Evaluation of Different Dose Application Techniques on the *In Vitro* Cutaneous Pharmacokinetics of Metronidazole from Topical Gel and Cream Products

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PURPOSE

The metamorphosis of a semisolid dosage form applied on the skin may have the potential to alter its drug delivery characteristics, either as a result of drying and the resulting changes in the composition of the formulation, or as a result of the physical shear stress and microstructural deformations associated with the techniques of dose dispensing and application.

OBJECTIVE

Our objective was to evaluate the influence of dose application techniques on the *in vitro* cutaneous pharmacokinetics of metronidazole from topical gel and cream products. In this study, the influence of different finite dose application methods on the rate and extent of metronidazole permeation through human skin was evaluated using a commercially available metronidazole gel, 0.75% (Metrogel®) and a metronidazole cream, 0.75% (Metrocream®) using *In vitro* Permeation Testing (IVPT).

METHODS

The IVPT experiments were performed using dermatomed human (posterior torso) cadaver skin from a single donor using franz diffusion cells with a dose (active diffusional) area of 2 cm^2. The receptor medium consisted of phosphate buffered saline (pH 7.4) and contained 0.01% gentamicin sulfate as an antibiotic agent to mitigate microbial decomposition of the skin during the study duration.

A finite dose (10 mg/cm^2) of the topical gel or cream product was applied within the dose area using three different application techniques:

Spatula Technique: The product was weighed on the spatula and applied directly on the skin.

Finger Technique: The product was weighed on the spatula, transferred onto a gloved forefinger and then applied on the skin.

Vial Technique: The product was weighed on the base of a HPLC vial and then applied on the skin.

Care was taken to apply uniform pressure during application.

Metronidazole was quantified using a validated HPLC method. The results were analyzed using student's t-test ($p<0.05$) and were expressed as mean ± SD.

RESULTS

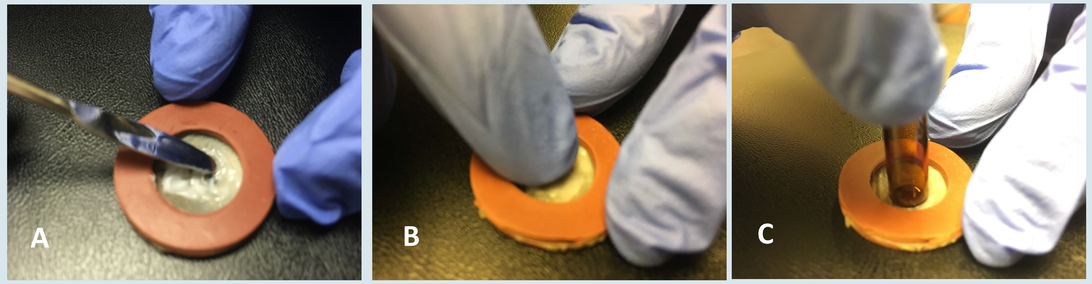

Fig. 1: Different dose application techniques A) Spatula, B) Finger and C) Vial

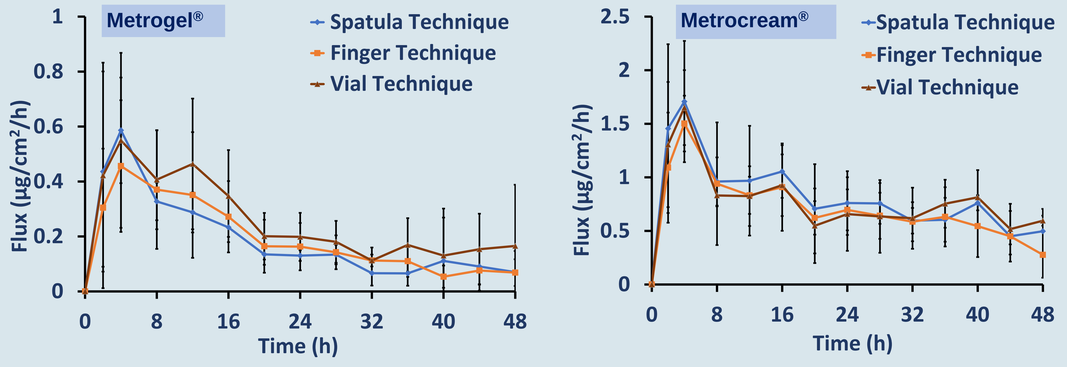

Fig. 2: Effect of method of dose application on topical bioavailability (n=4 replicates)

Product	Method	Area Under the Curve AUC (µg/cm²)	Maximum flux J_{max} (µg/cm²/h)
Metrogel®	Spatula	7.27 ± 4.58	0.67 ± 0.22
	Finger	7.50 ± 5.69	0.53 ± 0.17
	Vial	12.28 ± 2.50	0.69 ± 0.31
Metrocream®	Spatula	39.49 ± 11.84	1.85 ± 0.47
	Finger	34.65 ± 16.50	1.69 ± 0.15
	Vial	37.25 ± 8.53	1.80 ± 0.13

Table 1: In vitro cutaneous pharmacokinetics of metronidazole topical products (n=4 replicates)

The differences in J_{max} and AUC observed were not statistically significant (with $p<0.05$) among any of the three methods of application for either of the products evaluated in this limited dataset.

CONCLUSION

The results suggest that the cutaneous pharmacokinetics of metronidazole from the gel or cream products studied was relatively robust with respect to differences in the methods of dose application. The differential deformation and/or metamorphosis of the dosage forms did not significantly alter the drug delivery from either the gel or cream, which suggests that the technique of dose application may not be a critical study parameter in this instance, at this dose and with these products.

However, these results do not support a conclusion that the method of dose application will not matter in other situations. It may still be prudent to evaluate different dose application techniques during IVPT method development to identify the most suitable and precise method of dose application, and/or to identify study conditions that are the most clinically relevant and discriminating to differences in bioavailability.

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