

W4058

Characterization of the Cutaneous Pharmacokinetics of Three Metronidazole Topical Drug Products Evaluated by an In Vitro Permeation Test (IVPT) with Excised Human Skin

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PURPOSE

Metronidazole is used to treat rosacea and is available in oral dosage forms like capsules and tablets as well as in topical creams, gels and lotions. The primary goal of the present study was to characterize the rate and extent of metronidazole absorption through human skin from topical drug products using an In Vitro Permeation Test (IVPT), in order to evaluate whether such IVPT studies may provide cutaneous pharmacokinetic results that could support the evaluation of bioequivalence for topical drug products.

A further goal of this study was to evaluate whether IVPT results can correlate with in vivo results, and the intent was that the results of the current IVPT studies would ultimately be correlated with the results of an in vivo study performed with the same set of drug products under harmonized study conditions, to thereby establish an in vitro-in vivo correlation (IVIVC).

METHOD(S)

A metronidazole gel, 0.75% Reference Listed Drug (RLD) was selected as a reference product, to which a generic metronidazole gel, 0.75% and a generic metronidazole cream, 0.75% (different formulation at the same strength) were compared as a positive control and a negative control, respectively for bioequivalence. IVPT were conducted with a PermeGear® In-Line flow-through diffusion cell system. Three products each were applied onto a 0.95 cm² area of dermatomed human abdominal skin with transepidermal water loss values below 15.0 g/m²/h, using an inverted HPLC vial to achieve a target dose of 10 mg/cm². The surface temperature of skin was maintained at 32 ± 2°C using a circulating water bath. Isotonic phosphate buffer (pH 7.4 ± 0.1) was used as the receiver solution at a flow rate of 1.0 mL/h. Samples were collected every 2 h for 24 h. Metronidazole concentrations in all receiver solution were analyzed using a validated HPLC method.

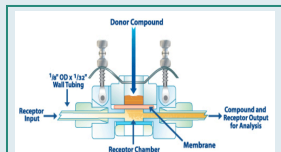


Figure 1. Cross-sectional view of an In-Line Cell with HPLC fittings (Source: PermeGear, <http://www.permegear.com/inline.htm>)

Flux profiles of metronidazole from the topical drug products were generated based on the sample concentrations collected across a 24 h study. In this study, each drug product was tested on skin from the same set of three different donors, with four replicate skin sections per donor per product.

RESULTS

The cutaneous pharmacokinetics of metronidazole was similar between the RLD and generic gels, while cutaneous pharmacokinetics of metronidazole from generic cream was different compared to both gels. The maximum flux (J_{max}) was observed at 4 h for both metronidazole gels, 0.93 ± 0.63 µg/cm²/h for the RLD gel and 1.22 ± 0.69 µg/cm²/h for the generic gel. Following the early peak in metronidazole flux from these gels, the flux of metronidazole from the gels declined thereafter. In contrast, the flux profile of metronidazole from the generic cream showed an increasing flux during the initial 12 h followed by a relatively steady flux during the remainder of the 24 h study period. The J_{max} for the generic cream was observed at ≥ 12 h.

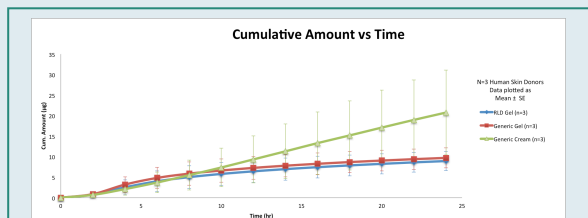


Figure 2. Cumulative cutaneous absorption of RLD gel, generic metronidazole gel and generic metronidazole cream over 24-h study duration.

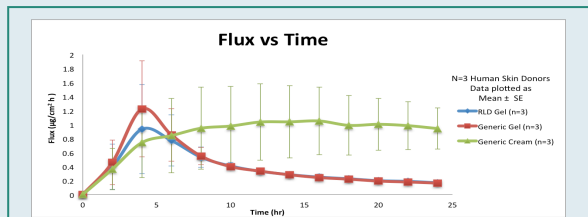


Figure 3. Flux profile of RLD gel, generic metronidazole gel and generic metronidazole cream over 24-h study duration.

RESULTS

The highest total cumulative amount of metronidazole delivered through the skin was observed from the generic cream (21.0 ± 10.32 µg) compared with 8.93 ± 2.33 µg and 9.70 ± 2.42 µg for the RLD and generic gels, respectively.

CONCLUSIONS

Three topical products with the same concentration of metronidazole were compared using IVPT studies. The IVPT cutaneous pharmacokinetic results for the gels (which were comparable to each other) and the cream (which was distinct with respect to both gels) were consistent with the expectation that differences in physical and structural critical quality attributes between topical semisolid drug products (e.g., between a gel and a cream) can alter the bioavailability of metronidazole. The results also suggested that IVPT studies may have utility to help support an evaluation of bioequivalence for topical drug products, since the IVPT results appropriately showed the two gels (which were positive controls for bioequivalence relative to each other) to have a similar rate and extent of metronidazole delivery, and discriminated the cutaneous pharmacokinetics of the cream (which was a negative control for bioequivalence relative to the reference gel) as being different from that for both gels.

ACKNOWLEDGEMENT

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