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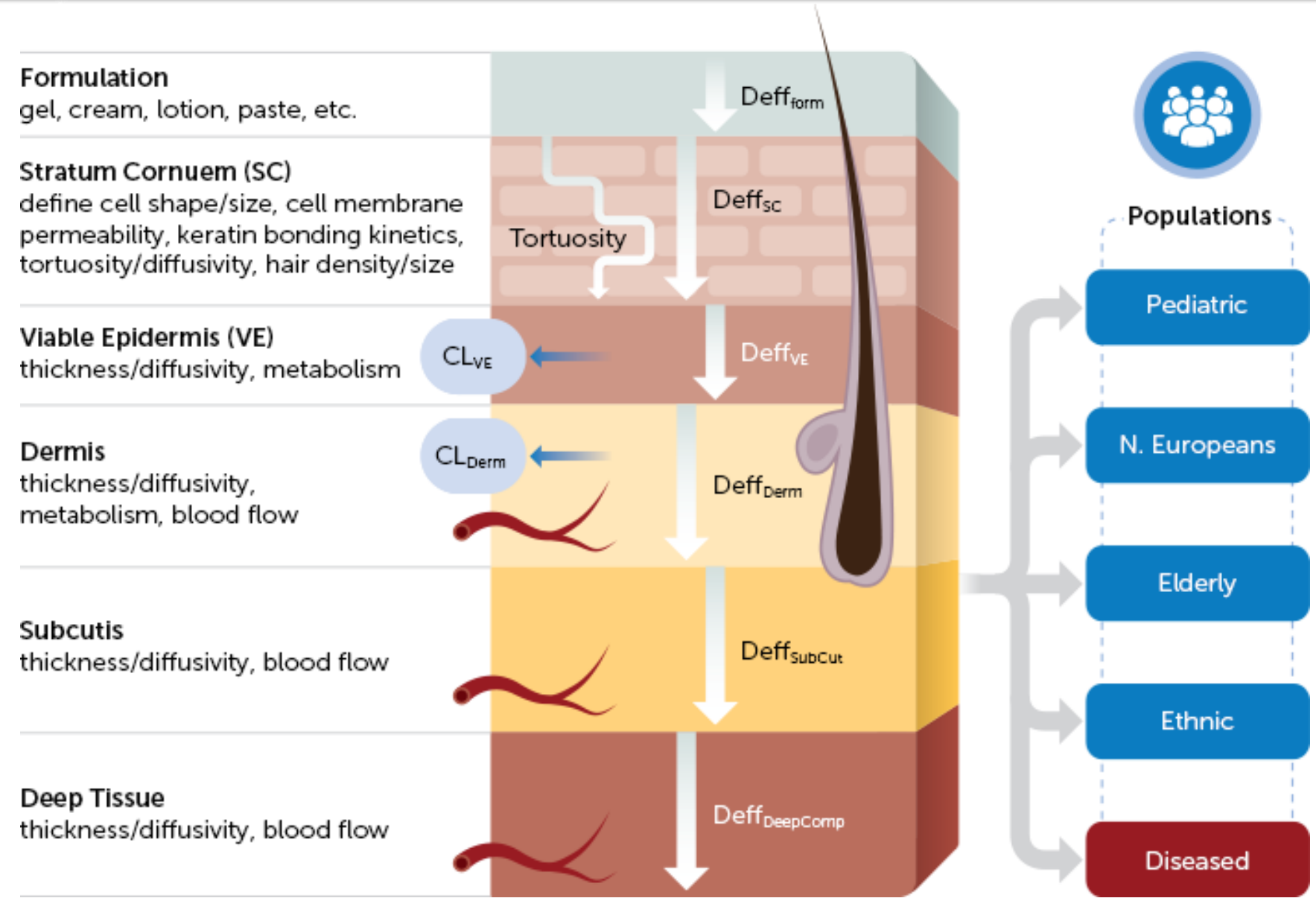
Simcyp

PBPK Modeling of Dermally Applied Drug Products to Support Clinical Development and Regulatory Assessment

Nikunjkumar Patel

Certara UK Limited

MPML-MechDermA Model



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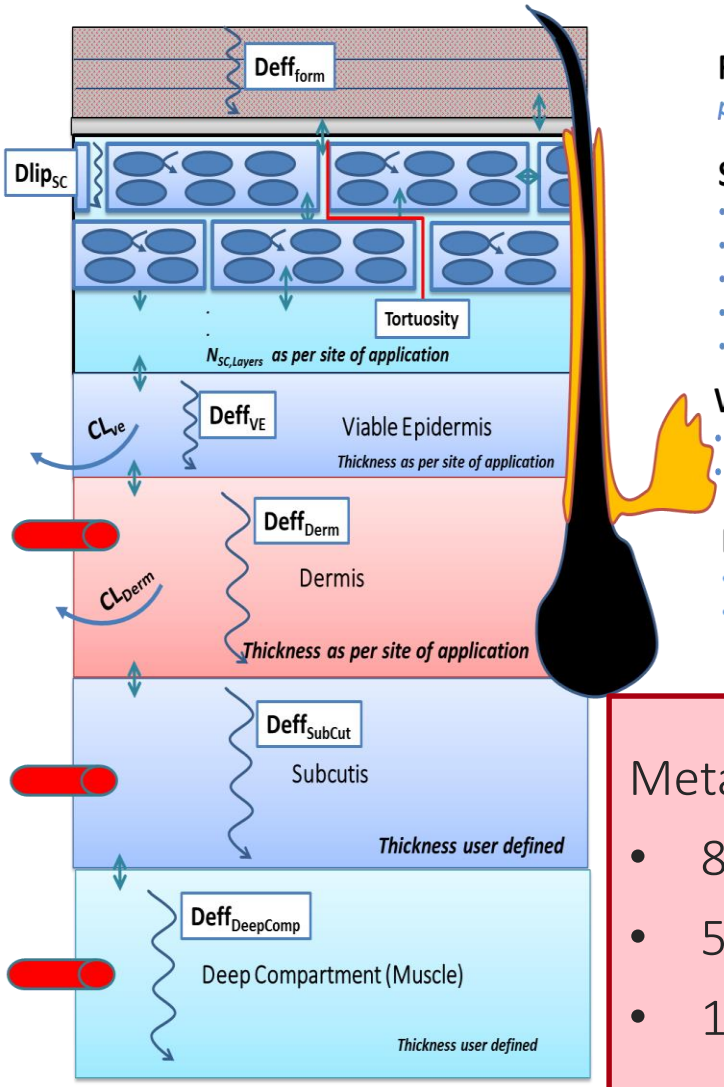
Simcyp MPML-MechDermA model – Structure and Parameters



Formulation *(Gel, cream, lotions, paste, patch, ointments, etc.)*

Stratum Corneum (SC)
- *Define cell shape and size*
- *Cell membrane permeability*
- *Keratin bonding kinetics*
- *Tortuosity and diffusivity*
- *Hair follicle density and size*

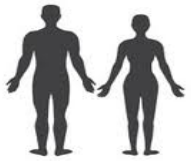
Viable Epidermis (VE)
- *Thickness, diffusivity*
- *Metabolism*

Dermis
- *Thickness, diffusivity*
- *Metabolism, blood flow*

Meta-analysis
- 8 anatomical locations
- 500+ publications
- 100+ parameter
- >2 person-years

Paediatric Population

Healthy NEurCaucasian

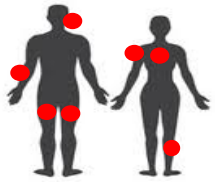


Elderly Subjects

Ethnic Population

East Asian (Chinese, Japanese, Korean)

Diseased Population (psoriasis)



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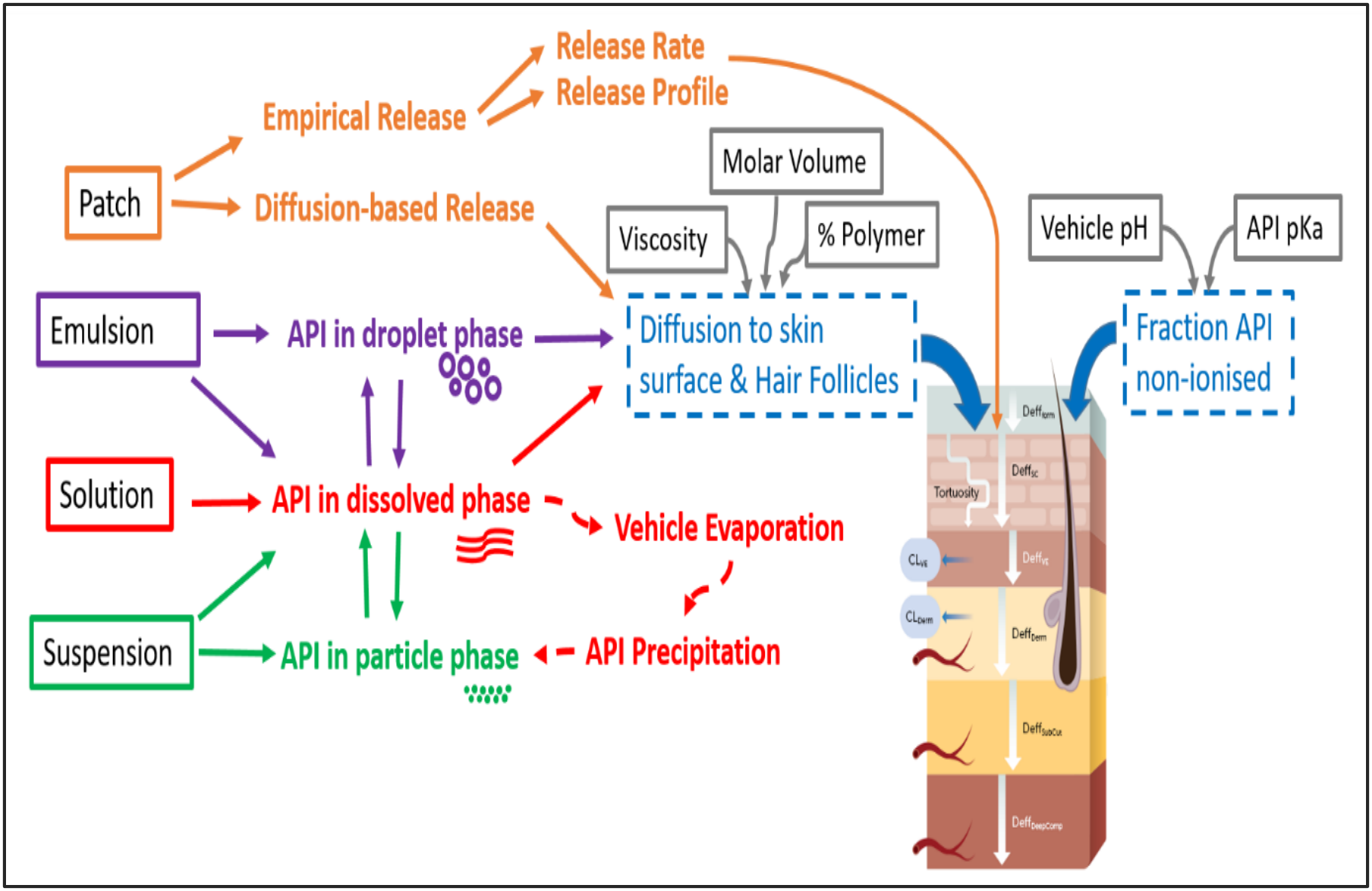
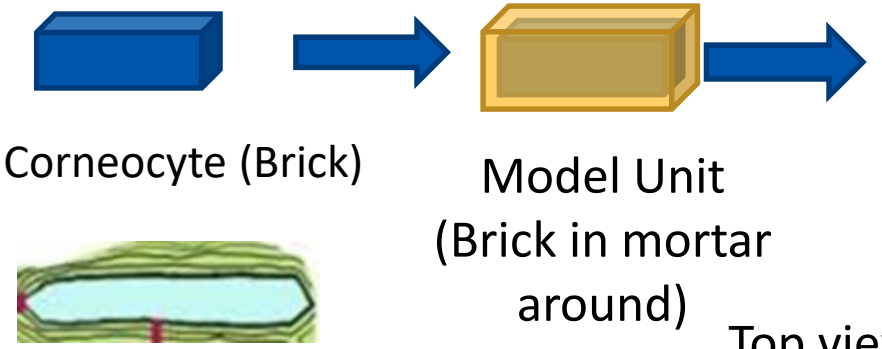
MPML-MechDermA Formulation Models



MPML-MechDermA – Brick and Mortar Model



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Intra-individual Variability

- Eight different locations
  1. Forehead
  2. Face (cheek)
  3. Volar Forearm
  4. Dorsal Forearm
  5. Upper Arm
  6. Lower Leg
  7. Thigh
  8. Back

- Various structural elements
  1. Skin surface
  2. **Stratum corneum**
  3. Viable epidermis
  4. Dermis
  5. Subcutis
  6. Muscle
  7. Hair

- Various parameters
  1. **Number of layers**
  2. Corneocyte pH
  3. Corneocyte size
  4. Fraction of p/w/l
  5. Tortuosity
  6. Lipids fluidity/th

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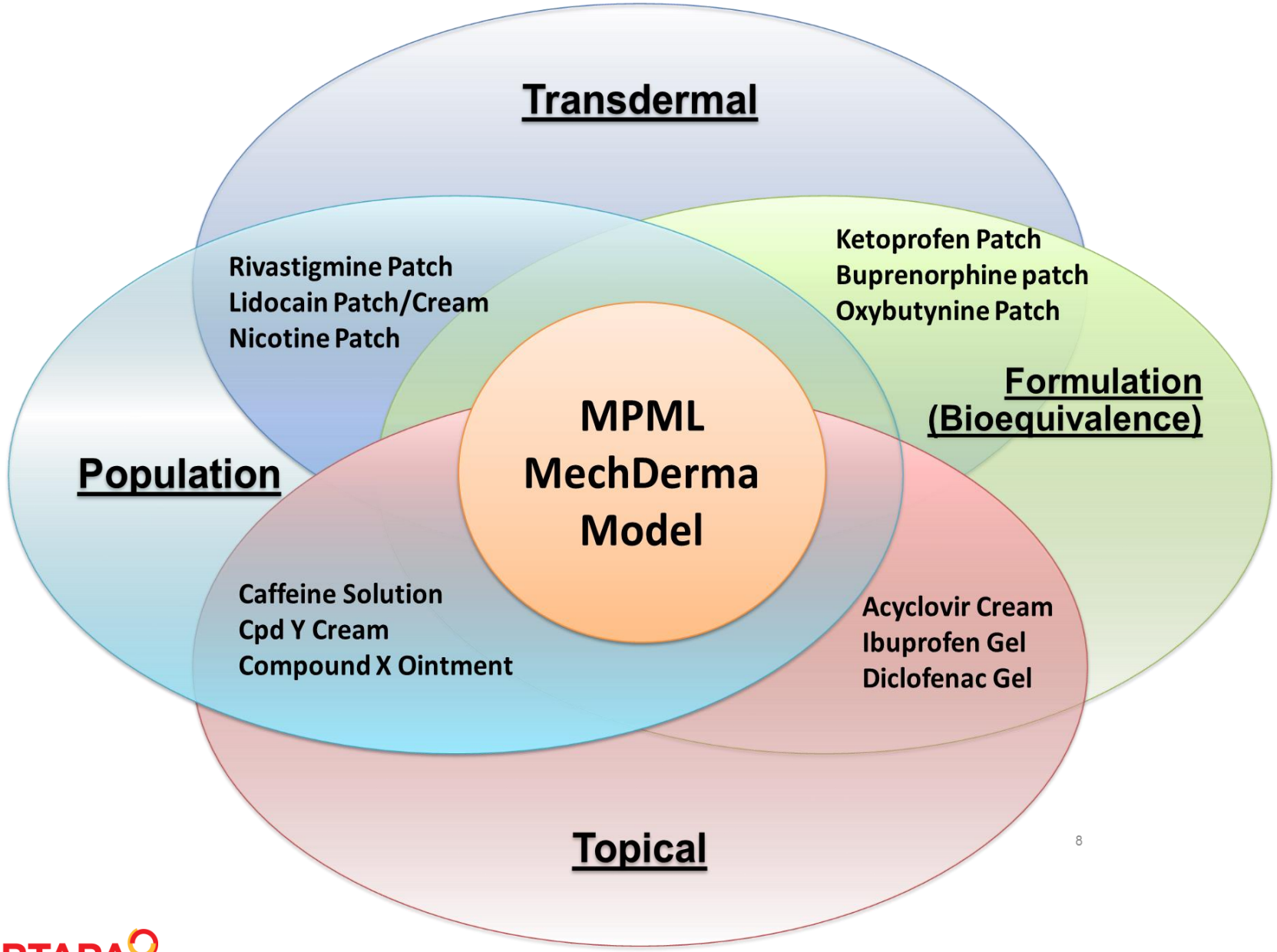
Model Verification and Application – 11 Different Case Examples



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Model Verification Dataset Profile

		1	2	3	4	5	6	7	8	9	10	11
	Compound	[redacted]										
Formulation type	solution		x		x	x				x	x	x
	emulsion					x		x (with particles)	x (paediatric)	x		
	paste										x	
	patch	x	x			x	x		x (adult)			x
Formulation reported	matrix patch	x				x	x				x	
	reservoir and other patches			x					x			
	gel				x	x				x		x
	cream		Not clear		x			x	x	x	x	
	ointment									x	x	
Place of application	forehead											
	inner forearm				x				x	x	x	
	outer forearm								x			
	upper arm	x					x		x			
	face				x			x		x	x	
	lower leg								x	x		
	upper leg						x		x		x	x
	back	x	x	x			x				x	x
Exposure data	plasma	x	x	x	x	x	x		x	x	x	x
	dermal flux and IVPT						x	x				x
	SC					x				x		
	subcutis					x						
	muscle					x					x	
	synovium fluid				x	x					x	
	synovium tissue					x					x	
	cerebrospinal fluid						x					
Chemical character	acid				x	x				x	x	
	ampholyte	x						x				
	base		x	x			x		x			x
	zwitterion											

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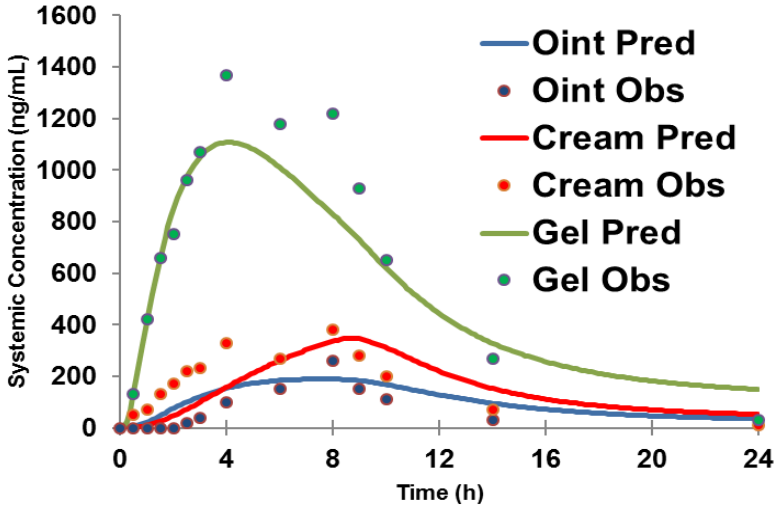
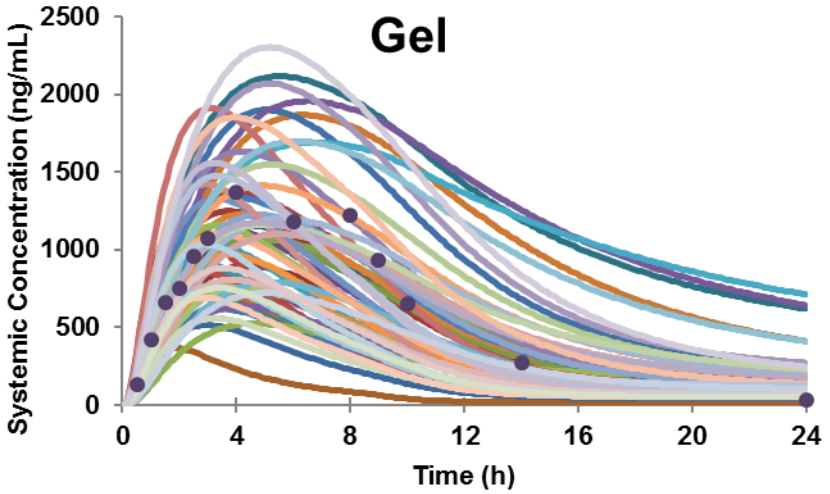
Studying Formulation Impact - Ibuprofen

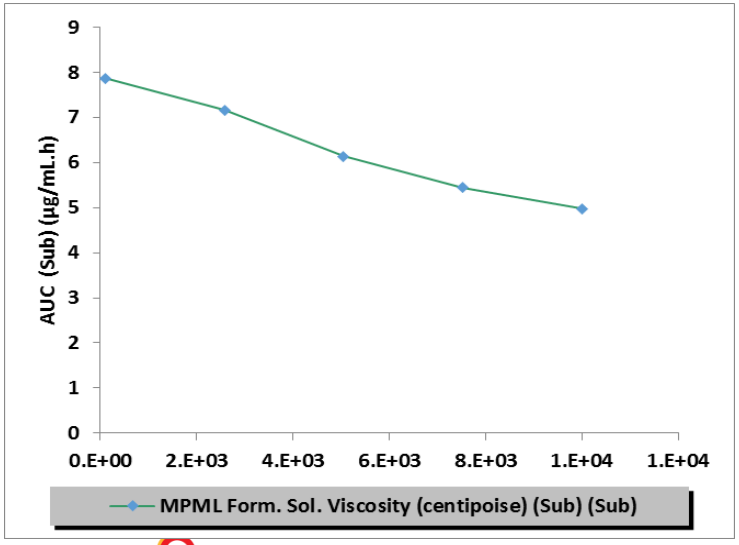
Compare Formulations

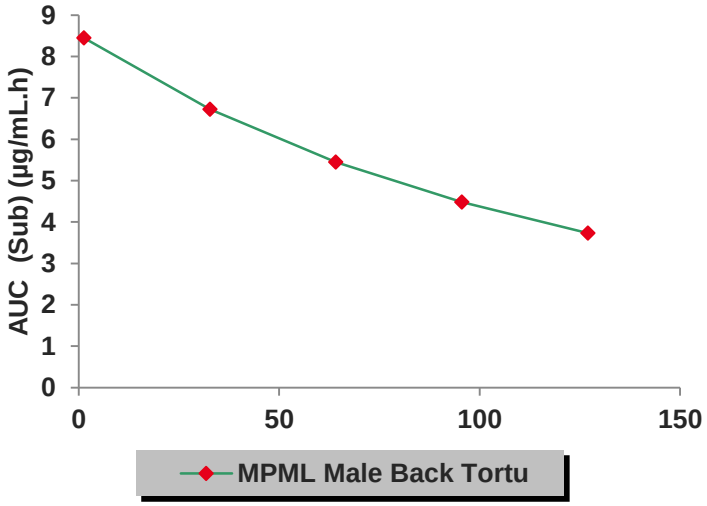


Simulate Population Variability



Identify clinically-relevant Critical Product Quality/Physiology Attributes





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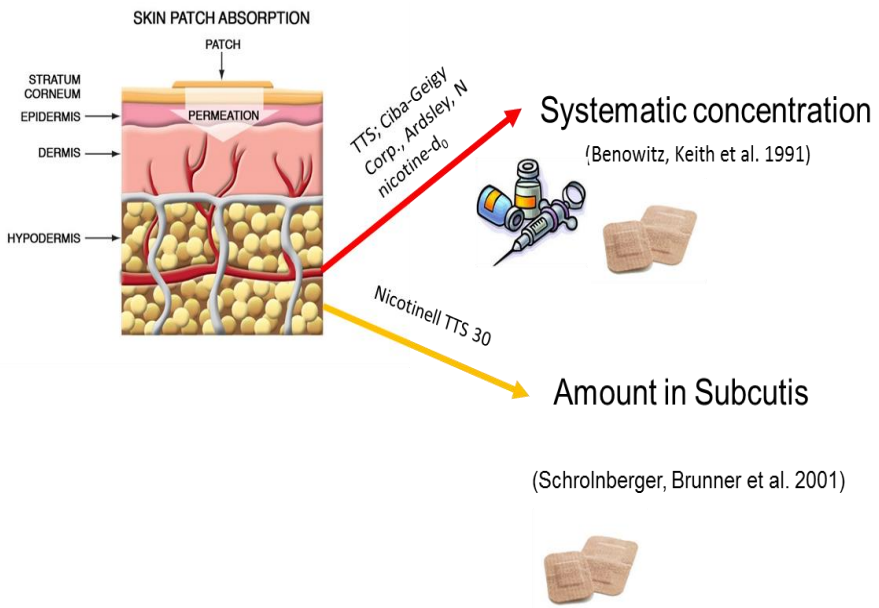
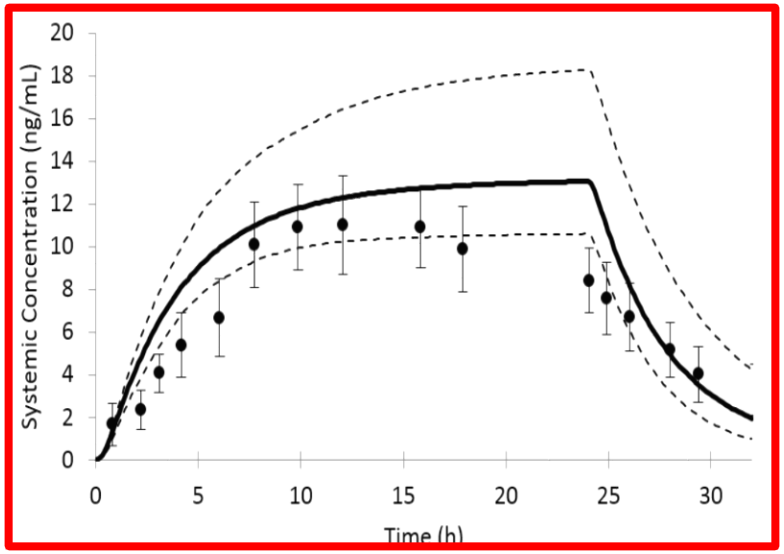
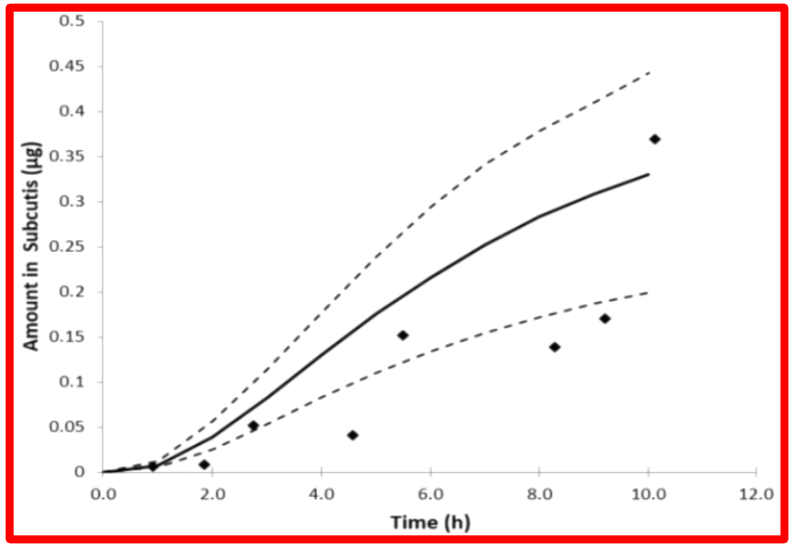
Predicting local and systemic exposure after nicotine patch





		Predicted		Observed data	
		Mean	SD	Mean	SD
Patch order zero release	T_{max} (h)	23.9	0	12.06	4.8
	C_{max} (ng/mL)	12.6	0.9	11.1	3.8
	AUC (ng/mL×h)	300	23.1	245.7	125

Martins *et al*. 2018



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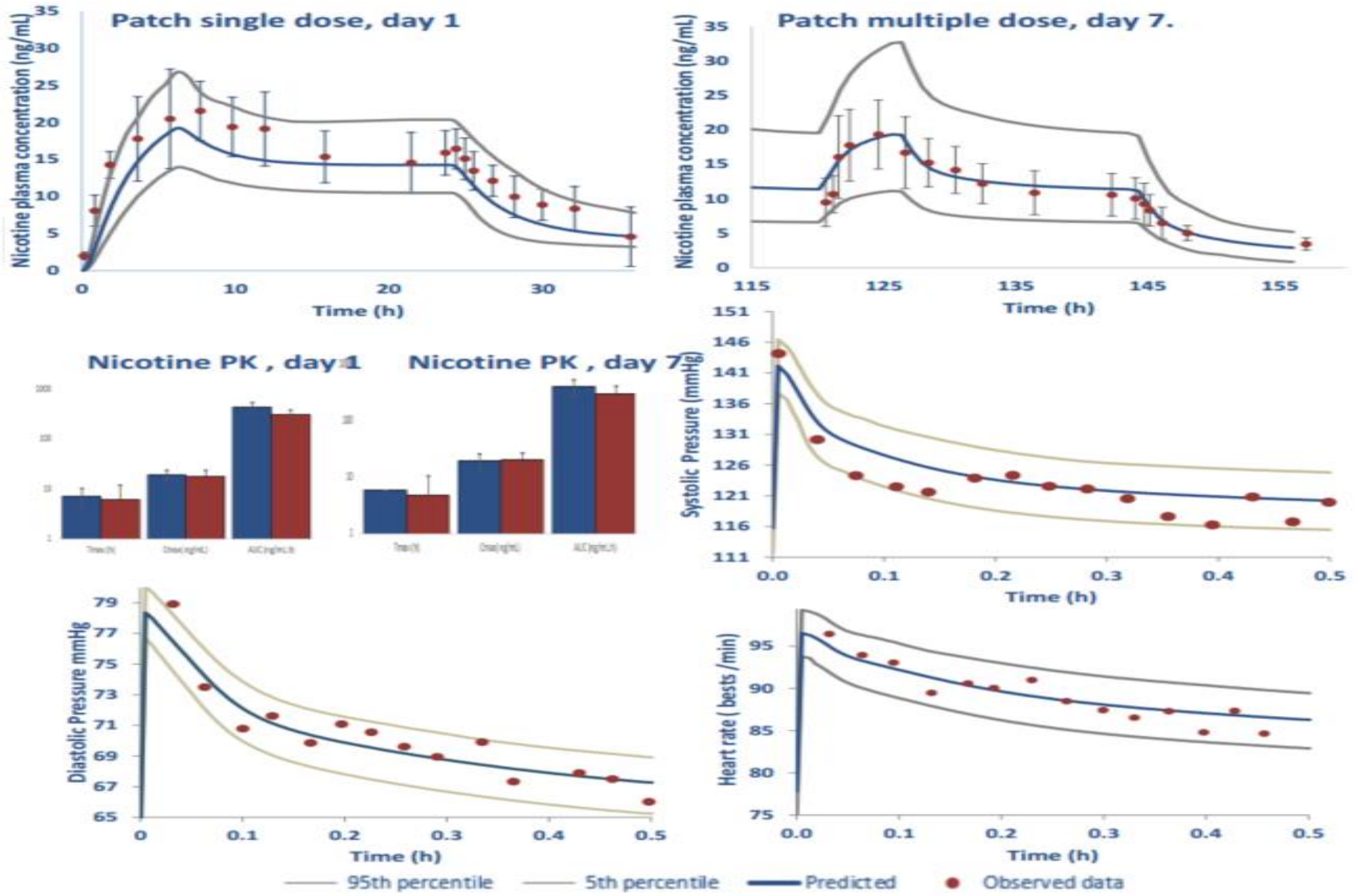
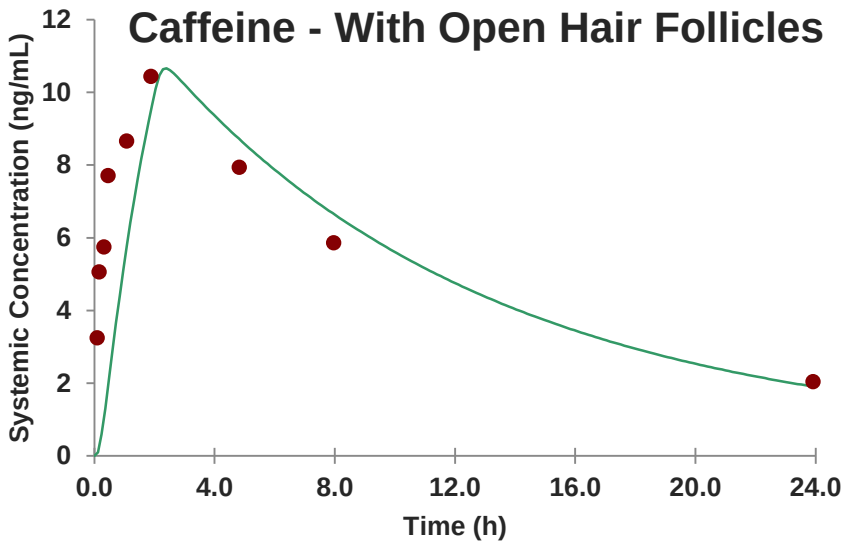
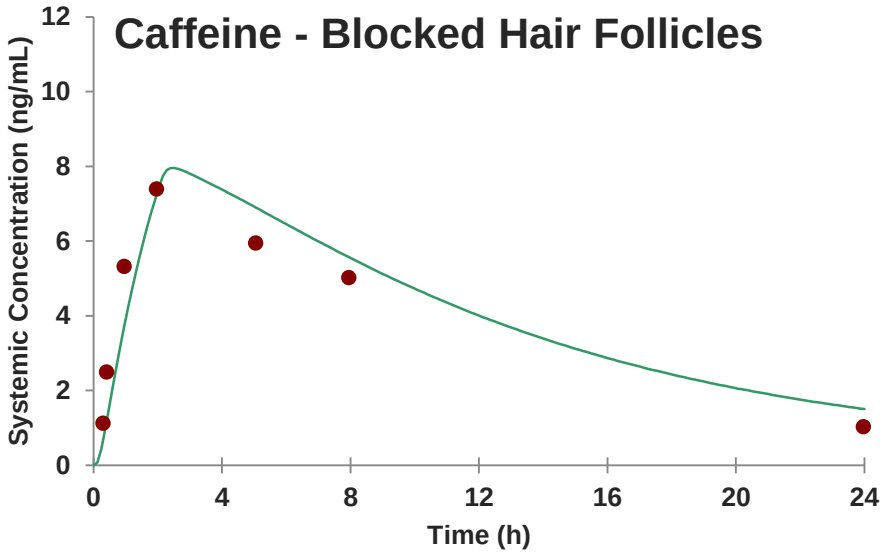
PBPK-PD Model for Therapeutic Equivalence



Martins *et al*. 2018

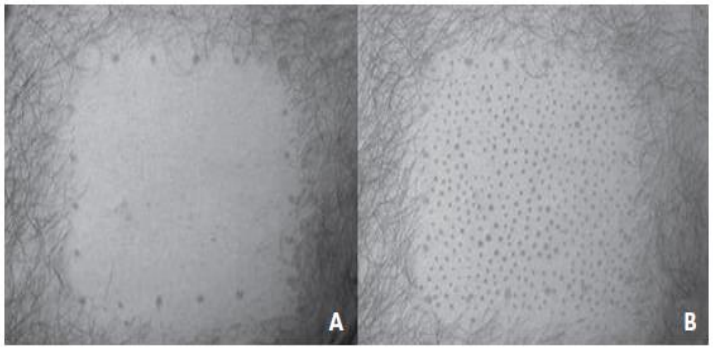
Caffeine Case Study – Predicting Contribution of Hair Follicle





Clinical data and trial design from Liu et al. BJCP, 2011, 72, 768

- When just the hair follicles are closed in model, predictions were higher than clinical measurement
- With reduction in area of block around the hair follicle by wax, the model predicted clinical observation



Otberg *et al*. 2007

Martins et al. 2017 ISSX Meeting

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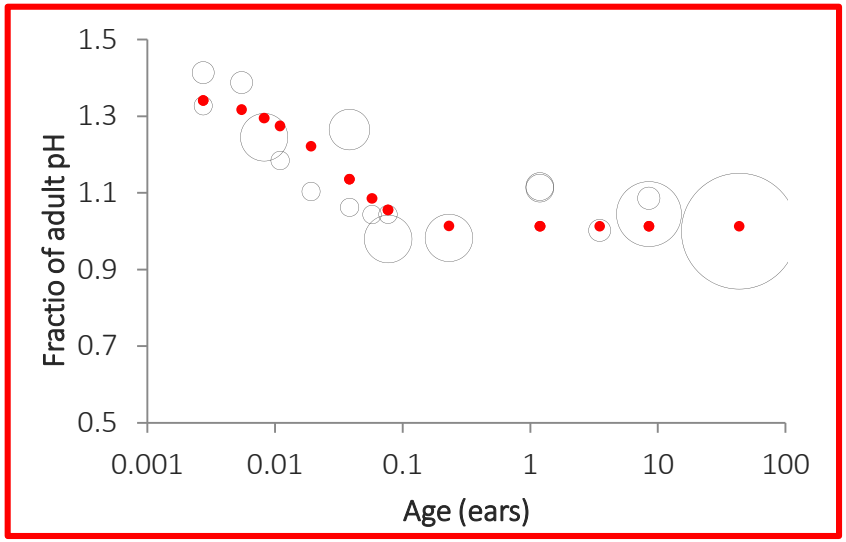
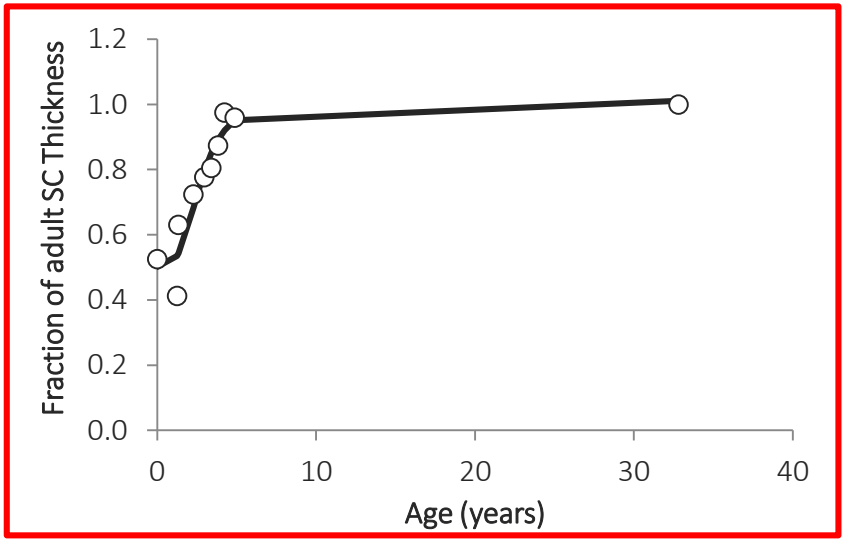
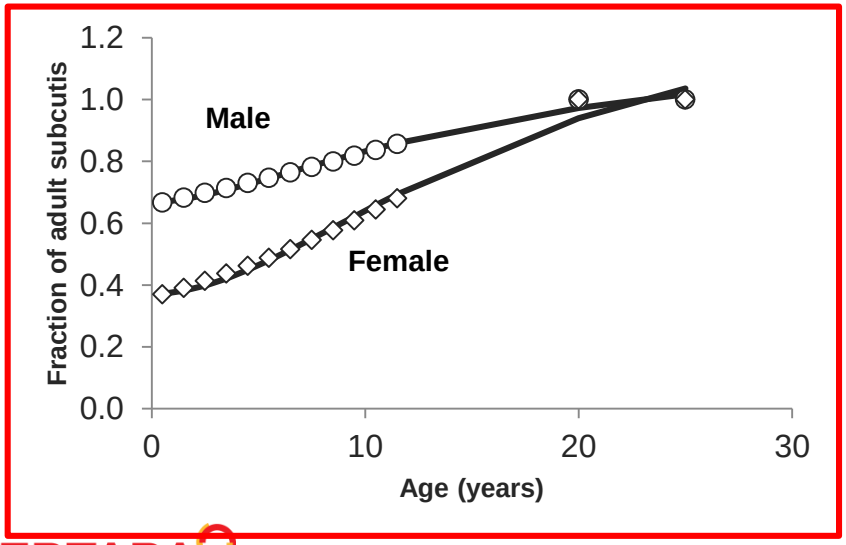
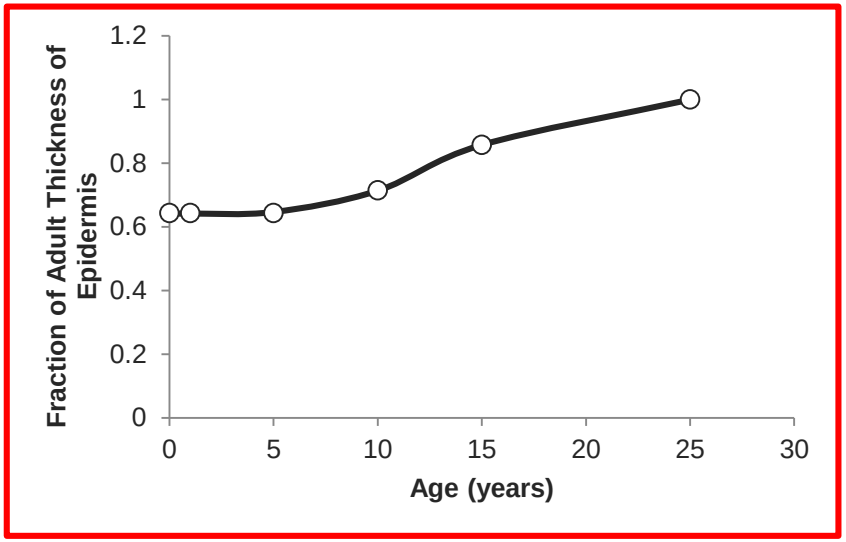
Age-related Changes in System Parameters

Age-related changes to system parameters (ontogeny) are introduced as a fraction of adult parameters.









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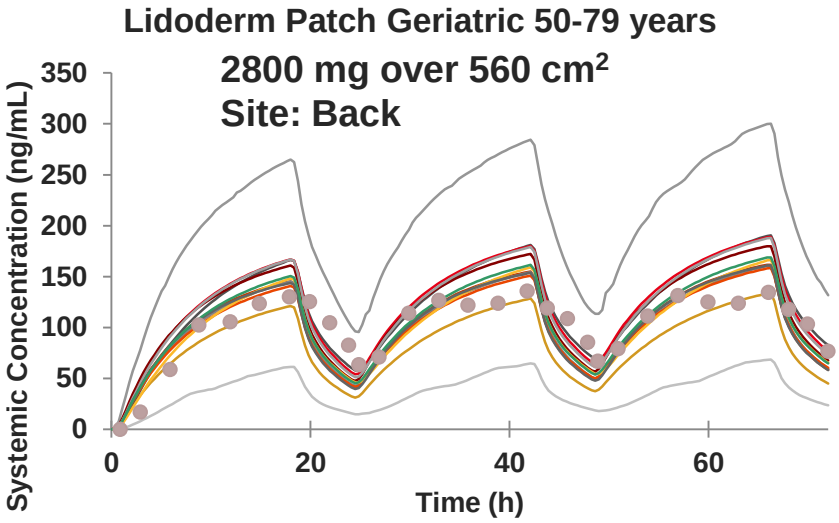
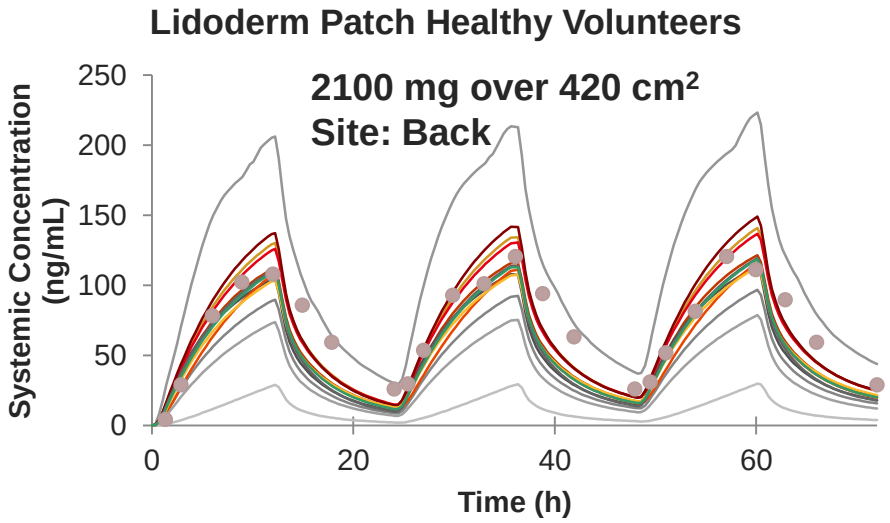
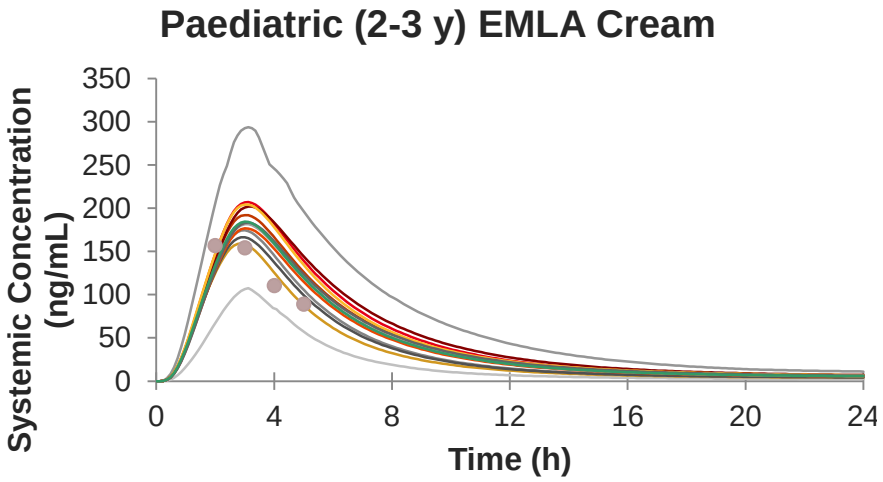
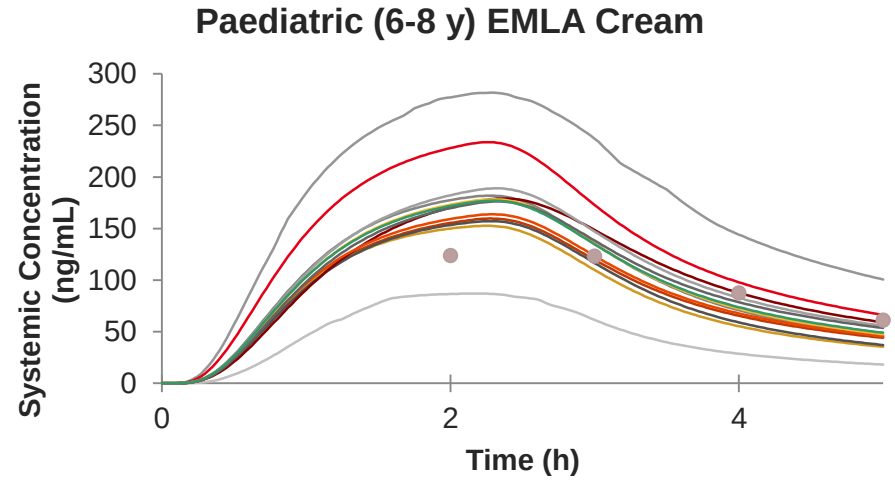
Special populations (geriatric and paediatric)

Lidocaine – simulating various formulation and populations









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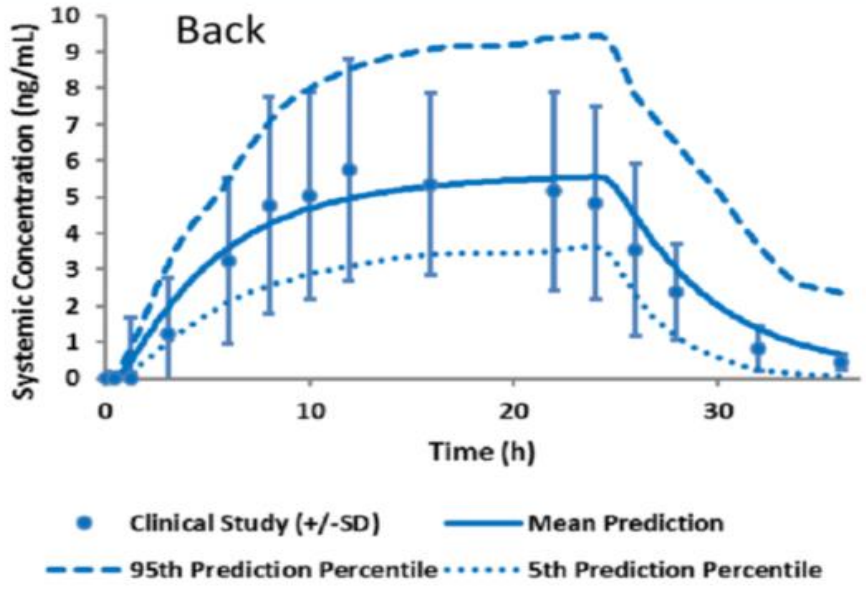
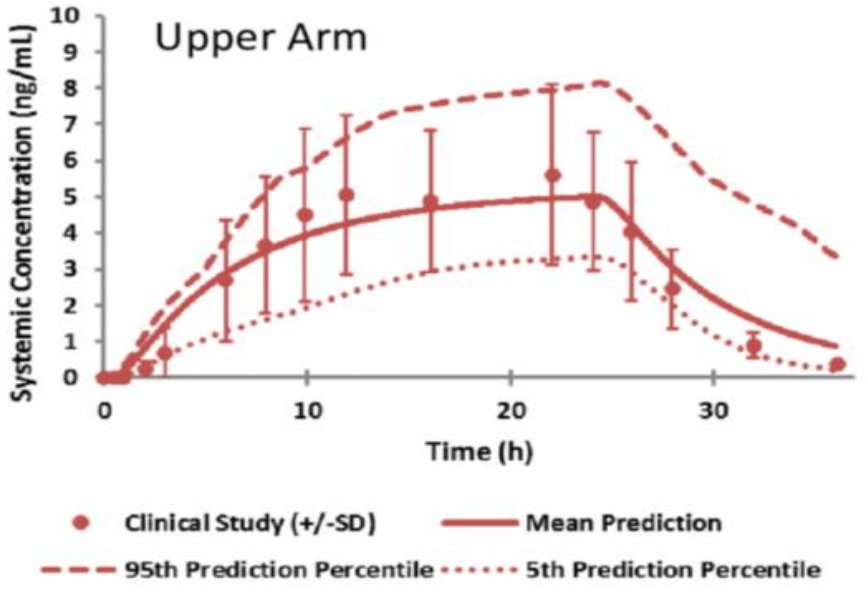
Salem *et al*. 2019 ASCPT Annual Meeting

Impact of site of application: Rivastigmine patch





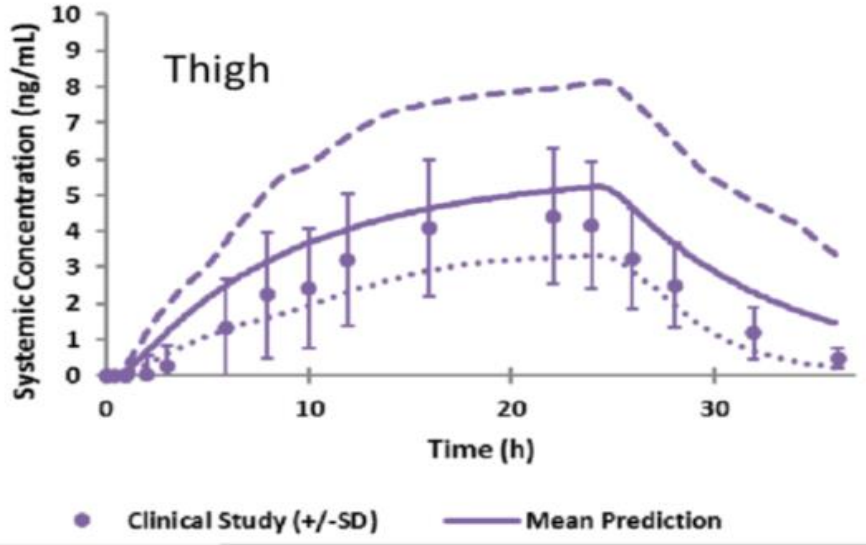


Figure 1. **Observed [2] and predicted PK profiles following 24h application of 10cm² (18mg) Rivastigmine TDS to Back (top left), Upper Arm (top right) and Thigh (bottom left)**

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Abdulla et al. 2017 AAPS Annual Meeting

Pharma Case 1: Support First In Human Exposure Prediction

- Neutral moderately lipophilic small (MW <500) drug formulated as oil in water emulsion with volatile components (~50%) in vehicle
- Animal studies (minipig) performed for topical cream formulation and systemic exposure measured after repeat dose
- PBPK Model developed based on Simcyp in-built QSAR to predict dermal absorption parameters
- PBPK simulated exposure level for high dose simulation was within 2-fold of empirical in-house animal to human extrapolation approach
- Building confidence in FIH dose exposure and formulation impact

LaButti *et al. (unpublished)*

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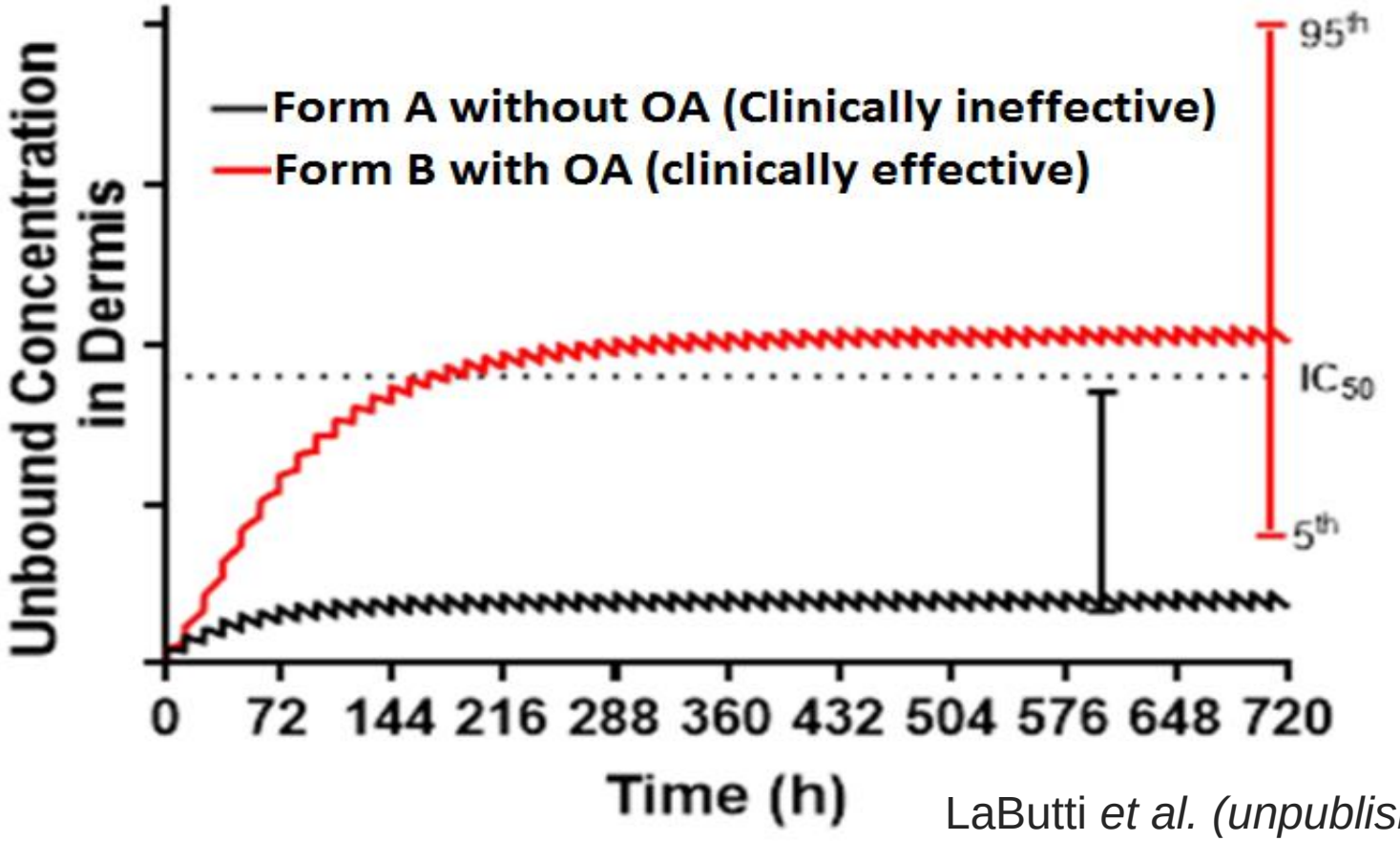
Pharma Case 2: Clinically Relevant Product Assessment

MechDermA Simulation of Drug X Concentrations in Dermis After Topical Administration

30 Psoriasis Patients, 300 cm^2, 0.9g ointment



LaButti *et al. (unpublished)*

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Pharma Case 3: DDI risk for safety of topical cream product

- Drug X is metabolised by CYP2C19, 2C9 and 3A4 with systemic exposure below LOQ (pg/mL) for 80% subjects as drug is locally acting hence by design systemic exposure is minimal
- There was a concern what would be exposure levels in presence of metabolic inhibitors as compared to safety margin of the drug
- PBPK model was developed and verified for two dose levels at single dose and steady state and predictive performance assessed at local tissue exposure level (SC and dermis) and systemic circulation
- The model was used to simulate DDI with metabolic inhibitors as well as worst case scenario where metabolism via CYP2C19 was completely blocked.

Patel et al. 2017 AAPS Annual Meeting

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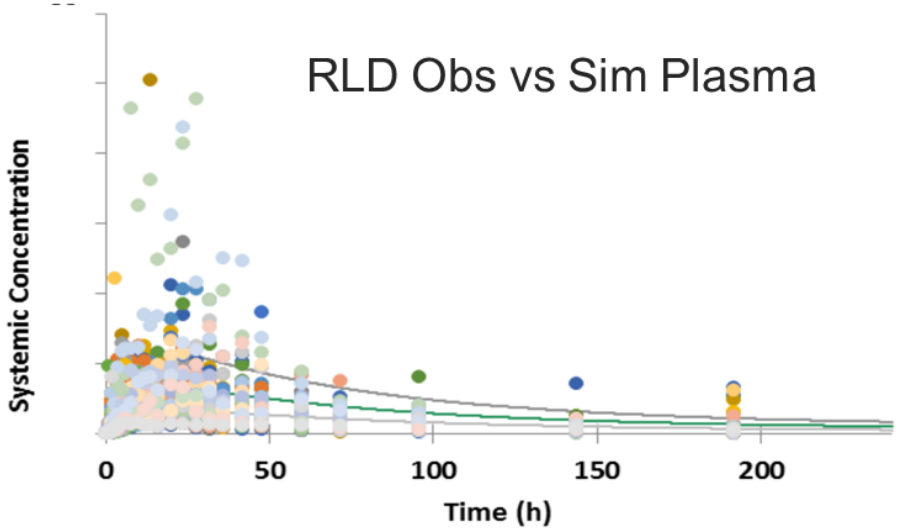
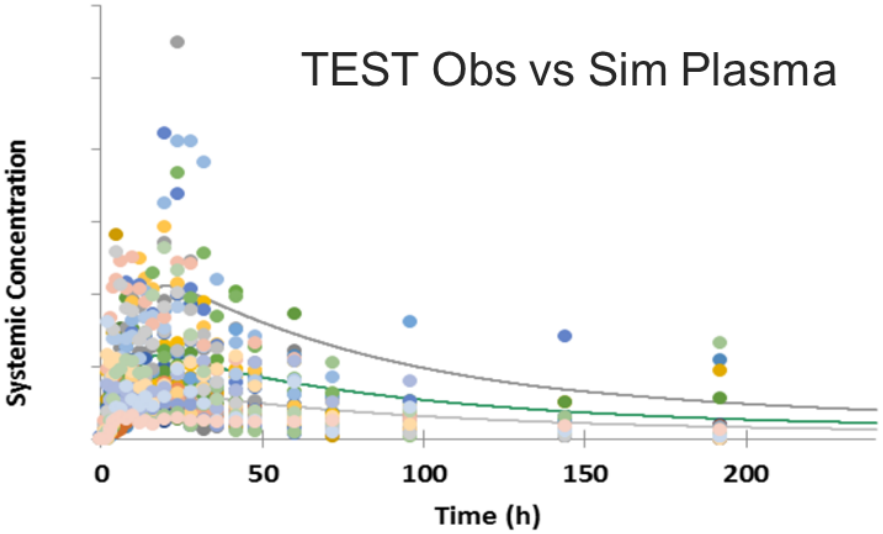
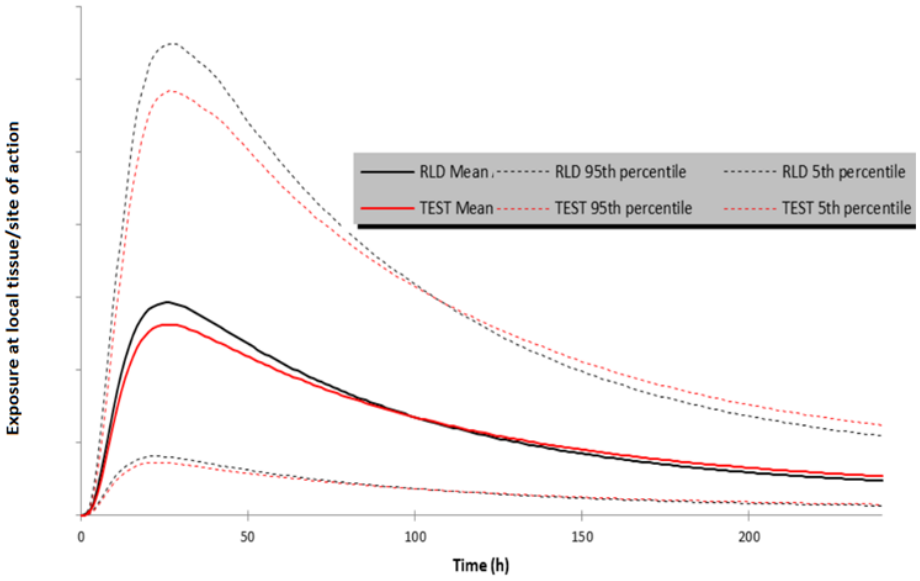
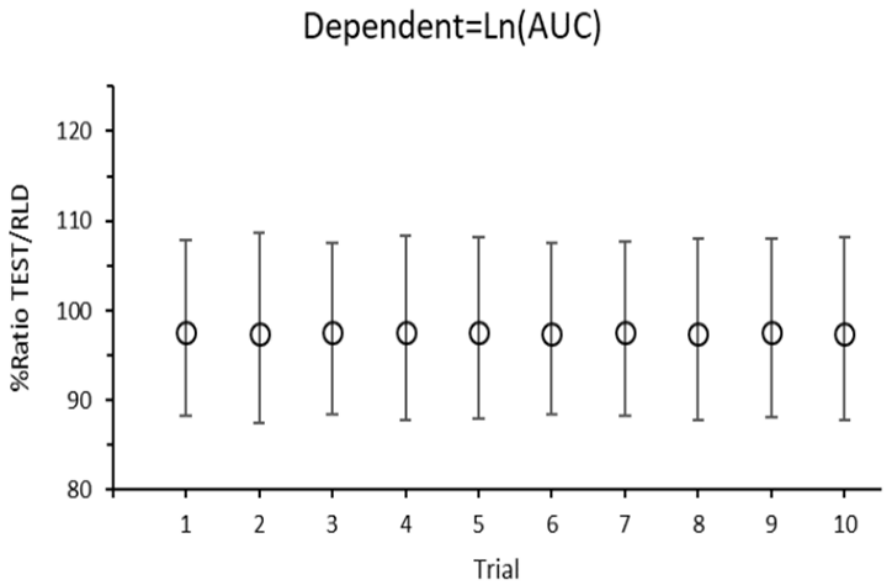
Pharma Case 4: Virtual BE Model Results









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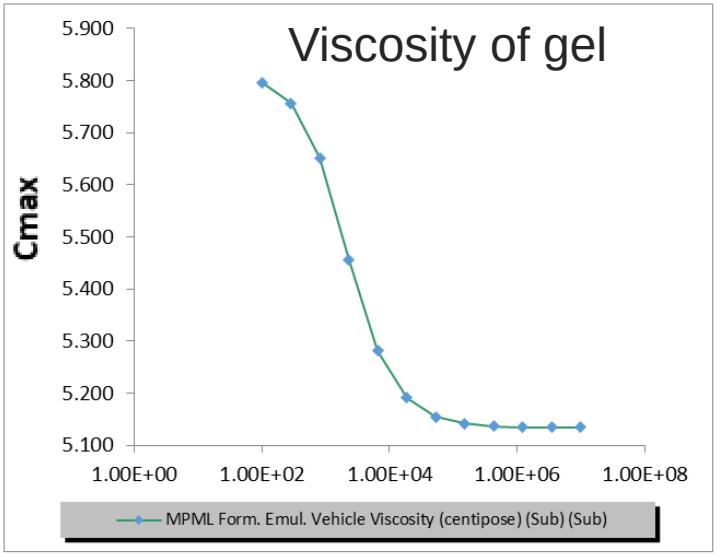
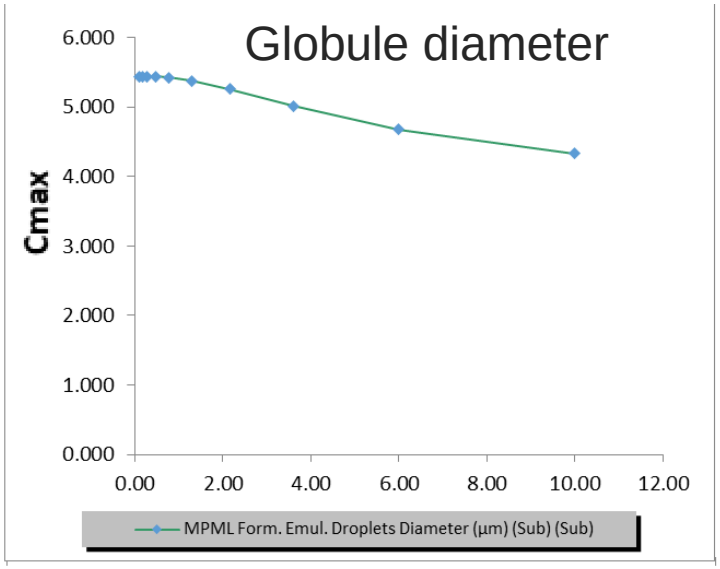
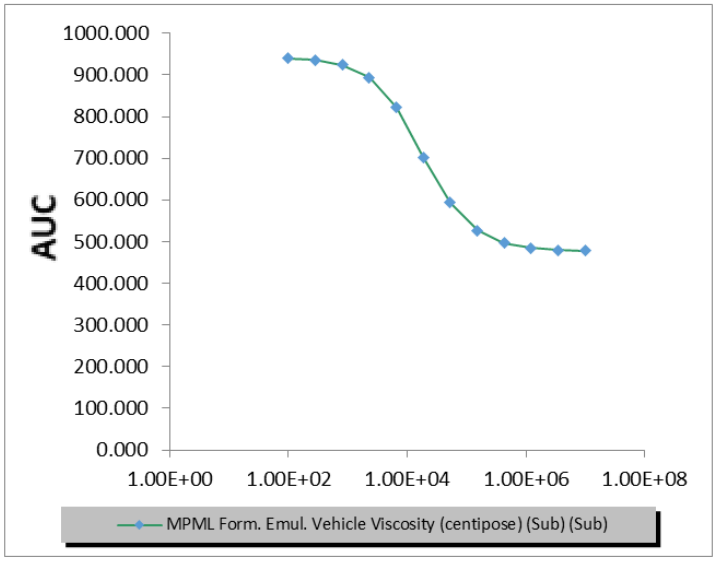
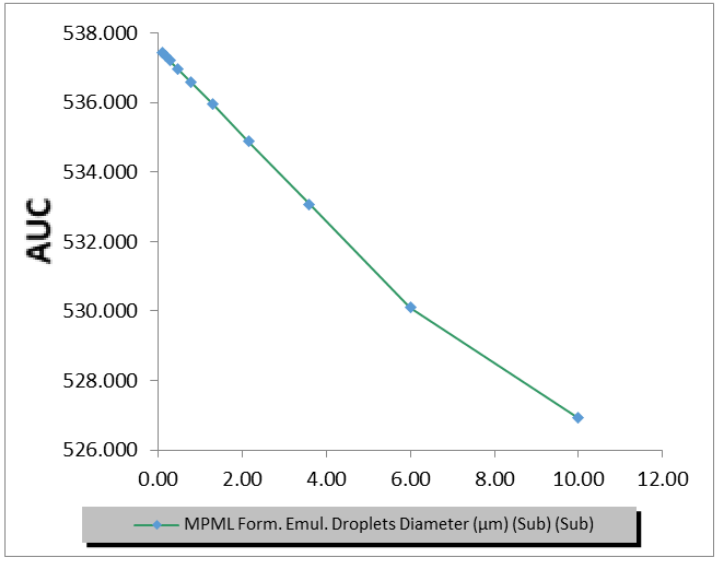
Identify clinically relevant critical product attributes – Sensitivity Analysis









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Acyclovir Products – Simulating Q3 Product Attributes

(Murthy 2015)

Molar Volume

Viscosity

% Polymer

(Murthy 2015)

Vehicle pH

API pKa

(Murthy 2015)

API in droplet phase

Diffusion to skin surface & Hair Follicles

Fraction API non-ionised

(Murthy 2015)

API in dissolved phase

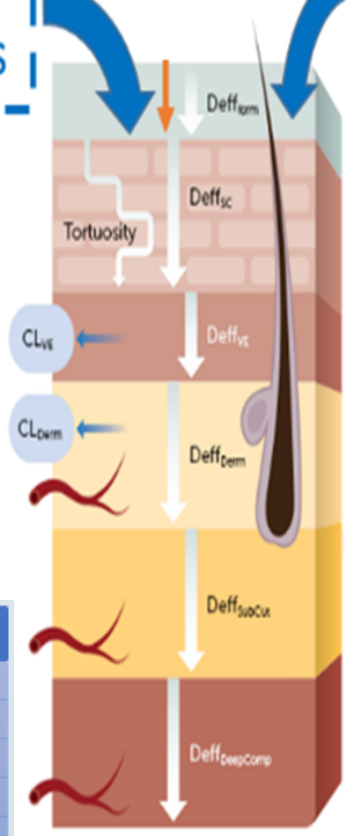
(Murthy 2015)

Vehicle Evaporation

API Precipitation

API in particle phase

(Murthy 2015)



Formulation Parameters	ZOVIRAX US	ACICLOSTAD
pH	7.74	4.58
Drug Solubility (mg/mL)*	0.492	0.365
Particle Size (d50) um	5.06	6.75
Viscosity (Pa.S @ 0.0025 s^{-1} shear)	8360	29300
Drying Rate (h^{-1})	0.02	0.07
Oil phase/Continuous Phase Ratio	1.76	2.67
Solid fraction^	0.973	0.987

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Acyclovir VBE Results and Future Direction

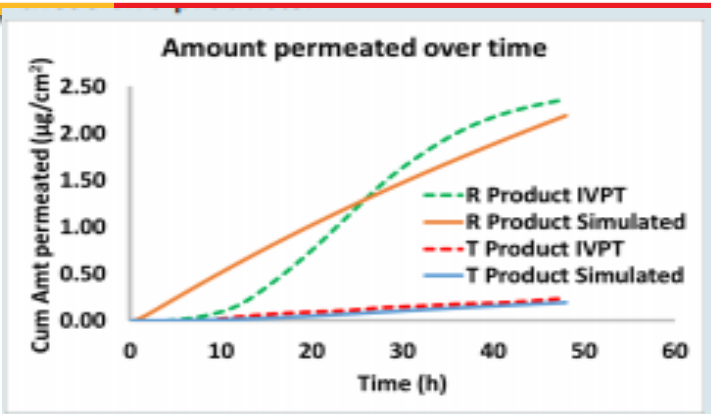

Figure 2. Cumulative amount permeated over time plots

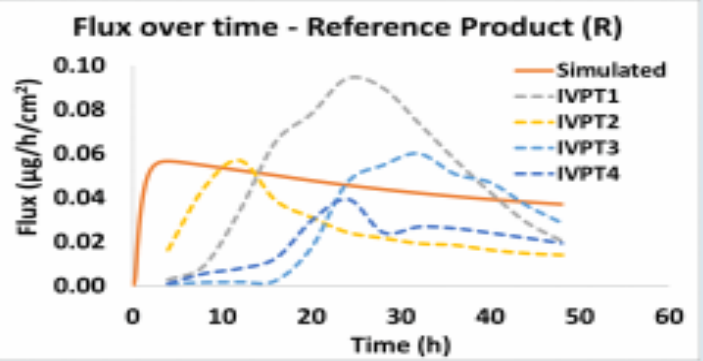

Figure 3. Permeation flux over time for the R Cream

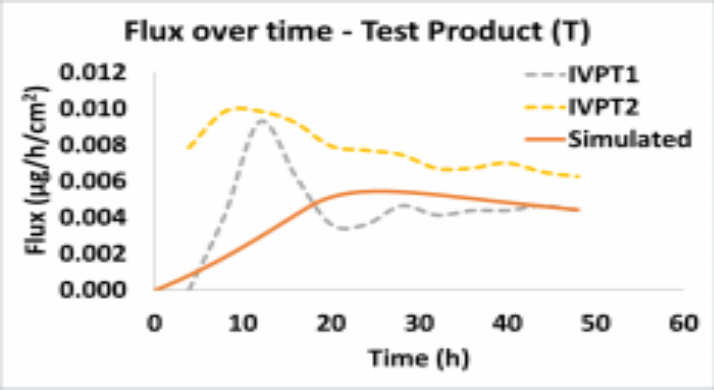

Figure 4. Permeation flux over time for the T Cream

Key Findings

1. PBPK modeling allows to translate the *in vitro* product characterization to *in vivo* situations in terms of local and/or systemic PK and identify impact of formulation differences on exposure
2. We assumed static maximal and minimal effect of PG on R and T formulations throughout the simulation period which lead to good prediction of steady state flux (establishes importance of excipient) but over- and under- estimates initial transient permeation flux for R and T products, respectively [Figs 2 -4].
3. More mechanistic dynamic modelling of excipient is needed in future as to mimic realistic time-varying impact of excipient rather than static effect from time zero onwards.
4. Kinetic modelling of super-saturation and precipitation is desirable to accurately model the formulations with significant vehicle evaporation leading to structural changes to the formulation.

Patel *et al*. 2017 AAPS

Collaboration with Uni of Queensland AUS

Formulation Meta-morphosis and Dermal Products CQA assessment

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- Masoud Jamei

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- Theunis C. Goosen

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- Eleftheria Tsakalozou
- Priyanka Ghosh
- Sam Raney
- Xinyuan Zhang
- Zhanglin Ni

University of Queensland

- Mike Roberts
- Jeff Grice
- Yousuf Mohammed

Many pharma collaborators

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