Simulated “in use” Conditions to Assess Semisolid Topical Products

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PURPOSE

Generic medicinal products can provide high quality, therapeutically equivalent options that reduce the cost of medical therapy to individuals and to the government. Typically, bioequivalence testing is used as a measure of product performance, making it possible to compare a generic product to the reference listed drug (RLD) product developed by the innovator. However, comparing two complex, semisolid topical or transdermal products may not be as straightforward as comparing other simpler dosage forms. The skin conditions and the products’ physicochemical characteristics (Critical Quality Attributes CQAs) may play a critical role in the performance of some topical products.

Moreover, it may be of value to simulate, where possible, “in use” product behaviour, when assessing topical products for comparative bioavailability. Particle size is one of the many critical quality attributes that influences the solubility of the active in the vehicle.

The objective of this work was to develop novel strategies and methodologies for comparison of microstructural characteristics (particle size) under static conditions and under simulated “in use” conditions for a topical dermatological 5% acyclovir cream.

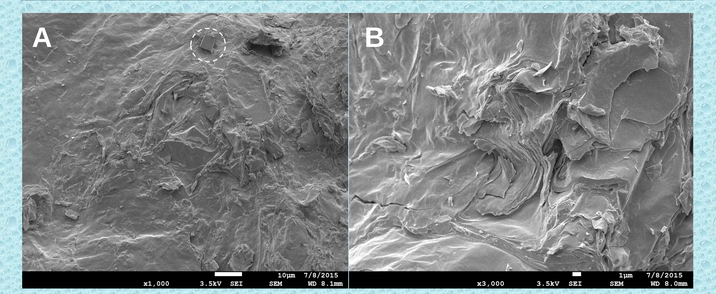

Figure 1 Scanning Electron Microscopy images of Acyclovir 5% cream (A) Crystal highlighted and (B) Microstructure of the cream bulk phase.

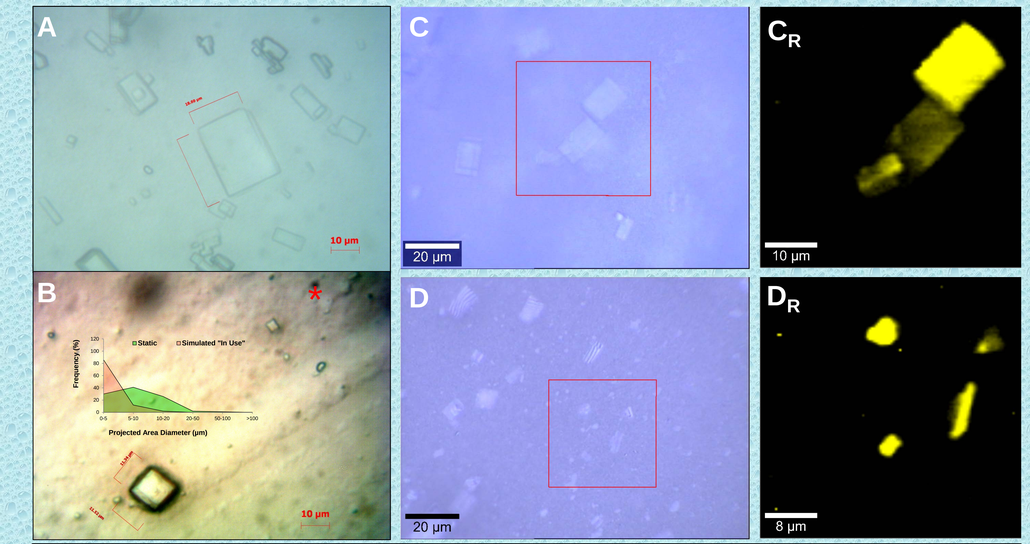

Figure 2 Acyclovir drug particles in 5% cream “at rest” (A &C) and after simulated “in use” conditions (B&D); Optical microscopy image (left) and chemically selective Raman image after processing (right- C_R&D_R). *insert (B) shows size distribution of particle projected area diameter. * “In use” image blurred as a result of a thin residual layer upon application.

METHODS

- The drug particle size distribution and the formulation microstructure were assessed by optical microscopy and confocal Raman microscopy.
- Samples were applied on a glass slide and spread evenly in a thin layer.
- For the simulated “in use” conditions, cream samples were applied with a defined mechanical stress.
- Images (40X, 100X) were acquired using a Zeiss Primostar optical microscope with a Zeiss AxioCam Erc 5S.
- At 40X, 4 microscopy images were acquired for each sample. A calibrated scale bar was used to measure the particle sizes
- In each image, approximately 25 particles were manually counted and measured.
- Particle size distribution plots were generated using the AxioVision software (Release 4.8.2).
- In addition, chemically selective images were acquired with Raman microscopy (alpha 300R+, WITec) with an excitation wavelength of 785 nm and a step size of 0.5 µm.
- Electron microscopy was employed to understand the morphology and microstructure of crystals and the formulation

RESULTS

- The drug particle size distributions for the static and simulated “in use” conditions were found to be substantially different.
- It was also noted that the spatial distributions of the product excipients and the drug were dissimilar after simulation of product application.
- The most significant finding was the considerable reduction in the number of crystals and an associated increase in dissolved drug seen after simulated “in use” application of acyclovir 5% cream.
- Raman microscopy was used to differentiate between drug particles and cream base in acyclovir 5% cream. Results acquired with Raman could be correlated to findings based on optical microscopy.

CONCLUSIONS

It is important to develop a better understanding of the relationship between product quality attributes that describe their microstructure and the resulting therapeutic performance and/or product failure modes that may arise from differences in critical quality attributes.

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 microstructural characteristics in the bulk manufactured semisolid topical products from those that arise “in use” are particularly relevant.

Here, we have presented a simple method to investigate product behaviour under an increased application stress simulating “in use” conditions.

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