Importance of formulation type, ionisation at skin surface, binding to keratin along with thickness and lipid levels of skin layers in quantitative prediction of human dermal absorption of diclofenac and ibuprofen

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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, dermal metabolism and binding to keratin (fu_{SC}). Validity of enhancements are assessed using two model compounds Diclofenac (DF) and Ibuprofen (IP), commonly used for dermal treatments. DF was administered as lotion whereas the IP was given as gel and cream formulations.

Materials and Methods:

All simulations were carried out in Simcyp version 13.2 using the enhanced mechanistic dermal absorption (**MechDermA**) model [Fig 1]. Due to the bottom-up nature of MechDermA, neither clinical nor animal dermal absorption data were necessary. Instead, a range of built-in QSAR models and prior *in vitro* data were used as model input. Simulation of plasma concentration-time profiles for DF and IP were carried out with both the enhanced and original models and were compared against each other. Dermal metabolism of both drugs was considered negligible. A clinical trial design is replicated by selecting an appropriate population from Simcyp Library and applying the trial design parameters [Table 1]. Predicted profiles and values of C_{max}, T_{max} and AUC were then compared with reported clinical results [2, 3].

Study Design	DF Lotion		IP Gel		IP Cream	
	Clinical	Simulation	Clinical	Simulation	Clinical	Simulation
Formulation	Lotion	Aq. base	Aq. Gel	Aq. base	Cream	Non-aq.
Site	Knee	Lower leg	Upper back	Upper arm	Upper back	Upper arm
Area (cm^2)	200	200	360	360	360	360
# subjects [Age] (% F)	4 [45-76] (NA)	4 [45-76] (50%)	6 [20-48] (100%)	6 [20-48] (100%)	6 [20-48] (100%)	6 [20-48] (100%)
Population	HCV	HCV	HCV	HCV	HCV	HCV

Table 1. Clinical and simulated trial designs; HCV – healthy Caucasian volunteers; simulations were replicated 10 times.

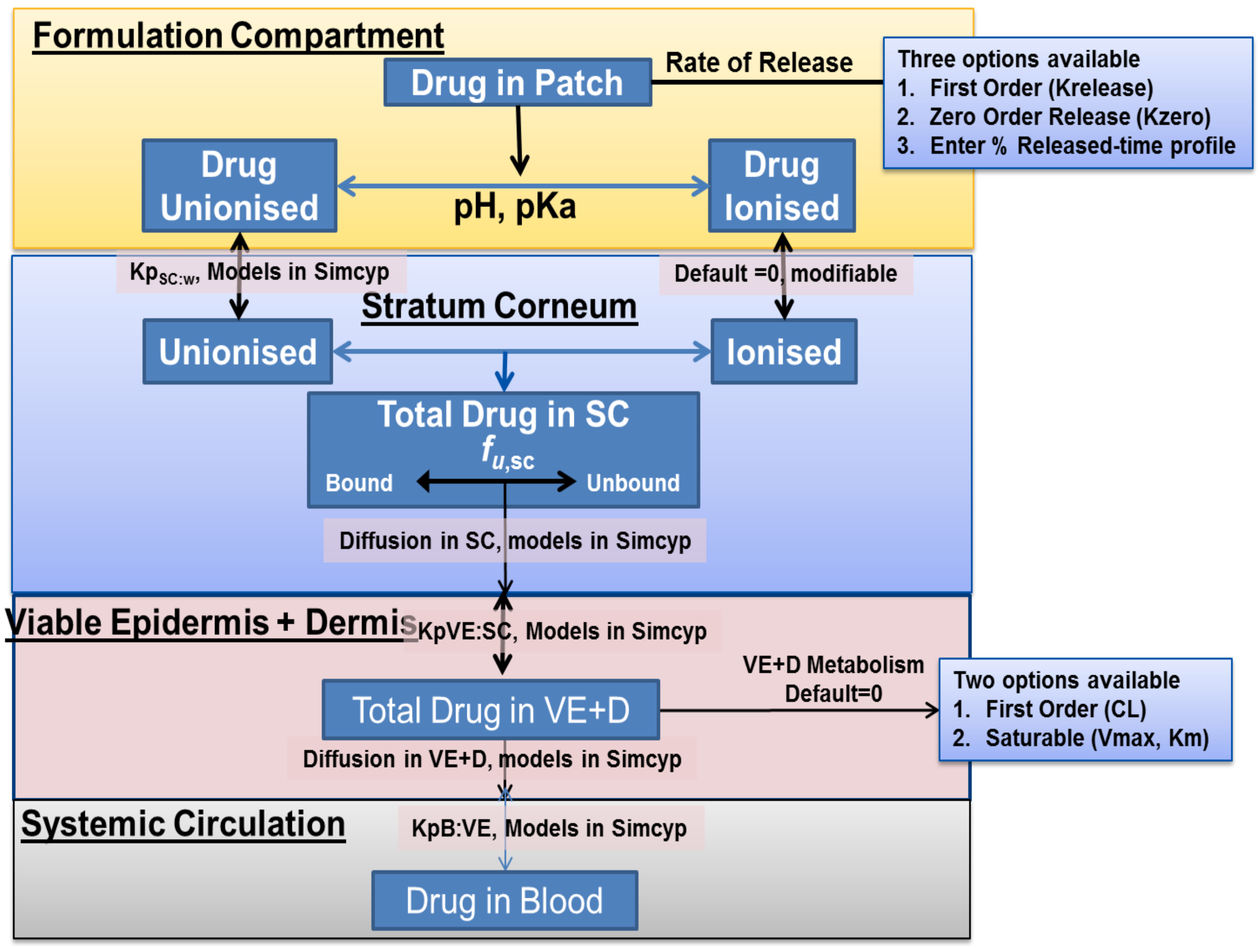

Figure 1. The Simcyp Dermal Absorption model (MechDermA)

RESULTS AND DISCUSSIONS:

DICLOFENAC: 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) showed improved outcome by using the enhanced MechDermA model (Table 2).

PK Parameters	Clinical	Predicted (Without Ionisation and f_{uSC})		Predicted (With Ionisation and f_{uSC})	
		Value	%PE	Value	%PE
C_{max} (ng/mL)	11.8	7.13	39.58	13.45	-13.97
T_{max} (h)	30	15.65	47.83	29.75	0.83
AUC (ng/mL.h)	717.6	533.86	25.60	721.08	-0.48

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

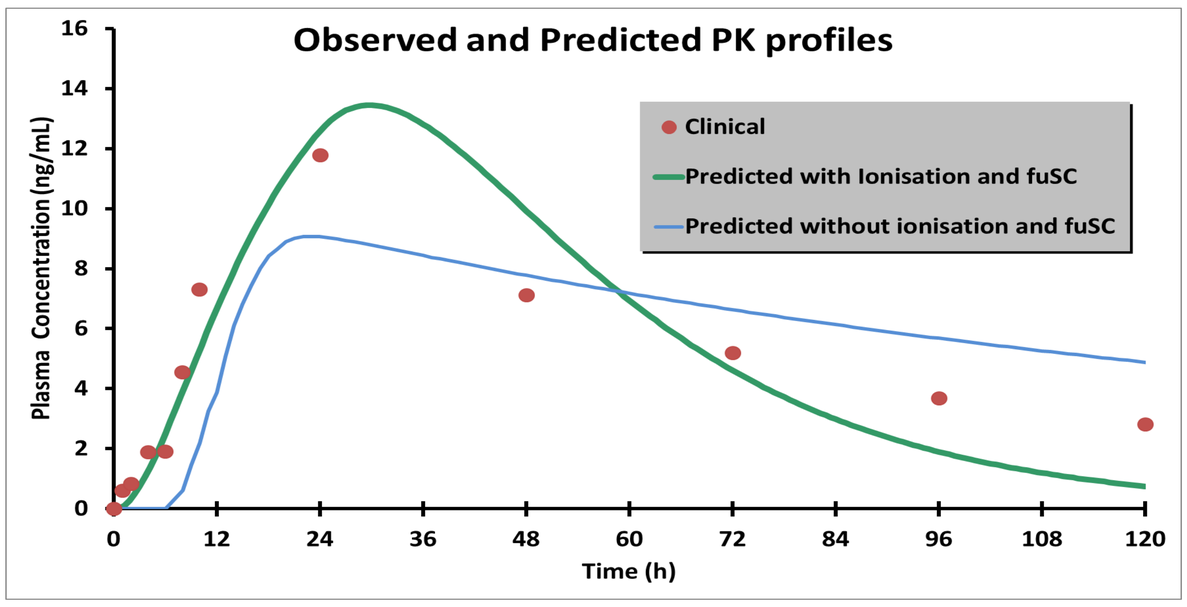

Figure 2. Observed and predicted PK profiles after 15mg DF lotion

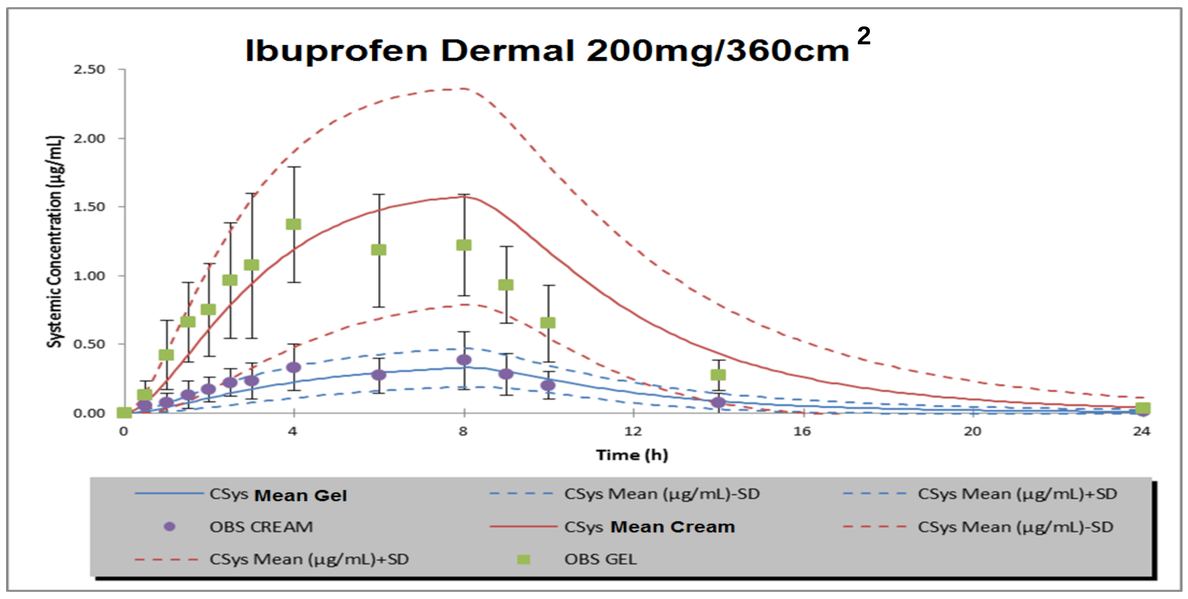

Figure 3. Observed and predicted PK profiles of Gel and Cream formulation of IP

IBUPROFEN: Similar to DF case, inclusion of ionisation and fuSC significantly improved predictions of two different formulations of IP (gel formulation was simulated as aqueous base vehicle; cream formulation was simulated as non-aqueous base vehicle). The results from predictions were compared to clinically measured pharmacokinetic profiles including the population variability of each of the formulations (Fig 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.

ACKNOWLEDGEMENTS: The Simcyp Simulator is freely available, following completion of the training workshop, to approved members of academic institutions and other non-for-profit organizations for research and teaching purposes.

REFERENCES: [1]. Polak *et al.* (2012), J. Pharm. Sci., 101: 2584–2595. [2] Hui *et al.* (1998), Pharm Res., 15(10): 1589-95. [3] Seth, P. L. (1993), Arzneimittel-Forschung 43(8): 919-921.