The Impact of Topical Semisolid Product Microstructure and Metamorphosis on Bioavailability and Bioequivalence

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Introduction

Topical semisolid drug products are complex dosage forms comprised of varying qualitative (Q1) and quantitative (Q2) compositions, and possessing specific physical and structural qualities (Q3). Stresses that alter Q3 properties when dispensing a product from a container, and/or during dose administration (rubbing into the skin), and/or during the loss of volatiles from the product on the skin can change both, the composition (Q2) and arrangement of matter (Q3). This can affect product performance and bioequivalence, even for products that are initially Q1 and Q2 the same. We investigated the impact of dispensing a product from a tube and a pump using acyclovir cream, 5% products marketed in the U.K. We also compared the effect of simulated “in use” application stresses on Q3 attributes and the permeation of acyclovir through excised human skin from acyclovir cream, 5% products marketed either in the U.S. or Austria.

Methodology

The innate microstructure of the product and its metamorphosis were comprehensively characterized by optical microscopy and confocal Raman microscopy (CRM). The impact on cream microstructure of dispensing from a tube vs. pump was assessed. Independently, the impact on bioavailability of rubbing the cream on the skin was investigated using an in vitro permeation test (IVPT) with heat-separated human epidermis mounted in Static Franz-type diffusion cells.

Results

Physical and structural (Q3) differences were evident in the acyclovir creams following dispensing of the product from a tube and a pump. This included the presence of small globules (coalesced oil phase containing dimethicone) after dispensing the cream from the pump that were not observed either in the canister prior to pumping or after the cream was dispensed from a tube. Independently, The acyclovir particle characteristics were altered following simulated “in use” conditions compared to static conditions. The bioavailability of acyclovir evaluated by IVPT was significantly higher ($P < 0.05$) when the product was dispensed from a tube compared to the pump, and following the application of simulated “in use” stresses compared to static conditions.

Conclusion

These findings highlight important considerations related to routine metamorphosis-inducing procedures associated with the use of topical semisolid drug products, which can alter the physical and structural (Q3) characteristics of the dosage form and affect the drug delivery to the skin. Clearly it is important to characterize Q3 attributes of topical semisolid drug products, to support determinations of both, pharmaceutical equivalence and bioequivalence. These findings have particular significance for the product development, testing, manufacturing and control of both, generic and reference listed drug products.

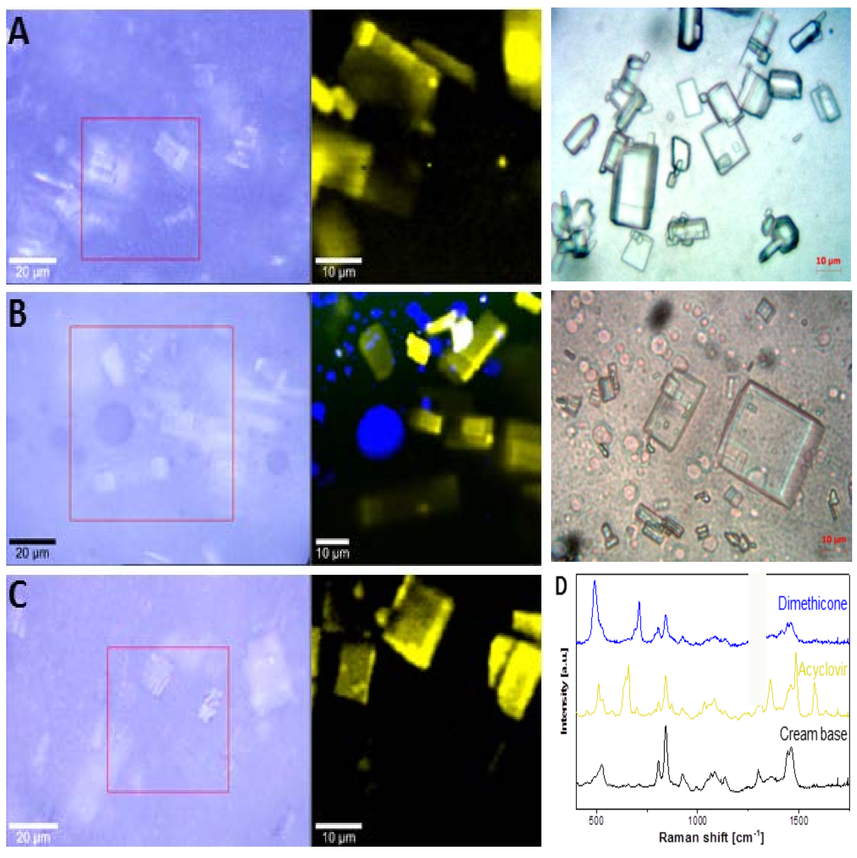

Figure 1: Light microscopy and CRM (attached first two columns, respectively), and optical microscopy images of acyclovir cream from a tube (A), pump (B) and opened pump dispenser (C). Panel C far right image shows the color coding of CRM spectra.

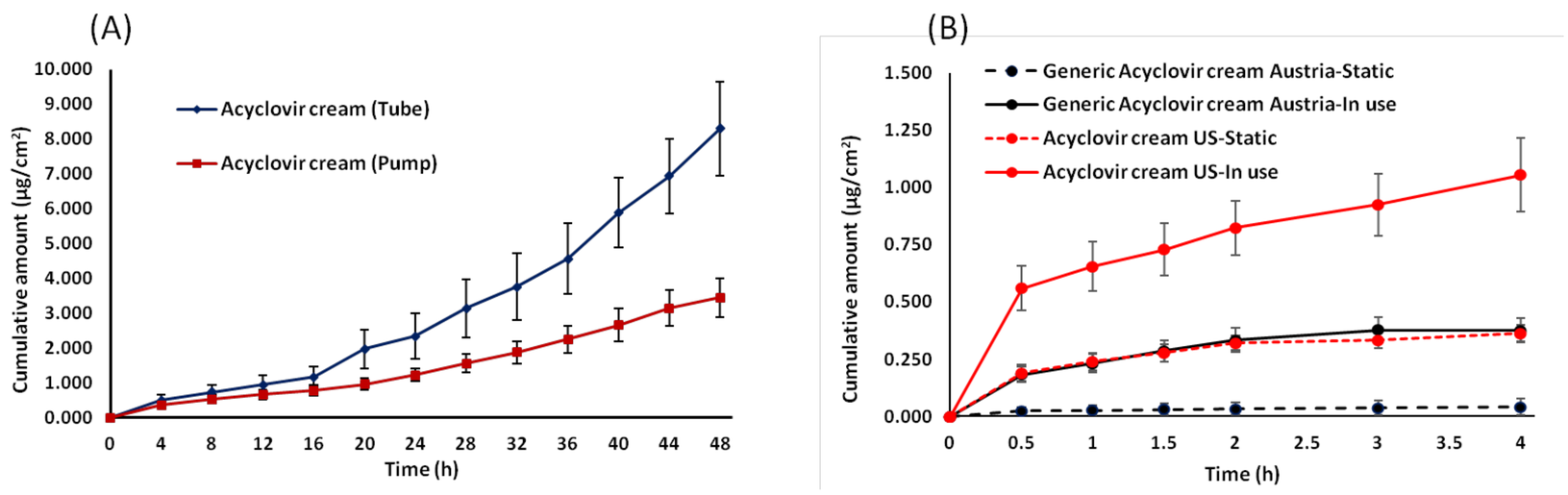

Figure 2: (A) Permeation profile of acyclovir from acyclovir cream, 5% (Zovirax® U.K.) dispensed from a tube or from a pump and evaluated in an IVPT study using heat separated human epidermis. Results are expressed as mean ± SEM; 3 donors with 3 replicates each, and (B) Permeation profile of acyclovir from acyclovir cream, 5% products (Zovirax® U.S. and an Austrian generic) using either of two different dose application techniques evaluated in an IVPT study using dermatomed human skin. Results are expressed as mean ± SEM; 3 donors with 3 replicates each

Acknowledgements Funding for this project was made possible, in part, by the Food and Drug Administration through grant U01FD005226. The views expressed in this abstract 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.