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Rheological Characterization of Topical Clobetasol Propionate Foams

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PURPOSE & OBJECTIVE

Pharmaceutical foams are thermodynamically, and mechanically unstable dosage forms comprised of a dispersion of gas within a liquid phase. Rheological characteristics of a drug product are generally dependent on the microstructure and may affect the application and product performance. Therefore, the rheological characterization of pharmaceutical foams can be utilized to understand and compare the stability and spread ability of this class of drug products, which in turn may impact performance. In this study, both, solution-based foam (CPF) and emulsion-based foam (CPEF) generic products and their corresponding reference listed drug (RLD) clobetasol propionate (CP) topical foam, 0.05% drug products were evaluated to understand the impact of physical state (solution vs. emulsion) on the rheological properties of the drug products.

METHODS

Approved drug products were obtained from the pharmacy. Rheological measurements were performed using a stress-controlled rheometer, DHR-2, TA Instruments. The experiments were conducted at 22°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. The temperature was precisely controlled using a Peltier system. A 20 mm parallel-plate geometry was used. To minimize sample slippage at the sample-rheometer plate interface, adhesive-backed sandpapers (grit number # 600) were attached to both upper and lower plates. The samples were placed on the bottom plate, and the top plate was brought into contact using a linear closure profile at 20 µm/sec. This step is important so that the foam sample does not collapse during loading. Experiments were performed with a gap of 500 µm. G' (storage modulus) and G" (elastic modulus) were measured from the tests. G' represents the elastic component or solid like behavior and G" represents the viscous component or liquid like behavior of the viscoelastic materials. When feasible, two sets of experiments were conducted on each of the four products.

Set 1:

- Time sweep test (time (t) =300 s, stress (σ)= 1 Pa, frequency (ω)= 1 Hz
- Frequency sweep test (σ=1 Pa, ω= 0.3-10 rad/s)
- Time sweep test (t=300 s, σ=1 Pa, ω=1 Hz)
- Amplitude sweep test (σ=0.1-10 Pa, ω=1 Hz)
- Time sweep test (t=300 s, σ=1 Pa, ω= 1 Hz)

Set 2:

- Time sweep test (t=300 s, σ=1 Pa, ω=1 Hz)
- Flow sweep test (shear rate ($\dot{\gamma}$)=0.002 s^{-1}-1 s^{-1})
- Time sweep test (t=300 s, σ=1 Pa, ω=1 Hz)

All experiments were performed using 4 independent samples. The data are presented as mean ± standard deviation (SD). The results were analyzed using an unpaired t-test for statistical significance with the p-value set at 0.05.

RESULTS

The yield stress of the generic CPF was 2.3 ± 0.1 Pa, and that of the corresponding RLD was 2.1 ± 0.2 Pa (p=0.67). Both the foam samples appear to have a relatively smaller yield stress value of around 2 Pa, which is at least an order of magnitude lower compared to other types of topical dermatological drug products, e.g., gels.

In the flow-sweep test, the CPF was found to have a viscosity value of 5454.2 ± 1001.7 Pa.s, whereas, the RLD foam had a viscosity value of 4824.3 ± 1402.2 Pa.s measured at the shear rate of 0.01 1/s. Although the CPF showed a slightly higher viscosity than the RLD, the difference was not statistically significant (p=0.49).

When the same protocol was applied to evaluate the rheological characteristics of the emulsion-based foams, the instrument was unable to record consistent data, likely due to the highly fragile nature of the emulsion-based foams. These foams collapsed immediately after coming in contact with the rheometer top plate and, in some instances, the collapsing phenomenon began as soon as the foam was dispensed on the rheometer bottom plate. Therefore, it was challenging to preserve the microstructure of the foam and to generate reliable rheological data for the emulsion-based generic and RLD foams.

Figure 1: Collapsed sample of CPEF

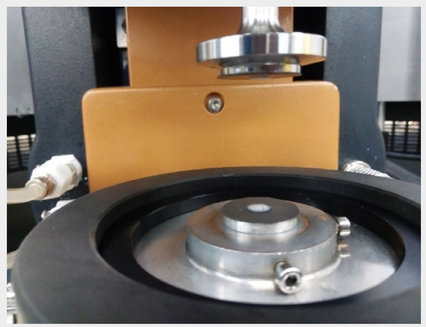


Figure 2: Yield stress for generic CPF

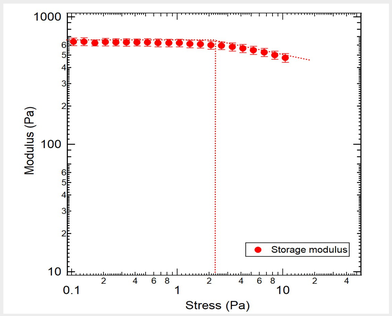


Figure 3: Yield stress for RLD CPF

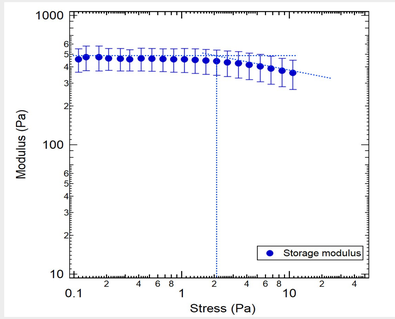


Figure 4: Frequency sweep for generic CPF

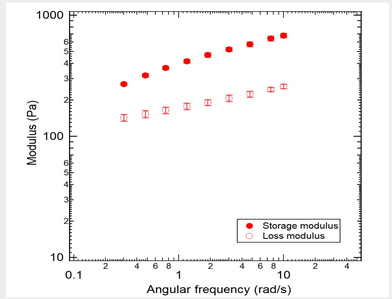


Figure 5: Frequency sweep for RLD CPF

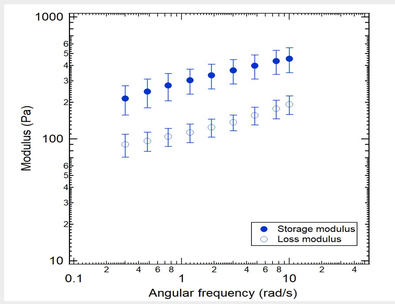


Figure 6: Flow sweep profile of generic and RLD CPF

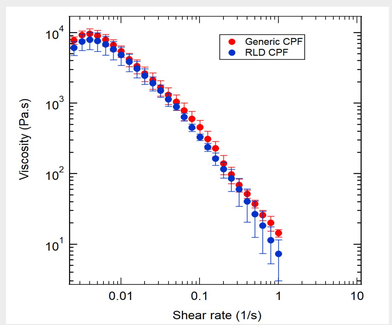
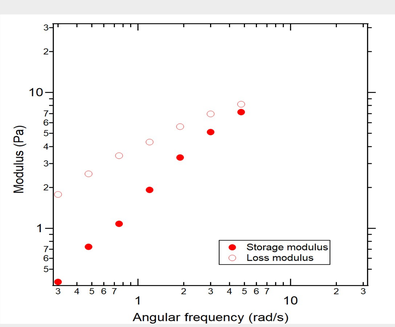


Figure 7: Frequency sweep for generic CPEF



CONCLUSIONS

The solution-based generic and RLD CPF products were found to exhibit consistent and relatively similar rheological properties in this study. These results also illustrate that a rheological characterization of solution-based foams is feasible and that such data can be utilized to compare the microstructure of generic and RLD clobetasol propionate solution-based foams. It is reasonable to conclude from this work that rheological characterization techniques that are routinely used to characterize topical semisolid dermatological products can be used to evaluate/compare the microstructure of solution-based topical dermatological foams.

By contrast, the emulsion-based foams evaluated in the study appeared to have a weak microstructure, and it was not possible to obtain consistent rheological data for these products (with intact foam) using a conventional rheometer. These results suggest that the rheological characterization of foams that disintegrate almost immediately following application on the surface of the skin may be challenging to perform, and/or that it may be challenging to interpret the results for such products. Additional research with other emulsion-based foams and other approaches to characterize the rheology of collapsed foams are warranted.

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