A Novel Strategy for the Efficient Modulation of Topical Drug Delivery to Validate the Sensitivity of an *In Vitro* Permeation Test (IVPT)

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PURPOSE

An IVPT method should be sensitive to differences in drug delivery, which may be modulated by the dose amount applied or the dose duration. To achieve controlled differences in drug delivery with which to validate the sensitivity of an IVPT study, the target dose amount may be increased and decreased to determine whether the flux profile is sensitive to any resulting changes in drug delivery. However, since topical bioavailability is variable, and not necessarily proportional to dose amount or duration, it may not be evident what magnitude of change in the dose could induce a discernible change in drug delivery.

We postulated that a relatively more rapid loss of volatile components (a faster drying rate for smaller doses of a thinner film of gel or cream) would more rapidly diminish the amount of soluble metronidazole available for partitioning into the skin, and correspond to a relatively lower peak flux and/or total permeation of metronidazole. Conversely, slower drying for larger, thicker doses, would correspond to a more sustained drug delivery, with higher peak flux and/or total permeation.

OBJECTIVE

The objective of this study was to develop an efficient, mechanistically based approach to estimate the range of the doses using which the sensitivity of an IVPT method may be validated.

METHODS

Two topical drug products, metronidazole gel, 0.75% and metronidazole cream, 0.75% were selected for the study, each of which contains volatile components. The drying rate of each product at 32˚C was determined by uniformly applying a dose of 3 mg/cm^2, 10 mg/cm^2, or 30 mg/cm^2 on the surface of an inverted weigh boat, and monitoring the weight over time. The duration for a 30% loss in weight (T_{30}) was determined for each product (n=3) to compare drying rates.

IVPT studies were performed with dermatomed posterior torso human cadaver skin (acquired from New York Fire Fighters Skin Bank) using 1 donor with 6 replicates per dose amount. The skin was mounted in Franz diffusion cells with a dose (active diffusion) area of 2 cm^2.

The cutaneous pharmacokinetic parameters, maximum flux (J_{max}) and area under the curve (AUC) of the incremental permeation profile, were used to compare the dynamic rate (flux profile) and extent of metronidazole bioavailability from each dose of each product. Metronidazole in the receptor solution samples was analyzed using a high performance liquid chromatography (HPLC) method.

RESULTS

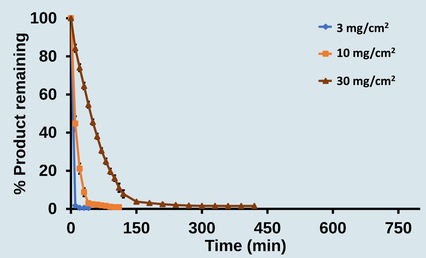

Fig 1: Rate of Drying of Metronidazole Gel, 0.75%

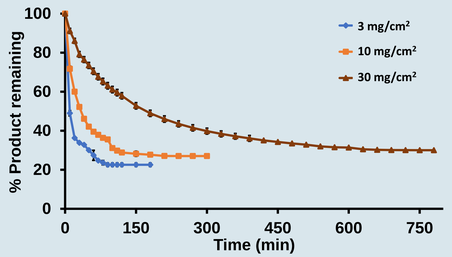

Fig 2: Rate of Drying of Metronidazole Cream, 0.75%

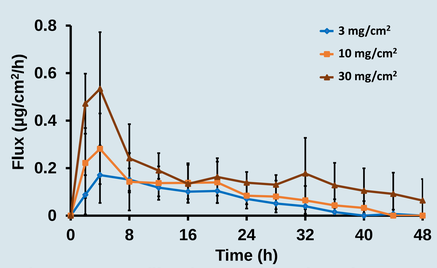

Fig 3: IVPT profile of Metronidazole Gel, 0.75%

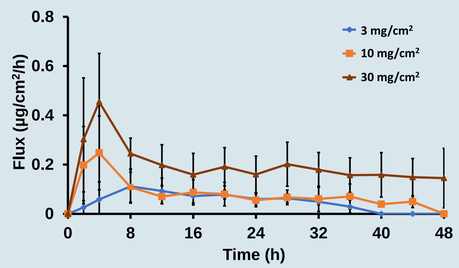

Fig 4: IVPT profile of Metronidazole Cream, 0.75%

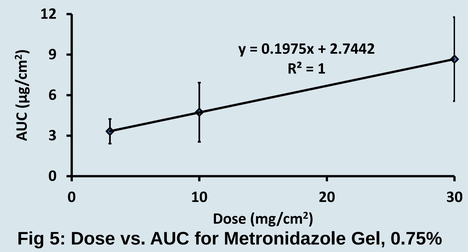

Fig 5: Dose vs. AUC for Metronidazole Gel, 0.75%

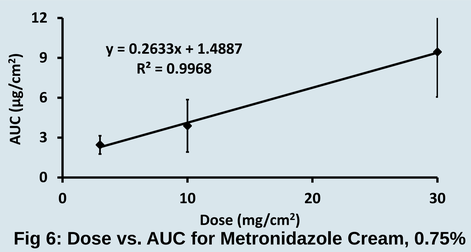

Fig 6: Dose vs. AUC for Metronidazole Cream, 0.75%

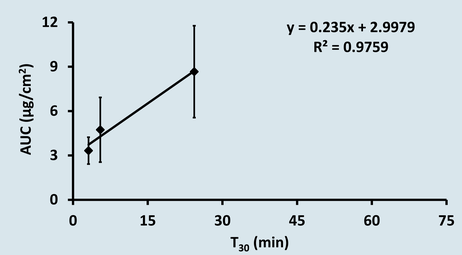

Fig 7: T_{30} vs. AUC for Metronidazole Gel, 0.75% at 3 mg/cm^2, 10 mg/cm^2, and 30 mg/cm^2 doses

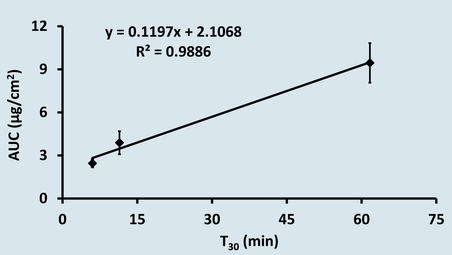

Fig 8: T_{30} vs. AUC for Metronidazole Cream, 0.75% at 3 mg/cm^2, 10 mg/cm^2, and 30 mg/cm^2 doses

Dose (mg/cm^2)	Metronidazole Gel, 0.75%		Metronidazole Cream, 0.75%	
	T_{30} (min)	AUC (µg/cm^2)	T_{30} (min)	AUC (µg/cm^2)
3	3.10 ± 0.00	3.32 ± 0.91	6.00 ± 0.10	2.45 ± 0.69
10	5.47 ± 0.45	4.74 ± 2.19	11.42 ± 1.15	3.89 ± 1.97
30	24.33 ± 2.02	8.66 ± 3.11	61.66 ± 5.13	9.45 ± 3.39

Table 1: T_{30} and AUC values of Metronidazole Gel, 0.75% and Metronidazole Cream, 0.75% at 3 mg/cm^2, 10 mg/cm^2 and 30 mg/cm^2 doses

CONCLUSION

The results of this study were consistent with the hypothesis that changes in the dose amount of a topical semisolid dosage form may be expected to lead to changes in drug delivery when the dosage form is reasonably volatile, whereby drying (and physicochemical metamorphosis) may alter the delivery of the drug into the skin. This effect may be mediated via changes in the amount, diffusion and/or partitioning of dissolved drug from the dosage form into the skin. The results suggest that for semisolid dosage forms with volatile components, it may be possible to efficiently estimate the dose levels that could provide differentiated levels of drug delivery based upon whether the drying curves at the different dose levels are well-differentiated. The further implication is that for ointments and other relatively non-volatile dosage forms, for which drying rate may not be dose dependent, a modulation of dose duration (rather than amount) may be more suitable to induce changes in drug delivery, which may be used to validate the sensitivity of an IVPT method.

ACKNOWLEDGEMENT & DISCLAIMER

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