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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Ongoing scientific and regulatory developments have further increased the importance of accurately predicting drug concentration-time profiles in the epidermis and dermis. Mechanistic physiologically based modelling has proven to be a reliable method for this purpose [1, 2]. We are currently comparing the novel MPML-MechDermA model with the current MechDermA model using the Simcyp simulator [3, 4].

Materials and Methods

The model performances have been assessed using data from a study reporting data for 0.4 mg erythromycin contained in 10 µL of lotion which was applied on a 1.96 cm² 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 fub,plasma [8]). By contrast, these calculations were based on physicochemical properties e.g. LogD 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.

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 RSMDS 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 other two 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


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