Modeling *in vitro* skin permeation experiments to mechanistically understand *in vivo* dermal absorption: Application of *in vitro-in vivo* extrapolation (IVIVE) and physiological based pharmacokinetic (PBPK) modeling using testosterone as model drug

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Background

IVIVE combined with PBPK modeling has increasingly been utilized for the prospective prediction of human pharmacokinetics in drug discovery and development. The present work illustrates an approach to derive key kinetic parameters from in *vitro* skin permeation (IVPT) experiments and parameterize multi-phase multi-layer mechanistic dermal absorption (MPML-MechDermA) model implemented within the Simcyp Simulator V18 to predict human pharmacokinetics of model drug testosterone following topical administration.

IVIVE (*In vitro-in vivo* extrapolation)

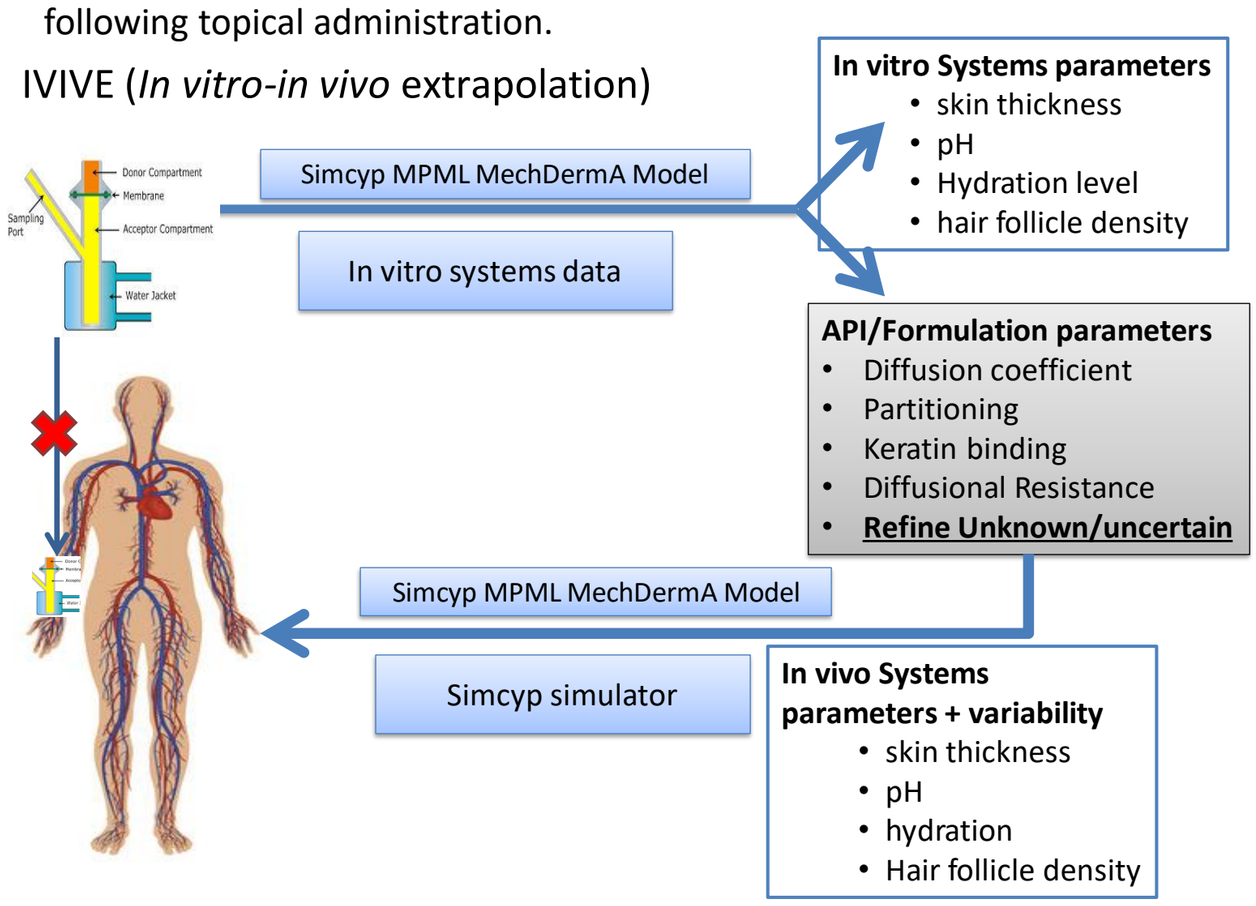

Fig 1. Simcyp IVIVE: Translating *in vitro* permeability to clinical situations

Methods

IVPT and *in vivo* exposure data used in this study was obtained from literature [1-3].Input data for testosterone included physicochemical MW 288.24, LogP 3.32, plasma clearance CL_{IV} 40.83 L/h (for *in vivo* predictions), volume of distribution V_{ss} 25.57 L/kg (predicted by Rodgers and Rowland Method), and the surface skin pH 5.5. For the simulation of the IVPT setup for skin permeation experiments, MPML MechDermA Model was adapted in terms of skin thickness (subcutis and muscle compartments were removed) and blood flow to dermis is set to mimic fluid flow in the *in vitro* setup. The drug get accumulated in the blood compartment.

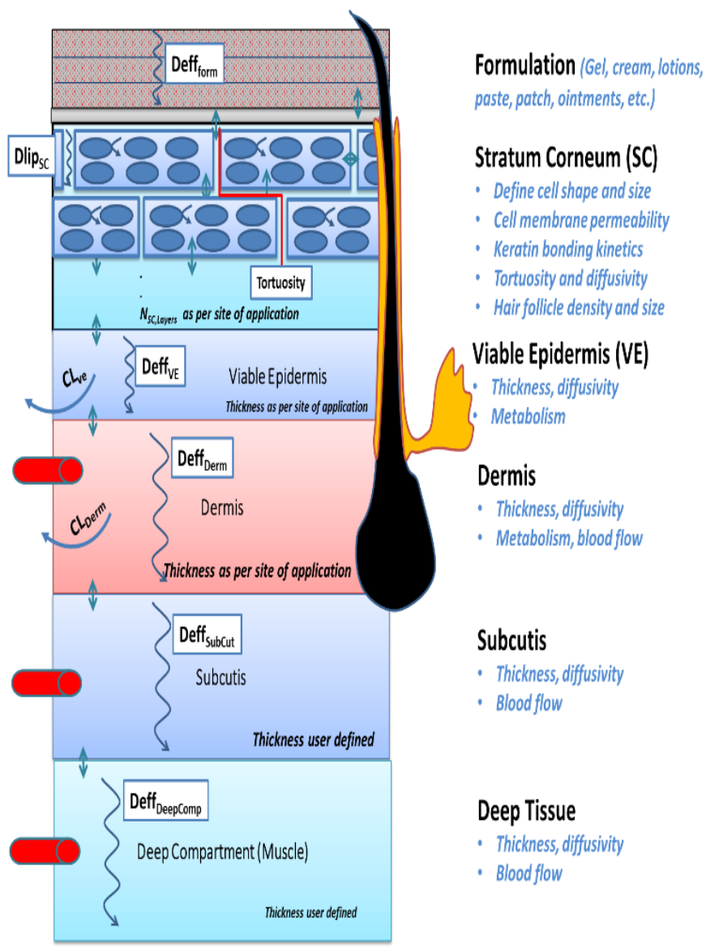

Fig 2. MPML MechDermA Model Structure

All kinetic parameters such as partition and diffusion coefficients through various layers of skin were either determined experimentally or predicted by QSAR (Table 1) except diffusional path length of testosterone through stratum corneum which was fitted against the *in vitro* cumulative permeation vs time profile reported by Bronaugh et al 1986. These parameters were then used as such to predict *in vivo* systemic exposure profiles of testosterone following topical administration by replicating the study design mentioned in the publications [1-3].

Methods

Table 1 QSAR Prediction of Testosterone Diffusion and Partition Coefficients through various skin layers

	Parameter	QSAR Prediction/ Experimental	QSAR Method
Partition Coefficient	Stratum Corneum: Vehicle	52	Experimental
	Sebum: vehicle	2170.74	Valiveti 2008
	VE:SC	10.15	Calculated
	Skin:blood	2.74	Shatkin and Brown 1991
Diffusion Coefficient (cm^2/h)	SC lipid	4.75×10^{-4}	Johnson 1996
	VE	8.8×10^{-4}	Modified Chen 2015
	Dermis	8.8×10^{-4}	
	Sebum	0.00059	Johnson 1996
Diffusional Resistance	Tortuosity	743.95	Fitted (*IVPT*)
Keratin Binding		Steady state	

Results

The results of the simulations are presented in Table 2 and Figure 3.

Table 2 Observed and Simulated exposure data of testosterone from *in vitro* and *in vivo* skin permeation studies by Bronaugh et al 1986

Parameter	% Dose/h (maximum)		% Absorbed	
	Observed	Simulated	Observed	Simulated
In vitro	1.8 ± 0.2	2.02	41.4 ± 6.8	45.86
In vivo	2.1 ± 0.3	1.68	49.2 ± 4.7	44.10

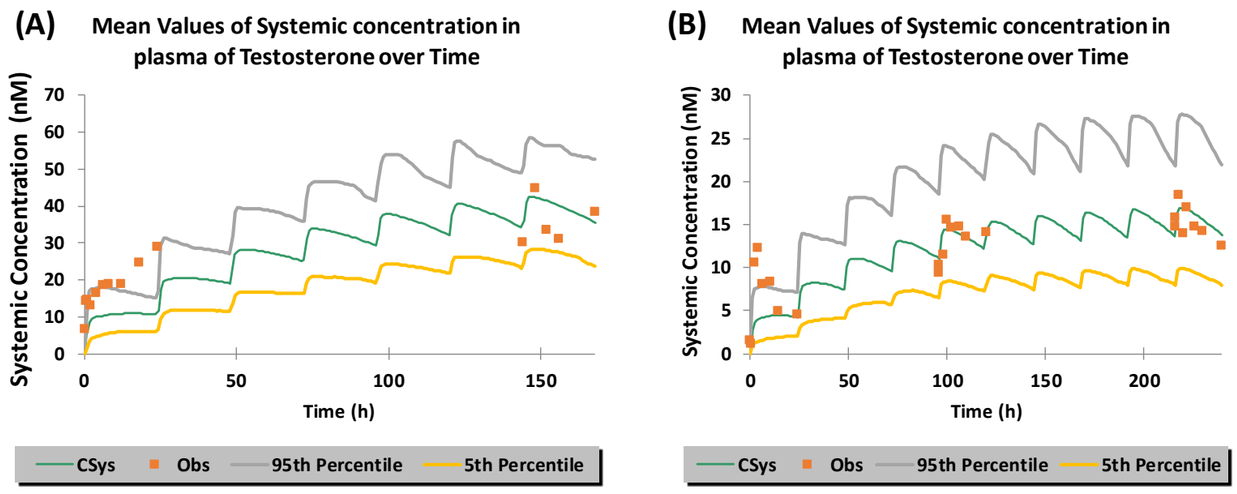

Fig 3. Observed and Simulated exposure data of testosterone from *in vivo* skin permeation studies (A) Wang et al 2000 and (B) Rolf et al 2002

Conclusions

- MPML MechDermA model can be modified to mimic *in vitro* flow through skin permeation experiments.
- Mathematical modeling of *in vitro* permeation experiments can provide understanding of the underlying mechanisms of skin permeation which could be translated to *in vivo*.
- Key kinetic parameters derived from IVPT experiments can be used to parameterize the *in vivo* MPML-MechDermA model which can improve confidence in the prediction of systemic exposure of topically applied drug products. This approach warrants more exploration with other molecules with different physico-chemical properties.

References

1. Bronaugh et al 1986, British Journal of Dermatology (1986) 115, I - II
2. Wang et al, JCE & M, 2000 Vol 85, No 3
3. Rolf et al, European Journal of Endocrinology (2002) 146 673–679