In Vitro – In Vivo Correlation (IVIVC) of Diclofenac Bioavailability from Three Topical Drug Products

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Background Demonstrating bioequivalence of topical products using clinical studies can be expensive and time-consuming. Potential alternative options to assess bioequivalence include IVPT (*in vitro* permeation tests) and DPK (dermatopharmacokinetics; *in vivo* tape stripping).

This work comprised IVPT and DPK studies that measured:

1. Drug permeation across excised porcine skin from diclofenac sodium gel 1% (Voltaren®), diclofenac sodium gel 3% (Solaraze®) and diclofenac sodium solution 2% (Pennsaid®).

2. Diclofenac in the stratum corneum (SC) of healthy volunteers at two discrete time points post-administration of the same three formulations.

Methods

In vitro

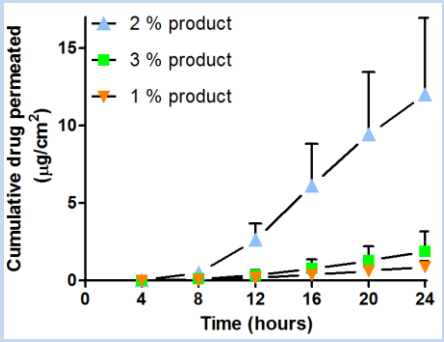
- Dermatomed (~750 µm) porcine skin
- Dose applied: 10 mg/cm² for the 1% and 2% products and 20 mg/cm² for the 3% product
- Duration: 24-h experiment during which the formulations were kept on the skin. Sampling every 4 h
- Flow-through (1 ml/h) Franz cells
- Receptor: pH 7.4 PBS + 0.01 % sodium azide

In vivo

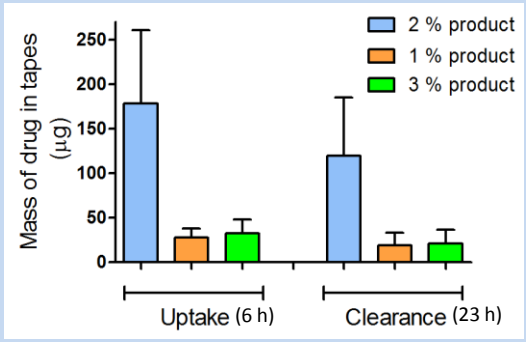
- 14 healthy adults, 12 treatment sites (8.25 cm²), 2 sites per formulation per arm
- Dose applied: 10 mg/cm² for the 1% and 2% products and 20 mg/cm² for the 3% product (differences reflect clinical recommendations and match *in vitro*)
- All sites cleaned after 6 h; half the sites were tape-stripped (Book tape, 3M, US) immediately ('**uptake**' sample); remaining sites stripped 17 h later ('**clearance**' sample). Stripped area (5 cm²) controlled by a template.
- 30 tapes from each site unless TEWL (AquaFlux, Biox, UK) ≥ 60 g/m²/h
- SC removed determined gravimetrically
- Diclofenac extracted from tapes and assayed (HPLC)

Results

Amount of drug permeated between 8 and 24 h was higher from the 2% product (contains DMSO) than from the other products (ANOVA; $p < 0.05$).



A greater mass of drug was found in the SC following application of the 2% product than following application of the other two products, at both uptake and clearance (two way ANOVA; $p < 0.05$).



In vitro - in vivo comparison

It was assumed that the decrease in the amount of drug present in the SC (*in vivo)* observed at the clearance samples was entirely due to drug moving into the underlying tissue (no desquamation effects).

The *in vivo* input of drug into the body was calculated and compared to the amount of drug reaching the receptor solution *in vitro* between 8-24 hours (see table).

(mean ± 90% confidence interval)		2% product	1% product	3% product
In vitro	Drug permeated between 8 hours and 24 hours (µg/cm²)	11.5 ± 5.7	0.83 ± 0.33	1.8 ± 1.4
In vivo	Drug cleared from stratum corneum between 6 and 23 hours (µg/cm²)	11.8 ± 5.3	1.7 ± 1.0	2.2 ± 1.6

Conclusion Both *in vitro* and *in vivo* results indicated that the bioavailability of diclofenac was significantly higher from the 2% solution compared to either of the two gel products. In contrast, the drug's bioavailability from the two gel products was very similar despite their difference in strength.

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