USE OF BIO-PREDICTIVE METHODS DURING EARLY FORMULATION SCREENING

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Acknowledgements

1X Dissolution / Simulations

- Paul Harmon
- Wei Xu
- Adam Socia
- Mike Socki
- Justin Pennington

Transfer Model

- Sanjay Patel
- Wei Zhu
- Binfeng Xia

ASD

- Christopher Polster
- David Sperry
- Lee Burns
- Karl Kovach
- Shobha Bhattachar

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Topics

- What is the intent of dissolution in the early space?
- Physiochemical properties and prediction of bio performance
- “Predictive” methodologies and case studies
- Areas for improvement and discussion

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What is the Intent of Dissolution in The “Early Development” Space?

Predict *in-vivo* performance of formulations (bio-predictive)

- In preclinical models
- In Phase I studies
- In Bio-comparison (BC) studies

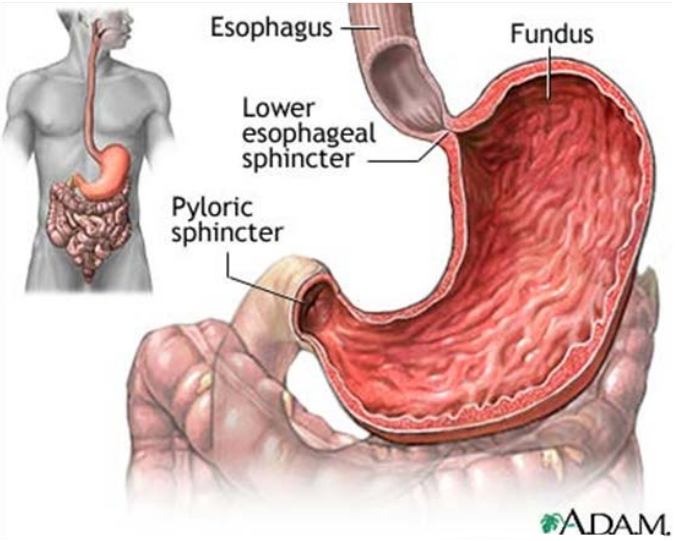
Establish a dissolution model for predicting the performance of formulations in-vivo to guide market formulation and process development.

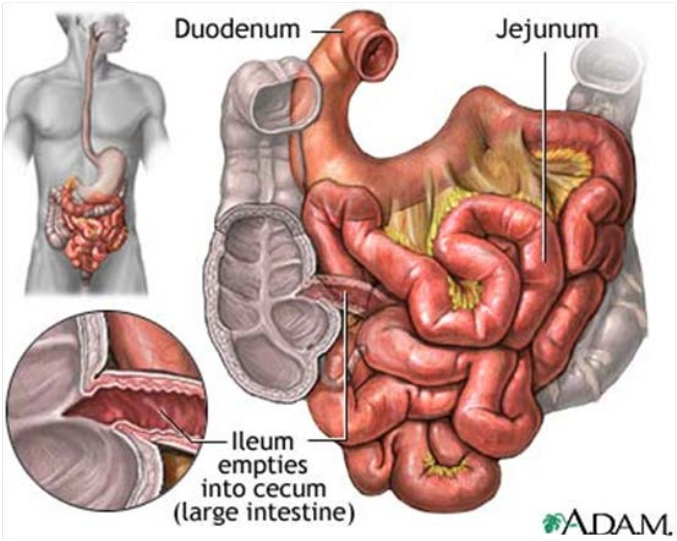
- Reduce number and complexity of animal studies.
- Take best formulations forward for human studies

Driving an understanding of what factors of the API/Formulation/Process are most important in developing bio-predictive methods

Assumption here is that dissolution is meaningful for PK performance…

When Bioavailability Depends on Dissolution…





Dissolution is the best surrogate for bio-performance if IVIVC can be established.

It enables selection/ rank ordering of formulation candidates in early development without the need to perform actual in vivo (animal or human) studies significantly accelerating development

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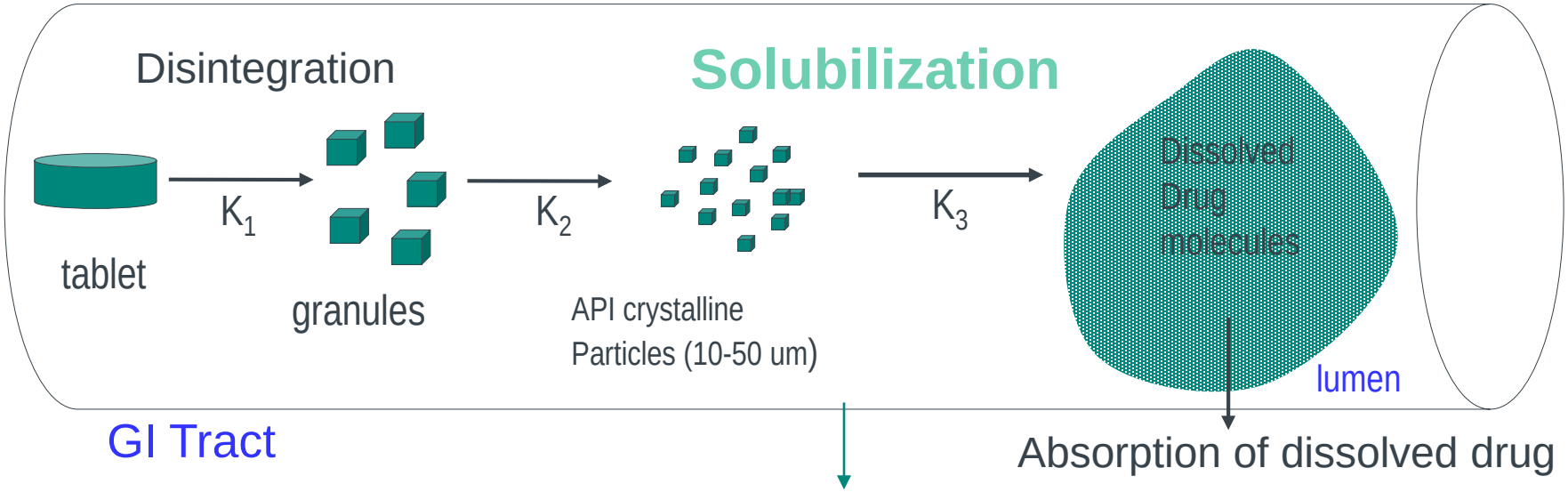
When Bioavailability Depends on Dissolution…

A simple view of dissolution…



flux drug removed = A(mem) [drug] in lumen X perm. rate const.

Dissolution ~ (Particle SA)(Diffusion Term)($C_{sol\ lim} - C(t)_{lum}$)

(Rate of API particle)

Sum of rates, K_1, K_2, K_3 is slower than rate of permeation

Oh D.M., Curl R.L., Amidon G.L. 1993. Estimating the fraction dose absorbed from suspensions of poorly soluble compounds in humans: a mathematical model. Pharm. Res. 10(2):264-270.

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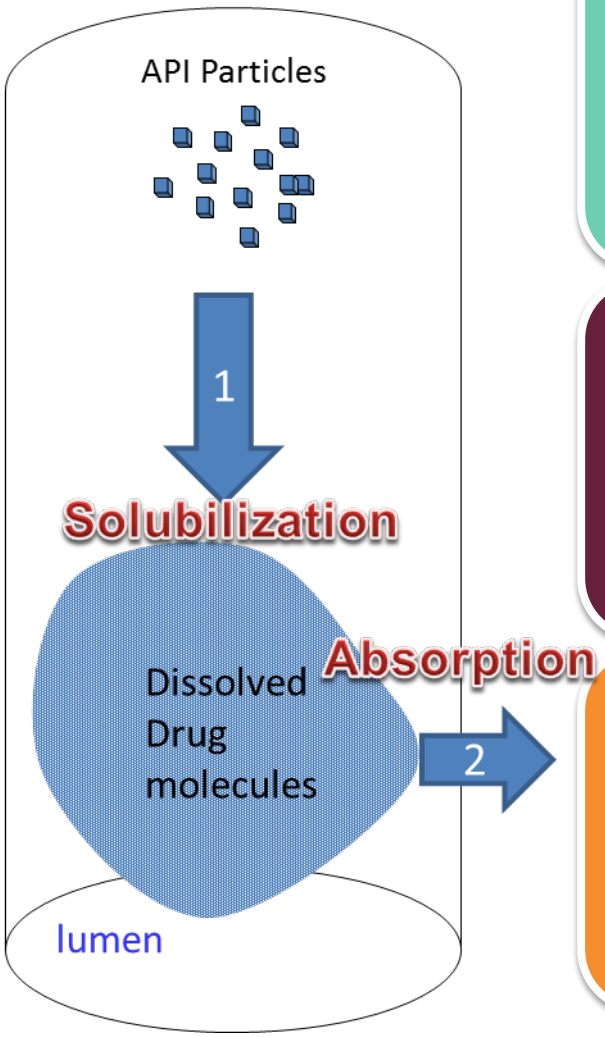
When Dissolution *Rate* Matters



If 1 > 2, then dissolved drug concentration in the GI is "pegged" at the solubility limit – this is *solubility/permeability limited* exposure. In this regime, different formulations of same API give similar AUC.

If 2 > 1, then dissolved drug concentration in GI is *below* the drug solubility limit, this is *dissolution rate limited* (disso rate can't keep up with permeability loses). In this regime AUC may be sensitive to formulation details...(API PSD, for example)

How to measure/compare "aggregate" API particle dissolution *rates* – as they dissolve in aggregate (from different formulations) as this dissolution drives the [API] in GI fluids to the its solubility limit?

This scenario is called "Dissolution Rate Limited AUC

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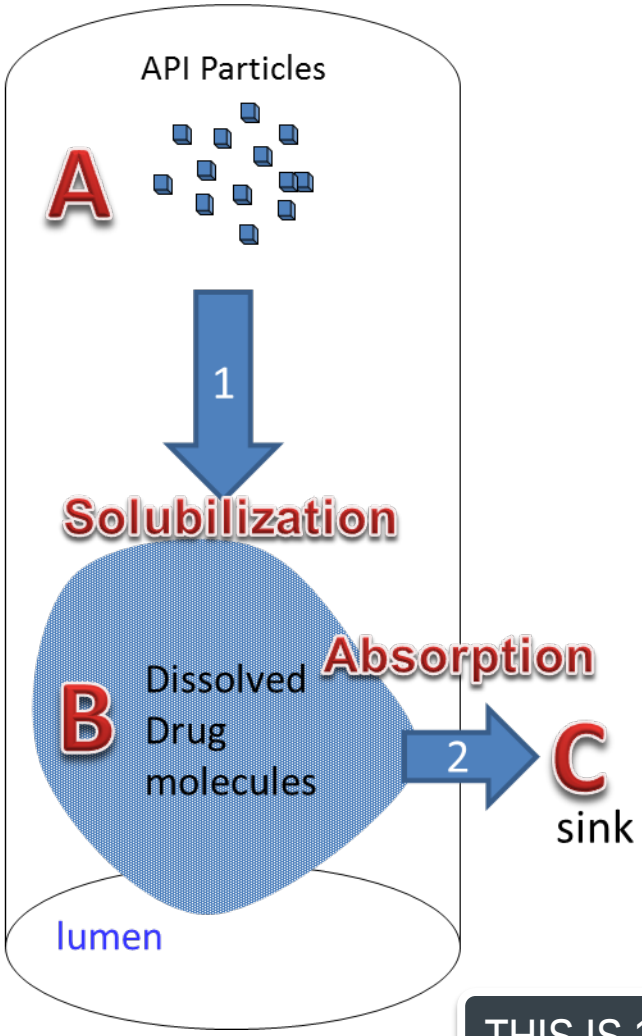
How to Measure Aggregate Flux – Whole Dose Must Dissolve



In the case where C provides constant sink for dissolved drug to go, the *rate* "1" of transition from A to B matters, regardless of amount dosed, therefore the dissolution behavior of the entire dose matters

How can this be measured? Mimic the system! Put the dose inside a permeable membrane (only drug in solution gets through) and have large volume on other side of membrane to keep [drug] below its solubility limit or some sort of way to remove drug outside membrane (inside always driving to sol limit). Also, biphasic dissolution (aqueous/organic)

Is there an even more simple way? Simply put a *portion* of dose into BR media AT the solubility limit, compare disso profile (rate) to get there!

THIS IS 1X BIORELEVANT DISSOLUITION

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The Case for Conducting Bio-Predictive Dissolutions at the Solubility Limit of the Drug

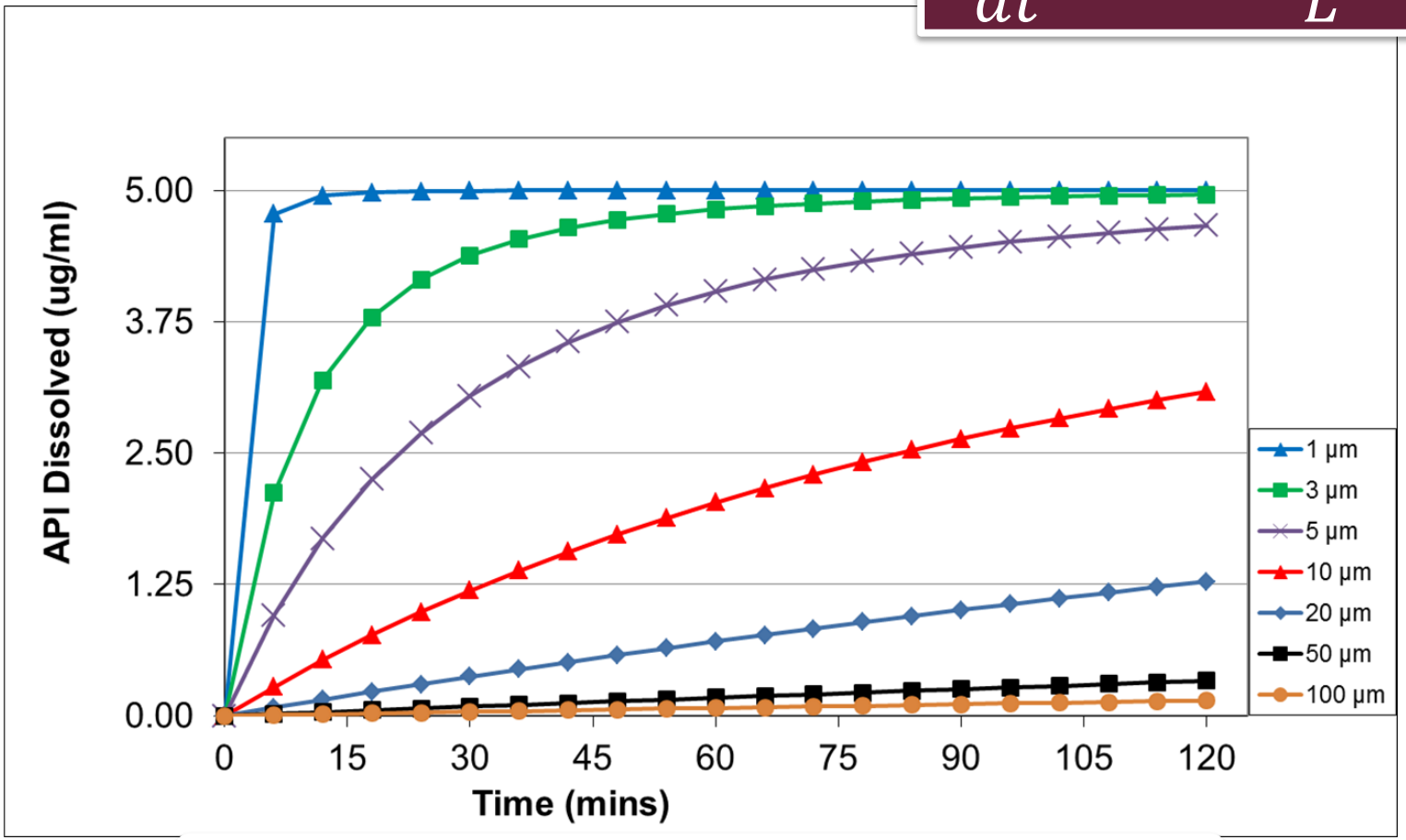
Called “1X” dissolution: have your target concentration = solubility limit of the drug.. ...then all drug particles must dissolve; formulation differences in rates of approach to solubility limit easier to see and whole “formulation response” is measured

you need to see all the API dissolve to compare formulations, since our % dose absorbed (hopefully) approaches 100%..

Simply comparing the rate of reaching the solubility limit in FaSSIF for all formulations at 1X

Simulation of Dissolution

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$



This simulation is done at the solubility limit of the drug

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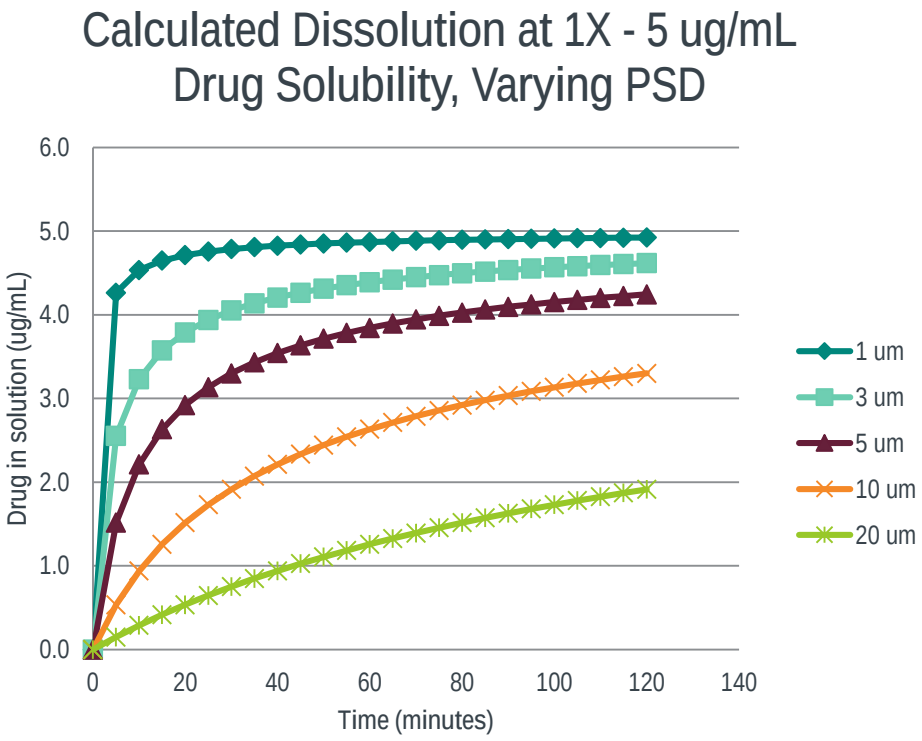
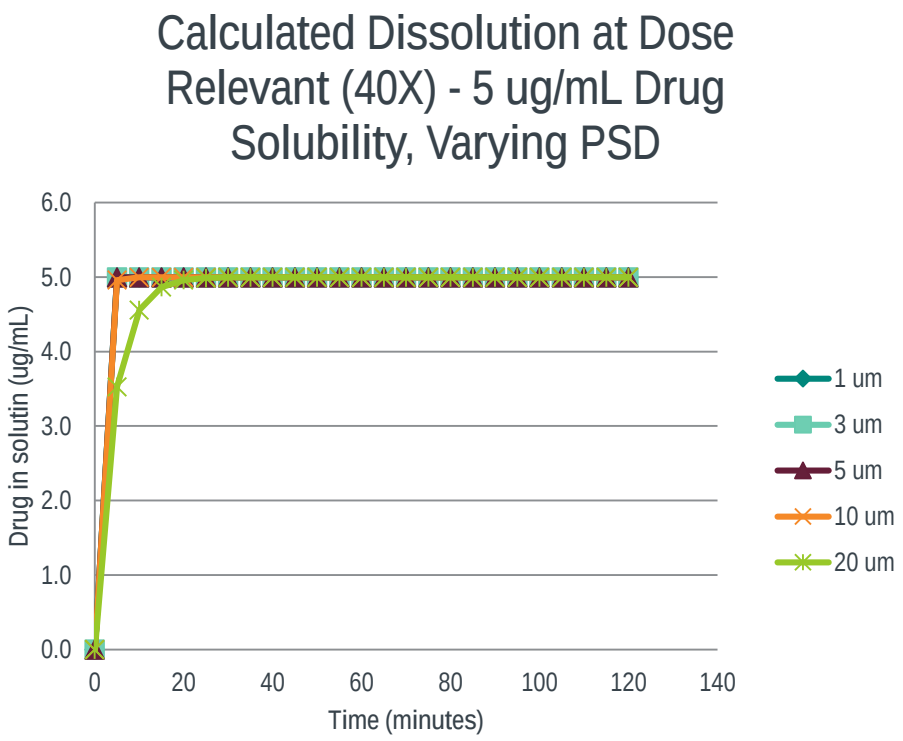
This Approach Allows Quantitative Comparisons Across Formulation Types





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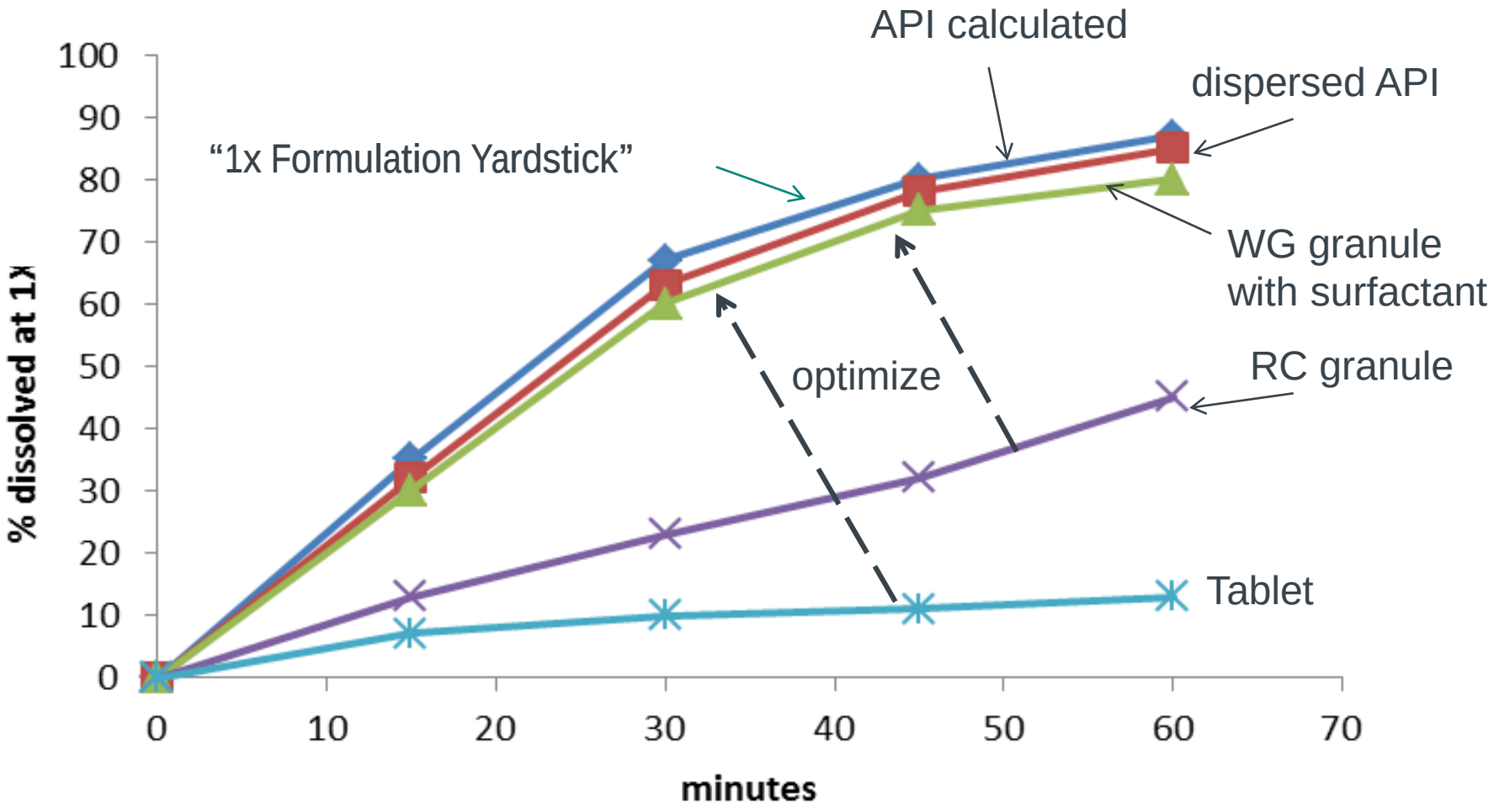
This Approach Allows Quantitative Comparisons Across Formulation Types

Understanding the dissolution rate of well dispersed API particles is the first step in evaluating dissolution performance – as a very well dispersed formulation with very fast granule dissolution will approach dispersed API dissolution rate.

Representative 1X Data Comparing Formulation Components



Practically, What Working at the Solubility Limit of the Drug Means

Using the 5 ug/mL solubility in FaSSIF example, and the 100 mg dose

To work at “1X” with a complete 100 mg tablet then would require a 20,000 mL volume

That’s a lot of FaSSIF!

How is this made practical?

We work with granules (example here, 1/40th weight of a tablet in 500 mL FaSSIF) or portions of tablets – or pre-disintegrated in SGF

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This Approach Allows Quantitative Comparisons Across Formulation Types

Formulation Attribute	1x Dissolution Response
Formulation processes strive to disperse the API particles to their primary size from a tablet	Formulations that do this better will have faster rates of dissolution than those that do this poorly
Granulation of API	Granulation can help with dispersion of particles in dissolution – also over granulation can add additional dissolution rate slowing (increase in r term (particle density)
Addition of Surfactants	Helping wet the particles may improve dissolution rate

Understanding the dissolution rate of well dispersed API particles is the first step in evaluating dissolution performance – as a very well dispersed formulation with very fast granule dissolution will approach dispersed API dissolution rate.

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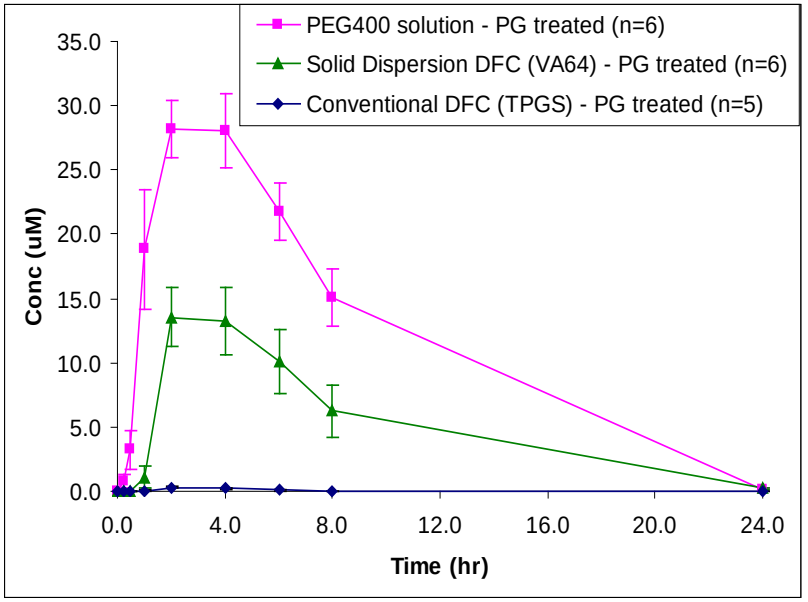
1X Dissolution – Case Study

1

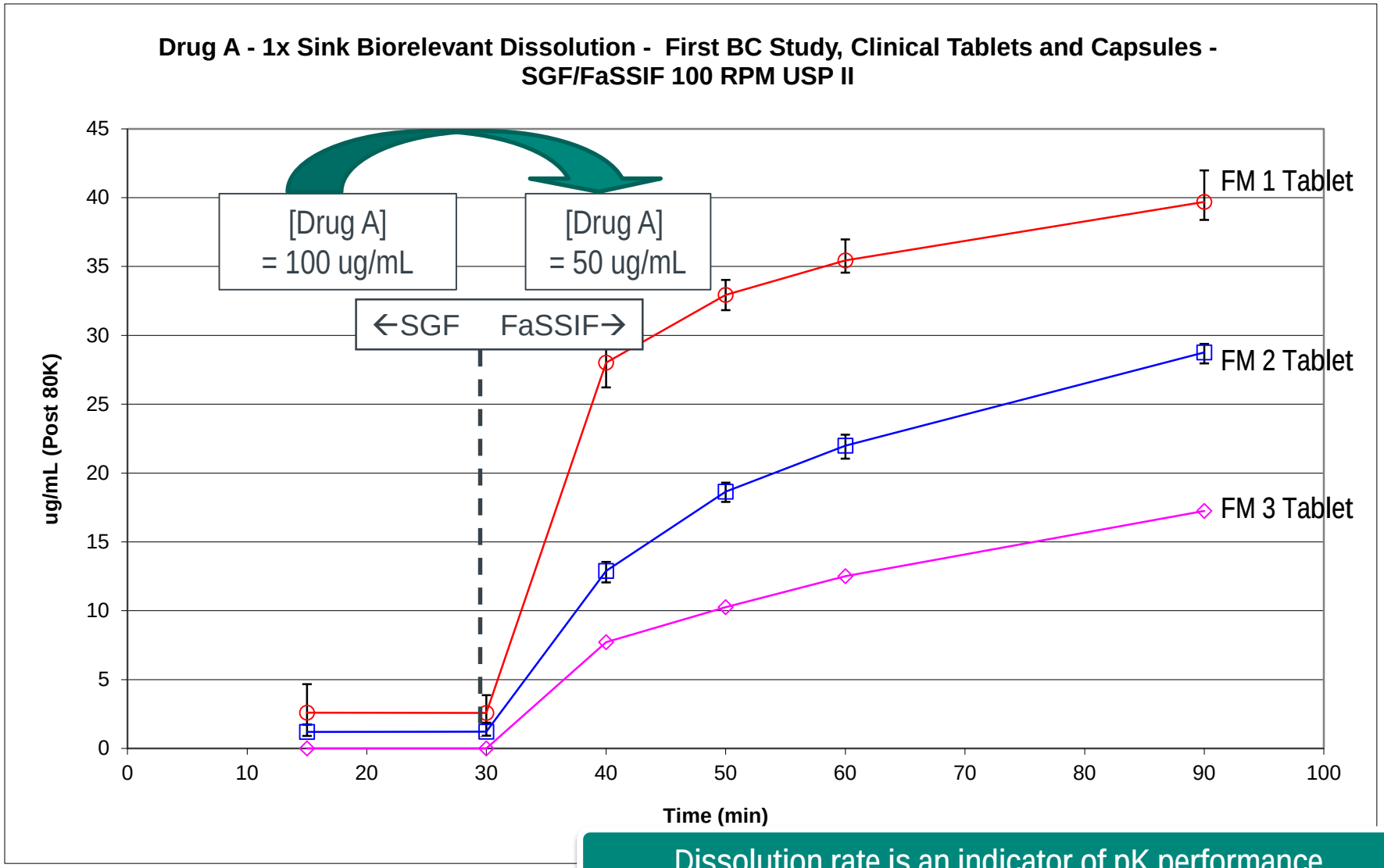
Amorphous by Spray drying (FFP Formulation)	
30% Drug A	API
65% Copovidone	Polymer
5% SLS	Surfactant



2

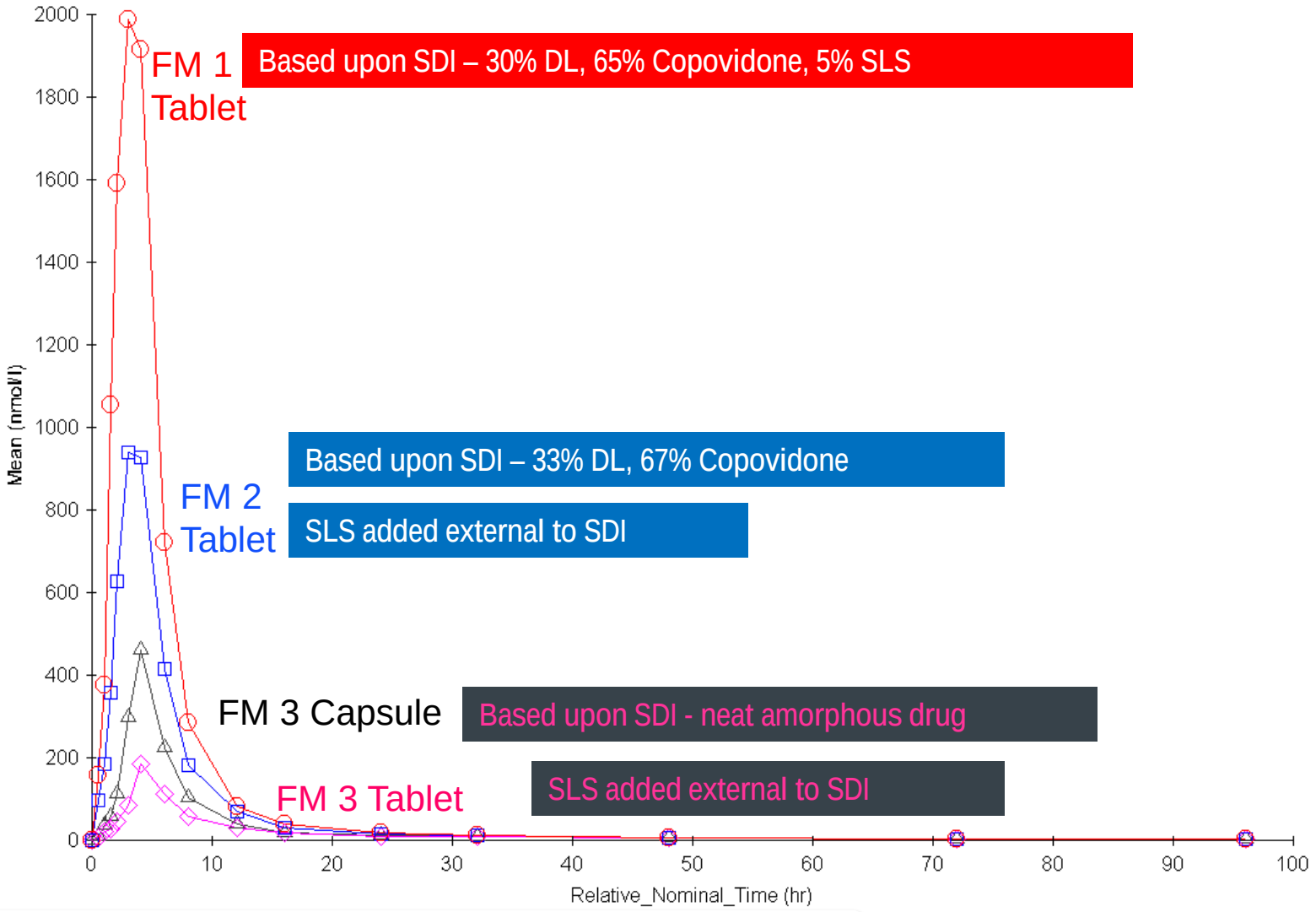
Formulation	Drug in SDI	SLS in SDI	PVPVA in SDI	SLS in tablet	Test Hypothesis
FM 1 Tablet	30%	5%	65%	0%	High Probably of Success based upon prior knowledge
FM 2 Tablet	33%	0%	67%	5%	Test necessity of SLS in SDI
FM 3 Tablet	99.5%	0%	0%	5%	Test whether supersaturation is enough to get adequate PK
FM 2 Capsule	99.5%	0%	0%	5%	Test whether supersaturation is enough to get adequate PK

Drug A – 1X Dissolution



Dissolution rate is an indicator of pK performance

Exploratory BC PK Data



Dissolution rate is an indicator of pK performance

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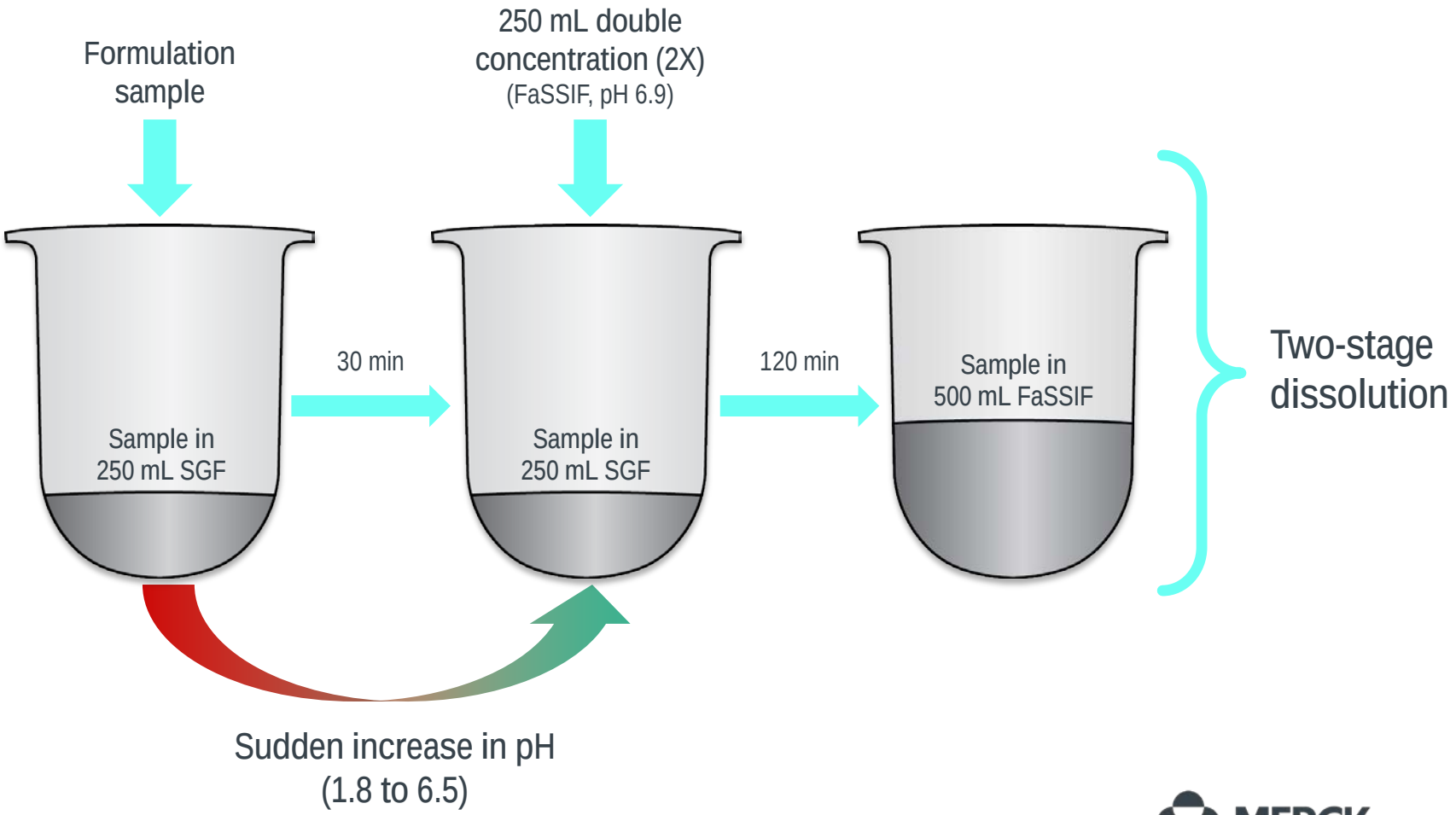
Two-Stage Dissolution

During the typical two-stage dissolution, 1X addition of FaSSIF creates sudden pH change for the 2nd stage. This may be especially problematic for weak bases, which may undergo precipitation in the 2nd stage.



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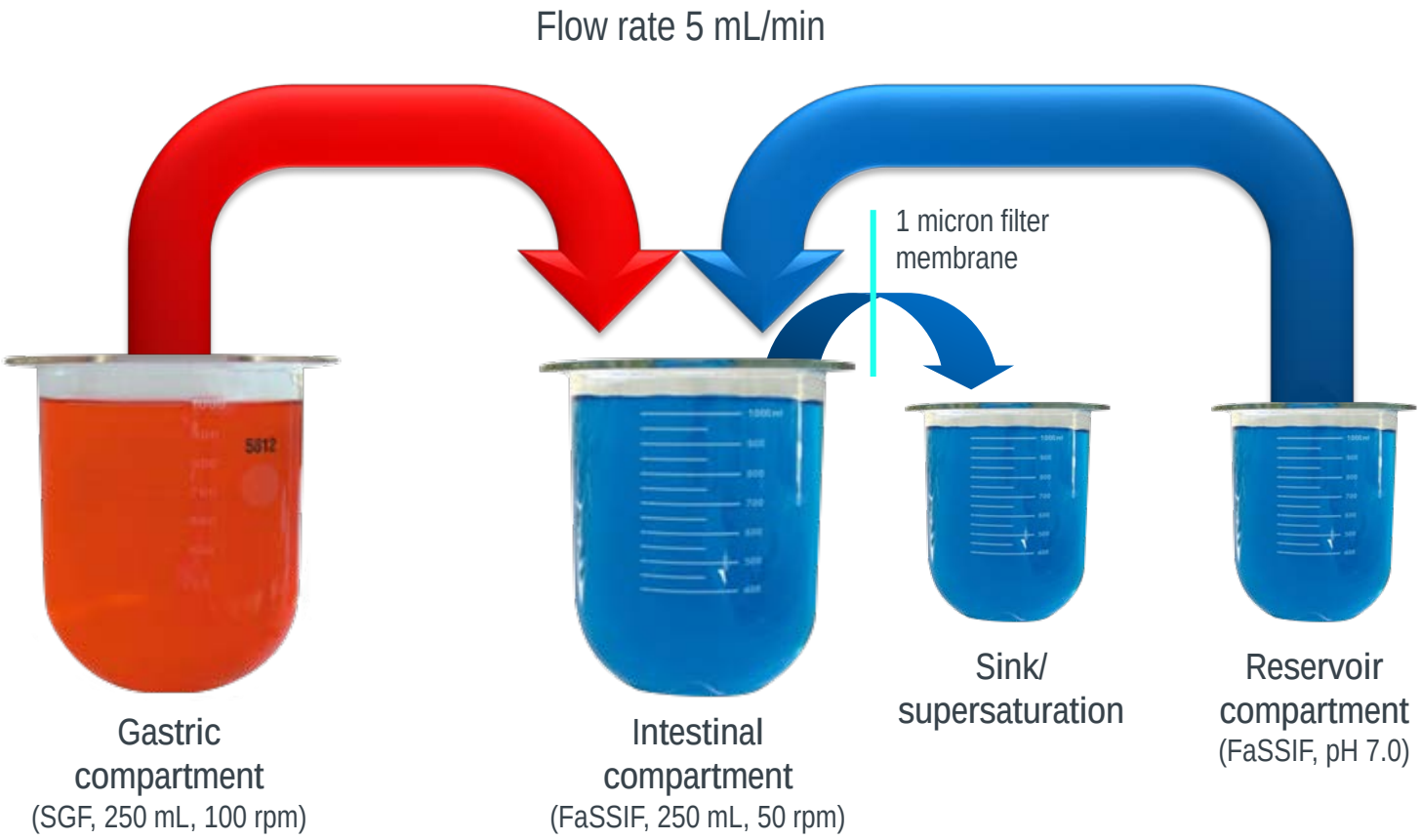
Multi-compartment Transfer Model to Predict Dissolution/Precipitation of Weakly Basic Drug



Case Study: Ketoconazole

Ketoconazole: Weak dibasic antifungal agent

pKa: 2.94, 6.51

BCS II

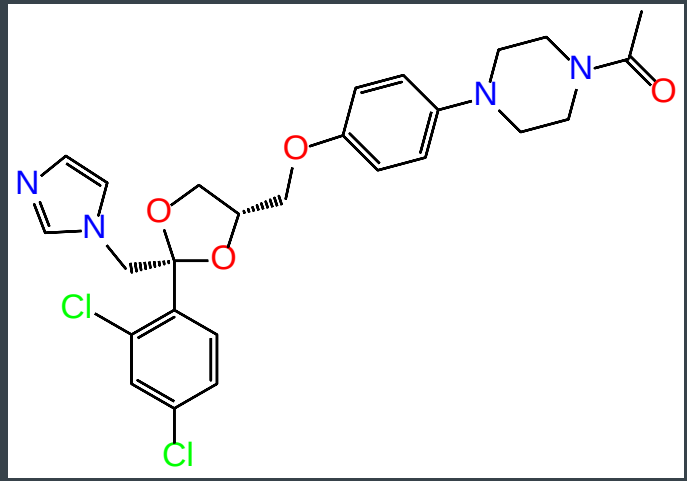
Permeability:
Caco-2 Peff=53x10^{-6} cm/sec

Solubility:

- Virtually insoluble at pH 5 or higher
- Detailed solubility profile (right)

Administration:

- Exposure was well known as being affected by elevated stomach pH
- Recommended to codose w/acidic cola drink



pH	Solubility (mg/mL)
1.6 (FaSSGF)	9
3 (buffer)	1.8
3.5 (buffer)	0.7
4.5 (buffer)	0.25
5 (buffer)	0.1
6.5 (buffer)	0.007
SGF	6
FaSSIF	0.02537

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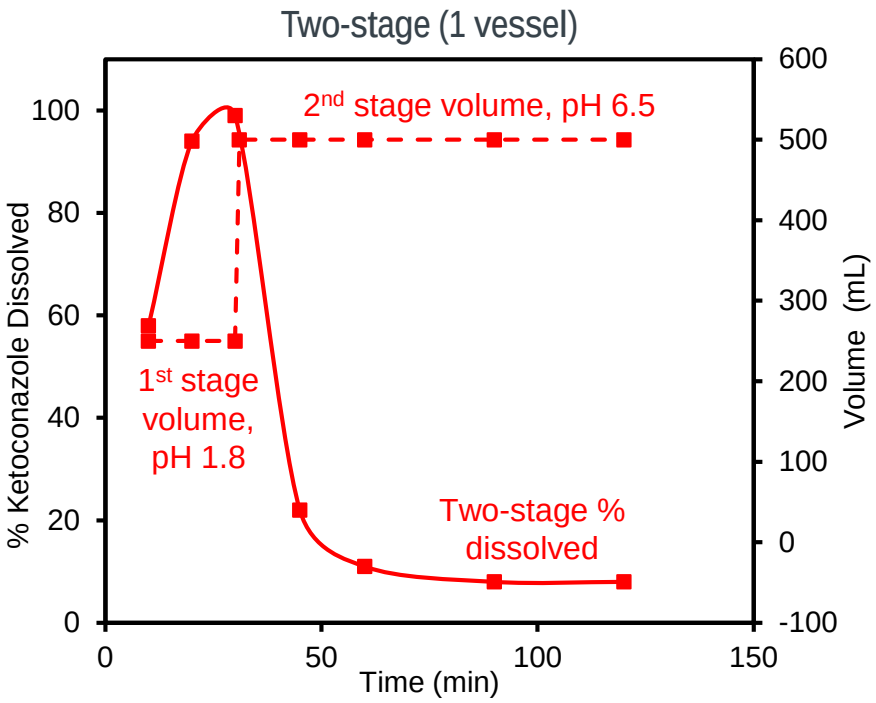
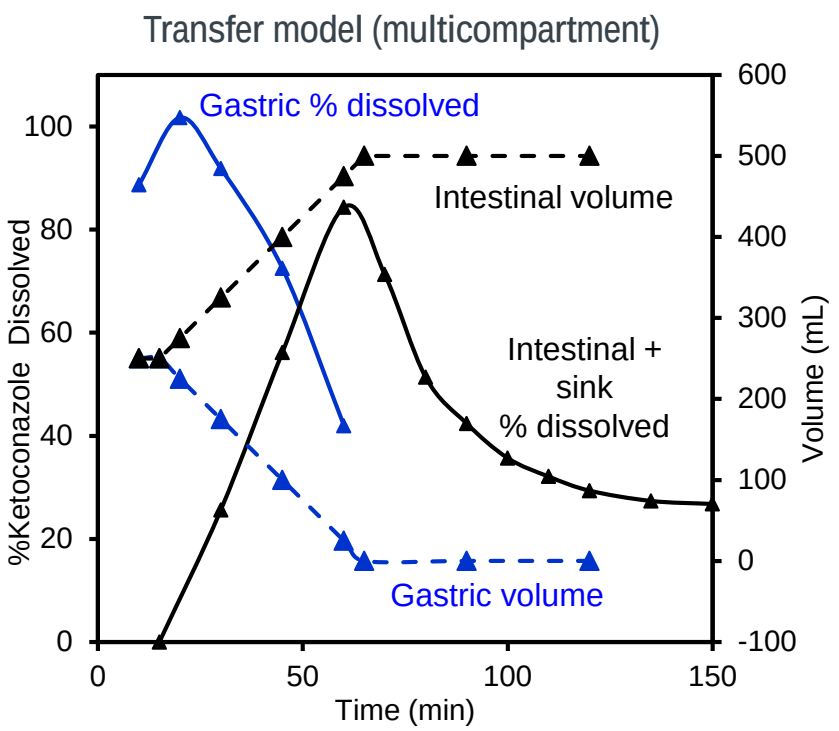
Ketoconazole Tablets: Transfer vs Two-Stage





Some precipitation observed in the transfer model; significant precipitation in two-stage dissolution

A *small amount of precipitation* was observed in fasted adult study

(Psachoulias D, et al. *Pharm Res.* 2011;28(12):3145-3158. doi: 10.1007/s11095-011-0506-6)

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Transfer Model Summary

A multicompartment transfer system was established to investigate the in vivo behavior of weak basic compounds

Preliminary data showed promising results to support transfer model as an alternative way to estimate in vivo precipitation in intestinal compartment for weak basic compounds

Opportunities:

- In silico model – Develop full mathematical model to describe simultaneous transfer/precipitation process
- Nanoparticle formers/enabling formulation

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ASD Motivation

- A tool for drug product development, including early phase formulation screening
- Help predict the in vivo impact of
  - salts,
  - solid forms,
  - formulation composition,
  - particle size,
  - process

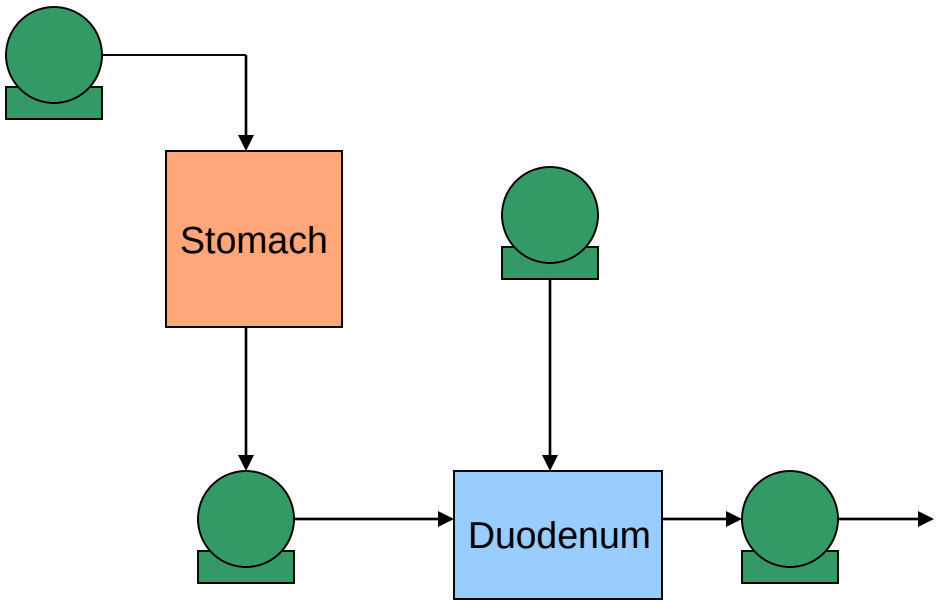
  using an in vitro system that mimics the dynamic conditions of the human gastrointestinal tract.

ASD Concept

- Capture supersaturation, precipitation and dissolution phenomena as they occur in vivo.
- Dynamic dissolution system designed to simulate the stomach and duodenum environment:

• fluid compositions	• fluid flows
• mixing (not peristalsis)	• pH
• transit times	• fluid volume

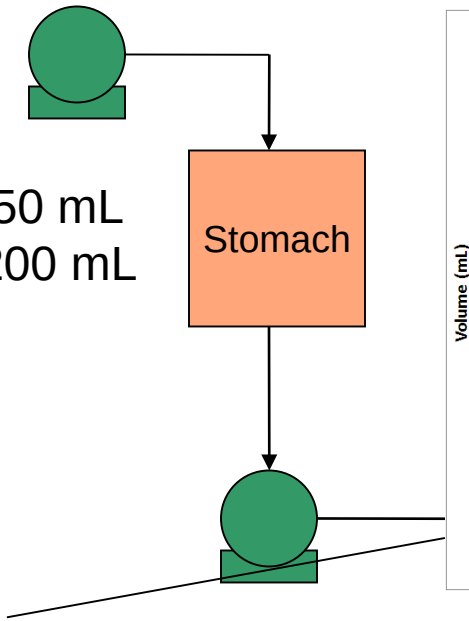
Physical Model

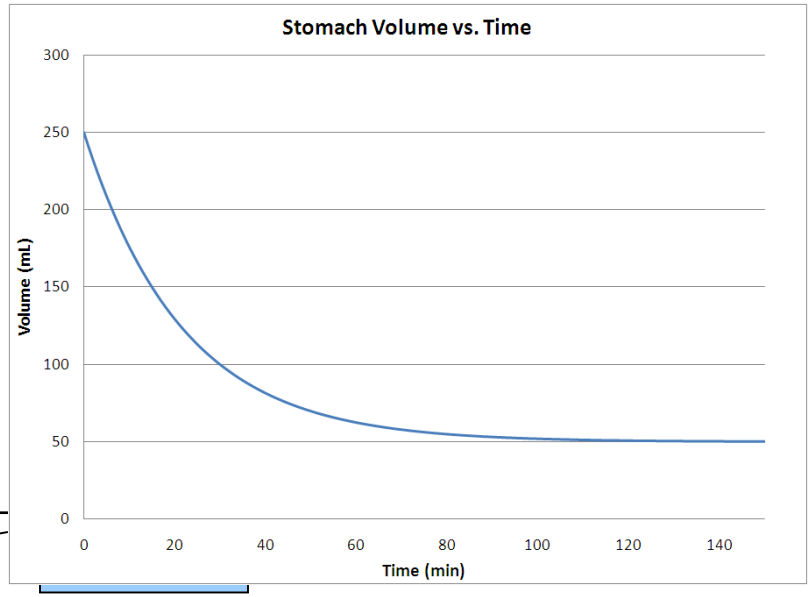


-UV-vis fiber optic probes and pH probes in both chambers for data acquisition.

Physiological Modeling

Stomach Secretion Rate = 2 mL/min





mL/min

Resting Volume = 50 mL
Dosing Volume = 200 mL

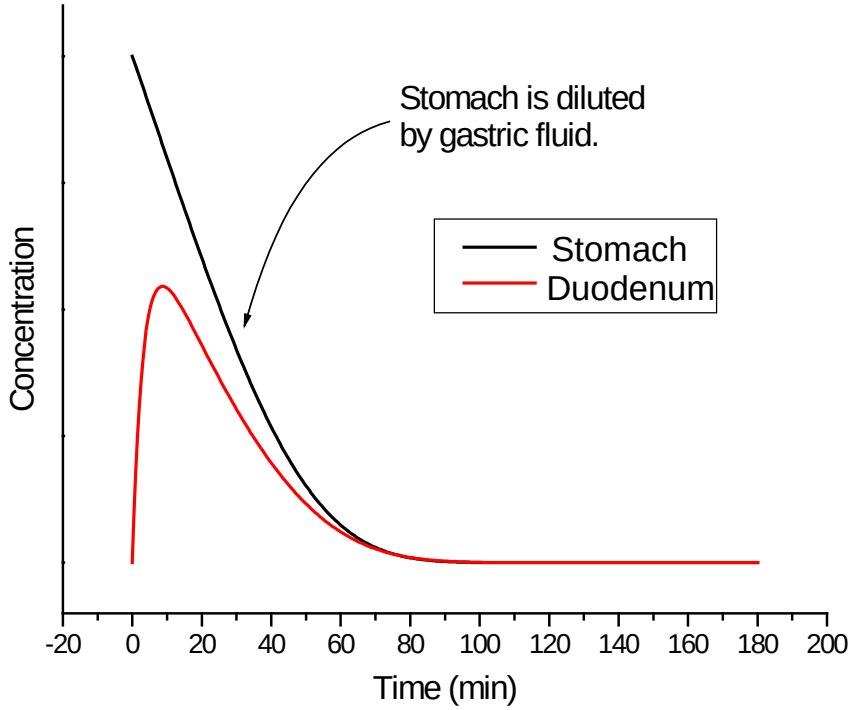
Stomach Emptying:
First order decay (w.r.t. Volume)
Emptying Half-life = 15 min

Duodenum:
Constant volume = 30 mL

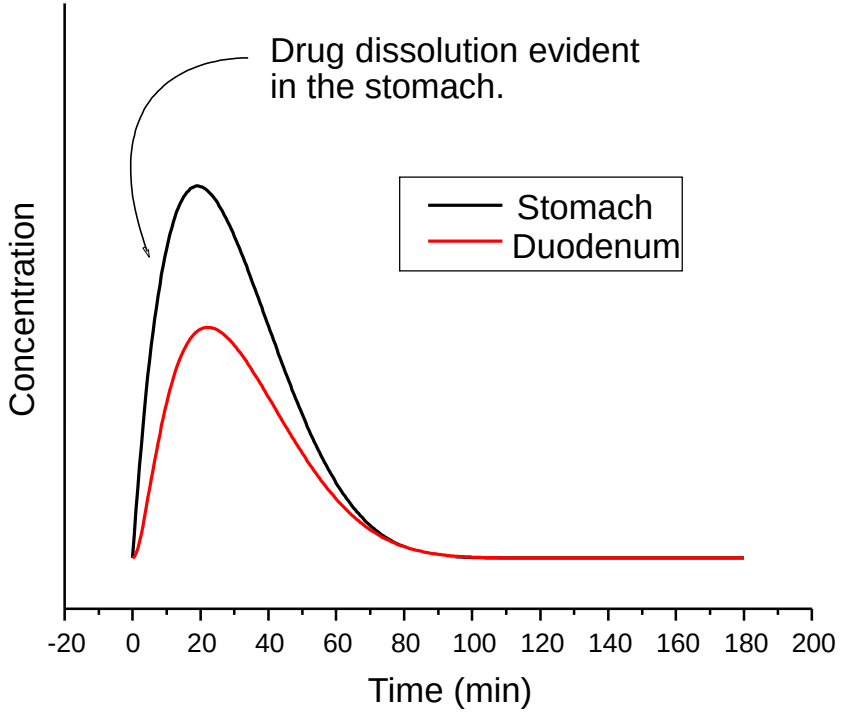
Fluids:
Stomach – 0.01 N HCl or higher pH buffer
Duodenum – Phosphate buffer, pH 6.8 or FaSSIF w/o lecithin

Typical Results

Gastric Emptying + Intestinal Fluid + Gastric Fluid

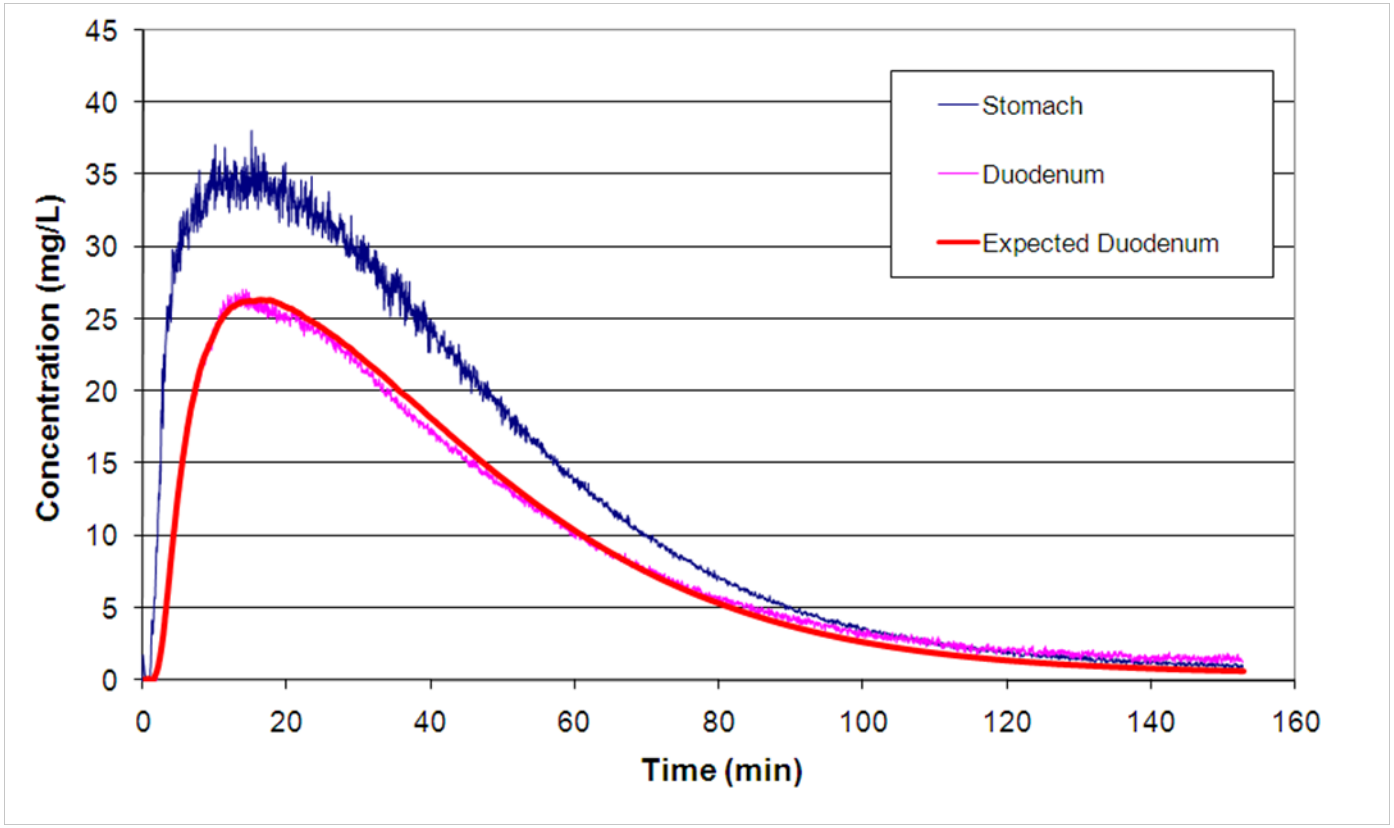


Dissolution + Gastric Emptying + Intestinal Fluid + Gastric Fluid



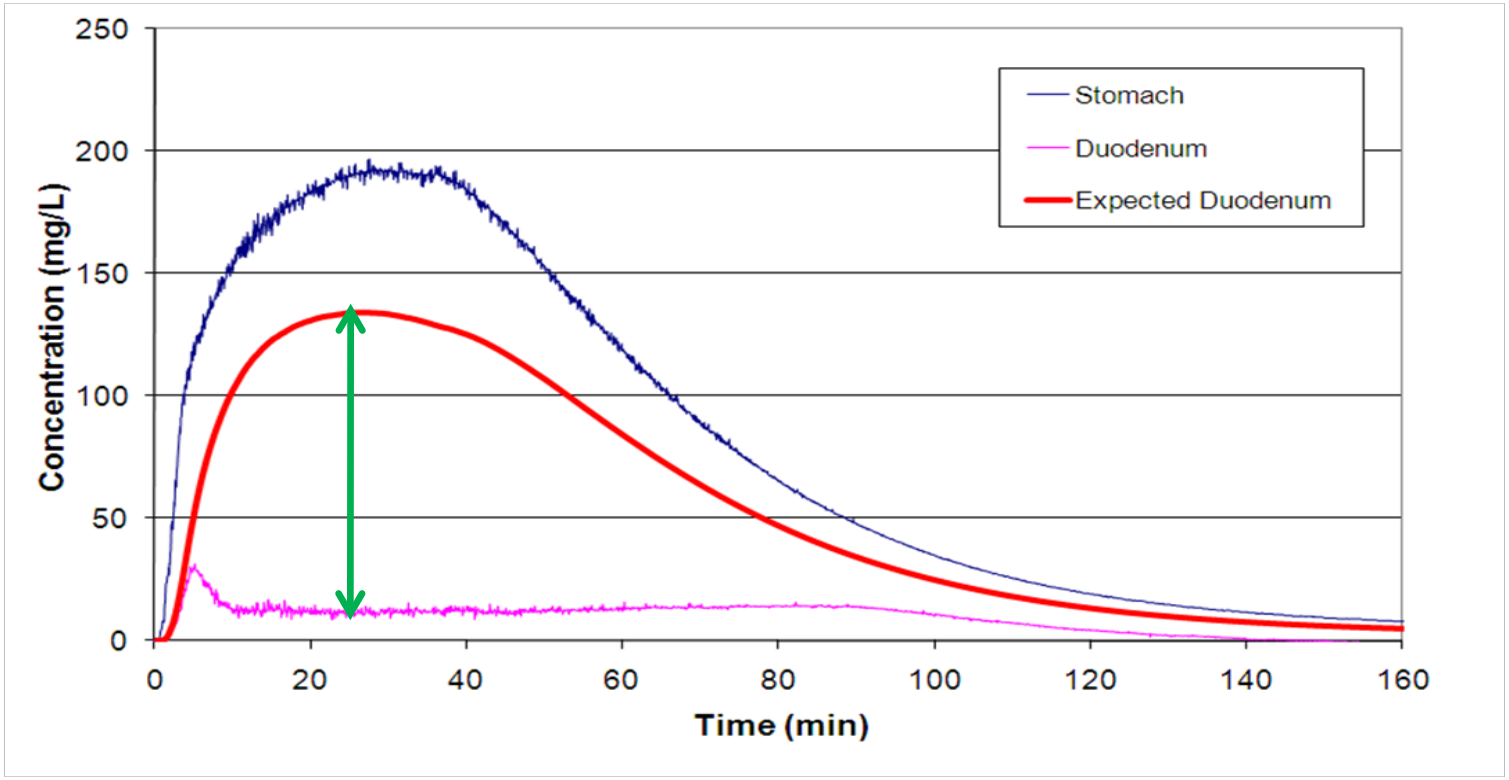
Drug-Concentration Profiles

- Expected duodenum concentrations can be calculated from experimental stomach data.

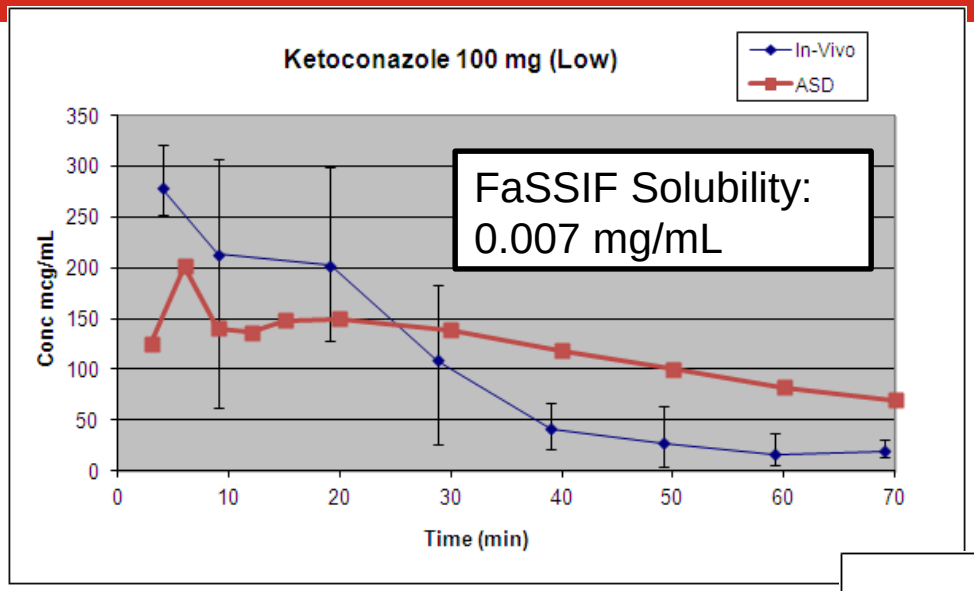


Dissolution and Precipitation

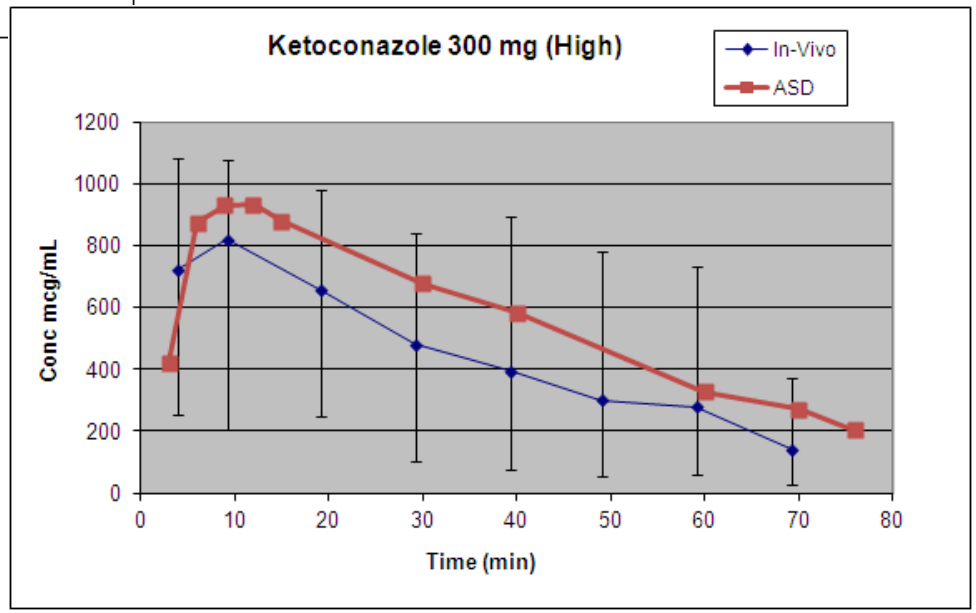
- Deviations from the expected duodenum profiles indicate either additional dissolution or precipitation.



ASD/Human Comparison



- In vitro data: Human ASD
- In vivo data: 12 Human volunteers.
  (Source: Psachoulias D, Vertzoni M, et al. Pharm Res. 2011; 28(12): 3145-3158)

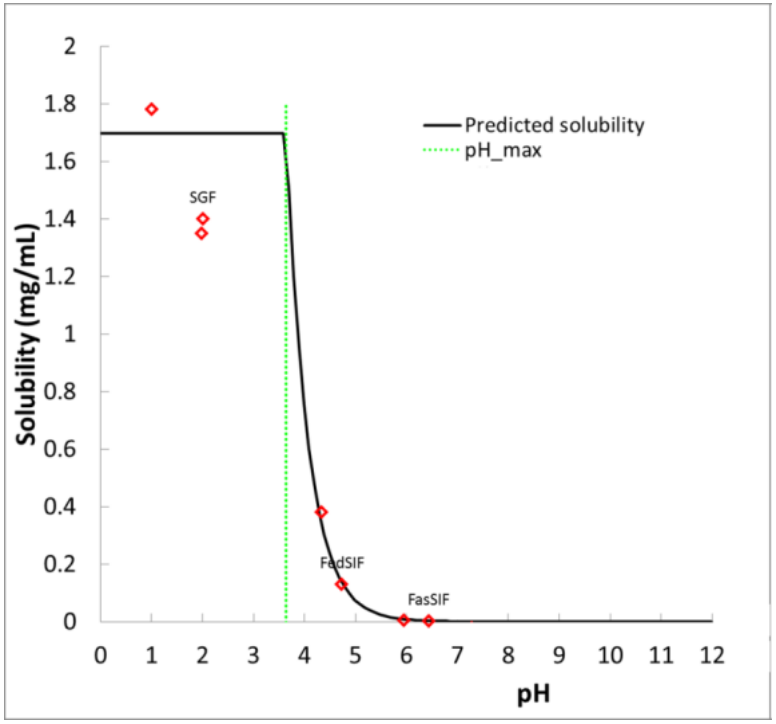


- Ketoconazole dosed as 240 mL of a solution acidified to pH 2.7

L. Burns, K. Kovach

Case Study– Free base conversion

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

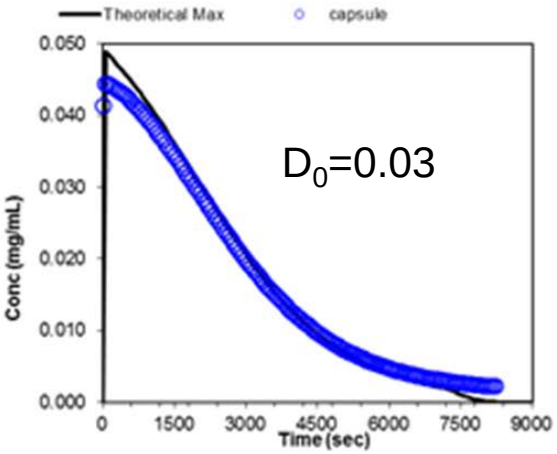


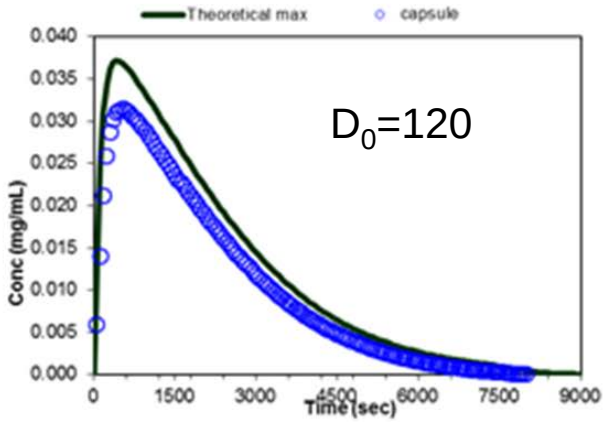
Case Study- Salt supersaturation and precipitation

Stomach concentrations

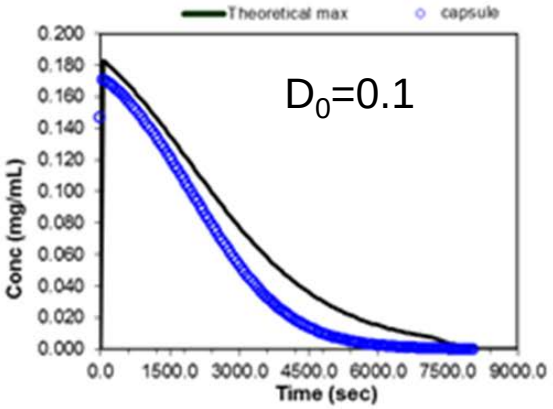
Duodenum concentrations

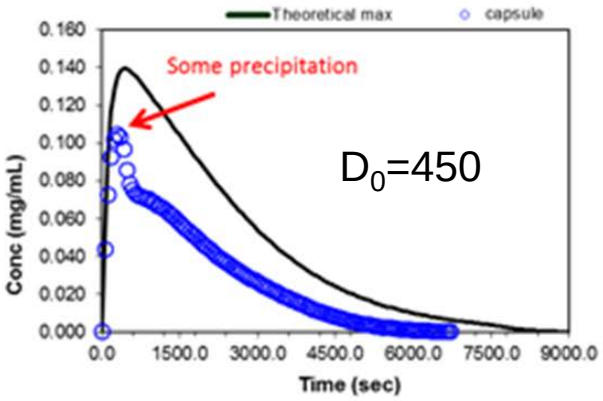
Low dose



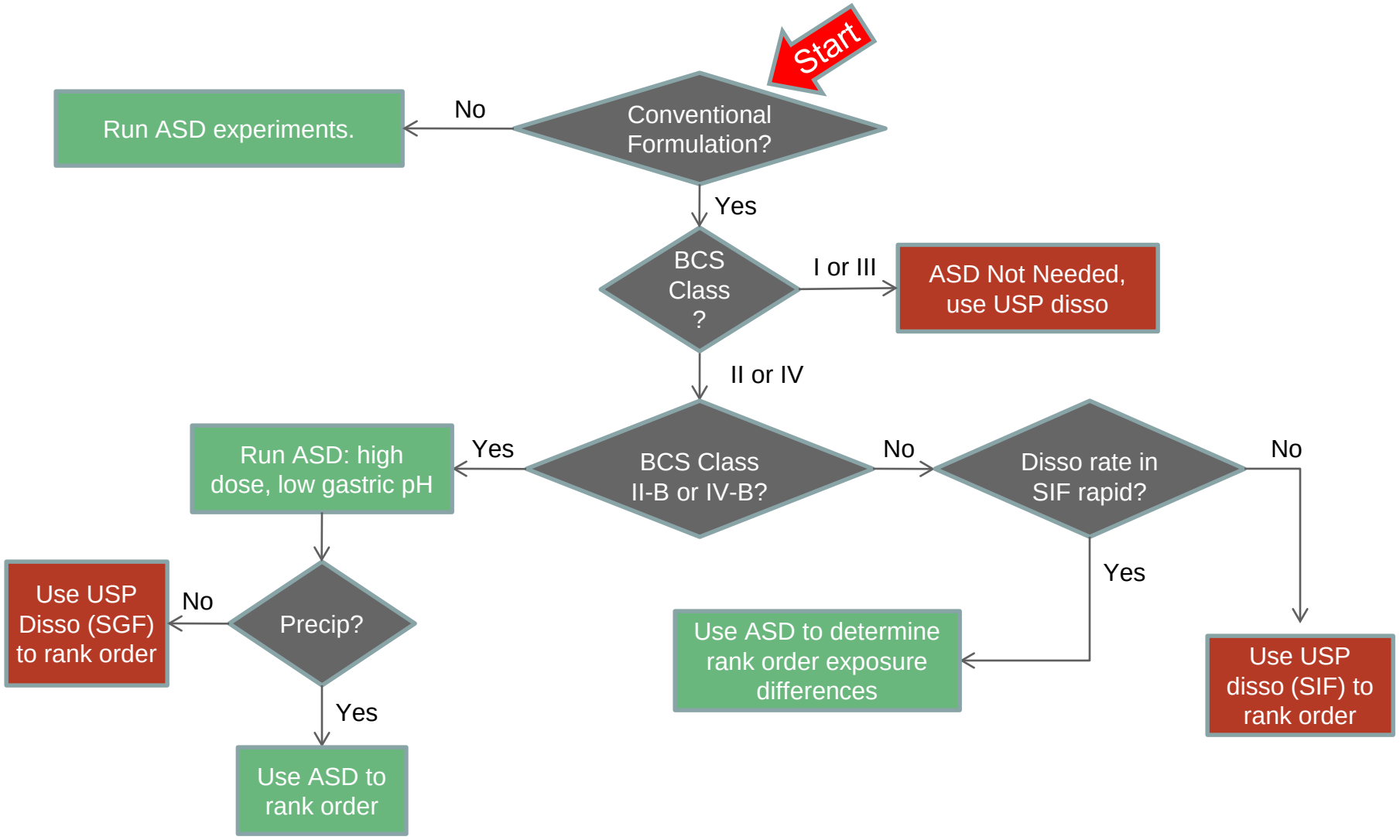


High dose





Decision Tree Guides Experiments



ASD Areas for Improvement

- Field of study would benefit from some standardization
  - Fluid compositions
  - Solids transport
  - Agitation
  - Fed vs. fasted simulations
- Enhancements to physical system
  - More compartments → transit time
  - Automated low-volume sampling
  - Methods to simulate removal of aqueous drug from system (absorption)

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M-CERSI Organizing committee and you!

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Background Slides

Physiochemical Properties and the Prediction of Performance

Noyes-Whitney Equation: $\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$

Rate of dissolution

- **A** is the surface area of the solid.
- **C** is the concentration of the solid in the bulk dissolution medium.
- **C_s** is the concentration of the solid in the diffusion layer surrounding the solid.
- **D** is the diffusion coefficient.
- **L** is the diffusion layer thickness.

Rate of dissolution is described by the Noyes-Whitney equation

The Noyes-Whitney equation represents the influence of key physiochemical properties on the dissolution rate

Influence of Physiochemical Properties on the Dissolution Rate

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

A is the surface area of the solid

- Surface are is directly related to particle shape and size
- Particle size naturally occurs as a distribution

C is the concentration of the solid in the bulk dissolution medium.

- At t=0, this is 0

C_s is the concentration of the solid in the diffusion layer surrounding the solid.

- This is the solubility limit of the drug.
- At t=0, the difference (C_S-C) represents the total capability of the particle to dissolve

D is the diffusion coefficient.

L is the diffusion layer thickness.

Commercial software packages can accurately simulate dissolution curves using these data

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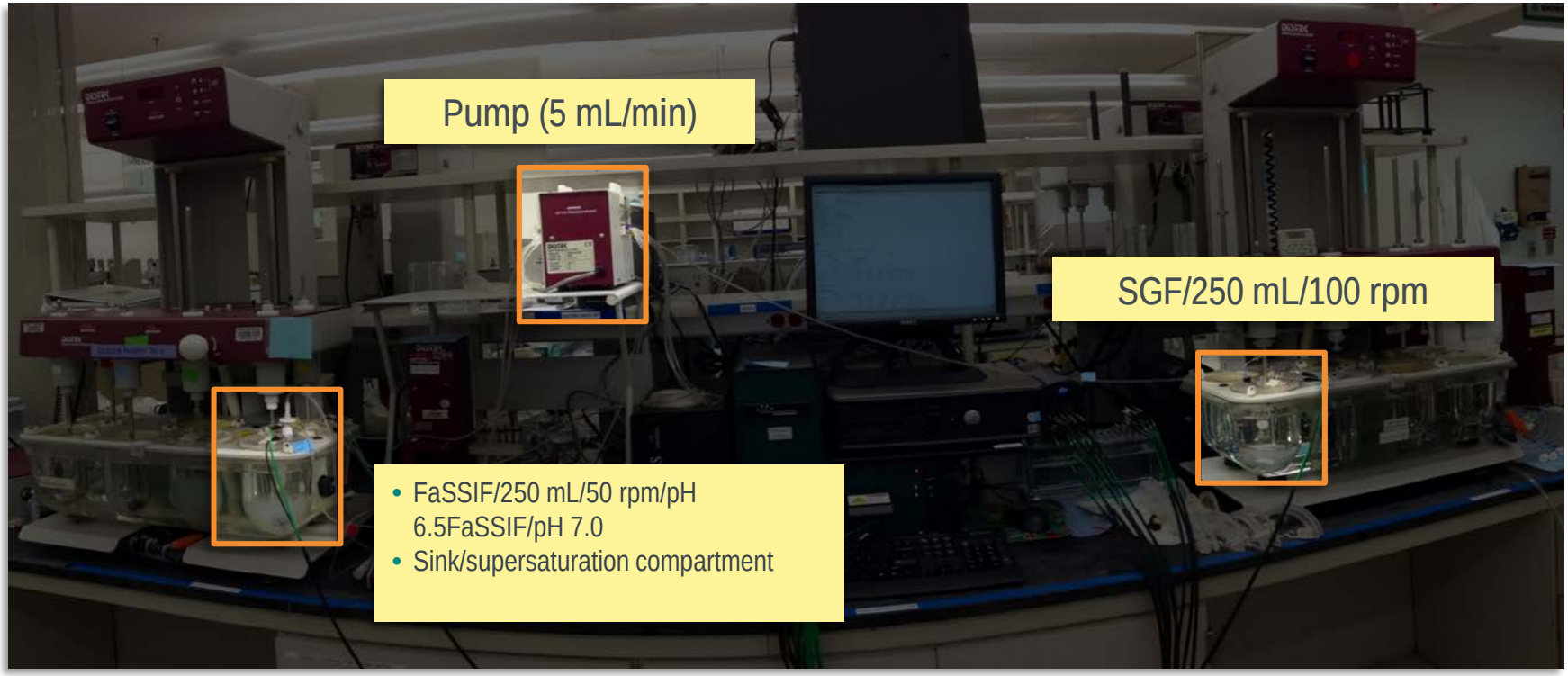

Pump (5 mL/min)
SGF/250 mL/100 rpm
• FaSSIF/250 mL/50 rpm/pH 6.5FaSSIF/pH 7.0
• Sink/supersaturation compartment

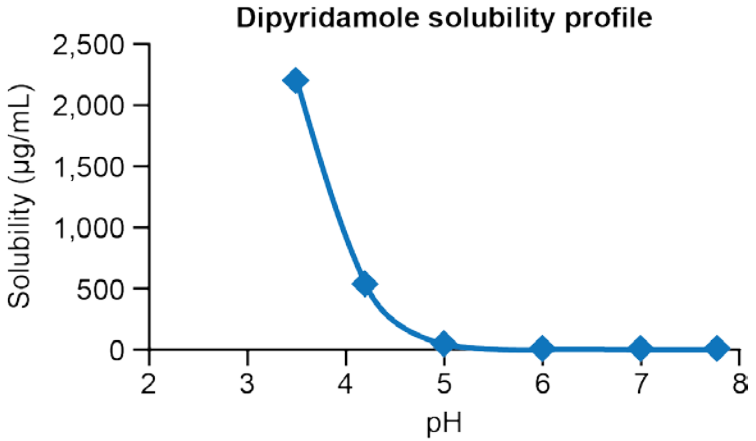
Case Study: Dipyridamole

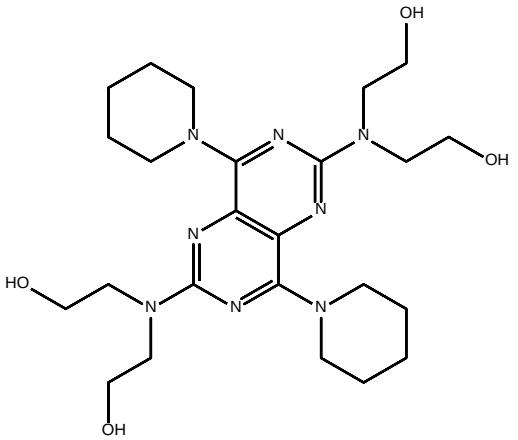
Characteristics

- Inhibits thrombus formation (antiplatelet)
- Free base with pKa of 6.4
- BCS Class II
- Permeability: Estimated human Peff 1.5 (cm/sec x 10^{-4})

Dose Information

- Tablets: 25 mg, 50 mg, 75 mg
- Recommended dose: 75-100 mg 4 times daily
- Significantly decreased exposure with famotidine-treated healthy elderly patients
- The absolute bioavailability is 27 +/- 5.5% (range 11% – 44%)





Molecular Weight: 504.6, pKa = 6.4

pH	Solubility (mg/mL)
3.5	2.2
4.2	0.5
5	0.0054
6	0.0010
7	0.0005
7.8	0.0006
SGF	8
FaSSIF	0.01148

Terhaag B, et al. *Int J Clin Pharmacol Ther Toxicol*. 1986;24(6):298-302.
Glomme A, et al. *J Pharm Sci.* 2005;94(1):1-16.

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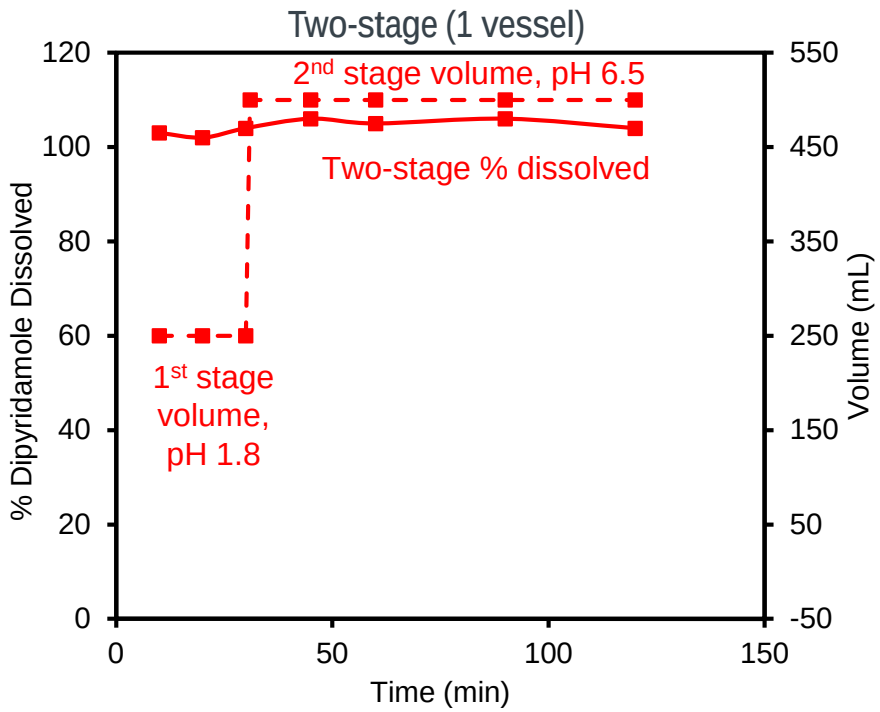
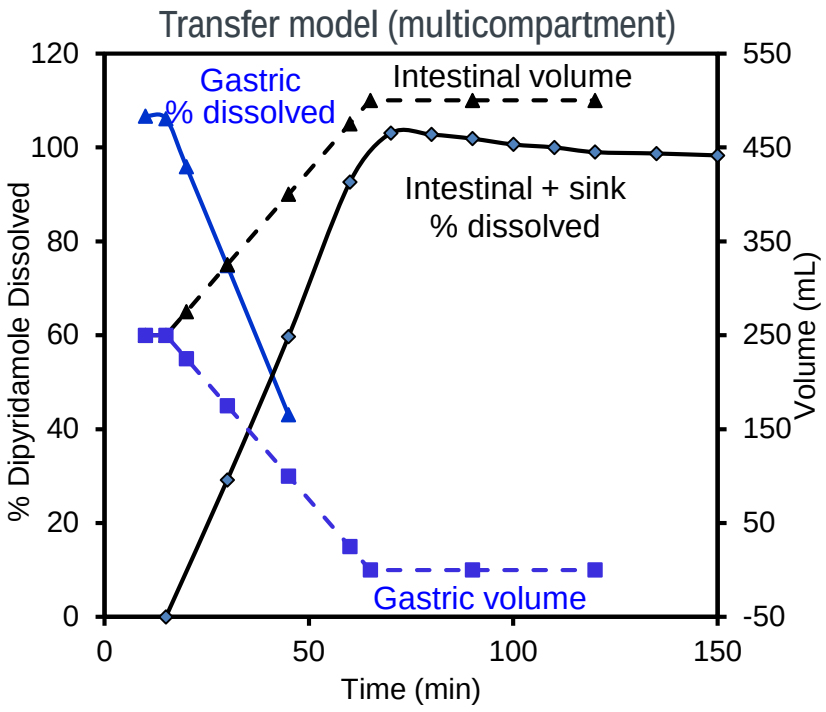
Dipyridamole Tablets: Transfer vs Two-Stage

Both models indicate dipyridamole does not undergo rapid precipitation

Absorption modeling studies also indicate a prolonged in vivo precipitation

Dipyridamole precipitation is concentration dependent (Box K, et al. Approaches for measuring intestinal precipitation rates of oral drugs [abstract])





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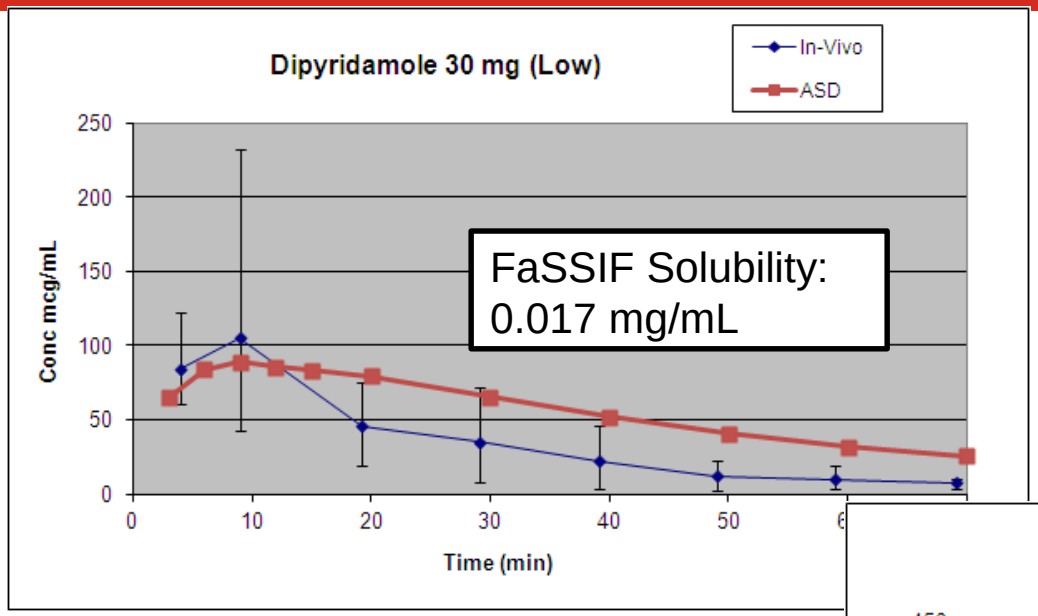
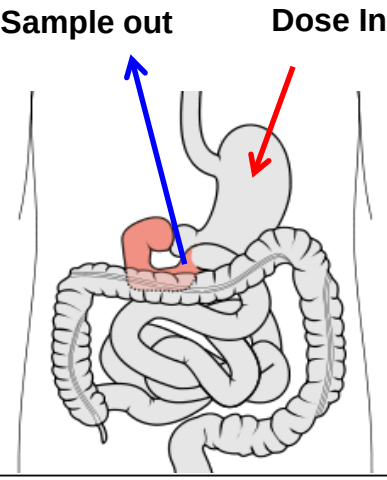
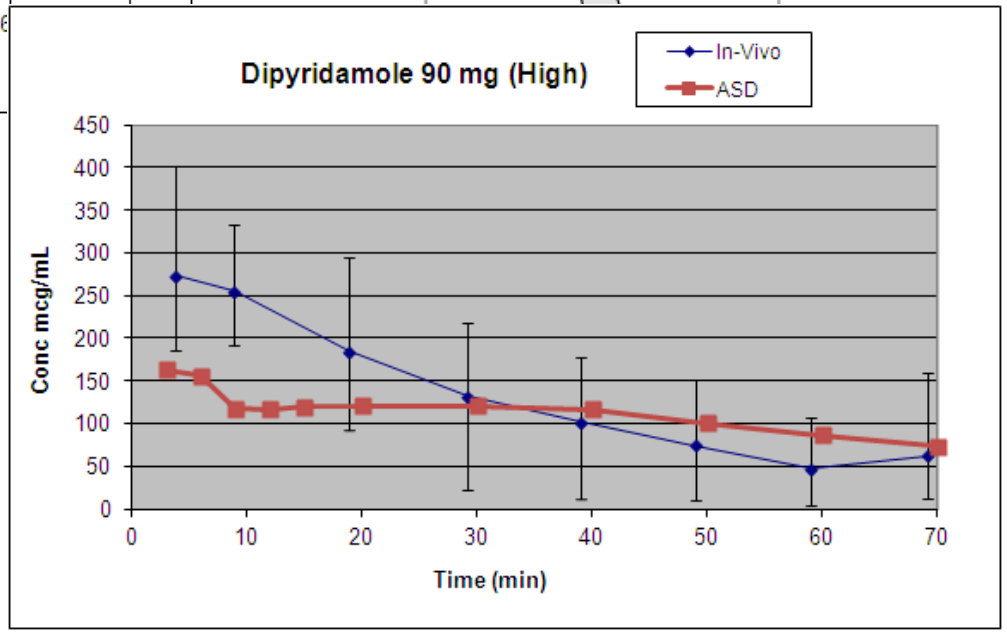
ASD/Human Comparison of Duodenal Concentration Profile







- In vitro data: ASD
- In vivo data: 12 Human volunteers. (Source: Psachoulias D, Vertzoni M, et al. Pharm Res. 2011; 28(12): 3145-3158)
- Dipyridamole dosed as 240 mL of a solution acidified to pH 2.7

L. Burns, K. Kovach