Computational Simulation of Complex Dermal Topical Formulations

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PURPOSE

By integrating systems of rate equations, the Transdermal Compartmental Absorption & Transit (TCAT) Model in GastroPlus® (Simulations Plus, Inc) simulates the dynamics of topical and transdermal dosage forms and the dermato-PK of compounds delivered from them. As part of an effort to expand the model's capabilities, we have developed case studies for several small molecules in gel and micro-emulsion formulations. Here, we describe our work on the steroid, clobetasol-17 propionate (**CP**).

OBJECTIVE

We simulated clinical results for an oil-in-water micro-emulsion formulation of CP (Dermovate® cream, 0.05% w/w, Glaxo Smith Kline) prescribed for the treatment of psoriasis and other inflammatory skin diseases. In the study by Bodenlenz *et al* (1), Dermovate cream was applied for 14 days under occlusion to lesional and healthy arm skin sites of psoriasis patients. CP concentrations in dermis interstitial fluid were sampled continuously by open-flow micro-perfusion (dOFM, **Figure 1**) on days 1 and 14. dOFM probe depths in the skin of study subjects were measured by ultrasound, with mean depth ~ 870 µm and 95% CI ~ 90 µm. After calibrating a baseline model, we explored the sensitivity of CP delivery to a range of formulation characteristics.

METHODS

The TCAT model uses well-mixed compartments and diffusive exchange pathways to describe skin permeation following application of a formulation to the skin surface (**Figure 2**). Concentration gradients in the skin can be treated by dividing compartments into sub-layers (***n***), and skin permeation can be linked to systemic PK models via blood and lymph perfusion.

Baseline values of the model input parameters, (**Table 1**), 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 Model.

RESULTS

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

Bodenlenz *et al* also reported values of dermis CP $AUC_{0\text{-}24h}$ on Day 1 for individual subjects. These are plotted in **Figure 4** vs. probe depth, along with predicted CP $AUC_{0\text{-}24h}$ for each dermis sub-layer. Simulated values passed through the upper range of the observed values, but displayed a steeper slope than suggested by the clinical results. We estimated the contribution of the sebum / hair pathways to $AUC_{0\text{-}24h}$, to be ~ 20%, by taking the difference between the baseline simulation and one in which these pathways were excluded.

As hydrophobic excipients of the o/w ME are varied, CP solubility in the dispersed phase may change. We explored the implications of this for a range of plausible values: $K_{veg\ oil,\ w} \leq K_{disp,w} \leq K_{o,w}$ (**Table 1**). Results are shown in **Figure 5**. As $K_{d,w}$ increased, CP solubility in the formulation as a whole also increased, reducing CP fractional saturation, the driving force for skin permeation. Further analyses (results not shown) indicated moderate dependence of dermis [CP] on φ_{disp}, and slight dependence on D_{eff}, D_{disp} and r_{disp}. The latter results are due to CP permeation through the skin being controlled primarily by the *stratum corneum*.

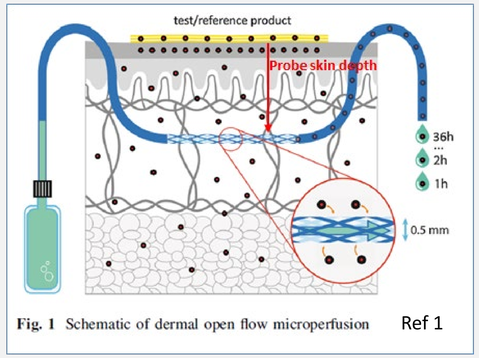

Fig. 1 Schematic of dermal open flow microperfusion Ref 1

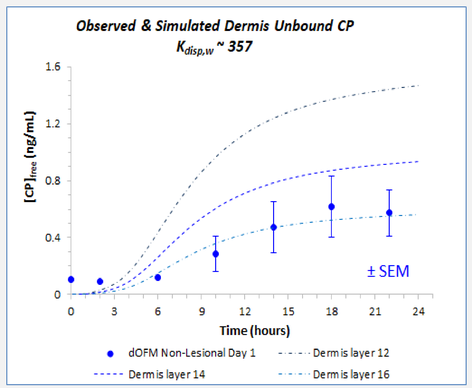

Figure 3. Predicted (---) and average of observed (•) [CP] in dermis interstitial fluid on day 1. Sub-layers 12-16 covered skin depths of 760-980 µm

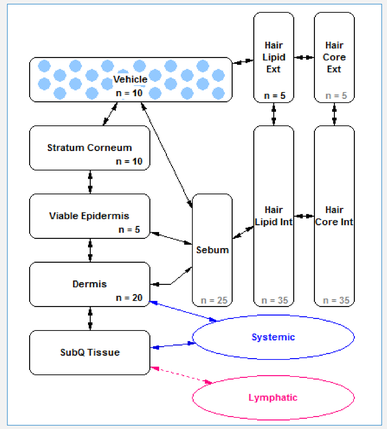

Figure 2. Schematic of the TCAT Module

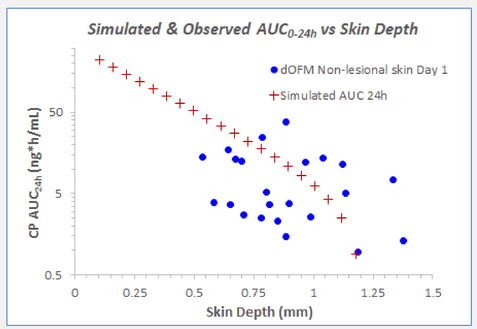

Figure 4. Free CP AUC_{24h} in dermis sub-layers 1-20 (+) plotted along with Day 1 AUC_{24h} measured for each subject (●) *vs* dOFM probe depth

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, $K_{disp,w}$	357		Baseline value: $K_{veg\ oil,w} = 1.115*LogP - 1.35$[C]
"	3162		Alternate value $K_{o,w} = 10^{LogP}$ ($LogP$ = 3.5, PubChem)
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}	2.61E-08	"	From *in vitro* release data using Higuchi's eqn[AD]
"	4.50E-09		From *in vitro* release data using a short time approx[AD]
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

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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

Table 1. Model Input Parameters - Baseline Values and Their Sources

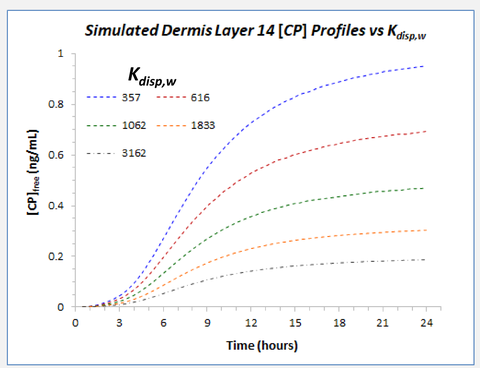

Figure 5. Dermis $[CP]_{free}$ *vs* dispersed phase - water partition coefficient. Min value = $K_{veg\ oil,w}$; Max = $K_{o,w}$

CONCLUSIONS

Using the TCAT Module in GastroPlus, we developed a model of CP skin permeation. Through careful determination of input parameter values, the model simulated published clinical data with reasonable 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 that modeling and simulation can play in the rational design of complex topical formulations.

REFERENCES

M Bodenlenz, C Dragatin, L Liebenberger *et al*, **Kinetics of Clobetasol-17-Propionate in Psoriatic Lesional and Non-Lesional Skin Assessed by Dermal Open Flow Micro-perfusion with Time and Space Resolution.** *Pharm Res* **33**, 2229-38 (2016)

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