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Are Topical Products Dispensed from Different Packaging Q3 Equivalent and Bioequivalent?

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PURPOSE

A topical semisolid drug product may be marketed in multiple packaging configurations for practical reasons such as the ease of dosing. Packaging or dispensing processes may have the potential to influence the product quality (Q3) attributes (i.e., microstructure) and the subsequent bioavailability of the active ingredient(s). The main objective of this work was to characterize whether any microstructural product quality (Q3) differences may arise when the same acyclovir 5% cream product is dispensed from a pump vs. a tube, and to compare the topical bioavailability of acyclovir from the creams in each packaging configuration.

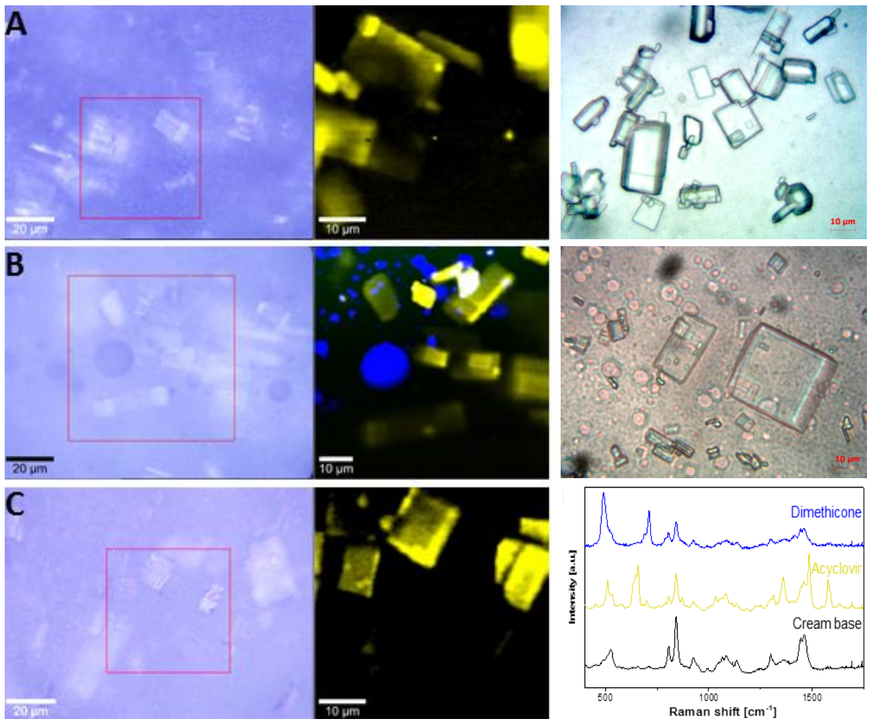
METHOD

We evaluated the differences in microstructural properties (e.g., particle/ globule size) and rheological behavior of a commercially available acyclovir cream 5% marketed in pump and tube packaging configurations in the U.K. Confocal Raman Microscopy (CRM) and confocal Raman spectroscopy (label-free) were used to selectively identify ingredients like acyclovir and dimethicone, as well as to characterize the associated microstructure in the product. *In Vitro* Permeation Tests (IVPT) using static Franz type diffusion cells were performed to assess the acyclovir bioavailability over 48 hours across heat separated human epidermis from a 15 mg/cm^2 dose of the acyclovir cream 5% dispensed from either a pump or a tube packaging configuration.

RESULTS

Differences in cream microstructure were evident between the pump and tube, with globules of coalesced oil phase identifiable only in the product dispensed through a pump (Fig 1B) and only after pumping. Fig 1 shows that confocal Raman spectroscopy confirmed the identity of the oil globules as being dimethicone (Fig 1B center panel) and identified the acyclovir crystals and the cream base (Fig 1C far right). As expected, dimethicone globules were also observed when imaged with cryo-SEM (Fig 3 B) in the cream sample dispensed from the pump (indicated by a black arrow), but not from the tube (Fig 3 A) although the morphology of the crystals (indicated by red arrows) and the internal microstructure (indicated by yellow arrows) were similar in both the products. Further, when the product was dispensed through a tube, it exhibited a lower yield stress (130 Pa) compared to that of the pump (225 Pa). 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. The cumulative amount of acyclovir permeated over a 48-hour period from the pump product was 3.4 ± 0.56 µg/cm^2 compared to 8.3 ± 1.3 µg/cm^2 from the tube product (Fig 2). The higher yield stress and lower acyclovir permeation through the skin for the cream dispensed from the pump may have been due to a coalescence of the larger dimethicone globules arising in that product.

Figure 1: Light microscopy and CRM (attached), 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



CONCLUSION

We observed clear microstructural product quality (Q3) differences in the acyclovir cream dispensed from the pump vs. the tube. A substantial difference in the in vitro skin permeation of acyclovir was also observed for the cream dispensed from the pump vs. the tube, demonstrating the potential influence of packaging configurations on Q3 product quality attributes and topical bioavailability.

Figure 2: Permeation profile of acyclovir from acyclovir cream 5% (UK) - tube and pump across heat separated human epidermis. Results expressed as mean ± SEM, 3 skin donors, 3 replicates each.

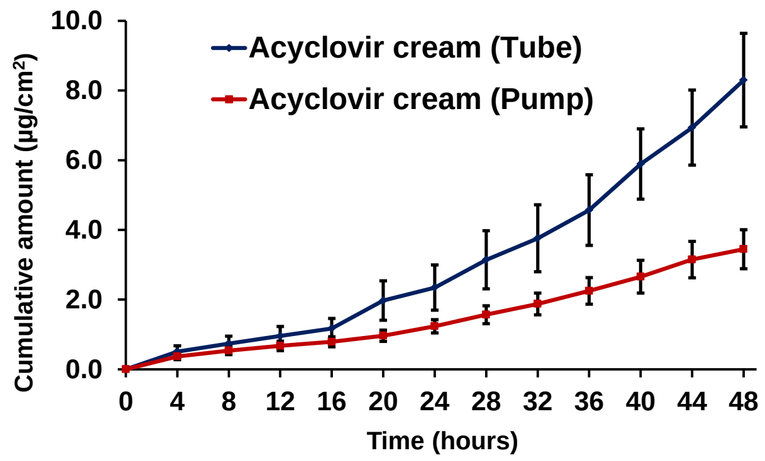


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Figure 3: Cryo-SEM images showing the internal microstructure of the acyclovir cream 5% (UK) dispensed from (A) tube and (B) pump (globules = black arrow, crystals = red arrow and background lamellar fabric = yellow arrow).