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Challenges and benefits of using PBPK to evaluate an IVIVC for drugs with non-ideal solubility and/or permeability

Bath, November 2014

Prof. Dr. Jennifer Dressman

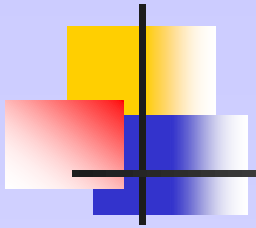
Why IVIVC and what are the challenges to establishing an IVIV relationship?

IVIVCs

- ***Support bridging studies during clinical studies***
- ***Support formulation and manufacturing changes after registration***

BUT,

- ***So far, most IVIVCs have been for MR dosage forms***
- ***Even for these, the in vitro results are usually generated with tests that resemble QC tests, so the IVIVC may not be very robust***
- ***IVIV relationships for IR dosage forms have been difficult to attain with classical methods***



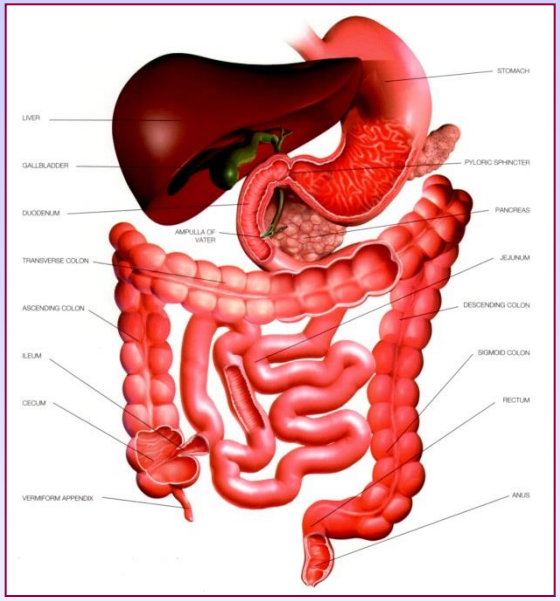
Recommendation: pay attention to the *in vitro* test design!

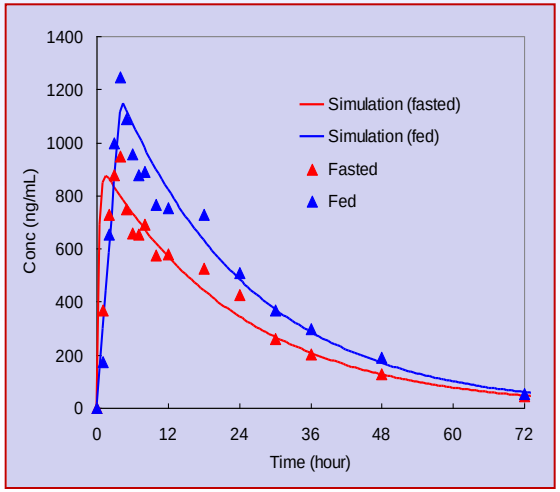
Part I: biorelevant dissolution tests – what are these?

General approach to dissolution testing

Hypothesis:

the closer the dissolution test conditions to the physiology, the better the chances of predicting product performance





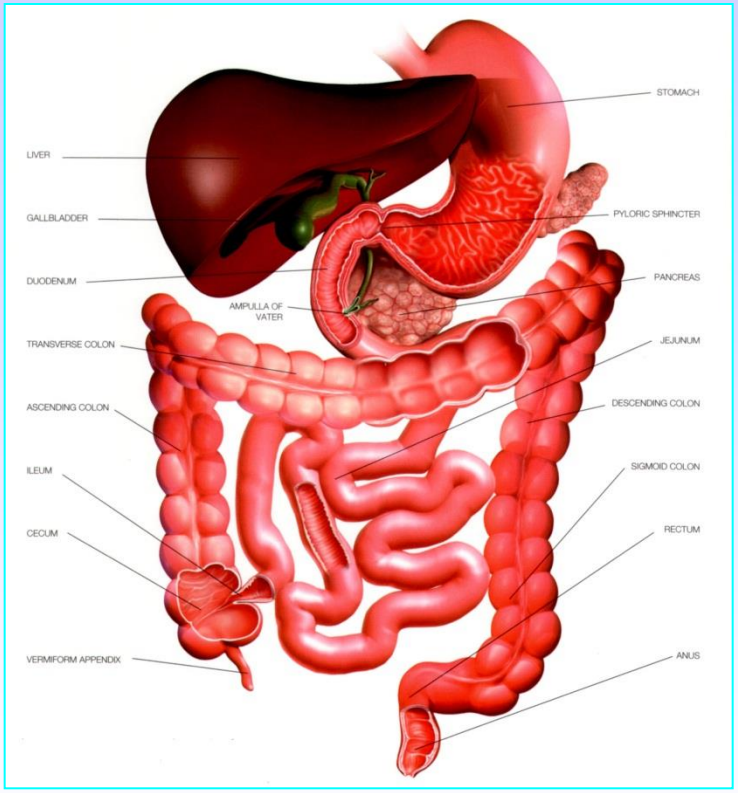
Finding the right dissolution test…..

THREE important considerations:

WHERE in the GI tract is drug released from the dosage form?

HOW LONG does the dosage form have to release the drug?

COMPOSITION of the fluids into which the drug is released?



Finding the right dissolution test…..

WHERE in the GI tract is drug released from the dosage form? This will vary with the drug product e.g.

- Immediate release dosage forms
- Enteric coated dosage forms
- Extended release dosage forms
- Pulsatile delivery….

The site(s) of release and/or % released at each site of release are often also dependent on whether the dosage form is given before or after a meal, so the dissolution test should also reflect the dosing conditions

Finding the right dissolution test…..

HOW LONG does the dosage form have to release the drug?

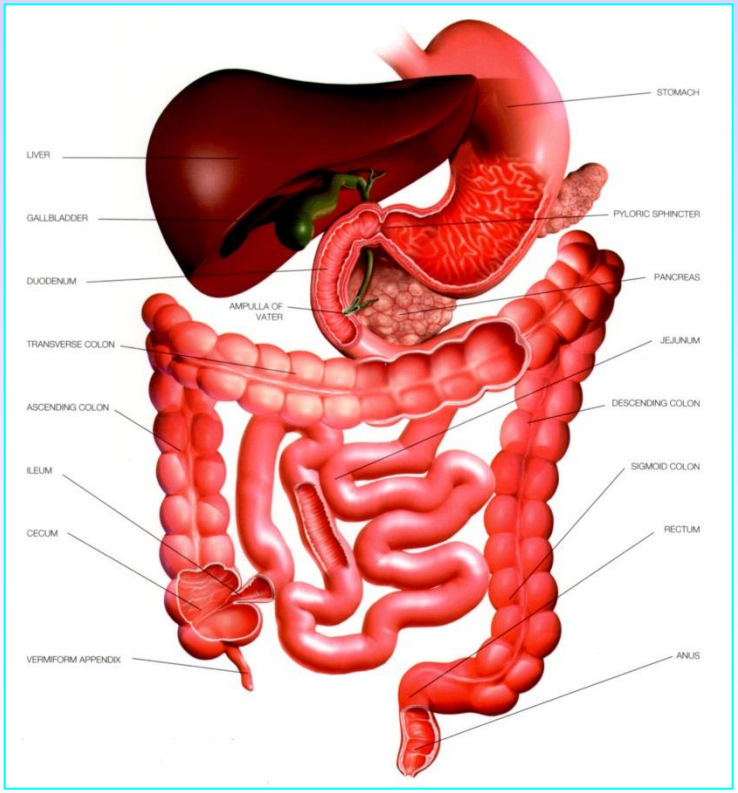
- The drug must be released before or at its site(s) of absorption, otherwise release will not result in absorption. So it is important to understand the permeability of the drug at various points in the gut.

- The passage of the dosage form through the stomach depends on unit size and prandial state.

Finding the right dissolution test…..

COMPOSITION of the fluids into which drug is released

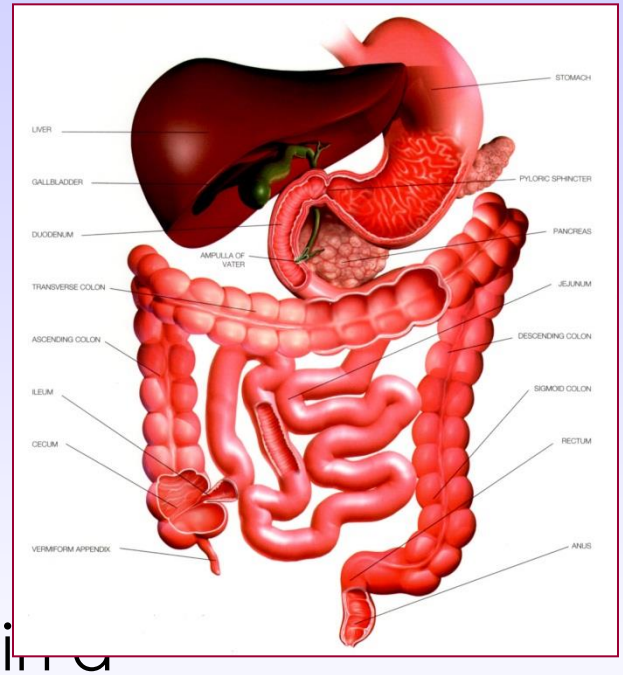
The foods and drinks we consume, gastric juices, bile, pancreatic juices, bacterial fermentation as well as water re-uptake all combine to influence the composition of the GI fluids at various points in the gut.



GI-appropriate media composition and volume: „biorelevant“ dissolution media

1. Fasted state

- Stomach:
  - **FaSSGF:** simulates reduced surface tension in the stomach
- Small intestine:
  - **FaSSIF** to simulate basal bile secretion in upper SI
- Colon:
  - **FaSSCOF** to simulate conditions in a fasted state PK study



Vertzoni et al. EJPB 2005, Dressman et al. Pharm.Res. 1998, Vertzoni et al. Pharm. Res. 2010

GI-appropriate media composition and volume: „biorelevant“ dissolution media

2. Fed State

- Stomach:
  - **FeSSGF**: Milk/buffer pH 5 combination to simulate gastric conditions after a standard breakfast
- Small intestine:
  - **FeSSIF-V2** to simulate postprandial bile secretion, lipolysis products, increased buffer capacity and osmolality in upper SI after food intake
- Colon:
  - **FeSSCOF** to simulate the ascending colon in the fed state

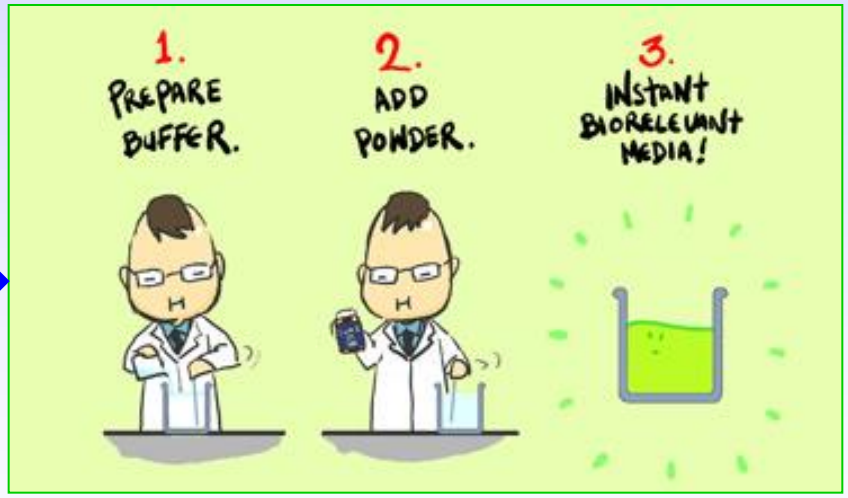
Jantratid et al., Pharm. Res. 2008, Vertzoni et al., 2010

Biorelevant dissolution media

Using „instant" powders to make the biorelevant media:

„Study of a Standardized Taurocholate–Lecithin Powder for Preparing the Biorelevant Media FeSSIF and FaSSIF"

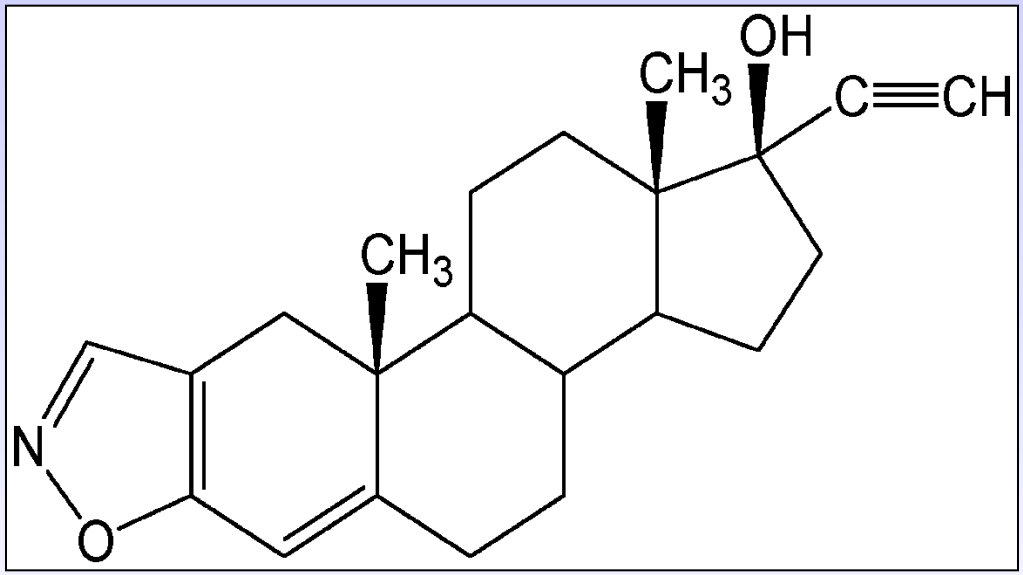
Dissolution Technologies



source: www.biorelevant.com

Case example 1: Relationship between dissolution and PK of Danazol (a poorly soluble but highly permeable drug)

Case example 1. danazol



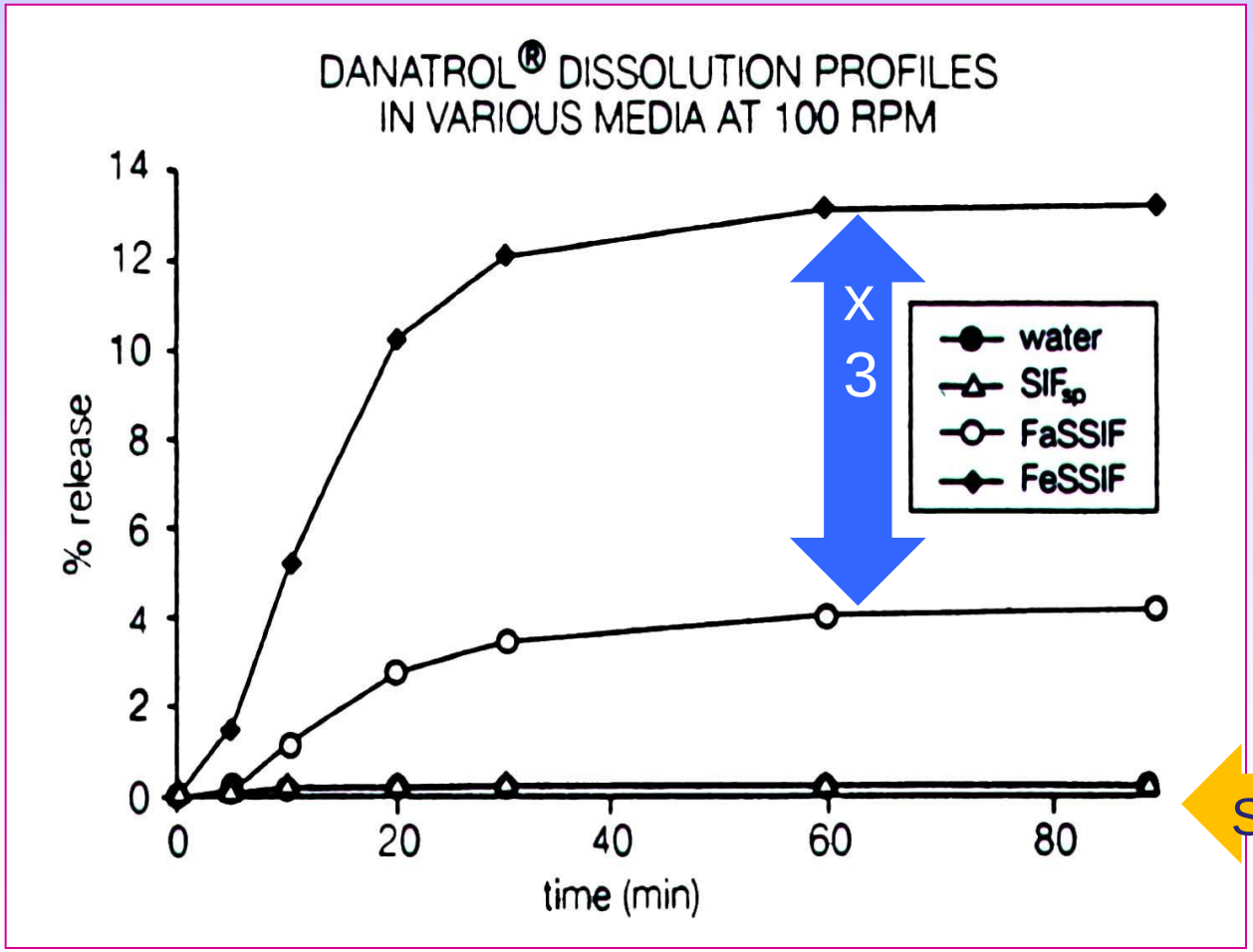
Aqueous solubility: 1µg/ml D:S 200 liters H_2O

Dose: 200 mg 20 liters FaSSIF

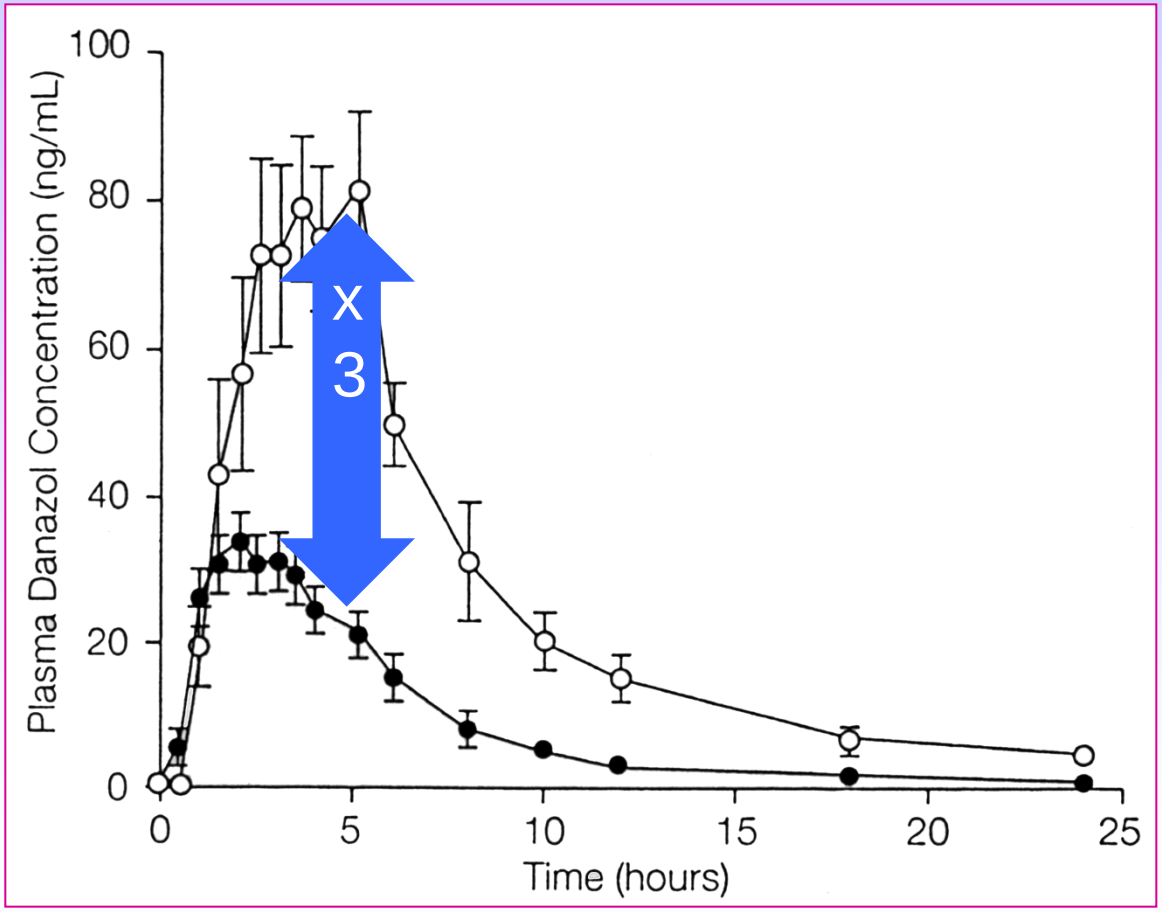
pKa: neutral 6 liters FeSSIF

log P: 4.53

Danatrol dissolution profiles in various media at 100 rpm

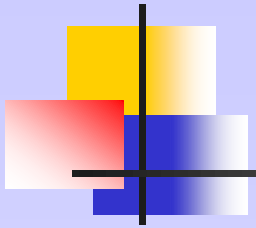


Danazol's food effect reflects its dissolution characteristics



Plasma profiles of danazol after administration in the fasted **(●)** and fed **(○)** state *(from Charman et al.)*

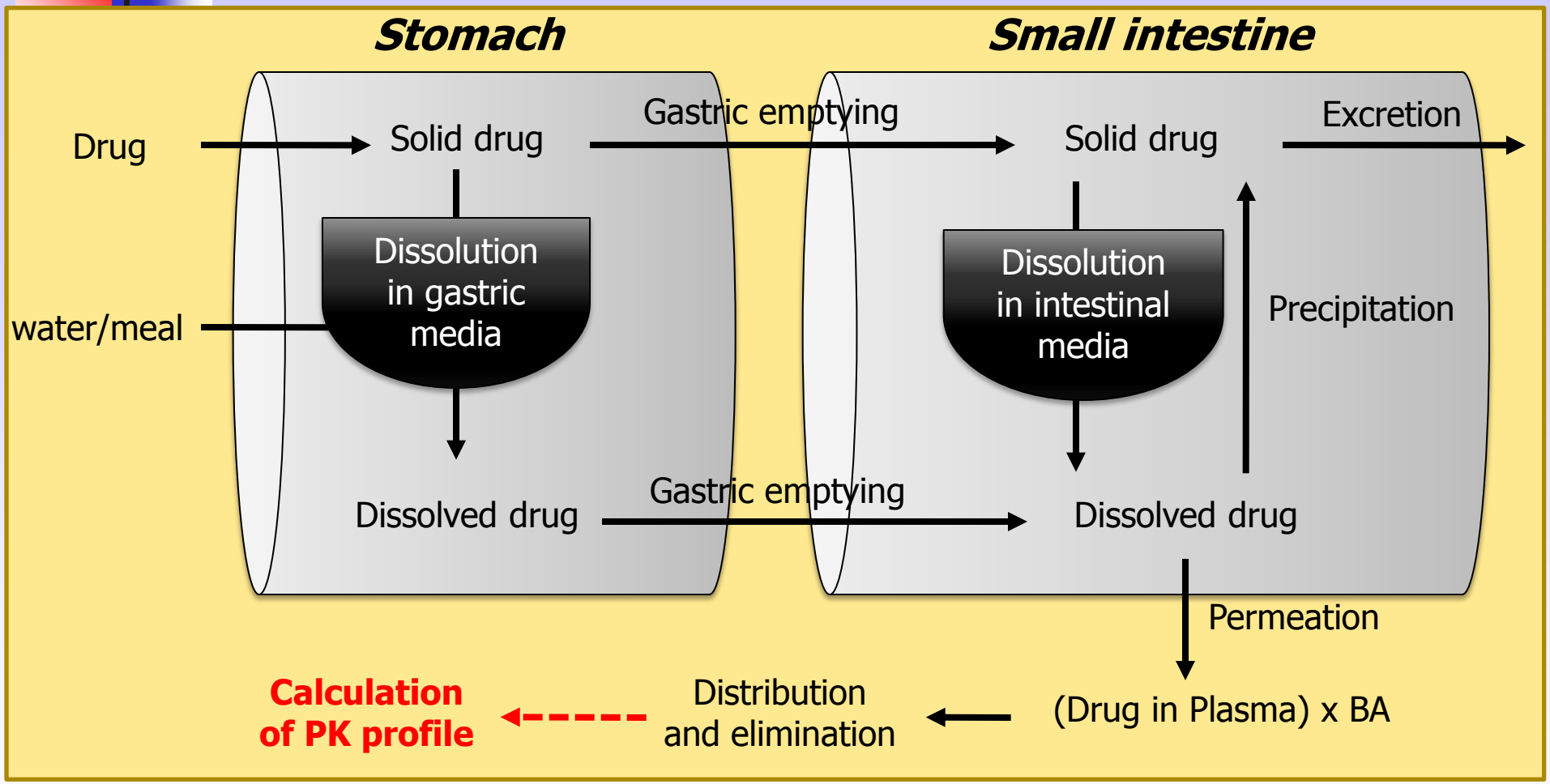
Part II: Combining biorelevant dissolution testing with PBPK modeling to achieve IVIV relationships for poorly soluble drugs



- **Biorelevant dissolution tests alone**:
- **Qualitative** forecast of food effects and formulation trends possible
- *But, how can we arrive at a more **quantitative** prediction??*

- **Coupling with PBPK models (IV-IS-IV-R)**:
- **Quantitative** forecast of food effects and formulation trends possible, since contributions of all steps affecting bioavailability can be addressed

PBPK Modeling and PK Simulation



Initial Assumptions in the model

- Negligible absorption from the stomach
- Simultaneous solid and liquid emptying from the stomach (disintegrating dosage form)
- No intestinal permeability restrictions (for high permeable drugs)

IV-IS-IV Strategy to predict oral absorption

Set up *in vitro* dissolution testing

Biorelevant media: fasted/fed, gastric/intestinal

Test parameters: apparatus, volume, hydrodynamics

Linkage

Understand *in vivo* performance

Further investigation to understand absorption mechanism and indentify key factor which affect on the *in vivo* performance

- **Development of a desired formulation**

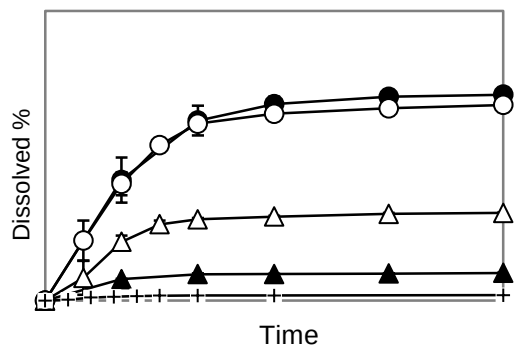
(no food effect, less variability, high BA)

- **Control strategy with a key attribute**

(design space, quality by design)

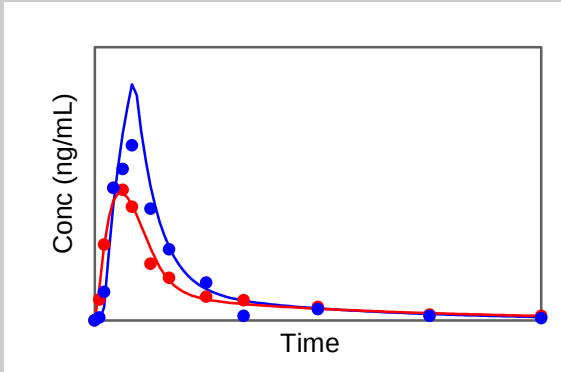
Predict *in vivo drug release*

Qualitative prediction based on the extent in dissolution, comparing with the *in vivo* data (AUC, ranking order)



Predict PK profile with *in silico* PBPK modeling

Quantitative prediction based on the extent in dissolution, comparing with the in vivo data (AUC, C_{max}, T_{max})



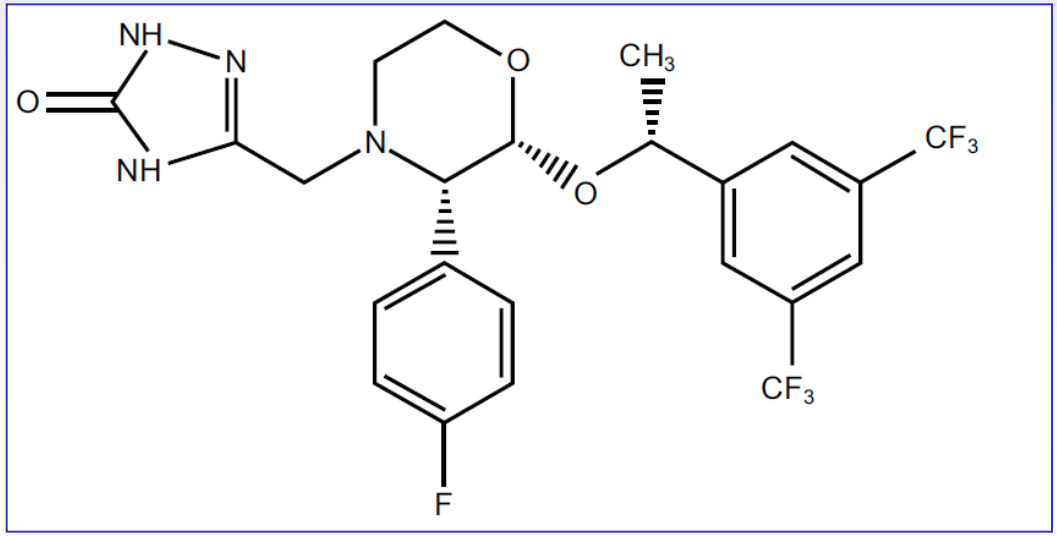
Case example 2: Coupling biorelevant dissolution with PBPK to understand the effect of particle size on PK of aprepitant (poorly soluble, highly permeable)

Case example: Aprepitant

BCS Class 2 (low solubility and high permeability)

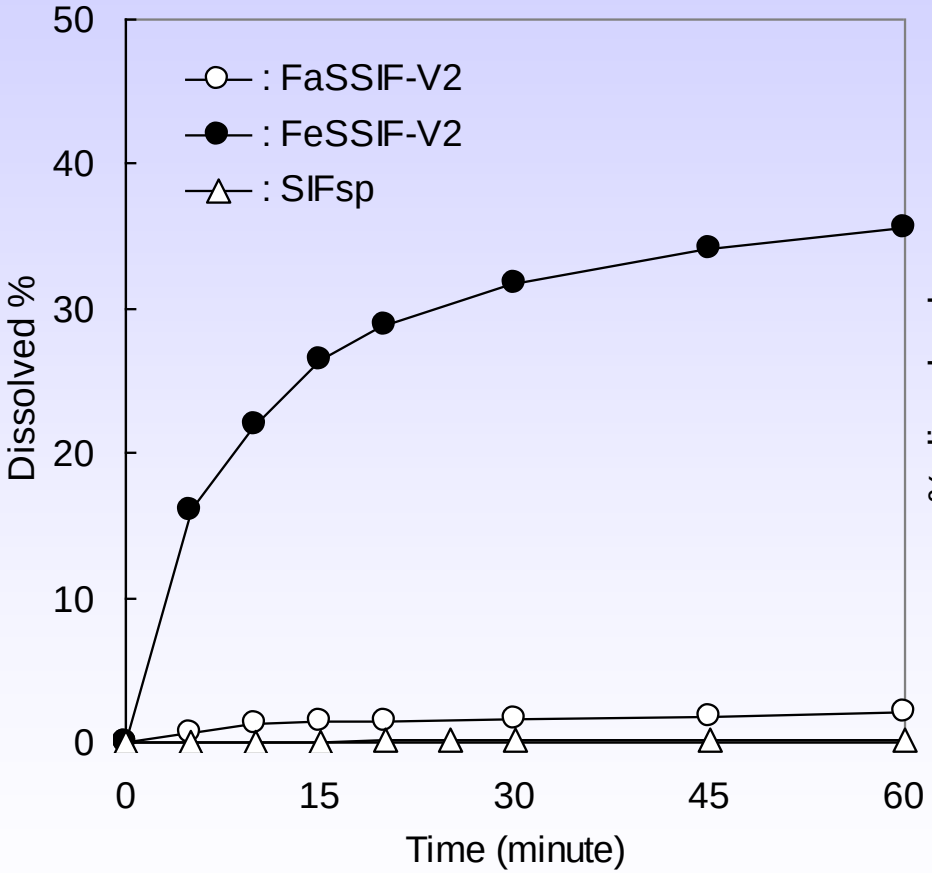
pK_a	: 9.7 (basic)
Cs	: 0.02 mg/mL in SGF_{sp} (pH1.2), 0.0007 mg/mL in SIF_{sp} (pH 6.8)
Log *P*	: 4.8
P_{app}	: 7.8 x 10^{-6} cm/sec (Caco-2)

Micronized, nanosized formulations
Indication: Emesis

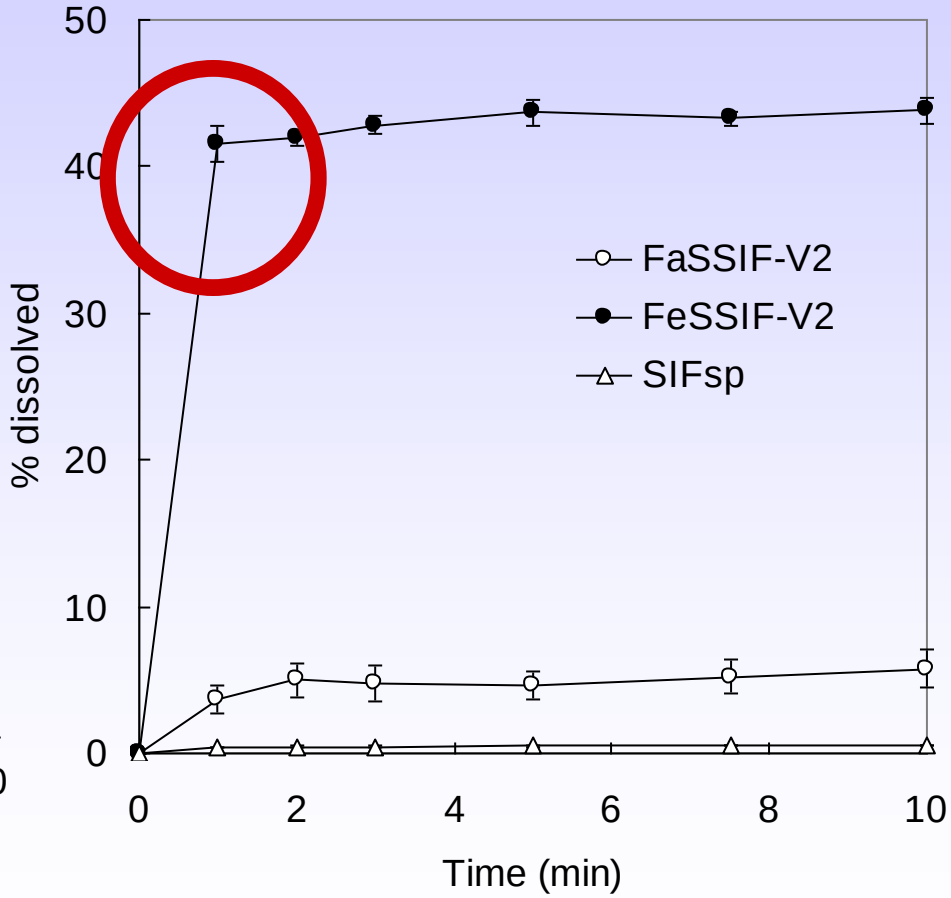


Dissolution of aprepitant 125mg in biorelevant media

Micronized

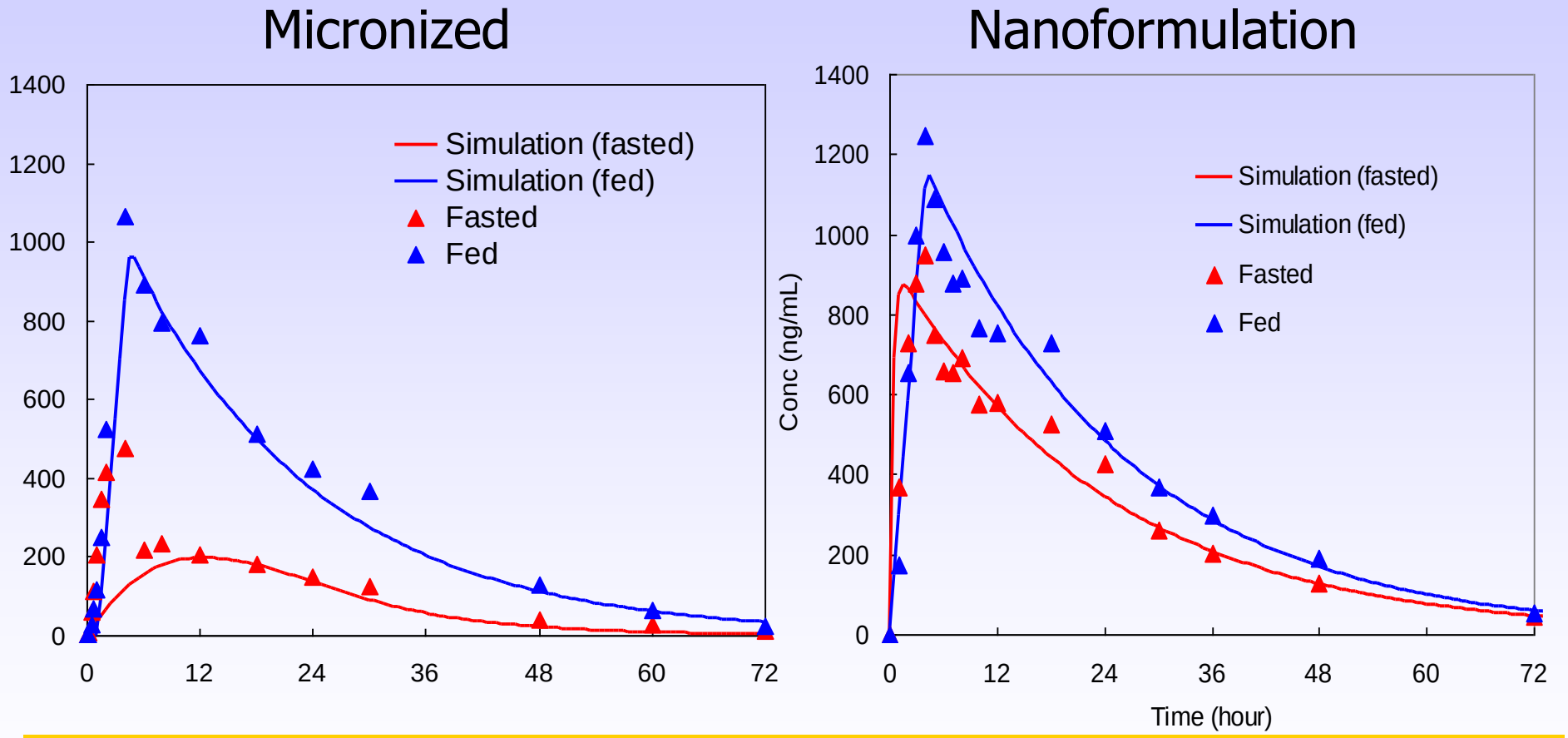


Nanoformulation



Dressman

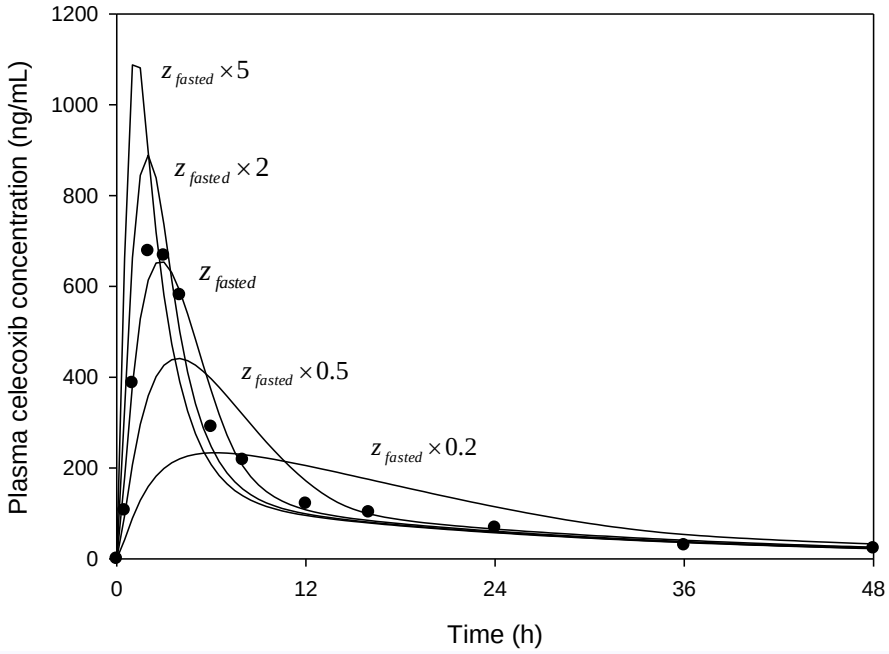
Simulated profiles of aprepitant in the fasted and fed state



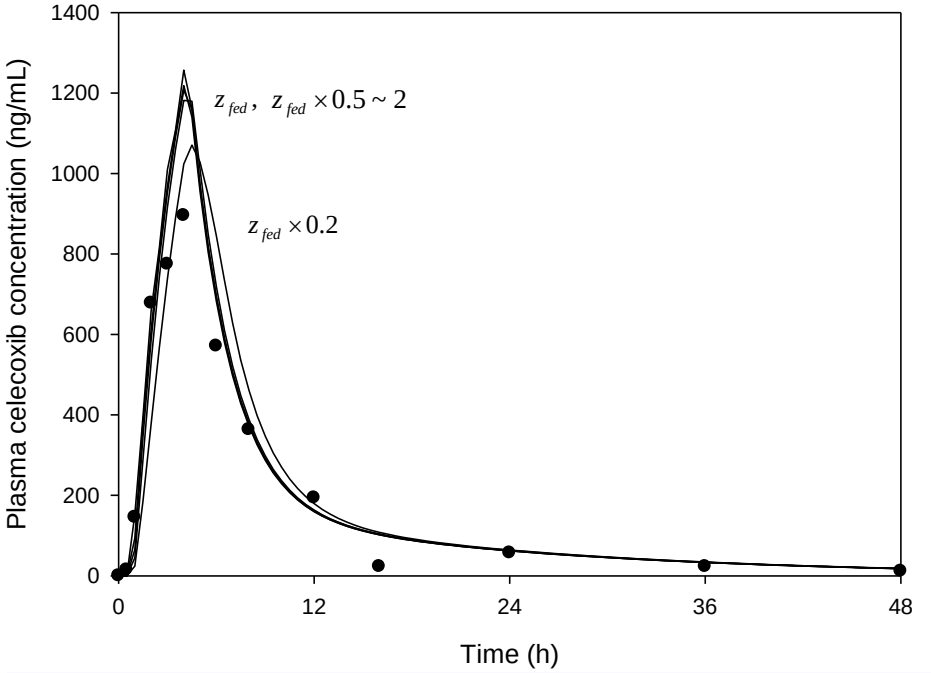
*Y. Shono et al. EJPB **76**:95-104 (2010)*
Value added: prediction of z value (=> particle size) at which food effect is eliminated

Value added of IVISIVC: mechanistic insight
1. Effects of dissolution rate (z) on PK profile

Fasted



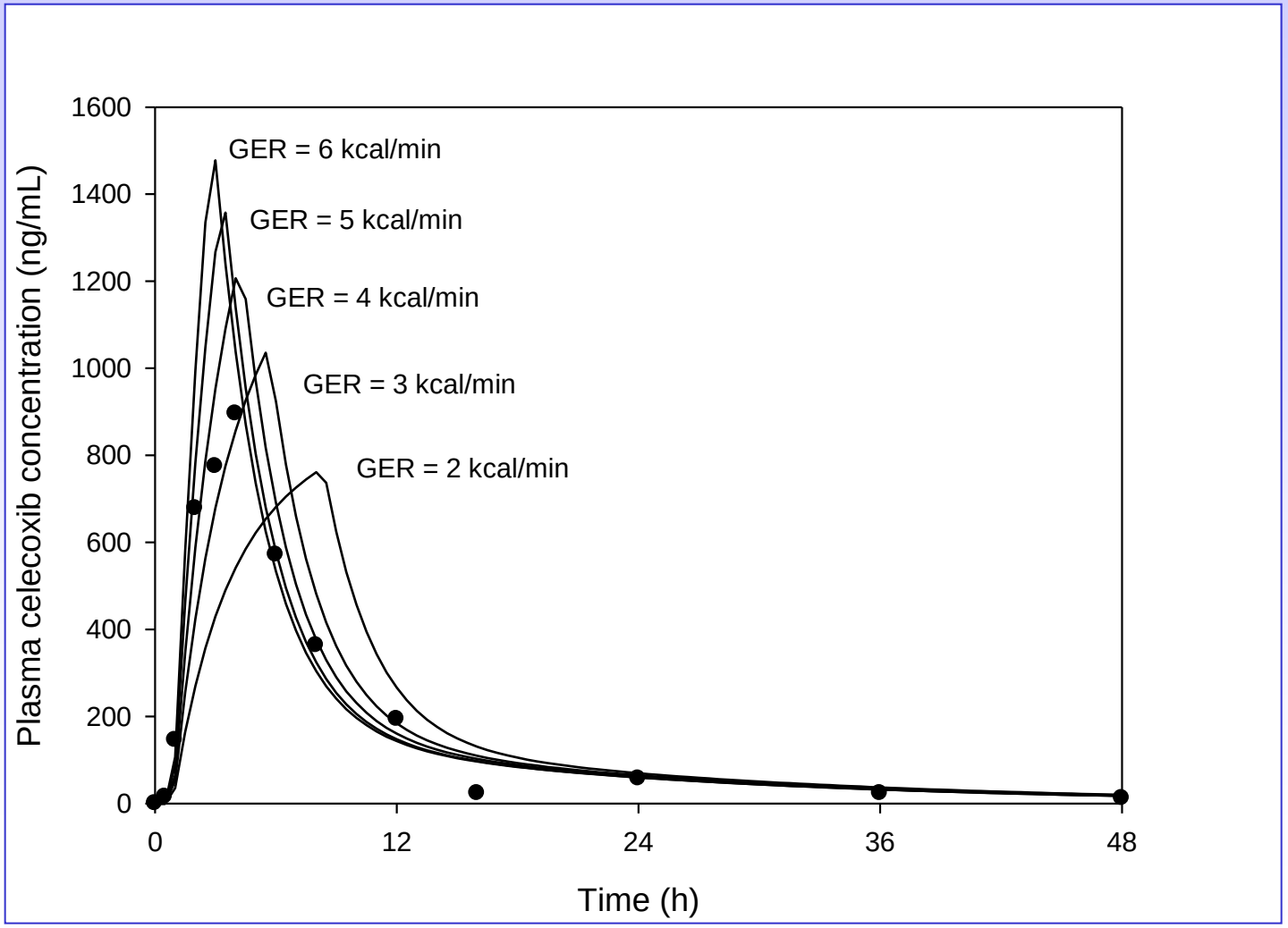
Fed

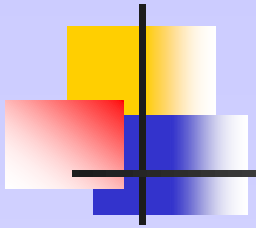


Fasted: highly dependent on dissolution rate in addition to solubility

Fed: no significant effect of dissolution rate ===> depends on gastric emptying

2. Effects of gastric emptying rate on PK profile in the fed state



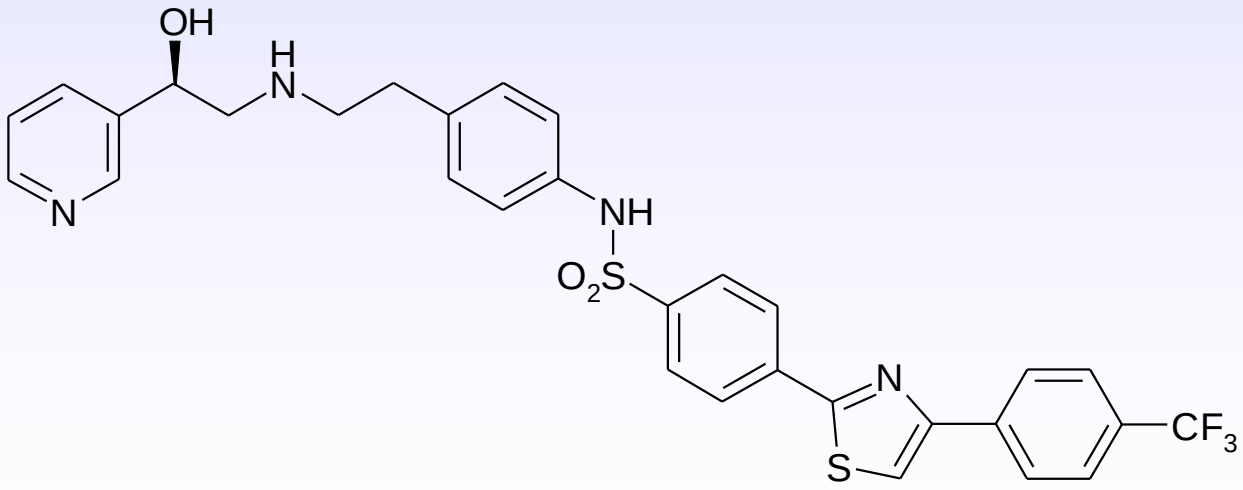


Case example 3: prediction of PK of a Merck & Co. development compound, which is neither highly soluble nor highly permeable and, being a weak base, might precipitate upon entry into the small intestine

Case example: Compound A

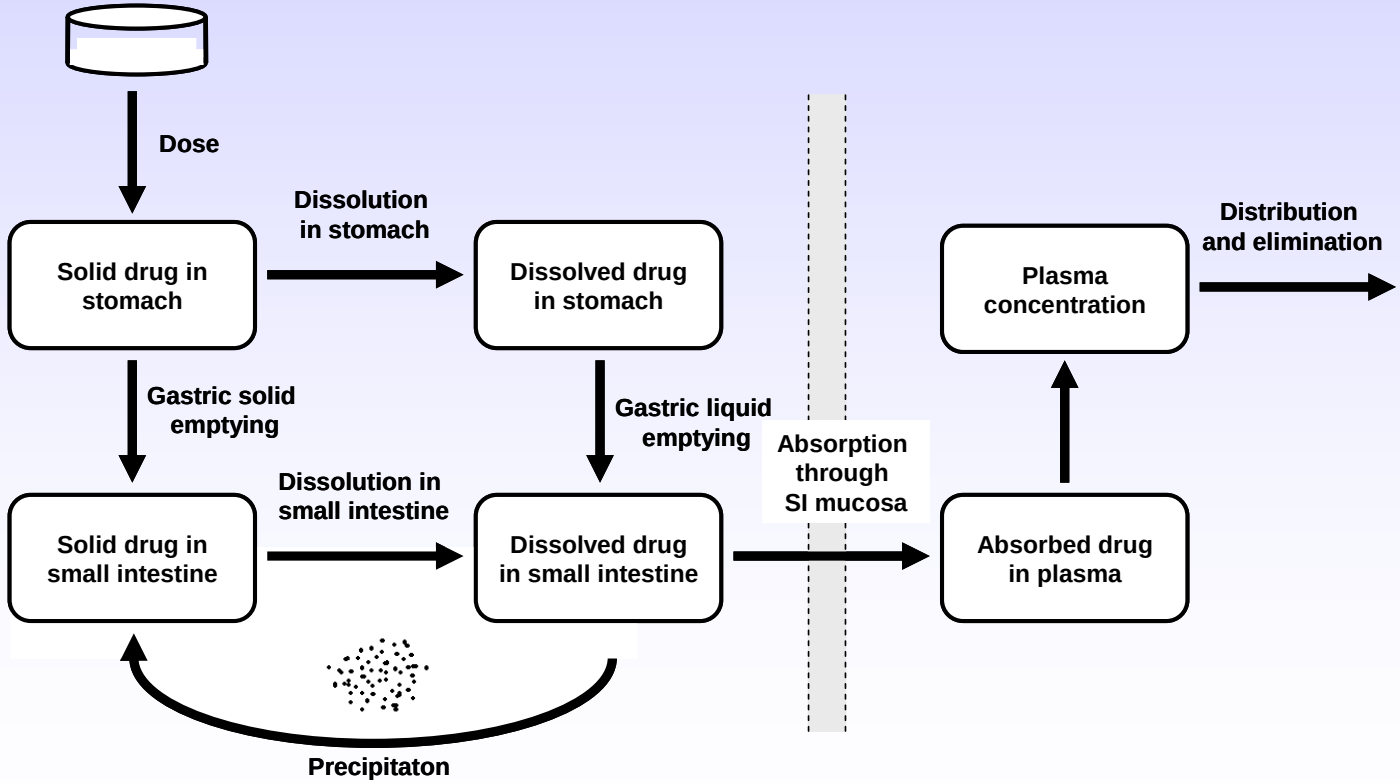
BCS Class 4 (neither solubility or permeability is high)

pK_a	: 4.2, 7.6, 9.1 (basic)
Cs	: 0.02 mg/mL in SGF_{sp} (pH1.2), 0.0007 mg/mL in SIF_{sp} (pH 6.8)
Log *D*	: 1.4 @ pH 1.5, 3.5 @ pH 7.4
P_{app}	: 0.8 x 10^{-6} cm/sec (Caco-2)



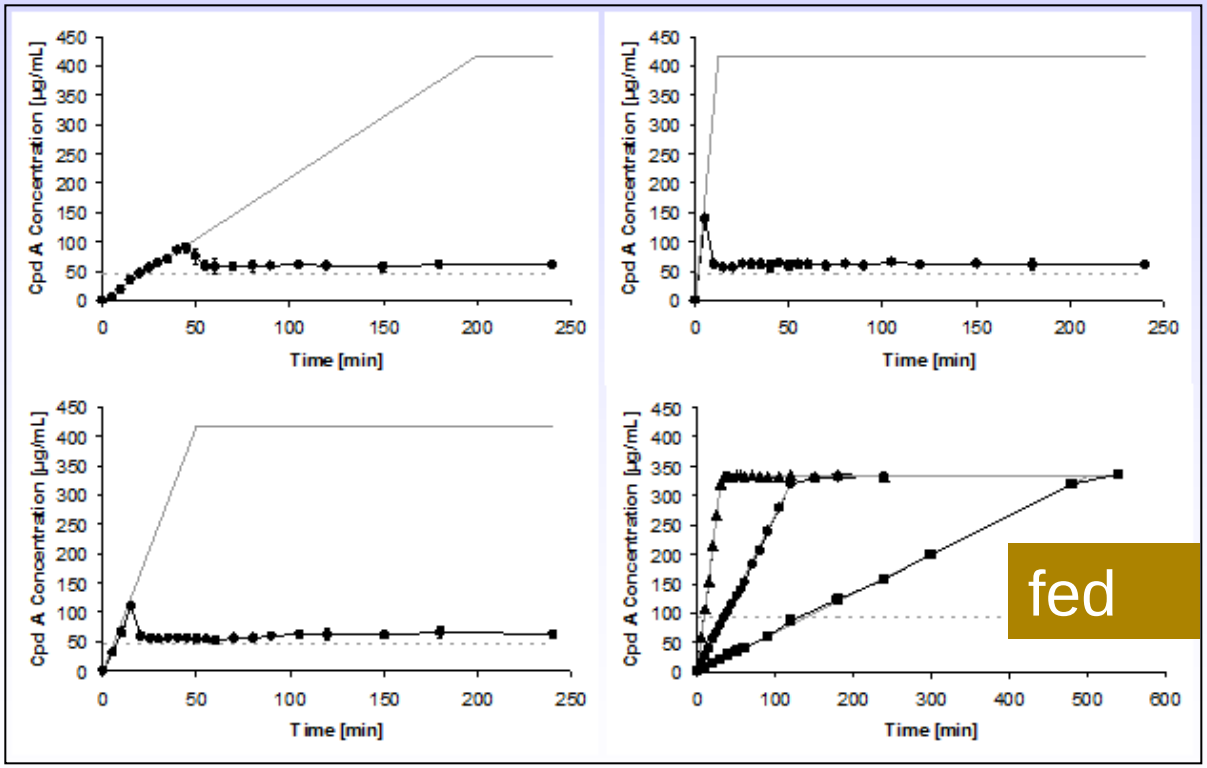
Compound A pharmacokinetic model

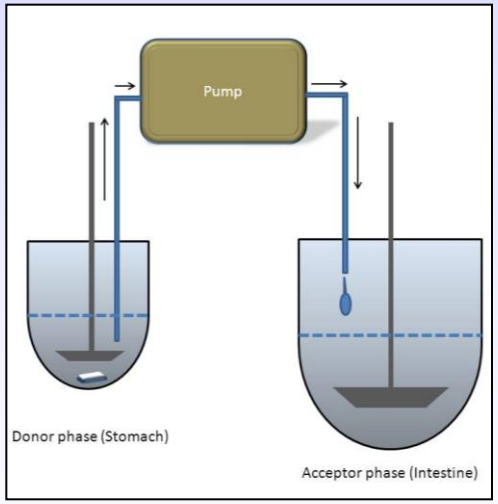
A precipitation step for the fasted state and a limitation to permeability were introduced into the Stella Model



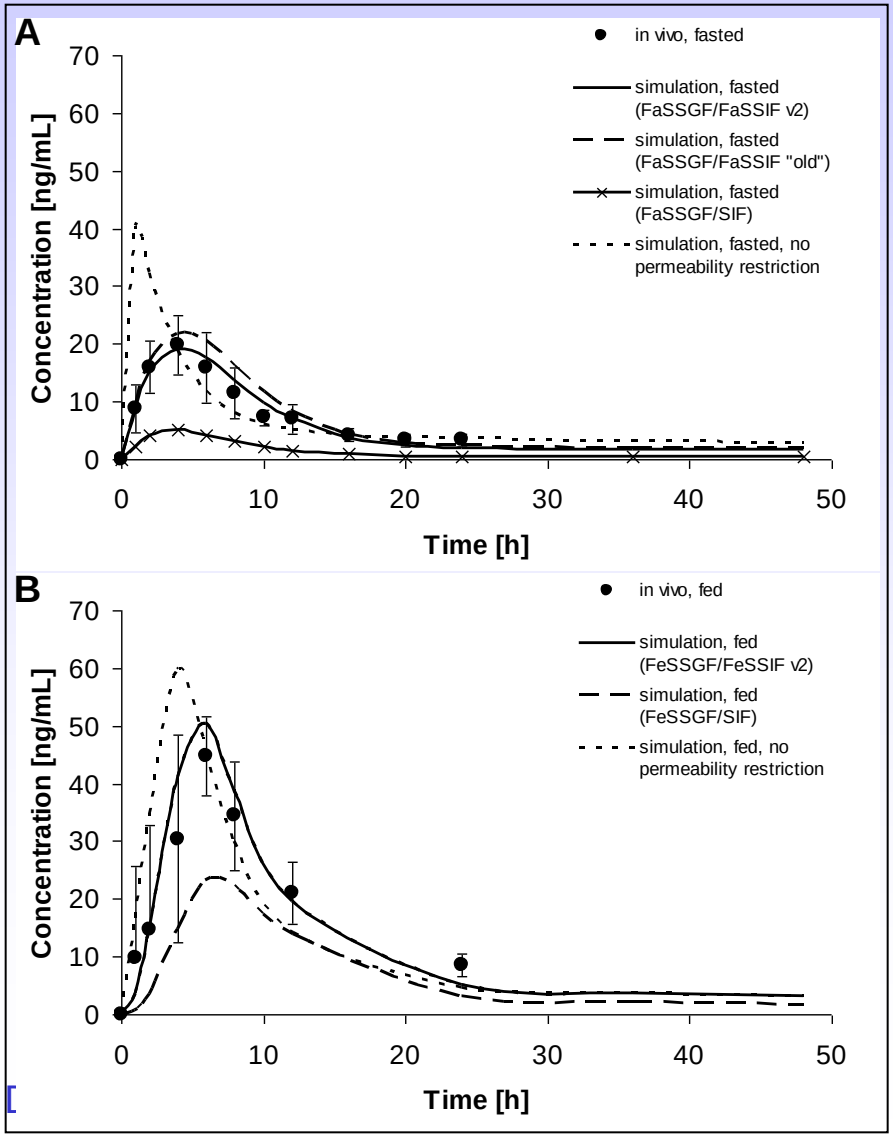
Compound A transfer model data

Transfer model data revealed transfer rate depedent precipitation in the fasted state, but no precipitation in the fed state

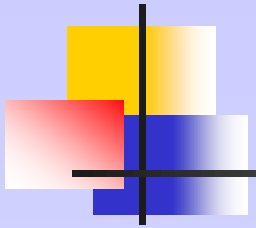




Compound A PBPK simulation

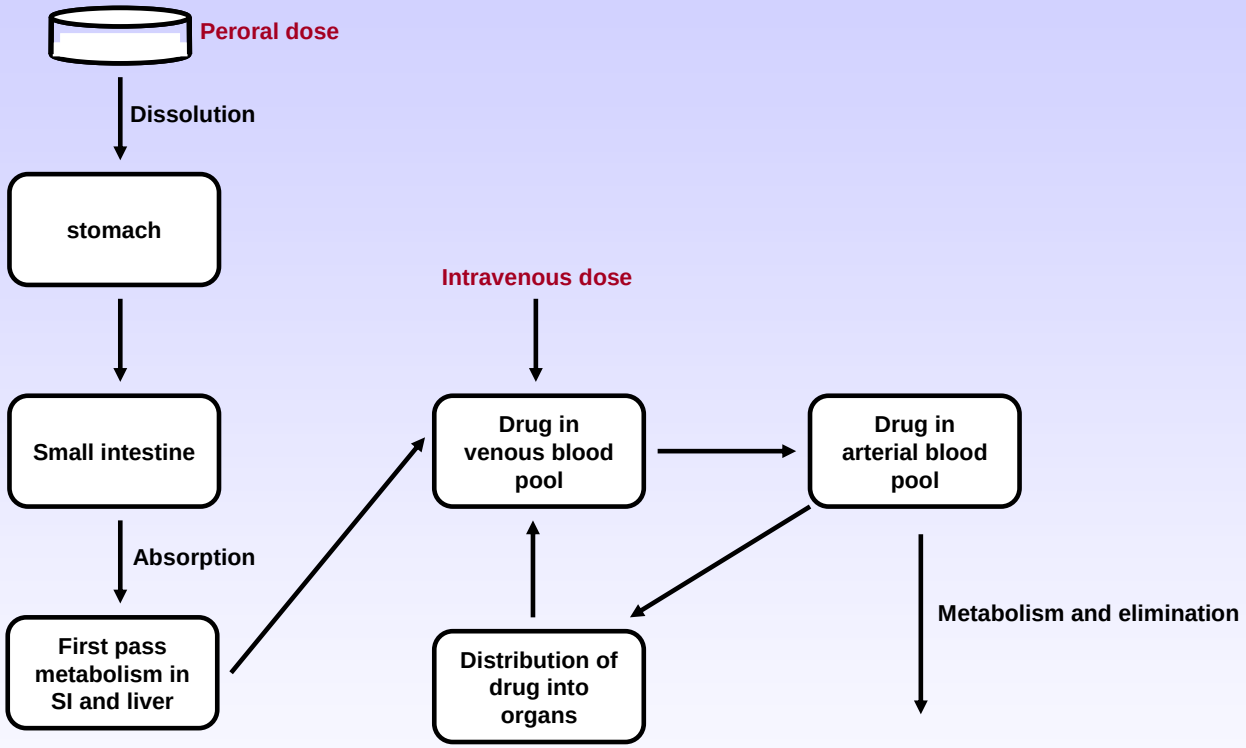


Only when biorelevant media are used and precipitation in the fasted state as well as a permeability restriction is invoked, is it possible to simulate the in vivo profiles accurately



Case example 4: prediction of nifedipine (poorly soluble, highly permeable, first pass substrate) PK after administration of the Adalat osmotic pump formulation

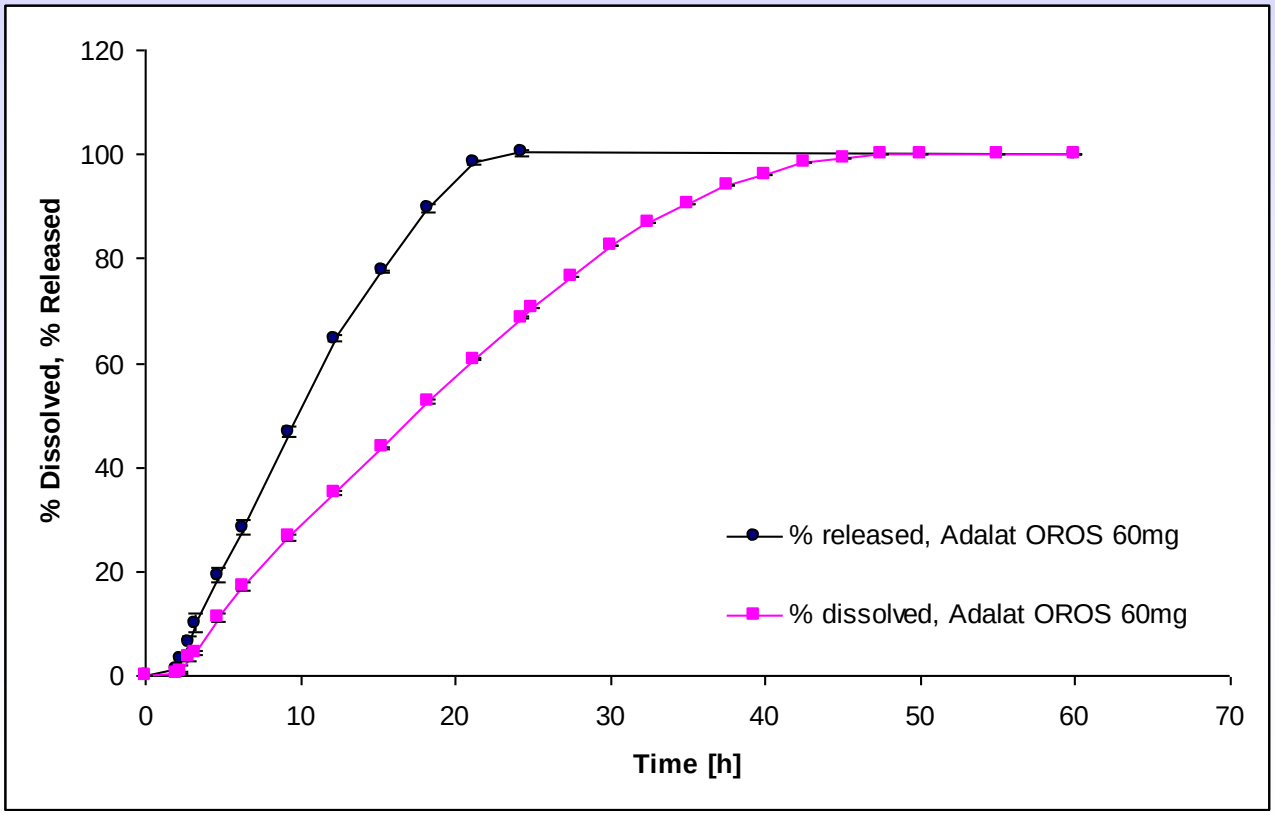
nifedipine pharmacokinetic model



Step 1: in silico description of nifedipine PK to account for first pass (using PK-SIM)

nifedipine release and dissolution in vitro

- *Step 2: release and dissolution in the Type 3 tester (BioDis) using a biorelevant media profile*

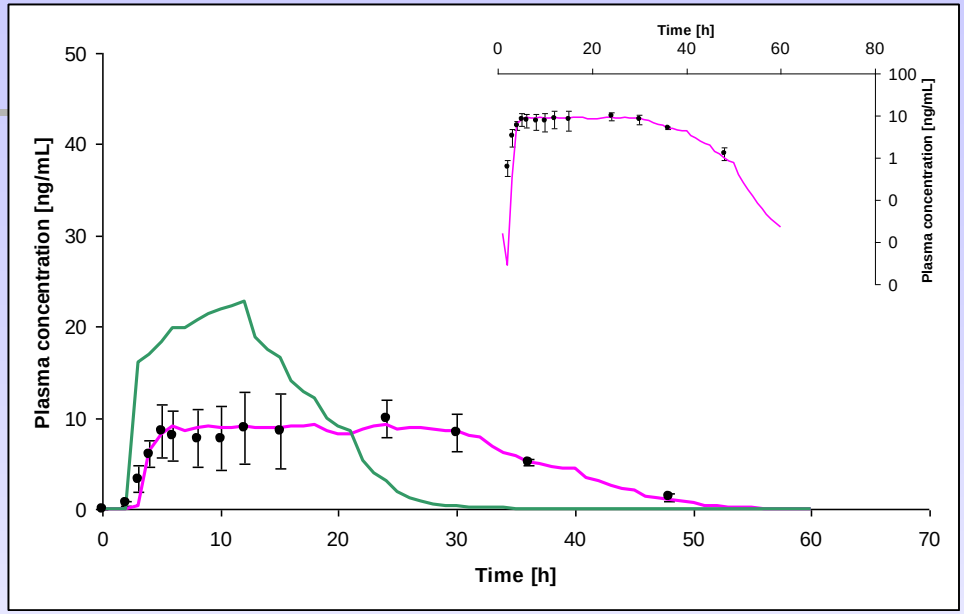


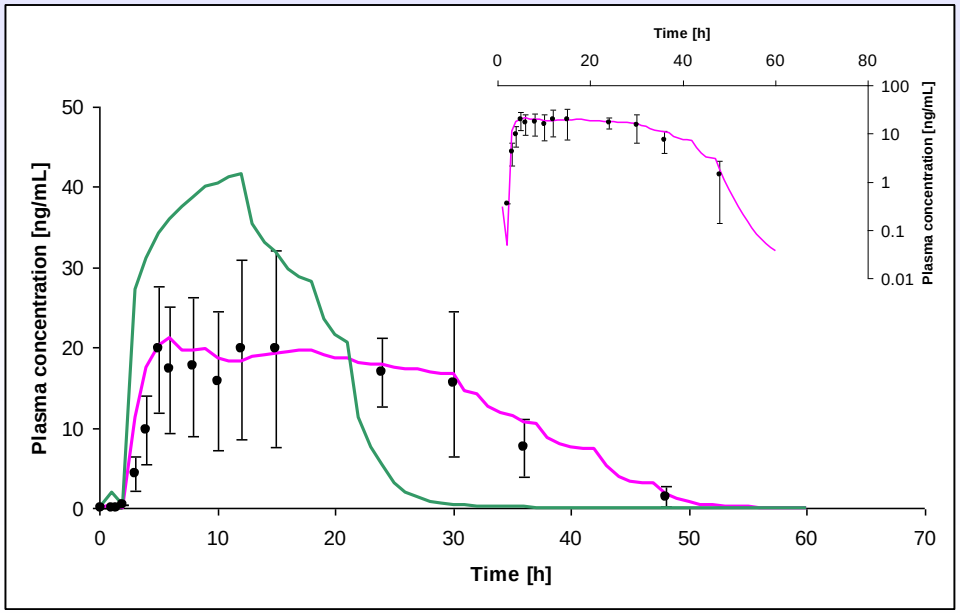
Nifedipine PK

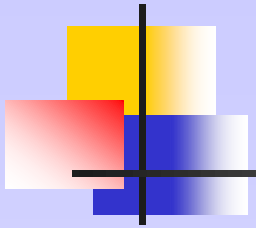
- *Step 3: prediction*

of PK profile based on PK-SIM model for first pass AND biorelevant dissolution testing

Conclusion: drug dissolution <u>after</u> release from the MR dosage form is rate-limiting to absorption







Strategy to understand and forecast oral drug absorption

Combine results from biorelevant dissolution tests with physiologically based pharmacokinetic modeling to create

„in vitro – in silico – in vivo“

relationships

IVIVC Challenges ahead

- Integration of appropriately biorelevant dissolution data (i.e. use the right level of biorelevant media)
- Appropriate integration of dissolution data into the commercial PBPK models (especially for MR dosage forms that do not have robust, zero-order release kinetics)
- Appropriate integration of precipitation data into commercial PBPK models

Acknowledgments

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- Dr.s Filippos Kesisoglou & Henry Wu (Merck & Co., Inc.)
- Dr. Christian Wagner (U-Frankfurt, now FDA)

…and Many Thanks for your attention!