Add your Assigned Poster Number by replacing this text

Multi-Phase Multi-Layer Mechanistic Physiologically based Pharmacokinetic Dermal Absorption Model verification including inter and intra individual variability assessment using nicotine as a model drug

Frederico Severino Martins[1], Nikunjkumar Patel[1], James Clarke[1], Sebastian Polak[1,2]

[1]Simcyp (a Certara company), Sheffield, United Kingdom, [2]Jagiellonian University Medical College, Kraków, Poland

CONTACT INFORMATION: Nikunjkumar.Patel@certara.com

aaps PharmSci 360 ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

Estimation of systemic exposure after skin absorption of any xenobiotic is very important in development of dermal pharmaceutical products as well as assessing exposures due to cosmetic products or environmental and occupational compounds. The Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MechDermA) model is a mechanistic absorption model with 4 formulation types and 8 application sites including specific skin physiology for these sites. The developed model is incorporated into the Simcyp simulator which is a 'bottom-up' IVIVE platform and database for mechanistic modelling and simulation of the drug disposition process using full body physiologically based pharmacokinetic modelling.

OBJECTIVE(S)

In this abstract, we describe scientific background to the Multi-Phase Multi-Layer (MPML) MechDermA Model implemented in Simcyp simulator V17 and its performance verification based on the clinical cases using nicotine as a model drug.

METHOD(S)

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, $f_{u,sc}$=0.42, $f_{ni,skin\ surface}$=0.01, CLiv =71.6 L/h, steady state volume of distribution V_{ss}= 3 L/kg, and the skin surface pH=5.5. Diffusion and partition coefficients were calculated using QSAR models (see Table 1).

Case 1: This study reported by (Benowitz, Keith et al. 1991) included results for fourteen male heavy smokers aged 27 to 64 years (mean age 39). According to the study settings, each individual was given an i.v infusion of 0.87 mg/h of deuterium-labelled nicotine (nicotine-d2) for 24 hours (total dose 20.88 mg, at the same time the patch (TTS; Ciba-Geigy Corp., Ardsley, N nicotine-d0) was applied on the skin (lower abdomen). The patch was loaded with 52.5 mg (declared release rate – 0.9 mg/h) of drug to provide continuous and controlled release of nicotine after its application to intact skin.

Case 2: 13 males, aged 26±3 years were treated single dose of nicotine patch (Nicotinell TTS 30, declared release rate of 0.87 mg/h). The biopsy of subcutis was taken using "biopsy needle device" in 5 different sampling times (Schrolnberger, Brunner et al. 2001).

Figure 1. MPML MechDermA Model Structure

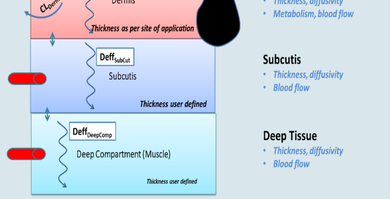

Table 1 : QSAR prediction of diffusion and partition coefficients of Nicotine in patch.

	Parameter	QSAR prediction
Partition Coefficient	Lipid: vehicle	5.0
	Sebum: vehicle	71.7
	VE:SC	6.5
	Skin:blood	1.0
Diffusion Coefficient (cm^2/h)	SC lipid	0.0008
	VE	0.014
	Subcutis	0.014
	Sebum	0.0009
Keratin binding	kon/koff	10.8/2.13

RESULTS

Figure 2 present the overlay of a predicted nicotine in plasma and subcutis over that observed by Benowitz et al 1991 and (Schrolnberger, Brunner et al. 2001). Table 2 compares predicted and observed pharmacokinetics (PK) parameters, the observed PK parameters for nicotine infused and transdermal delivered were similar to those predicted. The difference between the model prediction and clinical data is well within the variability of such clinical studies.

Benowitz et al 1991 observed that after the patch removal, the systemic absorption of nicotine was not suddenly interrupted, suggesting that some amount of drug remains in the skin, as it can be observed in Figure 1 with a slow plasma clearance after 24 hours. The subcutis concentration has a lag time of ~1 h compatible with lag time in plasma. The variability of skin physiology, biopsy technique and drug effect on skin blood flow could explain the over prediction of nicotine on subcutis.

Figure 2 : Nicotine Systemic and local concentration after i.v. infusion (a), patch application (b), Subcutis profile after patch application(c).

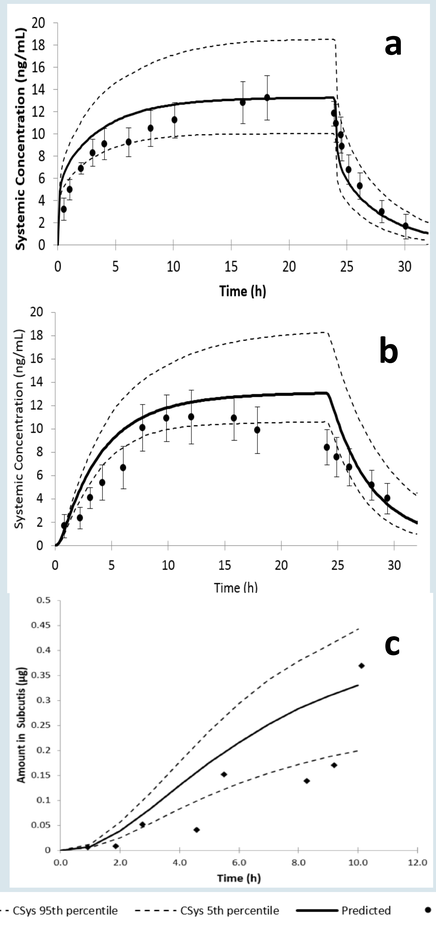

Table 3: Comparison of PK profile of predicted and observed data after nicotine infusion and transdermal delivery, Benowitz et al 1991

		Predicted		Observed data	
		Mean	SD	Mean	SD
Intravenous infusion	Tmax (h)	17	0.1	14.0	4.06
	Cmax (ng/mL)	12.78	0.88	17.3	2.38
	AUC (ng/mL×h)	303	20.9	287	80.6
Patch order zero release	Tmax (h)	23.9	0	12.06	4.8
	Cmax (ng/mL)	12.6	0.9	11.1	3.8
	AUC (ng/mL×h)	300	23.1	245.7	125

CONCLUSION(S)

The results demonstrate that the MPML MechDermA model prediction is in a good agreement with the reported clinical data for both the local exposure in subcutis as well as in systemic circulation. The impact of excipients on skin physiology was not directly accounted in this study, it is known that patch has multiple combinations of permeants to improve and control the drug release, but those were not reported in the papers. Once the excipients in formulation are known, a systematic modification of the skin physiology and drug parameters properties can be done to mimic more realistic scenario

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

Funding for the work presented here was made possible, in part, by the U.S. Food and Drug Administration grant 1U01FD005225-01.

CERTARA Simcyp