Exploiting Dual Solid State PBPK Tools to Assess the Bio(in)equivalence of Tacrolimus Amorphous Formulations with Various Degrees of Crystallization Arising During Storage

September 11th 2019

David Turner

IAPC-8, Split, Croatia

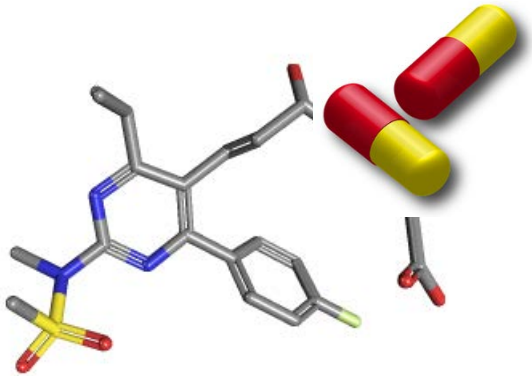
Outline

- Introduction
- Population PBPK Modelling / Mechanistic Modelling
- Interpreting & modelling of in vitro experiments
- Tacrolimus case study, towards virtual bioequivalence
- Summary

Population PBPK Modelling - Separation of system/drug data

Systems Data | Trial Design | Drug Data

Dose
Administration route
Frequency
Co-administered drugs
Populations
No of male/female



Mechanistic IVIVE-linked PBPK models

Prediction of drug PK (PD) in population of interest

Jamei (2016) ***Current Pharmacology Reports*** 2:161-169

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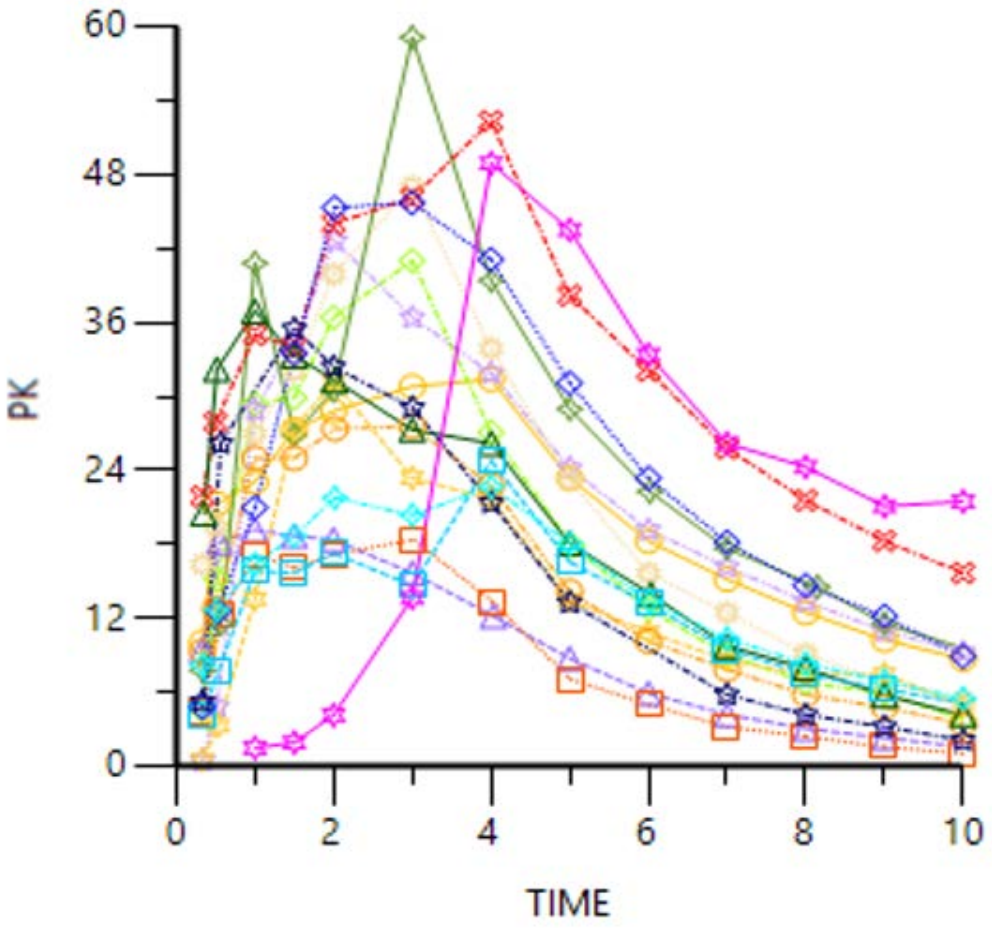
Population Variability: “Average” Subject vs Population Simulation

In Vivo Individual Plasma PK Profiles: An Extended Release Formulation

Conc



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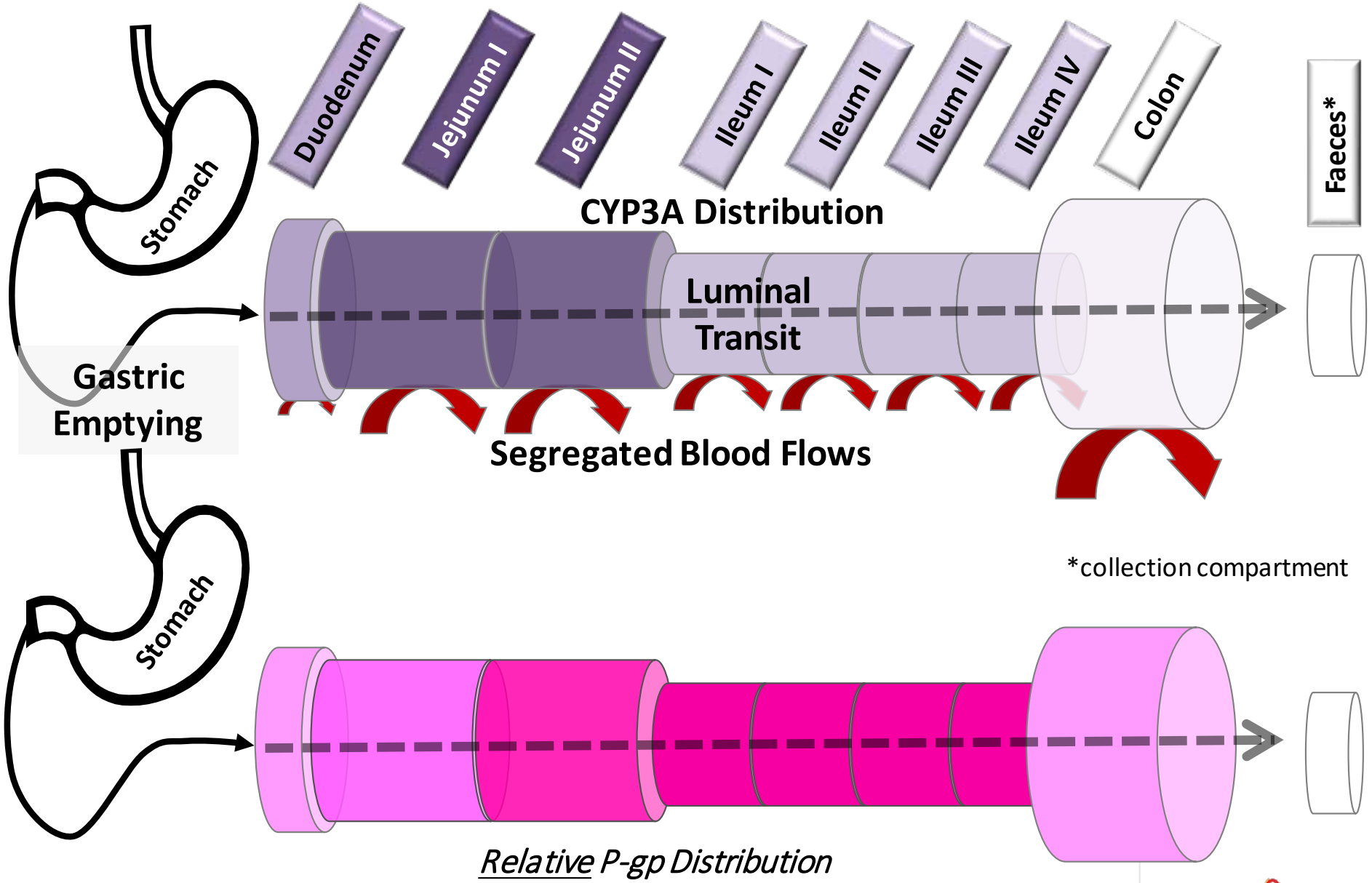
ADAM Model – Dissolution, Gut Wall Enzymes and Transporters



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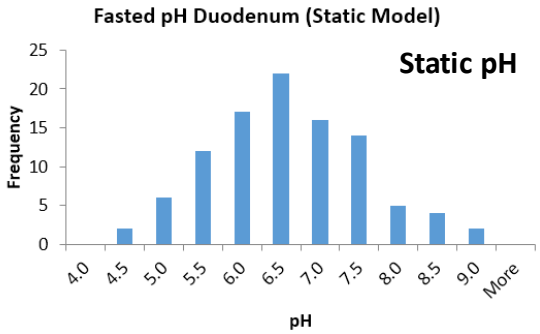
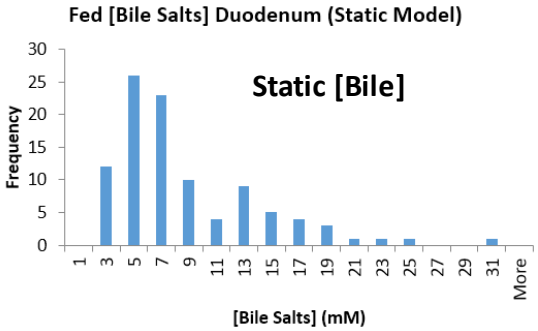
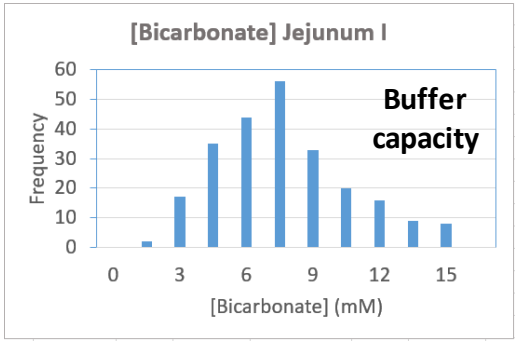
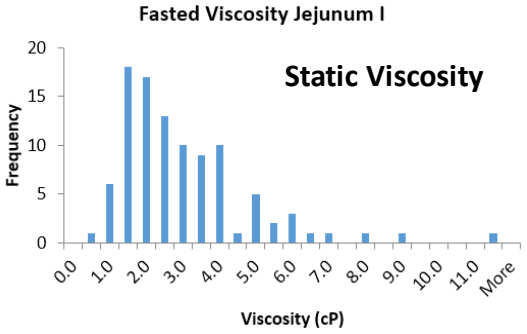
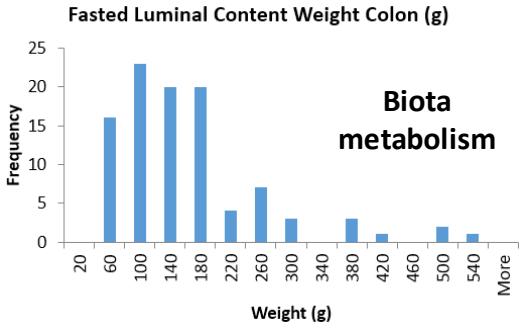
(Some of the) Gut-Related Parameters with BSV in Simcyp

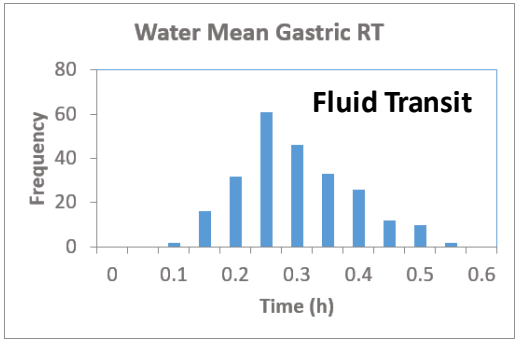




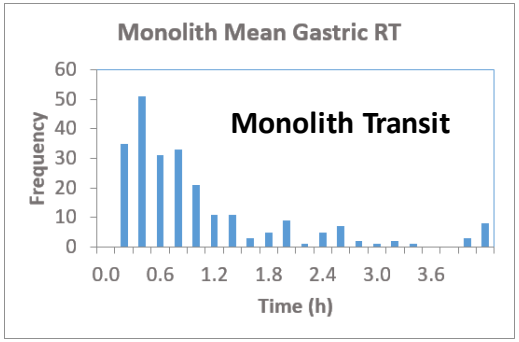








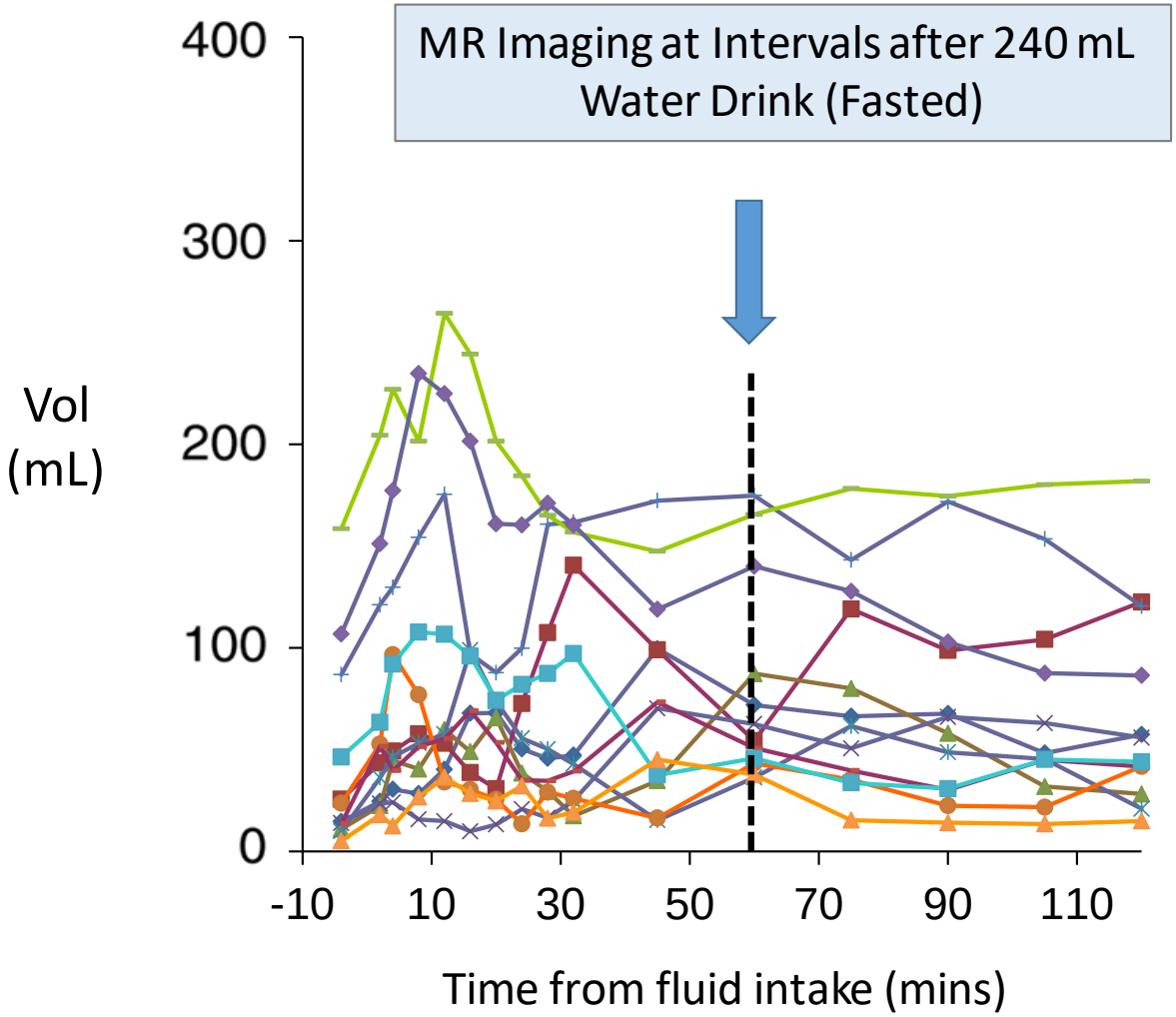
Moeity-specific transit



100 simulated HV subjects
Underlying data based on literature meta-analysis

BSV Between subject variability

Small Intestine: Luminal Water Volumes: Variability



12 subjects

Pop PBPK simulations have dynamic water volume profiles plus between subject variability

* Mudie, Marciani et al. 2014

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GIT Variability: Dipyridamole Example

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

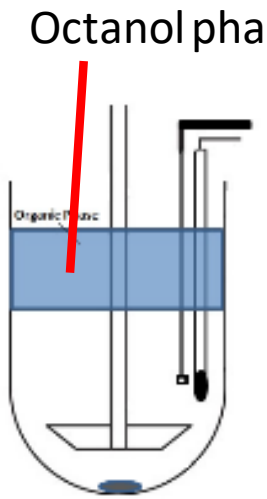
journal homepage: www.jpharmsci.org

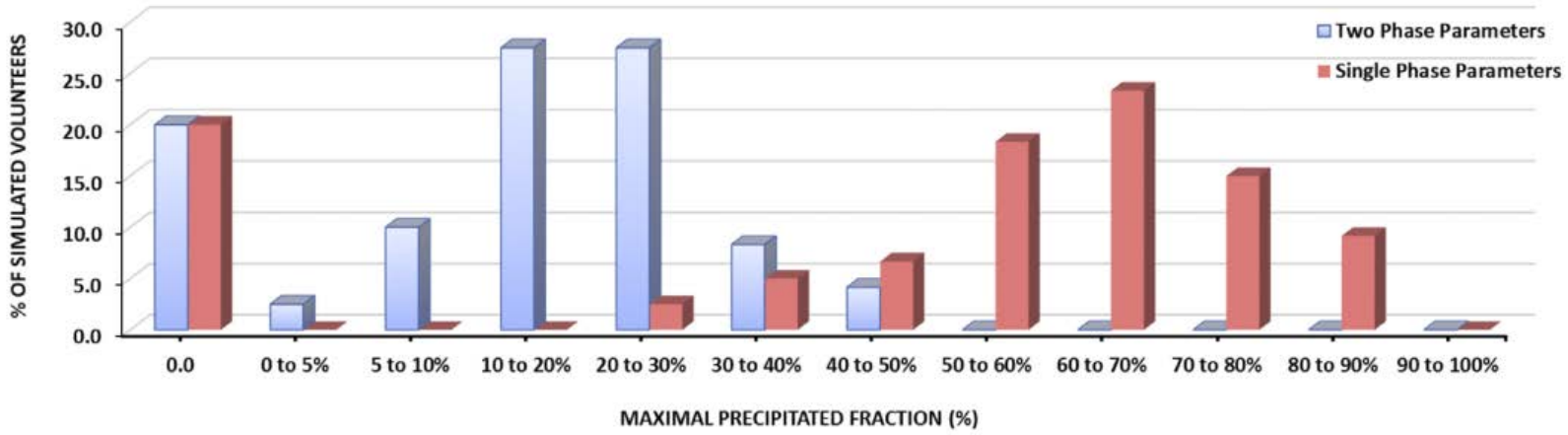
Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Biopharmaceutic *IVIVE*—Mechanistic Modeling of Single- and Two-Phase *In Vitro* Experiments to Obtain Drug-Specific Parameters for Incorporation Into PBPK Models

Shriram M. Pathak [1,*], Kerstin Julia Schaefer [2], Masoud Jamei [1], David B. Turner [1]

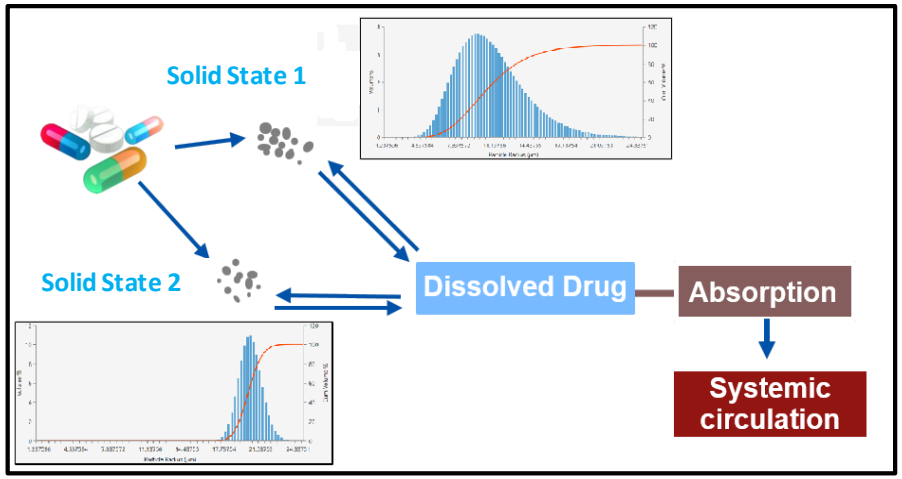
[1] *Certara UK Limited, Simcyp Division, Level 2-Acero, Sheffield, S1 2BJ, UK*
[2] *Pharmaceutical Development, Boehringer-Ingelheim Pharma GmbH & Co. KG, Germany*



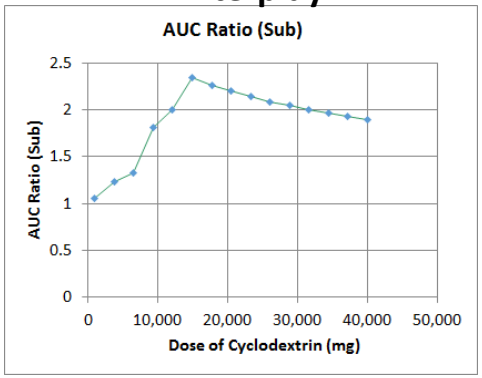


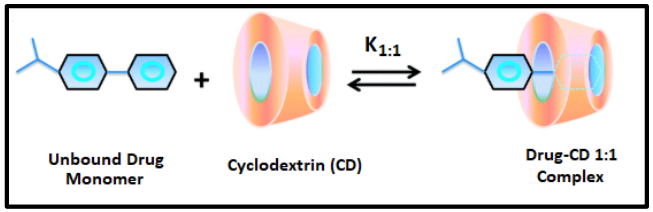
Recently Added Tools/Models

Particle Population Balance Model



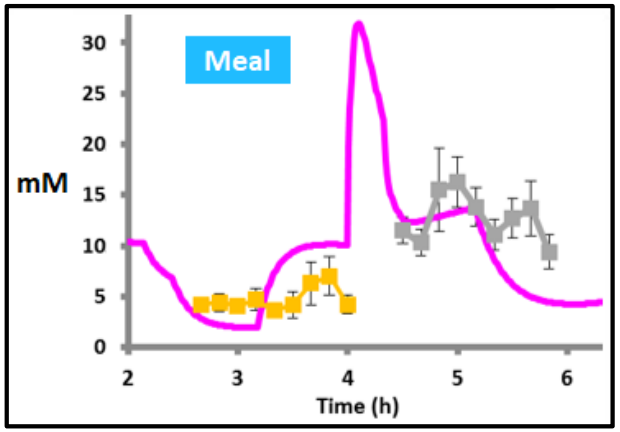
HPβCD Solubilisation-Permeability Interplay





Excipient Binding

Duodenum (Total Bile Salt vs time)



Solubility is not static

Dynamic Bile Salt Model (requires accurate luminal fluid volumes)

Nucleation Rate (1/s/m³)

$$J(t) = Z(t) \cdot f^* \cdot C^*(t)$$

Nucleation Model

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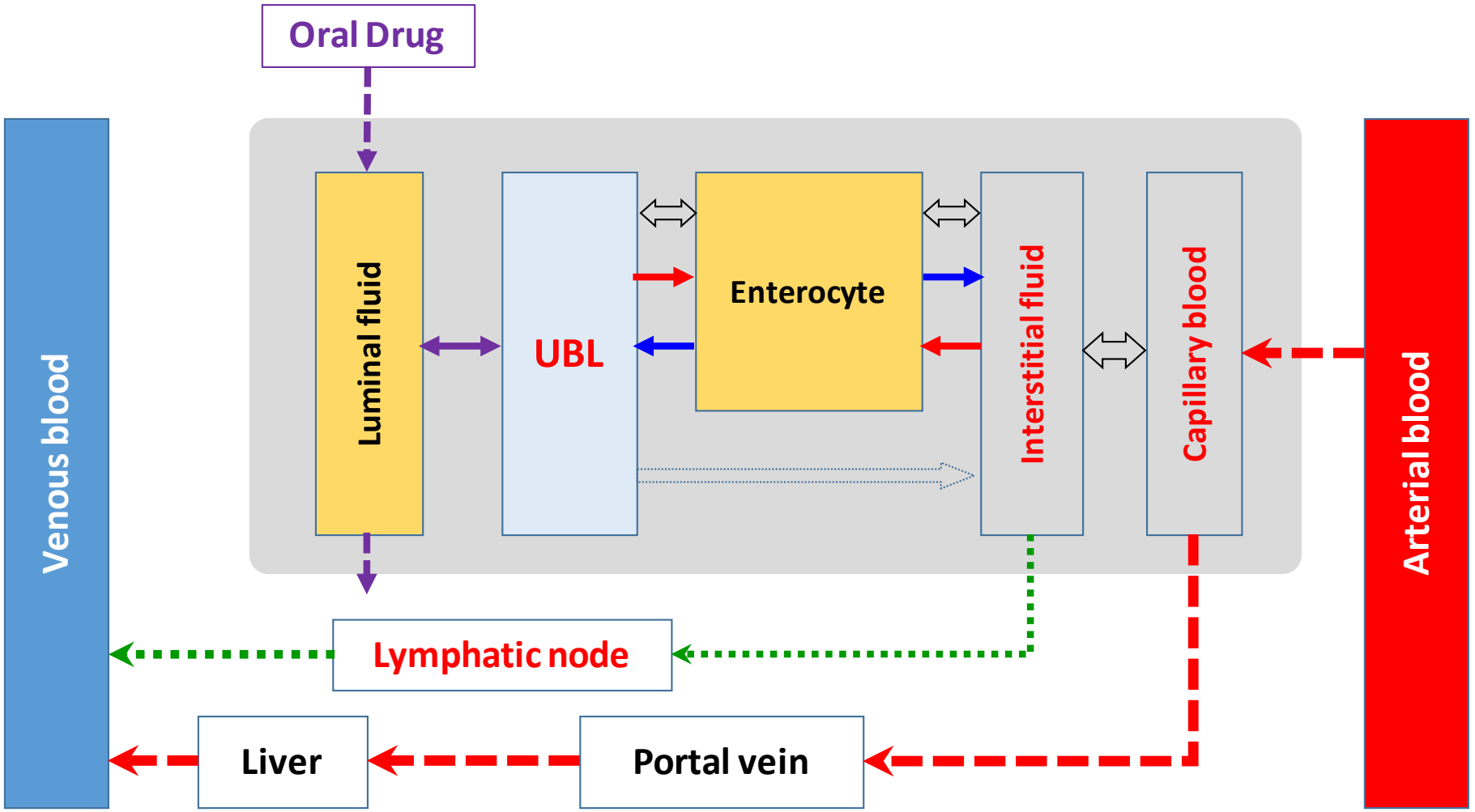
Multi-compartment Gut Wall ADAM (M-ADAM) Model



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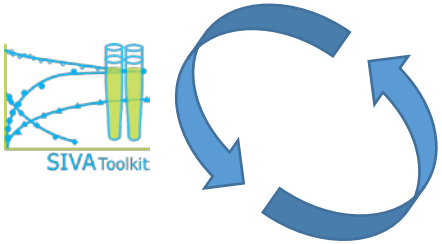
Handling Dissolution with PBPK Models

Either **Model Inputs: Particle size(s), solubility, pKa, fluid vols. *etc.***

$$DR(t) = -NS\frac{D_{eff}}{h_{eff}(t)}4\pi\, a(t)\,(a(t)+h_{eff}(t))(S_{surf}(t)-C_b(t))$$

Mechanistic model informed by in vitro experiment



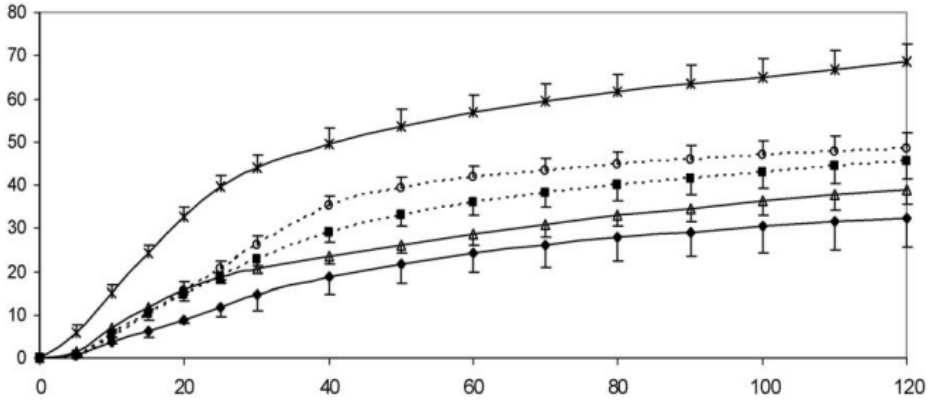
Modelling of *In Vitro* Dissolution (Estimate/Confirm)

In vivo physiology pH, fluid volumes etc. with variability

***In vivo* dissolution rate**

Or **Model Input(s): In vitro dissolution profile**

***In Vitro* % dissolved**



Time (mins)

In vivo physiology pH, fluid volumes etc. with variability

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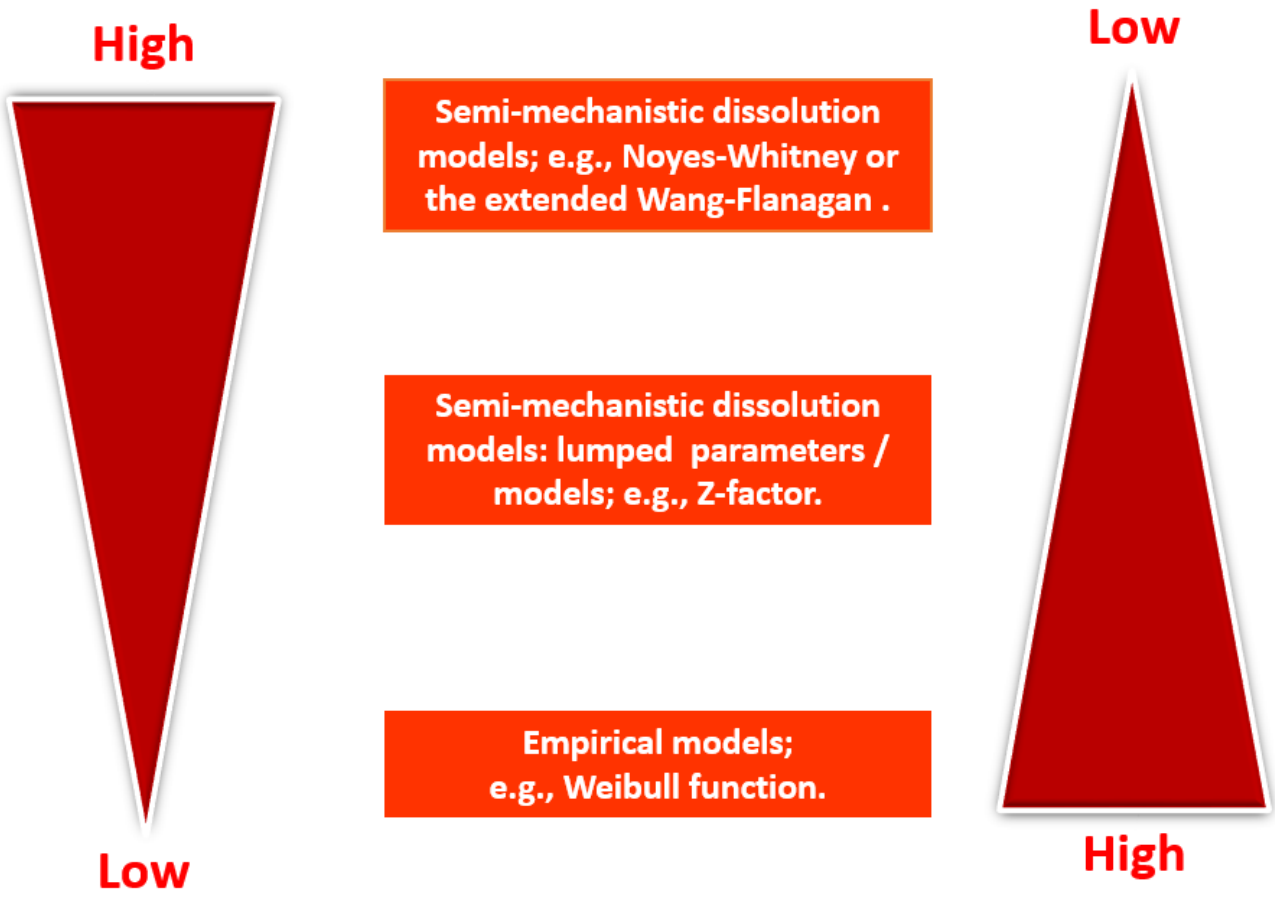
11

Predicting Oral Drug Absorption of Drug Products: Current Status

Sensitivity to physiological regional differences and BSV or WSV*.

Applicability to complex formulations within the current models



*BSV, WSV – Between, Within Subject Variability

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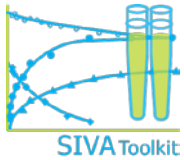
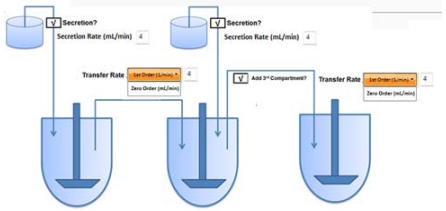
Running Theme

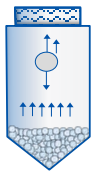
- PBPK Absorption modelling
  - Informed by *in vitro* experiments
  - Informed by <u>modelling of</u> *in vitro* experiments

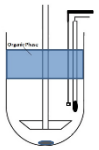
Biopharmaceutic Modelling



Estimated/Confirmed Parameters







USP-2, µDiss, USP-4,
Two-Phase,
Generic Dynamic transfer

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Accounting for Hydrodynamics: Effective Diffusion Layer Thickness, h_{eff}

$$DR(t) = \sum_{NBINs}^{i=1} -N_i \, S_{DR} \frac{D_{eff}(t)}{h_{eff,i}(t)} 4\pi a_i(t)\left(a_i(t) + h_{eff,i}(t)\right)\left(S_{surface}(t) - C_{bulk}(t)\right)$$

Fluid Dynamics h_{eff} Equations

shear

Apply viscosity models?

viscosity

radius

$$Re_{total} = \frac{\rho_f 2a(t)}{\mu_f}\left|\vec{U}_f - \vec{U}_p\right|$$

$$Sc = \frac{\upsilon}{D_{eff}} = \frac{\mu_f}{\rho_f D_{eff}}$$

$$Sh = 2 + 0.6 \cdot Re^{1/2} \cdot Sc^{1/3}$$

$$h_{eff} = 2a(t)/Sh$$

D'Arcy 2011 *JPS* 100 1102

$D_{eff} = f_{aq,N} \cdot D_{mono,N} + f_{aq,ion} \cdot D_{mono,ion} + f_{micelle} \cdot D_{micelle}$

Effective Diffusion Coefficients

Apply viscosity models?

Relative Velocity Terms?

Complex CFD Modelling → **Representative Velocities (USP2, µDiss) (axial and tangential)**

CFD models: USP 2: Bai et al. 2007 µDiss: Johansson et al. 2017

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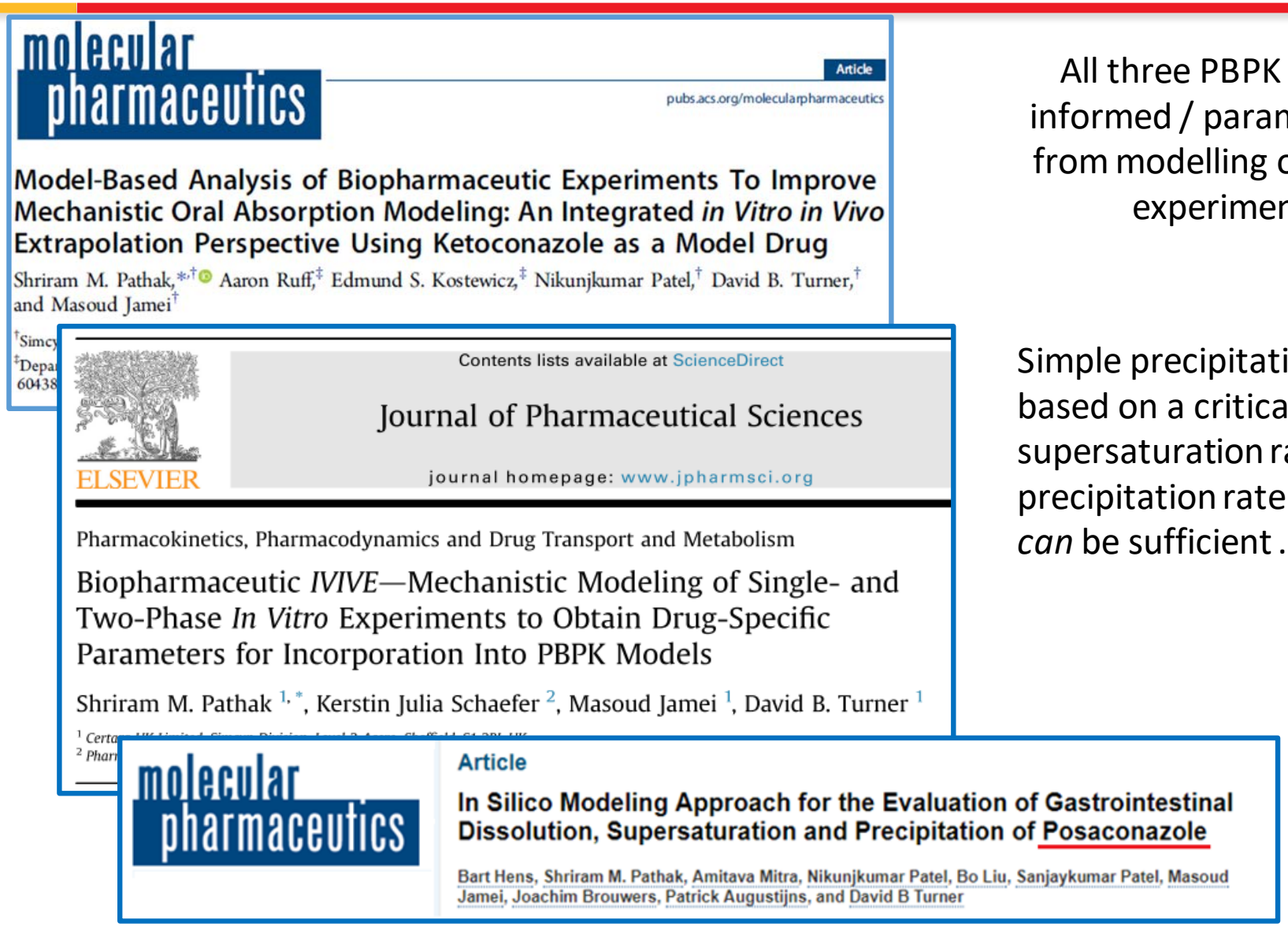
Examples of Application of PBPK Modelling to Supersaturating Drugs



molecular pharmaceutics

Article

pubs.acs.org/molecularpharmaceutics

Model-Based Analysis of Biopharmaceutic Experiments To Improve Mechanistic Oral Absorption Modeling: An Integrated *in Vitro in Vivo* Extrapolation Perspective Using Ketoconazole as a Model Drug

Shriram M. Pathak,*[†] Aaron Ruff,[‡] Edmund S. Kostewicz,[‡] Nikunjkumar Patel,[†] David B. Turner,[†] and Masoud Jamei[†]

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60438

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Shriram M. Pathak [1,*], Kerstin Julia Schaefer [2], Masoud Jamei [1], David B. Turner [1]

[1] Certa
[2] Phar

molecular pharmaceutics

Article

In Silico Modeling Approach for the Evaluation of Gastrointestinal Dissolution, Supersaturation and Precipitation of Posaconazole

Bart Hens, Shriram M. Pathak, Amitava Mitra, Nikunjkumar Patel, Bo Liu, Sanjaykumar Patel, Masoud Jamei, Joachim Brouwers, Patrick Augustijns, and David B Turner

All three PBPK models informed / parameterised from modelling of *in vitro* experiments

Simple precipitation models based on a critical supersaturation ratio and precipitation rate constant(s) *can* be sufficient …

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Sequential Modelling of In Vitro Experiments: Ketoconazole

Aqueous Phase Solubility Modelling

$$S_{pH} = min\left(S_o \cdot (1 + 10^{pKa-pH}),\ S_o \cdot SF\right)$$

Confirmed So, pKa & Salt Solubility Factors

Biorelevant Solubility Modelling

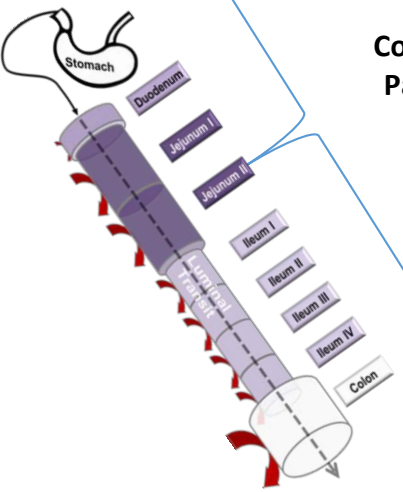
$$S_{(BS)Tot} = \left([BS] \cdot \frac{S_0}{C_{H_2O}} \cdot K_{m:w,unionised} + S_O\right) + \left([BS] \cdot \frac{S_i}{C_{H_2O}} \cdot K_{m:w,ionised} + S_i\right)$$

Confirmed Bile Micelle Partition Coefficients

USP-2 Dissolution Modelling

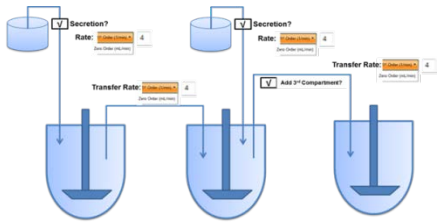
$$DR(t) = -NS\frac{D_{eff}}{h_{eff}(t)}4\pi a(t)\left(a(t) + h_{eff}(t)\right)\left(S_{surface}(t) - C_{bulk}(t)\right)$$

Confirmed DLM Parameters



Transfer Experiment Modelling

Determine precipitation model parameters



Pathak et al., *Mol Pharm*, 2017

Confirm and/or Estimate Parameters

An Application: Towards Virtual Bioequivalence: Tacrolimus ASD

- Tacrolimus was first approved in 1994 – Innovator Product Prograf® - Astellas Pharma
- Tacrolimus is poorly water-soluble - commercial formulations are Amorphous Solid Dispersions (ASD)

US FDA approved tacrolimus brand and generic products

FDA Application number	Therapeutic equivalence code	Label	Dosage form and route	Strength	Rx	Applicant
Prograf, NDA # 050708	AB	Label Available	Capsule; oral	Equivalent 0.1, 1 and 5 mg base	Prescription	Astellas
Prograf NDA # 050709	AB	Label Available	Injectable; Injection	Equivalent 5mg Base/ml	Prescription	Astellas
ANDA # 065461	AB	Label Available	Capsule; oral	Equivalent 0.1, 1 and 5 mg base	Prescription	Sandoz
ANDA # 090402	AB	Not Available	Capsule; oral	Equivalent 5mg base	Prescription	Watson labs
ANDA # 090509	AB	Not Available	Capsule; oral	Equivalent 0.1, 1 and 5 mg base	Prescription	Dr Reddys Labs Ltd
ANDA # 090596	AB	Not Available	Capsule; oral	Equivalent 0.1, 1 and 5 mg base	Prescription	Mylan
ANDA # 090802	AB	Not Available	Capsule; oral	Equivalent 0.1, 1 and 5 mg base	Prescription	Panacea biotec ltd
ANDA # 091195	AB	Not Available	Capsule; oral	Equivalent 0.1, 1 and 5 mg base	Prescription	Accord Healthcare

Rahman 2013 Tacrolimus: Effectiveness, Safety and Drug Interactions

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Rahman et al, Tacrolimus: Effectiveness, safety and drug interactions. Jan 2013

Formulation Details

Manufacturer	Powder weight (mg)	Tacrolimus (mg)	HPMC (mg)	Croscarmellose na (mg)	Lactose and other minor excipients (mg)
Astellas	138 (1)	5	5.3(0.6)	5.8	122
Mylan	100(1)	5	4.8 (0.1)	5.5	84
Dr. Reddy's	139(1)	5	5.2(0.8)	8.2	121
Accord	132 (2)	5	5.5(0.1)	21.5	100
Panacea	141 (1)	5	5.4(0.8)	4.1	126
Sandoz	242 (2)	5	4.9(0.4)	6	226

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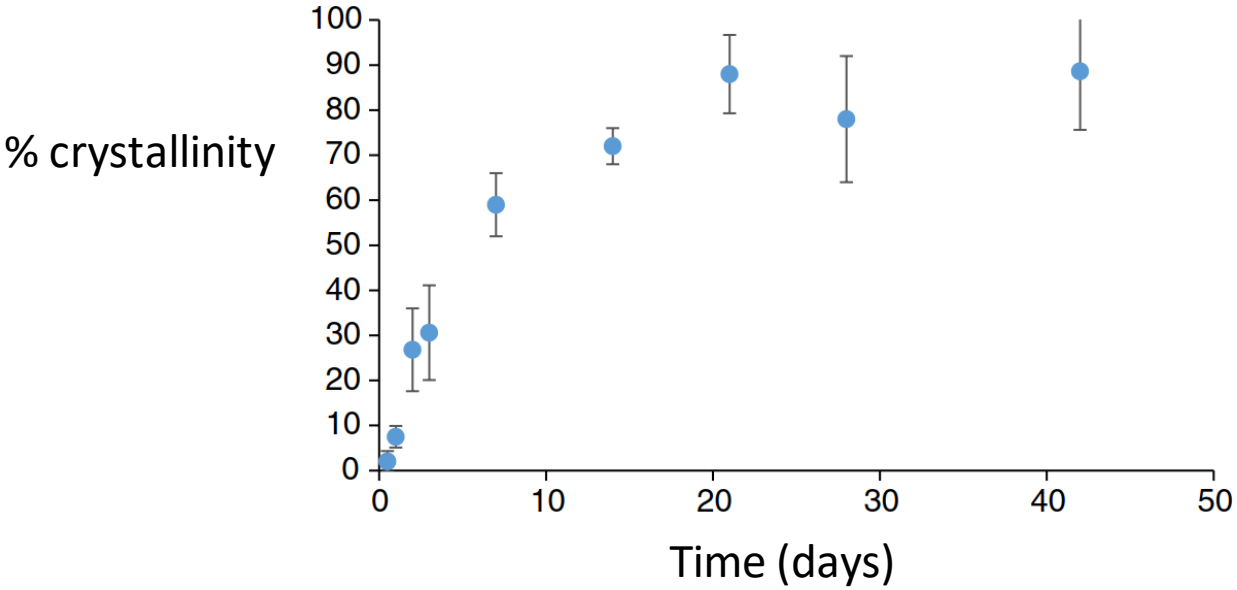
Crystallization of Tacrolimus in Generic Drug Products

Crystallisation Kinetics: Accord Powder after Capsule Storage at 40 C / 75% RH



Trasi et al. Pharm Res (2017) 34:2142

Accord

- Susceptible to crystallization under stress conditions
- Inter-batch differences in the extent of crystallisation

Q: Does (the extent of) crystallisation have implications for Bioequivalence ?

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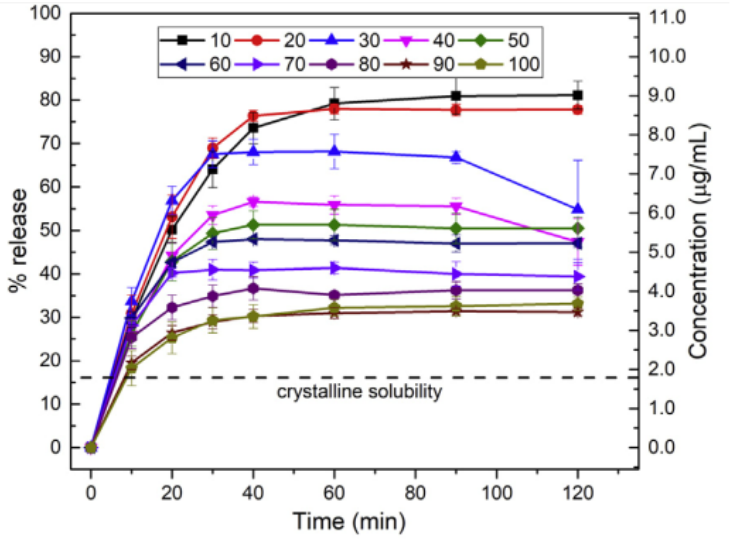
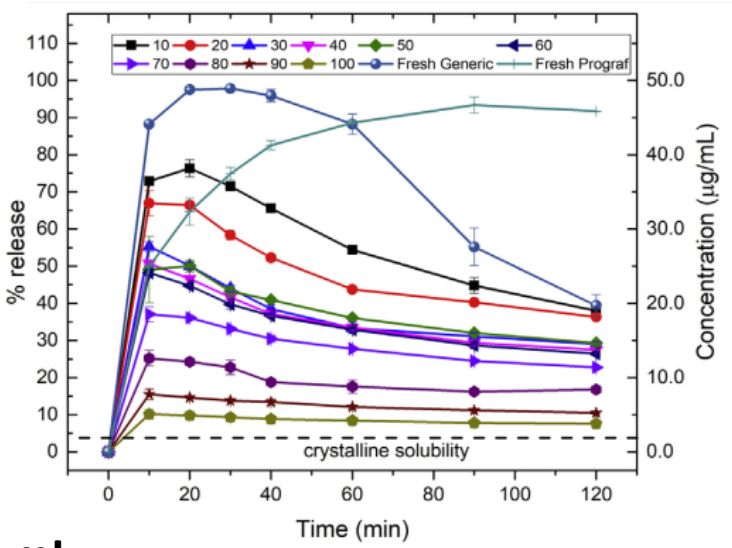
In Vitro Dissolution of Tacrolimus with Various Degrees of Crystallisation

V = 450 mL

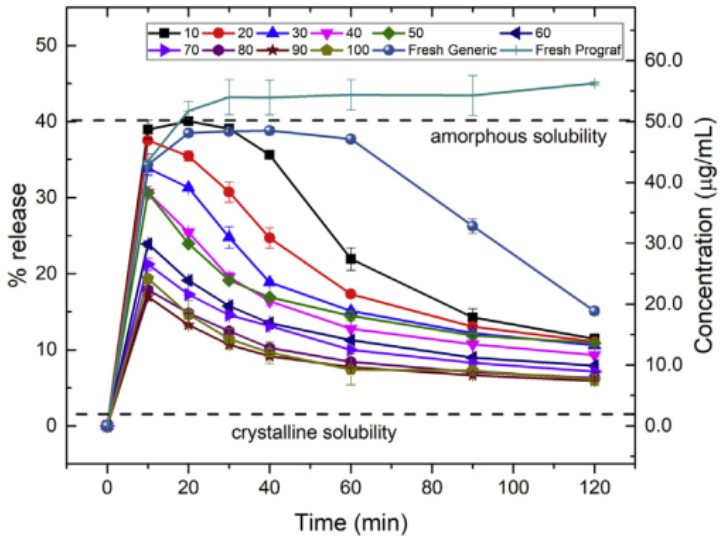


V = 100 mL



USP test medium I
50 mg/mL HPC
pH 4.5 (phosphoric acid) - Non-micellar

V = 40 mL



Purohit et al, J Pharm Sci 107 (2018) 1330

HPMC in formulation (5.5 mg)

V (mL)	HPMC Conc (ug/mL)
40	138
100	55
450	12

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Virtual Bioequivalence Analysis: Previous 3rd Party Study

Direct Input of In Vitro Dissolution Profiles into a PBPK Model

Purohit et al, J Pharm Sci 107 (2018) 1330

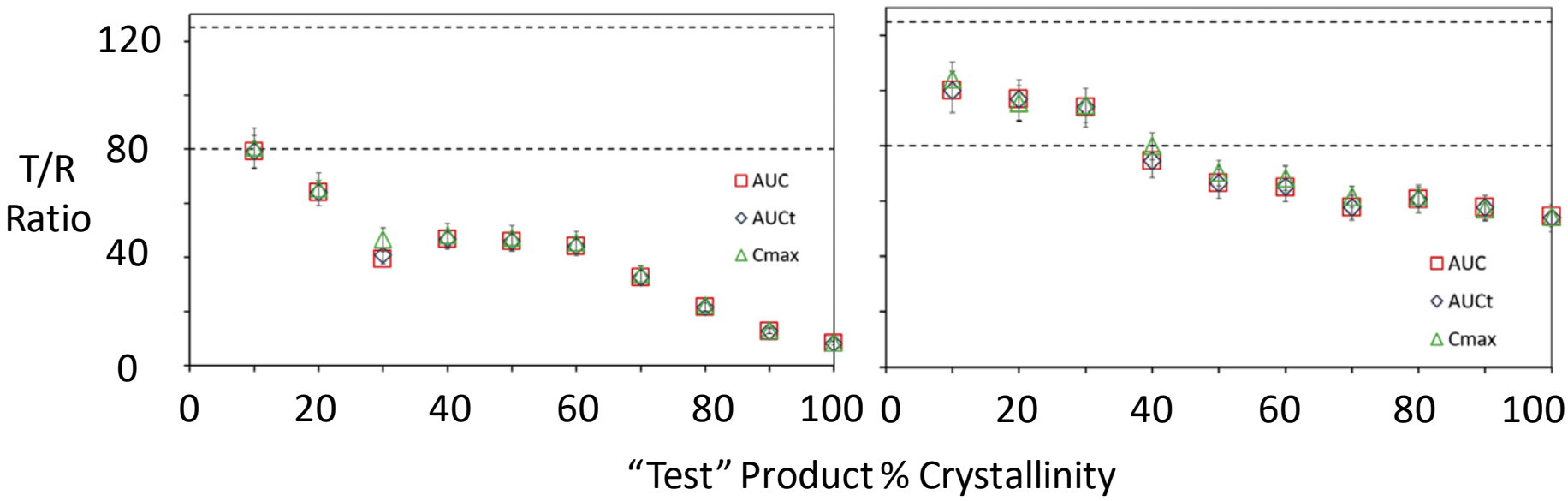
There is no absorptive phase / route in the in vitro experiments

Run the PBPK simulation,

Compare "Test" (partially crystallised) to fully amorphous "Reference" via simulated Cmax and AUC (Two-way crossover)

VBE based on 100 mL Dissolution Profiles

VBE based on 900 mL Dissolution Profiles



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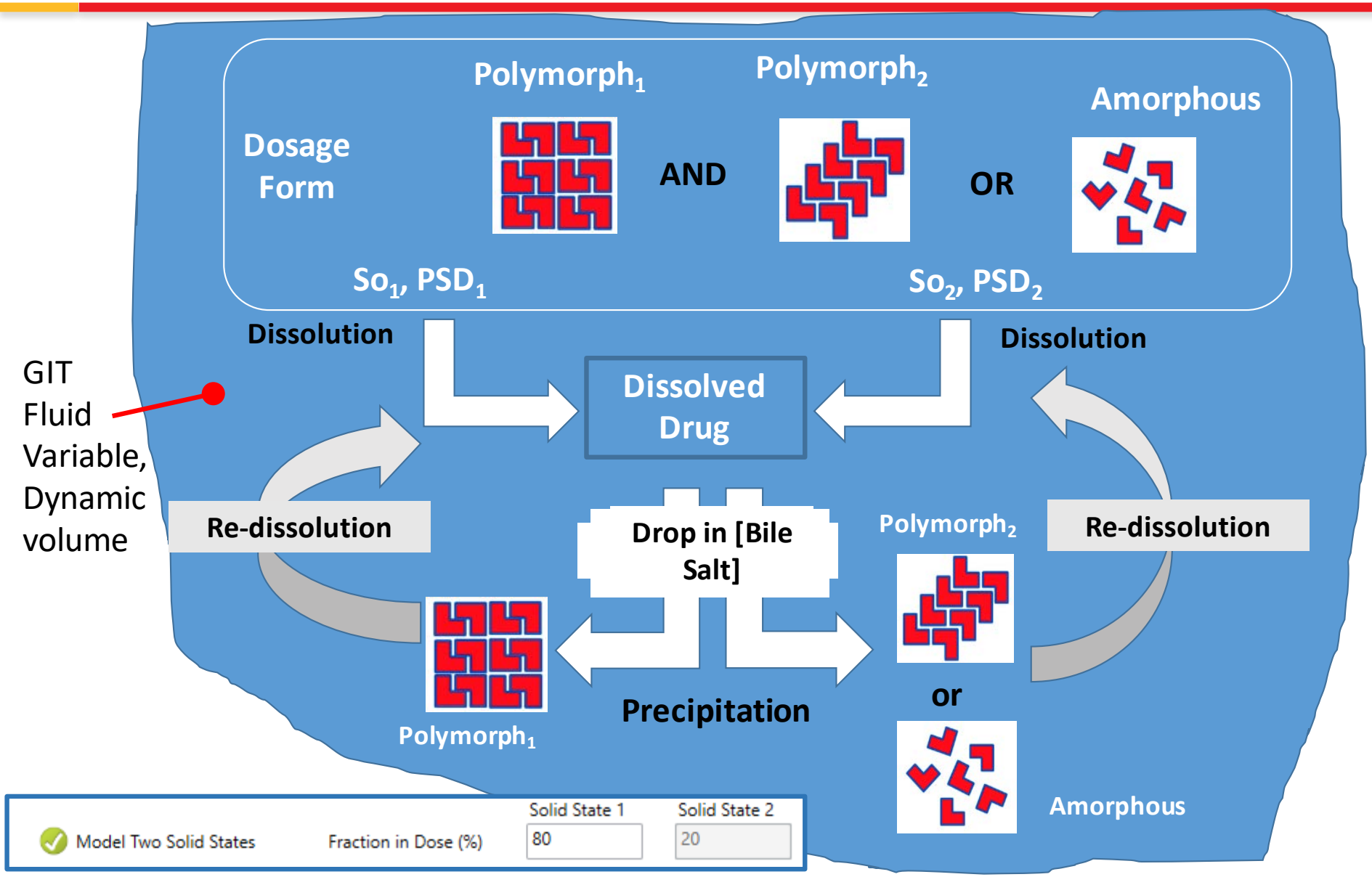
A More Mechanistic Approach: Simulation Tools for Handling Two Solid States



So – intrinsic solubility; PSD – particle size distribution

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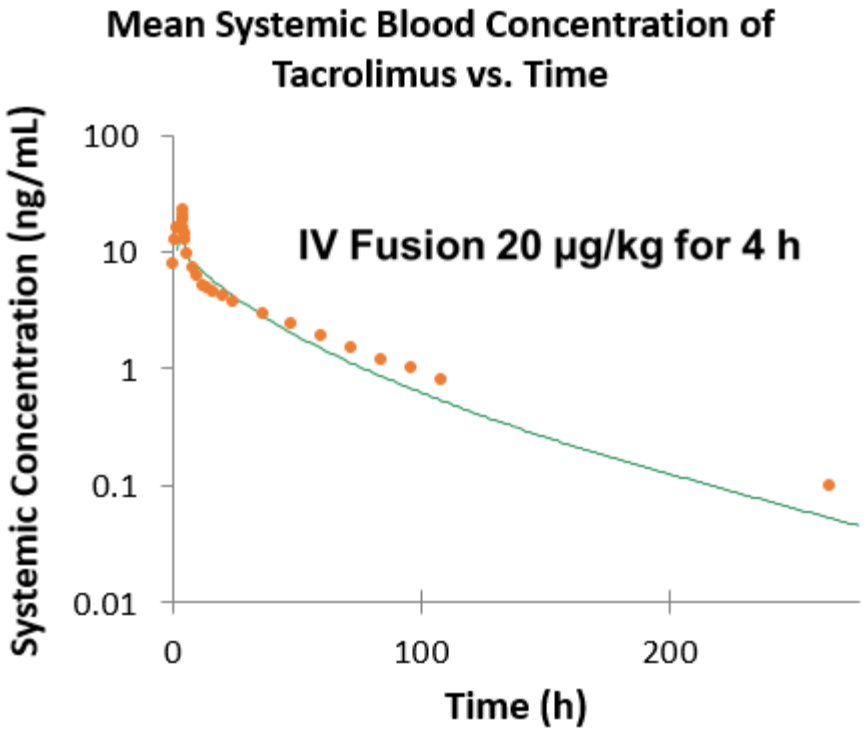
PBPK Simulations: Input Parameters

MWt 804 g/mol; logPow 3.3; Neutral

Plasma fu 0.013 (main binding protein HSA)

BP Ratio: Conc. dependent 5 - 80

Vss (L/kg) (Minimal PBPK)	17.1
Volume [Vsac] (L/kg)	1.43
SAC kin (1/h)	0.314
SAC kout (1/h)	0.048



Renal Clearance 0.048 L/h

CYP3A4/3A5 substrate with Vmax and Km for two pathways

High first pass GUT metabolism

Fg ~ 0.4

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PBPK Simulations: Gut Parameters

$P_{eff,man}$ (10^{-4} cm/s)	6.33
Formulation	Immediate Release
Dissolution Model	Diffusion Layer (DLM, W&F)
Particle Handling Model	Particle Population Balance
Intrinsic Solubility – Amorphous (Solid State 1)	50 µg/mL
Intrinsic Solubility – Crystalline (Solid State 2)	1.8 µg/mL
Particle radius (µm)	10 (sensitivity analysis)

Oral dosing (5 mg) simulations

- No precipitation to crystalline form (initial assumption)
- Amorphous solubility limit cannot be exceeded

  IF $C_{bulk,unbound} > So,amorphous$ THEN

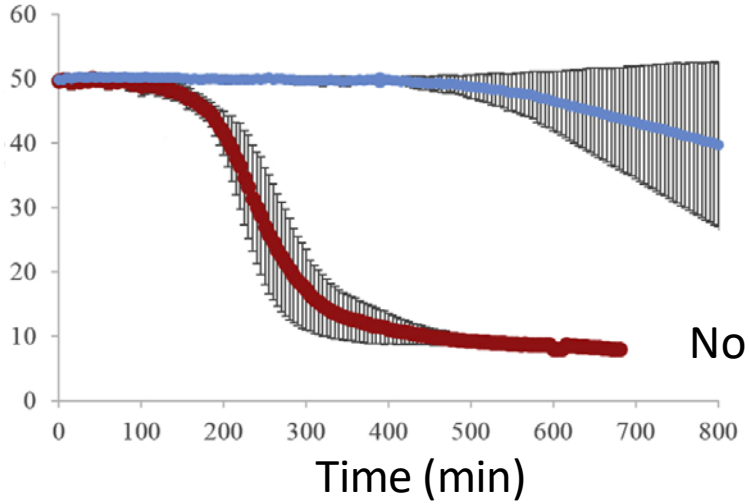
  ⇒ Immediate, rapid precipitation to amorphous material (solid? LLPS droplets?)

HPMC Impact and Anticipated HPMC In Vivo Concentrations

Induction Time for Tacrolimus Crystallisation

So,amorphous
= 50 µg/mL

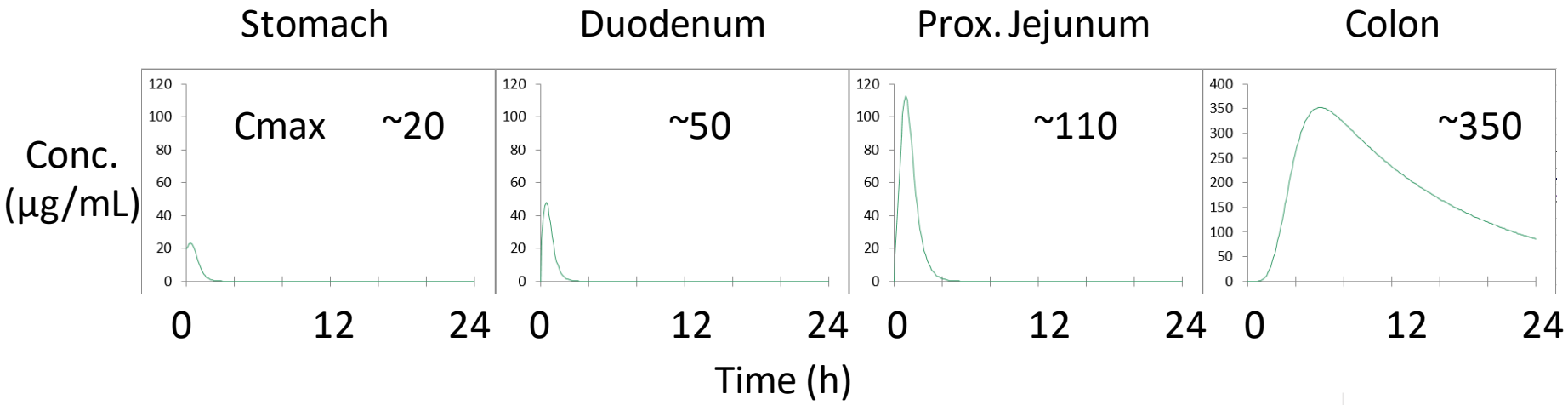
Conc.
(µg/mL)



[HPMC]
= 50 µg/mL

No HPMC

PBPK Simulated In Vivo HPMC Concentrations – 5.5 mg HPMC, 240 mL drink



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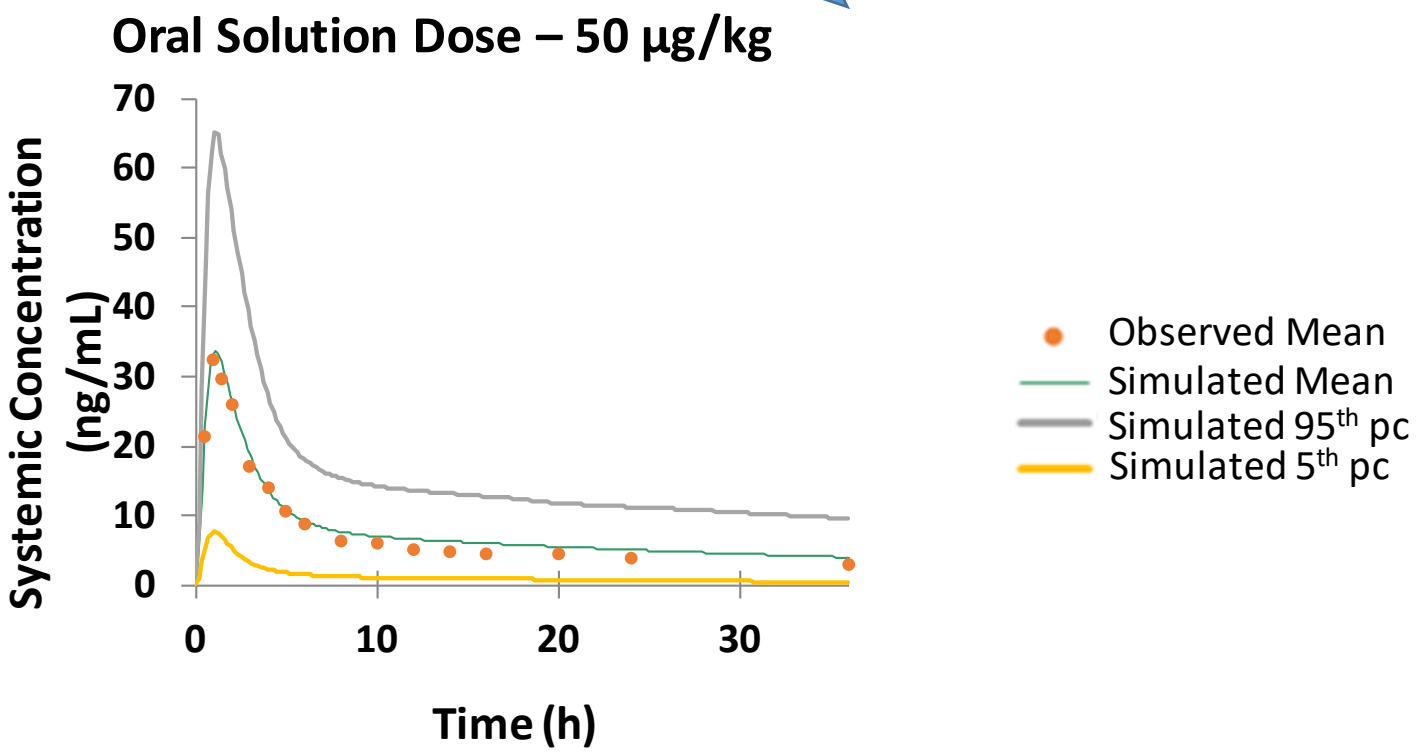
Initial Verification of the Tacrolimus File – Moller et al 1998

~ 4 mg for an 81 kg man



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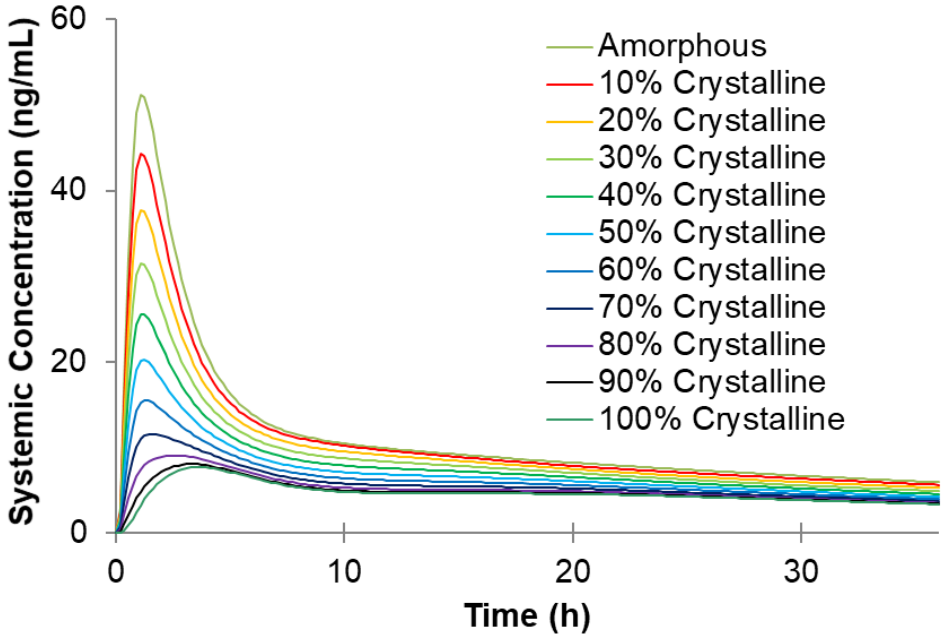
Implication of Crystallization of Tacrolimus in Generic Drug Products on BE

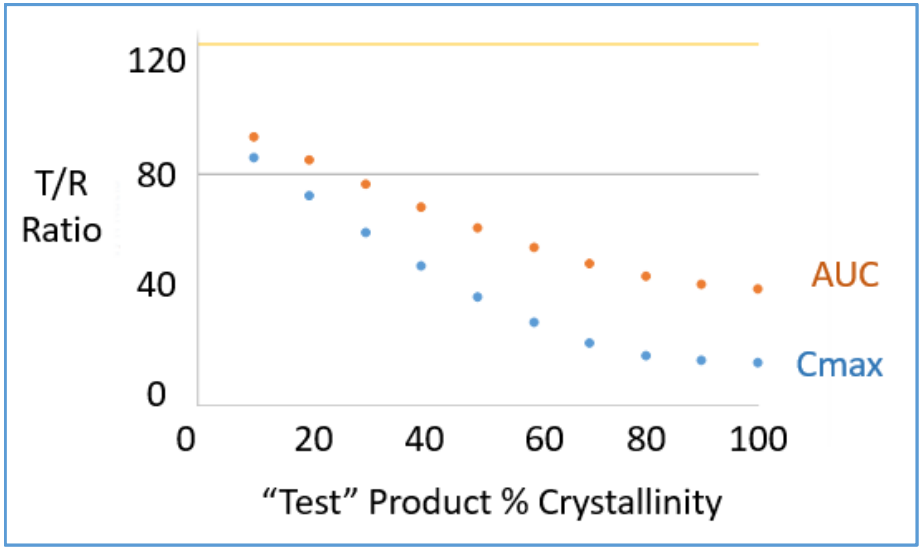
2-way Crossover VBE evaluating the PK metrics C_{max} and AUC_{0-t} of 50 Healthy Volunteers

(A) **Mean Values of Systemic concentration in blood of RV-Tacrolimus over Time**



Mean Profiles for 50 simulated subjects

(B) Test/Reference (T/R) Ratios



"Test" - partially crystallised in "dose"
"Reference" - fully amorphous

Note – Intra-occasion (within subject) variability was not included in the current BE assessment (future work)

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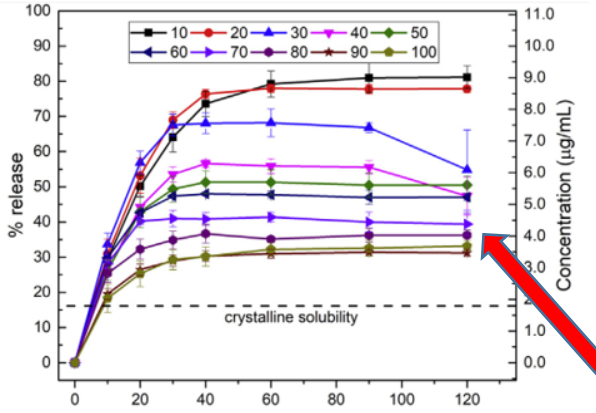
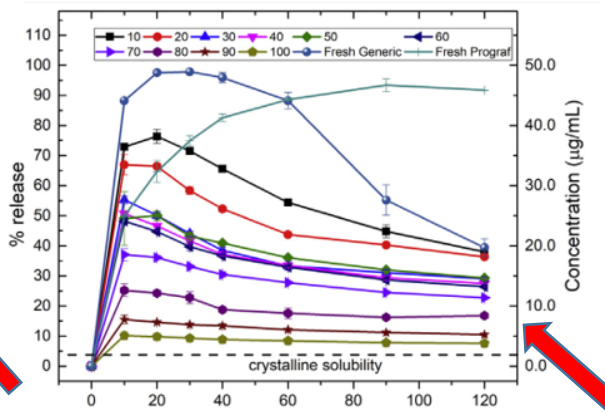
In Vivo vs. In Vitro Concentrations

In Vitro Data

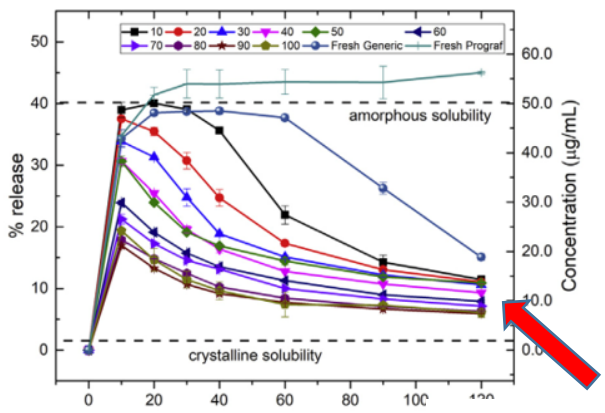
V = 450 mL



V = 100 mL

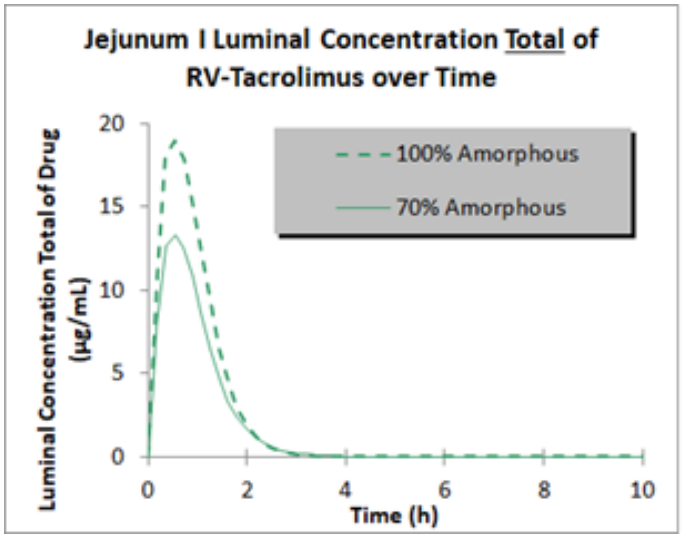


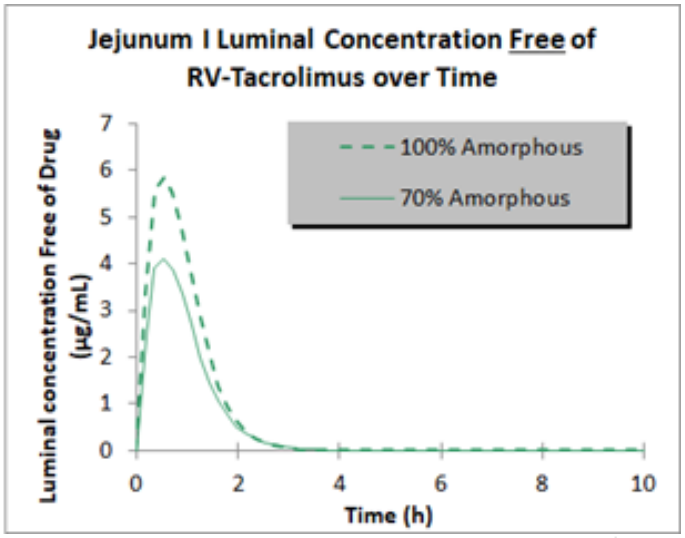
V = 40 mL



Final metastable concs 3 – 9 ug/mL 3 – 20 ug/mL 8 – 15 ug/mL

Jejunum I is Region with Maximum Luminal Fluid Concentration of Tacrolimus

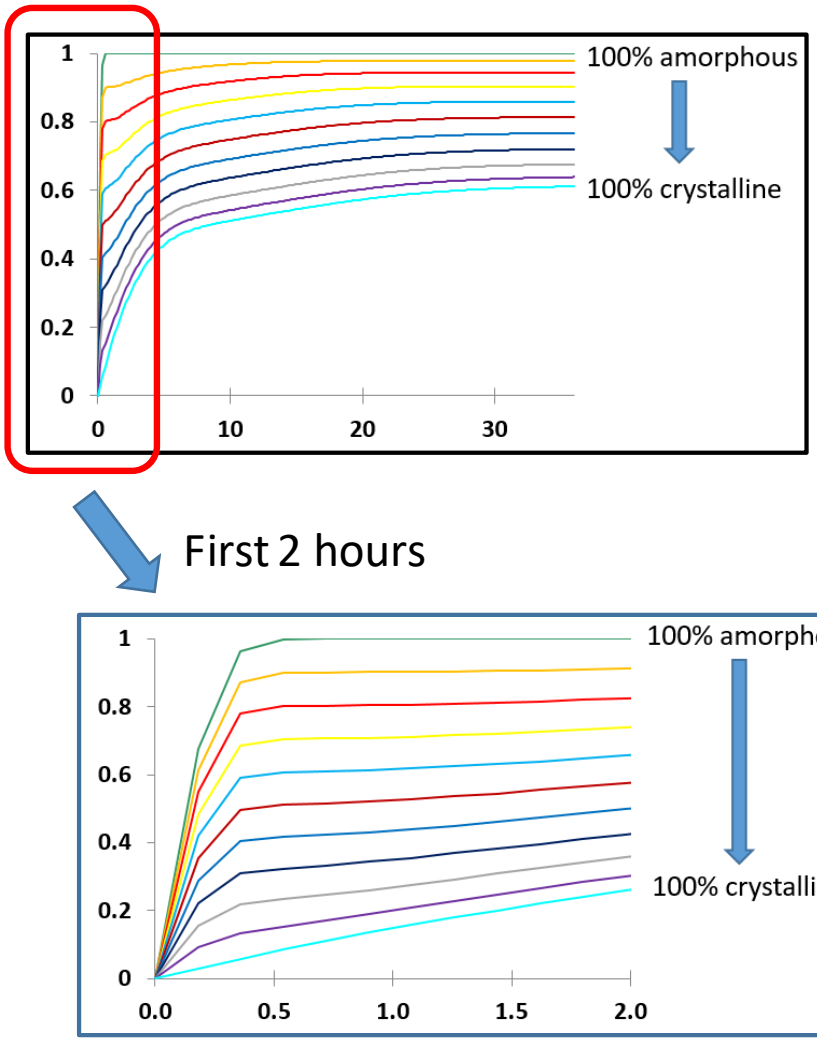




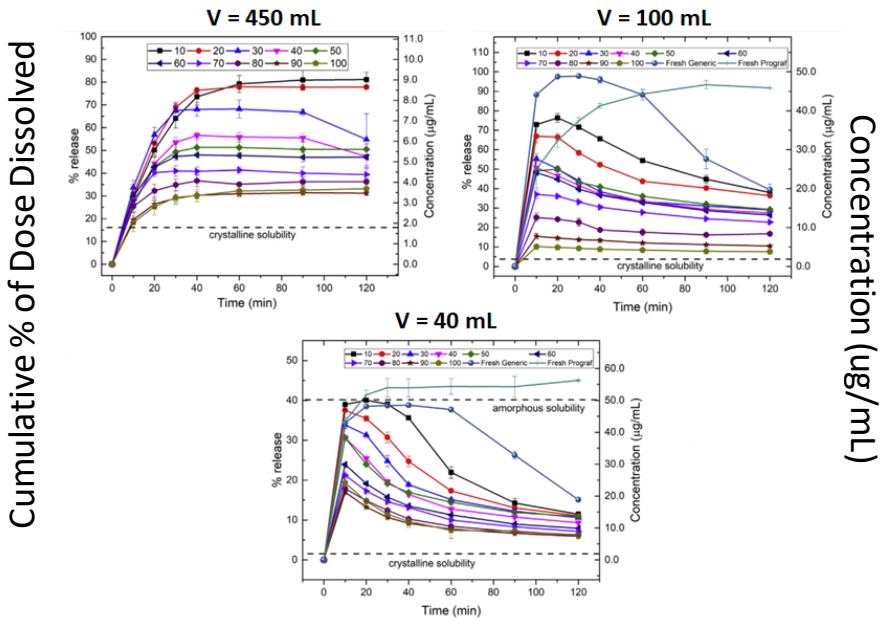
28

In silico Dissolution profiles vs Experimental Dissolution Profiles

Simulated In Vivo Dissolution



In Vitro Dissolution



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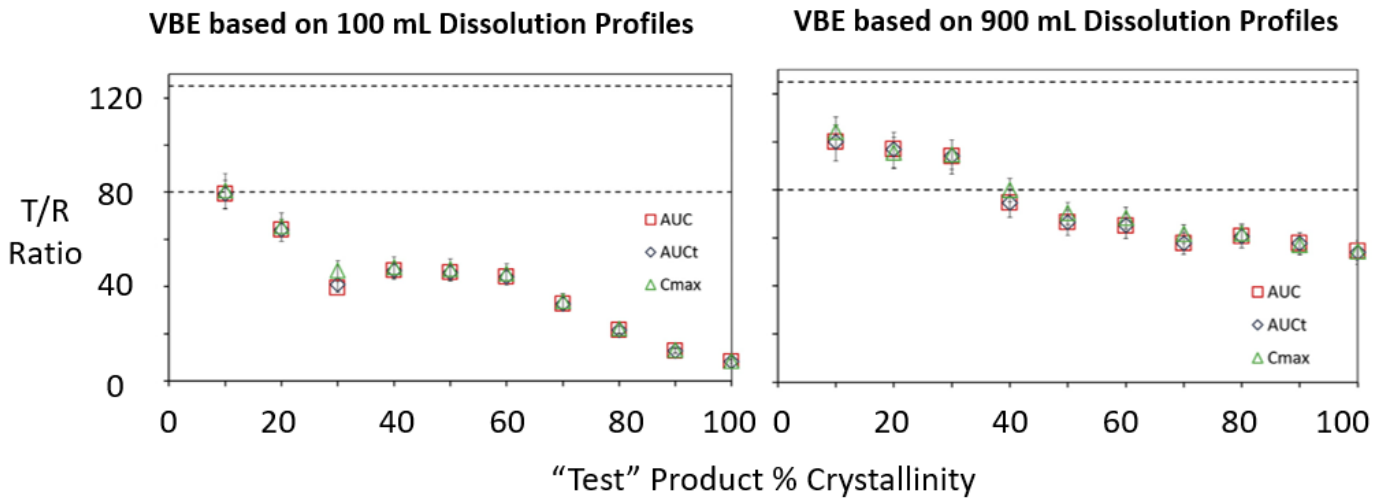
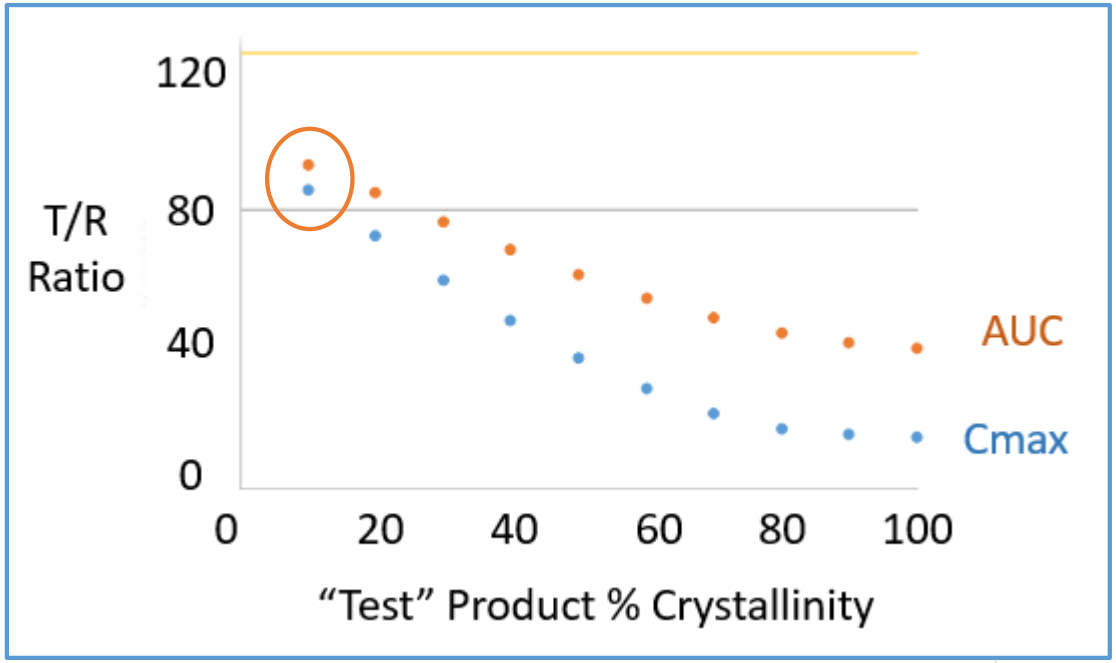
BE Comparison – Mechanistic DLM vs. Input Dissolution Profile

Direct input of In Vitro Dissolution Profiles (3rd party study)



Mechanistic Dissolution Model with two solid states



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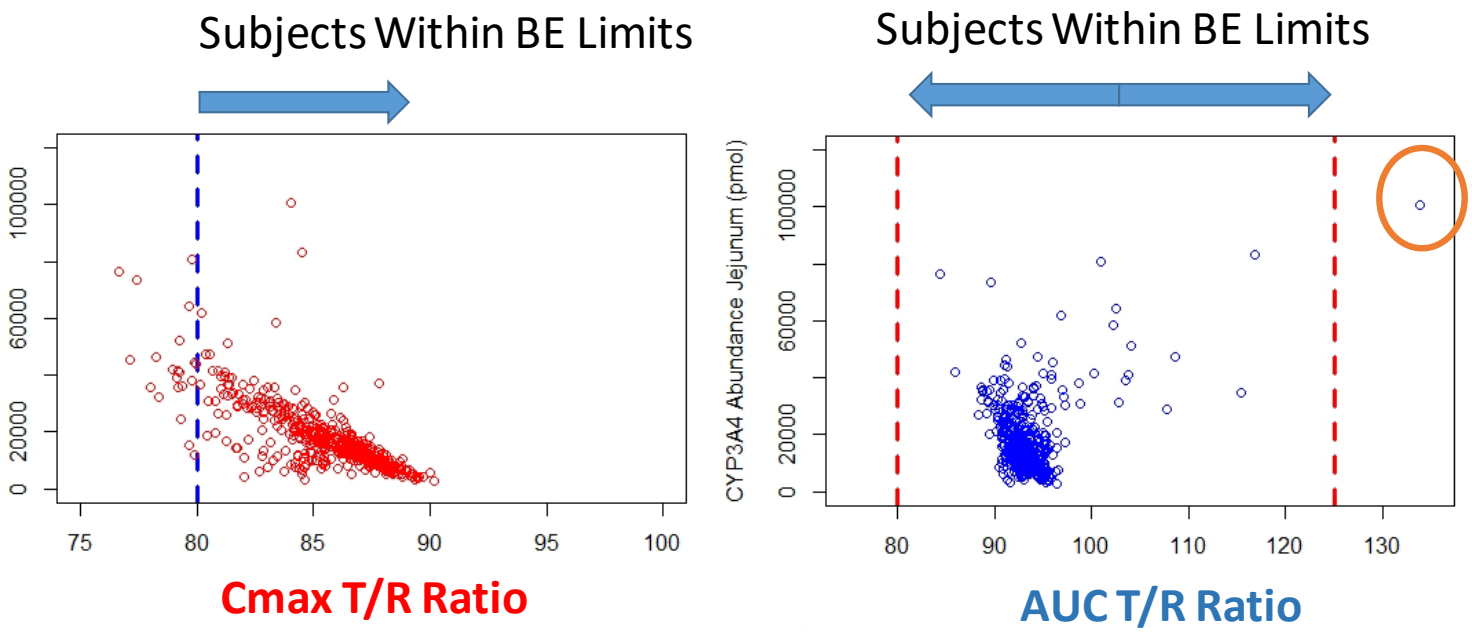
Exploration of Co-variates – CYP3A4/5 Jejunal Abundance

Simulation – Reference – Amorphous (100%)
– Test – Amorphous (90%) + Crystalline (10%)

Jejunum CYP3A4 Abundance (pmol)



Each marker point relates to a single subject

Residence time in the gut lumen is also a key covariate

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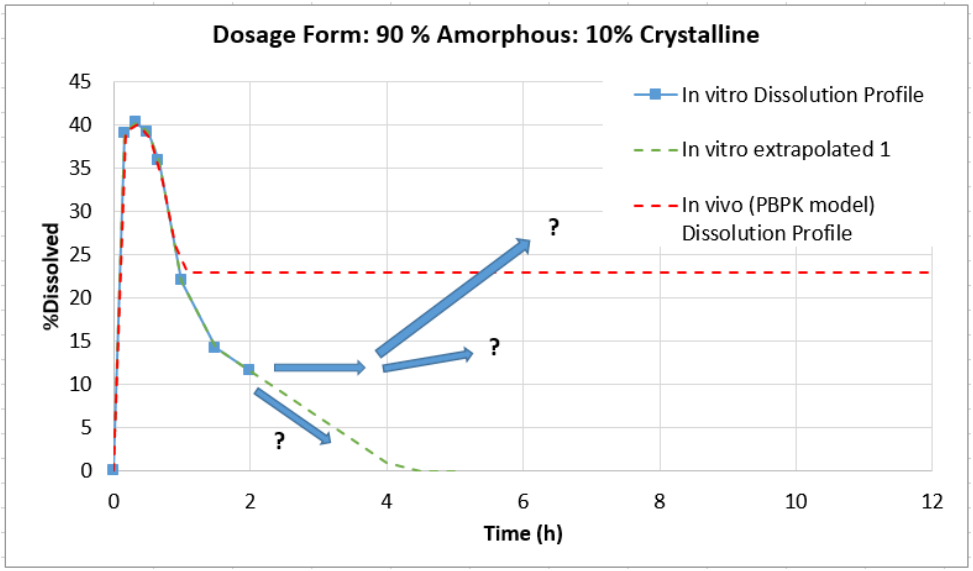
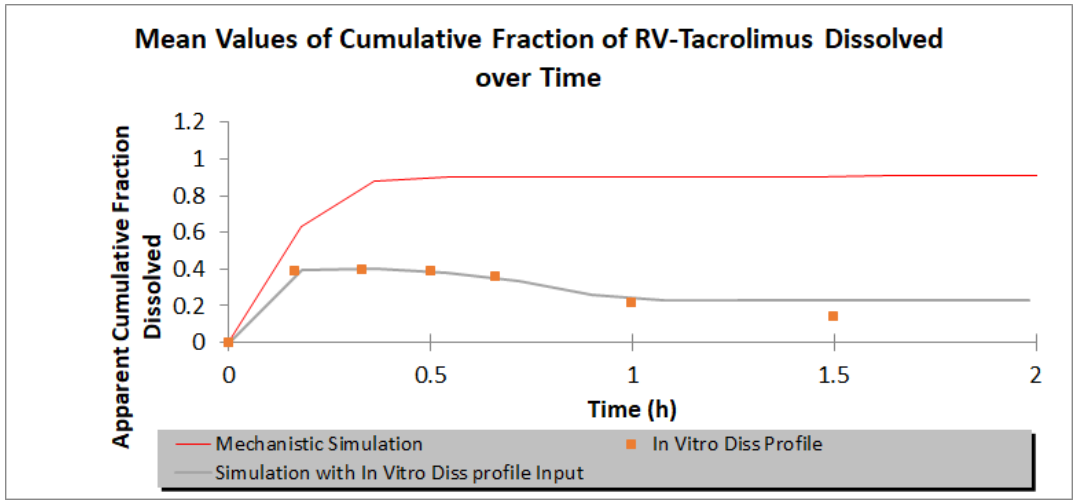
31

Tacrolimus: 90% Amorphous: 10% Crystalline Simulations





fa cannot exceed cumulative fraction dissolved

Summary

Further work tacrolimus

- Metastable concentrations observed in vitro ?
- Add in WSV, further analysis of covariates related to bioinequivalence
- Obtain clinical results to verify

Mechanistic PBPK Models

Can help interpret in vitro data and translate it to in vivo

Can capture regional and inter-individual differences in physiology

Can extrapolate to different physiologies (paediatric, disease, ethnic)

Can be used to define safe spaces for dissolution

Can be used to perform Virtual Bioequivalence analyses

PBPK modelling has come a long way …

… and has a long way to go … formulation, multiple excipients …

Acknowledgements

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NIH-003-ABSORPTION GRANT

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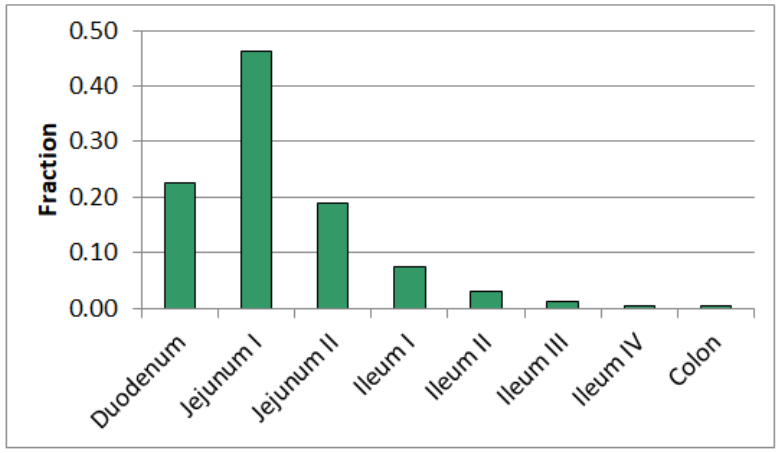
Questions?

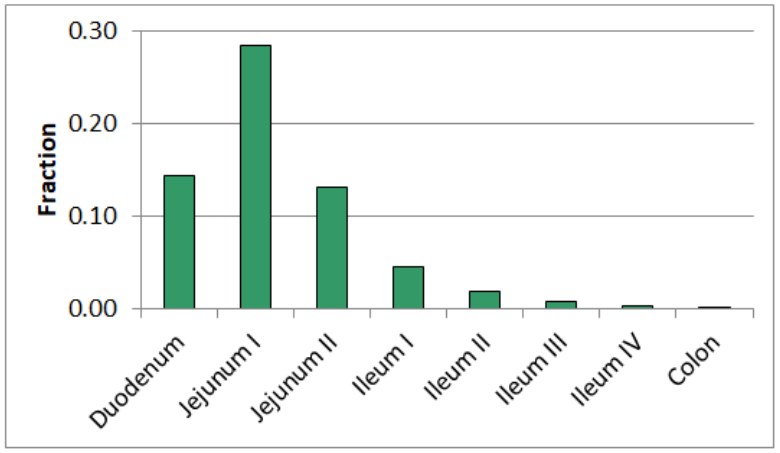
Regional fa and Fraction Metabolised (Population Representative)

Regional fa

Regional Fraction Metabolised

100% Amorphous

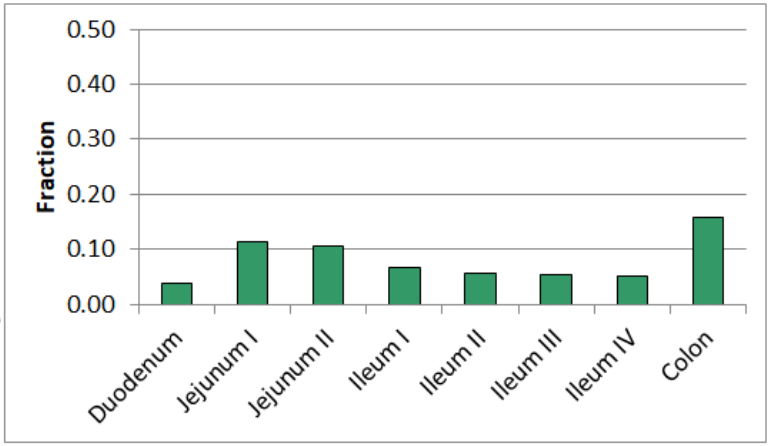


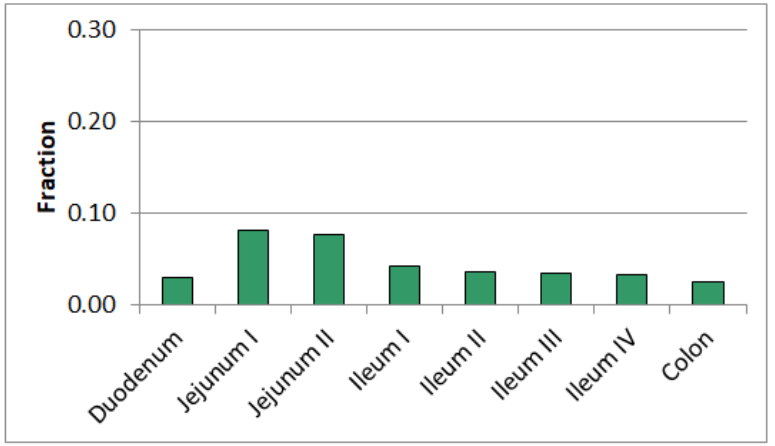


Overall fa: 1 (0.99-1)

Fg: 0.37 (0.13 – 0.72)

10% Amorphous / 90% crystalline





Overall fa: 0.64 (0.39-0.9)

Fg: 0.45 (0.24 – 0.72)

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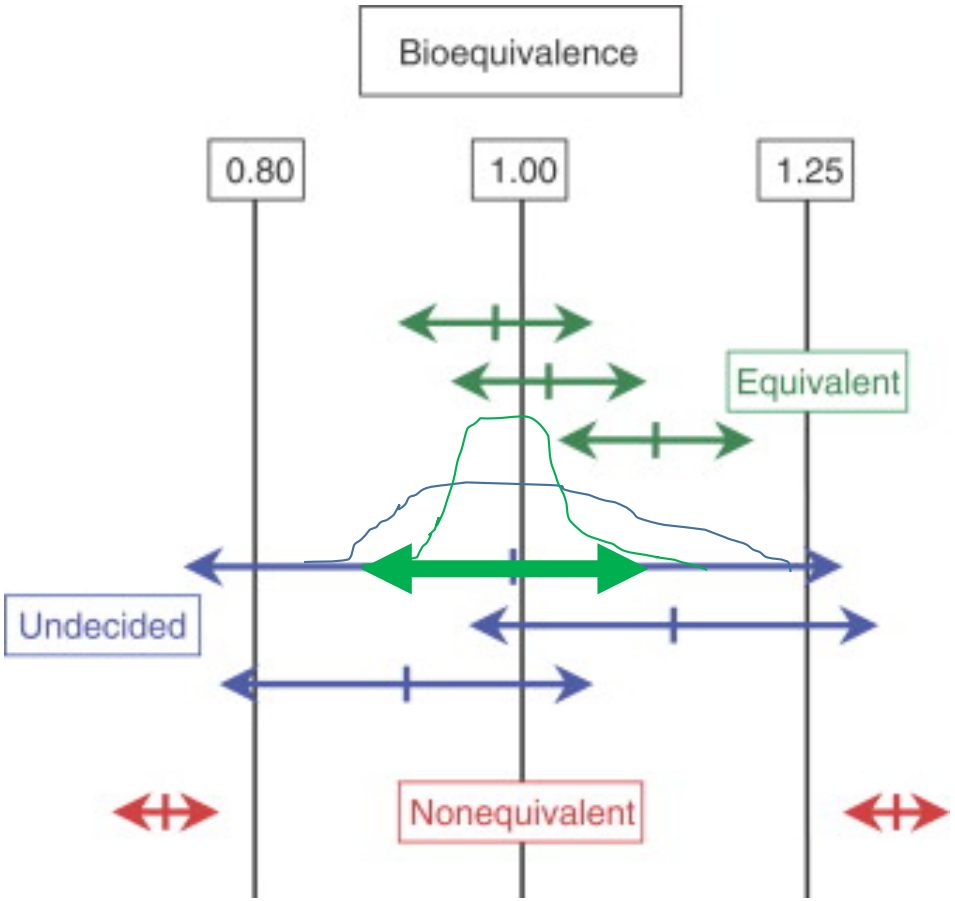
Bioequivalence is Simple ;O)

- Take the ratio between the geometric means of PK parameters for two formulations
- Calculate a 90% confidence interval around the geometric mean
- Does this fall within 0.8 – 1.25?
  - The limit may be scaled for highly variable or narrow therapeutic index drugs
- What if it it's undecided?



- As you know, when you increase the sample size, the confidence intervals get smaller
- Sample size calculations can be used to estimate the number needed, for a particular power
- Overpowering a study is frowned upon ("forced bioequivalence")
- 80% power is typical (note that this means 1 in 5 studies will fail to show bioequivalence just by chance)

Image: Tillement & Tremblay 2007

37