Computational Modeling of Absorption from Complex Topical Formulations

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July 23rd, 2020

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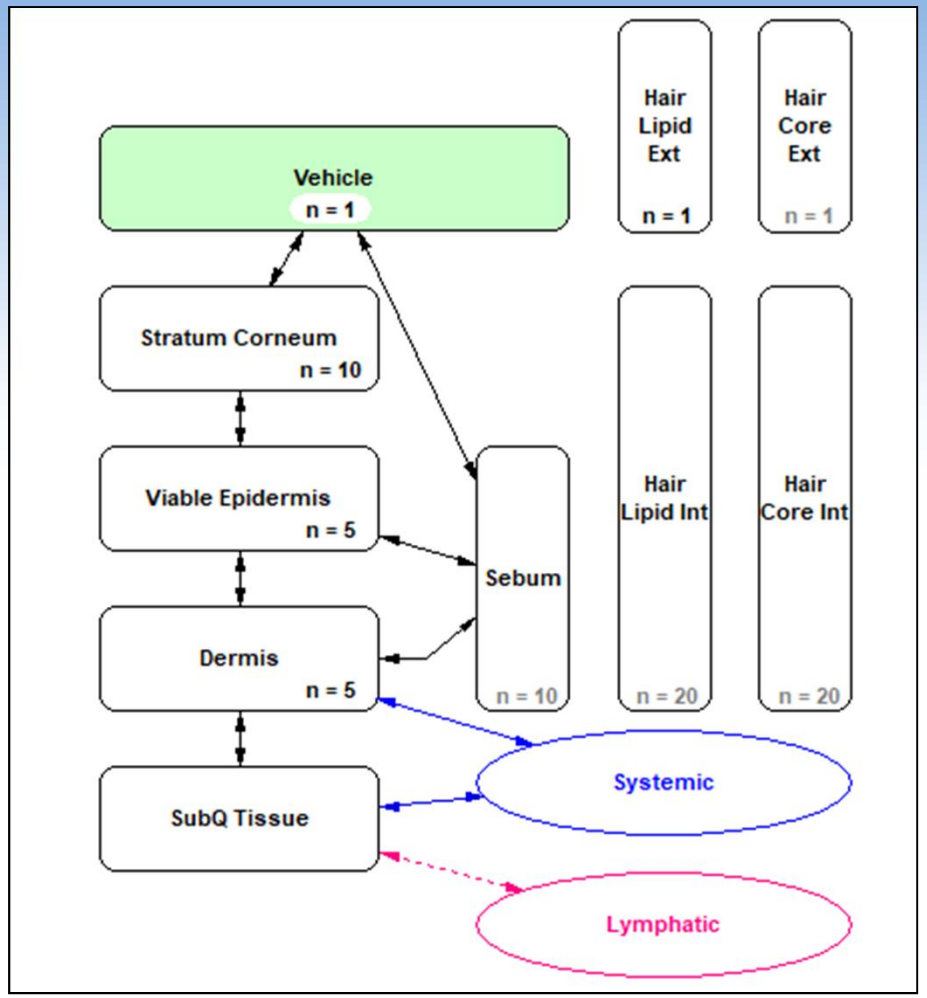
in silico Modeling of Dermal Exposure in GastroPlus

- The TCAT™ module within GastroPlus® was developed to predict drug disposition *in vivo* after topical or subcutaneous application
- The model includes the major skin layers as well as the pilosebaceous unit
- There are several options for modeling topical vehicles, including emulsion formulations



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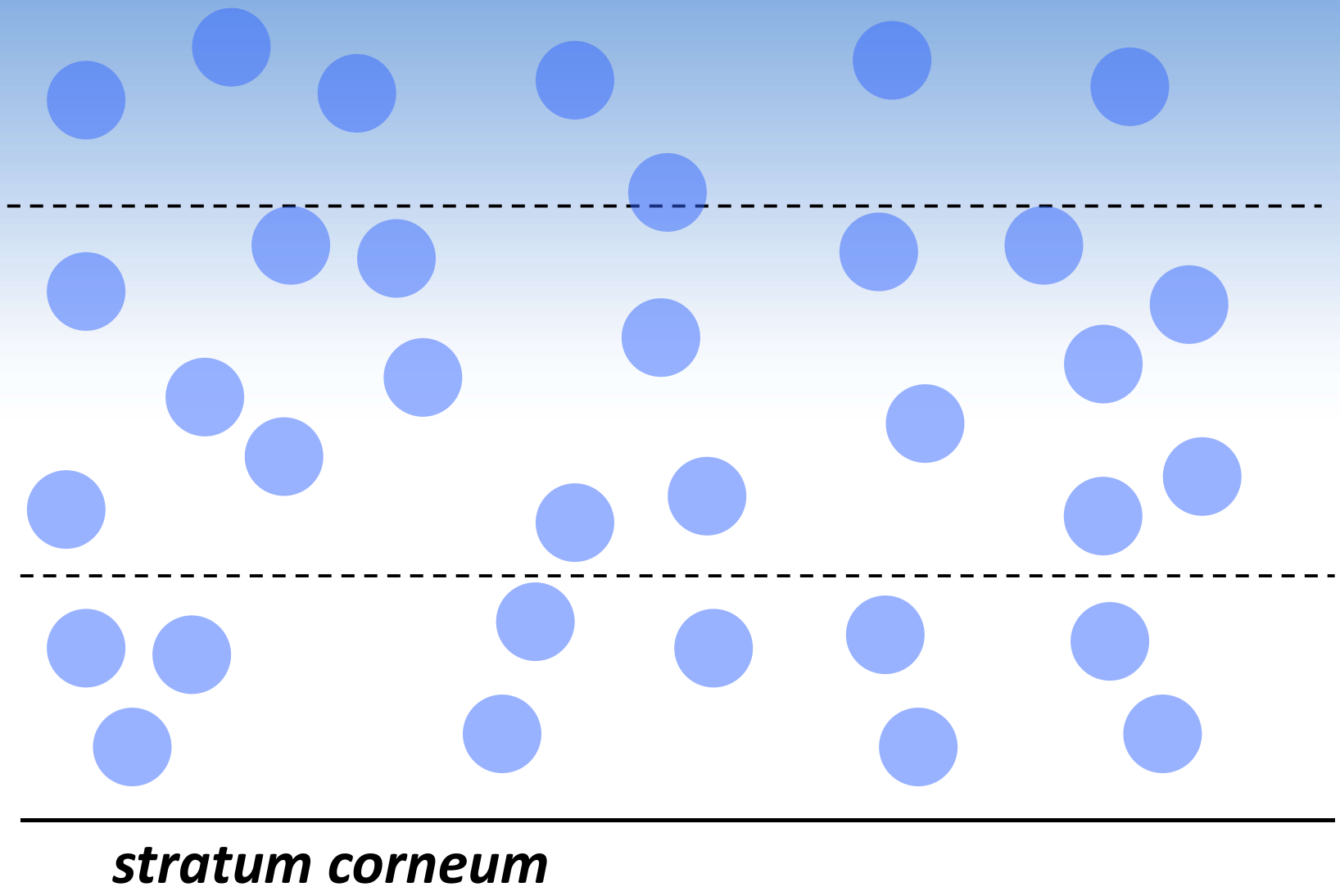
Modeling of Topical Emulsions in TCAT



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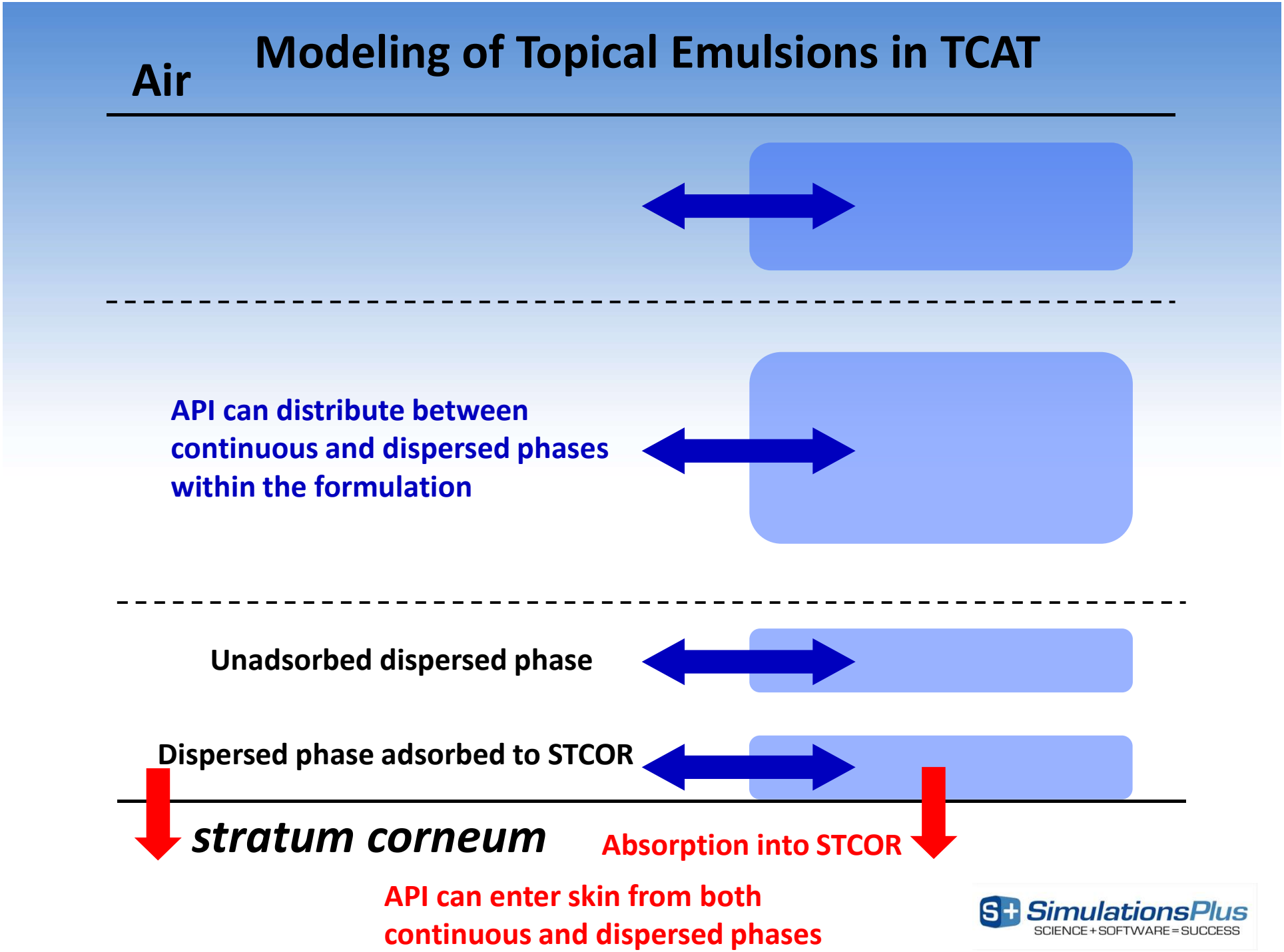
Modeling of Topical Emulsions in TCAT



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Modeling of Topical Emulsions in TCAT

- What is the best way to parameterize *in silico* models of complex topical formulations such as emulsions?
  - What is the best way to estimate parameters that cannot be directly measured?
  - What parameters are most important?
  - What are the sensitive ranges of these parameters?
- How well can these models simulate absorption and local skin concentrations of compounds dosed through these formulations?

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Case Study – Clobetasol Propionate

- Clobetasol is a corticosteroid that is commonly applied topically to treat plaque psoriasis and other inflammatory skin disorders

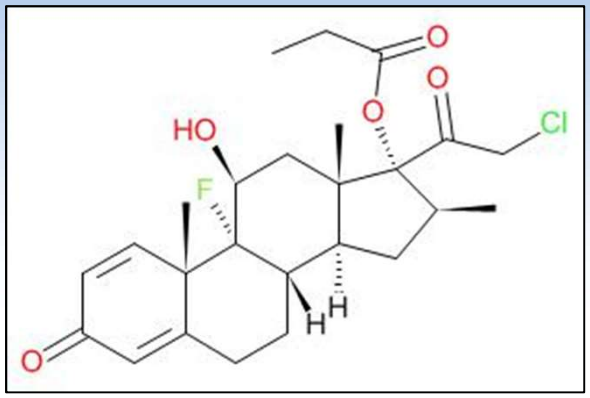
- S+logP = 3.7
- Exp logP = 3.5 (Sangster, 1994)

- No pKa's in the range pH 2-12

- S+Aq. Sol. = 3.15 μg/mL at pH 7
- Exp Aq. Sol. = 3.86 μg/mL

- S+Rbp = 0.84

- S+fup = 10.35
- Exp fup = 2.5 (Dawson et al, 2012)



S+: Parameter value estimated by ADMET Predictor 9.5
Exp: Parameter value determined experimentally

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Case Study – Clobetasol Propionate Cream

Pharm Res (2016) 33:2229–2238
DOI 10.1007/s11095-016-1960-y

RESEARCH PAPER

Kinetics of Clobetasol-17-Propionate in Psoriatic Lesional and Non-Lesional Skin Assessed by Dermal Open Flow Microperfusion with Time and Space Resolution

Manfred Bodenlenz[1] • Christian Dragatin[1] • Lisa Liebenberger[2] • Bernd Tschapeller[1] • Beate Boulgaropoulos[1,2] • Thomas Augustin[1] • Reingard Raml[1] • Christina Gatschelhofer[1] • Nathalie Wagner[3] • Khaled Benkali[3] • Francois Rony[3] • Thomas Pieber[1,2] • Frank Sinner[1,2]

- Evaluate the absorption kinetics of topically applied clobetasol-17-propionate (CP) in lesional and non-lesional psoriatic skin when released from a commercially available low-strength cream using dermal open-flow microperfusion (dOFM)
- 12 patients received Dermovate® cream (CP, 0.05%) once daily for 2 weeks on small lesional and non-lesional skin test sites
- On days 1 and 14, dOFM samples were taken continuously in the dermis for 24h and analyzed by LC-MS/MS. Probe depths were assessed by 50MHz ultrasound scanning

Bodenlenz M, Sinner F, et al. **Kinetics of Clobetasol-17-Propionate in Psoriatic Lesional and Non-Lesional Skin Assessed by Dermal Open Flow Microperfusion with Time and Space Resolution**. *Pharm Res*, 2016.

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Dermal Open-Flow Microperfusion

- Dermal open-flow microperfusion (dOFM) is a potential means to assess bioequivalence and bioavailability of topically applied products
- The dermis interstitial fluid is sampled over a period of up to 48 hours
- Provides information on local drug concentrations beneath the area of application (in this case, on the upper and lower arm)

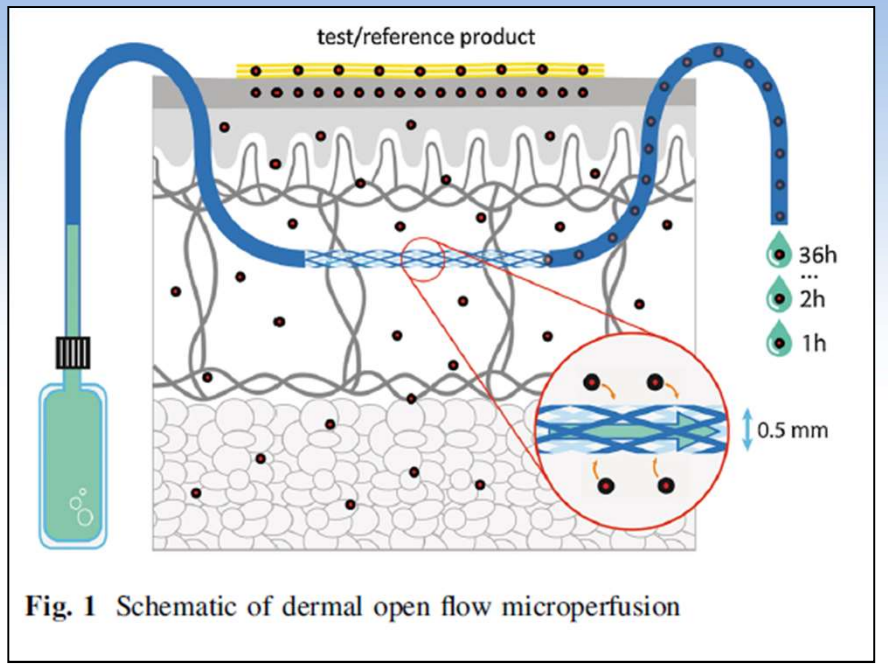

Fig. 1 Schematic of dermal open flow microperfusion

Bodenlenz et al, 2016

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dOFM Concentration Profiles and AUC Data

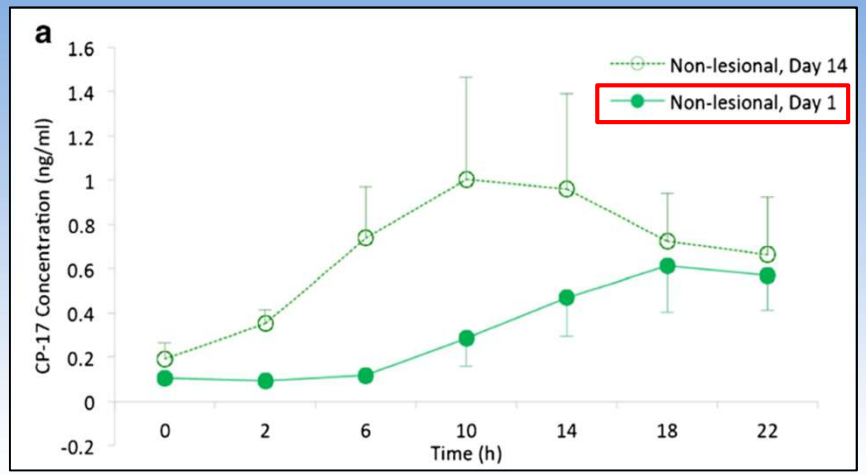

Figure 3. Mean CP concentration profiles from t_0 to 24h post dose on Day 1 (1st dose) and Day 14 (after 14th dose). (a) Non-lesional skin profiles. Data are mean ± sem

How well can we simulate these results using the TCAT Module?

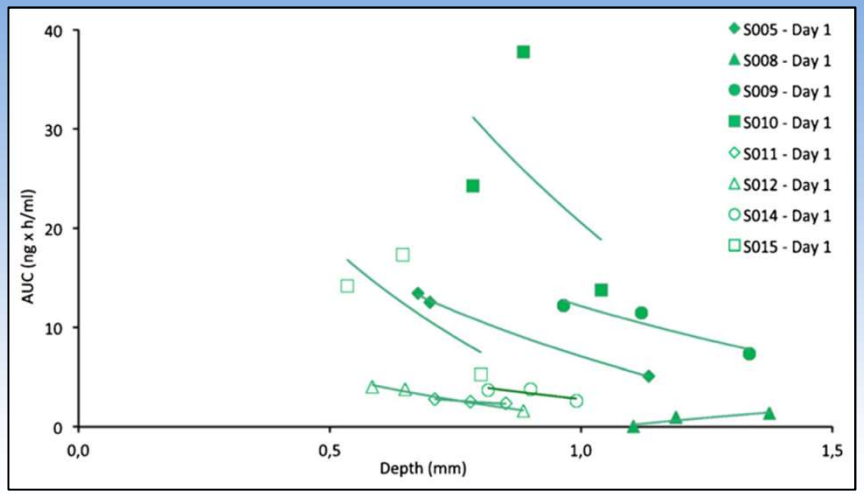

Figure 4. *AUC* data of non-lesional skin on day 1 plotted vs depth

- Regression lines are fitted to the *AUC*s of the 3 adjacent probes for each subject
- The illustration suggests a relationship between *AUC* and probe depth in 7 of 8 subjects (negative slopes)
- Most of the variability is inter-subject variability of CP penetration

Bodenlenz et al, 2016

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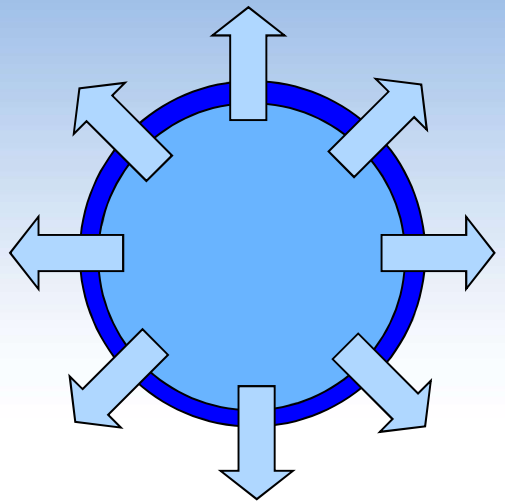
Parameterizing Creams in TCAT

- Continuous phase
  - Volume fraction
  - pH
  - API Diffusivity
  - API Partition coefficient (wrt water)
  - API Solubility
- Dispersed phase
  - Volume fraction
  - Droplet size distribution
  - API Partition coefficient (wrt water)
  - API Diffusivity in the membrane/surfactant layer

Diffusional Model



Diffusional release rate from entire dispersed phase is:

$$RelRate_j = v_j^{dis}\left(\frac{D^{mem}K_{d,c}}{L^{mem}}\right)\left(\frac{3\Psi}{r}\right)\left(\frac{c_j^{dis}}{K_{d,w}} - \frac{c_j^{con}}{K_{c,w}}\right)$$

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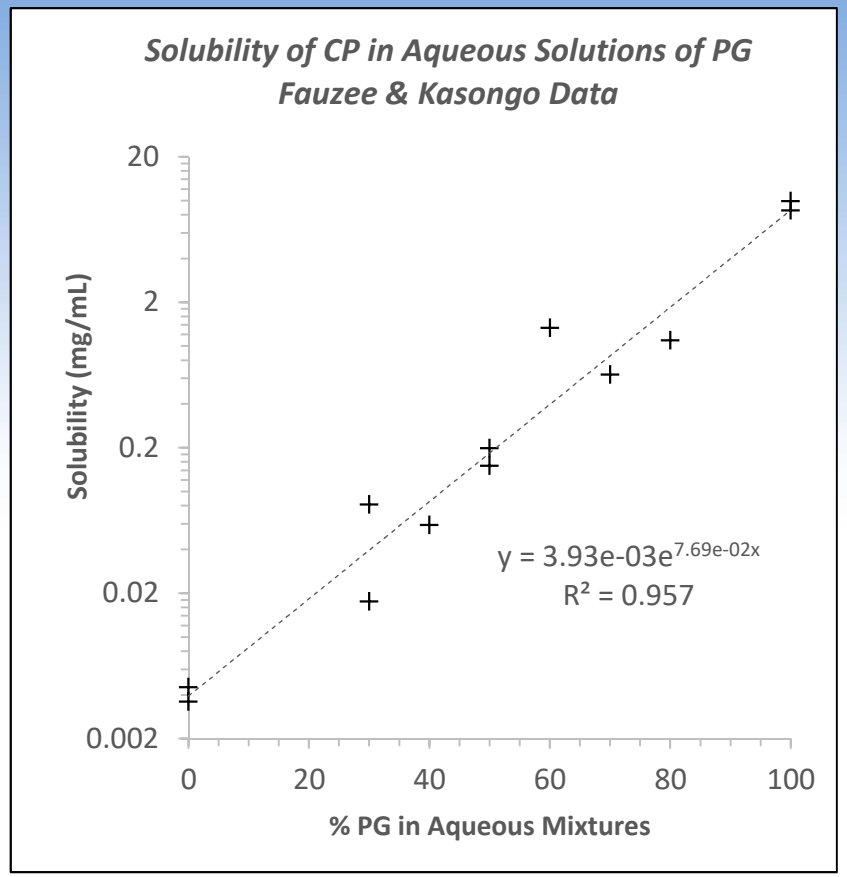
Characterization of Dermovate Cream

Component	*Density (g/mL)*	*% in Cream (% w/w)*	*mg in 100 g Cream*	*Volume (mL)*
Propylene glycol	1.04	47.5	47.5	45.67
Sodium citrate	1.66	0.05	0.05	0.030
Citric acid	1.66	0.05	0.05	0.030
Arlacel 165	0.97	1.50	1.5	1.55
Glyceryl monostearate	0.97	11.0	11	11.34
Cetostearyl alcohol	0.81	8.40	8.4	10.37
White beeswax	0.966	1.15	1.15	1.19
Chlorocresol	1.37	0.075	0.075	0.05
Distilled water	0.9958	30.225	30.225	30.35

- Dermovate® 0.05% w/w cream (batch # 274665, Sekpharma® Pty Ltd, Sandton, Gauteng, SA)
- Information about the commercial cream from which values of model parameters could be derived was taken from MS Theses and peer-reviewed literature
- Dispersed phase volume fraction, φ_{disp} ~ 0.243 (calculated from the aqueous and non-aqueous volumes)
- pH of the cream ~ 5.22 (Fauzee, 2011), and its density ~ 0.994 g/mL (calculated from total mass and volume)

AFB Fauzee, **Development, manufacture and assessment of clobetasol 17-propionate cream formulations**. MS Thesis, Rhodes University, 2011

Solubility of Clobetasol Propionate in Dermovate Cream



- The MS theses of Fauzee (2011) and Kasongo (2007) are two sources of data for the solubility of CP in water:PG mixtures
- Both sets of measurements are plotted at left, from which we derived an equation for CP solubility in the Dermovate aqueous phase, ~ 60% PG (v/v)
- CP continuous phase C_s ~ 0.40 mg/mL
- From the formulation composition and solubility data, and noting that CP is completely dissolved in the formulation, we calculate that $K_{cont/w}$ ~ 97.6, and use $K_{disp/w}$ ~ $K_{veg\ oil/w}$ or $K_{o/w}$
- Per 100 mg of the cream, one has the following

Non-aq Vol (mL)	24.45		
Aq Vol (mL)	76.14		
Cream Density (g/mL)	0.994		
Disp Phase φ	0.243		
PG% of continuous phase	60	~ F_{sat} *for* $K_{veg\ oil/w}$	~ F_{sat} *for* $K_{o/w}$
$[CP]_{cont}$ *(mg/mL)*	0.302	0.762	0.145
API Fraction $_{cont}$ *(%)*	46		
$[CP]_{disp}$ *(mg/mL)*	1.10	0.802	0.153

KW Kasongo, **Development and *in vitro* evaluation of a clobetasol 17-propionate topical cream formulation**. MS Thesis, Rhodes University, 2007

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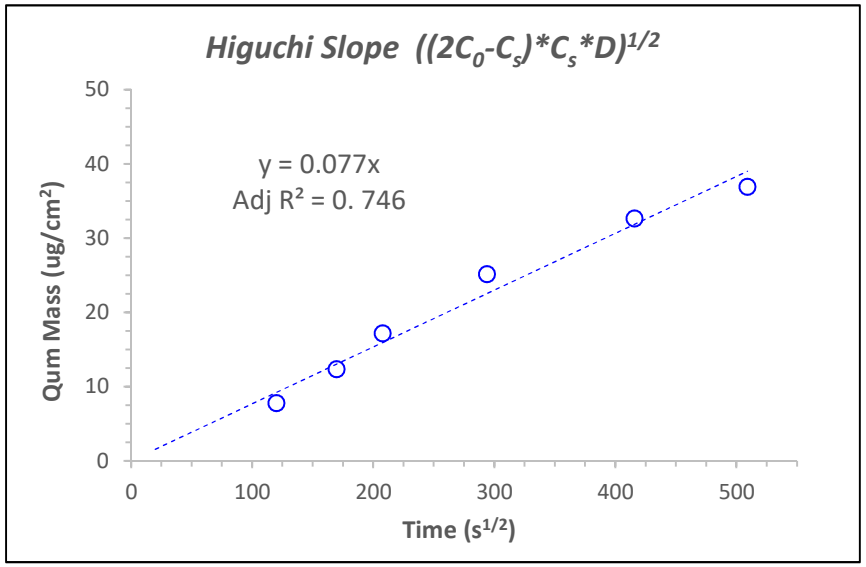
Diffusivity of Clobetasol Propionate in Dermovate Cream Continuous Phase

Table 4.6. Franz cell diffusion conditions for in vitro release of CP cream formulations

Apparatus	Glass Franz diffusion cell system
Sample number	6 cells
Average diffusional surface area (n=6)	2.063 ± 0.104 cm^2
Average receptor volume (n=6)	12.61 ± 0.25 ml
Temperature	32.0 ± 0.5°C
Synthetic membrane	0.025 µm nitrocellulose
Dosing conditions	300 mg
Sample occlusion/ non-occlusion	Occlusion
Magnetic stirrer	10 mm x 2.5 mm rectangular magnetic stirrer
Sampling time	2, 4, 8, 12, 24, 48, 72 hours
Sample analysis	HPLC with UV detection 239 nm



- Release of CP from Dermovate cream through nitrocellulose membranes was measured *in vitro,* under occlusion, in vertical Franz cells
- The experimental conditions are summarized at left
- The data plotted below left were digitized from Figure 4.9 in Fauzee, 2011
- The effective diffusivity of CP in the cream was calculated from Higuchi's equation

Calculated using data from Fig. 4.9		
Parameter	***Value***	***Units***
C_0	500	ug/mL
C_s	400	ug/mL
Slope	7.70E-02	$1/s^{1/2}$
+ 95% CI	8.37E-02	"
- 95% CI	7.02E-02	"
$D_{eff,\ cont}$	2.47E-08	cm^2/s
+ 95% CI	2.92E-08	"
- 95% CI	2.05E-08	"

Siepmann J & Peppas NA. **Higuchi equation: Derivation, applications, use and misuse**. *Intl J Pharm,* 2011

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Diffusivity of Clobetasol Propionate in Dermovate Cream Dispersed Phase

- CP diffusivity at the transition between phases was estimated from the ferrocene diffusivity measured by cyclic voltammetry for caffeine microemulsions
- The compositions and viscosities of the oil phases in the two cases were dissimilar
  - Caffeine: IPM, Labrasol, Cremophor EL
  - Clobetasol propionate: Beeswax, glyceryl monostearate, cetostearyl alcohol, POE 100 stearate
- φ_{cont} ~ 0.76 for Dermovate cream; one interpolates a $D_{ferrocene}$ ~ $9.85 \cdot 10^{-9}$ cm^2/s

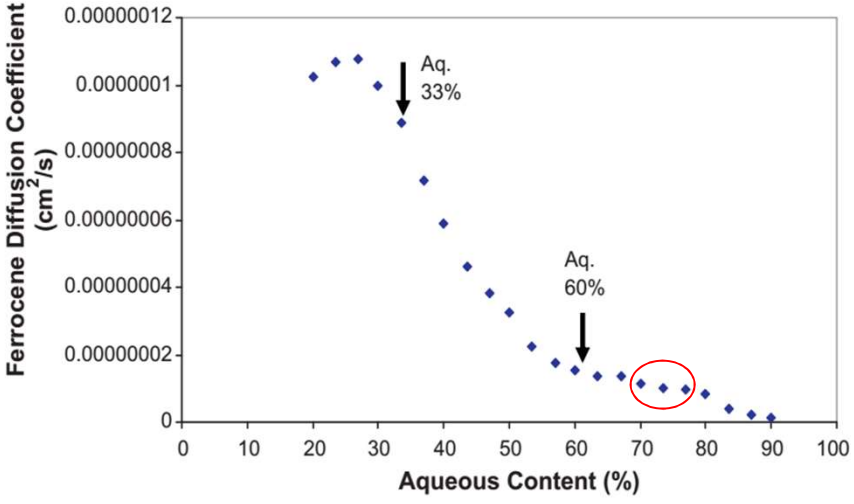

Fig. 4. The plot of apparent diffusion coefficient of ferrocene, *D* vs. aqueous content of microemulsions along the water dilution line of oil to surfactant ratio 1/9.

- We used the Stokes-Einstein equation to estimate CP diffusivity from that of ferrocene by the ratio of hydrodynamic radii
- Ferrocene radius from the reference below, CP value from GP 9.7

Compound	*r (m)*	*D_{disp} (cm^2/s)*
Ferrocene	2.60E-10	9.85E-09
CP	6.00E-10	4.27E-09

J Zhang, B Michniak-Kohn, **Investigation of microemulsion microstructures and their relationship to transdermal permeation of model drugs: Ketoprofen, lidocaine, and caffeine**. *Int J Pharm* 2011

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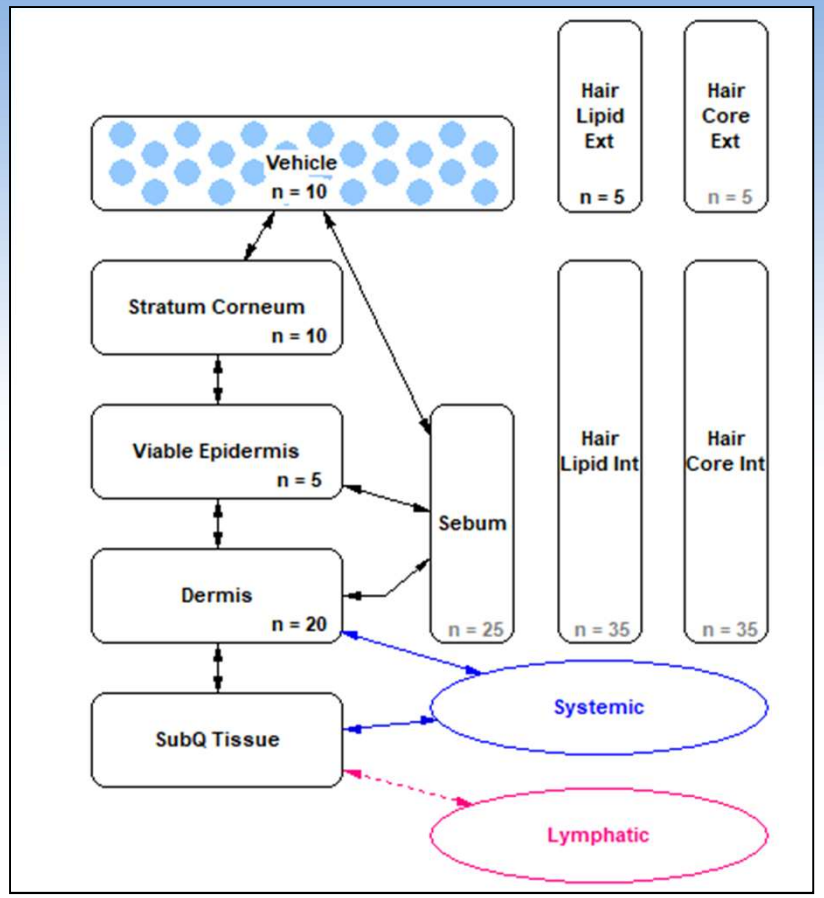
Summary of Formulation Input Parameters

- Administration
  - Dose = 0.05775 mg
  - Applied Volume = 0.1162 mL
  - Applied Surface Area = 7.7 cm^2
  - Application Time = 24h
- Continuous phase (water:PG)
  - pH = 5.22
  - Density = 1.03 g/mL
  - CP Solubility = 0.40 mg/mL
  - CP D_{cont} = 2.47e-8 cm^2/s
  - CP $K_{cont/w}$ = 97.6
- Dispersed phase
  - Volume Fraction, ϕ_{disp} = 0.243
  - Droplet diameter, d_{disp} = 3.8 µm
  - CP $K_{disp/w}$ = $K_{o/w}$ = 3162 or $K_{veg\ oil/w}$ = 357
  - CP D_{mem} = 4.27e-9 cm^2/s (disp ↔ cont phases)



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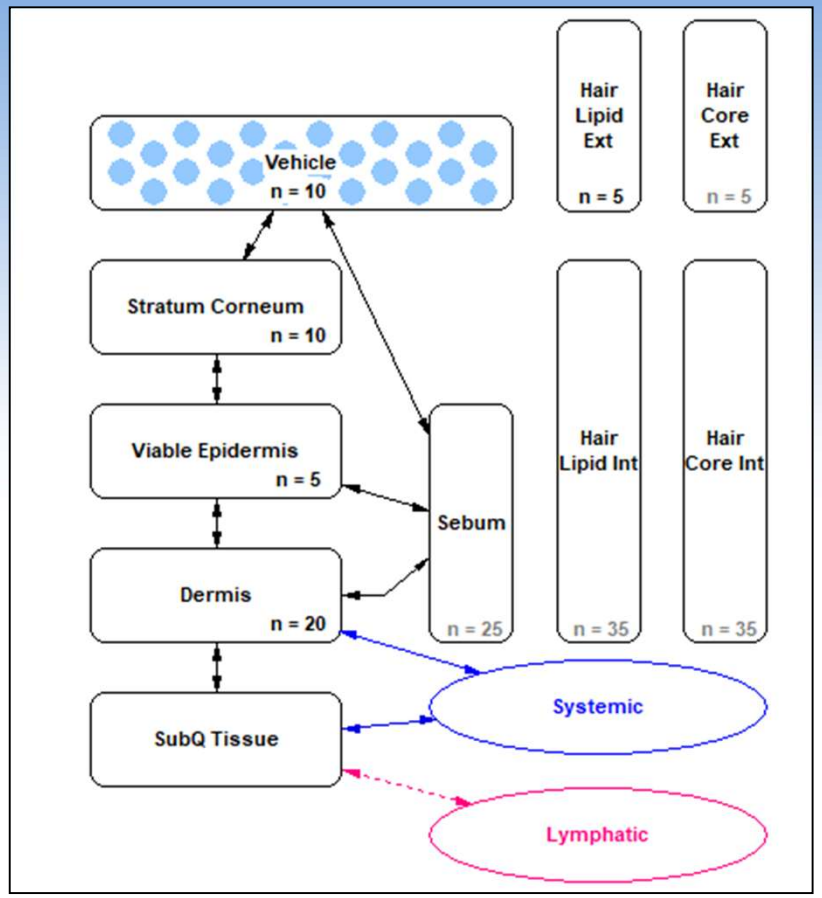
Summary of Skin Permeability Parameters

- Each skin layer has a diffusivity and a partition coefficient associated with it
- For stratum corneum, we estimate these properties using the Robinson model (Wilschut et al, 1995)
  - D_{STCOR} = 3.91e-12 cm^2/s
  - $K_{STCOR/w}$ = 63.46
- For viable epidermis and dermis, we use the Kretsos model (Kretsos et al, 2008)
  - $D_{VE} = D_{DE}$ = 1.26e-6 cm^2/s
  - $K_{VE/w} = K_{DE/w}$ = 0.7
  - 84% of CP bound to albumin and lipid in VE and DE
- For the sebum, we use the Yang-Lian model (Yang et al, 2018, 2019)
  - D_{SBM} = 3.28e-9 cm^2/s
  - $K_{SBM/w}$ = 556
- Transport from dermis to systemic circulation is calculated using the Ibrahim model (Ibrahim et al, 2012; Kapoor et al, 2016)



Dermis layer 14 corresponds to the geometric mean depth of the dOFM probes *in vivo*

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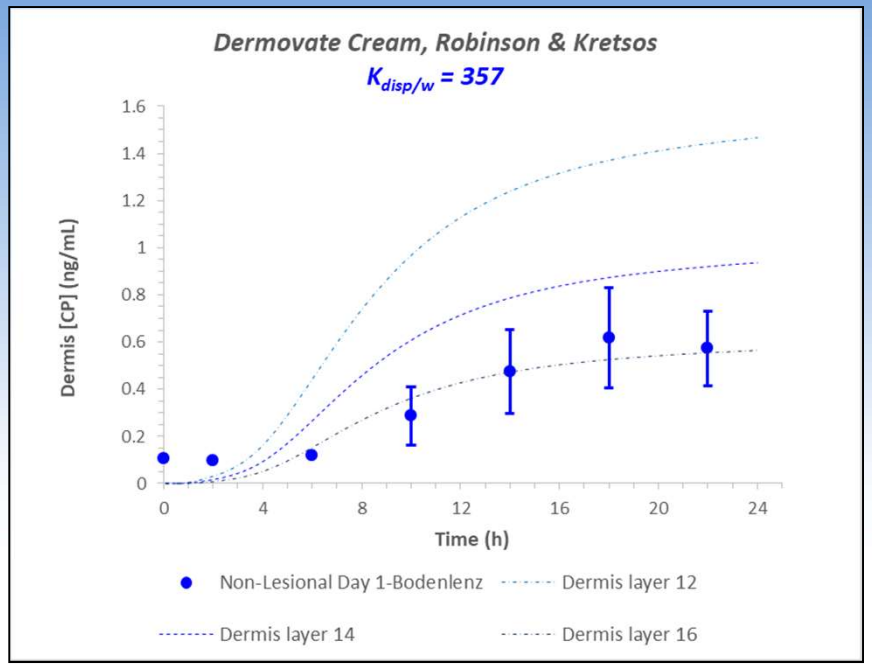
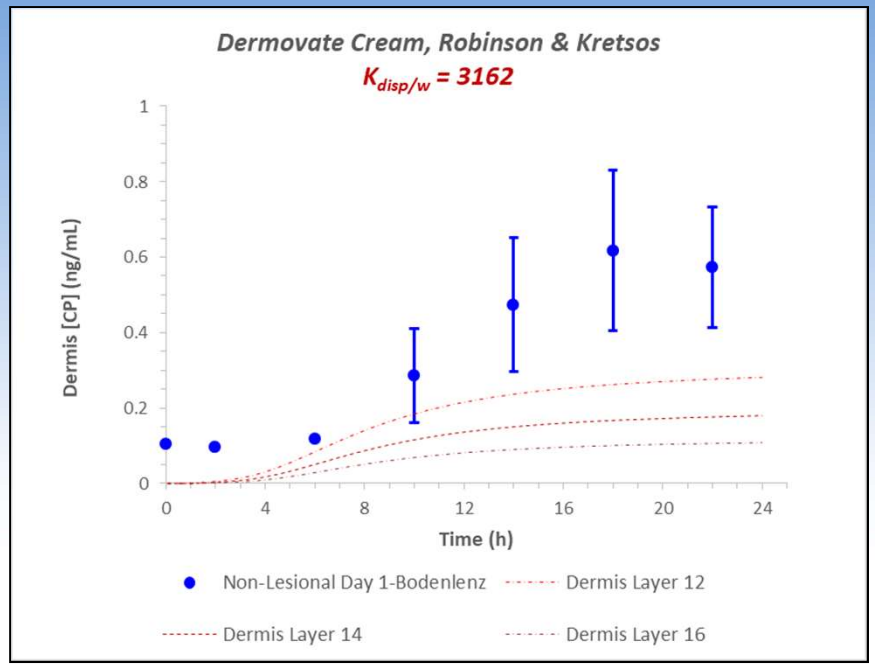
Comparison of *in silico* and *in vitro* Dermis Concentrations





• Sub-layer 14 corresponds to the geometric mean of dOFM probe depths (870 μm). Layers 12 and 16 cover the 95% confidence interval for probe depths (± 90 μm)

• **At left**, Using the Robinson and Kretsos permeability equations and $K_{disp/w} = K_{veg\ oil/w,}$ simulated unbound dermal CP concentrations in sub-layers 12, 14, and 16 are plotted with average concentrations measured *in vivo* by dOFM (± SEM)

• **At right**, results for the same simulation but with $K_{disp/w} = K_{o/w}$ (note that the ordinate scale differs)

• The differences in simulated $[CP]_{DE}$ between the two cases result from the 5-fold difference in fractional saturation of CP in the formulation due to the choice of $K_{disp/w}$: 0.76 vs 0.15, for $K_{veg\ oil/w}$ and $K_{o/w}$, respectively

• Using $K_{veg\ oil/w}$, we slightly over-predict the dermis concentration after 4 hours, but using $K_{o/w}$, we somewhat under-predict it. Vegetable oil is more predictive

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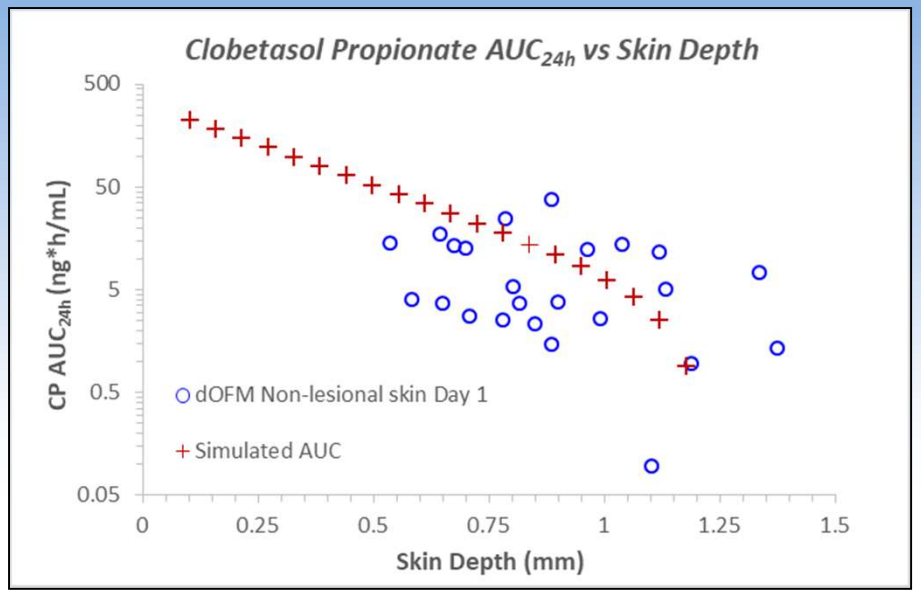
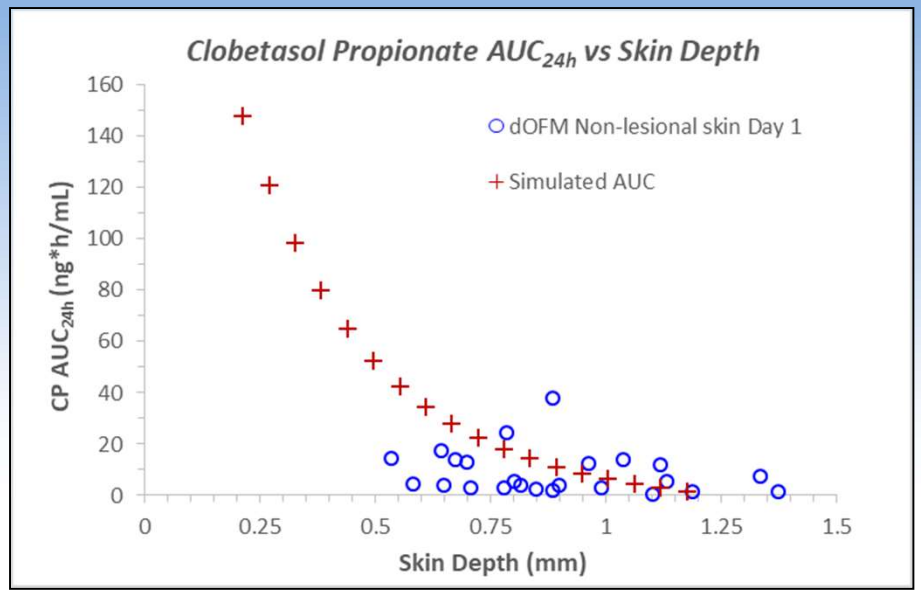
Comparison of *in silico* and *in vivo* Dermis AUC





dOFM data from Fig. 4 of Bodenlenz et al, 2016

- AUC_{24h}, calculated from the unbound CP concentration-time profiles in dermis layers 1-20 for the simulation in which $K_{disp/w} = K_{veg\ oil/w}$, is plotted above along with CP AUC_{24h} on Day 1 (○) for individual subjects vs dOFM probe depth
- Within the range of dOFM probe skin depths, the simulated values are within the range of observed values
  - Inter-subject variability in dermis thickness may be a source of variability in experimental AUCs

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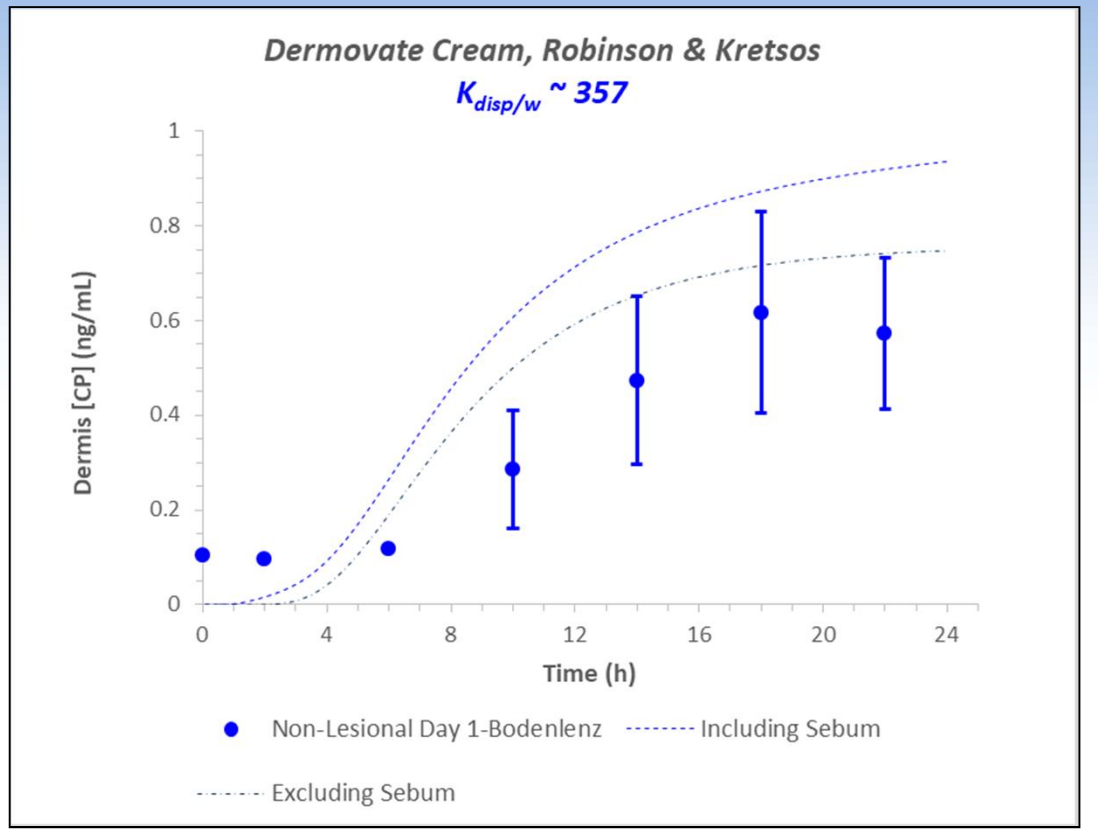
Effect of Sebum Pathway on Dermis Concentrations

- In the simulations, the permeability of the sebum pathway was ~ 1.53e-5 cm/s, and the surface area fraction covered by sebum was 1.44e-3 (~ 1 part in 700)
- Skin permeability was 1.86e-7 cm/s, about 80-fold lower than the sebum pathway
- We parsed out the contribution of the sebum pathway by nulling out its diffusivity
- Results of this simulation are plotted at right in comparison with the baseline simulation (using $K_{veg\ oil/w}$)
- Eliminating the parallel pathway induced a progressive delay in reaching a particular baseline CP concentration in dermis layer 14
- AUC_{24h} of unbound CP in dermis sub-layer 14 was reduced ~ 20%



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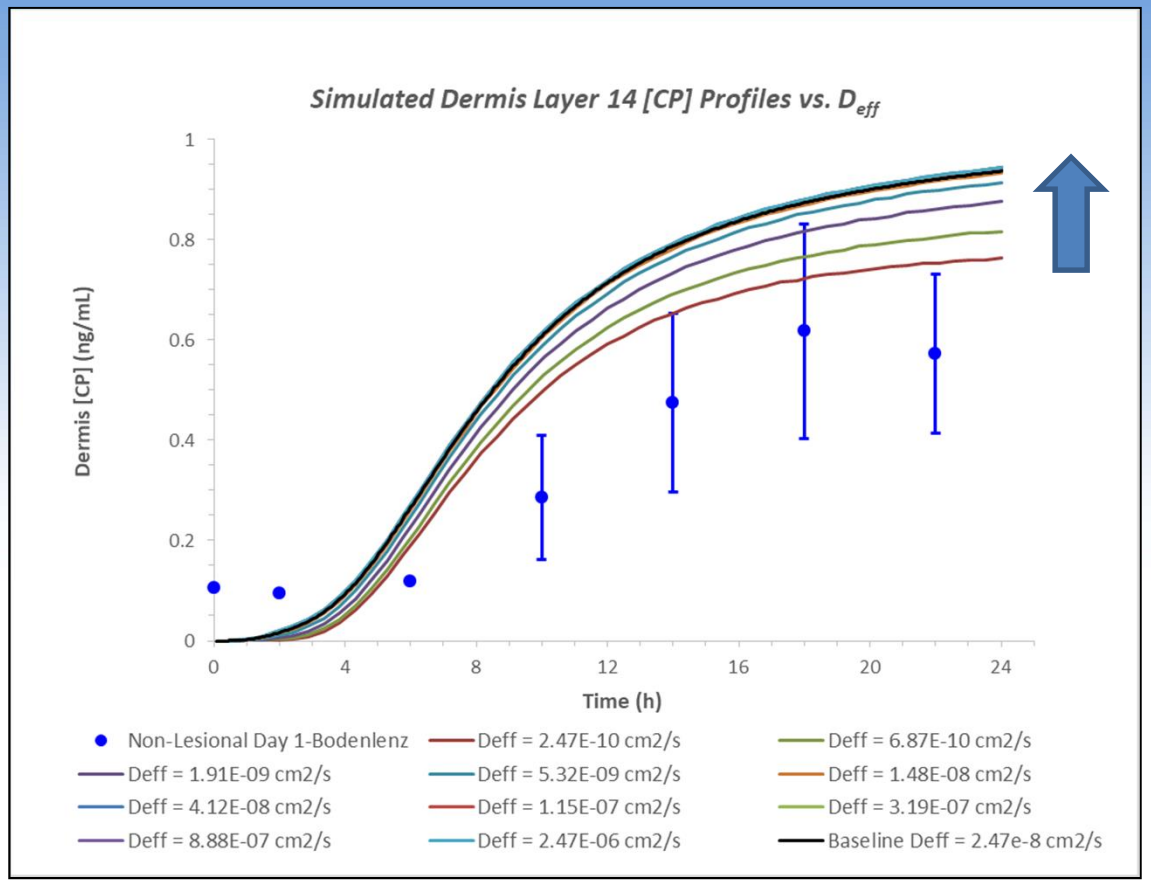
Sensitivity to Continuous Phase Diffusivity



• Dependence of the unbound CP concentration profile in the dermis on D_{eff} (effective diffusivity of CP in the continuous phase) was modest: Changing D_{eff} by four orders-of-magnitude produced ~20% change in $[CP]_{DE}$ at geometric mean probe depth, from 10 - 24h post dose

• Sensitivity is primarily in the lower range of values, with little change above 1.5e-8 cm^2/s

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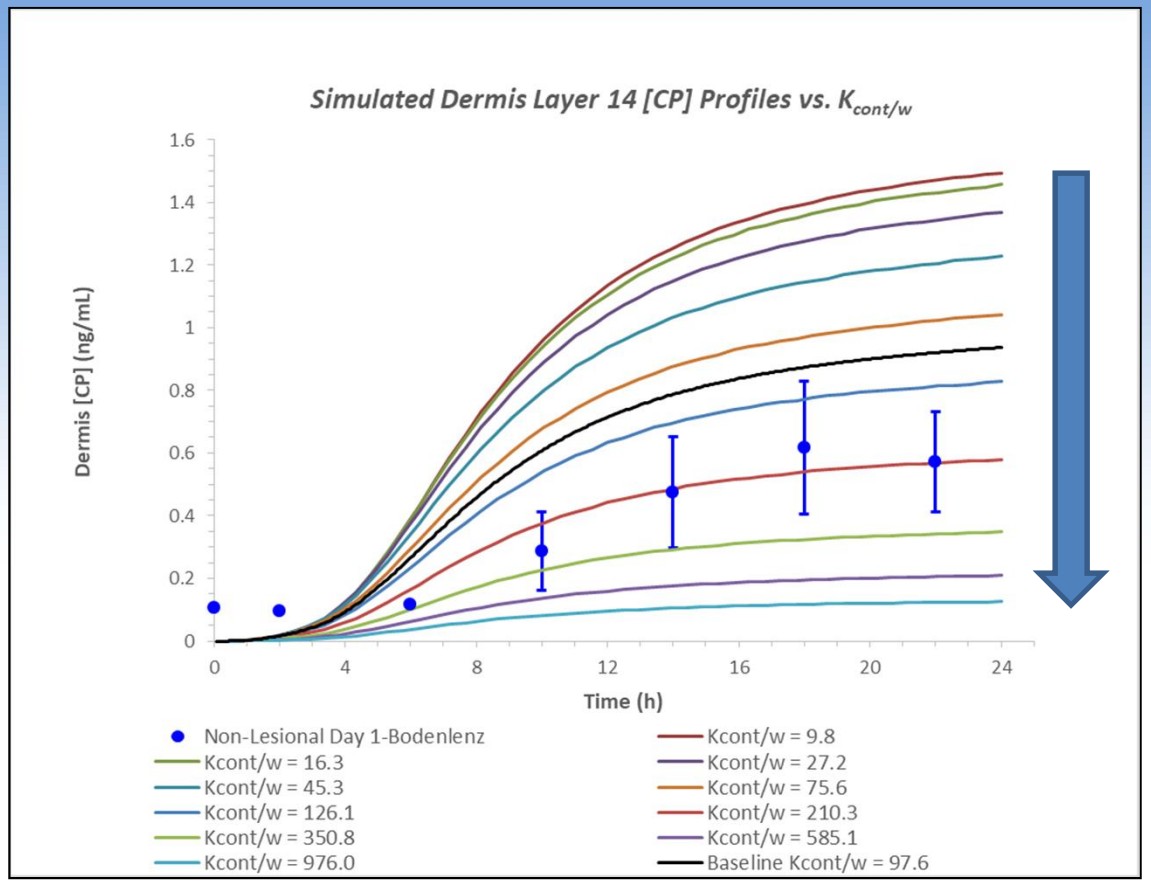
Sensitivity to Continuous Phase Partition Coefficient



• The unbound CP concentration profile in the dermis is highly sensitive to $K_{cont/w}$ (partition coefficient of CP between the continuous phase and water): A 10-fold change (±) in the baseline value of $K_{cont/w}$ produced >10-fold change in $[CP]_{DE}$ at geometric mean probe depth, from 16-24h post dose

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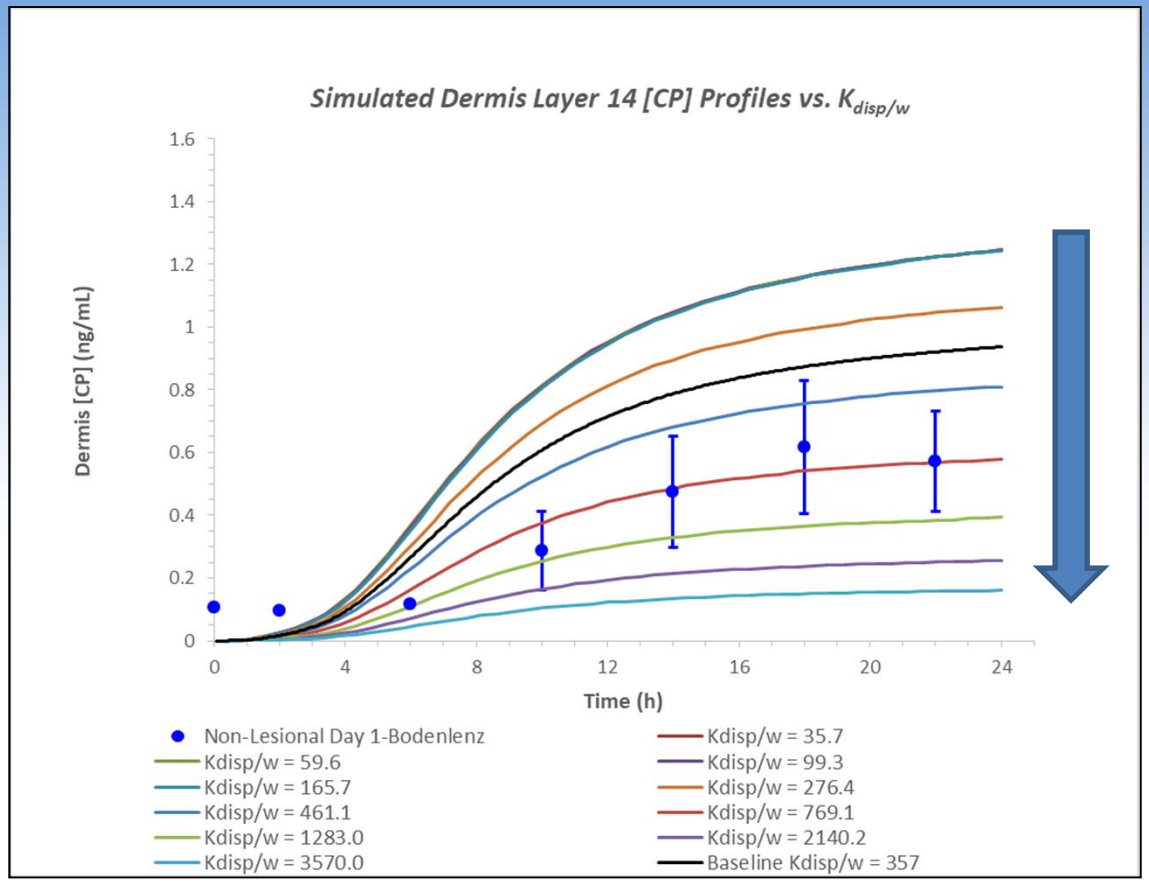
Sensitivity to Dispersed Phase Partition Coefficient



- The unbound CP concentration profile in the dermis is fairly sensitive to $K_{disp/w}$ (partition coefficient of the dispersed phase). Changing $K_{disp/w}$ by two orders-of-magnitude produced ~10-fold change in $[CP]_{DE}$ at geometric mean probe depth at 24h post dose
  - Sensitivity is primarily in the upper range of values, with little change below $K_{disp/w}$ = 165

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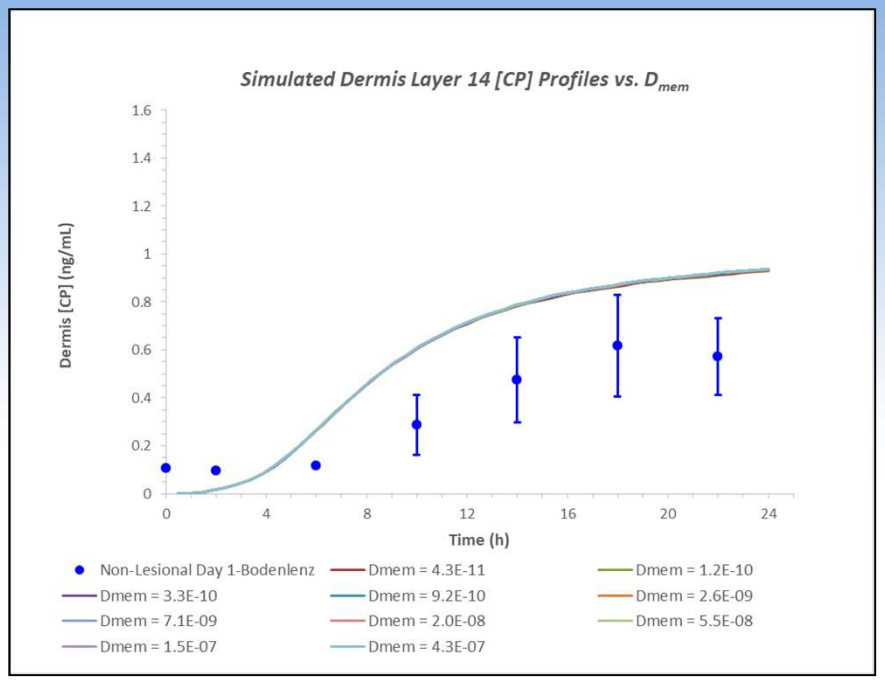
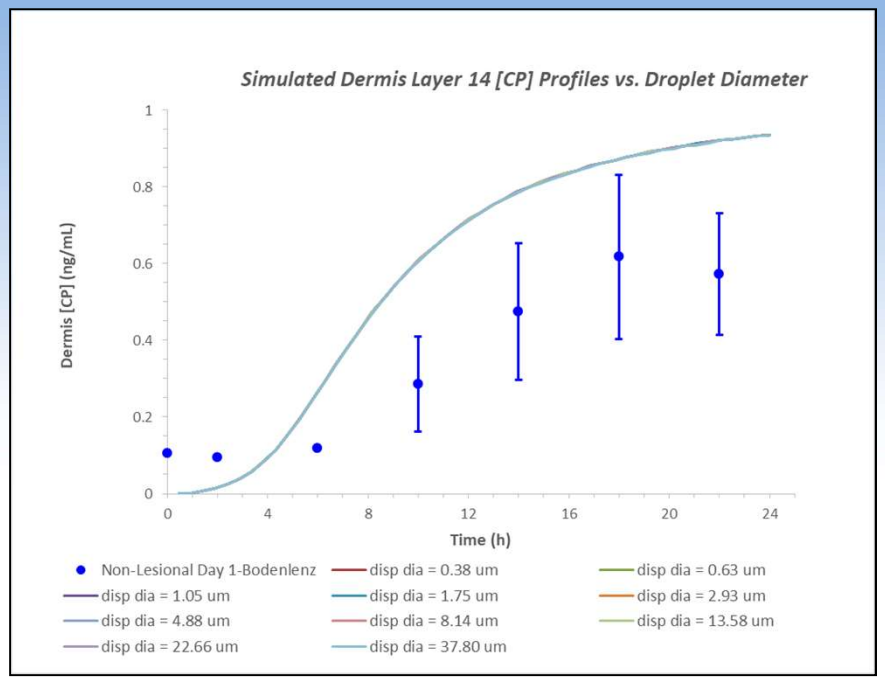
Sensitivity to Membrane Diffusivity and Dispersed Phase Droplet Diameter





- The model showed almost no sensitivity to D_{mem} or d_{disp} across a wide range of values

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in silico Modeling of Dermovate Cream Summary

- We were able to develop a model of Dermovate cream using the TCAT module in GastroPlus
  - The micro-emulsion formulation was defined via publicly available information and experimental data
  - Skin layer permeabilities were defined using built-in equations
- We simulated Day 1 of a clinical study conducted by Bodenlenz et al., 2016
  - Model predictions of $[CP]_{DE}$ and AUC_{24h}, as measured by dOFM, were reasonably accurate with respect to time and skin depth
- We identified the most sensitive formulation parameters as the partition coefficients of CP in the dispersed and continuous phases

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Thank you!

Simulations Plus Team

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Modeling Skin Permeability of Clobetasol Propionate

- Values of *stratum corneum* and viable epidermis permeability ($cm \cdot s^{-1}$), estimated by the models available in the TCAT module, are listed in the upper table
- Overall human skin permeabilities calculated from these values are listed in the lower table
- They are consistent with measurements for other steroids and their esters (references below)
- Robinson P_{STCOR} / Kretsos $P_{VE,DE}$ were used for baseline simulations

Permeability (cm/s) of CP in human skin layers via equations built into the TCAT module				
Model	***S Corneum***	***Model***	***VE***	***Dermis***
Wang-Kasting-Nitsche	1.67E-06	Kretsos	1.44E-04	7.83E-06
Potts-Guy	1.66E-07	Bunge-Cleek	5.33E-05	2.90E-06
Robinson	1.91E-07	Robinson	3.20E-05	1.74E-06

S Corneum	***VE / Dermis***	***Skin Perm (cm/s)***
WKN	Kretsos	1.36E-06
"	Bunge-Cleek	1.04E-06
"	Robinson	8.30E-07
Potts-Guy	Kretsos	1.62E-07
"	Bunge-Cleek	1.57E-07
"	Robinson	1.51E-07
Robinson	Kretsos	1.86E-07
"	Bunge-Cleek	1.79E-07
"	Robinson	1.71E-07

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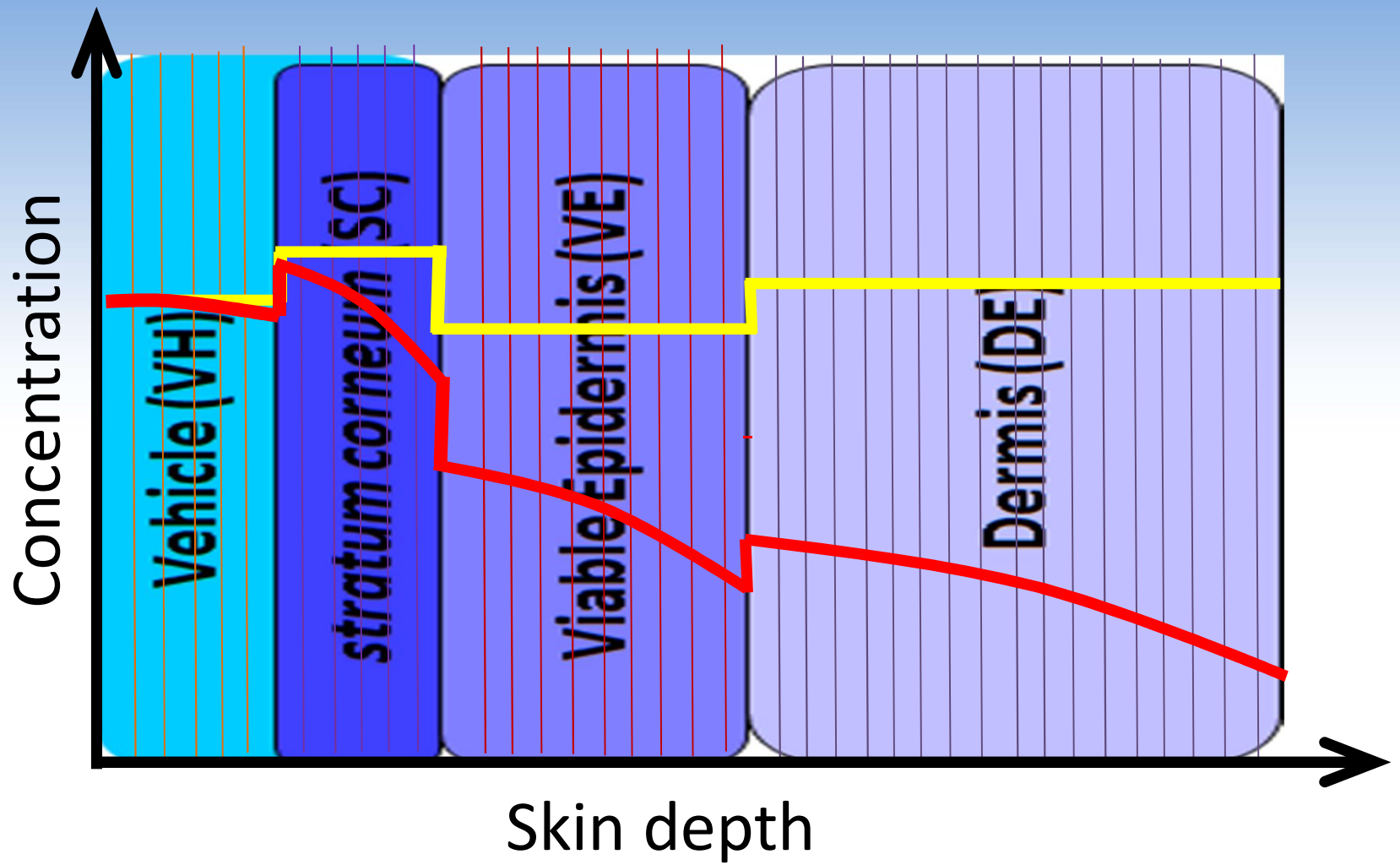
Diffusion Through Skin Layers



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