SimulationsPlus

MIDD+22

Model Informed Drug Development

In Silico QbD for Dermal Topical Formulations via TCAT Model Simulations

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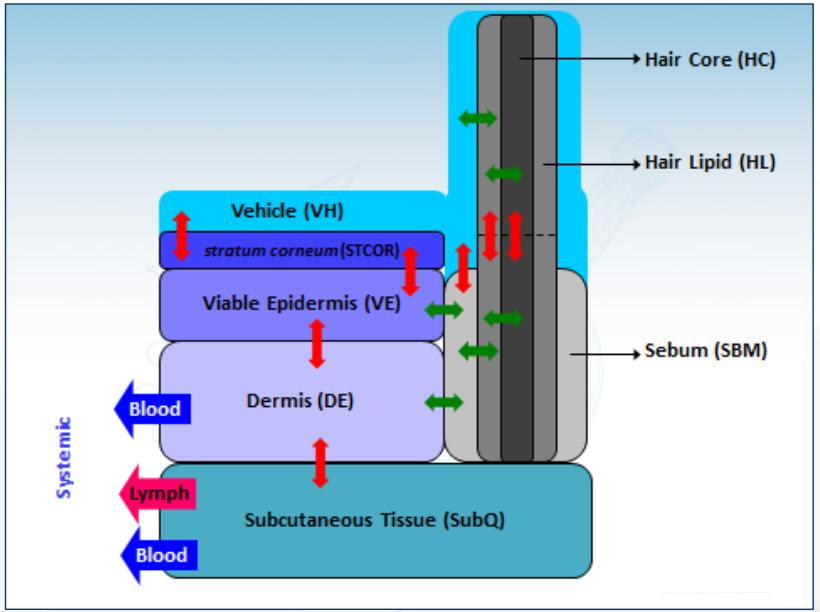
Please note: this presentation, including questions from the audience, is being recorded and may be made available.

PBPK Simulations to Support Dermal Formulation Design

- The composition of dermal topicals can affect the absorption of APIs through formulation attributes such as API solubility / diffusivity, excipient volatility, and rheology
- Critical quality attributes (CQAs) determine whether an API reaches therapeutic / toxic concentrations locally or systemically, and whether test formulations are bioequivalent to a reference formulation
- PBPK models that simulate the mechanisms by which these attributes influence dermal absorption can inform formulation development, reducing the need for animal and human testing

TCAT Model PBPK Simulations of Skin Permeation

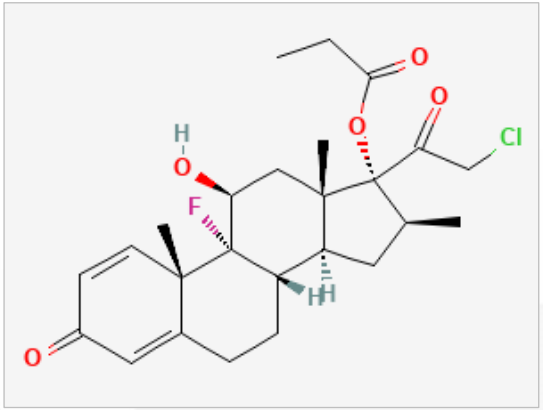
- The Transdermal Compartmental Absorption and Transit™ (TCAT) Model is a physiologically-based mathematical model in GastroPlus™ that simulates the dermal and systemic ADME-PK of topically applied compounds
  - The TCAT Model comprises well-mixed compartments and material exchange pathways
  - Concentration gradients within compartments can be treated by dividing them into sub-layers ($1 \leq n \leq 20$)
  - Skin permeation can be linked to systemic PBPK models via blood and lymph perfusion



- Designed experiments can be simulated by conducting parameter sensitivity analyses (PSA) to identify CQAs and quantify their role in local and systemic delivery

A Case Study: Clobetasol-17 Propionate

- Clobetasol-17 propionate (CP) is a highly potent glucocorticoid used topically to treat inflammatory skin conditions such as psoriasis and eczema
- CP is hydrophobic, of low aq solubility (~4 μg/mL) and P_{SC} largely controls its overall skin permeability
- We developed a model for CP formulated as an O/W ME (Dermovate Cream®) and used it to explore the role of formulation attributes in CP skin permeation
- When applied in such formulations (O/W ME), the dispersed phase can act as a reservoir to maintain CP concentrations in the aqueous continuous phase



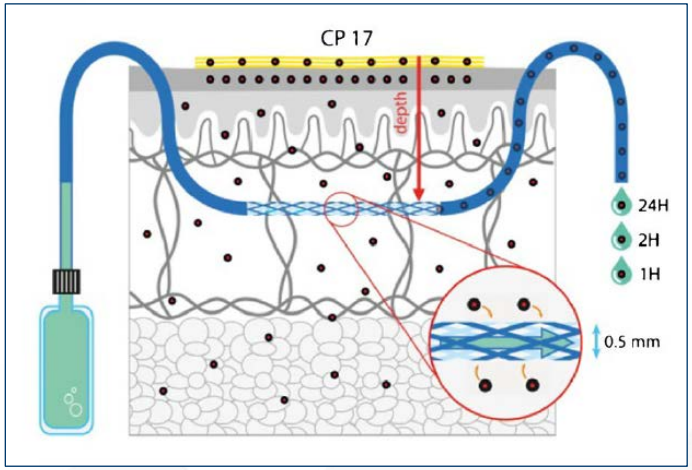
MW ~ 467 amu
Log P ~ 3.5 (experimental)
P_{SC} ~ 1.5e-7 cm/s (QSPR *stratum corneum* permeability)

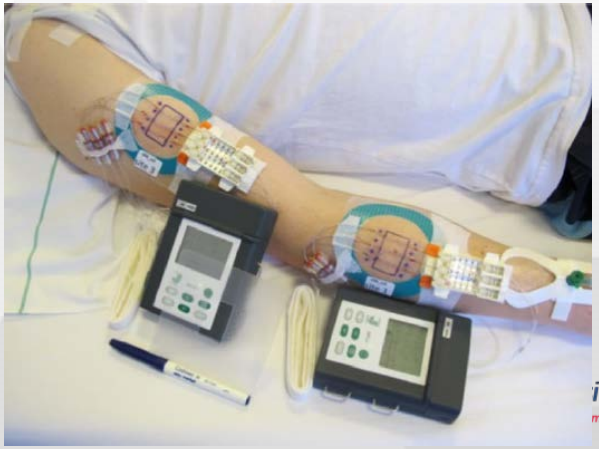
https://pubchem.ncbi.nlm.nih.gov/compound/32798

https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/019322s018lbl.pdf

Measuring CP Concentrations in the Dermis

- We simulated the results from Day 1 of a clinical study reported by Bodenlenz *et al*
- Dermovate was applied daily for 14 days to a lesional and a healthy arm skin site for each of 8 psoriasis patients
- Application for 24h on Days 1 and 14; 4h application on Days 2-13
- Dermis concentrations of CP were measured continuously via dermal open flow microperfusion (dOFM) on Days 1 and 14
- Probe skin depth was measured by ultrasound
- Geometric mean dOFM probe skin depth ~ 860 μm (95% CI ± 90 μm; range 535 - 1136 μm)





Bodenlenz, M, et al. *Pharm Res.* 33 (9); 2229–38, 2016

Baseline Model for Dermovate Cream

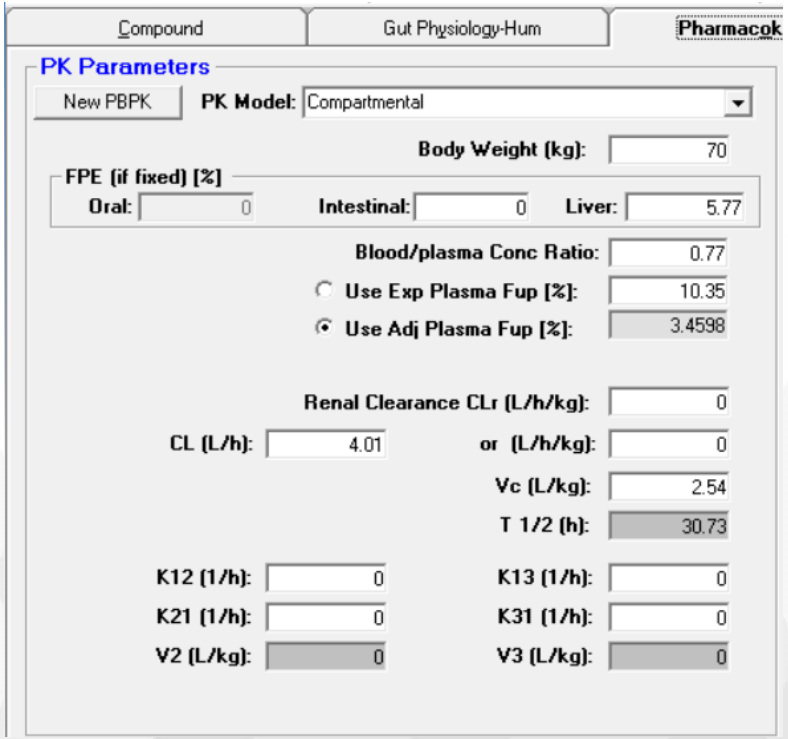
- Information on Dermovate Cream biopharmaceutic properties was obtained from several sources and used to estimate the values of model input parameters that describe the formulation
- We used QSPR models and standard equations in the TCAT Model to estimate CP permeability in the skin compartments, and protein binding in the viable epidermis (VE) and dermis

cont: continuous phase; ***disp***: dispersed phase
D_{eff}: effective diffusivity in the continuous phase
D_{disp}: diffusivity in the dispersed phase
D_w: aqueous diffusivity
φ_{disp}: volume fraction of dispersed phase in formulation
$K_{cont,w}$: partition coefficient between continuous phase and water
$K_{disp,w}$: partition coefficient between dispersed phase and water
P_{SC}: permeability in the stratum corneum
P_{VE} & P_{dermis}: permeability in the viable epidermis and dermis
P_{sebum}: permeability in the sebum

Parameter	Value	Units	Source
CP content	0.5	mg/g cream	Dermovate® Cream 0.05%, GSK Pharma GmbH, Vienna, Austria
φ_{disp}	0.243		AFB Fauzee and KW Kasongo, MS Theses,
CP aqueous solubility	4.06E-3	mg/mL	Rhodes University, 2011 and 2007
CP solubility cont phase	0.396	mg/mL	"
$K_{cont,w}$	97.6		Ratio of continuous phase and water solubilities
$K_{disp,w}$	357		Log $K_{veg\ oil,w}$ = 1.115*LogP - 1.35 (LogP ~ 3.5, ADMET Predictor 10.3)
CP D_w	5.90E-6	cm^2/s	Estimated via ADMET Predictor 9.5
CP D_{eff}	2.61E-08	"	Higuchi eqn analysis of IVRR data in AFB Fauzee, MS Thesis, Rhodes University, 2011
CP D_{disp}	4.25E-9	"	Zhang and Michniak-Kohn, Int J Pharm 421(1), 2011: 34–44
Droplet radius (r_d)	1.89	µm	Set to ½ of d_{50} measured for Zovirax cream
P_{SC}	1.91E-7	cm/s	Wilschut, A *et al*, Chemosphere 30(7): 1275-96, 1995
P_{VE} & P_{dermis}	1.44E-4, 7.83e-6	"	Kretsos, K, Kasting, GB *et al*, Int J Pharm 346(1-2): 64-79, 2008
CP bound in VE & Dermis	84	%	"
P_{sebum}	1.53e-5	cm/s	Yang S, Lian G *et al*, J Ph Sci, 108(9):3003-10, 2019

Compartmental Model for CP Systemic PK

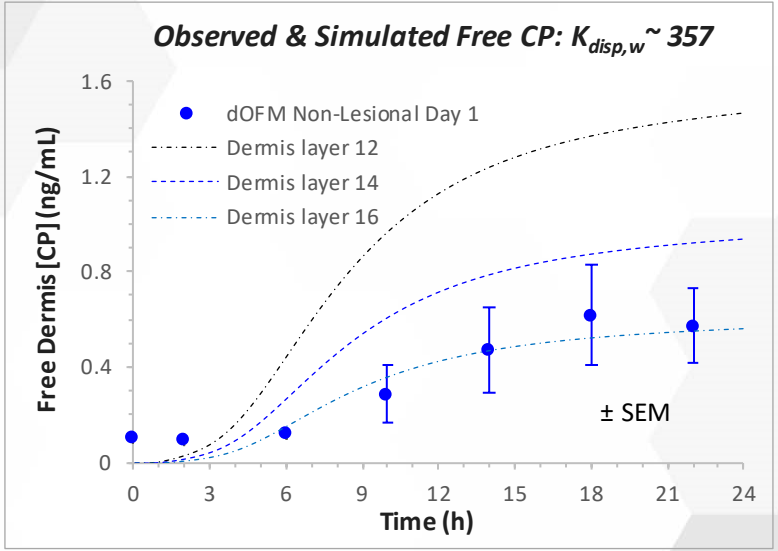
- Detailed human systemic PK for CP seems to be unavailable (CP is indicated solely for topical use)
- Systemic PK was simulated by a one-compartment model, with *CL*, V_d, $F_{u,p}$ and blood/plasma ratio estimated from 2D structure via ADMET Predictor
- The model for API exchange between dermis and systemic circulation was adapted from Ibrahim, Nitsche and Kasting, *J Pharm Sci*, 2012
- Dermis blood flow was set to 9.89 mL/min/g tissue, an average value for human arm skin
- 15 mg/cm^2 Dermovate Cream were applied to 7.7 cm^2 of each subject's two skin sites (58µg CP)
- With these model inputs the body acts as an infinite sink for systemic CP taken up from the dermis and subcutaneous tissue (see Additional Slides)

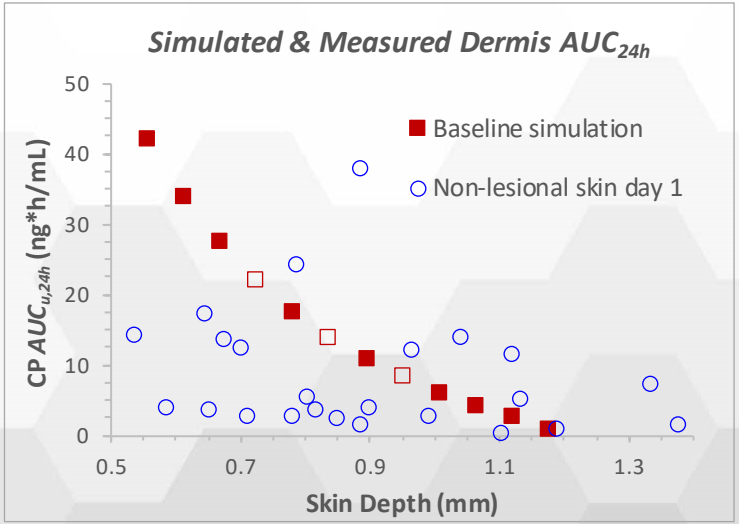


- The model does not account for vasoconstriction induced by CP (see Additional Slides)

Calibrating the Baseline Model

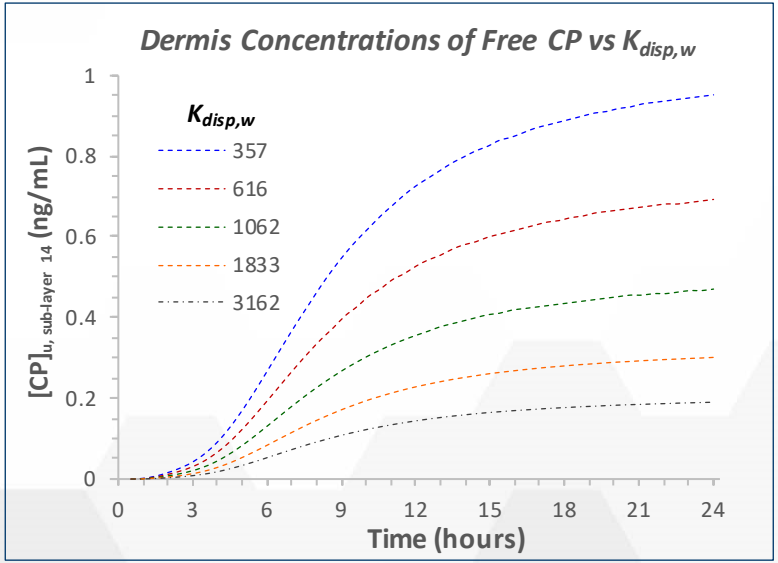
- Dermis sublayers 12-16 covered geometric mean probe depth ± 95% CI (860 ± 92 μm)
- Simulated concentrations of free CP in dermis at mean probe depth were within ~ 2-fold of the group average dOFM values and tracked the initial rise in mean dermis concentrations
- Simulated values of dermis CP $AUC_{0\text{-}24h}$ passed through the upper range of the observed values at each probe depth but displayed a steeper slope than suggested by the clinical results





Sensitivity to CP Dispersed Phase Solubility

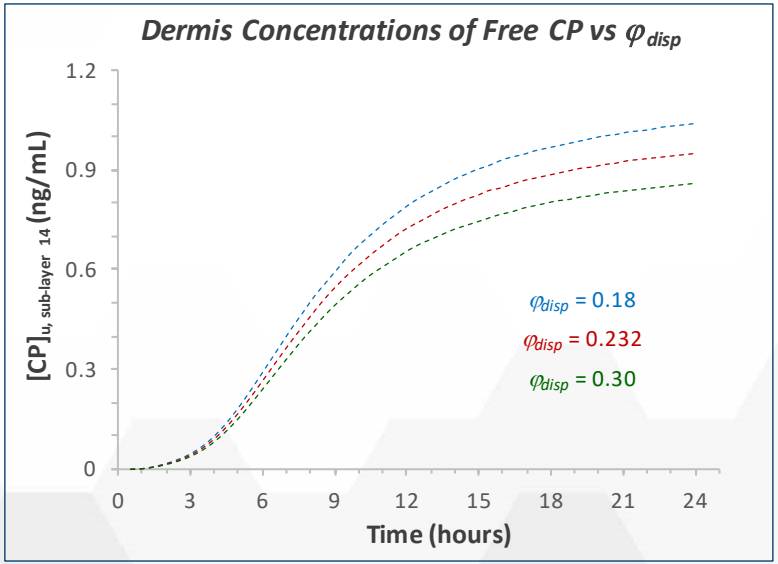
- We studied the effect of CP solubility in the dispersed phase by varying the dispersed phase-water partition coefficient, $K_{disp,w}$
  - One can vary CP solubility by the choice of hydrophobic excipients
  - $K_{disp,w}$ ($\sim c_{sat,disp}/c_{sat,w}$) changes directly with CP oil phase solubility
- We explored values of $K_{disp,w}$ ranging from $K_{veg\ oil,w}$ to $K_{o,w}$ (357 - 3162) while retaining baseline values for all other input parameters
- As $K_{disp,w}$ increases, more CP partitions into the dispersed phase, lowering CP concentrations in the continuous phase, thus reducing the driving force for CP partitioning into stratum corneum (SC)



- The simulations clearly show this, with reductions of dermis concentrations proportional to the relative changes in $K_{d,w}$

Sensitivity to Dispersed Phase Volume Fraction

- We also explored sensitivity of permeation to the dispersed phase volume fraction, φ_{disp}
- Its value was varied ± 25% from the value for Dermovate Cream (0.243)
- In practice, a formulation phase diagram indicates the range of values φ_{disp} can assume without loss of the ME phase structure
- As before, we compared free concentrations of CD in the dermis as φ_{disp} was varied
- Changing φ_{disp} has a similar effect as changing $K_{disp,w}$ – to alter CP concentrations in the continuous phase and thus the driving force for partitioning into SC

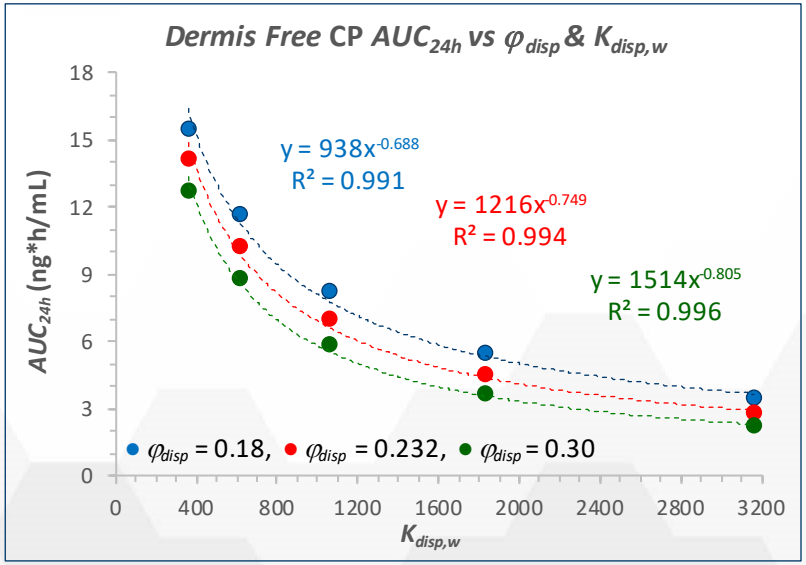


- Physically, changing φ_{disp} affects D_{eff}, CP diffusivity in the ME continuous phase: For φ_{disp} = 0.18, D_{eff} ↑ 35%; for φ_{disp} = 0.30, D_{eff} ↓ 21%
- These changes in D_{eff} have negligible effect on CP permeation, so they were omitted from the simulations

Cheng, SC & Vachon, RI (1969). *Int J Heat Mass Transfer* **12,** 249

Factorial Experimental Design: Simulation of $\varphi_{disp} \otimes K_{disp,w}$

- The combined effects of φ_{disp} and $K_{disp,w}$ on CP skin permeation can be quantified via a coupled (3D) PSA
- The simulation results allowed us to derive a response surface for the effects on AUC_{24h} and support predictions at interpolated values of (φ_{disp}, $K_{disp,w}$)
- The response surface (equation below), is non-linear in both parameters, and sensitivity to (φ_{disp}, $K_{disp,w}$) depends on your location on the surface
- c_1-c_4 are constants, and the adjusted r^2 for the fitted surface ~ 0.98

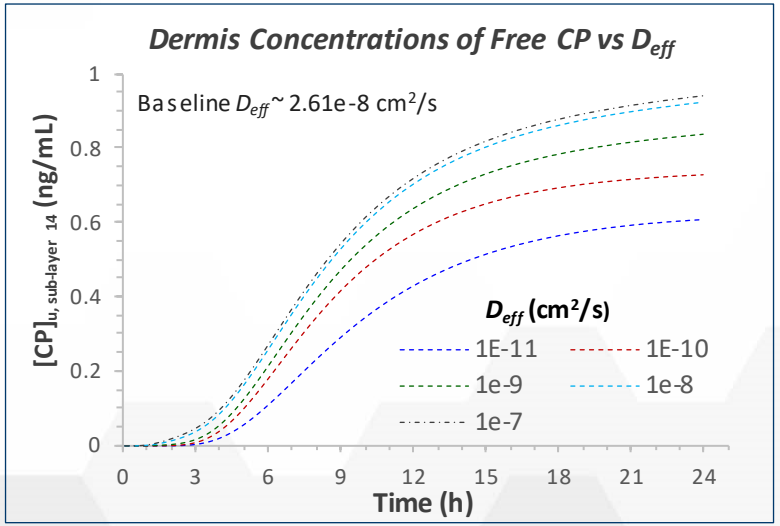


- The PSA was conducted over a broader range of φ_{disp} and $K_{disp,w}$ and in greater detail than might be tractable experimentally

$$AUC_{24h}(\varphi_{disp}, K_{disp,w}) \sim (c_1\varphi_{disp} + c_2)K_{disp,w}^{-(c_3\varphi_{disp}+c_4)}$$

Sensitivity to CP Diffusivity in the Continuous Phase

- Lastly, we discuss the dependence of CP skin permeation on its diffusivity in the ME continuous phase, D_{eff}
- In practice, D_{eff} can changed by
  - Adding a gelling agent to the continuous phase
  - Changing φ_{disp}, the dispersed phase volume fraction
  - Changing D_{disp}, API diffusivity in the dispersed phase
- As in the previous cases, input parameters other than D_{eff} retained their baseline values in this PSA
- Dermis concentrations of free CP depended modestly on D_{eff}: A 10^4-fold reduction produced $\lesssim$ 50% decrease in free CP concentrations at mean probe depth, over 8-24h simulation time



- And a 10-fold change ↕ in the baseline value of D_{eff}, produced ~ 10% change in $[CP]_u$ over 8-24h simulation time

Sensitivity to CP Diffusivity in the Continuous Phase

- This PSA probed the contributions of CP permeability in the continuous phase of the formulation, P_{cont}, and in SC, P_{SC}, to the overall rate of skin permeation
- If $D_{eff} \gtrsim$ 1e-8 cm^2/s, CP permeation through SC is the rate limiting process in skin permeation
- However, as D_{eff} declines, CP transport in the ME continuous phase begins to limit the rate of mass transfer into the SC
- This kinetic effect is mediated through the mass transfer rate boundary condition imposed at the formulation / SC interface‡
- $\boldsymbol{P_{cont} = D_{eff} \cdot K_{cont,w} / h_{cont,n}}$ ($\boldsymbol{h_{cont,n}}$ is the thickness of the skin-contacting formulation sub-layer)
- $\boldsymbol{P_{SC} = D_{SC} \cdot K_{SC,w} / h_{SC,1}}$ ($\boldsymbol{h_{SC,1}}$ is the thickness of the SC sub-layer at the skin surface)

$$dm/dt = \frac{2}{P_{cont}^{-1} + P_{SC}^{-1}} \cdot SA_{cont} \cdot \left(\frac{C_{cont,n}}{K_{cont,w}} - \frac{C_{SC,1}}{K_{SC,w}} \right)$$

‡ Chen T, Lian G and Kattou P. *Pharm Res.* 2016; **33**(**7**):1602-14

Carslaw HS and Jaeger JC, *The Conduction of Heat in Solids*, 2nd Edition, 1959

Conclusions

- PBPK simulation is a promising approach to study the sensitivity of drug absorption and disposition in the skin to changes in the thermodynamic and transport characteristics of the drug formulation
  - Particularly in relation to the rate-limiting steps in API skin permeability
- Sensitivity of drug skin permeation to formulation attributes can be assessed for single parameters, and the combined effects of multiple parameters can be quantified through coupled PSA
  - Bearing in mind the physical co-dependence of parameters
- These approach can inform the design of new formulations, and generic formulations with the goal of achieving bioequivalence
- In addition, combining PSA with virtual trial simulations can provide estimates of sample sizes required to detect differences in formulation performance
  - Essential to have good estimates of the variances in model input parameter values

Thank You!

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The views expressed here do not reflect official policies of the US FDA or DHHS, nor does any mention of trade names imply endorsement by the US Government

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Q&A

Questions & Answers

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Additional Slides

Clobetasol Propionate Systemic PK

- Hehir *et al* have published CP plasma profiles after application of Dermovate cream to the skin of psoriatic patients
- In some patients, plasma levels rose more rapidly than predicted by the model (next slide) perhaps due to inter-subject variability in skin permeability
- Or, in part, due to the large body surface dosed (~ 50%), leading to saturation of
  - Plasma protein binding
  - Metabolizing enzyme capacity
- The CP dose used was 1.3 - 1.6 μg /cm^2, whereas ~ 7.5 μg/cm^2 were applied in the Bodenlenz study

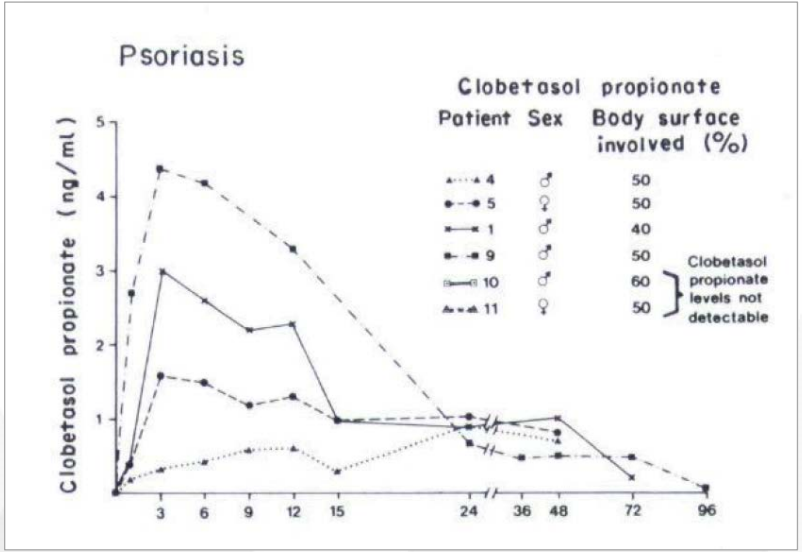
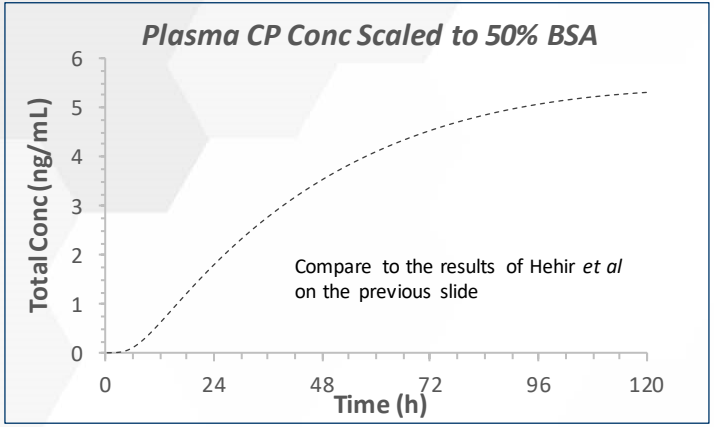


Figure 1. Plasma levels of clobetasol propionate after application of clobetasol propionate ointment to patients with psoriasis

Clin Exp Dermatol. 1983 Mar; **8**(**2**):143-51. M Hehir, A Du Vivier, L Eilon, MJ Danie, EV Shenoy

Clobetasol Propionate Systemic PK



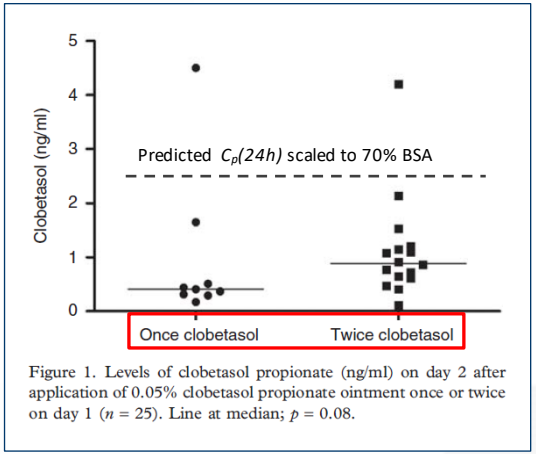
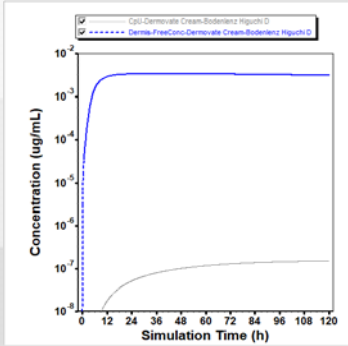


Figure 1. Levels of clobetasol propionate (ng/ml) on day 2 after application of 0.05% clobetasol propionate ointment once or twice on day 1 (n = 25). Line at median; p = 0.08.

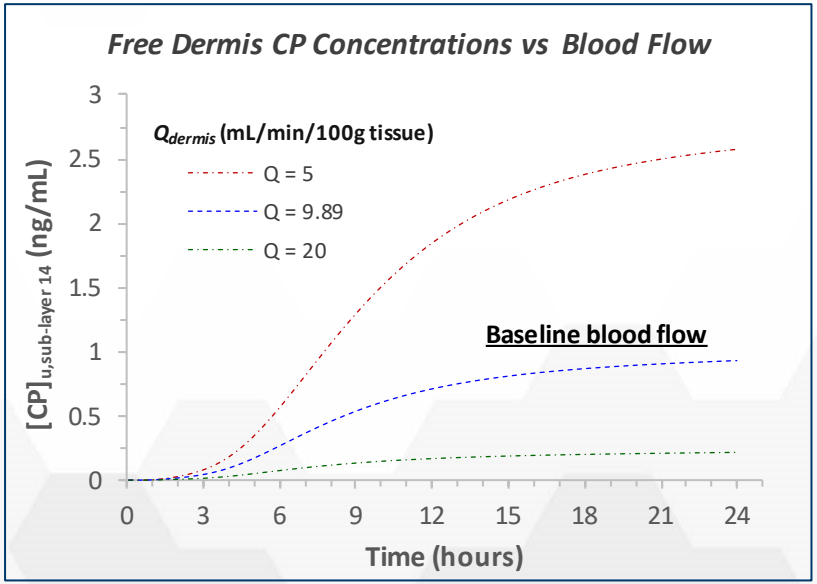
- In the study by van Velsen *et al*, atopic dermatitis patients were treated with 20 - 30 g of 0.05% CP ointment
- The applied CP dose was 0.66 - 1 mg/cm^2 for application at 80% of BSA
- Using a body surface area ~ 1.9·10^4 cm^2 (NHANES 2003), to 60-80% of which ointment was applied
- Scaling up C_p(24h) (~ 1.5·10^{-3} ng/mL per 7.7 cm^2 applied area) to 70% BSA yields 2.5 ng/mL (above, right---)
- Scaling up $C_{p,ss}$ (~ 4.4·10^{-3} ng/mL) yields 7.5 ng/mL, ~ 10x the median of observed values
- Simulated free CP plasma levels << free dermis levels due to $F_{u,p}$ ~ 3.5% and V_c ~ 2.5 L/kg (graph →)
- Thus, the body beyond the skin application site acted essentially as an infinite sink for CP



J Dermatolog Treat. 2012 Feb; **23**(1):16-20. SGA van Velsen, MP De Roos, IM Haeck, RW Sparidans, CAFM Bruijnzeel-Koomen

Vasoconstriction & Dermal Blood Flow

- The effects of dermis blood flow, $Q_{dermis,}$ can be simulated
- Two-fold changes (↕) in baseline blood flow induced time-dependent changes in dermis CP concentrations at mean probe depth ≳ 10x for $t \gtrsim$ 10h
- This range of Q_{dermis} cover much of the site-to-site variation observed over the human body
- Realistic accounting of vasoconstriction requires a pharmacodynamic (PD) model that encompasses the pharmacology of vasoconstriction by glucocorticoids and the intra-cellular uptake of CP as a function of time and skin depth



- GastroPlus has a PD module, but it may not accommodate a case in which the values of some model parameters change during a simulation

Vasoconstriction & Dermal Blood Flow

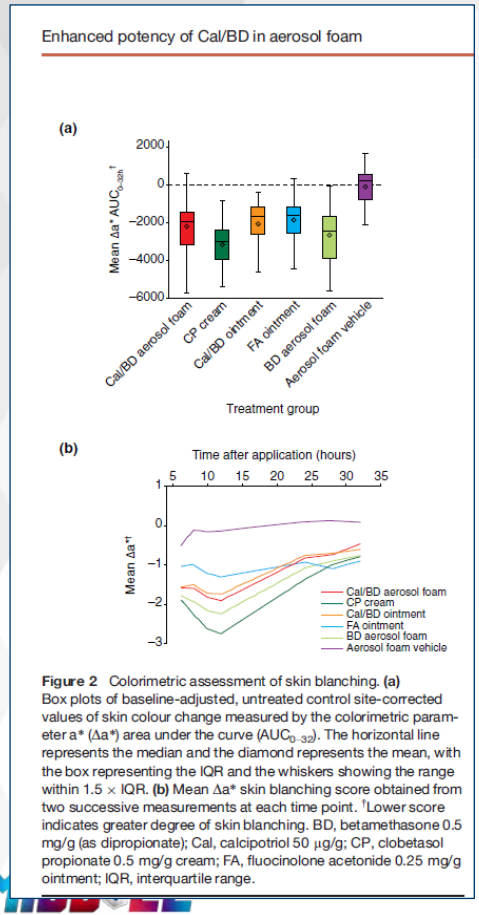


Figure 2 Colorimetric assessment of skin blanching. **(a)** Box plots of baseline-adjusted, untreated control site-corrected values of skin colour change measured by the colorimetric parameter a* (Δa*) area under the curve (AUC_{0-32}). The horizontal line represents the median and the diamond represents the mean, with the box representing the IQR and the whiskers showing the range within 1.5 × IQR. **(b)** Mean Δa* skin blanching score obtained from two successive measurements at each time point. †Lower score indicates greater degree of skin blanching. BD, betamethasone 0.5 mg/g (as dipropionate); Cal, calcipotriol 50 μg/g; CP, clobetasol propionate 0.5 mg/g cream; FA, fluocinolone acetonide 0.25 mg/g ointment; IQR, interquartile range.

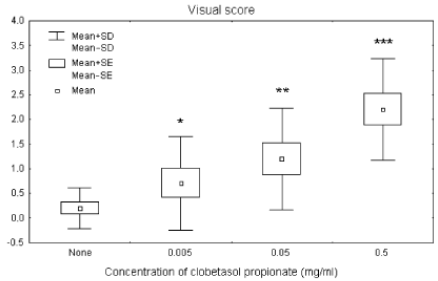


*Fig. 1. Intensity of dermal vasoconstriction assessed by the visual score after 19 h of steroid application in 10 subjects. The score rose with increase in the concentration of clobetasol propionate (ANOVA $P<0.0001$). The blanching was significantly greater at all concentrations than baseline. The significance of the findings is shown as follows: *$0.01<P\leq 0.05$, **$0.001<P\leq 0.01$, and ***$P\leq 0.001$.*

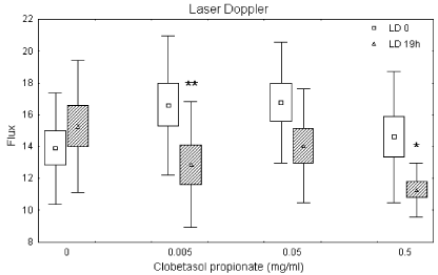


Fig. 2. The intensity of dermal vasoconstriction assessed by laser Doppler flowmetry before (LD 0) and 19 h (LD 19 h) after the application of steroid. The box whisker plots show the mean ± standard error and ± standard deviation of 20 assays in 10 subjects. The differences after the application of 0.005 and 0.5 mg/mL of clobetasol propionate were significant ($0.01<P\leq 0.05$, **$0.001< P\leq 0.01$).*

- Shown here are some published results for dermal vasoconstriction by CP and other glucocortocoids
- The extent of skin blanching, thought to be indicative of vasoconstriction, depends on the inherent potency of the steroid, applied dose, and time
- Blanching can be assessed visually (categorical scale, 0-4) or by colorimetry (continuous scale)
- Laser doppler flowmetry measures blood flow by light scattering off RBCs
- Neither article presents a quantitative PD model of Q_{dermis} as a function of local or regional exposure to a steroid over time

C Queille-Roussel, B Bang, F Clonier, J-P Lacour. *J Eur Acad Derm Vener*, 2016 Nov;**30**(**11**):1951-1956

L Emtestam, N Kuzmina, T Talme. *Skin Res Tech*. 2007 Feb;13(1):73-8