Performance verification of mechanistic dermal physiological based pharmacokinetic (PBPK) model for enhanced understanding of dermal absorption: prediction of local tissue exposure after topical application of acitretin

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Abstract

The present case study aims to verify the performance of the multi-phase multi-layer mechanistic dermal absorption (MPML-MechDermA) model implemented within the Simcyp Simulator V17 in terms of prediction of local tissue concentrations after topical application.

Acitretin, a second-generation retinoid, was used as a model drug. The input data included skin physiology parameters, acitretin physicochemical parameters relevant to skin permeation as well as volume of distribution and plasma clearance. No parameters were adjusted/fitted to match the clinical data, as the objective was "bottom up" prediction. The simulation results show that the MPML MechDermA model can predict the local dermal concentrations of acitretin reasonably well.

Background

Acitretin, the aromatic synthetic retinoid acid derivative, has been indicated for the treatment of severe psoriasis which includes erythrodermic and pustular types. In the early nineties, Surber *et al.* explored the potential of topical delivery of acitretin and carried both *in vitro* and *in vivo* studies investigating its dermal penetration kinetics. Availability of such data sets presents the opportunity to verify the prediction ability of novel PBPK models in terms of local tissue exposure.

Methods

The MPML MechDermA model accounts for longitudinal diffusion and distribution processes that consider skin physiology-related parameters and drug/formulation-specific parameters.

Input data of acitretin included physicochemical molecular weight (MW) = 192.19, acid-base dissociation constant (pKa) = 5.01, logP = 6.4, fusc = 0.09, fraction non-ionized skin (fniskin) surface = 0.39, intravenous plasma clearance (CL_{IV}) = 9.98 L/h, volume of distribution at steady state (V_{ss}) = 0.42 L/kg, surface skin pH=5.5, Site of application = back, and dose = 0.1485 mg. The vehicle used in the clinical study (Surber *et al.*, 1993) was isopropyl myristate (IPM).

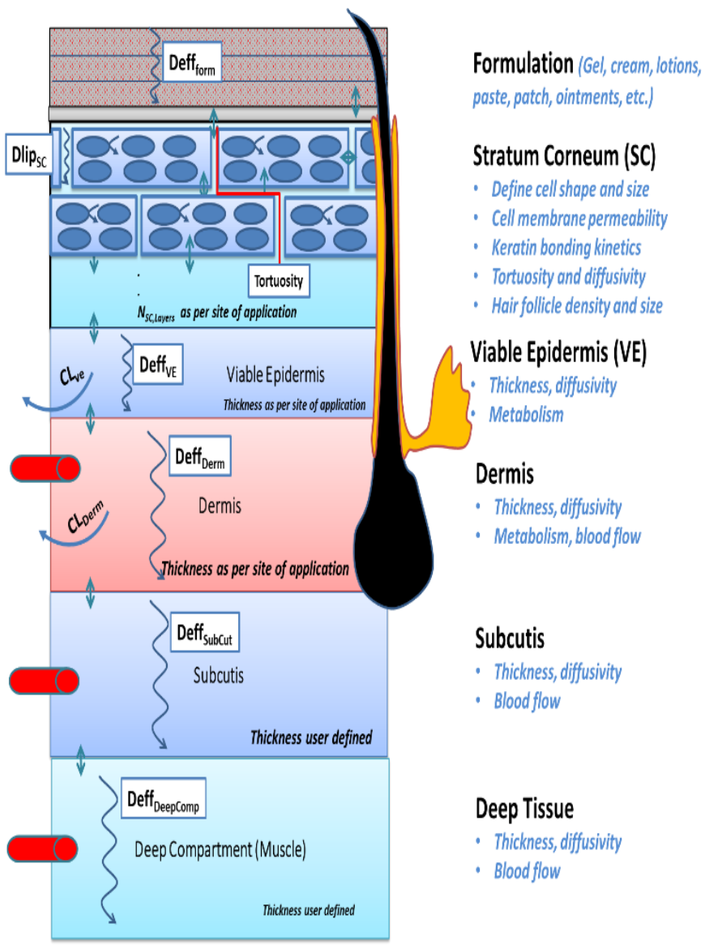

Figure 1. MPML MechDermA Model Structure

Different partition and diffusion coefficients of acitretin through various skin layers were predicted by a multitude of QSARs incorporated within the PBPK model (Table 1). The SC lipid : vehicle partition coefficient was estimated from the ratio of the SC : water partition coefficient (predicted by QSAR, Hansen 2013) to the IPM : water partition coefficient (calculated using the saturation solubility of acitretin in IPM, 330 µg/mL, and water, 0.073 µg/mL, Surber *et al.*, 1991).

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Methods

Table 1 QSAR Prediction of Acitretin Diffusion and Partition Coefficients through various skin layers from isopropyl myristate solution formulation

	Parameter	QSAR Prediction	QSAR Method
Partition Coefficient	Lipid: IPM	5.66	Calculated
	Lipid: water	25619	Hansen 2013
	Sebum: vehicle	15781.3	Valiveti 2008
	VE:SC	83.95	Kretsos 2008
	Skin:blood	1	Shatkin and Brown 1991
Diffusion Coefficient (cm^2/h)	SC lipid	5.58×10^{-7}	Mitragotri 2003
	VE	1.85×10^{-5}	Kretsos 2008
	Dermis	1.85×10^{-5}	Kretsos 2008
	Sebum	0.00055	Johnson 1996
	IPM vehicle	0.0079	Scheibel 1954
Keratin Binding		Steady state	

Results

The results of the simulations are presented in Table 2 and Figure 2.

Table 2 Comparison of the Observed and Simulated Acitretin Concentration (mean ± S.D.) after topical application of acitretin

Type of Biopsy	OBS (ng/g of tissue)	PRED (ng/g of tissue)	FE
Punch	155 ± 150	92 ± 106	0.6
Shave	358 ± 160	363 ± 402	1.01

Abbreviations: FE, fold error; OBS, observed value; PRED, predicted value

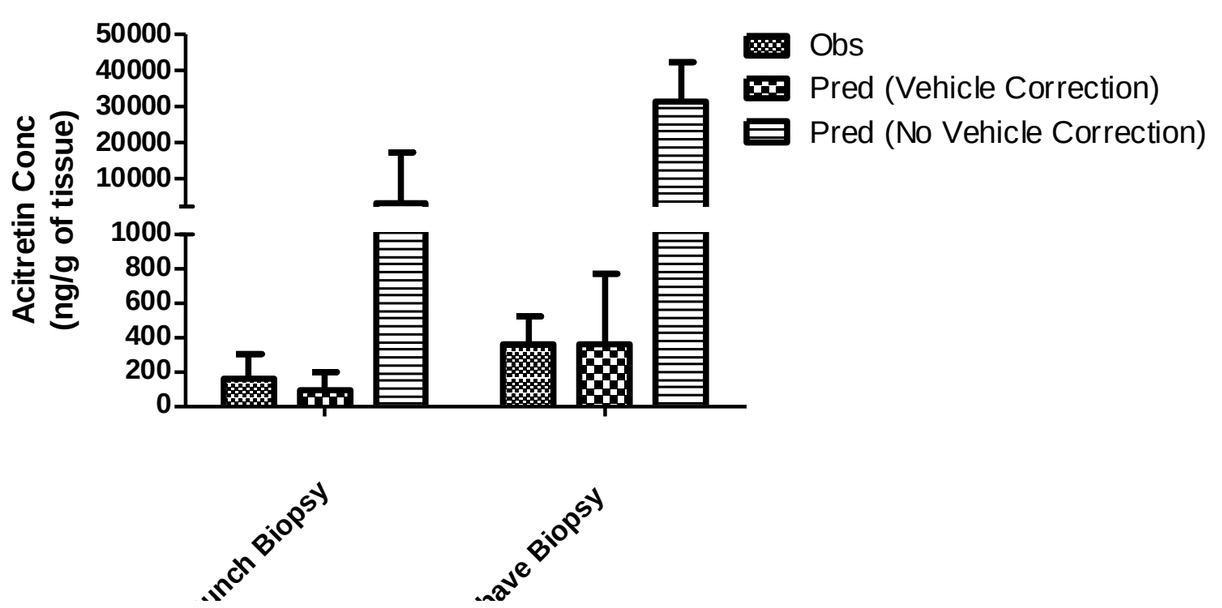

Figure 2 Observed and Simulated Acitretin Concentration After Topical Application. Error bars represent the standard deviation

Conclusions

- The simulation results show that the MPML MechDermA model can predict the local dermal concentrations of acitretin reasonably well following topical administration.
- Population simulations were able to capture the variances observed in the amount of acitretin per gram of skin tissue *in vivo*.
- Huge over-prediction of dermal concentration in absence of vehicle correction. Inclusion of the effect of the vehicle by determining the SC lipid: vehicle partition coefficient was important to correctly capture the dermal absorption of acitretin.

References

1. Surber C, Wilhelm KP, Bermann D, Maibach HI. Pharmaceutical research. 1993 Sep 1; 10(9):1291-4.
2. Surber C, Wilhelm KP, Maibach HI. 1991 Dec; 43(12):836-40.