Poster Number
W5081

Quantitative prediction of human dermal absorption from *in vitro/in silico* data using Simcyp Simulator – Importance of ionisation at skin surface and binding to keratin along with the thickness and lipid levels of skin layers

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PURPOSE:

Physiologically based pharmacokinetic (PBPK) models have a unique advantage in accounting for the drug and the formulation characteristics and the underlying inter- or intra-individual variability in physiology and biology. A mechanistic dermal absorption model informed by human physiology (skin layer thickness, lipid contents and blood flow rates, etc.) has been developed previously in the Simcyp Simulator to predict human dermal absorption of drugs [1]. Here we introduce new enhancements [Fig 1] which account for the impact of formulation type, ionisation at skin surface (f_{ni}), dermal metabolism and binding to keratin (fu_{SC}). Validity of enhancements are assessed using Diclofenac (DF), a commonly used drug for local pain treatments.

Materials and Methods:

All simulations were carried out in Simcyp version 14.0 using the enhanced mechanistic dermal absorption (**MechDermA**) model [Fig 1]. Four scenarios were simulated - M1 (Without considering fu_{SC} and f_{ni}); M2 (Considering only f_{ni}); M3 (Considering only fu_{SC}); and M4 (Considering both fu_{SC} and f_{ni}). Dermal metabolism of DF was assumed to be negligible. Binding to keratin was assumed to be equal to plasma protein binding of DF. A clinical trial design is replicated by selecting an appropriate population from Simcyp Library and the trial design parameters with representative subject (PopRep) [Table 1]. Predicted profiles [Fig.2] and values of C_{max}, T_{max} and AUC [Table 2] were then compared with reported clinical results [2].

RESULTS AND DISCUSSIONS:

The predicted PK profiles are overlaid with the clinically observed data (Fig 2). The predicted values and % prediction errors (%PEs) in C_{max} (ng/mL), T_{max} (h) and AUC (ng/mL×h) are reported in table 2. When no fu_{SC} and f_{ni} were considered in M1, the absorption is so rapid that the whole dose of drug was absorbed in few hours and due to high clearance (~15L/h), there was rapid decline in the profile. M2 model considered only ionisation (no fu_{SC}). When fu_{SC} is not considered, the drug passes through skin very quickly and as soon as drug is absorbed it gets metabolised due to high clearance. The drug was applied for 24 hours on skin. For M2, similar to M1, the drug absorption was very quick leading higher C_{max} and shorter T_{max} but once in systemic circulation it gets eliminated quickly leading to rapid drop after removing the formulation at 24 h. M3 (only fu_{SC}, no f_{ni}) very rapid initial flux. The significant binding of DF to the keratin in stratum corneum (SC) releases the drug very slowly into the systemic circulation and the kinetics is governed by the rate of entry into circulation than the clearance itself. Hence even when the drug was removed from skin surface at 24 h, the drug which has entered S.C. and bound to keratin gets released slowly into the circulation acting as a depot system. When both fu_{SC} and f_{ni} were considered in M4, the predicted kinetics were close to the clinically observed PK profile [Fig. 2, Table 2]. The population simulation of M4 also recovered the observed population variability reasonably well [Figure 3].

CONCLUSIONS:

Formulation type, drug ionisation at the skin surface and binding to keratin along with lipid content of skin layers and their thickness can significantly impact upon dermal absorption of ionisable compounds and should be considered during modelling for more realistic predictions. Further validation of the model on drugs with varying physicochemical characteristics and different types of formulation are warranted to improve confidence in such modelling strategy.

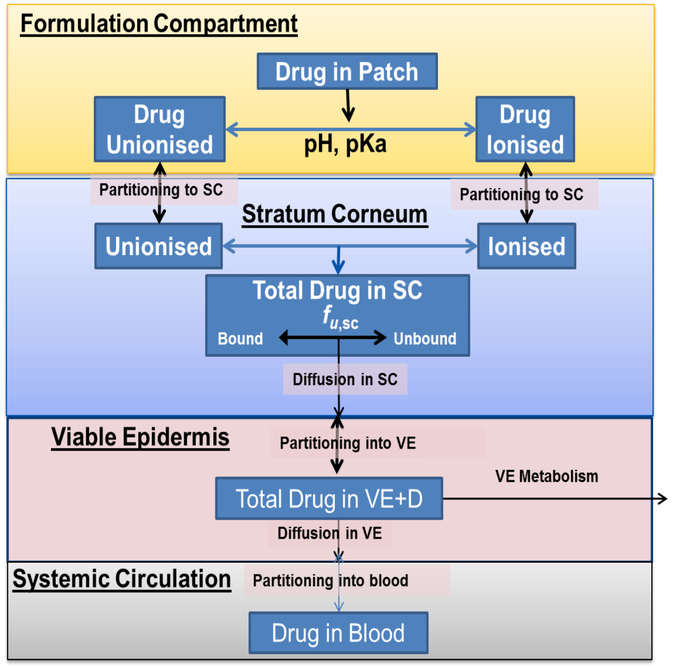

Figure 1. The Simcyp Dermal Absorption model (MechDermA)

Study Design	Trial parameters	
	Clinical	Simulation
Formulation	Lotion	Aq. base
Site	Knee	Lower leg
Area (cm^2)	200	200
Duration of Appl.	24 h	24 h
Thickness of applied drug layer (mm)	0.2	0.2
# subjects [Age] (% F)	4 [45-76] (NA)	10X4 [45-76] (50)
Population	Caucasian	NEurCauc

Table 1. Trial designs; NEurCauc– North European Caucasian

PK Parameter	Clinical	Predicted (%Prediction Error)			
		M1	M2	M3	M4
C_{max}	11.80	690 (-5749)	64.95 (-450)	12.38 (-4.88)	8.95 (24.16)
AUC	717.60	905 (-26.22)	779.56 (-8.63)	725.32 (-1.08)	612.23 (14.68)
T_{max}	30	0.7 (97.67)	1.85 (93.83)	3 (90)	24.07 (19.77)

Table 2. Comparison of predicted and observed C_{max}, T_{max} and AUC

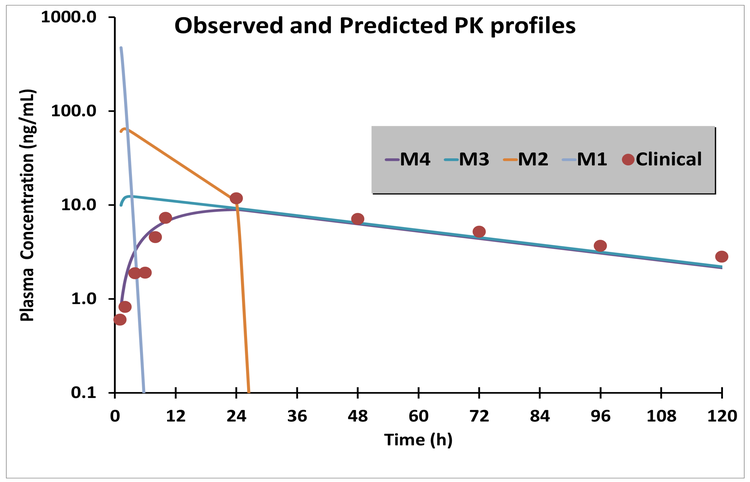

Figure 2. Observed and predicted PK profiles after applying 15mg DF lotion, M1 - Without considering fu_{SC} and f_{ni}; M2 – Considering only f_{ni}; M3 – Considering only fu_{SC}; and M4 – Considering both fu_{SC} and f_{ni}

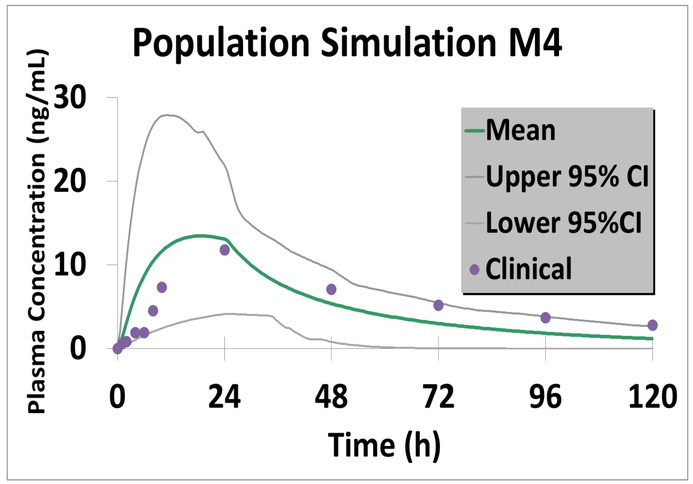

Figure 3. Population simulation of M4 overlaid with clinical profile (mean +/- SD)

REFERENCES: [1]. Polak *et al.* (2012), J. Pharm. Sci., 101: 2584–2595. [2] Hui *et al.* (1998), Pharm Res., 15(10): 1589-95.