Dermatopharmacokinetics as a tool for bioequivalence testing: a case study comparing acyclovir creams from the US and UK

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Background:

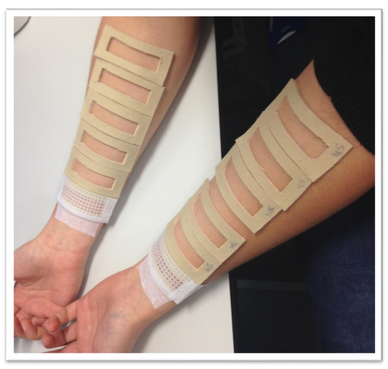
For many topical drug products, a clinical trial provides the principal evidence of bioequivalence for a generic product. However, such trials can be relatively insensitive, time-consuming and costly.

As drug diffusion across the stratum corneum (SC) is typically the rate-limiting step in skin absorption, this skin layer has been evaluated as an alternative matrix for bioavailability assessment.

Aim:

Here, a refined approach of the tape-stripping technique, which involves assessment of drug content in the SC after one uptake period and after a subsequent period of clearance, has been used to compare two formulations of acyclovir (ACV) cream 5% w/w (Zovirax®) which have been approved for use in the US (ACV-US) or the UK (ACV-UK).

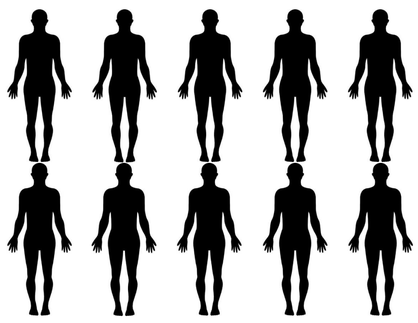
Healthy adults (n = 10). Six treatment sites (8.25 cm^2 each) were demarcated on each ventral forearm. ACV-UK cream was applied to 2 sites per arm, while ACV-US cream was applied to the remaining sites.

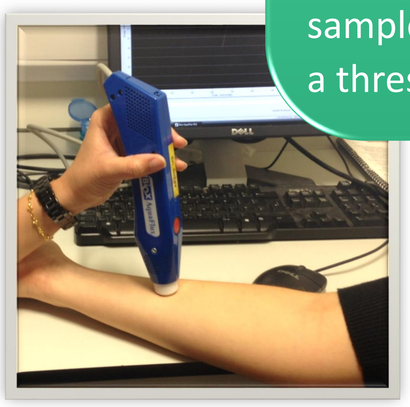


The creams were applied at clinically relevant doses (15 mg/cm^2) and were removed 6 hours later.

The SC at the treated sites were tape-stripped immediately following cream removal on one arm to assess drug "uptake", and 17 hours after cream removal on the other arm to assess "clearance".

Thirty tape-strips were removed from each site (5 cm^2 sample area) unless transepidermal water loss reached a threshold value (60 $g/m^2/h$).





The mass of SC removed on each tape was determined gravimetrically, and ACV extracted from the tapes was assayed by HPLC with UV detection. For each subject, the geometric mean of ACV mass in the SC in duplicate sites was calculated for uptake and clearance, as well as the clearance rate.

	ACV-US Ref	ACV-US	ACV-UK
Uptake ***(µg/cm²)***	0.69 (0.49-0.95)	0.60 (0.46-0.77)	0.42 (0.31-0.57)
Clearance ***(µg/cm²)***	0.45 (0.34-0.59)	0.42 (0.31-0.57)	0.28 (0.20-0.37)
Clearance Rate ***(ng/cm²/h)***	17.7 ± 11.6	10.1 ± 8.2	9.3 ± 8.0

Table 1. Average ACV amounts recovered from SC and the rate of ACV clearance over 17 hours in 10 subjects . Uptake and clearance reported as geometric mean (lower-upper 90% confidence interval); rate reported as arithmetic mean ± 90% confidence interval).

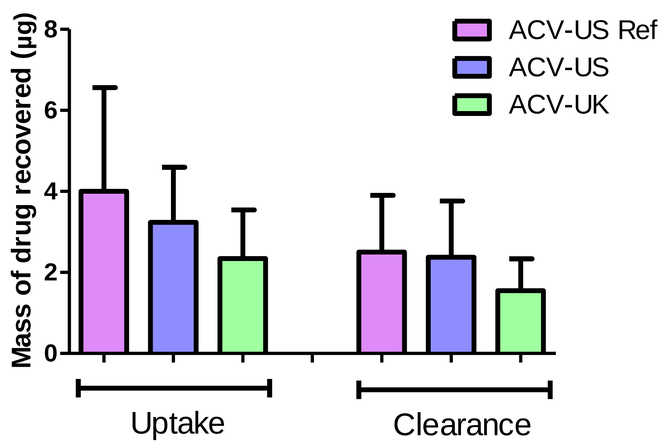


Fig. 1 Average of ACV mass (µg) recovered from the tapes in 10 subjects, (mean ± standard deviation).

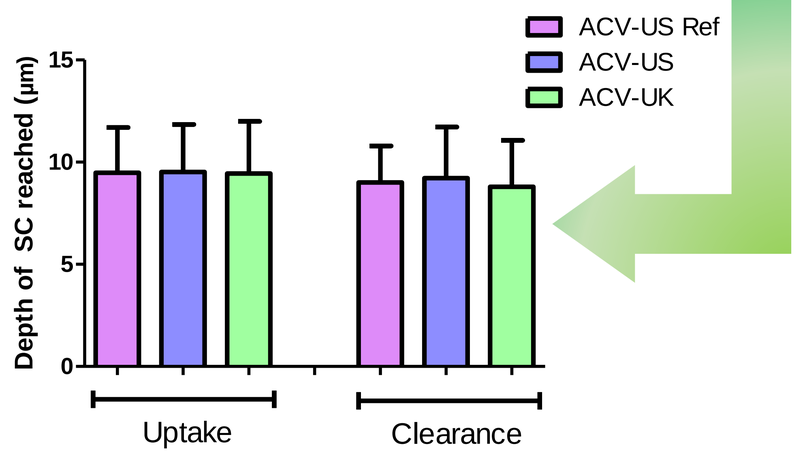


Fig. 2 Average of depth (µm) of SC reached after tape-stripping in 10 subjects, (mean ± standard deviation).

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Conclusions: At both uptake and clearance time points, there was a statistically significant difference between the ACV masses recovered from ACV-UK and both ACV-US sites, but no difference between ACV-US Reference and ACV-US test sites. No statistically significant difference between ACV clearance rates for any of the products was observed.