Multi-phase Multi-layer MechDermA model: Development, verification and application of a PBPK-PD model of dermal absorption for transdermal product assessment

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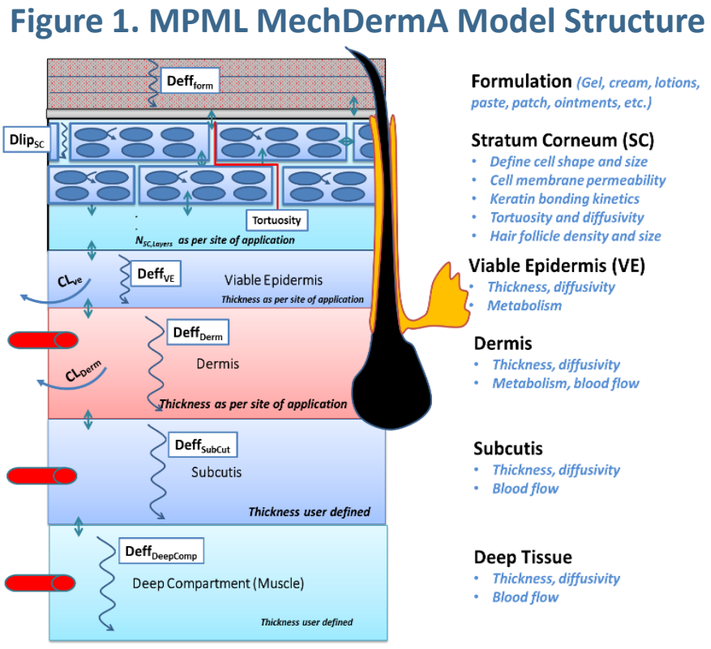
Dermal drug administration can be a preferred route for the delivery of drugs for local or systemic action, with numerous advantages over oral administration [1]. Mechanistic physiologically based pharmacokinetics models such as the Mechanistic Dermal Absorption (MechDermA) have a unique advantage in integrating both the drug and formulation characteristics and the underlying skin physiology [2,3]. Aim of the present work is to demonstrate the application of the Multi-Layer (MPML) MechDermA model [Figure 1] in predicting the dermal permeation of nicotine.

Figure 1. MPML MechDermA Model Structure



The SC is modelled as brick-and-mortar structure where bricks (corneocytes) are cuboid in shape embedded within the mortar of intercellular lipid matrix. The corneocyte is composed of a water and protein core encapsulated within a lipid envelope. The model can simulate partitioning and absorption through a hair follicular (HF) pathway depending on the drug's affinity to sebum and its molecular size. While the drug diffuses through the 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}). The drug present in the lipid matrix can diffuse to the next layer of SC. From the last layer of SC, drug can partition into the viable epidermis (VE) depending on SC:VE partition coefficient. The partition coefficient between VE and dermis was set as 1 (i.e. no difference in affinity). Blood flow to 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.

The model performance has been assessed using nicotine as a model drug. Input data included model and drug parameters such as MW=162.2, pKa1= 3.12, pKa2= 8.02 LogP = -0.87,fu_{sc}=0.42, $fni_{skin\ surface}$=0.01, $Cl_{i.v}$ =71.6 L/h, steady state volume of distribution Vss= 3 L/kg, and the skin surface pH=5.5. Diffusion and partition coefficients were calculated using QSAR models (see Table 1).

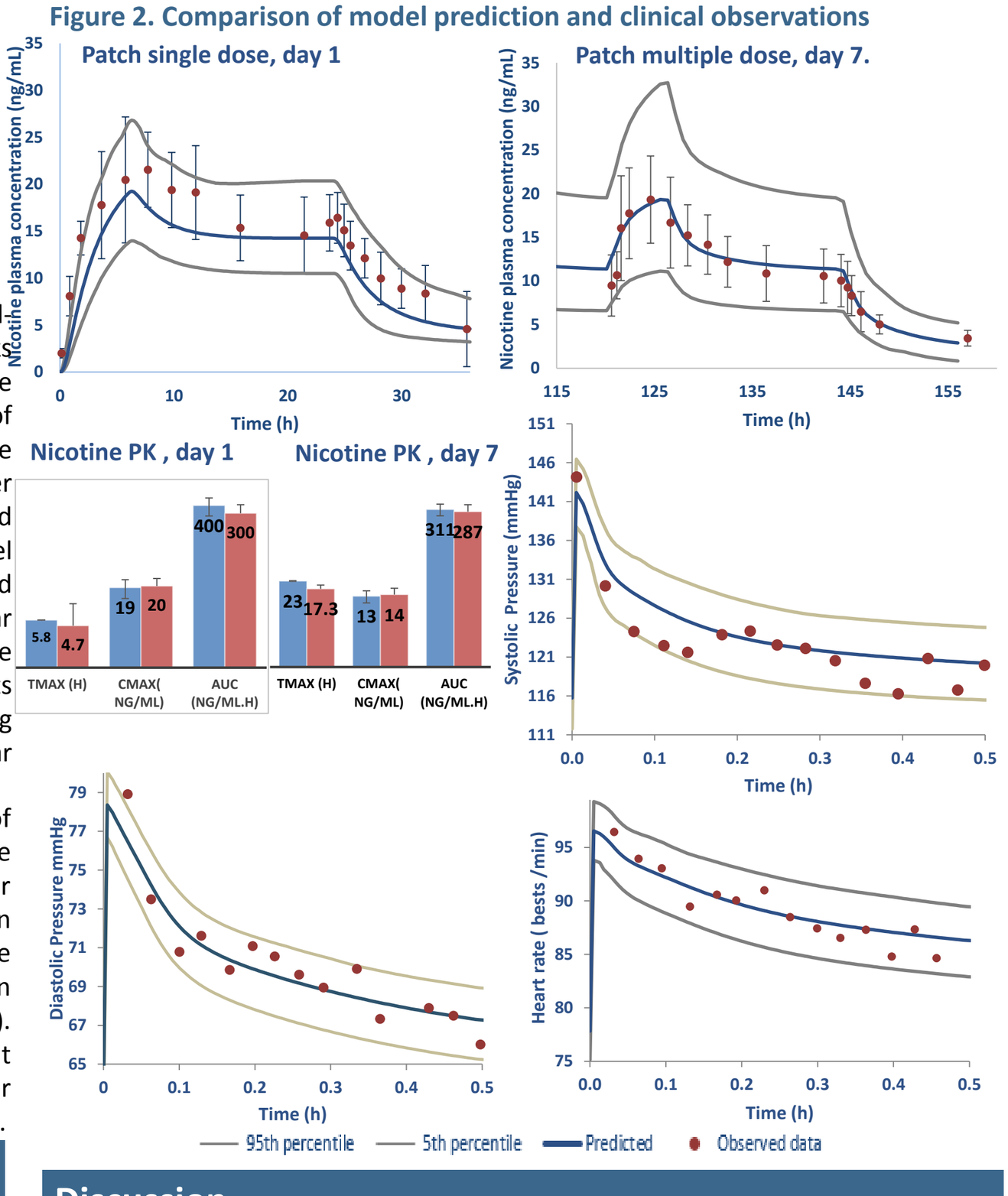
Gupta et al 1993 [3] described nicotine transdermal absorption in 13 volunteers after single and multiple dose for 7 days (every 24 hr). The active substance was released from the patches, 22 cm^2 (Nicoderm®, ALZA Corporation, Palo Alto) containing 36 mg of the nicotine, applied to the upper arm. The total dose released was 20.9 mg, C_{max} 18.1 ng/mL, AUC 304 ng/mL/h, and T_{max} 6.2 h. Jones et al 1998 described the physiological effects of nicotine on blood pressure for 0.043 mg/kg of i.v. nicotine in 3 women and 12 men [4] . Population PK and PK-PD models were developed using Simcyp V16, the best PBPKPD was characterized by a full PBPK model. The Sigmoid E_{max} (Hill) response model was applied to correlate plasma nicotine concentration,-blood pressure ($E_{0\ =}$ 116mmHg, $E_{max=}$ 150 mmHg to systolic and $E_{0\ =}$ 60 mmHg, $E_{max=}$ 80 mmHg to diastolic , EC_{50} = 0.41 uM) and heart rate $E_{0\ =}$85 bps , $E_{max=}$ 95 bps, EC_{50} = 0.96 uM . Both EC50 values were fitted by parameter estimation.

Table 1: QSAR prediction of diffusion and partition coefficients of Nicotine in patch.

	Parameter	QSAR prediction	Reference
Partition Coefficient	Lipid: vehicle	5.0	Hansen 2013 [5]
	Sebum: vehicle	71.7	Valiveti 2008[6]
	VE:SC	6.5	Kretsos 2008 [7]
	Skin:blood	1.0	Shatkin & Brown [8]
Diffusion Coefficient (cm^2/h)	SC lipid	0.0008	Mitragotri 2003 [9]
	VE	0.014	Kretsos 2008 [7]
	Dermis	0.014	Kretsos 2008 [7]
	Sebum	0.0009	Johnson 1996 [9]
Keratin binding	Kon/koff	10.8/2.13	Seif 2012 [10]

The predicted and observed nicotine plasma concentration after single and multiple patch application and PD profiles are compared in Figure 2.

Figure 2. Comparison of model prediction and clinical observations



Discussion

The study results show that the MPML MechDermA model can predict the absorption through the skin reasonably well and the results are encouraging. One third of the nicotine was shown by Gupta et al 1993 to be lost from the exposed edges of the system, most likely due to evaporation, considering the high volatility of nicotine. Ten percent of nicotine was estimated to be in the skin, this fact can explain the apparently longer half life of nicotine delivered by patch (3 h) in comparison to i.v. studies (2 h) (not shown. Nicotine can produce dose and time effects on BP and HR. The predominant cardiovascular effects of nicotine result from activation of the sympathetic nervous system [4]. MPML MechDermA model associated with a full PBPK disposition model can provide drug concentration in tissues where pharmacodynamics effects occur, such as the brain or heart as shown in this example. The kinetic penetration processes are likely to be dependent on the nature of the drug substance and properties of the formulation such as pH, viscosity, excipients, duration of application and evaporation of vehicle. Further validation of the model using drugs with various physicochemical characteristics, different types of formulations, and different anatomical sites of application are warranted to evaluate the validity of the model.

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