Critical Quality Attributes of Topical Clobetasol Propionate Foams

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PURPOSE

The objective of the study was to compare the physical and structural quality attributes of reference and generic clobetasol propionate (CP) topical foam, 0.05% drug products to identify critical quality attributes for the characterization of the dosage form. Commercially available solution-based (Olux) and emulsion-based (Olux E) clobetasol propionate foam, 0.05% (reference products), and approved generic products (designated as CPF and CPEF, respectively) were used for the study. Different quality attributes including bubble size distribution, density, drying profile, time to break, residual content, and foam firmness were evaluated for each product.

METHODS

Each drug product was assessed using the following techniques:

- The bubble size distribution of the foam products was measured using differential interference contrast microscopy. Bubble size distribution was determined and d_{10}, $d_{50,}$ and d_{90} values were calculated.
- The pH of the foam products was determined using the In-Lab microprobe.
- The foam density was measured by determining the average weight of the foam at five different volumes.
- The metamorphosis (drying profile) of the foams was evaluated thermogravimetrically by dispensing the foam products into the cavity of a rubber ring, placed on a pre-weighed glass slide. The excess foam was trimmed off with a scalpel blade, the rubber ring was removed, and the weight of the slide was noted. The slide was then placed in an incubator at 32˚C and the weight was monitored at 3-minute intervals, until a constant weight was reached. The percentage of product remaining at different time points was calculated, and the time taken for a loss of 50% weight of the foam was determined.
- The time to break for the emulsion-based foams was determined by placing samples in an incubator at 30°C, 32°C, 33°C, 35°C, and 40°C, at 40% relative humidity. The time to break for solution-based foams were determined at 23°C, 25°C, 28°C, and 30°C, at 40% relative humidity. The energy of activation required for the collapse of the foams was determined using the rate constant values obtained at the five different temperatures, assuming zero-order processes.
- The residual content of the foams was evaluated by drying each foam at an elevated temperature for a prolonged time. The weight of the slide was recorded every one hour until a constant weight was attained. The presence of any crystals in each sample was evaluated under a microscope.
- Foam firmness and work of adhesion (WOA) were determined using a TA-3 Texture analyzer.

RESULTS

Table 1: Comparative evaluation of topical clobetasol propionate foams

Quality Attribute	Olux	CPF	Olux-E	CPEF
Bubble size: D10 (µm)	24.43 ± 2.60	38.77 ± 2.44	111.33 ± 40.50	75.67 ± 24.01
Bubble size: D50 (µm)	51.40 ± 4.51	70.70 ± 5.29	185.67 ± 30.92	191.50 ± 23.34
Bubble size: D90 (µm)	94.87 ± 5.00	119.97 ± 7.91	276.17 ± 22.42	353.47 ± 15.10
Density (g/cm^3)	0.060 ± 0.004	0.084 ± 0.00	0.086 ± 0.003	0.080 ± 0.008
pH	5.99 ± 0.07	5.85 ± 0.05	5.75 ± 0.04	5.80 ± 0.01
Drying profile (T30) (min)	3.72 ± 0.90	6.07 ± 1.48	5.08 ± 0.63	3.98 ± 0.23
Drying profile(T50) (min)	6.37 ± 0.64	9.40 ± 0.69	26.67 ± 4.51	10.67 ± 1.44
Energy of Activation (KJ/Mol)	114.91 ± 4.84	114.33 ± 8.00	61.42 ± 5.65	51.80 ± 5.91
% Residual content (w/w)	3.34 ± 1.93	2.14 ± 1.42	41.13 ± 8.09	26.65 ± 5.73
Texture property: Firmness (g)	58.58 ± 3.48	60.23 ± 0.85	50.24 ± 2.56	50.99 ± 7.83
Texture property: WOA (g.sec)	85.61 ± 17.16	88.68 ± 5.42	67.56 ± 17.16	88.30 ± 12.7

- All the studies were conducted in triplicate and the data are reported as mean ± S.D. Test for significance was performed using unpaired Student-t test(95%confidence interval).
- The colored cells represent quality attributes that appear to differentiate between solution-based foams and emulsion-based foams.

Fig.1 Bubble size distribution of solution-based foams

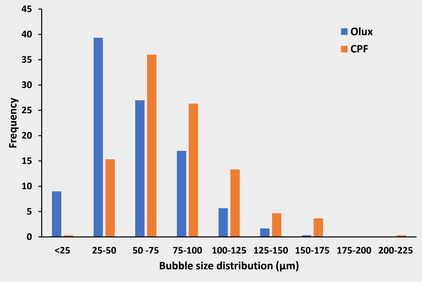


Fig.2 Bubble size distribution of emulsion-based foams

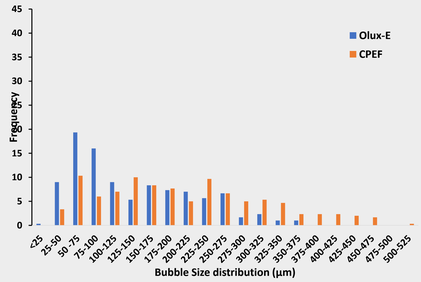


Fig.3 Drying profile of solution-based foams

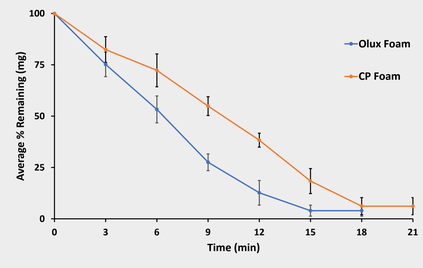
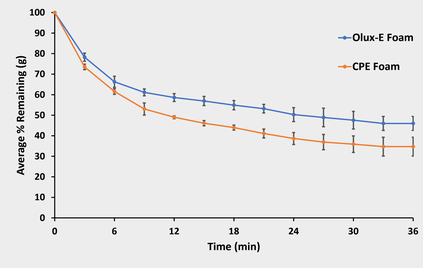


Fig.4 Drying profile of emulsion-based foams



CONCLUSIONS

- The data indicates that quality attributes such as bubble size distribution, the energy of activation, and % residual content appear to be comparable between the generic and corresponding reference products, but are able to distinguish between solution- and emulsion-based foams. Therefore, these quality attributes may provide some utility in the differentiation between certain generic and reference solution-based foams and generic and reference emulsion-based foams.
- Overall, our study demonstrates that quality attributes such as bubble size distribution, density, pH, drying profile, the energy of activation, and % residual content can be included in comparing the physicochemical attributes of generic and reference clobetasol propionate foams.
- Additional studies are needed to correlate the macro and micro-structure of these drug products with their performance.

FUNDING

Funding for this project was made possible, in part, by the U.S. Food and Drug Administration through Grant 1U01FD005223. The views expressed in this poster do not reflect the official policies of the U. S. Food and Drug Administration or the U. S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

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