Dissolution coupled with oral absorption modeling to predict clinically relevant performance

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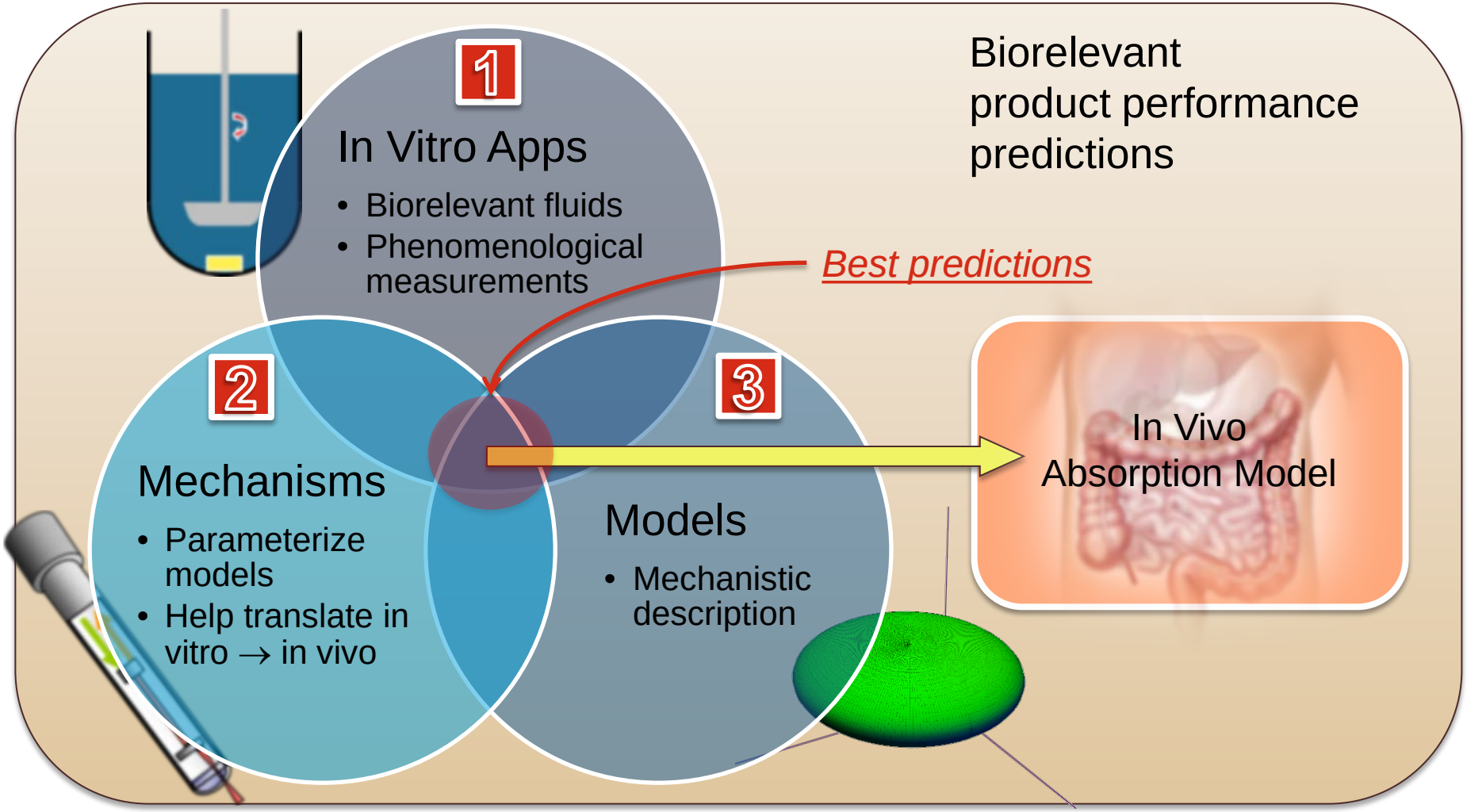
Outline

- Biorelevant tools useful for drug development
- Integrating in vitro and in silico models to predict in vivo performance
- Three case studies

Approach to biorelevant methods



Biorelevant tools

1. In vitro apparatuses
   - USP-type paddle methods
   - One-step and two-step
   - Artificial Stomach Duodenum (ASD) model
   - Scaled-down two-step dissolution
   - Microcentrifuge test

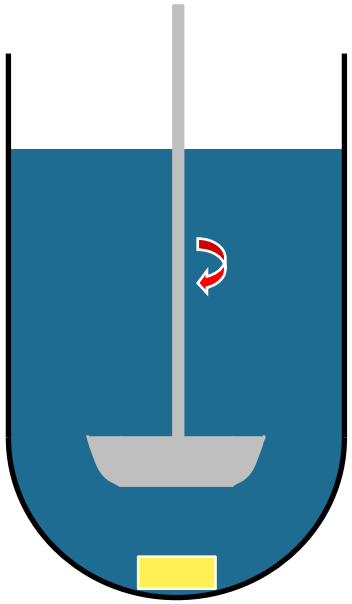
Biorelevant fluids
- SGF (FaSSGF, FeSSGF)
- FaSSIF, FeSSIF
- Simulated saliva

See, for example:
E. Jantratid and J. Dressman, “Biorelevant Dissolution Media Simulating the Proximal Human Gastrointestinal Tract: An Update,” *Diss. Tech.*, (2009) **16**(3), 21.

USP-type methods: Example

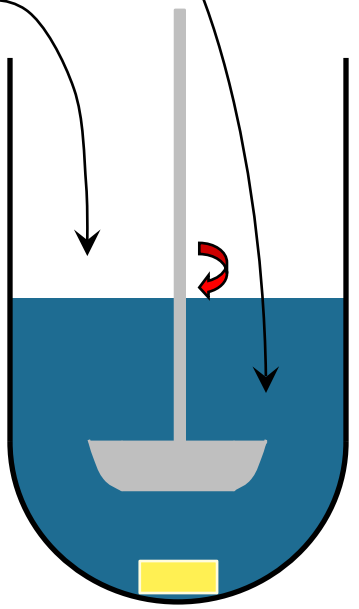
One-Step Dissolution

- 900 mL FaSSIF
- 75 rpm paddle

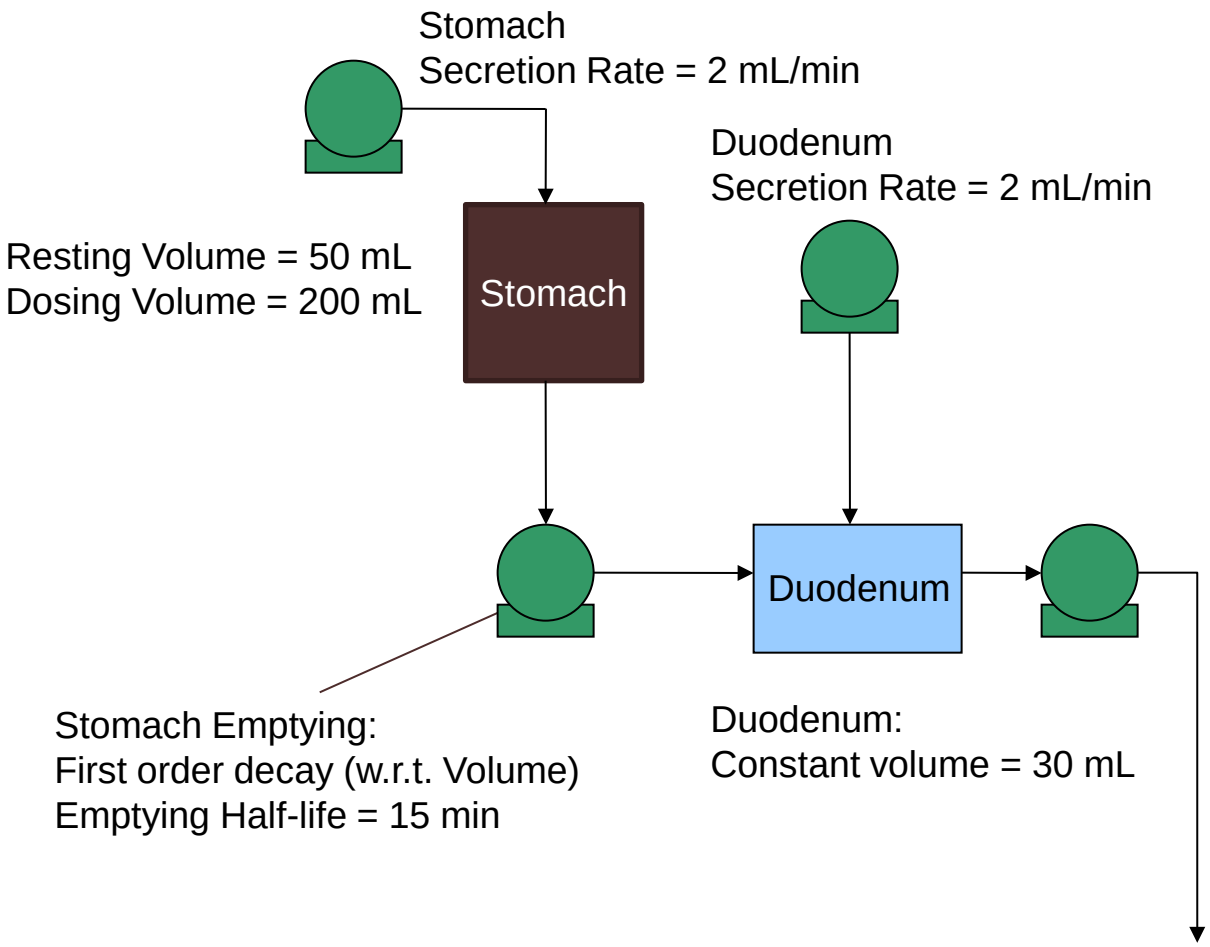


Two-Step Dissolution

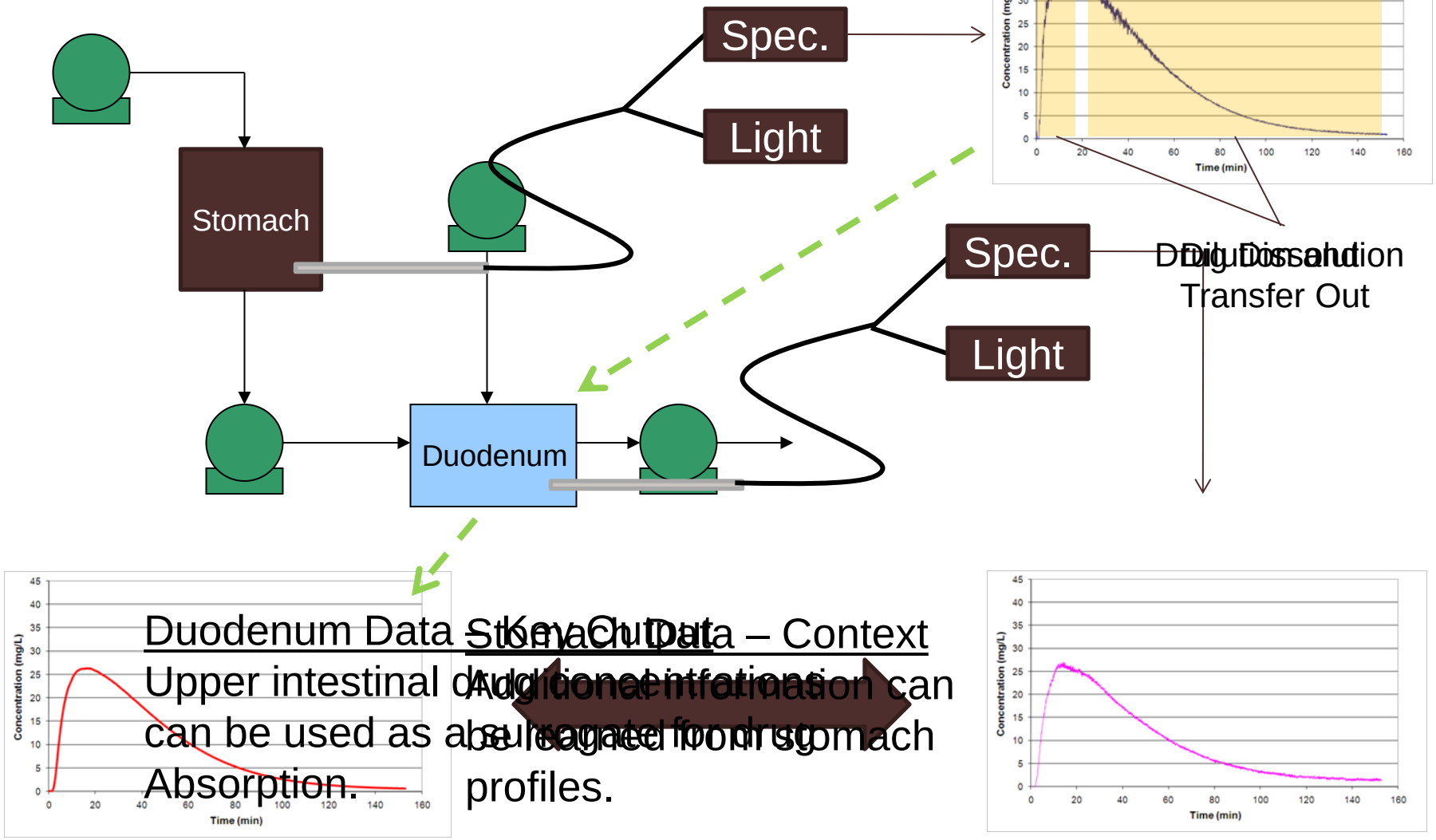
- 300 mL 0.01 N HCl
- 75 rpm paddle
  → 20 min
- 300 mL FaSSIF
- 75 rpm paddle
  → 260 min



ASD model



ASD measurements



Duodenum Data – Key Output

Upper intestinal data can be used as a surrogate for drug Absorption.

Stomach Data – Context

Additional information can be leveraged from stomach profiles.

Biorelevant tools

2. Mechanisms
   - Rotating disk dissolution (RDD, intrinsic dissolution)
   - Flow-through imaging
   - NMR
   - Focused beam reflectance measurement (FBRM)

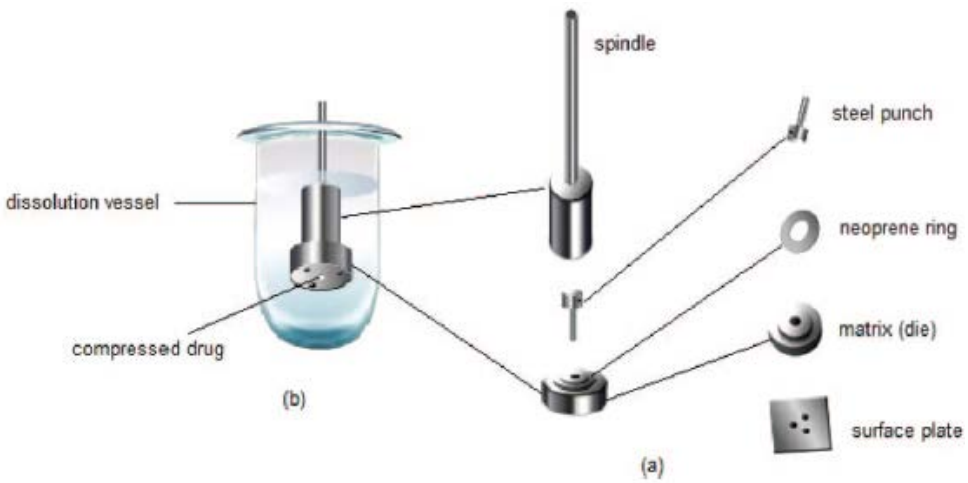
Diffusion coefficient

- Intrinsic dissolution rate: Solve Navier-Stokes for a rotating disk (Levich equation)

$$D_{IDR} = \left(\frac{IDR}{0.62 C_s}\right)^{\frac{3}{2}} \cdot \left(\frac{\eta}{\rho_f \cdot \omega^3}\right)^{\frac{1}{4}}$$

- Stokes-Einstein: laminar viscous drag on a spherical molecule

$$D_{SE} = \frac{k_B \cdot T}{6\pi \cdot \eta \cdot \left(\frac{3M_w}{4\pi \cdot N_A \cdot \rho}\right)^{\frac{1}{3}}}$$



Diffusion coefficient by other methods

- Flow-through UV Imaging (SDi300)

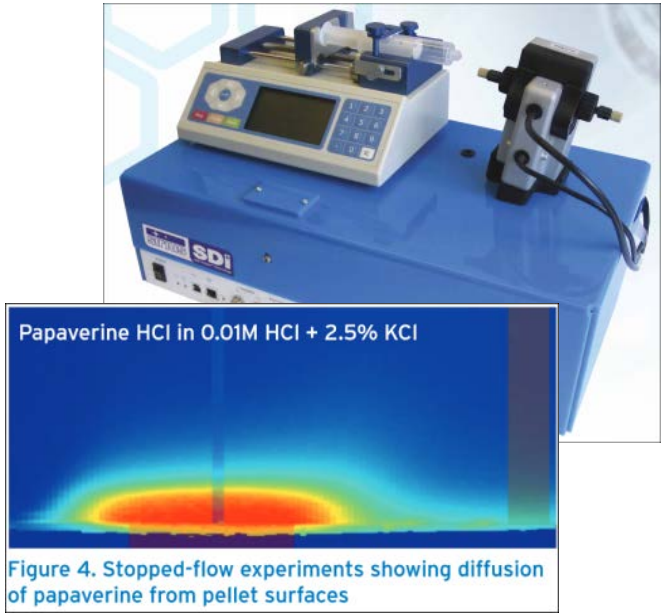
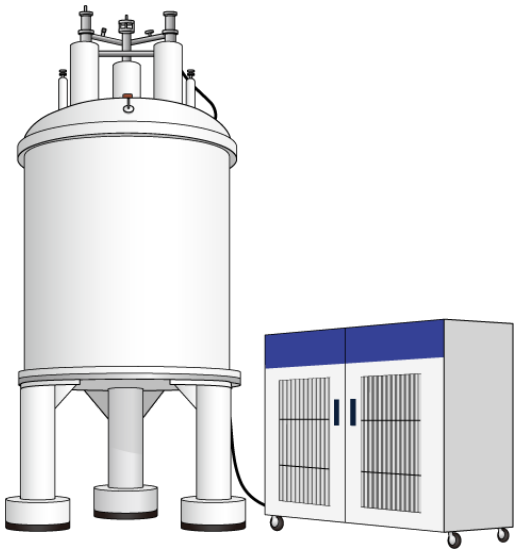


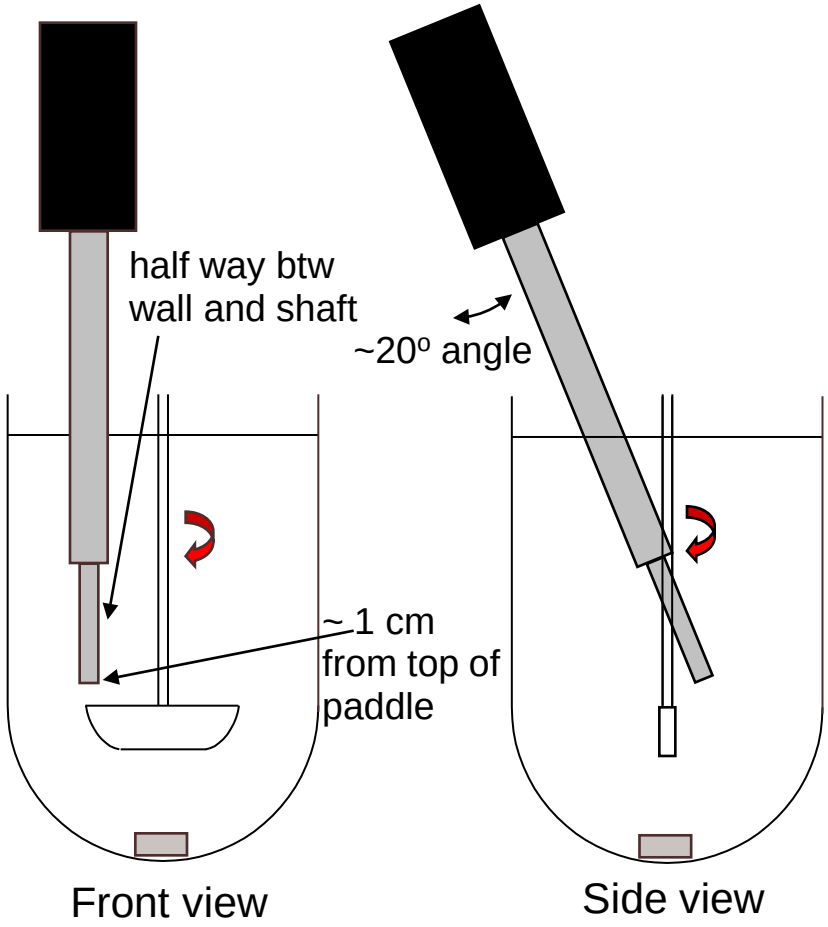
Figure 4. Stopped-flow experiments showing diffusion of papaverine from pellet surfaces

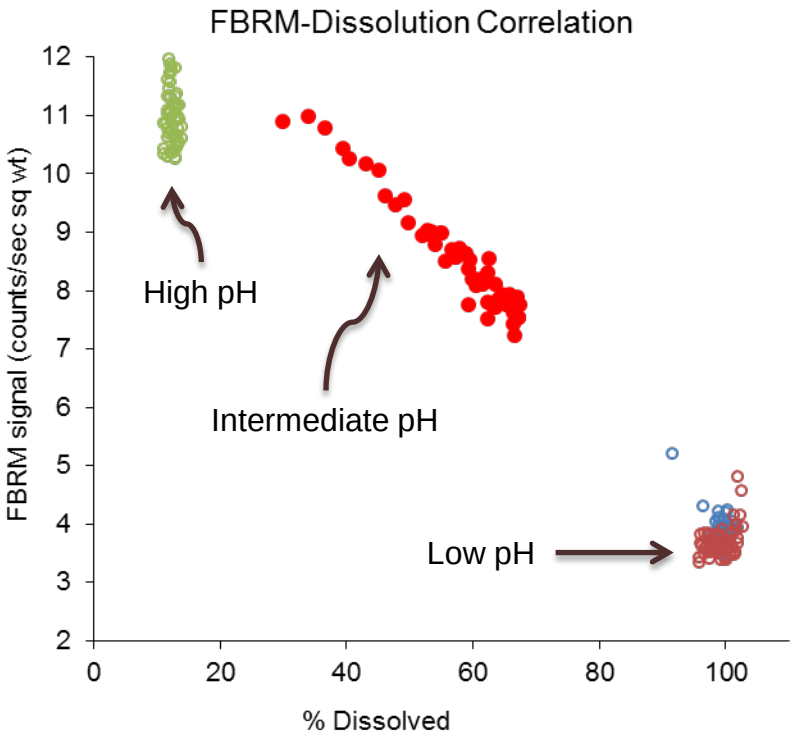
http://www.sirius-analytical.com/system/files/Sirius%20Application%20Note%20304-13%20UK%20web.pdf

- **D**iffusion-**O**rdered **S**pectroscop**y** 2D NMR



Lasentec® FBRM® experiments

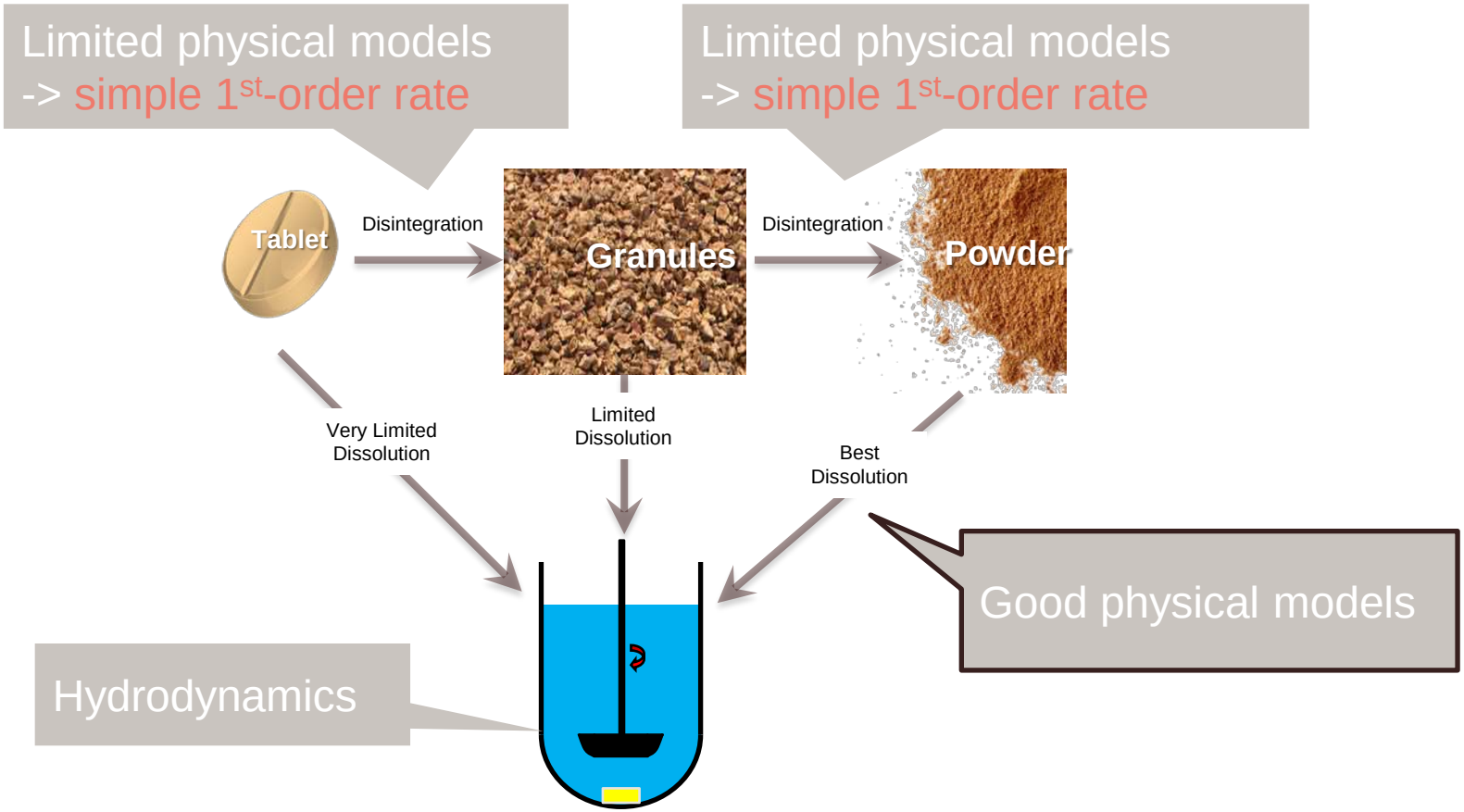




Slide courtesy of Carrie Coutant

Biorelevant tools

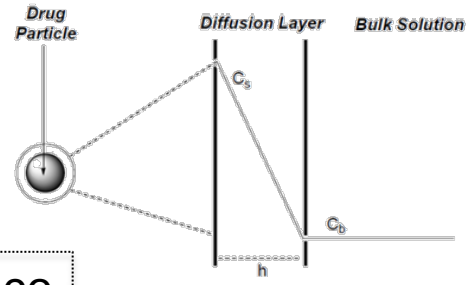
3 Dissolution Models



Dissolution model

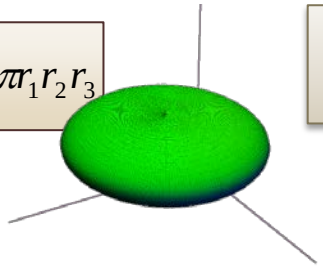
- Noyes-Whitney dissolution model, with several enhancements.

$$\frac{dC}{dt} = \frac{DS}{hV}(C_s - C_t)$$



Tablet and granule disintegration

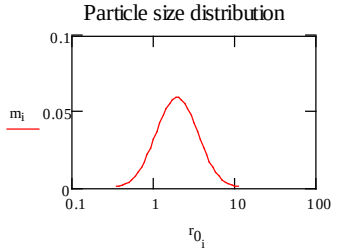
$$V = \frac{4}{3}\pi r_1 r_2 r_3$$



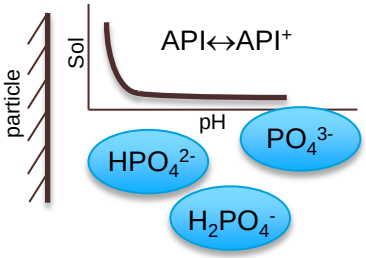
$$\left.\frac{\partial r_{1,2,3}}{\partial t}\right|_{\min(r_{1,2,3})>0} = -k_{tablet}$$

$$\left.\frac{\partial r_i}{\partial t}\right|_{r_i>0} = -k_{gran}$$

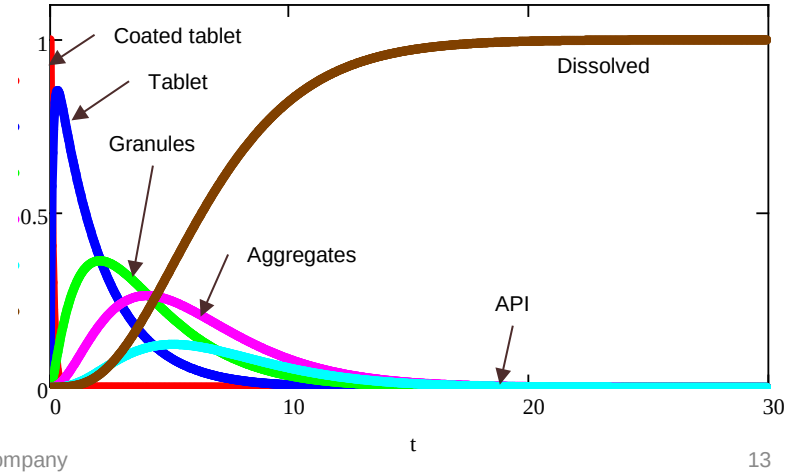
Population balance



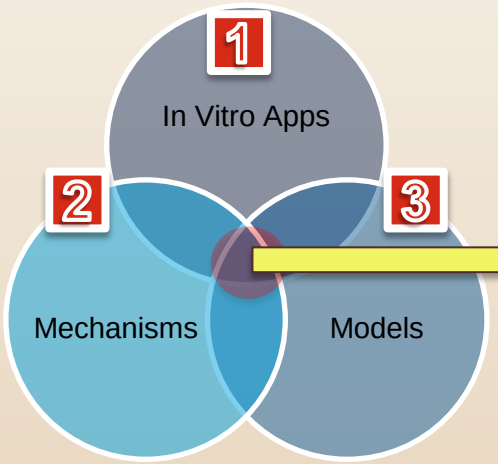
Surface concentration



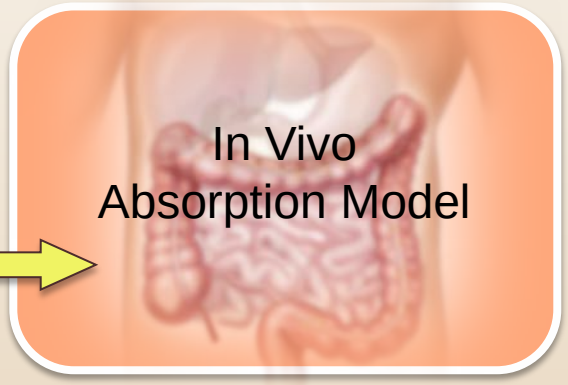
Henderson-Hasselbalch, pH and buffer capacity



In vitro-in silico approach



Biorelevant
product performance
predictions



Johnson model

Fitted D

z-factor

Fitted PSD

Input CR profile

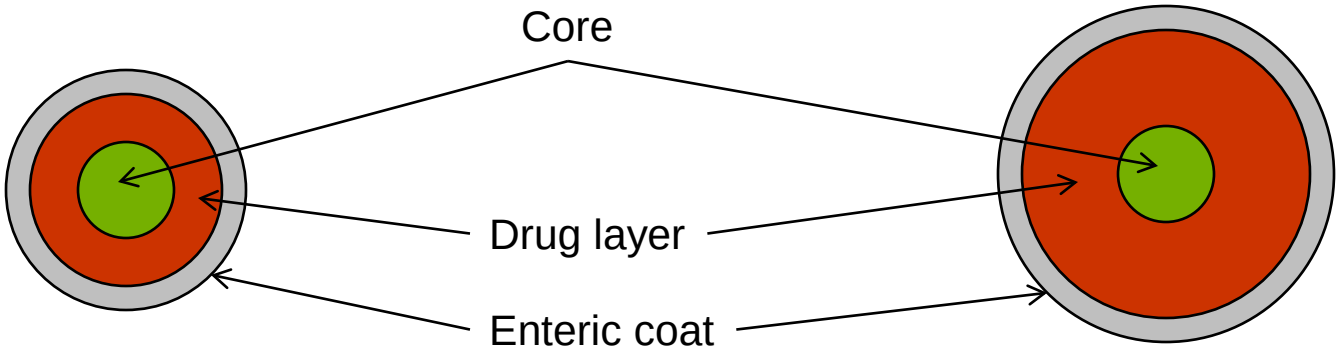
Mechanistic parameters

Case 1 – Modified release formulation

- Overall development challenge
  - Increase the throughput of the process by a simple formulation change: increase the drug-containing layer thickness thereby increasing the drug load.

- Formulation A
  - Spray-coated bead
  - Bead enteric coated

- "New" high-drug load formulation B
  - Drug load increased ~50% by spray-coating more drug on bead
  - Other aspects remain the same

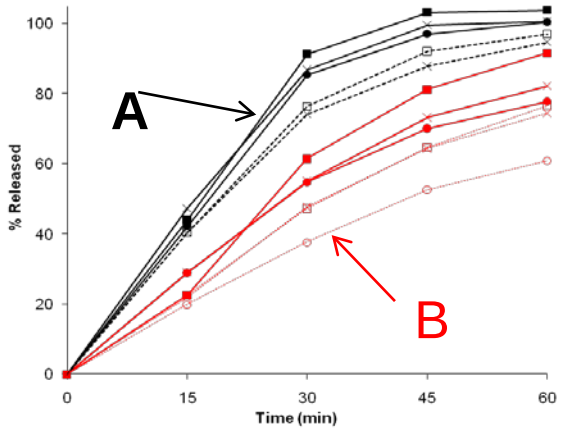


* Some details of formulation omitted for clarity

Sperry et al., *Molecular Pharmaceutics*, **2010**, *7*, 1450–1457.

In vitro dissolution

- Different strengths tested in vitro by different methods



- Many method conditions explored
  - e.g. Both paddles and baskets specifically investigated.

- Dissolution is different between formulations
- And difference is not an artifact of the test

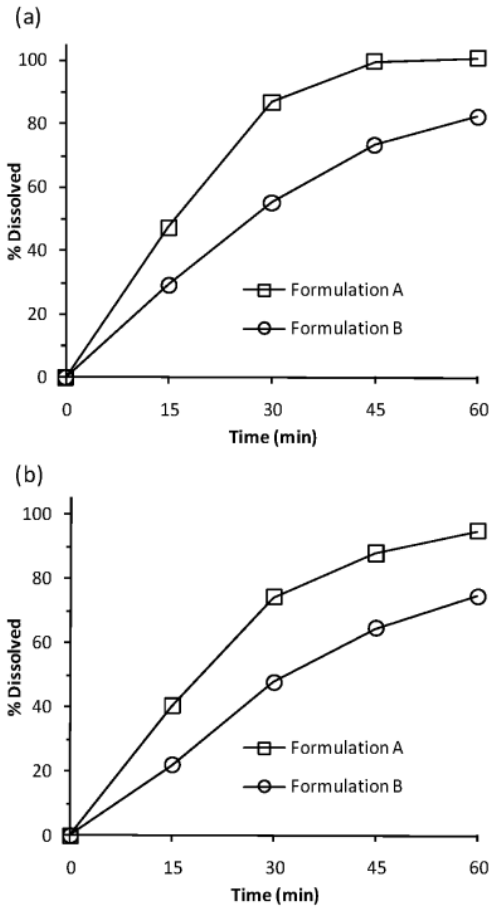
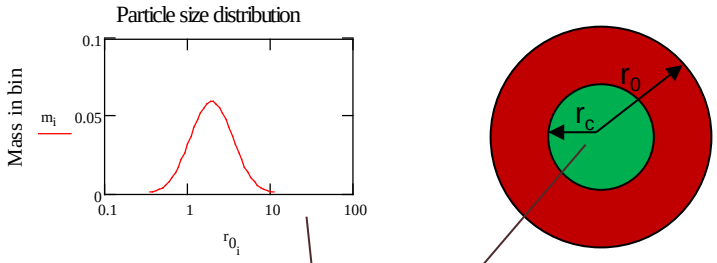


Figure 2. Average *in vitro* dissolution profiles ($n = 6$) of pellet formulations A and B by (a) USP method A and (b) USP method B. In all cases the standard error is 2% dissolved or less.

Sperry et al., *Molecular Pharmaceutics*, **2010**, *7*, 1450–1457.

In vitro modeling



$$\frac{dX_s}{dt} = \frac{-3 \cdot D \cdot X_0}{\rho \cdot h \cdot \left(r_0^3 - r_c^3\right)} \cdot \left[\frac{X_s}{X_0} \cdot \left(r_0^3 - r_c^3\right) + r_c^3\right]^{2/3} \cdot \left(C_s - \frac{X_d}{V}\right)$$

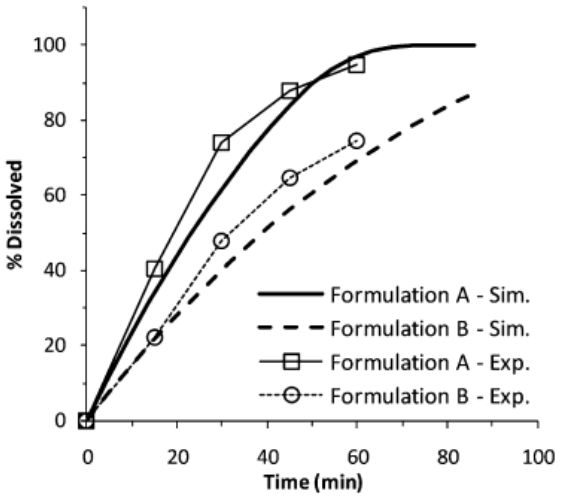


Table 1. Pharmacokinetic Parameter Results of Sensitivity Analysis Showing Impact of Changes to the Release Profile

	Weibull time-scale parameter (*A*)		
parameter	0.04	0.15[a]	1.1
time to reach 80% (min)[b]	41	56	114
relative C_{max}	1.00	1	0.91
relative AUC (0−∞)	1.00	1	0.99
t_{max} (h)	2.4	2.5	3.46

[a] The Weibull function fit to formulation A gives a time-scale parameter $A = 0.15$. [b] The time to reach 80% dissolved for the dissolution profile described by the Weibull function.

- Agreement suggests differences in release rate observed *in vitro* are due **purely to the difference in surface area**.

Sperry et al., *Molecular Pharmaceutics*, **2010**, *7*, 1450–1457.

Bioequivalence study

- **Met bioequivalence criteria** of 0.8 and 1.25

➢ **In this case, simple buffers and USP II method produced adequate biorelevant predictions.**

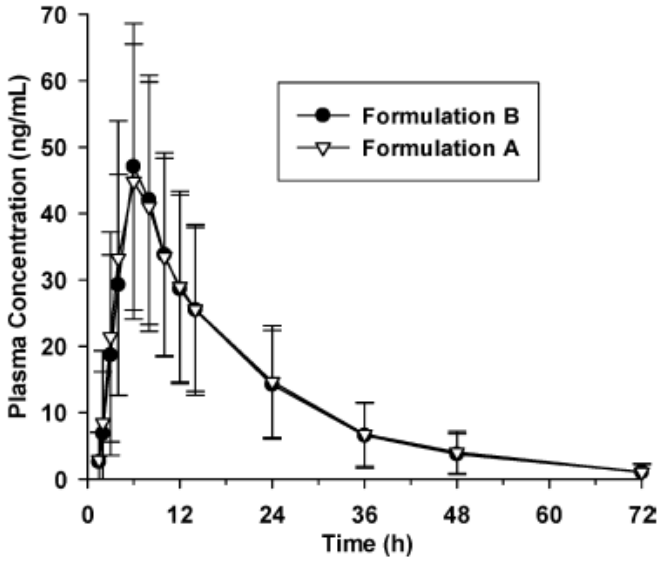


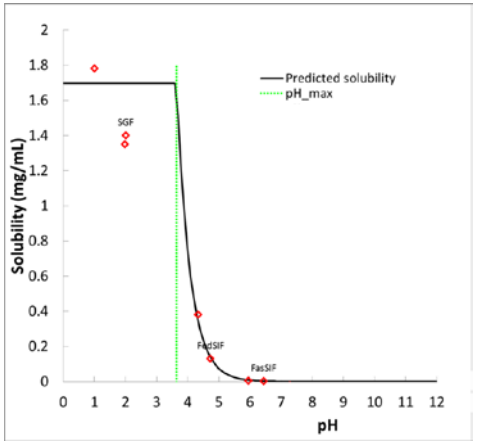
Table 2. Relative Pharmacokinetic Parameters and Confidence Intervals Comparing Formulations A and B

parameter	ratio of geometric mean (B/A)	90% confidence interval
C_{max}	1.03	(0.95−1.11)
AUC(0−∞)	0.98	(0.92−1.05)

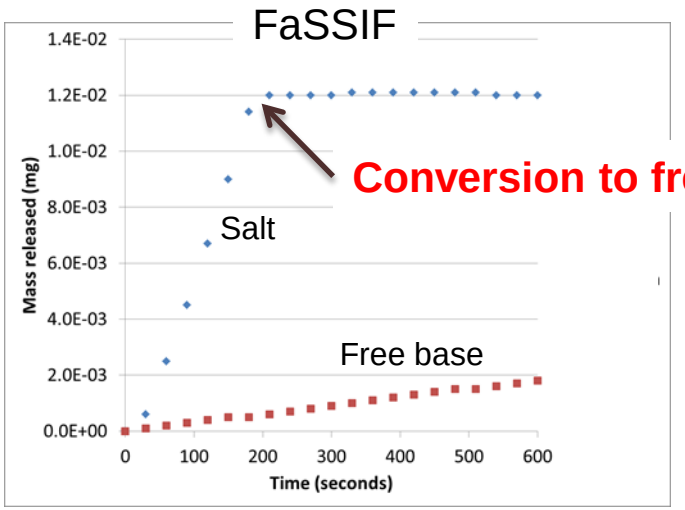
Sperry et al., *Molecular Pharmaceutics*, **2010**, *7*, 1450–1457.

Case 2 – Free base conversion

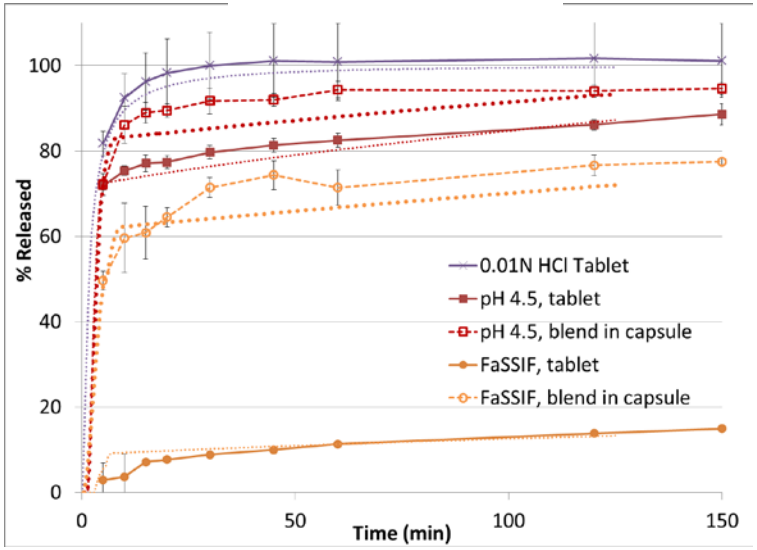
- Solid forms: free base & a salt
- Properties: Low solubility, pk_a ~7



Rotating Disk Dissolution



Salt Dissolution

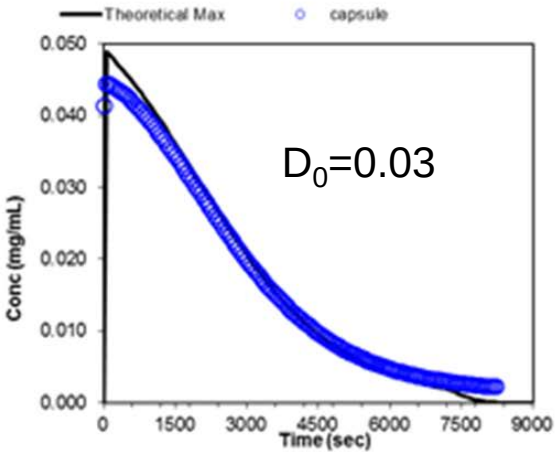


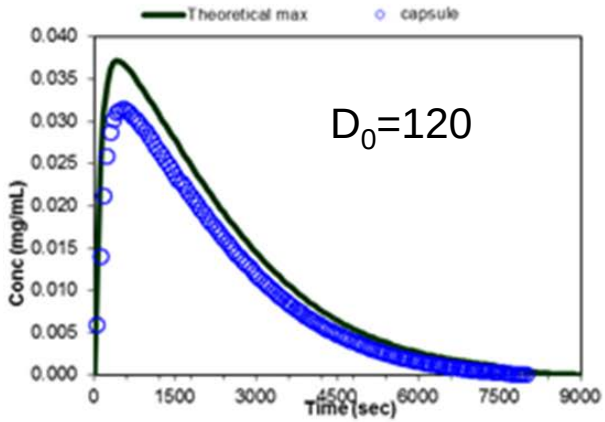
ASD: Salt supersaturation and precipitation

Stomach concentrations

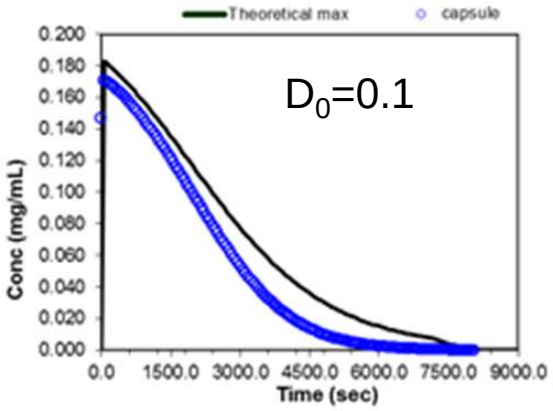
Duodenum concentrations

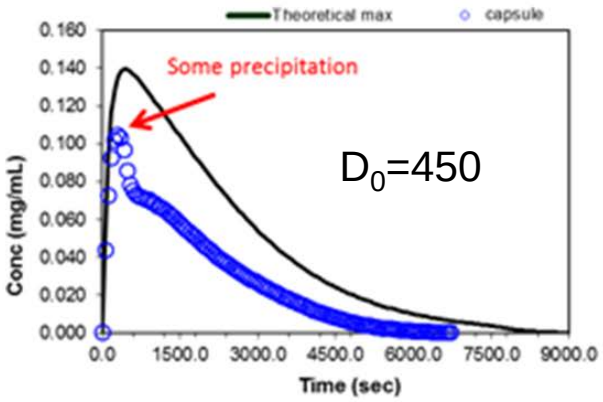
Low dose





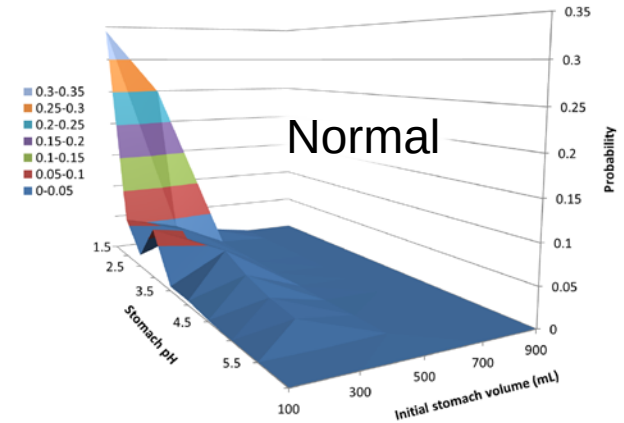
High dose



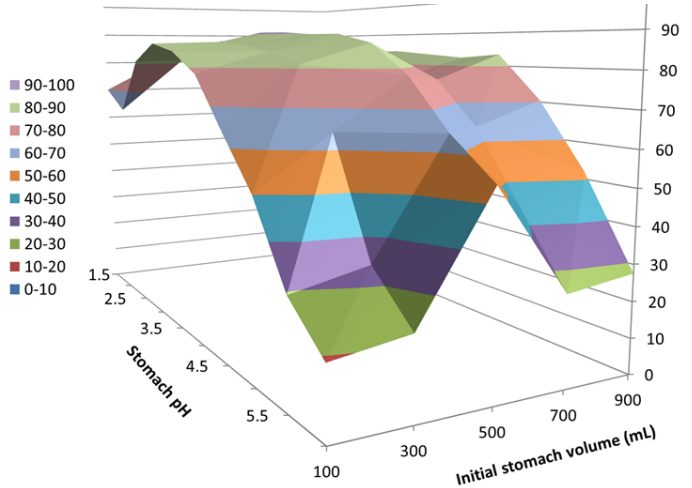


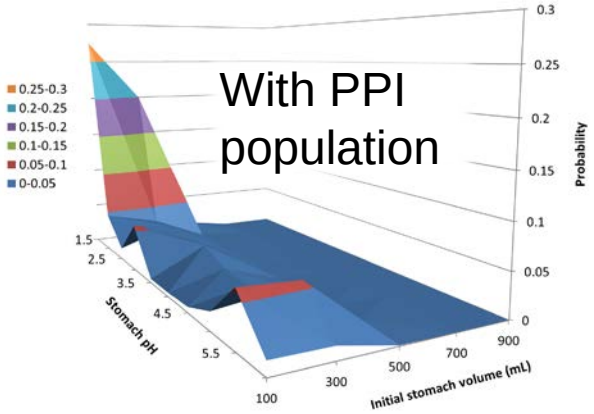
Distribution of gastric conditions

Map of Gastric conditions

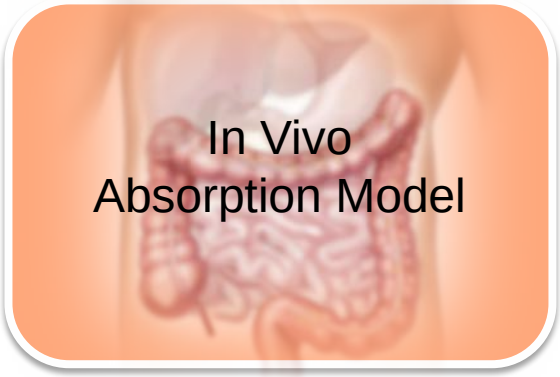


$$\frac{dC}{dt} = \frac{DS}{hV}(C_s - C_t)$$



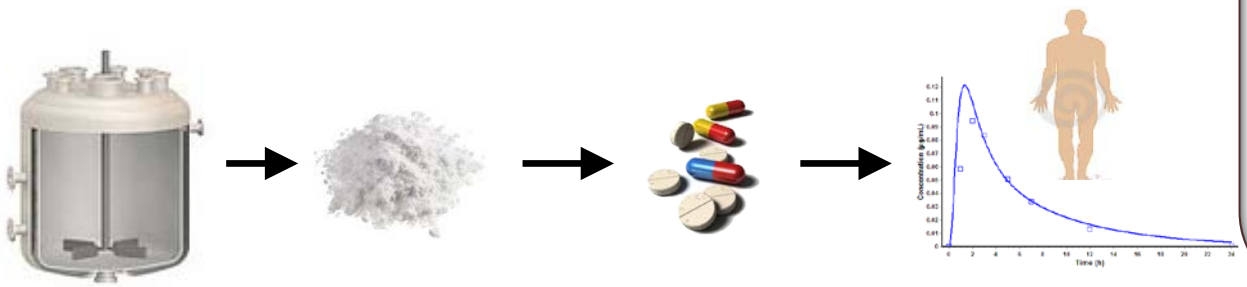


Dissolution input



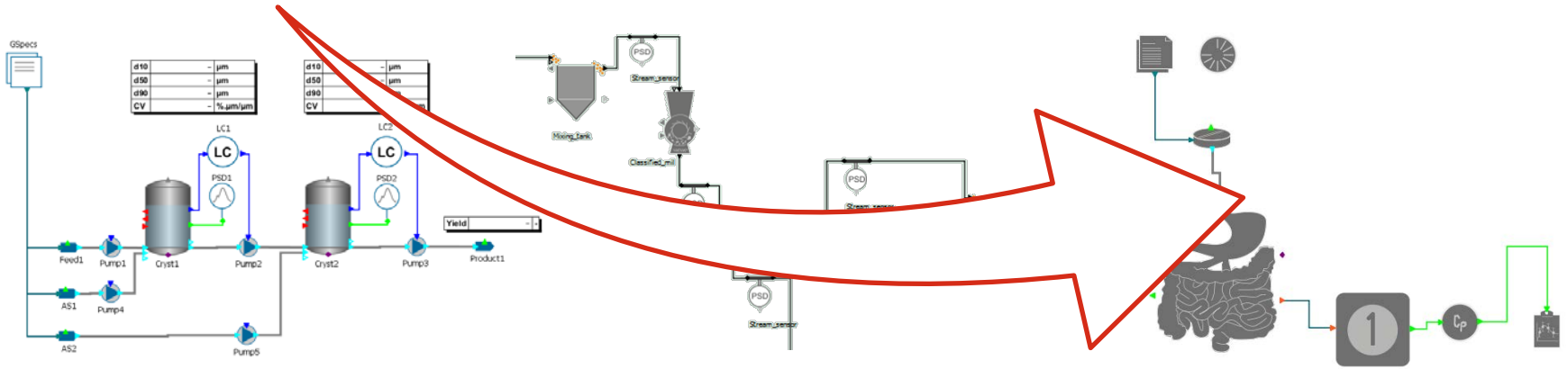
Systems-based Pharmaceutics

- *Linking manufacturing excellence with patient performance*



Lilly Pfizer PSE Roche gsk

Alliance



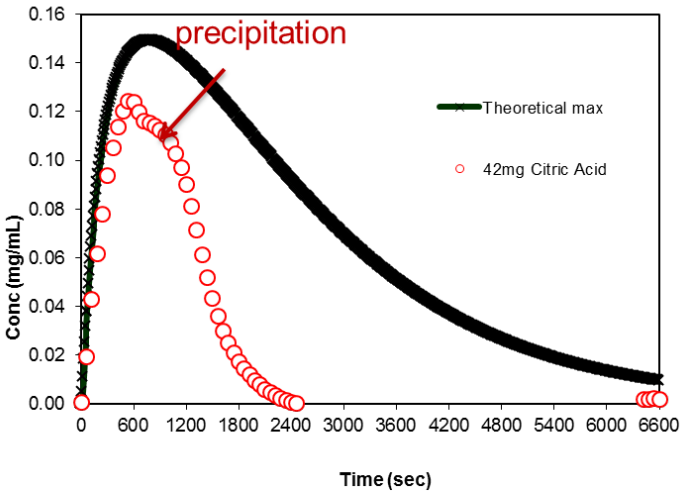
Case 3 – Integrating ASD data

- Low solubility base

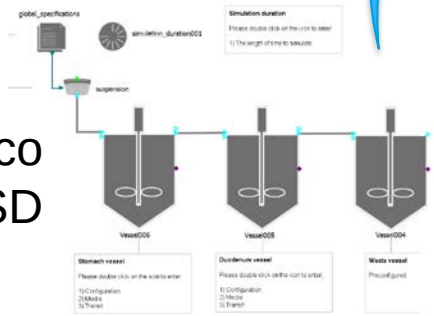
In vitro ASD

Dissolution/ precipitation parameters

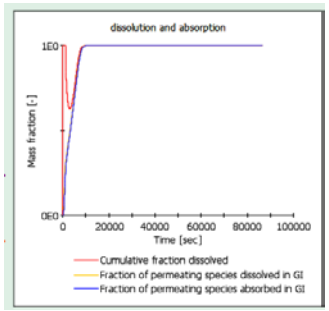
ASD Duodenum Concentration



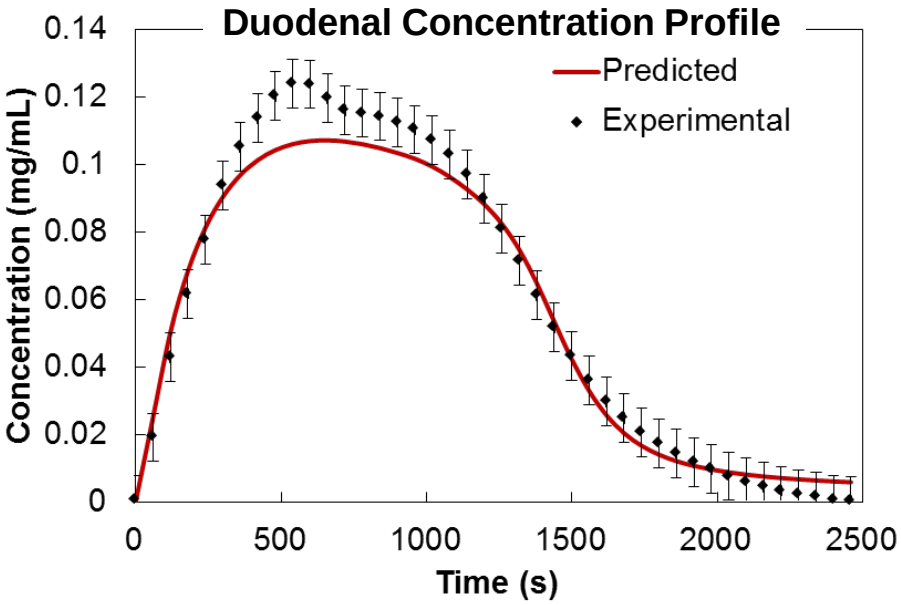
In silico ASD

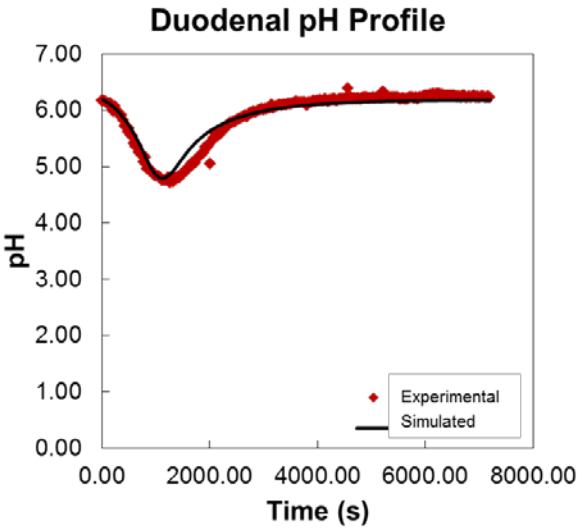


In Vivo Absorption Model



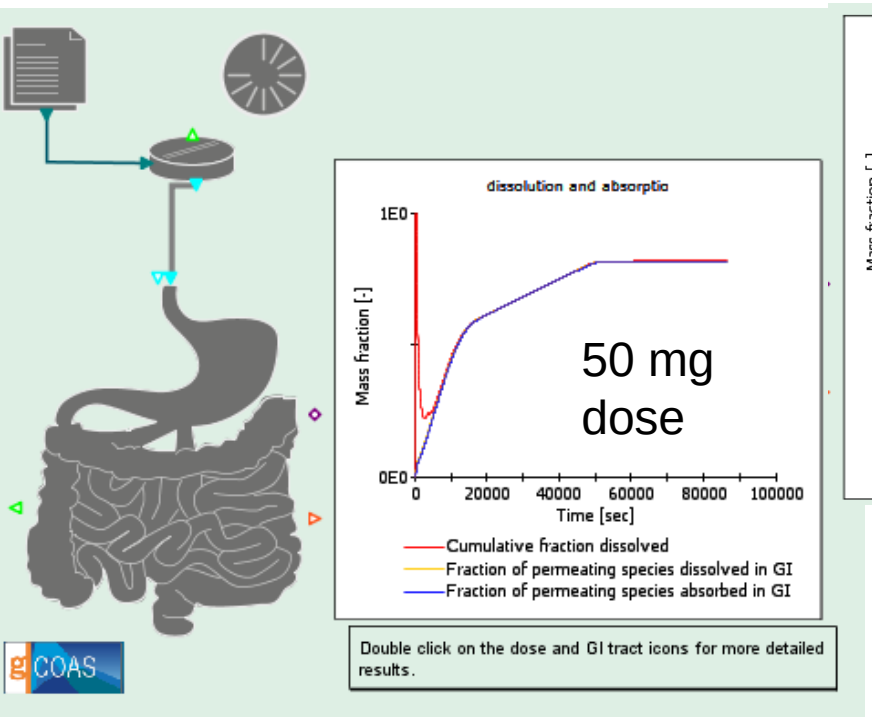
Precipitation rate parameters

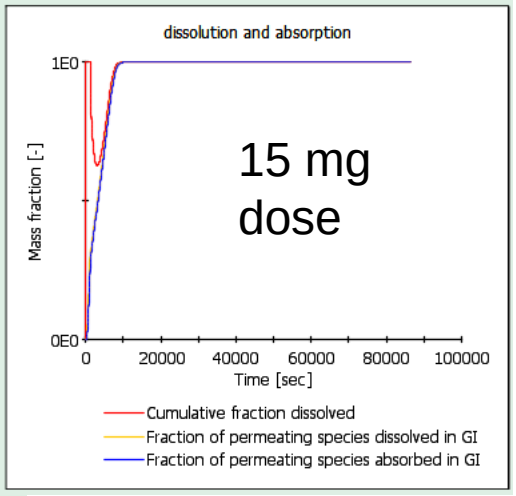




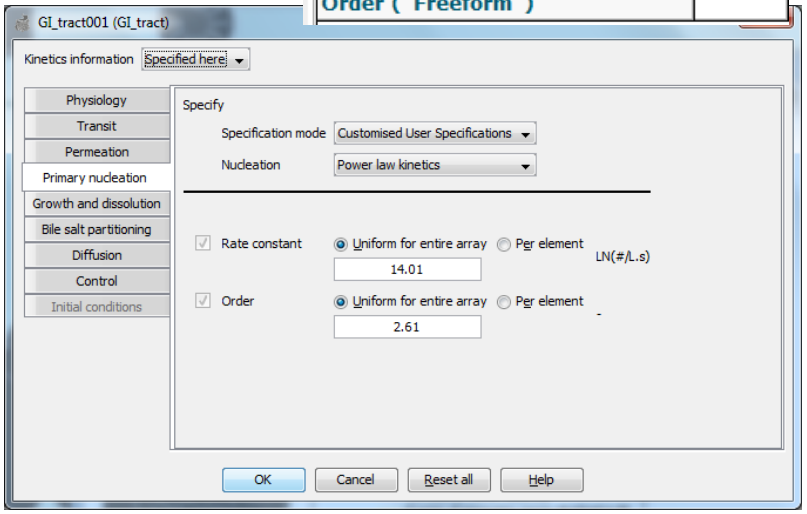
Model parameter	Final value	Initial guess	95% C.I	Standard deviation
Growth constant	0.55	0.36	1.42	0.70
Growth order	1.60	0.81	2.29	1.13
Nucleation coefficient	14.01	13.85	974.9	481.2
Nucleation order	2.61	2.77	399.3	197.1

Incorporating ASD results in gCOAS GI model





Model Parameter	Final Value
Vessel005 Integration constant ("Freeform")	0.55358
Vessel005 Integration order ("Freeform")	1.59909
Vessel005 Rate constant ("Freeform")	14.0132
Vessel005 Order ("Freeform")	2.60956



- 15 mg dose
  - Precipitation is predicted to be negligble. Fa =1
- 50 mg dose
  - Fa =0.82 due to precipitation in the small intestine

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- Lee Burns
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