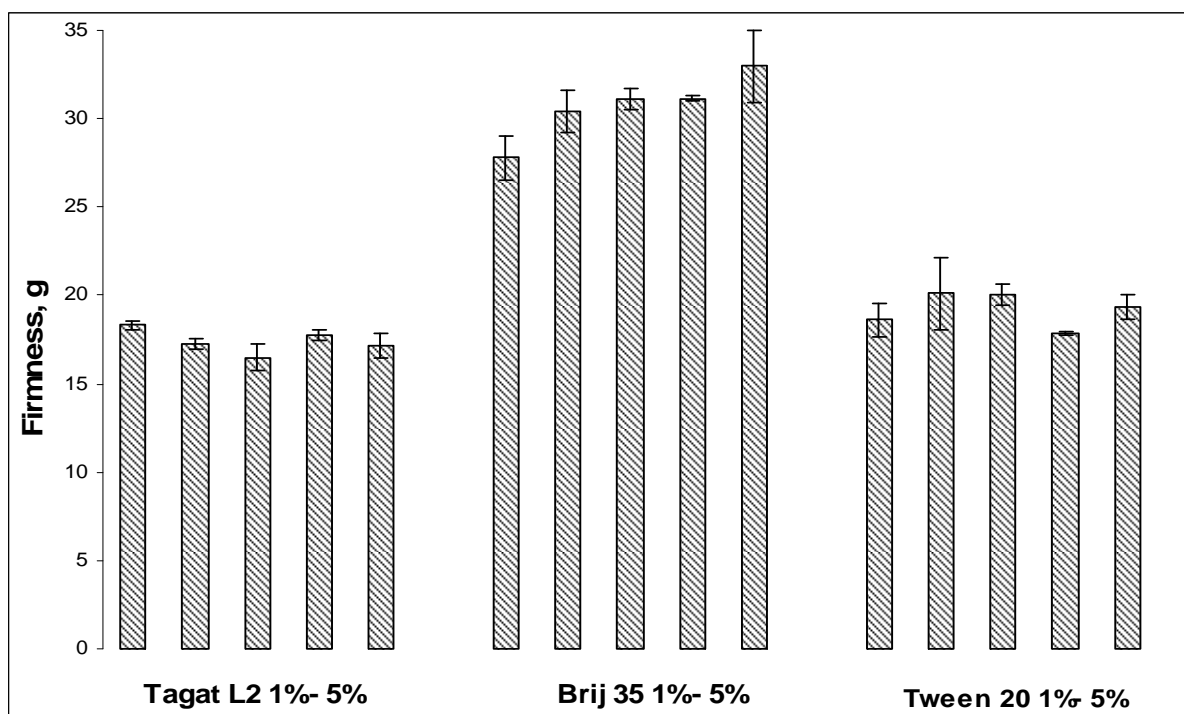
##### **4.1.2.1 Foam firmness**

The foam firmness was evaluated as the maximum penetration force during foam compression. Surface viscosity, bulk liquid viscosity, bubble size distribution and foam geometry are among the factors which influence foam firmness (Wijnen, 1997). Considering the data for foam firmness for the Tagat<sup>®</sup> homologue series, slightly higher values were determined for Tagat<sup>®</sup> O2.

No differences were observed between foams produced from Tagat<sup>®</sup> L2 and Tagat<sup>®</sup> S2 solutions (Figure 26). The foam which was produced from a Brij<sup>®</sup> 35 solution showed the highest values for foam firmness compared to the other two foaming agents containing lauric acid chain in their structure (Figure 27). Values for foam firmness for Tagat<sup>®</sup> L2 and Tween<sup>®</sup> 20 were similar. The higher values for Tagat<sup>®</sup> O2 and Brij<sup>®</sup> 35 foam were probably caused by the smaller bubble size or the higher gas volume fraction of the foam produced from these foaming agents. Smaller air bubbles execute more resistance during the compression cycle than larger bubbles, leading to higher values for foam firmness.



**Figure 26** Foam firmness within the Tagat<sup>®</sup> homologue series



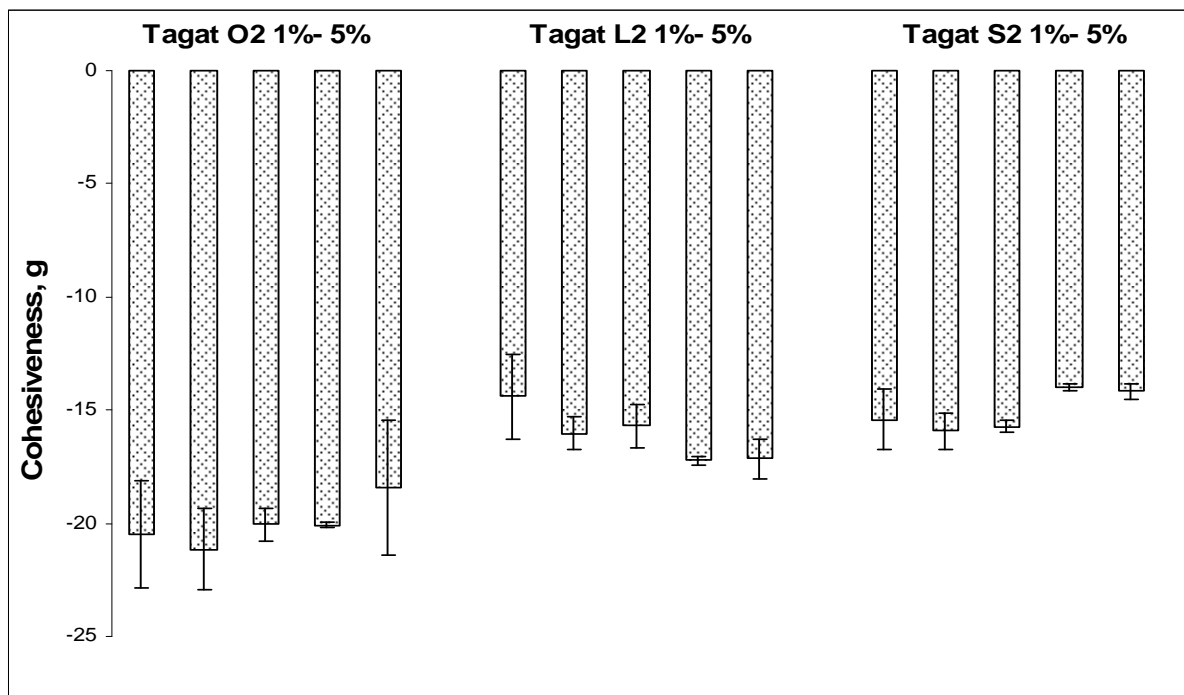
**Figure 27 Firmness of foams produced with foaming agents containing lauric acid in their structure**

No correlation between foam firmness and concentration of foaming agent was observed. This is again a confirmation that viscosity of the foaming agent solution does not affect the foam firmness as determined with the Texure Analyser.

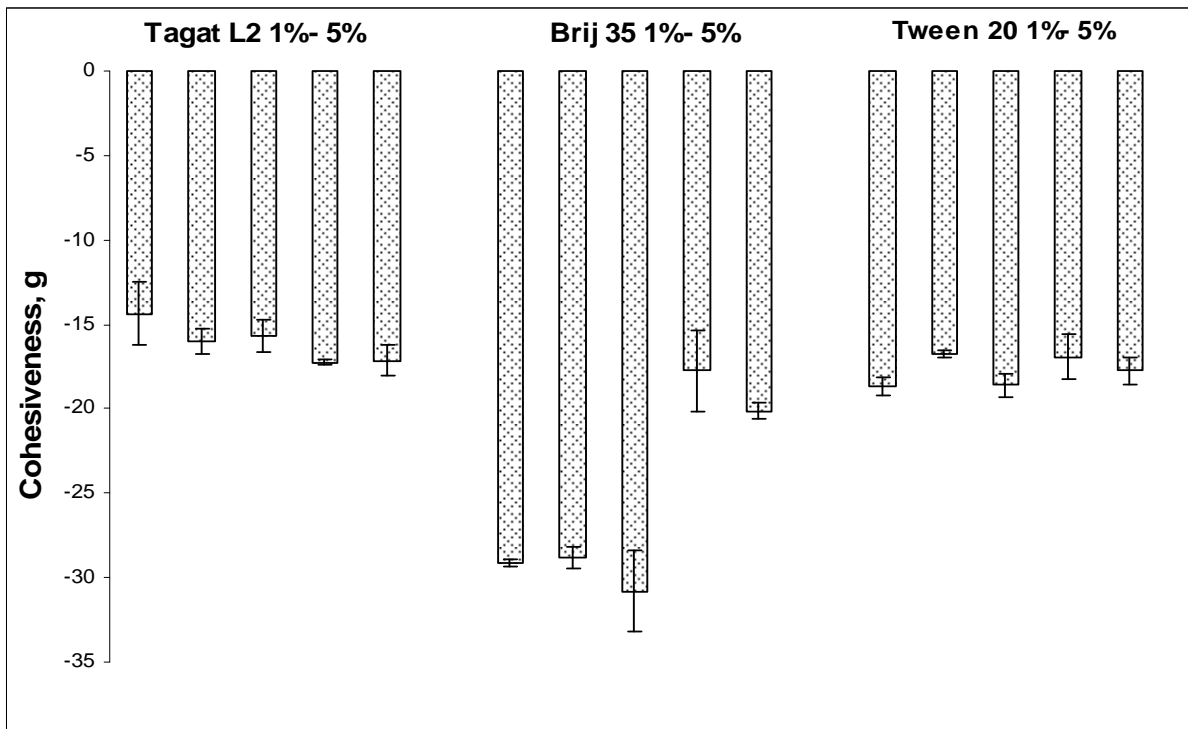
#### 4.1.2.2 Cohesiveness

Foam cohesiveness was determined as the minimum force when the sample was proceeded to withdraw from the disk. Foam cohesiveness corresponds to the force which is required to overcome foam stickiness. The same rank order of foaming agents involved into the test was observed for foam cohesiveness as already reported for firmness. The highest values were determined for foams produced from Tagat<sup>®</sup> O2 and Brij<sup>®</sup> 35 solutions (Figure 28 and 29). Higher values for cohesiveness for these foaming agents are probably based on worse wettability of the compression disc surface with solutions of these foaming

agents. The worse wettability can be explained by the high gas volume fraction of foams produced from Tagat<sup>®</sup> O2 and Brij<sup>®</sup> 35 solutions. This supposition correlates with the data for foam firmness. The cohesiveness values for Tagat<sup>®</sup> L2, Tagat<sup>®</sup> S2 and Tween<sup>®</sup> 20 were similar. No concentration dependence for cohesiveness values was observed.



**Figure 28** Foam cohesiveness within the Tagat<sup>®</sup> homologue series



**Figure 29** Cohesiveness of foams produced with foaming agents containing lauric acid in their structure

#### 4.1.2.3 Summary

Foam firmness in this study was determined as the maximum resistance of a foam against a standardised deformation (compression). It was possible to determine foam firmness and foam cohesiveness with the Texture analyzer method. These two parameters of foam quality were brought in connection with foam bubble size and foam gas fraction. This method is time-intensive and, in case, the foam structure is inhomogeneous, the measurements are not possible. Large air bubbles within the foam disrupt the measurement causing irregularities in the texture analyser force profile. However, the mechanical properties derived from the force-time curve can be used to assess the application ease of foam samples and adhesiveness of foam to the skin.

### 4.1.3 Light (back-) scattering method

#### 4.1.3.1 Backscattering profiles

The backscattering signal correlates with the growth of foam air bubbles which takes place as foam ages. Foam bubble growth taking place because of Ostwald ripening has nothing in common with bubble rupture which can be observed by means of FVS measurement with the cylinder test. Bubble rupture during light (back-) scattering method can be observed through a decrease of the foam meniscus in the measuring cell over the determination time.

Considering the data for the Tagat<sup>®</sup> homologue series, foams produced from Tagat<sup>®</sup> S2 showed a growth of air bubbles which was more pronounced compared to foams produced from Tagat<sup>®</sup> O2 and Tagat<sup>®</sup> L2. Foams produced from Tagat<sup>®</sup> L2 showed the lowest air bubble growth observed during determination time (Figure 30).

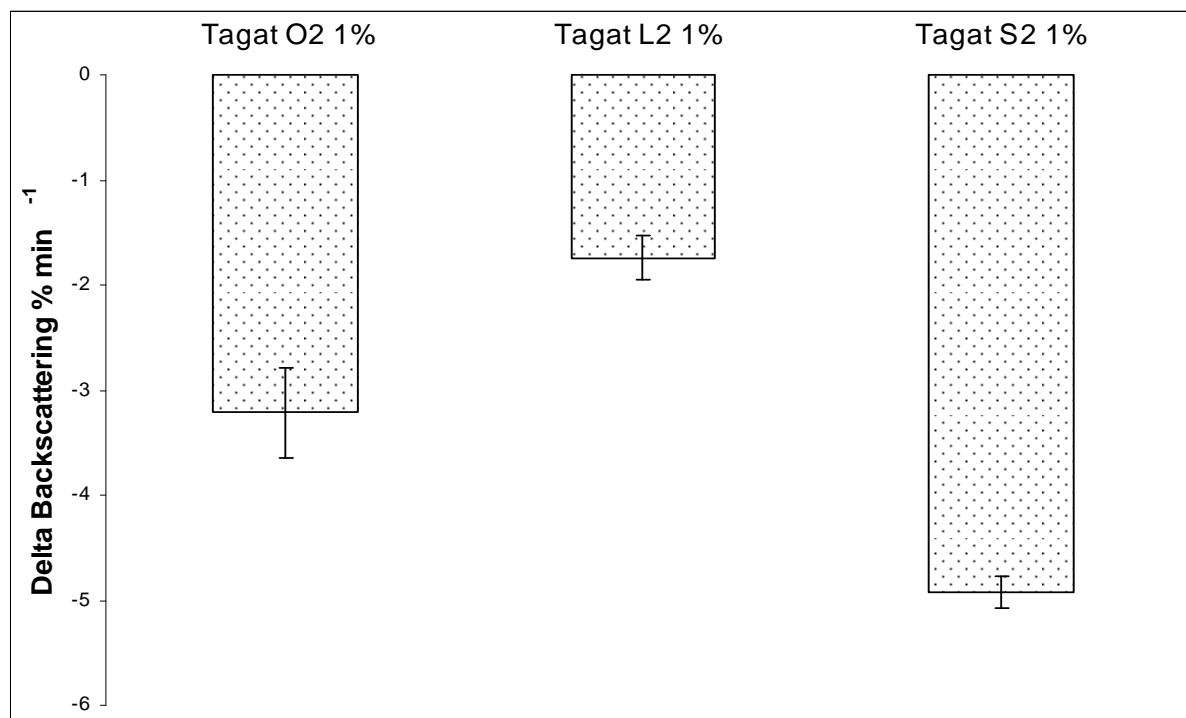
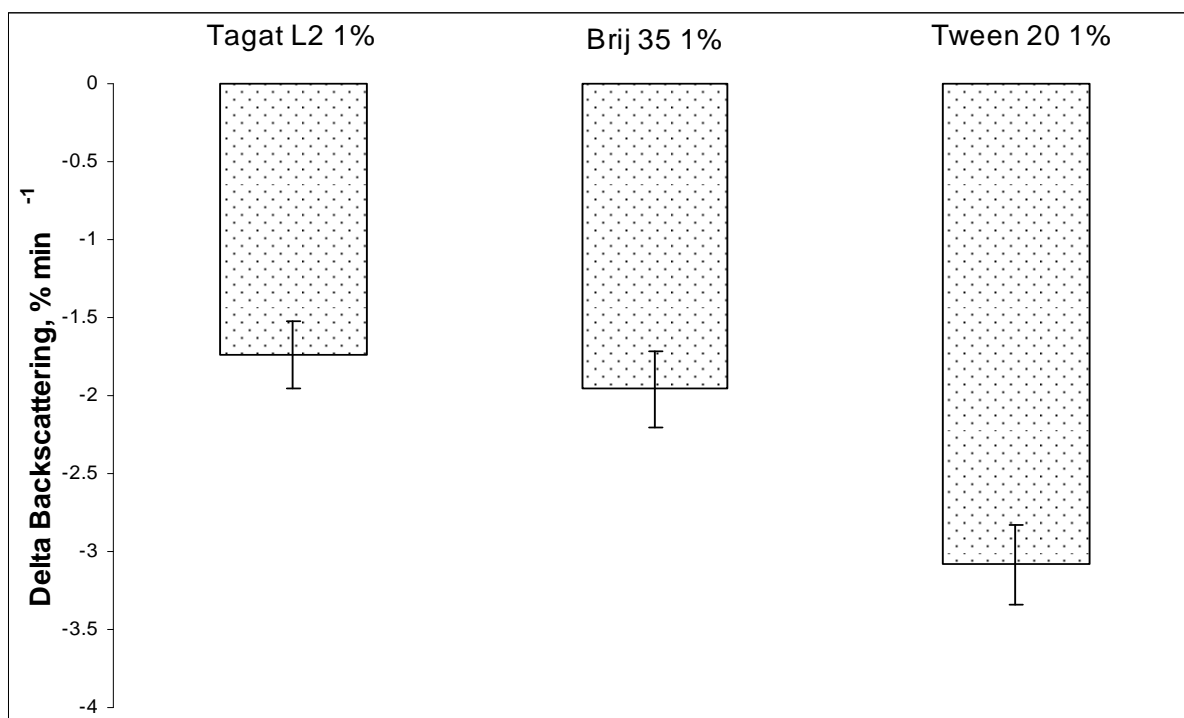


Figure 30 Delta Backscattering within the Tagat<sup>®</sup> homologue series



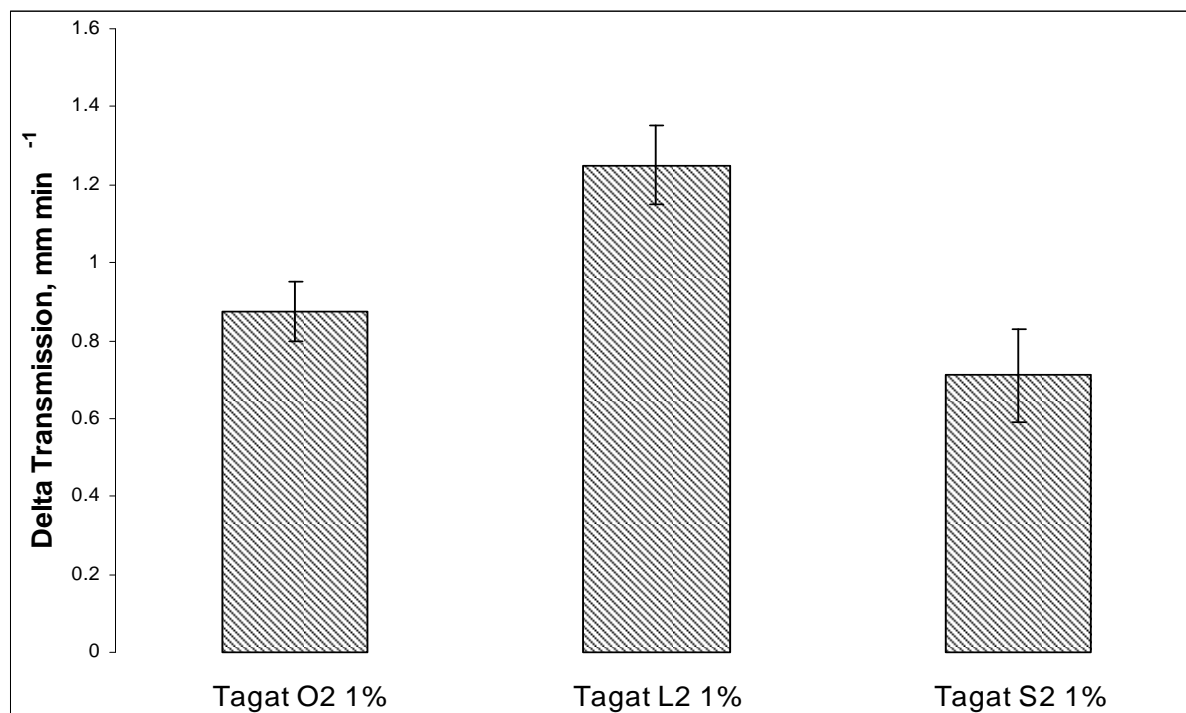
**Figure 31** Delta Backscattering of foams produced with foaming agents containing lauric acid in their structure

Considering bubble growth of foaming agents which contain lauric acid in their structure, it was more pronounced by use of Tween<sup>®</sup> 20 as foaming agent. No differences between foams produced from Tagat<sup>®</sup> L2 and Brij<sup>®</sup> 35 were observed (Figure 31). It can be concluded that Ostwald ripening happens to a greater extent in foams produced from Tagat<sup>®</sup> S2 and Tween<sup>®</sup> 20 as foaming agents.

#### 4.1.3.2 Transmission profiles

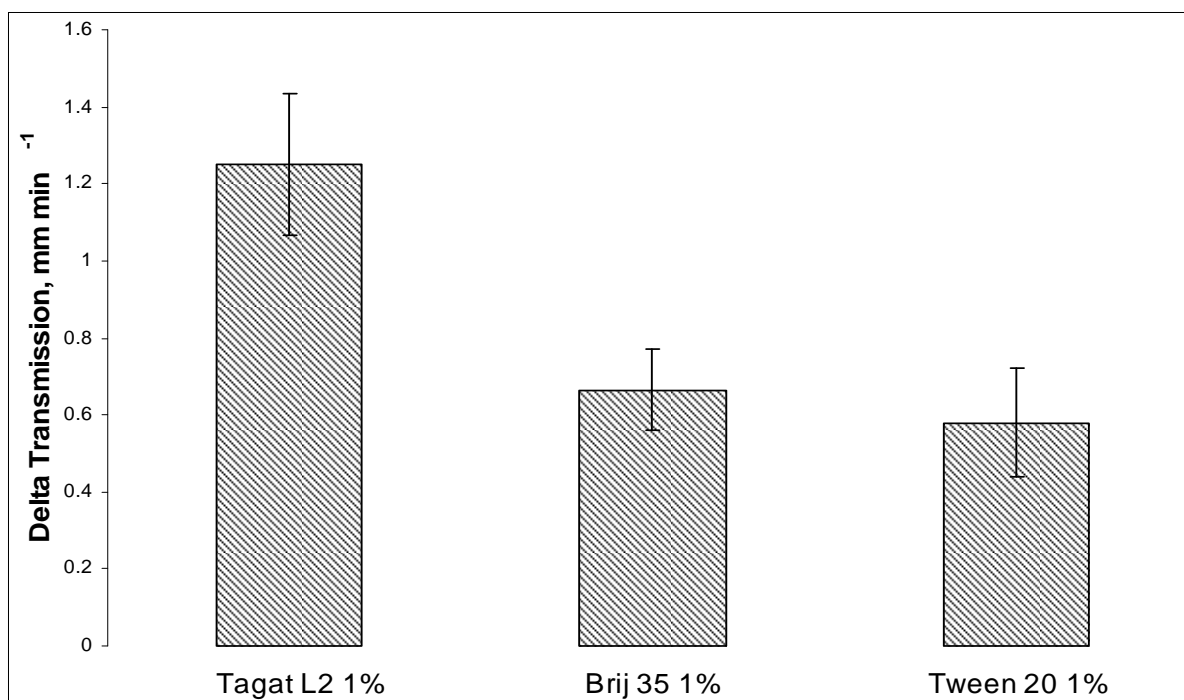
The intensity of the transmission signal should correlate with the data for foam liquid stability obtained with the cylinder test. In both cases, liquid drainage is evaluated. The results were, nevertheless, different from that obtained by the cylinder test. Liquid drainage of the foams produced from Tagat<sup>®</sup> S2 solutions was less pronounced than liquid drainage observed for foams produced from Tagat<sup>®</sup> O2 and Tagat<sup>®</sup> L2 solutions (Figure 32). Liquid drainage, observed by

the foam produced from Tagat<sup>®</sup> L2 solution was more pronounced than liquid drainage from foams produced from Brij<sup>®</sup> 35 and Tween<sup>®</sup> 20 solutions (Figure 33).



**Figure 32** Delta Transmission within the Tagat<sup>®</sup> homologue series





**Figure 33** Delta Transmission of foams produced with foaming agents containing lauric acid in their structure

#### 4.1.3.3 Summary

The light (back-) scattering method provides a fast and practical approach to characterize foam stability through detection of air bubble growth and liquid separation because of liquid drainage in a foam. Foamability of a formulation can, nevertheless, not be detected with this method. To detect foamability, the cylinder test described before, presents a timesaving alternative.

#### 4.1.4 Comparison of methods

Three methods were used for comprehensive foam characterization. A comparison of these methods according to their significance, determination time and ease of operation is given in Table 11.

**Table 11** Foam characterization: comparison of methods

<i>Method</i>	<i>Parameter</i>	<i>Significance</i>	<i>Determination time</i>	<i>Ease of operation</i>
<i>Cylinder method</i>	<i>Foamability</i>	+	+	+
	<i>FLS</i>	±	+	+
	<i>FVS</i>	±	+	+
<i>Texture Analyser</i>	<i>Firmness</i>	+	+	±
	<i>Cohesiveness</i>	+	+	±
<i>Turbiscan method</i>	<i>Bubble growth</i>	+	+	±
	<i>Liquid drainage</i>	±	+	±

+ good      ± acceptable      - poor

The cylinder method requires short determination time and is very easy to carry out. During the determination of foam firmness and cohesiveness by means of the Texture Analyser and transmission and backscattering signals by means of the light (back-) scattering method experimental skills are required for foam discharge into the measuring vessel. Incorporation of big air bubbles should be avoided, as it can lead to disruption of the force-time curve in the Texture Analyser method and increased transmission values in the light (back-) scattering method. Short determination times are required for these kinds of analysis. Determination of liquid drainage through transmission is not possible for foams produced from highly opaque solutions, as it leads to low transmission intensities.

#### **4.1.5 Recommendation of a comprehensive approach for foam characterization**

A comprehensive approach for foam characterization was developed. The proposed approach presents a time saving alternative to the methods proposed by Eur. Ph. 6.0. Moreover, the developed methods consider the determination of foam stability which is not included in the Eur. Ph. The methods are easy to carry out, nevertheless, certain experimental skills are required. The methods are supposed to be used in routine analysis for the formulation development stage.

The following set of tests is proposed. It is proposed to determine foamability of formulations with the cylinder method. Foam firmness and cohesiveness can be determined using the Texture Analyser method. Foam stability caused by liquid drainage can be determined through observation of transmission intensities by means of the light (back-) scattering method, if the drained solution is not opaque. In case of opaque solutions, liquid drainage can be determined through calculation of FLS from the cylinder method. Foam bubble rupture can be determined through FVS by means of the cylinder method. The increase of the foam bubble size can be determined through observation of backscattering intensities using the light (back-) scattering method. The combining of these analytical techniques for foam characterization allows for a fast and extensive screening of potential formulation candidates as well as for routine drug product quality control.

## **4.2 Formulation development**

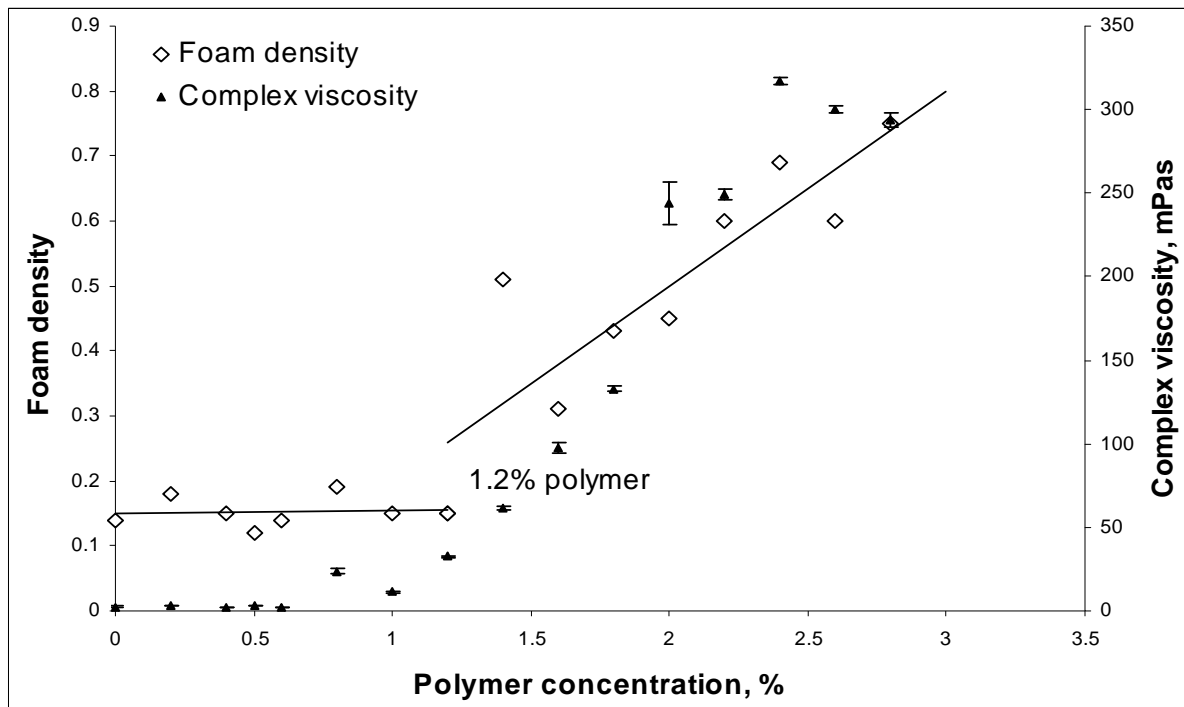
### **4.2.1 Development of a low viscous O/W emulsion**

#### **4.2.1.1 Optimum viscosity for the foam generation with the Airspray<sup>®</sup> foam dispenser**

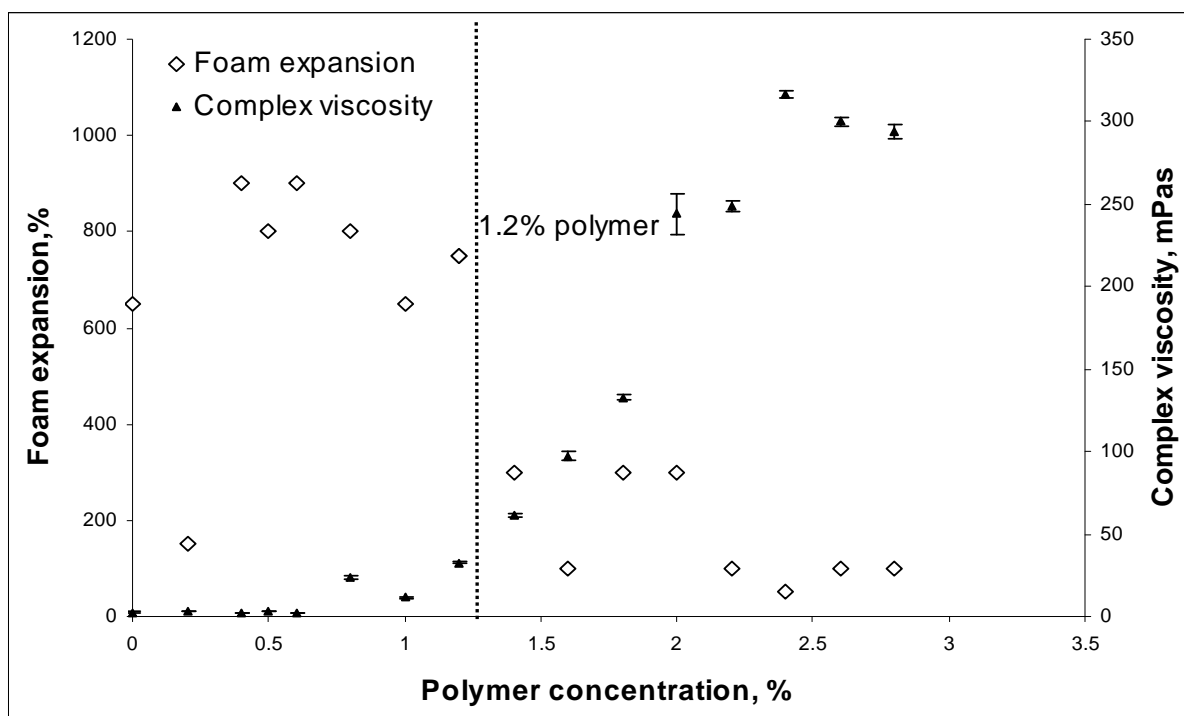
High viscous liquids can not be foamed by means of Airspray<sup>®</sup> foam dispenser because the process of mixing the formulation with air in the metering chamber is complicated due to the high viscosity. This leads either to failure of foam generation or to the generation of an inhomogeneous foam. Therefore, the optimum viscosity interval for foam generation had to be determined. Sodium lauryl sulfate (Texapon K 12) dissolved in water at a concentration of 0.5% was used as a model foaming agent for these investigations. Hydroxypropyl methyl cellulose (Metolose 60 SH 50) at concentrations from 0 to 3.0% was added to the solution of the foaming agent and used as a standard gelling agent for foam stabilization. Foam was generated using Airspray<sup>®</sup> dispenser and foam density (determination according to Ph. Eur. 6.0) and foam expansion parameters were

determined which are appropriate indicators for foamability. The complex viscosity of the solutions was measured by oscillation rheometry. A dependence between solution viscosity and foam quality was observed and the optimal viscosity interval for this kind of foam generator was determined: At HPMC concentrations of 1.0-1.2%, an increase in foam density was observed (Figure 34). Higher values for foam density indicate a low gas volume fraction in the foam and correlate with fast destabilization of the foam.

At the same HPMC concentrations a reduction of foam expansion was observed (Figure 35) which can be taken as an indicator for a worsened foamability of formulations. The optimum values for foam expansion were observed at HPMC concentrations of 0.4%-0.8%. By means of this test, an upper viscosity limit for the Airspray<sup>®</sup> dispenser was determined. It was defined to be approximately 30 mPa·s (equates to the HPMC concentration of 1.2%).



**Figure 34** Influence of polymer concentration on foam density and complex viscosity



**Figure 35 Influence of polymer concentration on foam expansion and complex viscosity**

At higher viscosity an effective passage of the formulation through the double sieve is hindered or completely impossible. In the first case, it leads to production of a foam with high foam density and, therefore, a low gas volume fraction which leads to a decreased foam stability. In the second case, no foam production takes place.

The optimum viscosity interval was, therefore, determined to be between 3 and 30 mPa·s which equates to HPMC concentrations of 0.2 to 1.2%.

#### 4.2.1.2 Foaming agents

The ability of different surfactants to foam was screened with the foamability method after Jellinek (1959). Shaking was used as a foam generation method. The results of this preliminary test are summarized in the Appendix.

All anionic surfactants involved at concentrations from 1% to 5% showed good foamability and foam stability after 15 and 30 min (scale values between 7 and 3). Nevertheless, nonionic agents were preferred as the toxicity potential of these substances is reported to be lower than that of anionic surfactants. The irritant potency *e.g.* of Tween<sup>®</sup> 20 was shown to be lower than that of sodium lauryl sulfate (Effendy and Maibach, 1996). Using Hostapon<sup>®</sup>, Medialan<sup>®</sup>, Serwet<sup>®</sup> WH 172 and Rewopol<sup>®</sup> SB CS 50K as foaming agents led to production of a very stable fine pored foam which was stable over the whole test period. However, the best foamability and foam stability was obtained with sodium lauryl sulfate. These observations supported the information that anionic surfactants are good foaming agents. Moreover, all surfactants from the anionic group are widely used for cosmetic application but are not approved for pharmaceutical application yet (with the exception of sodium lauryl sulfate). Therefore, it was decided to decrease the number of surfactants in the study to those surfactants which are approved for pharmaceutical use. Polyoxyethylene containing surfactants (Tagat<sup>®</sup> - series, Brij<sup>®</sup> - series and Tween<sup>®</sup> - series) with different length of fatty acid side chains in their structure were chosen for further investigations. Especially Tagat<sup>®</sup> L2, Brij<sup>®</sup> 35 and Tween<sup>®</sup> 20, all three containing the ester of lauric acid, showed good values for foamability (see Appendix).

The rule after Traube corroborates these findings. This experimental rule postulates that the velocity of the interfacial occupancy correlates with the length of the fatty acid side chain in the structure of a homologous series of surface active substances. The longer the fatty acid side chain, the faster the interface will be occupied with the surfactant molecules and, therefore, the faster

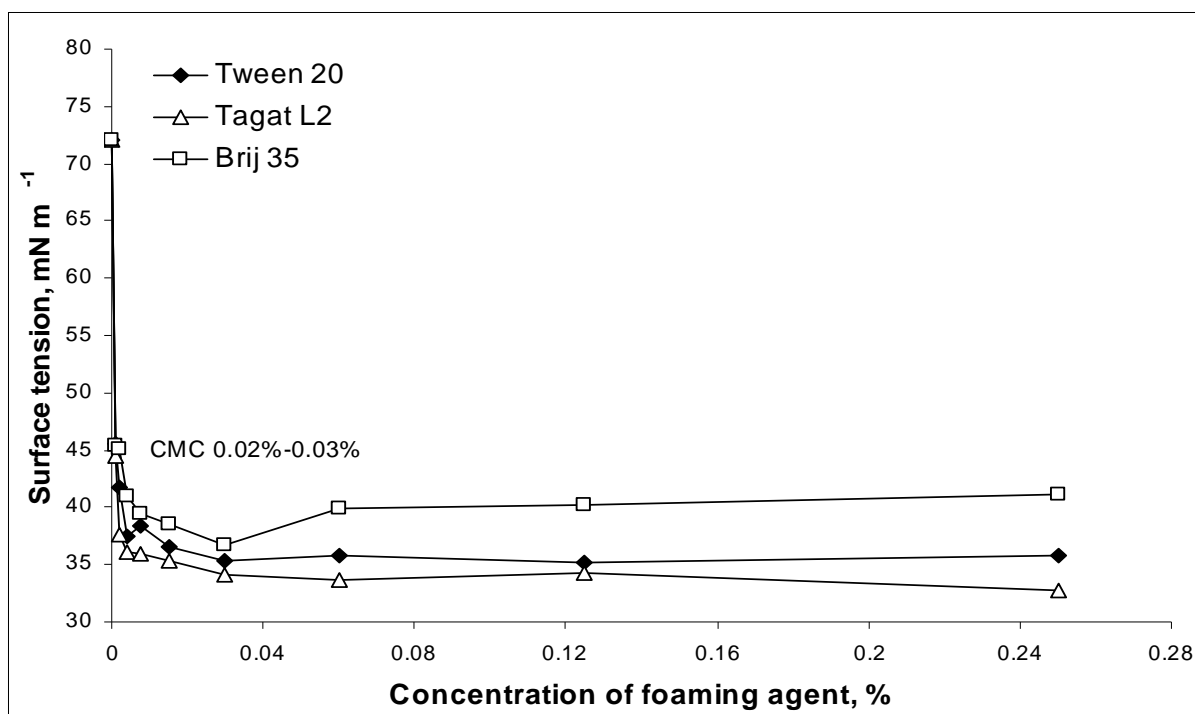
the CMC is reached in a solution, because formation of micelles is thermodynamically preferred for these molecules. In the case of shorter fatty acid side chains occupation of the interface would take place more slowly. For foam production, when a huge interface is created in a short period of time, slow occupation of newly created interfaces may be beneficial. The series of the foaming agents used in this test contained stearic acid ( $C_{18}$ ), oleic acid ( $C_{18}$ , double bond), cetyl alcohol ( $C_{16}$ ), palmitic acid ( $C_{16}$ ) and lauric acid ( $C_{12}$ ). Lauric acid contains the shortest hydrocarbon chain, leading to a lower CMC and, therefore, to better values of foamability.

A shorter fatty acid side chain leads to a slow occupation / enrichment in the interface according to the rule after Traube. However, a shorter fatty acid chain length causes more flexibility and diffusivity of the molecule. The latter characteristic is in this case considered to be dominant over the CMC because diffusivity in the interface and film flexibility are more relevant to foam stability. Tween<sup>®</sup> 20, Brij<sup>®</sup> 35 and Tagat<sup>®</sup> L2 were chosen for further formulation development.

#### **4.2.1.2.1 CMC of foaming agents**

Foaming agents should be used in concentrations above their CMC. For three surfactants which were chosen in the preliminary test for further investigations (Tween<sup>®</sup> 20, Brij<sup>®</sup> 35 and Tagat<sup>®</sup> L2), the CMC was determined by means of plotting the surface tension of surfactant solution vs. surfactant concentration ( $n=3$ ), (Figure 36).

For these foaming agents, the CMC was determined to be in the range of 0.02% to 0.03% which is in accordance to literature data.



**Figure 36** Critical micelle concentration of foaming agents (SD are too low to be seen on the plot; graphical CMC determination is not shown)

#### 4.2.1.3 Foam stabilizing agents

Concentrations of foam stabilizing agents were determined analogically to the optimum viscosity determinations for the foam generation with the Airspray<sup>®</sup> dispenser (see 4.2.1). The complex viscosity was determined with oscillation rheometry. HPMC was used at concentrations of 0.4%, 0.6%, 0.8% and 1.0%. MC was used at concentrations of 0.1%, 0.2 and 0.4%. Xanthan gum was used at a concentration of 0.05%. Also, combinations of two foam stabilizing agents such as HPMC / Xanthan (0.6% / 0.01%) and MC / Xanthan (0.2% / 0.01%) were used. It was assured with oscillation measurements that the use of the respective surfactant / polymer combination did not lead to a solution complex viscosity of more than 30 mPa·s.

The surface tension of the foam stabilizing agents was determined by means of tensiometry. The results are summarized in Table 12.



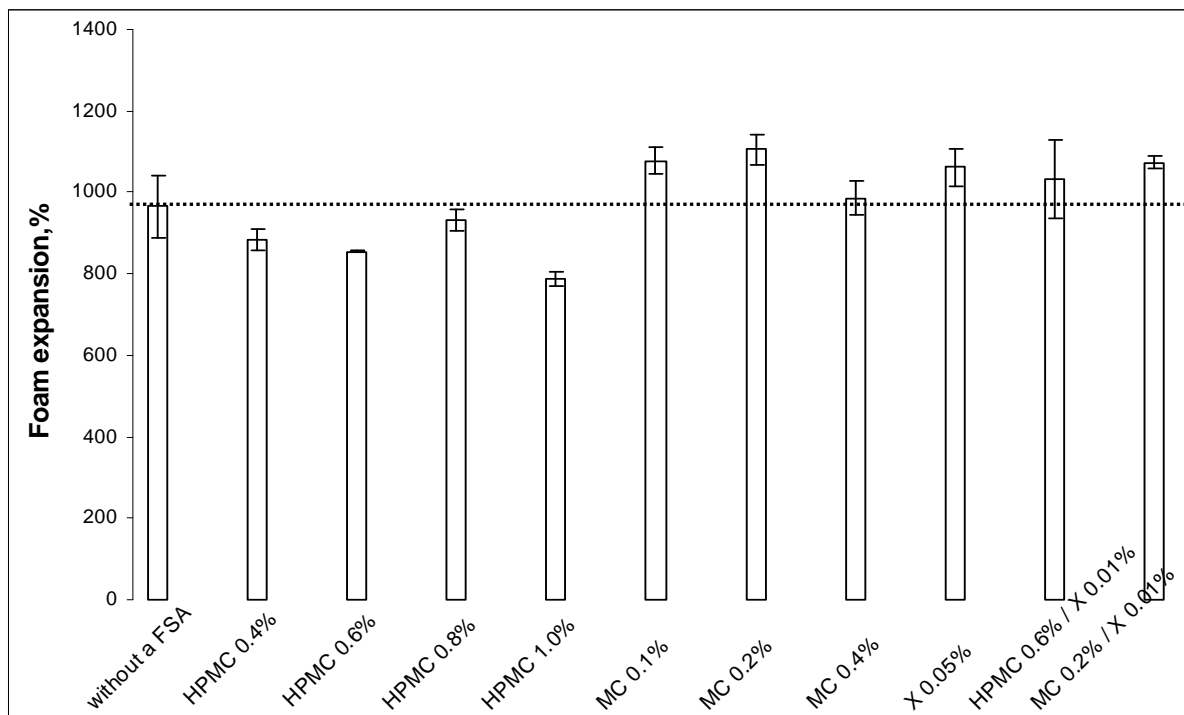
**Table 12 Surface activity of foam stabilizing agents**

<i>Polymer concentration, %</i>	<i>Surface tension, mN·m<sup>-1</sup> mean ± SD</i>
<i>HPMC 1.0%</i>	<i>46.2 ± 0.1</i>
<i>MC 0.4 %</i>	<i>45.1 ± 0.6</i>
<i>Xanthan 0.05%</i>	<i>58.3 ± 0.5</i>
<i>HPMC 0.6% / Xanthan 0.01%</i>	<i>44.6 ± 0.1</i>
<i>MC 0.2% / Xanthan 0.01%</i>	<i>44.4 ± 0.3</i>

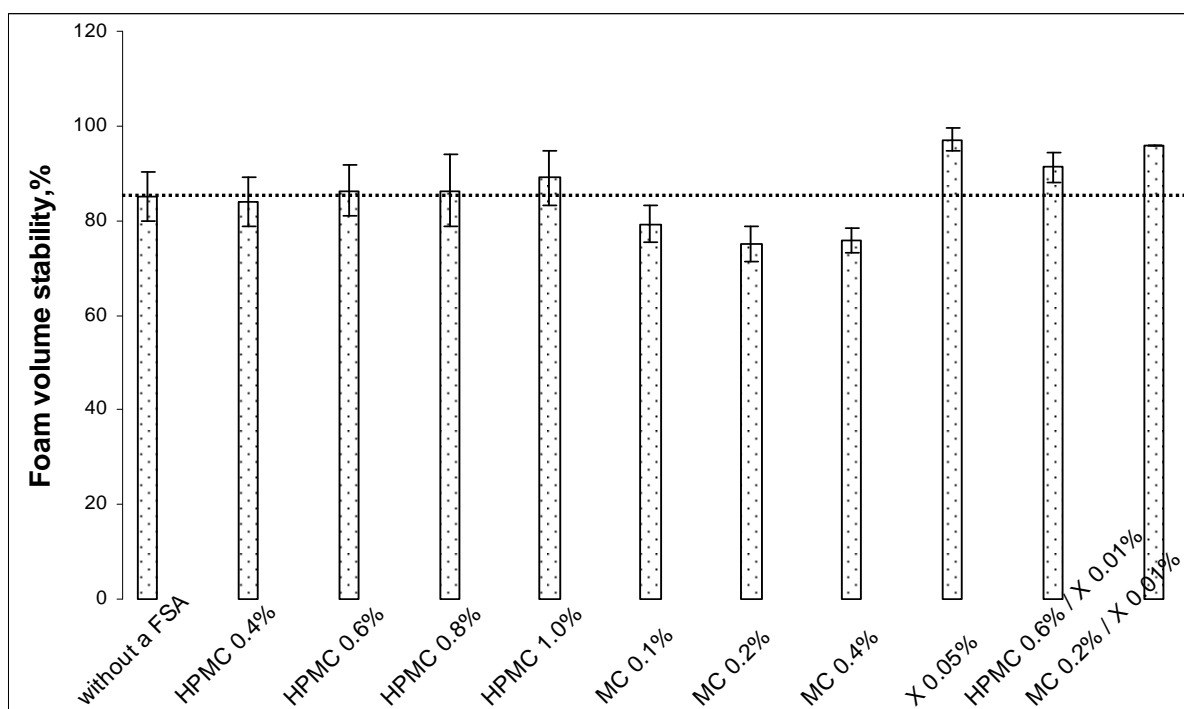
It is desired for foam stabilization that foam stabilizing agents have an affinity to occupy the interface. The chosen polymers have this affinity which can be observed through the reduction of surface tension. The highest HPMC and MC concentrations used for further stabilization studies, namely 1.0% and 0.4% respectively, as well as combinations of these polymers with xanthan gum led to a reduction of the surface tension of approximately 27 mPa·s. Xanthan gum alone also has an affinity to occupy the interface, which is, nevertheless, pronounced to a lesser degree.

#### **4.2.1.3.1 Effect of different foam stabilizing agents / combinations of foam stabilizing agents on foam quality**

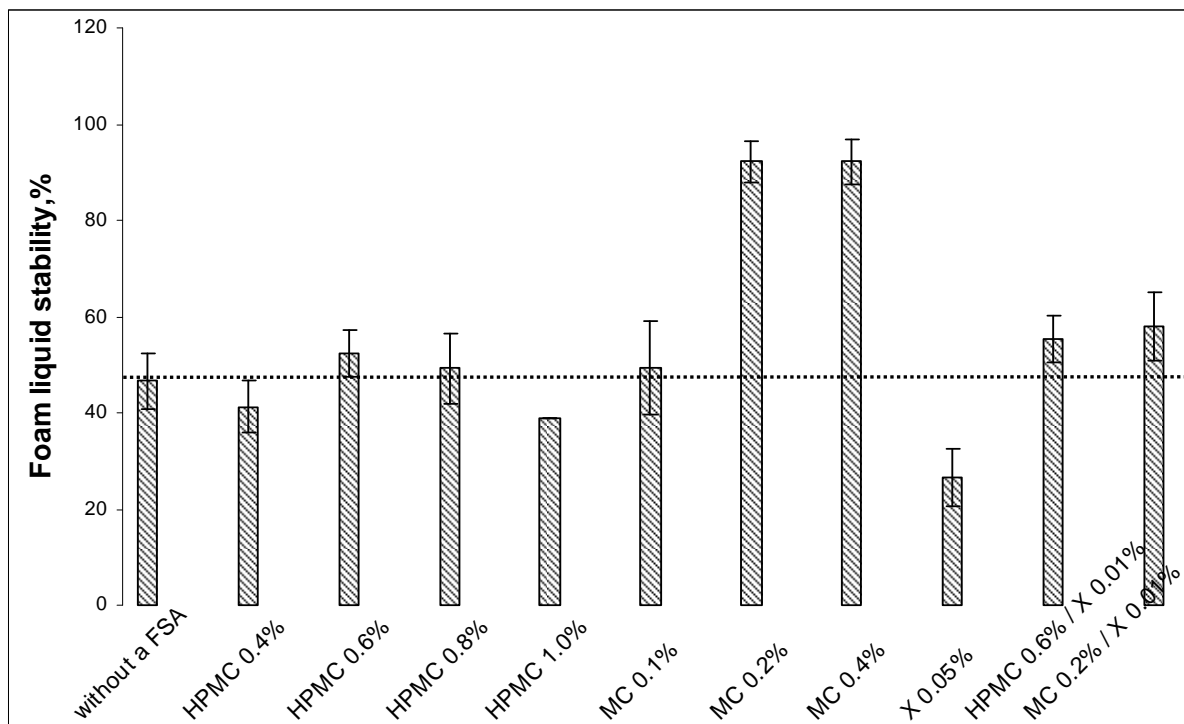
Solutions containing 3% Tween<sup>®</sup> 20 and optimized polymer concentrations (see 4.1.2) or their combinations were produced. The foams were generated by means of the Airspray<sup>®</sup> dispenser. The cylinder test was performed in triplicate. Foam density was not determined as it was supposed to be similar for all used foam stabilizing agents (FSA), as the complex viscosity of the formulations were held approximately at the same level. Results are summarized in Figure 37, 38, 39 and 40, respectively.



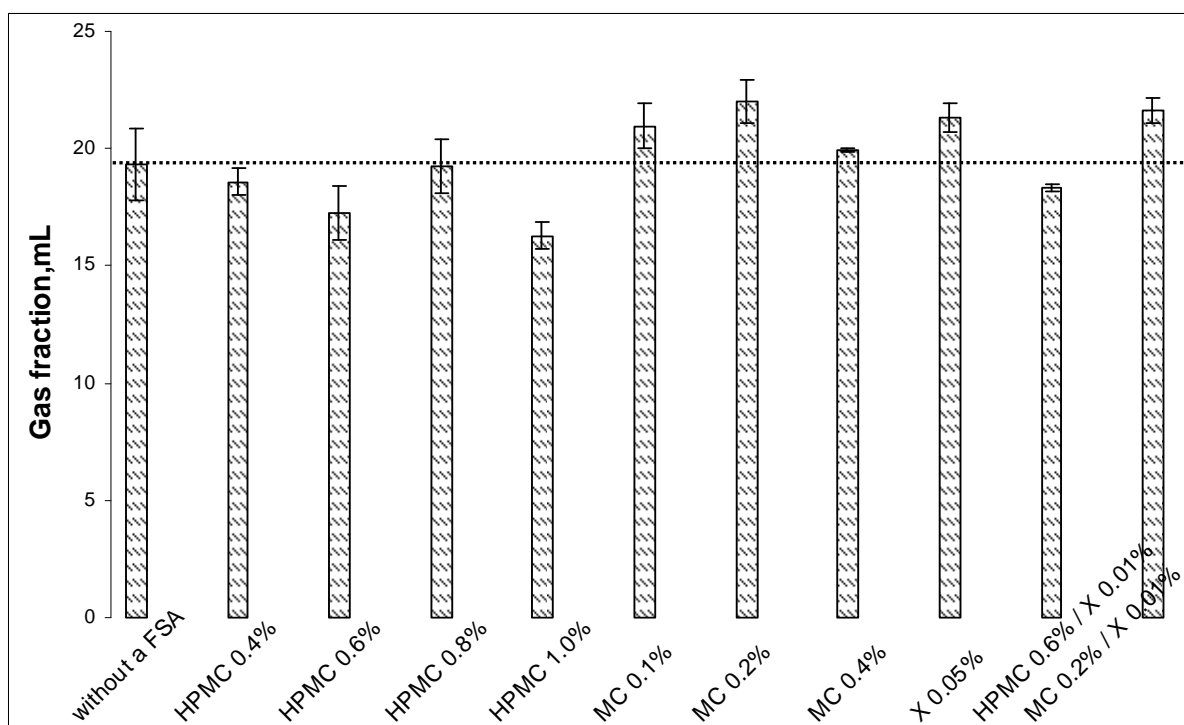
**Figure 37** Foam expansion of Tween<sup>®</sup> 20, 3% solution under the influence of different foam stabilizing agents



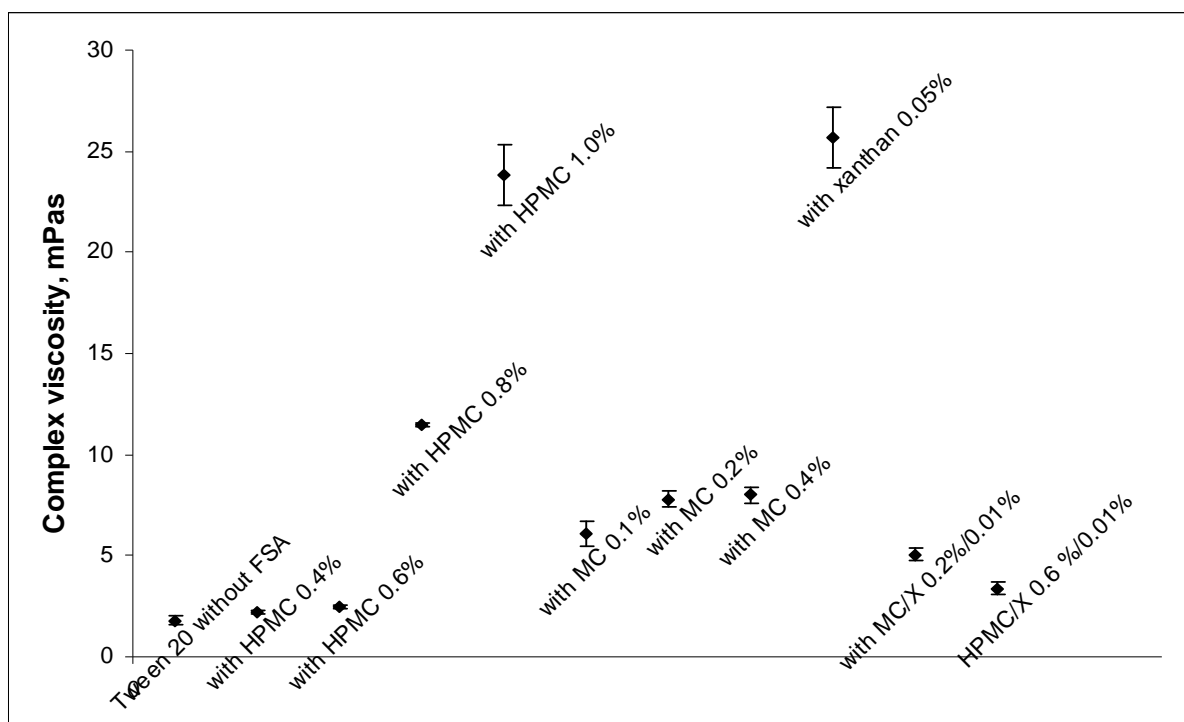
**Figure 38** Foam volume stability of Tween<sup>®</sup> 20, 3% foam under the influence of different foam stabilizing agents



**Figure 39** Foam liquid stability of Tween<sup>®</sup> 20, 3% foam under the influence of different foam stabilizing agents



**Figure 40** Gas fraction of Tween<sup>®</sup> 20, 3% foam under the influence of different foam stabilizing agents



**Figure 41** Complex viscosity depending on polymer concentration

The foam expansion of a 3% Tween<sup>®</sup> 20 solution was shown to be influenced only marginally through the addition of stabilizing agents or their combinations within the limits of optimal solution viscosity. Slightly higher values for foam expansion were observed while using MC, xanthan gum and polymer combinations as foam stabilizing agents. This data is in accordance to the surface activity of these polymers (Table 13), with exception of xanthan gum, but do not correlate to the viscosity of the solutions (Figure 41). This is an indication that foam expansion does not depend on the solutions' viscosity, as foam stability does, but is more connected to the nature of a foam stabilizing agent.

Higher values for foam volume stability should be aimed at as in this case foam destabilization mechanisms are slowed down. Slightly higher values for foam volume stability were determined while using xanthan and polymer combinations and slightly lower values while using MC as foam stabilizing agents (Figure 38).

The velocity of foam destabilization is directly dependent on the viscosity of solutions. Solutions' viscosity while using MC is in the range of 6 to 8 mPa·s which seems to be a disadvantageous range for liquid drainage. The same trend is observed for foam liquid stability. Low values for this parameter are indicators for slow liquid drainage and, therefore, good foam stability. With MC, especially in concentrations of 0.2% and 0.6%, nearly twice as high values for foam liquid stability were observed compared to the application of other polymers or without polymer application (Figure 39).

While using xanthan gum alone, slightly higher values for foam volume stability and lower values for foam liquid stability were observed than compared to the other polymers. It seems that the presence of xanthan gum in the formulation would slow down the processes of foam destabilization. The reason for better foam stability in presence of xanthan gum may be its low surface activity. HPMC and MC as surface active substances compete against molecules of foaming agent in the interface. This competition for the interfacial occupation leads to a decreased foam stability. Xanthan gum being a substance with low surface activity does not practice this kind of competition. Its presence, therefore, leads to a better foam stability.

Considering the gas fraction of produced foams no definite trends through application of foam stabilizing agents could be observed (Figure 40). All values were in the range of  $19.5 \text{ mL} \pm 1.9 \text{ mL}$ . The gas fraction parameter is desired to be high as it indicates a high gas amount incorporated into the foam and, therefore, lowers the velocity of foam destabilization mechanisms based on gravitational force such as liquid drainage.

According to the results xanthan gum 0.05% as well as combinations of HPMC 0.6% / xanthan gum 0.01% and MC 0.2% / xanthan gum 0.01% were chosen for further formulations studies.

#### 4.2.1.3.2 Effect of a foam stabilizing agent on foam characteristics produced from three different foaming agents

In this part of the study, HPMC 0.4% – 1.0% was used to investigate the influence of a stabilization agent on the foam characteristics produced from three different foaming agents: Tween<sup>®</sup> 20, Brij<sup>®</sup> 35 and Tagat<sup>®</sup> L2. Concentration of foaming agents was held at 3% (0.024 mol/L, 0.025 mol/L and 0.026 mol/L respectively). These foaming agents were chosen as they showed good results in the foaming test after Jellinek (1959), (see 4.2.1.2). Considering foamability characteristics (foam expansion) and foam stability characteristics (foam volume stability, foam liquid stability and gas fraction) of these three foaming agents without addition of HPMC, the following rank order was determined: Tween<sup>®</sup> 20 performed slightly better than Tagat<sup>®</sup> L2 and Brij<sup>®</sup> 35. The same trend can be observed for these foaming agents considering foamability characteristics under addition of HPMC, whereas differences between Brij<sup>®</sup> 35 and Tagat<sup>®</sup> L2 by the addition of 0.8% and 1.0% HPMC cannot any more be observed (Figure 42). The same ranking of the foaming agents was observed considering the plot of gas fraction in produced foams (Figure 43).

Since gas incorporation into the foam structure happens during the process of foam generation, this trend was expected.

Better values for Tween<sup>®</sup> 20 and Tagat<sup>®</sup> L2 could be explained based on the chemical structure of these foaming agents as these foaming agents were used in the same molar concentration. Moreover, they have similar molecular weight (Tween<sup>®</sup> 20 1276 g·mol<sup>-1</sup>, Brij<sup>®</sup> 35 1198 g·mol<sup>-1</sup> and Tagat<sup>®</sup> L2 1154 g·mol<sup>-1</sup>), similar HLB values and are used in concentrations above CMC.

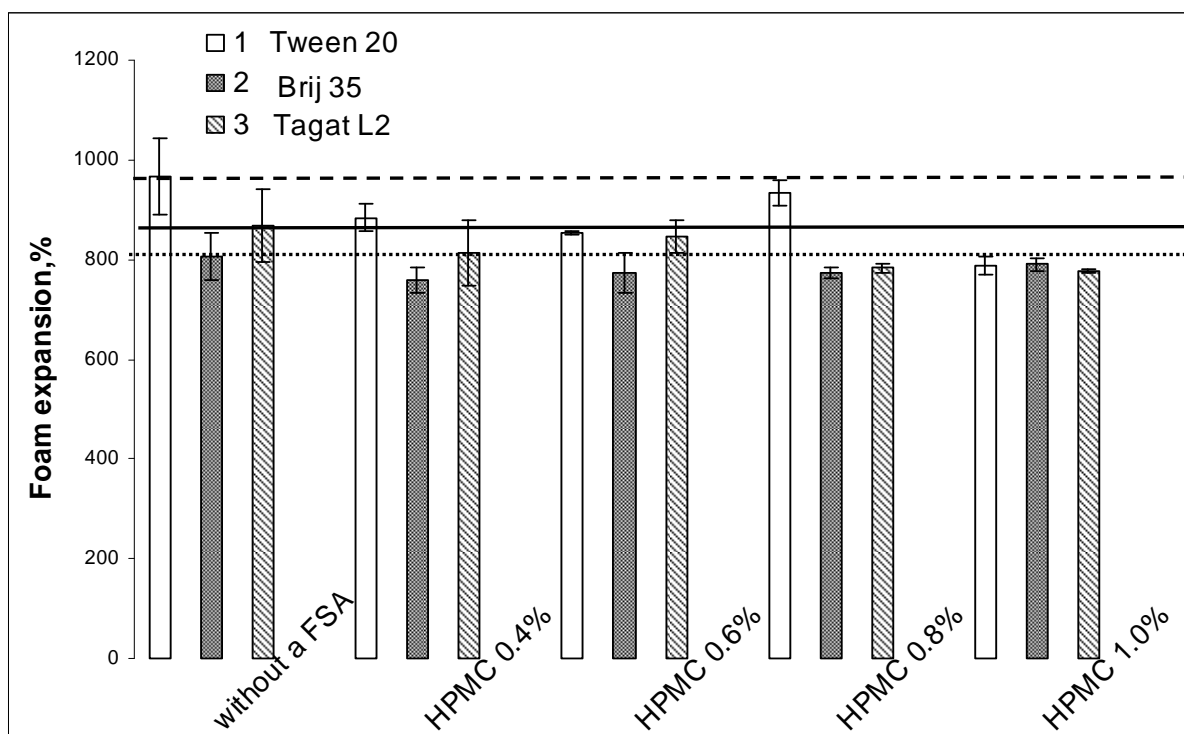
Different chemical structures of these foaming agents, such as longer polyethylene oxide chain within the structure of Brij<sup>®</sup> 35 structure or presence of hydrophilic units such as sorbitane and glycerol in the structure of Tagat<sup>®</sup> L2

and Tween<sup>®</sup> 20, can lead to different velocities of the interfacial occupation during the process of interface generation during foam production.

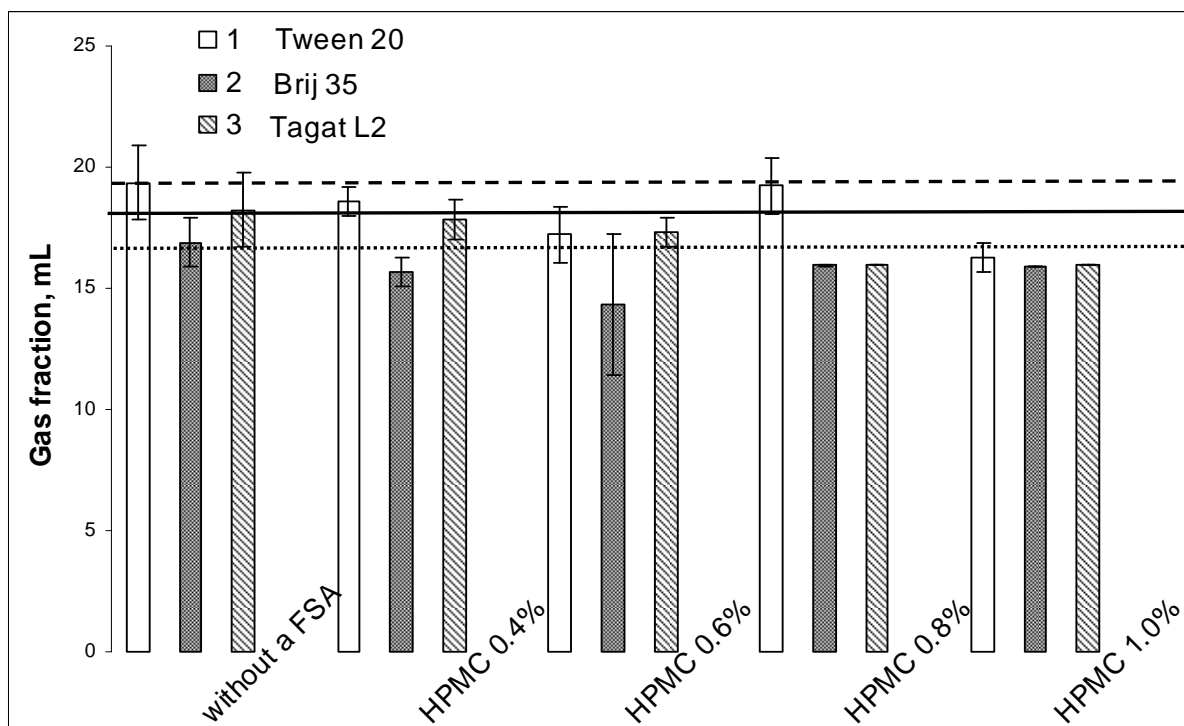
The parameter of foam volume stability describes a process of air bubble coalescence and, therefore, reduction of height of the foam column. This process seems to be independent from the viscosity of a formulation, as nearly no differences or no trend were observed considering the parameter of foam volume stability (Figure 44).

Foam liquid stability, on the other hand, is directly dependent on the viscosity. Liquid separation from foam structure (liquid drainage) processes slower at higher viscosities of foamable solutions.

Through addition of HPMC, viscosity of colloidal solutions increases. The increase of viscosity leads to a slowdown of liquid drainage which results in a decrease of the foam liquid stability. This can clearly be followed by addition of HPMC to Brij<sup>®</sup> 35 and Tween<sup>®</sup> 20 solutions (Figure 45).

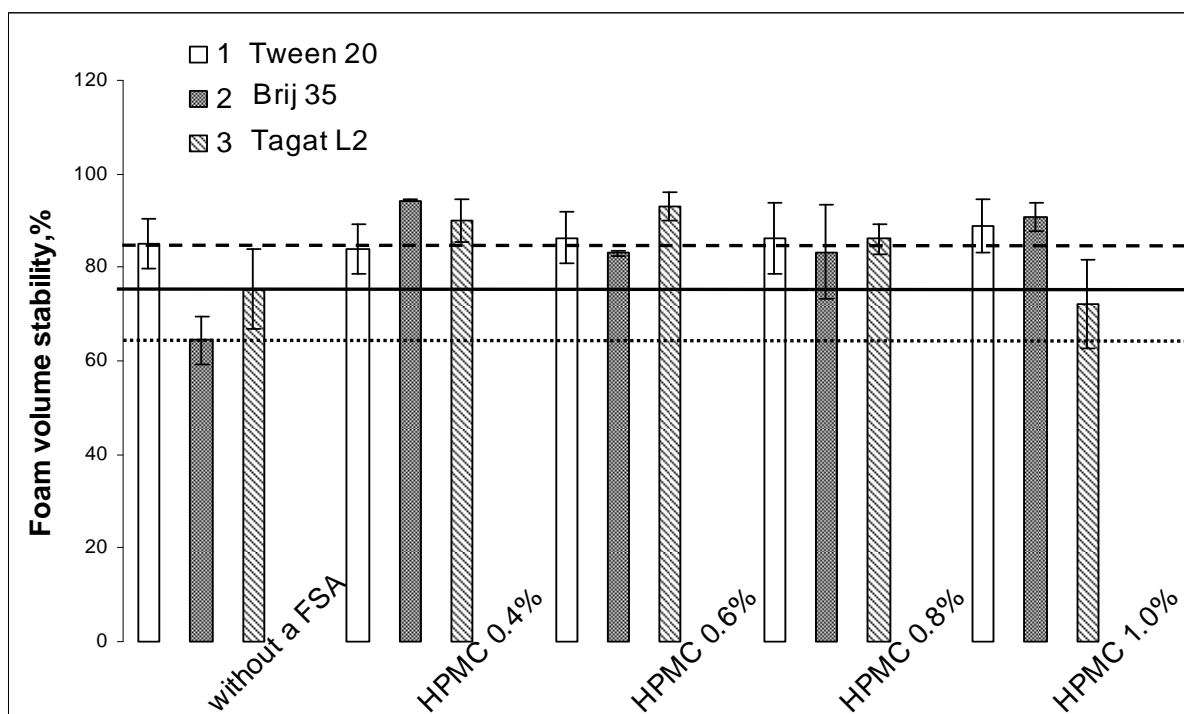


**Figure 42** Foam expansion of 3% solution of three different foaming agents under the influence of HPMC

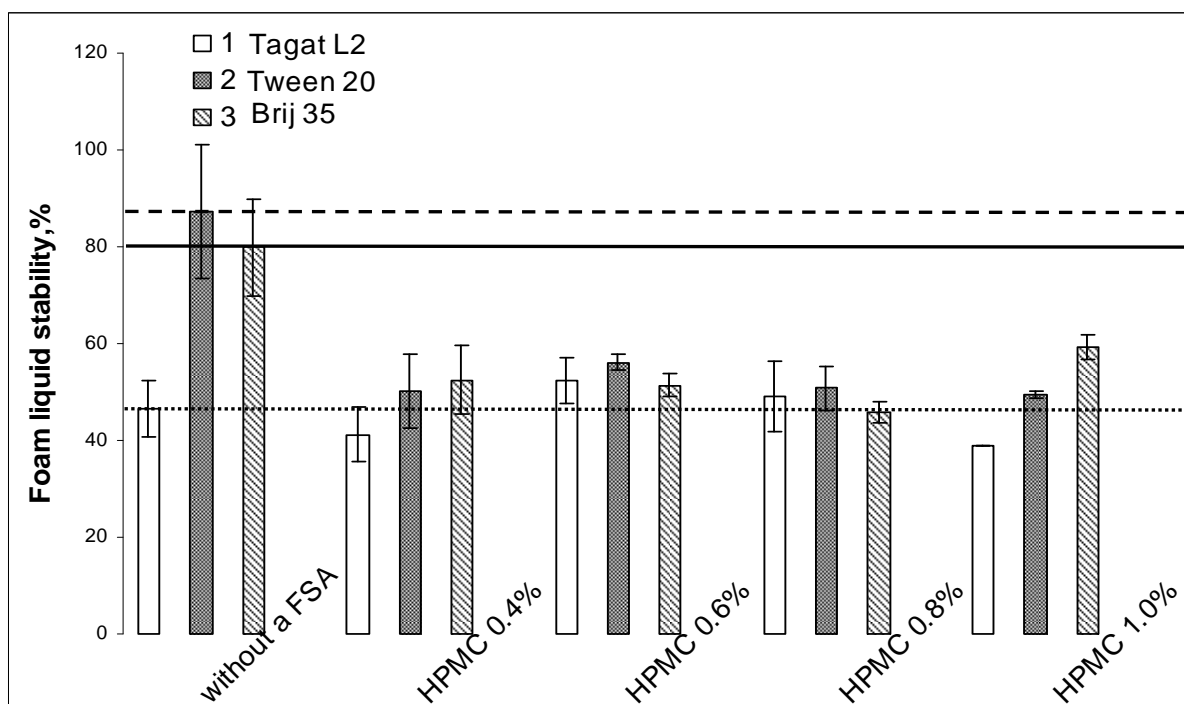


**Figure 43** Gas fraction of three different foaming agents, 3%, under the influence of HPMC





**Figure 44** Foam volume stability of three different foaming agents, 3%, under the influence of HPMC



**Figure 45** Foam liquid stability of three different foaming agents, 3%, under the influence of HPMC

#### 4.2.1.4 Oil phase

Viscosity and polarity of the oil phase in emulsions have an influence on the emulsion stability. Liquid oils from different chemical groups and different origin were used for formulation development and classified according to their viscosity and polarity. The viscosity of the emulsion should not exceed the upper limit of 30 mPa·s.

##### 4.2.1.4.1 Viscosity of the oil phase

Viscosity values of oil components are summarized in Figure 46. Abil<sup>®</sup> 100, olive oil and soybean oil showed the highest viscosity values whereas viscosity values of isopropyl palmitate, isopropyl myristate and cyclomethicone were comparatively low.

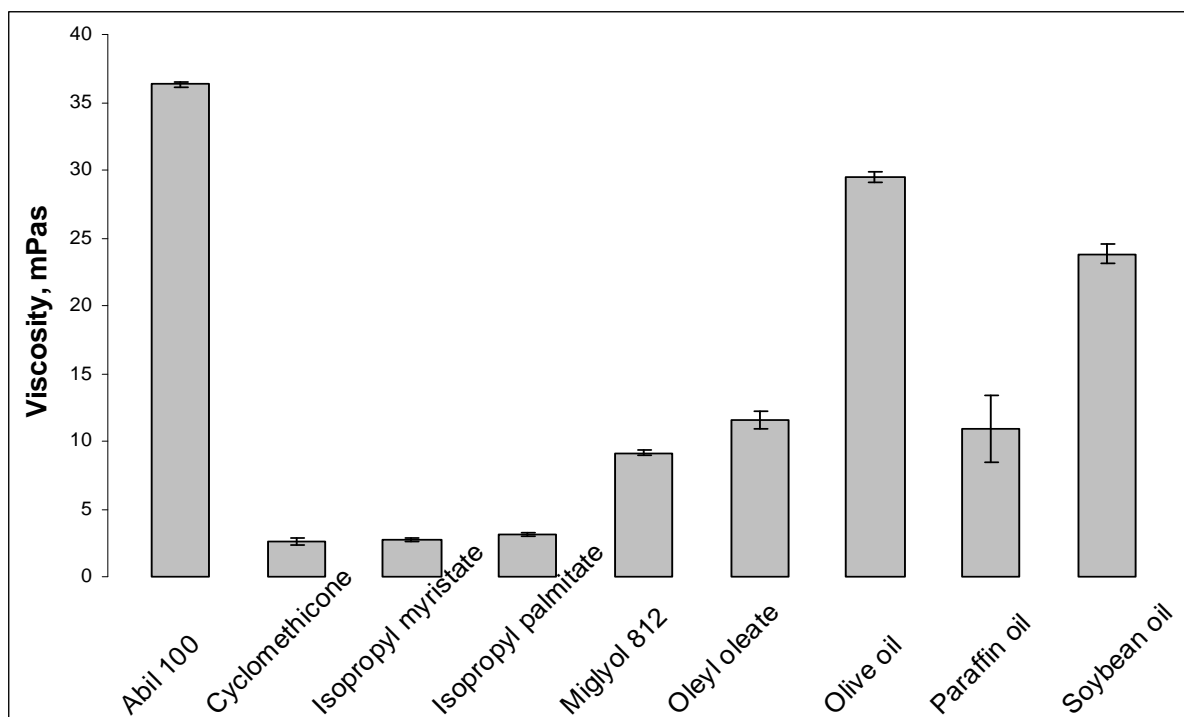
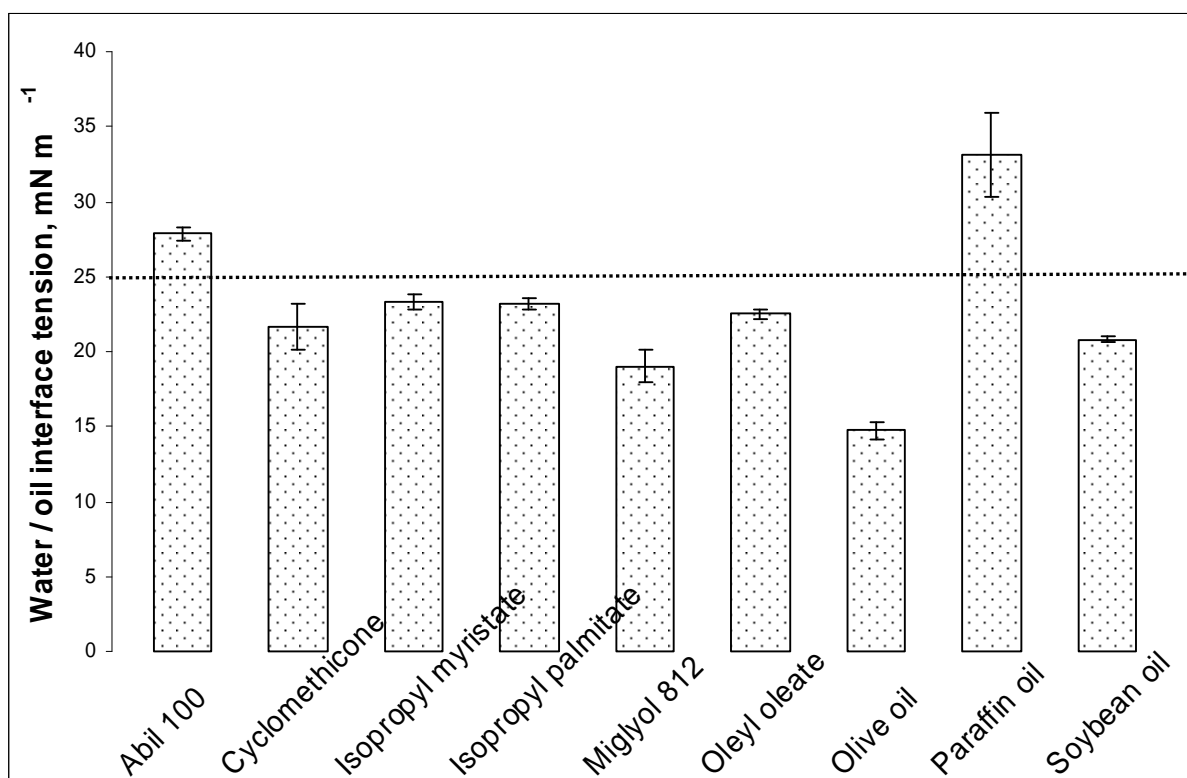


Figure 46 Viscosity of oil components



**Figure 47** Interfacial tension between oil components and water

#### 4.2.1.4.2 Polarity of the oil phase

The polarity values reported as the interfacial tension between water and the respective oil are summarized in Figure 47. High values for the interfacial tension between water phase and oil phase point to the low polarity of the respective oil. The oils were classified as polar when the interfacial tension values were lower than  $25 \text{ mN}\cdot\text{m}^{-1}$  (see 3.2.1.4). Interfacial tension between water and such oils as paraffin oil and Abil<sup>®</sup> 100 were the highest. This indicates a low polarity of these oils. Contrary, olive oil and Miglyol<sup>®</sup> 812 showed comparatively high polarity.

The following oil components were used for further formulation development (Table 13). This choice was based on the combination of polarity and viscosity values to evaluate the influence of different oil properties on emulsion stability.

**Table 13 Oil components for further formulation development**

<i>Parameter</i>		<i>Oil component</i>
<i>Polarity</i>	<i>Viscosity</i>	
<i>Nonpolar</i>	<i>High viscosity</i>	<i>Abil<sup>®</sup> 100</i>
<i>Nonpolar</i>	<i>Low viscosity</i>	<i>Paraffin oil</i>
<i>Polar</i>	<i>High viscosity</i>	<i>Olive oil</i>
<i>Polar</i>	<i>Low viscosity</i>	<i>Miglyol<sup>®</sup> 812</i>
<i>Polar</i>	<i>Low viscosity</i>	<i>Cyclomethicone</i>

**4.2.1.4.3 O/W emulsions and their characteristics**

The basic composition for a foamable o/w emulsion is presented in Table 14. The choice of foaming agents and foam stabilizing agent was based on preliminary tests as described earlier (see 4.2.1.2 and 4.2.1.3).

**Table 14 Basic composition for a foamable o/w emulsion**

<i>Phase</i>	<i>Component</i>	<i>Amount</i>
<i>Oil phase</i>	<i>e.g. Miglyol<sup>®</sup> 812</i>	<i>0.1% - 1.0 %</i>
<i>Foaming agent</i> <i>Foaming agent blend (1:1)</i> <i>(emulsifier)</i> <i>(solubilization agent)</i>	<i>e.g. Tween<sup>®</sup> 20</i>	<i>5.0% - 10.0 %</i>
<i>Co-emulsifier</i>	<i>e.g. Span<sup>®</sup> 20</i>	<i>1.0% - 4.5%</i>
<i>Emulsion stabilization agent</i>	<i>e.g. Pemulen<sup>®</sup> solution 0.1%</i>	<i>1.0%</i>
<i>Foam stabilization agent</i>	<i>e.g. HPMC</i>	<i>0.4% - 1.0%</i>
<i>Preservative agent</i>	<i>Sodium benzoate</i>	<i>0.1%</i>
<i>Topical corticosteroid</i>	<i>BMV</i>	<i>0.025% - 0.1%</i>
<i>Phosphate buffer pH 4.5</i>		<i>q. s. ad 100%</i>

Formulation development was proceeded with the foaming agents containing lauric acid chain rests in their structure, namely Tween<sup>®</sup> 20, Brij<sup>®</sup> 35 and Tagat<sup>®</sup> L2 or combinations thereof. HPMC (0.4%-1.0%), MC (0.1%-0.4%), xanthan gum in concentrations up to 0.05% and combinations of two stabilizing agents were used for foam stabilization. All combinations were produced and evaluated due to their optical appearance. The stability of the produced emulsions was examined with the centrifuge test and a high temperature-low temperature cycle test. The appearance of the emulsions after stability tests was evaluated by means of the scheme after Quack *et al.* (1975). Emulsions evaluated with note 8 were assessed as stable (see 3.2.2.2.). It was possible to produce stable low viscous emulsions with the following components and their fractions (Table 15).

**Table 15**                      **Compositions of stable low viscous o/w emulsions**

<i>Phase</i>	<i>Component</i>	<i>Amount</i>
<i>Oil phase</i>	<i>Miglyol<sup>®</sup> 812</i>	<i>0.1% - 1.0 %</i>
<i>Foaming agent</i>	<i>Tween<sup>®</sup> 20</i>	<i>7.0%</i>
<i>Foaming agent blend (1:1)</i> <i>(emulsifier)</i> <i>(solubilization agent)</i>	<i>Brij<sup>®</sup> 35</i> <i>Tagat<sup>®</sup> L2</i> <i>Tween<sup>®</sup> 20 : Brij<sup>®</sup> 35</i>	
<i>Foam stabilization agent</i>	<i>HPMC</i> <i>MC</i> <i>HPMC / Xanthan gum</i> <i>MC / Xanthan gum</i> <i>Xanthan gum</i>	<i>1.0%</i> <i>0.4%</i> <i>0.6% / 0.01%</i> <i>0.2% / 0.01%</i> <i>0.03% - 0.05%</i>
<i>Preservative agent</i>	<i>Sodium benzoate</i>	<i>0.1%</i>
<i>Topical corticosteroid</i>	<i>BMV</i>	<i>0.025% - 0.1%</i>
<i>Phosphate buffer pH 4.5</i>		<i>q. s. ad 100%</i>

Surfactants or their blends were used in the formulation for following purposes:

- as solubilization agent for BMV
- as emulsifier
- as foaming agent.

Relatively high amounts of surfactant were essential to solubilize BMV (preliminary test, data not shown). At the same time, it was possible to incorporate up to 1% of a low viscous polar oil (Miglyol<sup>®</sup> 812) into the formulation. The concentration of foam stabilizing agents could not be further increased because of the upper viscosity limit of the Airspray<sup>®</sup> dispenser. Addition of w/o emulsifiers such as Span<sup>®</sup> 20, Span<sup>®</sup> 60, Span<sup>®</sup> 80 and Brij<sup>®</sup> 72 at a low concentration did not result in stable formulations. Addition of these co-emulsifiers in concentrations up to 4.5% led to an increase of formulation

viscosity so that it was not possible to produce a foam. The use of emulsion stabilizing agents such as Pemulen<sup>®</sup> or Carbopol<sup>®</sup> (solutions 0.1%) also led to a viscosity increase.

The droplet size distribution of the oil phase of produced emulsions was in the range of  $134.3 \pm 1.5$  to  $320.5 \pm 5.6$  nm (nanoemulsions) which is typical for emulsions produced with the ultra-turrax method (Urban *et al.*, 2006). Moreover, a bimodal particle size distribution was observed. Particles with a size in the range of  $6.9 \pm 0.3$  nm were attributed to the size of the micelles of surface active substances. This is in accordance to the literature data (Kumbhakar *et al.*, 2004; Chumakov *et al.*, 2006).

#### 4.2.1.4.4 Influence of the oil component on foam quality

Foamability, foam stability characteristics and firmness of foams produced from stable emulsions were evaluated (Table 16). Formulations of the same polymer-surfactant composition but without an oil fraction were also produced to investigate the influence of the oil component on foam quality. BMV was also excluded from the composition.

**Table 16** Foam quality produced from o/w emulsions and formulations without oil phase

<b><i>Characteristics, mean <math>\pm</math> SD</i></b>	<b><i>O/W emulsion</i></b>	<b><i>Without oil fraction</i></b>
<i>FE, [%]</i>	<i>1095.5 <math>\pm</math> 111.1</i>	<i>1077.9 <math>\pm</math> 43.4</i>
<i>FVS, [%]</i>	<i>43.3 <math>\pm</math> 5.8</i>	<i>94.4 <math>\pm</math> 2.4</i>
<i>FLS, [%]</i>	<i>87.6 <math>\pm</math> 5.2</i>	<i>43.1 <math>\pm</math> 4.5</i>
<i>GF, mL</i>	<i>19.5 <math>\pm</math> 0.6</i>	<i>20.3 <math>\pm</math> 0.6</i>
<i>Foam firmness, [g]</i>	<i>25.3 <math>\pm</math> 2.5</i>	<i>24.8 <math>\pm</math> 1.8</i>
<i>Liquid drainage, [mm·min<sup>-1</sup>]</i>	<i>-2.63 <math>\pm</math> 0.25</i>	<i>-1.82 <math>\pm</math> 0.23</i>
<i>Bubble growth, [%·min<sup>-1</sup>]</i>	<i>0.92 <math>\pm</math> 0.04</i>	<i>0.59 <math>\pm</math> 0.02</i>

Foamability of formulations as well as foam firmness was not influenced through addition of an oil phase. Nevertheless, an almost 50% decrease of foam stability (liquid drainage from FLS and height of foam column from FVS, cylinder test) was observed.

The light (back-) scattering method showed similar results. The liquid drainage rate of the emulsion was higher compared to the oil free formulation. The bubble growth rate of the emulsion also had higher values than the bubble growth rate of the oil free formulation.

The reduced stability of foams produced from emulsions can be explained through the presence of the oil phase. Oil droplets orientate themselves at the foam lamellae which leads to an increase of surface pressure and reduction of film elasticity. This ends up in the reduction of foam stability (Roberts *et al.*, 1975).

#### 4.2.1.4.5 Influence of foaming agent combinations on foam quality

The influence of foaming agent combinations on foam quality was investigated using the example of an o/w composition with 10% foaming agent fraction.

The results are summarized in Table 17.

**Table 17** Foam quality produced from o/w emulsions with single and combined foaming agent fraction

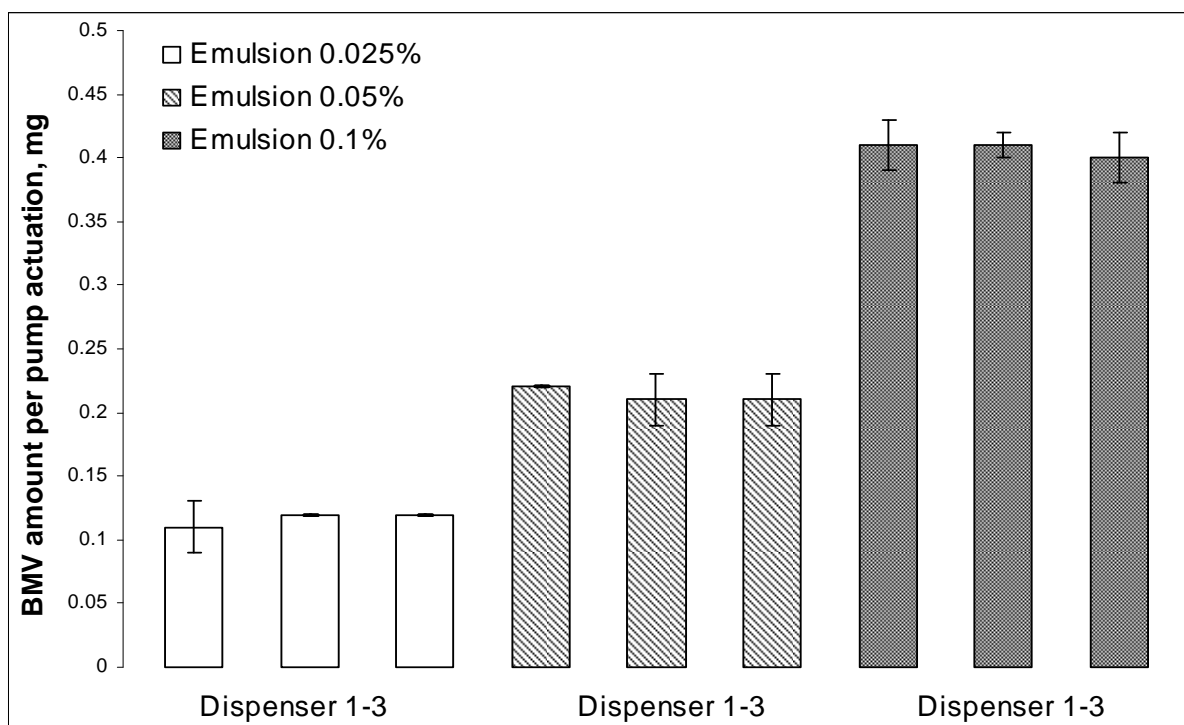
<b>Characteristics, mean <math>\pm</math> SD</b>	<b><i>Tween</i><sup>®</sup> 20 10%</b>	<b><i>Tween</i><sup>®</sup> 20 : <i>Brij</i><sup>®</sup> 35 (1:1) 10%</b>	<b><i>Tagat</i><sup>®</sup> L2: <i>Brij</i><sup>®</sup> 35 (1:1) 10%</b>
<i>FE</i> , [%]	1095.5 $\pm$ 99.1	986.3 $\pm$ 4.7	991.3 $\pm$ 22.6
<i>FVS</i> , [%]	43.3 $\pm$ 5.8	62.1 $\pm$ 2.1	43.4 $\pm$ 0.6
<i>FLS</i> , [%]	87.6 $\pm$ 5.2	74.4 $\pm$ 3.5	81.5 $\pm$ 7.1
<i>GF</i> , mL	19.5 $\pm$ 0.6	19.1 $\pm$ 0.5	19.6 $\pm$ 0.6
<i>Foam firmness</i> , [g]	25.3 $\pm$ 2.5	24.3 $\pm$ 2.1	25.6 $\pm$ 2.3
<i>Liquid drainage</i> , [mm·min <sup>-1</sup> ]	-2.63 $\pm$ 0.25	-2.21 $\pm$ 0.20	-2.58 $\pm$ 1.89
<i>Bubble growth</i> , [%·min <sup>-1</sup> ]	0.92 $\pm$ 0.04	0.75 $\pm$ 0.05	0.89 $\pm$ 0.04



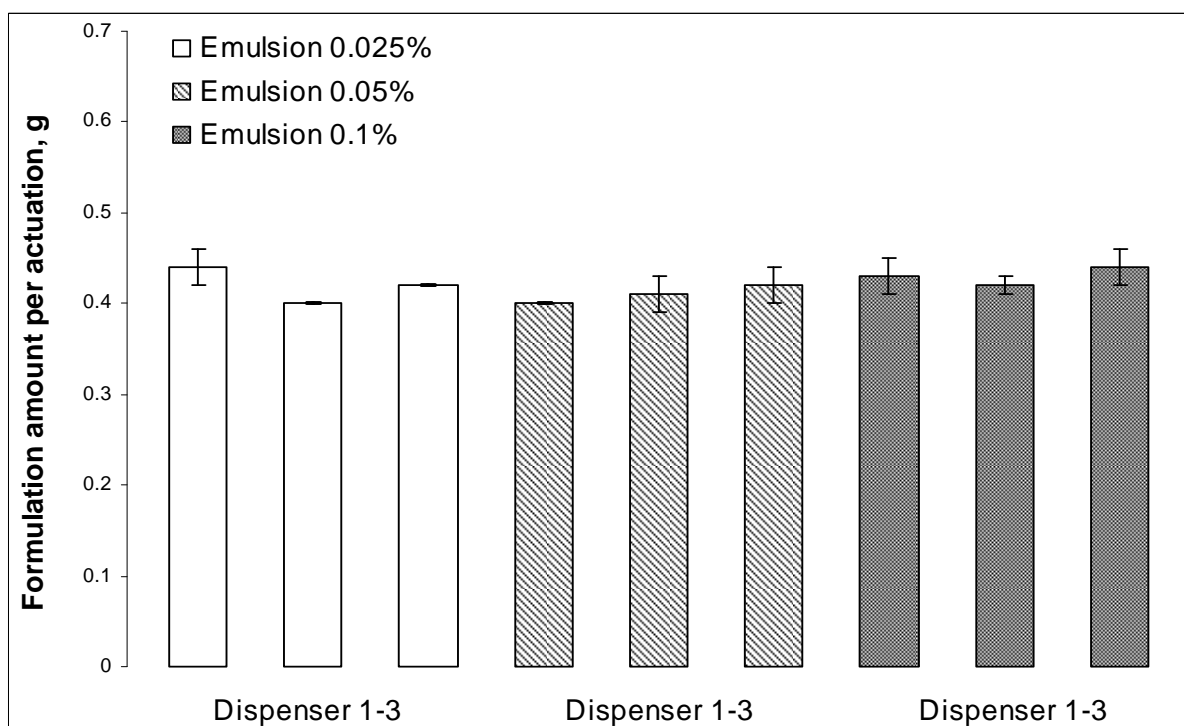
The use of a Tween<sup>®</sup> 20 : Brij<sup>®</sup> 35 (1:1) combination in the composition of the foamable o/w emulsion led to an increase of FVS and a decrease of FLS and, therefore, to a better foam stability. This phenomenon is also described by Jellinek (1959). Other parameters were not changed through a combined foaming agent application.

#### **4.2.1.5 "Dose uniformity" of the Airspray<sup>®</sup> foam dispenser**

The Airspray<sup>®</sup> foam dispenser was tested considering its ability to deliver uniform doses of the corticosteroid. Three different concentrations of BMV were used for this test (0.025%, 0.05% and 0.1%). Each concentration was tested with three dispensers. Three actuations of dispenser pump dosing system were performed with each dispenser. The results are presented in Figure 48 and 49. It was possible to deliver a uniform amount of BMV using the Airspray<sup>®</sup> foam dispenser.



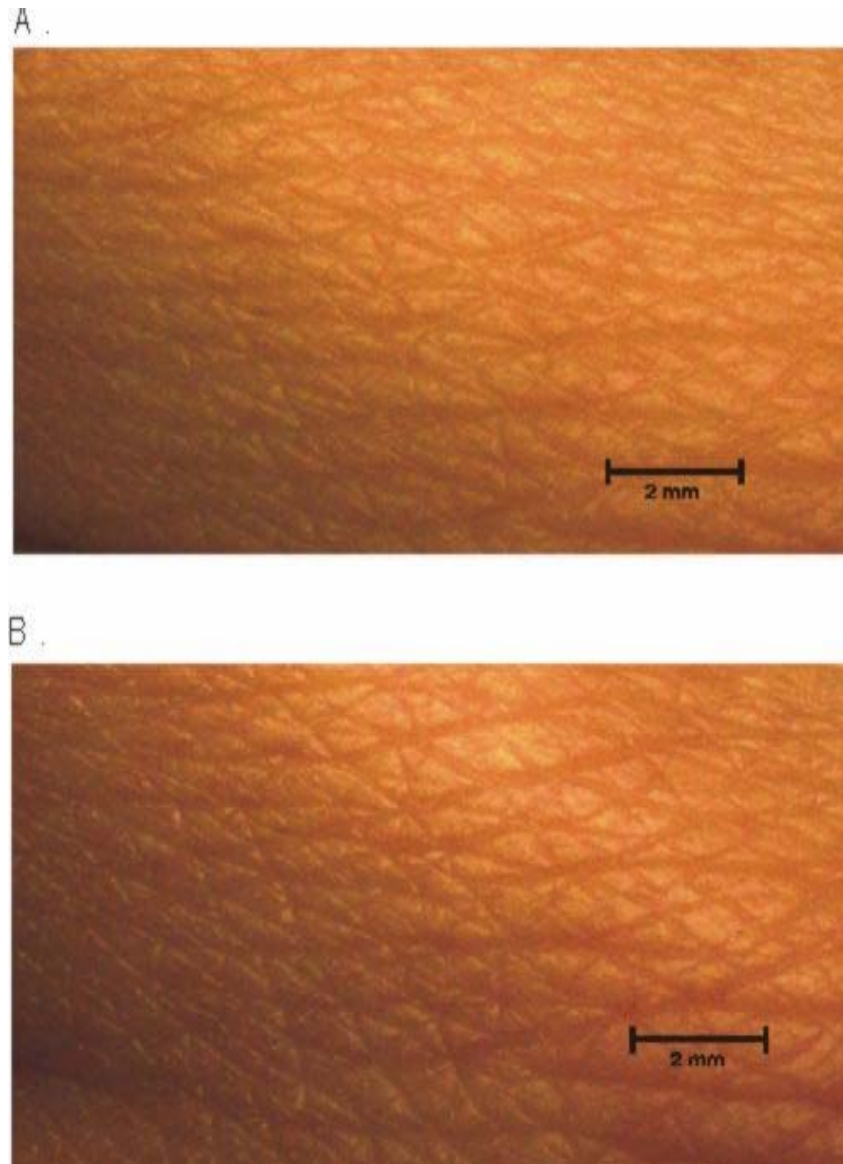
**Figure 48** Amount of BMV per pump actuation



**Figure 49** Formulation amount per pump actuation

#### **4.2.1.6 Microscopic evaluation of skin status after application of a foam vehicle**

To identify possible residues of the foam vehicle after application on the skin surface, microscopic imaging was performed. The foam vehicles are expected to leave little residue on the skin surface after application as fluid foam components evaporate. Residues may consist of oil components and surfactants. For this test a composition with the highest oil and surfactant fraction was chosen. A foam vehicle was applied onto a cleaned dry surface of the hand. The vehicle was distributed on the surface and the skin was dried at room temperature for approximately 1 min at ambient humidity. The skin area where the formulation was distributed was visually compared to untreated area. No differences between these two areas were detected (Figure 50).



**Figure 50** Microscopic assessment of skin surface:  
**A.** Before application of foam vehicle  
**B.** After application of foam vehicle

## 4.2.2 Solution based foams

### 4.2.2.1 Formulation development steps

The solubility of BMV in different solvents (see 3.1.4) was determined as described in 3.2.1.5. As BMV was dissolved, it was possible to reduce the foaming agent fraction. Combined surfactant use was also abdicated. Foamable formulations of the following compositions were produced (Table 18). All combinations were tested. These formulations passed through temperature and centrifuge stress stability tests.

**Table 18** Compositions for foamable solutions of BMV

<i>Phase</i>	<i>Component</i>	<i>Amount</i>
<i>Solvent</i>	<i>Propylene glycol</i>	$\geq 11.3\%$
	<i>Hexylene glycol</i>	$\geq 5.6\%$
	<i>Pharmasolve<sup>®</sup></i>	$\geq 0.8\%$
	<i>Arlasolve<sup>®</sup></i>	$\geq 1.9\%$
<i>Foaming agent</i>	<i>Tween<sup>®</sup> 20</i>	3.0%
<i>Foam stabilization agent</i>	<i>HPMC</i>	1.0%
	<i>MC</i>	0.4%
	<i>HPMC / Xanthan gum</i>	0.6% / 0.01%
	<i>MC / Xanthan gum</i>	0.2% / 0.01%
	<i>Xanthan gum</i>	0.03% - 0.05%
<i>Preservative agent</i>	<i>Sodium benzoate</i>	0.1%
<i>Topical corticosteroid</i>	<i>BMV</i>	0.1%
<i>Phosphate buffer pH 4.5</i>		<i>q. s. ad 100%</i>

#### 4.2.2.2 Evaluation of formulation stability

Foam stability was determined by means of the light (back-) scattering method. Formulations containing HPMC at a concentration of 1.0% and xanthan gum at a concentration of 0.05% as foam stabilizing agents and different solvents for BMV in minimal possible concentrations to dissolve BMV (see Table 18) were compared to each other. The results are summarized in Figure 51, 52, 53 and 54, respectively.

Considering the rate of foam bubble growth and the rate of liquid drainage, no effect of different solvents on foam stability was observed, whereas the solvents were used in different concentrations. In contrast, different foaming agents were shown to have an effect on these parameters. The foams with xanthan gum as foam stabilizing agent showed a growth of air bubbles which was pronounced to a lesser degree than by the foams produced with HPMC as foam stabilizing agent. The liquid drainage rate was also determined to be lower for the foams with xanthan gum. This phenomenon was already discussed in 4.2.1.3.1.

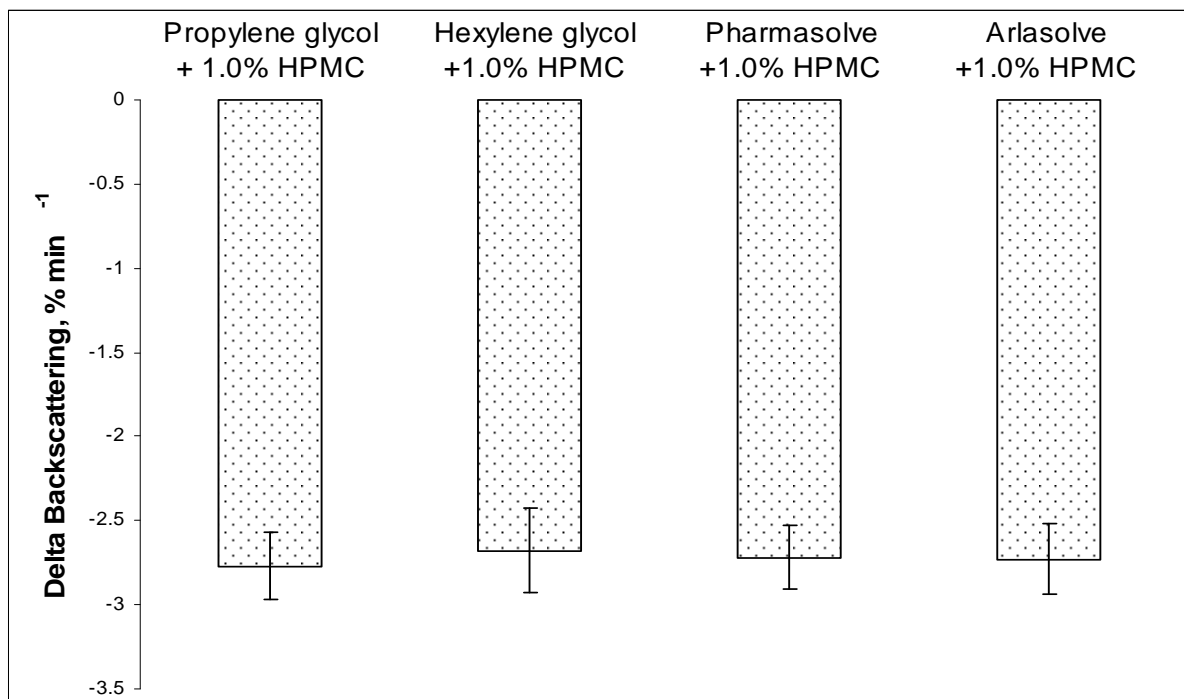


Figure 51 Foam bubble stability (foams with 1.0% HPMC)

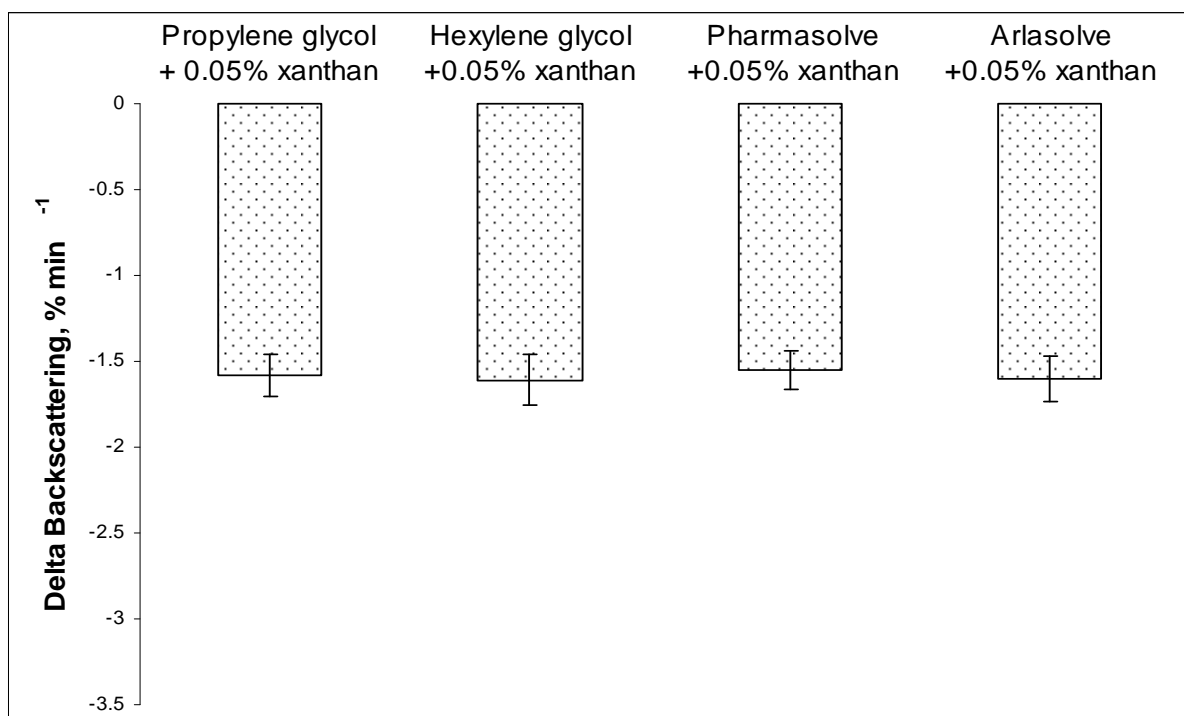


Figure 52 Foam bubble stability (foams with 0.05% xanthan gum)

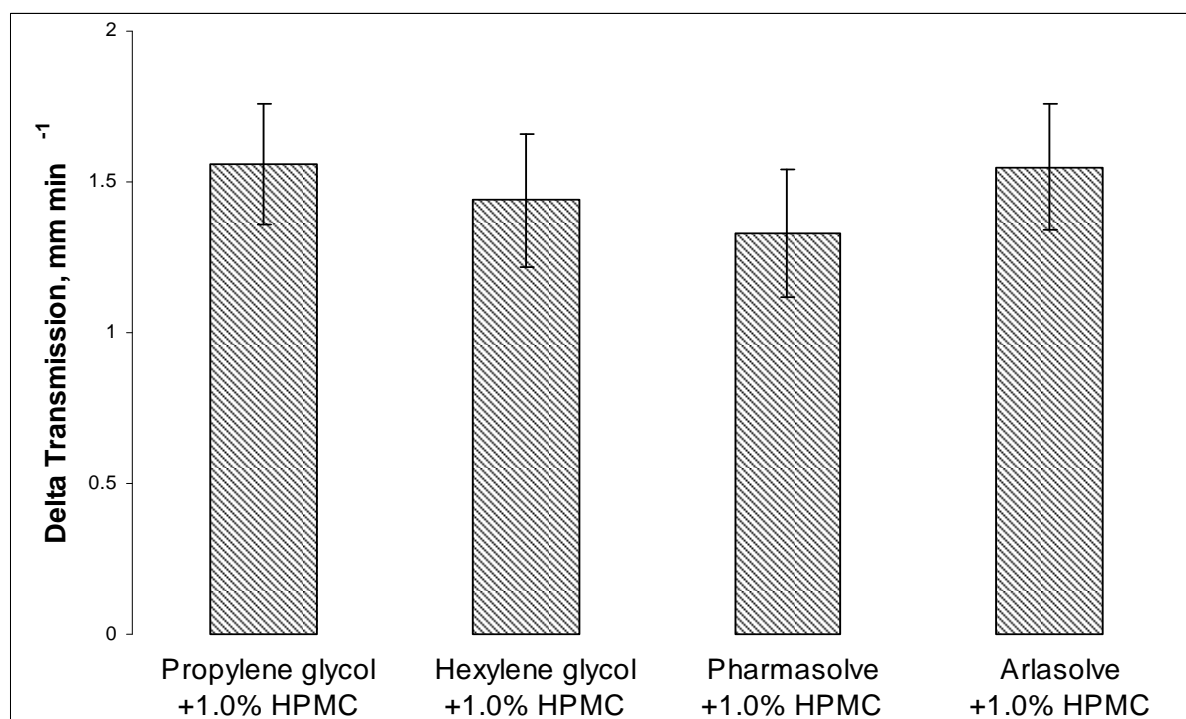
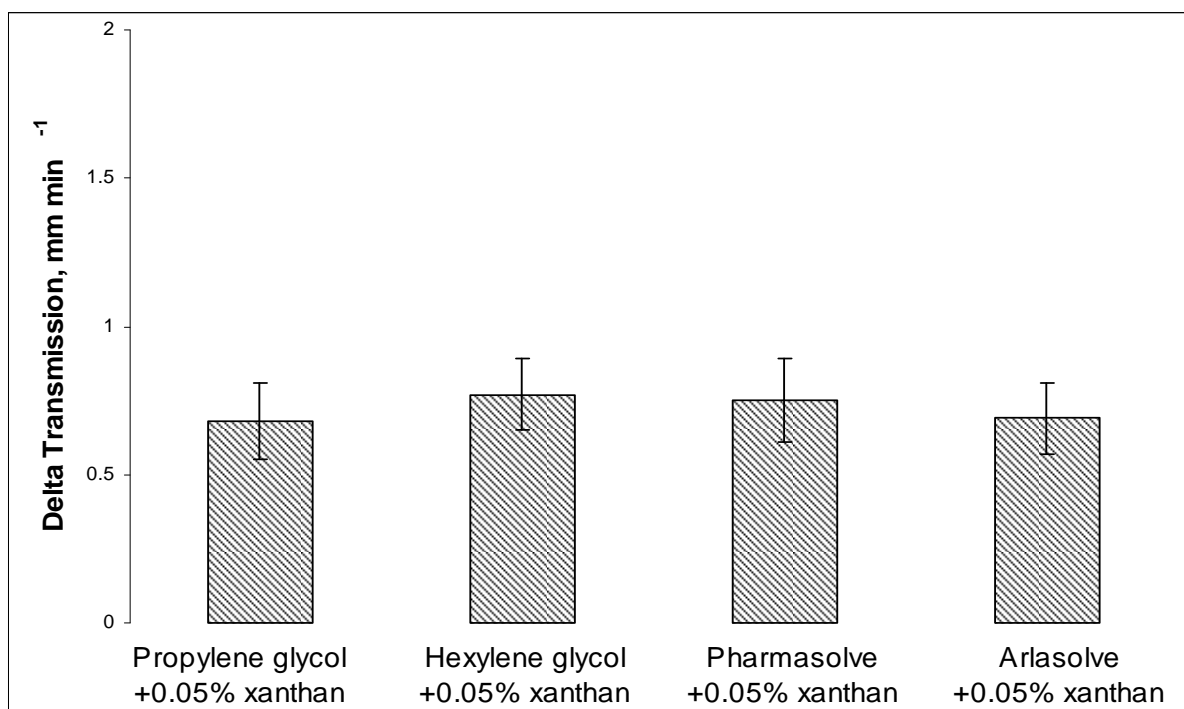


Figure 53 Liquid drainage rate (foams with 1.0% HPMC)



**Figure 54** Liquid drainage rate (foams with 0.05% xanthan gum)

### 4.2.3 Summary

It was shown during the preliminary tests that foamability of different foaming agents and their combinations as well as foam stability characteristics could be influenced through the addition of polymers. High concentrations of polymers causing an increase of viscosity above 30 mPa·s should be avoided. This leads to a worse foamability of formulations because of the construction of the Airspray<sup>®</sup> foam generator. Foam stability can be increased through the addition of low concentrations of polymers or their combinations. The differences between polymers in their capacity for foam stabilization could be explained through their different surface activity.

The Airspray<sup>®</sup> dispenser was shown to be an appropriate device for foam generation for pharmaceutical needs. The dispenser is able to deliver uniform doses of the corticosteroid within the generated foam.

Stable low viscous o/w emulsions were produced using a low viscous polar oil such as Miglyol<sup>®</sup> 812 as an oil phase. Surfactants containing lauric acid and



combinations thereof were used as foaming agents and emulsifiers. BMV was solubilized by means of the same surfactants. The produced emulsions were nano-emulsions which was reached by the method of high-energy emulsification (high-shear stirring with ultra turrax). Sufficient formulation stability during storage as well as delivery of the equivalent active ingredient dosage within the application was assured. Incorporation of oil into compositions of foamable formulations resulted in reduced stability of foams. The combined use of two foaming agents led to better values of foam stability of produced of o/w emulsions. Application of the emulsions onto the skin resulted in no visual residues.

By the production of solution based foamable formulations, BMV was dissolved in different solvents. Such solvents as propylene glycol, hexylene glycol, Pharmasolve<sup>®</sup> and Arlasolve<sup>®</sup> were used. The use of ethanol as solvent was avoided as it may enhance drug penetration into the skin leading to undesired side effects. The presence of ethanol in the formulation may also lead to skin irritation. Surfactant amount in solution-based formulations could be reduced.

As well as for emulsion-based foams and solution-based foams, HPMC, MC, xanthan gum and their combinations were used as foam stabilizing agents. Formulations were preserved with sodium benzoate. Stability of BMV was assured through the use of phosphate buffer with pH 4.5.

All developed compositions showed satisfactory foaming properties which resulted in the generation of foams of sufficient cosmetic properties and stability.

A new platform propellant free vehicle for topical drug delivery was developed. The new developed vehicle platform offers two different formulation proposals: a low viscous o/w emulsion based foam and a solution based foam. Therefore, a propellant free foam generation mechanism was presented and evaluated. The later choice of the appropriate vehicle should be dependent on the application

site and skin condition. Abdication of propellant allows a reduction of the production cost and the number of production steps.

### 4.3 Formulation development / Pressurized aerosol foams

#### 4.3.1 Emulsion based foams

##### 4.3.1.1 Formulation development steps

The formulation development was based on a foamable formulation as developed for the Airspray<sup>®</sup> dispenser. The surfactants used for formulation development should fulfil the following functions:

- foam generation
- solubilization of BMV
- emulsification of oil phase
- emulsification of liquefied propellant

The following formulation development steps were carried out to reach the product targets named above (Table 19).

**Table 19** Formulation development steps

<i>Step</i>	<i>Target</i>
<i>Reduction of surfactant fraction</i>	<i>Reduction of skin exposure</i>
<i>Reduction of water fraction</i>	<ul style="list-style-type: none"> <li>· <i>Emulsification of liquefied propellant</i></li> <li>· <i>Development of a homogenous emulsion</i></li> </ul>
<i>Addition of a w/o surfactant</i>	
<i>Addition of polyacrylic acid polymers</i>	
<i>Increase of oil phase / Exchange of oil phase</i>	<i>Dissemination improvement</i>

The following components and portions thereof were used for pressurized aerosol foam development (Table 20). The viscosity of the formulation is not a limitation factor for the development of aerosol foams, as far as the formulation is not semisolid. All combinations were produced and evaluated due to their optical appearance.

#### **4.3.1.2 Evaluation of formulation stability**

After conducting the temperature stress test for all formulations, only formulations with a score of 7 and 8 according to the scheme after Quack *et al.* (1975), (see 3.2.2.2.2) were described as stable (Table 21).

Formulations which became a score of 8 were described as a "one-phase" system; formulations which became a score of 7 were described as "two-phase" systems. Completely homogenous emulsions were evaluated as a "one-phase" system. Such formulation was produced when 8% of the propellant was added to the formulation shown in Table 22.

The "two-phase" systems showed optically a strip line as the propellant phase was not completely emulsified in the formulation. However, it was easily possible to homogenize the "two-phase" systems to a homogenous emulsion through slightly shaking. Centrifuge test was not carried out because the formulations were filled into aerosol cans not applicable to a centrifuge. All formulations that are listed in Table 21 showed good foamability (optical determination) and foam stability characteristics (light (back)-scattering method). Addition of Span<sup>®</sup> 80 resulted in the generation of very coarse foams (optical determination) which collapsed immediately. This was explained through the presence of oleic acid in the structure of the surfactant (see 4.1.1.2). Foam stability of these foams was not analytically determined.

**Table 20** Formulation ingredients as used for the development of pressurized aerosol foams

<i>Phase</i>	<i>Component</i>	<i>Amount</i>
<i>Oil phase</i>	<i>Miglyol<sup>®</sup> 812</i>	<i>1.0% - 10.0 %</i>
	<i>Olive oil</i>	
	<i>Cyclomethicone</i>	
	<i>Isopropyl palmitate</i>	
	<i>Paraffin oil</i>	
	<i>Abil 100</i>	
<i>Foaming agent blend (1:1) (emulsifier) (solubilization agent)</i>	<i>Tween<sup>®</sup> 20 : Brij<sup>®</sup> 35</i>	<i>5.0%-10.0%</i>
<i>Co-emulsifier</i>	<i>Lanette<sup>®</sup> O</i>	<i>2.0%-5.0%</i>
	<i>Span<sup>®</sup> 20</i>	
	<i>Span<sup>®</sup> 80</i>	
	<i>Brij<sup>®</sup> 72</i>	
<i>Emulsion stabilization agent</i>	<i>Pemulen<sup>®</sup> solution 0.25%</i>	<i>1.0%-10.0%</i>
	<i>Carbopol solution 0.25%</i>	
<i>Foam stabilization agent</i>	<i>Xanthan gum</i>	<i>0.05%</i>
<i>Preservative agent</i>	<i>Sodium benzoate</i>	<i>0.1%</i>
<i>Topical corticosteroid</i>	<i>BMV</i>	<i>0.1%</i>
<i>Phosphate buffer pH 4.5</i>		<i>q. s. ad 100%</i>
<hr/>		
<i>Propellant</i>		<i>8.0%</i>
<hr/>		

Table 21 Stable pressurized aerosol foams

<i>Phase</i>	<i>Component</i>	<i>Amount</i>
<i>Oil phase</i>	<i>Miglyol<sup>®</sup> 812</i>	<i>1.0% - 10.0 %</i>
	<i>Olive oil</i>	<i>1.0% - 5.0 %</i>
	<i>Cyclomethicone</i>	<i>1.0% - 5.0 %</i>
<i>Foaming agent blend (1:1) (emulsifier) (solubilization agent)</i>	<i>Tween<sup>®</sup> 20 : Brij<sup>®</sup> 35</i>	<i>4.5%-10.0%</i>
<i>Co-emulsifier</i>	<i>Span<sup>®</sup> 20 Brij<sup>®</sup> 72</i>	<i>2.0%-5.0%</i>
<i>Emulsion stabilization agent</i>	<i>Pemulen<sup>®</sup> solution 0.25%</i>	<i>5.0%-10.0%</i>
<i>Foam stabilization agent</i>	<i>Xanthan gum</i>	<i>0.05%</i>
<i>Preservative agent</i>	<i>Sodium benzoate</i>	<i>0.1%</i>
<i>Topical corticosteroid</i>	<i>BMV</i>	<i>0.1%</i>
<i>Phosphate buffer pH 4.5</i>		<i>q. s. ad 100%</i>
<i>Propellant</i>		<i>8.0%</i>

**Table 22 Basic composition for pressurized aerosol foam (emulsion based)**

<i>Phase</i>	<i>Component</i>	<i>Amount</i>
<i>Oil phase</i>	<i>Miglyol<sup>®</sup> 812</i>	<i>1.0 %</i>
<i>Foaming agent blend (1:1) (emulsifier) (solubilization agent)</i>	<i>Tween<sup>®</sup> 20 : Brij<sup>®</sup> 35</i>	<i>10.0 %</i>
<i>Foam stabilization agent</i>	<i>Xanthan gum</i>	<i>0.05%</i>
<i>Preservative agent</i>	<i>Sodium benzoate</i>	<i>0.1%</i>
<i>Topical corticosteroid</i>	<i>BMV</i>	<i>0.1%</i>
<i>Phosphate buffer pH 4.5</i>		<i>q. s. ad 100%.</i>

#### 4.3.1.3 Stability of generated foams

The stability of generated foams was evaluated as described in 3.2.1.1.3. Liquid drainage rate of those formulations which stability was evaluated with a score of 7 could not be determined with the light (back-) scattering method as the drained liquid was not transparent enough to transmit light. Air bubble growth of formulations containing Miglyol<sup>®</sup> 812 and olive oil was within the range of  $-2.11 \text{ \%}\cdot\text{min}^{-1} \pm 0.25\%\cdot\text{min}^{-1}$ . Formulations which contained cyclomethicone as oil phase showed twice as high air bubble growth, namely  $-4.66 \text{ \%}\cdot\text{min}^{-1} \pm 0.39\%\cdot\text{min}^{-1}$ . Silicone oils are known to function as foam inhibitors (see 2.1.3).

#### 4.3.1.4 Pressurized aerosol foam vs. foam generated by Airspray<sup>®</sup> foam dispenser

The stability of two foams of the same composition but generated by different methods determined by means of light (back-) scattering method as described in 3.2.1.1.3 was compared to each other (Table 23). It was possible to determine liquid drainage rate in this case as light could be transmitted through a layer of drained liquid as the formulation was not opaque. The composition of the tested formulation is shown in Table 22.

**Table 23 Stability of foams produced by two different methods**

<i>Characteristics</i>	<i>Airspray<sup>®</sup> dispenser mean <math>\pm</math> SD</i>	<i>Pressurized aerosol foam mean <math>\pm</math> SD</i>
<i>Bubble growth, [<math>\% \cdot \text{min}^{-1}</math>]</i>	<i>-1.82 <math>\pm</math> 0.23</i>	<i>-4.80 <math>\pm</math> 0.50</i>
<i>Liquid drainage, [<math>\text{mm} \cdot \text{min}^{-1}</math>]</i>	<i>2.37 <math>\pm</math> 0.30</i>	<i>0.44 <math>\pm</math> 0.10</i>

The pressurized aerosol foam showed a lower foam bubble stability in comparison to the foam of the same composition generated with the Airspray<sup>®</sup> foam dispenser. Bubble growth within pressurized aerosol foam was approximately twice as fast as within the mechanically generated foam. The reason for this is an abrupt evaporation of a propellant blend at atmospheric pressure. The bubbles of a pressurized aerosol foam contain propellant which evaporates instantaneously. A pressure increase within the bubbles causes them to burst. In the case of mechanically generated foams, the foam bubbles contain air. Therefore, the bubbles of foams generated with the Airspray<sup>®</sup> dispenser are more stable to rupture. Nevertheless, the liquid drainage rate was approximately five folds higher within mechanically generated foam than within pressurized aerosol foam. A higher liquid drainage rates within the mechanically generated foams are connected with a lower gas fraction of such foams than of pressurized aerosol foams. The same volume of a foam produced with the Airspray<sup>®</sup> dispenser contains percental more liquid than a pressurized aerosol foam.

This leads inevitably to a higher liquid drainage rate. Foam stability is, therefore, dependent on the foam generation mechanism.

### 4.3.2 Solution based foams

#### 4.3.2.1 Formulation development steps

Basic compositions of formulations are shown in Table 24. All combinations were formulated and resulted in all cases in good foamability and foam stability.

All produced "two-phase" systems (see 4.3.1.2) passed the temperature stress stability test.

**Table 24 Basic composition of pressurized aerosol foams (solution based)**

<i>Phase</i>	<i>Component</i>	<i>Amount</i>
<i>Solvent</i>	<i>Propylene glycol</i>	$\geq 11.3\%$
	<i>Hexylene glycol</i>	$\geq 5.6\%$
	<i>Pharmasolve</i> <sup>®</sup>	$\geq 0.8\%$
	<i>Arlasolve</i> <sup>®</sup>	$\geq 1.9\%$
<i>Foaming agent</i>	<i>Tween</i> <sup>®</sup> 20	3.0%
<i>Foam stabilization agent</i>	<i>HPMC</i>	1.0%
	<i>MC</i>	0.4%
	<i>HPMC / Xanthan gum</i>	0.6% / 0.01%
	<i>MC / Xanthan gum</i>	0.2% / 0.01%
	<i>Xanthan gum</i>	0.03% - 0.05%
<i>Preservative agent</i>	<i>Sodium benzoate</i>	0.1%
<i>Topical corticosteroid</i>	<i>BMV</i>	0.1%
<i>Phosphate buffer pH 4.5</i>		<i>q. s. ad 100%</i>
<i>Propellant</i>		8.0%



#### **4.3.2.2 Evaluation of formulation stability**

The stability of produced pressurized aerosol foams was detected by means of light (back-) scattering methods. Formulations containing HPMC at a concentration of 1.0% and MC at a concentration of 0.4% as foam stabilizing agents and different solvents for BMV in minimal possible concentrations to dissolve BMV were compared to each other. The results are summarized in Figures 55 and 56.

No differences were found in such foam stability characteristic as foam bubble growth within the foams produced with different solvents. The foam bubble stability of foams stabilized with 1.0% HPMC and 0.4% MC was just slightly different. Actually, no difference between these two stabilizing agents was expected because of their similar surface activity.

No transmission peaks were detected during stability determination. In the case of formulations where the layer of separated liquid is not opaque and can transmit light, absence of a transmission peak is an evidence for the absence of drained liquid. The absence of drained liquid is an evidence for good formulation stability against separation of liquid phase within a foam.

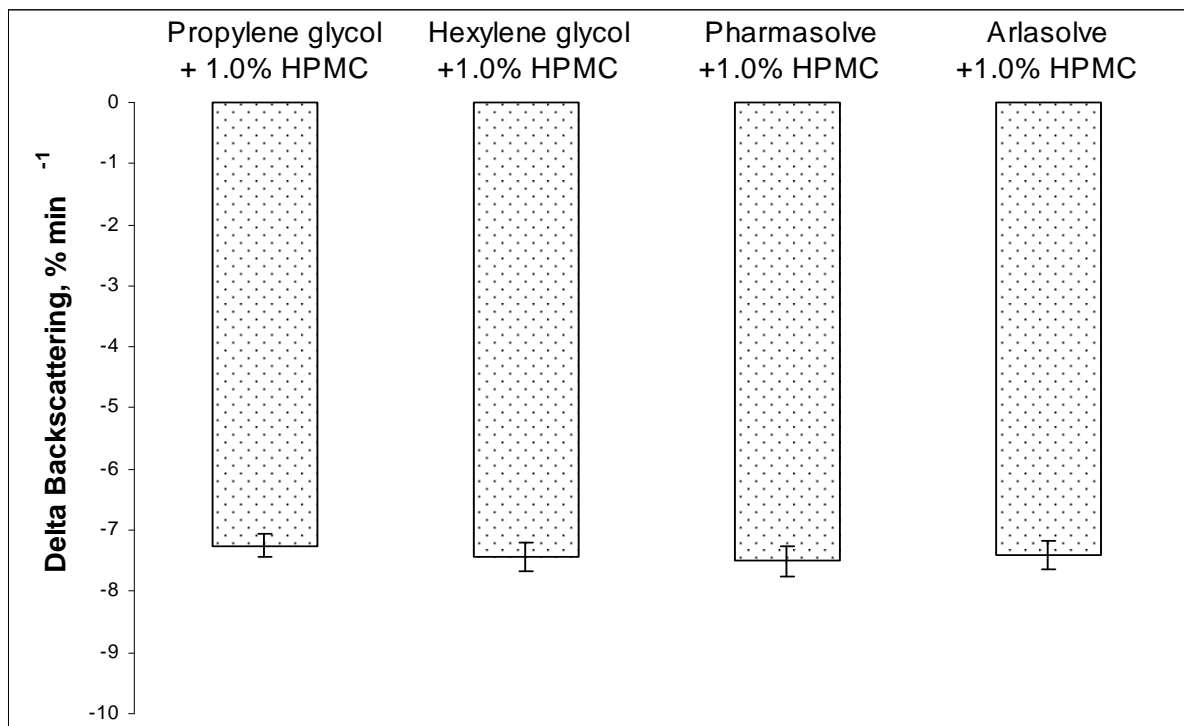


Figure 55 Foam bubble stability (foams with 1.0% HPMC)

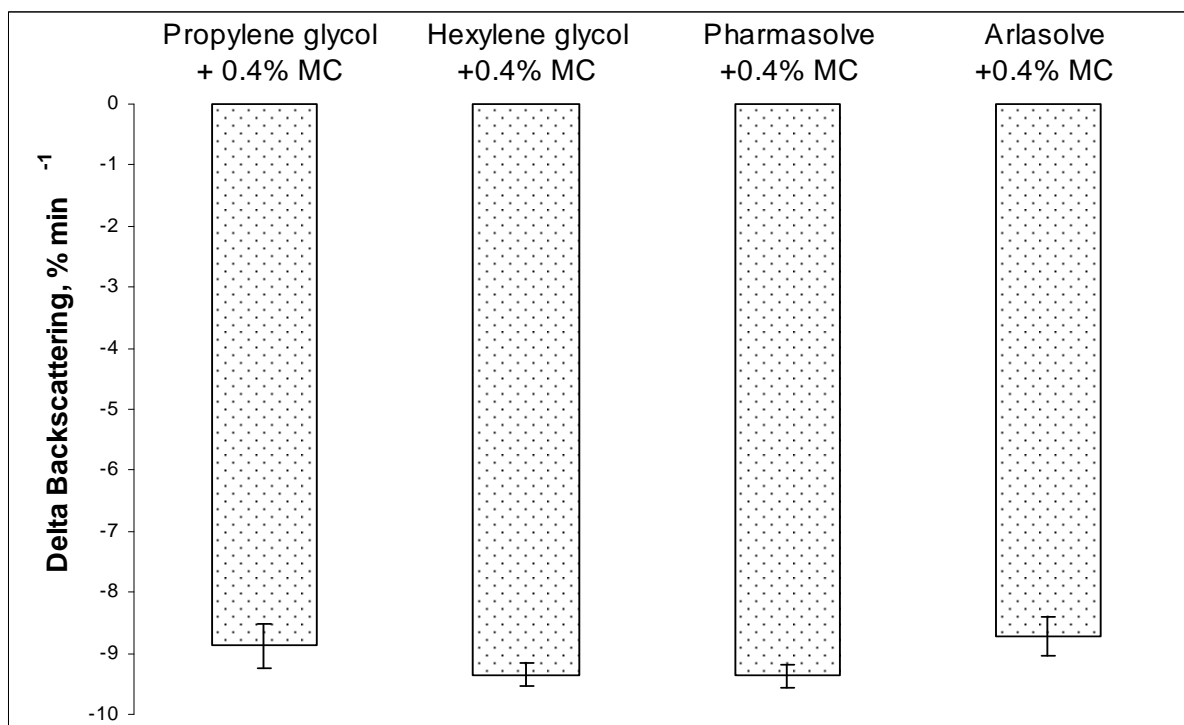


Figure 56 Foam bubble stability (foams with 0.4% MC)

### 4.3.2.3 Pressurized aerosol foam vs. foam generated by Airspray<sup>®</sup> foam dispenser

Formulations containing HPMC at a concentration of 1.0% as foam stabilizing agent and different solvents for BMV in minimal possible concentrations to dissolve BMV and generated with two different methods were compared to each other. The results are summarized in Table 25.

In comparison to foams of the same composition generated with the Airspray<sup>®</sup> foam dispenser, pressurized aerosol foams showed lower foam bubble stability. Bubble growth rate by pressurized aerosol foam was more than twice as high compared to mechanically generated foam. Nevertheless, a liquid drainage was not detected at all for pressurized aerosol foams. This phenomenon was described before (see 4.3.1.4). It was confirmed that foam stability is dependent on the foam generation mechanism.

**Table 25** Stability of foams produced by two different methods

<i>Characteristics</i>	<i>Airspray<sup>®</sup> dispenser mean ± SD</i>	<i>Pressurized aerosol foam, mean ± SD</i>	<i>Solvent</i>
<i>Bubble growth, [%·min<sup>-1</sup>]</i>	<i>-2.77 ± 0.20</i>	<i>-7.25 ± 0.19</i>	<i>Propylene glycol</i>
	<i>-2.68 ± 0.25</i>	<i>-7.44 ± 0.24</i>	<i>Hexylene glycol</i>
	<i>-2.72 ± 0.19</i>	<i>-7.50 ± 0.25</i>	<i>Pharmasolve<sup>®</sup></i>
	<i>-2.73 ± 0.21</i>	<i>-7.41 ± 0.23</i>	<i>Arlasolve<sup>®</sup></i>
<i>Liquid drainage, [mm·min<sup>-1</sup>]</i>	<i>1.56 ± 0.20</i>	<i>0</i>	<i>Propylene glycol</i>
	<i>1.44 ± 0.22</i>	<i>0</i>	<i>Hexylene glycol</i>
	<i>1.33 ± 0.21</i>	<i>0</i>	<i>Pharmasolve<sup>®</sup></i>
	<i>1.55 ± 0.21</i>	<i>0</i>	<i>Arlasolve<sup>®</sup></i>

### 4.3.3 Summary

Foaming formulations as pressurized aerosol foams on the base of o/w emulsions were successfully developed. It was possible to reduce the surfactant fraction so that it was still possible to solubilize BMV. It was also possible to increase the oil fraction in the formulations and to integrate oils of different viscosity and polarity such as olive oil and cyclomethicone. A co-emulsifier application was, nevertheless, essential. Stability of emulsions could be increased through addition of Pemulen<sup>®</sup> solution. Produced formulations were either "one-phase" or "two-phase" systems.

It was also possible to produce pressurized aerosol foams on the basis of a solution of BMV using such solvents as propylene glycol, hexylene glycol, Pharmasolve<sup>®</sup> and Arlasolve<sup>®</sup> in different concentrations, considering the solubility of BMV. These systems were "two-phase" systems.

HPMC, MC, xanthan gum and combinations thereof were used as foam stabilizing agents for development of both emulsion-based and solution-based foams. All formulations were preserved with sodium benzoate. Stability of BMV was assured through the use of a phosphate buffer pH 4.5.

8% propellant was sufficient to generate foams with good optical appearance.

It was observed that such parameters as foamability and foam stability are dependent on foam generation mechanism. In comparison to foams generated with the Airspray<sup>®</sup> dispenser, no dependency of formulation composition on foam quality and formulation viscosity was observed for pressurized aerosol foams for the tested viscosity interval.

The developed foam vehicles present platform formulation vehicles for different active substances and skin conditions. This platform was developed using a model drug BMV. Developed foam vehicles are supposed to be used for the treatment of such skin conditions as psoriasis and seborrheic dermatitis of haired body regions. Beside corticosteroids, other therapeutical agents such as

antimycotics or antibiotics can be integrated into a foam vehicle. Emulsion based formulations as well as oil-free formulations were produced. Dependent on skin condition foams with different oil fractions can be used when the vehicle is supposed to be applied on the body region beside scalp. When the vehicle is supposed to be used on the scalp, oil free formulations are available. It was also possible to reduce the fraction of foaming agents to decrease the risk for skin irritation.

#### **4.4 BMV release studies**

##### **4.4.1 Artificial membranes**

BMV release studies were carried out during 12 hours as described in 3.2.2.3. Commercially available Deflatop<sup>®</sup> foam and Betagalen<sup>®</sup> lotion were used as comparator formulations. The Deflatop<sup>®</sup> foam contains ethanol in its composition. The release of BMV may, therefore, be enhanced through addition of this excipient. Betagalen<sup>®</sup> lotion was used as an example for a BMV formulation in a conventional vehicle. Because of the difficulties to dose a uniform vehicle amount onto the membrane, it was decided to carry out the release studies using not a foam itself but the foamable formulation from which foams can be generated. Therefore, it was reasonable to include only formulations for the Airspray<sup>®</sup> dispenser into the study. The composition of the formulation used for release studies is shown in Table 22. Deflatop<sup>®</sup> foam was dispensed and destroyed. The liquid formulation which was left was used for the study. Betagalen<sup>®</sup> lotion was dosed directly as a semisolid formulation. All three formulations contained BMV in a concentration of 0.1%. To avoid the technical problem that the limited solubility of the lipophilic drug in the acceptor medium affects the rate of BMV release, phosphate buffer pH 4.5 containing 25% methanol (v/v) was used as acceptor medium. Release profiles are shown in Figures 57 and 58.

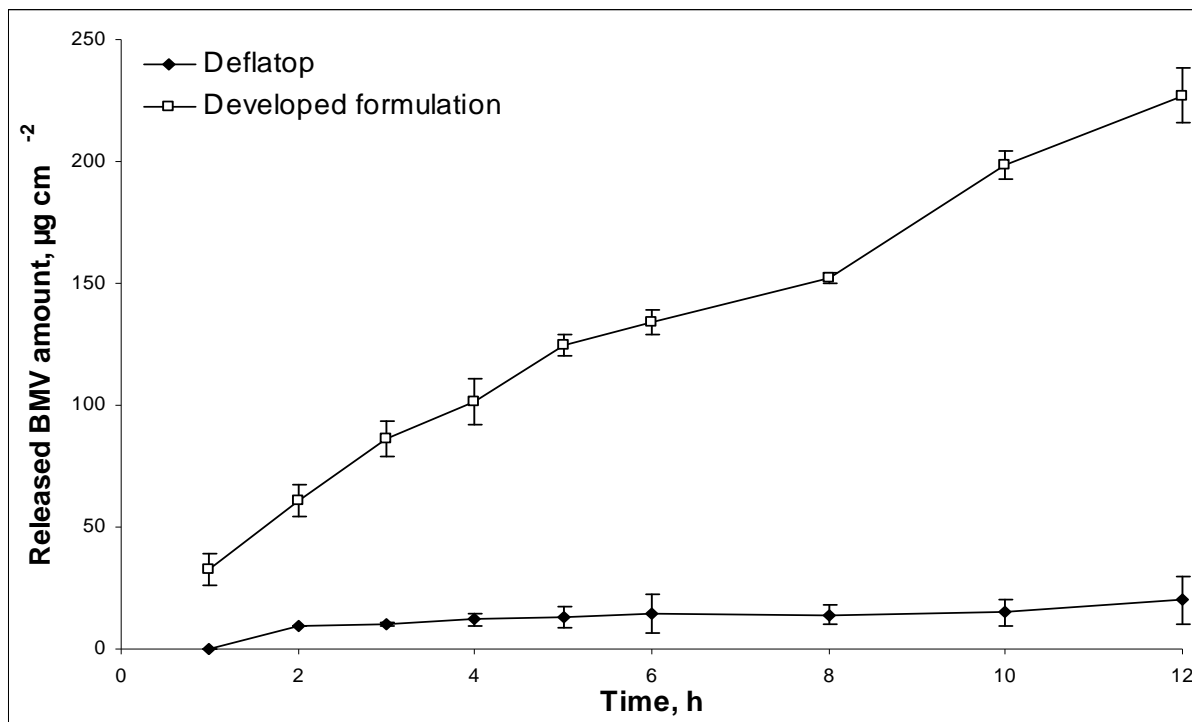


Figure 57 Release of BMV through an artificial membrane

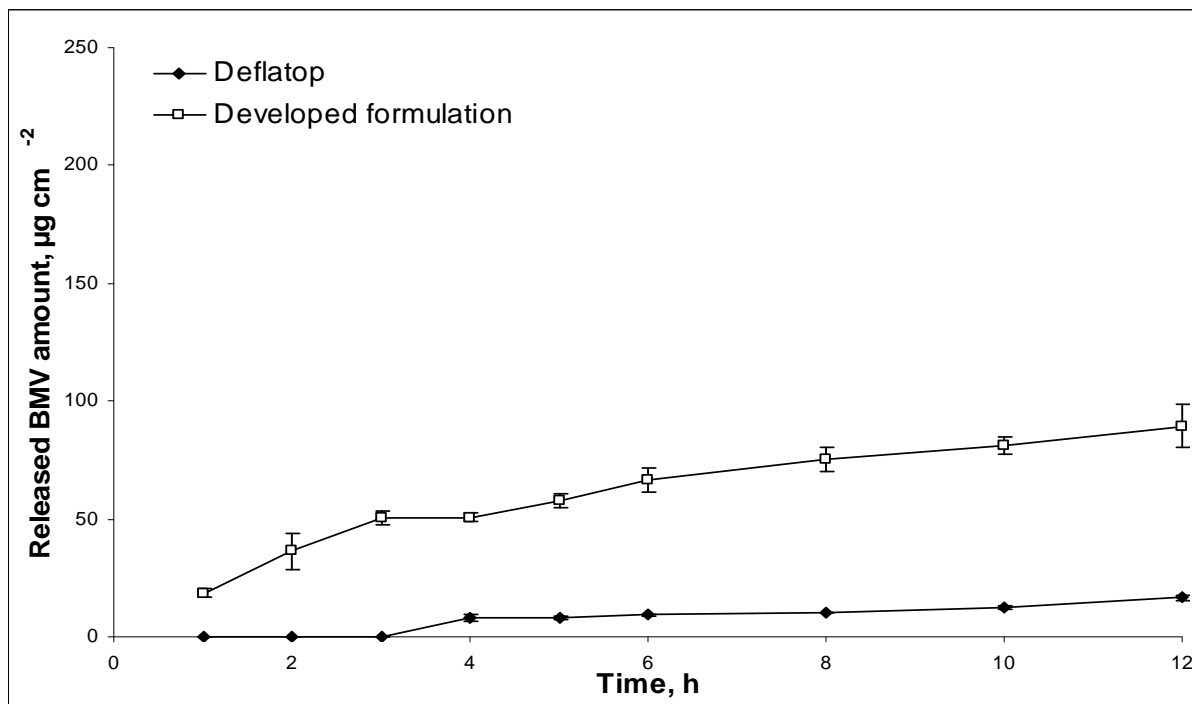


Figure 58 Release of BMV through artificial membrane, saturated with isopropyl myristate

On the ordinate the cumulative BMV amount in acceptor medium is presented. No BMV was found in the acceptor compartment when released from Betagalen<sup>®</sup> lotion.

BMV was released faster from the developed formulation than from the commercial Deflatop<sup>®</sup> formulation. Further on higher BMV amounts were released within the same time period from developed formulation compared to the Deflatop<sup>®</sup> formulation. After 12 hours 20.0 µg BMV (4.0% of the amount applied on the membrane) were found in the acceptor compartment in the case of Deflatop<sup>®</sup> foam and 226.9 µg BMV (45.4% of the applied amount) were found in the case of the developed formulation. Differences in the release profiles when using unsaturated artificial membranes and membranes saturated with isopropyl myristate were observed. Using unsaturated membranes, approximately an 11 fold higher amounts of BMV were released from the developed formulation than from Deflatop<sup>®</sup> within 12 hours (45.4% vs. 4.0% of the applied amount). On the other hand using membranes saturated with isopropyl myristate, the released BMV amount from the developed formulation was only 5 fold higher (17.9% vs. 3.3% of the applied amount). Using membranes saturated with isopropyl myristate, the overall drug release was found to be slower. The saturation of the membrane with a lipophilic fluid such as isopropyl myristate leads to an increase of the membrane lipophilicity reducing drug diffusion.

These differences in the release profiles result from the differences in the compositions of used formulations and drug distribution in it. In Deflatop<sup>®</sup> foam BMV is dissolved in ethanol (99.7% v/v). In Betagalen<sup>®</sup> lotion BMV is dissolved in the lipophilic components of the vehicle (see Appendix). In the developed formulation the drug is solubilized in micelles. The size of the micelles is approximately  $6.9 \pm 0.3$  nm (see 4.2.1.4.3). After the release studies the acceptor medium was analyzed by means of PCS measurements. In case of the developed formulation, micelles of the same size were found in the acceptor

fluid. This was an evidence that the micelles with the solubilized BMV take a pass through the pores of the used membranes to a higher degree than a dissolved BMV either in a hydrophilic or in a lipophilic vehicle. Saturation of the membranes with isopropyl myristate hinders the passage of the micelles through the pores of the membrane. Dissolution of the drug in ethanol (Deflatop<sup>®</sup>) hinders drug release from the vehicle. Saturation of the membrane with isopropyl myristate has then no effect on the drug release from the Deflatop<sup>®</sup> vehicle (16.5  $\mu\text{g}$  vs. 20.0  $\mu\text{g}$  of BMV after 12 hours). Dissolution of the drug in the lipophilic phase of Betagalen<sup>®</sup> lotion leads to a decrease of the drug release from this vehicle. In the case of this study, the released drug amount was below the detection limit of used analytics (HPLC).



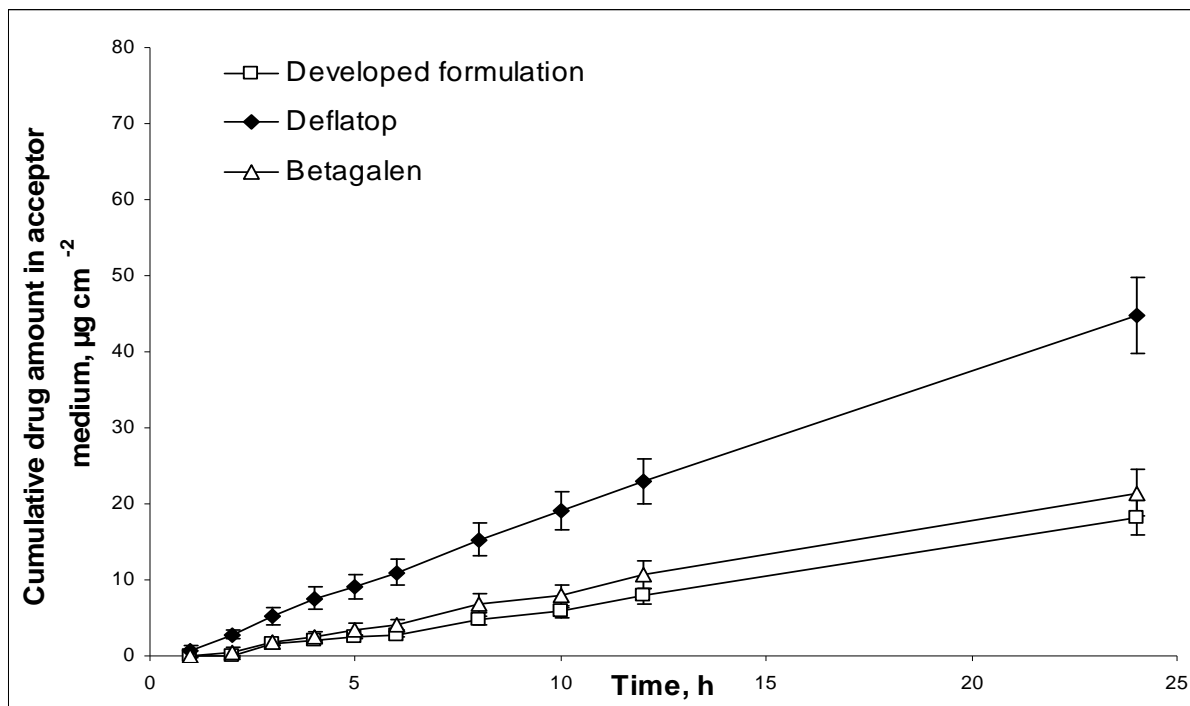
#### **4.4.2 Summary**

The use of artificial membranes was shown to be inappropriate for release studies when the active drug is solubilized in micelles which sizes are smaller than the pore size of the used membranes. The release profiles differ strongly from each other when using unsaturated membranes and membranes saturated with lipophilic fluids such as isopropyl myristate considering the release profiles of BMV from the developed formulation. Diffusion of surfactants through the artificial membrane also leads to a solubilization effect in the acceptor fluid which is responsible for the overall higher drug release. Saturation of the membrane led to a decreased amount of drug found in the acceptor compartment as lipophilic properties of the membrane were more pronounced and, therefore, the barrier properties of the *St. corneum* were better mimicked.

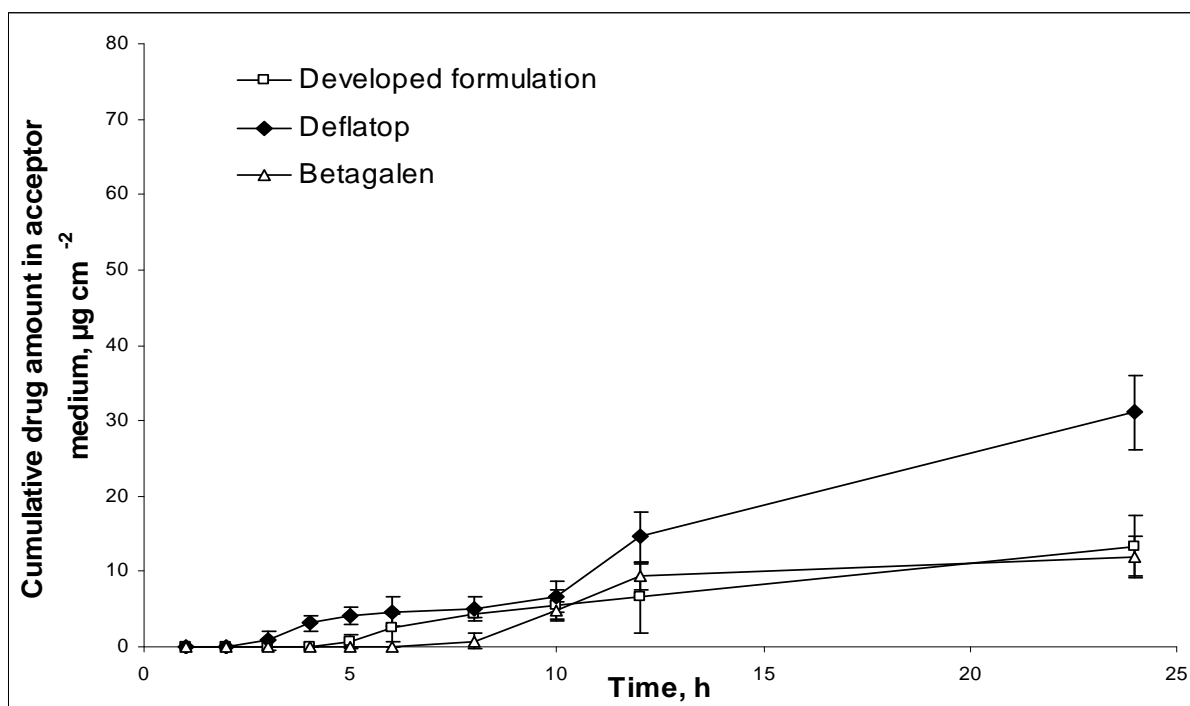
### **4.5 BMV permeation studies**

#### **4.5.1 Porcine ear skin**

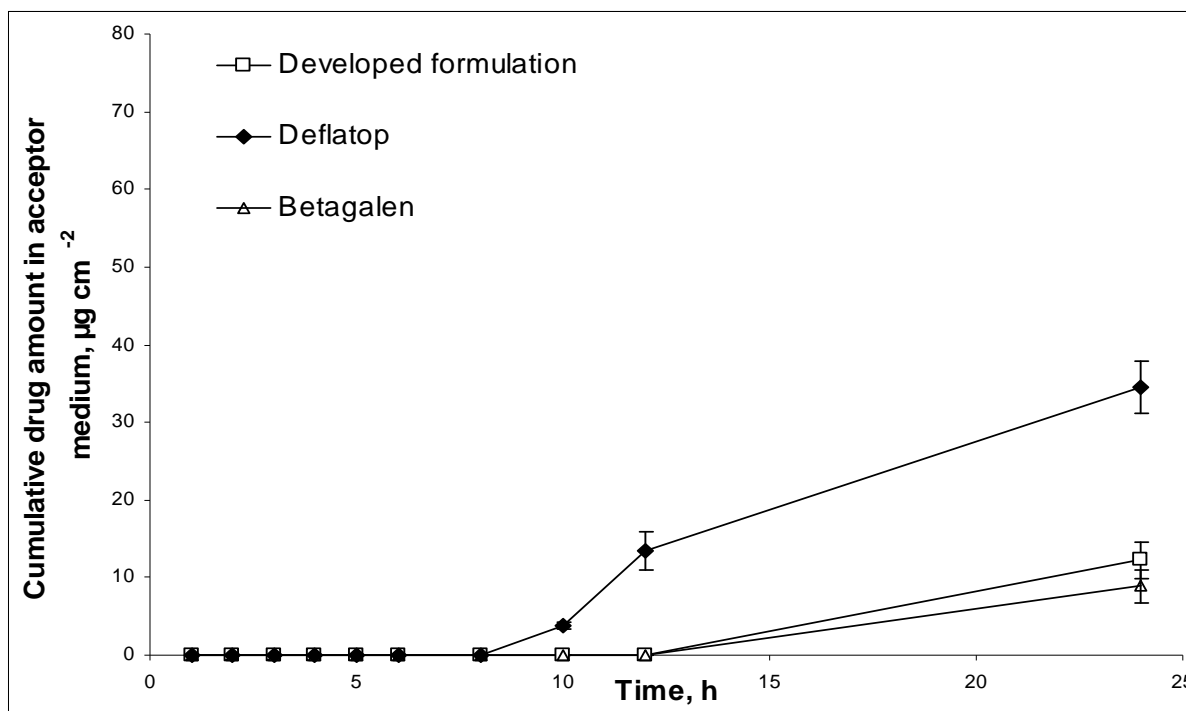
Pig ears were taken from the slaughterhouse. Permeation studies were carried out as described in 3.2.2.4 over 24 hours. Two other acceptor media were used additionally to examine the influence of the acceptor medium composition on the permeation profiles of BMV. Drug permeation profiles are shown in Figures 59, 60, 61 and 62.



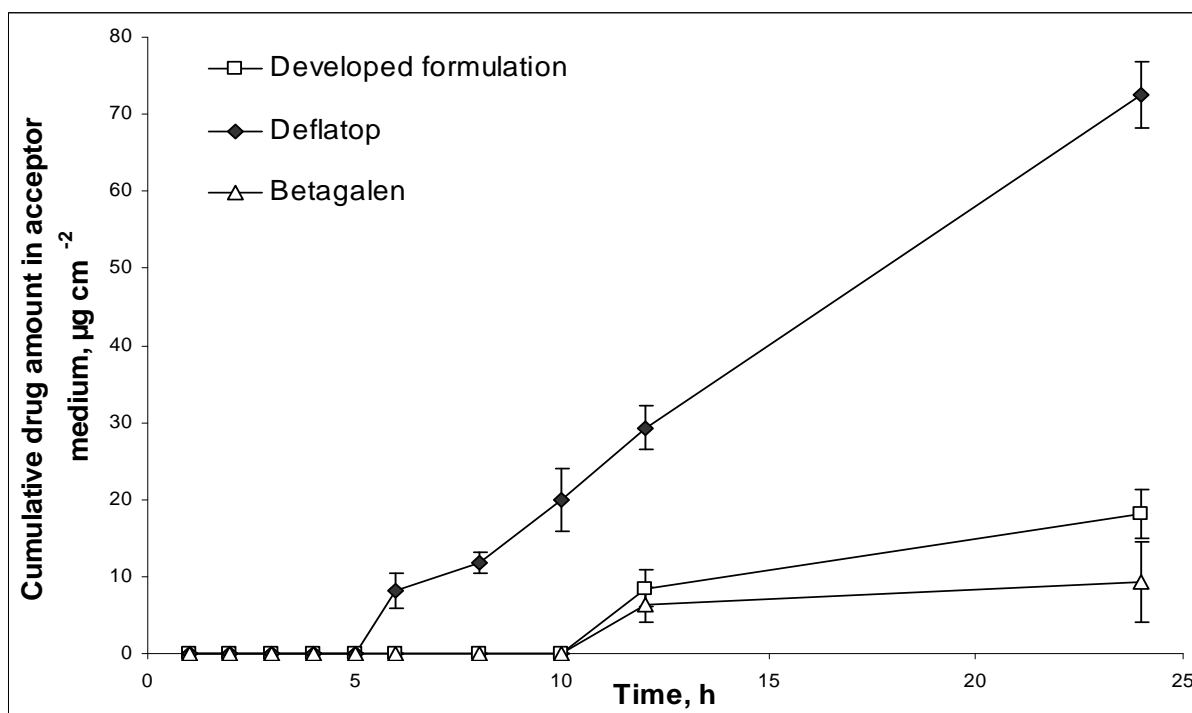
**Figure 59** Permeation of BMV through excised pig ear skin (phosphate buffer pH 4.5 + 25% (v/v) methanol), internal part of the ear



**Figure 60** Permeation of BMV through excised pig ear skin (phosphate buffer pH 4.5 + 25% (v/v) methanol), external part of the ear



**Figure 61** Permeation of BMV through excised pig ear skin (phosphate buffer pH 4.5), internal part of the ear



**Figure 62** Permeation of BMV through excised pig ear skin (phosphate buffer pH 4.5 + 0.1% methyl- $\beta$ -cyclodextrine), internal part of the ear

The skin from the internal part of the pig ear was used for permeation studies. For the acceptor medium with ethanol the external part of the pig ear was also used to evaluate differences in the permeation profiles (Figure 59 and 60). Permeation of BMV from Deflatop<sup>®</sup> was found to be higher in all three different acceptor media. No differences in the BMV penetration profiles were found in case of the developed formulation and Betagalen<sup>®</sup> lotion. Using skin from the internal part of the pig ear, the following amounts of BMV were found in the acceptor compartment after 24 hours using phosphate buffer pH 4.5 containing 25% (v/v) methanol: 8.9%, 4.3% and 3.6% for Deflatop<sup>®</sup>, Betagalen<sup>®</sup> and the developed formulation, respectively (in % of the applied amount). BMV was found in the acceptor medium already after 2 hours after beginning of the study (lag-time). When using phosphate buffer pH 4.5 alone as acceptor medium, the first drug amounts were found in the acceptor compartment after 10-12 hours. After 24 hours 6.9% (Deflatop<sup>®</sup>), 1.8% (Betagalen<sup>®</sup>) and 2.5% (developed formulation) of the applied drug amount were found in the acceptor medium. When using phosphate buffer pH 4.5 with 0.1% methyl- $\beta$ -cyclodextrine, BMV could be detected in the acceptor medium after 6-12 hours (depending on the formulation). After 24 hours 14.5% (Deflatop<sup>®</sup>), 1.8% (Betagalen<sup>®</sup>) and 3.6% (developed formulation) were found in the acceptor medium.

Using skin from the external part of the pig ear and phosphate buffer pH 4.5 with 25% (v/v) methanol as acceptor medium, the following amounts of BMV were detected in the acceptor compartment after 24 hours: 6.2%, 2.4% and 2.7% for Deflatop<sup>®</sup>, Betagalen<sup>®</sup> and the developed formulation, respectively. It was possible to detect BMV in the acceptor medium after 2 hours after study begin. No particles or micelles were found in the acceptor media when they were analyzed by means of PCS.

Lower amounts of permeated BMV were found when using skin from the external part compared to skin from the internal part of the ear. Differences in the permeation profiles in this case are dependent on the skin thickness.

BMV permeates to a greater extent through thinner skin, namely the skin from the internal part of the ear.

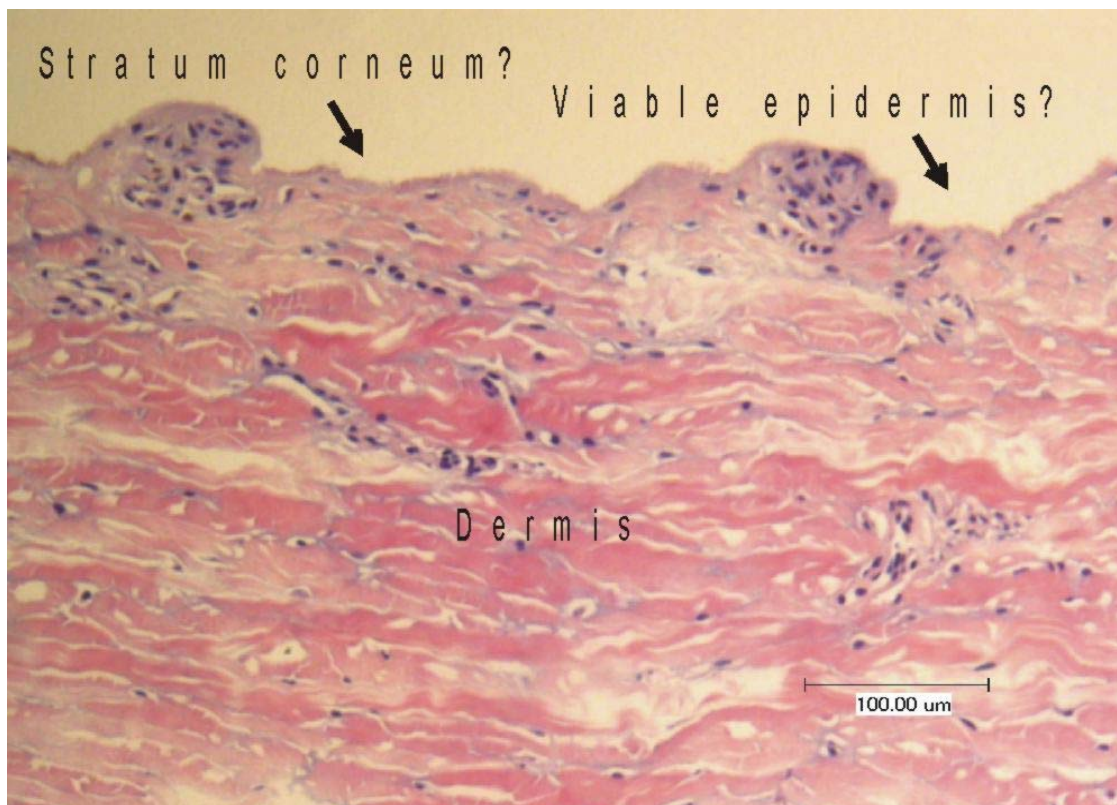
Differences in the permeation profiles during application of three different acceptor media can be explained through a different solubility of BMV in these media. Addition of methanol and methyl- $\beta$ -cyclodextrine leads to an increase of BMV solubility in the acceptor medium and, therefore, to a faster access of the drug in the acceptor compartment.

The BMV permeation profiles obtained using pig ear skin were compared to the permeation profiles reported in the literature. Simonsen and Fullerton (2007) found between 4 and 20  $\mu\text{g}\cdot\text{cm}^{-2}$  BMV permeated through pig ear skin into the acceptor medium after 70 hours from a conventional vehicle. Degim *et al.* (1999) showed that about 2.5  $\mu\text{g}\cdot\text{cm}^{-2}$  BMV was permeated across canine skin after 48 hours. About 1-3  $\mu\text{g}\cdot\text{cm}^{-2}$  (Kubota and Maibach, 1993) and 8  $\mu\text{g}\cdot\text{cm}^{-2}$  BMV (Kubota *et al.*, 1992) were found in acceptor medium after 72 hours using human split thickness skin as a natural permeation membrane. Huang *et al.* (2005) reported 50  $\text{ng}\cdot\text{cm}^{-2}$  BMV in the acceptor compartment permeated across excised human skin after 24 hours from a foam vehicle. Anyway, all these data for BMV permeation reported much lower amounts of the drug permeated across different natural membranes from different vehicles.

#### **4.5.2 Biopsy and microscopy of the pig ear skin**

The histology of biopsies of pig ear skin which was used for permeation studies was examined to find the reason for a higher permeated BMV amount than reported in the literature. Biopsies were taken from the skin, fixated in formaldehyde solution and prepared following standard histological procedures (see Appendix). Sections of biopsies were investigated using microscopy (Figure 63). The only skin layer, which could be microscopically detected, was a dermis layer. An epidermis layer was not present at the border of the *St. basale*.

The dermal papillae could still be detected. It was obvious that the epidermis layer with the *St. corneum* was somehow removed between the time of slaughter and picking up the skin from the slaughterhouse. After literature analysis no special references were found considering the skin preparation and the exact time of the ears displacement from the rest of the carcass of the slaughtered animal.



**Figure 63** Histology of porcine skin as used for permeation studies

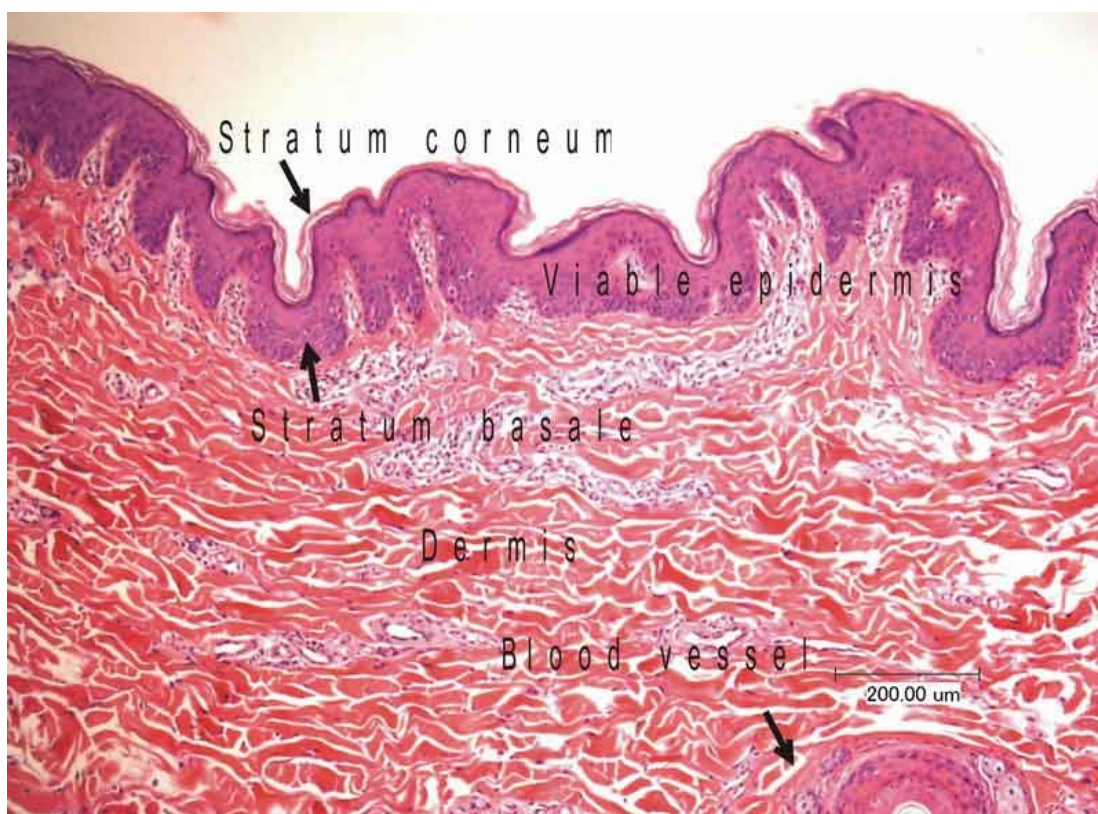
Such descriptions as "pig ears were obtained no more than a few hours post-mortem", "pig ears were obtained from a local abbatoir", "ears were obtained from pigs slaughtered on the day of the experiment" or no detailed instructions at all were found in the literature (Dick and Scott, 1992; Meyer, W., 1996; Sekkat *et al.*, 2002; Jacobi *et al.*, 2007). Even in the test guidelines for *in vitro* assessment of dermal absorption and percutaneous penetration of cosmetic

ingredients (Diembeck *et al.*, 1999), no detailed descriptions were given for the process of skin displacement in the slaughterhouse.

The carcasses of the slaughtered animals are exposed to the high-temperature cleaning procedure prior to further processing. This cleaning procedure causes a displacement of the upper skin layer up to the basal cells, which makes the skin inappropriate for the use for permeation studies as the main permeation barrier, namely the *St. corneum*, is destroyed. The ears of the animals should, therefore, be displaced from the carcass directly after slaughter and before high-temperature cleaning. More detailed instructions for a skin obtaining procedure should be given in the literature and the guidelines for performing the permeation studies.

### 4.5.3 Full thickness pig ear skin

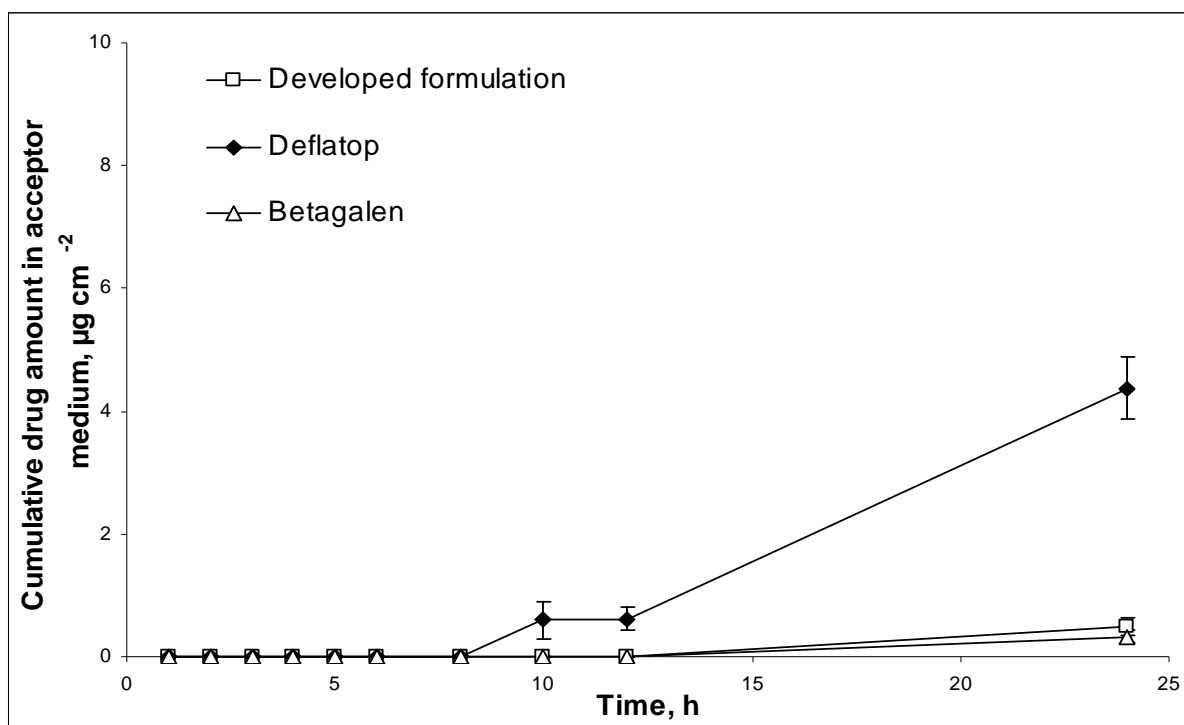
It was assured that the animals were not scaled with hot water before the ears were separated. Otherwise, the epidermis would be completely removed. The skin was histologically investigated. The *St. corneum* consisted of compactly organized keratinocytes (Fig. 64). The most prominent layer of the viable epidermis beneath was the *St. granulosum* also containing keratinocytes. At the border to the dermis, basal cells were determined. The dermal papillae were numerous and prominent in the epidermis.



**Figure 64** Histology of porcine full thickness skin

The permeation studies were performed again using the phosphate buffer pH 4.5 containing 25% methanol (v/v) as acceptor medium and the internal part of the pig ear skin. Following permeation profiles were obtained (Figure 65).





**Figure 65** Permeation of BMV through full thickness porcine skin (acceptor medium: phosphate buffer pH 4.5 + 25% (v/v) methanol), internal part of the ear

The highest BMV amount was found after 24 hours in the acceptor medium when Deflatop<sup>®</sup> was applied into the donor compartment (4.4 µg, which makes out a 0.9% of the applied amount). No difference in the permeation profiles of BMV across the membrane was found, when the developed formulation and Belagalen<sup>®</sup> lotion were used (0.5 µg and 0.3 µg, respectively). Permeation of BMV took place after an 8-hours lag-time using Deflatop<sup>®</sup> and after 12-hours lag-time using the developed formulation and Betagalen<sup>®</sup>. No particles were found in the acceptor media when they were analyzed by means of PCS. The amount of BMV found in the acceptor compartment actually reflects the drug amount which reaches the systemic circulation. In case of topically used corticosteroids, the systemic drug absorption should be avoided to exclude a risk of side effects development. Permeation of BMV across the skin from the developed formulation and Betagalen<sup>®</sup> lotion took place to a minor degree.

#### 4.5.4 Summary

It could be shown by means of performed permeation studies using porcine skin as a model for human skin that the permeation of BMV and, therefore, the risk of systemic absorption is lower when using one of the developed formulations with high surfactant fraction or Betagalen<sup>®</sup> lotion than the marketed Deflatop<sup>®</sup> foam. The increased permeation rate of BMV from Deflatop<sup>®</sup> can be explained through the presence of ethanol in the composition which acts as a typical permeation enhancer. Ethanol is known to increase the flux of the lipophilic drugs across the skin by extracting the *St. corneum* lipids (Williams *et al.*, 1992).

The relatively high surfactant fraction in the developed formulation does not seem to influence the drug permeation rate to a greater extent than ethanol does, although, surfactants are also used as skin-permeation enhancers in the galenical formulation development. Anionic surfactants, *e.g.* sodium lauryl sulfate, are shown to cause swelling of the *St. corneum* and interact with keratin. Nonionic surfactants which were used for formulation development are reported to act as weaker permeation enhancers (Ritschel and Hussain, 1988; Williams *et al.*, 1992).

It was also shown that a detailed description of the skin preparation procedure is necessary to be given at least in such regulatory papers as guidelines to avoid a faulty comparative data interpretation of the permeation studies.

## 5 Overall summary

As a first achievement of this work, a new comprehensive approach for routine characterization of foams as drug vehicles in the formulation development stage was developed. This approach was proposed as an alternative to the methods of Eur. Ph. 6.0 and is extended to the determination of foam stability - a parameter which is not considered in the monograph. A simple cylinder test is proposed to be used for the determination of foamability. Firmness and cohesiveness of the produced foams can be determined using texture analysis. Foam stability as a function of liquid drainage can be brought in connection to the transmission intensity detected with the light (back-) scattering method or determined through calculation of foam liquid stability using the cylinder method. Foam stability as a function of bubble rupture can be described with the foam volume stability parameter utilizing the same method. Observation of backscattering intensities with the light (back-) scattering method helps to evaluate foam bubble size growth caused by the Ostwald ripening within foams. A fast and extensive screening of potential formulations during galenical development or quality control is possible when this developed set of analytical tests is combined.

Two new formulation platforms were developed during this work: propellant-free foams and pressurized aerosol foams as vehicles for topical drug delivery. These developed foam vehicles present platform formulation vehicles for different active substances and skin conditions. The platform was developed using the model drug betamethasone-17-valerate. The developed vehicles are supposed to be used for the treatment of such skin conditions as psoriasis and seborrheic dermatitis of haired body regions. Besides corticosteroids, other therapeutical agents such as antimycotics or antibiotics can be also integrated into these foam vehicles.

Two formulation approaches were employed within the both platforms: development of foams based on low viscous o/w emulsion and solution-based

foams. The appropriate vehicle can then be chosen dependent on the application site and skin condition such as skin moisture content and degree of hair-growth.

Nano-emulsions with a low oil phase fraction were developed using the high-energy emulsification method for their production. Sufficient formulation stability during storage as well as delivery of the equivalent active ingredient dose when applied was assured.

In the developed solution-based foamable formulations, betamethasone-17-valerate was dissolved in such solvents as propylene glycol, hexylene glycol, N-methyl-2-pyrrolidone and dimethyl isosorbide.

All developed compositions showed satisfactory foaming properties which resulted in the generation of foams of sufficient cosmetic properties and stability.

During the studies, the Airspray<sup>®</sup> dispenser was approved as a device for the generation of propellant-free pharmaceutical foams. The dispenser was able to deliver uniform doses of the corticosteroid in the generated foam. An upper viscosity limit was also established for the Airspray<sup>®</sup> dispenser – a maximal viscosity value up from which the foam generation with the Airspray<sup>®</sup> dispenser is not possible. This limit was determined to be 30 mPa·s.

During pre-formulation studies it was shown that foamability and foam stability of the developed formulations could be improved through the addition of such polymers as hydroxypropyl methyl cellulose, methyl cellulose, xanthan gum and their combinations.

By the means of permeation studies across porcine ear skin it could be shown that the systemic absorption of BMV is lower using one of the developed formulations than the systemic absorption of BMV from the commercially available Deflatop<sup>®</sup> foam and similar to the systemic absorption of BMV from Betagalen<sup>®</sup> lotion.

## 6 Summary (German version)

Einer der Gegenstände der vorliegenden Arbeit war die Entwicklung eines neuen umfassenden Verfahrens zur routinemäßigen Charakterisierung von Schäumen als therapeutische Vehikel während der Phase der Formulierungsentwicklung. Dieses Verfahren sollte als eine Alternative zu dem im Arzneibuch (6.0) beschriebenen Verfahren dienen und um die Bestimmung der Schaumstabilität erweitert sein. Die Bestimmung der Schaumstabilität ist im Arzneibuch nicht vorgesehen. Die Zylindermethode war zur Bestimmung der Aufschäumbarkeit einer Formulierung vorgesehen. Die Festigkeit und die Kohäsion eines Schaums konnten mit dem Texture Analyser bestimmt werden. Die Stabilität des Schaums als Funktion der Flüssigkeitsdrainage konnte mit der Transmissionsintensität eines Lichtstrahles in Verbindung gebracht werden oder durch die Bestimmung des FLS-Parameters (Foam Liquid Stability) während der Zylindermethode erfasst werden. Die Transmissionsintensität wurde mit dem Licht (Rück)Streuungs-Verfahren gemessen. Die Stabilität eines Schaums als Funktion der Stabilität der Schaumblasen konnte durch die Berechnung des FVS-Parameters (Foam Volume Stability) bestimmt werden. Durch die Beobachtung der Rückstreuintensitäten des Lichtes mit dem Licht (Rück)Streuungs-Verfahren konnte die Zunahme der Größe der Schaumblasen als das Resultat der Ostwaldreifung in einem Schaum erfasst werden. Durch die Kombination dieser Methoden ist eine schnelle und umfangreiche Selektion der potentiellen Formulierungen während der galenischen Entwicklung oder während einer Qualitätskontrolle möglich.

Zwei neue Formulierungsplattformen zur Therapie topischer Krankheiten konnten auch entwickelt werden: der treibgasfreie Schaum und der Schaum in einer Aerosoldruckgaspackung. Diese neuen Formulierungsplattformen stellen neue Grundlagen für verschiedene Arzneistoffe und Hautzustände dar. Diese Formulierungen wurden unter der Anwendung des Modellarzneistoffes, Betamethasonvalerat entwickelt. Die neuen entwickelten Formulierungen

können zur Therapie solcher Hautkrankheiten wie Psoriasis und seborrhoische Dermatitis auf behaarten Körperarealen angewendet werden. Außer Kortikosteroiden können auch Arzneistoffe aus anderen therapeutischen Gruppen, wie zum Beispiel Antimykotika oder Antibiotika, in diese Schaumvehikel eingearbeitet werden.

Zwei Formulierungsansätze wurden für beide Plattformen eingesetzt: Die Entwicklung eines Schaums auf der Basis einer niedrig-viskosen O/W-Emulsion und Entwicklung eines lösungsbasierten Schaums. Das entsprechend geeignete Vehikel kann dann in Abhängigkeit von dem Applikationsort und dem Hautzustand, wie zum Beispiel Hauthydratationszustand und Behaarungsdichte, gewählt werden.

Nanoemulsionen mit einem niedrigen Gehalt einer Ölphase wurden mit dem Verfahren der Hochenergieemulgierung entwickelt und hergestellt. Sowohl eine ausreichende Stabilität der Formulierungen während der Lagerung als auch die Abgabe einer äquivalenten Dosis des Wirkstoffes wurde gewährleistet.

Bei der Herstellung von lösungsbasierten Schäumen wurden Lösungsmittel wie Propylenglykol, Hexylenglykol, N-Methyl-2-Pyrrolidon und Methylisosorbid verwendet. Die entwickelten Formulierungen waren sowohl durch eine zufrieden stellende Aufschäumbarkeit als auch eine ausreichende Schaumstabilität und ausgezeichnete kosmetische Eigenschaften gekennzeichnet.

Es konnte gezeigt werden, dass der Airspray<sup>®</sup> Schaumspender zur Herstellung pharmazeutischer treibgasfreier Schäume gut geeignet ist. Der Schaumspender ist in der Lage, eine uniforme Dosis des Kortikosteroids abzugeben. Die obere Viskositätsgrenze wurde für den oben genannten Schaumspender festgestellt; sie betrug 30 mPa·s. Oberhalb dieser Grenze ist keine Schaumproduktion möglich.

Während der Formulierungsentwicklung wurde gezeigt, dass die Zugabe von Polymeren wie Hydroxypropylmethylcellulose, Methylcellulose, Xanthan und

deren Kombinationen zu den Rezepturen eine Verbesserung der Aufschäumbarkeit und der Schaumstabilität hervorrufen kann.

Anhand der durchgeführten Permeationsstudien durch Schweinehaut wurde gezeigt, dass die systemische Absorption des Modellwirkstoffes aus einer der entwickelten Formulierung geringer als die systemische Absorption des Modellwirkstoffes aus Deflatop<sup>®</sup> Schaum und vergleichbar zur systemischen Absorption des Modellwirkstoffes aus Betagalen<sup>®</sup> Lotion ist.

## 7 Appendix

### HPLC analysis

Betamethsone-17-valerate was assayed by HPLC on a reverse phase column with external calibration and UV detection (Kontron, Kontron Instruments, Italy). The measurements were carried out under isocratic conditions. The mobile phase consisted of solvents in HPLC-quality and double distilled water from a Finn Aqua 75-E-4 distillery (FinnAqua, Finland). The mobile phase was degassed at ambient temperature.

<u>Precolumn:</u>	LiCroChart 4-4
	Merck KGaA, Germany
<u>Column:</u>	LiCroChart 125-4; 12.5 cm
	Merck KGaA, Germany
<u>Stationary phase:</u>	LiCrospher 100 RP-18 (5 $\mu$ m)
<u>Mobile phase:</u>	Acetonitrile      450 ml
	Water                550 ml
<u>Wavelength:</u>	254 nm
<u>Flow rate:</u>	1.2 mL/min
<u>Injected volume:</u>	80 $\mu$ l



### **Skin biopsy and microscopy**

Skin biopsies were taken from the both sides of pig ear. They were fixed in formaldehyde solution (Alfa Aesar GmbH & Co., Germany), dehydrated (Tissue-Tek<sup>R</sup> VIP, Sakura, Germany), treated with ethanol 50%, 60%, 70%, 96% (v/v, C. Roth GmbH CoKG, Germany), isopropanol (C. Roth GmbH CoKG, Germany), xylol (Alfa Aesar GmbH & Co., Germany) and subsequently embedded in paraffin (MKR & Co. Ltd, UK). Sections of approx. 4 µm thickness were cut vertically to the surface using a microtome (Jung AG, Germany). The paraffin layer was removed through tempering the samples in a heated cabinet for 40 min at 68°C. The sections were immersed subsequently in xylol, ethanol 96% (v/v), ethanol 70% (v/v) and distilled water dips. Afterwards, the sections were stained with haematoxyline (Gill III, Shandon, Germany) / eosine (Abbey Color, USA) following standard histological procedures. Images were taken using a digital microscope (VHX-500, Keyence, Japan).

### Foamability method, modified after Jellinek (1959) / Foaming agents

<i>Trade name</i>	<i>Group</i>	<i>C, %</i>	<i>Scale_1<sup>1</sup></i>	<i>Scale_2<sup>2</sup></i>	<i>Scale_3<sup>3</sup></i>
<i>Medialan<sup>®</sup></i>	<i>Anionic</i>	1	4.5	4.0	3.0
		2	4.0	3.0	2.0
		3	4.5	4.0	2.0
		4	5.0	4.5	4.0
		5	2.0	2.0	1.5
<i>Hostapon<sup>®</sup></i>	<i>Anionic</i>	1	4.5	4.3	4.0
		2	4.0	4.0	4.0
		3	4.5	4.3	4.2
		4	5.0	4.8	4.5
		5	3.5	3.0	1.2
<i>Serwet<sup>®</sup> WH 172</i>	<i>Anionic</i>	1	6.5	6.0	6.0
		2	5.8	5.0	4.8
		3	5.0	5.0	5.0
		4	6.0	5.5	5.5
		5	5.5	5.2	5.0
<i>Rewopol<sup>®</sup> SB CS 50K</i>	<i>Anionic</i>	1	4.5	4.2	4.0
		2	4.2	4.0	4.0
		3	4.5	4.2	4.0
		4	4.3	4.0	4.0
		5	4.0	3.8	3.5
<i>Texapon<sup>®</sup> K 12</i>	<i>Anionic</i>	1	7.0	5.0	5.0
		2	7.0	6.0	5.0
		3	7.0	6.0	6.0
		4	7.0	6.0	6.0
		5	7.0	6.0	6.0
<i>TEGO Betain<sup>®</sup> L7</i>	<i>Amphoteric</i>	1	4.8	4.5	4.5
		2	5.1	5.0	5.0
		3	5.5	5.5	5.5
		4	5.2	5.0	5.0
		5	5.3	5.2	5.1
<i>TEGO Betain<sup>®</sup> 810</i>	<i>Amphoteric</i>	1	3.0	1.5	1.2
		2	2.0	1.8	1.7
		3	4.2	1.2	0
		4	4.0	3.8	3.5
		5	4.2	3.8	3.2
<i>TEGO Care<sup>®</sup> CG90</i>	<i>Nonionic</i>	1	2.0	2.0	2.0
		2	1.5	1.5	1.5
		3	1.5	1.5	1.5
		4	-	-	-
		5	-	-	-
<i>Plantaren<sup>®</sup> 818 UP</i>	<i>Nonionic</i>	1	5.0	4.5	4.5
		2	5.5	5.3	5.0
		3	6.0	5.8	5.8
		4	5.5	5.2	5.0
		5	6.0	5.5	5.5
<i>Sucrose laurate</i>	<i>Nonionic</i>	1	2.0	2.0	1.8
		2	2.2	2.2	2.0
		3	2.0	2.0	1.8
		4	2.5	2.3	2.2
		5	3.5	3.0	2.8
<i>Imwitor<sup>®</sup> 380</i>	<i>Nonionic</i>	1	1.3	1.2	1.2
		2	1.3	1.2	1.2
		3	1.5	1.3	1.2
		4	1.5	1.3	1.3
		5	1.5	1.3	1.2

<i>Trade name</i>	<i>Group</i>	<i>C, %</i>	<i>Scale_1<sup>1</sup></i>	<i>Scale_2<sup>2</sup></i>	<i>Scale_3<sup>3</sup></i>
<i>ABIL<sup>®</sup> Care 85</i>	<i>Nonionic</i>	1	1.4	1.0	0
		2	1.4	1.0	0
		3	1.1	1.1	0
		4	1.1	1.1	0
		5	1.1	1.1	0
<i>Teginacid<sup>®</sup>C</i>	<i>Nonionic</i>	1	2.1	1.8	1.5
		2	2.3	2.1	2.0
		3	2.5	2.2	2.1
		4	2.5	2.2	2.0
		5	2.8	2.3	2.1
<i>Eumulgin<sup>®</sup>B2</i>	<i>Nonionic</i>	1	2.0	1.8	1.5
		2	1.3	1.2	1.1
		3	3.8	2.0	1.5
		4	2.5	1.5	1.2
		5	2.0	1.5	1.3
<i>TAGAT<sup>®</sup> CH 40</i>	<i>Nonionic</i>	1	1.5	1.2	1.1
		2	1.5	1.2	1.2
		3	1.8	1.3	1.2
		4	1.8	1.5	1.3
		5	1.8	1.5	1.3
<i>TAGAT<sup>®</sup> S2</i>	<i>Nonionic</i>	1	1.2	1.2	1.2
		2	1.2	1.2	1.2
		3	1.5	1.3	1.2
		4	1.5	1.3	1.2
		5	1.5	1.4	1.2
<i>TAGAT<sup>®</sup> 02</i>	<i>Nonionic</i>	1	2.1	2.0	1.9
		2	2.1	2.1	2.0
		3	2.1	2.0	1.8
		4	2.5	2.3	2.0
		5	2.3	2.0	2.0
<i>TAGAT<sup>®</sup> L2</i>	<i>Nonionic</i>	1	3.0	2.8	2.5
		2	2.5	2.2	2.0
		3	3.0	2.5	2.2
		4	3.0	2.5	2.2
		5	2.3	2.0	1.8
<i>TEGO<sup>®</sup> SML</i>	<i>Nonionic</i>	1	1.2	1.2	1.2
		2	1.2	1.1	1.1
		3	1.2	1.1	1.1
		4	1.2	1.1	1.1
		5	1.5	1.3	1.2
<i>Brij<sup>®</sup> 35</i>	<i>Nonionic</i>	1	6.0	4.0	4.0
		2	7.0	2.0	1.3
		3	5.5	2.0	1.3
		4	6.0	2.0	1.4
		5	5.0	2.0	1.5
<i>Brij<sup>®</sup> 58</i>	<i>Nonionic</i>	1	2.0	2.0	1.8
		2	2.0	1.8	1.6
		3	2.3	1.8	1.5
		4	3.0	3.0	3.0
		5	2.0	1.5	1.5
<i>Brij<sup>®</sup> 98</i>	<i>Nonionic</i>	1	4.0	3.2	3.0
		2	2.0	2.0	2.0
		3	5.0	4.0	3.5
		4	4.0	3.5	3.5
		5	4.0	4.0	4.0

<i>Trade name</i>	<i>Group</i>	<i>C, %</i>	<i>Scale_1<sup>1</sup></i>	<i>Scale_2<sup>2</sup></i>	<i>Scale_3<sup>3</sup></i>
<i>Tween<sup>®</sup> 20</i>	<i>Nonionic</i>	<i>1</i>	<i>3.0</i>	<i>2.5</i>	<i>2.2</i>
		<i>2</i>	<i>4.0</i>	<i>3.8</i>	<i>3.8</i>
		<i>3</i>	<i>4.2</i>	<i>4.0</i>	<i>3.8</i>
		<i>4</i>	<i>4.0</i>	<i>4.0</i>	<i>3.6</i>
		<i>5</i>	<i>4.0</i>	<i>3.8</i>	<i>3.8</i>
<i>Tween<sup>®</sup> 40</i>	<i>Nonionic</i>	<i>1</i>	<i>1.5</i>	<i>1.3</i>	<i>1.3</i>
		<i>2</i>	<i>1.5</i>	<i>1.3</i>	<i>1.3</i>
		<i>3</i>	<i>2.0</i>	<i>1.8</i>	<i>1.5</i>
		<i>4</i>	<i>1.5</i>	<i>1.5</i>	<i>1.3</i>
		<i>5</i>	<i>1.5</i>	<i>1.5</i>	<i>1.3</i>
<i>Tween<sup>®</sup> 60</i>	<i>Nonionic</i>	<i>1</i>	<i>1.5</i>	<i>1.5</i>	<i>1.4</i>
		<i>2</i>	<i>1.8</i>	<i>1.5</i>	<i>1.4</i>
		<i>3</i>	<i>1.5</i>	<i>1.3</i>	<i>1.3</i>
		<i>4</i>	<i>1.4</i>	<i>1.4</i>	<i>1.2</i>
		<i>5</i>	<i>1.5</i>	<i>1.3</i>	<i>1.2</i>
<i>Tween<sup>®</sup> 80</i>	<i>Nonionic</i>	<i>1</i>	<i>1.8</i>	<i>1.8</i>	<i>1.6</i>
		<i>2</i>	<i>2.0</i>	<i>1.8</i>	<i>1.8</i>
		<i>3</i>	<i>3.0</i>	<i>3.0</i>	<i>3.0</i>
		<i>4</i>	<i>1.8</i>	<i>1.5</i>	<i>1.5</i>
		<i>5</i>	<i>2.0</i>	<i>1.8</i>	<i>1.6</i>

**1 – direct after foam production**

**2 – after 15 min**

**3 – after 30 min**

**Composition of Deflatop<sup>®</sup> foam**

0.1% Betamethasone-17-valerate

Hexadecan-1-ol

Stearyl alcohol

Poylsorbat 60

Ethanol 99.7%

Purified water

Propylene glycol

Citric acid

Potassium citrate

Pressurized with a hydrocarbon (butane/propane/2-methylpropene) propellant

**Composition of Betagalen<sup>®</sup> lotion**

0.1% Betamethasone-17-valerate

Phenoxy ethanol

Decyl oleate

Cetyl stearyl alcohol

Cetomacrogol 1000

Propylene glycol

Dimeticon 20

Citric acid

Sodium monohydrogene phosphate

**Equipment**

Analytical balance	Sartorius A200S, Sartorius AG, Germany
Autosampler / HPLC	Kontron Autosampler 565, Kontron Instruments, Italy
Detector / HPLC	Kontron HPLC-Detector 540, Kontron Instruments, Italy
Microanalytical balance	Sartorius 4501 micro, Sartorius AG, Germany
pH-meter	pH 540 GLP, WTW GmbH & Co. KG, Germany
Pump / HPLC	Kontron, Kontron Instruments, Italy
Software / HPLC	Kontron Data System, Kontron Instruments, Italy
Thermometer	VOLTCRAFT® Data-Logger Thermometer 306 Voltcraft AG, Germany
Thermostat bath	HAAKE K, HAAKE, Germany
Thermostatic unit	Rumed 3501, Rubarth Apparate GmbH, Germany
Timer	Hanhart, Hanhart, Germany
Ultrasound bath	Bandelin Sonorex Super RK 106, Bandelin electronic, Germany
Ultra-turrax	T25 basic IKA Labortechnik, Germany
Volumetric pipette	Eppendorf AG, Germany

**Chemicals**

Acetonitrile	C. Roth GmbH CoKG, Germany
Kalium dihydrogen phosphate monohydrate	Merck KG, Germany
Methanol	C. Roth GmbH & CoKG, Germany
Methyl- $\beta$ -cyclodextrine	Chemos GmbH, Germany
Sodium benzoate	Riedel-de Haen AG, Germany
Sodium dihydrogen phosphate	Merck KG, Germany

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