PBPK Modeling of Dermal Penetration from Topical Formulations

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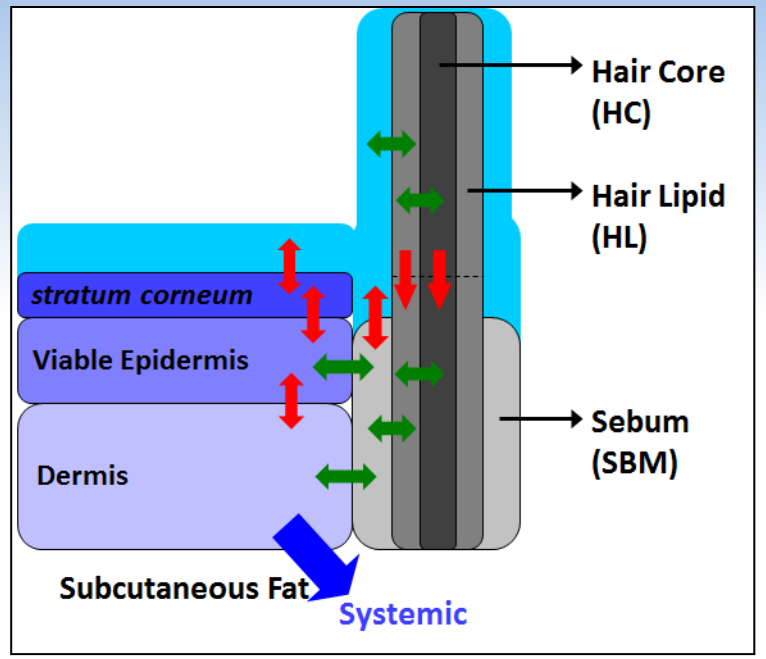
Physiologically-based modeling to support dermal formulation design

- Absorption of topically applied compounds into the skin is heavily affected by the composition of the topical formulation, through attributes such as the solubility and diffusivity of the compound in the formulation, partitioning from the formulation into skin, etc.
- The composition and related attributes of topical formulations will therefore affect whether the compound reaches therapeutic concentrations in the skin and/or systemic circulation, and whether test formulations are bioequivalent with a reference formulation
- Physiologically-based modeling that simulates the mechanisms by which these attributes affect absorption can be used to inform formulation development, reducing the need for animal and human testing

Physiologically-based modeling of skin with the TCAT model

- The Transdermal Compartmental Absorption and Transit™ (TCAT) model in GastroPlus™ is a physiologically-based modeling platform used to simulate absorption and disposition of compounds in the skin. It can be used to identify critical formulation qualities and attributes and model their effect on absorption into the skin and/or uptake into systemic circulation
- By using parameter sensitivity analysis in conjunction with physiologically-based modeling, we can simulate factorial designed experiments to identify the most critical formulation attributes and quantify their effects on absorption and local and/or systemic concentrations



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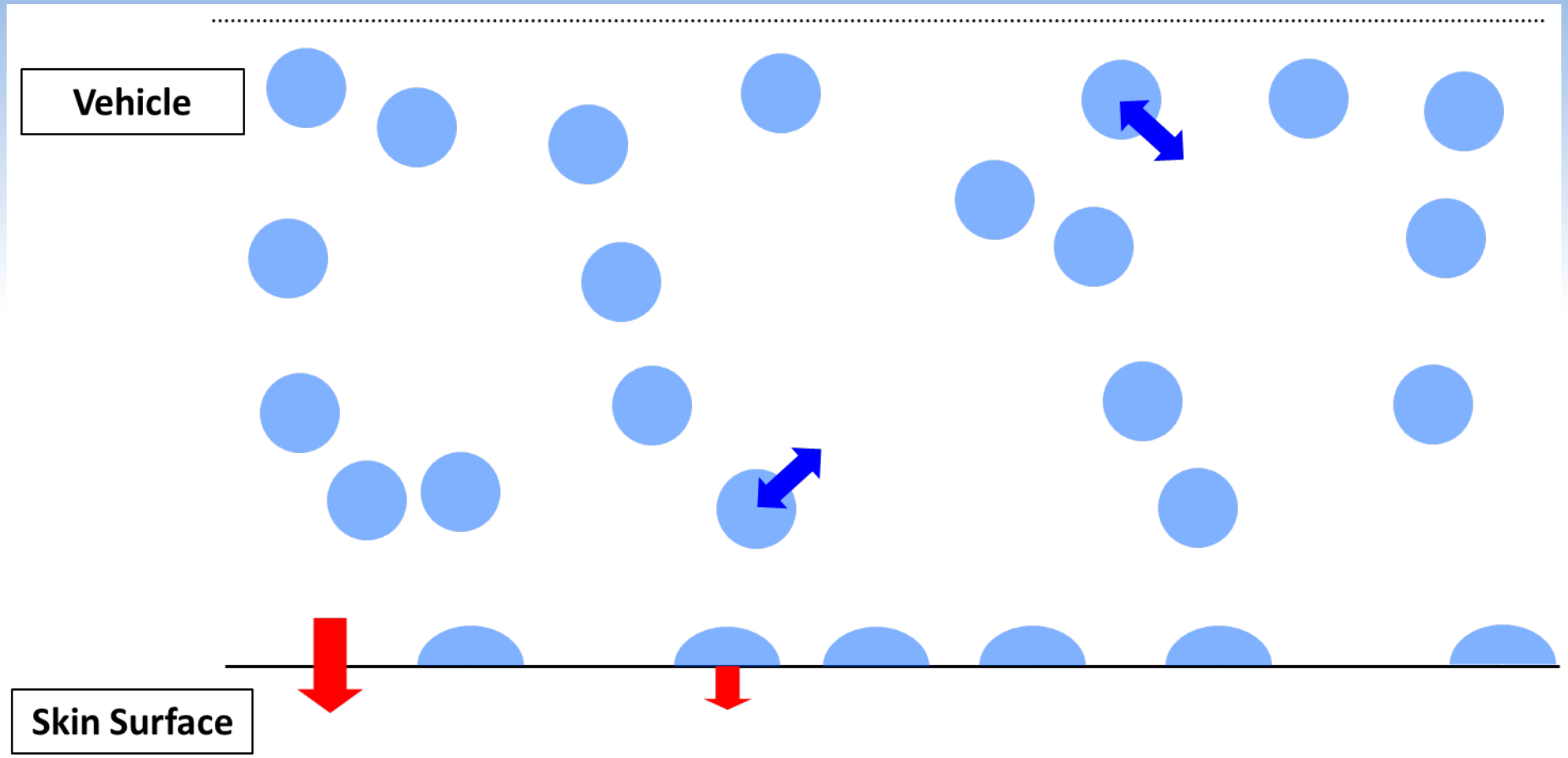
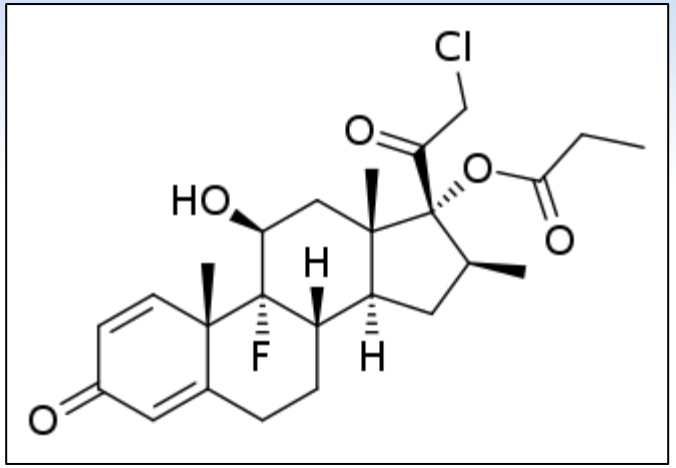
Modeling emulsions in TCAT

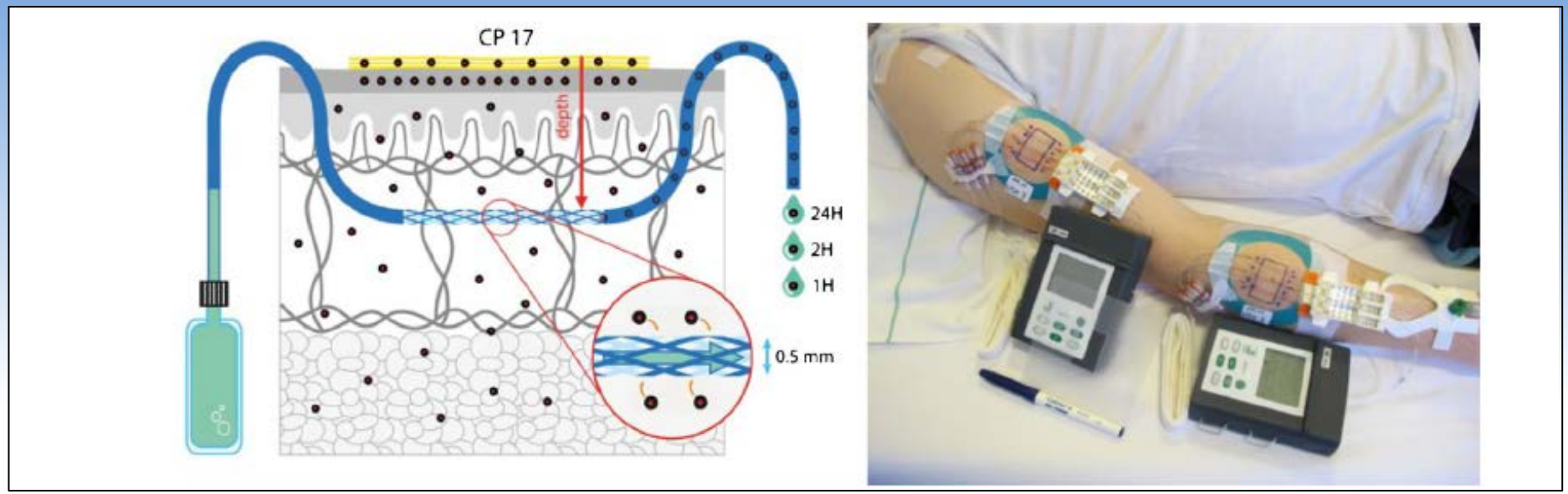


Example compound: Clobetasol-17 propionate

- Clobetasol-17 propionate (CP) is a topical steroid used to treat conditions such as psoriasis
- When applied in formulations such as oil/water microemulsions, dispersed phase droplets can act as a reservoir for CP to maintain drug saturation in the continuous phase
- We can build a baseline model of CP and use it to explore the effect of formulation changes



Measuring CP concentration in the dermis



- CP was applied to the surface skin in the form of Dermovate® Cream, an oil/water microemulsion
- CP concentration was directly measured in the dermis for 24 hours after application on the surface of the skin, using dermal open-flow microperfusion (dOFM) technique, at an average probe depth of 0.87 mm

Bodenlenz, M, et al. *Pharm Res.* 33, no. 9 (September 2016): 2229–38.

Baseline model of CP in Dermovate Cream

- Information on the composition of Dermovate Cream was taken from a variety of sources and used to derive formulation parameters
- Standard equations were used to model distribution in the skin—Robinson equation for stratum corneum, Kretsos equation for viable epidermis and dermis

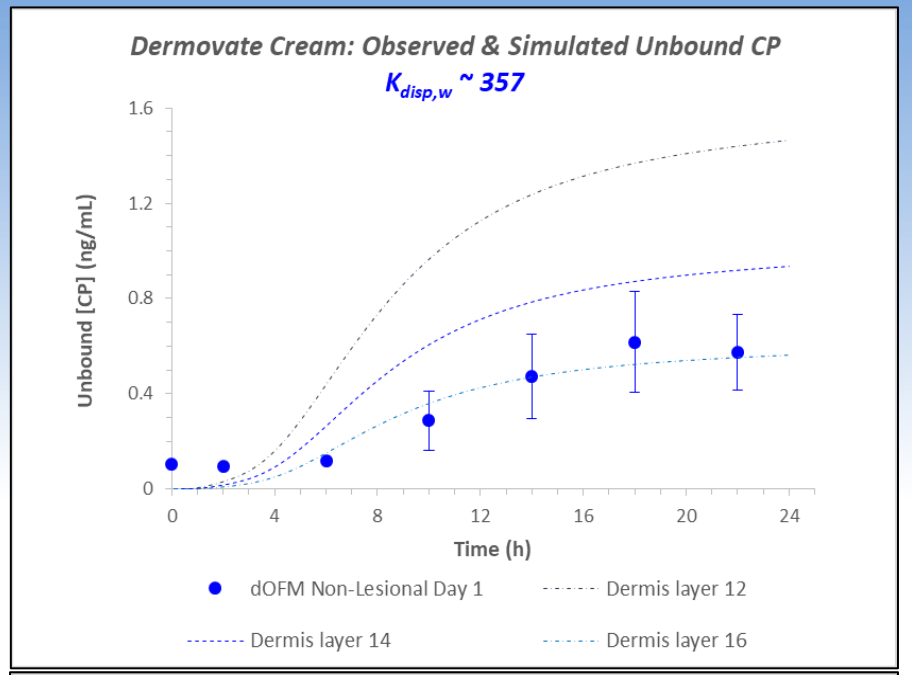
Parameter	Value	Units	Source
CP content	0.5	mg/g cream	CLOBEX® (clobetasol propionate) Lotion, 0.05%, prescribing information
f_{disp}	0.243		Calculated from the composition
CP aqueous solubility	4.06E-03	mg/mL	Solubility data for water:PG mixtures
CP solubility cont phase	0.396	mg/mL	"
$K_{cont,w}$	97.6		The ratio of continuous phase and water solubilities
$K_{disp,w}$	357		Log $K_{veg\ oil,w}$ = 1.115*LogP - 1.35 (LogP ~ 3.5)
CP D_w	5.90E-06	cm^2/s	Estimated via ADMET Predictor 9.5
CP D_{eff}	2.61E-08	"	From analysis of IVR data in Fauzee thesis via the Higuchi equation
CP D_{disp}	4.25E-09	"	Zhang and Michniak-Kohn
Droplet radius (r_d)	1.89	mm	Set to half of d50 measured for Zovirax cream

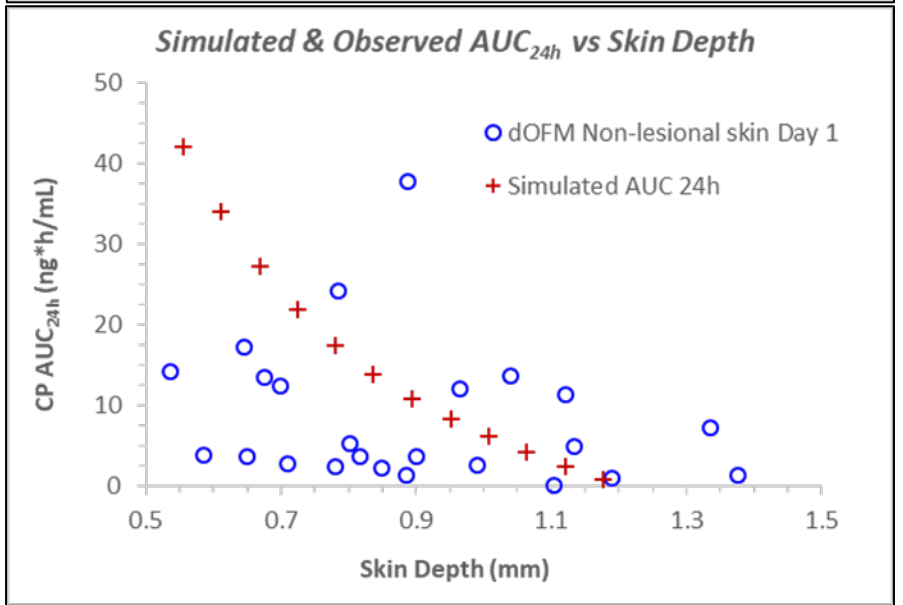
Fauzee AFB. Master of Science (Pharmacy), Rhodes University, 2011.
Zhang J, Michniak-Kohn B. *Int J Pharm* 421, no. 1 (December 12, 2011): 34–44.

cont: continuous phase
D_{eff}: effective diffusivity in the cont phase
D_{disp}: diffusivity in the disp phase
D_w: aqueous diffusivity
disp: dispersed phase
f_{disp}: volume fraction of disp phase in formulation
$K_{cont,w}$: partition coefficient between cont phase and water
$K_{disp,w}$: partition coefficient between disp phase and water

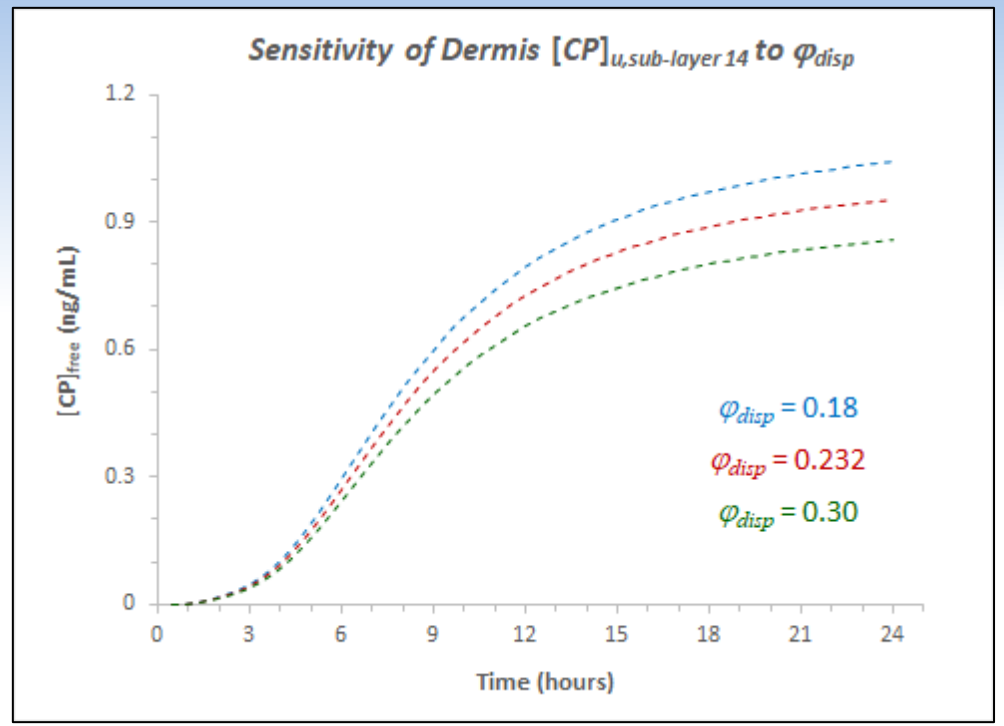
Validation of the baseline model

- Dermis sublayers 12-16 correspond to the probe depth—we were able to match the dOFM probe data, with close matching of simulated concentrations in sublayer 16
- The study also measured AUC_{24h} at different skin depths—simulation results passed through the experimental values
- We can use this model to explore the effect of formulation characteristics on the dermis concentration-time profile and AUC_{24h}





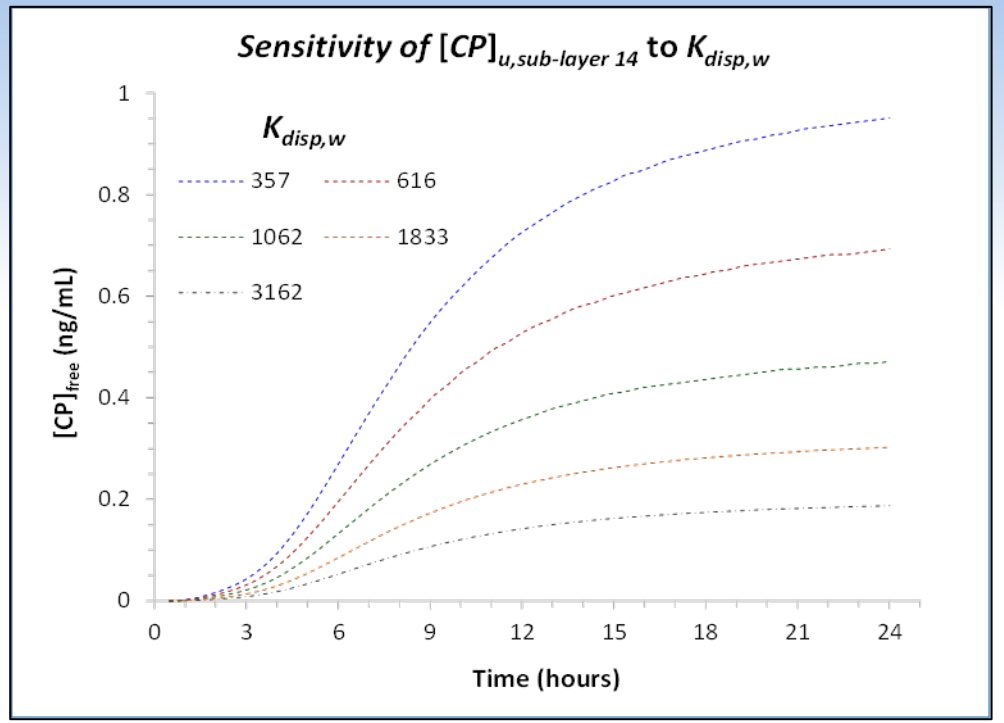
Sensitivity to dispersed phase fraction



- The dispersed phase volume fraction of the formulation was varied by ±25% from the baseline value for Dermovate Cream
- Increasing the dispersed phase fraction had the effect of increasing overall CP solubility in the formulation, decreasing the fractional saturation and reducing the transdermal flux

Sensitivity to dispersed phase solubility

- The effect of CP solubility in the dispersed phase can be explored through the dispersed phase-water partition coefficient $K_{disp,w}$
  - $K_{disp,w}$ increases as solubility increases
  - This solubility can be varied by hydrophobic excipients
- We explore the range from $K_{veg\ oil,w}$(~357) to $K_{o,w}$ (~3162)
- Concentration in dermis decreases as $K_{disp,w}$ increases
  - This change is primarily driven by reducing the fractional saturation in the formulation



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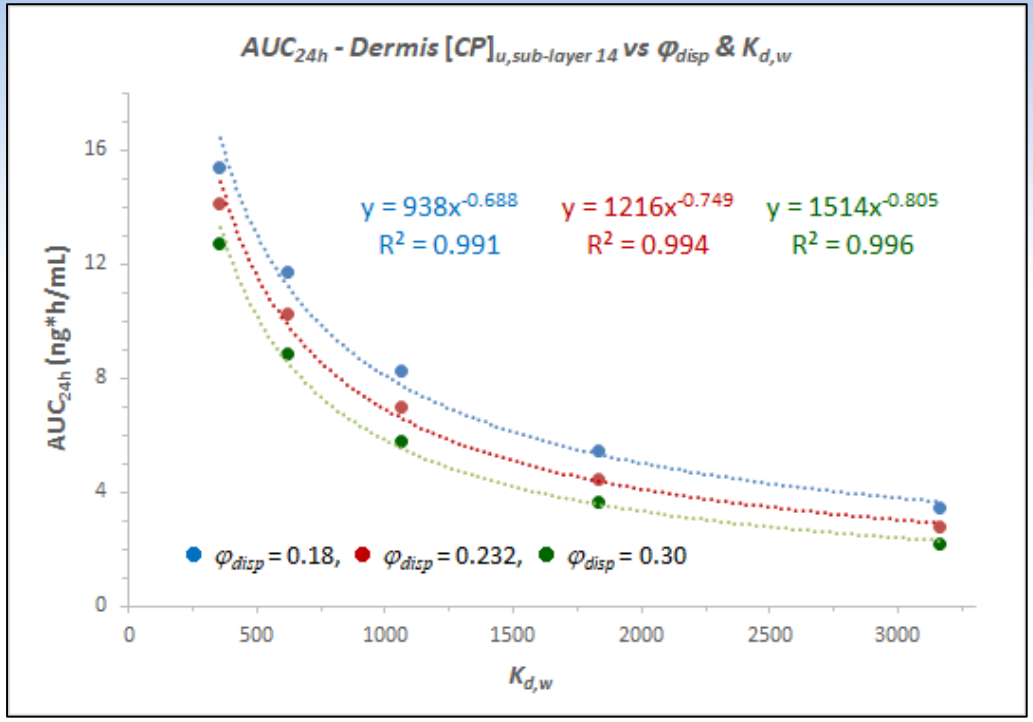
Combined effect of dispersed phase volume and $K_{disp,w}$ – Simulation of factorial experiment design



- The combined effect of both factors can be explored through coupled parameter sensitivity analysis
  - We examine the effect on AUC_{24h} of the unbound CP concentration in the dermis at the dOFM probe depth
- A response surface for the two parameters can be derived to quantify the sensitivity of AUC_{24h} to changes

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

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Conclusions

- Physiologically-based modeling and simulation of topical and transdermal formulations provides a promising approach to test and predict the effect of formulation changes on drug absorption and disposition in the skin
- Sensitivity to formulation attributes can be assessed for single parameters, and combined effects of multiple parameters can be quantified through coupled parameter sensitivity analysis
- These approaches can then be used to inform design of generic formulations with the goal of achieving bioequivalence
- In the future, coupling models to virtual population simulations may also help to indicate sample sizes needed to detect differences between formulations in a statistically rigorous way

Thank you!

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