Integrating Topical Drug Product Quality Attributes Within Physiologically-based Pharmacokinetic Models

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Session Description and Objectives

- This talk will discuss the considerations/key parameters needed to develop and verify/validate a mechanistic dermal absorption model capable of explaining observed *in vitro* and *in vivo* permeation of drugs across skin from topical applied drug products

- List data requirements in developing and verifying/validating dermal Physiologically Based Pharmacokinetic (PBPK) models
- Understand the utility of PBPK models in identifying critical product quality attributes of topical/transdermal drug products influencing skin permeation
- Appreciate the utility of *in vitro* verified PBPK models in predicting *in vivo* dermal exposure (*in vitro in vivo* extrapolation, IVIVE) of topically applied drug products

Biography and Contact Information

- Senior Research Scientist (Virtual Bioequivalence) in the modeling and simulation group at Certara Simcyp
- Project lead of the FDA awarded grant investigating the integration of formulation drug product quality attributes in dermal physiologically based pharmacokinetic models for topical/transdermal drug products
- Expertise in the field of biopharmaceutics for oral and dermal drug products and in the field of Physiologically Based Biopharmaceutics Modeling (PBBM)

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Disclaimer

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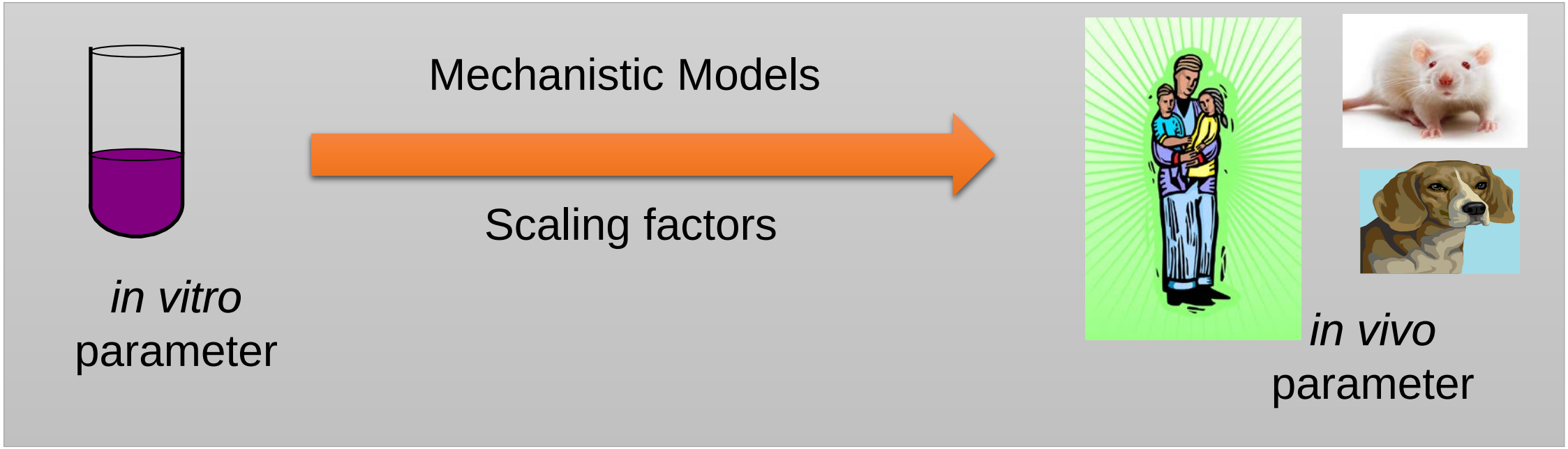
Outline of the Presentation

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 – Metronidazole commercial formulations (MetroGel®)
5. Conclusion(s)

Understanding *In vitro* to Predict *In vivo* – IVIVE with PBPK Modeling



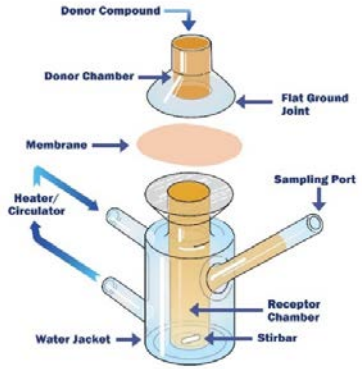
- Information obtained from surrogate *in vitro, ex vivo* or animal studies is used to provide quantitative solutions to predict the *in vivo* behavior of drugs in a target human population prior to undertaking a clinical study

- 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.

Dermal IVIVE – A step towards Virtual Bioequivalence for Complex Topical Products

Input



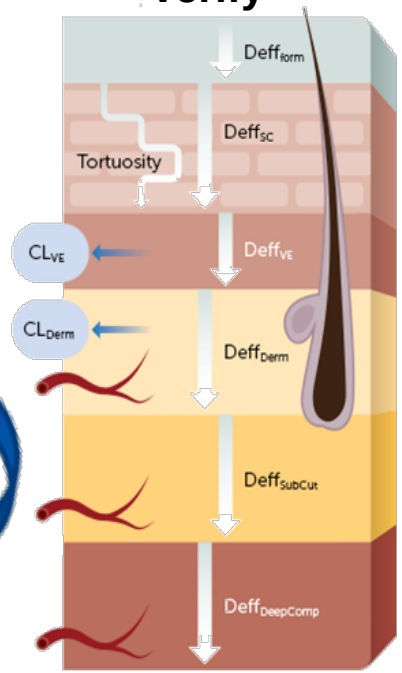
***In vitro* Release/Permeation Studies**

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 permeation

Confirm & Learn Approach

Verify

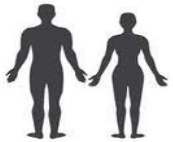


Mechanistic Dermal Absorption Model

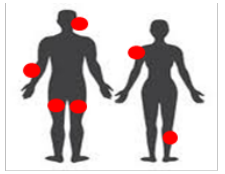
- Confirm key drug/formulation parameters: partition and diffusion coefficients
- Verify model performance with challenge formulations (different strengths, non-Q1, Q2, Q3 formulation)

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

Extrapolate



Healthy NEurCaucasian



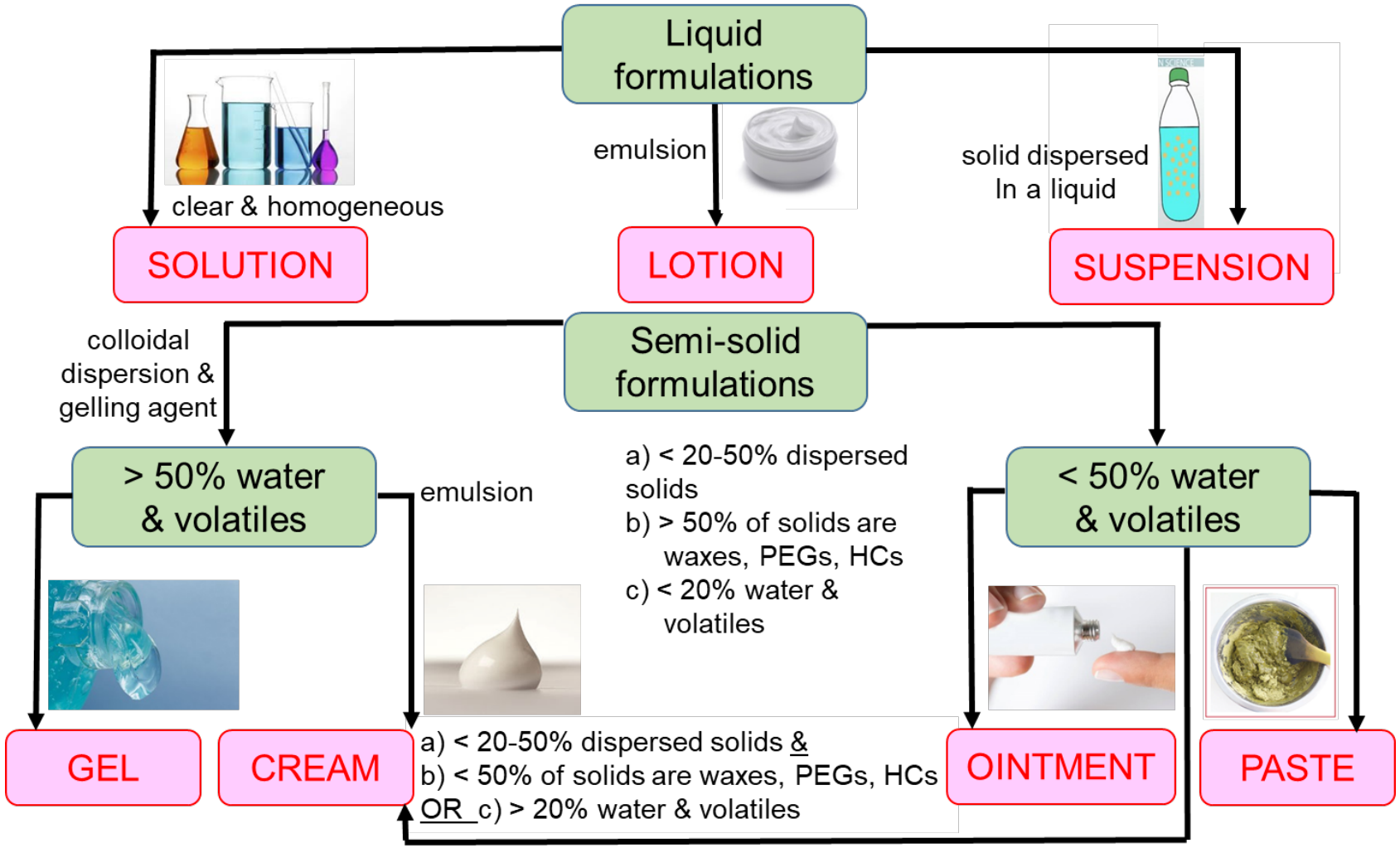
Diseased Population

Elderly Subjects

Paediatric Population

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

Topical Formulations/Products for Dermatological Applications

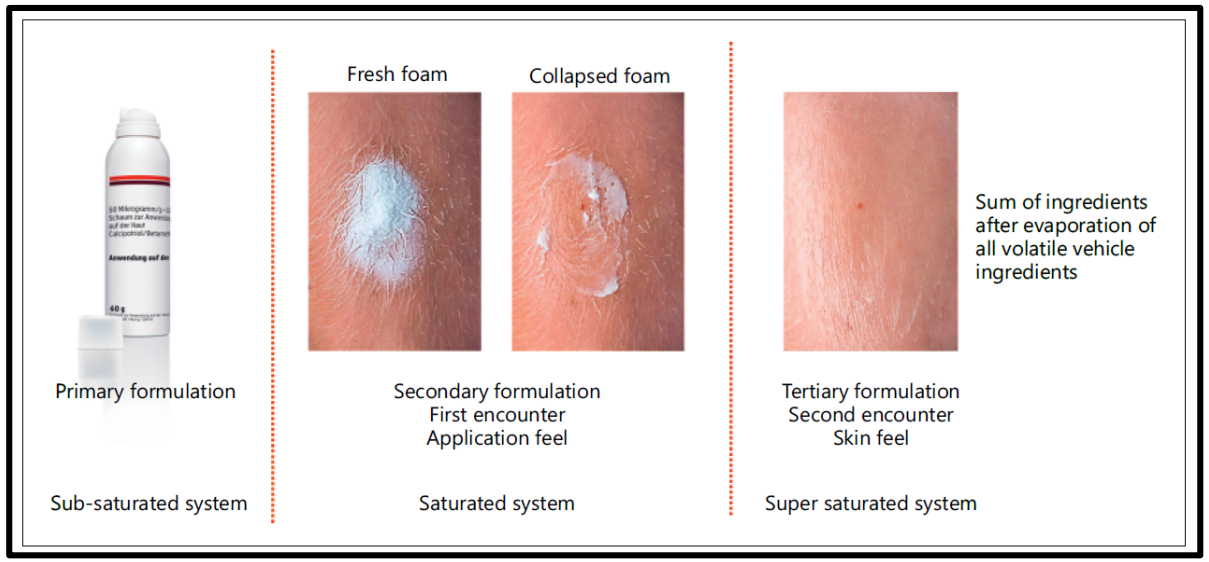


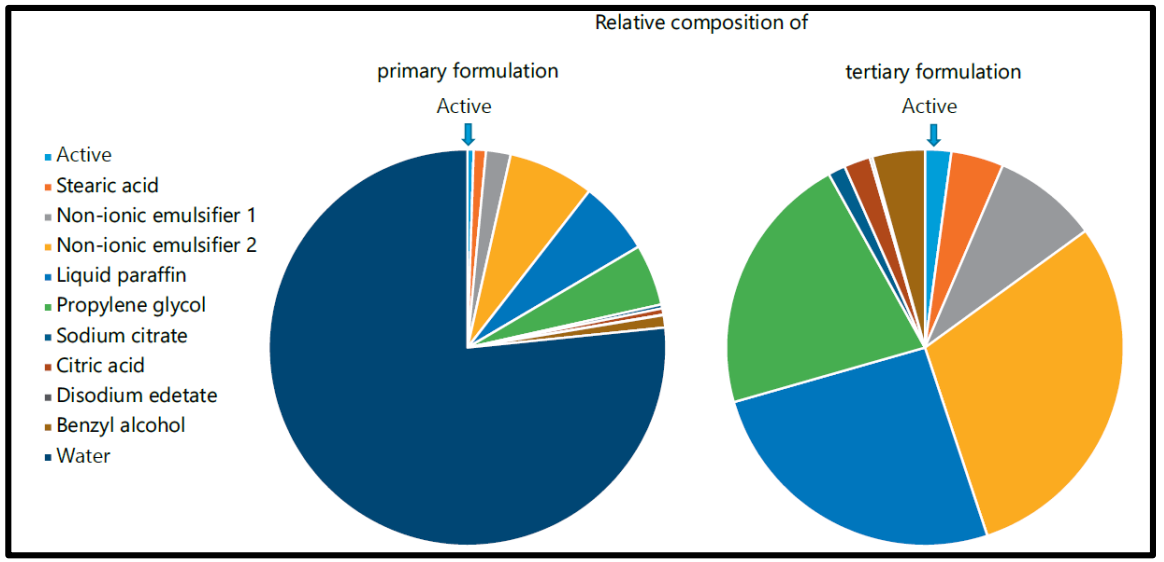
All these products can broadly be classified as –

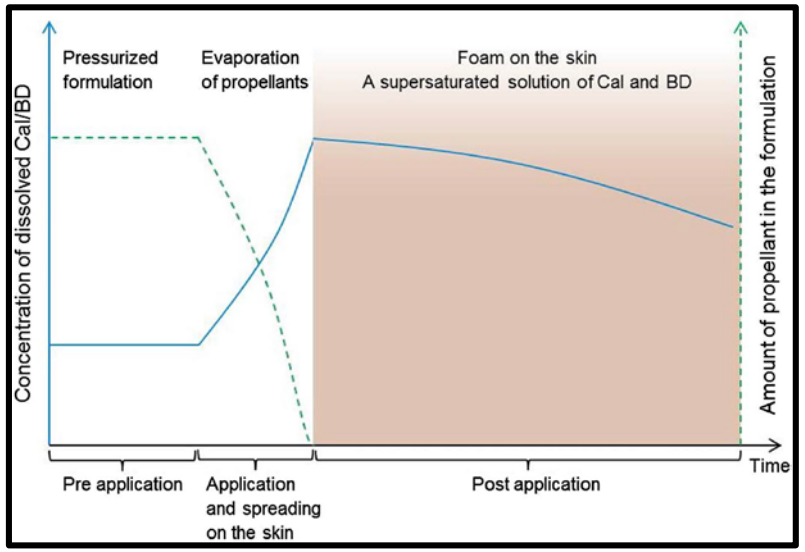
1. Solutions
2. Emulsions
3. Suspensions

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

Metamorphosis of Topical Formulations



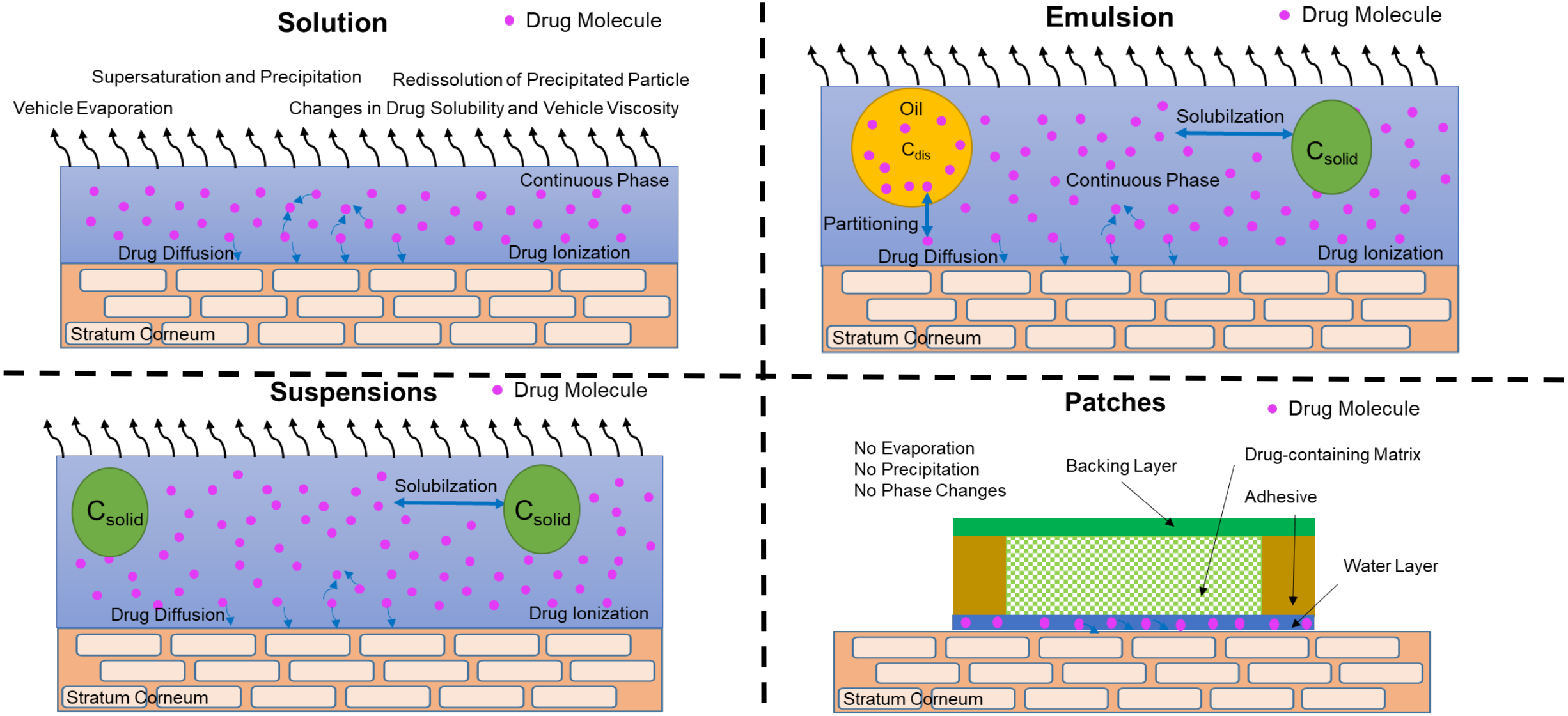




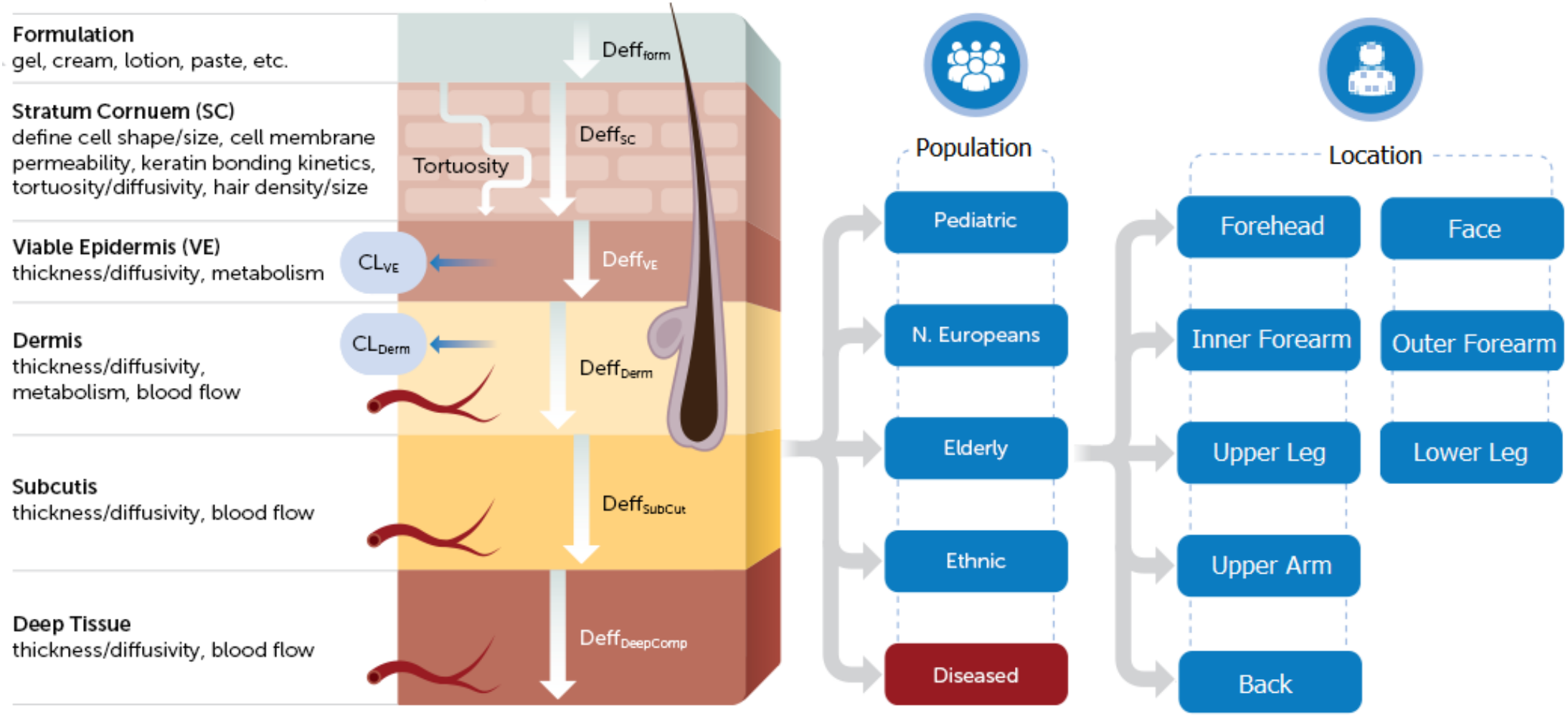
Change in concentration of active ingredients dissolved in the aerosol form formulation over application time.
BD Betamethasone dipropionate, Cal calcipotriene

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

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.

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

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

Q3 data for MetroGel needed for model parameterization

1. Gels can be treated as **solutions** if they are monophasic systems (in case of MetroGel®, metronidazole is completely solubilized in the formulation)

2. We need understanding of following Q3 properties –

   a) pH of the formulation.

   b) Drying rate at 32°C (relevant to skin temperature) – loss of volatile ingredients of the formulation.

   c) Rheology – understanding the viscosity of formulation at rest conditions (lower shear rates).

   d) Metronidazole solubility in formulation (in this case since more than 95% v/v of formulation is water, solubility of metronidazole in water is required).

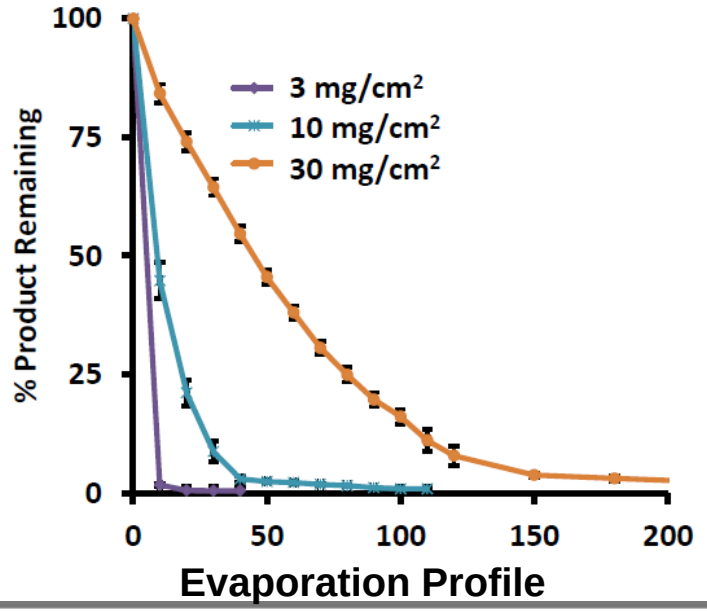
   e) If precipitation of drug is observed, we need to parametrize the precipitation model.

MetroGel® (0.75%) Structural and Physical Characterization Data – Murthy et al. 2015

Parameter	MetroGel®
Formulation Simulation Option	Solution
Dose of Cream Applied (mg/cm^2)	10
Density of formulation (g/cm^3)	1.01
Dose of Drug Applied (µg)	74
Volume of Formulation (mL)	0.01
Thickness of Formulation (cm)	0.01
Viscosity (cP)	12779
pH of formulation	5.23
Drug Solubility in Continuous Phase (mg/mL)	8.7
Evaporation Profile	User Input Profile
Precipitation Model	Empirical
CSR	1
PRC (h^{-1})	11

Product	Initial Viscosity (@0.01/S^{-1})	Yield Stress
MetroCream®	9541 ± 284	94 ± 0.00
Generic cream	6830 ± 1166	70 ± 3.00
MetroGel®	12779 ± 1215	50 ± 4.04
Generic gel-1	10534 ± 263	50 ± 0.00
Generic gel-2	12489 ± 1692	49 ± 5.20

Viscosity Measurements



In Vitro Permeation Test (IVPT)

Figure 3: Metronidazole concentration in the donor compartment vs time from finite and infinite volume IVPT (n=6)

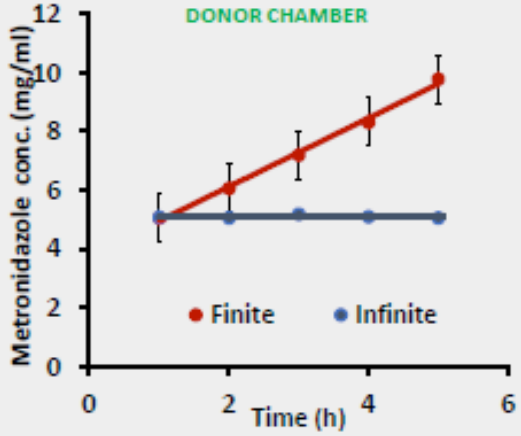
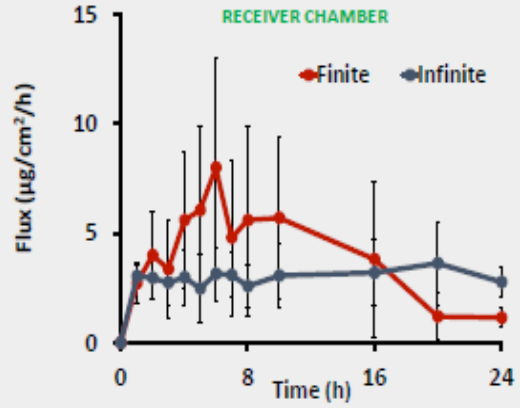
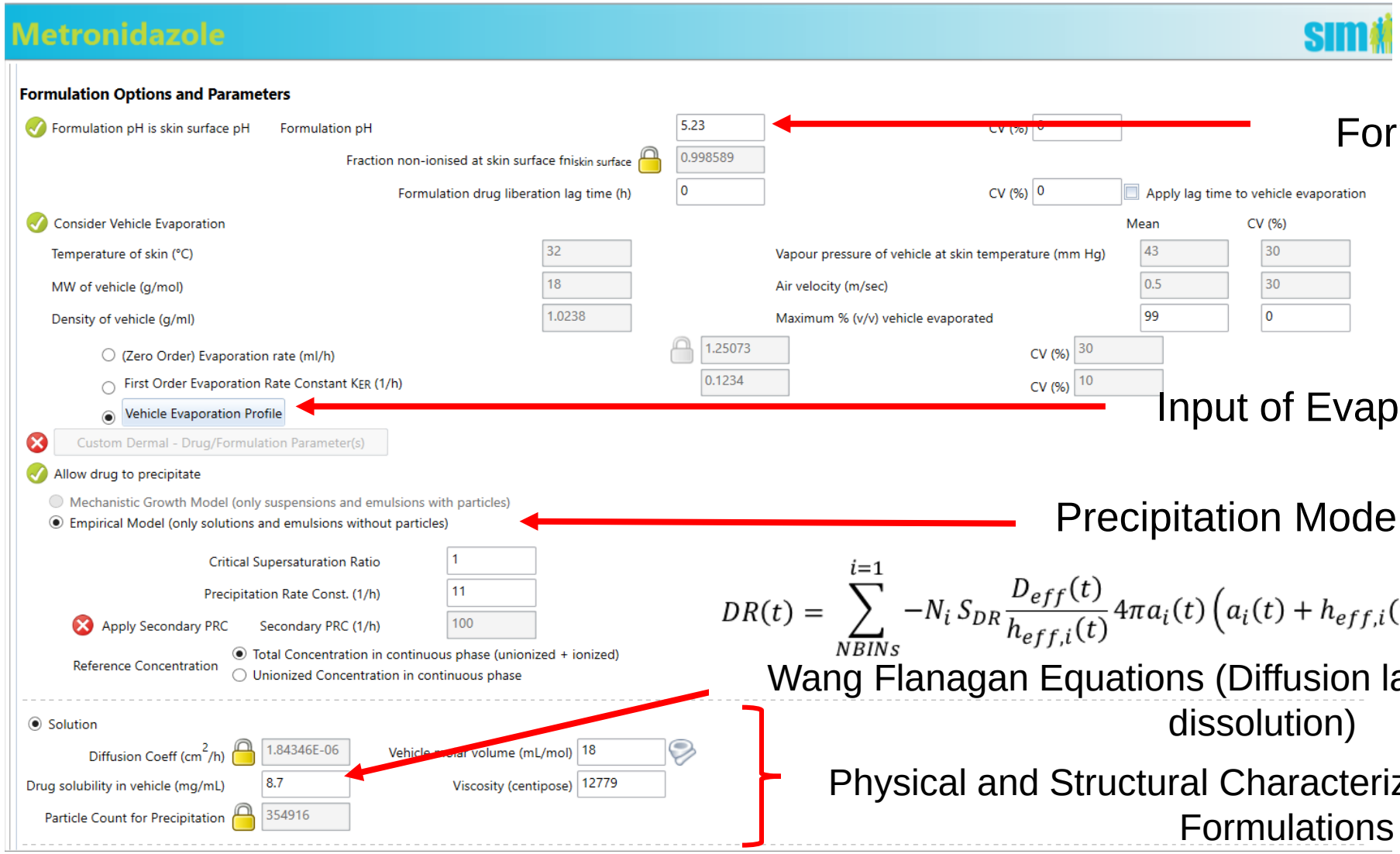


Figure 4: Metronidazole flux vs time profiles from finite and infinite volume IVPT (n=6)



Parameterization of Formulation Parameters for MetroGel® in MPML MechDermA Model



Formulation pH Input

Input of Evaporation Profile

Precipitation Model *CSC* (*CSR* x Eq.Sol)

$$DR(t) = \sum_{NBINs}^{i=1} -N_i S_{DR} \frac{D_{eff}(t)}{h_{eff,i}(t)} 4\pi a_i(t) \left(a_i(t) + h_{eff,i}(t)\right)\left(S_{surface}(t) - C_{bulk}(t)\right)$$

Wang Flanagan Equations (Diffusion layer model for particle dissolution)

Physical and Structural Characterization Data of Topical Formulations

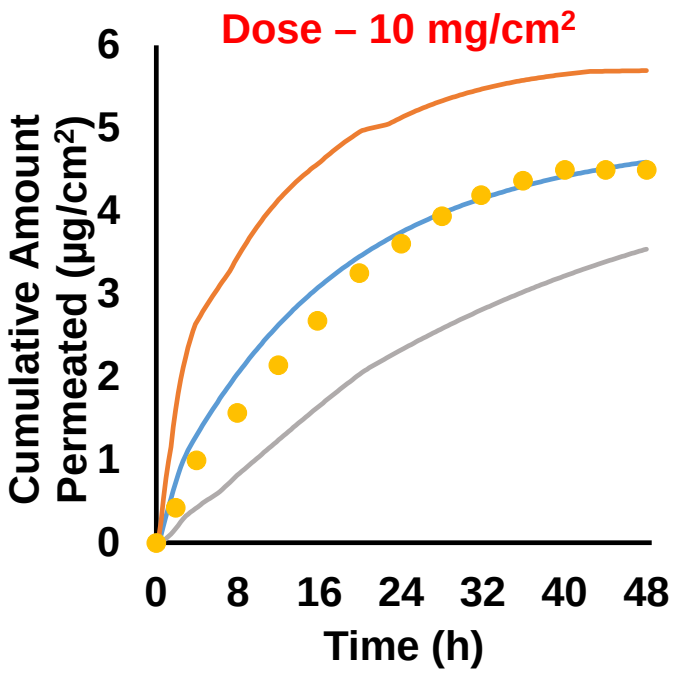
Simulation of *in vitro* skin permeation of metronidazole – Diffusion and Partition Parameters – 3 dose application 3, 10 and 30 mg/cm²

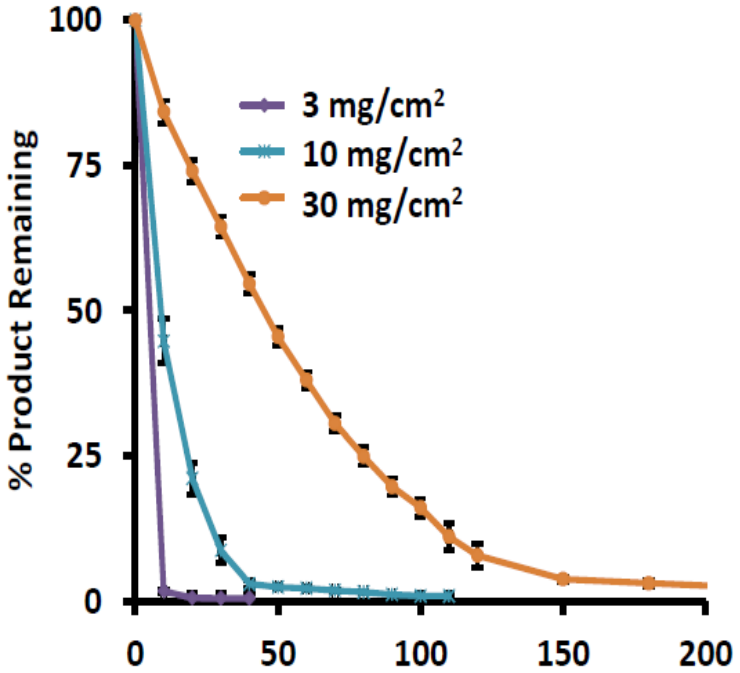
- MW – 171.56, log P -0.02, Compound type – Monoprotic Base, pKa 2.38
- Compound is non-ionized at skin surface pH
- Back as skin site, Dose = 10 mg, Dose Volume = 2 mL, Trial Design = 10 trials X 6 individuals

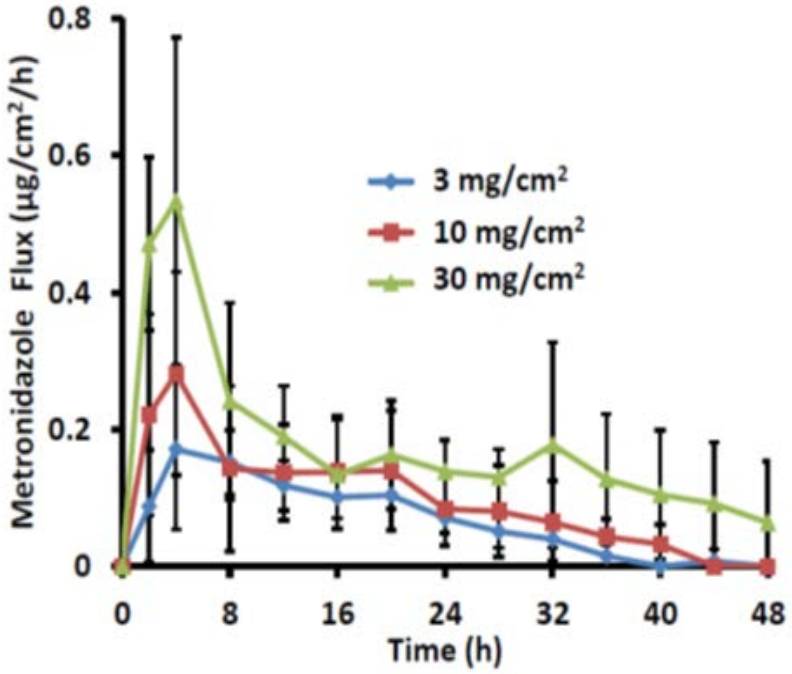
Partition and diffusion coefficient of metronidazole across various tissue layers

Parameter	Value	Unit of measure	Method
$K_{lip/water}$	5	NA	Optimized using finite dose aqueous solution IVPT data
$K_{sebum/water}$	0.816	NA	Yang 2019
$K_{SC/VE}$	0.995	NA	Shatkin and Brown QSAR
$K_{Dermis/VE}$	0.729	NA	Modified Chen 2015
$K_{Dermis/Sebum}$	0.891	NA	Modified Chen 2015
$K_{Receptor:Dermis}$	1	NA	Assumed
$P_{corneocyte}$	1E-05	cm/h	Default
D_{sclip}	1.28E-04	cm^2/h	Optimized using 10 mg/cm² IVPT data
Tortousity	2336.06	NA	Johnson QSAR
D_{Dermis}	0.0102	cm^2/h	Modified Chen 2015
D_{ve}	0.0102	cm^2/h	Modified Chen 2015
$D_{Receptor}$	1	cm^2/h	
Fraction unbound in SC	0.488		Polak et al. 2016

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





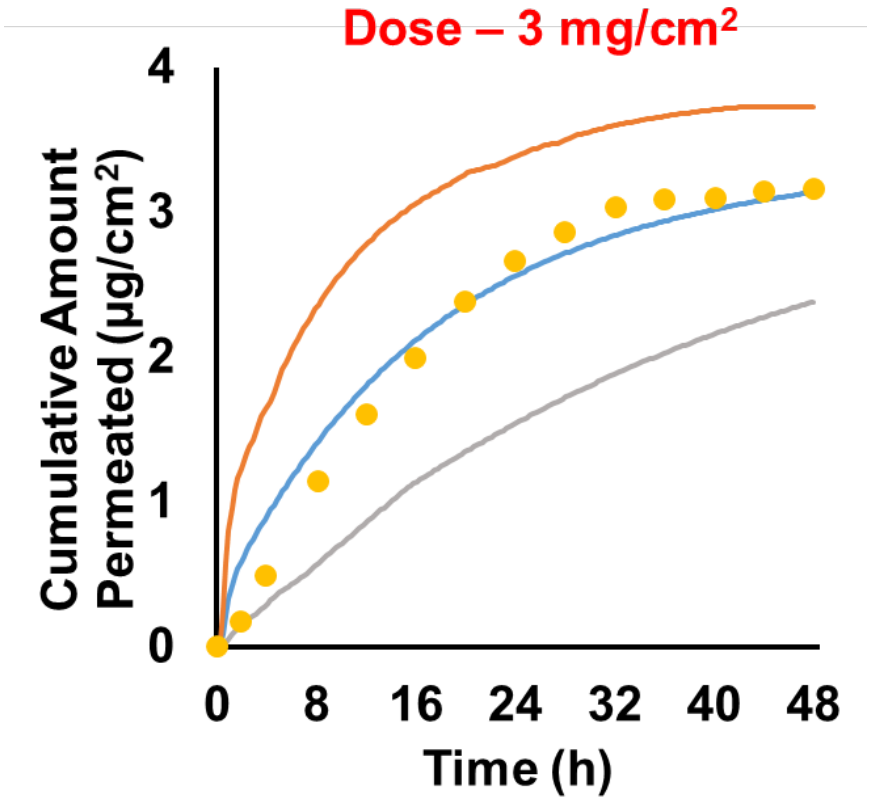


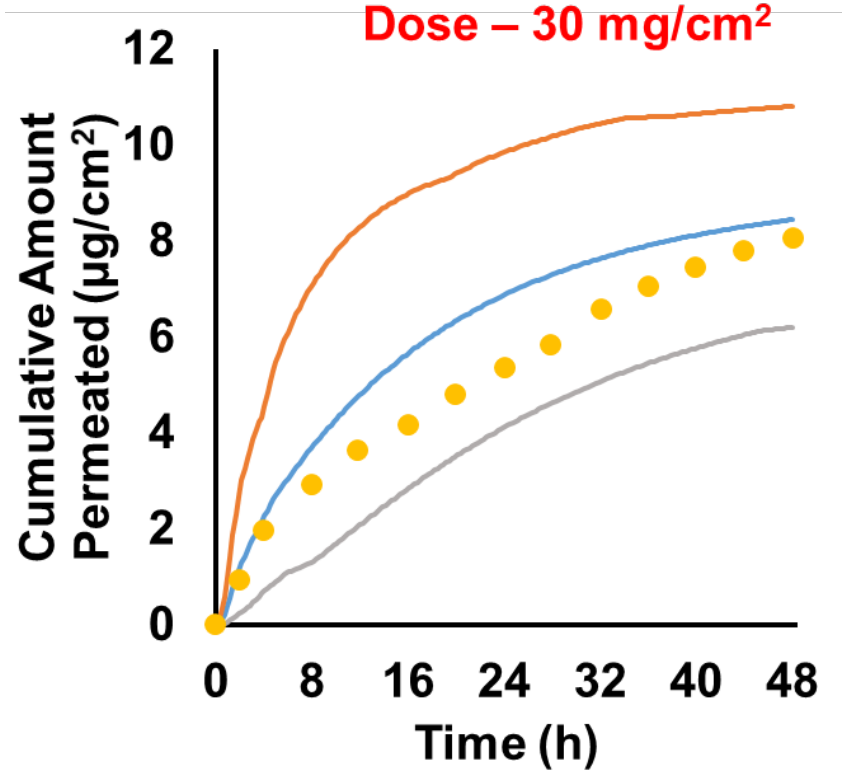
Optimized model was able to simulate metronidazole cumulative amount permeated from 10 mg/cm² dose application. We need additional verification of the model with other two challenge doses since these show very different formulation metamorphosis

Murthy SN. et al. AAPS 2015

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

- In all these gel simulations, duration of drug application was set when nearly 99% of the water is evaporated



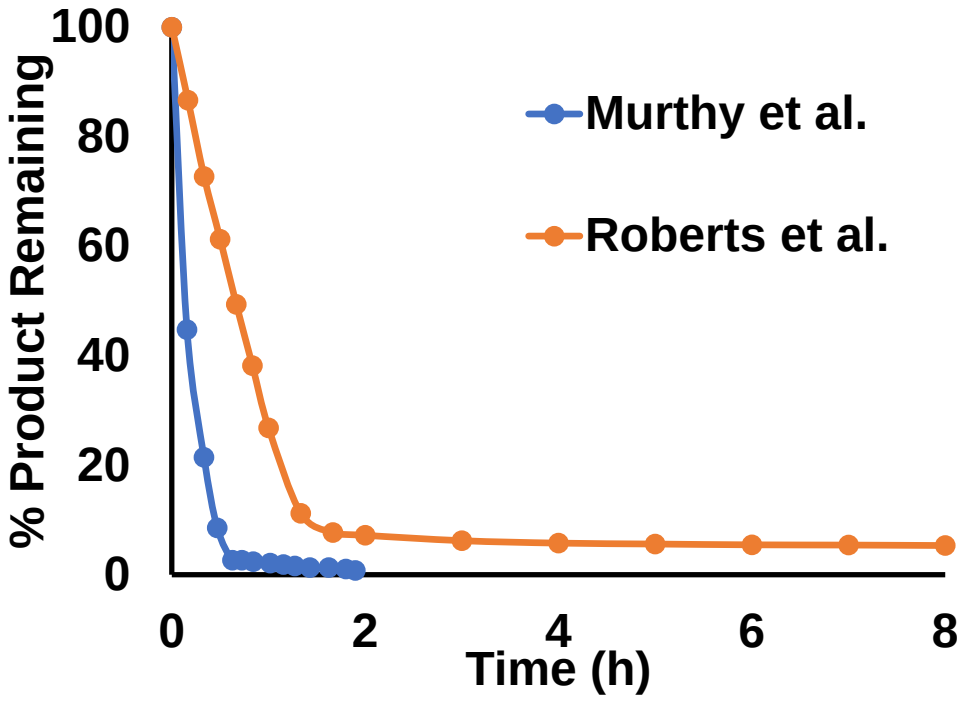


Optimized PBPK model was able to **predict** cumulative amount permeated (µg/cm²) observed from the challenge formulation (different dose volumes)

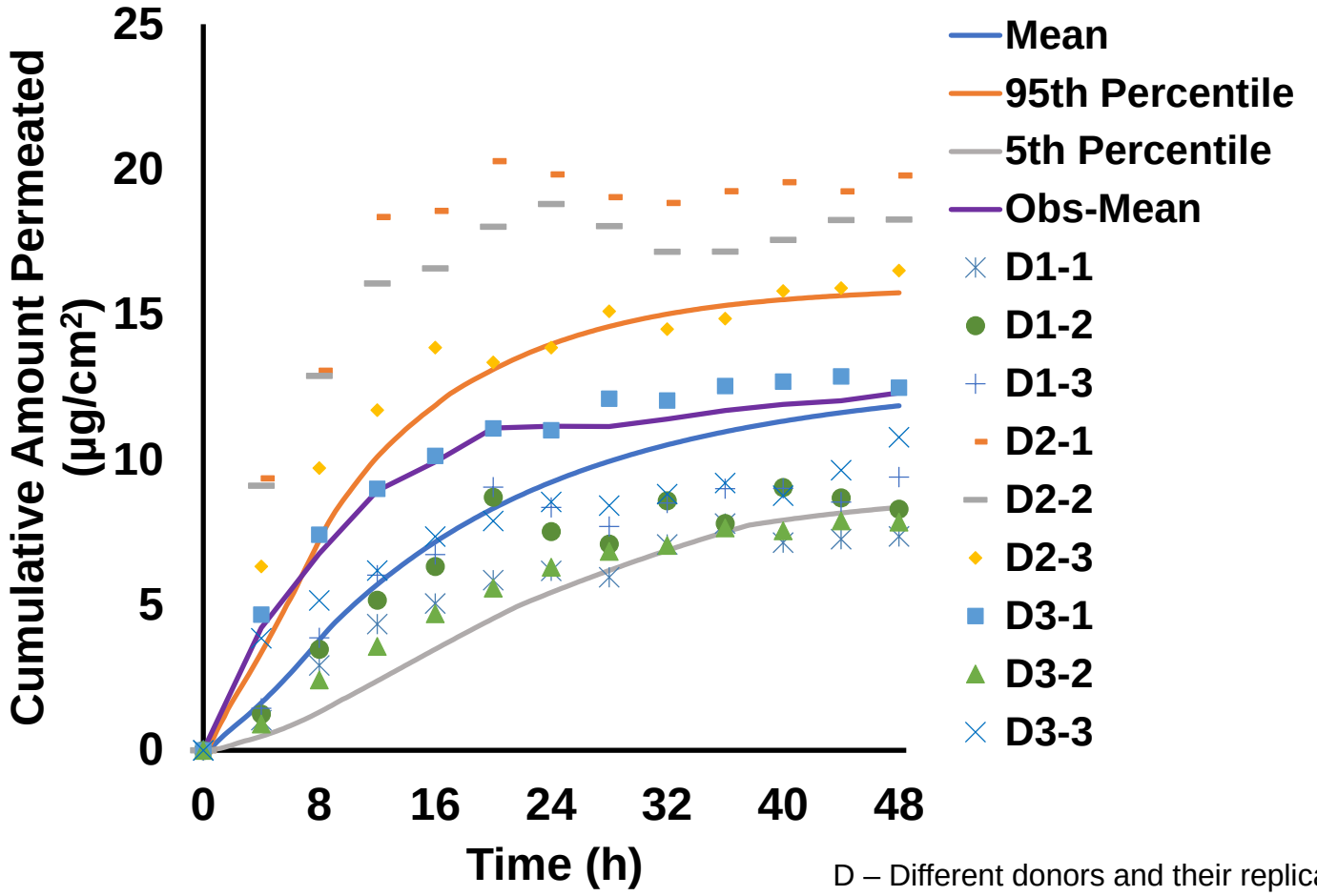
Murthy SN. et al. AAPS 2015

Simulation of *in vitro* skin permeation of metronidazole from MetroGel ® - Roberts et al. Q3 Characterization - Dose 10 mg/cm^2

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



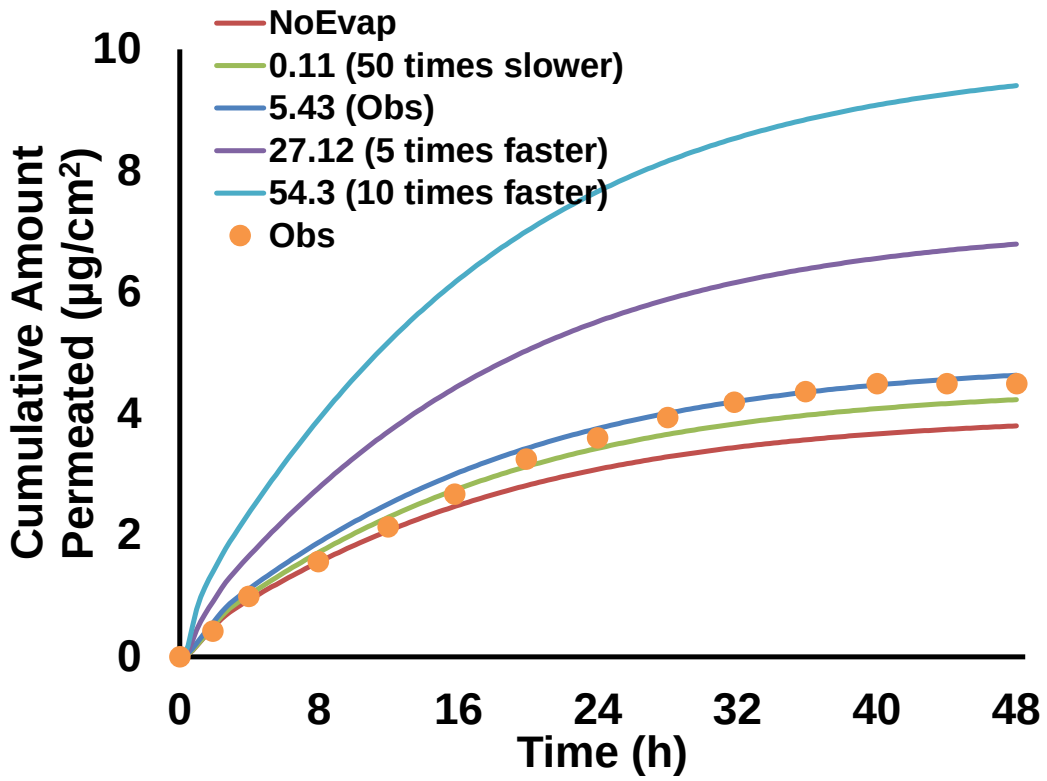
The model was able to **predict** mean cumulative amount permeated (µg/cm^2) as well as variability from 10mg/cm^2 dose determined by another lab.



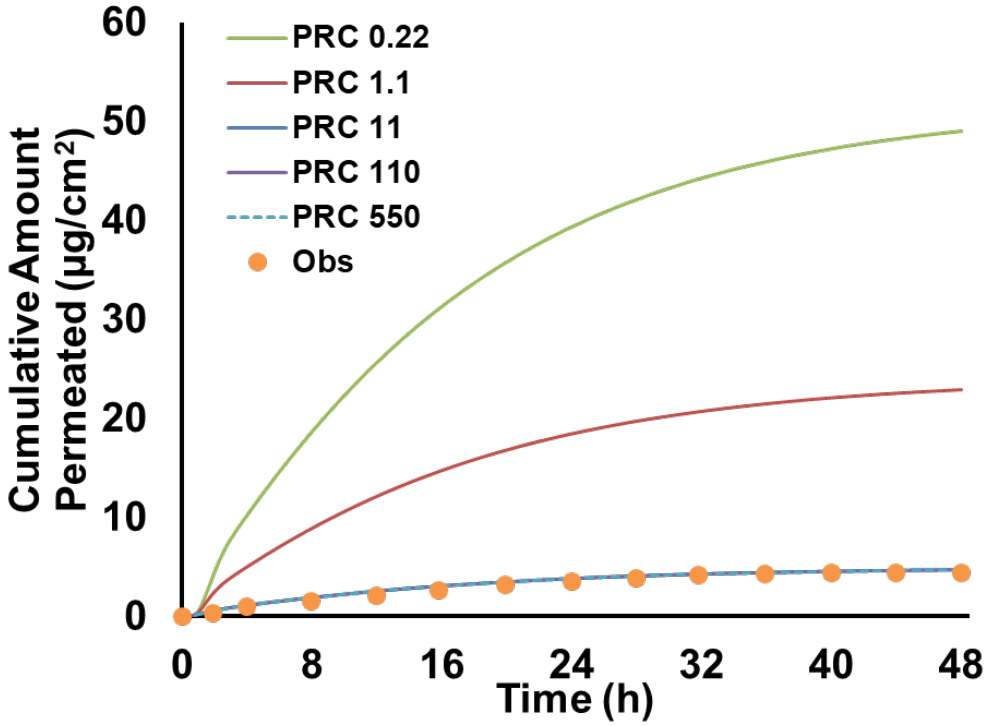
D – Different donors and their replicate

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

Parameter Sensitivity Analysis of Critical Formulation Parameters of MetroGel®

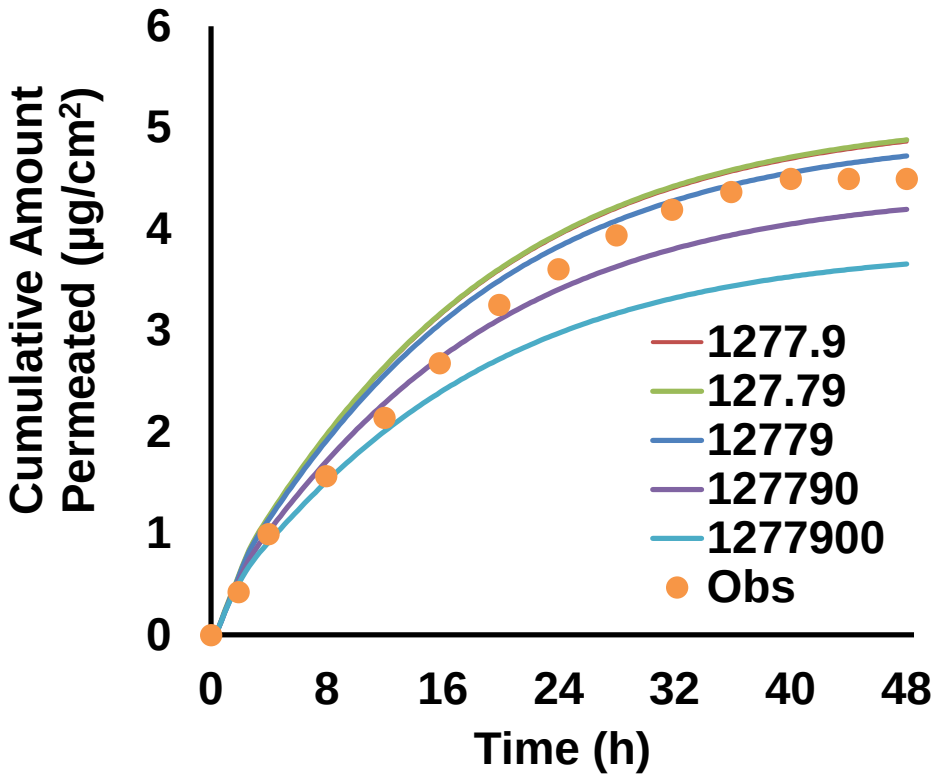


Evaporation Rate Constant

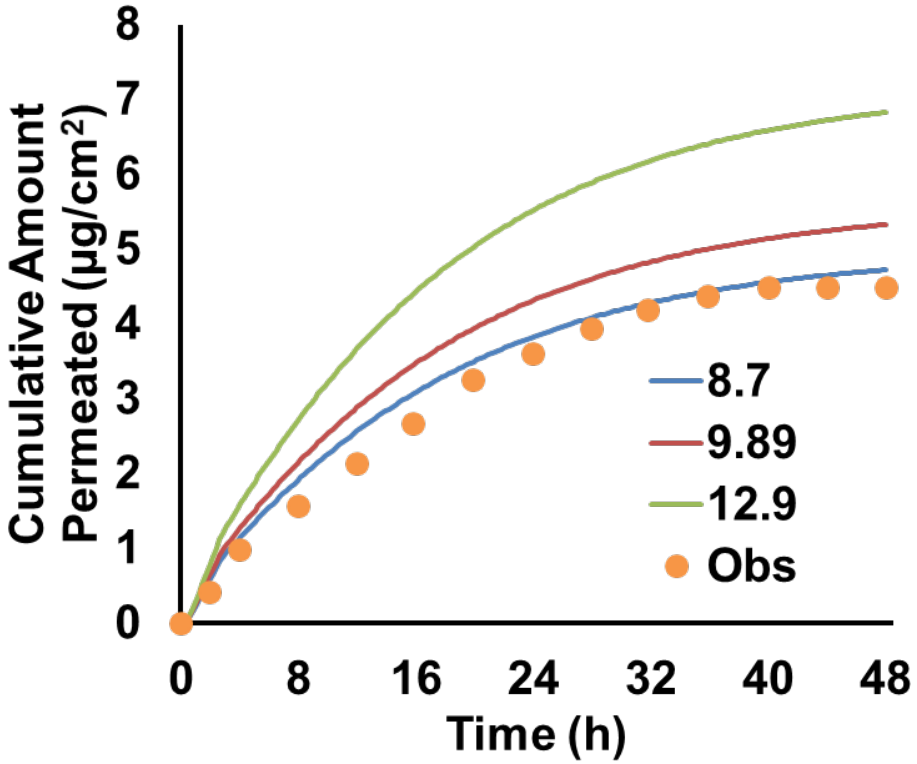


Precipitation Rate Constant

Parameter Sensitivity Analysis of Critical Formulation Parameters of MetroGel®



Vehicle Apparent Viscosity

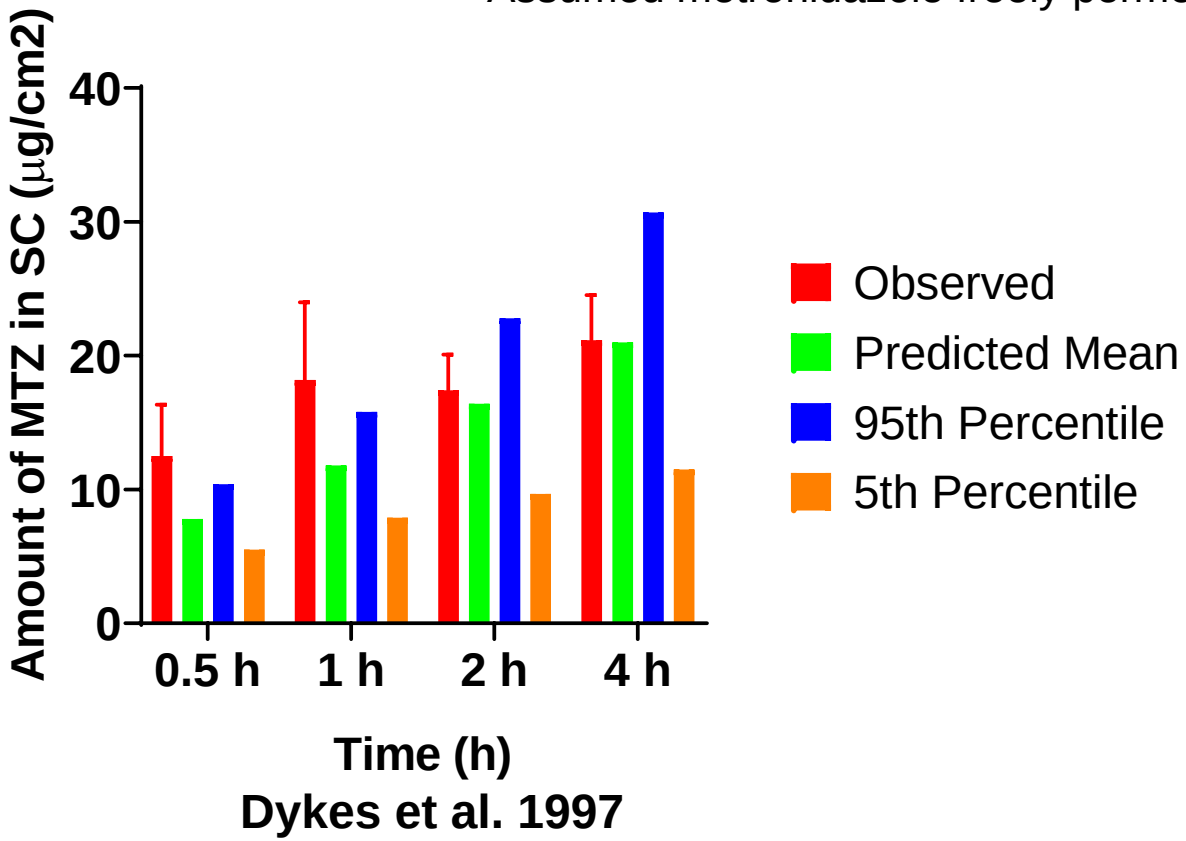


Drug Solubility in Continuous Phase (mg/mL)

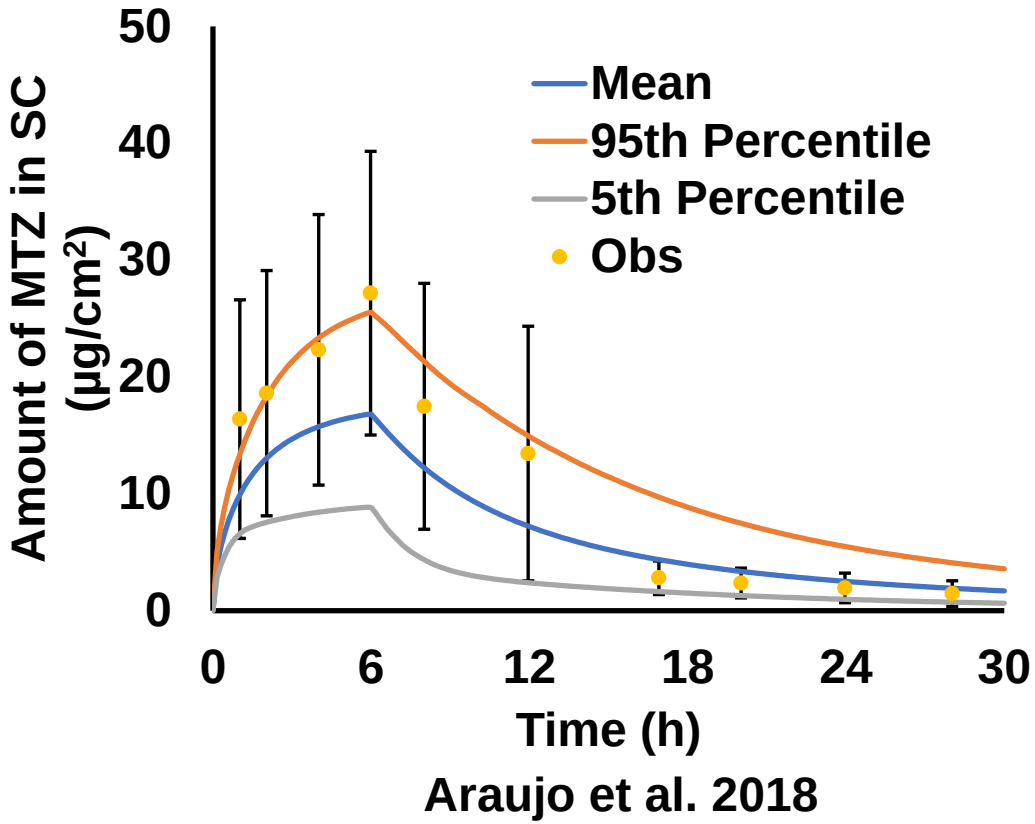
Simulation of *in vivo* skin permeation of metronidazole from MetroGel® and Rosex®

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/cm^2) in the stratum corneum observed *in vivo* demonstrating successfully IVIVE in this case.

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 metronidazole from gels formulation provided these models are adequately parameterized with respect to physical and structural characterization of formulations.

- We validated this approach for other drugs and formulations.

- These models present an opportunity to understand the impact of differences in formulation attributes between reference and test products on their *in vivo* performance.

- IVIVE was demonstrated for metronidazole gel formulations – Consistency in terms of dose applied and conditions of application between *in vitro* and *in vivo* scenarios is needed to further understand/evaluate capability of PBPK modelling approaches in predicting *in vivo* exposure from *in vitro* verified models.

Thank you and Questions?

Email – sumit.arora@certara.com

Please feel free to be in touch via the email if you have additional questions and want to know more about our work

The Simcyp Simulator is freely available, following completion of the relevant workshop, to approved members of academic institutions and other not for -profit organizations for research and teaching purposes. “