Mechanistic Evaluation of Microstructure and Performance Attributes of Medicated Topical Shampoos

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Ishanka A. Liyanage[1], Megan Kelchen[2], Tannaz Ramezanli[2], Priyanka Ghosh[2], Muhammad Ashraf[1], Ahmed Zidan[1]

[1] Office of Pharmaceutical Quality Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993.

[2] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993.

INTRODUCTION

Medicated topical foams and shampoos are described as thermodynamically and mechanically unstable dispersions of gas in liquid containing surfactants and are characterized by a vast interface, which tends to shrink through foam drainage at the air-liquid interface due to the breakdown of bubbles. Surfactants are a dispersant component allowing for better accommodation of an active pharmaceutical ingredient (API) in both ionic and non-ionic form friendly components of skin and hair. The local and systemic availability of the API from foam or shampoo products may vary depending on how the foam is generated, microstructure attained after actuation, stability and decay kinetics, residual formulation attributes after breakdown, physicochemical characteristics of drug substance and complexity of inactive ingredients contributing to the arrangement of matter. It is essential to understand the performance attributes of topical foam and shampoo formulations and identify appropriate sensitive and discriminating characterization techniques that can be used to understand their microstructure. Additionally, there is an unmet research need to understand the relationship between microstructure and performance of foams following application to skin. Accordingly, this study aimed at evaluating and identifying appropriate characterization techniques and tools for assessing the critical performance attributes of complex foam formulations using ketoconazole shampoos as model products.

MATERIALS AND METHODS

Two approved ketoconazole topical (2%) shampoos and ketoconazole topical (2%) foams were purchased. Foam height and structure was evaluated using KRÜSS Dynamic Foam Analyzer (DFA100) using a prism column with a filter plate and sparging (air) sample holder at 23 ± 1°C instead of 32°C, the temperature at the surface of the skin, due to experimental limitations associated with the foams evaluated in the current study. Experimental details of the study are listed in **Table 1**.

Table 1. Experimental details of the foam products studied.

Product	Parameters	Dilution (v/v)[1]			Flow rate (L/min)[2]		
Shampoo 1	Foam height and structure	1:25	1:50	1:100	0.20	0.35	0.50
Shampoo 2	Foam height and structure	1:25	1:50	1:100	0.20	0.35	0.50
Foam 1	Foam structure	N/A			N/A		
Foam 2	Foam structure	N/A			N/A		

N/A = not applicable, [1]x mL (x = 2.0, 1.0 and 0.5) of shampoo is diluted in 50 mL of water (diluent) to achieve 1:25, 1:50 and 1:100 (v/v) dilutions, respectively. [2] Flow rate = Rate of air flowing through the liquid (i.e., water), ** Each experiment was triplicated, and data was presented as average ±SD.

Definitions of foam height and structure parameters analyzed in this study

1. **Foam height:** Height of the foam layer between the liquid phase at the bottom and the gas phase at the top
2. **Bubble count per mm²:** Number of bubbles per mm² of the predefined imaging area
3. **Mean bubble area:** Mean value of the area of total number of bubbles in the predefined imaging area
4. **Average bubble radius:** Average of the radius of total number of bubbles in the defined imaging area
5. **Bubble count half-life time:** Time at which the bubble count in the predefined imaging area reduce to 50% of its initial value.

RESULTS AND DISCUSSION

Both shampoos produced a stable and intact foam layer with a transparent liquid layer after 30 seconds of foaming phase and remained stable for 15 minutes (900 seconds) for all analyzed dilutions and at all applied flow rates (**Figure 1**). However, both shampoos at the highest dilution (1:100) studied showed a few random dissections of the foam layer during the last 5 minutes of data acquisition (see arrow in **Figure 1B**). Foam height was independent of the dilution for both shampoos at all flow rates and at the same time stable over 15 minutes for all dilutions and flow rates applied (**Figure 2**). A gradual increase in foam height was observed with the increase in the flow rate applied (**Figure 3**). Bubble count per mm² was a function of dilution and flow rate applied and decreasing trends of bubble structure attributes could be observed over time at higher dilutions at relatively lower flow rates (**Figure 4**). Foam products were also evaluated for similar bubble structure attributes and only the bubble size distributions (bubble count per mm² vs. bubble area) of foam products over time is shown (**Figure 5**). Further method optimization is in progress.

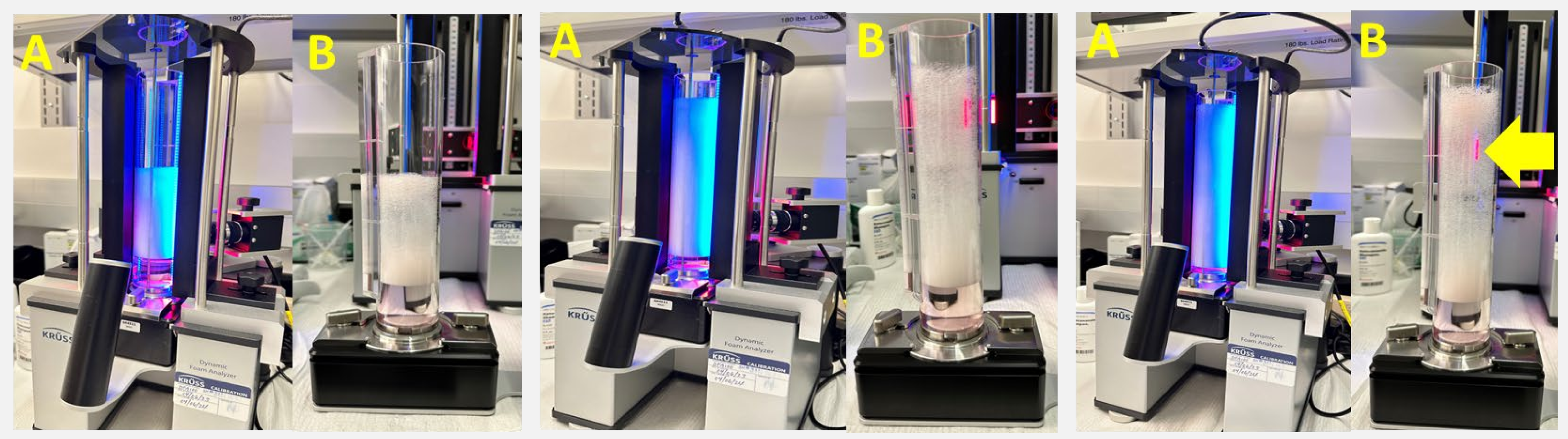

Figure 1. DFA100 prism column (A) at the end of the foaming phase and (B) at the end of the 15-minute experiment at 0.2, 0.35 and 0.5 L/min flow rates (left to right) at a dilution of 1:50 (v/v) for Shampoo 1.

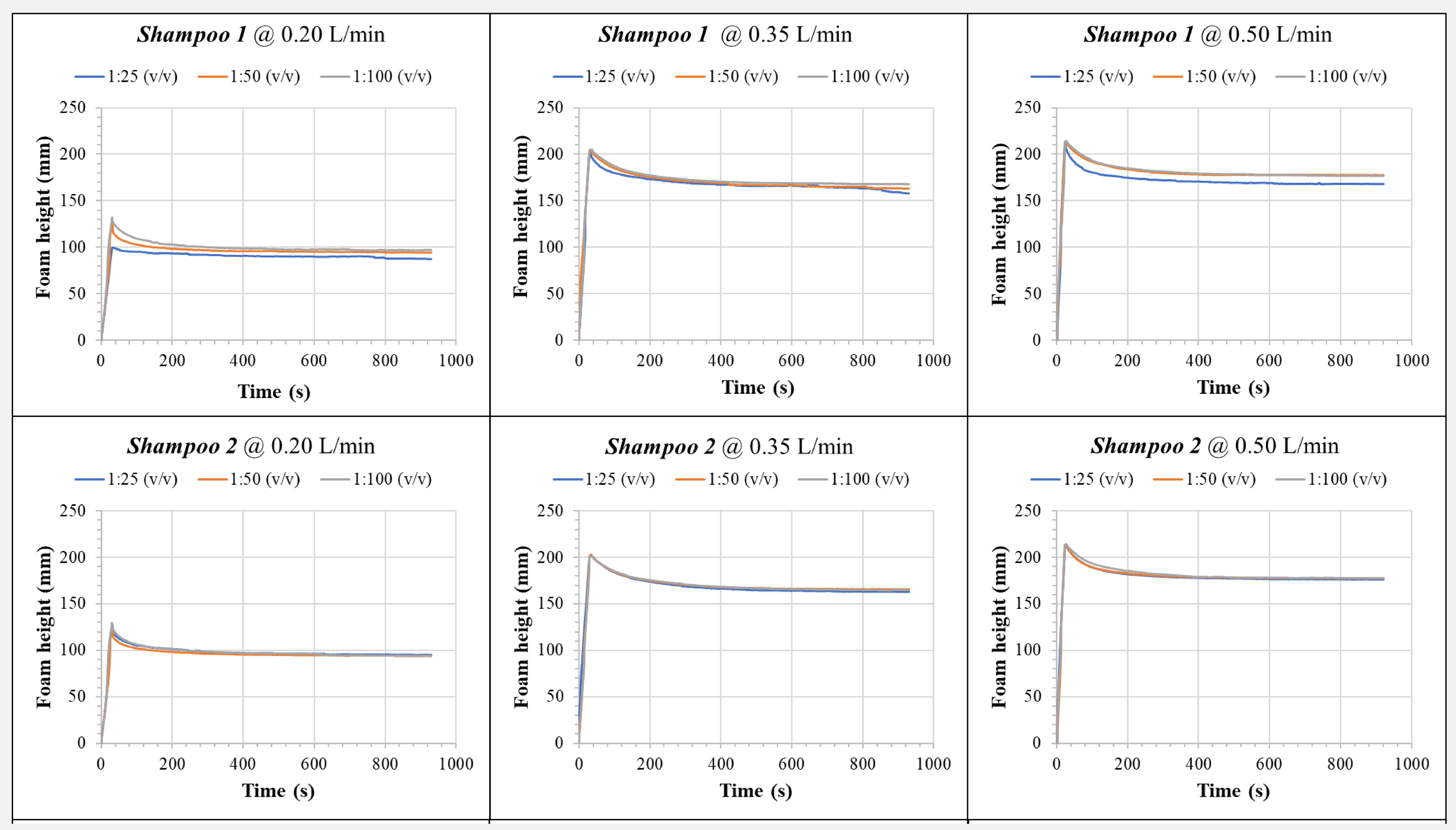

Figure 2. Representative plots of foam height vs. time at each flow rate (0.20, 0.35 and 0.50 L/min) at each dilution (1:25 v/v, 1:50 v/v and 1:100 v/v) for Shampoo 1 and Shampoo 2.

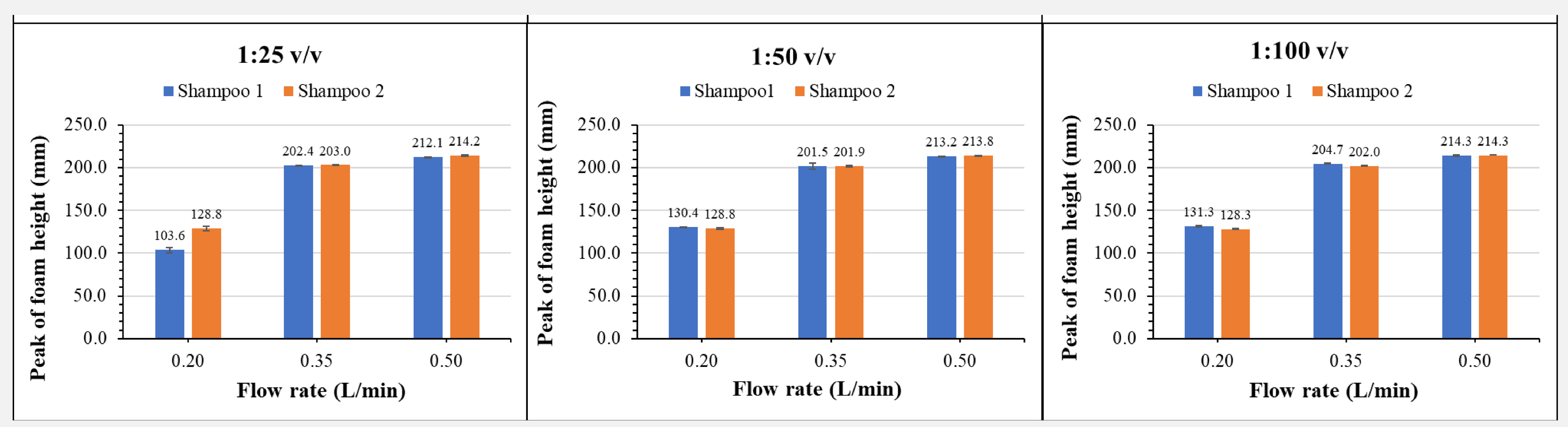

Figure 3. Average (± SD) maximum foam height vs. flow rate at each dilution (1:25 v/v, 1:50 v/v and 1:100 v/v) for Shampoo 1 and Shampoo 2 (n=3).

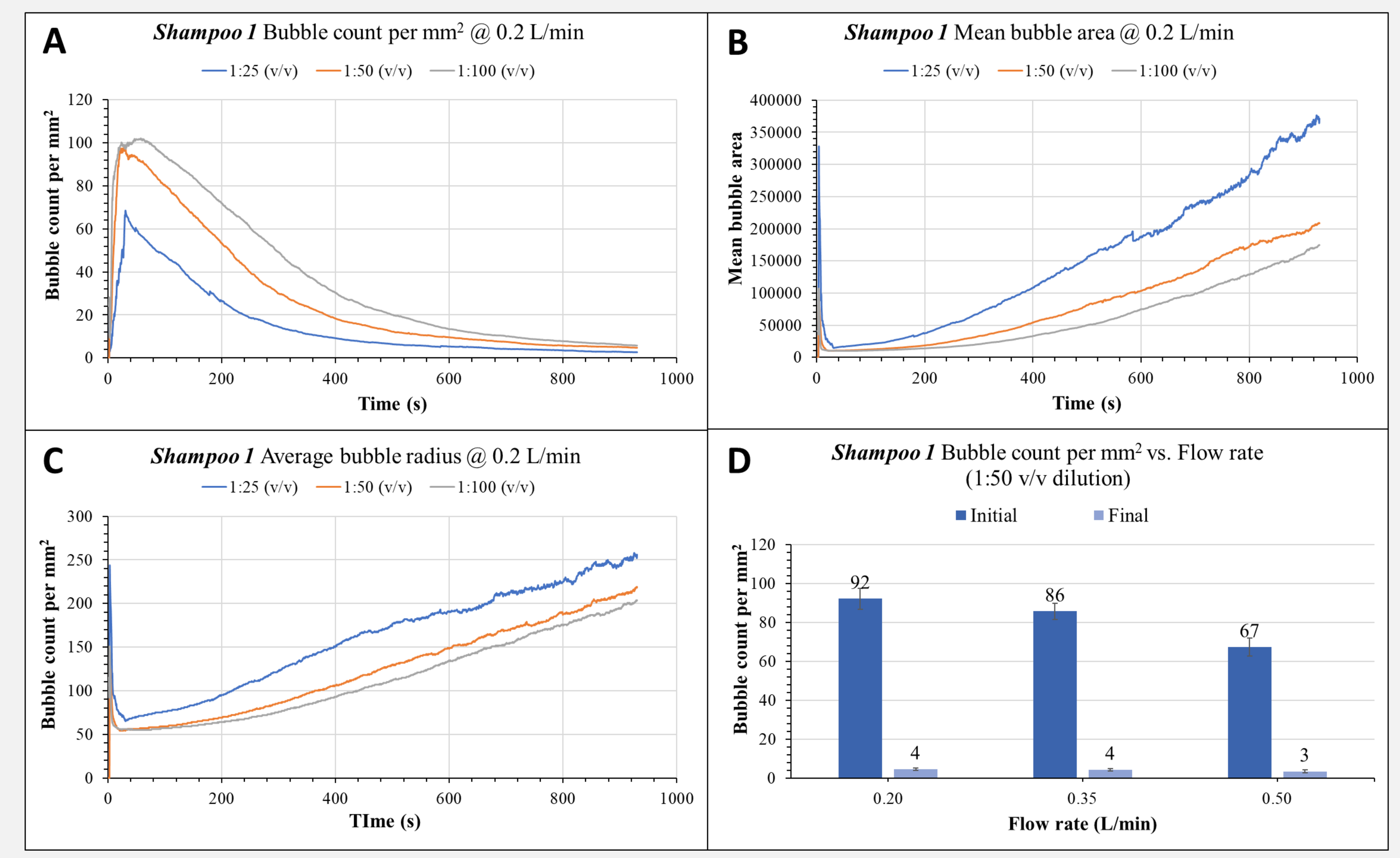

Figure 4. Representative plots of (A) bubble count per mm² and (B) mean bubble area and (C) average bubble radius at different dilutions at a flow rate of 0.2 L/min. (D) Average (± SD) bubble count per mm² vs flow rate at 1:50 v/v dilution for Shampoo 1 .

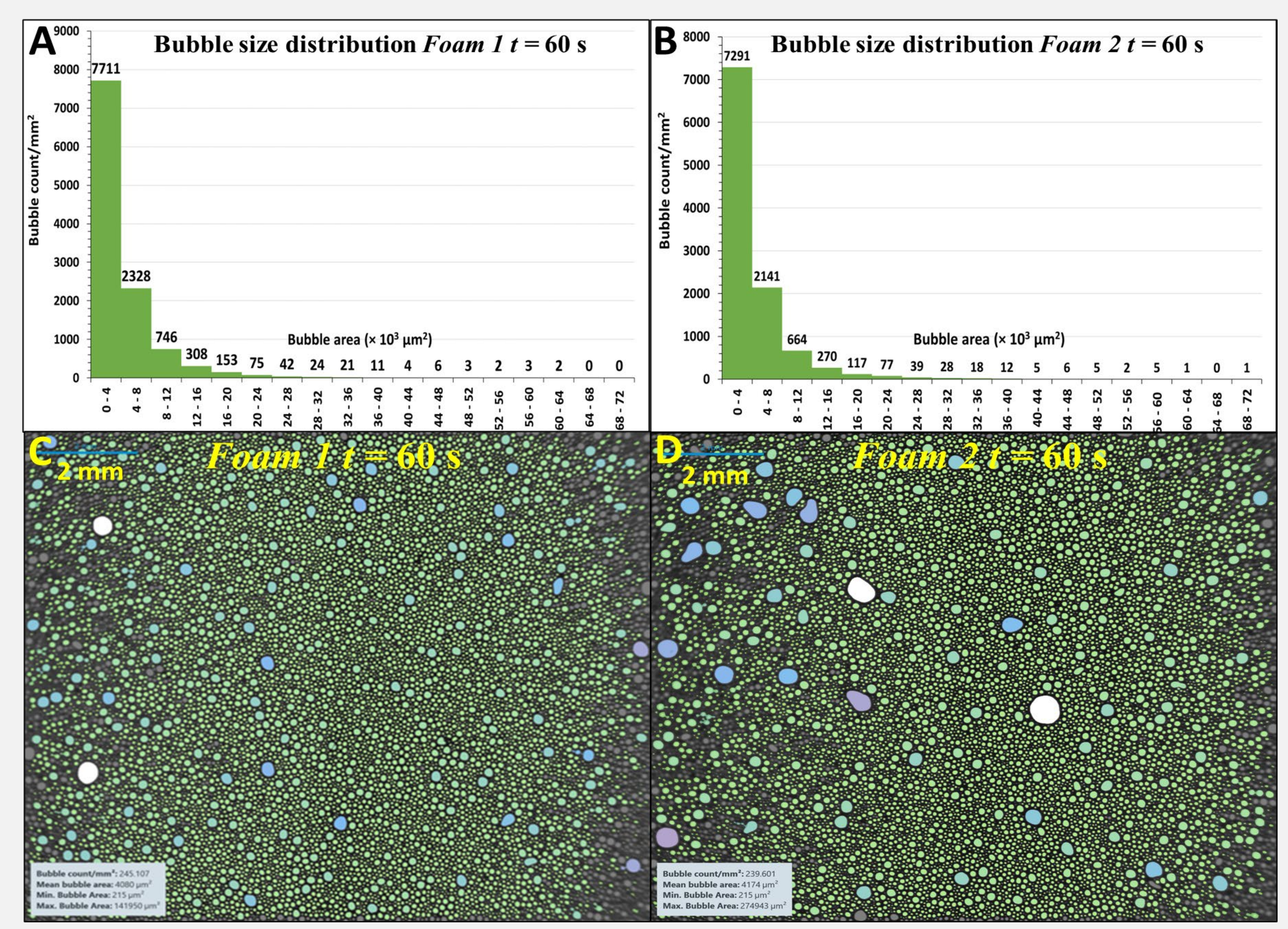

Figure 5. Representative plots of bubble size distributions at 60 second (1 minute) for (A) *Foam 1* (B) *Foam 2* products. Images of Foam 1 and Foam 2 at 60 second (1 minute) are shown in (C) and (D), respectively.

CONCLUSIONS

Based on the products studied, dilution of the shampoo and flow rate applied for foaming have a direct impact on the foam characteristics such as foamability, foam stability and kinetics and foam microstructure. Dilution at lower flow rates (0.20-0.35 L/min) improve the foamability and foam stability of the shampoo. However, it is important to emphasize that the above derived trends are specific to the products that were evaluated.

Foamability and foam stability are critical performance attributes of foam formulations. These attributes could be evaluated by assessment of microstructure parameters using standardized and optimized dynamic characterization methods in terms of dilution percent, sparging rate and time. The foam height- and structure-driven characteristics may be useful in comparison of different foam formulations.

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