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Water Content and Product Drying Rate as well as the Amount of Propylene Glycol may Impact the Topical Bioavailability of Acyclovir from Cream Products

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PURPOSE

Generic drug products can provide high quality, therapeutically equivalent options that reduce the cost of medical therapy to individuals and to health care systems. Product quality attributes may play a pivotal role impacting topical bioavailability. The objective of this work was to develop a framework for measurement of specific quality attributes (QAs) and to relate them to the cutaneous bioavailability (BA) of acyclovir from topical acyclovir creams.

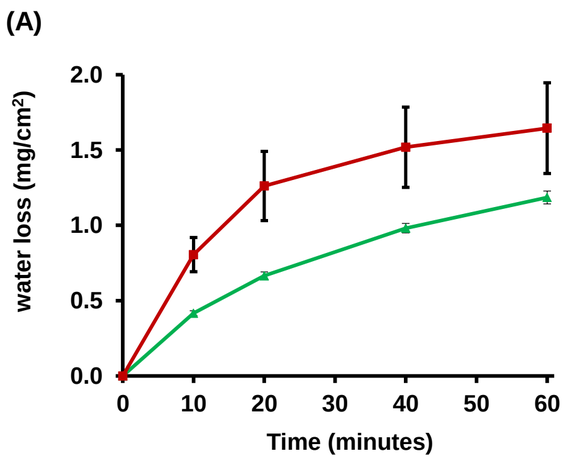
METHODS

The total amount of water present in the reference (R) and the test (T) creams was measured using a Karl Fischer titration. The rate of passive evaporation of water (at 32°C) from the R and T creams was measured using a novel method developed with a modified BIOX-AquaFlux system. Thermogravimetric analysis (TGA) was used to quantify propylene glycol. *In Vitro* Permeation Tests (IVPT) with reference (R) and test (T) acyclovir 5% creams were performed to assess the acyclovir bioavailability (BA) over 48 hours across heat separated human epidermis from a 15 mg/cm^2 dose.

RESULTS

The total percentage of water and the corresponding rate and extent of water evaporation from the T cream was higher compared to the R cream (Fig 1A and Table 1). The estimated propylene glycol content in the formulations was approximately 35-40% in the R cream and 13-15% in the T cream based upon the percentage weight loss from the cream in the 125-225°C region of the TGA curves during a temperature ramp. The cumulative skin permeation of acyclovir over 48 h from the R cream (4.6 ± 0.46 µg/cm^2) was higher than from the T cream (1.02 ± 0.15 µg/cm^2) (Fig 1 B). We hypothesize that, among other possible mechanisms, the higher rate of water evaporation from the T cream may result in faster drying of the product on the skin, leading to a more rapid crystallization of acyclovir and concomitant decrease in the amount of solubilized drug available for diffusion and permeation.

Figure 1: (A) Water loss (mg/cm^2) comparison between the Test (-) and Reference (-) creams; (B) Permeation profile of acyclovir from creams across heat separated human epidermis. Results are expressed as mean ± SEM based upon 3 skin donors with 3 replicate skin sections each.



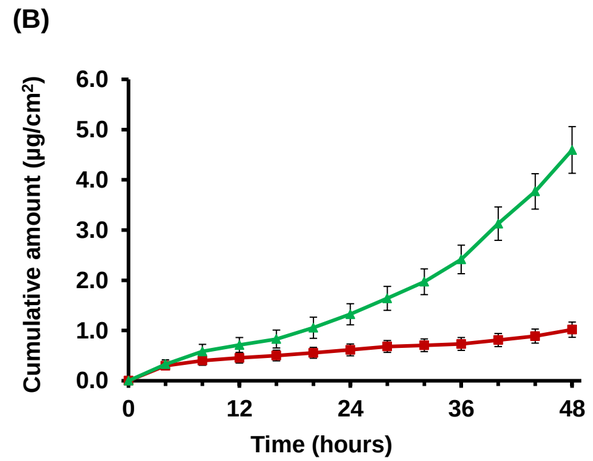


Table 1: The total amount of water (%) in reference and test creams

Water content (%)	Reference cream	Test cream
	26.3	60.5

CONCLUSION

The influence of propylene glycol on the performance of acyclovir products has been previously reported.[1] Here we observed that beyond the potentially reduced penetration enhancement due to a lower propylene glycol content, a higher water content and faster drying rate were associated with a reduced topical bioavailability of acyclovir from the T cream. This suggests that the water content and rate of evaporative water loss may be critical quality attributes for topical semisolid drug products like acyclovir cream.

REFERENCE

1. Trottet L, Owen H, Holme P, Heylings J, Collin IP, Breen AP, Siyad MN, Nandra RS, Davis AF. Are All Acyclovir Cream Formulations Bioequivalent? Int J Pharm 2005; 304, 63-71.

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