Modeling Dermal Drug Absorption from Complex Semisolid Formulations: Insights from Multi-Phase, Multi-Layer MechDermA Model

Topical Drug Development - Evolution of Science and Regulatory Policy II

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Disclaimer

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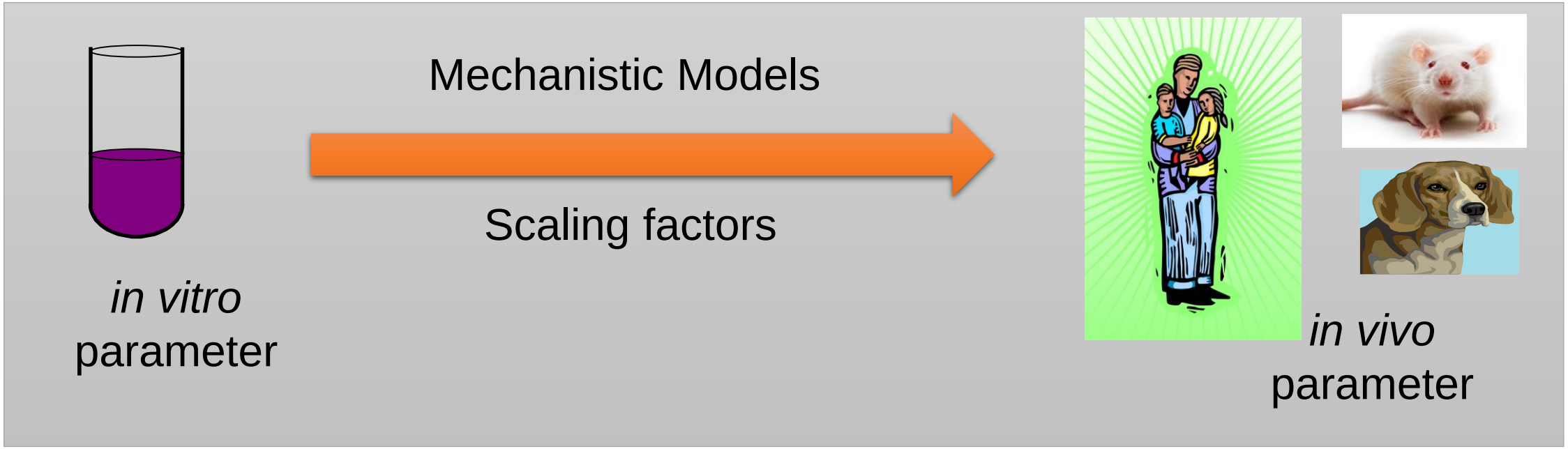
Outline of the Presentation

1. Introduction of IVIVE and its application for dermal drug delivery
2. Metamorphosis of topically applied formulations – Modeling Challenges
3. Skin PBPK model structure and input parameters required
4. Case Study 1 – Metronidazole commercial formulations (Gel and Cream)
5. Case Study 2 – Acyclovir commercial formulations (Cream)
6. Conclusions

Understanding *In vitro* to Predict *In vivo – In vitro In vivo Extrapolation* (IVIVE) *with Physiologically Based Pharmacokinetic (PBPK) Modeling*



- Information obtained from surrogate *in vitro, ex vivo* or animal studies is used to provide quantitative solutions to predict the *in vivo* behavior of drugs in a target human population prior to undertaking clinical study
- This approach is widely used now in field of metabolic clearance/drug-drug interaction prediction and gastrointestinal absorption.

A Rostami-Hodjegan et al. Clin Pharmacol Ther. 2012 Jul;92(1):50-61. doi: 10.1038/clpt.2012.65.

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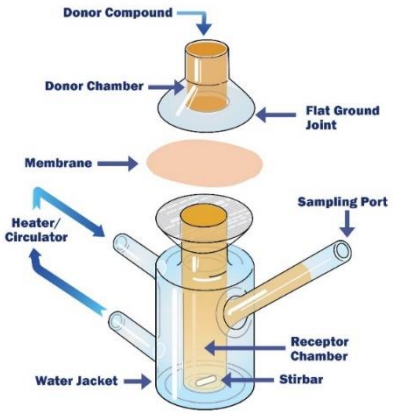
Dermal *in vitro in vivo* extrapolation (IVIVE) – A step towards Virtual Bioequivalence Complex Topical Products

Input



***In vitro* Release/Permeation Studies**

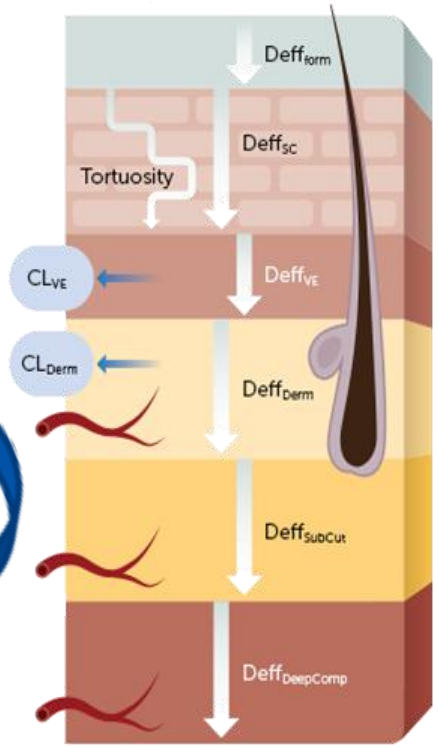
+

Understanding Q1, Q2 and Q3 properties of topical products

- **Composition**
- **Drug Solubility in different phases**
- **Drying Rate (weight loss)**
- **Specific gravity**
- **Particle size (solid particles/droplets)**
- **Rheology**
- **Precipitation characterization**
- **Excipient penetration**

Confirm & Learn Approach

Verify

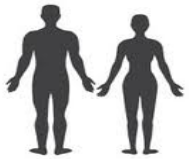


Mechanistic Dermal Absorption Model

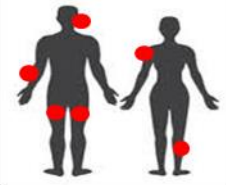
- **Confirm key drug/formulation parameters: partition and diffusion coefficients**
- **Verify model performance with challenge formulations (different strengths, non-Q1, Q2, Q3 formulation)**

IVPT verified PBPK model combined with *In vivo* physiology to predict *in vivo* local and systemic exposure

Extrapolate



Healthy NEurCaucasian



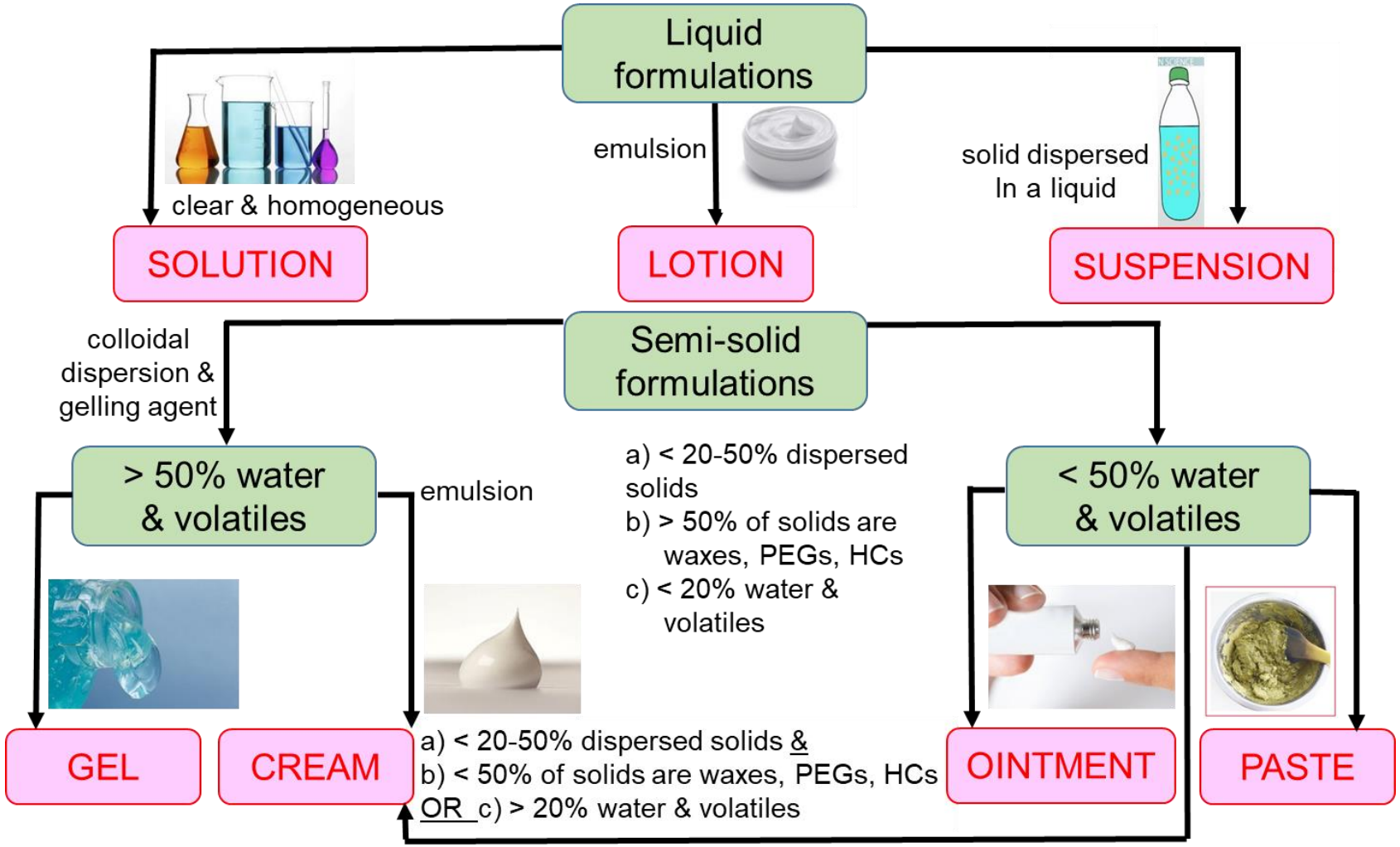
Diseased Population

Elderly Subjects

Paediatric Population

Q1 – Qualitative Sameness Q2 – Quantitative Sameness Q3 – Microstructure sameness

Topical Formulations/Products for Dermatological Applications

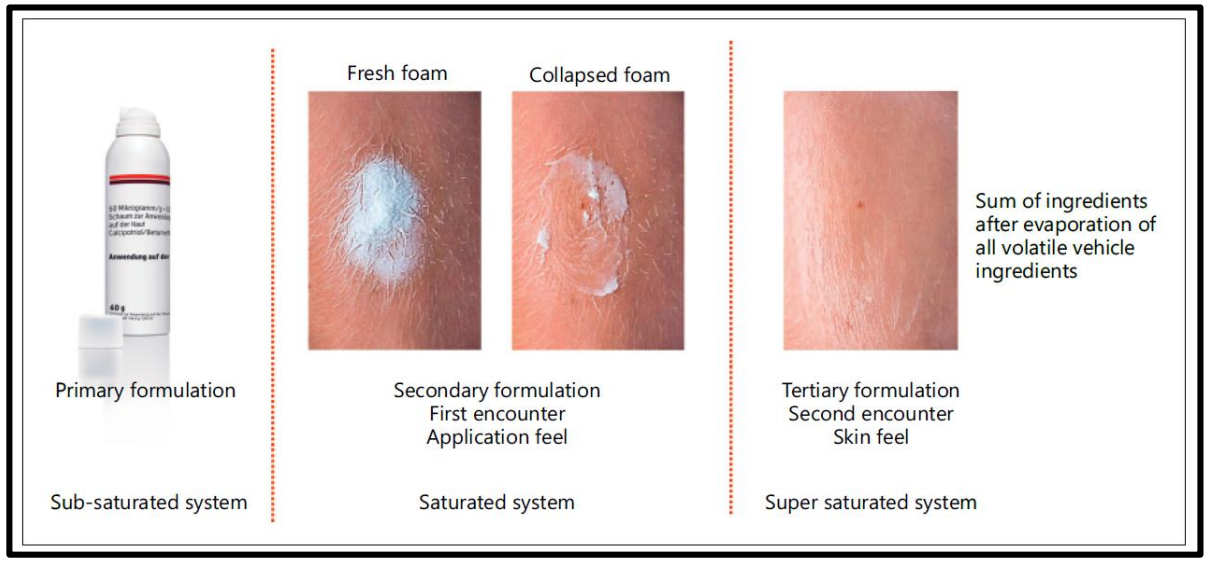


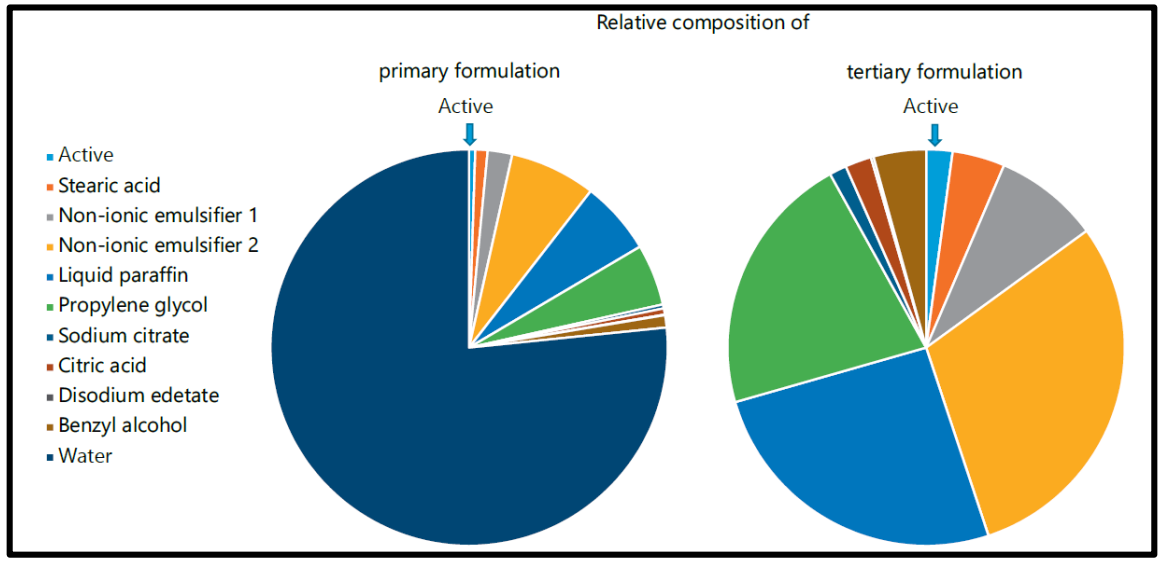
All these products can broadly be classified as –

1. Solutions
2. Emulsions
3. Suspensions

Adapted from SR Chaudhuri, AAPS Workshop Nov. 2017 San Diego (co-organisers: S. Raney & SR Chaudhuri)

Metamorphosis of Topical Formulations





Change in concentration of active ingredients dissolved in the aerosol form formulation over application time. BD Betamethasone dipropionate, Cal calcipotriene

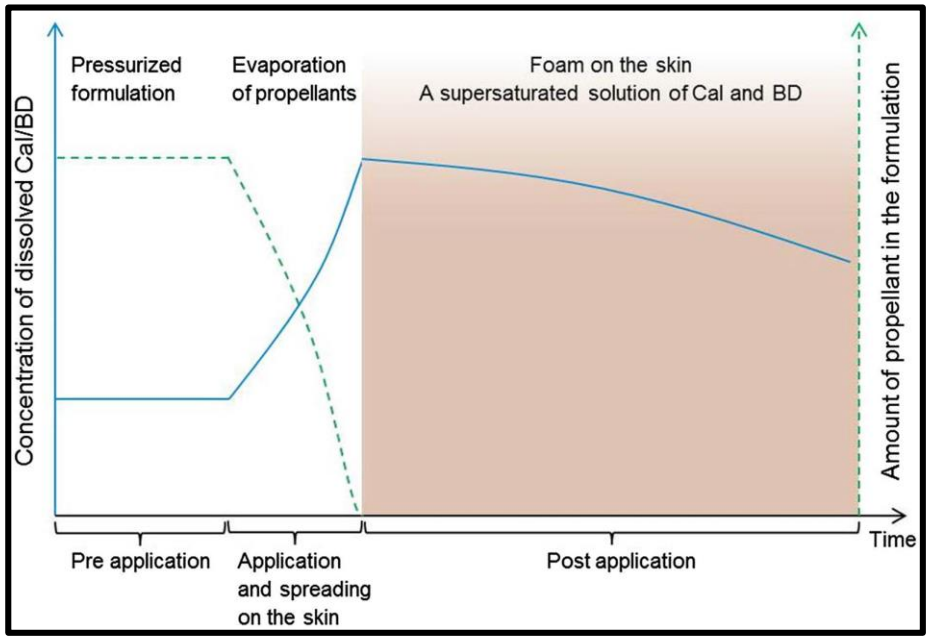


Image adapted from Lind et al, Dermatol Ther (Heidelb) 2016; 6: 413–425.;Suber et al, Curr Probl Dermatol. Basel, Karger, 2018, vol 54, pp 152–165

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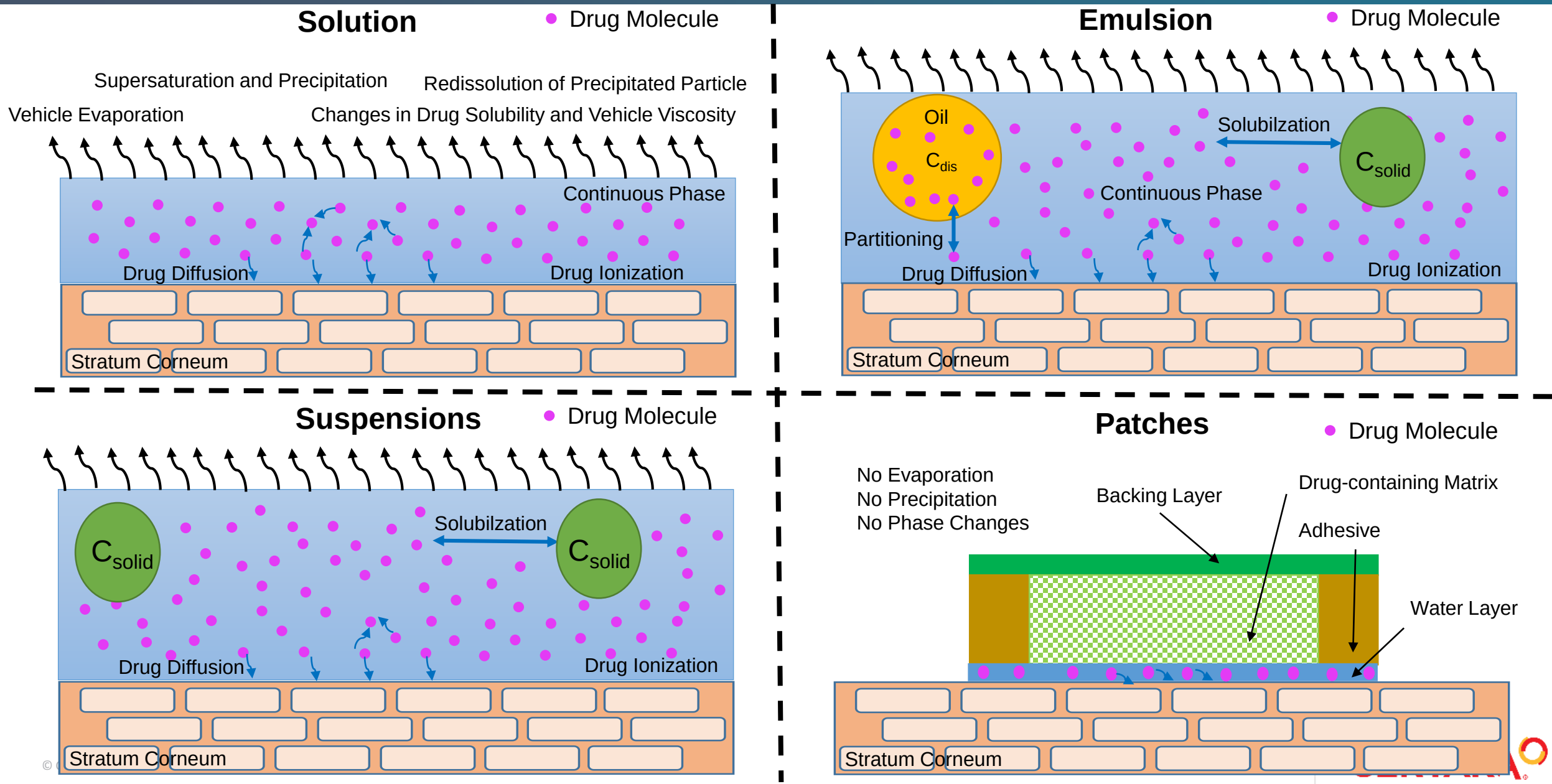
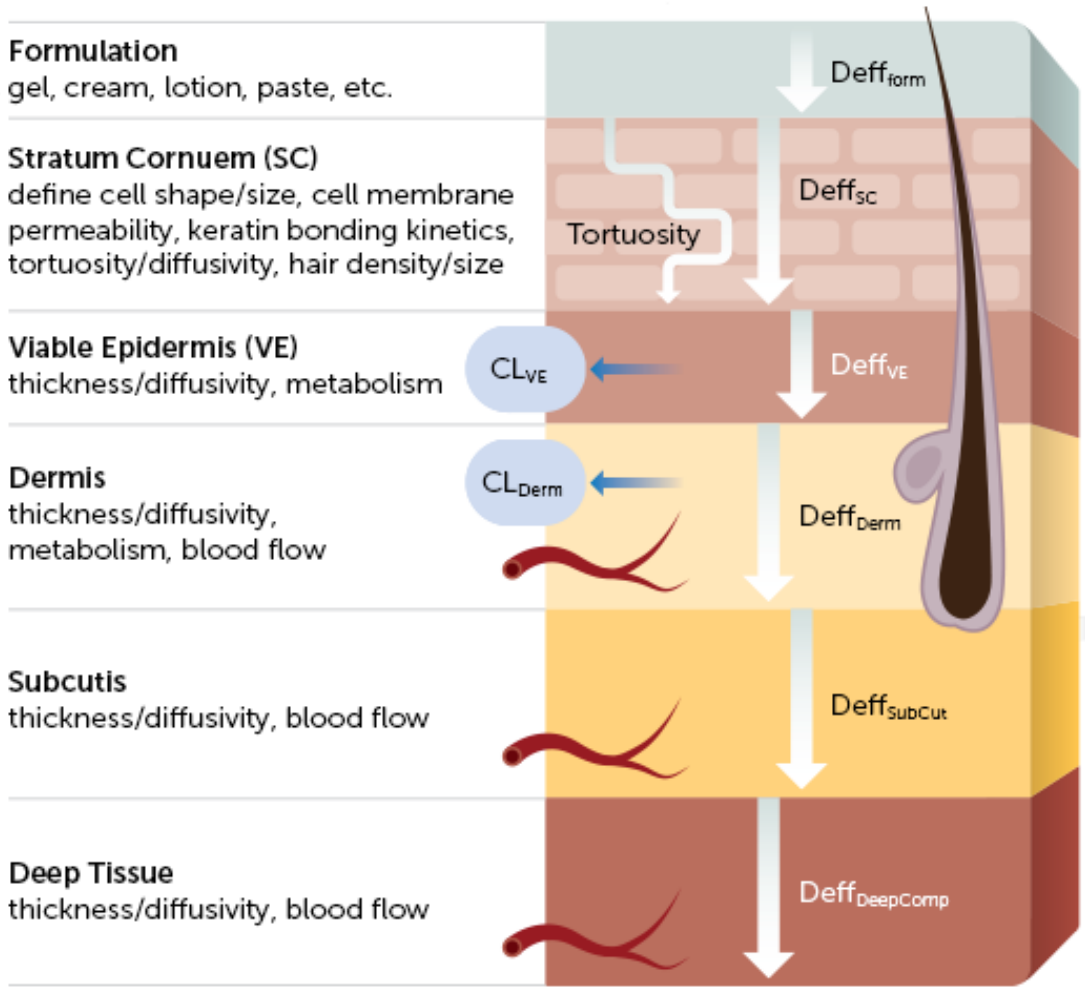
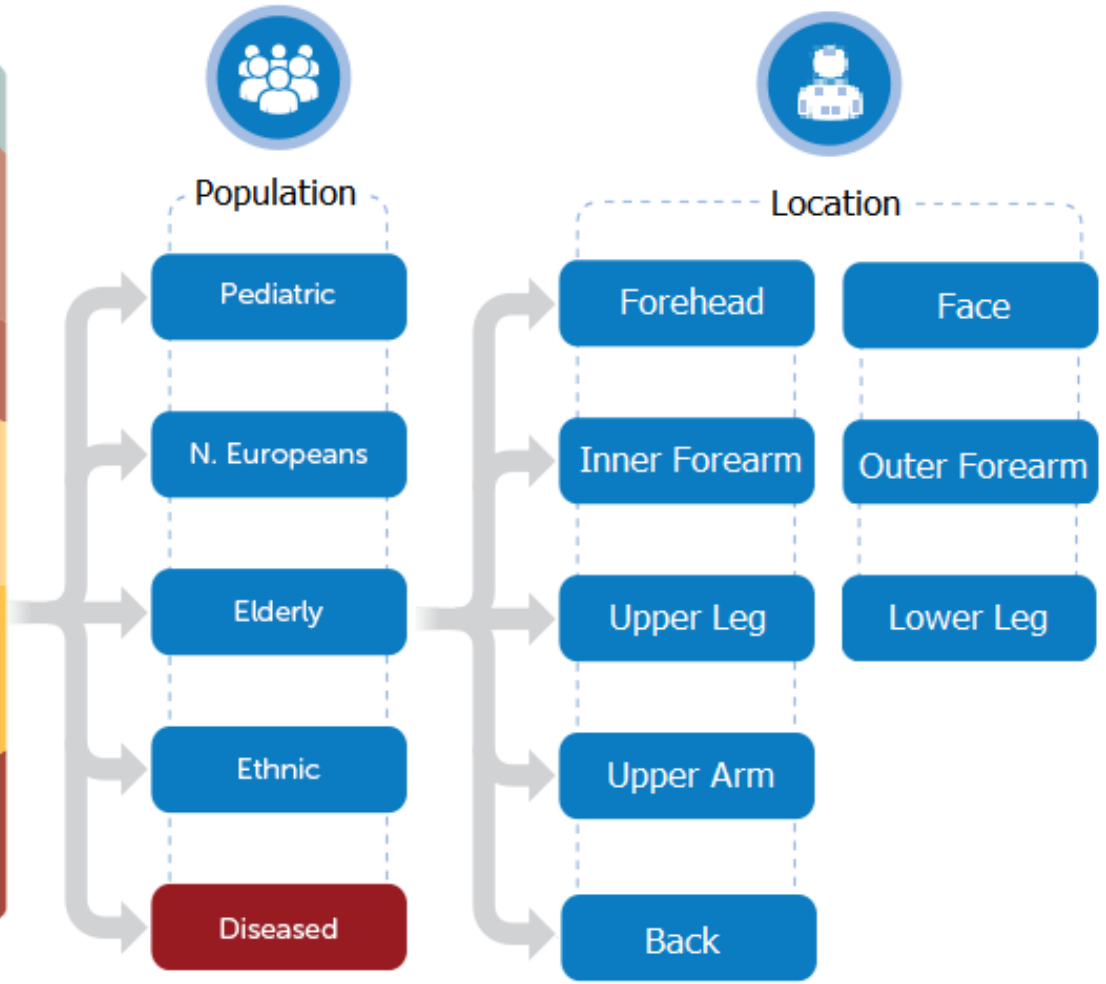
Modeling Metamorphosis of Topical/Transdermal Formulations – Even Simple Formulations Are Not That Simple !!!



Simcyp' s Multi-Phase Multi-Layer (MPML) MechDermA Model





Martins et al. GRC - Barrier Function of Mammalian Skin, NH, USA, August 13 - 18, 2017.

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Input Parameters Needed to Parameterize the Model

Systems Data | **Trial Design** | **Drug Data** | **Formulation**

Systems Parameters

In vitro Simulation

- Static or flow through
- Anatomical region
- Type of skin sample
- Thickness of skin sample
- Area of diffusion cell
- Volume of receptor fluid

In vivo Simulation

- Site of application
- Physiology is then populated from database generated from meta-analysis (can be modified by the user)

Trial Design

- Number of subjects
- Demographics (age range, gender)
- Dose and volume of formulation applied
- Duration of simulation

Drug Parameters

- MW
- Log P
- pKa
- f_u (QSAR)

Skin Model Inputs (Partition and Diffusion Coefficient)

- $K_{SClip:Water}$ (QSAR)
- $K_{SC:VE}$ (QSAR)
- $K_{Dermis:VE}$ (QSAR)
- $K_{Dermis:Blood}$ (QSAR)
- D_{SClip} (QSAR)
- D_{VE} (QSAR)
- D_{Dermis} (QSAR)
- fu_{SC} (QSAR)

Formulation Data

- Type of Formulation
  - ✓ Solution
  - ✓ Emulsion (w/wo particles)
  - ✓ Suspension
  - ✓ Patch
- Composition
- Drug solubility in different phases
- Drying rate (weight loss)
- Specific gravity
- Particle size (solid particles/droplets)
- Rheology
- Precipitation characterization

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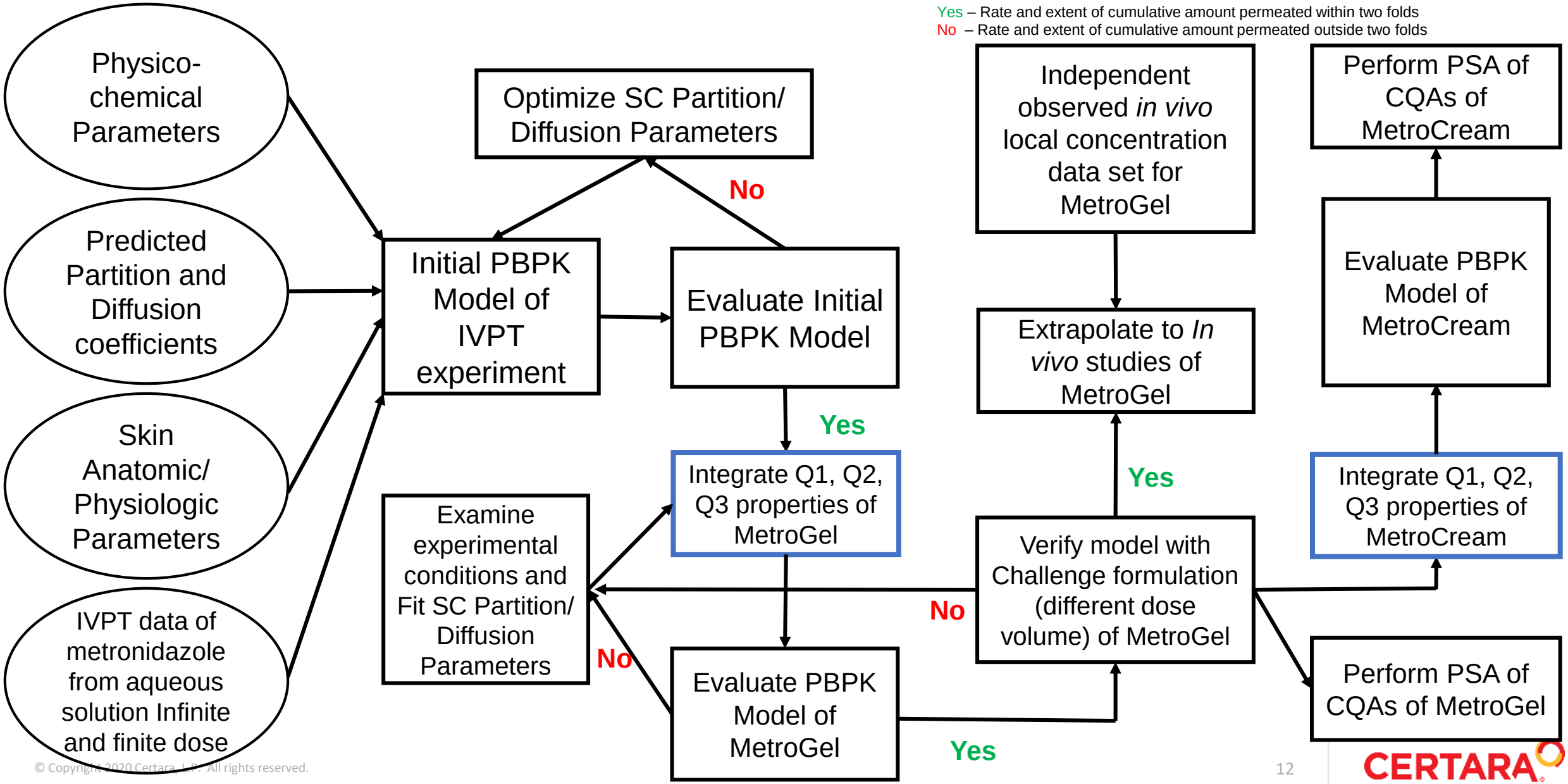
Case Example 1 – Modeling *In Vitro* and *In Vivo* Skin Permeation of Metronidazole Commercial Formulations (MetroGel® and MetroCream®)

Experimental Data and a Modeling Plan for Metronidazole



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MetroGel® (0.75% w/w Gel)

Data Available

a. IVPT data - Infinite and Finite dose from aqueous metronidazole solution.

b. A battery of Q3 characterization data such as pH of formulation, viscosity, evaporation profile, drug solubility in continuous phase from two different laboratories.[a.b]

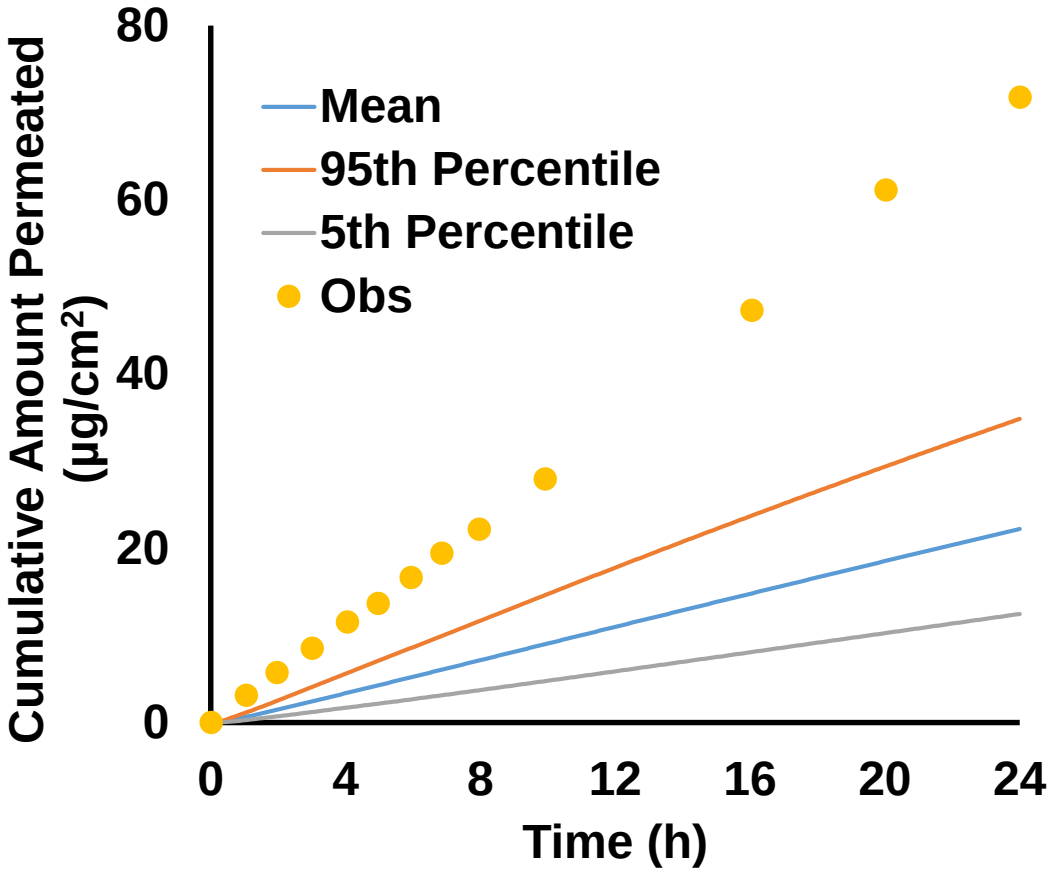
c. IVPT data – three doses 3, 10 and 30 mg/cm^2 from Ajjarapu et al.[c]

d. IVPT data – one dose 10 mg/cm^2 from Roberts et al.[b]

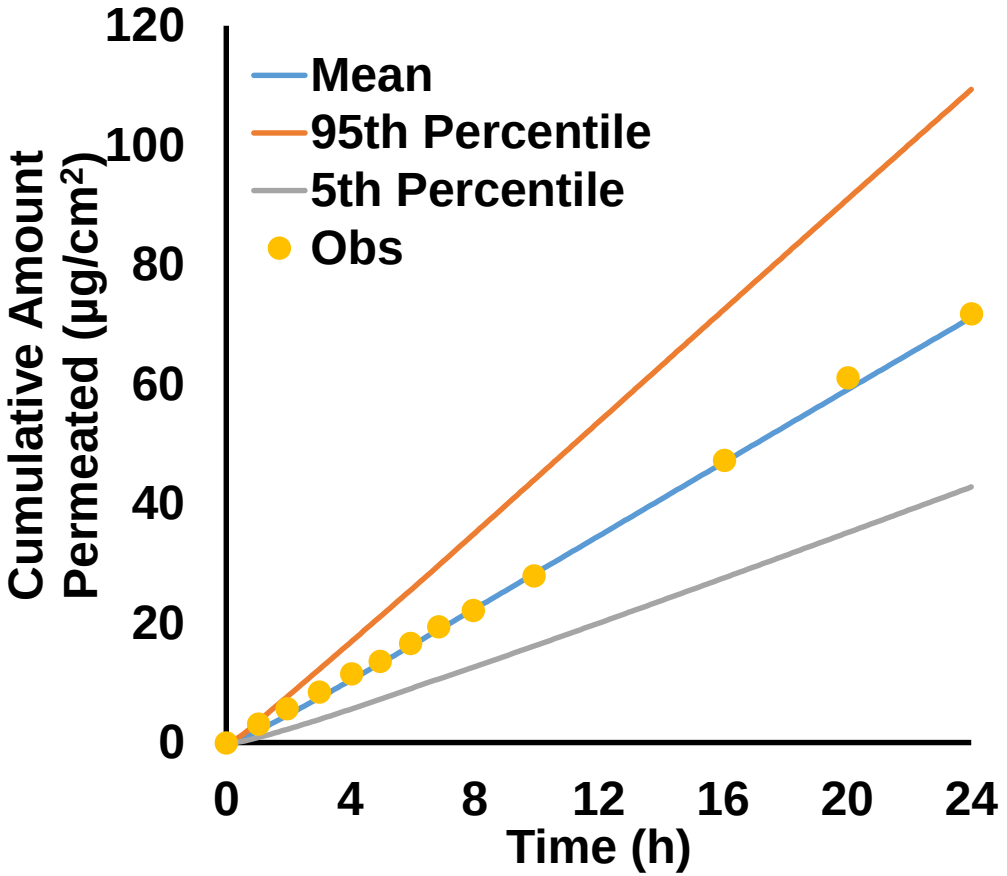
e. *In vivo* stratum corneum permeation data from two clinical studies reported in literature.

[a]Murthy SN. et al. AAPS 2015; [b]Roberts et al. (unpublished); [c]Ajjarapu et al. Poster Presentation. AAPS 2019

Simulation of *in vitro* skin permeation of metronidazole from aqueous solution – Infinite Dosing Conditions



Optimized $Kp_{sclipid:water}$



Bottom-up predictions led to nearly four fold under prediction of the extent of permeation

Simulated cumulative amount permeated (µg/cm²) captured the observed profile

$Kp_{sclipid:water}$ = Partition coefficient between SC lipids:water

*Observed data is n = 6

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2019

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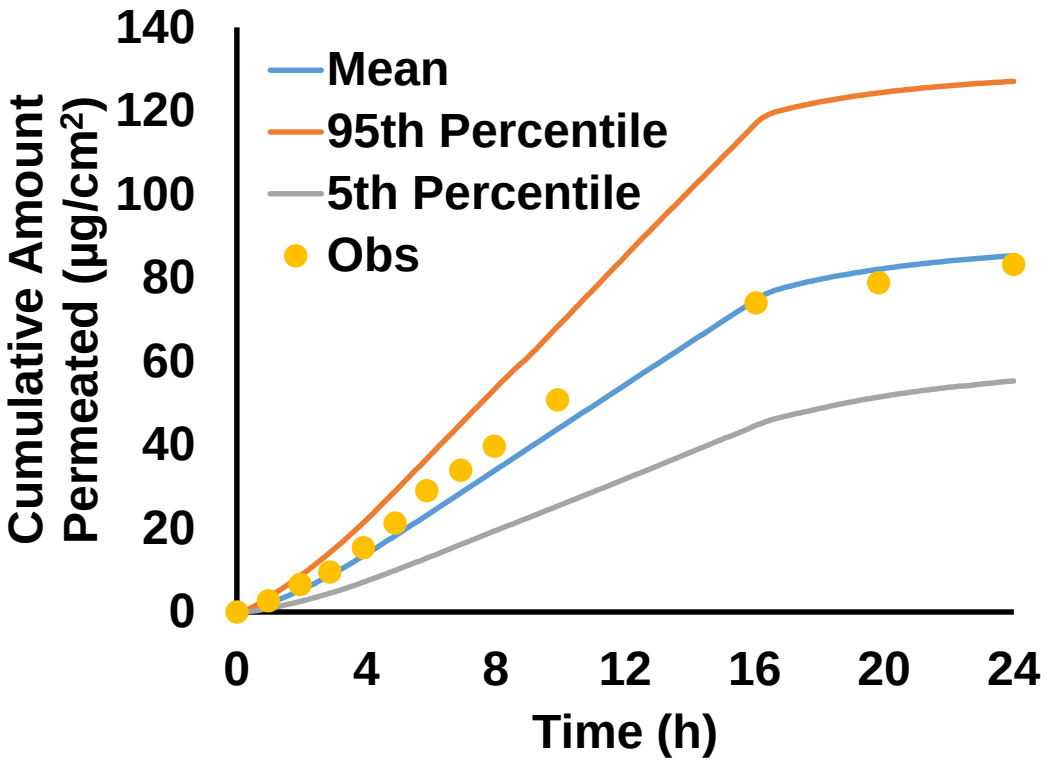
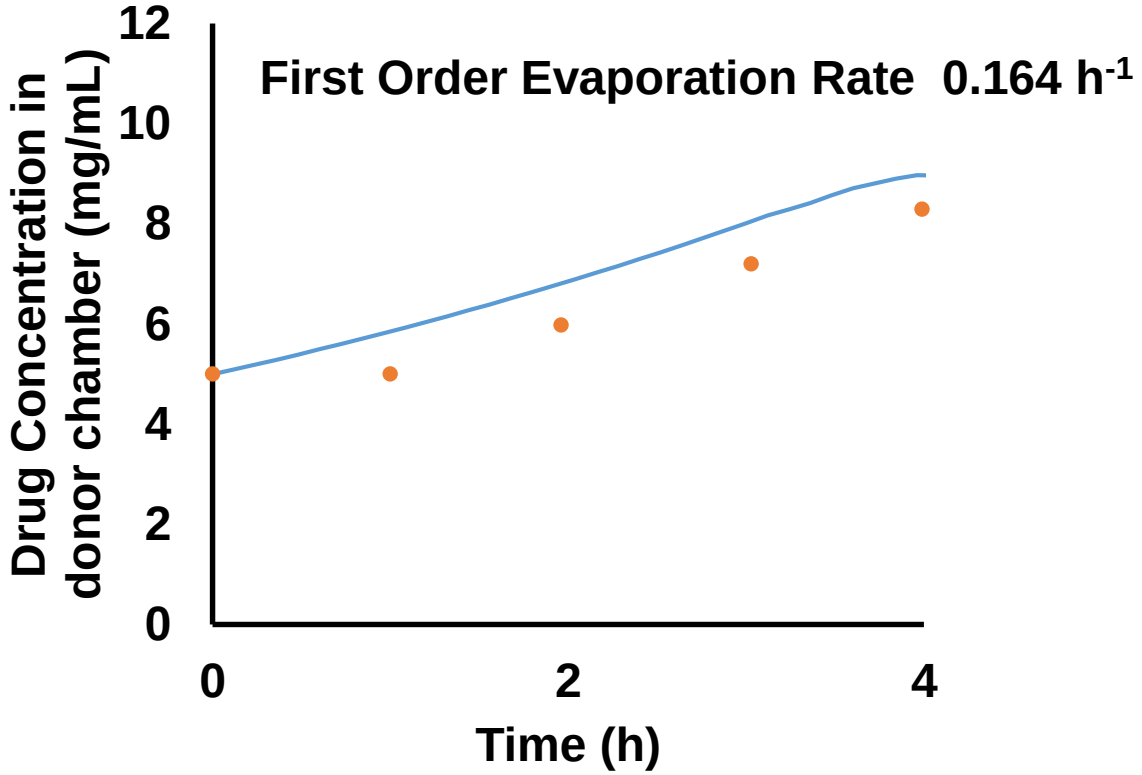
Simulation of *in vitro* skin permeation of metronidazole from aqueous solution – Finite Dosing Conditions

- Back as skin site, Dose = 1.5 mg, Dose Volume = 300 µL, Trial Design = 10 trials X 6 individuals





Predicted profile closely matches to the observed data. This steps serve to verify the fitting of $Kp_{sclipid:water}$

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2019

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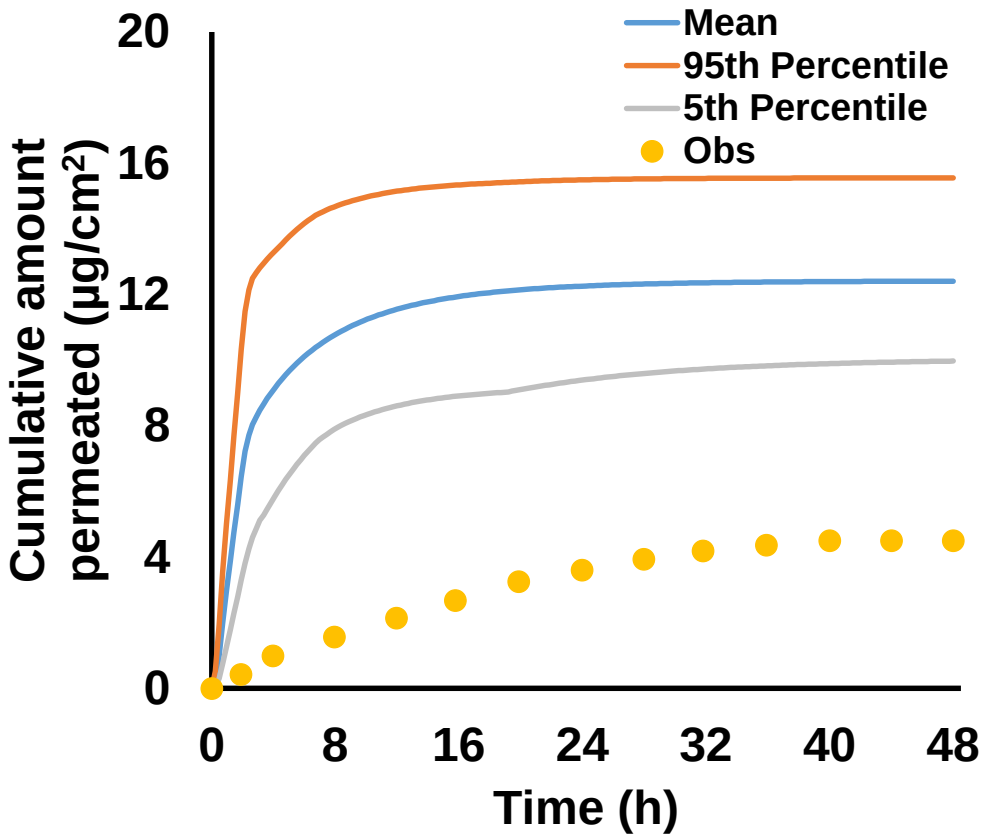
Simulation of *in vitro* skin permeation of metronidazole from MetroGel® - Murthy et al. Q3 Characterization - Dose 10 mg/cm²

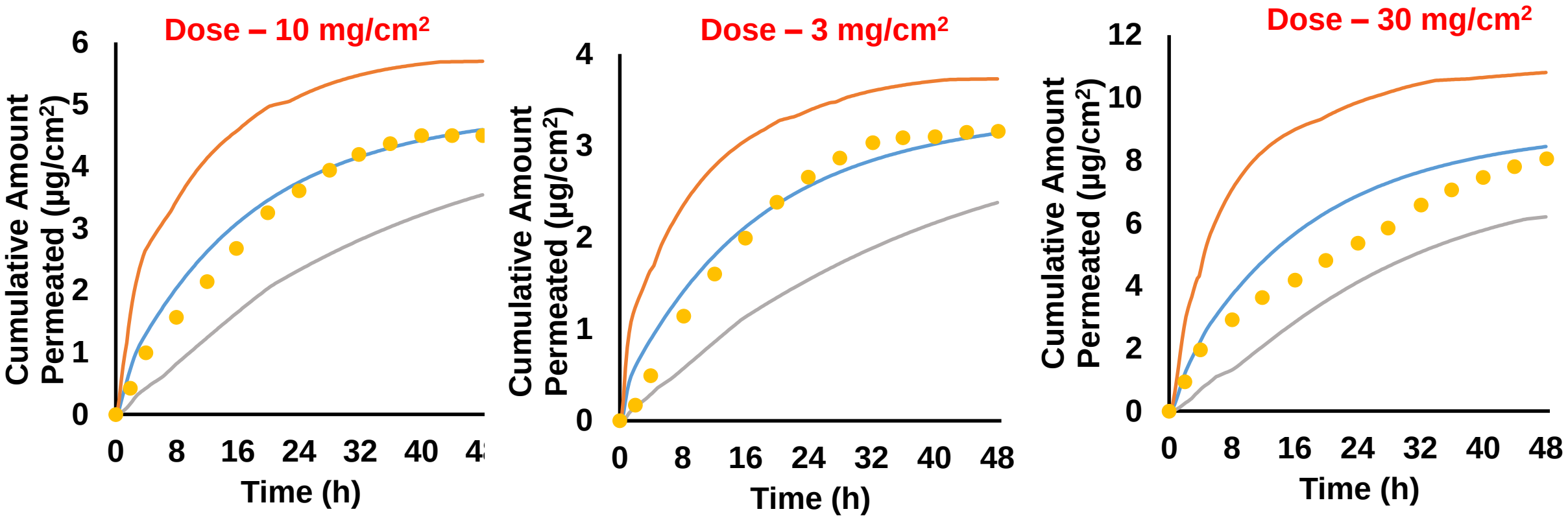


- Significant overprediction was observed both for the rate and extent of metronidazole permeation from Metrogel®
- Clearly, the translation of model parameters from simple aqueous based infinite and finite dosing conditions to complex formulation was not straight forward
- A closer look at the experimental conditions revealed differences in hydration conditions between the aqueous IVPT experiments where large dose volume was used (around 2mL in infinite dosing conditions) vs IVPT experiments for gel where 10µL dose volume was applied in the experiment.
- **Skin hydration is known to effect the diffusion of the drug through stratum corneum[a] and thus, we decided to optimize diffusion coefficient of metronidazole using IVPT data for 10 mg/cm² for MetroGel formulation.**

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2017; [a]Yuosef et al. AAPS J . 2017 Jan;19(1):180-190.

Simulation of *in vitro* skin permeation of metronidazole from MetroGel® - Murthy et al. Q3 Characterization - Dose 3, 10 and 30 mg/cm²

- Optimized $D_{sclipid}$ using 10 mg/cm² IVPT data
- 3 mg/cm² and 30 mg/cm² IVPT dataset serves as model verification



Optimized PBPK model was able to **predict** cumulative amount permeated (µg/cm²) observed from the challenge formulation (different dose volumes).

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2017

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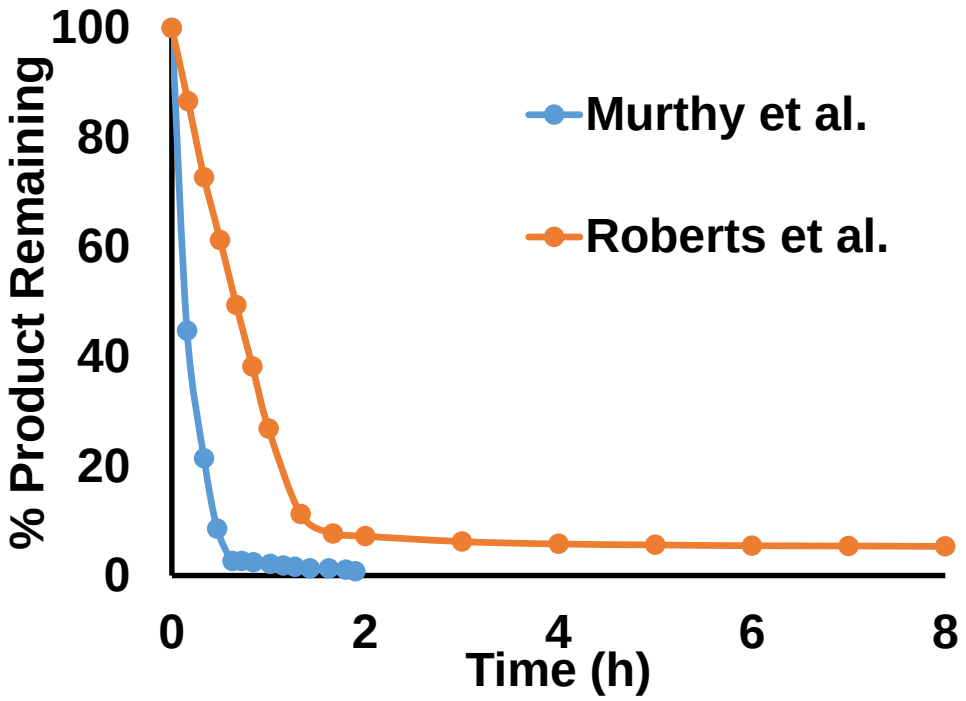
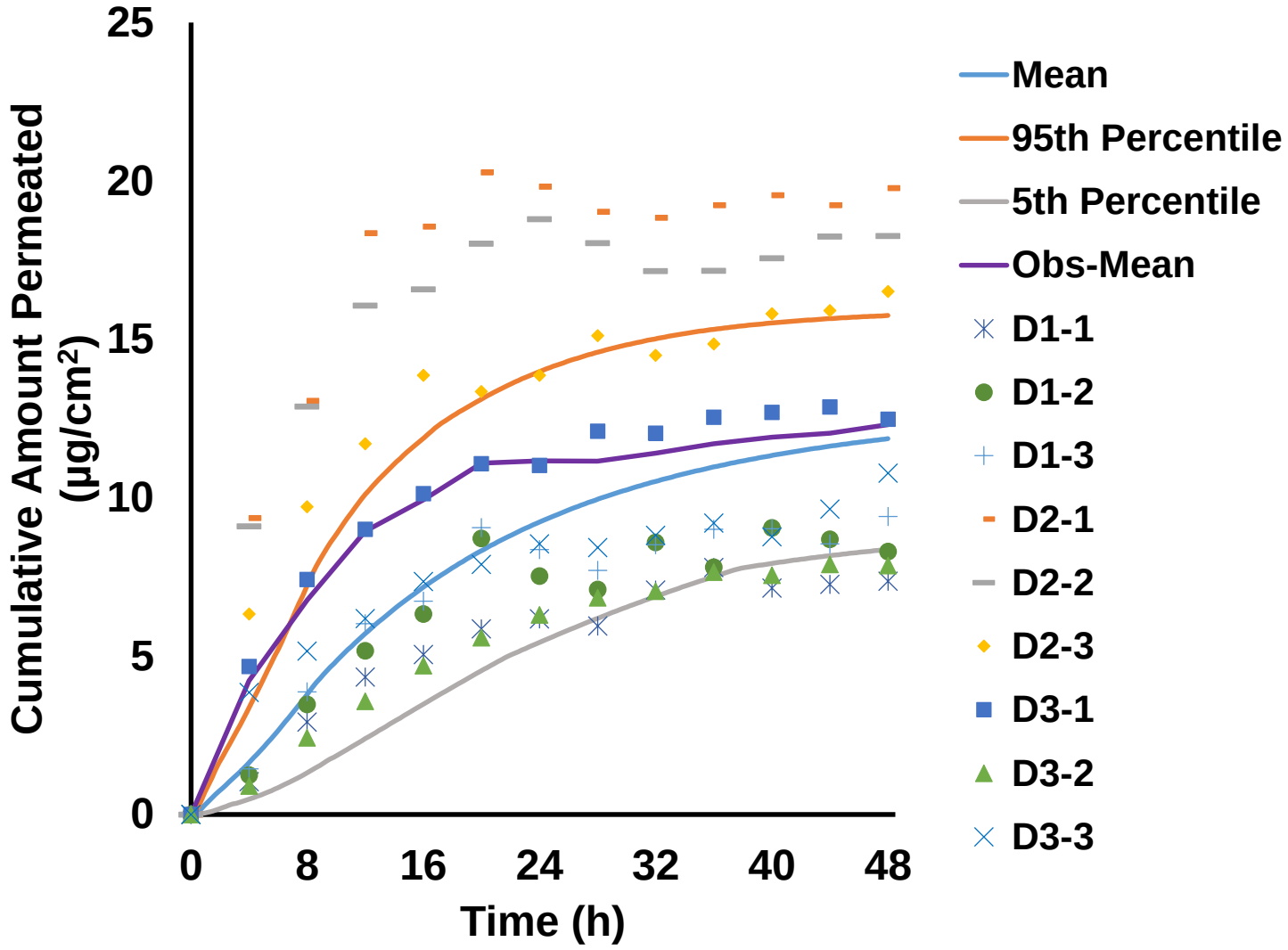
Simulation of *in vitro* skin permeation of metronidazole from MetroGel® - Roberts et al. Q3 Characterization - Dose 10 mg/cm²

All the parameters are similar except pH of formulation (pH 4.8) and evaporation profile

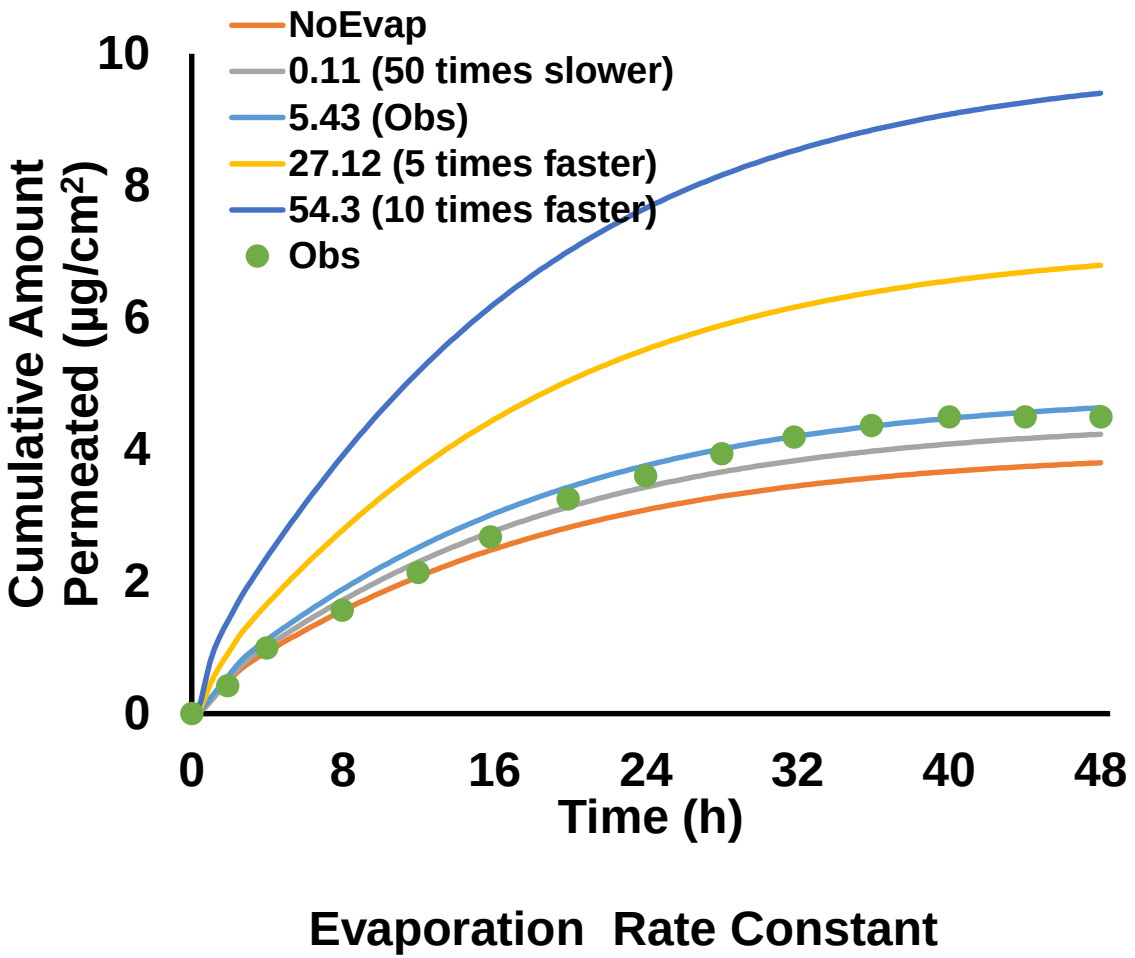




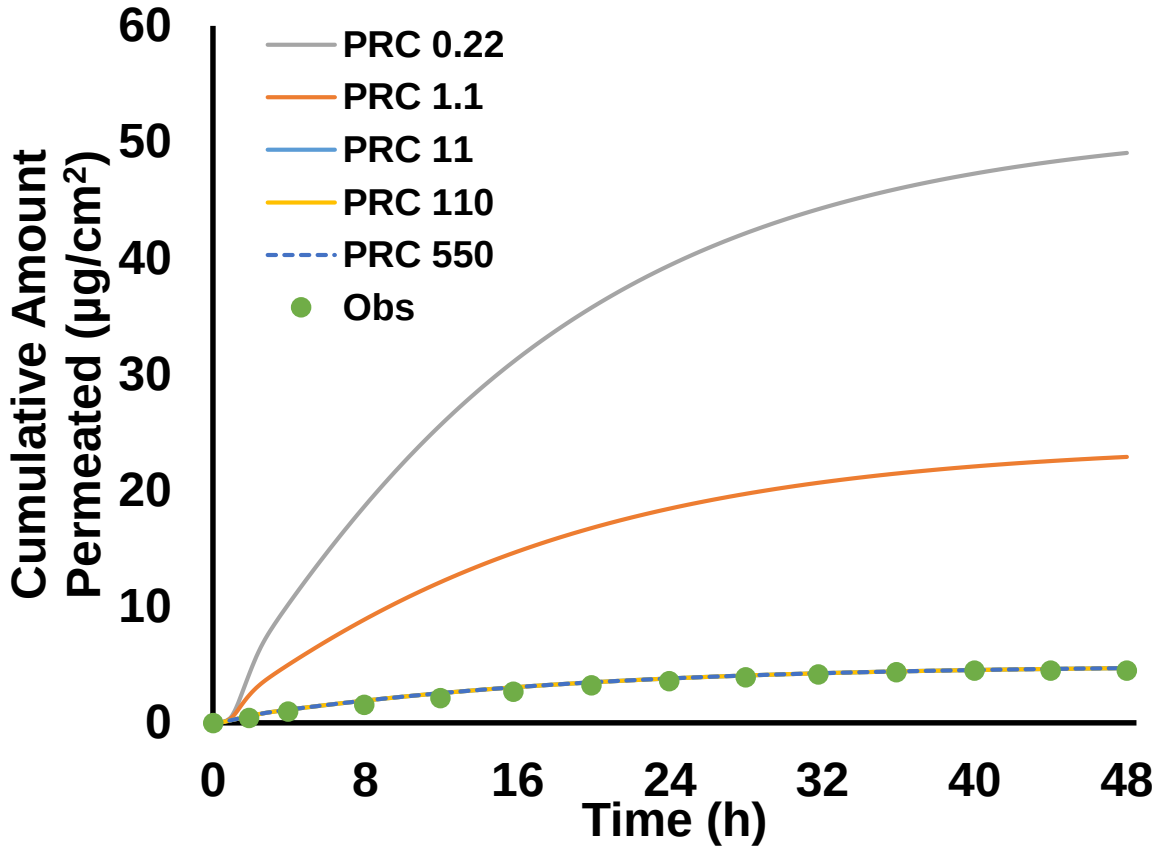
The model was able to **predict** mean cumulative amount permeated (µg/cm²) as well as variability from 10mg/cm² dose determined by another lab.

Murthy SN. et al. AAPS 2015; Roberts et al. (unpublished)

Parameter Sensitivity Analysis of Critical Formulation Parameters of MetroGel®



Evaporation Rate Constant



Precipitation Rate Constant

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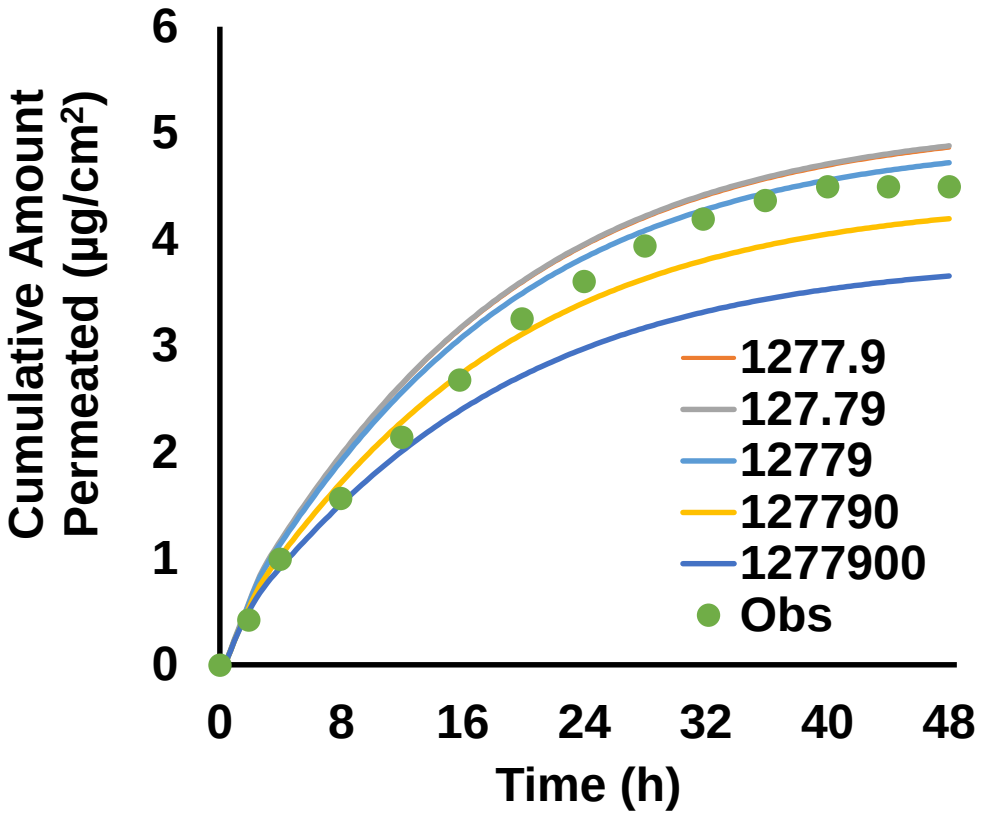
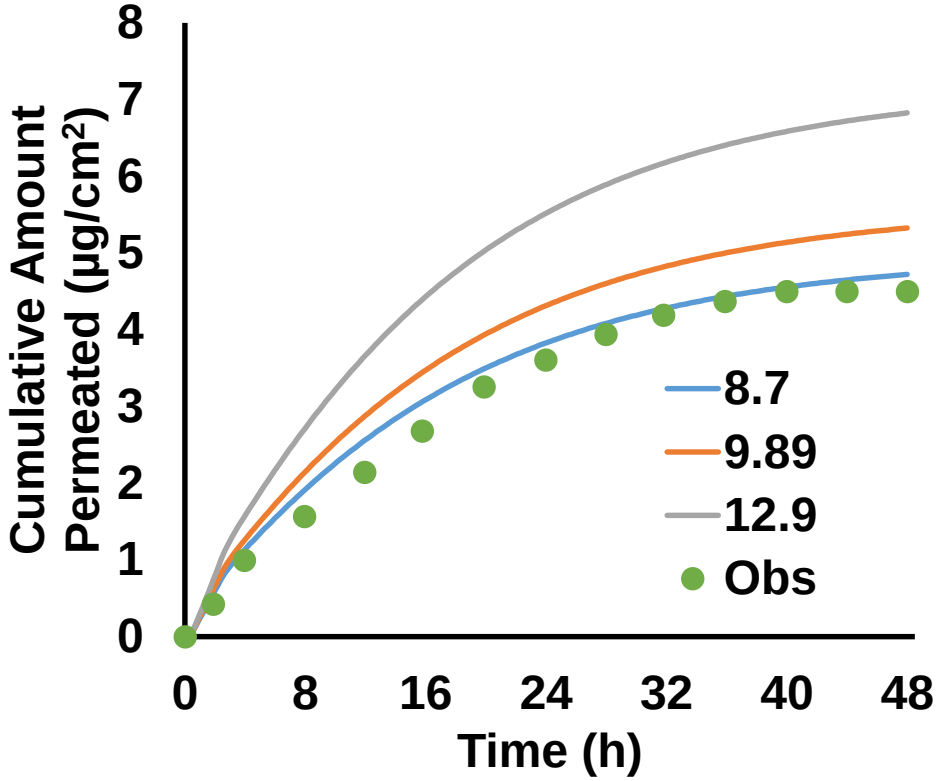
Parameter Sensitivity Analysis of Critical Formulation Parameters of MetroGel®



Vehicle Viscosity



Drug Solubility in Continuous Phase (mg/mL)

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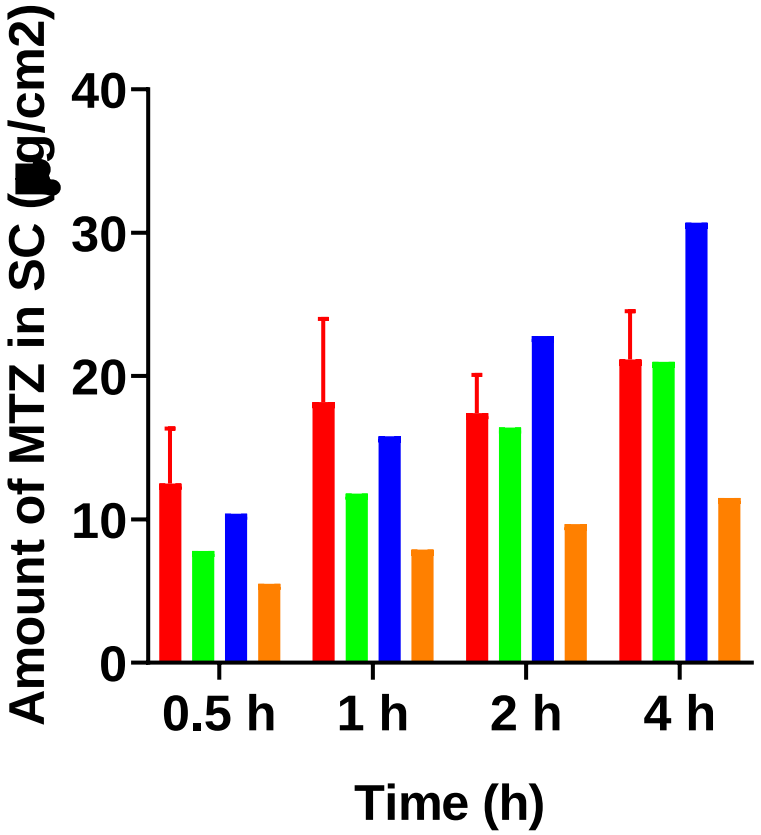
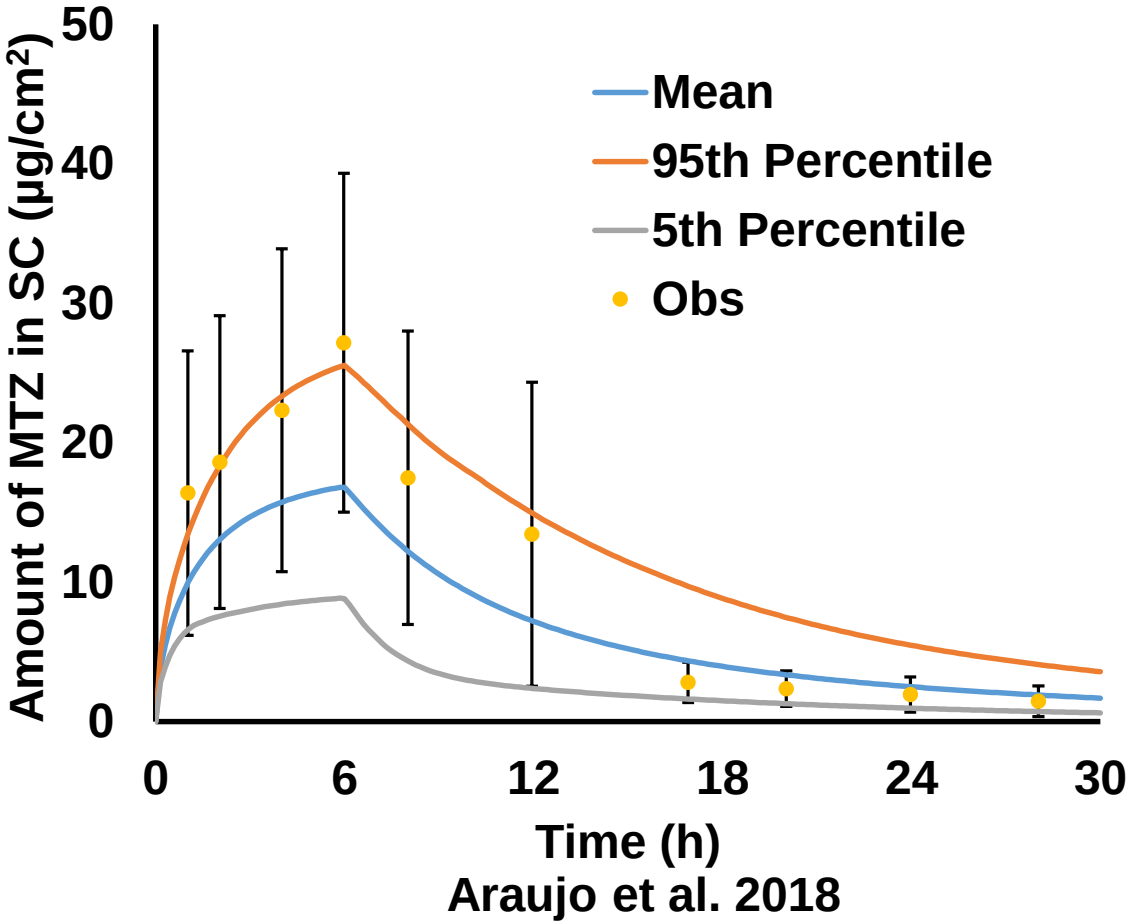
Simulation of *in vivo* skin permeation of metronidazole from MetroGel® and Rosex®

Rosex was assumed to be similar to the Metrogel. Both are 0.75% w/w gels of metronidazole with similar Q1 properties

Assumed metronidazole freely permeates through corneocyte



Dykes et al. 1997



Araujo et al. 2018

The model was able to **predict** metronidazole amount permeated (µg/cm²) in the stratum corneum observed *in vivo* demonstrating successfully IVIVE in this case.

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MetroCream® (0.75% w/w Gel)

Data Available

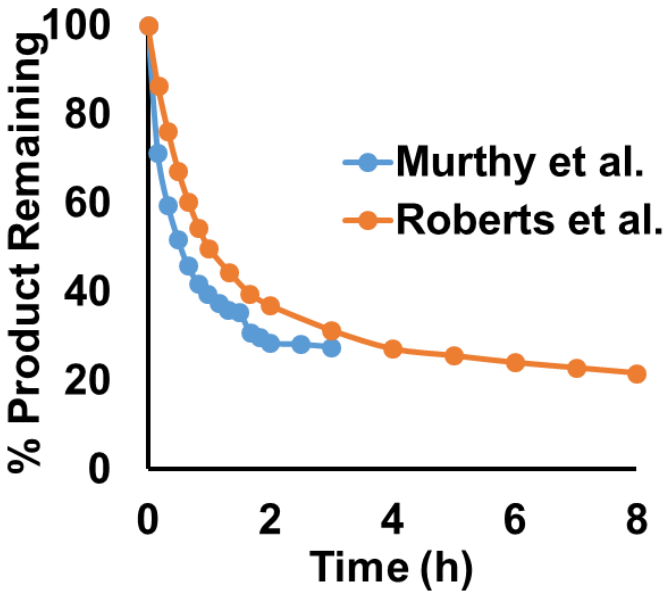
a. A battery of Q3 characterization data such as pH of formulation, viscosity, evaporation profile, drug solubility in continuous phase from two different laboratories.[a,b]

b. IVPT data –10 mg/cm^2 from three different laboratories.[a,b,c]

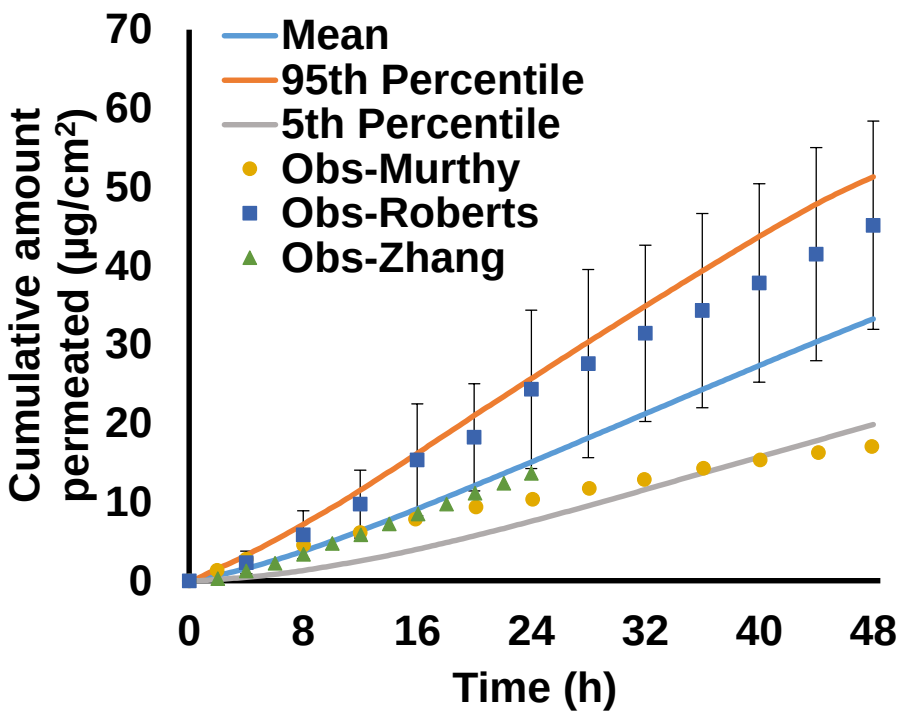
[a]Murthy SN. et al. AAPS 2015; [b]Roberts et al. (unpublished), [c]Zhang et al. Poster Presentation. AAPS 2019

Simulation of *in vitro* skin permeation of metronidazole from MetroCream ® (10 mg/cm2)

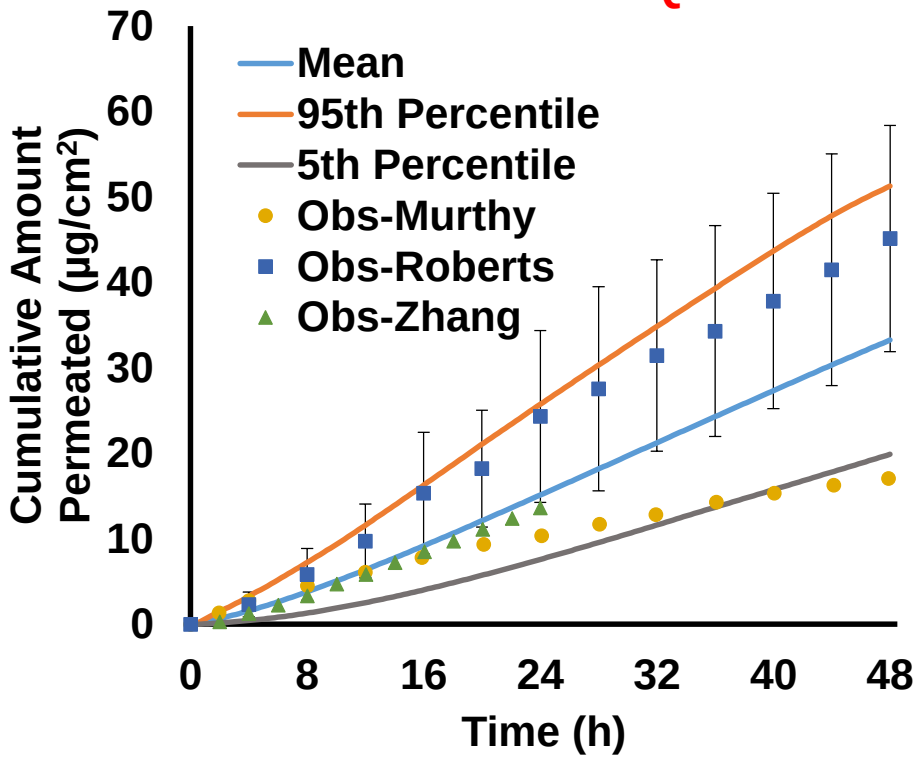
- Back as skin site, Dose = 0.074 mg, Dose Volume = 10 µL, Trial Design = 10 trials X 6 individuals
- Diffusion and partition parameters are kept same as that for MetroGel



Murthy et al. Q3



Roberts et al. Q3



Simulated cumulative amount permeated (µg/cm²) was able to successfully **predict** the observed data from three different laboratories **bottom up**

*Note – Simulations are done using Franz diffusion setup based on Murthy et al. and Roberts et al. Q3 properties, Data from Zhang et al. is obtained using flow through setup, It is overlayed on the same graph for comparison purpose only

[a]Murthy SN. et al. AAPS 2015; [b]Roberts et al. (unpublished), [c]Zhang et al. Poster Presentation. AAPS 2019

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Case Example 2 – Modeling *In Vitro* Skin Permeation of Acyclovir Commercial Formulations (Zovirax and Aciclostad)

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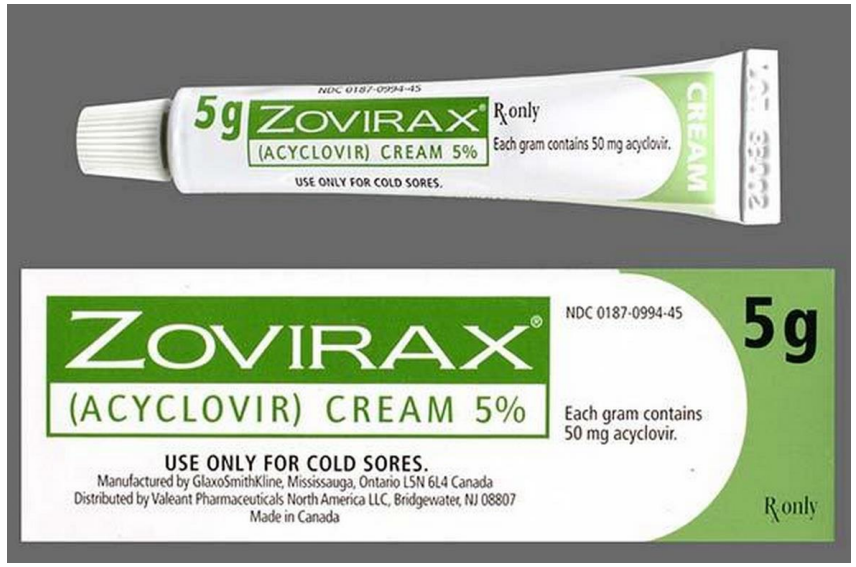
Zovirax (Approved in US) and Aciclostad (Approved in Austria)

Data Available

a. Good understanding of Q1 and Q2 properties of both products

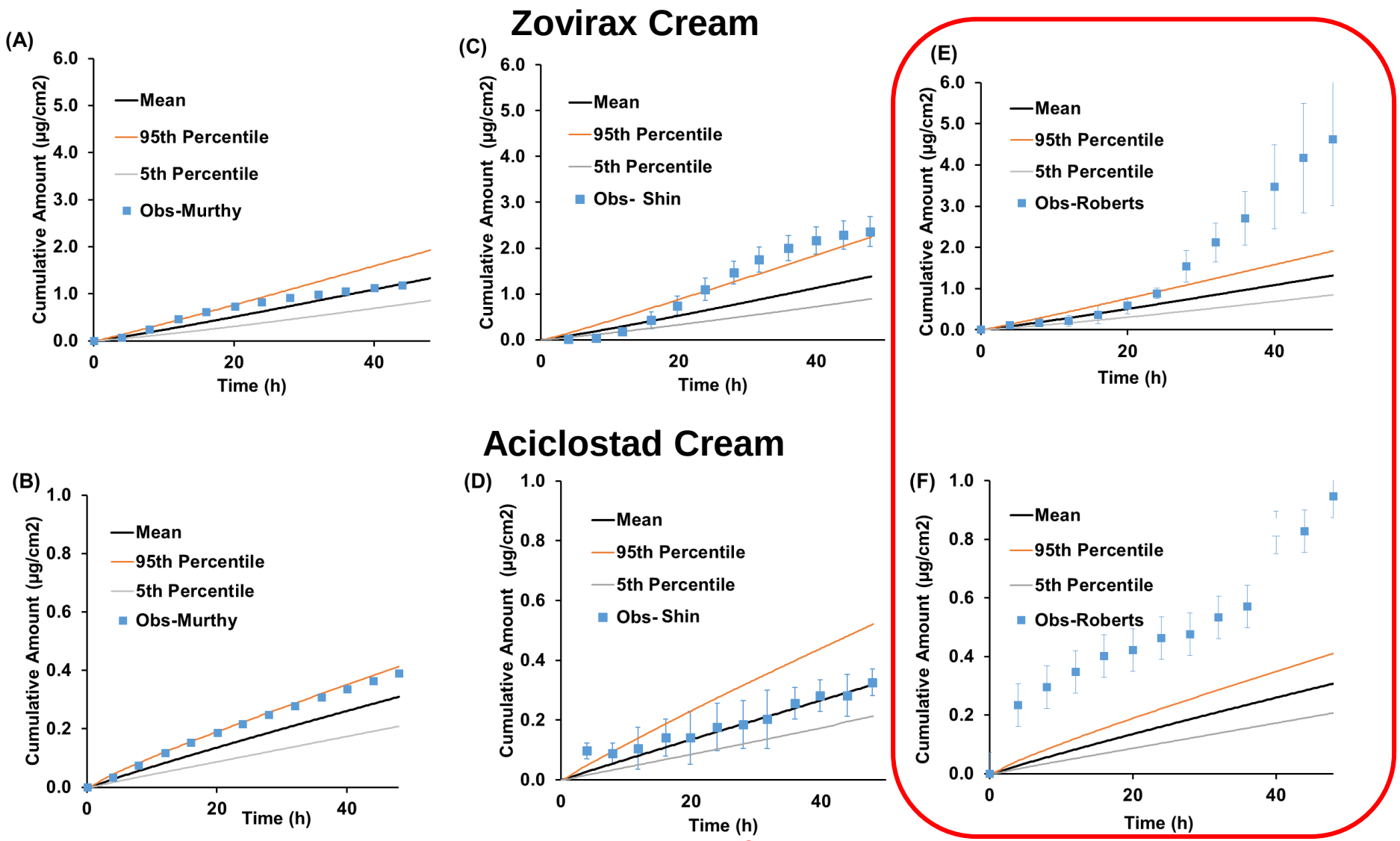
b. A battery of Q3 characterization data such as pH of formulation, viscosity, evaporation profile, drug solubility in continuous phase from two different laboratories.[a,c]

c. IVPT data –15 mg/cm^2 from three different laboratories.[a,b,c]



[a]Murthy SN. et al. AAPS 2015; [b]Shin et al. Poster Presentation. AAPS 2015; [c]Roberts et al. (unpublished)

Simulation of *in vitro* skin permeation of acyclovir from Zovirax and Aciclostad



This work was presented at CRS Annual Virtual Meeting 2020 and will also be discussed as poster at upcoming AAPS PharmSci Annual Meeting 2020

Simulated cumulative amount permeated (µg/cm^2) was able to successfully **predict** the observed data from two different laboratories **bottom up**

Murthy SN. et al. AAPS 2015; Shin et al. Poster Presentation. AAPS 2015; Roberts et al. (unpublished)

Conclusions

- PBPK models can be immensely helpful in dermal drug development. The developed models, with limited datasets, was able to capture the *in vitro* skin permeation of drug(s) from gels and creams formulation provided these models are adequately parameterized with respect to physical and structural characterization of formulations.

- These models presents an opportunity to understand the differences between the reference and test products.

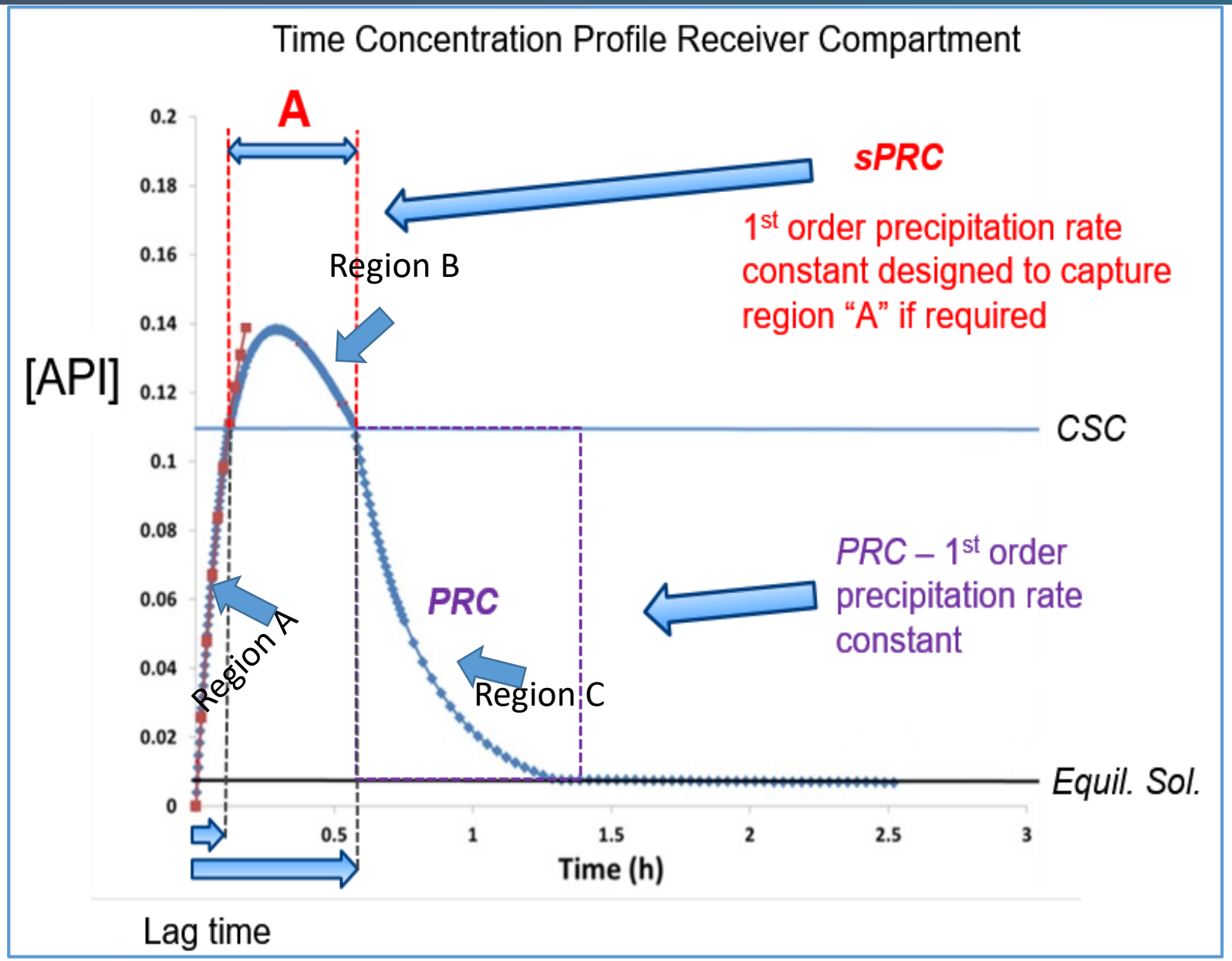
- IVIVE was demonstrated for metronidazole gel formulations – Consistent datasets in terms of dose applied and conditions of application between *in vitro* and *in vivo* scenario is needed to further understand/evaluate capability of PBPK models to predict *in vivo* exposure from *in vitro* verified models.

Thank you

Email address – sumit.arora@certara.com

Back Up Slides

Empirical Supersaturation/Precipitation Model



Empirical Model

IF supersaturated conditions encountered THEN

Dissolution stops

Precipitation can only begin when CSC is reached

***CSC* is a critical conc. at which precipitation starts**

[Drug] may continue to rise due to slow permeation of drug from skin

Supersaturated conc. may exceed *CSC* (*CSR* x Eq.Sol)

CSC – Critical Supersaturation Concentration
CSR – Critical Supersaturation Ratio
PRC – Precipitation Rate Constant (1/h)
sPRC – Secondary Precipitation Rate Constant (1/h)

Metronidazole Equil.Sol = 8.7 mg/mL
CSR – 1
PRC - 11

US Patent Number 8,877,792 B2

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