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Investigation of the effect of polymers on dermal foam properties using the QbD approach

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ABSTRACT

Dermal foams are promising drug delivery systems due to their many advantages and ease of application. Foams are also considered a novelty in the field of dermatology. In particular, they are beneficial for the treatment of skin conditions where patients have highly inflamed, swollen, infected and sensitive skin, as the application of the foam to the skin surface to be treated minimizes the need for skin contact. In order to formulate foams, it is necessary to know which material and process parameters influence the quality characteristics of foams and which methods can be used to study foams; this part of the research is assisted by the QbD approach. By using the QbD concept, it contributed during the development process to ensure quality-based development. With initial risk assessment, the critical material attributes (CMAs) and the critical process parameters (CPPs) were identified to ensure the required critical quality attributes (CQAs). During the initial risk assessment, five high-risk CQAs, namely foam volume stability, foam expansion, cross point, the initial values of the number and size of bubbles, and three medium-risk CQAs, namely spreadability, relative foam density and viscosity of the liquid system were identified and investigated. In this research, different types of polymers (xanthan gum, hydroxyethylcellulose, different types of hyaluronic acids) were used to improve the properties of foam formulations. The formulations containing xanthan gum and high molecular weight hyaluronic acid had good foam properties and will be appropriate delivery systems for an active pharmaceutical ingredient. Overall, the polymer content had a great effect on the properties of the foams. Different polymers affect the properties of foams in different ways. When used in combination, the methods reinforce each other and help to select a formula for dermal application.

1. Introduction

Foams are part of our daily lives in the field of cosmetics, as well as in the pharmaceutical and food industries. Pharmaceutical foams are usually applied topically (Zhao et al., 2010) as dermal, vaginal, or rectal administration, but there are other special applications such as parenteral and oral (Farkas et al., 2019; Hoc and Haznar-Garbacz, 2021). It is a preferred delivery system used to improve wound healing and to treat sunburn or skin diseases such as psoriasis and is also used in the pediatric field (Velasco et al., 2019).

Foams have many beneficial properties over conventional carrier systems. Their high rate of expansion allows large skin surfaces to be covered rapidly. It is really advantageous for patients who need to treat highly inflamed, swollen, abraded, infected and sensitive skin because the application of foam minimizes the need for touch, resulting in enhanced patient compliance (Parsa et al., 2019). Dermal foams are used to treat the skin or specific mucosal surfaces in order to exert their effects locally or by absorption through the skin. By applying liquid foams dermally, a local effect can be easily achieved. The transdermal delivery route allows a smaller amount of drugs to be used. It avoids not only the destructive effect of the gastrointestinal tract but also the enterohepatic circulation of the drug, making it less likely to cause systemic side effects. However, the main limitation of using foams is that they are thermodynamically unstable, therefore foams are prone to decay. The composition, both excipients and active ingredients, may affect the stability and quality of foams (Parsa et al., 2019; Cantat and Cohen-Addad, 15 June 2021).

In terms of their structure, foams are produced by dispersing a gaseous substance in a solid or liquid dispersion medium. Before formulation, it is essential to select suitable excipients, which greatly

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Table 1
Composition of different formulations.

	Foam 1 (F-0polymer)	Foam 2 (F-XANT_0.1)	Foam 3 (F-XANT_0.2)	Foam 4 (F-HEC_0.2)	Foam 5 (F-HEC_0.4)	Foam 6 (F-HA_{LMW}_0.1)	Foam 7 (F-HA_{LMW}_0.2)	Foam 8 (F-HA_{HMW}_0.1)	Foam 9 (F-HA_{HMW}_0.2)	Foam 10 (F-HA_{CL}_0.1)	Foam 11 (F-HA_{CL}_0.2)
Phase A											
Labrasol ALF /surfactant/	+	+	+	+	+	+	+	+	+	+	+
Kolliphor RH40 /surfactant/	+	+	+	+	+	+	+	+	+	+	+
Phase B											
Xanthan gum (Xant.) /polymer/	–	0.1%	0.2%	–	–	–	–	–	–	–	–
Hydroxyethyl-cellulose (HEC) /polymer/	–	–	–	0.2%	0.4%	–	–	–	–	–	–
Low-molecular-weight hyaluronic acid /polymer/	–	–	–	–	–	0.1%	0.2%	–	–	–	–
High-molecular-weight hyaluronic acid /polymer/	–	–	–	–	–	–	–	0.1%	0.2%	–	–
Cross-linked hyaluronic acid /polymer/	–	–	–	–	–	–	–	–	–	0.1%	0.2%
Purified water /solvent/	+	+	+	+	+	+	+	+	+	+	+
Phase C											
Phenoxyethanol /preservative/	+	+	+	+	+	+	+	+	+	+	+

affect foam stability. They usually contain surface-active agents, solvents, foam stabilizers, preservatives and may also include penetration enhancers (Parsa et al., 2019). Aerosols are pressurized in cans. These containers are capable of ex tempore foam formation. Propellant-free liquid foams are produced by adding air to a polymer solution with stirring or a propellant-free pump device. Liquid foams have many unique properties thanks to their ability to exhibit both liquid and solid behavior (Cantat and Cohen-Addad, 15 June 2021).

As noted above, the lifetime and the stability of the foam can be increased by using surfactants and foam stabilizing excipients (Langevin 2017; Bureiko et al., 2015). Increasing the viscosity of the liquid phase with polymers may lead to the stabilization of the foam structure. For instance, polymers used in foams can be naturally occurring polymers such as xanthan gum, agar-agar, tragacanth gum; acidic polymers such as palmitic acid, stearic acid; and semi-synthetic polymers such as cellulose ethers (Parsa et al., 2019). In addition to conventional polymers, there is a lack of literature on the effect of hyaluronic acid on foam stability. Hyaluronic acid plays a crucial role in skin moisture and helps the tissue regeneration process. Furthermore, it has an anti-aging effect and reduces dermatitis (Draelos 2011; Berkó et al., 2013).

There are four different main parallel mechanisms that occur when foam is decaying. These are: drainage, coalescence, disproportionation (Ostwald ripening) and bursting of bubbles. Drainage is when the liquid drains off through the Plateau borders due to gravity. These Plateau borders act as paths for the liquid to flow down through. As this happens, the lamellas of each bubble will get thinner and the foam will dry out. This results in the liquid getting to the bottom, which increases over time. In the case of coalescence, surface tension acts as a driving force when two bubbles get close to each other. Then they will conjoin and form a single bubble. The next way of foam decay is similar to coalescence but the mechanism is slightly different. Both coalescence and Ostwald ripening describe the formation of large masses. Coalescence is the process in which a few smaller masses merge with each other to form a large mass. These small masses can be droplets, bubbles, particles, and so on. When they come in contact, they tend to fuse and form a single drop, particle, or bubble. The main reason for Ostwald ripening is that large particles are thermodynamically more favorable than small particles. For the same reason, the process of Ostwald ripening is a spontaneous process. However, during Ostwald ripening the small particles dissolve in the solution and re-deposit to form large masses. Finally, the bubble form is not a stable state so they burst after a certain time. The bursting of foam lamellas leads to the elimination of air from the foam (Arzhavitina and Steckel, 2010; Karakashev et al., 2012; Guerrero et al., 2013).

Stabilization and thus the right quality is the first and the leading requirement for pharmaceuticals in development (Sivaraman and Banga, 2015; Anita Kovács et al., 2020). Nowadays, the Quality by Design approach in the design stage helps the development in pharmaceutical industry (Radhakrishnan et al., 2018). Generally, QbD aims to improve the efficiency of the design process, reducing costs in different stages of development. Initially, it records the critical quality attributes and critical process parameters that affect the quality of the product. In summary, QbD is science-based and risk-based drug development that begins with predetermined goals. If the design and testing of the active substance and pharmaceutical form are based on the QbD approach in the research phase, the results obtained during the research can be more effectively integrated into the development process. The first step of the QbD approach is to define the Quality Target Product Profile (QTTP), which is the goal of the development. The next step is to identify critical quality attributes (CQA), critical material attributes (CMAs) and critical process parameters (CPPs), and then parameters that potentially affect product quality are selected by risk assessment (A Kovács et al., 2017.; Visser et al., 2015; Yu, 2008). Although, the QbD approach is an innovative method in the field of drug development, its implementation is

Table 2
Quality target product profiles (QTPPs).

QTPP parameters	Target	Justification
Route of administration	Dermal	The dermal delivery of drugs is an opportunity to avoid systemic side effects. It is non-invasive, thus increasing patient compliance.
Dosage form	Foam	The good spreadability of the foams on the skin ensures the immediate release of the active ingredient, no rubbing on the skin is necessary (Parsa et al., 2019).
Site of action	Topical	Most medicated foams contain antiseptic, antifungal, anti-inflammatory, local anesthetic agents, as well as skin moisturizers and emollients (Parsa et al., 2019; Tamarkin et al., 2006). Absorption into the systemic circulation is not the aim of these formulations.
Stability of liquid system	There is no sign of instability, homogenous	Stability is an important parameter of the liquid system as it can affect foaming and foam stability.
Appearance of liquid system	Transparent or white, homogeneous	An esthetic preparation needs to be formulated for good patient adherence.
Stability of foam system	Adequate stability for the dermal route of administration	Adequate stability of the foam system is required for the foam to remain at the site of application.
Appearance of foam system	White	To increase patient compliance.
Polymer content	Increasing foam stability	Increasing the viscosity of the liquid phase with polymers can lead to the stabilization of the foam structure.

Table 3
Critical quality attributes (CQAs) of the foams.

CQA	Target	Justification
Bulk liquid properties		
pH	4–8	Ideal pH of topical formulations for the safety of the product and the skin. (Lambers et al., 2006).
Viscosity	20–200 mPas	Viscosity influences the stability of foam systems and their applicability to the skin.
Surface tension	27–30 mN/m	The surface tension of the initial liquid is important for bubble growth. The lower the surface tension of the initial liquid, the less force is required for the bubbles to blow (Farkas et al., 2021).
Foam properties		
Size of bubbles (initial value)	200–500,000 μm^2	The unique bubble size provides information on the stability and homogeneity of the foam (Farkas et al., 2021).
Number of bubbles (initial values)	100 <	The number of bubbles provides information on the stability of the foam.
Foam volume stability (FVS %)	50% ≤	This parameter indicates the rate of foam collapse. Stability is important to ensure that the active substance has a sufficient contact time (Kamal 2019).
Foam expansion (FE%)	100 ≤	Foam expansion is necessary to make the preparation suitable for treating large surfaces (Bikard et al., 2007).
Relative foam density (RFD)	≤ 0.5	One of the foam stability parameters. It also indicates the firmness of the foam (Mirtič et al., 2017).
Rheology: Cross point	Detectable within the strain value range of 0.1% to 100%	The presence of the cross point ensures that the foam has a coherent structure.
Spreadability	The force required to spread a cream is about 500 mN (Yadav et al., 2014).	In the case of foams, the goal is to spread on their own.

challenging for developers, as the incorporation of elements of the QbD concept varies from one pharmaceutical formulation to another.

The aim of our research was to design stable foam compositions based on the QbD approach and to determine the proper methods to investigate their physicochemical and structural properties and to compare the results of different methods. A further aim was to investigate the effect of different polymers on foam stability as well as on foam structure.

2. Materials and methods

2.1. Materials

Kolliphor RH 40 was obtained from BASF SE Chemtrade GmbH (Ludwigshafen, Germany). Labrasol ALF was from Gattefossé (Saint-Priest Cedex, France), Xantural® 180 was provided by CP Kelco A Huber Company (Atlanta, GA, USA). Verstatil PC was purchased from Biesterfeld GmbH (Hamburg, Germany). Hydroxyethylcellulose (Ph. Eur. 9.) was supplied by Molar Chemicals Ltd. (Budapest, Hungary). Purified and deionized water was used (Milli-Q system, Millipore, Milford, MA, USA). HyaCare50, HyaCare Filler CL and HyaCare Tremella were product samples from Evonik Industries AG (Essen, North Rhine-Westphalia, Germany).

2.2. Methods

2.2.1. Quality by design methodology

2.2.1.1. Definition of quality target product profile (QTPP). The first step in QbD-based development is to define the target product and to summarize the quality characteristics of the product. This determines the efficiency, the delivery route, the dosage form, the packaging, the appearance and therapeutic indication, etc. During development, QTPP parameters form the basis of development (Grangeia et al., 2020; Bakonyi et al., 2018; Kis et al., 2019).

2.2.1.2. Definition of CQA, CMA, CPP. In order to ensure the desired quality of the pharmaceutical product during development and production, the second step is to define the quality attributes. In the case of medicated foam formulations, the pH and viscosity of the bulk liquid, the homogeneity of bubble size and the skin penetration of the active pharmaceutical ingredient (API) etc. can also be critical quality parameters.

As a third step, it is necessary to determine the material and process parameters that can affect the critical quality attributes of the foams. The determination of these parameters helps to find the relationship between material properties and process parameters that are related to critical product quality parameters (Kovács et al., 2017; Charoo et al., 2012).

2.2.1.3. Risk assessment: quality tools. The QbD concept is based on risk assessment. Risk assessment can be used to identify critical parameters that have an impact on critical quality attributes. In our research, we applied quality tools such as the risk estimate matrix (REM), Pareto analysis and Ishikawa diagram. We started the risk assessment with a

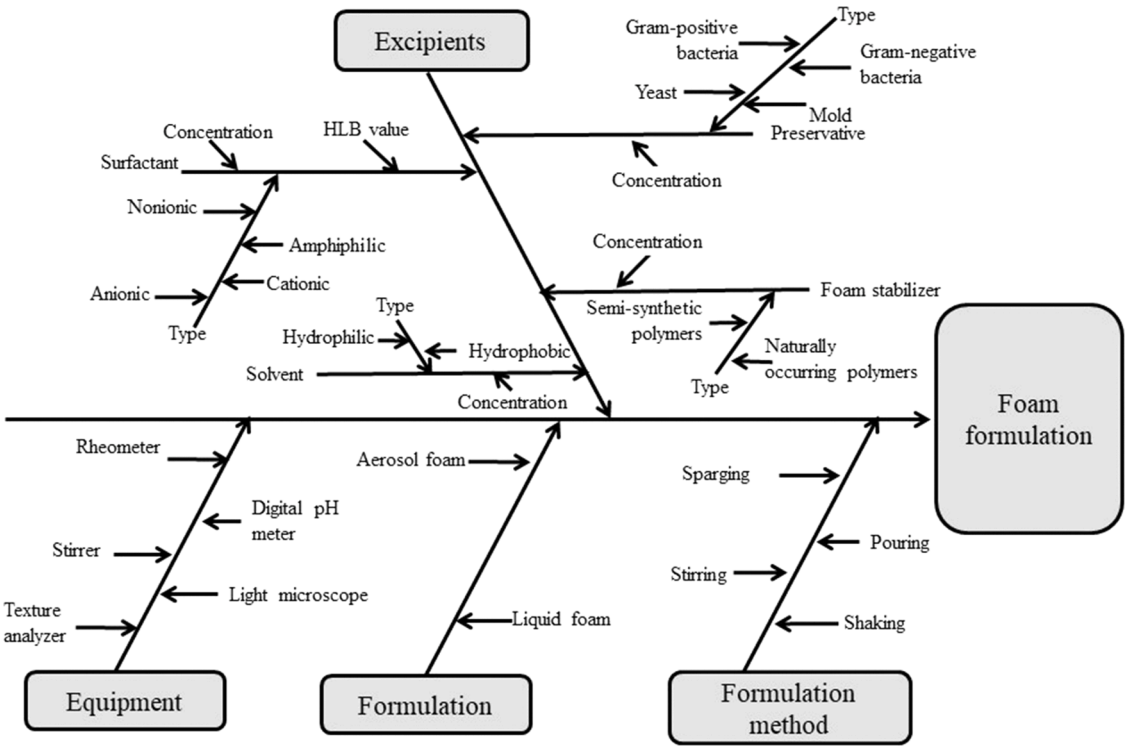

Fig. 1. Ishikawa diagram.

Table 4
Risk estimation matrix of QTPP and CQA parameters (LeanQbD™ Software) Low = low-risk, Medium = medium-risk, High = high-risk parameters during formulation.

	Route of administration (M)	Dosage form (M)	Site of action (M)	Stability of liquid system (M)	Appearance of liquid system (M)	Stability of foam system (M)	Appearance of foam system (M)	Polymer content (M)
pH	Low	Low	Low	Medium	Low	Medium	Low	Low
Viscosity of liquid system	Low	Low	Low	Medium	Medium	Medium	Low	High
Surface tension	Low	Low	Low	Medium	Low	Medium	Low	Medium
Size of bubbles (initial)	Low	High	Low	High	Low	High	Low	Medium
Number of bubbles (initial)	Low	High	Low	High	Low	High	Low	Medium
Foam volume stability	Medium	Medium	Low	High	Low	High	Low	High
Foam expansion	Medium	Medium	Low	High	Low	High	Low	High
Relative foam density	Medium	Medium	Low	Medium	Low	Medium	Low	High
Cross point	High	Medium	Low	Low	Low	High	Medium	High
Spreadability	Medium	High	Low	Medium	Low	High	Low	Medium

popular quality tool method called the Ishikawa diagram. This method helps to collect the possible root causes influencing the quality of foams. The next step was to determine the critical parameters with Pareto analysis, which is also called ABC analysis (Kovács et al., 2017). The items in Category A are the high-risk parameters, in Category B the medium-risk parameters and in Category C the low-risk parameters (ICH Guideline Q9 on Quality Risk Management, 2021). REM was used to define the level of the risk parameters and the connection between quality attributes and CPPs, CMAs. The LeanQbD™ software (QbD Works LLC, Fremont, CA, USA) was used for risk assessment.

2.2.2. Preparation of foams

Different foam compositions (Foam 1-Foam 11) were prepared (Table 1.) The lifetime of the foam can be extended by increasing the viscosity of the liquid phase among the air bubbles. One possible solution is the use of polymers in the composition. Therefore, the formulated foams contain different types of polymers in different concentrations (Phase B) (Vandewalle et al., 2011). The foaming agents are mainly surfactants (Phase A). All formulations contain the same amount of surfactants. Phase C contains the microbiological preservative.

The first step of foam preparation was to prepare Phase B, where the swelling of polymers lasted for 2 h in purified water. Phase C was then added to Phase A. The last step was the addition of Phase B to the mixture of Phases A and C. After the preparation of the samples, the liquids were stored in a well-sealed jar until the start of the examination. Before each investigation, 30 g of bulk liquid was stirred with an IKA stirrer for 5 min at 2000 rpm based on preformulation studies.

2.2.3. Investigation of foam properties

2.2.3.4. Macroscopic characterization of foams. The macroscopic properties of the foams were determined by using the cylinder method

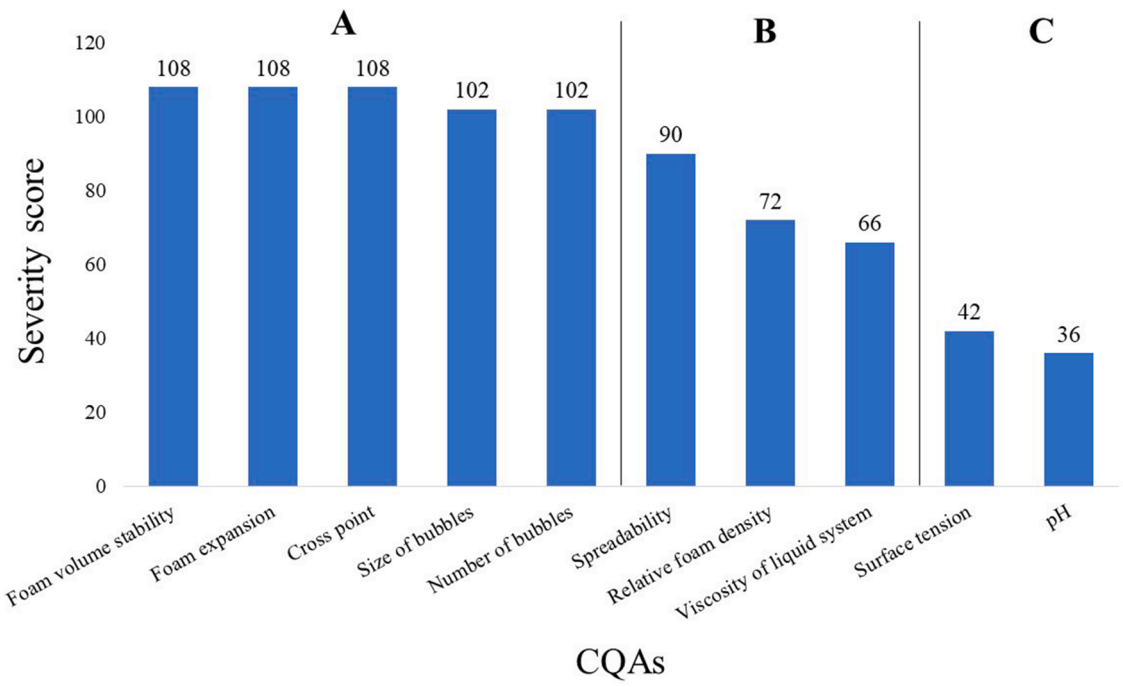

Fig. 2. Pareto chart of CQA parameters.

Table 5
Risk estimation matrix of CPPs/CMAs and CQA parameters (LeanQbD™ Software) Low = low-risk, Medium = medium-risk, High = high-risk parameters during formulation.

	Composition					Production		
	Polymer concentration	Polymer type	Surfactant concentration	Surfactant type	Preservative type	Stirring speed	Stirring time	Stirring temperature
pH	Low	High	Low	Low	Medium	Low	Low	Low
Viscosity of liquid system	High	High	Medium	Medium	Medium	Medium	Medium	Medium
Surface tension	Low	Medium	Low	Low	Low	Low	Low	Low
Size of bubbles (initial)	High	Medium	Medium	Medium	Low	High	High	Low
Number of bubbles (initial)	High	Medium	Medium	Medium	Low	High	High	Low
Foam volume stability	Medium	High	Low	Low	Low	Medium	Medium	Low
Foam expansion	High	Medium	Medium	Medium	Low	High	High	Low
Relative foam density	High	Medium	Medium	Medium	Low	High	High	Low
Cross point	High	High	Medium	Medium	Medium	Medium	Medium	Low
Spreadability	High	High	Medium	Medium	Low	Medium	Medium	Low

(Parsa et al., 2019). After stirring the bulk liquid for 5 min, the foam was filled into a glass measuring cylinder and the initial and the aged volumes of the foam after 30 min were recorded. The following parameters can be determined by macroscopic tests:

- relative foam density (RFD)
- foam expansion (FE,%)
- foam volume stability (FVS,%).

These parameters were calculated using the formula below (Arzhavitina and Steckel, 2010; Mirtič et al., 2017).

$$RFD = \frac{m(foam)}{m(water)} \quad (1)$$

The European Pharmacopoeia describes RFD in the Monograph "Medicated foams". It equals the weight of the test sample of foam compared to the weight of the same volume of water.

$$FE(\%) = \frac{V(foam) - V(formulation)}{V(formulation)} \cdot 100\% \quad (2)$$

where V(formulation) is the volume of the formulation [ml] required to produce V(foam) [ml] (Parsa et al., 2019).

$$FVS(\%) = \frac{V(foam,\ 30\ min)}{V(foam)} \cdot 100\% \quad (3)$$

where V(foam,30 min) is the foam volume after 30 min [ml].

2.2.4. Microscopic examination

The microscopic measurements were performed with Leica DM6 B Fully Automated Upright Microscope System (Leica Biosystems GmbH, Wetzlar, Germany) The structure of the foam from the microscopic images was analyzed after a predetermined time (0, 10, 20, 30 min).

Through microscopic examination, we can determine the structure and bubble size of the foams, providing information about the foam kinetics.

Foam uniformity can also be determined with this method as the homogeneity of air bubbles (Zhao et al., 2009). The size, roundness, and the aspect ratio of incorporated air bubbles as well as bubble amount in a predetermined area are the parameters of interest in foam

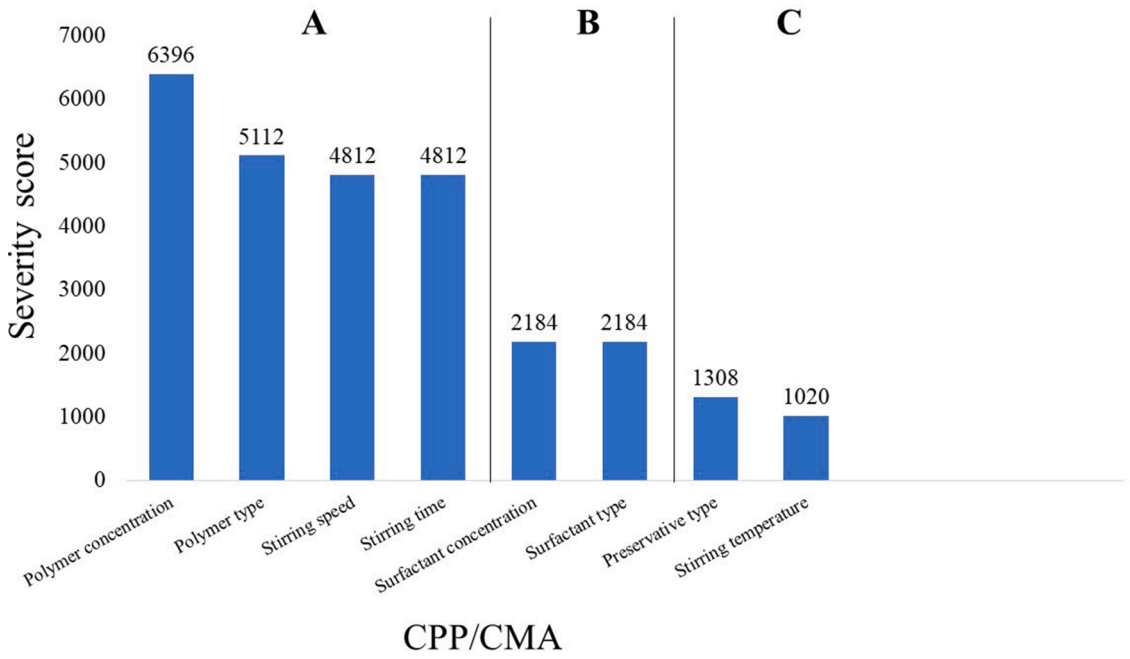

Fig. 3. Pareto chart of CPP/CMA parameters.

characterization.

With the microscopic method, the temporal stability of foams as well as the kinetics of the destabilization mechanism were determined. During the examination, the change in bubble size over time was also observed, which gave information about the stability of the foam samples.

2.2.5. Rheology

The rheological properties were studied with an Anton Paar Physica MCR302 Rheometer (Anton Paar, Graz, Austria). The measuring device was of the parallel plate type (diameter 50 mm, gap height 2 mm). The flow curves were recorded over the shear rate range from 0.1 to 100 and from 100 to 0.1 1/s at 25 °C for the liquid formula.

The foams were analyzed by means of amplitude sweeps, where the strain value was increased from 0.1% to 100%, and the angular frequency was 10 rad/s (Kealy et al., 2008).

2.2.6. Spreadability

The dermal application of any semi-solid dosage forms can be modeled with a texture analyzer. The forces required to spread the product on the skin were measured. The spreadability of the foams was investigated with a TA.XT plus Texture Analyzer (Stable Micro Systems Ltd., Vienna Court, Lammas Road, Godalming, Surrey, UK. GU7 1YL) using a TTC Spreadability Rig, which comprises a male 90° cone probe and a precisely matched female perspex cone-shaped product holder (Bayarri et al., 2012). During the test, the male cone immerses into the sample in the female cone until a gap of 1 mm is reached. The product is forced to flow outward at 45° between the male and female cone surfaces during the test, the ease of which indicates the degree of spreadability. The spreadability of the sample characterized the maximum force (firmness) recorded in the force-distance curve.

3. Results and discussion

3.1. Determination of QTPP and CQAs

The QTPP of the foams containing polymers includes the route of administration, dosage form, site of action, appearance of the drug delivery system, stability of the liquid system and the foam system, appearance of the liquid and the foam system and the polymer content of the foam for stability and skin application. The properties of the liquid system and the foam formed depend on the characteristics of the excipients used. The properties of the foams are influenced by several excipients, from which the polymer content was selected, and the influence of them was investigated. The polymer content can influence the stability of the foams. CQAs are defined from QTPPs. The CQAs were defined with the consideration of the attributes of the liquid system and the formed foam, too. On the one hand, the properties of the liquid systems are, for example, physical properties, viscosity, pH, surface tension. On the other hand, the formed foam system has attributes such as bubble size, foam stability, foam expansion, foam density, rheological properties, spreadability Tables 2. and 3 show the QTPP and CQA parameters with their targets and their justifications.

After the determination of QTPPs and CQAs, the following step is to determine the critical material attributes (CMAs) and the critical process parameters (CPPs) of the foams containing polymer with risk assessment.

3.2. Initial risk assessment

Risk assessment is the determination of the risks related to foams. Risk assessment tools can be utilized to rank and identify parameters based on their risk. An Ishikawa diagram represents the effect of the primary attributes and parameters of foams. It interprets the causes and sub-causes affecting the quality attributes of foam systems (Fig. 1).

The risk estimate matrix (REM) was used to assess the connection between CQAs and QTPPs (Table 4). A three-step scale was applied to rate the link between the CQA and QTPP parameters for the foam formulations: Low (low-risk parameters), Medium (medium-risk parameters), High (high-risk parameters) were the alternative levels. Based on the results of the REM, a Pareto chart (Fig. 2) was created to represent the severity scores of the CQAs

Our results show that five foam properties such as macroscopic foam stability, foam expansion, cross point, size of the bubbles and number of the bubbles are the most critical parameters, called Category A, with the highest severity score (> 100) during development. The next is Category B with a severity score of 60–90, which includes spreadability, relative foam density and viscosity of the liquid system. The third category of

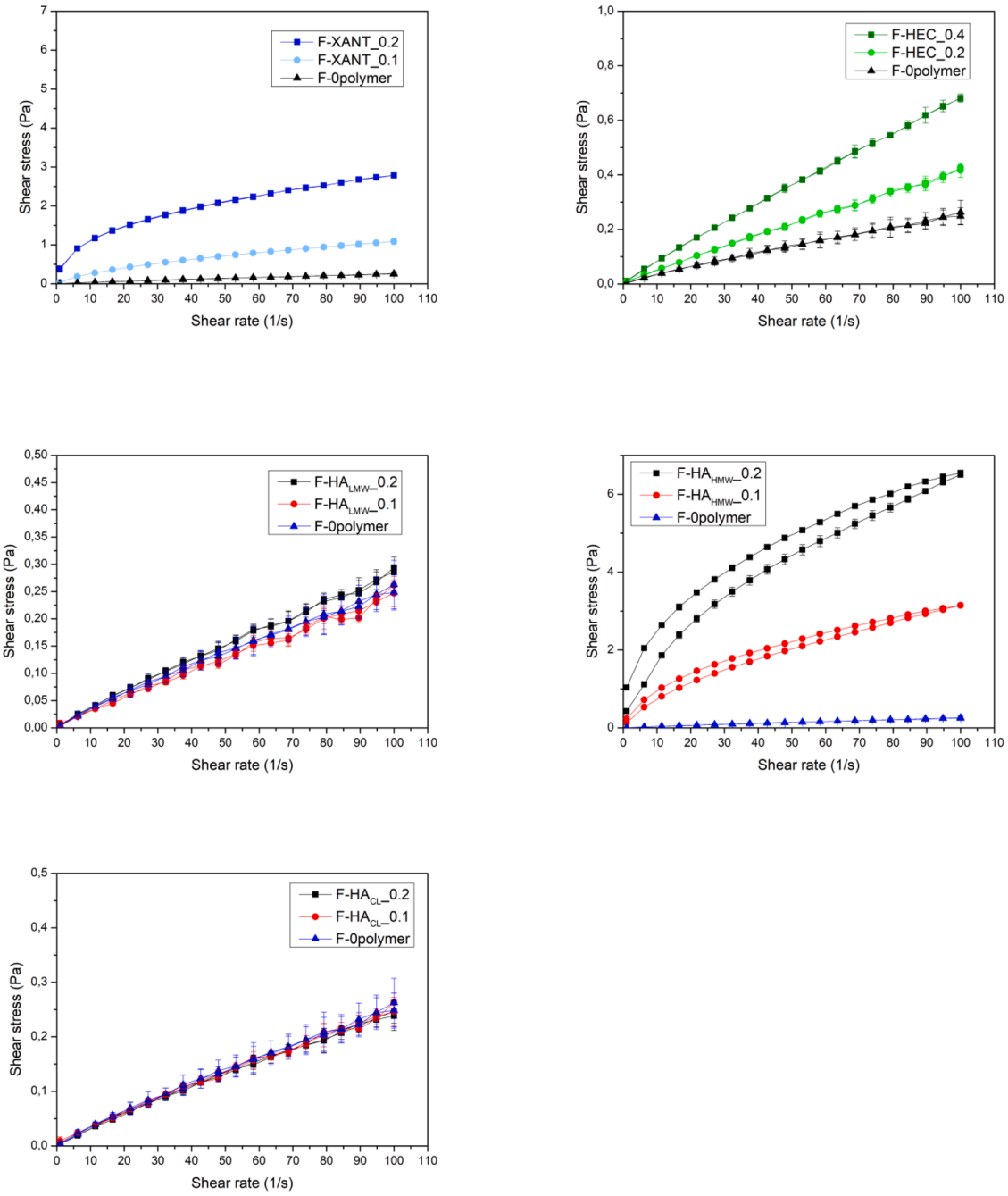

Fig. 4. Flow curves of bulk liquids.

severity scores is Category C (below 60), including parameters which have a low impact on product quality. High (Category A) and medium (Category B) risk parameters indisputably have an effect on the quality of foam systems. Therefore, these parameters were investigated.

The second REM (Table 5) presents the relationship between CQAs, CMAs and CPPs. The same scale was used for assessment (low, medium, high). The critical material attributes are polymer concentration and type, surfactant concentration and type, preservative type. The critical process parameters are the following: stirring speed, time and temperature.

In the light of the results of the initial risk assessment (Fig. 3), there are three groups of parameters regarding the risk level. In Category A, the critical parameters are both material and process parameters: polymer concentration and type, stirring speed and time with the highest severity score (> 4000). Category B includes surfactant concentration and type with a severity score of 2000–4000, which have a medium effect on quality. The parameters considered above are the parameters investigated during the experiment. Category C has the lowest impact (< 2000) on the quality of the foams: preservative type, stirring temperature. Based on the risk assessment, the critical (A) and medium critical (B) quality attributes, defined above, were investigated by varying the critical material and process parameters (A).

Among the QbD tools, the Ishikawa diagram was used to collect from literature and current knowledge all the material and process parameters, affecting the foam properties, from which the critical parameters were selected by REM and Pareto analysis.

According to the results, five CQAs, namely foam volume stability, foam expansion, cross point, the initial size of bubbles and the initial number of bubbles, were found to be critical attributes for the foam system. Moreover, three CQAs, namely spreadability, relative foam

Table 6
Effect of mixing time and speed on foam volume.

F-0polymer	1000 rpm	1500 rpm	2000 rpm
5 mins	×	×	✓
10 mins	×	×	✓
15 mins	×	×	✓
F-XANT_0.2			
5 mins	×	×	✓
10 mins	×	✓	✓
15 mins	×	✓	✓
F-HEC_0.4			
5 mins	×	×	✓
10 mins	×	×	✓
15 mins	×	×	✓
F-$HA_{lmw\_}$ 0.2			
5 mins	×	×	✓
10 mins	×	×	✓
15 mins	×	×	✓
F-$HA_{hmw\_}$ 0.2			
5 mins	×	×	✓
10 mins	×	✓	✓
15 mins	×	✓	✓

density, the viscosity of the liquid system, were found to be attributes of medium influence. These parameters were investigated in the course of the research work. Thus, the number of ten quality attributes of foams, determined based on prior knowledge and literature, was reduced to five with initial risk assessment. Then, test methods were developed to investigate these five critical quality attributes.

Furthermore, the initial risk assessment showed that there were two highly critical material parameters for CQAs that were the concentration and type of polymers, and two highly critical process parameters were found in this development, namely the stirring speed and time. Consequently, the number of eight material and process parameters, influencing the quality attributes of foams, was reduced to four with initial risk assessment and the effect of varying these parameters was investigated.

3.3. Preformulation studies of bulk liquid–Rheological investigation

Based on the results of the risk assessment, the viscosity of the bulk liquids was tested first. Rheological parameters are sensitive indicators of changes within liquid, semi-solid, foam formulations, e.g., they are suitable for characterizing the spreadability, consistency, and stability of the formulation.

The viscosity of the initial liquid preparation can have an effect on the formation of foam. Too high viscosity can hinder foam formation, while too low viscosity can lead to fast destabilization.

Polymer solutions are characterized by a shear-thinning flow due to the shear orientation of the macromolecules. For xanthan gum and HEC-containing solutions, a more significant jump in values can be seen with increasing concentration. The rheological behavior of low molecular weight hyaluronic acid and cross-linked hyaluronic acid-containing solutions was similar to that of the polymer-free solution, no significant increase in rheological parameters was observed with the polymer content. In contrast, high molecular weight hyaluronic acid behaves similarly to xanthan gum, the polymer is characterized by a thinning flow to solution shear, and even slight thixotropy is observed (Fig. 4).

3.4. Preformulation studies of foams of CPPs

Preformulation tests were carried out to select the appropriate mixing time and speed. These were essential to produce a foam with the right consistency. The bulk liquid was stirred at different speeds (1000 rpm, 1500 rpm, 2000 rpm) for different lengths of time (5, 10, 15 min). Our goal was to produce a foam macroscopically suitable for testing purposes. We aimed to have a foam with twice the volume of the liquid to carry out the tests (✓: complies with the criteria, ×: does not comply with the criteria). Based on the results (Table 6), a foam of sufficient consistency for the tests was obtained at 2000 rpm after 5 min.

3.5. Investigation of foam properties

3.5.1. Macroscopic properties

Through the determination of macroscopic properties (cylinder method), we can acquire information on the stability of foam formulations (foam expansion, foam volume stability, relative foam density). Based on the macroscopic tests, polymer-containing foams are more stable formulations than the polymer-free one. In the tested formulations, F-XANT_0.1, F-XANT_0.2, F-HA_{HMW}_0.1 and F-HA_{HMW}_0.2 had the highest stability but the lowest foam expansion values. In general, the results show that the greater the foam expansion, the higher its foamability, and the higher the foam volume stability value, the more stable the resulting foam. From the tested formulations, the well-foaming composition was foams with an expansion above 150%. The most stable formulations are the formulations with foam volume stability above 70%, and in this case these were F-XANT_0.2 and F-HA_{HMW}_0.2 (Table 7).

The macroscopic examinations showed that the polymer-free composition had a high value of foam expansion but a low value of foam stability, which was also apparent because the structure of the foam was broken down quickly. Similarly to the polymer-free formulation, F-HEC_0.2, F-HA_{LMW}_0.1 and F-HA_{LMW}_0.2 showed high foam expansion and low foam stability. F-HA_{CL} showed low foam stability at both concentrations tested, however, its foam expansion was not high either. F-XANT and F-HA_{HMW} formulations showed high foam stability at both concentrations tested.

As the polymer concentration was increased, foam density increased for all polymers used, however, based on the results, it did not correlate with foam stability and foam expansion results.

3.5.2. Microscopic properties

3.5.2.5. Structure and homogeneity. The structure of each foam containing different polymers can be observed with the help of microscopic

Table 7
Results of macroscopic investigations and the viscosity of bulk liquid.

	Viscosity of bulk liquid [mPa•s] (50 1/s)	FE [%]	FVS [%]	RFD
F-0polymer	3.06 ± 0.56	172 ± 15.7	14 ± 1.81	0.2028
F-XANT_0.1	14.32 ± 0.96	158 ± 3.84	95 ± 0.78	0.3879
F-XANT_0.2	42.05 ± 0.22	134 ± 1.92	100 ± 0	0.4265
F-HEC_0.2	4.38 ± 0.19	177 ± 0	15 ± 1.39	0.3614
F-HEC_0.4	7.27 ± 0.22	164 ± 1.92	29 ± 1.28	0.3781
F-HA_{LMW}_0.1	2.67 ± 0.26	179 ± 1.92	14 ± 0.09	0.3585
F-HA_{LMW}_0.2	3.00 ± 0.23	177 ± 0	14 ± 0.35	0.3614
F-HA_{HMW}_0.1	44.22 ± 0.24	130 ± 3.33	77 ± 14.22	0.4348
F-HA_{HMW}_0.2	97.79 ± 1.44	126 ± 3.85	94 ± 0.09	0.4434
F-HA_{CL}_0.1	2.57 ± 0.15	130 ± 3.33	15 ± 0.87	0.4348
F-HA_{CL}_0.2	2.64 ± 0.06	130 ± 3.33	14 ± 0.21	0.4348

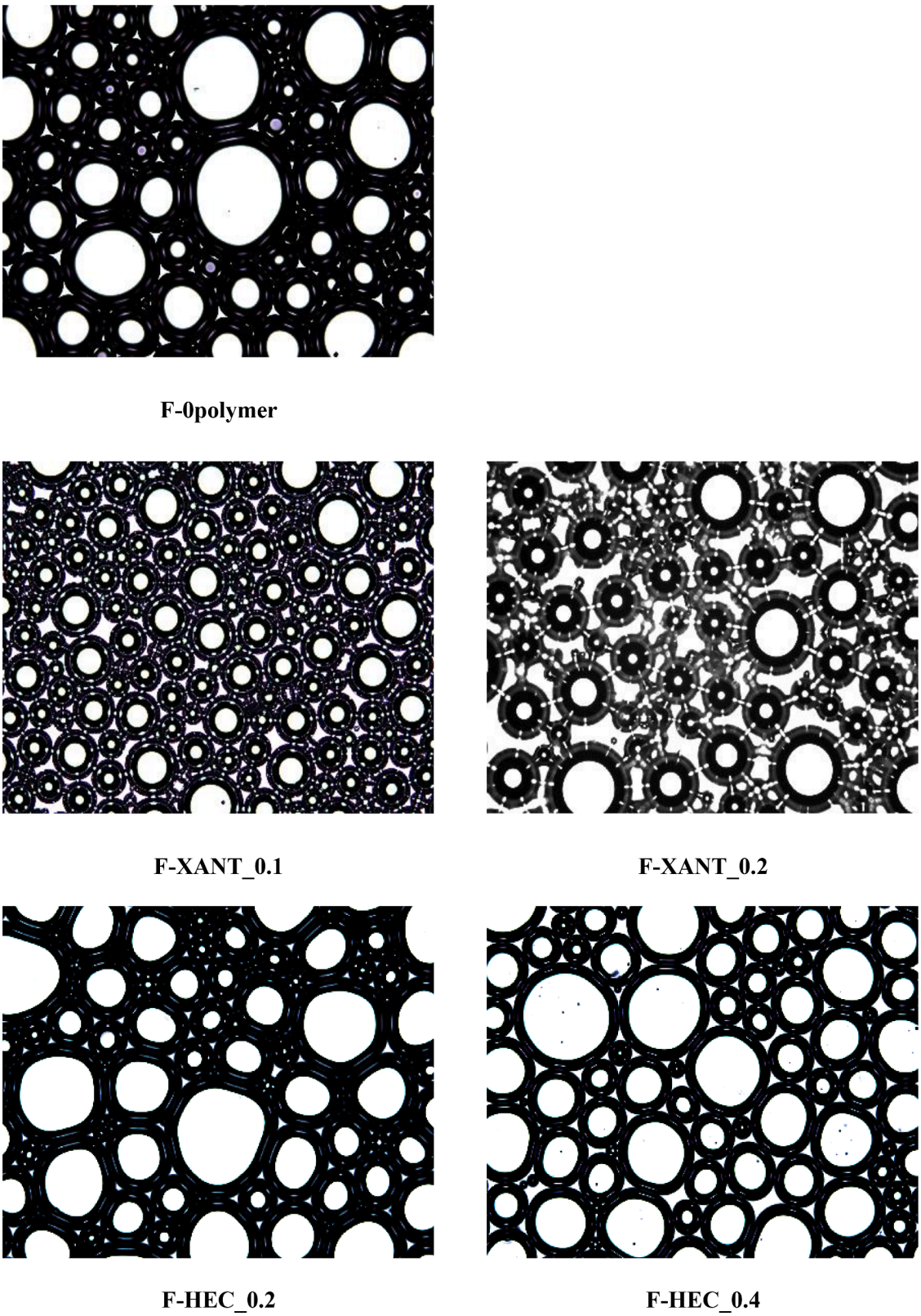

Fig. 5. Microscopic images.

images (Fig. 5). Foams which contain larger bubbles from the beginning are more friable. The size of the bubbles depends on the concentration of the polymer. In the case of F-XANT, F-HA_{HMW}, and F-HA_{CL} with increasing polymer concentration, the initial size of the bubbles was also larger. The lamellas between two bubbles are thinner in F-HEC than in formulations containing xanthan gum and high molecular weight and cross-linked hyaluronic acid.

The homogeneity of formulations can be determined by bubble size

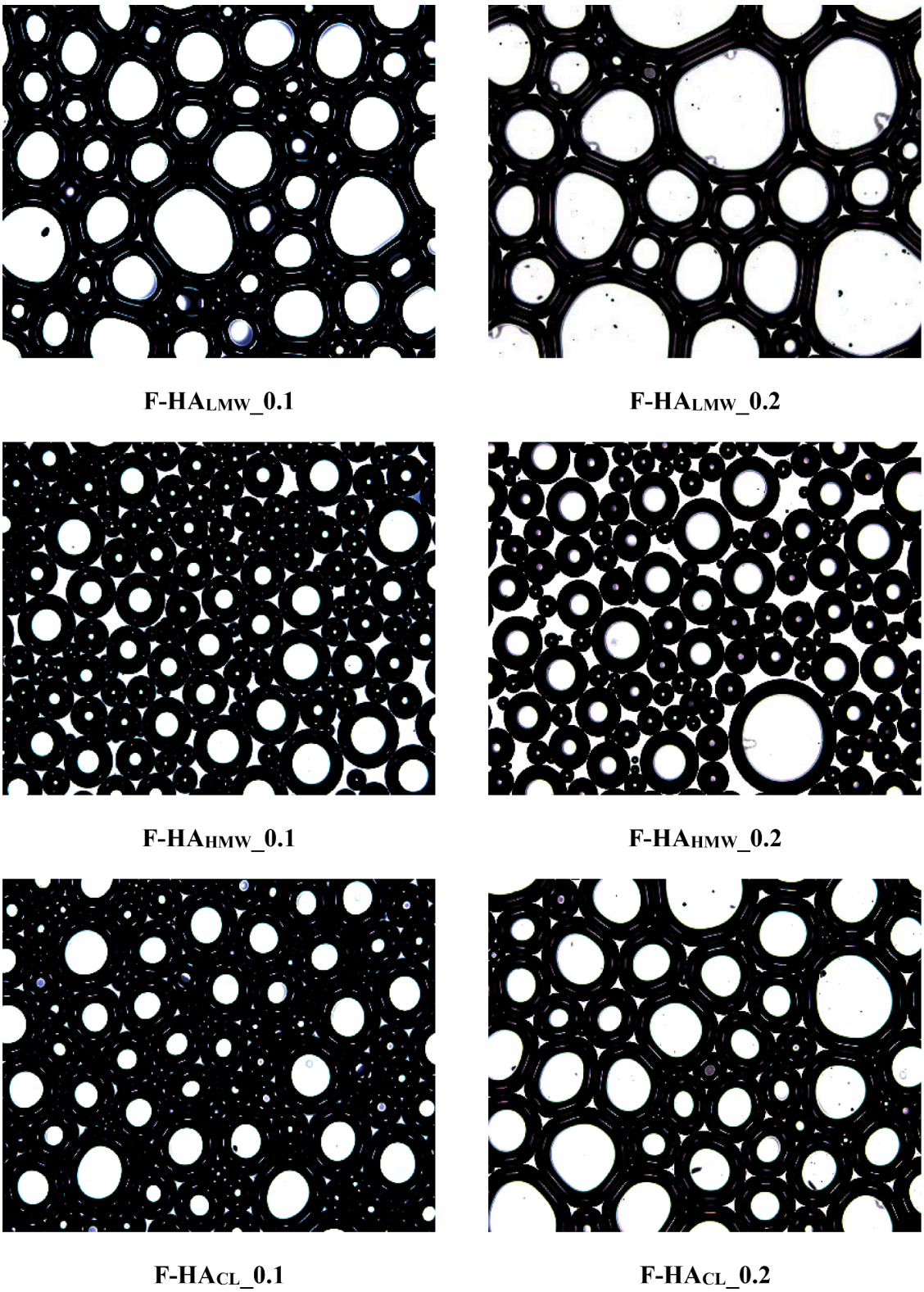

Fig. 5. (*continued*).

analysis (Table 8). An example of bubble size analysis performed by the software is shown in Fig. 6. During editing the bar charts, the data were plotted in the range between the minimum and maximum areas. All foam systems are polydisperse.

3.5.2.6. Kinetics of foam stability. The kinetics of foam destabilization was observed with microscopic examinations. Bubble sizes were detected in microscopic images taken after a predetermined time (0, 10, 20, 30 min). The microscopic pictures showed that the increasing size of the bubbles leads to the destabilization of the foam over time. The stability of the foams could be determined by kinetic analysis Fig. 7. shows the number of bubbles versus time. Foams with an initial bubble count

Table 8
Results of microscopic investigations.

	Minimum area (μm^2)	Maximum area (μm^2)	Mean (μm^2)	Std Dev
F-0polymer				
0 min	**505**	**306 477**	**63 957**	**63 726**
F-XANT_0.1				
0 min	**1339**	**88 659**	**23 718**	**17 973**
F-XANT_0.2				
0 min	**1494**	**174 564**	**26 346**	**31 479**
F-HEC_0.2				
0 min	**3114**	**277 779**	**53 018**	**54 914**
F-HEC_0.4				
0 min	**1015**	**243 753**	**47 054**	**45 447**
F-HA$_{LMW}$_0.1				
0 min	**8574**	**235 000**	**69 631**	**50 716**
F-HA$_{LMW}$_0.2				
0 min	**10 593**	**366 345**	**115 178**	**94 767**
F-HA$_{HMW}$_0.1				
0 min	**456**	**103 582**	**22 721**	**22 420**
F-HA$_{HMW}$_0.2				
0 min	**382**	**286 301**	**23 700**	**31 159**
F-HA$_{CL}$_0.1				
0 min	**5796**	**120 204**	**46 715**	**30 937**
F-HA$_{CL}$_0.2				
0 min	**8281**	**245 578**	**73 323**	**47 835**

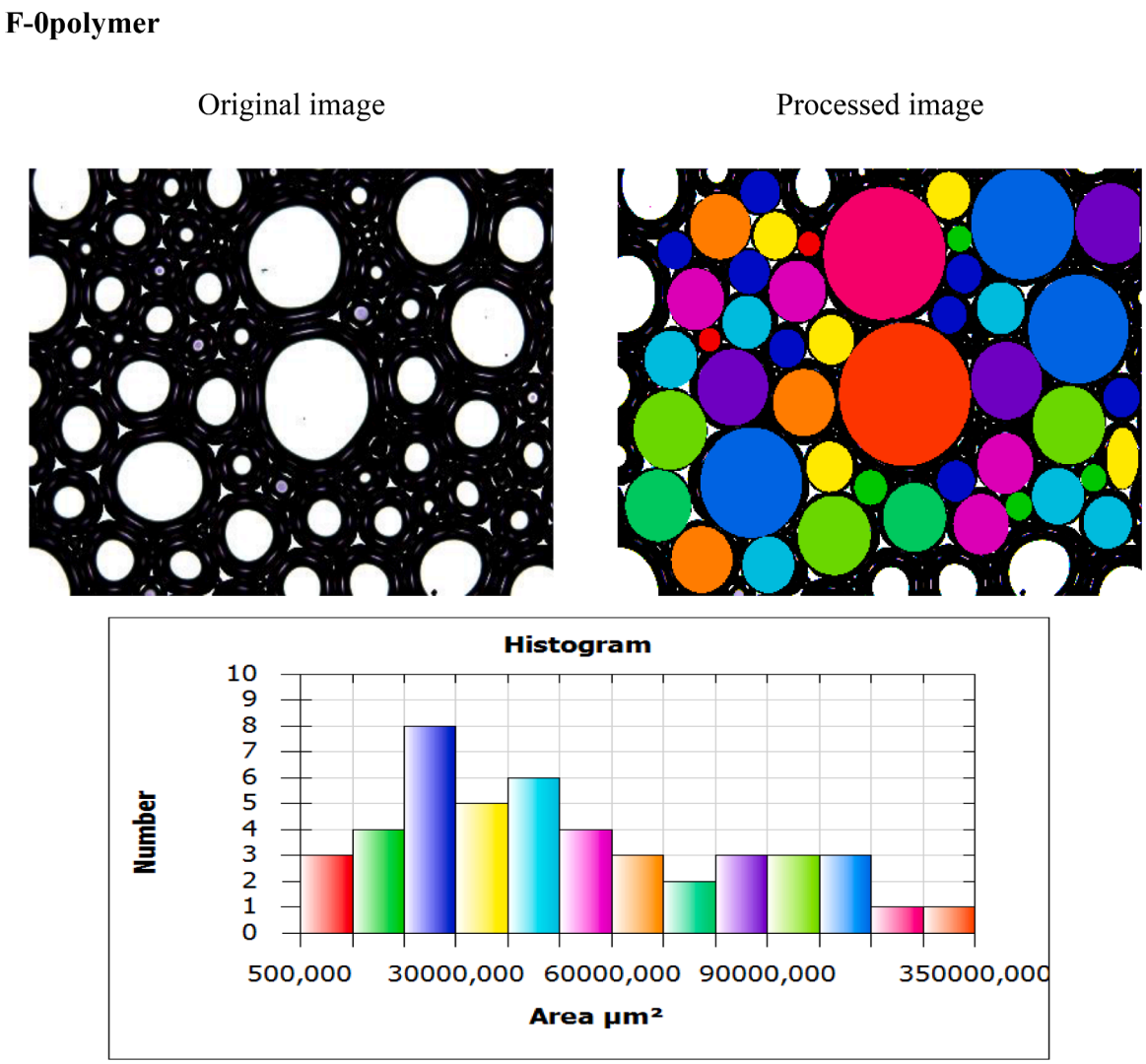

Fig. 6. The method of bubble size analysis in the case of F-0polymer.

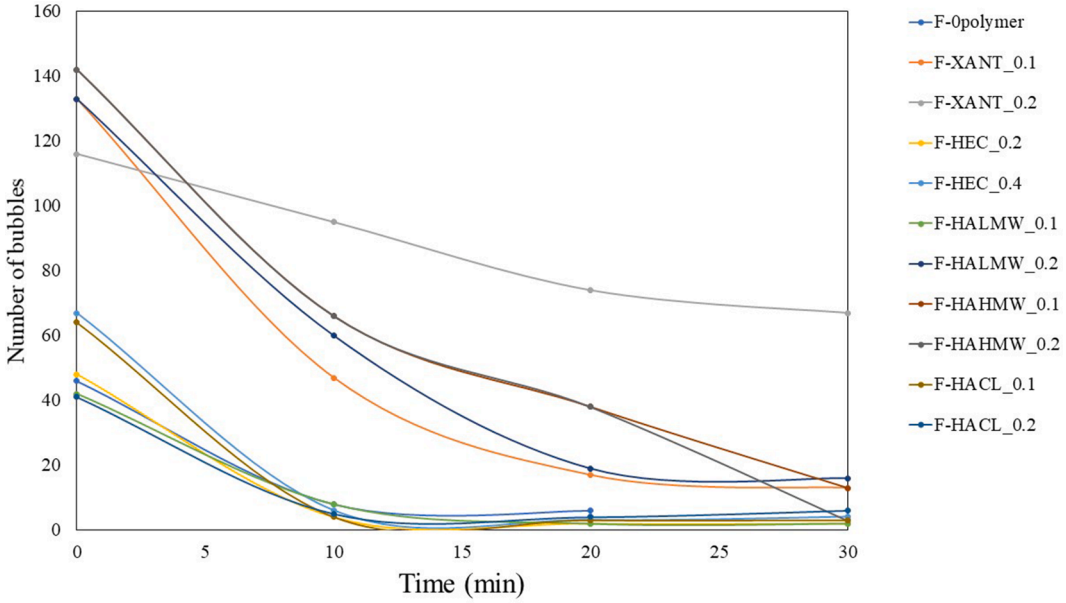

Fig. 7. Kinetics of foam destabilization.

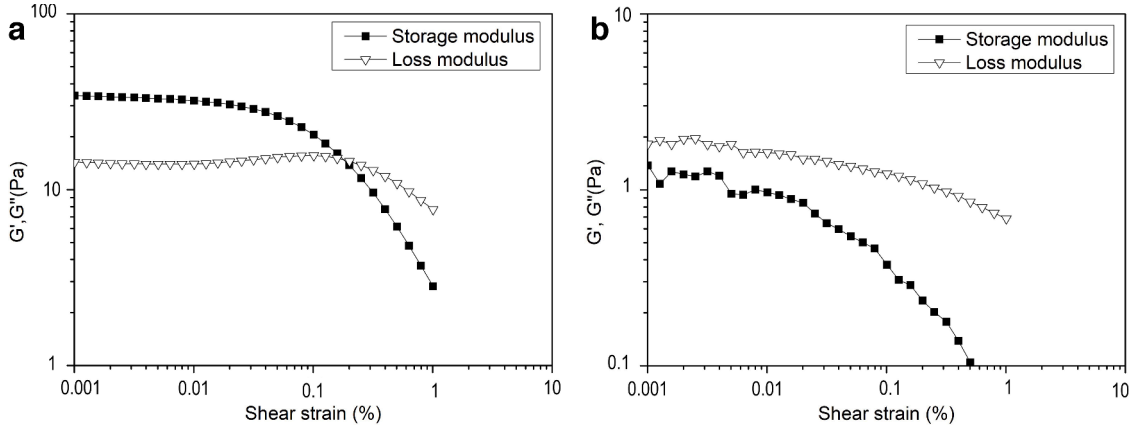

Fig. 8. Typical rheological behavior of the formulated foams; stable (a) and unstable (b) foams.

above 100 were microscopically stable. These are F-XANT_0.1, F-XANT_0.2, F-HA_{LMW}_0.2, F-HA_{HMW}_0.1 and F-HA_{HMW}_0.2, which shows that the results correlated well with the stability determined by the macroscopic FVS% method.

3.5.2.7. Rheology–Oscillometric measurement. The structure of the foam is built up of a network of bubbles. A coherent structure can be formed due to the cohesive dispersion medium formed among the bubbles. This structure can be analysed by oscillatory rheology (Dollet and Raufaste, 2014), (Thurston and Martin, 1978). The viscoelastic property of a material can be expressed by the value of the G' (storage modulus) and G" (loss modulus) parameters and their relationship to each other. In the case of amplitude sweep, the point of intersection of the two curves can be interpreted as a flow point (γ_f). The linear viscoelastic (LVE) range and its limit (yield point, γ_y), which indicate the stability of a coherent structure, can be also determined. In this range, G' and G" are constant, the structure is maintained. The wider this range, the more stable the structure.

Two typical amplitude sweep curves can be distinguished: one which represents a wider LVE range, the elastic modulus is higher than the viscous one, and the moduli are constant up to higher strain values, indicating a more stable coherent structure (Fig. 8.a). The other type of rheological behavior of the foam is when G" dominates over G' in the entire strain range, and a crossover point cannot be detected (Fig. 8.b). These preparations did not form a real coherent foam structure.

The measurable rheological parameters of the foams are summarized in Table 9.

Some foam formulations showed that G" values were higher than G' in the LVE region. These samples had a yield point (detectable limit of LVE range) but no flow point because the structure of these foams did not form a coherent structure, they behaved like liquids. There were other cases where it was not measurable due to foam instability. The polymer-free foam has no flow point, which means it flows from the beginning. The limit of the LVE range was the highest after 10 min due to liquid drainage from the interspace between the bubbles.

F-XANT_0.1 and F-XANT_0.2 have higher γ_y and γ_f values than the polymer-free foam. With increasing concentration, the values of flow point also showed an increase. F-XANT_0.1 was still stable after 30 min, however, higher concentration results in a less stable formulation after 30 min. This can be explained by the fact that too high a polymer content can cause the destabilization of the foam.

The structure of F-HEC_0.2 and F-HEC_0.4 was less coherent than that of F-XANT. Stability decreased over time. Rheological values changed in direct proportion to polymer concentration.

Table 9
Rheological parameters derived from the amplitude sweep curves.

	γ_f (%)	γ_y (%)
F-0polymer		
0 min	×	0.202
10 min	×	0.49
20 min	×	0.205
30 min	not measurable	not measurable
F_XANT_0.1		
0 min	15.9	0.43
10 min	4	0.192
20 min	7.98	0.196
30 min	7.98	0.204
F-XANT_0.2		
0 min	10.1	0.23
10 min	12.7	0.237
20 min	15.9	0.255
30 min	20.1	0.73
F-HEC_0.2		
0 min	×	0.245
10 min	0.318	0.104
20 min	×	101
30 min	not measurable	not measurable
F-HEC_0.4		
0 min	×	0.421
10 min	0.318	0.163
20 min	0.159	0.152
30 min	not measurable	not measurable
F-HA_{LMW}_0.1		
0 min	2.01	0.199
10 min	×	0.311
20 min	×	0.136
30 min	not measurable	not measurable
F-HA_{LMW}_0.2		
0 min	×	0.22
10 min	×	0.112
20 min	×	1.07
30 min	not measurable	not measurable
F-HA_{HMW}_0.1		
0 min	×	0.248
10 min	12.7	0.309
20 min	15.9	0.283
30 min	20.1	0.369
F-HA_{HMW}_0.2		
0 min	0.634	0.157
10 min	25.2	0.79
20 min	31.8	0.69
30 min	31.8	0.658
F-HA_{CL}_0.1		
0 min	0.798	0.206
10 min	×	0.13
20 min	×	0.334
30 min	not measurable	not measurable
F-HA_{CL}_0.2		
0 min	×	0.221
10 min	×	0.331
20 min	not measurable	not measurable
30 min	not measurable	not measurable

x: no cross point.
not measurable: the foam sample was immeasurable due to destabilization.

F-HA_{LMW} formulations were measurable for 20 min. The foam containing the lower concentration of polymer started to lose its coherent structure after 10 min. The increase in the amount of polymer made it more stable after 20 min.

F-HA_{HMW} had the best rheological properties among our formulations. Both concentrations had a decrease in the rheological values after 20 min. However, after 30 min, F-HA_{HMW}_0.1 proved to be more coherent. As with the xanthan gum-containing foam, higher polymer concentration caused the breakage of the coherent structure of the foam.

Cross-linked hyaluronic acid also caused the early breakage of the structure of the foam. The higher the polymer concentration, the earlier the breakage of the coherent structure occurs.

The long-term stability of the foam is insufficient for possible application to the skin. Our results indicate that xanthan gum-containing and high molecular weight hyaluronic acid foams met this requirement. These results correlated well with FVS% values.

3.5.2.8. Spreadability. Spreadability is the ability of foam to spread on the skin. If spreadability values decrease, the application of the foam is easier (Djiobie Tchienou et al., 2018).

The force is applied with a male cone probe, which penetrates through the foam to a certain depth. During penetration, the force gradually increases to the maximum penetration depth. The maximum force (firmness) is obtained during the measurement. Primarily, the factors that affect the firmness of the foam are the viscosity of the bulk liquid, the interactions between the bubbles, the distribution of the bubbles and the geometry of the bubbles. The results show that the lower the detected force, the easier for the foam to spread. Secondly, the greater the force required to spread, the more stable the foam.

The spreadability of the polymer-free foam is not-compliant, it starts to flow very quickly. On the basis of the results, in general, the polymer content improved the firmness of the foam (Fig. 9), which would prevent the formulation from flowing off the skin. As the concentration increases, the force required to spread the foam is also greater. In the case of high molecular weight hyaluronic acid-containing foams, the greatest force was required to spread the foam formulation. Our results indicate that xanthan gum-containing and high molecular weight hyaluronic acid foams met this requirement and correlated with the macroscopic investigations.

4. Conclusions

The aim of our study was to find, develop and compare the test methods that are suitable for the investigation of foam compositions, and with their help to select the appropriate composition during the development of a foam formula. The application of the QbD concept, including risk assessment, was of great help in the development of methods for testing foams.

The purpose of this research work was to acquire a better knowledge of the properties of API free foams as a delivery system and to establish control methods suitable for testing the foams.

Considering the results of initial risk assessment, eleven compositions were formed and investigated.

During the initial risk assessment, five CQAs, namely foam volume stability, foam expansion, cross point, size of bubbles and number of bubbles were found to be highly critical attributes, and three CQAs, namely spreadability, foam density and the viscosity of the liquid system were found to be medium critical attributes in the development of foam formulations. These parameters were investigated. The initial risk assessment also showed that there are two material parameters, polymer concentration and polymer type, which were highly critical parameters for CQAs, while surfactant had a medium impact on CQAs.

In summary, the polymer content has a great effect on the properties of the foams. Different polymers affect the properties of foams in different ways Table 10. summarizes and compares the results obtained on the basis of the previously established requirements (Table 3). When used in combination, the methods reinforce each other and help to select a formula for dermal application. Based on our results, formulations F-XANT_0.1, F-XANT_0.2, F-HA_{HMW}_0.1 and F-HA_{HMW}_0.2 have good foam properties and will be appropriate delivery systems for an active pharmaceutical ingredient. The results of the different methods showed good correlation and can be used in preformulation studies. The appropriate formula can be selected by using macroscopic method of foam stability (FVS), the investigation of the number of bubbles with a light microscope, and the oscillometric measurement methods of cross-point determination. While previous research papers have used these test methods separately, the selection protocol of an appropriate foam formula has been developed based on the results of the present research

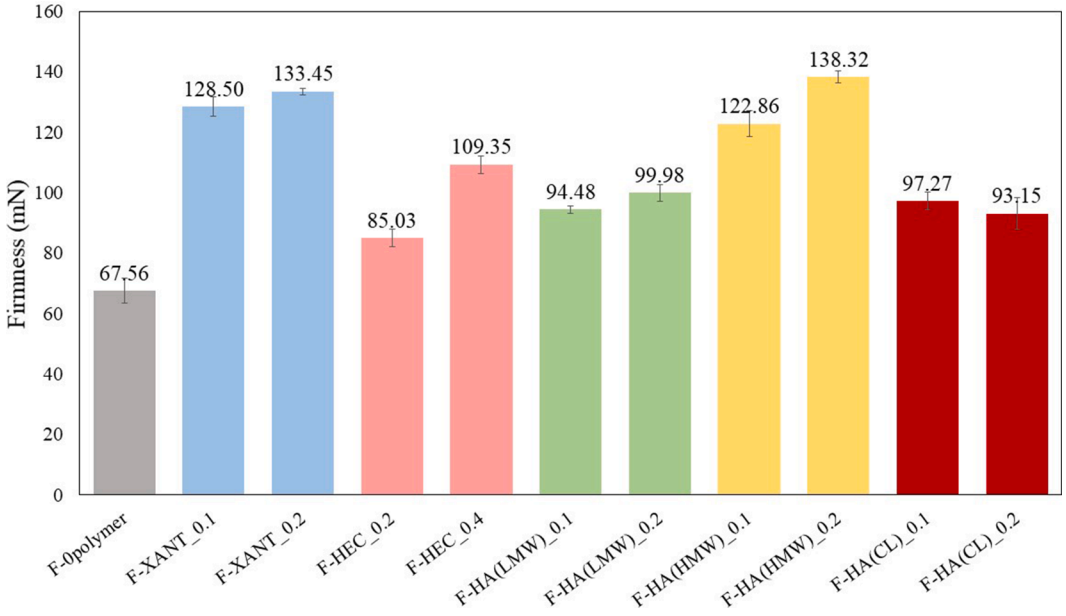

Fig. 9. Foam firmness.

Table 10
Summary of the investigation of foams; ✓✓: Exceptionally good result, ✓: The result meets the target requirement, ×: The result does not meet the target requirement.

Investigation	Target	F-0polymer	F-XANT_0.1	F-XANT_0.2	F-HEC_0.2	F-HEC_0.4	F-HA_{LMW}_0.1	F-HA_{LMW}_0.2	F-HA_{HMW}_0.1	F-HA_{HMW}_0.2	F-HA_{CL}_0.1	F-HA_{CL}_0.2
Foam expansion	100% ≤	✓✓	✓✓	✓	✓✓	✓✓	✓✓	✓✓	✓	✓	✓	✓
Foam density	≤ 0.5	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Number of bubbles (Initial values)	100 <	×	✓	✓	×	×	×	✓	✓	✓	×	×
Spreadability	< 500 mN	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cross point	Detectable	×	✓	✓	×	×	✓	×	×	✓	✓	×
Foam volume stability	50% ≤	×	✓✓	✓✓	×	×	×	×	✓✓	✓✓	×	×
Viscosity of liquid system	20–200 mPas	×	×	✓	×	×	×	×	✓	✓	×	×

and these results assist in the development of pharmaceutical foams to determine the control strategy. Furthermore, the results of the present research on foams have expanded the knowledge space. Based on the results, we plan to develop an experimental design for API-containing foams in the future.

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CRediT authorship contribution statement

Fanni Falusi: Writing – original draft, Methodology, Investigation, Visualization. **Mária Budai-Szűcs:** Software, Methodology. **Erzsébet Csányi:** Supervision, Writing – review & editing. **Szilvia Berkó:** Methodology, Writing – review & editing. **Tamás Spaits:** Methodology. **Ildikó Csóka:** Conceptualization. **Anita Kovács:** Supervision, Conceptualization, Writing – review & editing.

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