

Development and validation of Dermal PBPK model towards virtual bioequivalence assessment: Prediction of dermal drug absorption of various Ibuprofen formulations using Simcyp MechDerMA model

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simulator | consultancy | education

Introduction Dermal drug application can be a route of choice for the delivery of drug for local and systemic action due to numerous advantages over oral administration [1]. However, skin is a tough barrier to the penetration of many drug substances [2]. Estimation of the absorption of drugs from the skin is an important parameter assessed during the development of dermal formulations. Animal models have been used to assess dermal drug absorption. However, due to the frequent divergence between animal and human data along with ethical and regulatory requirements towards reduction of animal experiments, *in vitro* and *in silico* models are becoming important alternatives. Within *in silico* approaches mechanistic physiologically based pharmacokinetic (PBPK) models have a unique advantage in integrating both the drug and formulation characteristics and the underlying skin physiology [3,4]. Aim of the present work is to demonstrate the application of multi-phase and multi-layer (MPML) mechanistic dermal absorption (MechDerMA) model in predicting the clinical observed pharmacokinetics of three ibuprofen formulations.

Materials and Methods The model performance has been assessed using ibuprofen as a model drug. Input data included physico-chemical ($pK_a=4.4$, $\log P=3.68$) and disposition parameters (plasma clearance = 3.88 L/h, and volume of distribution $V_{ss}=0.129$ L/kg, obtained after IV dosing of the drug to healthy human volunteers [5]).

Diffusion coefficients through the formulation and skin layers were calculated using either QSAR models for the current MechDerMA or also using Stokes-Einstein equation. Three formulations - gel, cream and ointment - were simulated and compared with clinical data [5].

Results and Discussion The observed mean ointment, cream and gel plasma AUC values were 1.35, 3.19, and 12.48 h $\cdot\mu$ g/mL respectively; the predicted values were 1.17, 2.34, and 17.8 h $\cdot\mu$ g/mL respectively. The T_{max} for the gel formulation was over-predicted and the potential reason could be the permeability modifying excipients present in the original formulation which were not considered in the current simulations. For example, ethanol used to solubilize ibuprofen in gels has been widely used as a skin permeation enhancer in many transdermal therapeutic systems [6]. In accordance with Bommannan et al., ethanol extracted appreciable amounts of lipid and ceramides from the stratum corneum [7], increase lipid fluidity especially near the polar interface [8], and allows formation of the pores [9], causing the enhance on ibuprofen permeation.

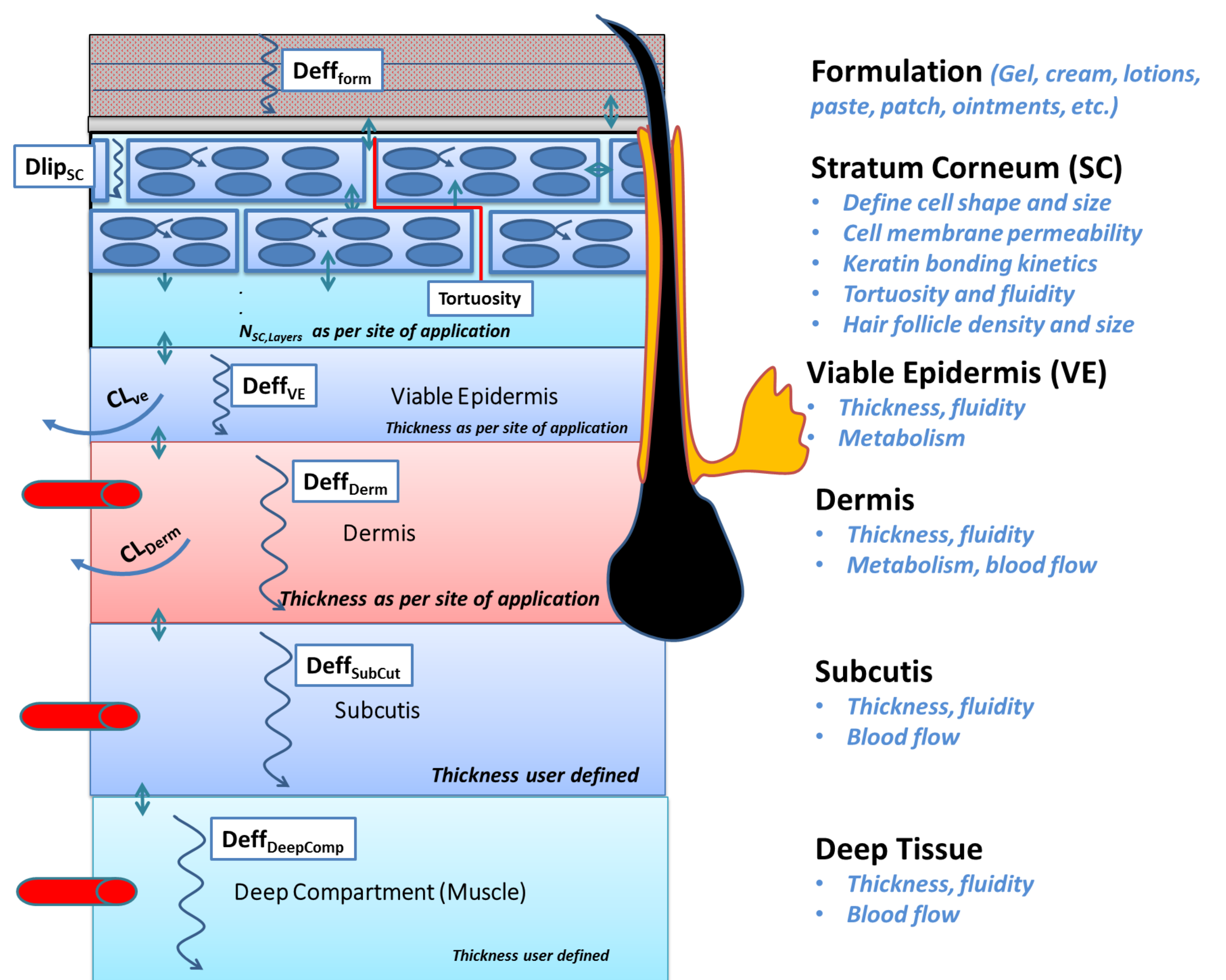
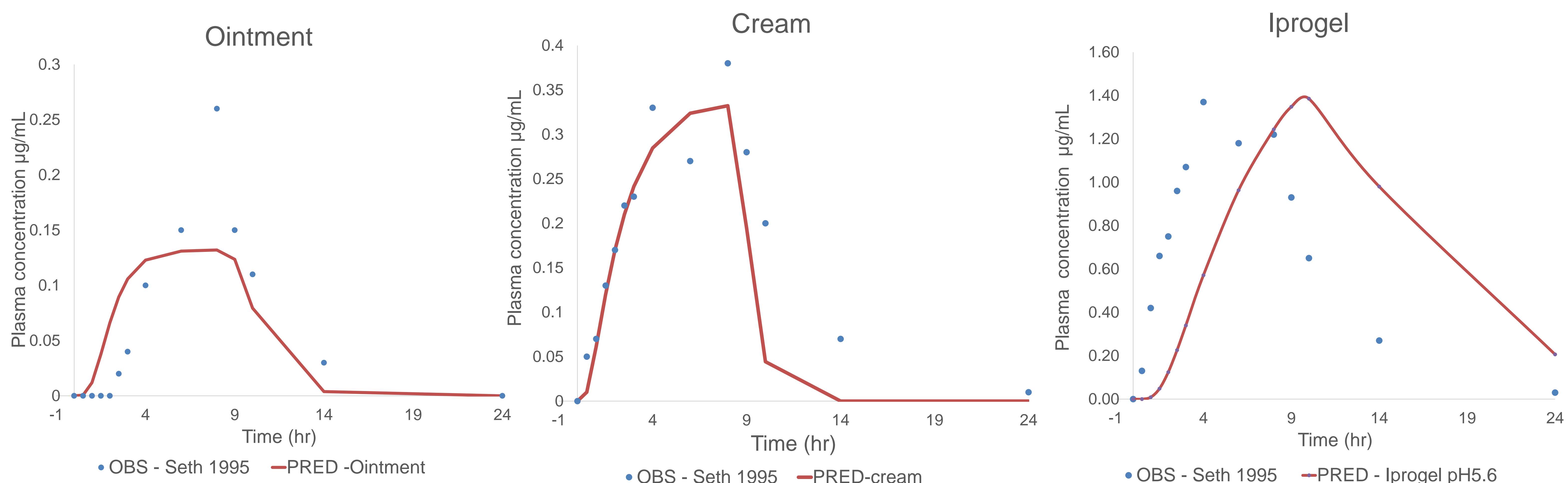


Figure 1. MPML - MechDerMA Model Structure



Conclusions The results are encouraging and the study indicates the predictive performance of the model. Further validation of the model using drugs with various physico-chemical characteristics and different types of formulations are warranted to improve confidence in such a modelling strategy. Accounting for between and within subjects variability will be another future element which will help to design studies to compare bioequivalence.

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