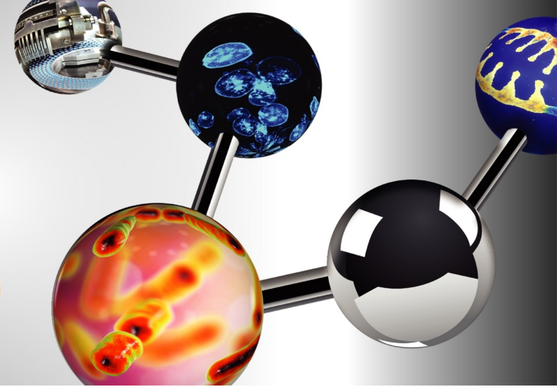
1053373

A Cross-Species Retrospective Percutaneous IVIVR for Topical Dermatological Products Containing Metronidazole

Sharareh Senemar, Benjamin A. Kuzma and Grazia Stagni

Division of Pharmaceutical Sciences, Long Island University, Brooklyn, NY, USA

Contact Information: HS 623 75 DeKalb Ave, Brooklyn NY 11201, Long Island University
email: sharareh.senemar@my.liu.edu



PURPOSE

- The availability of in vitro - in vivo relationships (IVIVR) have helped to streamline the development and optimization of oral dosage forms in the past 20 years.
- The development of IVIVR for topical dermatological drug products (TDDP) might bring similar advantages to this important category of therapeutics, like a better comprehension of the permeation process and a quality by design approach for a targeted permeation profile.
- In this study, we explored the possibility to develop a retrospective IVIVR for metronidazole (MTZ) topical formulations (brand cream, generic cream, brand gel, and generic gel) between in vitro permeation testing (IVPT) and in vivo dermal microdialysis data.

OBJECTIVES

1. To compare the in vivo cumulative amount permeated from MTZ formulations between in vivo (rabbit) and IVPT (human cadaver skin) to establish a point-to-point correlation between in vitro and in vivo profiles (Level A IVIVR).
2. To verify the developed IVIVR by predicting the rabbit dermal concentration-time profiles, via convolution

METHODS

Metronidazole products evaluated: Gel-Reference: MetroGel® (metronidzole) topical gel, 0.75%; Prasco Lab.; Gel-Test: metronidazole topical gel, 0.75%;Tolmar; Cream-Reference: MetroCream® (metronidazole) topical cream, 0.75% from Galderma Laboratories Cream-Test: metronidazole topical cream, 0.75%, Fougera Pharm.

In vivo Data:

- **Bioavailability:** In a previous study [1], the same product dose (10 mg/cm^2) of each MTZ formulation was applied in seven rabbits and dermal pharmacokinetic (dPK) profiles measured using dermal microdialysis (dMD).
- **Estimation of dUIR:** Six probes were inserted on the dorsum of one New Zealand albino rabbit and were perfused with 1, 5, or 10 µg/mL MTZ in lactated Ringer's, in duplicate, at a flow rate of 0.5 µL/min for 4 hours with a sampling interval of one hour. At the end of the fourth hour, the perfusion solution was switched to plain lactated Ringer's solution and sampling continued for 5 hours. Dermal disposition parameters were calculated. [2]

In vitro Data:

- IVPT studies [3] were performed on human cadaver skin with same product dose and formulations.

IVIVR Model Development:

- The dPK profiles were numerically deconvolved with the estimated dUIR to assess the cumulative amount permeated (CA) for each formulation (Phoenix®; Certara®, Princeton, NJ), where the effective dose was calculated based upon the amount applied on the area immediately above the dialysis window (0.068 cm^2) of the dMD probe (Figure 1).

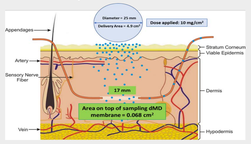


Figure 1 - Schematic representation of the dosed area

- The in vivo fractional input in rabbit was correlated with the human IVPT fractional input using an inverse Weibull function to apply a non-linear time scale
- The IVPT data were convolved with the rabbit dUIR to predict the in vivo MTZ dermal concentration time profile.
- Predicted in vivo concentration-time profiles were compared to the observed profiles, and an extent scaling factor between rabbit and human skin of 1.5 for MTZ,[4] was applied to predict concentration time profiles
- Model suitability was evaluated by calculating the percentage prediction error (%PE) for bioavailability parameters ($AUC_{0\text{-}20}$ and C_{max}).

RESULTS

Dermis Unit Impulse Response

- Dermis concentrations declined mono-exponentially following the delivery phase as the concentrations decreased in a straight line on a semi-log-scale
- Dermis disposition parameters are reported in Table 1
- The following MTZ dermal unit impulse response (dUIR) was obtained:

$$\mathrm{dUIR} = \frac{1}{Vd}\left(e^{-Ket}\right) = 6.53e^{-0.61t}$$

- Figure 2 shows the time-course of MTZ concentrations observed in dermis from the TDDPs and the dermal infusion

IVIVR

- Comparison of the in vitro and in vivo amount permeated via Levy plots (Figure 3) indicates that the non-linear time-scaling was successful in three out of the four formulations.
- Figure 4 shows the predicted and observed cumulative MTZ permeated into dermis from gel and cream formulations
- Figure 5 presents the rabbit observed concentration-time profiles and the predicted concentration-time profiles (using human IVPT data and rabbit dUIR) for MTZ in both cream and gel formulations.
- Table 3 reports the %PE for $AUC_{0\text{-}20}$ and C_{max}; the extent of absorption (AUC) is reasonably predicted and close to the the FDA guidelines recommendations, whereas the %PE for C_{max} is quite outside.
- The IVIVR predicts a delayed T_{max} compared to the in observed data (Figure 5).

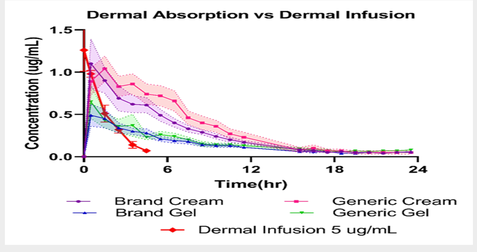


Figure 2. Time-course profile of MTZ in dermis from TDDPs absorption vs dermal infusion.

Dose (µg/mL)	Half-Life (hr)	Cl (mL/hr)	Vd (mL)
1	1.185	0.090	0.150
5	1.070	0.090	0.150
10	1.175	0.110	0.190

Table 1. The dermal disposition parameters, (mean ,n=2) for each dose

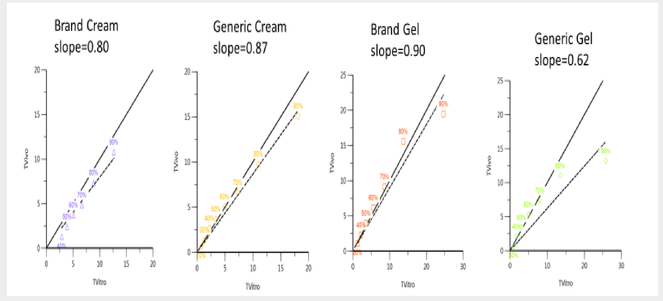


Figure 3 - Levy Plots for the MTZ formulations after non-linear time scale application. An inverse Weibull function was applied to the in vitro data. In vitro (n=6) is on the x-axis while in vivo (n=7) is on the y-axis as the in vivo is the predicted parameter.

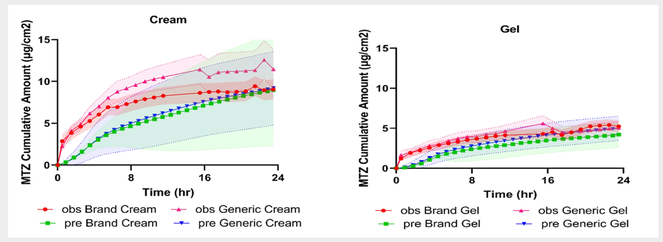


Figure 4 – Observed (is scaled based on the probe area (0.068 cm^2)) and IVIVR predicted cumulative amount of MTZ in rabbits' dermis (n=6 for predicted profiles while n=7 for observed ones)

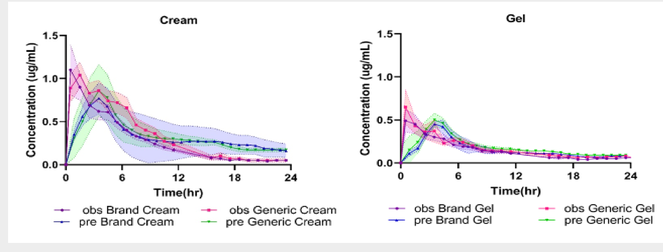


Figure 5 - Observed and IVIVR predicted concentration-time profile of MTZ in rabbits' dermis (n=6 for predicted profiles while n=7 for observed ones)

Formulation	Prediction Error % $AUC_{0\text{-}20}$	Prediction Error % C_{max}
Brand Cream	-0.91	72.91
Generic Cream	23.32	74.44
Brand Gel	16.29	75.11
Generic Gel	5.90	63.98

Table 3- Percentage prediction error of rabbit dermal exposure using the developed IVIVR.

CONCLUSIONS

- An exploratory IVIVR was developed to predict exposure of MTZ in rabbit dermis from human IVPT data.
- The retrodialysis/microdialysis (dermal infusion) is a practical technique to estimate dermal disposition parameters and thus to assess the dUIR that is essential to develop an IVIVR.
- The IVIVR required a non-linear time scaling and an extent scaling factor.
- The developed IVIVR adequately predicted the extent of absorption (%PE <20 % for $AUC_{0\text{-}20}$ for three (3) metronidazole formulations (brand cream, brand gel, generic gel), whereas for the generic cream was only slightly above the 20 %.
- The rate of absorption (C_{max}) as well as T_{max} were poorly predicted; possibly due to a faster absorption rate across rabbit skin compared to human skin. The identification of a rate scaling factor based on anatomical and physiological differences between the two species may help to reduce the %PE.
- Further studies are necessary to better understand the effect of species differences in percutaneous PK.

FUNDING

Funding for this project was made possible, in part by the food and drug administration through grant USFDA U01FD005862. The views expressed in this abstract/poster do not reflect the official policies of the U.S. Food and Drug Administration or the department of U.S. Health and Human Services.

ACKNOWLEDGMENTS

The authors would like to acknowledge the valuable discussions and advice from Dr. Tannaz Ramezanli, Dr. Priyanka Ghosh, and Dr. Sam G Raney from the Division of Therapeutic Performance Office of Research and Standards CDER, US FDA. A great appreciation to Dr. N. Murthy for sharing IVPT data and Dr. Kerry Weinberg for her consistent support for ultrasound imaging.

REFERENCES

1. Sharareh Senemar et Al., Evaluating the Bioequivalence of Topical Dermatological Drug Products Containing Metronidazole Using Dermal Microdialysis: Preliminary Studies in Rabbits, in AAPS Pharm Sci 360 November 2019: San Antonio, Texas.
2. Benjamin A. Kuzma, et Al. Estimation of In Vivo Percutaneous Permeation (Flux) and Cumulative Amount Input of Metronidazole Formulations in Mini-Pigs' Dermis, in AAPS PharmSci 360. November 2019: San Antonio, Texas.
3. Murthy, S.N., Characterizing the Critical Quality Attributes and In Vitro Bioavailability of Acyclovir and Metronidazole Topical Products, in Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. 2017: White Oak, MD.
4. Bartek MJ, LaBudde JA, Maibach HI. Skin permeability in vivo: comparison in rat, rabbit, pig and man. J Invest Dermatol. 1972;58(3):114-23.