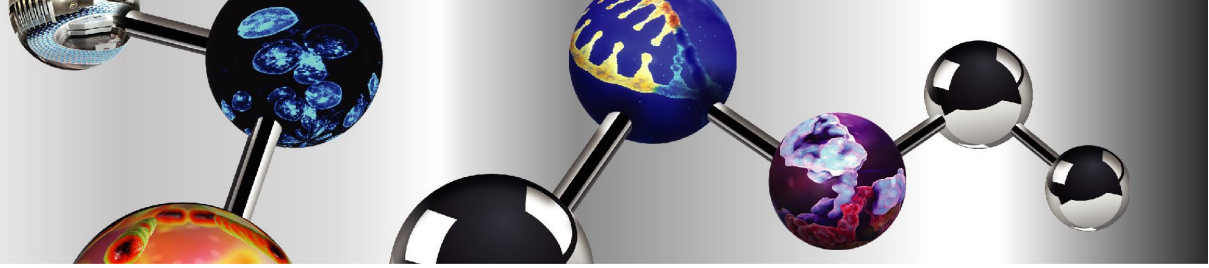
aaps PharmSci 360 OCT 17-20 2021



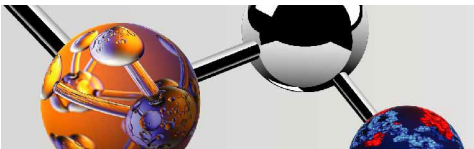
Applicability of Existing Prediction Methods to Non-Oral Routes of Delivery

On Demand

Viera Lukacova, Ph.D

SimulationsPlus

SCIENCE + SOFTWARE = SUCCESS



Session Description and Objectives

Description:

- Discuss advances made with PBPK modeling for both oral and non-oral routes for the first in human predictions

Objectives:

- Learn how to parameterize PBPK models using in silico and/or in vitro data for accurate predictions
- Identify current limitations of PBPK models in predicting local and systemic exposures for non-oral delivery routes
- Define areas for further development to increase the predictability of PBPK models for non-oral delivery routes

Biography and Contact Information

- **Viera Lukacova,** Chief Scientist – Lancaster Division, Simulations Plus
  - viera@simulations-plus.com

- Ph.D. in Pharmaceutical Sciences
- 16+ years of experience in mechanistic absorption and PBPK modeling
- Development of GastroPlus®, DDDPlus™, MembranePlus™
- Application of mechanistic absorption and PBPK models throughout the drug development process

PBPK Modeling for FIH

ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2006; 45 (5): 511-542
0312-5963/06/0008-0511/$39.95/0

2006

A Novel Strategy for Physiologically Based Predictions of Human Pharmacokinetics

Hannah M. Jones,[1] *Neil Parrott,*[1] *Karin Jorga*[2] and *Thierry Lavé*[1]

1 Drug Metabolism and Ph
2 Clinical Pharmacology, F

0090-9556/07/3510-1766–1780$20.00
DRUG METABOLISM AND DISPOSITION

DMD 35:1766–1780, 2007

2007

Prediction of Human Pharmacokinetics Using Physiologically Based Modeling: A Retrospective Analysis of 26 Clinically Tested Drugs

Stefan S. De Buck, Vikash K. Sinha, Luca A. Fenu, Marjoleen J. Nijsen, Claire E. Mackie, and Ron A. H. J. Gilissen

Johnson & Johnson Pharmaceutical Research and Development, Discovery ADME-Tox Department, Beerse, Belgium

Received March 5, 2007; accepted July 3, 2007

ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2011; 50 (5): 331-347
0312-5963/11/0005-0331/$49.95/0

2011

Simulation of Human Intravenous and Oral Pharmacokinetics of 21 Diverse Compounds Using Physiologically Based Pharmacokinetic Modelling

Hannah M. Jones,[1] *Iain B. Gardner,*[1] *Wendy T. Collard,*[2] *Phil J. Stanley,*[3] *Penny Oxley,*[3] *Natilie A. Hosea,*[4] *David Plowchalk,*[5] *Steve Gernhardt,*[6] *Jing Lin,*[6] *Maurice Dickins,*[1] *S. Ravi Rahavendran,*[4] *Barry C. Jones,*[1] *Kenny J. Watson,*[1] *Henry Pertinez,*[1] *Vikas Kumar*[5] and *Susan Cole*[1]

1 Department of Pharmacokinetics, Dynamics and Metabolism, Pfizer Worldwide R&D, Sandwich, UK
2 Department of Metabolism and Safety, Pfizer Animal Health, Kalamazoo, Michigan, USA
3 Department of Research Statistics, Pfizer Worldwide R&D, Sandwich, UK
4 Department of Pharmacokinetics, Dynamics and Metabolism, Pfizer Worldwide R&D, La Jolla, California, USA
5 Department of Clinical Pharmacology
6 Department of Pharmacokinetics, Dy

RESEARCH ARTICLE – *Drug Discovery-Development Interface*

2015

Prospective Predictions of Human Pharmacokinetics for Eighteen Compounds

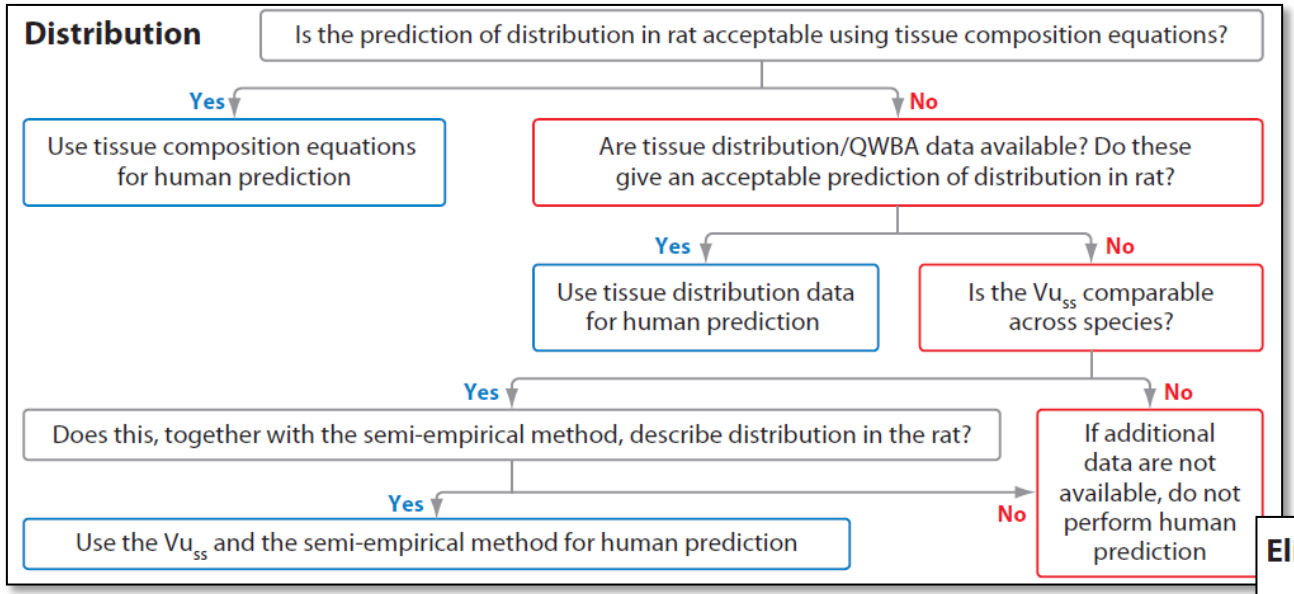
TAO ZHANG, TYCHO HEIMBACH, WEN LIN, JIN ZHANG, HANDAN HE

Drug Metabolism and Pharmacokinetics, Novartis Institutes for Biomedical Research, East Hanover, New Jersey 07936

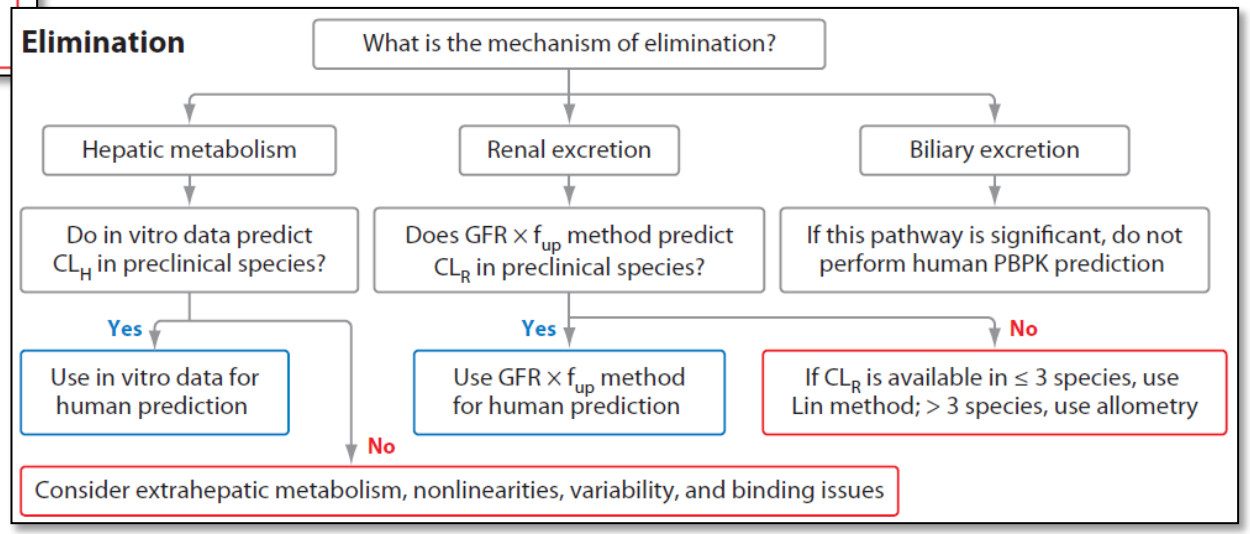
Received 26 August 2014; revised 2 January 2015; accepted 8 January 2015

Published online 17 February 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24373

Early Decision Trees:
Distribution & Elimination



- Focus mainly on systemic disposition
- Number of scenarios where using PBPK for FIH was not recommended



Rowland et al. (2011) Annu. Rev. Pharmacol. Toxicol. 51: 45–73

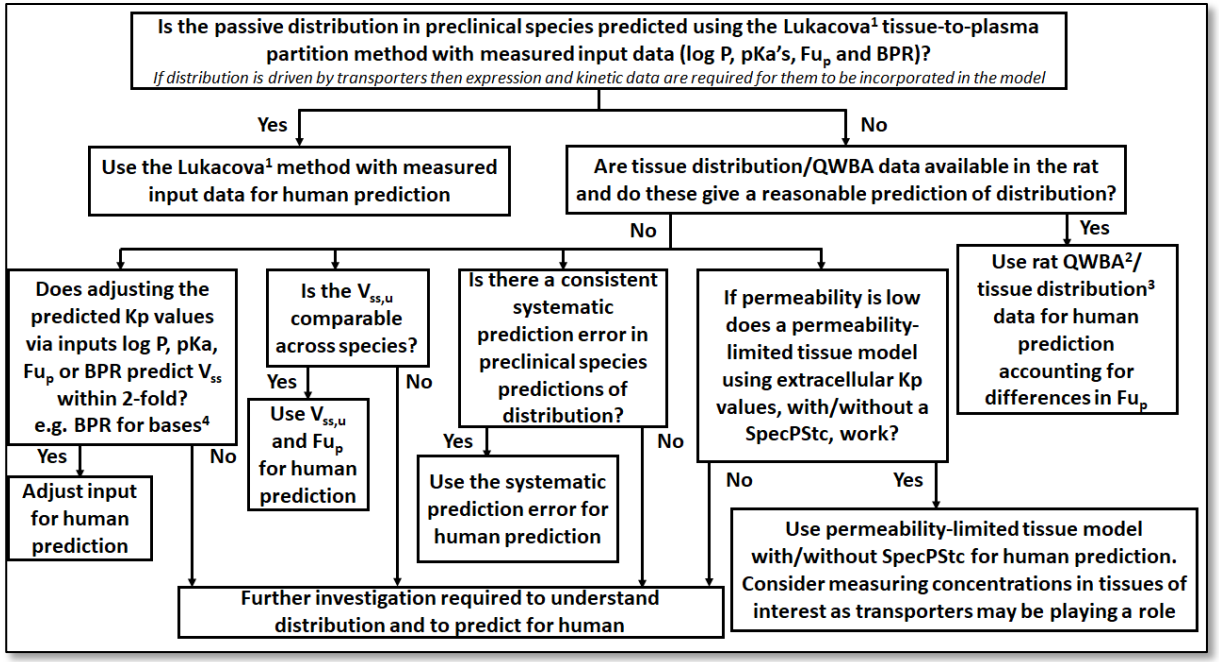
Industry Case Studies

Focus changed from “What portion of compounds we can predict accurately” to “How can we predict the complex cases”

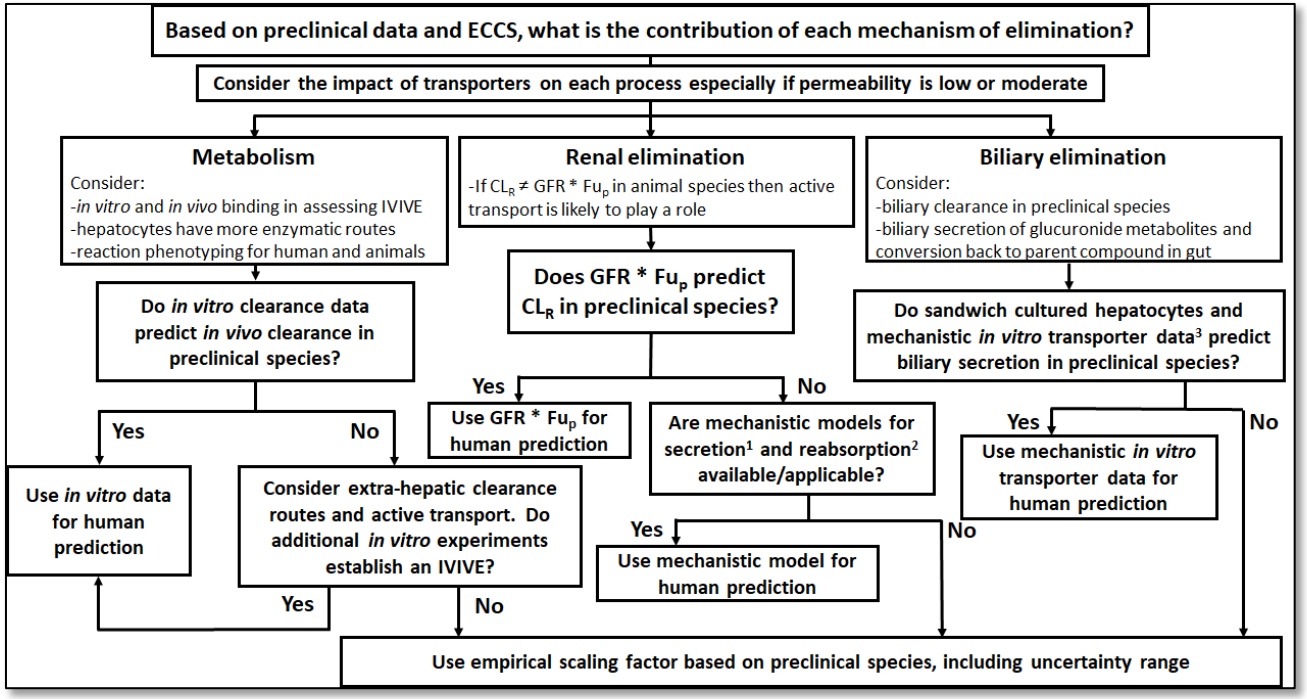
- Empirical PBPK model factors from preclinical species enable First-in-Human prediction
- Impact of Blood/Plasma ratio in predicting volume of distribution at steady state for basic compound in a retrospective analysis
- Challenging lipophilic weak acid
- High molecular weight compound with expected slow passive diffusion through membranes

Miller et al. (2019) Clinical Pharmacokinet. 58:727-746

Updated Decision Trees:
Absorption, Gut Metabolism, Distribution & Elimination

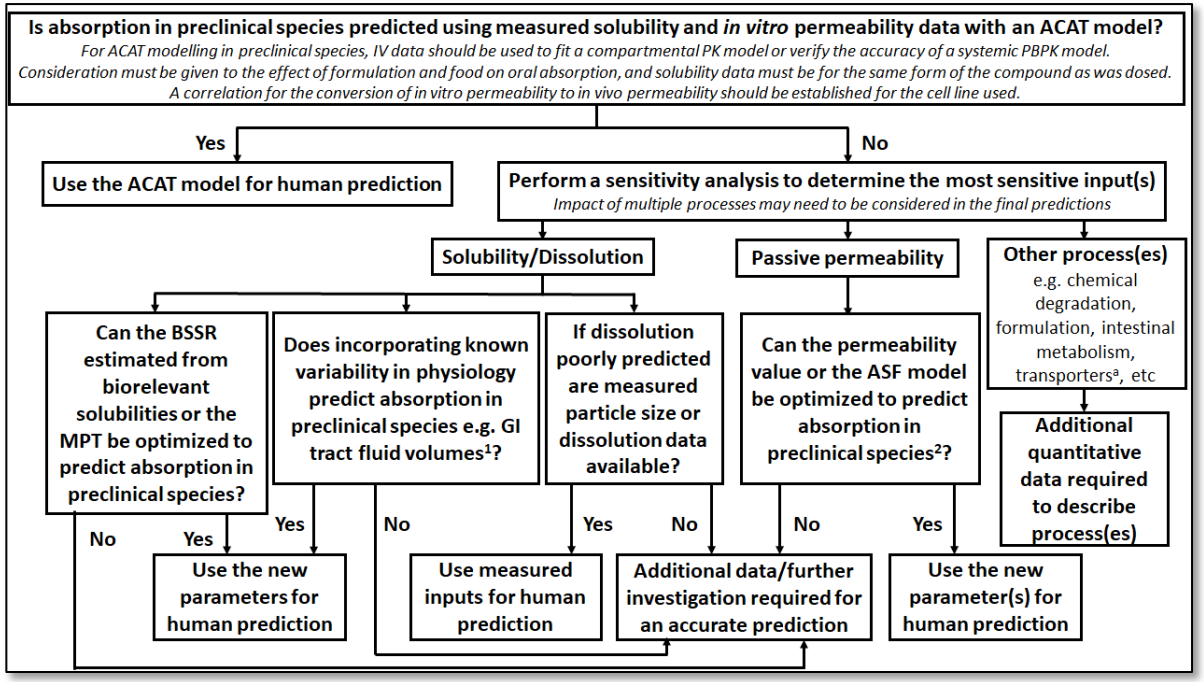


- Expanded scenarios for the more complex cases

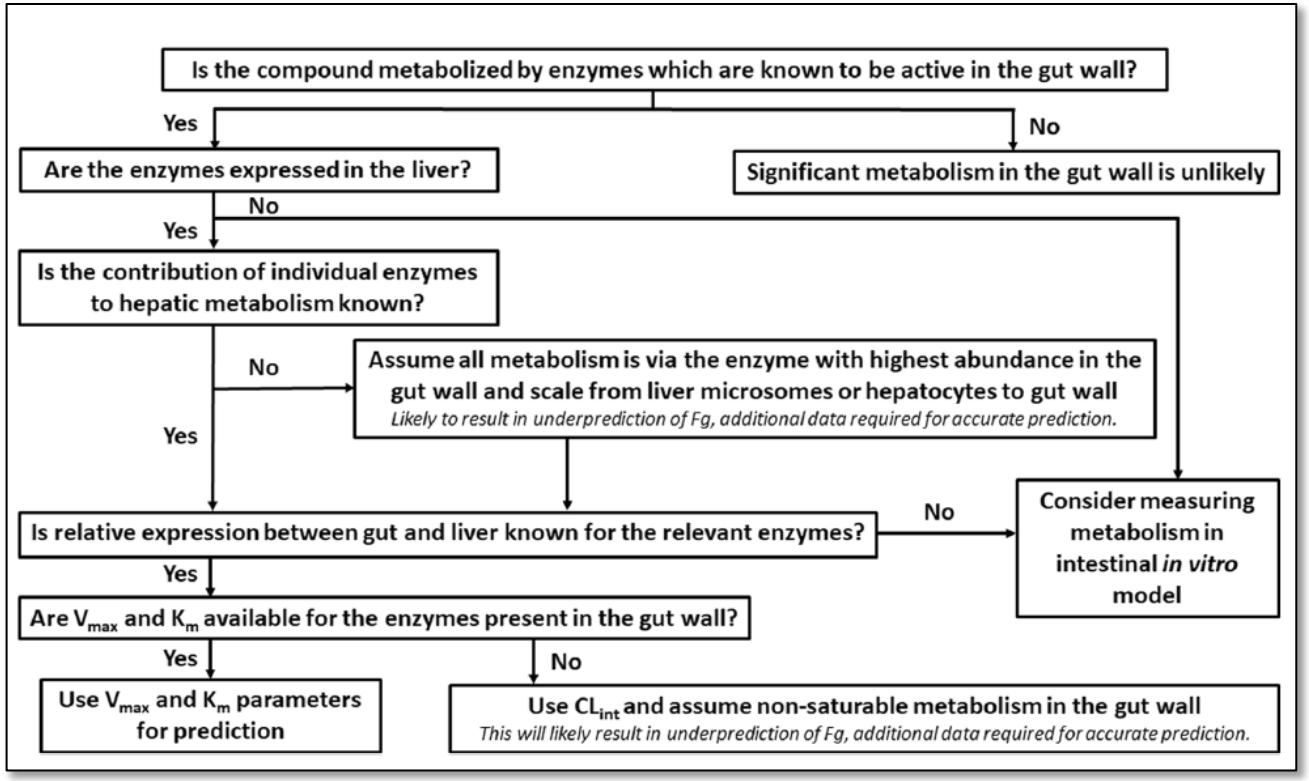


Miller et al. (2019) Clinical Pharmacokinet. 58:727-746

Updated Decision Trees:
Absorption, Gut Metabolism, Distribution & Elimination

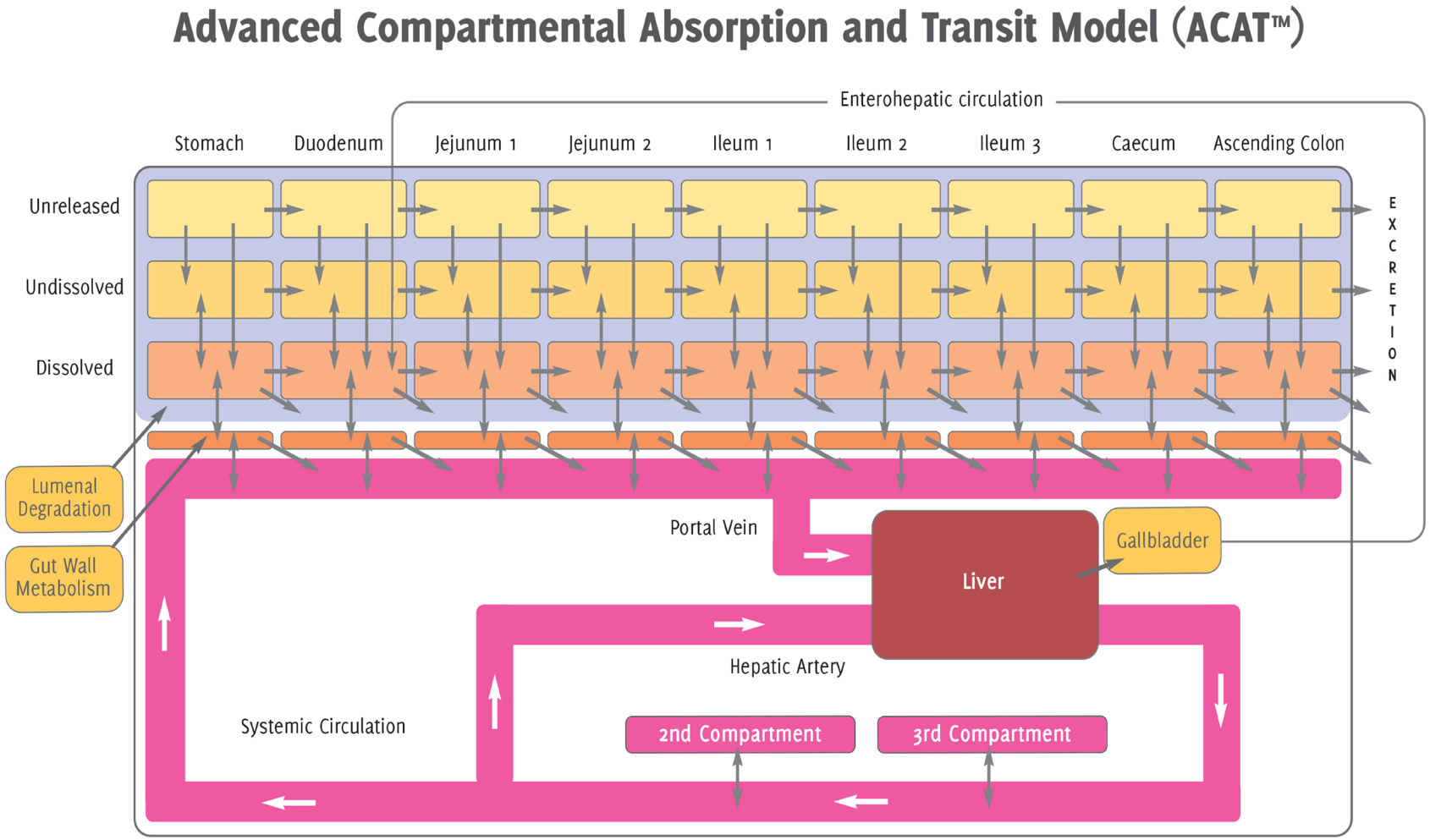


- Added decision trees for absorption and gut metabolism

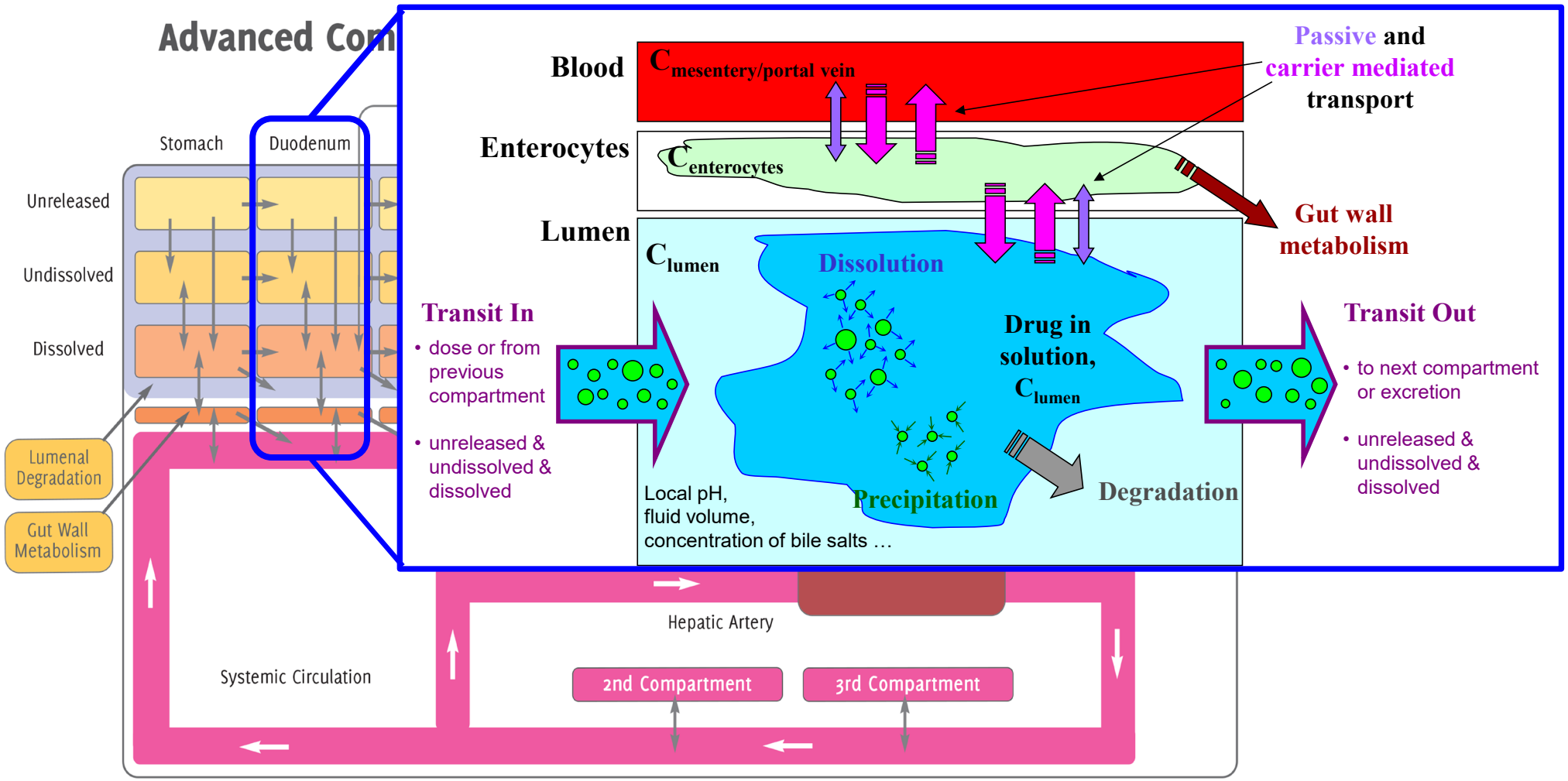


Miller et al. (2019) Clinical Pharmacokinet. 58:727-746

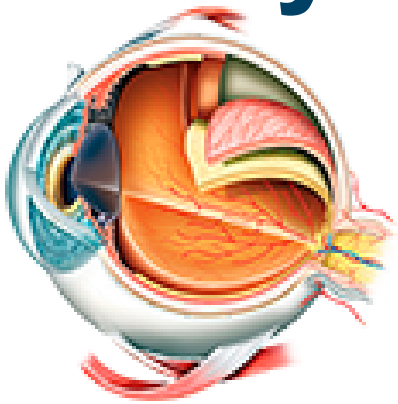
Oral Absorption

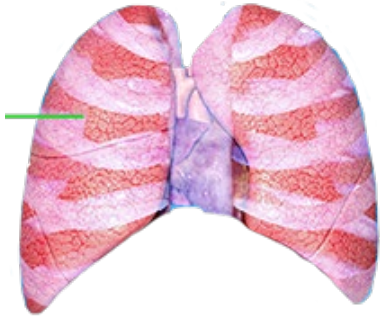


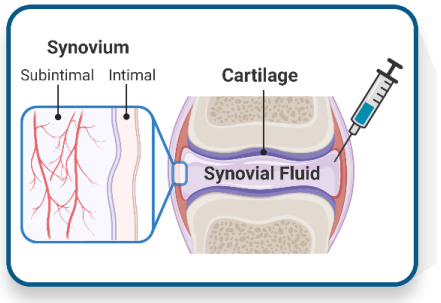
Oral Absorption

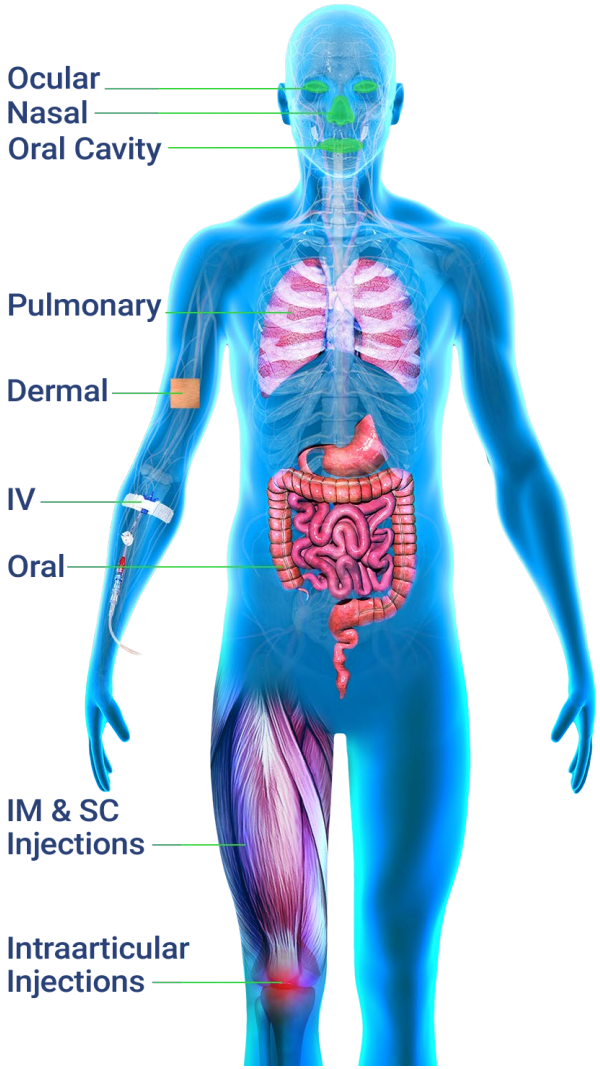


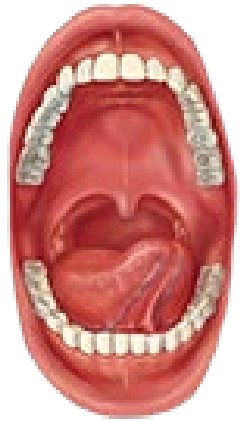
Pathways beyond oral absorption …

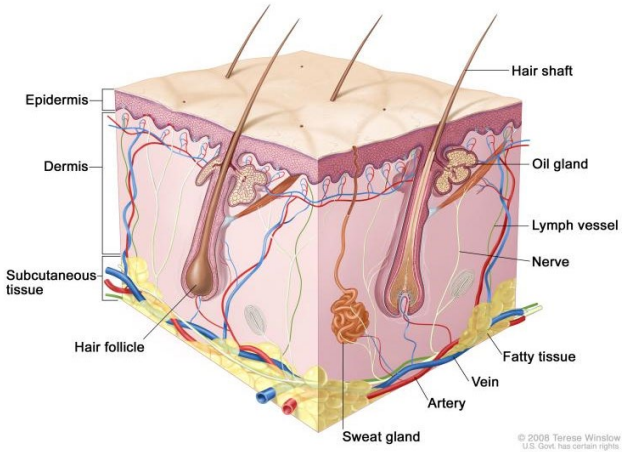




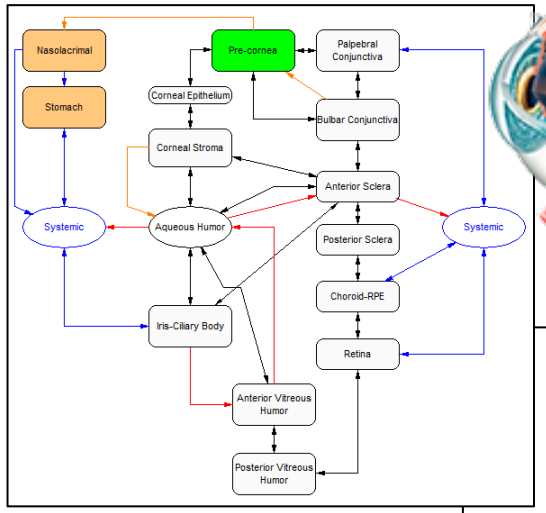


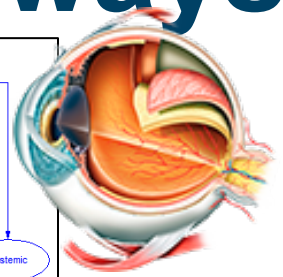


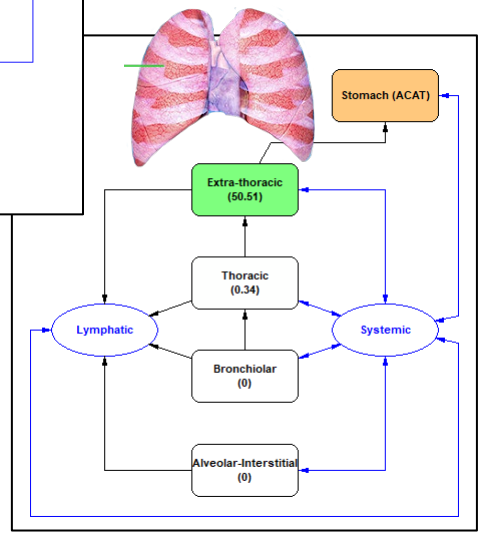


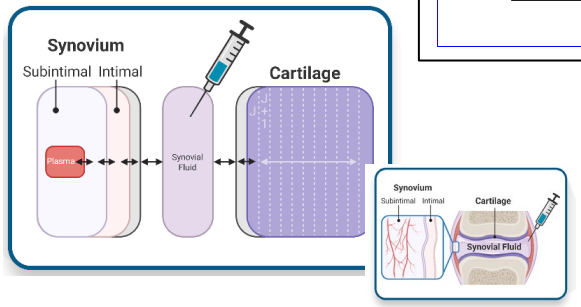


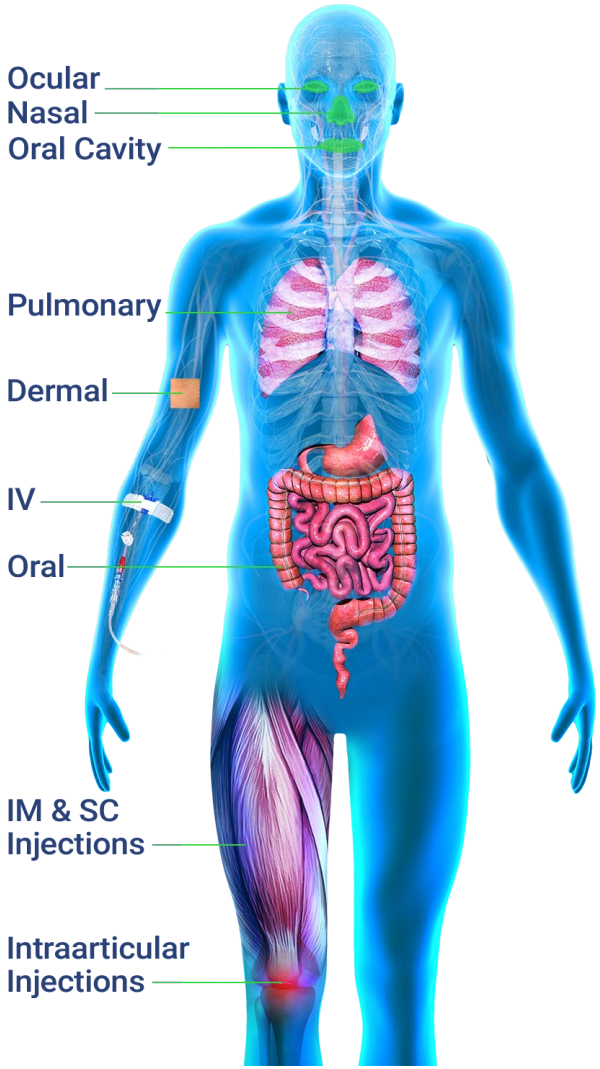
Pathways beyond oral absorption …

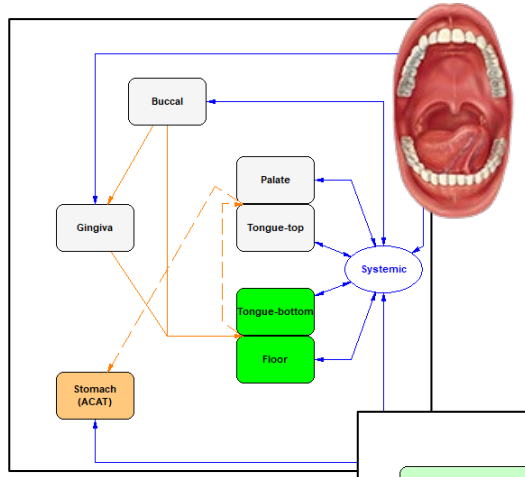


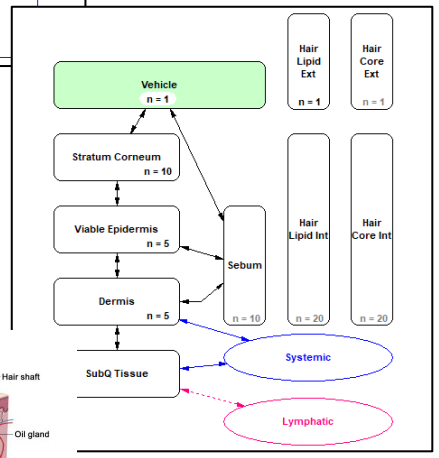


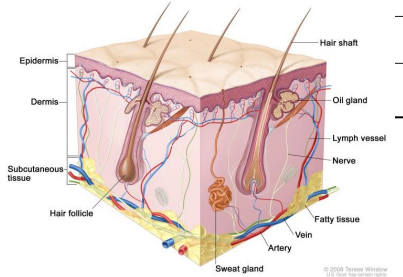




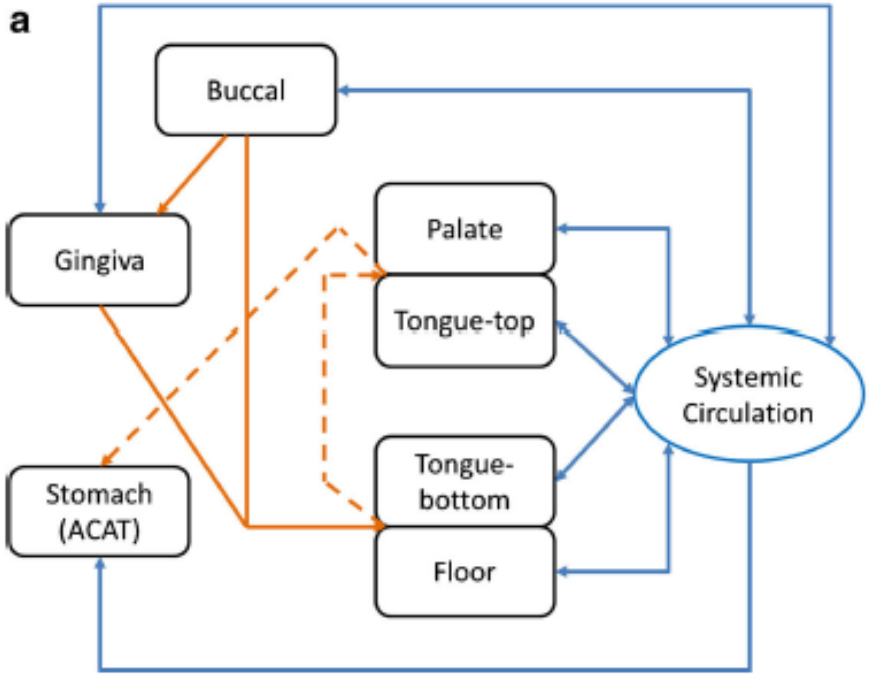


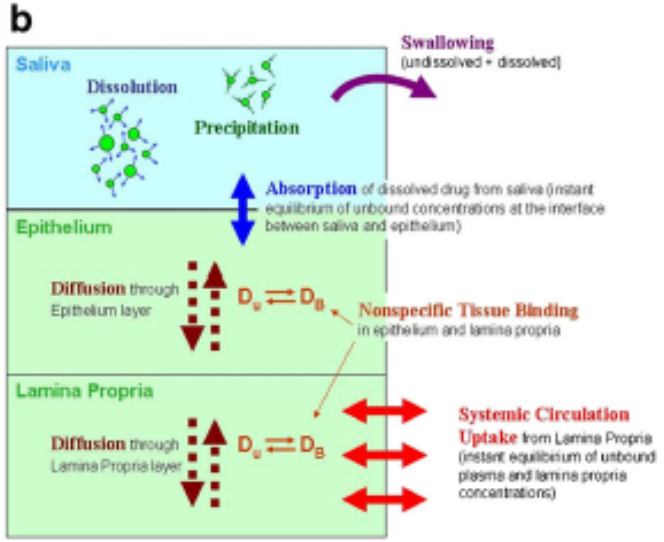






Oral Cavity Absorption





Processes:

- Dissolution/precipitation
- Dilution with saliva
- Transit/Swallowing
- Absorption into oral mucosa
- Diffusion and binding in oral mucosa
- Metabolism
- Uptake into systemic circulation

Oral Cavity Absorption

The AAPS Journal, Vol. 17, No. 3, May 2015 (© 2015)
DOI: 10.1208/s12248-015-9727-7

Research Article

Development of a Novel Oral Cavity Compartmental Absorption and Transit Model for Sublingual Administration: Illustration with Zolpidem

Binfeng Xia,[1,3] Zhen Yang,[1] Haiying Zhou,[2] Viera Lukacova,[2] Wei Zhu,[1] Mikolaj Milewski,[1] and Filippos Kesisoglou[1]

- Publication described structure and application of OCCAT™ model
- Main focus was analysis of zolpidem absorption after sublingual administration
- Prediction of Fa from oral cavity after sublingual administration for 4 additional compounds with promising results

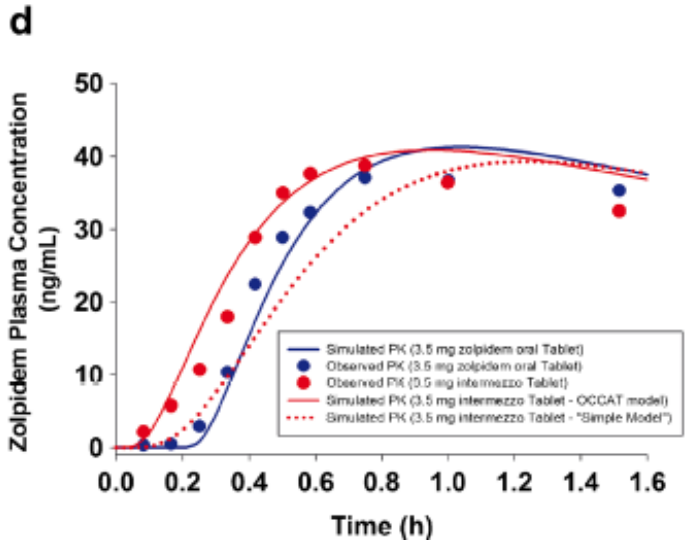


Table IV. The F_{a_IO} bioavailability for sublingual administrated tablets in a clinic study

Drugs	Dose (mg)	"Observed" F_{a_IO}[a] (%)	Methods for obtaining the "observed" F_{a_IO}	OCCAT model predicted F_{a_IO} (%)	Reference
Zolpidem	3.5	13.3	F_{PO}: 70%; F_{PO+IO}: 74% Eq. 8[b]	18.9	[18]
Asenapine	5	35	F_{PO}: 1%; F_{PO+IO}: 35% Eq. 8[b]	35.9	[39]
Verapamil	40	35	F_{PO}: 35%; F_{PO+IO}: 58% Eq. 8[b]	31.5	[40]
Propranolol	40	25–40	PBPK model with a single oral cavity compartment	30.9	[8]
Nicotine	2	53	F_{PO}: 25%; F_{PO+IO}: 65% Eq. 8[b]	14.8	[41, 42]

[a] "Observed" F_{a_IO} was calculated using Eq. 8 based on the absolute bioavailability of the oral only formulation (F_{PO}) and the absolute bioavailability of intraoral drug products (F_{IO+PO}) reported in literature unless specified (e.g., estimated using PBPK model published in literature)
[b] Fraction absorbed in oral cavity calculated by $F_{a\_IO}+(1-F_{a\_IO})\times F_{PO}=F_{PO+IO}$

Be Careful About Generic Assumptions!!

- Possibly faster onset of action is one of the advantages of intraoral administration
- But **not every compound** shows faster absorption after intraoral administration compared to PO

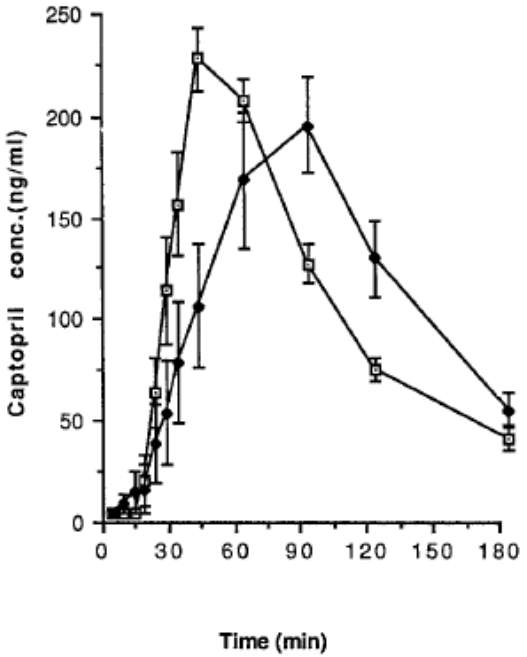


Fig. 1. Plasma unchanged captopril profiles after peroral (—◆—) and sublingual (—□—) administration of captopril (25 mg). [Data quoted are the mean (SEM) for eight healthy volunteer subjects]

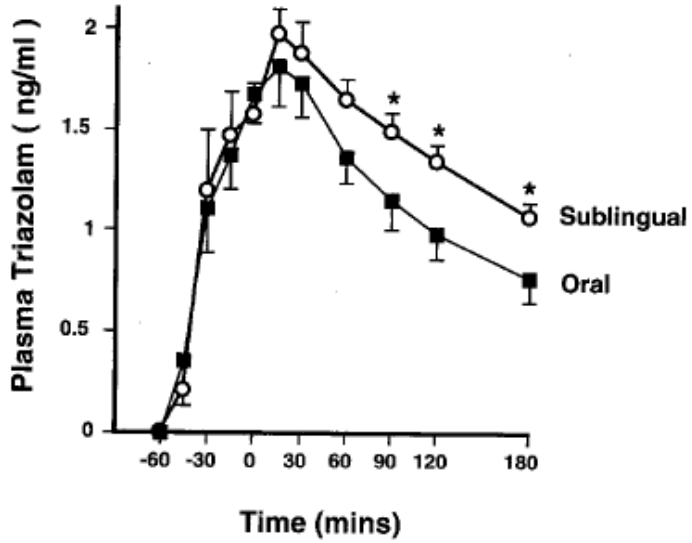
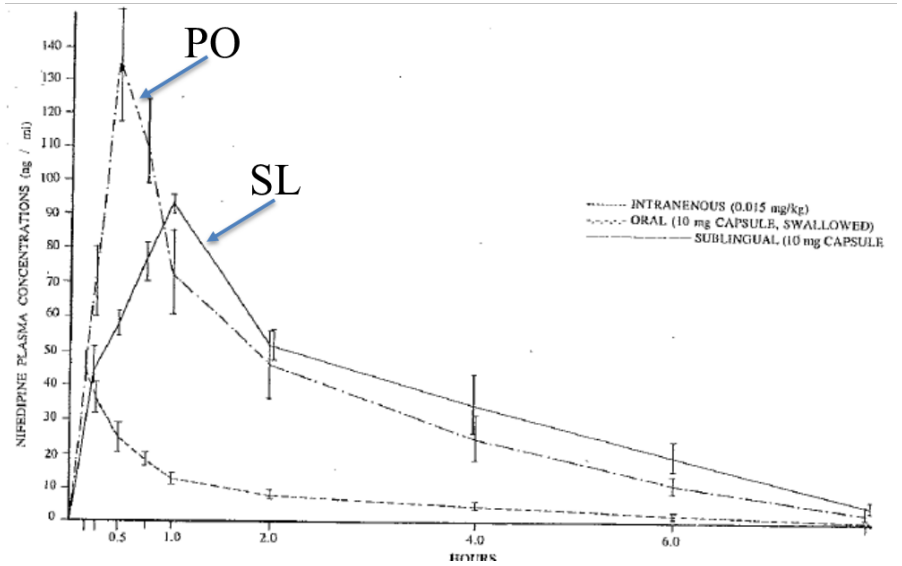
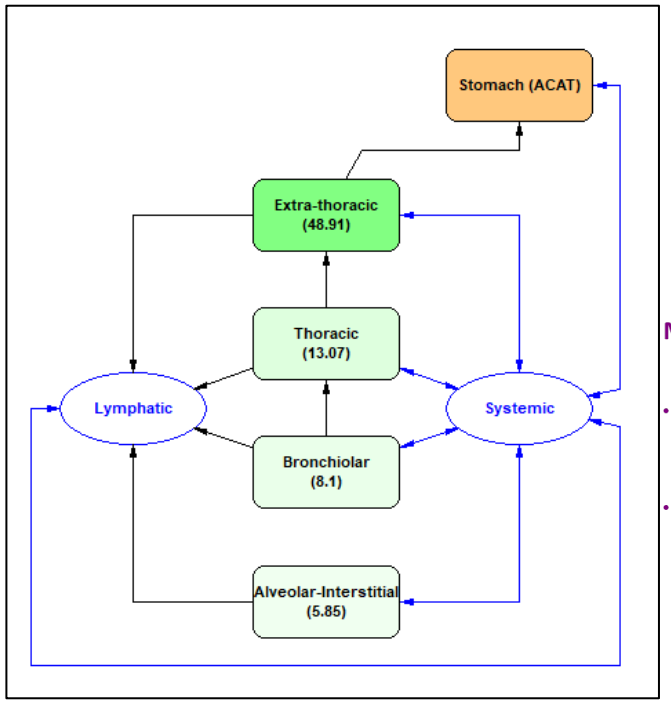


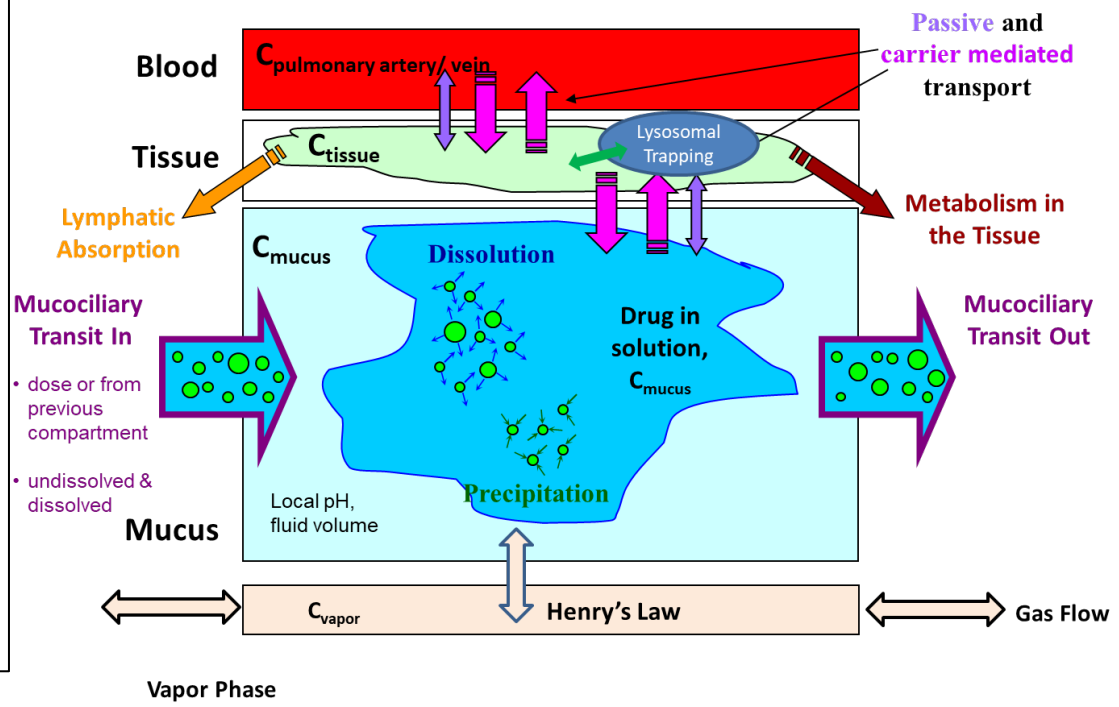
Fig. 3. Plasma triazolam levels measured from time of administration (–60 minutes) through 180 minutes from the start of surgery in the two groups of subjects who received the active drug.



Al-Furaih – Eur J Clin Pharmacol 1991, 40: 393-398; Berthold – Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997, 84: 119-124; Palma-Aguirre – Archiv Invest Med 1989, 20: 129-135

Inhaled Administration





Processes:

- Deposition
- Transit
- Dissolution/Precipitation
- Absorption into lung tissue
- Lysosomal trapping
- Metabolism
- Absorption into systemic circulation
- Evaporation/Exhalation

Inhaled Administration

Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-021-01066-2

ORIGINAL RESEARCH ARTICLE

Physiologically Based Pharmacokinetic Modelling of Inhaled Nemiralisib: Mechanistic Components for Pulmonary Absorption, Systemic Distribution, and Oral Absorption

Neil A. Miller[1] · Rebecca H. Graves[1] · Chris D. Edwards[2] · Augustin Amour[2] · Ed Taylor[3] · Olivia Robb[2] · Brett O'Brien[2] · Aarti Patel[3] · Andrew W. Harrell[3] · Edith M. Hessel[4]

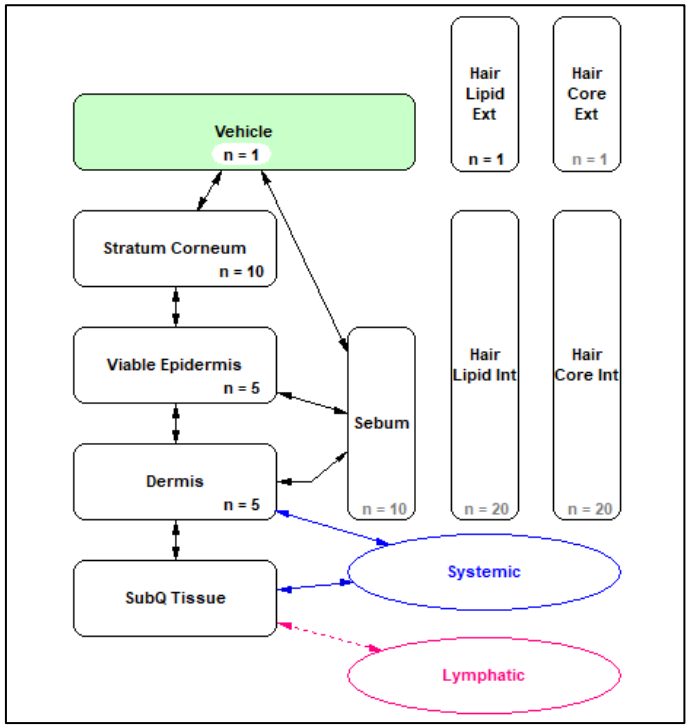
Table 2 Predicted versus observed AUC_t and C_{max} following an inhalation dose of nemiralisib

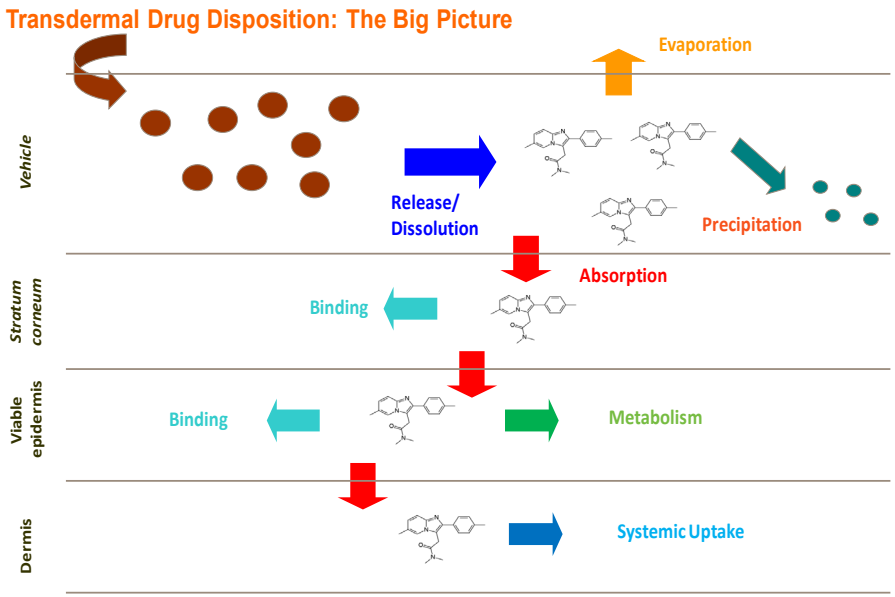
Subject	Predicted AUC_t (pg h/mL)	Observed AUC_t (pg h/mL)	AUC_t Fold error	Predicted C_{max} (pg/mL)	Observed C_{max} (pg/mL)	C_{max} Fold error
1001	3.324E+4	2.528E+4	+ 1.3	4551	3237	+ 1.4
1002	3.876E+4	4.477E+4	− 1.2	4477	5609	− 1.3
1003	2.562E+4	2.419E+4	+ 1.1	4330	3903	+ 1.1
1004	4.265E+4	4.042E+4	+ 1.1	5690	8283	− 1.5
1005	1.500E+4	1.834E+4	− 1.2	4813	2866	+ 1.7
1006	1.952E+4	2.708E+4	− 1.4	4924	1.257E+4	− 2.6

AUC_t area under the plasma concentration–time curve from time zero to time *t*, *C_{max}* maximum concentration

- Systemic disposition and intestinal absorption calibrated/validated against IV and PO data
- Inhaled parameters:
  - Deposition – predicted from MPPD model and subsequently scaled based on observed inhalation dose
  - Solubility – measured
  - Permeability – measured (MDCK-MDR1)
  - Systemic absorption rate constant – estimated from lung blood flows
  - Binding in mucus and cells – assumed the same as plasma

Dermal Delivery





Processes:

- Dissolution/Precipitation
- Evaporation
- Absorption into Stratum Corneum
- Diffusion and binding in different skin layers
- Metabolism
- Absorption into systemic circulation

Dermal Delivery

New Journal and we have not received input yet 19 (2021) 100177

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.sciencedirect.com/journal/computational-toxicology

Cosmetics Europe evaluation of 6 *in silico* skin penetration models

Sébastien Grégoire [a,*], Ian Sorrell [b,1], Daniela Lange [c], Abdulkarim Najjar [c], Andreas Schepky [c], Corie Ellison [d], John Troutman [d], Eric Fabian [e], Hélène Duplan [f], Camille Genies [f], Carine Jacques-Jamin [f], Martina Klaric [g,2], Nicola J. Hewitt [g]

- Several mechanistic skin penetration models of varying complexity have been described in literature and/or are available commercially
- Recently published study by Cosmetics Europe evaluated 6 of these models and identified required improvements
- Predictions were compared with *in vitro* skin penetration studies and focus was on chemicals rather than drugs, but the results provide good guidance on future improvements needed for these skin penetration models

Dermal Delivery: Evaporation

New Journal and we have not received input yet 19 (2021) 100177

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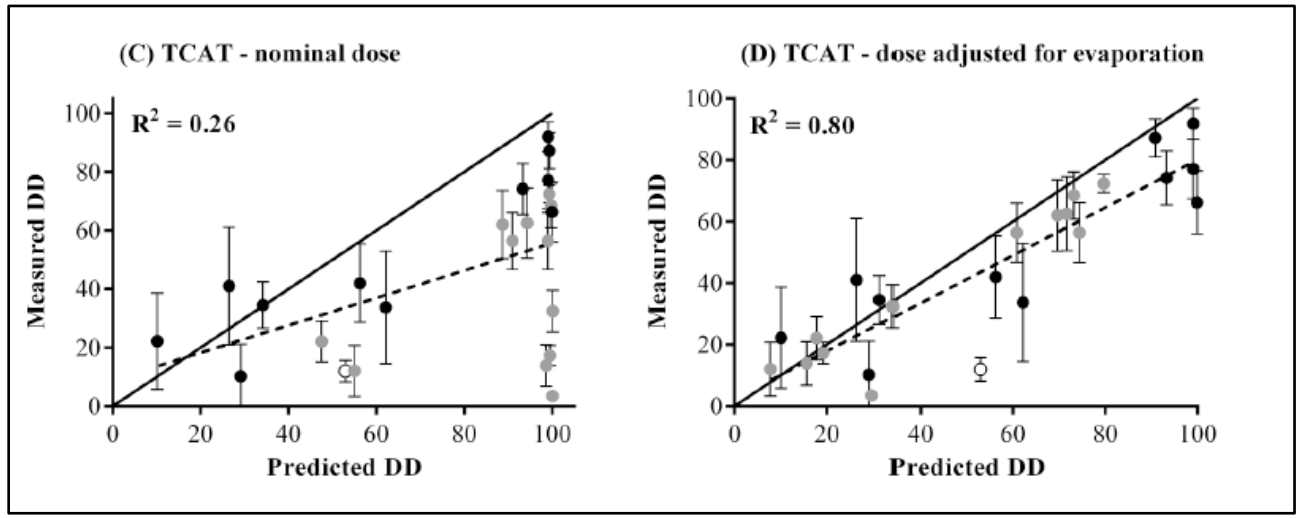

Evaporation was critical for accurate prediction of dermal delivery

- The models either did not include model to predict the evaporation or the accuracy of predicting evaporation rate was not sufficient
- However, after adjusting the administered dose for the evaporated dose, the quality of prediction improved with several tested models (for clarity, results for only one of the models shown in this slide)

Dermal Delivery: Parameter Estimates

New Journal and we have not received input yet 19 (2021) 100177

Contents lists available at ScienceDirect

Computational Toxicology

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Cosmetics Europe evaluation of 6 *in silico* skin penetration models

Sébastien Grégoire [a,*], Ian Sorrell [b,1], Daniela Lange [c], Abdulkarim Najjar [c], Andreas Schepky [c], Corie Ellison [d], John Troutman [d], Eric Fabian [e], Hélène Duplan [f], Camille Genies [f], Carine Jacques-Jamin [f], Martina Klaric [g,2], Nicola J. Hewitt [g]

Table 3
Impact of measured and QSAR $K_{SC/buffer}$ and Dsc values on correlation coefficients (R^2) between predicted and measured values of DD of 24 chemicals applied in PBS as a preliminary criterion of performance.

Model	Condition (Table 2)	R^2 using $K_{SC/buffer}$ and D_{sc}	
		QSAR	Measured
TCAT	T1	0.80	0.53
Surrey	Su2 (2D Model)	0.29	-
	Su4 (1D Model)	-	0.28
DSkin	D2	0.60	0.14
SimCyp	SC1	0.23	0.58

Impact of measured or *in silico* parameter inputs for Stratum Corneum partitioning and diffusivity yielded mixed results:

- Measured values improved predictions with one model
- *in silico* parameter inputs resulted in better predictions with two other models (including the highest overall R^2)

Dermal Delivery: Local Concentrations

New Journal and we have not received input yet 19 (2021) 100177

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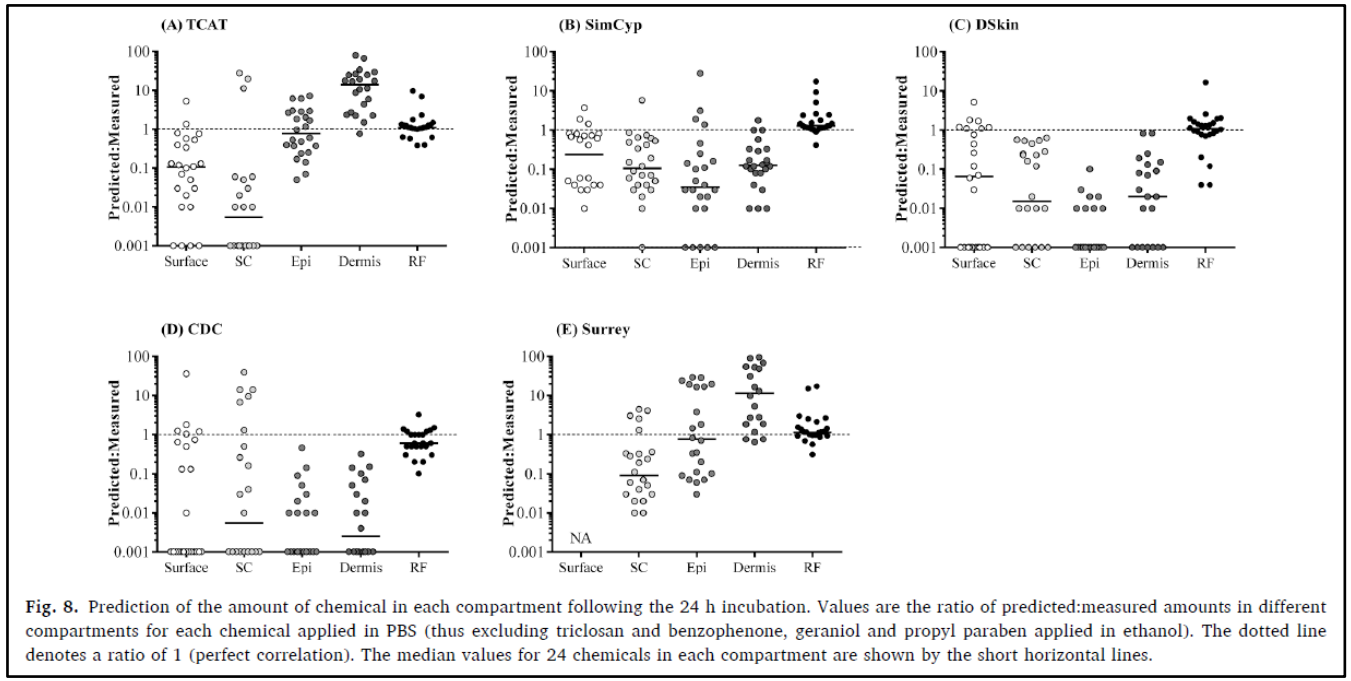


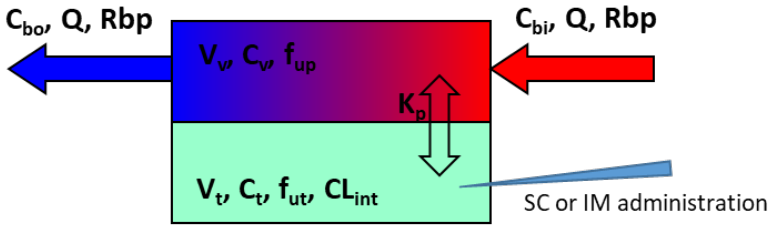
Fig. 8. Prediction of the amount of chemical in each compartment following the 24 h incubation. Values are the ratio of predicted:measured amounts in different compartments for each chemical applied in PBS (thus excluding triclosan and benzophenone, geraniol and propyl paraben applied in ethanol). The dotted line denotes a ratio of 1 (perfect correlation). The median values for 24 chemicals in each compartment are shown by the short horizontal lines.

Prediction of compound accumulation in different skin layers :

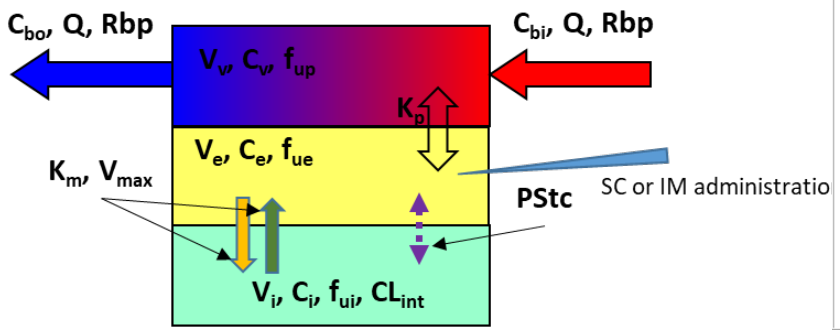
- Accuracy varied for different models and layers
- There is room for improvement with all tested models – important especially for locally acting drugs

Intramuscular and Subcutaneous Injections

Perfusion Limited:



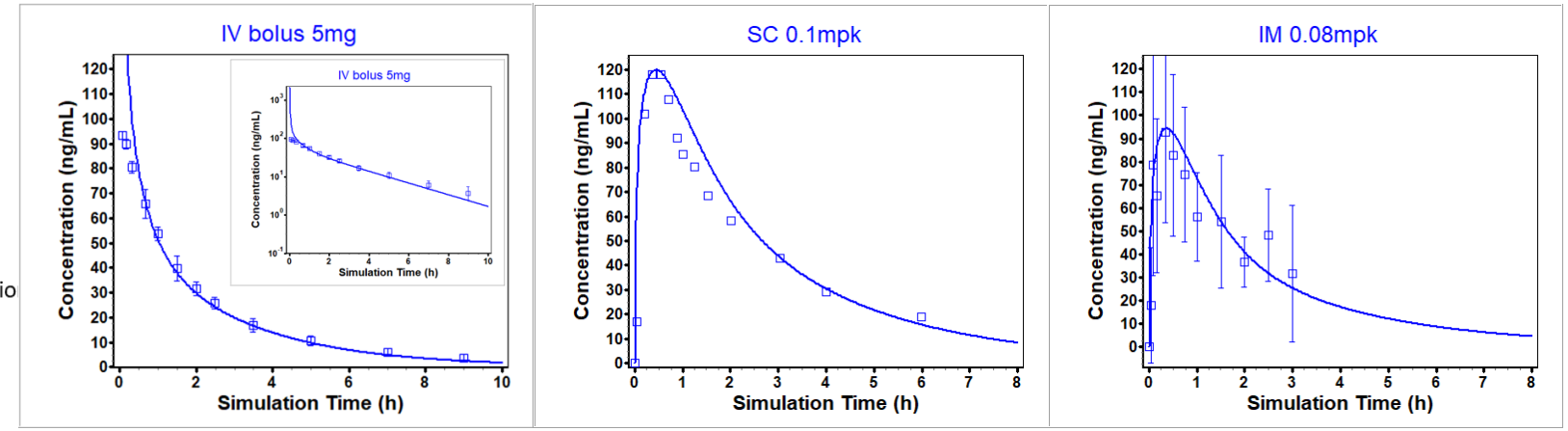
Permeability Limited:



- Tissue plasma partition coefficients and tissue blood flow account for drug uptake from injection site into systemic circulation
- Works well with solution injections (if precipitation is not a significant factor)

Midazolam administration in healthy volunteers

- The same model correctly described PK after IV, SC solution and IM solution administration



Observed data from:
Pecking – Br J Clin Pharmacol 2002, 54:357; Alfonzo Echeverri – Anesth Prog – 1990, 37:277; Kupferschmidt – Clin Pharmacol Ther 1995, 58:20

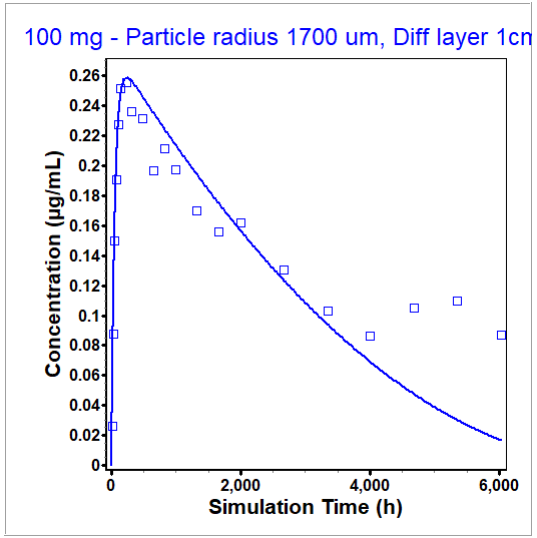
Intramuscular and Subcutaneous Injections

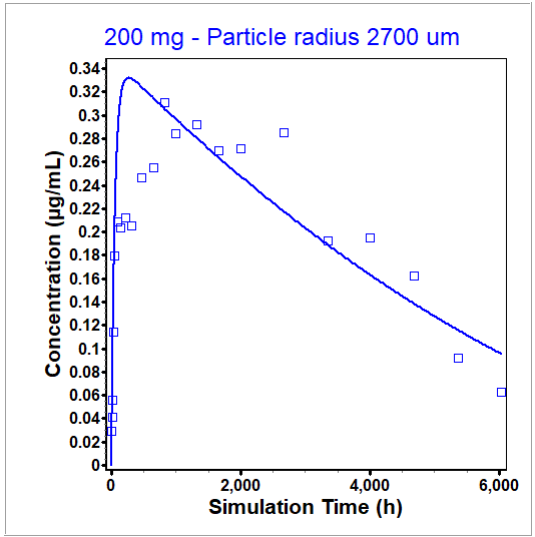
Intramuscular and subcutaneous injection of crystalline suspension of low solubility compound cabotegravir

Simulation used Johnson dissolution equation with: $$\frac{dM_D}{dt} = \frac{D_w}{\rho h r_t}\frac{(1+2s)}{s}(C_s - C_l)M_{u,t}$$

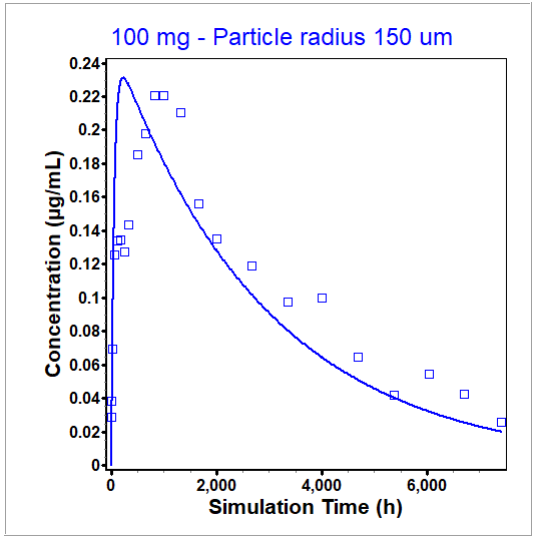
- Large particle size (might be indicative of aggregation at the injection site)
- Large diffusion layer surrounding particles (might be indicative of static tissue environment)

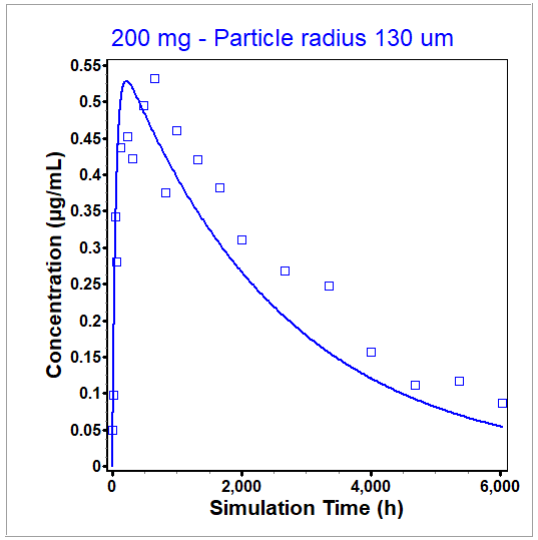
Intramuscular





Subcutaneous





Observed Data:
Spreen - J Acquir Immune Defic Syndr, 2014, 67(5):481

Intramuscular and Subcutaneous Injections

Tissue response may further complicate the apparent behavior of injected formulation:

I. Acute phase of the inflammatory response

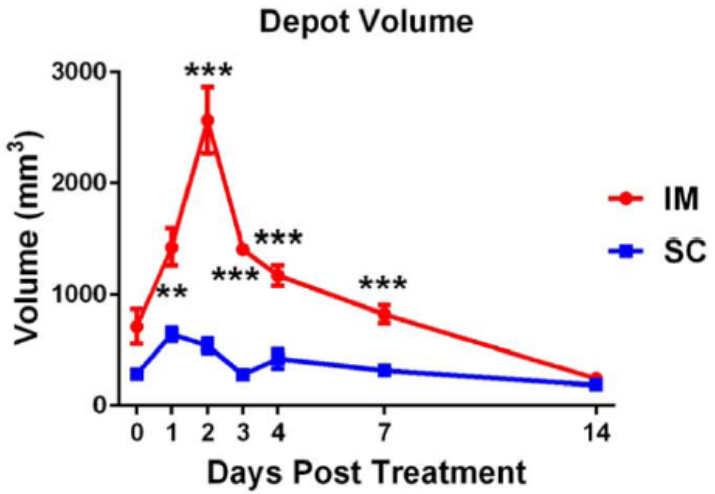
Occurs within one week following administration and is characterized by the presence of neutrophils in the area of the injection or implant.

II. Onset of the chronic phase of inflammation

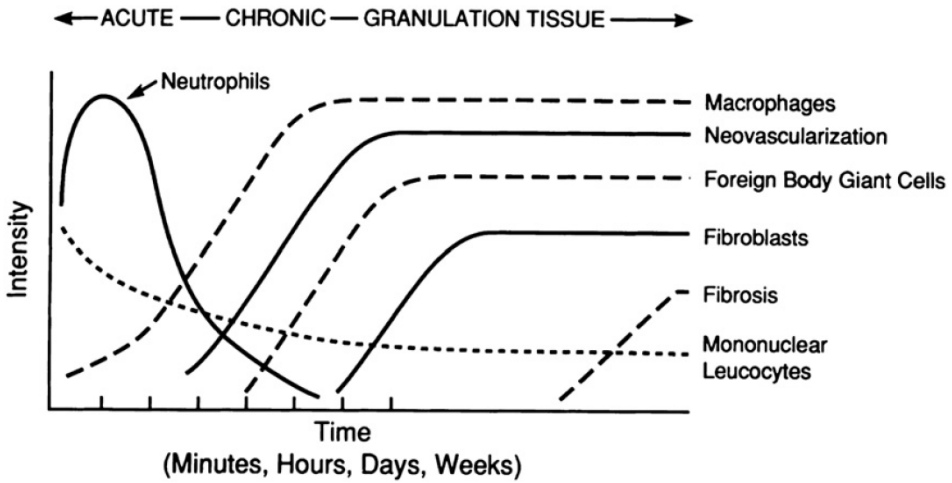
Onset of the chronic phase of inflammation, is characterized by the appearance of monocytes and macrophages

III. Fibroblasts infiltration and collagen deposition

Fibroblasts infiltrate the site and collagen deposition is initiated to form a fibrous capsule. Neo-angiogenesis is also observed during this period



Jucker – J Contr Rel 2017, 268: 102-112



Anderson et. al., Advanced Drug Delivery Reviews 64 (2012), 2012

The temporal variation in the three phases of inflammatory response resulting from administration of biodegradable microspheres

Summary

- Significant progress was made in development of *in vitro* systems and models to predict intestinal absorption
- Similarities in processes impacting absorption from oral and non-oral routes of delivery provide path towards improved predictions from non-oral routes of delivery
- Additional route-specific processes impact predictions for non-oral routes of delivery:
  - Deposition with inhaled administration
  - Evaporation and impact of excipients on drug absorption with dermal administration
  - Potential aggregation and physiological response with IM or SC injectables
  - Contribution of intestinal absorption with oral cavity, ocular, and inhaled administration
  - ...

Questions

Viera Lukacova, Chief Scientist – Lancaster Division, Simulations Plus

viera@simulations-plus.com

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