Towards development and validation of the Dermal PBPK model for virtual bioequivalence - model description and validation case studies

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Introduction

Mechanistic, physiology based pharmacokinetic (PBPK) models could be used to disentangle the impact of drug, formulation and physiology specific parameters on dermal drug delivery. The newly developed transient, multi-phase multi-layer (MPML-) Mechanistic Dermal Absorption (MechDermA) model (Figure 1) :

(1) differentiates between formulations: gels, emulsions, patches, suspensions, pastes

(2) accounts skin physiology related parameters (i.e. tortuosity of the diffusion pathway, keratin adsorption kinetics, SC hydration state, pH at the skin surface and within the SC layers, etc.)

(3) Simulates partitioning and absorption through the hair follicular pathway.

Materials and Methods

The predictive performance of the model was verified against clinical data published in 3 study cases of drugs with different physicochemical properties and formulations. A summary of the study conditions is provided in Table 1. Formulation parameters such as pH and viscosity, unless provided in the original publication, were assumed based on the formulation composition. Diffusion and partition coefficients into the skin layers together with keratin binding parameters of the studied drugs were either obtained from literature (*in vitro* experiments) or predicted by Quantitative Structure Activity Relationship (QSAR) models. Other required pharmacokinetic (PK) disposition parameters (volume of distribution and clearance) were obtained from intravenous dosing in healthy volunteers.

Drug	Dose (mg)	Formulation	Skin area (cm^2)	Skin location	Reference
Diclofenac (DICLO)	300	Solution gel Emulsion gel	400	Back	[1]
Timolol (TIMO)	24	Patch 40 µm thick	5x6 (patch area)	Upper arm	[2]
Erythromycin (ERY)	0.4	Lotion (10 µl)	1.96	Back Upper arm	[3]

Table1. *Summary of clinical studies used for performance validation*

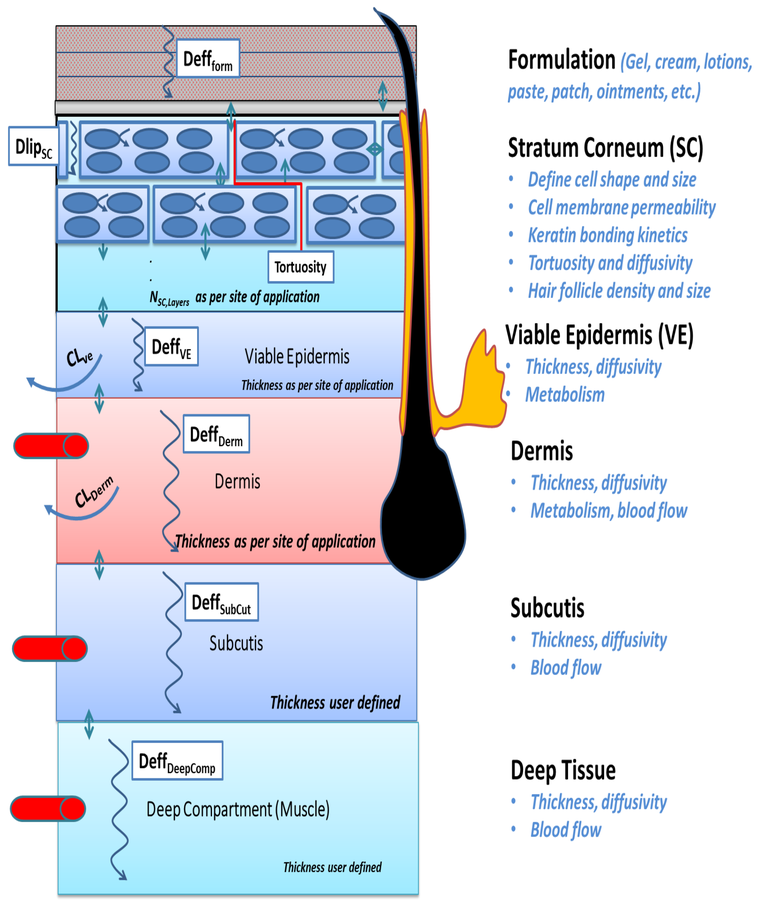

Figure 1*. MPML MechDermA Model with a a brick (cuboid corneocytes)-and-mortar (intercellular lipids) structure*

Results and Discussion

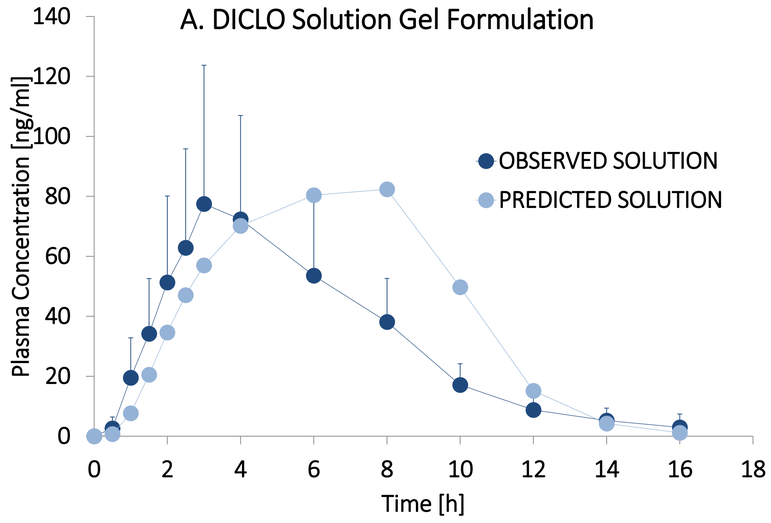

Figure 2. *Observed vs. Predicted plasma DICLO conc. (A) after solution gel application and (B) after emulsion gel application*

PK profiles of DICLO after applying either solution or emulsion gels are represented above (Figure 2).

- Predicted solution/emulsion AUC and Cmax ratios were consistent with the observed clinical values (1.63 and 1.62 vs. 1.54 and 2.07 respectively)
- Predicted relative bioavailability (F_{AUC}) of 4.5% (solution) and 2.8% (emulsion) were similar to the clinically observed F_{AUC} (3.3% and 2.2%).

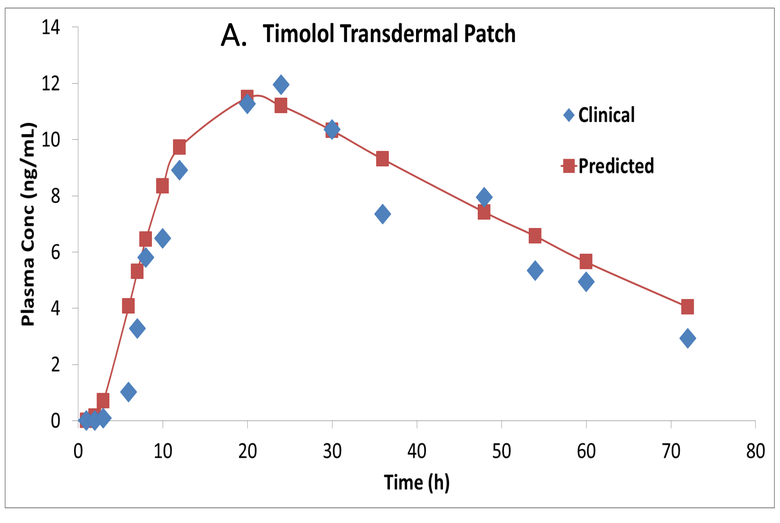

Figure 3*. (A)Simulated plasma TIMO conc. overlaid with clinical data and (B) TIMO conc. changing with depth of SC*

The overlaid profiles of predicted and clinically observed PK for TIMO are represented above (Figure 3 A).

- The predicted C_{max} (ng/ml) and AUC (ng/ml.h) of 11.48 and 633.33 respectively were very similar to the observed clinical values (12.7 and 613 respectively).
- The predicted and observed F_{AUC} were consistent:74.3% and 74.4% respectively.

TIMO concentrations in the SC layers (µg/cm^2) are simulated at various time points (Figure 3 B)

- Steady-state flux through SC is reached after 23-16 h after patch application

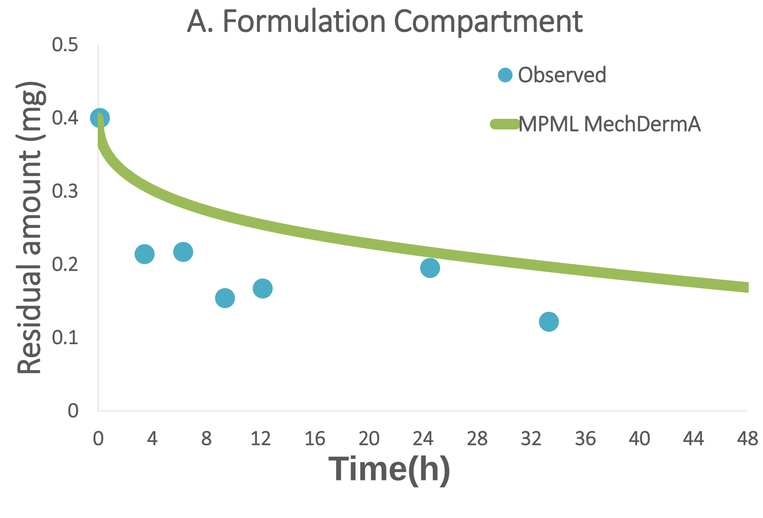

Figure 4. *(A) Predicted versus observed conc. of ERY at skin surface and (B ERY SC tissue concentrations in SC layers vs. tape stripping*

Figure 4 represents a two-step validation for the ERY case study by:

A. The amount of drug remaining at the skin surface represented as the simulated decline of the drug on the skin (formulation) compared to clinically measurements.

B. The amount of drug in each SC layer (stripping experiment) from surface to viable epidermis (VE). The simulations matched the clinically measured tape stripping data from two locations reasonably well.

The observations and the predictions in the whole SC are similar to the actual observations: 27.2% vs. 21.4% (back) and 23.2% (upper arm).

Conclusions

- The MPML-MechDermA model was predictive of local and systemic concentrations of drugs with varying nature and types of formulation (gel, cream, emulsion, and patch).
- Further validation using drugs with diverse physicochemical characteristics and other types of formulations are warranted to improve confidence in this modelling strategy.

References: [1] Seth BL (1992) Arzneim.-Forsch., 42(1): 120-122; [2] Kubota et al. (1993), Eur J Clin Pharmacol 44: 493-495; [3] Van Hoogdalem EJ, et al. (1996) Skin Pharmacol.; 9(2):104-110

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