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Influence of the Method of Dose Application on the In Vitro Permeation Profile of Acyclovir Permeation from Topical Creams

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PURPOSE

The goal of the study was to evaluate the effect of different methods of dose application on the flux profile (topical bioavailability) of acyclovir. In the study, the influence of different finite dose application methods on the permeation of acyclovir from two acyclovir 5% creams (both marketed in Austria) was evaluated by in vitro permeation testing (IVPT).

METHOD

The IVPT experimental protocol evaluated six replicate skin sections per treatment group using dermatomed human posterior torso cadaver skin from a single donor (acquired from New York Fire Fighters skin bank) and was performed in Franz diffusion cells with an active diffusional area of 2 cm^2. The receptor medium consisted of phosphate buffered saline (pH 7.2) with 0.008% gentamycin sulfate. A finite dose (15 mg/cm^2) of the acyclovir cream 5% (Austrian Zovirax® as Reference or Aciclovir 1A as Test) was applied on the active diffusion area using one of three different application methods: 1) applied by rubbing upon the skin using the flat underside of a glass vial, or 2) applied using a spatula, or 3) applied using a positive displacement pipette. The complete receptor volume of 10 ml was collected at sequential 4 h intervals for 48 h and analyzed for acyclovir using a validated high performance liquid chromatography method.

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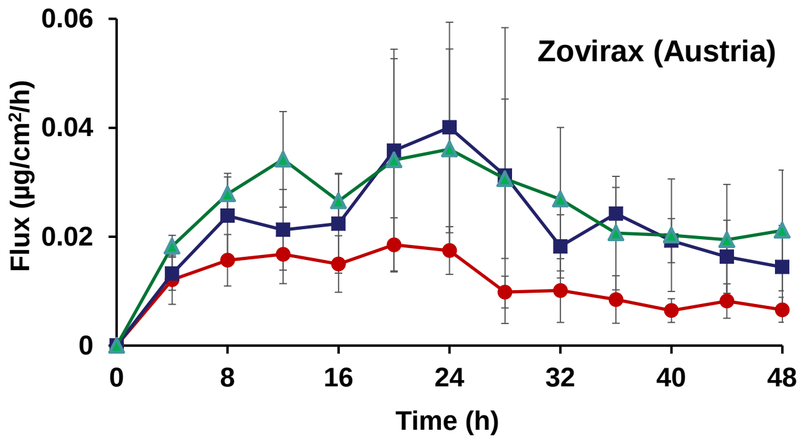
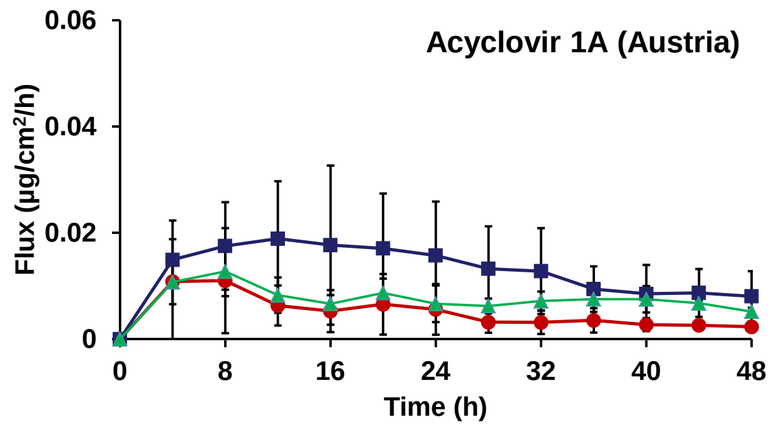
RESULTS





Method	AUC_{0-t}	Jmax (µg/cm^2/h)	Tmax (h)
Spatula method	1.22±0.38	0.04±0.01	16.67±8.54
Pipette method	0.57±0.16	0.02±0.001	18.67±5.46
Vial method	1.09±0.24	0.05±0.02	28.00±6.69

Method	AUC_{0-t}	Jmax (µg/cm^2/h)	Tmax (h)
Spatula method	0.36±0.06	0.01±0.003	19.20±5.59
Pipette method	0.25±0.19	0.01±0.02	7.33± 3.01
Vial method	0.63±0.31	0.02±0.01	12.67±4.67

The average maximum flux (J_{max}) of acyclovir across human skin in the case of the acyclovir cream 5% (Zovirax, Austria) was 0.05 (±0.01), 0.04 (±0.01) and 0.02 (±0.001) µg/cm^2/h for the vial, spatula and pipette methods respectively. The average J_{max} in the case of acyclovir cream 5% (Acyclovir 1A, Austria) was 0.02 (±0.01), 0.01 (±0.003) and 0.01 (±0.02) µg/cm^2/h using the vial, spatula and pipette methods respectively. Similarly, the different methods of dose application also resulted in flux profiles with different J_{max} and T_{max} and different total amounts of acyclovir permeated (AUC). (n=6 ± SD)The differences in permeation observed were not statistically significant ($p>0.05$) among the three methods of application for the two products evaluated in this limited dataset.

CONCLUSION

The results suggest that the method of application of a semisolid drug product may influence the shear forces, consistency or thickness of the applied dose and that the resultant influence upon the metamorphosis of the dosage form during drying may alter the permeation profile of the drug. These results suggest that the method of dose application may be an important procedural control parameter, to be kept constant throughout a study, and to be considered carefully when reporting or comparing results between studies, whether in vitro or in vivo.