

# Is Water Activity the Primary Determinant of Metamorphosis for Topical Creams?

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## PURPOSE

The ratio of the partial vapor pressure of water in a formulation to its vapor pressure in the pure form is its "water activity". Following dose application, topical cream formulations can undergo complex compositional and microstructural changes on the skin surface. The hypothesis of the present study was that water activity may be a critical quality attribute that determines the rate of loss of volatile (aqueous) contents from the cream, and is thereby a key factor modulating the metamorphosis of the cream as it dries at the site of application.

## METHOD

An AquaLab<sup>®</sup> 3TE was used to measure the water activity with three acyclovir cream 5% (Zovirax<sup>®</sup>) Reference Products marketed in different countries (U.S., U.K., and Austria (AUT)) and two acyclovir cream 5% Test Products marketed in Austria, (Aciclostad and Aciclovir 1A). The rate of loss of water from the creams following application on the skin was also measured by a Vapometer<sup>®</sup>. For these assessments, human cadaver skin was mounted on Franz diffusion cells with phosphate buffered saline (PBS) at pH 7.2 in the receptor compartment, and after equilibration for 30 minutes a baseline water evaporation rate was recorded. Creams were then applied on the skin at a dose of 15 mg/cm<sup>2</sup> and the water evaporation rate was recorded using a Vapometer<sup>®</sup> at predetermined time intervals. The metamorphosis (drying) of the creams was recorded using a high resolution Nikon camera.

## FUNDING

Funding for this project was made possible, in part, by the Food and Drug Administration through grant 1U01FD005223. The views expressed in this poster 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.

## RESULTS

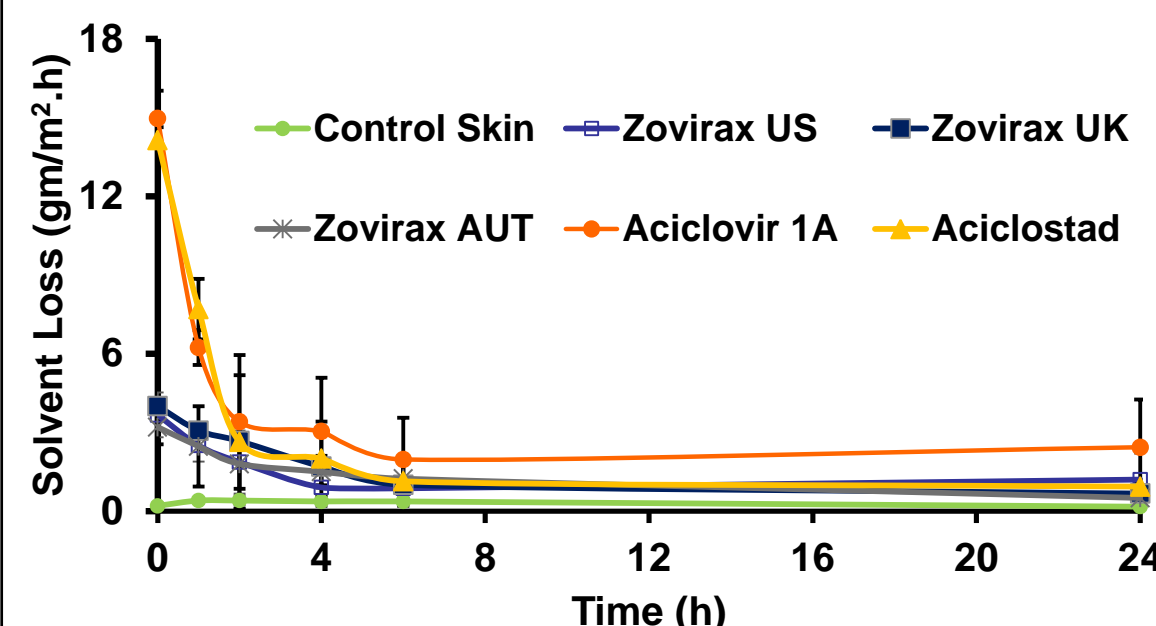


Figure 1: The rate of water loss in acyclovir creams. n=6 ± SD

Product	Water Activity (a <sub>s</sub> )
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732 ± 0.002
Aciclovir – 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

The water activity of the Reference Creams was similar, in the range of 0.732±0.002 to 0.753±0.003. This range was relatively lower than the water activities of the Test Creams which were 0.948±0.001 and 0.948±0.003. The corresponding flux of acyclovir across human cadaver skin from the Test Creams was also significantly lower compared to the Reference Creams (data not shown here). The topical bioavailability of acyclovir from these creams in vitro correlated inversely with the water activity values obtained for the creams. The rate and extent of solvent (water) mass lost from the Test Creams was greatest within the first 2 h. By contrast, the Reference Creams lost substantially less mass (water) in the first 2 h.

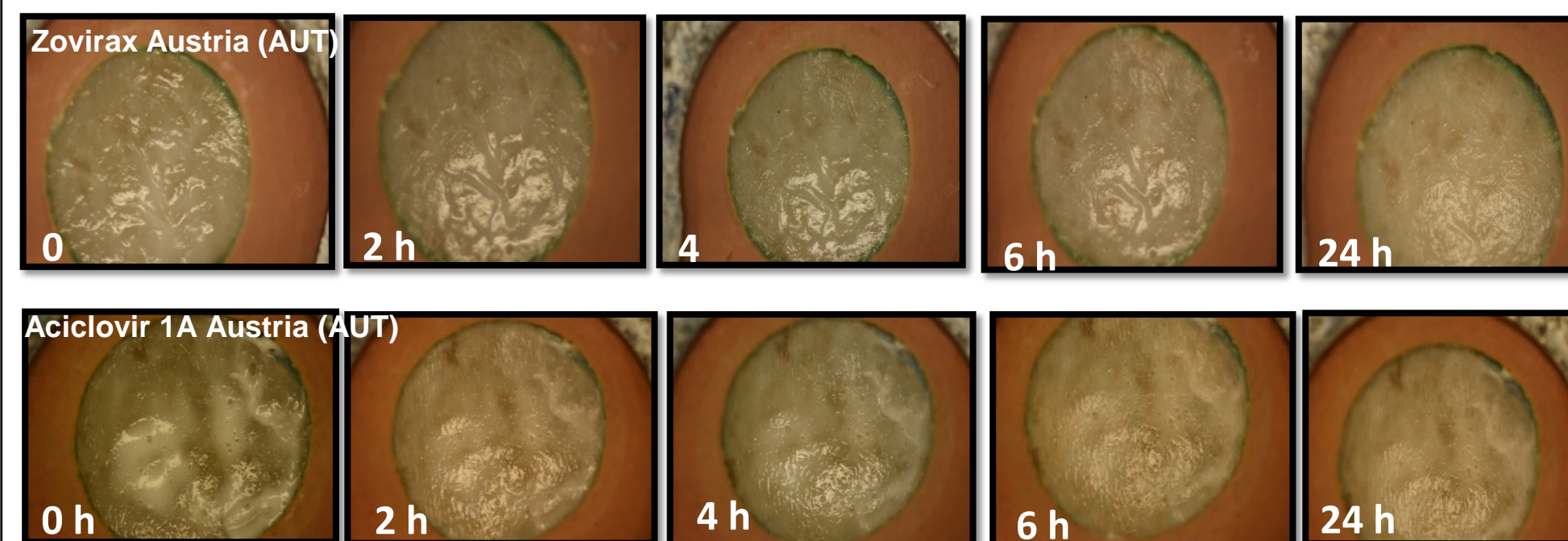


Figure 2: The metamorphosis (drying) of acyclovir creams on the human cadaver skin

These differences in water activity and in the correspondingly different rates of water loss may be expected to modulate the rate of metamorphosis of the cream, which would likely influence the solubility, thermodynamic activity and topical bioavailability of an aqueous drug like acyclovir. A mechanistic study performed to investigate morphological changes associated with solvent (water) loss showed that the Test Creams, which exhibited a higher water activity compared to the Reference Creams, also exhibited a faster drying rate compared to the Reference Creams.

## CONCLUSION

The results of the study showed that water activity correlated with the rate of drying (metamorphosis) for topical creams. A cream with relatively higher water activity would be predicted to undergo a more rapid metamorphosis compared a cream with a lower water activity. Nonetheless, since the acyclovir cream 5% products evaluated did not have identical compositions, the differences in quality attributes and metamorphosis among the creams cannot be uniquely associated with their water activities, and other quality attributes may also have been influential. Still, these data suggest that in addition to the dose, the water activity of the formulation may warrant consideration as one of the important factors to determine the frequency of application of topical dosage forms.