Topical Semisolid Product Bioequivalence- A Case for Product Quality and Performance Assessment as Evaluation Tools

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Purpose

Semisolid drug products for topical use are complex systems comprised of active and inactive ingredients organized within a well-defined physical and structural arrangement of matter (Q3). The structural and physical properties of pharmaceutical/cosmetic creams, gels, lotions etc. can be measured by utilizing sensitive and robust techniques. A complete rheological profiling along with measurement of loss of volatiles and water and microscopic assessment of semisolid products can aid in microstructural evaluation. Further, *in vitro* permeation testing using excised human skin can be utilised to evaluate performance and correlate physical and structural properties to performance.

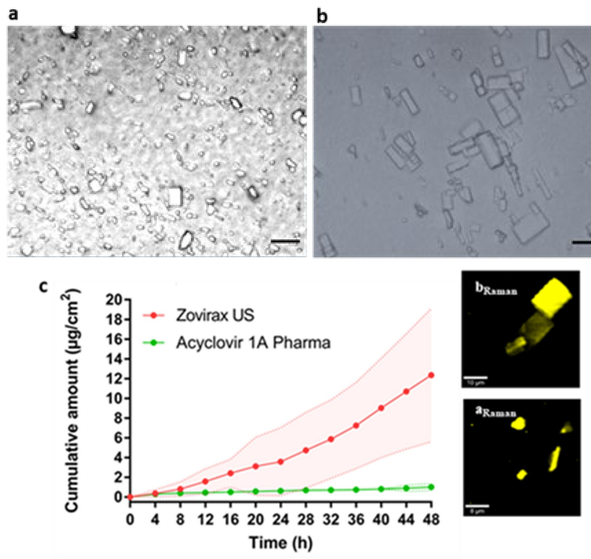

Figure 1: Differences in particle geometry visualized by optical microscopy (a) Irregular sized particles in Acyclovir 1A Pharma cream and (b) Regular rectangular particles in Zovirax® cream US. Chemically selective Raman image after processing (Right – b_r and a_r) and associated performance differences between the two products determined by IVPT (3 skin donors and 3 replicates)

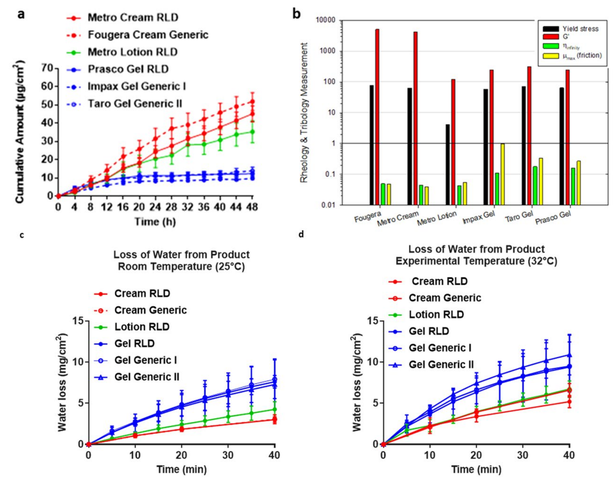

Figure 2: Differences in Q3 attributes such as (a) rheological properties (b) loss of water at 25°C and (c) loss of water at 32°C between reference and generic metronidazole products and the associated performance differences between metronidazole products of different microstructures as determined by IVPT (3 skin donors and 3 replicates)

Methods

The innate microstructures of multiple products from 3 active pharmaceutical ingredients (APIs) comprising of reference and generics and three dosage form types (microstructures) were comprehensively characterized by optical microscopy, confocal Raman microscopy and cryo-scanning electron microscopy. The shear response on product microstructure, flow and lubrication properties were evaluated with a sensitive and precise rheometer and tribometer and *in vitro* permeation tests (IVPT) was performed using static Franz-type diffusion cells and flow through diffusion system across heat-separated human epidermis.

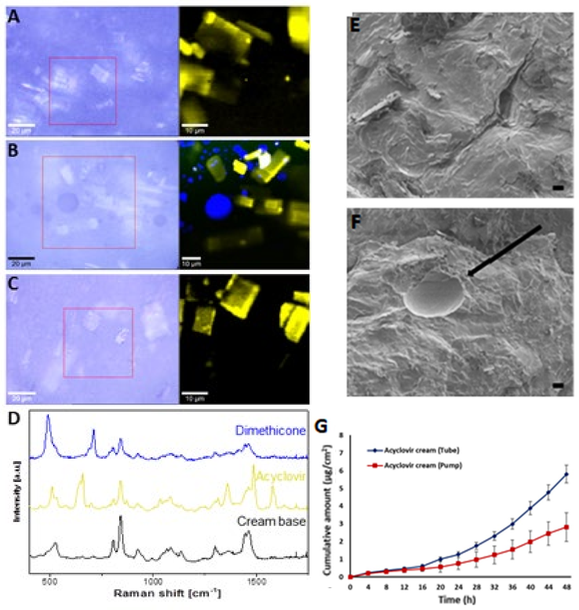

Figure 3: Confocal Raman microscopy (CRM) analysis of acyclovir formulations from different dispensers. Light microscopic images and corresponding Raman false color images of the areas indicated by the red square of samples from (A) tube , (B) pump and (C) a sample removed from the pump container without dispensing. The false color images show the cream base (black), acyclovir crystals (yellow) and dimethicone globules (blue): and the corresponding single spectra of these components (D). On the right panel Cryo-SEM images showing the internal microstructure of the acyclovir cream dispensed from (E) tube and (F) pump (globules - black arrow Scale bar = 5 µm and (G) permeation profile of acyclovir from Zovirax® cream (UK) - tube and pump (6 skin donors, n=3)

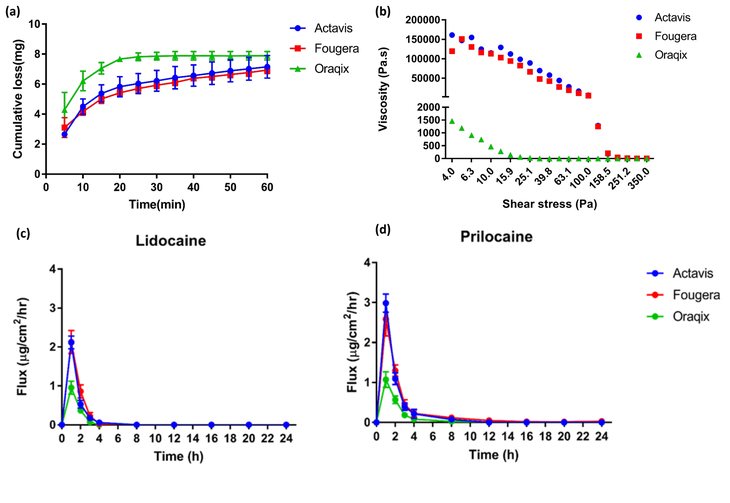

Figure 4: Differences in Q3 attributes such as (a) cumulative weight loss at 32°C (b) viscosity as a function of shear stress and performance differences between products for (d) lidocaine and (e) prilocaine

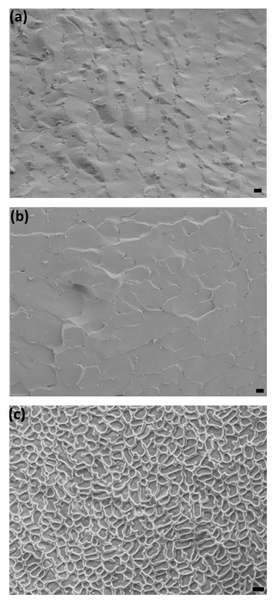

Figure 5: Cryo-SEM images at 3000X depicting the internal microstructures of (a) Actavis cream (b) Fougera cream and (c) Oraqix gel. Scale bar - 1µm

Results

- Our results suggested that the toolkit we developed for characterization of Q3 attributes was sensitive in determining differences between different topical microstructures such as creams, gels and lotion. (Figs 1-5)
- Some Q3 differences that we established led to performance differences among products of the same strength e.g. metronidazole products (Fig 2) where the water loss from the gels was highest followed by the lotion and creams.
- Differences in cream microstructure were evident after dispensing through a pump and tube, with globules of coalesced oil phase identifiable only in the product dispensed through a pump (Fig 3B, E and F) and only after pumping by CRM and cryo-SEM. Fig 3 also shows that CRM confirmed the identity of the oil globules as being dimethicone (Fig 3B and D). A comparison of these products by IVPT with human epidermal membranes determined that the bioavailability of acyclovir from the cream dispensed by the pump was lower than from that dispensed from the tube. (Fig 3G)
- Differences in Q3 attributes such as rate of drying, viscosity and the innate microstructure (as visualized by cryo-SEM) were also seen between lidocaine-prilocaine cream and gel products. (Figure 4 and 5)
- The cutaneous pharmacokinetics (PK) of the creams was comparable for lidocaine and prilocaine. By contrast, the gel exhibited a different cutaneous PK for both active ingredients.

Conclusion

It is important to develop a better understanding of the relationship between product quality attributes (Q3 attributes) that can describe the microstructure of complex semisolid dosage forms and the resulting therapeutic performance and/or product failure modes that may arise from differences in physical and structural characteristics. Furthermore, since the microstructure of semisolid dosage forms can be altered by the dynamic physical stresses imposed during the application of the dosage form upon the skin, methodologies that can discriminate between these characteristics in the bulk manufactured semisolid topical products from those that arise when product is “in use”, are particularly relevant.

Acknowledgements

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