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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Introduction

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).

Methods

A metronidazole gel, 0.75% Reference Listed Drug (RLD) was selected for study as a reference product, to which a generic metronidazole gel, 0.75% was compared as a positive control for bioequivalence. In addition, a different formulation (cream vs. gel) at the same strength, generic metronidazole cream, 0.75% was selected for study as a negative control for bioequivalence. The two gel products and one cream product evaluated in these IVPT studies were dosed upon a 0.95 cm^2 area of skin. IVPT studies were conducted with a PermeGear® In-Line flow-through diffusion cell system; samples were collected every 2 h for 24 h, and the study was performed at a skin surface temperature of 32± 2°C, maintained using a circulating water bath. Dermatomed human abdominal skin samples with transepidermal water loss values below 15.0 $g/m^2/h$ were cut into pieces for use in the IVPT studies. Isotonic phosphate buffer (pH 7.4± 0.1) was used as the receiver solution at a flow rate of 1.0 mL/h.

Methods (cont.)

The metronidazole gel or cream formulation was applied onto the skin using an inverted HPLC vial to achieve a target dose of 10.5 mg/cm^2. Metronidazole concentrations in all receiver solution samples were analyzed using a validated HPLC method. Metronidazole flux profiles from the topically applied drug products were generated based on the receiver solution 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 the cream was different compared to both gels. The maximum metronidazole flux (Jmax) was observed at 4 h for both metronidazole gels, 0.93 ±0.63 µg/cm^2/h for the RLD gel and 1.22 ±0.69 µg/cm^2/h for the generic metronidazole 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 metronidazole 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 highest total cumulative amount of metronidazole delivered through the skin was observed from the generic cream (21.0 ±10.27 µg) compared with 8.95 ± 2.31µg and 9.81 ± 2.42µg for the RLD and generic metronidazole gels, respectively.

Figure

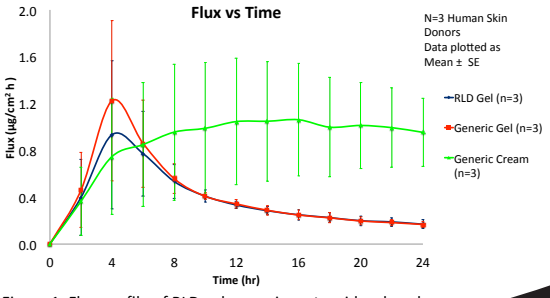

Figure 1. Flux profile of RLD gel, generic metronidazole gel, and generic metronidazole cream over 24-h study duration.

Conclusions

Three metronidazole topical products with the same concentration of metronidazole were compared using IVPT studies. The RLD and generic gel products were both observed to achieve a maximum flux at 4 h, while the maximum flux was observed at ≥ 12 h with the metronidazole cream, and was more sustained thereafter. 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.

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