Prediction of cutaneous PK profiles after topical application - a comparison between the novel MPML-MechDermA model and the current MechDermA model in Simcyp Simulator
Case Study: Erythromycin

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Introduction Mechanistic, physiologically based modelling can be useful in the assessment of various factors influencing drug delivery and it is able to distinguish between parameters associated with the drug, the anatomy and physiology of the skin and surrounding tissues, and population variability and characteristics. The present work compares two PBPK models, namely, the current model within the Simcyp Simulator - Mechanistic Dermal Absorption (MechDermA) model [1], based on the model of Shatkin and Brown [2] and a new, enhanced, transient multi-phase multi-layer model (MPML - MechDermA) [3][4]. The latter is substantially refined and incorporates numerous additional physiological parameters (i.e. tortuosity, hydration level, follicular transport, keratin adsorption, pH at skin surface and the gradient throughout the SC layers, etc.) as well as parameters relevant to the drug/formulation (i.e. ionization at skin surface, lipophilicity, vehicle viscosity, particle size, droplet size in the case of emulsions, etc.). The stratum corneum (SC) is represented by multiple layers of cuboid corneocytes with water and protein (keratin) components, embedded in an intercellular lipid matrix (the "brick – and – mortar" concept) rather than a simple one compartment approach. While the current MechDermA model does provide a few simple options for aqueous, non-aqueous (lipid) or patch formulations interacting with a simple construct of the skin, the novel MPML - MechDermA model was developed with the capability to predict the behavior of more varied types of formulations (i.e. cream, gel, ointment, patch, etc.) in a more comprehensive and sophisticated physiologically - based model.

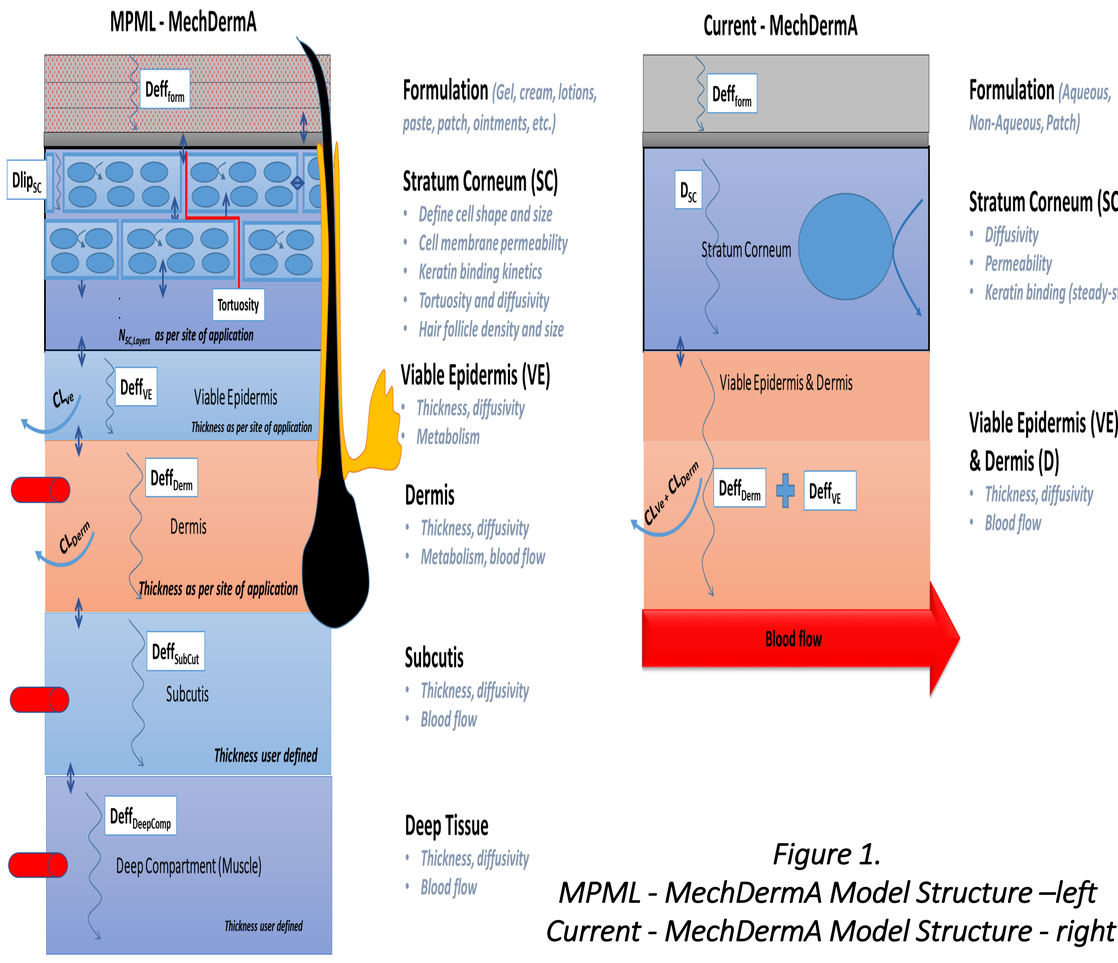

Figure 1.
MPML - MechDermA Model Structure –left
Current - MechDermA Model Structure - right

Materials and Methods The model performances have been assessed with the use of a study reporting data for 0.4 mg erythromycin contained in 10 µL of lotion which was applied on a 1.96 cm^2 skin area of the back and upper arm [5]. Input data included physicochemical properties of the model drug (pKa=8.88, logP=3.06, logD at pH 5.75 = 1.62) under the assumption that the drug was applied on the back (Ya-Xian et al 1999 found the same number of skin layers for the two localizations [6]). Diffusion coefficients through the formulation and skin layers were calculated using either QSAR models for the current MechDermA or also using Stokes-Einstein equations, in the novel MPML model. The major differences between the two models are as follows: the MechDermA uses a simplistic approach (a permeability coefficient 50x larger for SC and VE+D than the literature values) to mimic the formulation influence on active compound behaviour, does not account for ionization at the skin pH and the fraction unbound is assumed to be 0.31 (equal to fu,plasma [6]). By contrast, these calculations were based on physicochemical properties e.g. LogP in the novel MPML model. None of the absorption model parameters in the new model were fitted using clinical data. The hair follicular pathway contribution for the topical drug absorption was considered negligible at this stage.

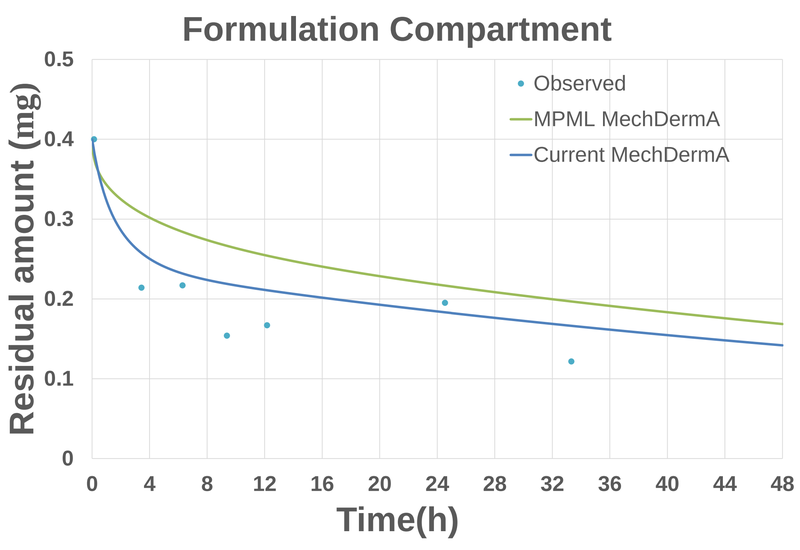

Figure 3. *Simcyp vs. MPML MechDermA from skin Predictions vs. Observations*

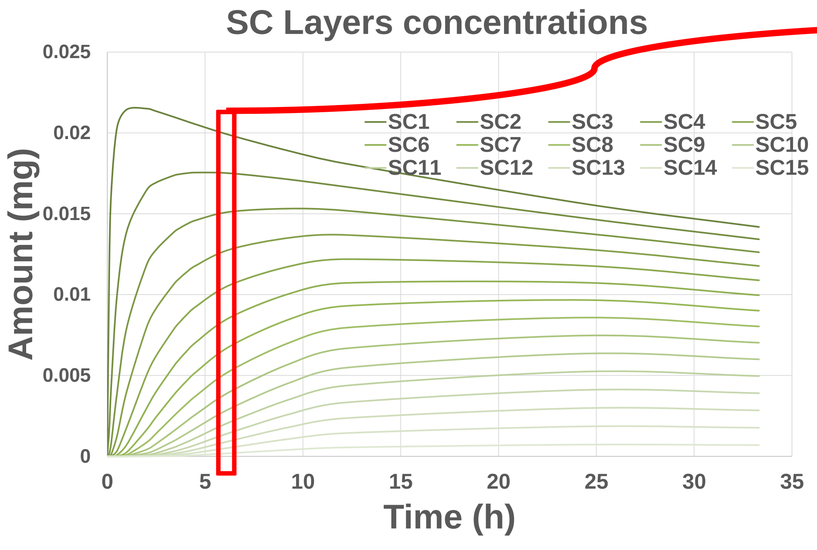

Figure 2. *Erythromycin SC individual layers PK profiles.*

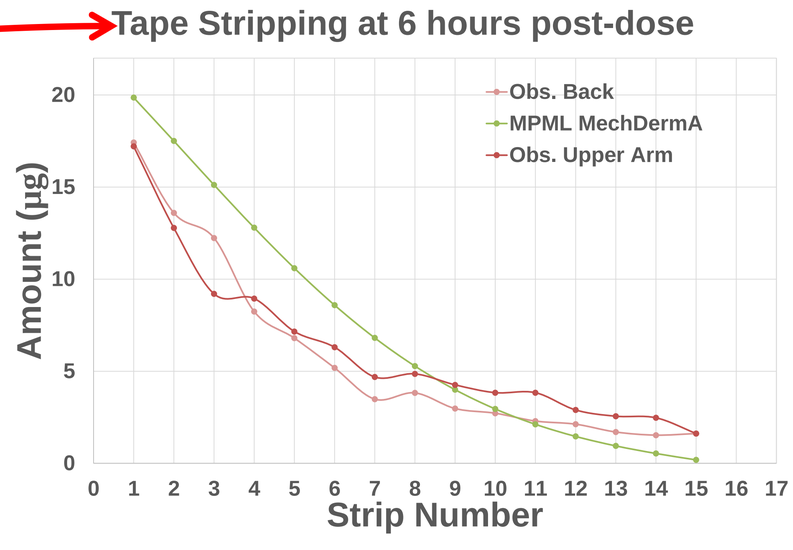

Figure 4. *MPML MechDermA skin stripping experiments Predictions vs. Observations*

Results and Discussion The novel MPML model is more realistic in simulating initial transient phase leading to steady state diffusion compared to the steady state single compartment SC approach (Figure 2). The output of the two models was assessed by RMSD by the % amount recovered from the skin surface and, additionally, in the strips. As illustrated in Figure 3, the MPML model predicts a slower dermal absorption of drug from the formulation than the current MechDermA model and does not match as well with the observed data on drug remaining on the skin surface (RMSD of 0.075 vs. 0.038). Skin stripping is used to determine the drug concentration in the stratum corneum by consecutive removal of thin layers of the skin. Each strip was assumed to account for the amount present in one skin layer. The MPML – MechDermA model allows predicting the drug concentration in each strip and the predictions are similar to the actual observations (27.2% vs. 21.4% (back) and 23.2% (upper arm) (Figure 4)). The total SC concentration profile was calculated by adding the amounts from all the strips and comparing the result to the current MechDermA model prediction. The latter over-predicted the initial drug concentrations probably due to its steady-state nature (37.5% vs. 27.2%). The present results are obtained with no fitting/adjustments done in the MPML model to empirically account for excipient impact in a similar manner as the 50 - fold higher permeability is used in the current MechDermA model simulations. There seems to be more drug remaining on the surface of the skin and an over prediction of the concentrations of the first half of the simulated tape strips followed by an under-prediction of the second half. This could be explained by a higher retention of the drug in the SC (keratin binding) or a smaller diffusion coefficient through the SC. The excipient may restrict the penetration of the drug into deeper layers of the skin or induce changes in the skin physiological parameters (i.e. hydration level, pH gradient). Currently we assume the same hydration levels and pH for all SC layers. More *in vitro* experimental data is necessary to clearly determine the individual impact of these two processes on the model predictions. The present results together with two other case studies for timolol [3] and diclofenac [4] show reasonable predictive performance of the new MPML – MechDermA model. The model development and validation work is ongoing and there is still a need to validate this approach using a wider range of drugs incorporated in more varied formulations to increase confidence in this modelling technique.

References [1] Polak S. et al. (2012) J. Pharm. Sci., 101: 2584–2595. [2] Shatkin JA, Brown HS. (1991) Environ Res., 56(1): 90-108. [3] Patel N. et al. 14th Barrier Function of Mammalian Skin Gordon Research Conference, Waterville Valley, NH, US, August 16-21, 2015. [4] Polak S. et al. 14th Barrier Function of Mammalian Skin Gordon Research Conference, Waterville Valley, NH, US, August 16-21, 2015. [5] Van Hoogdalem EJ, et al. (1996) Skin Pharmacol.; 9(2):104-110. [6] Ya-Xian Z. et al. (1999) Arch Dermatol Res. Oct; 291(10):555-9. [6] Barre J. et al. (1987) Br J Clin Pharmacol. Jun; 23(6): 753–757.

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