In vitro – in vivo extrapolation of dermal absorption of topically applied drug products using physiologically based pharmacokinetic (PBPK) modeling

Adebiotech

Alternatives to Animal Experimentation

6 June 2023

Yuri Dancik

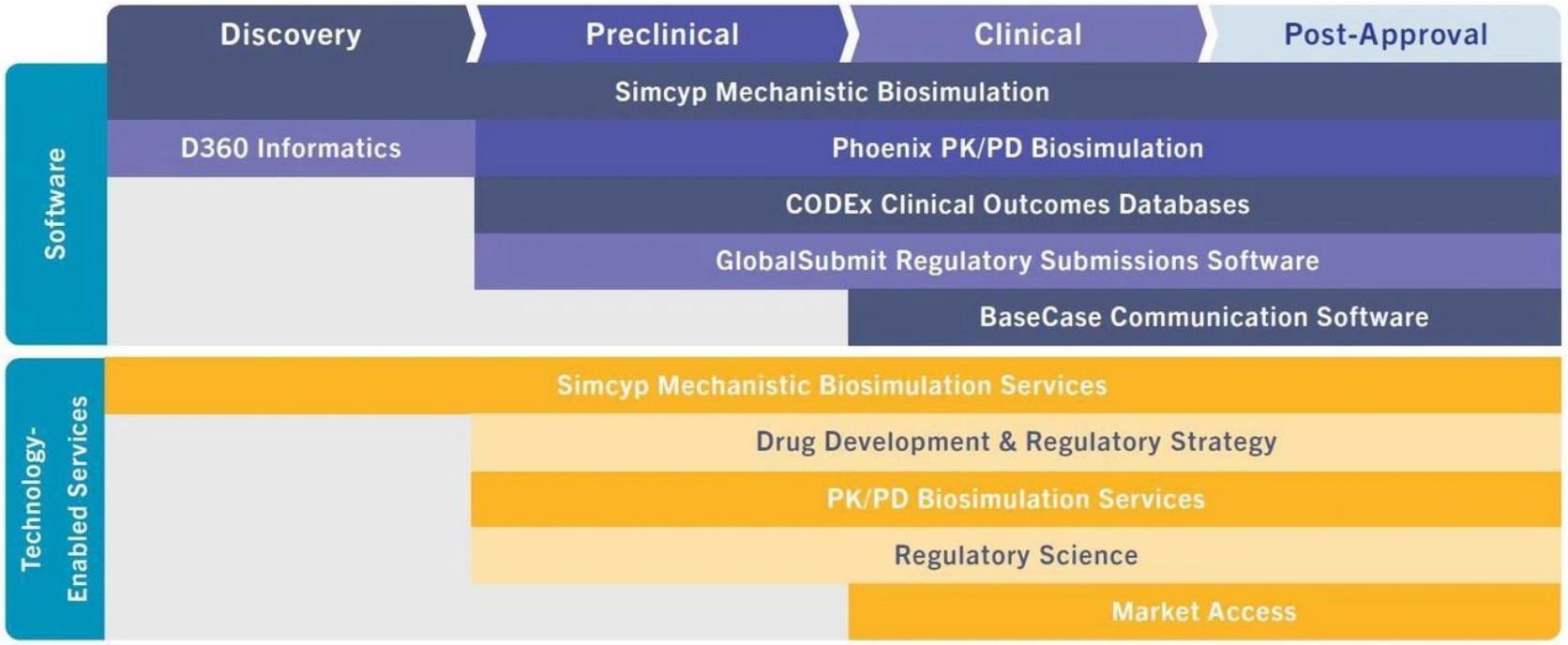
Certara UK Ltd, Simcyp Division

yuri.dancik@certara.com

Overview of Certara

- Support drug delivery and development decision-making
- End-to-end platform with biosimulation, technology-driven, regulatory science and market access solutions
- 1100+ scientists and experts

Certara End-to-End Platform



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Overview of Certara Simcyp

- Certara Simcyp based in Sheffield, UK. 200+ scientists, software developers, administrators
- Whole body PBPK simulator platform
- Developed and updated over the past 20 years *via* the Simcyp Consortium of 35 leading pharma companies
- Activities include:
  - Consultancy and support (incl. regulatory documents preparation, meetings) for companies of varying sizes and stages of product development
  - Research and Development of PBPK modelling platform through research grants
  - Peer-reviewed publications
  - Online and in-person workshops

- **Simcyp 100**:
  Regulatory-accepted predictions enabling sponsors to add prescribing information to the drug label

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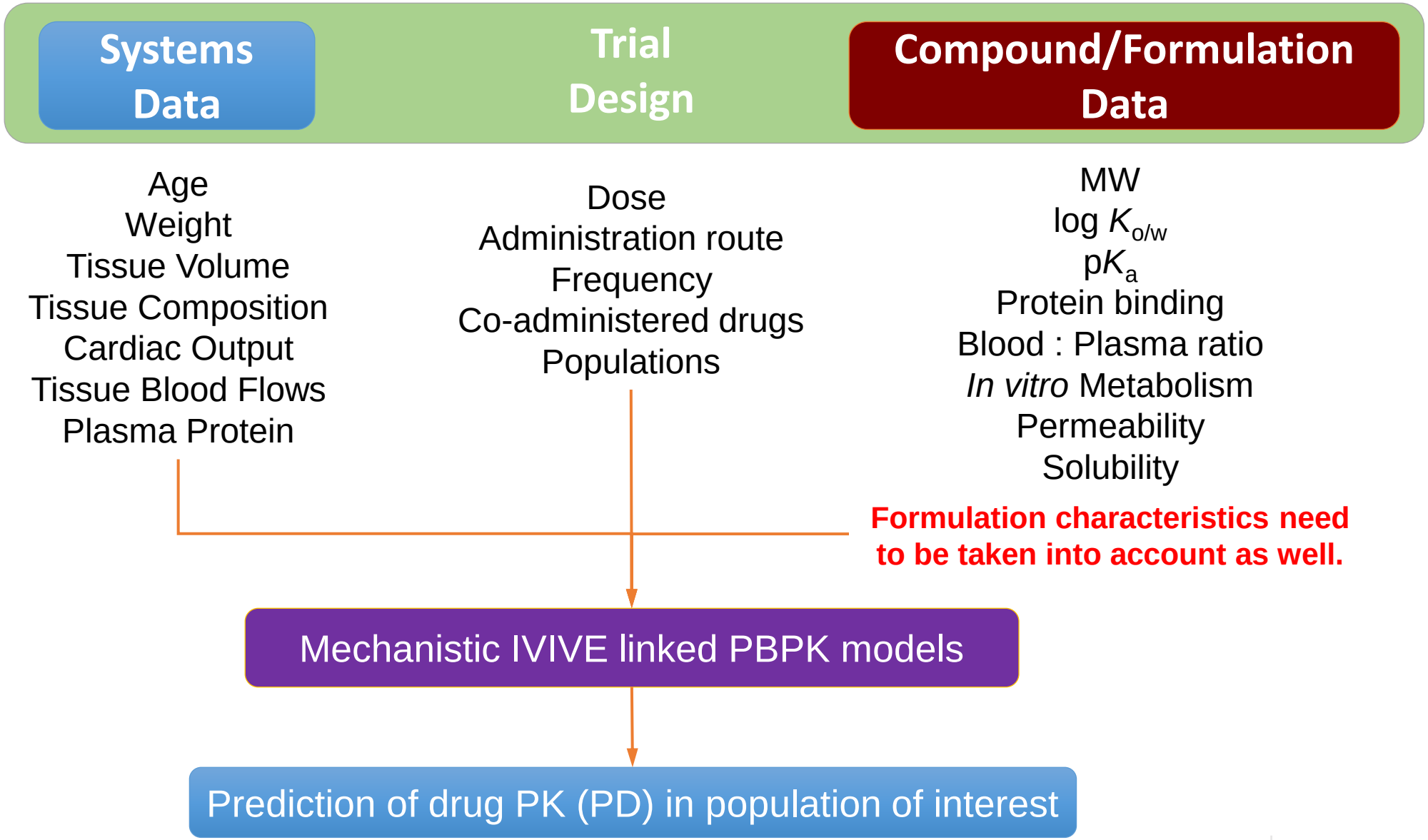
PBPK method: Separating Systems & Drug Information



Jamei *et al.*, DMPK, 2009; Rostami-Hodjegan, CPT, 2012

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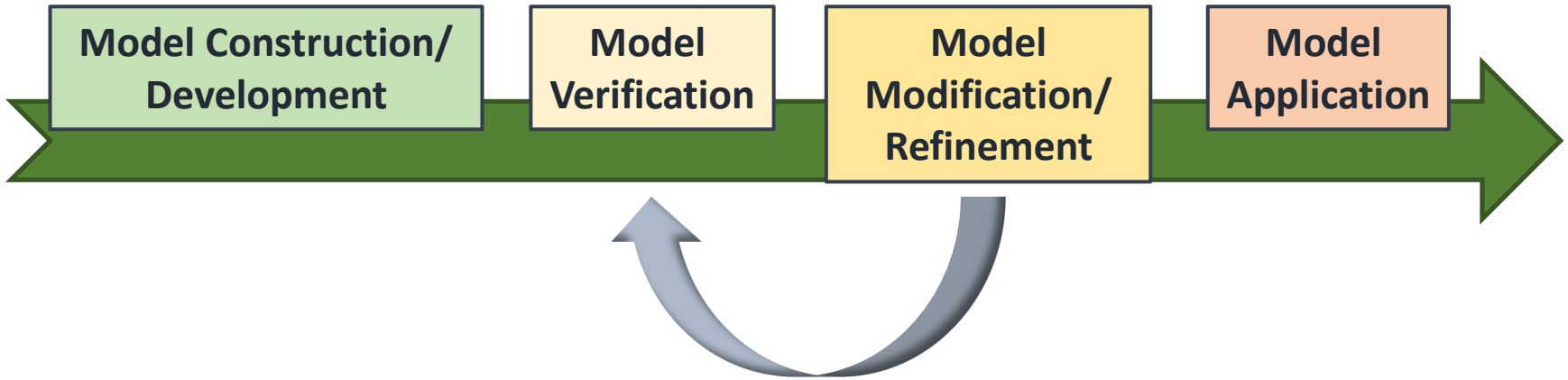
Workflow and Best Practice for PBPK Model Development

A Predict, Learn, Confirm, and Apply paradigm!



Zhao *et al.*, Clin Pharmacol Ther 2012

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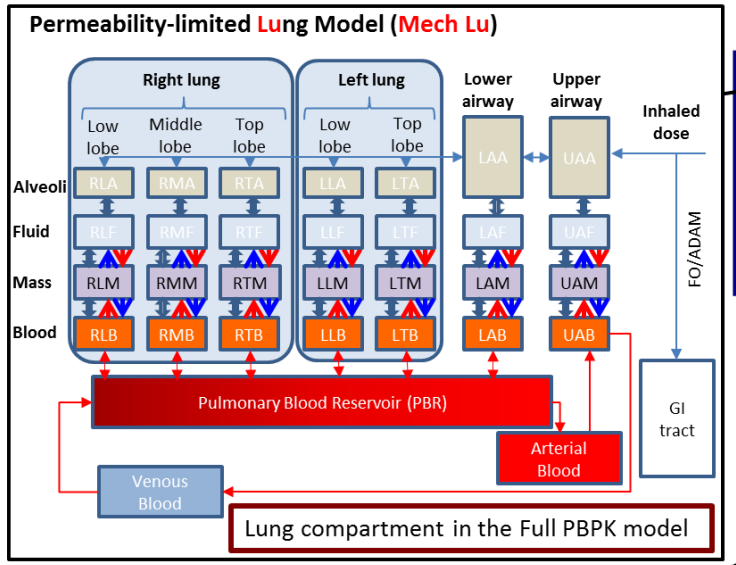
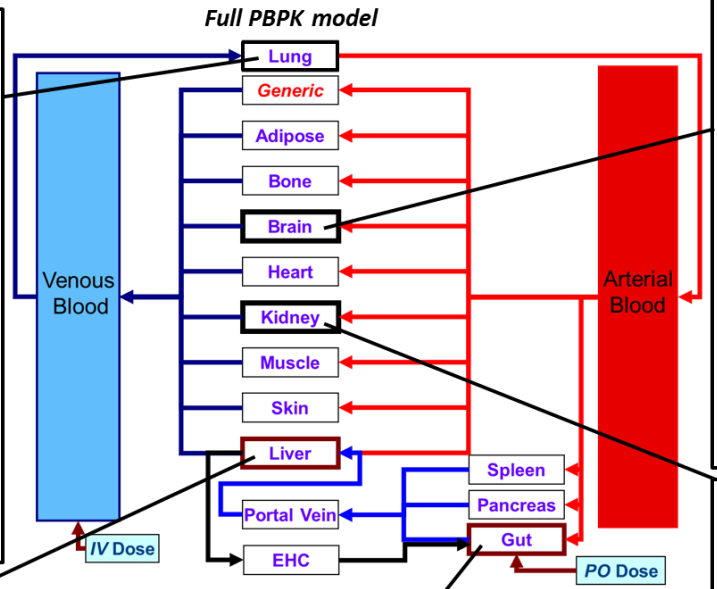
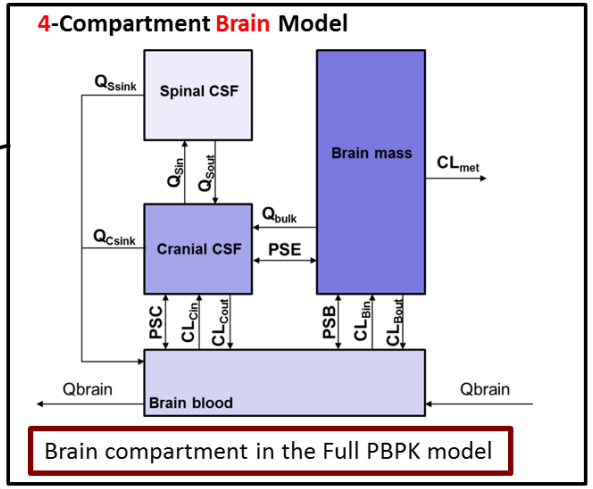
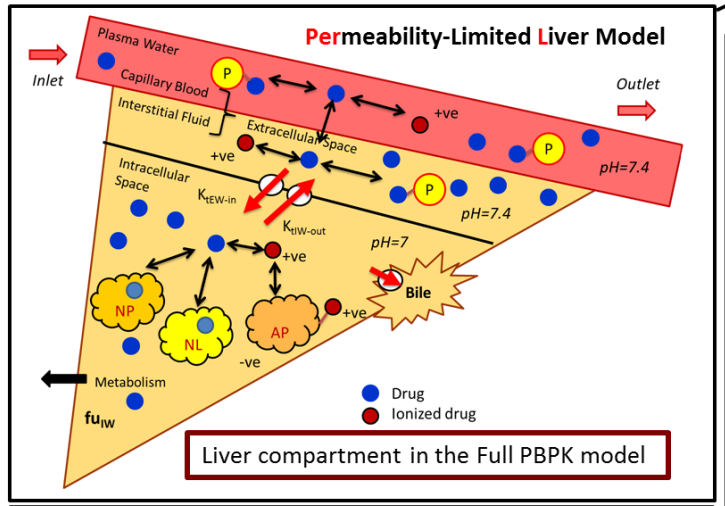
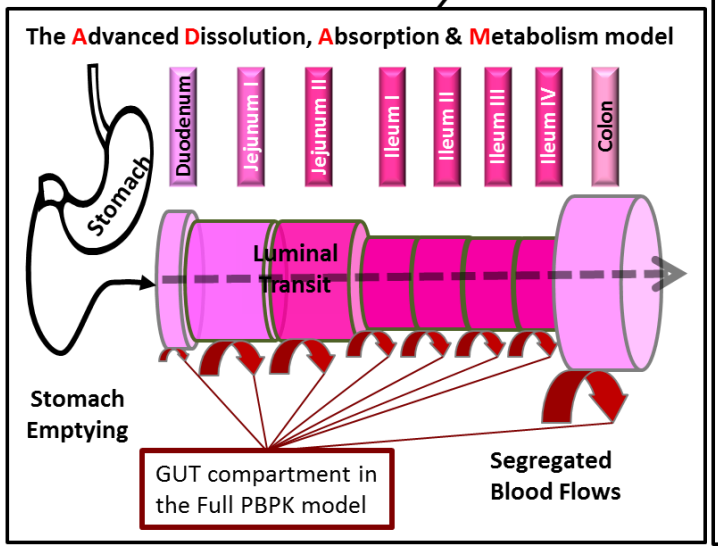
Simcyp permeability-limited models

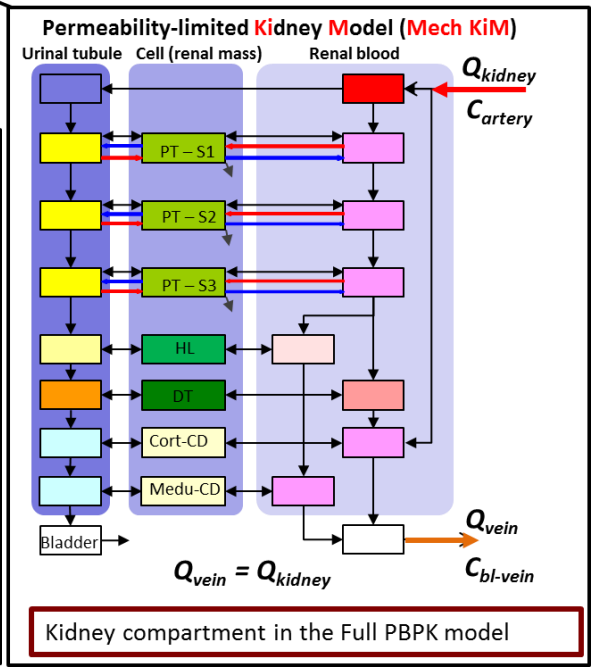












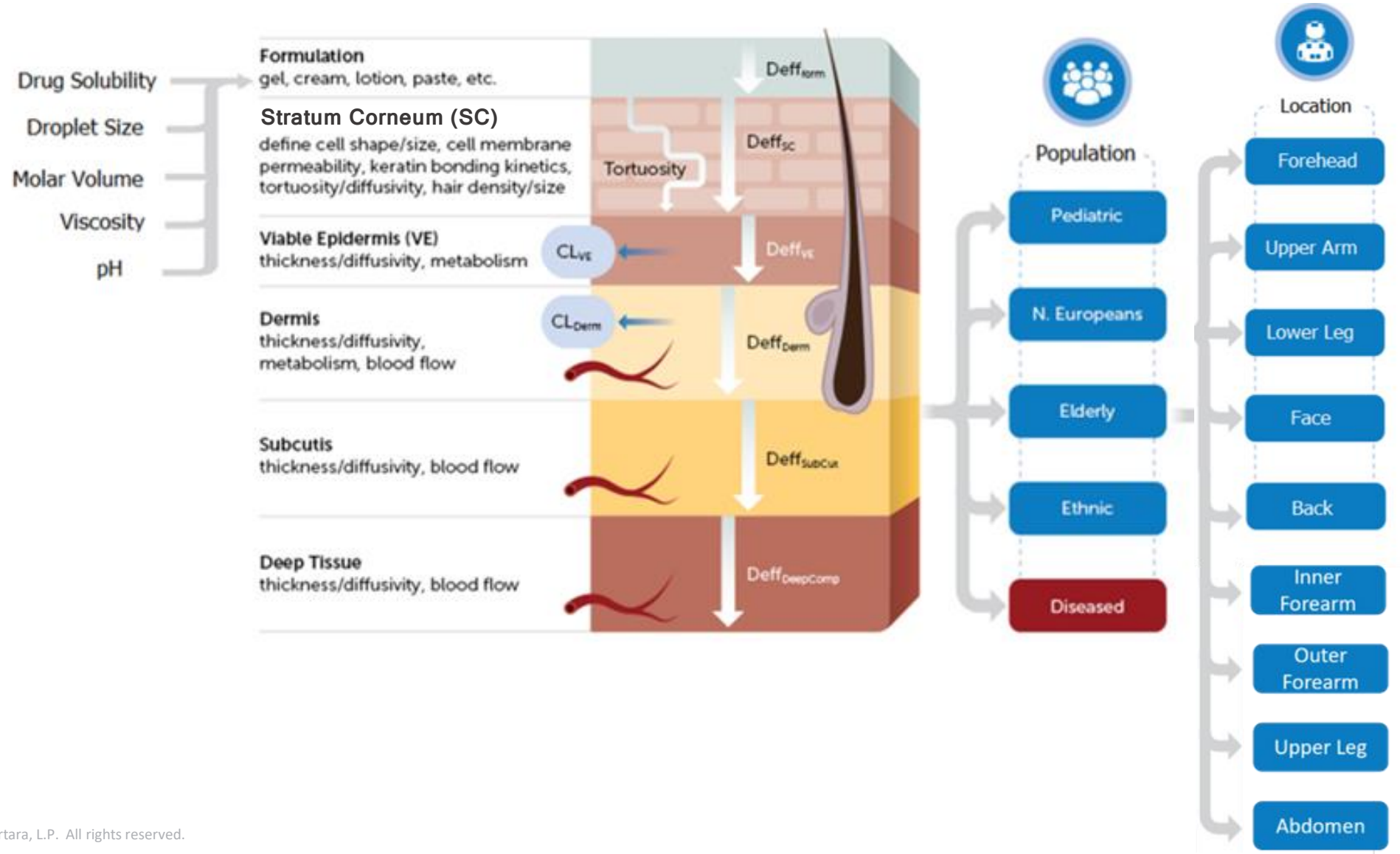
- Replacement and additional organ

Permeability-limited models available for:

- Intestine
- Liver
- Kidney
- Brain
- Lung
- Skin
- Feto-placental
- Etc.

Multi-Phase Multi-Layer Mechanistic Dermal Absorption model

- MPML MechDermA for *in vivo* simulations



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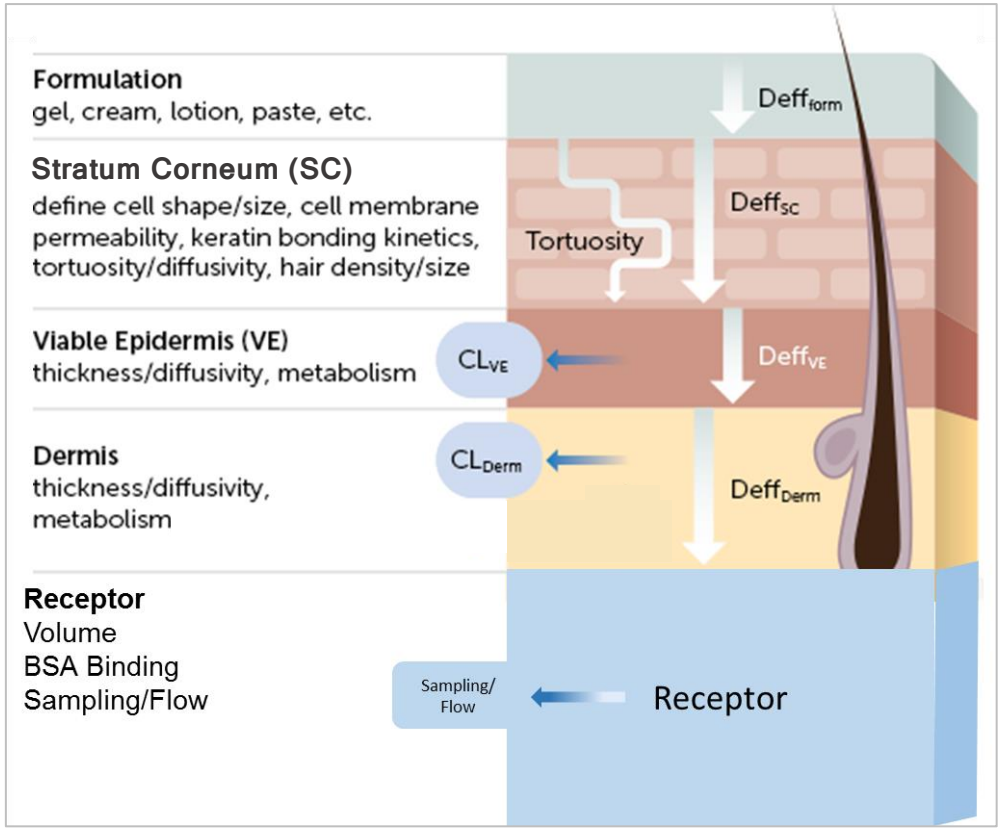
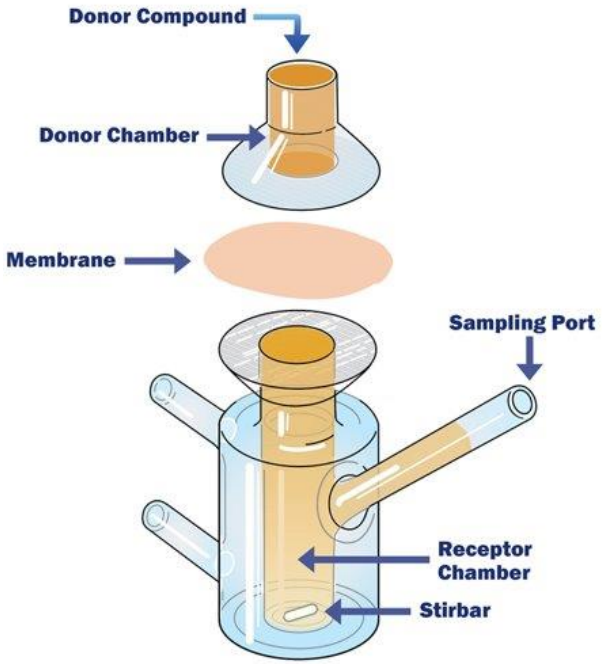
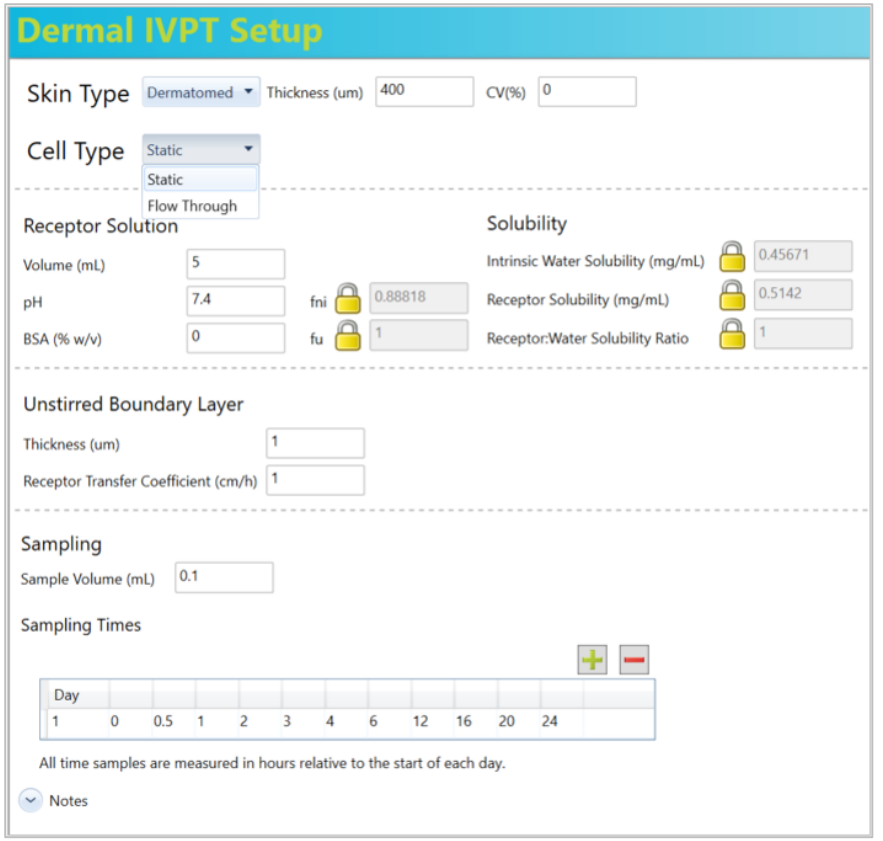
MechDermA IVPT module - *Ex vivo* skin physiology

- Physiology is assumed to be the same as *in vivo* except for excision related differences:
  - No blood or lymph flow in the dermis
  - No subcutis or muscle compartments
  - No hair follicle if isolated epidermis is selected



Franz diffusion cell





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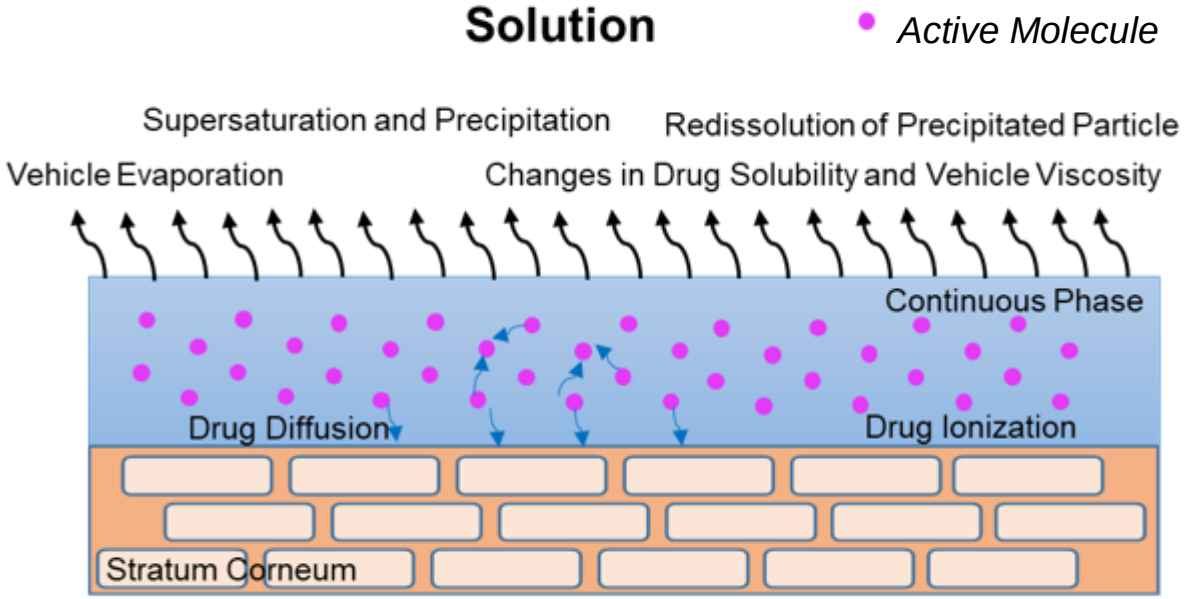
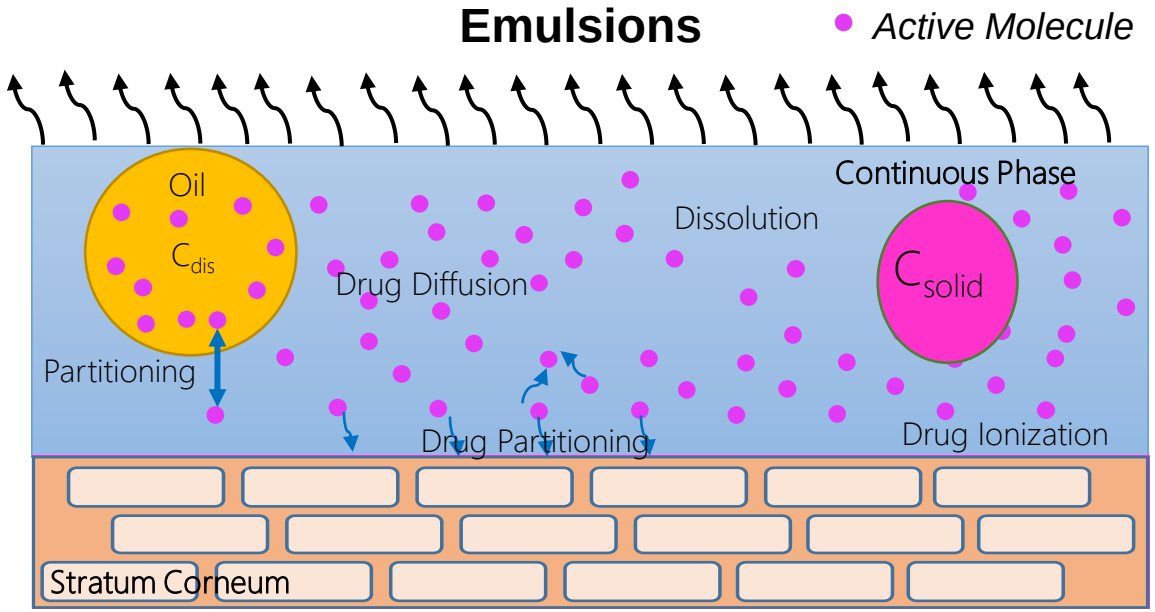
Modelling topical drug products in Simcyp

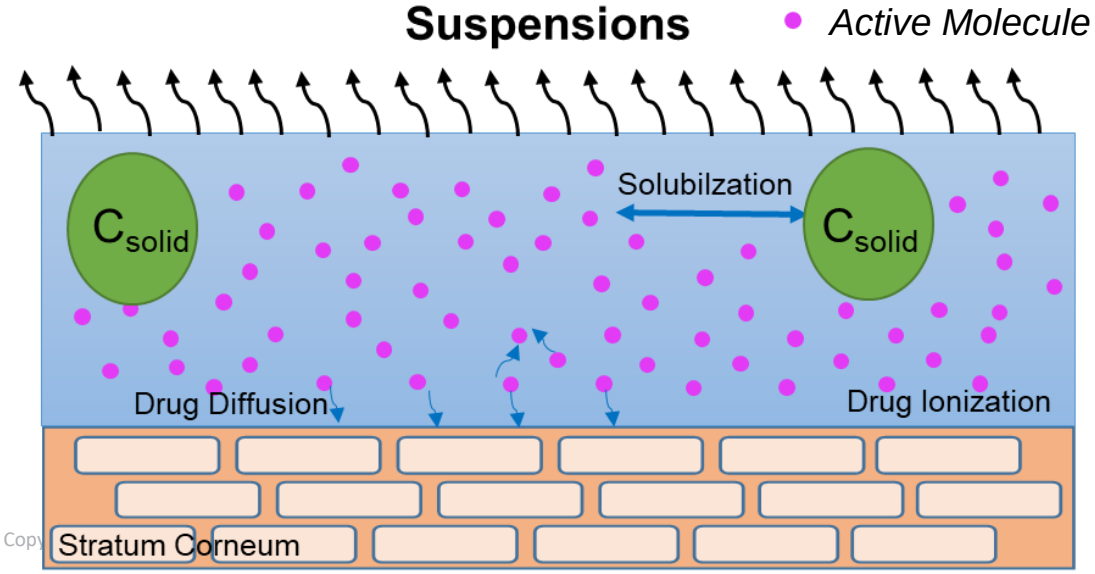
Solution



Emulsions



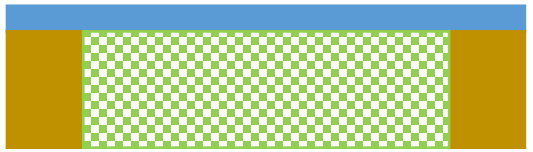
Suspensions



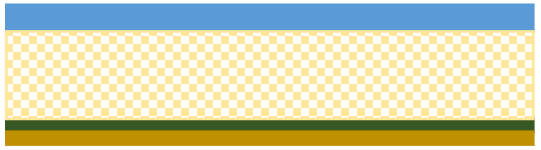
Patches

Drug in adhesive

Matrix



Reservoir



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Modelling *in vitro* and *in vivo* skin permeation of commercial Metronidazole formulations

- Available experimental data:
  - Q3 characterization data, i.e., formulation pH, viscosity, evaporation profile, drug solubility in continuous phase from two different laboratories [a,b]
  - IVPT : infinite and finite dose from aqueous metronidazole solution
  - IVPT at three doses (3, 10 and 30 mg/cm^2) from Ajjarapu *et al*. [c]
  - IVPT at one dose (10 mg/cm^2) from Roberts *et al.* [b]
  - *In vivo* stratum corneum permeation data from two clinical studies reported in literature

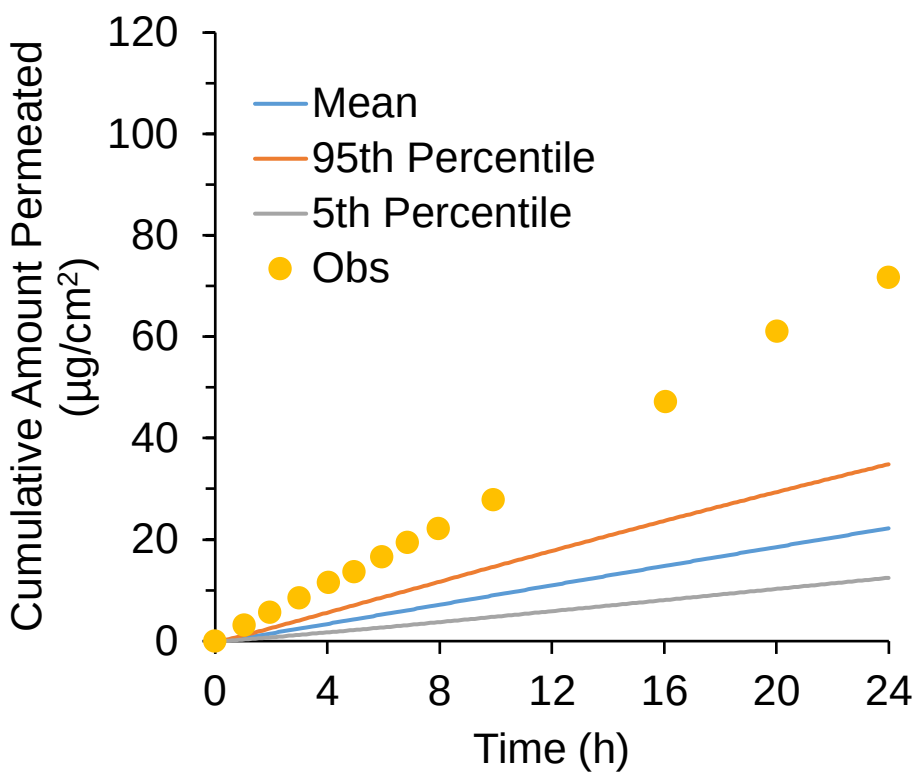
[a] Murthy *et al.* AAPS 2015; [b] Roberts *et al*. (unpublished); [c] Ajjarapu *et al*. Poster Presentation. AAPS 2019

Simulation 1

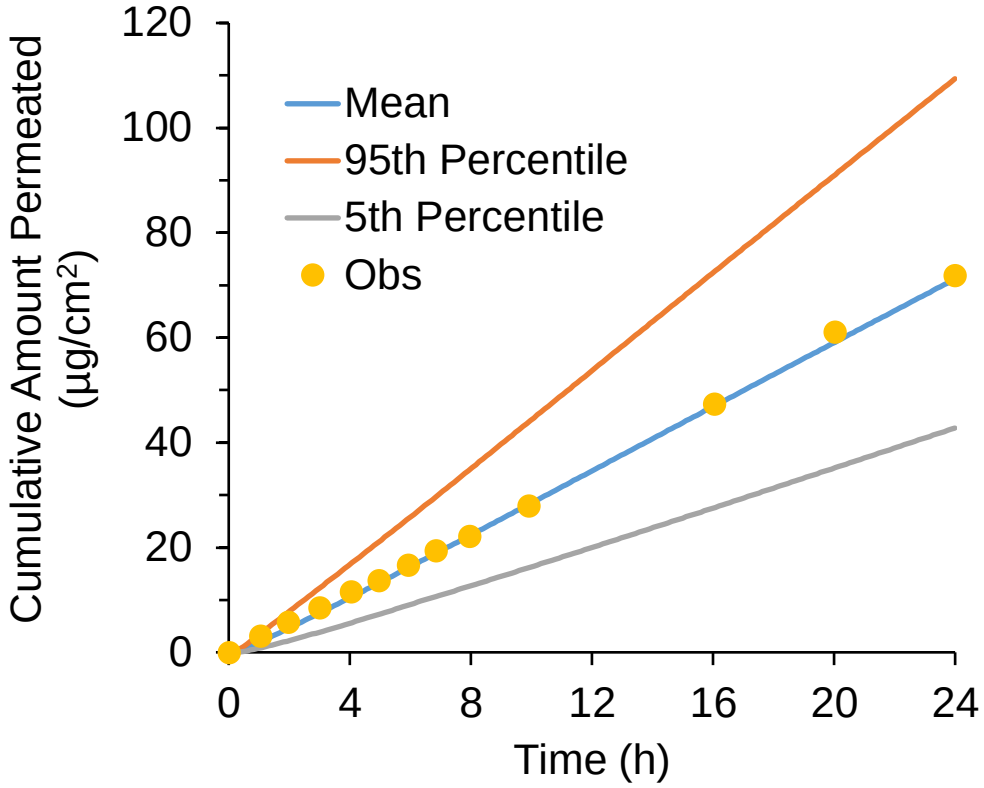
- Simulate IVPT experiment, drug in aqueous solution at infinite dose
- Physico-chemical parameters
  - MW: 171.56 g/mol, log $P_{o:w}$ = - 0.02, pKa 2.38 (monoprotic base)
  - Non-ionized at skin surface pH
  - Skin site = back; dose = 10 mg, dose volume = 2 mL, trial design: 10 trials x 6 individuals
- QSAR predictions of partition and diffusion coefficients in skin:

Parameter	Value	Unit	Method
$K_{lipid/water}$	1.279	NA	Hansen 2013
$K_{sebum/water}$	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}	$7.7 \cdot 10^{-4}$	cm^2/h	Johnson QSAR
Tortuosity	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	NA	Polak et al. 2016

Simulation 1



Optimized $Kp_{sclipid:water}$



Bottom-up predictions led to nearly 4-fold underprediction of the extent of permeation

Simulated cumulative amount permeated captured the observed profile

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

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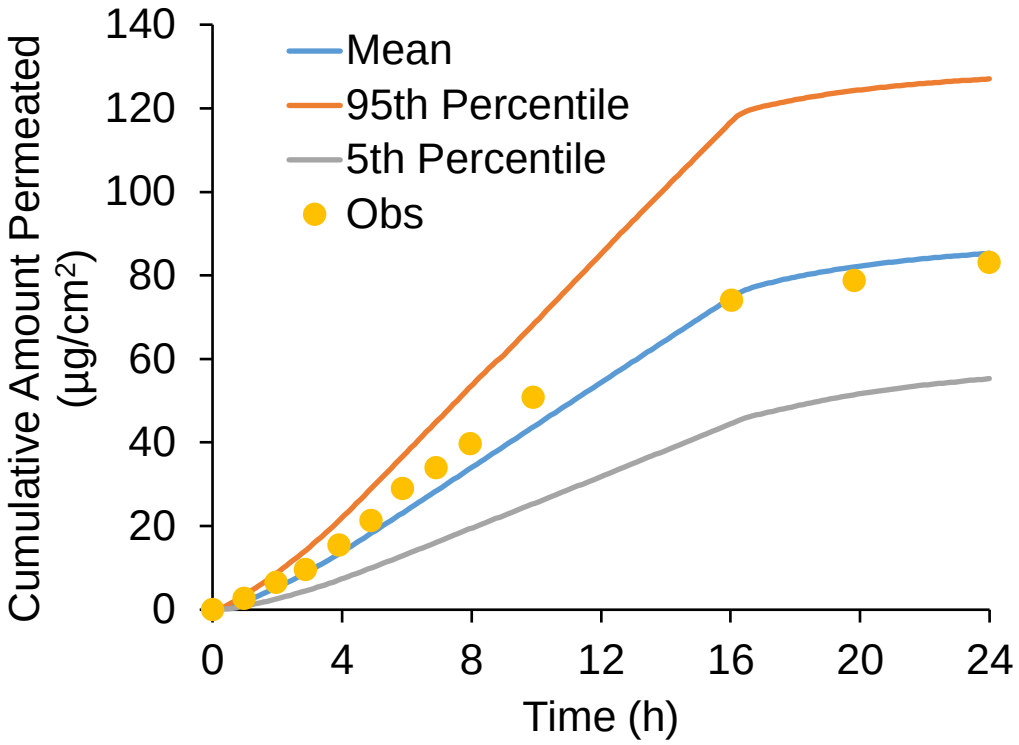
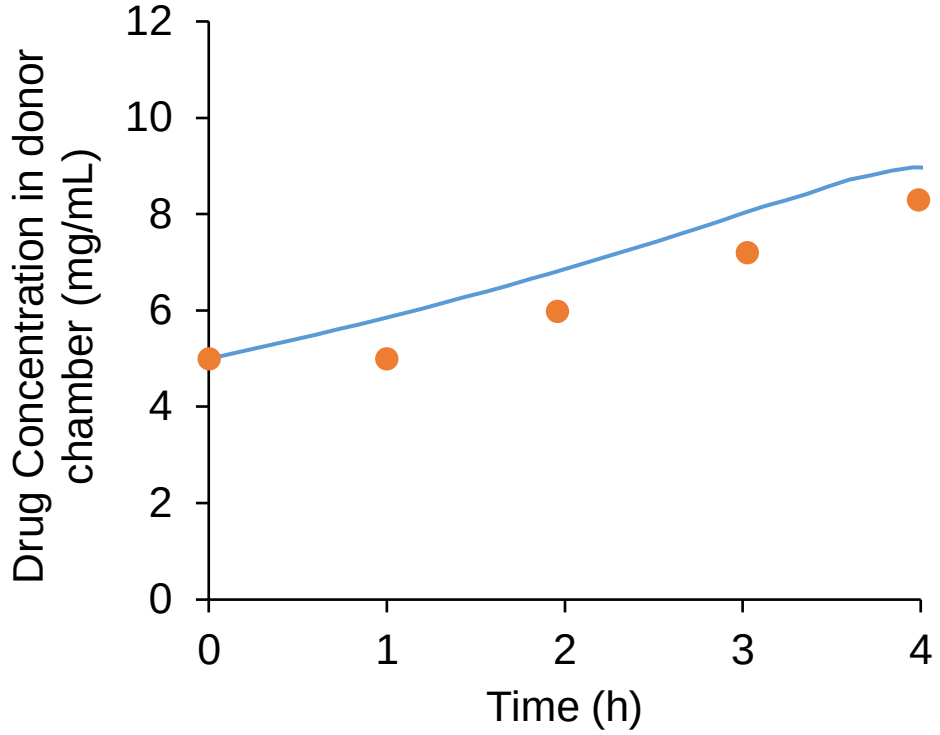
Simulation 1

- Skin site = back, dose = 1.5 mg, volume applied = 300 µL, trial design = 10 trials X 6 individuals





Predicted profile closely matches the observed data. This step verifies the fitting of $Kp_{sclipid:water}$.

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

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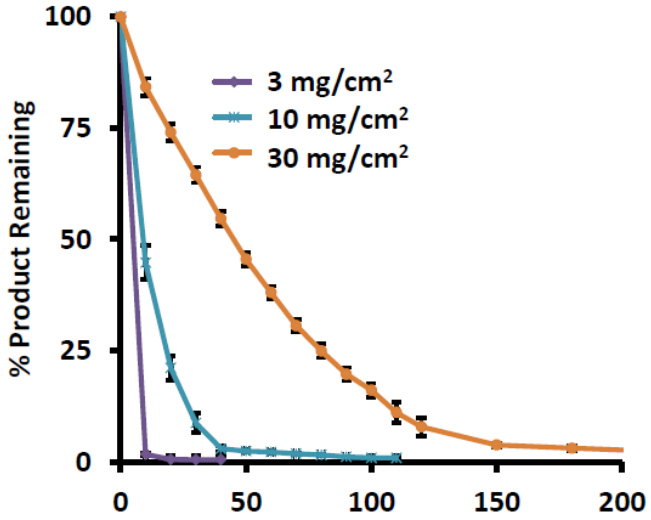
Simulation 2

Parameter	MetroGel®
Formulation	Solution
Applied dose (mg/cm^2)	10
Formulation density (g/cm^3)	1.01
Applied drug dose (µg)	74
Formulation volume (mL)	0.01
Formulation thickness (cm)	0.01
Viscosity (cP)	12779
Formulation pH	5.23
Drug solubility in continuous phase (mg/mL)	8.7
Evaporation profile	User Input Profile
Precipitation model	Empirical
CSR	1
Precipitation rate constant (h^{-1})	11

Viscosity measurements

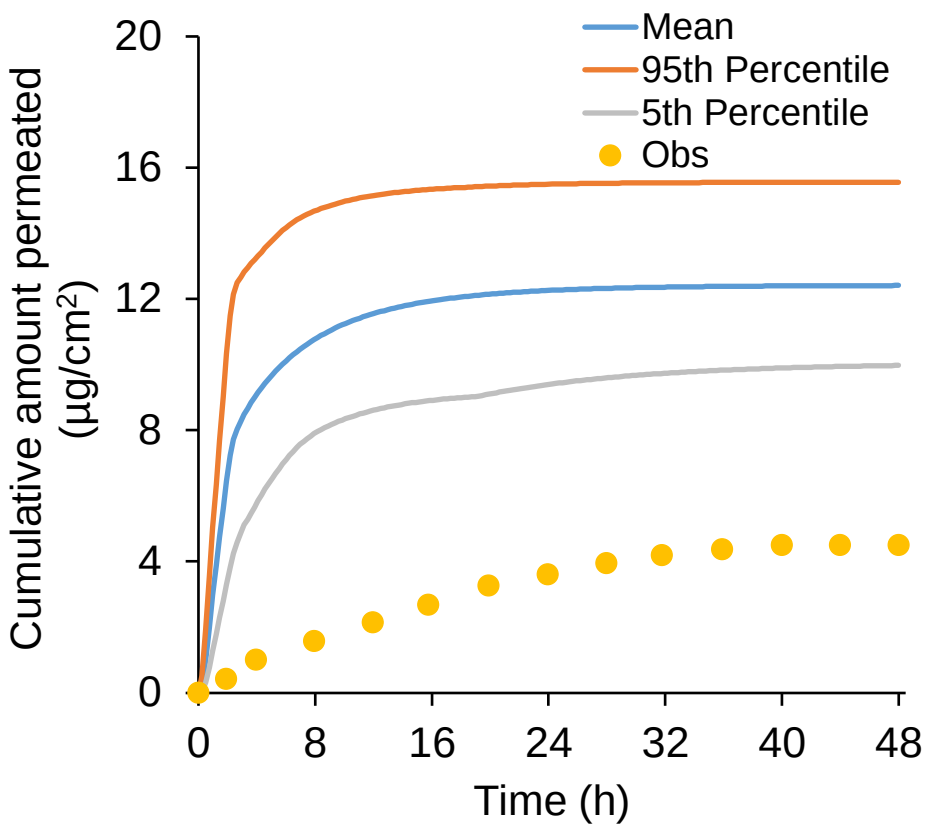
Product	Initial Viscosity (@0.01/S^{-1})	Yield Stress
MetroCream®	9541 ± 284	94 ± 0.00
Generic cream	6830 ± 1166	70 ± 3.00
MetroGel®	12779 ± 1215	50 ± 4.04
Generic gel-1	10534 ± 263	50 ± 0.00
Generic gel-2	12489 ± 1692	49 ± 5.20

Loss on drying measurements

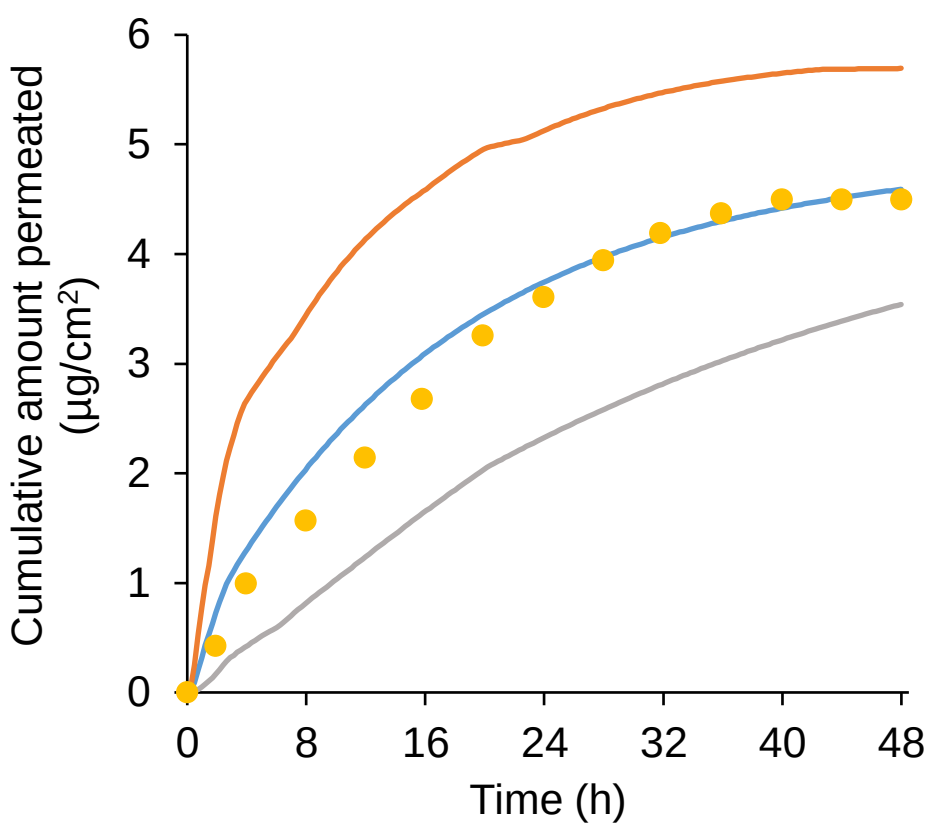


Murthy *et al*. AAPS Annual Meeting. Orlando, Florida, USA, 25-29 October 2015

Simulation 2



Optimized $Kp_{sclipid:water}$



Observed data from Murthy *et al*. FDA presentation. 2017

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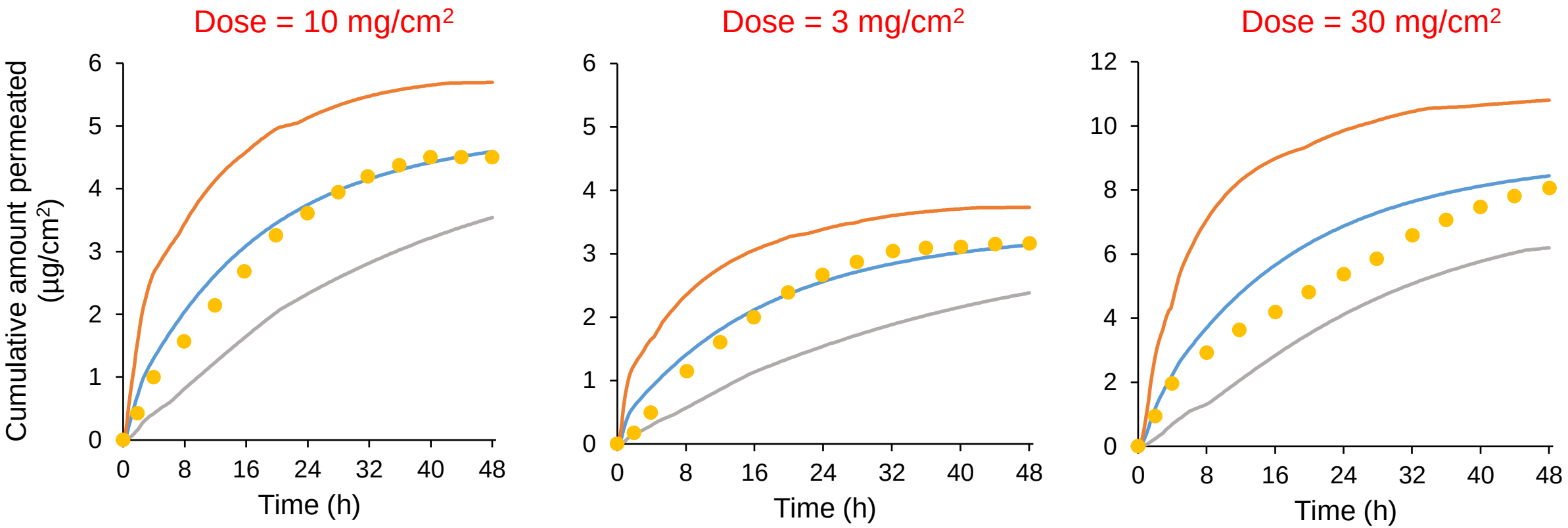
Simulation 2

- Optimized $D_{SC\ lipid}$ using 10 mg/cm^2 IVPT data
- 3 mg/cm^2 and 30 mg/cm^2 IVPT dataset serves as model verification



Optimized PBPK model was able to **predict** cumulative amounts permeated observed from the challenge formulations (different dose volumes).

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

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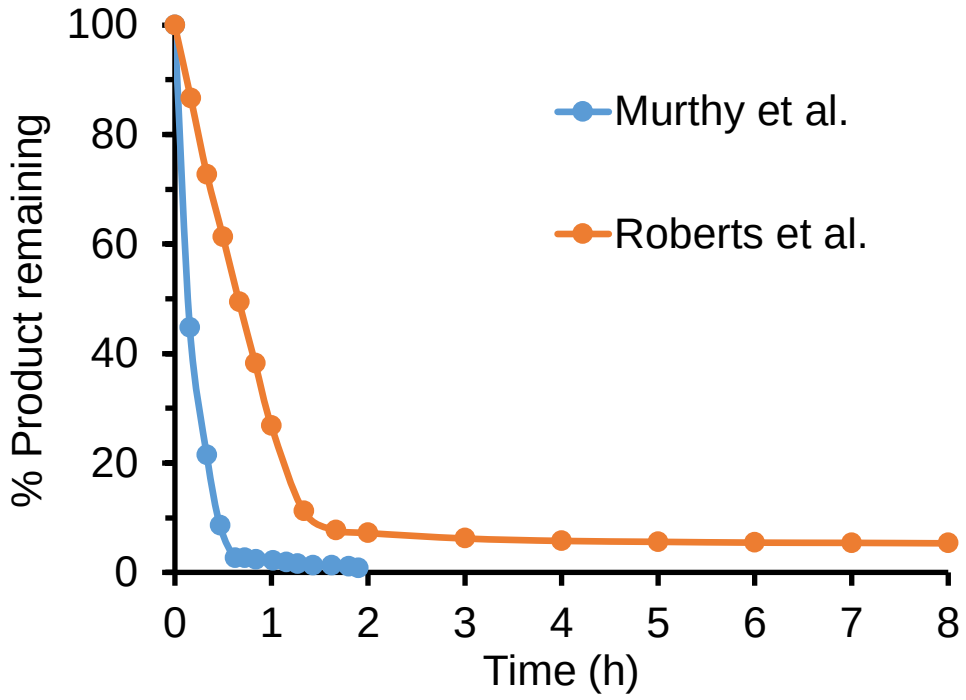
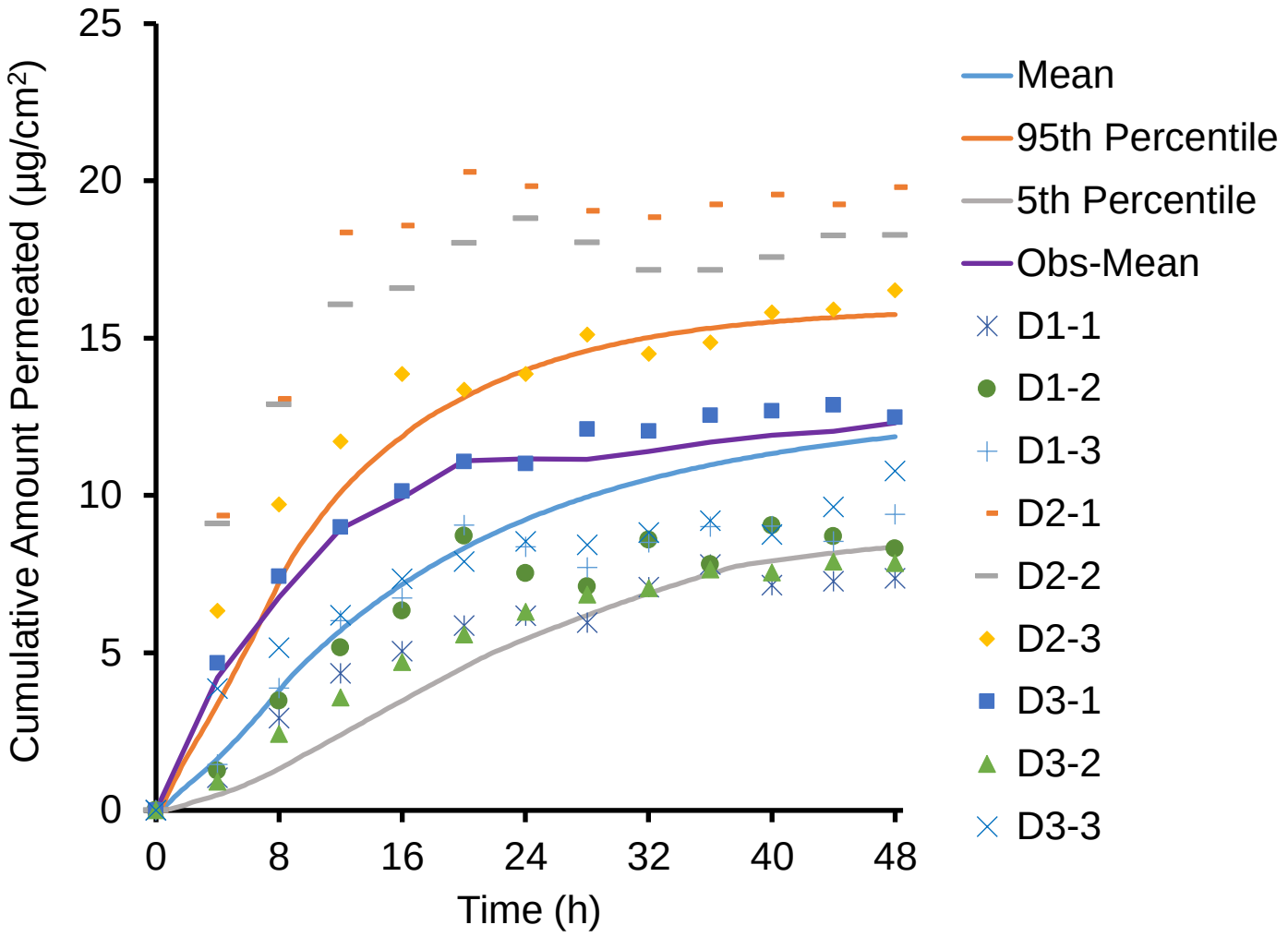
Simulation of *in vitro* skin permeation of metronidazole from MetroGel ®
Roberts *et al*. Q3 characterization - dose 10 mg/cm²

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





The model **predicts** mean cumulative amount permeated and variability from 10 mg/cm² dose determined by another lab.

Observed data from Murthy *et al*. AAPS 2015; Roberts *et al*. (unpublished)

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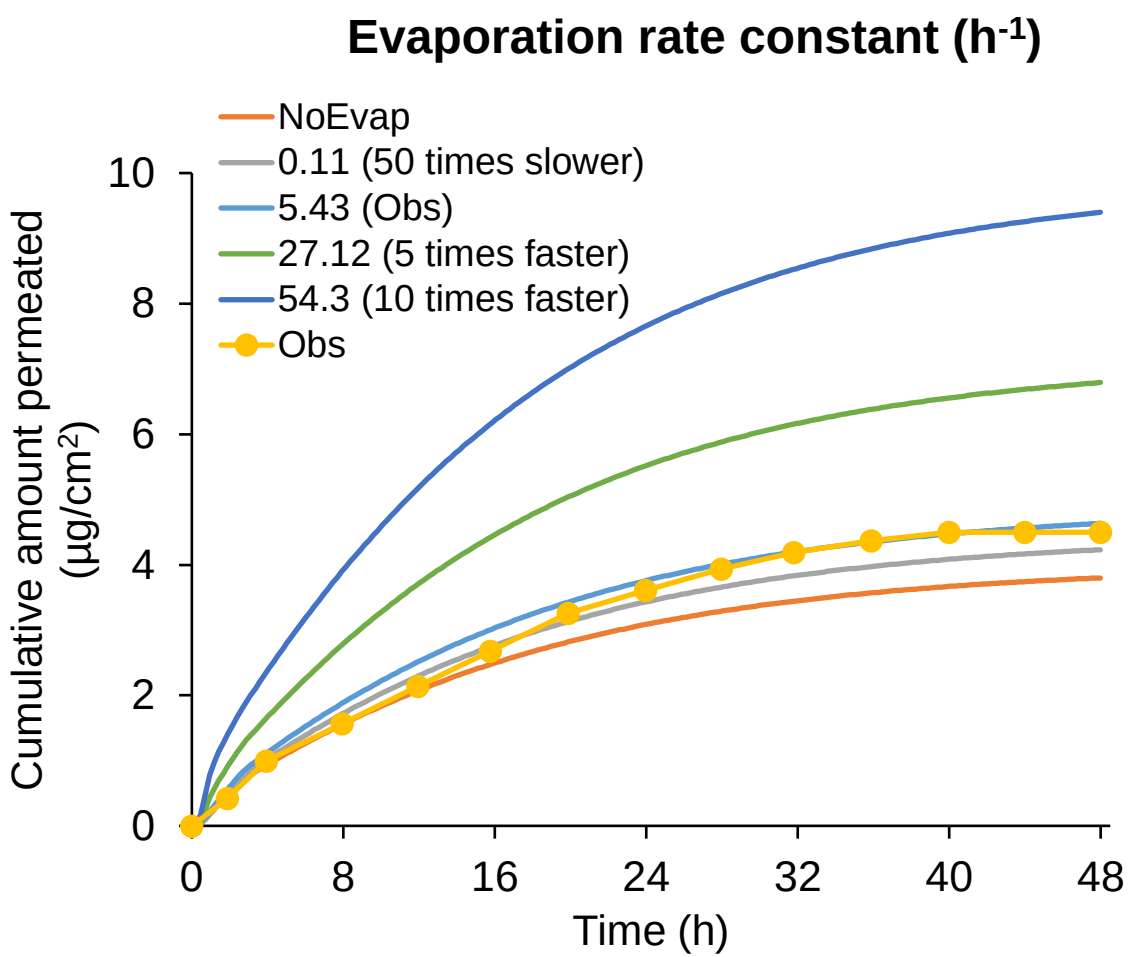
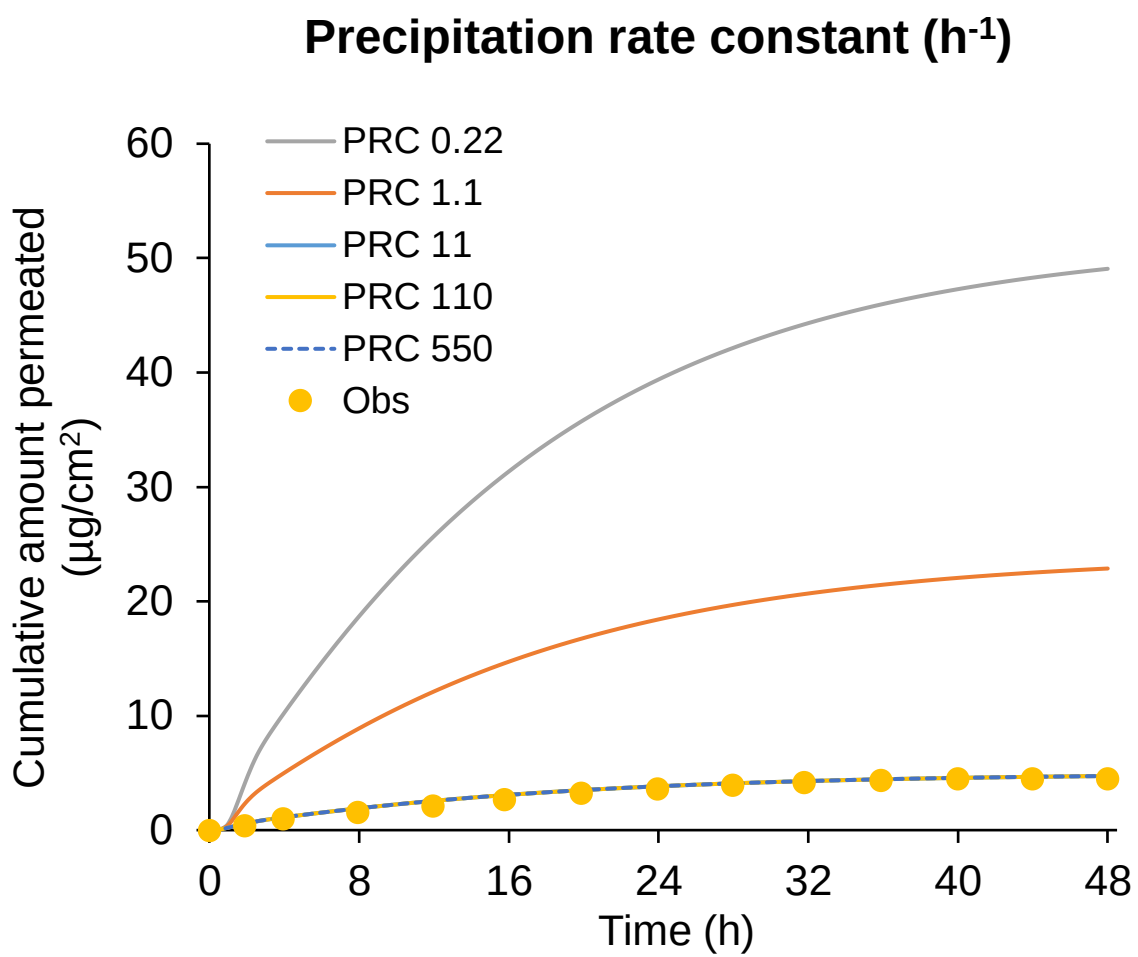
Sensitivity analysis of critical formulation parameters of MetroGel®





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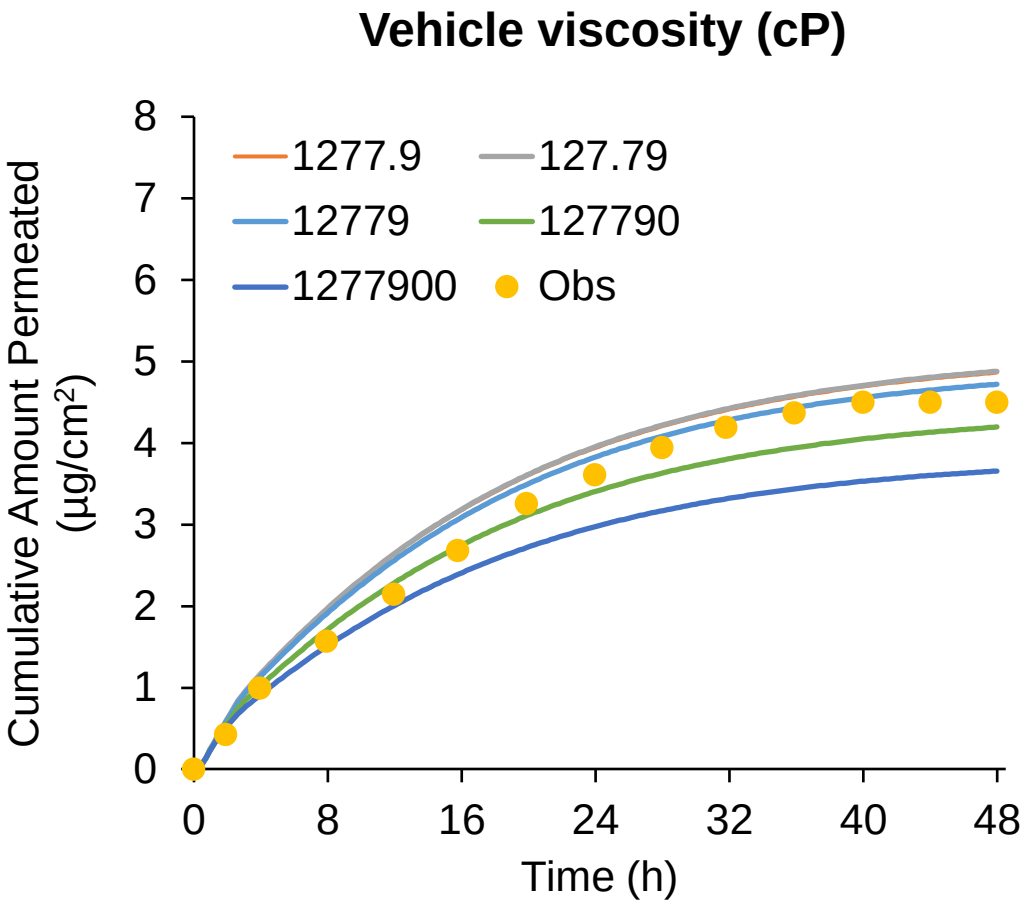
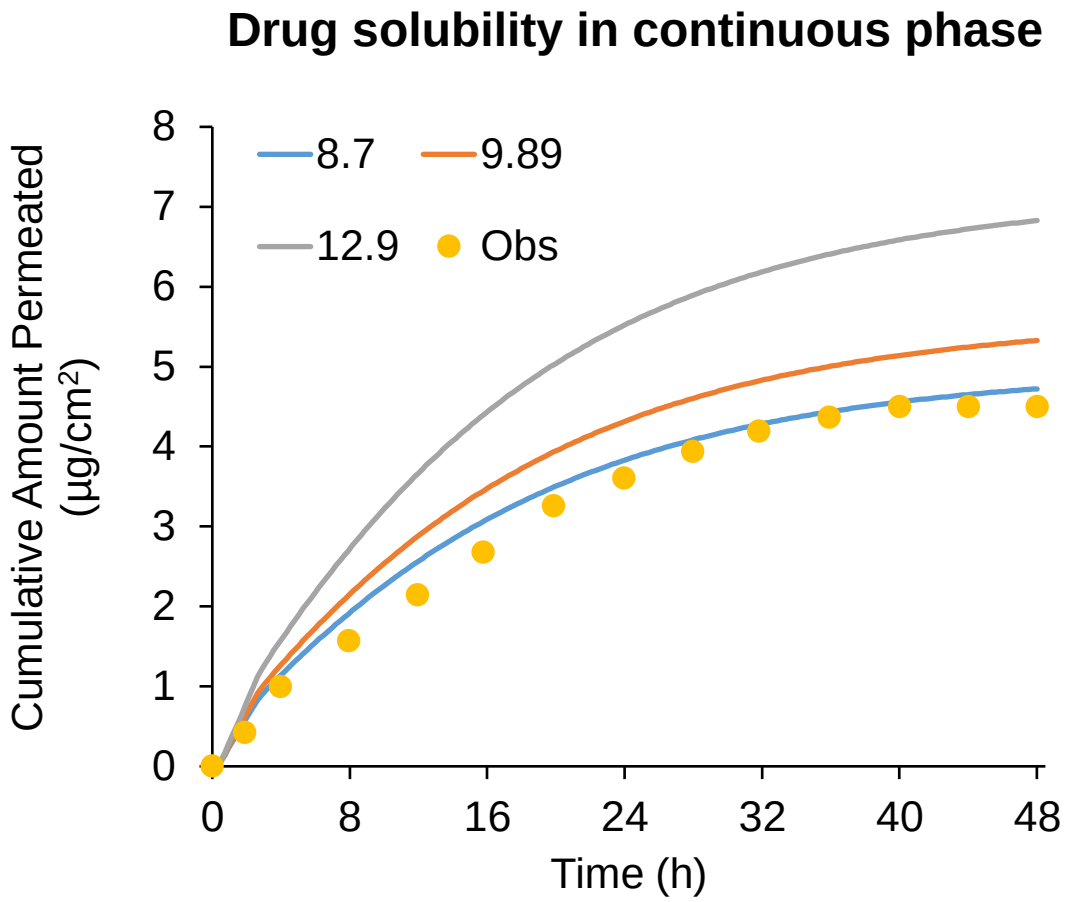
Sensitivity analysis of critical formulation parameters of MetroGel®





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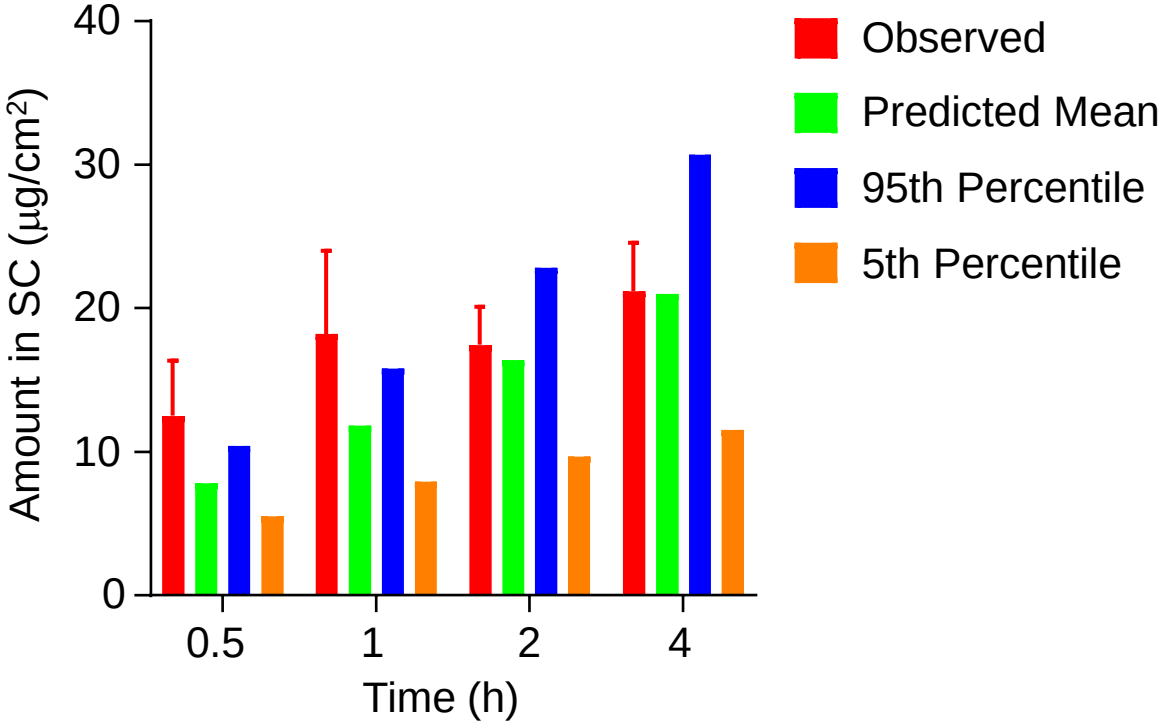
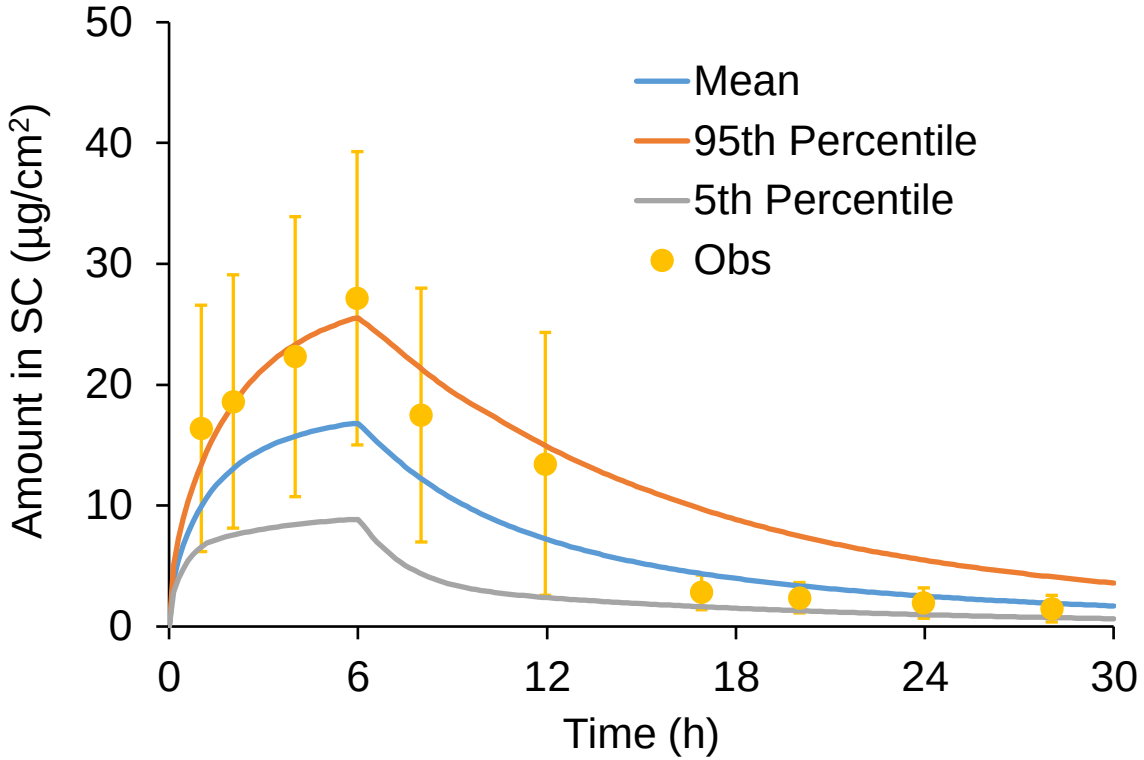
Simulation of *in vivo* skin permeation of metronidazole from MetroGel® and Rosex®

- 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 **predicts** metronidazole amount permeated in the stratum corneum observed *in vivo,* successfully demonstrating IVIVE in this case.

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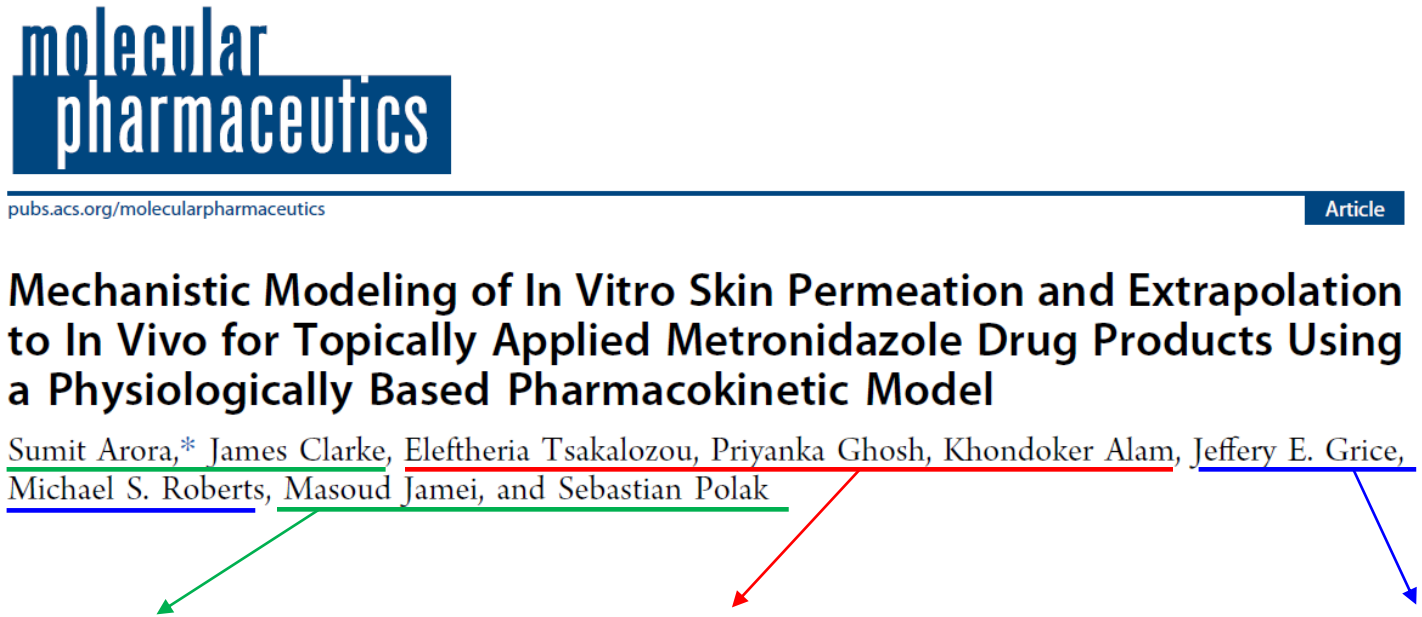
Simcyp publication on modelling metronidazole skin permeation



Certara Simcyp

Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research
U.S. Food and Drug Administration (FDA)
Silver Spring, Maryland 20993, United States

Therapeutics Research Centre, Diamantina Institute, University of Queensland
Brisbane 4102, Australia
Clinical and Health Sciences, University of South Australia, Adelaide 5005, Australia

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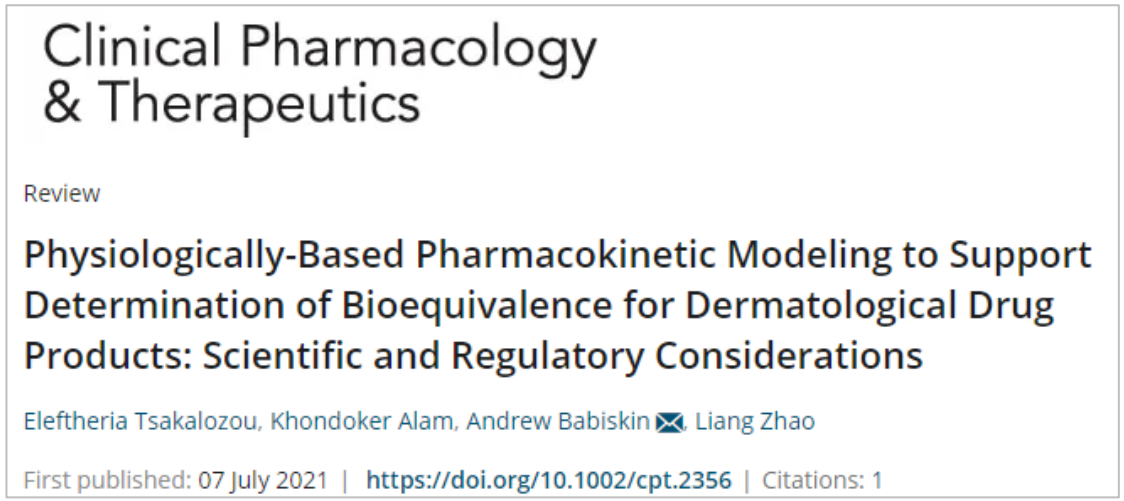
Conclusion: Applications of PBPK modelling skin absorption/permeation

- Prediction of tissue and/or systemic pharmacokinetics based on mechanistic simulations of absorption, distribution, metabolism and elimination (ADME)
- Simulations of application scenarios difficult to implement experimentally
  - Long exposure times
  - Repeated dose applications
  - Differences between applications at various body sites
  - Diseased skin (specific populations)
- Drug and/or formulation development, dose selection / optimization
- *In vitro – in vivo* extrapolation
- Risk assessment
- Drug virtual bioequivalence, generic *vs*. reference product

Regulatory interest in dermal PBPK modelling

- *In silico* PBPK modelling results increasingly used in regulatory submissions to replace clinical studies, e.g. for virtual bioequivalence
- FDA publications :



Clinical Pharmacology & Therapeutics

Review

Physiologically-Based Pharmacokinetic Modeling to Support Determination of Bioequivalence for Dermatological Drug Products: Scientific and Regulatory Considerations

Eleftheria Tsakalozou, Khondoker Alam, Andrew Babiskin, Liang Zhao

First published: 07 July 2021 | https://doi.org/10.1002/cpt.2356 | Citations: 1

CPT: Pharmacometrics & Systems Pharmacology

REVIEW | Open Access

Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%

Eleftheria Tsakalozou, Andrew Babiskin, Liang Zhao

First published: 06 February 2021 | https://doi.org/10.1002/psp4.12600 | Citations: 11

CERTARA

Recent Simcyp publication using MPML MechDermA

CPT: Pharmacometrics & Systems Pharmacology

ARTICLE | Open Access

Multi-phase multi-layer mechanistic dermal absorption (MPML MechDermA) model to predict local and systemic exposure of drug products applied on skin

Nikunjkumar Patel, James F. Clarke, Farzaneh Salem, Tariq Abdulla, Frederico Martins, Sumit Arora, Eleftheria Tsakalozou, Arran Hodgkinson, Omid Arjmandi-Tash, Sinziana Cristea, Priyanka Ghosh, Khondoker Alam, Sam G. Raney, Masoud Jamei, Sebastian Polak

ELSEVIER

Toxicology and Applied Pharmacology

Volume 459, 15 January 2023, 116357

Physiologically based modelling of dermal absorption and kinetics of consumer-relevant chemicals: A case study with exposure to bisphenol A from thermal paper

Barbara Wiśniowska [a], Susanne Linke [b c], Sebastian Polak [a d], Zofia Bielecka [a d], Andreas Luch [b c], Ralph Pirow [b]

ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics

Volume 178, September 2022, Pages 140-149

Modelling and simulation approaches to support formulation optimization, clinical development and regulatory assessment of the topically applied formulations – Nimesulide solution gel case study ☆

Naresh Mittapelly [a], Sebastian Polak [a b]

frontiers in Pharmacology

Front Pharmacol. 2022; 13: 1007496.

Published online 2022 Dec 1. doi: 10.3389/fphar.2022.1007496

PMCID: PMC9756572

PMID: 36532731

A mechanistic physiologically based model to assess the effect of study design and modified physiology on formulation safe space for virtual bioequivalence of dermatological drug products

J. F. Clarke [1,2,*], K. Thakur [1] and S. Polak [1,2]

Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model

Sumit Arora*, James Clarke, Eleftheria Tsakalozou, Priyanka Ghosh, Khondoker Alam, Jeffery E. Grice, Michael S. Roberts, Masoud Jamei, and Sebastian Polak

Cite this: *Mol. Pharmaceutics* 2022, 19, 9, 3139−3152

Publication Date: August 15, 2022

https://doi.org/10.1021/acs.molpharmaceut.2c00229

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Physiologically Based Pharmacokinetic Modeling of Transdermal Selegiline and Its Metabolites for the Evaluation of Disposition Differences between Healthy and Special Populations

by Santosh Kumar Puttrevu [1,*], Sumit Arora [1], Sebastian Polak [1,2] and Nikunj Kumar Patel [1]

[1] Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield S1 2BJ, UK

[2] Pharmacoepidemiology and Pharmacoeconomics Unit, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, str., 30-688 Krakow, Poland

* Author to whom correspondence should be addressed.

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