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Influence of Relative Humidity on Time to Break Analysis of Pharmaceutical Foams

S. Rangappa[1], S. Ajjarapu[1], P. Ghosh[2], M.N. Kelchen[2], S.G. Raney[2], M.A. Repka[1], H. Maibach[3], S. Narasimha Murthy[1]

[1]Department of Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi, Oxford, MS 38677, USA

[2]Division of Therapeutic Performance, 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, USA

[3] University of California San Francisco, School of Medicine, San Francisco, CA 94143, USA.

CONTACT INFORMATION: Srinath Rangappa: Email: srinath@olemiss.edu

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PURPOSE & OBJECTIVE:

Pharmaceutical foams are a dispersion of gas in a liquid phase and the dosage forms are typically thermodynamically and mechanically unstable once they are dispensed from the container closure system. An analysis of the time to break (i.e., collapse) is one of the techniques recommended for in vitro characterization of topical foams, where time to break is defined as the time required for the foam to collapse completely. Currently, time to break analysis is performed at 30˚C, 33˚C, 35˚C, and 40˚C. The objective of this study was to evaluate the influence of relative humidity (RH) on the results obtained during this analysis. The study was performed using an oil-in-water (O/W) emulsion-based foam formulation (Azelaic acid topical aerosol foam, 15%) and a hydro-alcoholic solution-based foam (Clindamycin phosphate topical aerosol foam, 1%) as model foam drug products.

METHODS:

- A rubber ring, scalpel blade and a glass slide were equilibrated in a pre-set incubator (at the specified temperature and RH).
- The foam was actuated from the canister per the instructions on the label and dispensed into the ring cavity. The excess foam was trimmed off using a scalpel blade and the rubber ring was removed.
- The initial weight was recorded, and the time was noted. The slide was immediately placed into a pre-heated incubator set at the desired RH.
- The RH was controlled using a saturated sodium chloride solution. The breakup of bubbles was observed through the glass window until the foam completely collapsed. The time to break for the bubbles was defined as the total time from the moment the foam was dispensed until its complete collapse.
- Two sets of experiments were performed. In the first set of experiments, the two foams were evaluated at a constant RH of 40% with varied temperatures of 30˚ C, 32˚ C, 33˚ C, 35˚ C, and 40˚ C, while in the second set of experiments, relative humidity was adjusted to 30%, 45%, 60%, or 75% while maintaining the temperature constant at 32˚ C.
- The energy of activation (E_a) required for the collapse of the foams was determined using the rate constant values obtained at 5 different temperatures, assuming zero-order processes.
- All the studies were conducted in triplicate and the data are reported as mean ± standard deviation (SD).

RESULTS

Figure 1: Preparation of foam for time to break analysis

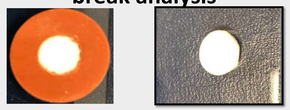


Figure 2: Structural metamorphosis of the foam during time to break analysis

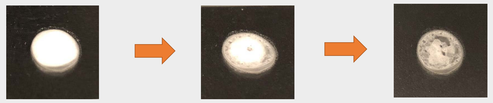


Table 1: Mean (± SD) time to break analysis of O/W emulsion and hydroalcoholic solution based foams at different % RH at a constant temperature (n=3)

Temperature (°C)	RH (%)	Time to break (min)	
		O/W emulsion foam	Hydroalcoholic foam
32	30	22.21 ± 1.00	10.06 ± 0.53
32	45	28.80 ± 2.37	28.99 ± 2.31
32	60	89.96 ± 3.71	100.20 ± 9.99
32	75	273.06 ± 10.81	238.22 ± 9.52

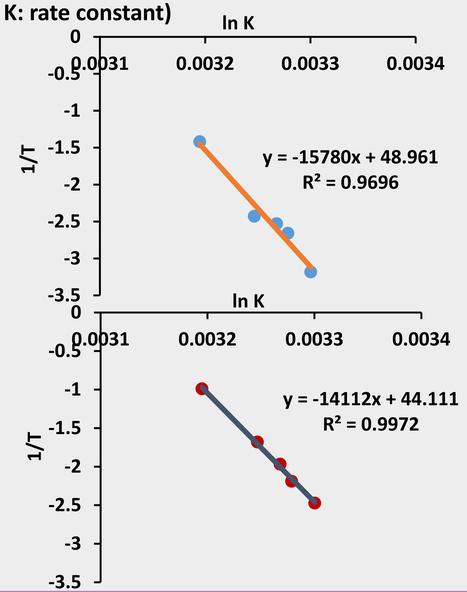
Table 2: Mean (± SD) time to break analysis of O/W emulsion and hydroalcoholic solution based foams at different temperatures at a constant % RH (n=3)

Temperature (°C)	RH (%)	Time to break (min)	
		O/W emulsion foam	Hydroalcoholic foam
30	40	40.22 ± 1.69	19.76 ± 1.61
32	40	23.80 ± 1.15	14.90 ± 0.62
33	40	20.92 ± 0.45	11.93 ± 0.31
35	40	18.93 ± 0.54	8.95± 1.01
40	40	6.69 ± 0.54	4.49± 0.54

Table 3: Energy of activation of the foams following time to break analysis at various temperatures and a constant 40% RH

	O/W emulsion foam	Hydroalcoholic foam
E_a (kJ/mol)	133.75 ± 8.27	117.58 ± 12.09

Figure 3: Energy of Activation of O/W emulsion foam (top) and hydro-alcoholic foam (bottom) (T: absolute temperature in Kelvin; K: rate constant)



CONCLUSIONS

- From this study, it can be concluded that in addition to temperature, RH is also a critical parameter that should be controlled during the evaluation of pharmaceutical foams – particularly when performing a time to break analysis of the foams.
- The results indicate that time to break analysis studies at multiple temperatures should be conducted at a constant RH, to be able to use the data generated from such studies to characterize formulations and enhance our understanding of the differences in microstructure between products.
- The E_a value for a given foam product may be potentially used as a quantitative attribute for comparing foam formulations, and to correlate the physical characteristic of the foam with the performance of the product.

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Contact Information:
Murthy Research Group
http://home.olemiss.edu/~murthy
Email ID: murthy@olemiss.edu
Phone No.: 662-915-5164