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Development and validation of Dermal PBPK model towards virtual bioequivalence assessment

Nikunj Patel, Senior Research Scientist

DMDG Symposium: 100 Years of Drug Delivery, GSK, Ware
06/10/2015

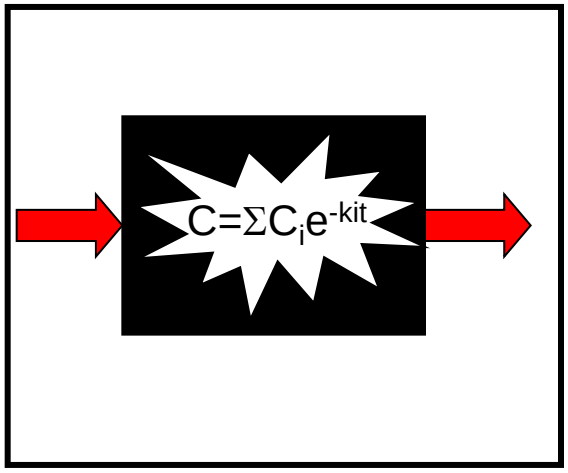
Tripos SIMCYP Pharsight

Outline

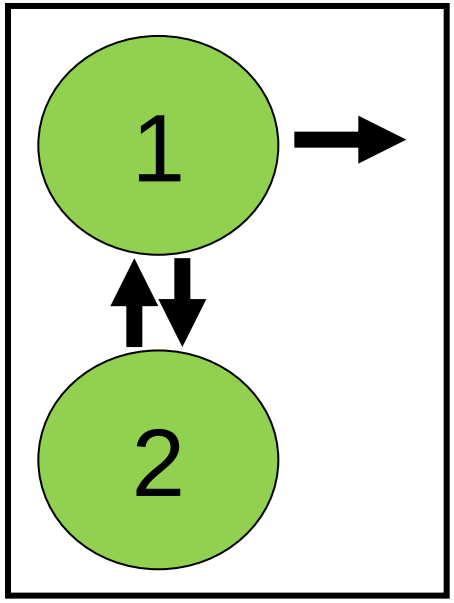
- PBPK Modelling and its Increasing Utilisation
- Dermal PBPK Modelling towards Virtual BE
- Case Studies

Typical Models Used to Describe Pharmacokinetics

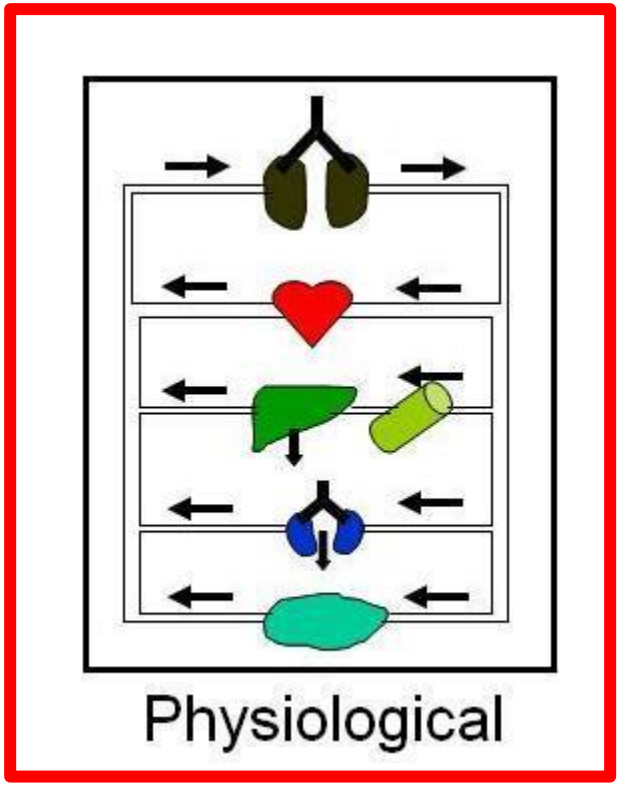
Three type of models can be used to describe concentration time profiles.



Empirical



Compartmental



Physiological

Physiological model is the best if building the model from scratch and with *in vitro* data available.

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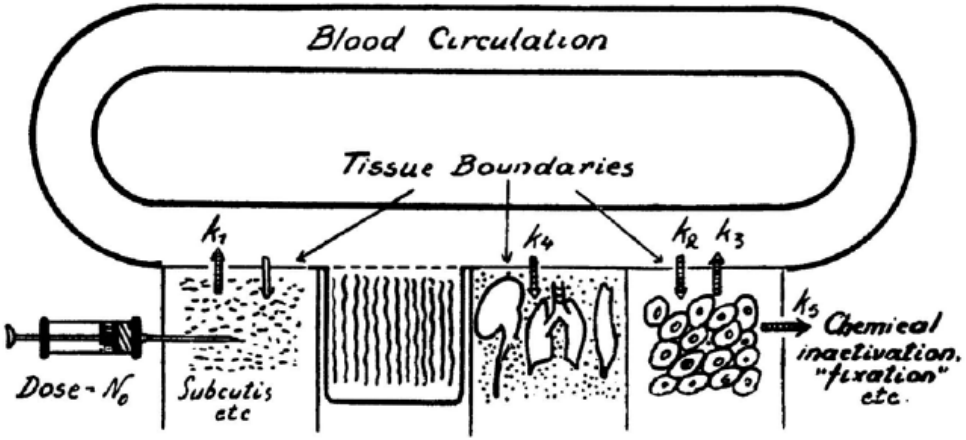
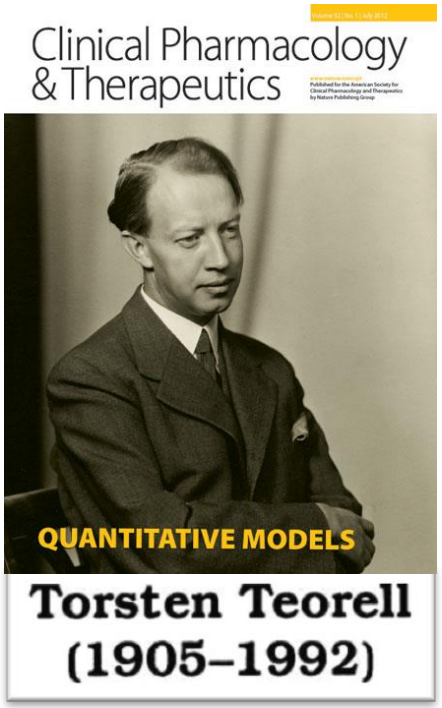
PBPK Modelling is not new



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	—	V_3	—
Concentration	x/V_1	y/V_2	—	z/V_3	—
Perm. coeff	k_1'	—	k_4'	k_2'	—
Velocity constant out	$k_1 = k_1'/V_1$	—	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	—	not existing	$k_2 = k_2'/V_2$	—
Name of process	Resorption	—	Elimination	Tissue take up -"- output	Inactivation

FIG. 1

Scheme of the Concept of Drug Distribution used in this paper.
Instead the *injection* pictured in the figure, the administration of the drug depot can be made *per os*, *per rectum*, *by inhalation*, etc.



The Father of Pharmacokinetics

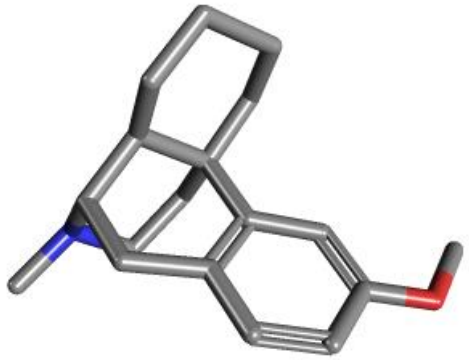
(Teorell, 1937)

Separating systems & drug information

Systems Data

Drug Data

Trial Design



Dose
Administration route
Frequency
Co-administered drugs
Populations

Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

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

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Recent Publications on the use of PBPK Modelling

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.33

PERSPECTIVE

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

FDA

C Wagner[1], P Zhao[1]*, Y Pan[2], V Hsu[1], J Grillo[1], SM Huang[1] and V Sinha[1]*

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.30

ORIGINAL ARTICLE

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

EMA

T Shepard[1]*, G Scott[2], S Cole[1], A Nordmark[3] and F Bouzom[4]

Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development: A Pharmaceutical Industry Perspective

Industry

HM Jones[1], Y Chen[2], C Gibson[3], T Heimbach[4], N Parrott[5], SA Peters[6], J Snoeys[7], VV Upreti[8], M Zheng[9] and SD Hall[10]

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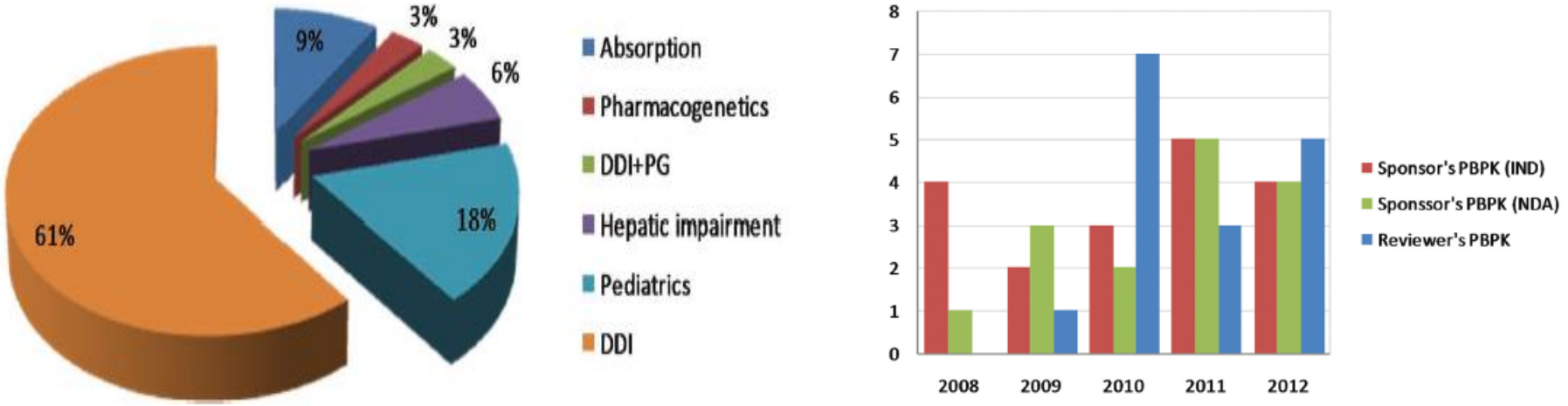
PBPK Impact on 16 US Drug Labels in Last 2 Years

Revatio (Sildenafil) Pulmonary Arterial Hypertension	Xarelto (Rivaroxaban) Deep Vein Thrombosis and Pulmonary Embolism	Edurant (Rilpivirine) infection	Iclusig (Ponatinib) Chronic Myeloid Leukemia
Olysio (Simerprevir) Hepatitis C	Opsumit (Macitentan) Pulmonary Arterial Hypertension	Imbruvia (Ibrutinib) Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia	Movantik (Naloxegol) Opioid Induced Constipation
Cerdelga (Eliglustat) Gaucher Disease	Jevtana (Cabazitaxel) Prostate Cancer	Zykadia (Ceritinbi) Metastatic Non-Small Cell Lung Cancer	Bosulif (Bosutinib) Chronic Myelogenous Leukemia
Lynparza (Olaparib) Advanced Ovarian Cancer	Farydak (Panobinostat) Multiple myeloma	Lenvima (Lenvatinib) Thyroid cancer	Odomzo (sonidegib) basal cell carcinoma

Need for Dermal PBPK Models towards Virtual BE of Generic Products



PBPK Modelling in NDA Submissions Huang et al. J. Pharm Sci. 102(9):2912-23 (2013)

- Low utility in ANDA / Generic Drug Applications
  - PBPK models needed for complex products, topical and locally acting drugs
  - Improvements needed for BA/BE Assessment e.g. WS variability
  - GDUFA – 7 grants for PBPK model development for non-oral drug delivery

Zhang & Lionberger 2014 CPT; Lionberger 2014, AAPS AM

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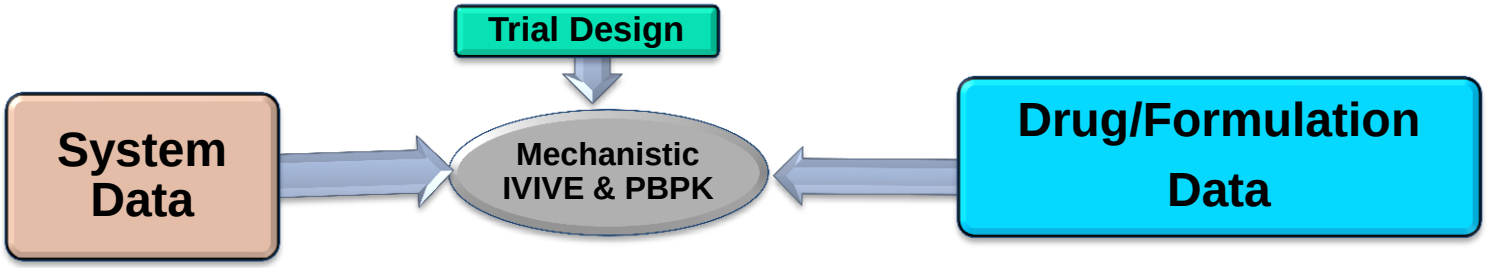
Dermal absorption modelling in systems pharmacology context



- Stratum corneum thickness
- Viable epidermis thickness
- Stratum corneum fat amount
- Viable epidermis fat amount
- Skin blood flow

- Molecular weight
- LogP
- Hydrogen bond donor
- pKa
- $fu_{,SC}$
- Dermal metabolism
- Formulation type

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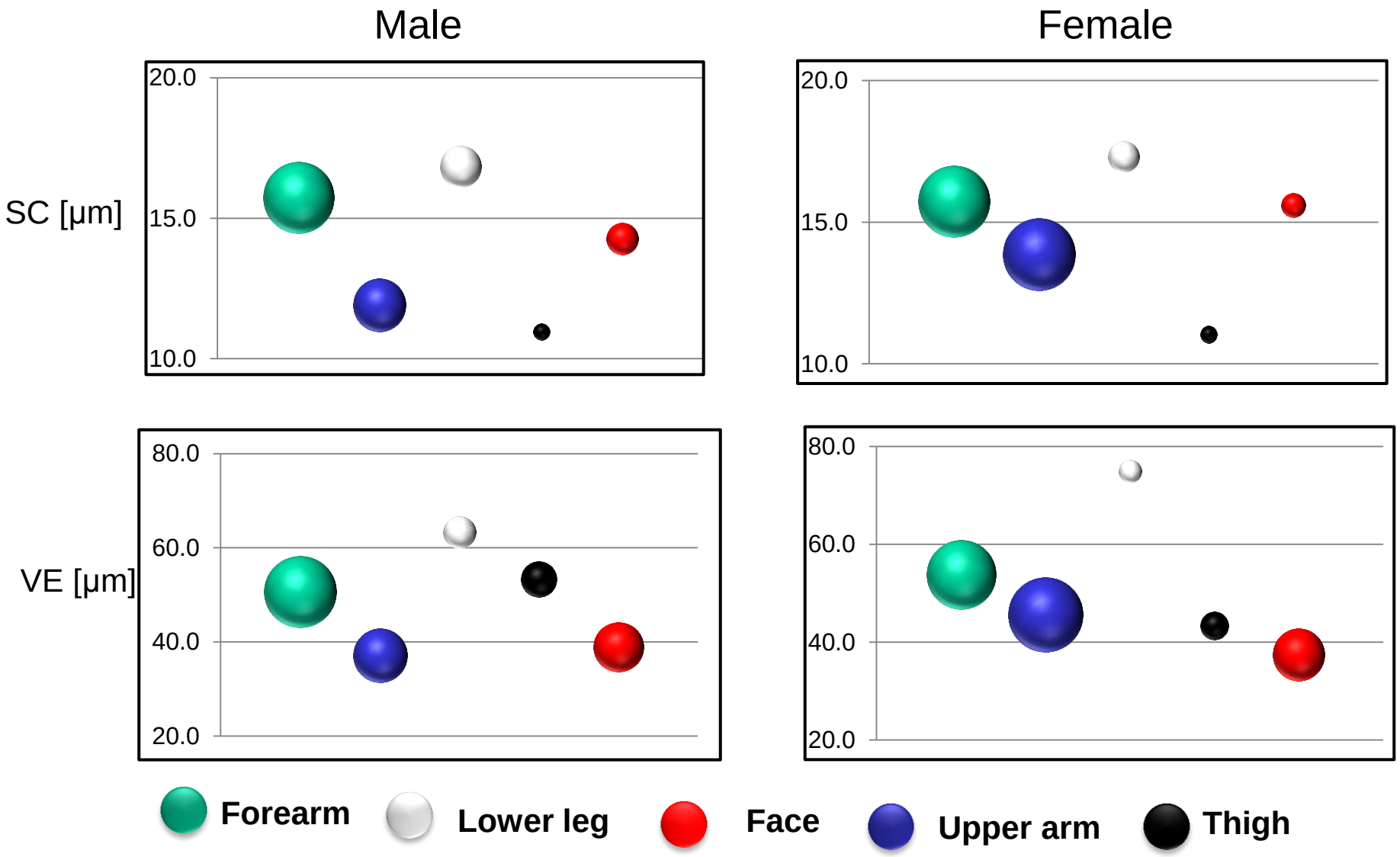
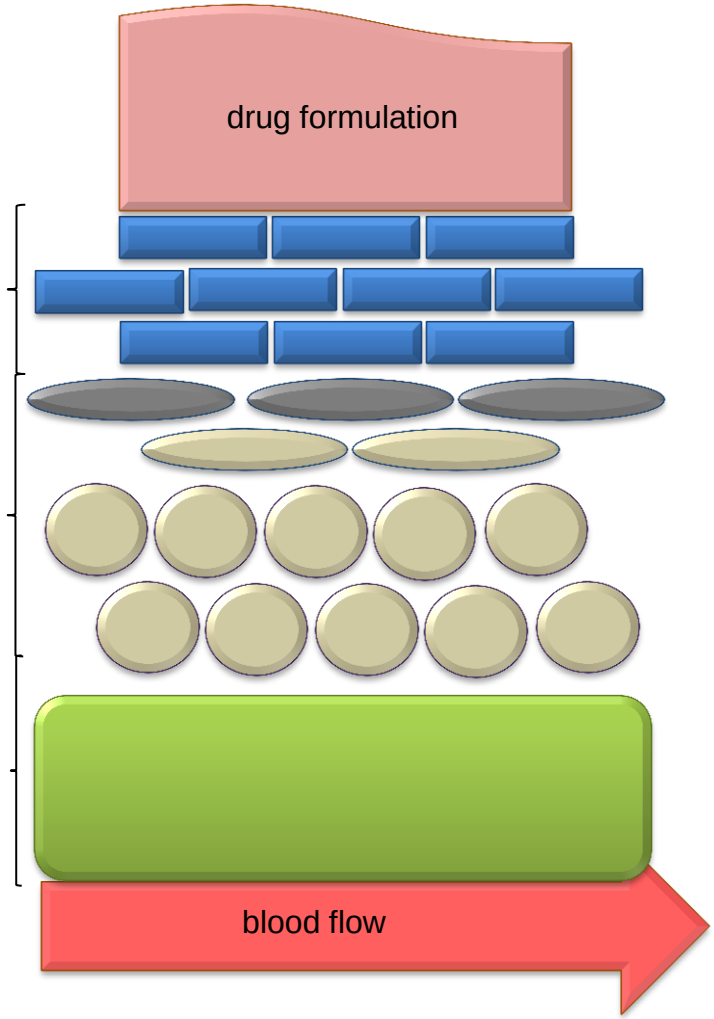
Dermal Absorption – Accounting for population variability

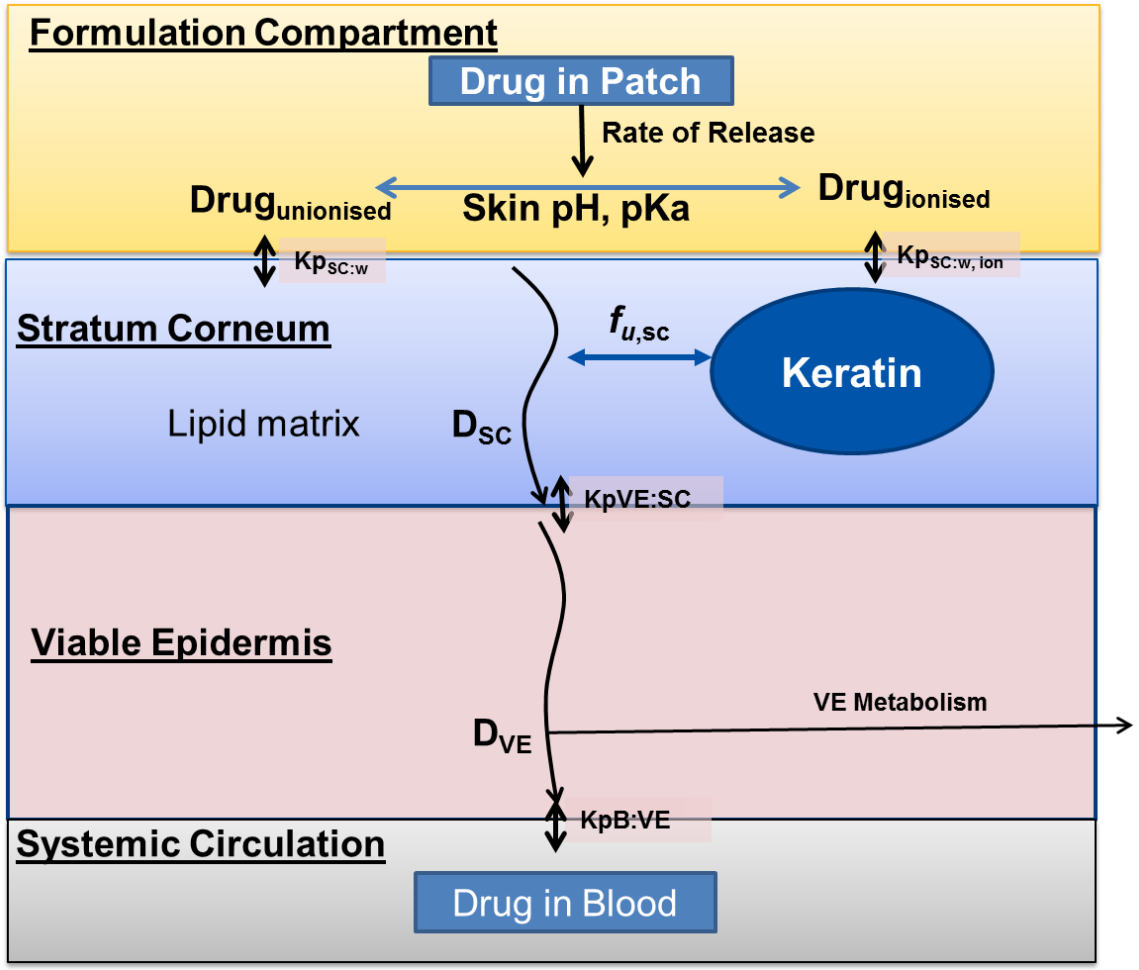
Inter Individual Variability: Skin Thickness (5 Locations)



Polak 2012 JPS 101(7), 2584

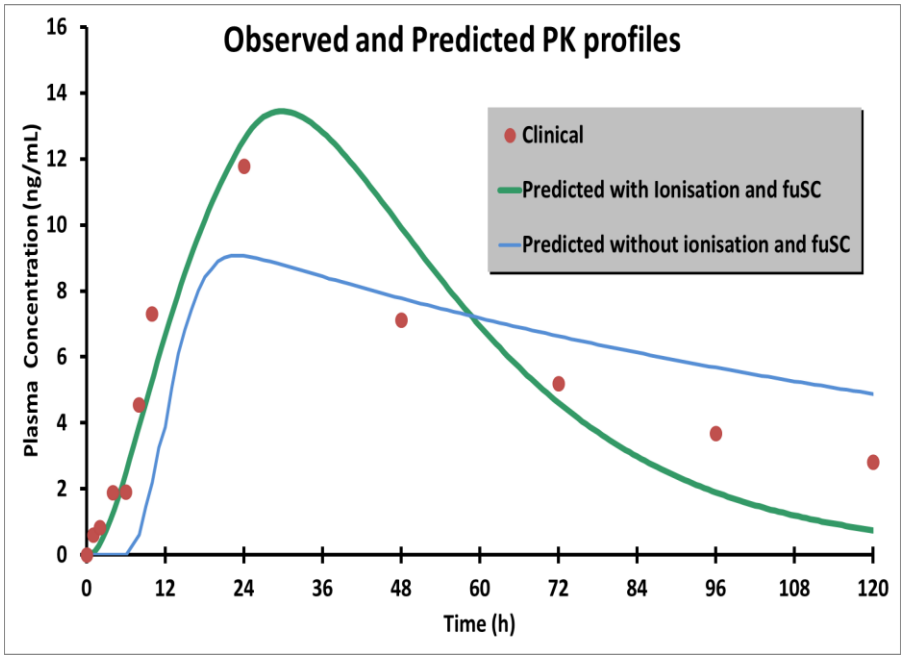
Single Layer Multi-phase SC

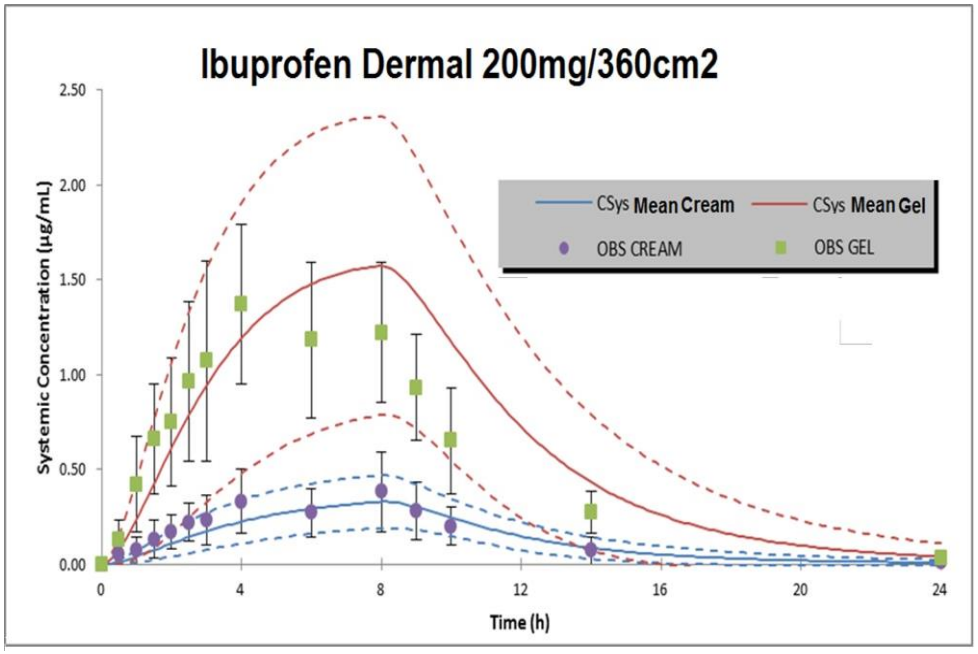




Case study: Diclofenac Lotion & Ibuprofen Gel vs Cream

Study Design	DIC Lotion		IBU Gel		IBU Cream	
	Clinical	Simulation	Clinical	Simulation	Clinical	Simulation
Formulation	Lotion	Aq. base	Aq. Gel	Aq. base	Cream	Non-aq.
Site	Knee	Lower leg	Upper back	Upper arm	Upper back	Upper arm
Area (cm^2)	200	200	360	360	360	360
# subjects [Age] (% F)	4 [45-76] (NA)	4 [45-76] (50%)	6 [20-48] (100%)	6 [20-48] (100%)	6 [20-48] (100%)	6 [20-48] (100%)
Population	HCV	HCV	HCV	HCV	HCV	HCV





Patel 2014 Skin Forum, Prague

Further Enhancements as part of the USFDA OGD GDUFA Grant

Awarded up to 3 years FDA OGD grant in September 2014.

'Development and validation of dermal PBPK modelling platform towards virtual bioequivalence assessment considering population variability'

The project aims to develop a physiologically-based dermal absorption and disposition model along with the supporting database of physiology and its variability for not only the healthy Caucasian volunteers but also special populations such as paediatric, geriatric, other races such as Asian and diseased populations.

The new model will also take into account other mechanisms that play an important role in dermal absorption, such as skin surface pH, dermal hydration, skin appendages, binding to keratin, and the effect of permeability-modifying formulation ingredients and drug-physiology interactions

http://www.simcyp.com/News/2014/October/20141023_FDA_Grant.htm?p=1

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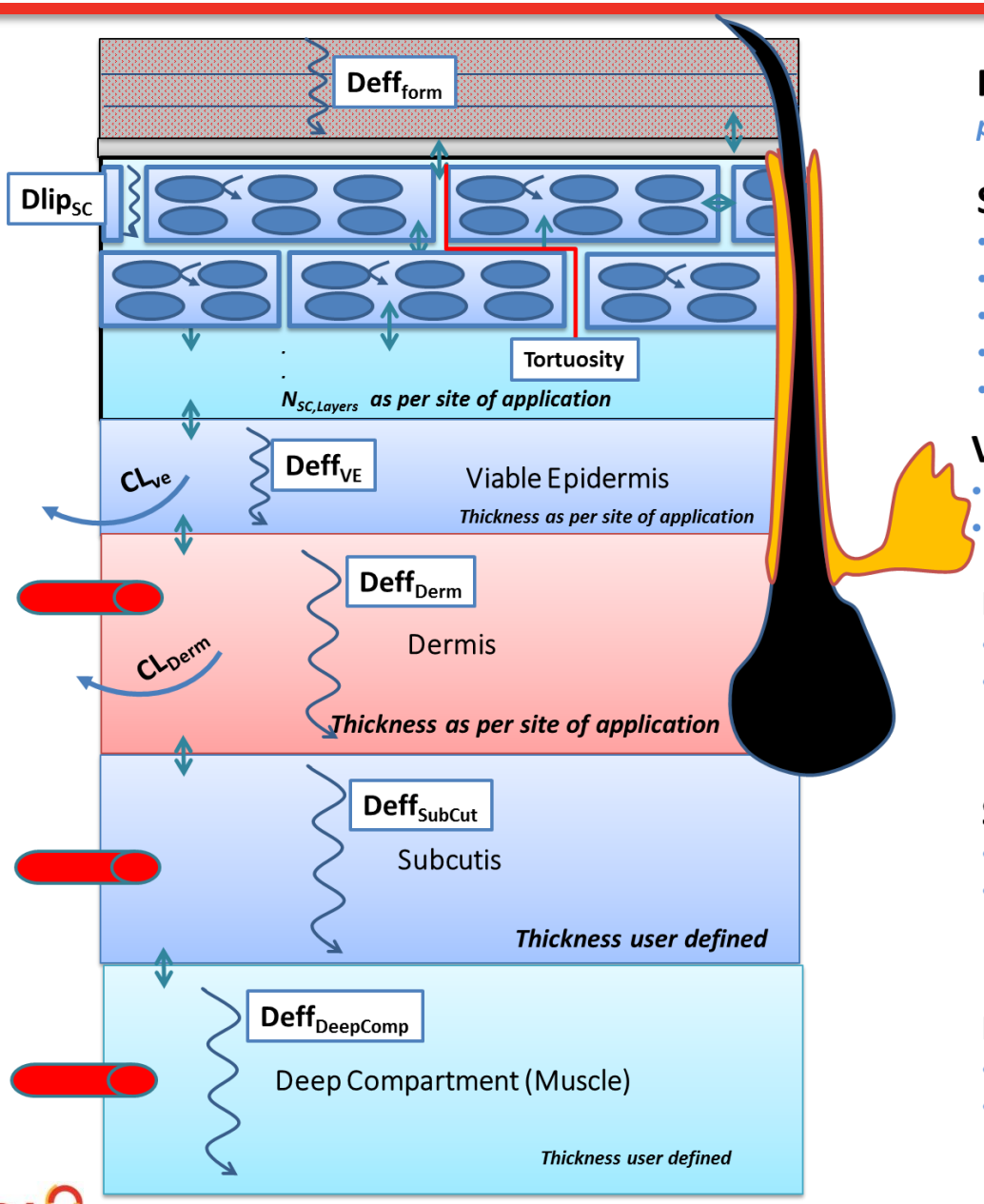
MPML MechDermA Model



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

Stratum Corneum (SC)

- *Define cell shape and size*
- *Cell membrane permeability*
- *Keratin bonding kinetics*
- *Tortuosity and fluidity*
- *Hair follicle density and size*

Viable Epidermis (VE)

- *Thickness, fluidity*
- *Metabolism*

Dermis

- *Thickness, fluidity*
- *Metabolism, blood flow*

Subcutis

- *Thickness, fluidity*
- *Blood flow*

Deep Tissue

- *Thickness, fluidity*
- *Blood flow*

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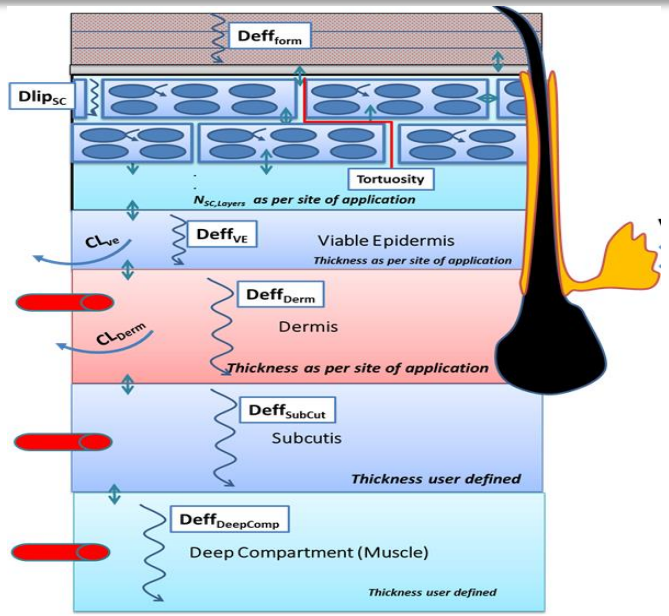
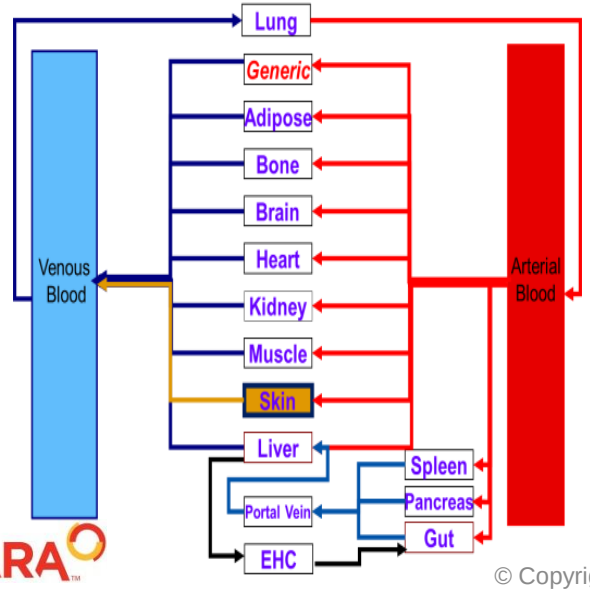
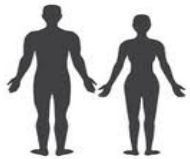
Meta-analysis of Systems Data





Paediatric Population

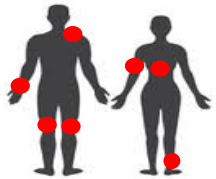
Healthy NEurCaucasian



Elderly Subjects

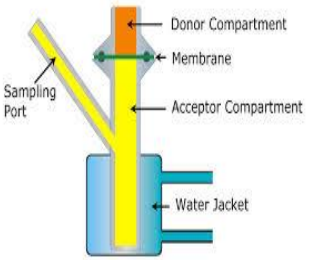
Ethnic Population

Diseased Population



Simcyp IVIVE: Translating in vitro permeability to clinical situations

IVIVE (*In vitro-in vivo* extrapolation)

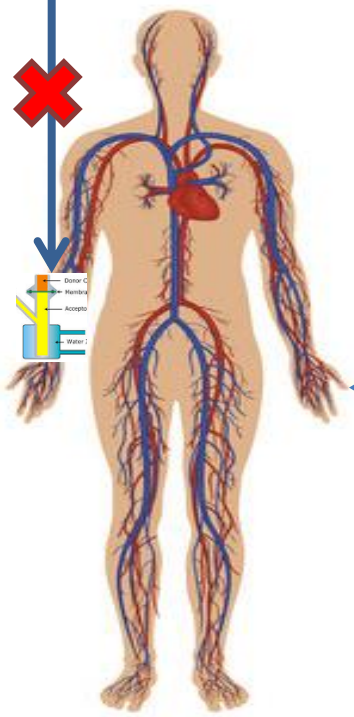


Simcyp MechDermA Model

In vitro systems data

In vitro Systems parameters
- skin thickness
- pH
- Hydration level
- hair follicle density

API/Formulation parameters
- Diffusion coefficient
- Partitioning
- Keratin binding
- **<u>Refine Unknown/uncertain</u>**



Simcyp MechDermA Model

Simcyp simulator

In vivo Systems parameters + variability
- skin thickness
- pH
- hydration
- Hair follicle density

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Model Performance Verification in vitro – Three Beta-blockers

Evaluation of β-Blocker Gel and Effect of Dosing Volume for Topical Delivery

Zhang, Chantasart, and Li, JOURNAL OF PHARMACEUTICAL SCIENCES

β-Blocker	log $K_{o/w}$[a]	log $K_{o/w}$[b]	Gel pH	f_{union}
Propranolol	3.3	3.48 ± 0.02	7.4	0.0079
Betaxolol	2.8	2.80 ± 0.02	7.4	0.0108
Timolol	2.1	1.79 ± 0.02	7.4	0.0153

β-Blocker	Molecular Weight (g/mol)	p*K*a	log $K_{o/w}$
Propranolol	259.3	9.5 ± 1.2[a]	3.3[a]
Betaxolol	307.4	9.4[b]	2.8[b]
Timolol	316.4	9.2[c]	2.1[c]

Table 2. Experimental Conditions Used in the Franz Cell Experiments of the β-Blockers

β-Blocker	Donor Concentration	Experimental Condition	Dosing Volume (mL)
Propranolol	4 mg/mL propranolol hydrochloride	Nonocclusive	0.15
		Occlusive	0.03, 0.07, 0.15, 0.5
Betaxolol	5 mg/mL betaxolol hydrochloride	Nonocclusive	0.15
		Occlusive	0.03, 0.07, 0.15
Timolol	5 mg/mL timolol maleate	Nonocclusive	0.15
		Occlusive	0.03, 0.07, 0.15

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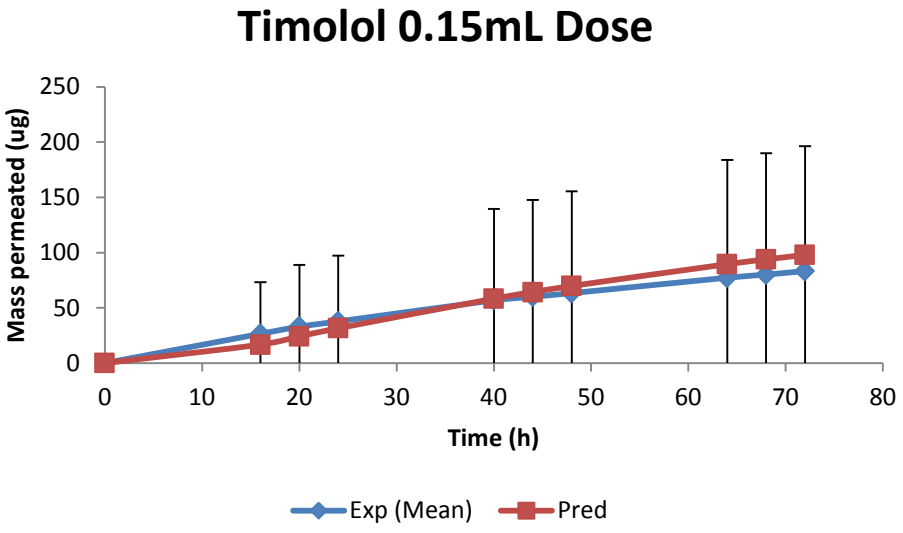
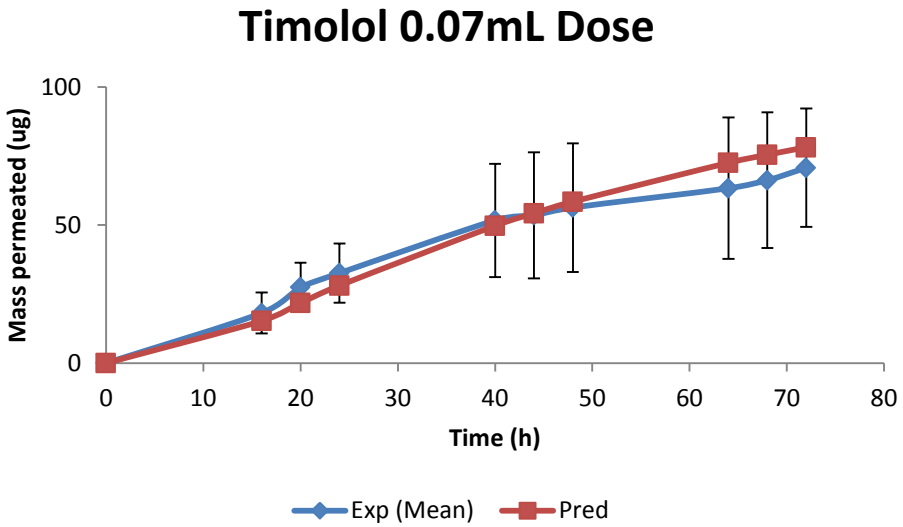
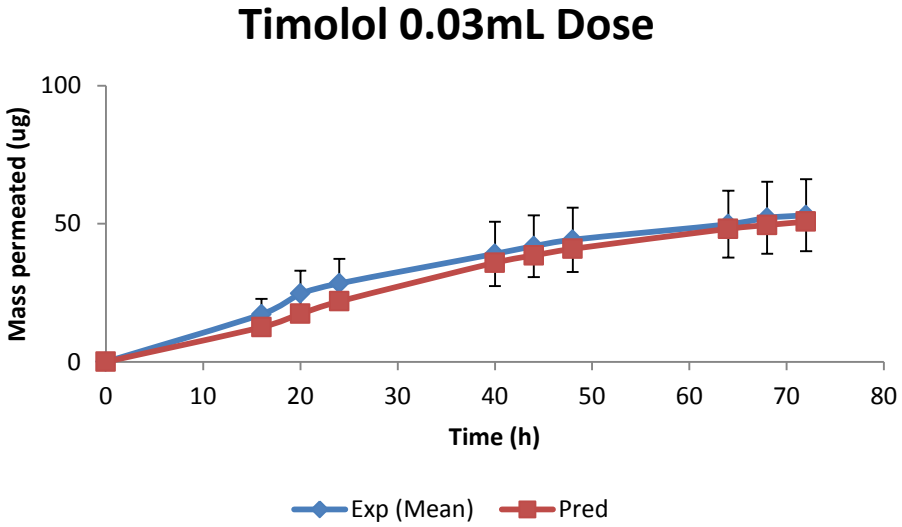
Timolol Prediction for three doses







- Thickness of skin layers not reported
  - ✓ Assumed SC thickness 10um (Simcyp value for back is 9um)
  - ✓ Assumed VE thickness 100um (value typical for split-thickness skin)
- Hydration expansion of SC (2.5-fold)
- **Tortuosity (1.5-fold) –** fitted parameter to match observations (but within the limits of reported value)

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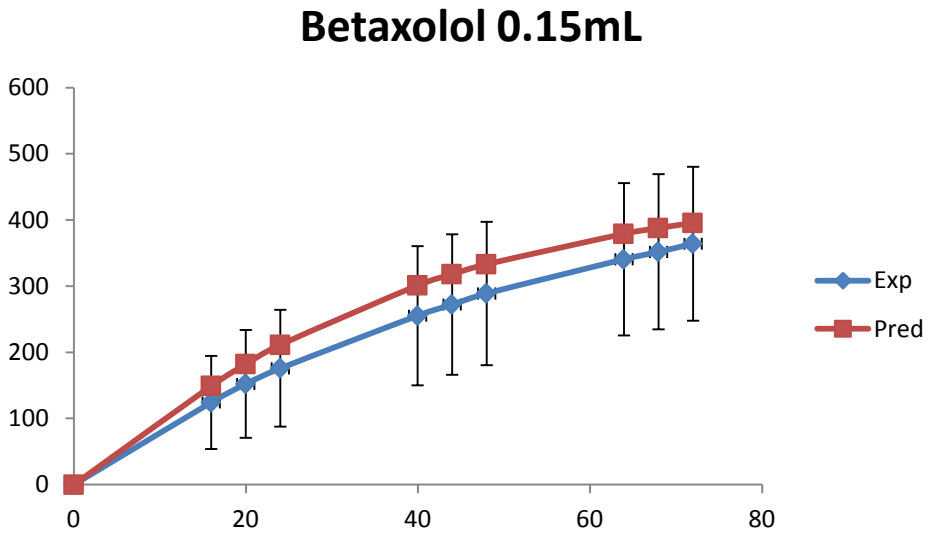
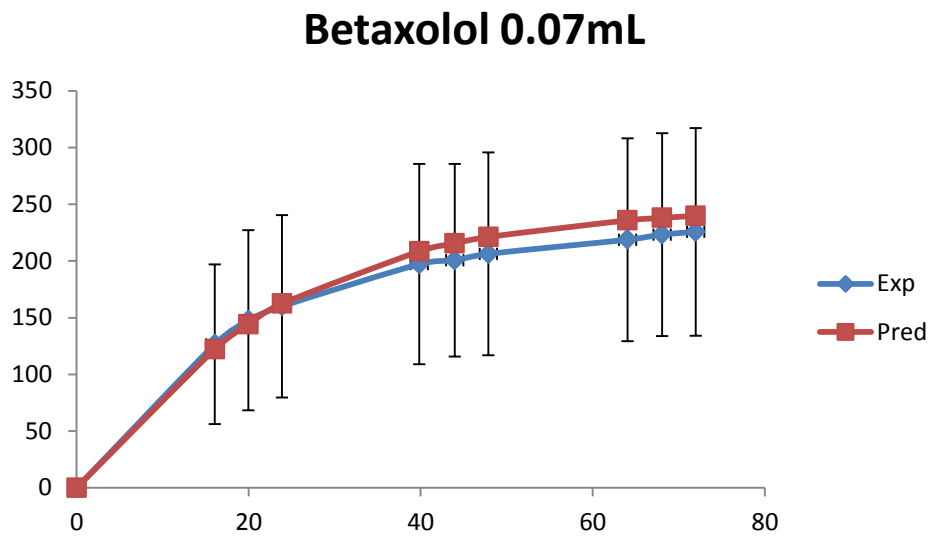
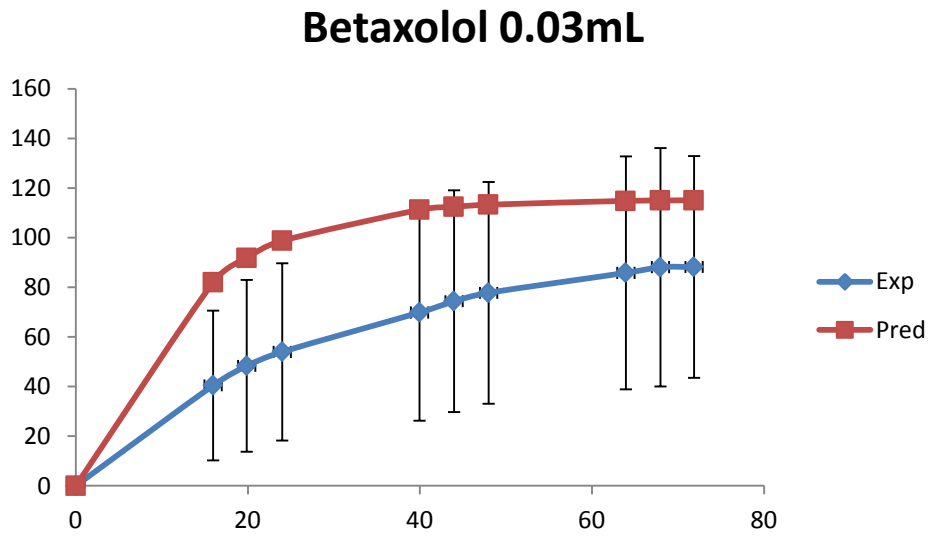
Betaxolol Prediction for three doses







- Thickness of skin layers not reported
  - ✓ Assumed SC thickness 10um (Simcyp value for back is 9um)
  - ✓ Assumed VE thickness 100um (value typical for split-thickness skin)
- Hydration expansion of SC (2.5-fold)
- **Tortuosity (2.5-fold) –** fitted parameter to match observations (but within the limits of reported value)

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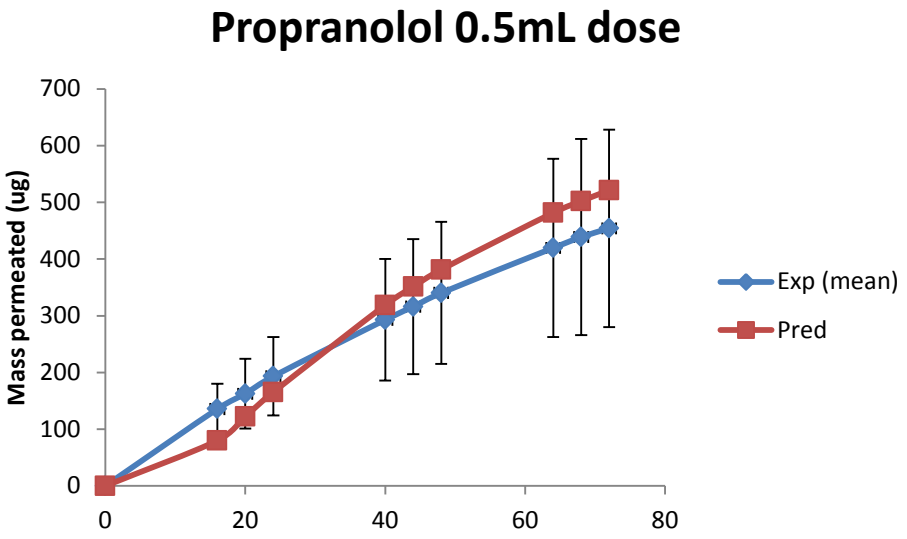
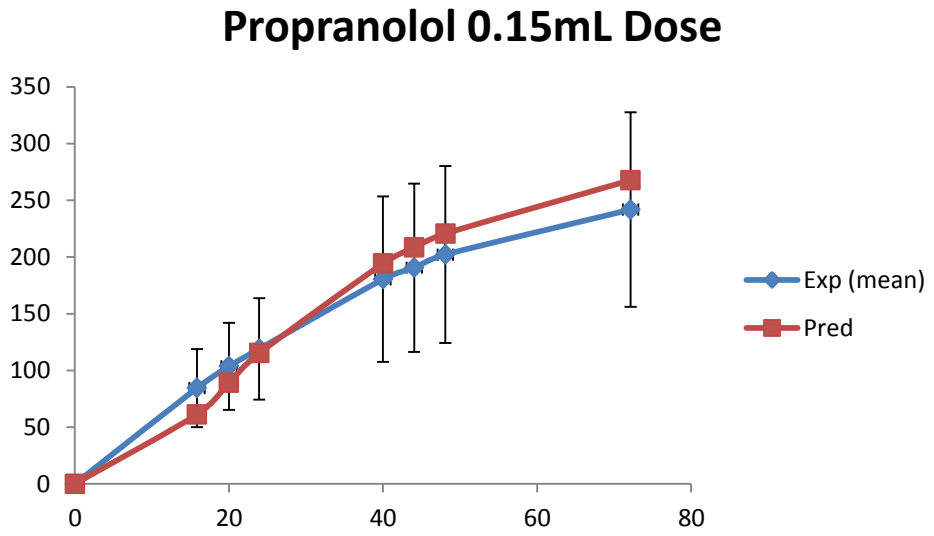
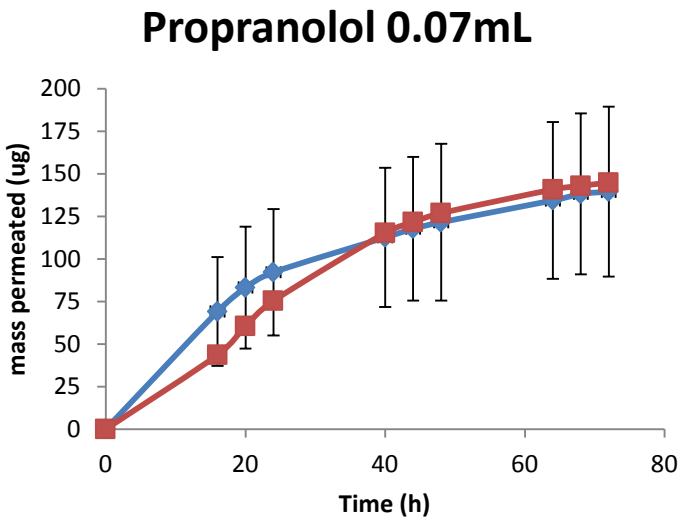
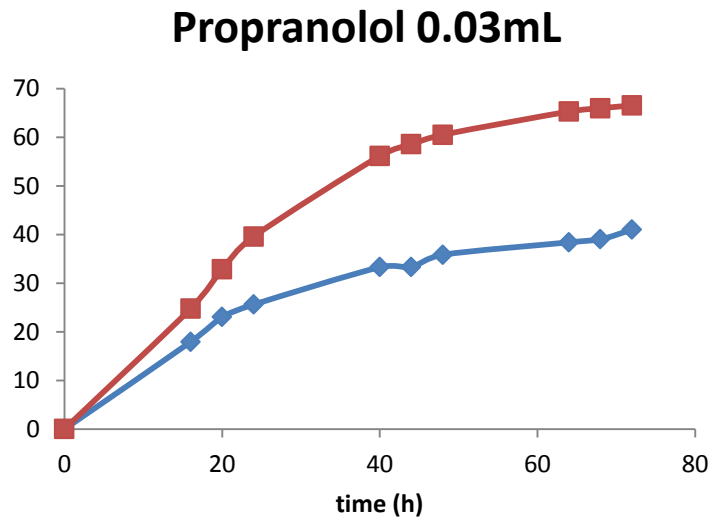
Propranolol Prediction for four doses









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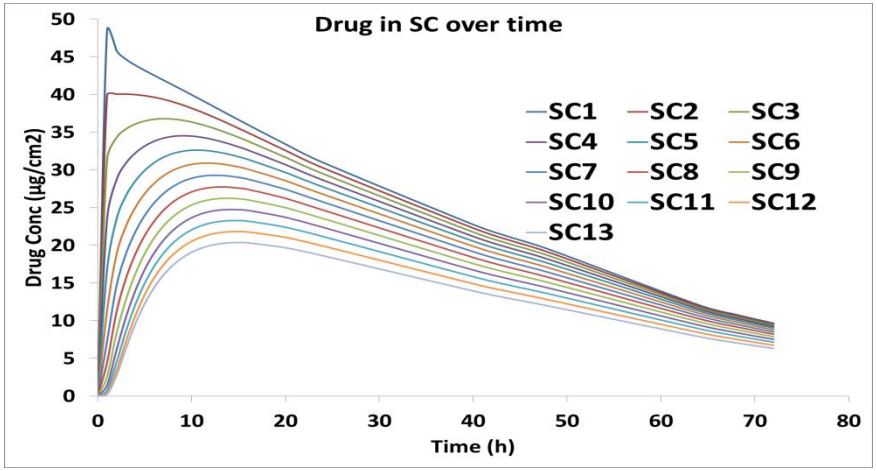
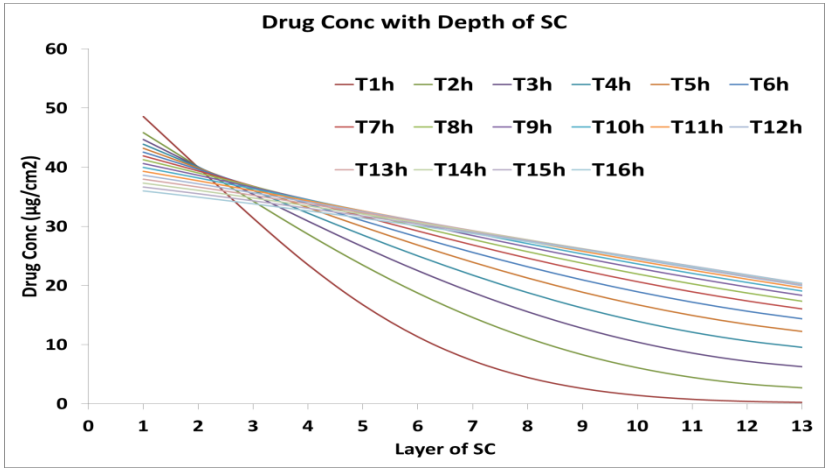
Timolol – Matrix-type Patch formulation

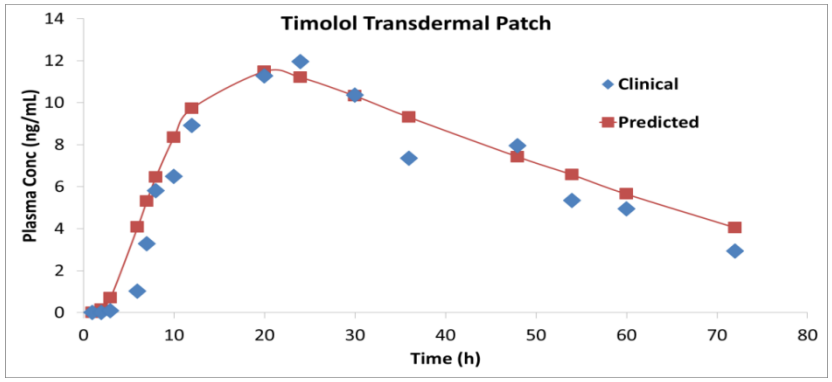


Drug conc. in layers of SC changing with time



Drug conc. changing with depth of SC

- Able to simulate the transient phase and transition to steady-state diffusion
- 12-16 h to achieve steady state diffusion



Simulated plasma drug conc. overlaid with clinically observed data

PK Parameter	Clinical	Simulated	%PE
C_{max} (ng/mL)	12.7	11.48	9.63
T_{max} (h)	22.9	21	8.3
AUC_{inf} (ng/mL.h)	613	633.33	-3.3
F_{AUC}	74.4	74.3	0.13
Lag time (h)	3	2	33.3

Comparison of Observed and Predicted PK parameters and %prediction errors

Patel et al. 2015 GRC Dermal Barrier Conference

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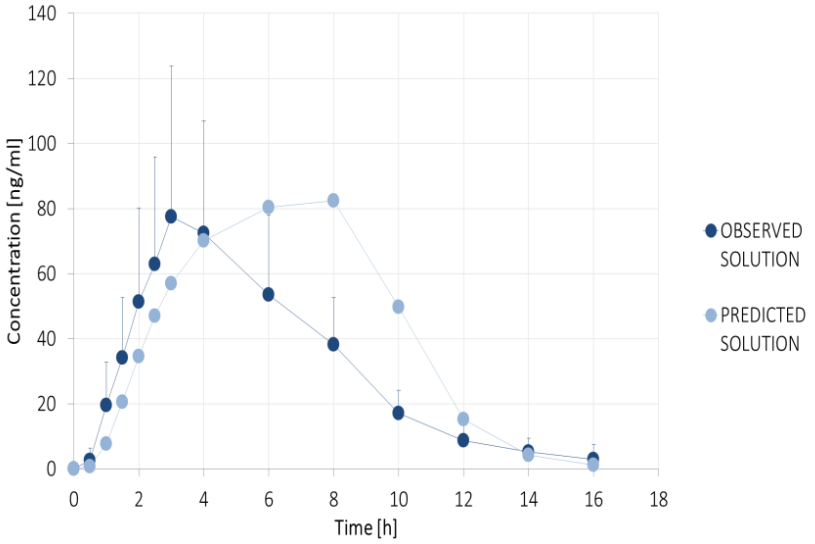
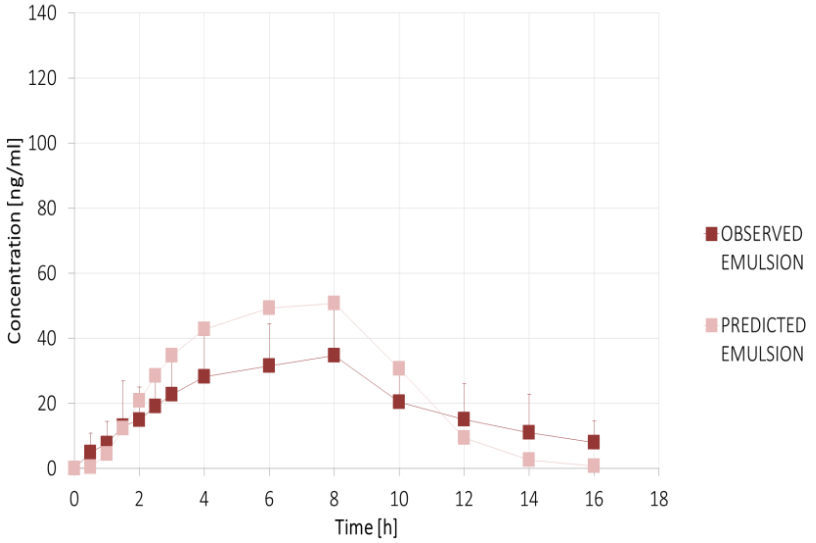
Diclofenac – solution gel vs. emulsion gel



Observed vs. Predicted drug concentration after solution gel application



Observed vs. Predicted drug concentration after emulsion gel application

- Predictions using as input physicochemical properties of the drug and formulation characteristics
- T_{max} over-predicted for the solution gel
- Diffusion coefficients: QSAR predicted / Stokes Einstein equation

Parameter	Observed	Simulated
S/E Cmax ratio	1.54	1.63
S/E AUC ratio	2.07	1.62
F_{AUC}	4.5% (S); 2.8% (E)	3.3% (S); 2.2% (E)

S – solution gel; E – emulsion gel

Polak et al. 2015 GRC Dermal Barrier Conference

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Topical Erythromycin Solution

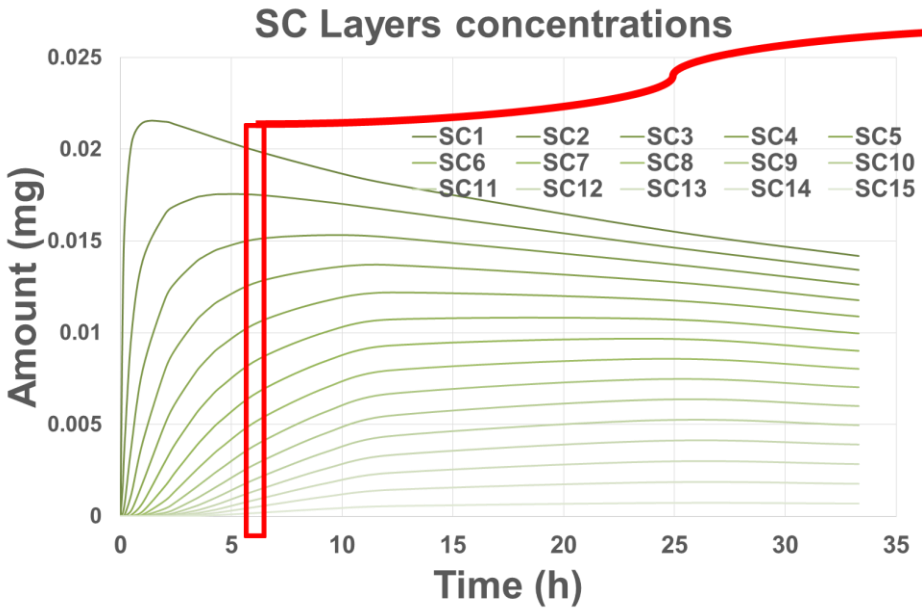

Figure 2. Erythromycin SC individual layers PK profiles.

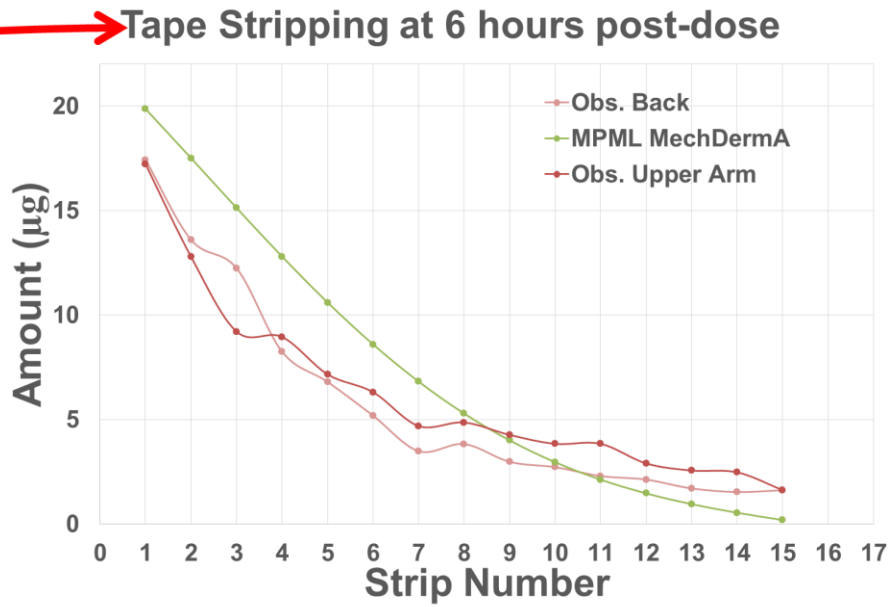

Figure 4. MPML MechDermA skin stripping experiments Predictions vs. Observations

- The MPML Model produces outputs that can be validated against tape-stripping

For More Details: Please visit Poster Cristea et al. Prediction of cutaneous PK profiles after topical application

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Conclusions & Future Direction

- PBPK M&S has a strong potential in assessment of virtual BE for Dermal Products
- Further validation of the approach for various drugs and different formulations is required to improve confidence in such approach
- Modelling of excipient effects is crucial for BE but very challenging
- Consideration of inter-occasion variability mechanistically can be difficult but essential for BE assessment
- Providing PD models to PK for assessment of therapeutic equivalence

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Thank You

Questions?