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Bioequivalence of Topical Products in Excised Human Skin Assessed with dermal Open Flow Microperfusion (dOFM)

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Background

There are a limited number of established approaches by which to demonstrate the bioequivalence (BE) of a prospective generic topical drug product to its reference listed drug product. In recent years, novel, accurate, sensitive, reproducible and efficient tools and methods to evaluate topical BE have been developed in collaborative research projects funded by the FDA. Several research facilities around the world investigated different acyclovir cream products to characterize their quality attributes[1,2,3], release rates[4], skin permeation[5] and in vivo cutaneous pharmacokinetics in human subjects[6]. The results of these studies are enhancing our mechanistic understanding of cutaneous bioavailability (BA) and BE. Our research group investigated the utility of ex vivo dermal Open Flow Microperfusion (dOFM) studies for evaluating BE. We performed an ex vivo dOFM study using a study design that was identical to a previous in vivo dOFM study (in human subjects)[6]. A key objective of this work was to explore the utility of ex vivo dOFM studies for the purposes of evaluating BE.

Material and Methods

- 40 excised human skin sections from 16 skin donors (healthy skin)
- 3 treatment sites per skin section
- 2 dOFM probes per treatment site were inserted into the dermis and perfused for interstitial fluid (ISF) sampling at 1 µL/min
- T=0 hours: Topical application of two 5% acyclovir creams (Figure1):
  - Reference product (R) applied on two treatment sites
  - Test product (T) applied on the third treatment site
- T=–1hours…36 hours: Continuous dermal sampling in 4 hour intervals
- Controlled environmental conditions: 22±1°C, 40–60% relative humidity
- Bioanalytical method: UHPLC-MS for quantification of acyclovir in dermal samples
- Statistical evaluation:
  - Pharmacokinetic endpoints: $AUC_{0\text{-}36h}$ and C_{max}
  - All tests are based on log-transformed data
  - Reference-scaled average BE (SABE) approach
  - Positive control test for BE: R vs. R
  - Negative control test for BE: T vs. R

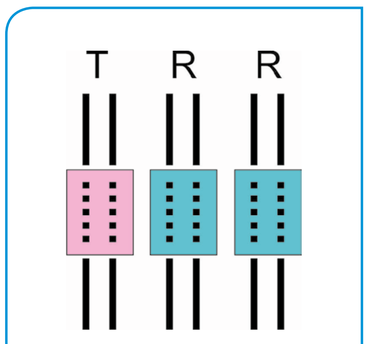

Figure 1: *Ex-vivo treatment sites on one skin section*

Results and Discussion

Dermal acyclovir concentration time profiles (Figure 1) were used to calculate the cutaneous pharmacokinetic (PK) endpoints: Area under the concentration vs. time curve (AUC) and maximum concentration (Cmax). These endpoints were used to evaluate BE by using the SABE approach (see info box 1).

BE was demonstrated for the two reference treatments (R vs. R, positive control). For the negative control (T vs. R) the two products were discriminated as not being BE (Table 1).

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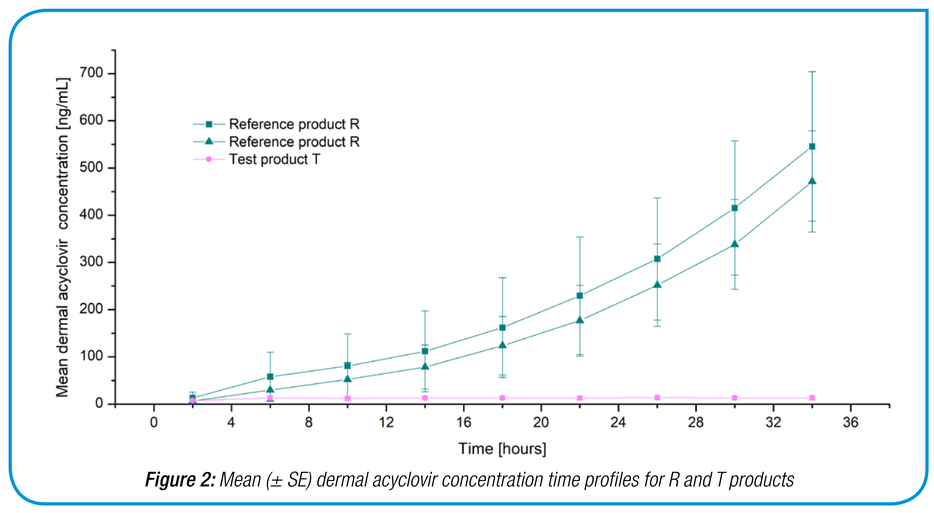

Figure 2: *Mean (± SE) dermal acyclovir concentration time profiles for R and T products*

Table 1: *Results for BE evaluations using the SABE approach*

Comparison	PK endpoint	Within-reference variability	Point estimate	Upper bound of the 95% confidence interval	SABE
R vs. R (positive control)	AUC	0.6824	1.1771	-0.159	Passed
	C_{max}	0.6033	1.1918	-0.094	Passed
T vs. R (negative control)	AUC	0.6825	0.0764	8.989	Failed
	C_{max}	0.6033	0.0293	16.050	Failed

Conclusion and Outlook

- **On the basis of the dermal PK parameters BE was successfully determined by comparing the reference product against itself (R vs.R) using the SABE approach. The negative control (T vs. R) was discriminated as not being BE.**
- **The ex vivo dOFM methodology was found to be very discriminating to evaluate the topical BA and BE of acyclovir.**

Info box 1:

SABE approach [1)]

The acceptance BE limits are scaled on the within-subject variability of the reference product:

$$\frac{(\mu_T-\mu_R)^2}{\sigma^2_{WR}} \leq \theta_s$$

μ_T = Population average of the log-transformed PK endpoints for the test product T
μ_R = Population average of the log-transformed PK endpoints for the reference product R
σ^2_{WR} = Population within-subject variance for the reference product R
$\theta_s = \frac{(\ln(1.25))^2}{(0.25)^2}$

Requirement: Within-reference standard deviation (s_{WR}) is above the cutoff value of 0.294 (correspond CV ≥ 30%)

Two products are BE if for both PK endpoints

1. the point estimator of the T/R geometric mean ratios fall within the limits of 0.8 and 1.25 and
2. the upper bound of the 95% confidence interval for $(\mu_T-\mu_R)^2-\theta_S\sigma^2_{WR}$ is less than or equal to 0.

1) According to FDA's ‚Draft Product Specific Guidance on Acyclovir, 5 % cream (Dec 2016)' [7]

References

[1] Anegundha, S. et al. Clinical Relevance of Rheological Characteristics of Topical Creams : Relationship between Yield Stress and Dose Spreading Area. Poster presentation at the 2016 AAPS Annual Meeting and Exposition. Poster 26M0900.

[2] Sharma, P. K. et al. Determination of pH for an Oil-in-Water Based Semisolid Cream : Method Development and Standardization. Poster presentation at the 2016 AAPS Annual Meeting and Exposition. Poster 24W0400.

[3] Namjoshi, S. M. et al. Water Content and Product Drying Rate as Well as the Amount of Propylene Glycol May Impact the Topical Bioavailability of Acyclovir from Cream Products. Poster presentation at the 2016 AAPS Annual Meeting and Exposition. Poster 25M0930.

[4] Tiffner, K. et al. A comprehensive approach to qualify and validate the essential parameters of an in vitro release test (IVRT) method for acyclovir cream, 5%. Int. J. Pharm. 35, 217-227 (2018).

[5] Shin, S. H. et al. Assessing Bioavailability and Estimating Bioequivalence of Acyclovir Creams by In Vitro Permeation Tests with Excised Human Skin. Poster presentation at the 2015 AAPS Annual Meeting and Exposition. Poster R6024.

[6] Bodenlenz, M. et al. Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. Clin. Pharmacokinet. 56, 1–8 (2016).

[7] U.S. FDA Draft Product Specific Guidance on Acyclovir, 5 % cream (Dec 2016)