Towards mechanistic simulation and prediction of bioequivalence studies of topical formulations case study with two diclofenac formulations

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Introduction

Animal models have been used to evaluate dermal drug absorption for a long time. However, frequent disparities between animals and human absorption kinetics together with ethical and regulatory requirements necessitate reduction of animal experiments. Therefore, a significant increase in the role of in vitro and in silico based methods to assess dermal drug absorption has been observed. In silico models span a wide range of available algorithms: from quantitative structure–activity relationship (QSAR) to semi-mechanistic and mechanistic physiologically based pharmacokinetic (PBPK) models. Physiologically based pharmacokinetic (PBPK) models have a unique advantage in integrating both the drug and formulation characteristics and the underlying skin physiology, along with its variability within a population, when predicting drug absorption, distribution, metabolism and excretion. Accounting for between- and within-subject variability is an important element of PBPK modelling when the model is used to simulate the population variability in dermal absorption or to design studies to compare bioequivalence. Another important advantage of the PBPK approach is its extrapolation capability. Once the model performance is verified for a particular drug/formulation in one population, it can be assessed with increased confidence for another population, since the formulation remains the same and only the underlying physiological characteristics changes. This facilitates translating the product performance from the healthy population to special populations such as elderly patients, provided that the physiological differences between healthy and elderly populations are well characterised. A mechanistic dermal absorption model informed by human physiology (e.g. skin layer thickness, lipid contents, blood flow rates, etc.) has been previously developed and integrated in the Simcyp Simulator to predict human dermal absorption of drugs [1].

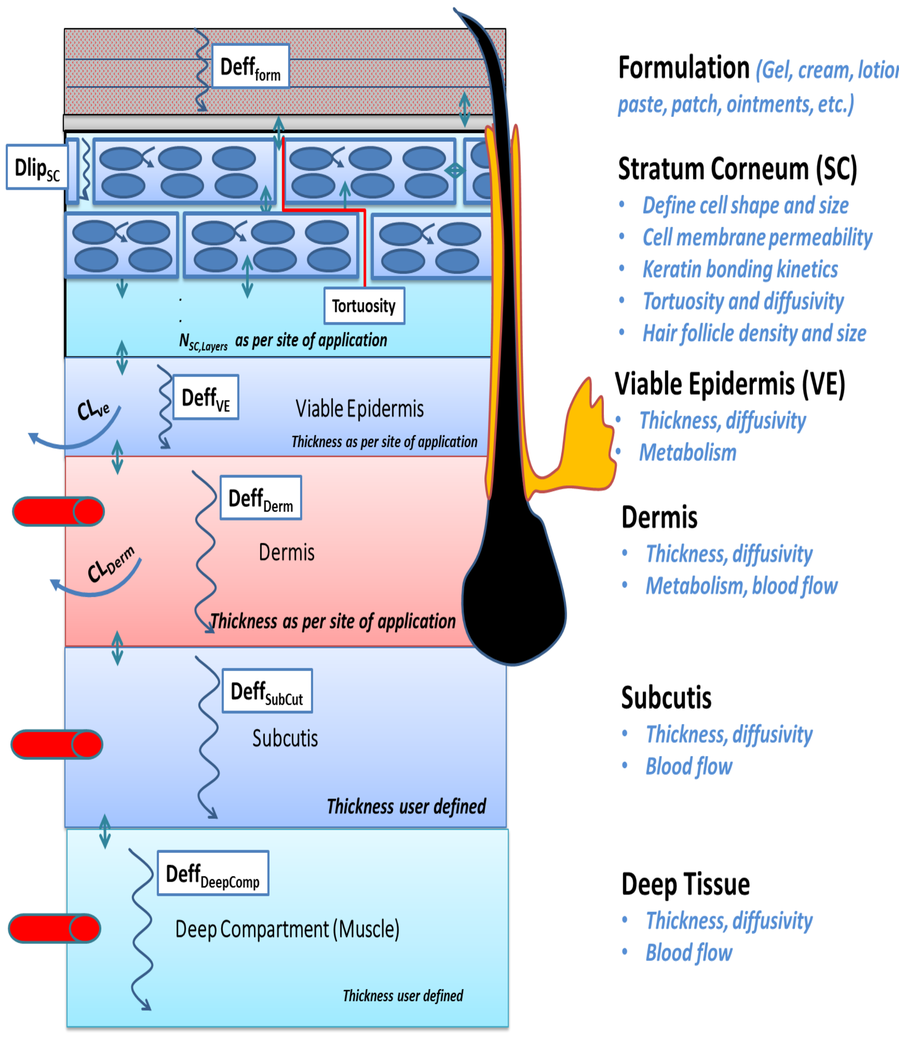

Figure 1. *MPML MechDermA Model Structure.*

The present work demonstrates application of the newly developed transient, multi-phase and multi-layer (MPML) mechanistic dermal absorption (MechDermA) model in predicting the clinical observed pharmacokinetics of two diclofenac formulations. The MPML MechDermA model which is currently under development comprises a series of significant improvements and modifications as compared with the original compartmental model within Simcyp simulator [1] developed based on the Shatkin and Brown work [2]. The new model accounts for longitudinal diffusion and distribution processes considering skin physiology related parameters such as: skin hydration and its change with depth, skin follicles and tortuosity, the pH of the skin surface, and drug affinity to keratin binding. Structural differences account for multilayer SC which is heterogeneous (multi-phasic) in nature containing protein, lipid and water fractions that allow simulation of complex diffusion through the SC for chemicals different in nature. The model can simulate and differentiate between formulations such as a gel, a cream (emulsions of different types), a patch, and a suspension or paste. The ultimate aim of the project is to build a framework facilitating virtual bioequivalence study simulations, therefore, the model would ideally be able to differentiate between various formulations and account for inter-subject variability.

Materials and Methods

The model performance has been assessed using diclofenac as a model drug. Input data included physico-chemical (pKa = 4.01, logP = 4.5, logD at pH 5.5 = 2.99) and distribution parameters (plasma clearance = 19.44 L/h, and volume of distribution = 30 L, obtained after intramuscular dosing of the drug to healthy human volunteers). Diffusion coefficients for different skin layers and partition coefficients were calculated with the use of Stokes Einstein equation or available QSAR models. None of the absorption model parameters were fitted using clinical data. Contribution of hair follicular pathway for trans-dermal drug absorption was considered negligible in this work. Two formulations, a solution gel and an emulsion gel, were tested as in the clinical study [3]. Solution was characterized by viscosity whereas, information describing emulsion included droplets size, number, volume and area.

Results and Discussion

The observed mean solution gel/emulsion gel ratios for AUC and C_{max} (1.54 and 2.07 respectively) were reasonably consistent with the predicted values (1.63 and 1.62 respectively). The predicted relative bioavailability (FAUC) of 4.5% and 2.8% for the solution and emulsion formulations were also close to the clinically observed mean FAUC (3.3% and 2.2% for the solution and emulsion formulations, respectively). The T_{max} for the solution formulation is over-predicted may be because the actual formulation may have some permeability modifying excipients which the current model did not consider. The initial results are encouraging and the study indicates the predictive performance of the model. Further validation of the model using drugs with various physicochemical 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.

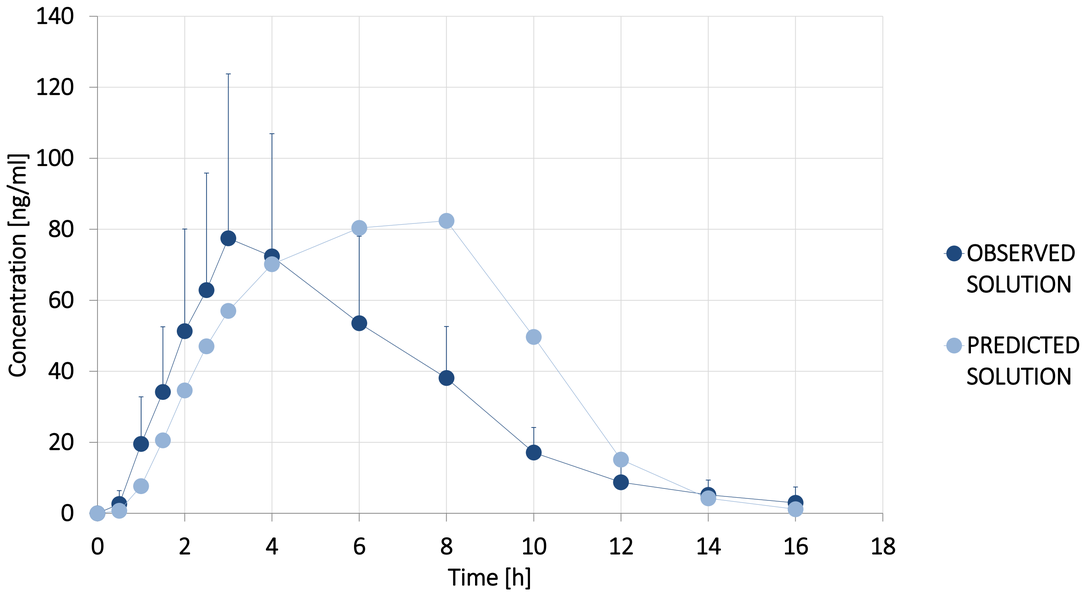

Figure 2. *Observed vs. Predicted drug concentration after solution gel application.*

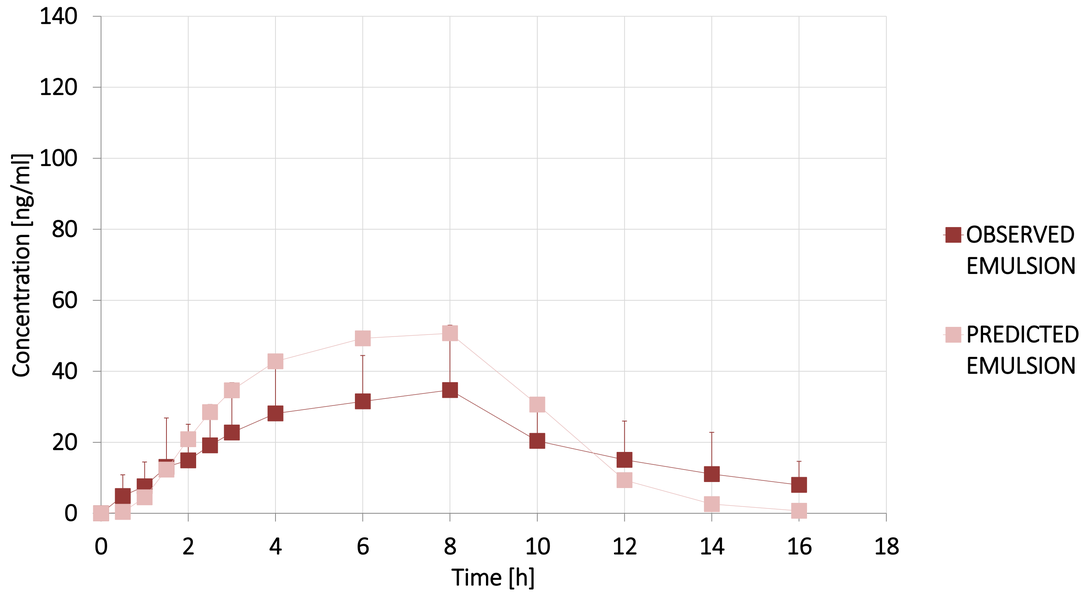

Figure 3. *Observed vs. Predicted drug concentration after emulsion gel application.*

References

[1] Polak S. et al. (2012), Prediction of concentration–time profile and its inter-individual variability following the dermal drug absorption. J. Pharm. Sci., 101: 2584–2595. [2] Shatkin JA, Brown HS. (1991) Pharmacokinetics of the dermal route of exposure to volatile organic chemicals in water: a computer simulation model. Environ Res., 56(1): 90-108. [3] Seth BL (1992) Comparative pharmacokinetics and bioavailability study of percutaneous absorption of diclofenac from two topical formulations containing drug as a solution gel or as an emulsion gel. Arzneim.-Forsch., 42(1): 120-122.

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