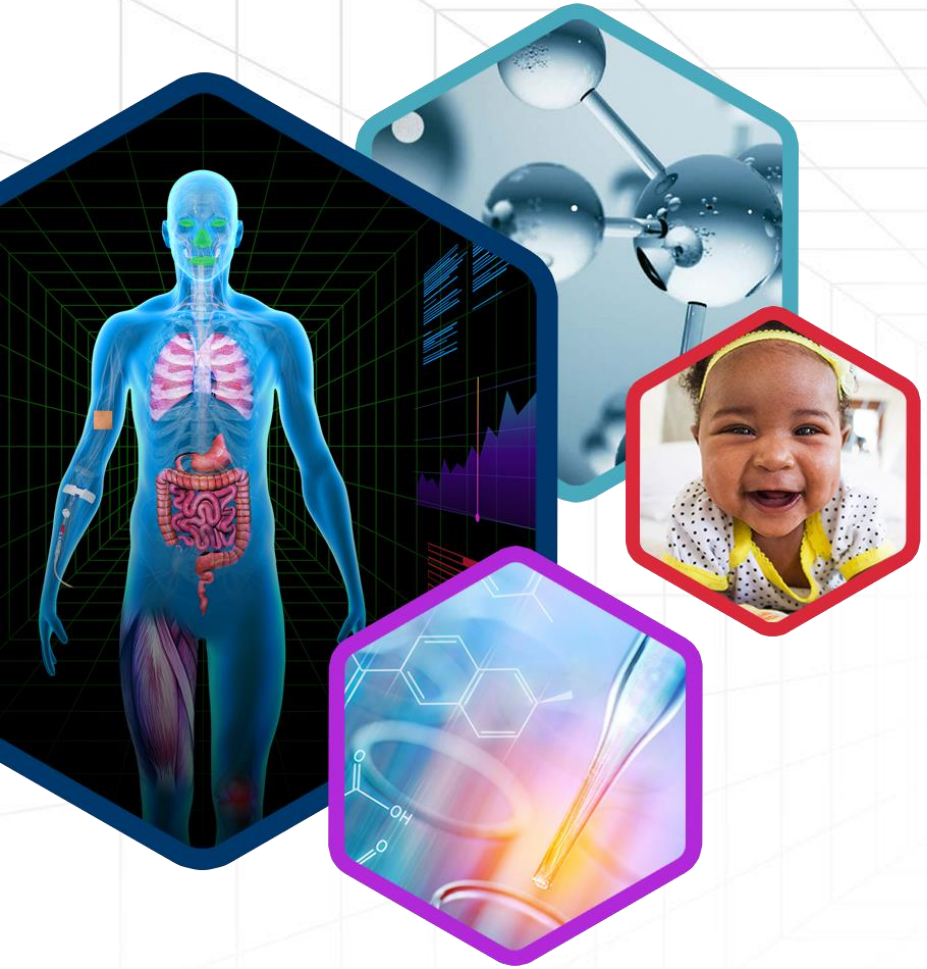

Absorption Predictions: Current Capabilities and Knowing the Gaps

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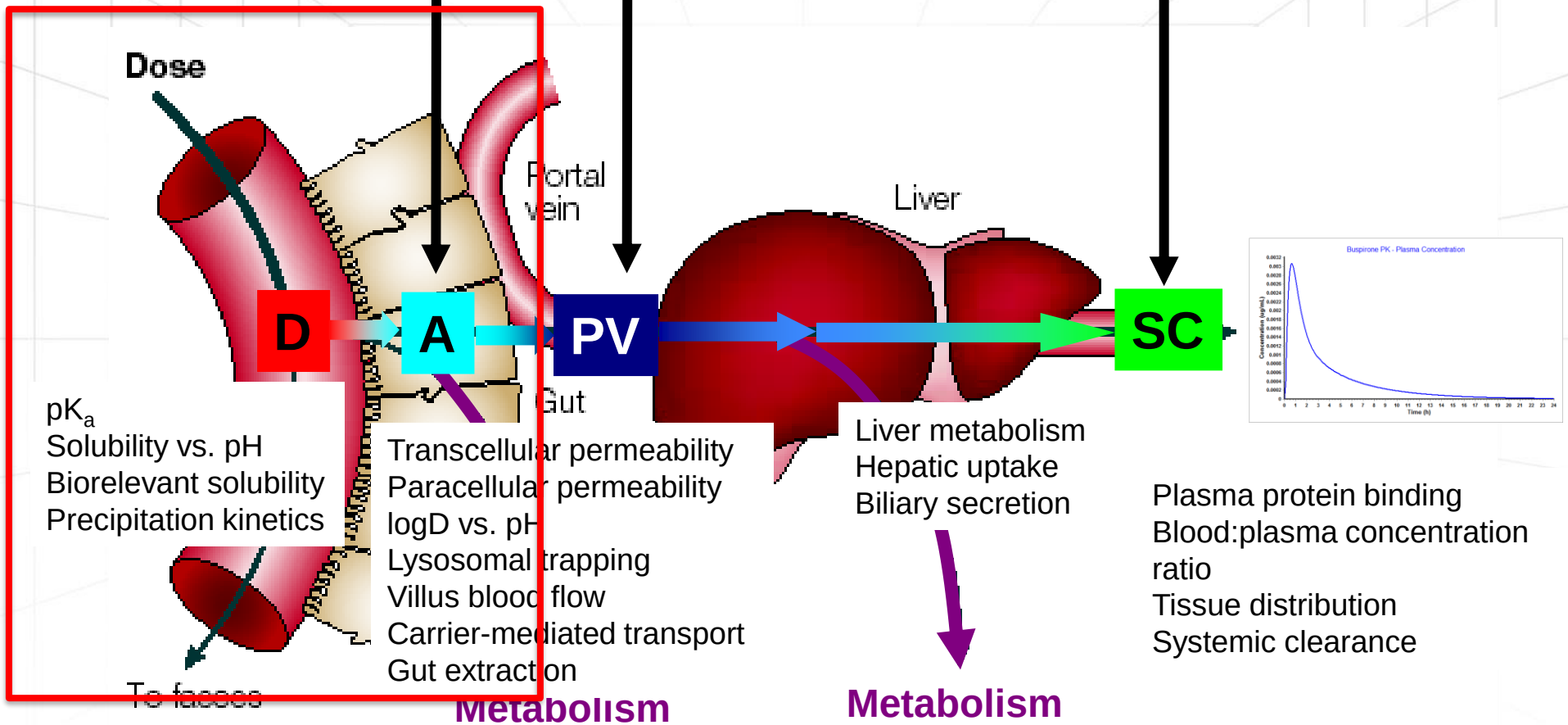
September 2022

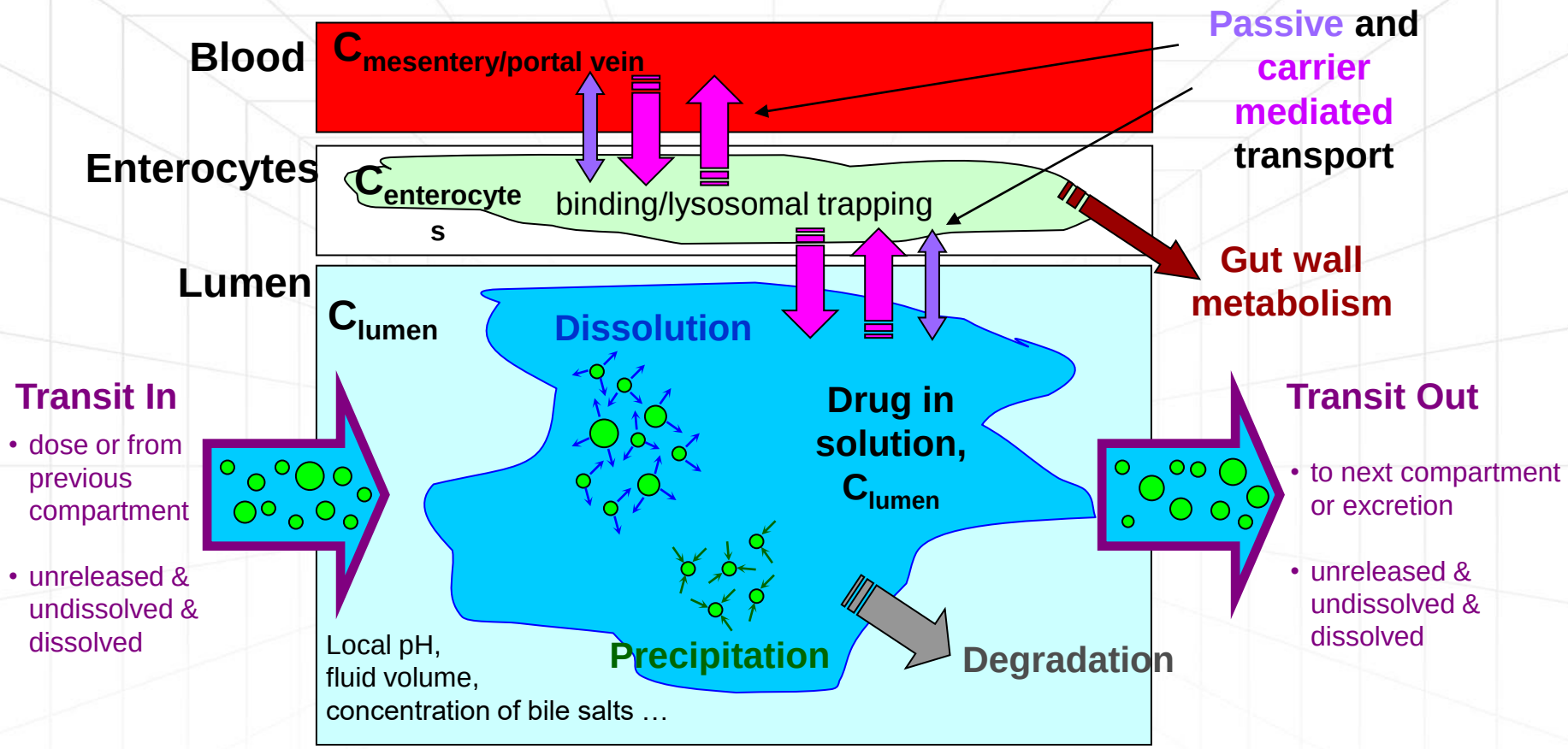
What's Happening *in vivo*?

Fa% **FDp%** **F%** (not Fa%)



* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

Processes Involved in Oral Absorption



These phenomena:

- **are happening simultaneously**
- **are repeated in each of the compartments of the gastrointestinal tract**

Some of the Important Interactions

Dissolution–Absorption

Faster absorption can promote faster dissolution

Degradation-Absorption

Degradation reduces lumen concentration, decreasing absorption

Solubility–Absorption–Dissolution

Low solubility can limit concentration gradient and limit absorption

Higher solubility increases dissolution rate

Plasma Protein Binding–Absorption

High plasma protein binding = less resistance to drug crossing the basolateral membrane

Plasma Protein Binding–Metabolism

High plasma protein binding limits metabolism

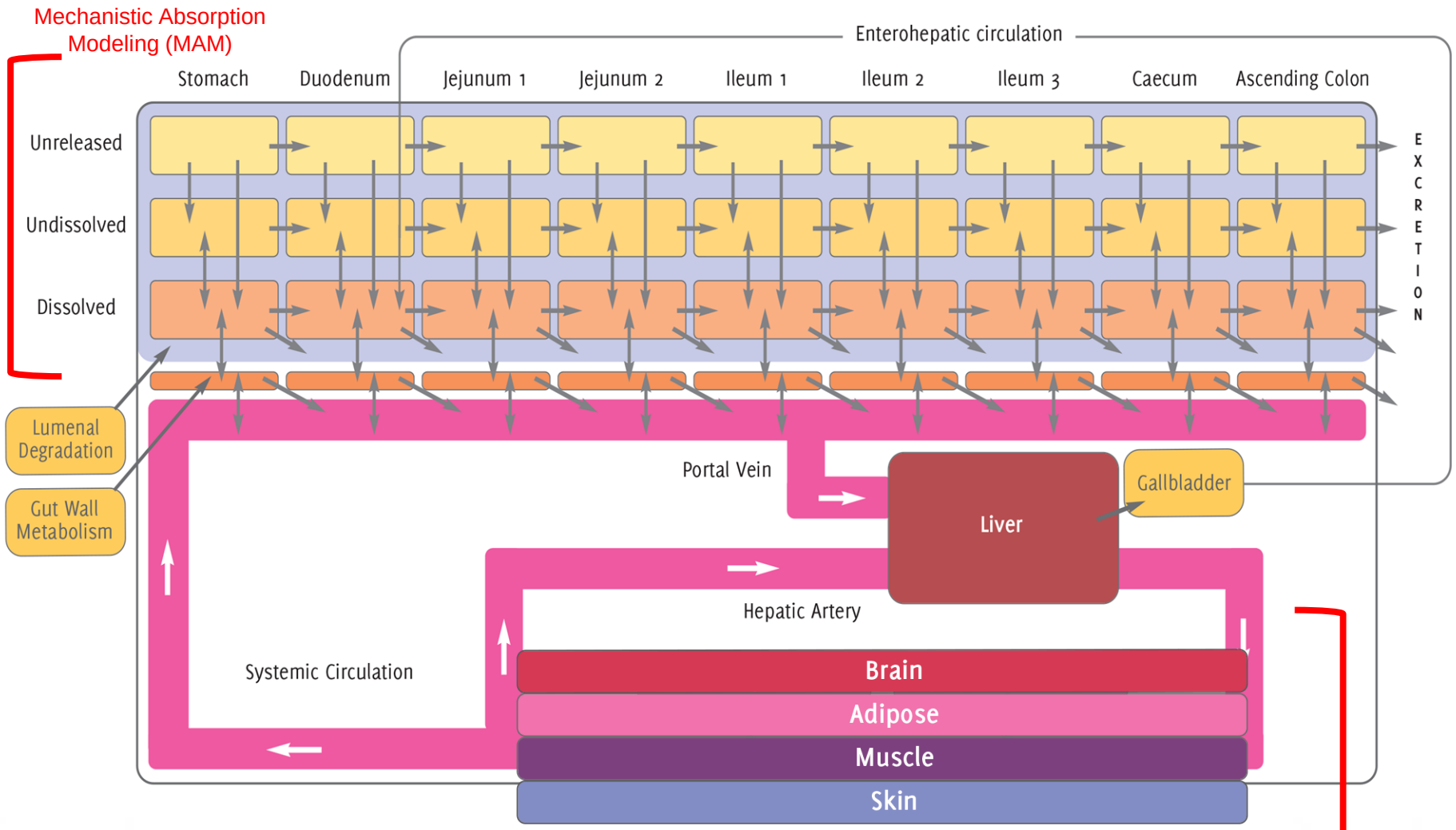
Meal (food) effects

Increased hepatic blood flow rate

Gall bladder emptying

Caecum emptying into colon

Advanced Compartmental Absorption and Transit Model (ACAT™)



Intestinal Physiology

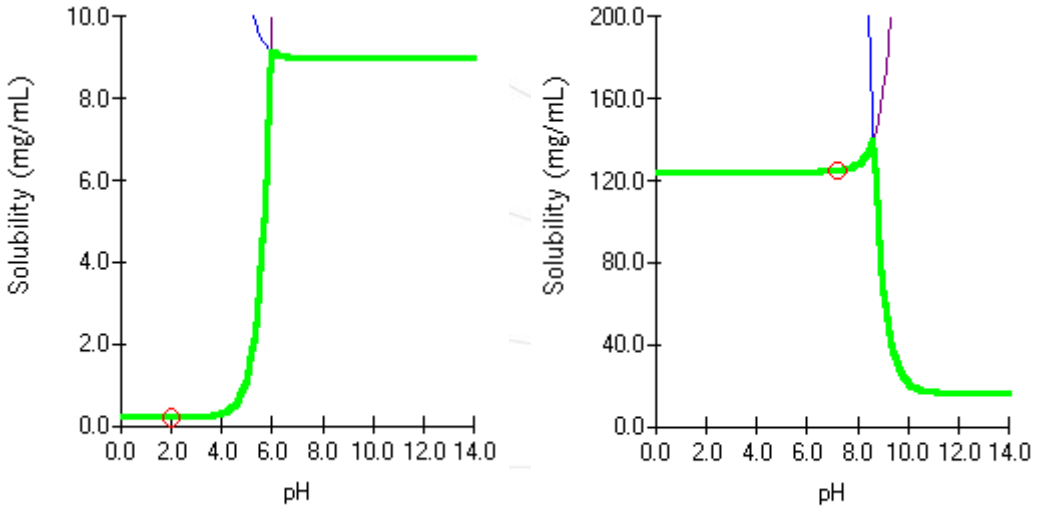
in silico model needs to account for changes in conditions along gastrointestinal tract, between prandial states, and between species:

- pH
- Bile salt concentrations
- Volume of fluid
- Absorptive surface area
- Pore sizes and porosity (for paracellular absorption)
- Enzyme and transporter expression levels
- …….

Solubility

Solubility - pH

Changes in ionization result in chanes in solubility in different regions of the intestine



Changes in bile salt concentrations in different regions of the intestine may result in changes in solubility (especially for more lipophilic compounds)

$$Sol_{bile,pH} = Sol_{aq,pH}\left(1+\frac{MWt_{H_2O}}{\rho_{H_2O}}\times SR\times C_{bile}\right)$$

Mithani, Pharm Res 1996, 13:163-167

pH and bile salt concentrations

fasted:

human:

Compartment Data		
Compartment	pH	Bile Salt (mM)
Stomach	1.30	0.0
Duodenum	6.00	2.800
Jejunum 1	6.20	2.330
Jejunum 2	6.40	2.030
Ileum 1	6.60	1.410
Ileum 2	6.90	1.160
Ileum 3	7.40	0.140
Caecum	6.40	0.0
Asc Colon	6.80	0.0

rat:

Compartment Data		
Compartment	pH	Bile Salt (mM)
Stomach	3.90	0.0
Duodenum	5.89	20.00
Jejunum 1	6.13	17.29
Jejunum 2	6.13	6.980
Ileum 1	5.93	2.820
Ileum 2	5.93	1.300
Ileum 3	5.93	1.240
Caecum	6.58	0.0
Asc Colon	6.23	0.0

dog:

Compartment Data		
Compartment	pH	Bile Salt (mM)
Stomach	3.00	0.0
Duodenum	6.20	5.000
Jejunum 1	6.20	4.050
Jejunum 2	6.20	1.820
Ileum 1	6.40	0.610
Ileum 2	6.60	0.440
Ileum 3	6.68	0.310
Caecum	6.75	0.0
Asc Colon	6.45	0.0

fed:

human:

Compartment Data		
Compartment	pH	Bile Salt (mM)
Stomach	4.90	0.0
Duodenum	5.40	14.44
Jejunum 1	5.40	12.02
Jejunum 2	6.00	10.46
Ileum 1	6.60	7.280
Ileum 2	6.90	5.990
Ileum 3	7.40	0.730
Caecum	6.40	0.0
Asc Colon	6.80	0.0

rat:

Compartment Data		
Compartment	pH	Bile Salt (mM)
Stomach	3.20	0.0
Duodenum	5.00	20.00
Jejunum 1	5.10	17.29
Jejunum 2	5.10	6.980
Ileum 1	5.94	2.820
Ileum 2	5.94	1.300
Ileum 3	5.94	1.240
Caecum	5.90	0.0
Asc Colon	5.51	0.0

dog:

Compartment Data		
Compartment	pH	Bile Salt (mM)
Stomach	5.00	0.0
Duodenum	6.20	15.40
Jejunum 1	6.20	12.50
Jejunum 2	6.20	5.600
Ileum 1	6.40	1.900
Ileum 2	6.60	1.340
Ileum 3	7.05	0.950
Caecum	7.50	0.0
Asc Colon	6.45	0.0

Solubilization Ratio (SR)

in vitro value:

1. measure *in vitro* solubility in media with bile salts with well defined pH and bile salt concentration (e.g. in FaSSIF or FeSSIF media) or use *in silico* estimates of these solubilities

$$Sol_{bile,pH} = Sol_{aq,pH}\left(1+\frac{MWt_{H_2O}}{\rho_{H_2O}}\times SR\times C_{bile}\right)$$

in vivo solubility in compartment with specific pH and bile salt concentration

Buffer solubility at given pH (calc from reference solubility, pKa(s) and solubility factor(s))

$$\frac{Sol_{Biorel}-Sol_{aq}}{Sc_{aq}\times M_w} = SR\times C_{bile}$$

Bile salt solubilization ratio – represents drug's affinity to bile salt miceles

This parameter is required to account for physiological effect of bile salts on solubility and dissolution rate

in vivo concentration of bile salts in given compartment (physiological parameter)

theoretical value:

- if *in vitro* (or *in silico*) FaSSIF and FeSSIV values are not available, SR can be estimated from *logP*

$$\log SR = 2.23 + 0.61\times \log P$$

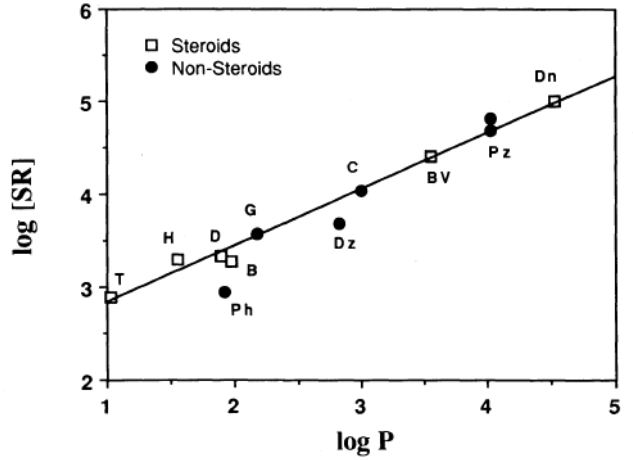


Fig. 1. Log [Solubilization Ratio] in aqueous solution taurocholate solutions as a function of log [octanol/water partition coefficient] for the non-steroidal compounds (circles; Ph = phenytoin, G = griseofulvin, Dz = diazepam, C = cyclosporin A, Pz = pentazocine), along with the prediction line based on steroid data (squares; T = triamcinolone, H = hydrocortisone, D = dexamethasone, B = betamethasone, BV = betamethasone 17-valerate, Dn = danazol); log [SR] = 2.23 + 0.60 log [P].

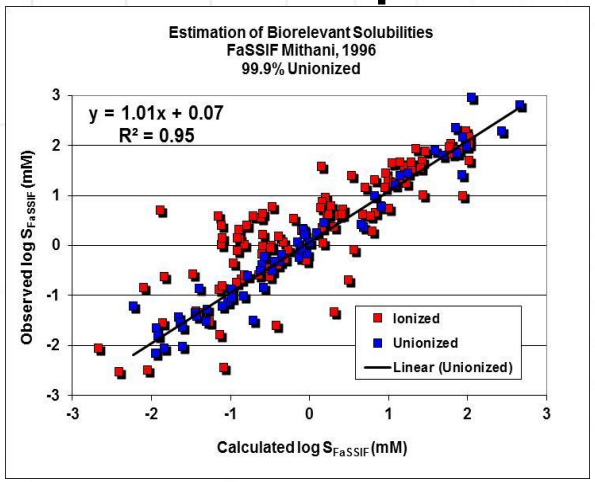
Mithani, Pharm Res 1996, 13:163-167

Predicting Solubilization Ratio

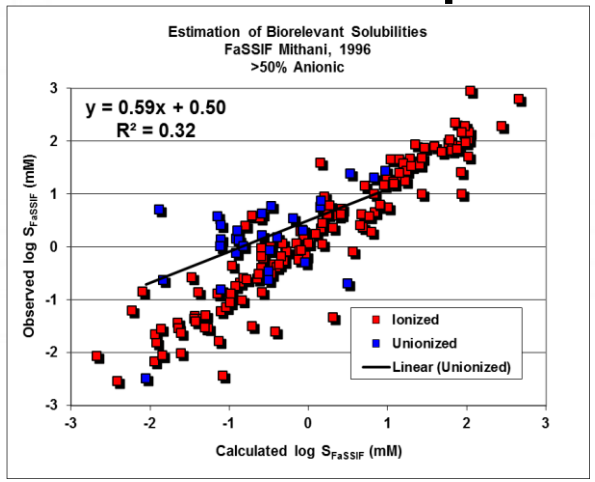
- The simple model for prediction of solubilization ratio from logP of the compound was evaluated using larger set of compounds (160 drug like molecules)
- The model performed well for neutral compounds, but resulted in higher errors of prediction for ionized compounds
- To estimate SR for ionized compounds, use experimental FaSSIF or FeSSIF solubilities, or *in silico* model that accounts for the ionization effects (i.e. model that was included ionized compounds in the training set)

Blue points represent different types of compounds in individual plots below

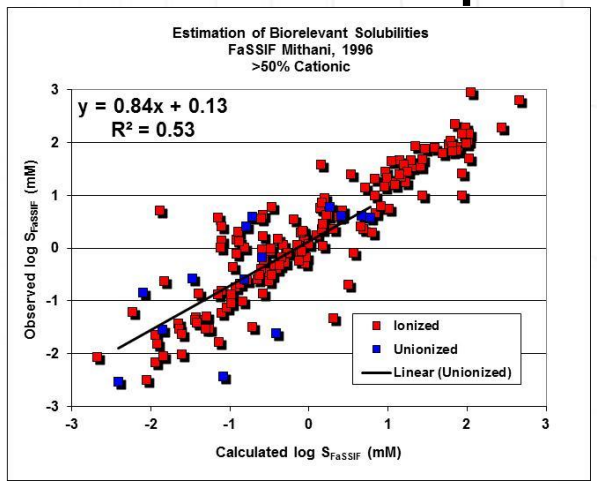
Un-ionized at pH = 6.5



>50% anionic at pH = 6.5



>50% cationic at pH = 6.5

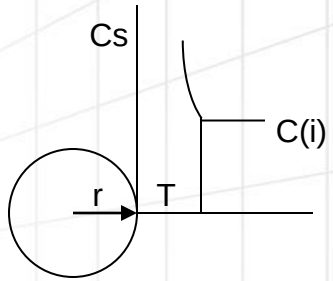


Dissolution

Dissolution

Dissolution rate coefficient (not a constant because it changes at every time step) in intestinal lumen compartment number *i* for particle size bin *j:*

$$\frac{dM_D}{dt} = \frac{D_w}{\rho r_t T}\frac{(1+2s)}{s}(C_s - C_l)M_{u,t}$$



$T = r_{0j}$

D = diffusion coefficient

C_S = solubility at *local* pH

$C_{(i)}$ = lumen concentration in compartment *i*

ρ = particle density (***density of API crystals***)

r_j = spherical particle *radius* for particle size bin *j*

T = diffusion layer thickness (= particle radius up to a limit)

s = shape factor (***Length/diameter****) **–** for spherical particles = 1

*in the original Johnson equation, *s'=Length/radius* and the term is $\frac{2(1+s')}{s'}$

Dissolution Models

1. Johnson (Nernst-Brunner model expanded by accounting for changing particle size due to dissolution and for non-spherical particles)

$$\frac{dM_D}{dt} = \frac{D_w}{\rho r_t T}\frac{(1+2s)}{s}(C_s - C_l)M_{u,t}$$

Lu, Pharm Res 1993, 10:1308-1314

1. Wang-Flanagan (applies only to ***spherical*** particles)

$$\frac{dM_D}{dt} = \frac{3D_w}{\rho}\frac{1}{r_t}\left(\frac{1}{r_t}+\frac{1}{T}\right)(C_s - C_l)M_{u,t}$$

Wang, J Pharm Sci 1999, 88:731-738

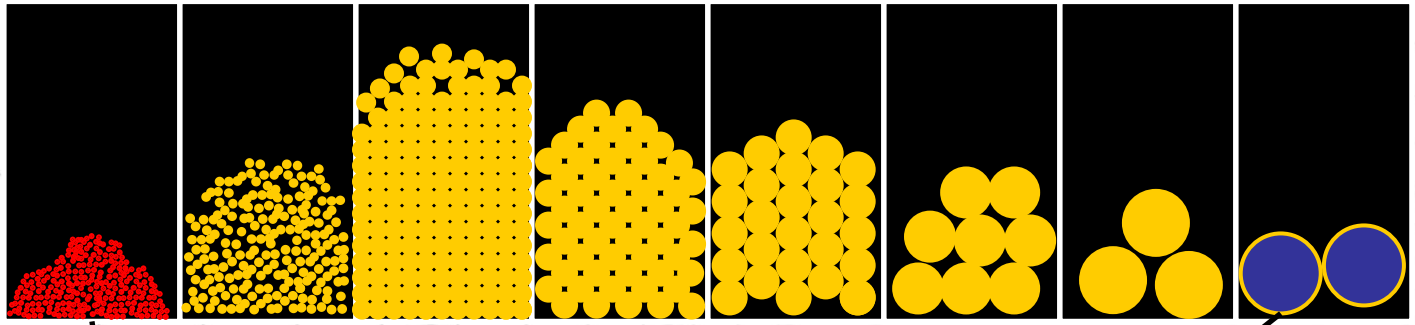
2. Z-Factor (Takano) (particle size applies ONLY through adjustment of solubility)

$$\frac{dM_D}{dt} = Z(C_s - C_l)M_{u,t}$$

Takano, Pharm Res 2006, 23:1144-1156

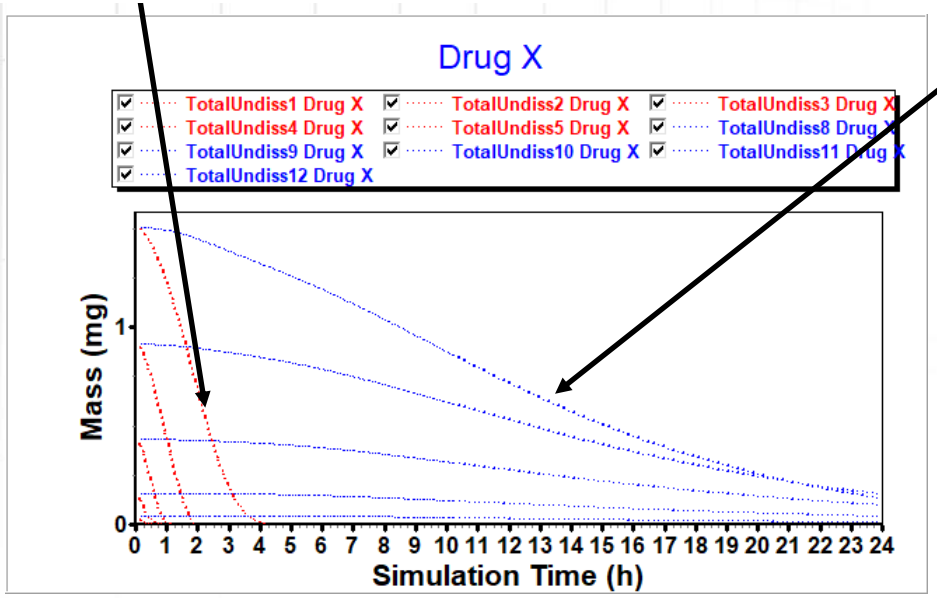
z represents $\frac{3D_w}{\rho r T}$ and is determined by fitting to *in vitro* dissolution data.

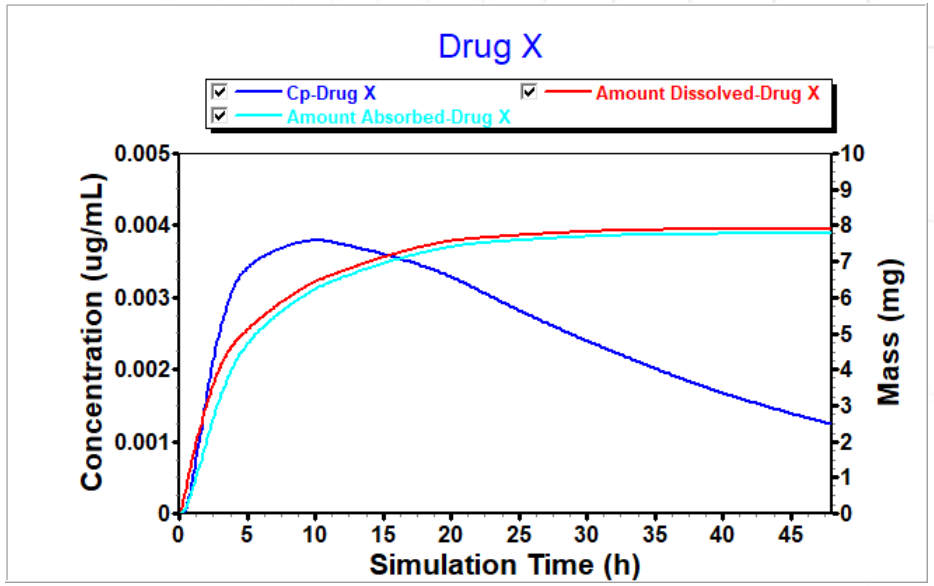
Dissolution with Particle Size Distribution



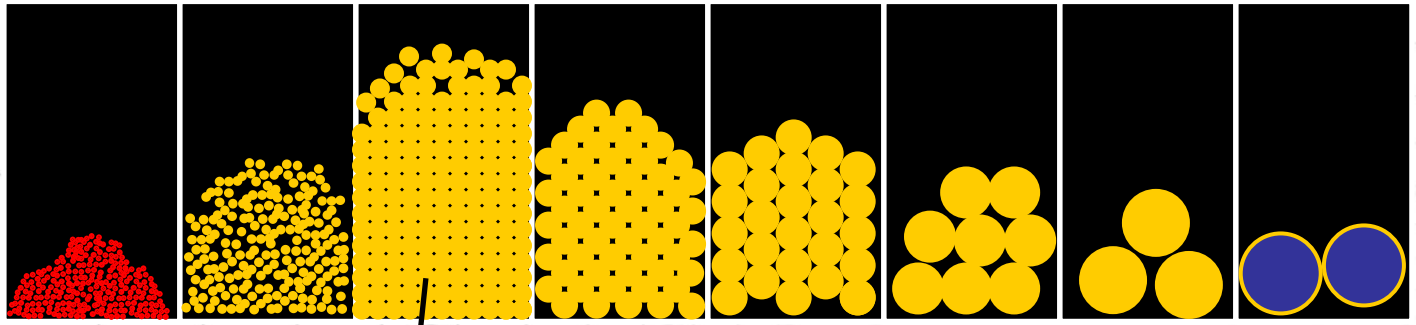
Small particles will be dissolving quickly

The large particles may take time to dissolve

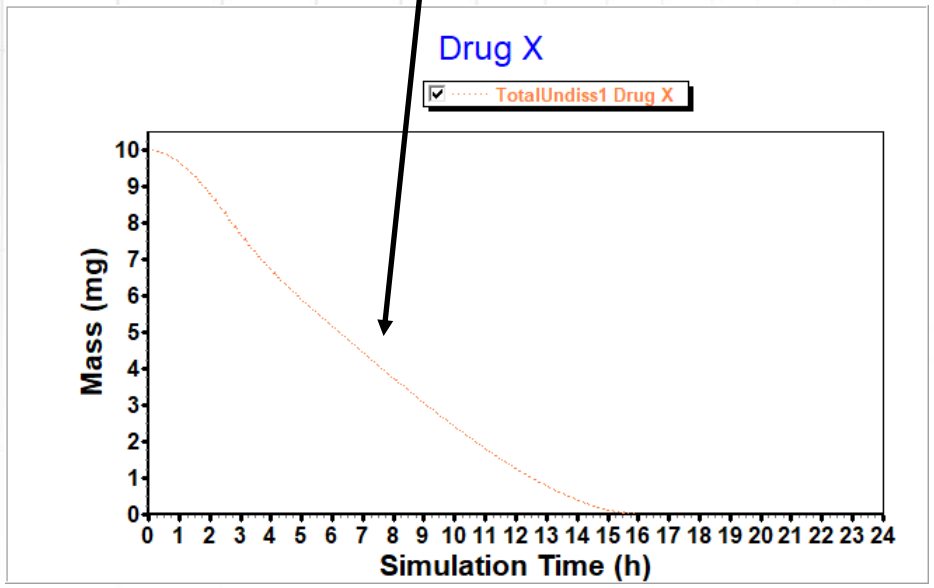


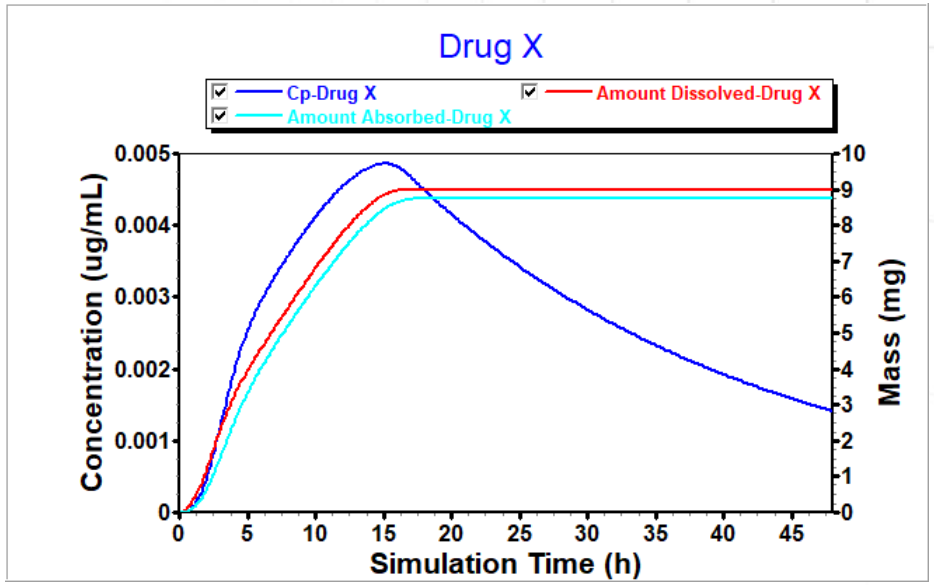


Dissolution with Particle Size Distribution



Representing all particles with mean radius





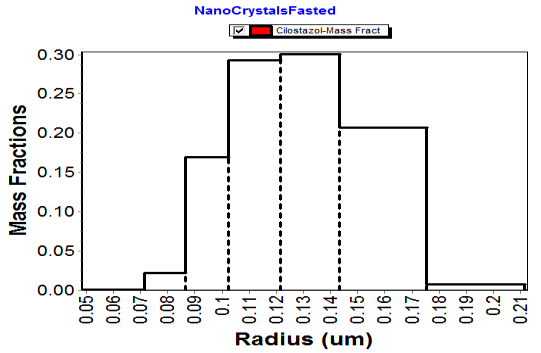
Predicting *in vivo* Dissolution: Particle Size Distribution

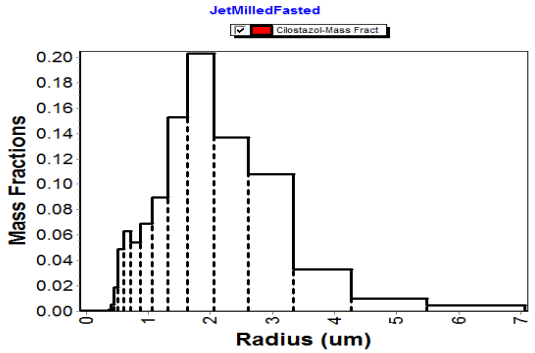
$$\frac{dM_D}{dt} = \frac{D_w}{\rho r_t T}\frac{(1+2s)}{s}(C_s - C_l)M_{u,t}$$

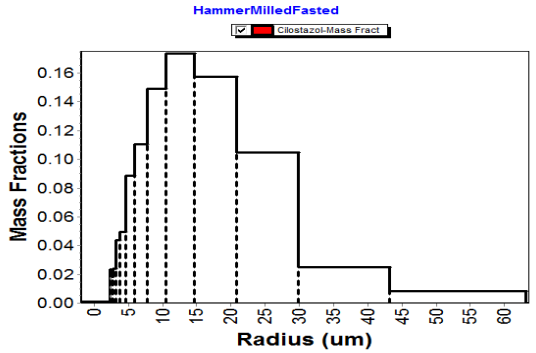
Lu, Pharm Res 1993, 10:1308-1314

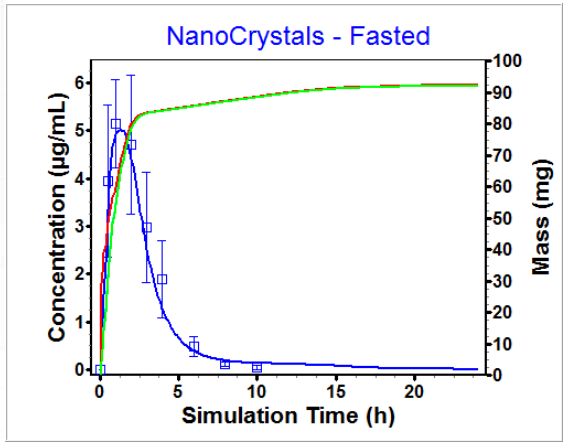
Prediction of *in vivo* performance for 3 cilostazol formulations with different API particle size distributions administered in dog

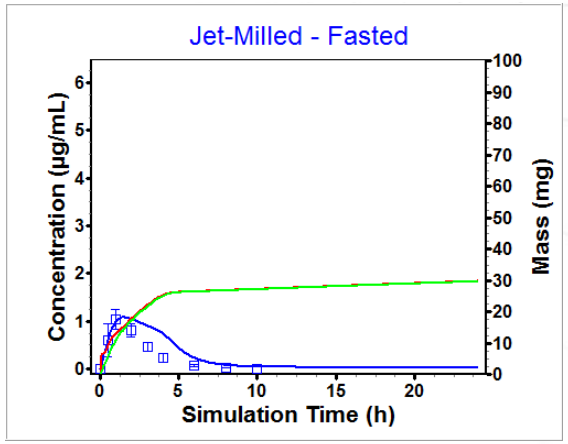
- *in vivo* dissolution rate and extent is calculated from particle size distribution for each formulation and *in vivo* drug solubility
- *in vivo* drug solubility is changing to account for changes in pH and bile salt concentration as the drug is moving through the intestine

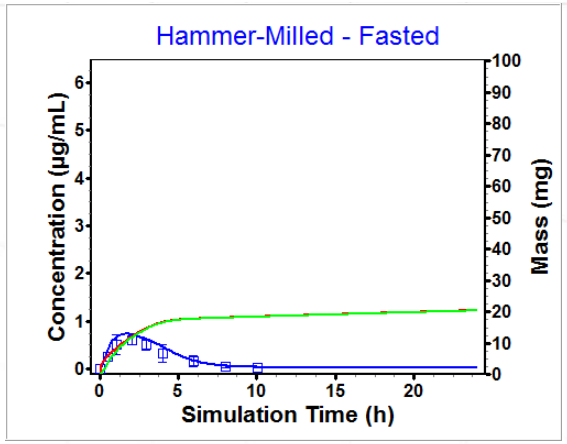












Observed data from Jinno, J Contr Rel 2006, 111: 56-64

Simulation results from GastroPlus v9.0

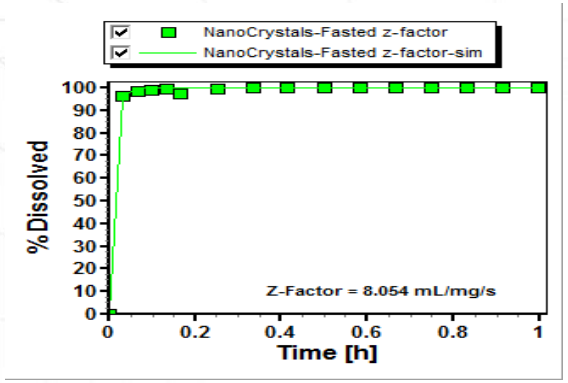
Predicting *in vivo* Dissolution: z-factor

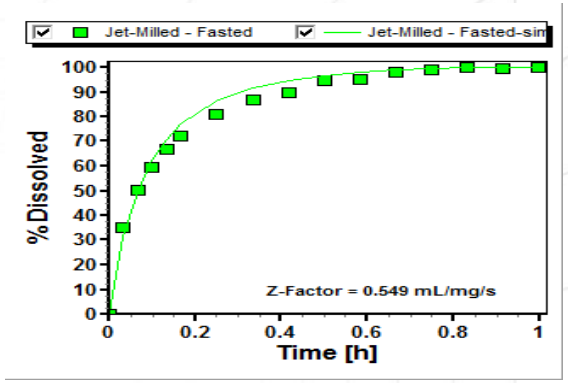
$$\frac{dM_D}{dt} = Z(C_s - C_l)M_{u,t}$$

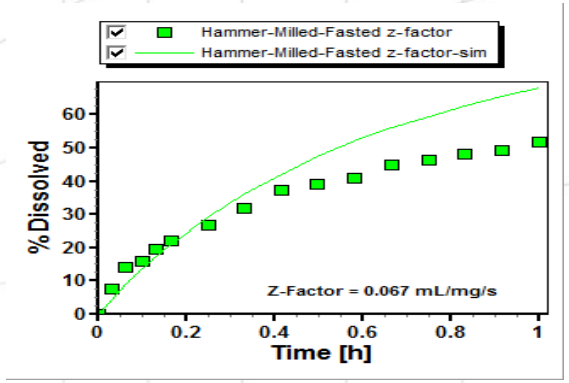
Takano, Pharm Res 2006, 23:1144-1156

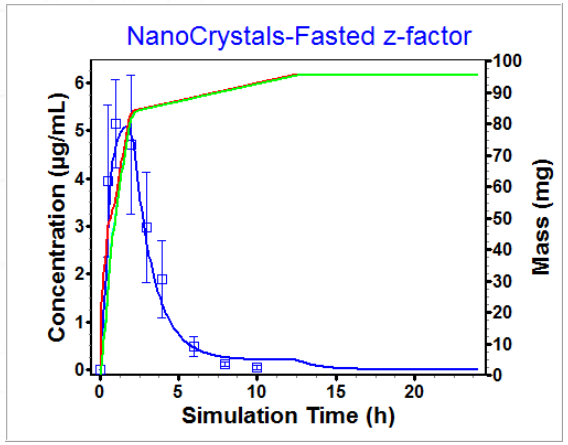
- *in vivo* dissolution rate and extent is calculated from z-factor fitted to *in vitro* dissolution profile for each formulation and *in vivo* drug solubility
- *in vivo* drug solubility is changing to account for changes in pH and bile salt concentration as the drug is moving through the intestine

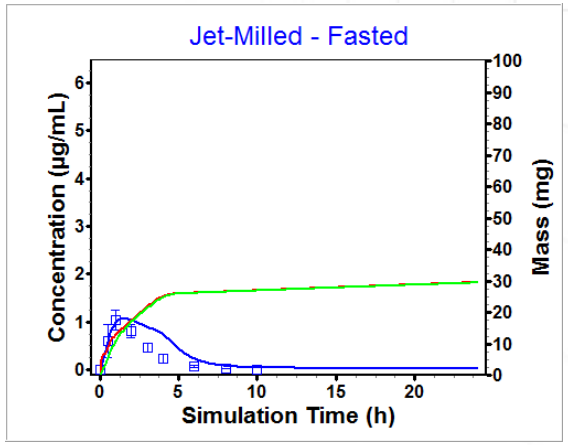
Prediction of *in vivo* performance for 3 cilostazol formulations with different API particle size distributions administered in dog

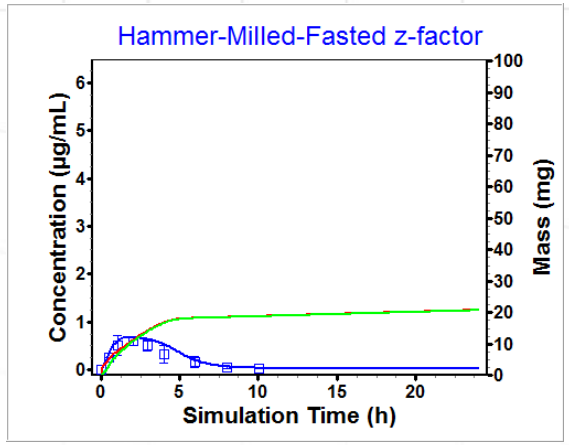












Observed data from Jinno, J Contr Rel 2006, 111: 56-64

Simulation results from GastroPlus v9.0

Predicting *in vivo* Dissolution: P-PSD

- The *in vitro* dissolution profiles showed multi-phasic behavior
- Single z-factor is not able to describe the entire dissolution profile for any of the tested batches

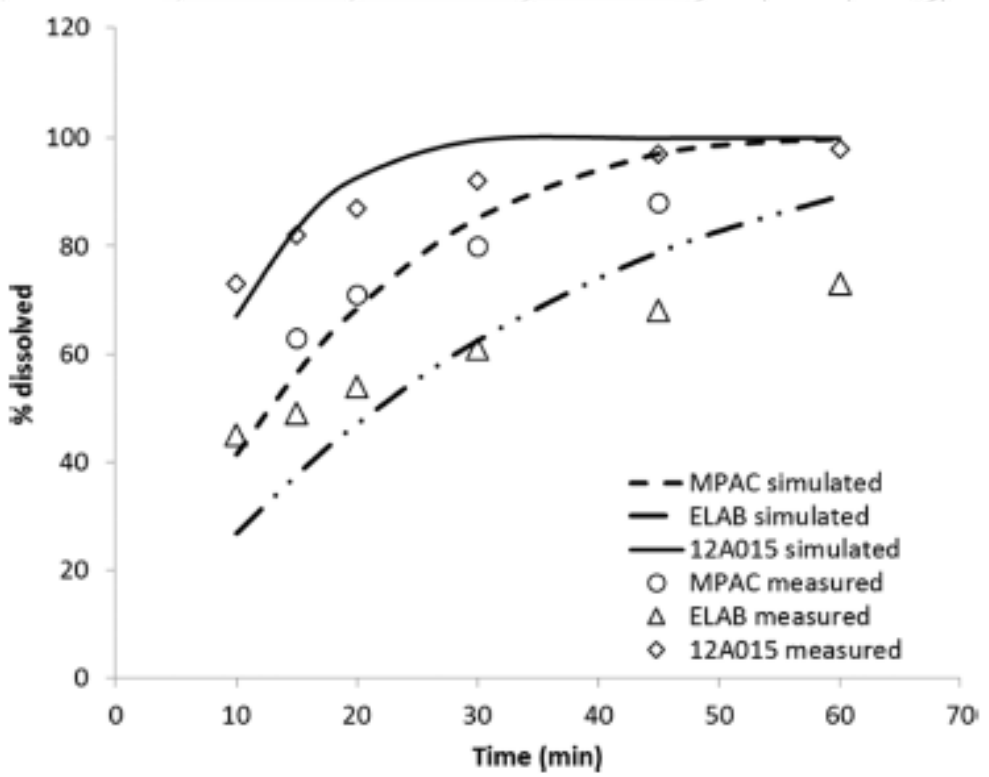
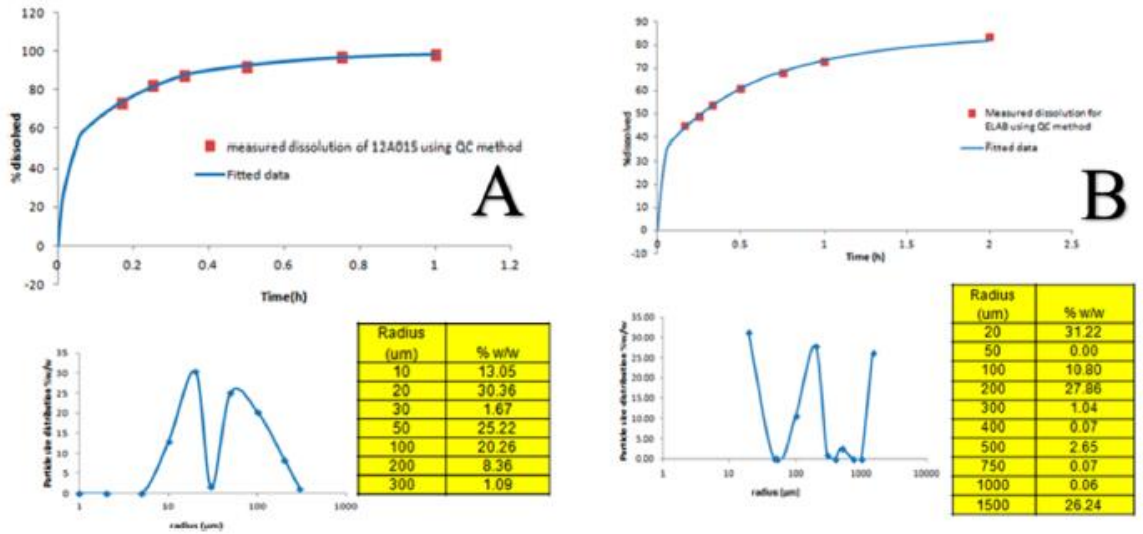


Figure 8. Z-factor fit for batches 12A015 ($Z = 1 \times 10^{-3}$ mL/mg/s), ELAB ($Z = 3.74 \times 10^{-4}$ mL/mg/s), and MPAC ($Z = 5e\text{-}4$ mL/mg/s).

Pepin et al. Mol Pharmaceutics 2016, 13:3256-3269

Predicting *in vivo* Dissolution: P-PSD

- Theoretical particle size distribution was fitted to one set of *in vitro* dissolution data
- The applicability of the fitted PSD was validated by predicting *in vitro* dissolution under different conditions
- The fitted PSD was used as an in put in *in vivo* simulation



Radius (um)	% w/w
10	13.05
20	30.36
30	1.67
50	25.22
100	20.26
200	8.36
300	1.09

Radius (um)	% w/w
20	31.22
50	0.00
100	10.80
200	27.86
300	1.04
400	0.07
500	2.65
750	0.07
1000	0.06
1500	26.24

Figure 4. Fitting of dissolution profile for batch 12A015 (A) and ELAB (B) in the QC dissolution method with a theoretical particle size distribution. Note: the value presented at the 2 h time point for batch ELAB is from an infinity spin (15 min, 250 rpm).

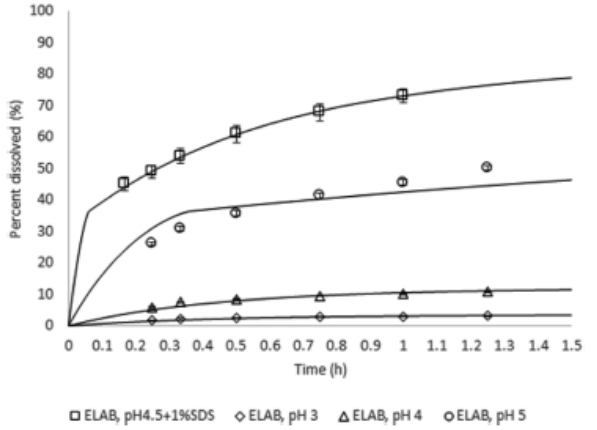


Figure 5. Simulation of ELAB dissolution in pH 3, pH 4, and pH 5 using particle size distribution derived from QC dissolution method profile (pH 4.5 + 1% SLS) vs observed data ±1 SD.

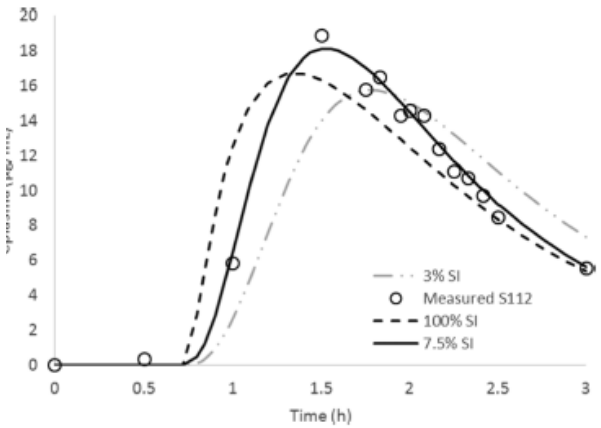
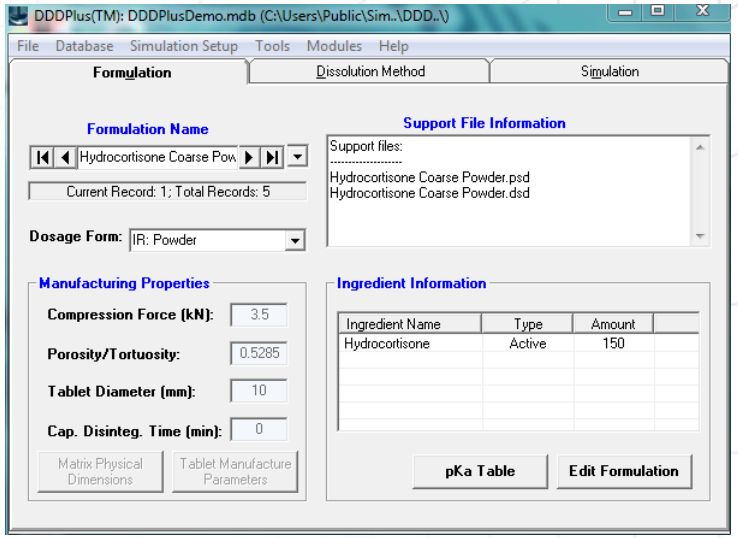


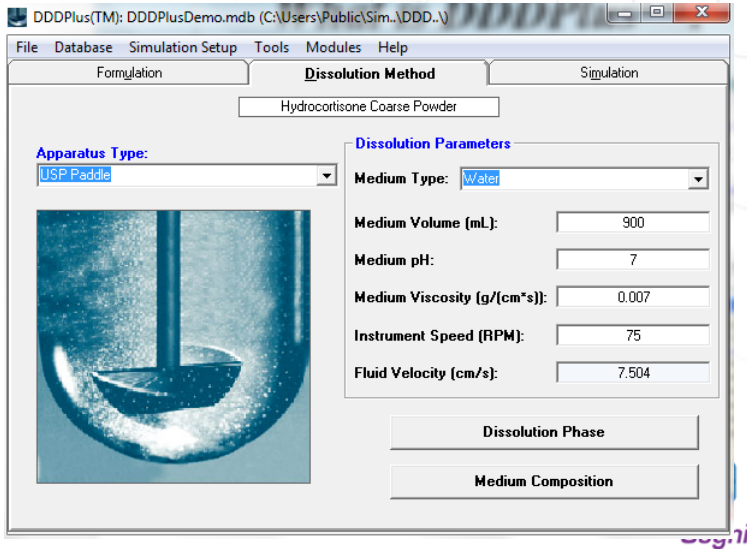
Figure 7. Simulated PK profile vs measured plasma concentrations for S112 following administration of 400 mg 12A015 tablet using Option A.

Pepin et al. Mol Pharmaceutics 2016, 13:3256-3269

Mechanistic Models are Important for *in vitro –in vivo* Extrapolation

- Extent and rate of *in vitro* dissolution for active pharmaceutical ingredient (API) and excipients:
  - Multiple particle size distributions for ingredients
  - Dynamic microclimate pH calculation
  - pH of buffers from composition of acids, bases, and salt equivalents.
  - Selection of USP and user defined experimental apparatus
  - Micelle-facilitated dissolution through addition of surfactants in medium
  - Multiple experimental phases allow for dissolution experimental design
- Differences in dosage forms:
  - IR powders, tablets, capsules, and coated beads
  - CR polymer matrix and bilayer tablet systems
  - DR coated tablets





Precipitation

When Precipitation Plays a Role

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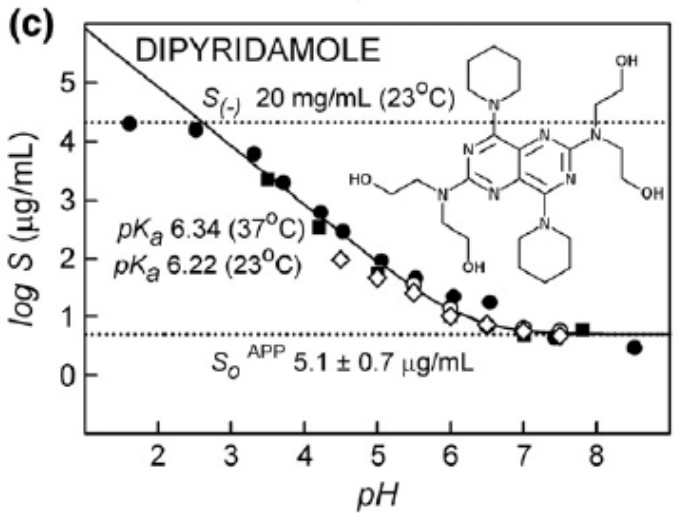
Solubility of sparingly-soluble ionizable drugs ☆

Alex Avdeef *

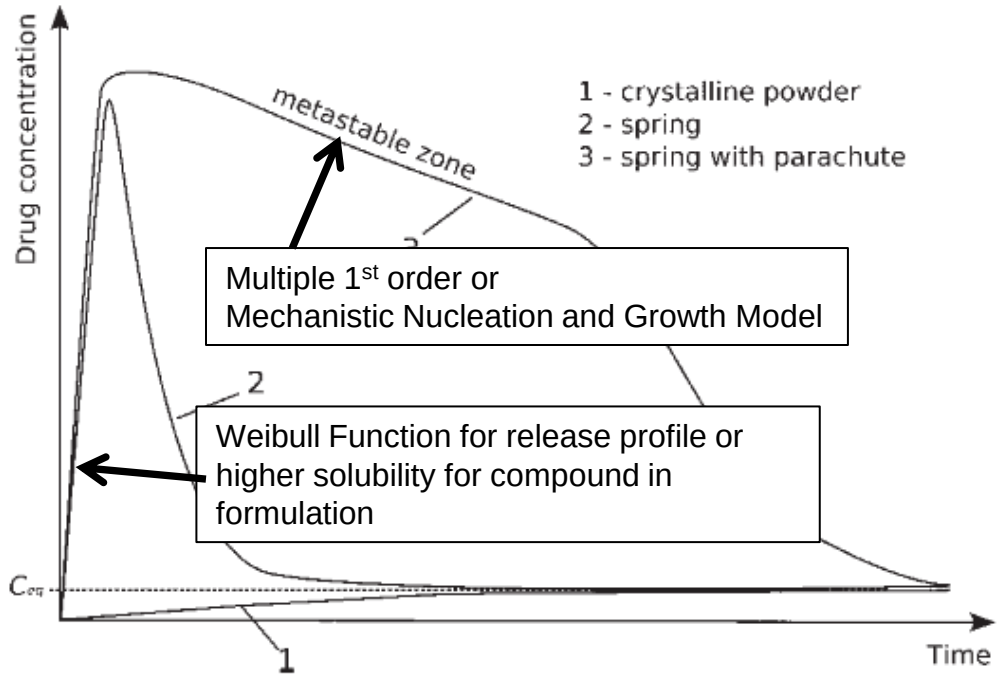
pION INC, 5 Constitution Way, Woburn, MA 01801 USA

Received 23 March 2007; accepted 10 May 2007
Available online 29 May 2007



Compartment Data		
Compartment	**pH**	**Bile Salt (mM)**
Stomach	1.30	0.0
Duodenum	6.00	2.800
Jejunum 1	6.20	2.330
Jejunum 2	6.40	2.030
Ileum 1	6.60	1.410
Ileum 2	6.90	1.160
Ileum 3	7.40	0.140
Caecum	6.40	0.0
Asc Colon	6.80	0.0

- Supersaturating Drug Delivery Systems (Salts, Cocrystals, Lipid formulations, SMEDDS, SNEEDS, Solid Dispersions …)



Brouwers J, J. Pharm. Sci. 98(8):2549 (2009)

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- **De Yoreo JJ, (2003):** "Whether considering nucleation or growth, the reason for the transformation from solution to solid is the same, namely the free energy of the initial **bulk** solution phase is greater than the sum of the free energies of the crystalline **solid** phase plus the final solution phase (Gibbs 1876, 1878).

Principles of Crystal Nucleation & Growth

$$\Delta g = \Delta g_b + \Delta g_s$$
$$= -\{[(4/3)\pi r^3]/\Omega\}\Delta\mu + 4\pi r^2\alpha$$

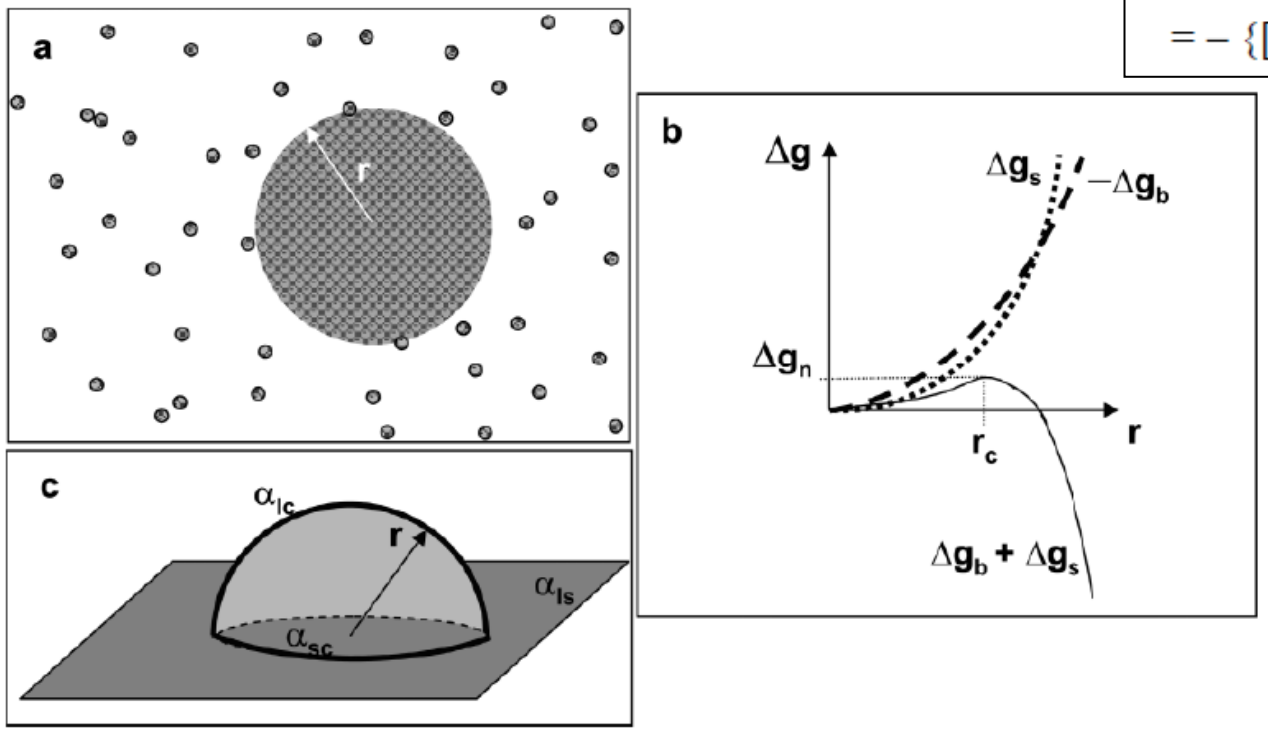


Figure 6. (a) Formation of a spherical nucleus of radius r from a solution leads to the free energy changes shown in (b). The cross-over of the bulk and surface terms combined with their opposing signs leads to a free energy barrier. (c) Heterogeneous formation of a hemispherical nucleus at a foreign substrate.

Ω = Molar Volume
α = interfacial free energy
$\Delta\mu$ = change chemical potential of crystal species
lc = liquid-crystal
sc = substrate-crystal
ls = liquid-substrate

De Yoreo JJ, Rev. Mineralogy Geochem. 54:57 (2003)

Precipitation Models

GastroPlus® First Order Precipitation:

$$\frac{dM_i}{dt} = \left(\frac{V_i}{T_{precip}}\right)\left(C_i - S_i\right)$$

M_i – Mass in compartment i
V_i – Volume of compartment i
T_p – Precipitation Time

Mechanistic Nucleation and Growth (different forms of this model are presented in literature):

$$\frac{dN_{nc}}{dt} = \left(\frac{R^*}{\lambda + R^*}\right) D_{mono} N_A C_{aq}^2 \left(\frac{k_B T}{\gamma}\right)^{1/2} \ln\left(\frac{C_{aq}}{S_{aq}}\right)$$

$$\times \exp\left[-ECF \times \frac{16\pi}{3}\left(\frac{\gamma}{k_B T}\right)^3 \left\{\frac{(\nu_m)}{\ln\left(C_{aq}/S_{aq}\right)}\right\}^2\right]$$

- D_{mono} = diffusion coefficient of the monomer (3.42E-4 cm^2/min)
- N_A = Avogadro's number (6.02E+23 molecs/mole)
- C_{aq} = Conc. of free monomer (moles/cm^3)
- S_{aq} = Solubility at the current pH
- k_b = Boltzman's constant (1.38E-21 cJoules/Deg. K)
  (Note: Joule = Newton-meter)
- T = 310° K
- γ = Interfacial tension (Newtons/cm)
- ν_m = Molecular volume = (V_m/N_A = XX cm^3/molec / 6.02E+23 molec/mole)
- R^* = Critical radius (cm)
- λ = Effective radius from Lindfors (cm)
- ECF = exponential correction factor

How Do We Account for Excipient Effects on Nucleation?

- Lindfors, 2008
  - If the rate of association/dissociation is entirely controlled by the diffusive flow of monomers from the cluster surface to the bulk and vice versa, the net flow of monomers to a cluster is: $Q = 4\pi R D_0 (C_b - S_0)$
  - Where R is the cluster radius, D_0 is the monomer diffusion coefficient, C_b is the monomer concentration in the bulk solution, and S_0 is solubility.

$$\varphi = \frac{R^*}{R^* + \lambda}$$

  - Effective size = λ
  - $Q = \varphi 4\pi R D_0 (C_b - S_0)$
  - If $R^* >> \lambda$ the transport is controlled by diffusion,
  - but if $R^* << \lambda$ the surface integration is the limiting process.
  - λ = 0.006 to 6.0 microns without nucleation inhibitors
  - λ = 6 to 1000 microns without PVP

in vitro Precipitation Experiments

Transfer assay

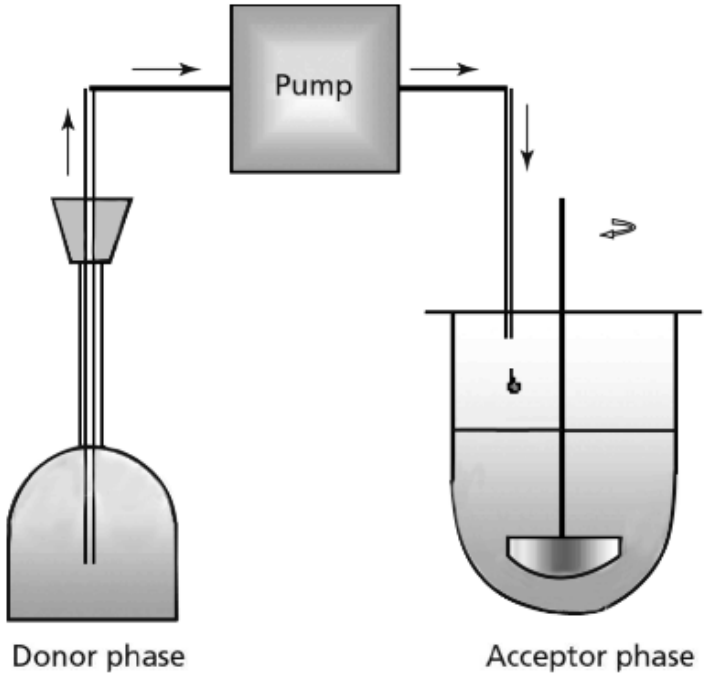
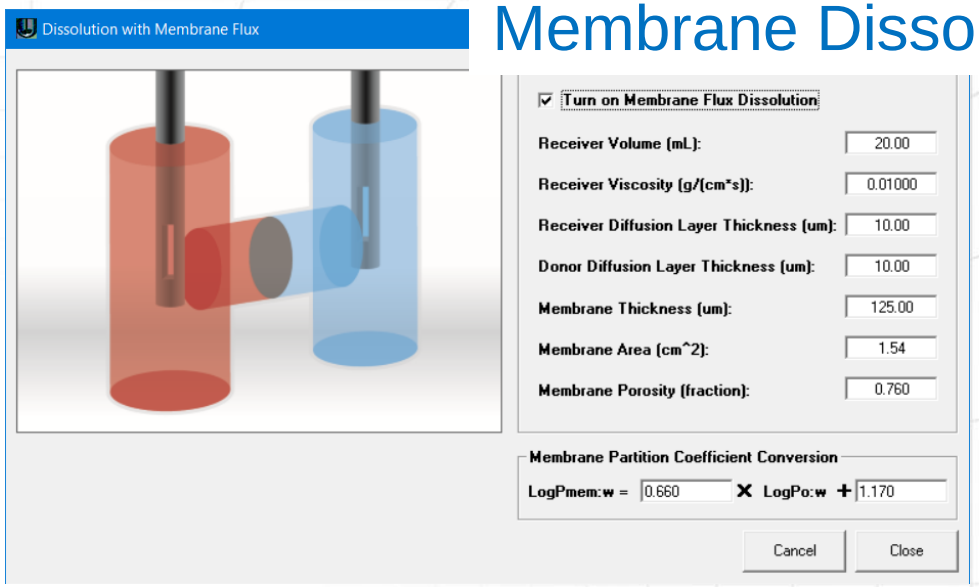


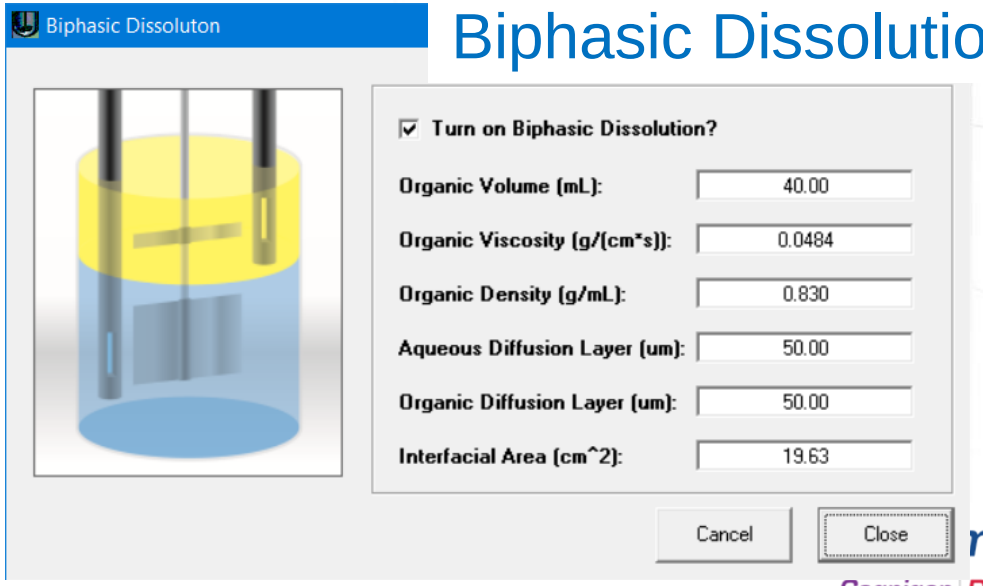
Figure 2 Experimental set-up to examine precipitation.

Figure from Kostewicz E, et al., J. Pharm. Pharmacol. 56:43 (2004)

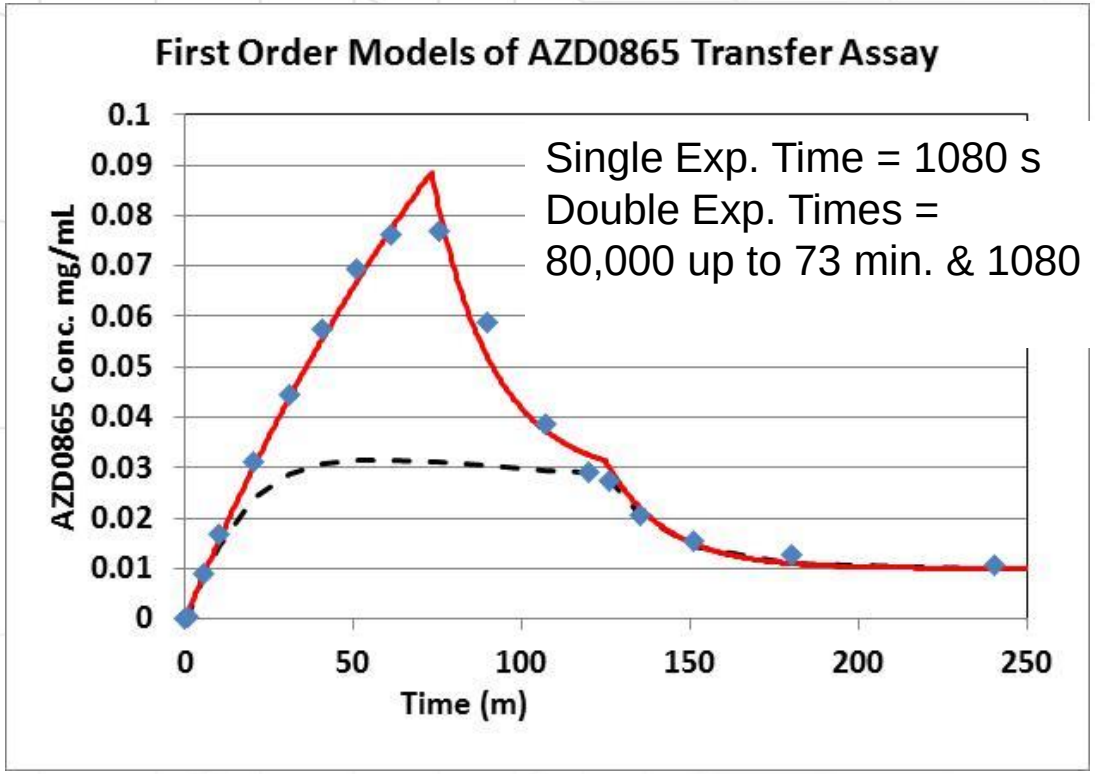
Membrane Dissolution

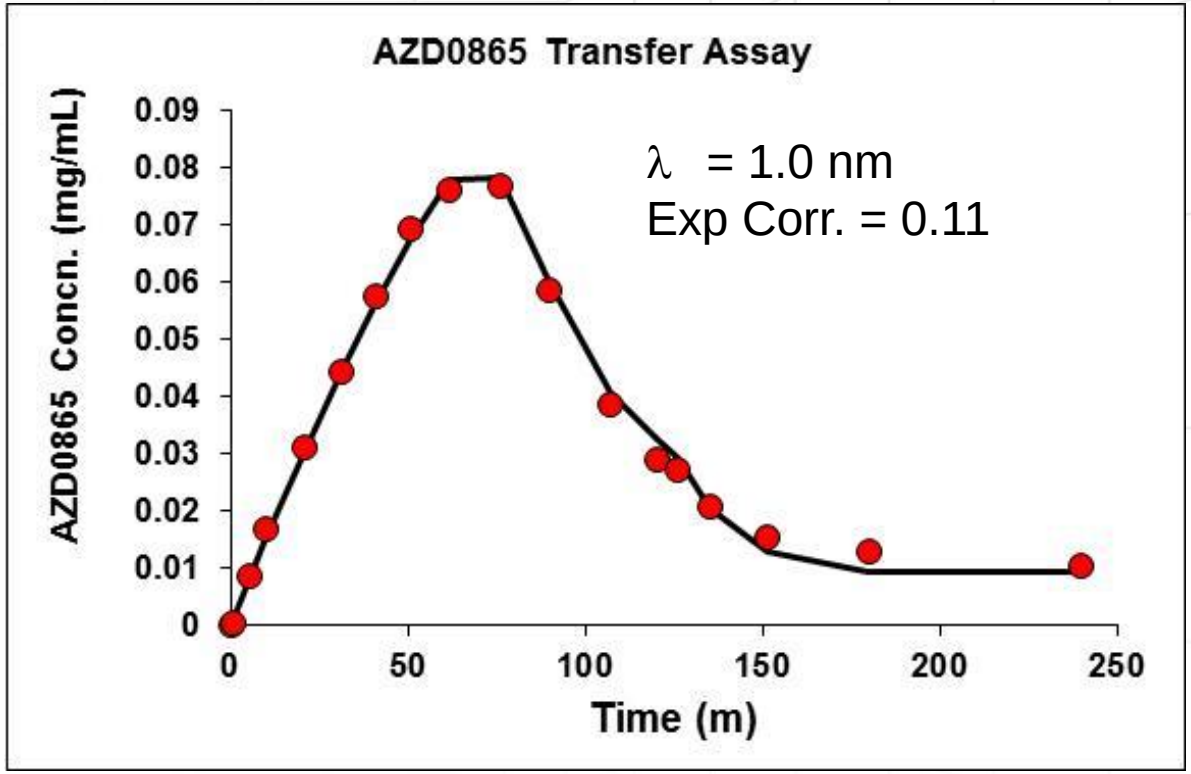


Biphasic Dissolution



Transfer Assay

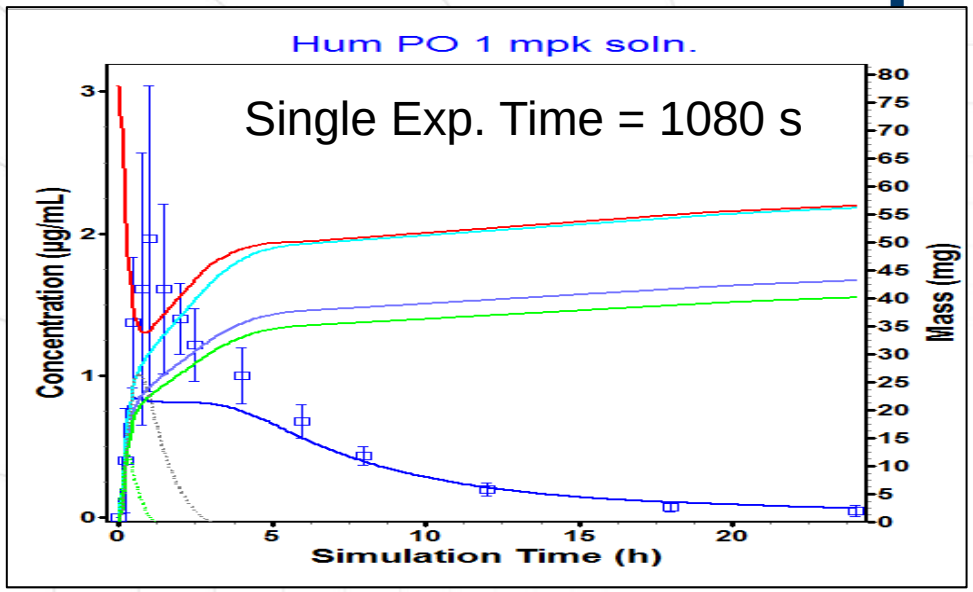


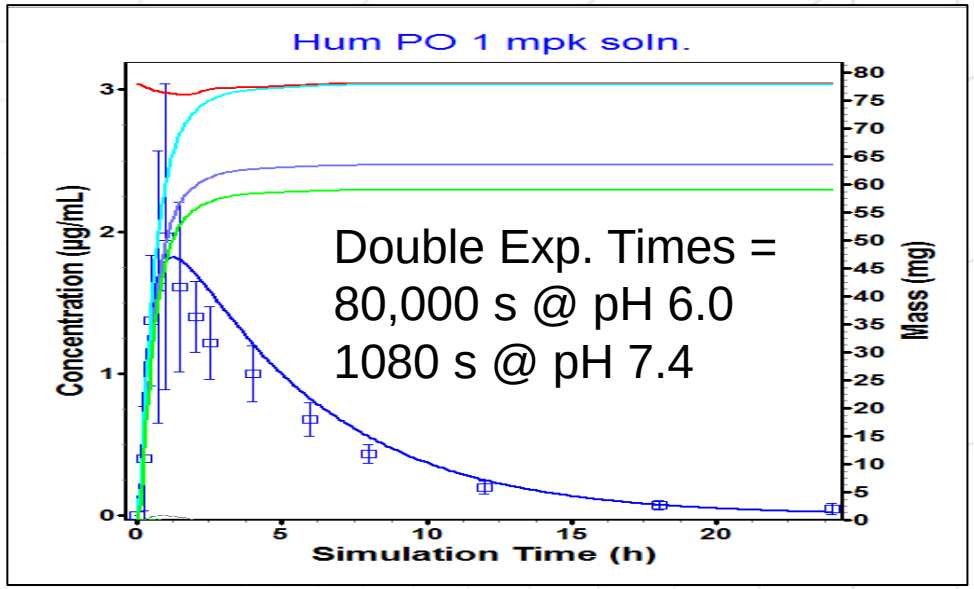


Data from Carlert S. Pharm. Res. 27:2119 (2010)

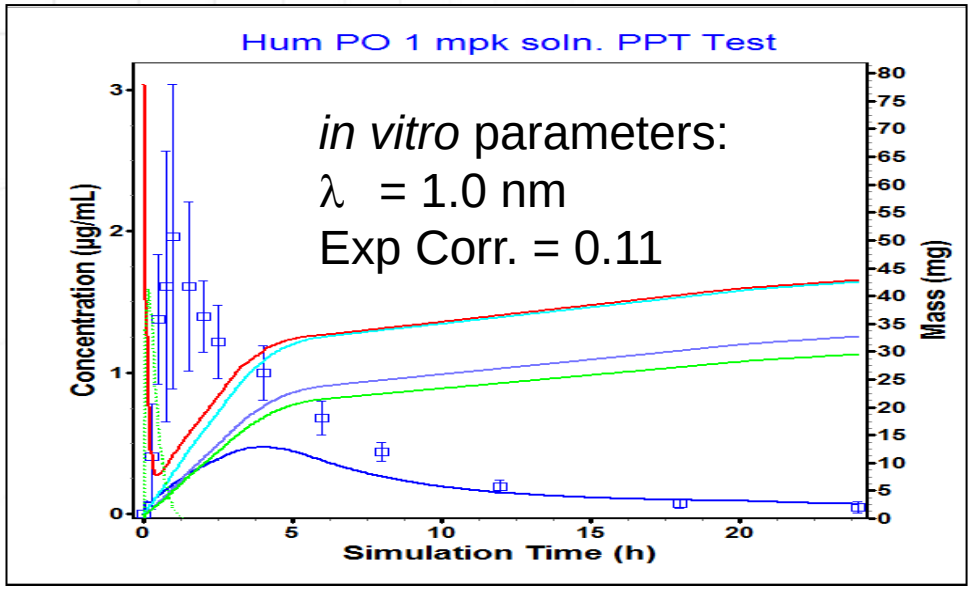
AZD0865 Precipitation *in vivo*

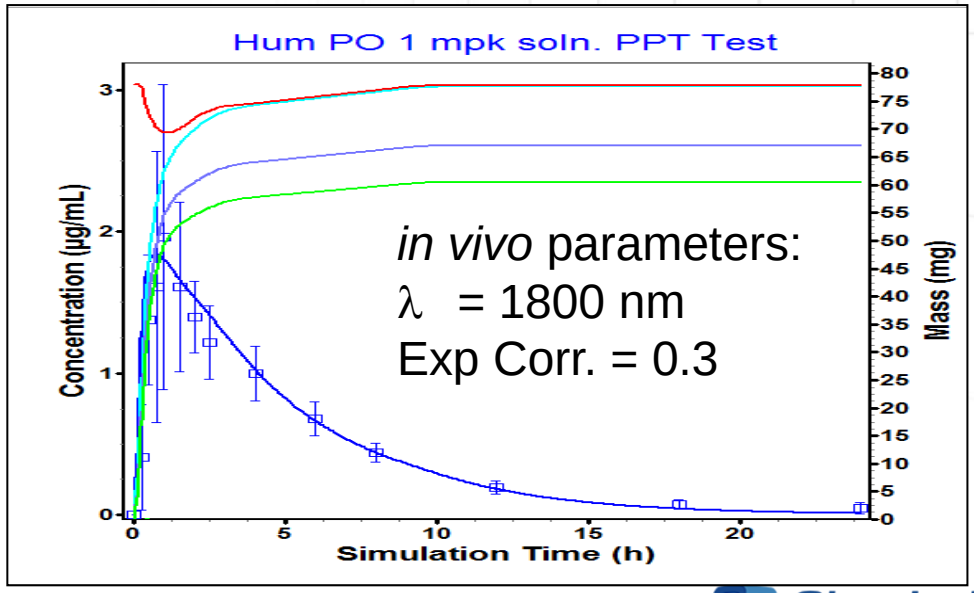
First order model





Mechanistic model

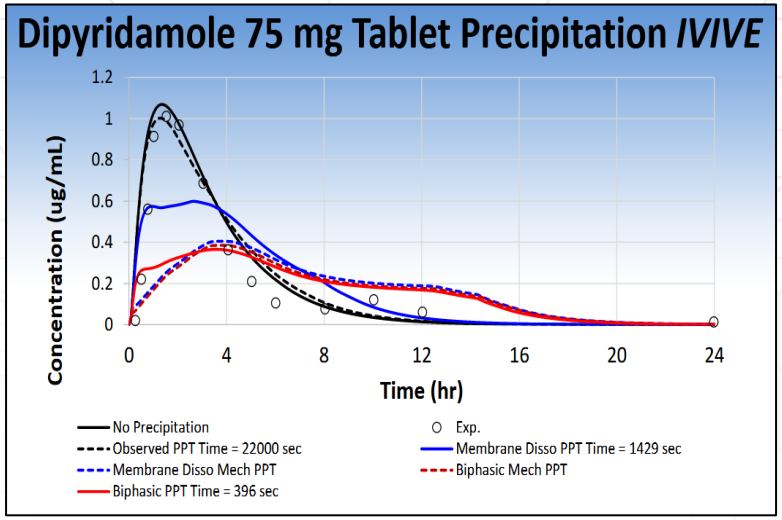


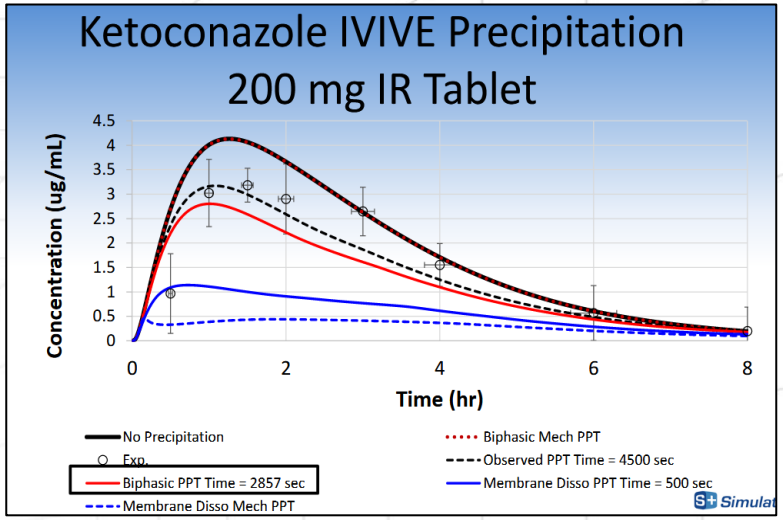


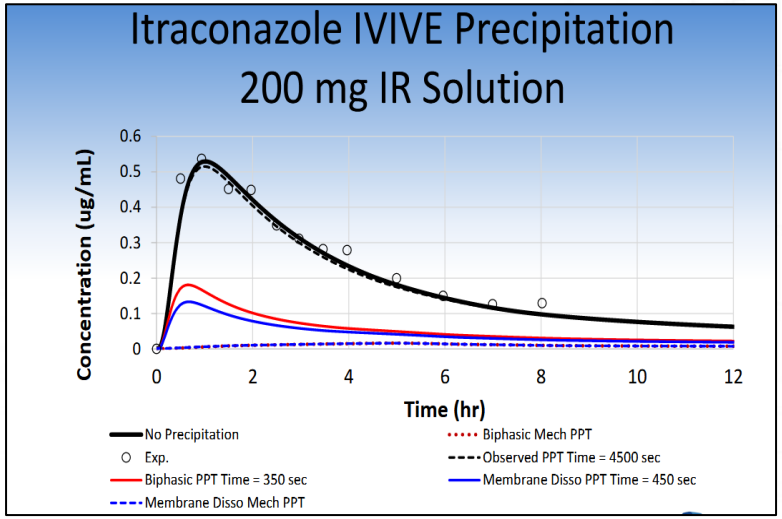
Amounts: red-dissolved, cyan-absorbed, blue-enteric portal vein, green-entering systemic circulation
Dark blue line and points – plasma concentration

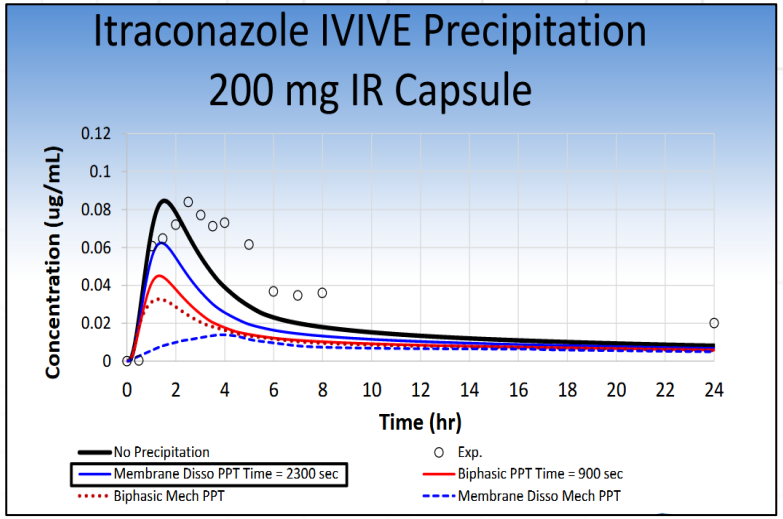
Biphasic and Membrane Dissolution

- Two-stage biphasic or membrane dissolution experiment were used to measure *in vitro* precipitation behavior
- DDDPlus™ was used to analyze the *in vitro* data using first order and mechanistic precipitation models
- The *in vitro* parameters were used to predict the *in vivo* exposure
- Different *in vitro* experiment and model provided accurate *in vivo* prediction for different compound/formulation





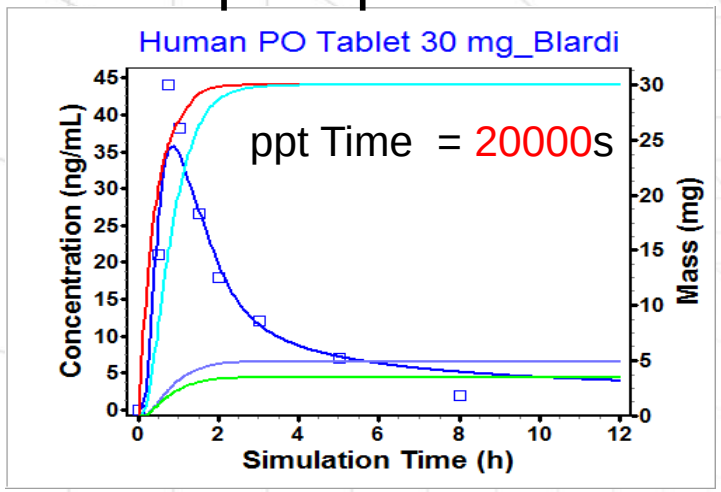


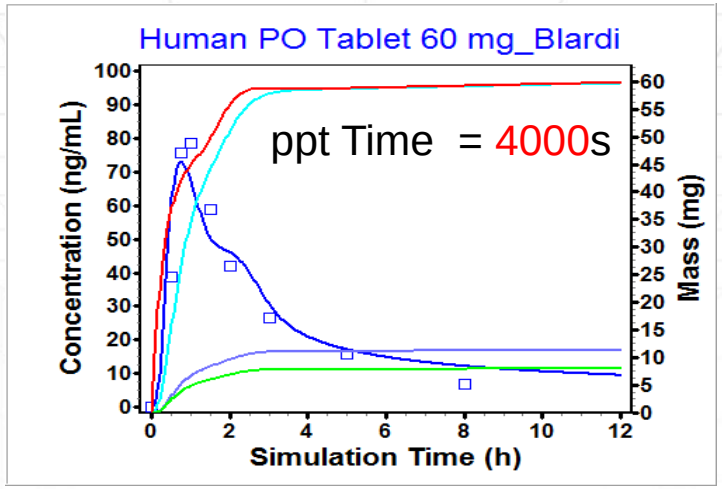


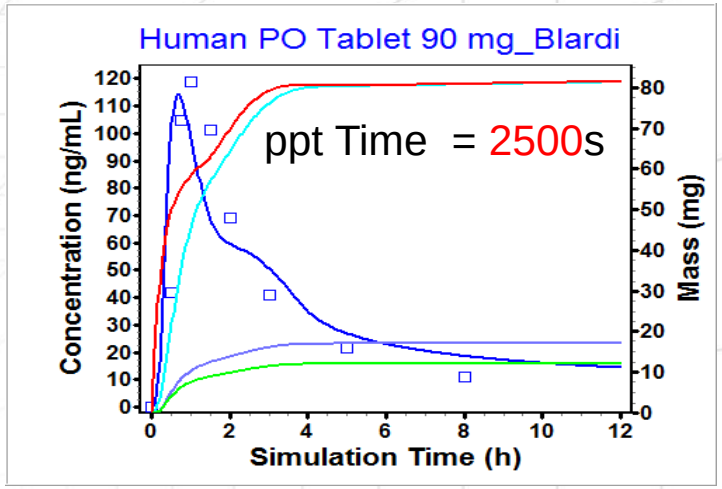
Webinar: Mullin – Best Practices for Membrane & Biphasic In Vitro Dissolution with DDDPlus™ & GastroPlus®
https://www.simulations-plus.com/resource/best-practices-for-membrane-biphasic-in-vitro-dissolution-with-dddplus-gastroplus/

Nimodipine Solid Dispersion

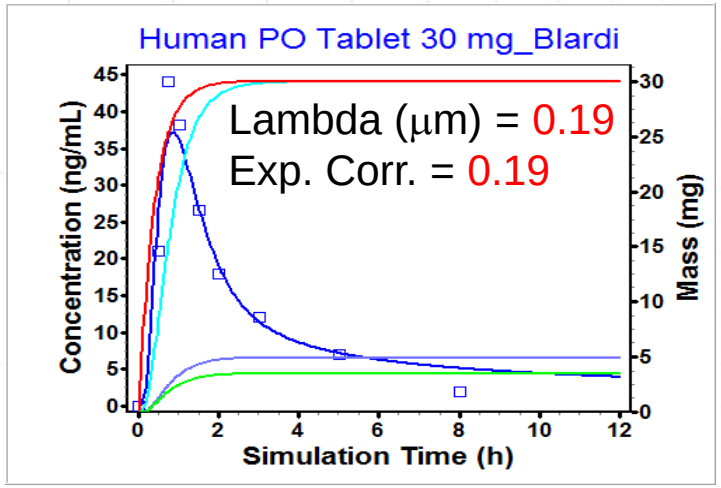
1st order precipitation

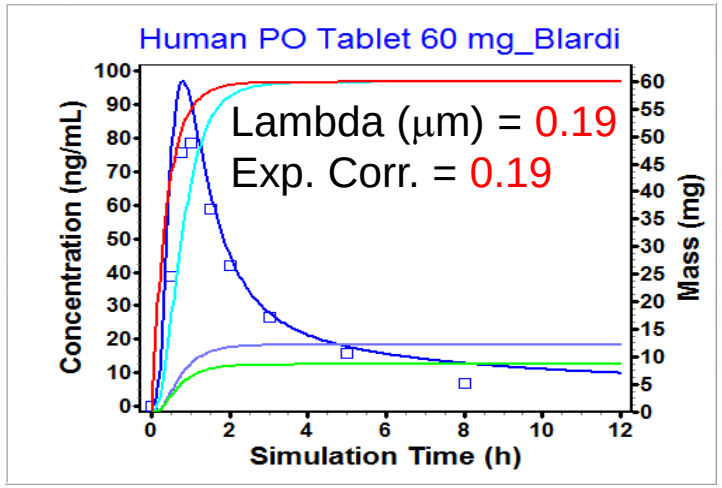


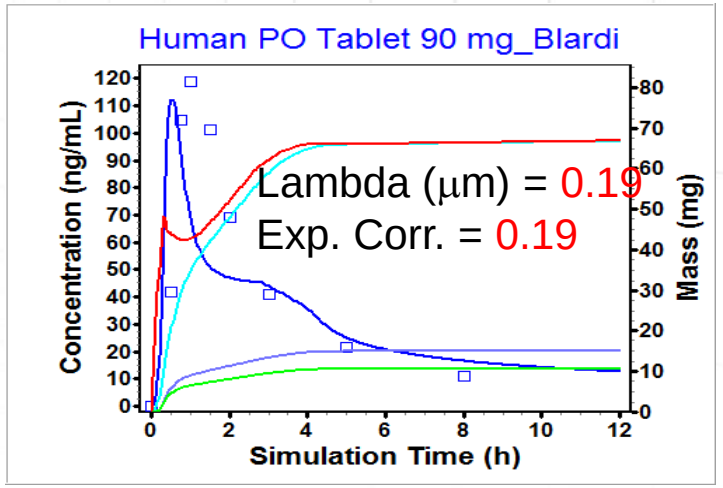




Mechanistic nucleation







Simulation results from GastroPlus v9.0

Amounts: red-dissolved, cyan-absorbed, blue-enteric portal vein, green-entering systemic circulation
Dark blue line and points – plasma concentration

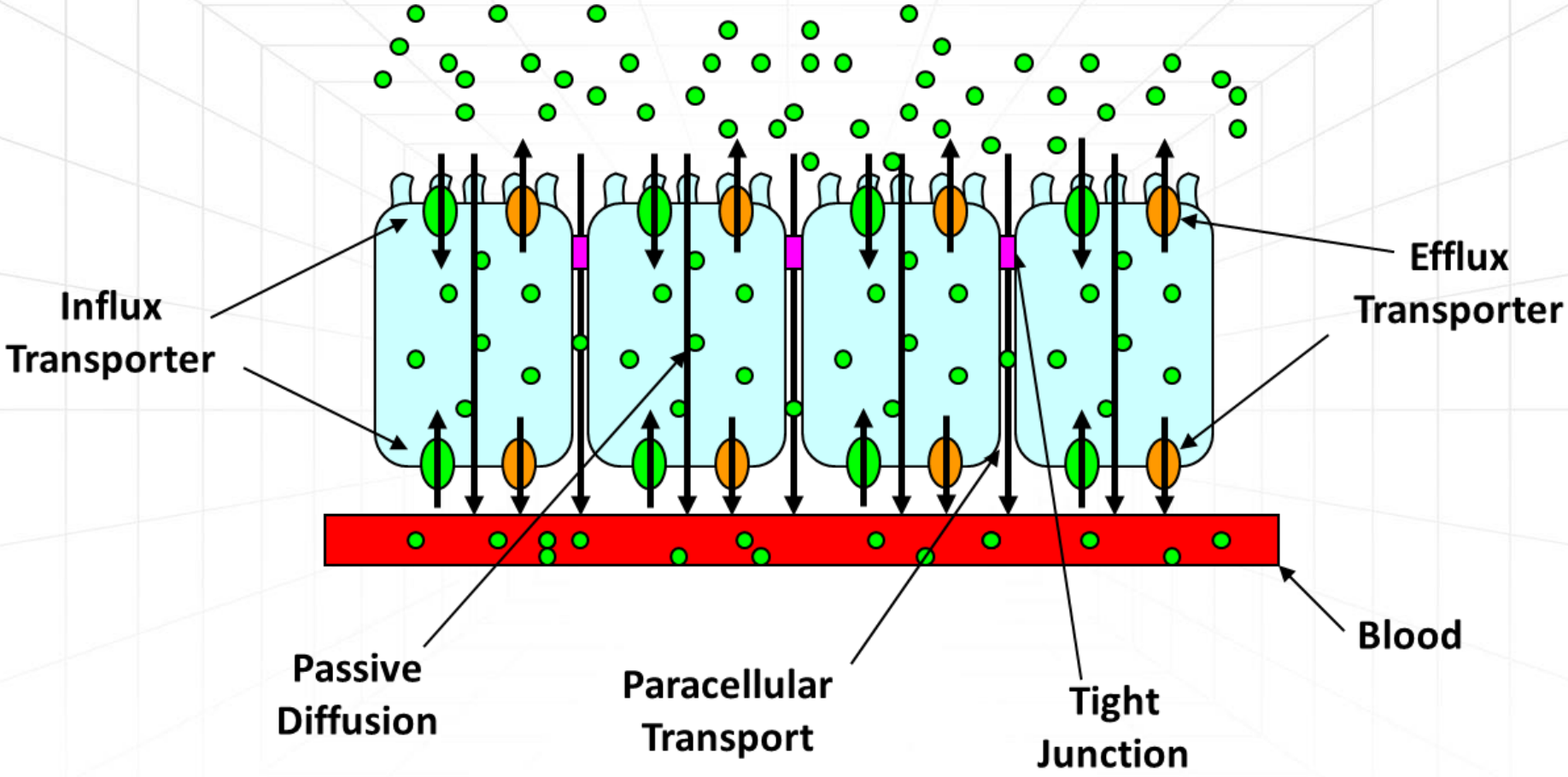
Data from Blardi – Clin Pharm Ther 72:556 (2002)

Precipitation Models

- Mechanistic nucleation and particle growth are important concepts for formulation of poorly soluble APIs.
- Testing *in vitro* is valuable for predicting the tendency to supersaturate and the relationship between supersaturation ratio and precipitation time.
- Simple 1st order methods have proven to be useful in understanding *in vivo* precipitation.
- Mechanistic nucleation and growth theory provides a more detailed understanding of the impact of chemistry and formulation on *in vivo* performance.
- First order precipitation time may need to change for each dose because the degree of supersaturation is different.
- One setting for Mechanistic Nucleation and Growth will explain all doses of enabled formulations.

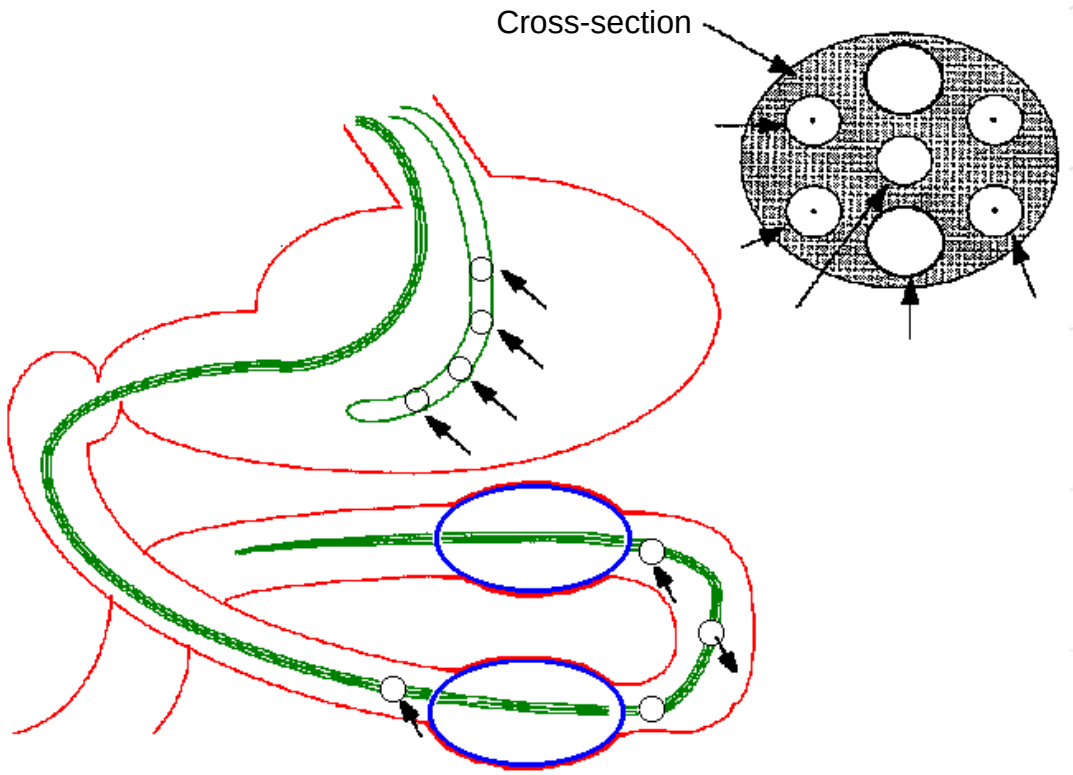
Absorption

Absorption Processes



Effective Permeability (P_{eff}): Measurements in Human

- Measure *disappearance* of drug from donor side
- Factors affecting permeability:
  - individual subject variations
  - adsorption to the tubes



Peff = Q(Cin - Cout) /(2 π r L Cin)

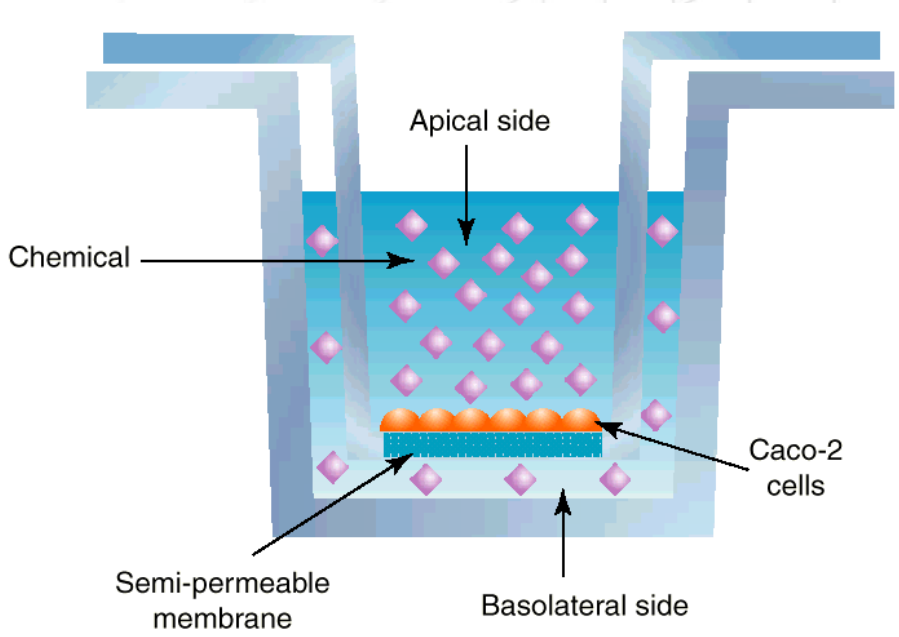
r=1.75 cm, L=10 cm

Peff = 0.0091*Q(Cin - Cout) /Cin

H. Lennernas, G.L. Amidon, et al.Capsugel Library, 1995

in vitro Permeability (P_{app}) Experiments

- Measure *appearance* of drug on receiver side
- Many factors affect *in vitro* permeability (P_{app}):
  - pH on each side of the membrane
  - solvents (e.g., DMSO)
  - amount of protein on receiver side
  - concentration in donor side
  - shaking rate
  - nonspecific binding to plasticware

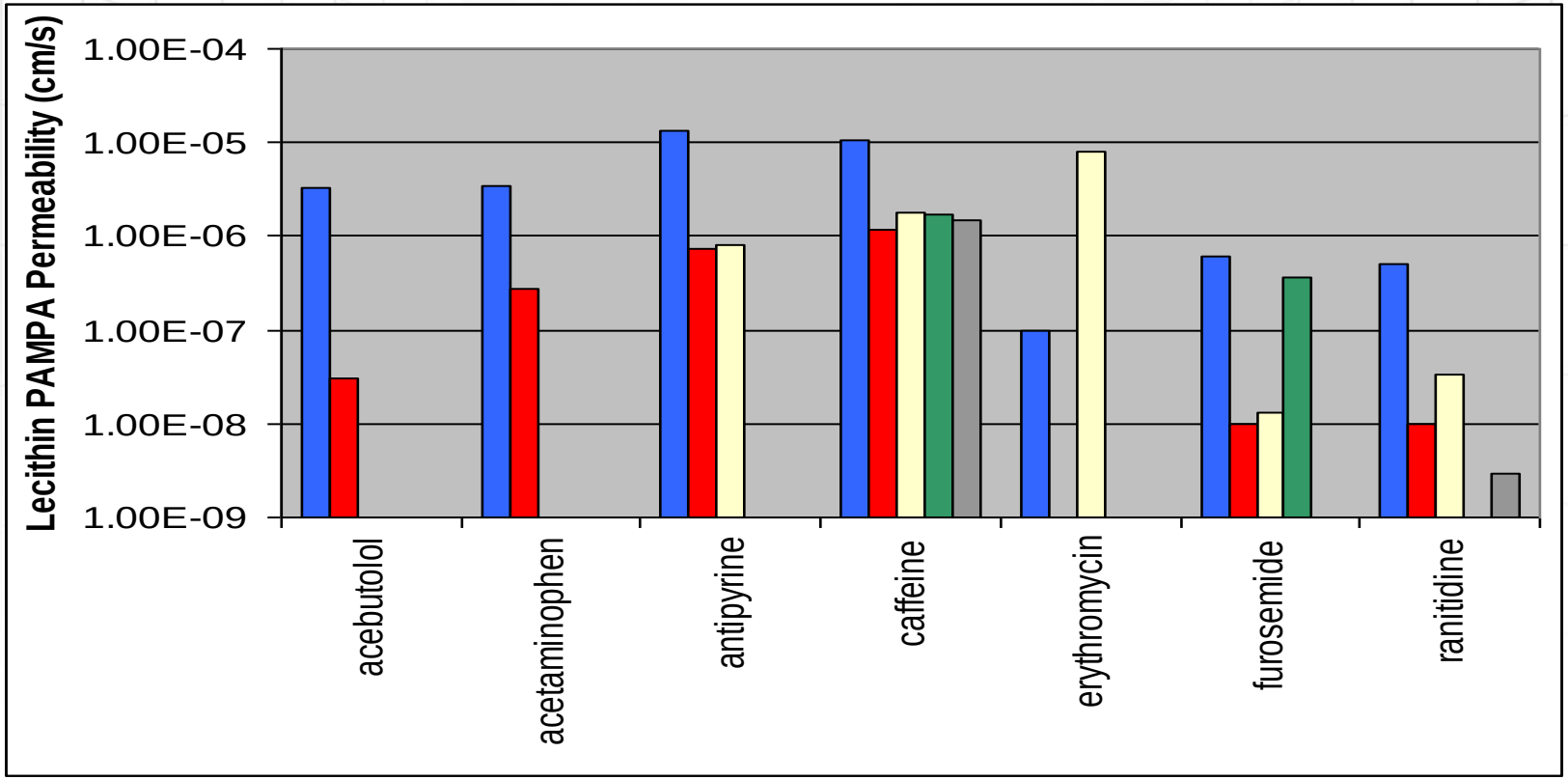


Li, A.P., DDT, 6(7):339-348

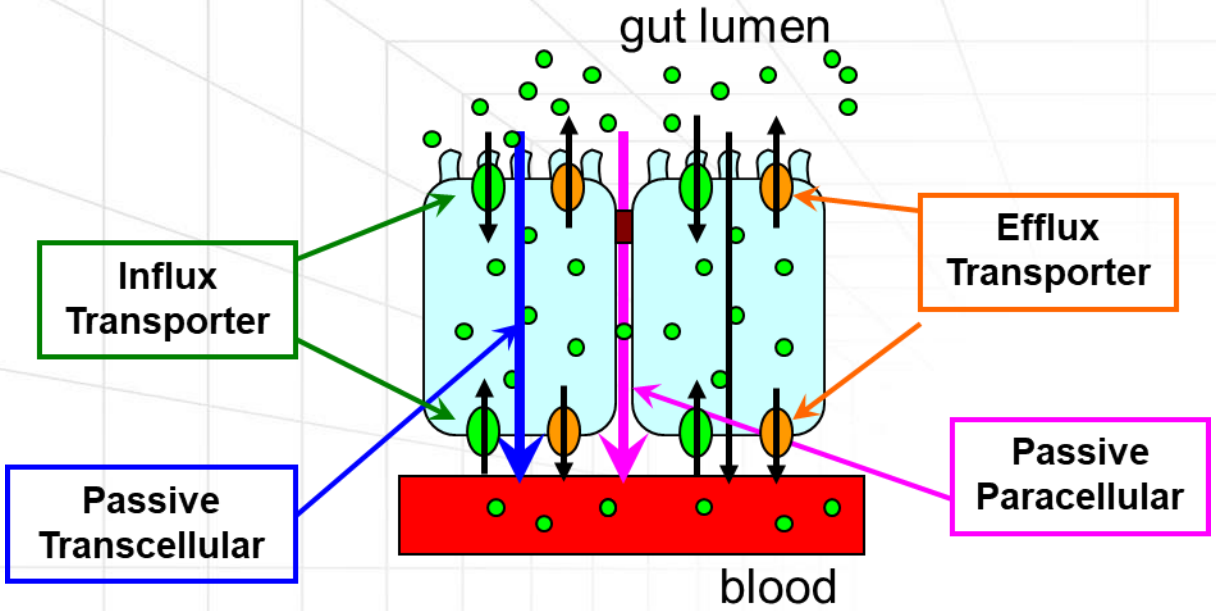
Variability of *in vitro* Permeability

PAMPA Permeability values for selected drugs collected from literature
All data are for Lecithin solution in dodecane and pH=7.4

Blue – Zhu Ch. EurJMedChem 2002, 37:399; Red – Ruell J.A. pION; Yellow – Kerns E.H. JPharmSci 2004, 93:1440; Green – Avdeef A. EurJPharmSci 2001, 14:271; Grey – Du C. pION



Paracellular Permeability in Absorption

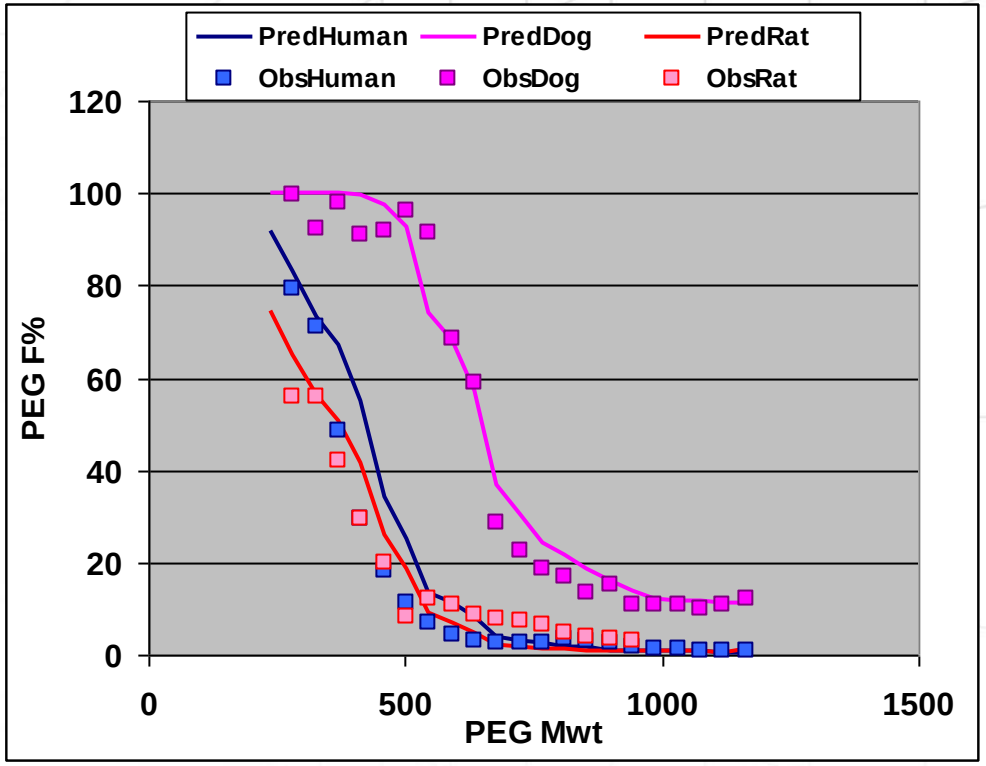


$$P_{trans} = P_{total} - P_{para}$$

Calculated from drug-dependent (user input) and physiological parameters

$$P_{para} = \frac{\varepsilon D_w F(r/R)}{\delta}\left(\frac{\kappa}{1-e^{-\kappa}}\right)$$

$$\kappa = \frac{ez|\Delta\Psi|}{k_B T}$$



Data from He-JPharmSci 1998, 87: 626-633

Carrier-Mediated Absorption

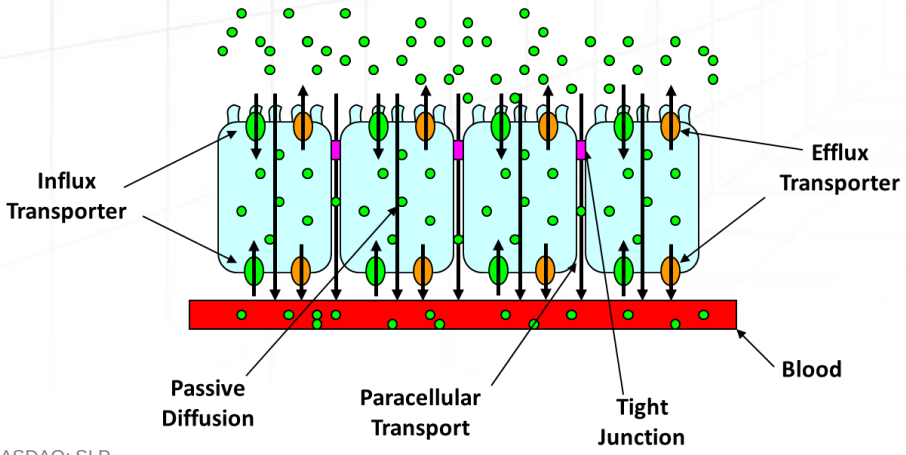
- Transporter expressions vary along the intestine
- Transporter expression patterns vary among species and differ from *in vitro*
- Considerable variability in reported expression patterns from different sources
- New measurements are being reported

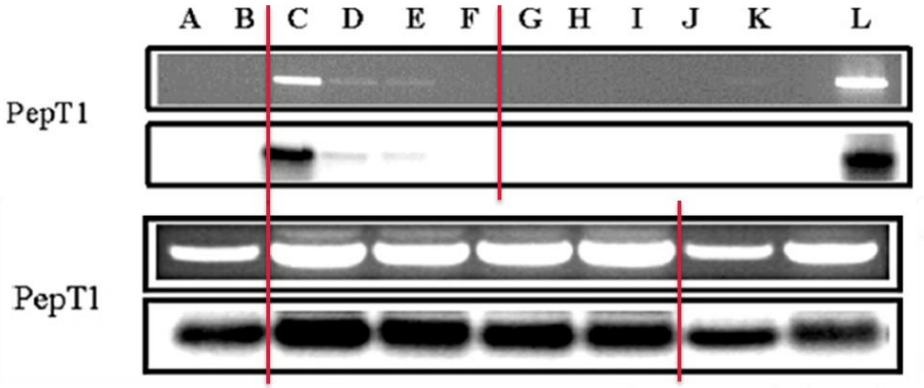
Table II. RT-PCR Northern Blot of Transporter Expressions (relative to Ileum as 1.0) Used in the GastroPlus Simulations

Compartment	PepT1[a]	PepT1[b]	PepT1[c]	HPT1[b]	P-gp[a]	P-gp[d]	OCTN1[c]	LAT2[e]	OATP 1A2[c]
Duodenum	0.72	8.42	1.02	1.06	0.16	0.70	0.42	0.74	0.07
Jejunum1	0.92	1.48	1.01	1.17	1.23	0.84	0.71	4.57	0.07
Jejunum2	0.92	1.48	1.01	1.17	1.23	0.94	0.71	4.57	0.07
Ileum1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ileum2	1.00	1.00	1.00	1.00	1.00	1.09	1.00	1.00	1.00
Ileum3	1.00	1.00	1.00	1.00	1.00	1.07	1.00	1.00	1.00
Caecum	0.02	0	0.04	1.36	0.36	1.3	0.34	0	0.13
Asc. Colon	0.02	0	0.04	1.70	0.36	1.3	0.34	0	0.17

Bolger MB, AAPS Journal, 11(2):353 (2009)

Be mindful of the effective concentration when determining Km

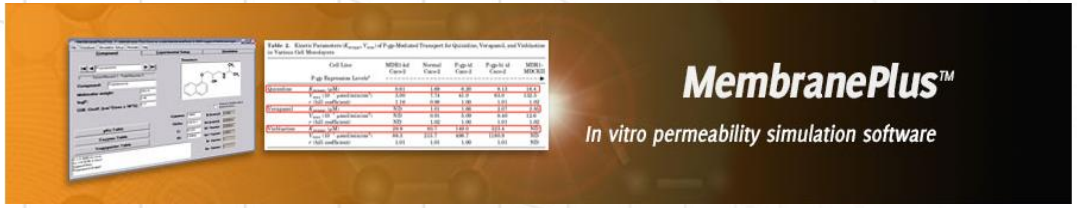


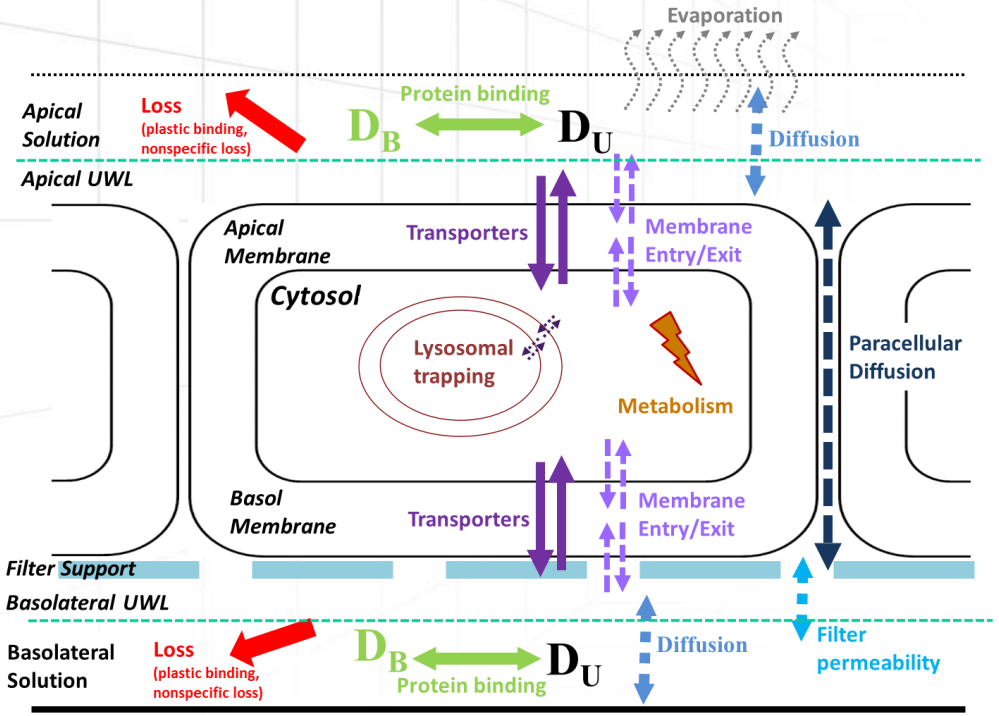


- RT-PCR analysis of human (top) and rat (bottom) PepT1
- Red lines mark small intestine (duodenum-ileocaecal junction)

Herrera-Ruiz AAPS Pharmsci 2001; 3 (1) article 9
(http://www.aapspharmaceutica.org)

Mechanistic Models are Important for *in vitro –in vivo* Extrapolation

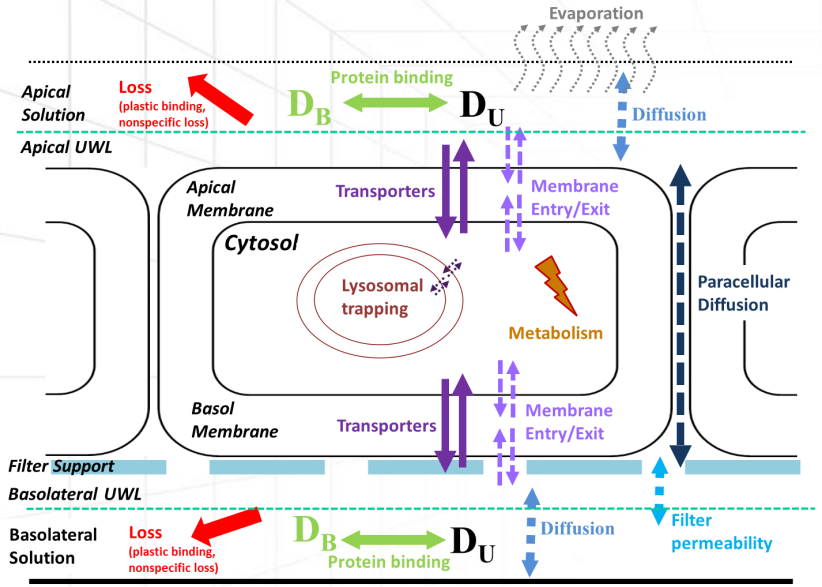


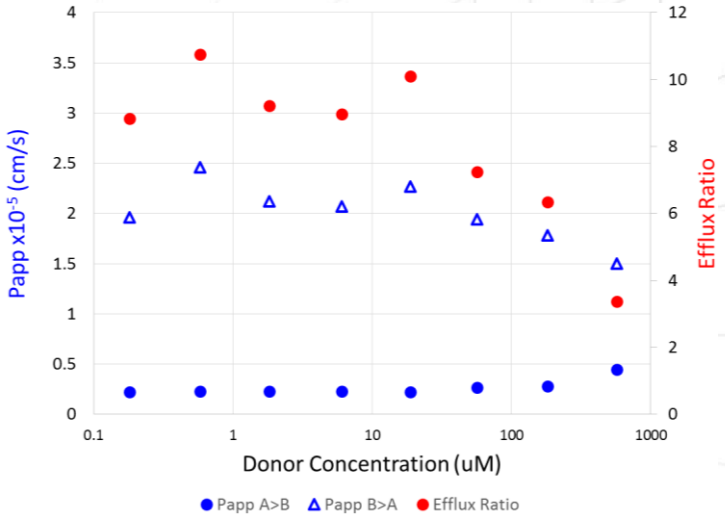


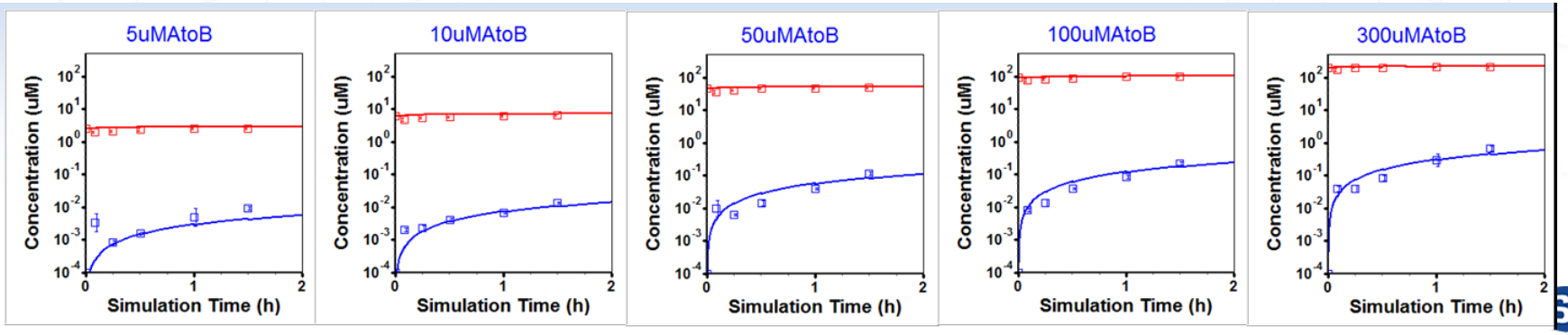
- Predict *in vitro* Papp and analyze measured data to unlock important information related to absorption
- Number of different processes affecting apparent *in vitro* permeability can be included in the simulation:
  - Passive transcellular diffusion
  - Passive paracellular diffusion
  - Carrier mediated influx and/or efflux
  - Metabolism in the cells
  - Binding to albumin
  - Accumulation in cell membranes or intracellular compartments
  - Experimental conditions (e.g., shaking rate, pH)

in vitro-in vivo Extrapolation of Digoxin Efflux – Determining Intracellular Unbound Km

The intracellular unbound P-gp K_m for digoxin was found to be 95.3 μM by fitting B->A Papp with MembranePlus™ across experiments run at eight different concentrations and validated in a separate experiment using kinetic data at five concentrations







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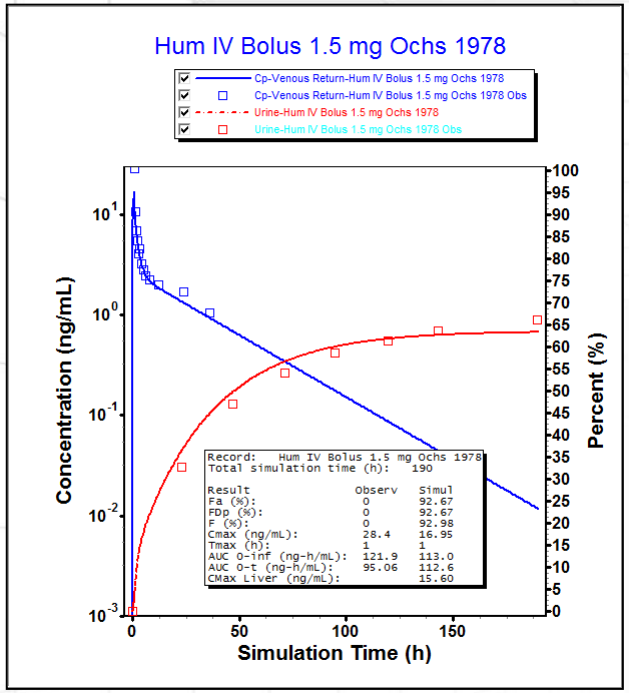
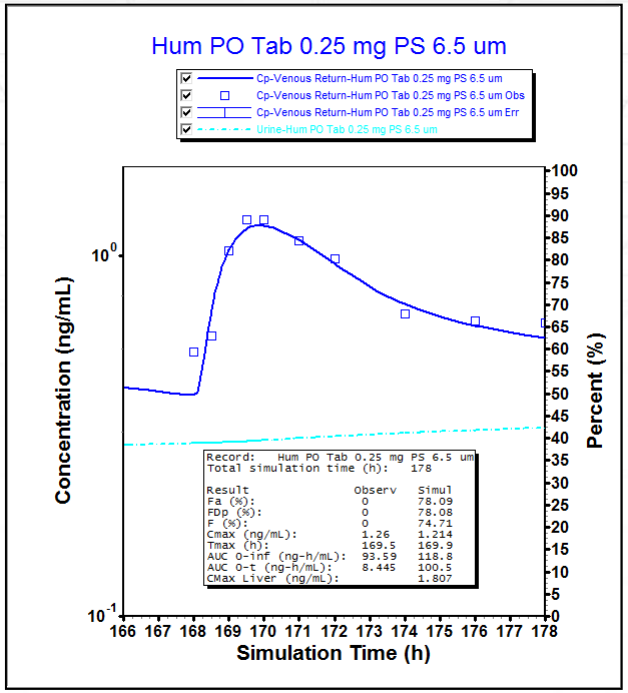
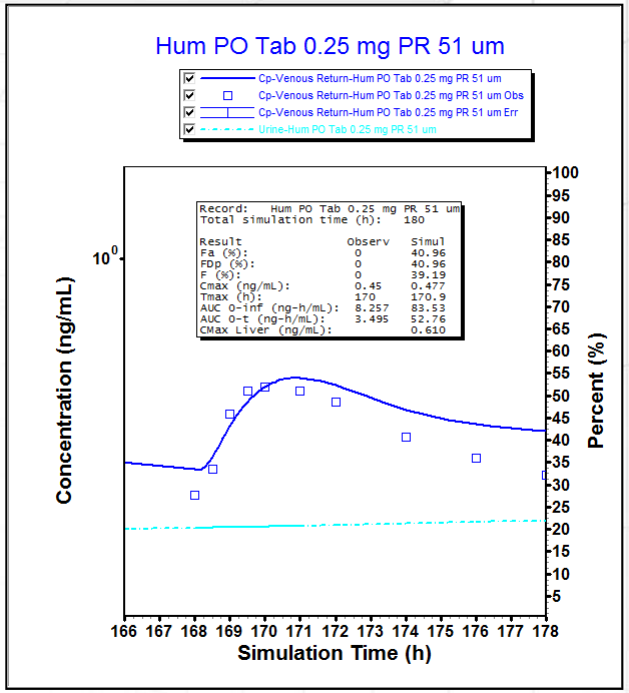
in vitro-in vivo Extrapolation of Digoxin Efflux – Predicting *in vivo* Absorption



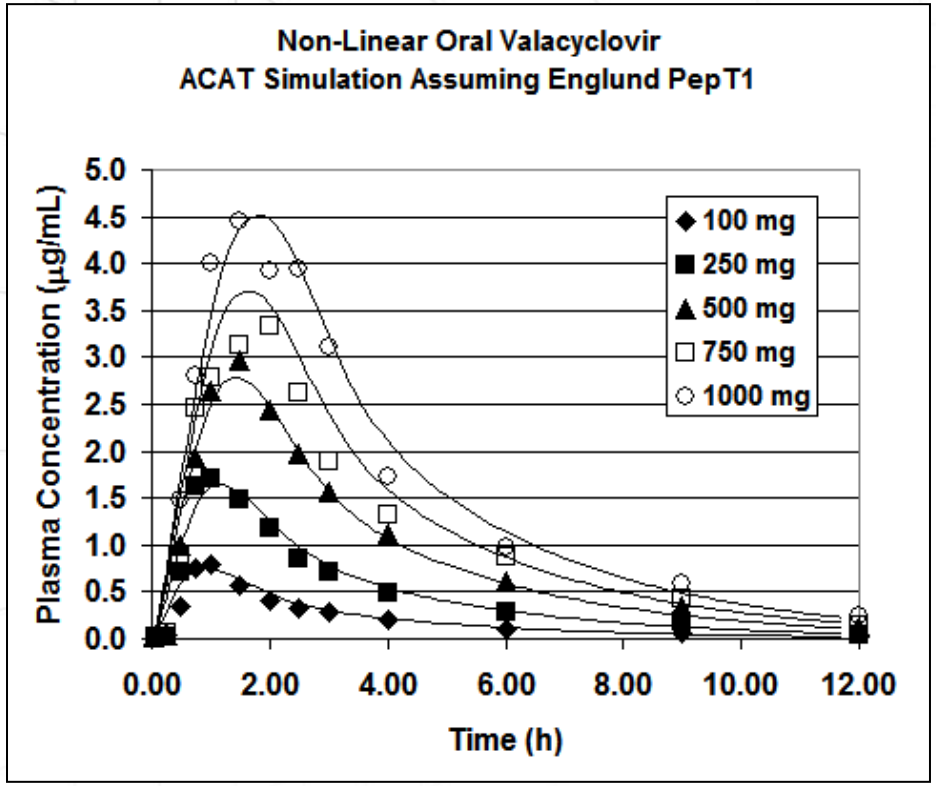


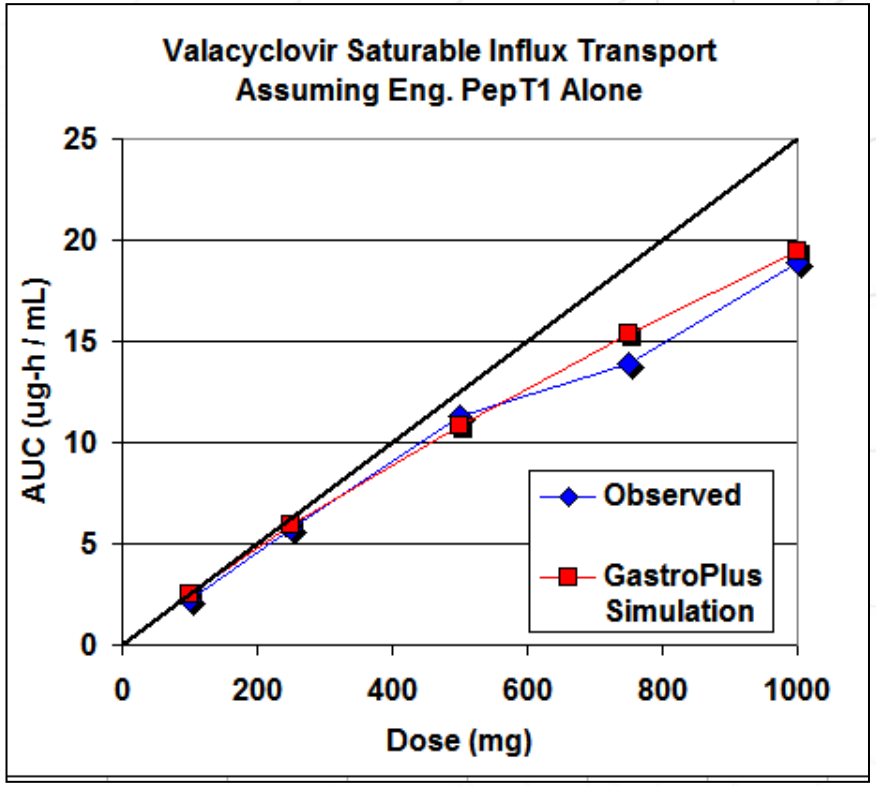


A **B** **C**

A: Observed (symbols) vs. predicted plasma conc. (blue) and urinary excretion (red) of digoxin (Ochs, 1978).
B: Observed (symbols) vs. predicted plasma conc. (blue) of digoxin for a PO formulation with 6.5 μm radius particle size (Jounela, 1975).
C: Observed (symbols) vs. predicted plasma conc. (blue) of digoxin for a PO formulation with 51 μm radius particle size (Jounela, 1975).
All simulations are using the fitted intracellular unbound P-gp Km value of 95.3 mM

GastroPlus Simulation of Nonlinear Dose Dependence for Influx Transport of Valacyclovir



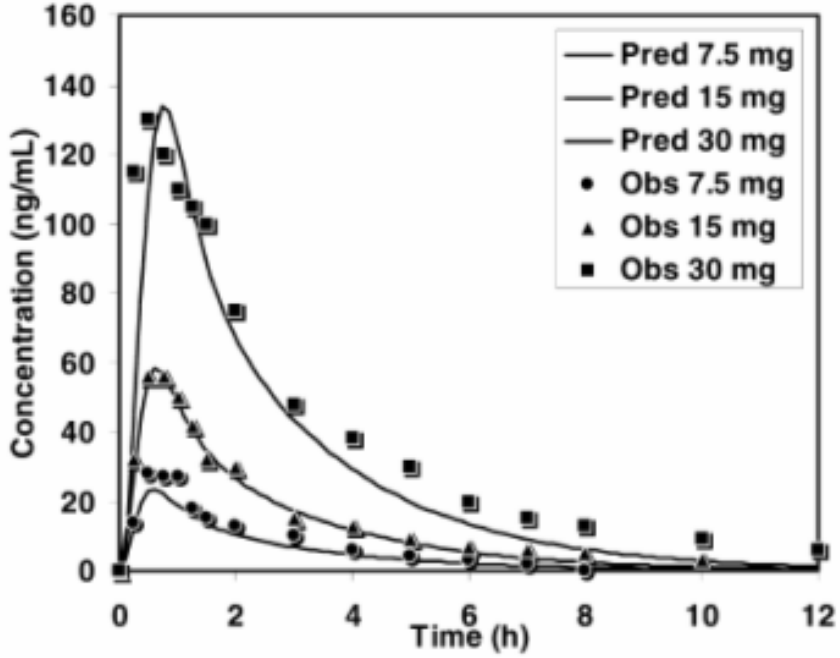


Bolger MB, et al. AAPS Journal 11(2):353 (2009)
GastroPlus results were first reported in Feb. 2003
at AAPS Drug Transport Workshop, Peachtree City, GA

Remember the Impact of Intestinal Metabolism

- Enzyme expressions vary along the intestine
- Enzyme expression patterns vary among species
- *in vitro-in vivo* extrapolation is established better than for transporters
- Compound elimination in the intestine affects the concentration and impacts the other processes

GastroPlus simulations of nonlinear dose dependence for midazolam using *in vitro* K_m and V_{max} and *iv* PK (Agoram et al., 2001)



Experimental			GastroPlus Compartmental Simulated				
Dose	Cmax	AUC	Cmax	AUC	Fa%	FDP%	Fb%
7.5	0.028	69	0.021	65	99	45	24
15	0.056	154	0.052	158	99	55	29
30	0.13	453	0.120	369	99	64	34

Summary

- Number of different processes contribute to net drug absorption
- Different *in vitro* assays are available to determine input parameters for individual processes
- Mechanistic simulations of *in vitro* assays are an important tool to 'deconvolute' parameter values and aid in *in vitro* – *in vivo* extrapolation
  - Accuracy of *in vitro* – *in vivo* extrapolation varies between the processes
- To predict the overall *in vivo* absorption, the interplay of all relevant processes needs to be considered

Small Sample of Published Examples

Journal of Pharmaceutical Sciences 000 (2021) 1–11

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Establishing the Bioequivalence Safe Space for Immediate-Release Oral Dosage Forms using Physiologically Based Biopharmaceutics Modeling (PBBM): Case Studies

Tycho Heimbach[a], Filippos Kesisoglou[a,*], Jasmina Novakovic[b], Christophe Tistaert[c], Martin Mueller-Zsigmondy[d], Sivacharan Kollipara[e], Tausif Ahmed[e], Amitava Mitra[f], Sandra [illegible][g]

Journal of Pharmaceutical Sciences xxx (2018) 1-15

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Drug Discovery—Development Interface

Prediction of ARA/PPI Drug-Drug Interactions at the Drug Discovery and Development Interface

Stephanie Dodd [1, *], Sivacharan Kollipara [2], Manuel Sanchez-Felix [1], Hyungchul Kim [1], Qingshuo Meng [4], Stefania Beato [5], Tycho Heimbach [3]

AAPS PharmSciTech (2020) 21: 102
DOI: 10.1208/s12249-020-01643-x

Check for updates

Research Article

Understanding the Oral Absorption of Irbesartan Using Biorelevant Dissolution Testing and PBPK Modeling

Navpreet Kaur,[1] Poonam Singh Thakur,[2] Ganesh Shete,[3] Rahul Gangwal,[4] Abhay T. Sangamwar,[5] and Arvind Kumar Bansal[5,6]

The AAPS Journal, Vol. 18, No. 6, November 2016 (© 2016)
DOI: 10.1208/s12248-016-9957-3

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Research Article

Physiologically Based Absorption Modeling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Alectinib

Neil J Parrott,[1,5] Li J Yu,[2] Ryusuke Takano,[3] Mikiko Nakamura,[4] and Peter N. Morcos[2]

The AAPS Journal (2020) 22:78
DOI: 10.1208/s12248-020-00463-y

Check for updates

Research Article

Theme: Use of PBPK Modeling to Inform Clinical Decisions: Current Status of Prediction of Drug-Food Interactions
Guest Editor: Filippos Kesisoglou

Physiologically Based Absorption Modelling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Entrectinib

Neil Parrott,[1,5] Cordula Stillhart,[2] Marc Lindenberg,[3] Bjoern Wagner,[1] Karey Kowalski,[4] Elena Guerini,[1] Nassim Djebli,[1] and Georgina Meneses-Lorente[1]

AAPS PharmSciTech (2021) 22:54
DOI: 10.1208/s12249-021-01923-0

Check for updates

Research Article

Exploratory Study on Lercanidipine Hydrochloride Polymorphism: pH-Dependent Solubility Behavior and Simulation of its Impact on Pharmacokinetics

Ilia Alekseevich Repin,[1] Raimar Loebenberg,[2] John DiBella,[3] António C. L. Conceição,[4] Manuel E. Minas da Piedade,[5,6] Humberto G. Ferraz,[1] Michele G. Issa,[1] Nadia A. Bou-Chacra,[1] Catharine F. M. Ermida,[1] and Gabriel L. B. de Araujo[1,6]

Small Sample of Published Examples

Received: 15 January 2021 | Revised: 2 March 2021 | Accepted: 12 March 2021
DOI: 10.1002/psp4.12634

ARTICLE

Application of physiologically based biopharmaceutics modeling to understand the impact of dissolution differences on in vivo performance of immediate release products: The case of bisoprolol

Joyce S. Macwan[1] | Grace Fraczkiewicz[1] | Mauro Bertolino[2] | Phillip Krüger[3] | Sheila-Annie Peters[2]

AAPS J (2022) 24:17
https://doi.org/10.1208/s12248-021-00663-0

Research Article

Theme: Integrating In Vitro Systems and Physiologically-Based Pharmacokinetics Modeling to Optimize Drug Product Development
Guest Editors: Rodrigo Cristofoletti and Lawrence Yu

Dissolution Challenges Associated with the Surface pH of Drug Particles: Integration into Mechanistic Oral Absorption Modeling

Bart Hens[1,6], Nidhi Seegobin[1,2], Marival Bermejo[3], Yasuhiro Tsume[4], Nicola Clear[1], Mark McAllister[1], Gregory E. Amidon[5], Gordon L. Amidon[5,6]

European Journal of Pharmaceutical Sciences 47 (2012) 375–386

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Application of PBPK modeling to predict human intestinal metabolism of CYP3A substrates – An evaluation and case study using GastroPlus™

Aki T. Heikkinen, Guillaume Baneyx, Antonello Caruso, Neil Parrott *

F. Hoffmann-La Roche AG, pRED, Pharma Research & Early Development, Non-Clinical Safety, Basel, Switzerland

pharmaceutics MDPI

Article

BCS Class IV Oral Drugs and Absorption Windows: Regional-Dependent Intestinal Permeability of Furosemide

Milica Markovic [1], Moran Zur [1], Inna Ragatsky [1], Sandra Cvijić [2] and Arik Dahan [1,*]

European Journal of Pharmaceutical Sciences 155 (2020) 105552

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

A combined in vitro in-silico approach to predict the oral bioavailability of borderline BCS Class II/IV weak base albendazole and its main metabolite albendazole sulfoxide

Maximo Pettarin[a], Michael B. Bolger[b], Maja Chronowska[a], Edmund S. Kostewicz[a,*]

[a] *Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany*
[b] *Simulations Plus, Inc., Lancaster, CA 93534, United States*

pharmaceutics MDPI

Review

PBPK Modeling as a Tool for Predicting and Understanding Intestinal Metabolism of Uridine 5′-Diphospho-glucuronosyltransferase Substrates

Micaela B. Reddy [1,*], Michael B. Bolger [2], Grace Fraczkiewicz [2], Laurence Del Frari [3], Laibin Luo [4], Viera Lukacova [2], Amitava Mitra [5], Joyce S. Macwan [2], Jim M. Mullin [2], Neil Parrott [6] and Aki T. Heikkinen [7]

AAPS J (2022) 24:17
https://doi.org/10.1208/s12248-021-00663-0

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The AAPS Journal (© 2009)
DOI: 10.1208/s12248-009-9111-6

Research Article

Theme: Towards Integrated ADME Prediction: Past, Present, and Future Directions
Guest Editors: Lawrence X. Yu, Steven C. Sutton, and Michael B. Bolger

Simulations of the Nonlinear Dose Dependence for Substrates of Influx and Efflux Transporters in the Human Intestine

Michael B. Bolger,[1,2,3] Viera Lukacova,[1] and Walter S. Woltosz[1]

The AAPS Journal (2020) 22:134
DOI: 10.1208/s12248-020-00511-7

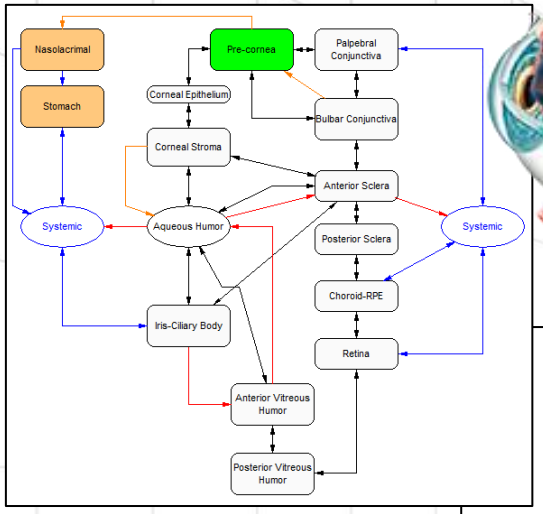
Research Article

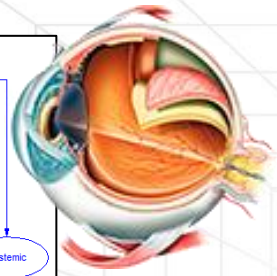
Theme: Use of PBPK Modeling to Inform Clinical Decisions: Current Status of Prediction of Drug-Food Interactions
Guest Editor: Filippos Kesisoglou

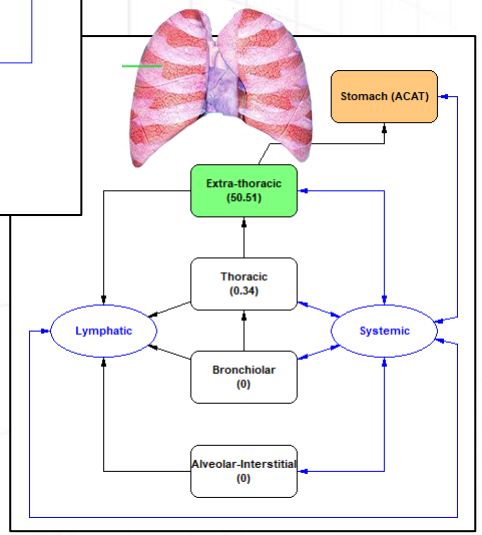
Physiologically Based Pharmacokinetic Modeling of Oral Absorption, pH, and Food Effect in Healthy Volunteers to Drive Alpelisib Formulation Selection

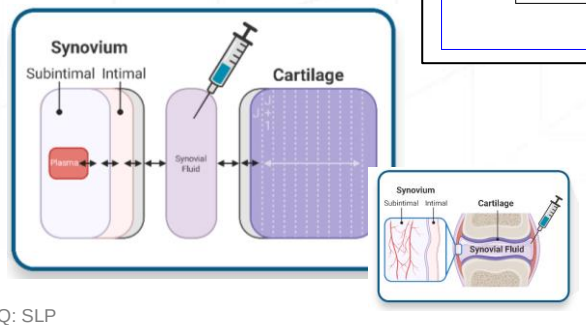
Monika Gajewska,[1] Lars Blumenstein,[1] Alexandros Kourentas,[2] Martin Mueller-Zsigmondy,[2] Sebastien Lorenzo,[3] Angela Sinn,[4] Maria Velinova,[5] and Tycho Heimbach[6,7]

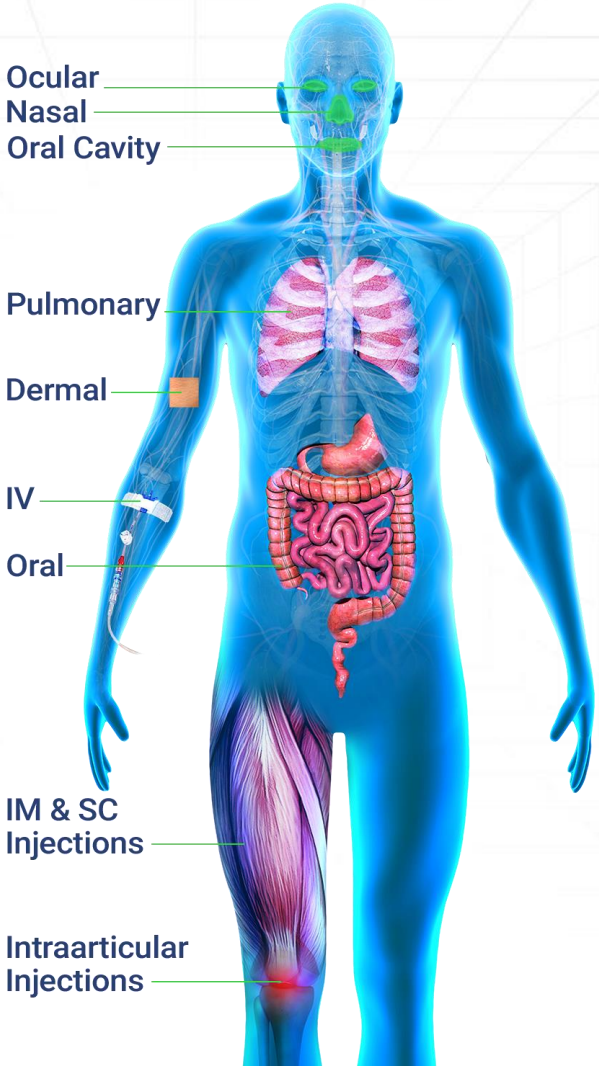
Similar Considerations Apply to Other Routes of Administration…

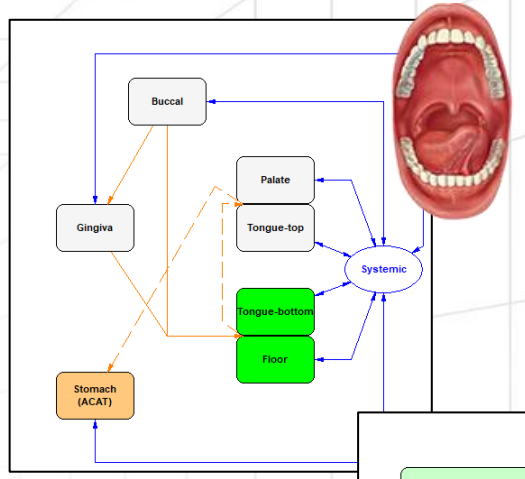


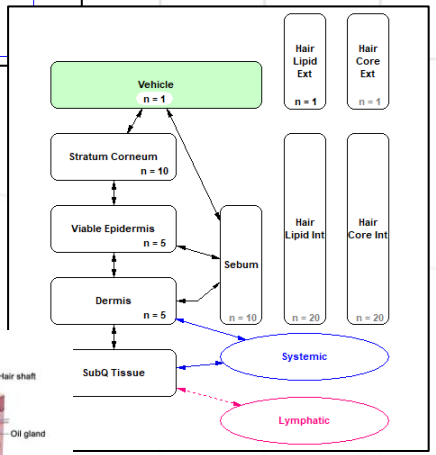


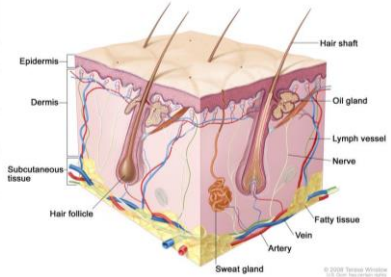












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