Mechanistic modelling of dermal drug absorption using the Simcyp Multi-phase Multi-layer MechDermA model: Case study of a transdermal patch formulation of weak base drug timolol

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Introduction:

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]. Here we introduce an enhanced model which is a transient, multi-phase and multi-layer (MPML) mechanistic dermal absorption model (MechDermA). The MPML MechDermA model (Fig. 1) accounts for longitudinal diffusion and distribution processes considering skin physiology related parameters (i.e. tortuosity of the diffusion pathway, keratin adsorption kinetics, stratum corneum (SC) hydration state, hair follicular transport, pH at the skin surface and within the SC layers, etc.) and drug/formulation specific parameters (i.e. ionization at the skin surface, lipophilicity, vehicle viscosity, etc.). The model can be developed, and is planned, to account for variability in dermal physiology to simulate within-subject and between-subject variability.

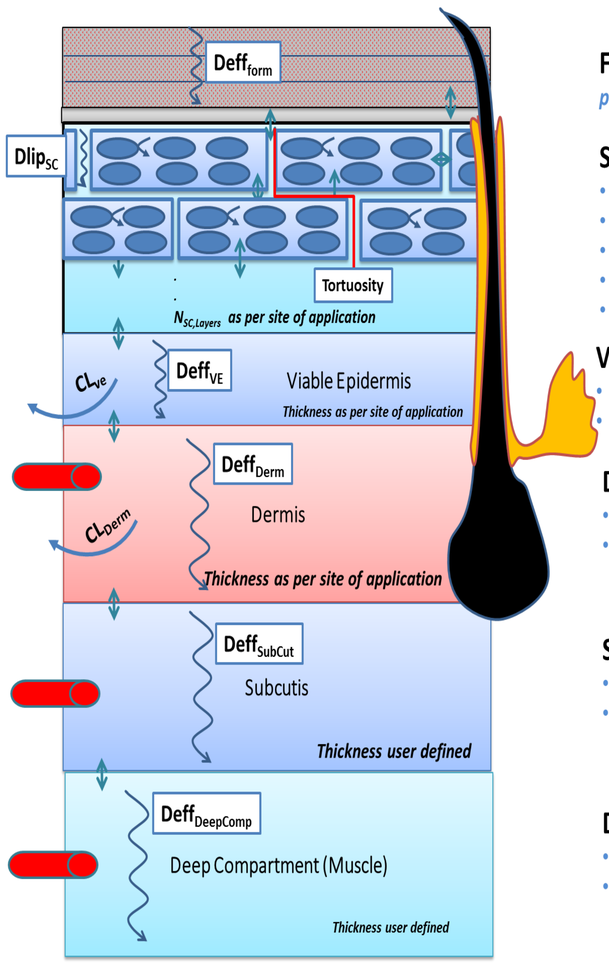

Figure 1. MPML MechDermA Model Structure

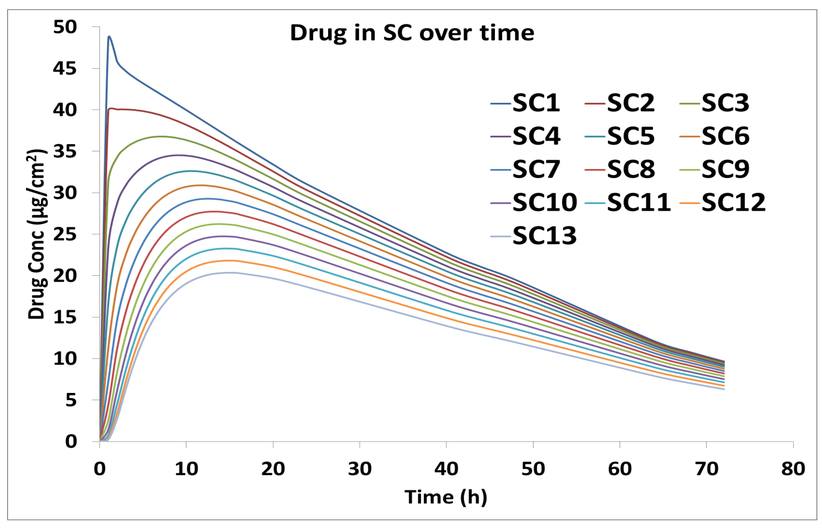

Figure 2. Drug conc. in layers of SC changing with time

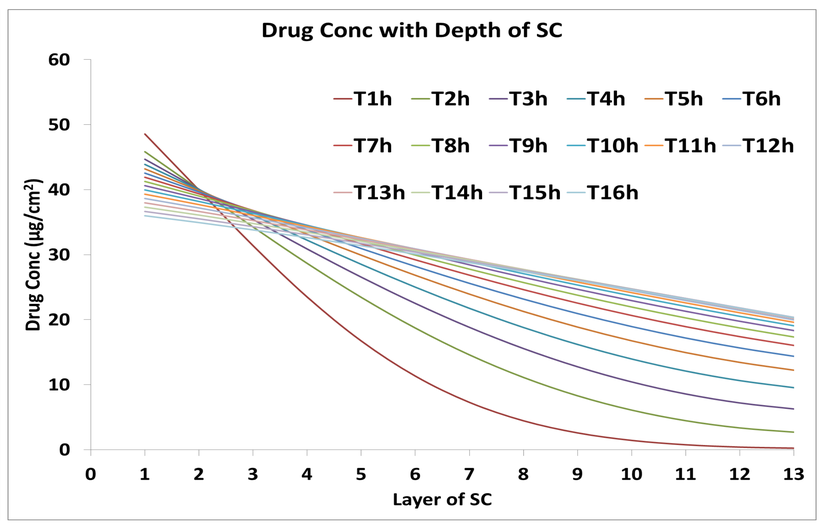

Figure 3. Drug conc. changing with depth of SC

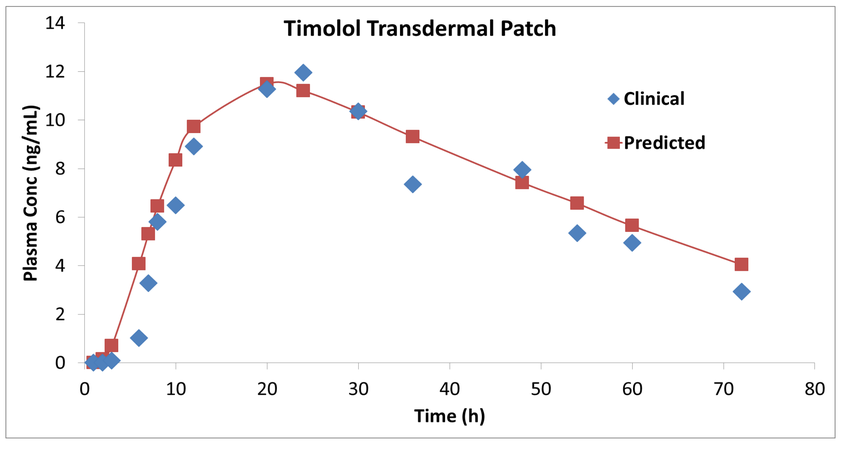

Figure 4. Simulated plasma drug conc. overlaid with clinically observed data

PK Parameter	Clinical	Simulated	%PE
C_{max} (ng/mL)	12.7	11.48	9.63
T_{max} (h)	22.9	21	8.3
AUC_{inf} (ng/mL.h)	613	633.33	-3.3
F_{AUC}	74.4	74.3	0.13
Lag time (h)	3	2	33.3

Table 1. Comparison of Observed and Predicted PK parameters and %prediction errors

Methodology:

In current work the model performance has been assessed using a transdermal patch of timolol, a weakly basic drug, using typical human healthy skin physiology of the upper arm; contribution of hair follicular pathway and skin metabolism were considered negligible at this time. The disposition parameters, namely plasma clearance and volume of distribution, were obtained after intravenous dosing of the drug to human volunteers [2].

Formulation: Matrix-type Patch formulation of 40 µm thickness was simulated. The pH and diffusivity of the patch was not disclosed in the report [2] hence the pH and viscosity of polymer were selected from the reported range that best described the clinical data to model diffusion and release from the patch onto skin surface.

Skin: SC is modelled as brick-and-mortar structure where bricks (corneocytes) can be hexahedron or cuboid embedded within the mortar of intercellular lipid matrix. For simplicity, we considered cuboid geometry in this work. The model automatically calculates the number of corneocytes that can be accommodated in the skin surface area where the formulation is applied, accounting for the tight-packing mosaic arrangement of cells with intercellular lipid thickness. Effect of hydration state of skin on the dimensions and composition of the corneocyte can be modelled. We considered corneocyte size and lipid bilayer thickness for partially hydrated SC in this work [3]. The corneocyte is composed of water and protein core encapsulated within a lipid envelope. Drug released from patch onto skin surface can be partitioned into the lipid matrix of the first layer of SC depending on lipophilicity (LogP) and ionisation (pK_a) of the drug. Model can simulate partitioning and absorption through hair follicular pathway, however the contribution has been neglected for this study. Fluidity of the SC lipids was not reported in literature, hence, we considered it to be half of the reported value for viable human epidermal cells [4]. Furthermore, drug diffusion is modelled as per Newtonian kinetics; however contradictory reports exist in literature on whether biological membranes should be modelled based on conventional fluid dynamics principles. While the drug diffuses through intercellular lipid matrix, depending on the drug to cell affinity and the concentration gradient, it can permeate into or out of the cells. Once inside the cell, the drug can get adsorbed onto the keratin. The adsorption can be modelled as steady state (fu_{SC}) or transient nonlinear adsorption/desorption kinetics (K_{on}/K_{off}). This mechanism can help to explain depot characteristic of SC for certain drugs such as steroids. The drug present in the lipid matrix can diffuse to the next layer of SC. The number of SC layers is well characterised for humans at various sites of the body and here we used 13 layers to simulate the upper arm physiology. Tortuosity of the diffusion pathway was taken from the experimentally reported value for *in vivo* human skin [5]. From the last layer of SC drug can partition into the VE depending on SC:VE partition coefficient which we calculated from QSAR model in Simcyp simulator V14. VE is considered a homogeneous diffusion layer with thickness of 56.7 µm. Metabolism within VE was considered negligible for timolol. The partition coefficient between VE and dermis was set as 1 (i.e. no difference in affinity) and thickness of dermis for upper arm was 1.2 mm with negligible metabolism. Blood flow to the dermis was modelled as a function of cardiac output, body weight and body surface area as per the Simcyp PBPK model framework. Further longitudinal diffusion into the subcutis and deep tissue was neglected in this work.

Results and Discussion:

The MPML MechDermA model was able to predict the observed lag time and absorption flux reasonably well using only physicochemical properties of drug and formulation characteristic (Figs. 2-4). The model was able to simulate the transient phase and transition to steady-state diffusion. It took about 12-16 hours to achieve steady state diffusion [Figs. 2&3]. The %prediction errors in AUC, C_{max} and T_{max} were 3.26%, 6% and 12.7% respectively considering mean values from clinical study as reference (Table 1). The predicted bioavailability (F_{AUC}) of 74.29% was also close to the clinically observed mean F_{AUC} (74.4%). The initial results are encouraging and the study confirms the predictive performance of the model. Further validation of the model using drugs with varying physicochemical characteristics and different types of formulations are warranted to improve confidence in such modelling strategy.

References: [1] Polak et al. (2012), J. Pharm. Sci., 101: 2584–2595; [2] Kubota et al. (1993), Eur J Clin Pharmacol 44: 493-495; [3] Wang et al. (2006), J. Pharm. Sci., 95:620-648; [4] Dunham et al. (1996), Spectrochimica Acta A, 52: 1357-1368; [5] Talreja et al. (2001), AAPS PharmSci, 3, 48-56.

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