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Modeling Metamorphosis: Advancing Dermal PBPK Modeling – A Metronidazole Case Study

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PURPOSE

To understand how formulation metamorphosis (changes after topical application) impacts drug bioavailability in the skin.

To demonstrate how Physiologically Based Pharmacokinetic (PBPK) dermal models can reliably capture these processes to support formulation development and bioequivalence assessments for topical drug products.

OBJECTIVES

To integrate post-application metamorphosis (e.g., solvent evaporation, drug precipitation) into dermal PBPK models and their impact on formulation microstructure and drug thermodynamic activity in an effort to improve the prediction of skin absorption.

Use metronidazole (MTZ) as a model compound and a series of binary and tertiary aqueous and gel formulations to study how formulation attributes and metamorphosis can affect PBPK model-based predictions of skin bioavailability for topical products.

METHODS

Modeling: The Transdermal Compartmental Absorption & Transit (TCAT™) model in GastroPlus® v9.9 [1] was used to simulate MTZ *in vitro* permeation testing (IVPT) studies in Franz diffusion cells (Table 1). The TCAT™ model was applied to the following:

	Formulation	MTZ concentration
MTZ solution [2]	50:50 v:v water, propylene glycol (PG)	21.1 mg/mL
MTZ Gels (Infinite dosing condition) [3]	1% polyethylene glycol (PEG 200), water, and hydroxyethyl cellulose (HEC)	2.5, 5.0 or 7.0 mg/mL
MTZ Gels (Finite dosing condition) [3]	1, 10 or 20% PEG 200, water, and HEC	5.0 mg/mL

Input parameters: MTZ physicochemical properties were obtained from the literature. Separate values of the MTZ diffusion coefficient and partition coefficient relative to water were estimated using the Potts–Guy and Bunge–Cleek (Method 4) for the stratum corneum and viable epidermis/dermis, respectively [2-4]. The partition coefficients were not adjusted for non-aqueous vehicles.

Formulation-specific parameters: The dosage form, volume applied, surface area of application, MTZ initial concentration, and experimentally determined MTZ solubility in the initial vehicle (Table 1), along with experimentally determined water evaporation rates were included in the models. Under finite dosing, rapid MTZ precipitation (within 1 s) was assumed whenever MTZ amounts exceeded the MTZ solubility in the corresponding mixture.

Evaluation of simulation performance: Simulated MTZ amounts in SC, viable skin, and in the receptor solution in the case of MTZ solutions [5], and simulated flux profiles in the case of MTZ gels under finite and infinite dosing [6] were compared with published data.

RESULTS

MTZ PG:water solution

Simulations underestimated MTZ in the SC and viable skin [5] but predictions for the receptor compartment were within experimental variability (Fig 1, blue).

Increasing the SC-vehicle partition coefficient (Ksc) improved prediction of SC levels but overestimated MTZ delivery into the receptor (Fig 1, green and red).

Results suggest that propylene glycol (PG) may enhance MTZ partitioning and diffusivity within the SC, which is supported by previous reports [7]. However, these effects are not captured by the Potts–Guy equation, which is based only on data from aqueous vehicles [2].

Additional IVPT data in aqueous-only vehicles are needed to characterize PG effects on MTZ permeation and improve the model predictability.

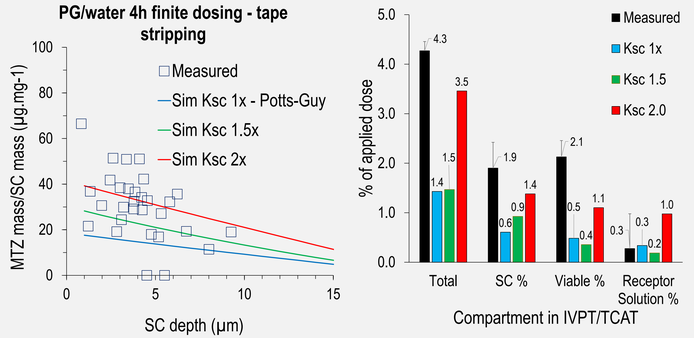

Figure 1. Simulations were compared with IVPT data from a 4-hour application of MTZ in a PG:water solution, using a standard Franz cell setup after unoccluded application of the formulation (dose: 110 µL/1.77 cm²). **Left**: Measured (squares) vs. simulated (solid lines) at 1xKsc (Ksc predicted by the Potts-Guy equation – light blue), 1.5xKsc (green) and 2xKsc (red) MTZ concentrations at different SC depths. **Right:** Measured mean ± SD (n=3) (black) vs. simulated % of the applied dose delivered into the different skin layers and into the receptor solution at 1xKsc (light blue), 1.5xKsc (green) and 2xKsc (red).

MTZ PEG200:water:HEC gels

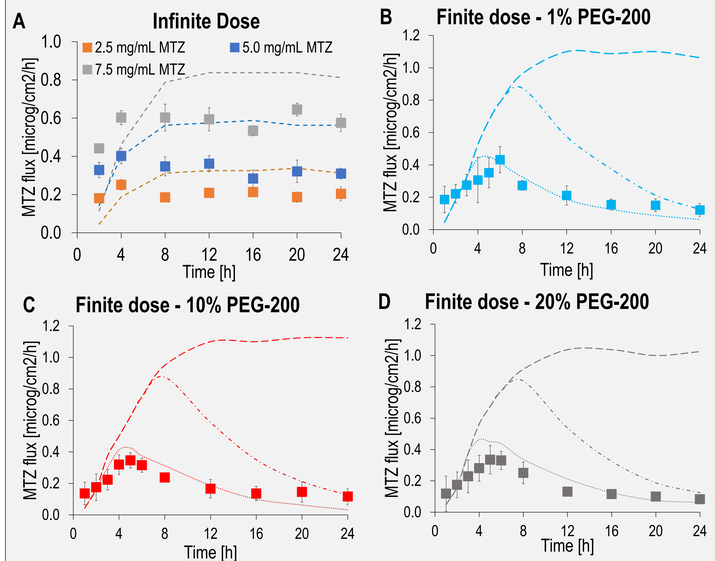

Figure 2. Simulations compared with IVPT data following 24-h applications of MTZ in PEG200:HEC in a standard Franz-cell setup. **A:** Measured ± SD (n=3) (☐) (dose:2 mL/cm²) vs. simulated (dashed) MTZ flux profiles from PEG200:HEC gels at different doses of MTZ under infinite dosing. **B, C, D**: Measured ± SD (n=3) (☐) MTZ flux from 0.5% MTZ in HEC gels with (B) 1%, (C) 10%, and (D) 20% PEG200 under finite dosing (dose:300µL/cm²) vs. simulated profiles at 24-h (dashed), 6-h (dash-dotted), and 2-h (dotted) duration of application.

Infinite dosing (Fig 2A):

Simulations of PEG200:water:HEC gels with 1% PEG200 and 2.5, 5.0, or 7.5 mg/mL MTZ yielded predictions within 1.5-fold of the observed values of the steady-state flux predictions under infinite dosing [6].

Finite dosing (Figs 2B-D):

Initial simulations (dashed lines) consistently overestimated MTZ flux beyond 6 hours, regardless of PEG200 content. In these simulations, evaporation, based on rates from gravimetric measurements [6], was assumed to reduce the volume on the skin surface to ~1% of the original volume. This assumption likely underestimated the actual residual phase volume, which according to experimental data [6] may range from ~6% to 25% of the initial formulation, depending on PEG200 content. The model also did not explicitly account for changes in MTZ solubility as the PEG200:water ratio evolved during evaporation. Incorporating such compositional effects could influence the predicted degree of MTZ saturation and precipitation behavior.

Reducing the product application time in the simulations resulted in a more accurate prediction of the observed flux for all gels (dotted lines). These results suggest that formulation metamorphosis (involving changes in viscosity, phase composition, together with MTZ precipitation) may have prevented further skin uptake from the residual formulation on the skin surface at around 2 hours.

Table 1. IVPT experimental conditions

Formulation composition	Dosing conditions	MTZ conc. (mg/mL)	Solubility (mg/mL)	Applied dose (mL)	Application area (cm²)
Solution – Water : PG (50:50 v/v)	Finite, 4 h, unoccluded	21.1	23.4	0.11	1.77
Gel[a] – 1% PEG200	Infinite, 24 h, occluded	2.5 5.0 7.5	10.4	2.00	1.00
Gel[a] – 1% PEG200	Finite, 24 h, unoccluded	5.0	10.4	0.30	1.00
Gel[a] – 10% PEG200	Finite, 24 h, unoccluded	5.0	10.4	0.30	1.00
Gel[a] – 20% PEG200	Finite, 24 h, unoccluded	5.0	10.4	0.30	1.00

[a]All gels contained hydroxyethyl cellulose (HEC) as the gelling agent at 5%.

CONCLUSIONS

This work demonstrates the utility of PBPK modeling in understanding and predicting the interplay between formulation properties, metamorphosis, and skin permeation.

For **PG:water solutions**, receptor delivery was predicted accurately, but SC uptake was underestimated. Results suggest PG enhances MTZ partitioning/diffusivity in the SC that may be addressed by dynamically adjusting the relevant parameters in the simulation.

For **PEG200:HEC gels**, MTZ flux was successfully modelled following infinite dosing. Under finite dosing, however, the model predictions highlight that solvent evaporation and MTZ precipitation in the absence of liquid may limit further MTZ uptake into the skin.

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