Simulating the Dermal Permeation of Clobetasol-17 Propionate from a Topical Formulation

Poster 301

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Introduction: By integrating systems of rate equations, the Transdermal Compartmental Absorption & Transit (TCAT) Module™ in GastroPlus® (Simulations Plus, Inc) simulates the dynamics of topical and transdermal dosage forms and the dermato-pharmacokinetics of small molecules delivered from them. As part of an effort to expand the module's existing capabilities, we have developed models for a range of small molecules in various formulations. Here, we describe our work on clobetasol-17 propionate (CP).

Methods: The TCAT Module uses well-mixed compartments and diffusive exchange pathways to describe skin permeation following application of a formulation to the skin surface (Figure 1). Concentration gradients compartments can be approximated by dividing compartments into sub-layers (n), and skin permeation can be linked to minimal or whole body PBPK model.

We simulated clinical results for an emulsion-based formulation of the immuno-suppressive steroid cobetasol-17 propionate (Dermovate® cream, 0.05% w/w, Glaxo Smith Kline) prescribed for the treatment of psoriasis**.** In the study by Bodenlenz *et al* (1), Dermovate® cream was applied under occlusion to lesional and non-lesional arm skin sites of psoriasis patients for 14 days. On days 1 and 14, application duration was 24 hours; on intermediate days, 4 hours. CP concentrations in dermis interstitial fluid were sampled continuously by open-flow microperfusion (dOFM) on days 1 and 14. Given the complexity of the dosing, we simulated Day 1 results for non-lesional skin.

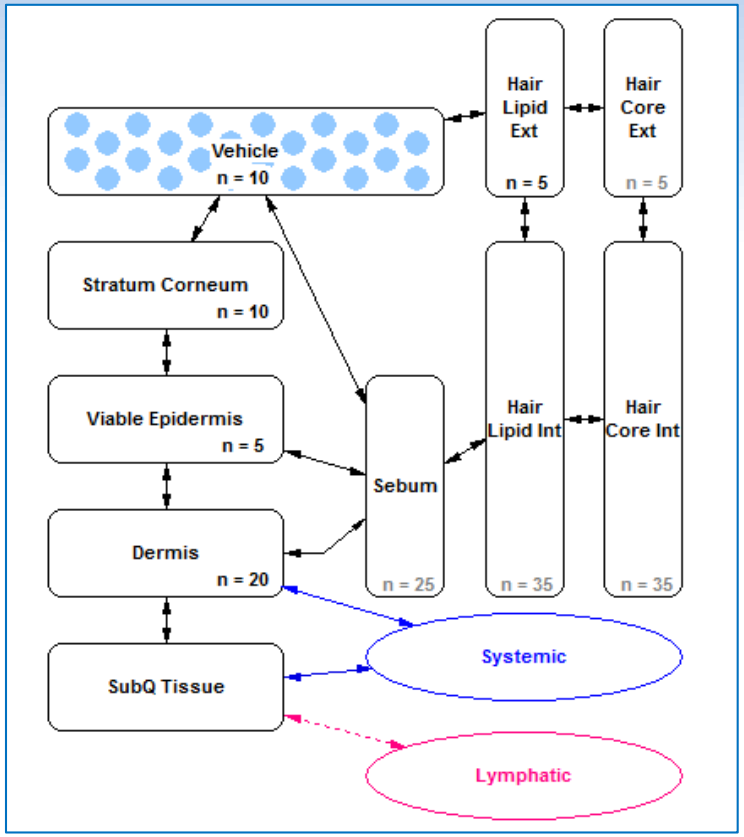

Figure 1. Schematic of the TCAT Module

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Methods (cont): Baseline values of the model input parameters, tabulated below, were defined from publicly available experimental data. We parameterized human arm skin and CP skin permeability using information and QSAR models built into The TCAT Module. dOFM probe depths in the skin of study subjects were measured by ultrasound (mean depth ~ 870 μm; 95% CI ~ ± 90 μm) (1).

Parameter	*Value*	*Units*	*Source*
Cream composition			AYB Fauzee, MS Thesis, Rhodes University, 2011[A]
CP content	0.5	mg/g cream	CLOBEX® (clobetasol propionate) Lotion package insert
Dispersed phase volume fraction	0.243		Calculated from the composition
CP solubility in water	4.06E-03	mg/mL	KW Kasongo MS Theses, Rhodes University, 2007[B]
CP cont phase solubility	0.396	mg/mL	"
Cont phase / water partition coeff, $K_{cont,w}$	97.6		Calculated as the ratio of the respective solubilities
Disp phase / water partition coeff, $K_{disp,w}$	3162		Calculated as $K_{o,w} = 10^{LogP}$ (*LogP* = 3.5, PubChem)
"	357		Alternate value: $K_{veg\ oil,w} = 1.115*LogP - 1.35$[C]
CP Diffusivity in water, D_w	5.90E-06	cm^2/s	ADMET Predictor 9.5, Simulations Plus
CP Effective diffusivity in cont phase, D_{eff}	2.47E-08	"	Calculated from *in vitro* release data using Higuchi's eqn[A,D]
CP diffusivity in the disp phase, D_{disp}	4.25E-09	"	Extrapolated from cyclic voltammetry data on ferrocene[E]
Disp phase droplet radius, r_{disp}	1.89	μm	A typical value
Evaporation time	NA	h	dOFM studies were done under occlusion
CP permeability - Stratum corneum	1.91E-07	cm/s	Wilschut, A *et al*, Chemosphere 30(7): 1275-96, 1995
CP permeability - Viable epidermis	1.44E-04	"	Kretsos, K, *et al*, Int J Pharm 346(1-2): 64-79, 2008
CP Permeability - Dermis	7.83E-06	"	"
CP permeability - Sebum hair	1.53E-05	"	Yang S, Lian G, *et al*, J Ph Sci, 108(9): 3003-10, 2019
CP bound in VE & Dermis	83.7	%	Kretsos, K, *et al*, Int J Pharm 346(1-2): 64-79, 2008
Dermis clearance model			Ibrahim, R *et al*, J Pharm Sci 101(6): 2094-2108, 2012
A: https://core.ac.uk/download/pdf/145045772.pdf			
B: https://core.ac.uk/reader/145042966			
C: Leo, A, Hansch, C, *et al* (1971), Chem Rev 71(6): 525-616, 1971			
D: Siepmann, J & Peppas, NA, Intl J Pharm 418: 6-12, 2011			
E: Zhang J, Michniak-Kohn B, Int J Pharm, 12;421:34-44, 2011			

Table1. Model input parameter values and their sources or derivations

Results

Results of our initial simulation, matched to clinical dose and applied area, are shown in Figure 2. Calculated unbound CP concentrations in dermis sub-layer 14 (corresponding to the average depth of measurement) were within 2-3 fold of the measured values and tracked the initial rise in mean dermis concentrations fairly well. But, the simulations also predicted more protracted CP delivery than suggested clinically, with time to steady state ~ 72h, by which time ~ 0.5% of the dose had been absorbed.

Bodenlenz *et al* also reported values of CP $AUC_{0\text{-}24h}$ on Day 1 for individual subjects. These are plotted in Figure 3 vs. measured skin

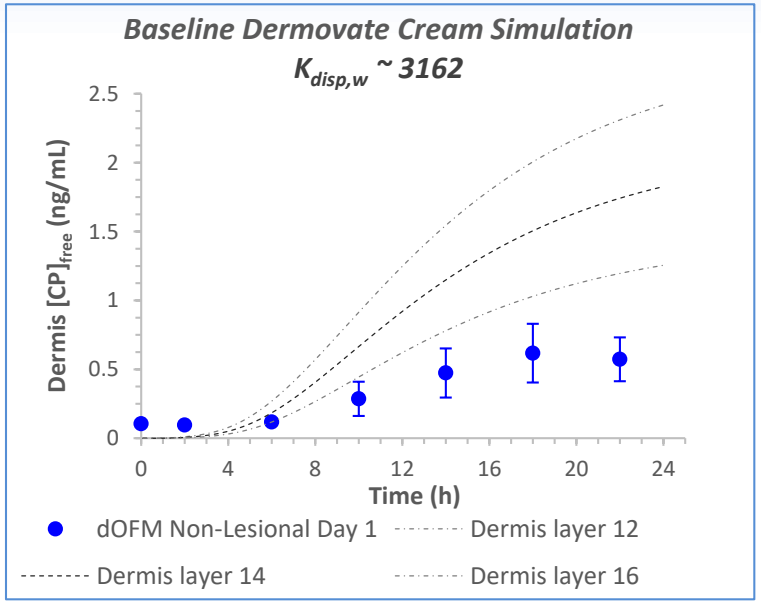

Figure 2. Predicted (---) and mean observed (•) dermis [CP]. In the human arm skin physiology, sub-layers 12-16 covered skin depths of 760-980 μm

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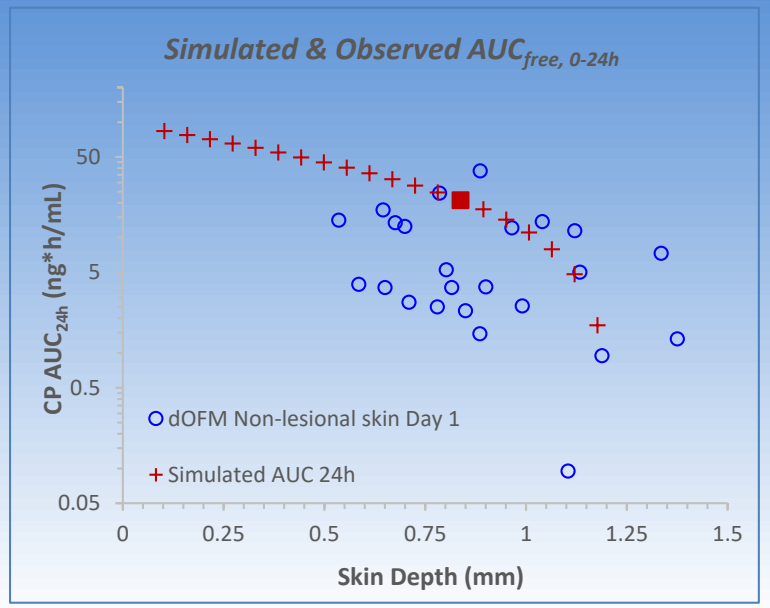

Figure 3. Simulated (+) and observed (○) CP $AUC_{0\text{-}24h}$ on Day 1

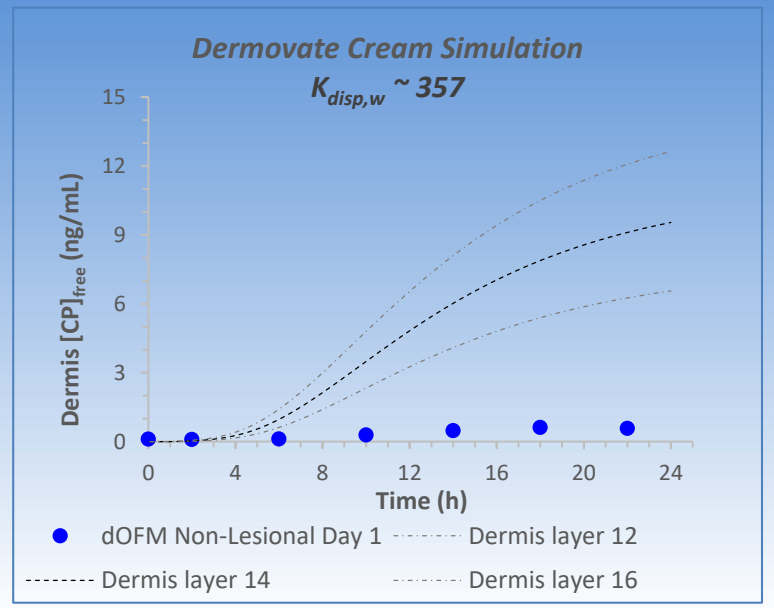

Figure 4. The same plot as Figure 2, but from simulating a less hydrophobic dispersed phase

Results (cont)

depth, along with the predicted values of $AUC_{0\text{-}24h}$ for dermis sub-layers 1-20. The latter passed through the upper range of the observed values, but displayed a steeper spatial gradient over the entire dermis than suggested by the clinical results. By setting their CP permeabilities to zero, we estimated the contribution of the sebum / hair pathways, to $AUC_{0\text{-}24h}$ in sub-layer 14 to be ~ 20%.

A measured value of CP solubility in the dispersed phase was unavailable. Hence, we explored an alternate value for $K_{disp,w}$: $K_{veg\ oil,\ w}$ instead of $K_{o,w}$ (Table 1). Figure 4 plots these simulation results. Free CP concentrations in the dermis increased just over 5-fold, the same factor by which CP fractional saturation in the formulation increased. The shape of the simulated CP dermis profiles was unchanged. Additional sensitivity analyses revealed weak dependence of dermis CP profiles on D_{eff}, D_{disp} and r_{disp}, indicating that the kinetics of CP delivery were controlled primarily by skin permeability.

Conclusions

Using the TCAT Module in GastroPlus, we have developed a model of CP skin permeation. Through careful determination of input parameter values, the model simulated published clinical data with moderate accuracy. The limited data precluded confirmation of the model over broader spatial and temporal ranges. Nonetheless, sensitivity analyses of formulation parameters indicated greater dependence of CP delivery on emulsion thermodynamics (CP solubilities in continuous and dispersed phases) than on kinetics (effective CP diffusivity, and the rate of CP diffusive exchange between phases) or drug product microstructure (r_{disp}). Thus, this work exemplifies a role for modeling and simulation in the rational design of complex topical and transdermal formulations.

References: M Bodenlenz, C Dragatin, L Liebenberger *et al*, *Pharm Res* **33**, 2229-38 (2016)

Acknowledgements: Funding for this project was made possible, in part, by the US FDA through grant 1U01FD006526-01. Views expressed here do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices or organization imply endorsement by the United States Government.