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

Frederico S. Martins[1*], Nikunjkumar Patel[1], Sinziana Cristea[1#] and Sebastian Polak[1,2]

[1]Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; [2]Faculty of Pharmacy, Jagiellonian University Medical College, Poland; [#]currently at Leiden Academic Centre for Drug Research
*Frederico.Martins@Certara.com

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, i*n 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.

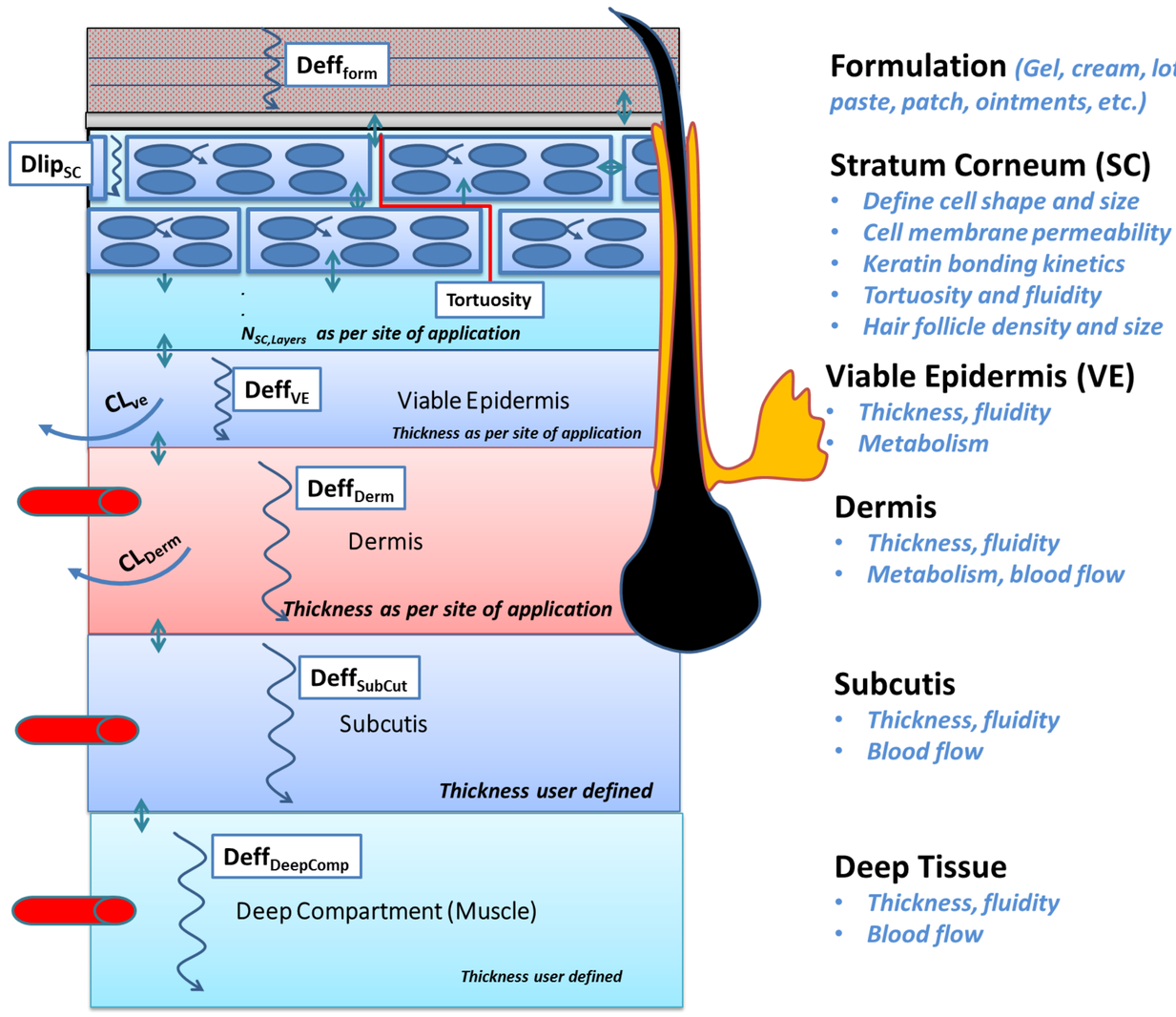
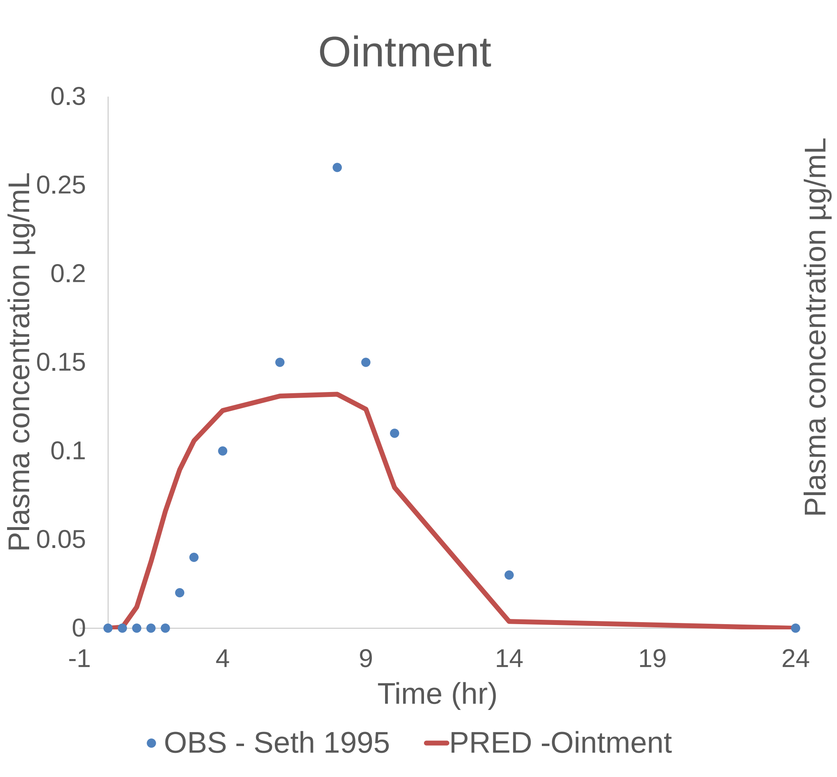
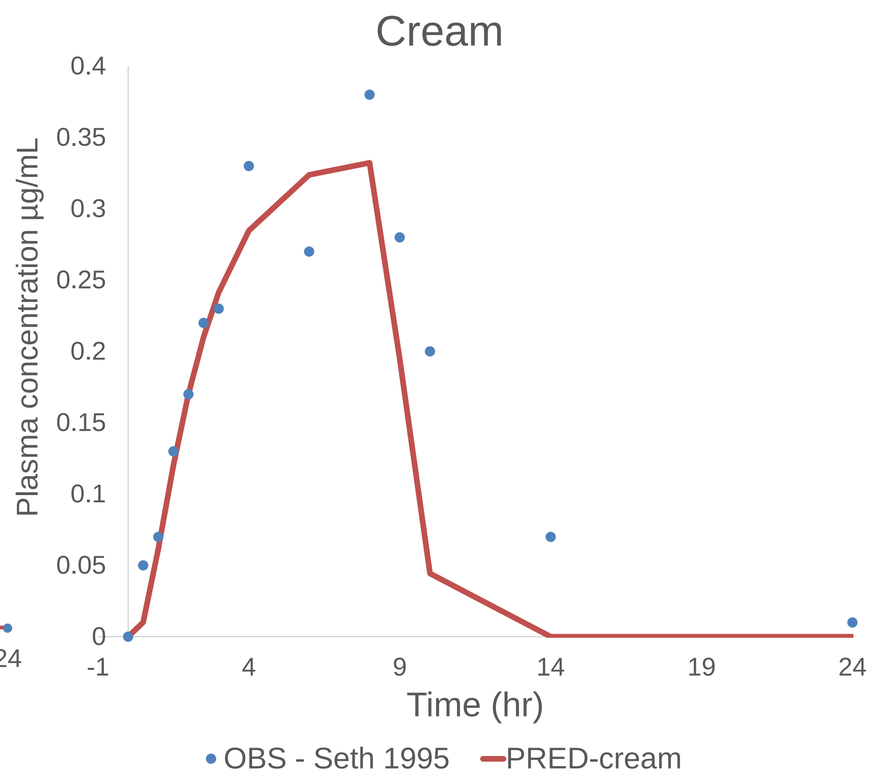


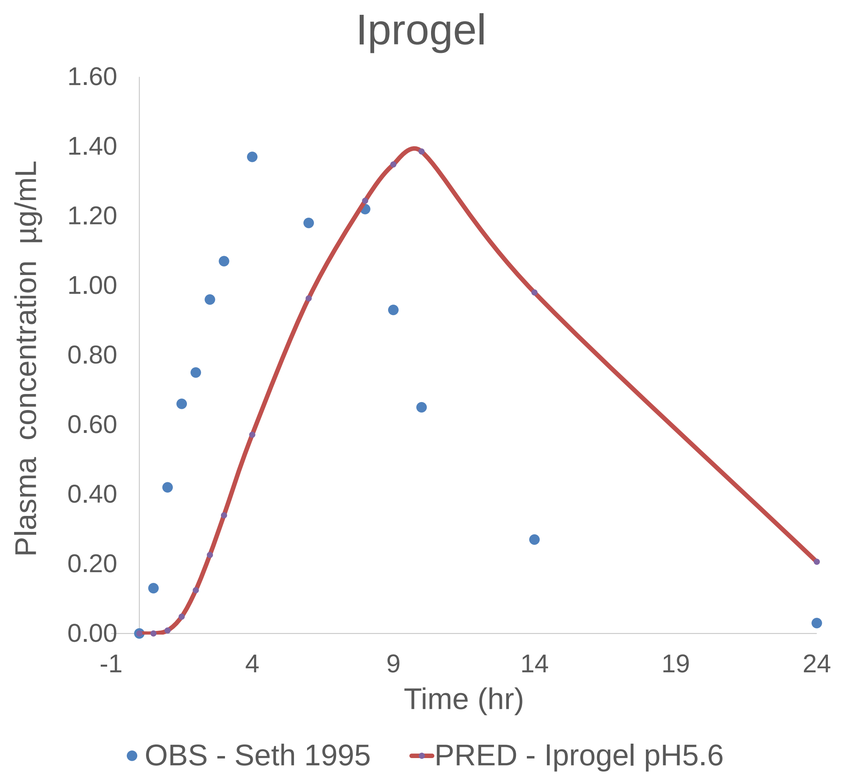
Figure 1. MPML - MechDermA Model Structure

Materials and Methods The model performance has been assessed using ibuprofen as a model drug. Input data included physico-chemical (pKa=4.4, logP=3.68) and disposition parameters (plasma clearance = 3.88 L/h, and volume of distribution Vss=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_µg/mL respectively; the predicted values were 1.17, 2.34, and 17.8 h_µg/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.







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.

References

[1]. Verma, P. and K. Pathak, *Therapeutic and cosmeceutical potential of ethosomes: An overview.* J Adv Pharm Technol Res, 2010. **1**(3): p. 274-82.
[2]. Prausnitz, M.R. and R. Langer, *Transdermal drug delivery.* Nat Biotechnol, 2008. **26**(11): p. 1261-8.
[3]. Polak, S., et al., *Prediction of concentration-time profile and its inter-individual variability following the dermal drug absorption.* J Pharm Sci, 2012. **101**(7): p. 2584-95.
[4]. Rowland, M., C. Peck, and G. Tucker, *Physiologically-based pharmacokinetics in drug development and regulatory science.* Annu Rev Pharmacol Toxicol, 2011. **51**: p. 45-73.
[5]. Seth, P.L., *Percutaneous absorption of ibuprofen from different formulations. Comparative study with gel, hydrophilic ointment and emulsion cream.* Arzneimittel-Forschung, 1993. **43**(8): p. 919-921.
[6]. Krishnaiah, Y.S., V. Satyanarayana, and P. Bhaskar, *Influence of limonene on the bioavailability of nicardipine hydrochloride from membrane-moderated transdermal therapeutic systems in human volunteers.* Int J Pharm, 2002. **247**(1-2): p. 91-102.
[7]. Bommannan, D., R.O. Potts, and R.H. Guy, *Examination of the effect of ethanol on human stratum corneum in vivo using infrared spectroscopy.* Journal of Controlled Release, 1991. **16**(3): p. 299-304.
[8]. Krill, S.L., K. Knutson, and W.I. Higuchi, *Ethanol effects on the stratum corneum lipid phase behavior.* Biochim Biophys Acta, 1992. **1112**(2): p. 273-80.
[9]. Inamori, T., et al., *Macromolecule transport in and effective pore size of ethanol pretreated human epidermal membrane.* International Journal of Pharmaceutics, 1994. **105**(2): p. 113-123.

Acknowledgement Funding for the work presented here was made possible, in part, by the Food and Drug Administration through grant 1U01FD005225-01, views expressed here by the authors of the work do not necessarily reflect the official policies of the Food and Drug Administration; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.