Case Studies of Mechanistic Absorption Modelling and IVIVC

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A Case Study in Avoiding Relative Bioavailability Studies for a BCS2 Drug

Neil Parrott

Parrott N, Hainzl D, Scheubel E, Krimmer S, Boetsch C, Guerini E, et al. Physiologically Based Absorption Modelling to Predict the Impact of Drug Properties on Pharmacokinetics of Bitopertin. The AAPS journal. 2014:1-8.

Background to the case study

- In 2010, a drug being developed for treatment of schizophrenia, is entering Ph 3 trials
- Roche held an EOP2 meeting with the FDA and requested waiver of an absolute bioavailability study for registration
- FDA agreed but requested a relative bioavailability study comparing the market formulation with a solution or suspension
- In 2011 Roche submitted a PBPK modelling report arguing that the relative BA study could be avoided

Biopharmaceutical properties

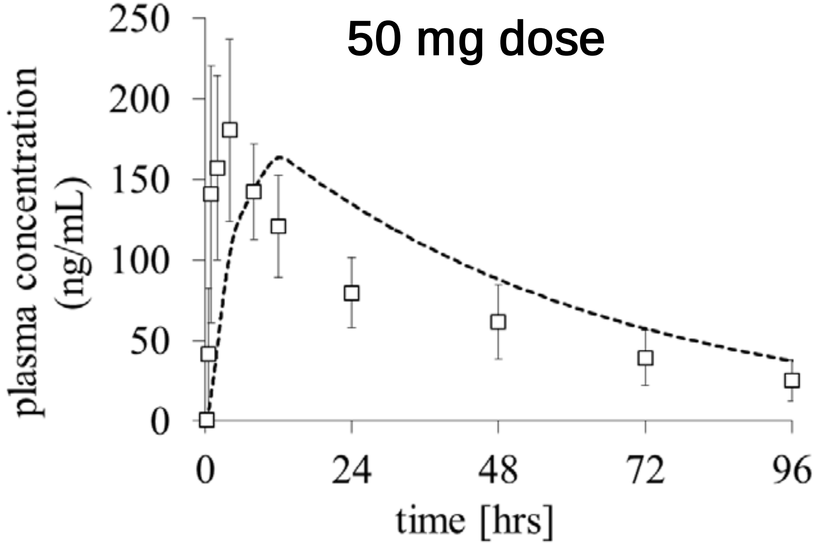
Lipophilicity logD at pH 7.4	3.0
Ionization constant	Neutral
Caco2 permeability scaled to HPeff	3.5 $*10^{-4}$ cm/s

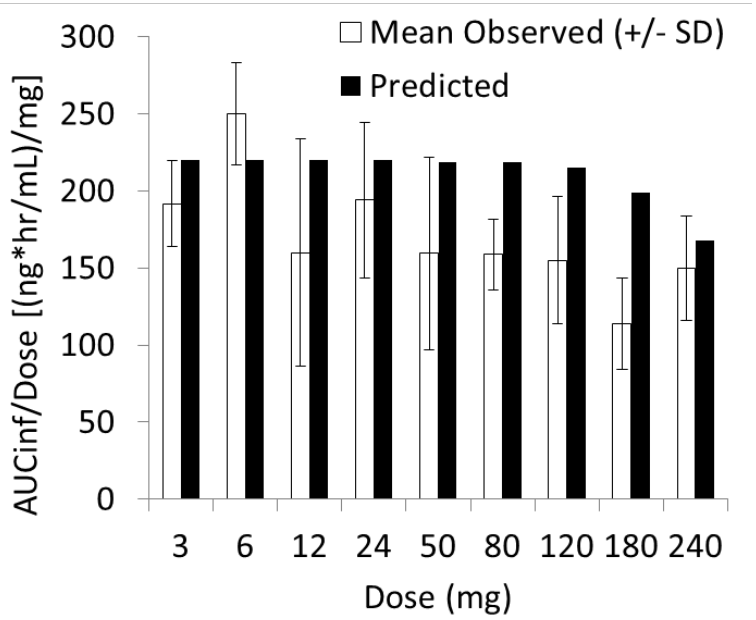
Solubility	**µg/mL**
Aqueous buffer pH 7	5
FaSSIF	25
FeSSIF	100
SGF	25

Clinical dose	~**20 mg**

Physiologically based model prediction and SAD

- PBPK was developed based on pre-clinical data and used to predict the human pharmacokinetics prior to the first in human studies in 2005
- Predicted : CL: 1 mL/min/kg; Vss = 3 L/kg; F% (< 80 mg) = 90%
- The predicted pharmacokinetics were found to be in good agreement with the clinical data from the single ascending dose study at 3, 6, 12, 24, 50, 80, 120, 180 and 240 mg.

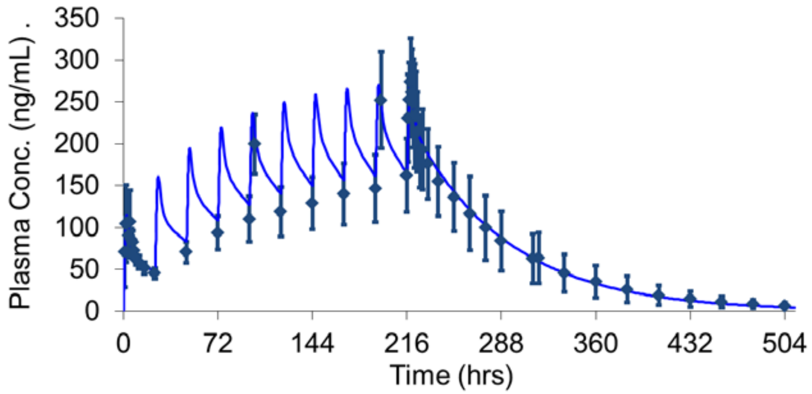




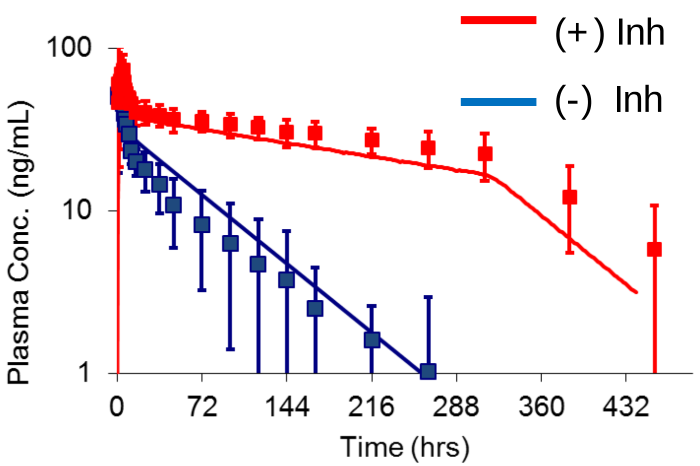
Further model verification - MAD and DDI

- High simulated fraction absorbed is in line with mass balance study.
  - 86% recovery of 80 mg dose only 5 to 15% parent in feces

- Multiple dose PK well predicted confirming time independent PK



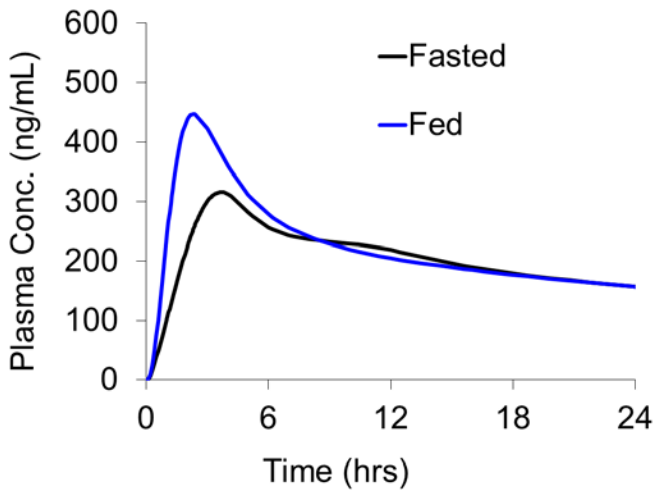
- DDI studies with strong CYP3A inhibitor well simulated confirming very minor role of hepatic and intestinal first pass metabolism



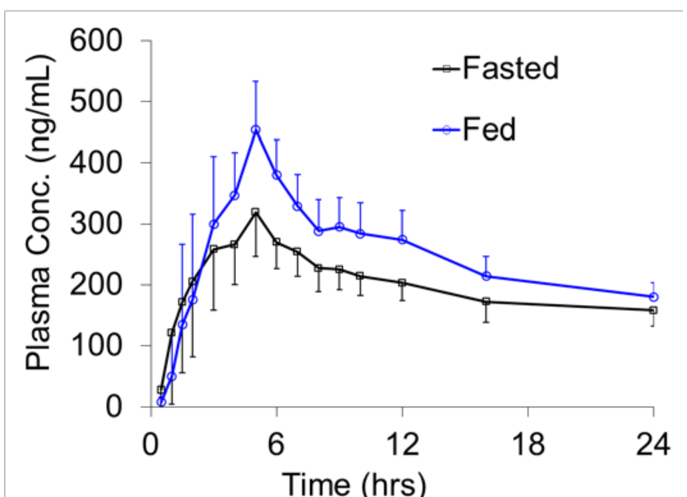
Further model verification - food effect

- Simulation of the effect of a high fat/high calorie breakfast on PK after a single 80 mg dose

simulation



observation



	fasted	fed
Gastric emptying	0.25 hr	1 hr
Solubility (µg/mL)	25	100

fed/ fasted	Cmax ratio	AUC ratio
Simulated	1.4	1.0
Observed	1.4	1.1

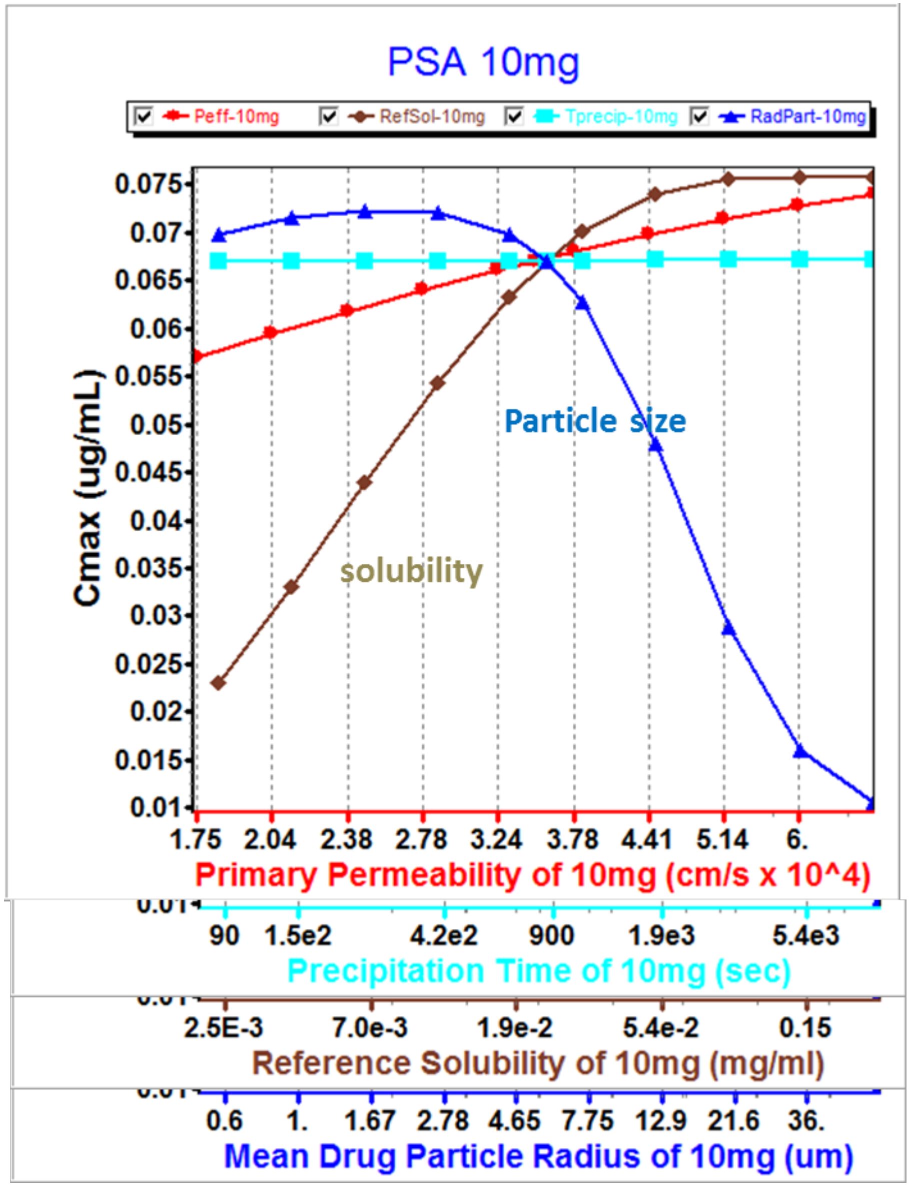
Parameter sensitivity analysis

GastroPlus Baseline parameters

Permeability scaled from Caco2 **3.5 *10-4 cm/s**

Solubility in fasted state simulating fluid **25 ug/mL**

Particle size **6 um radius**

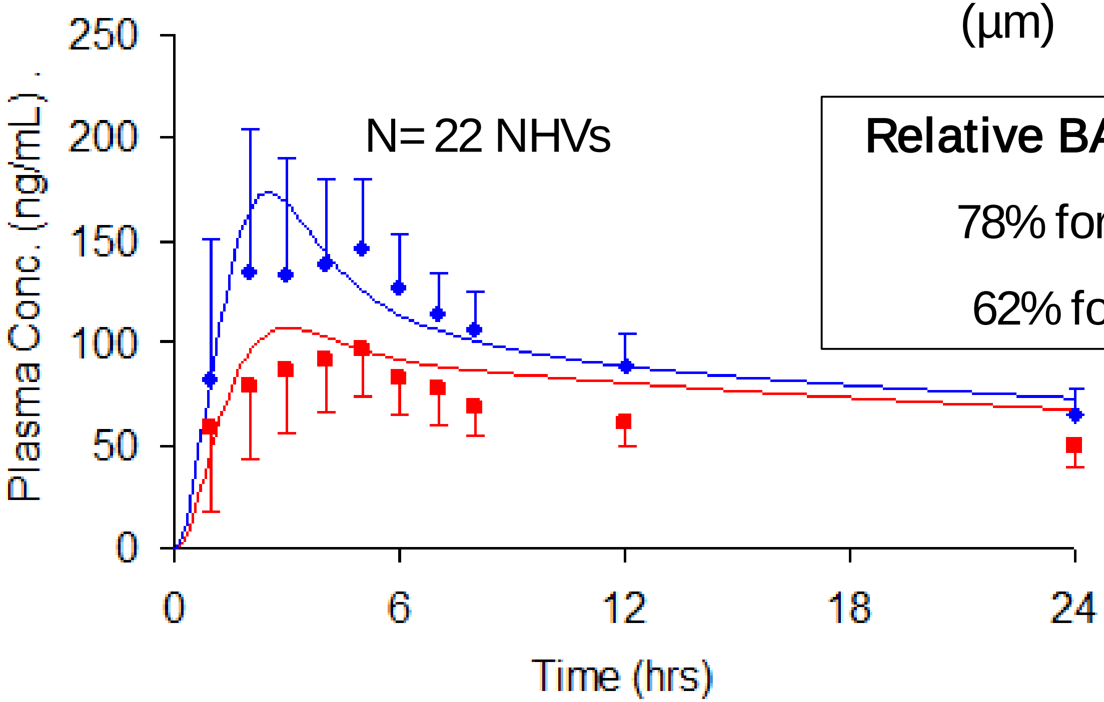


Further model verification – particle size

Relative BA study performed to bridge from capsules to tablets

Also compared 30 mg tablets containing powder prepared with either jet milling or hammer milling

	JET milled	HAMMER milled
Particle radius (µm)	1.8	12.5

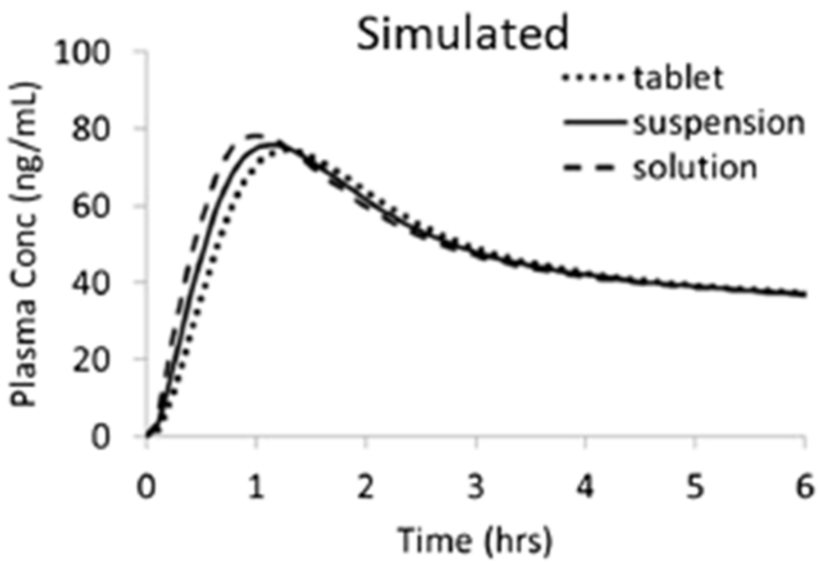


Relative BA of HAMMER to JET (90% CI)

78% for AUCinf/dose (72% – 80%)

62% for Cmax/dose (57% – 67%)

PBPK model prediction of an oral suspension vs tablet



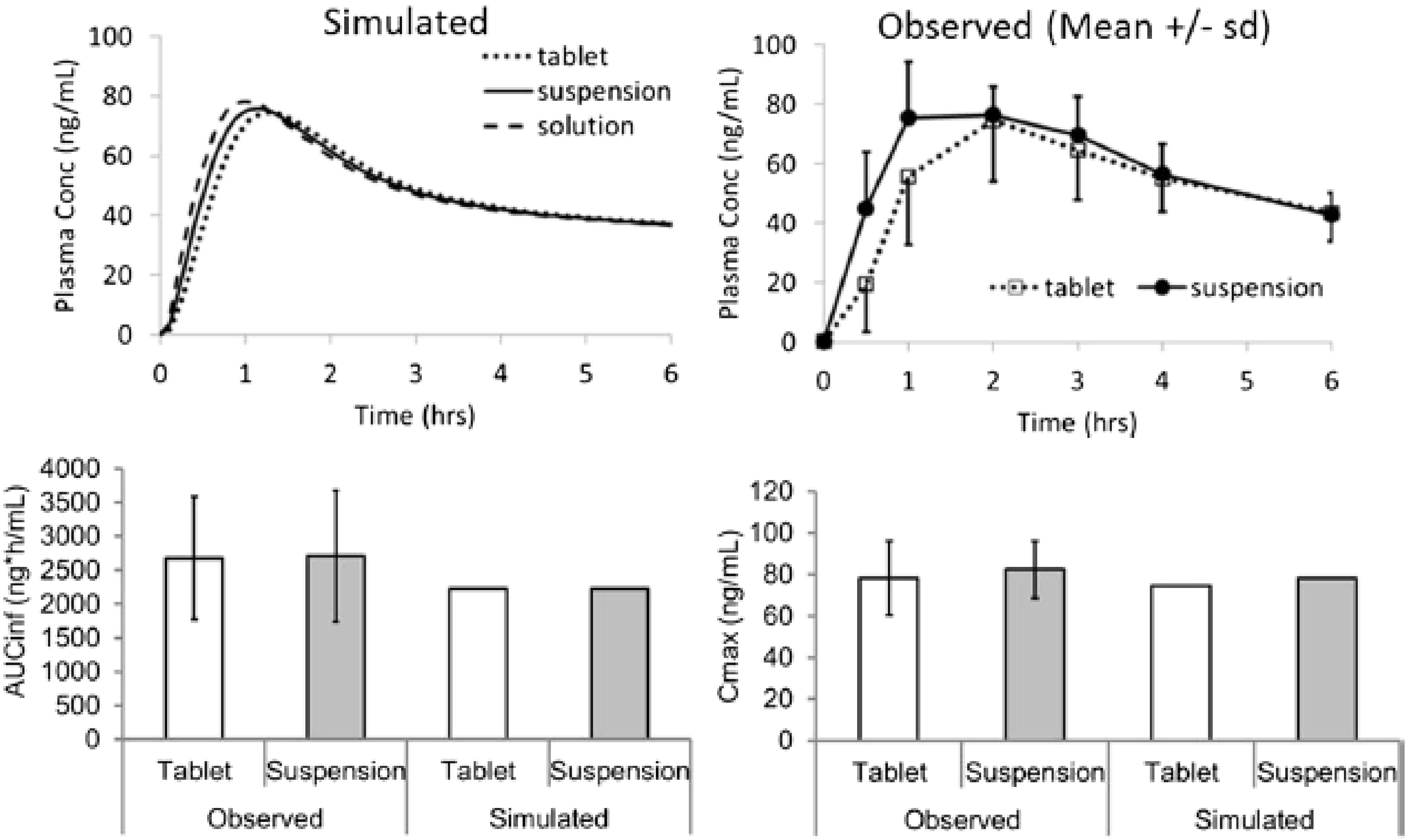
	C_{max}	AUC
	(ng/mL)	(ng.hr/mL)
Tablet	74	2200
Suspension	78	2200

At this time the FDA did not consider modelling was sufficient to waive the relative BA study

Predicted and observed suspension vs tablet

Bioequivalent

90% CIs Cmax and AUC0-inf within 80% to 125%.



Discussion

- We considered that the simulation of the relative bioavailability of a solution vs tablet should be reliable because the PBPK model captured the pharmacokinetics well.

- In particular absorption related factors were well captured as shown by particle size and food effect studies.

- 1^{st} pass metabolism was well described and simulations of ascending doses indicated that the prediction of solubility limited absorption at higher dose was valid.

- Therefore in this dose range exposures are unlikely to be increased substantially through a different oral formulations.

Use of oral absorption modelling to characterize drug release and absorption of a BCS II compound from IR formulations

Cordula Stillhart

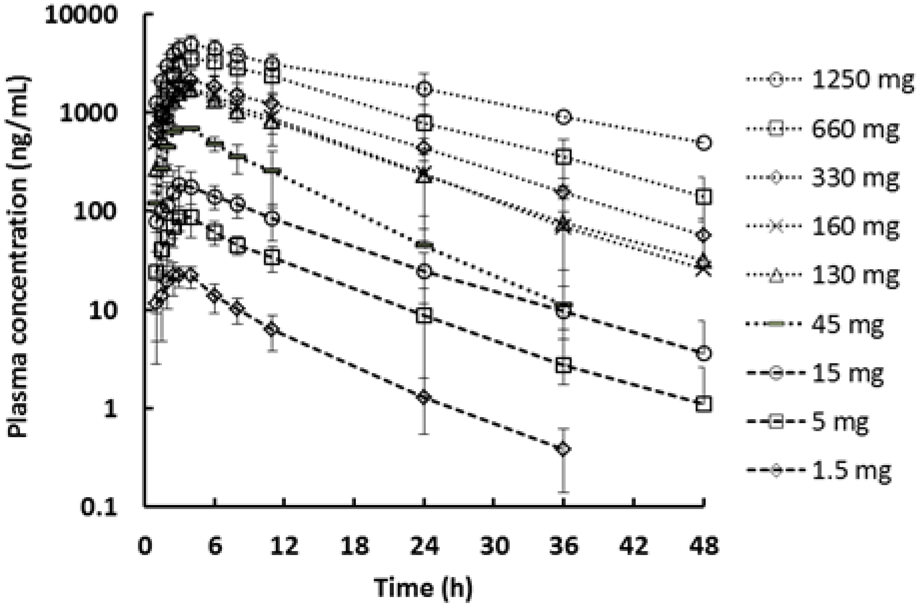
Stillhart C, Parrott NJ, Lindenberg M, Chalus P, Bentley D, Szepes A. Characterising Drug Release from Immediate-Release Formulations of a Poorly Soluble Compound, Basmisanil, Through Absorption Modelling and Dissolution Testing. The AAPS journal. 2017;19(3):827-36.

Compound properties and clinical formulations

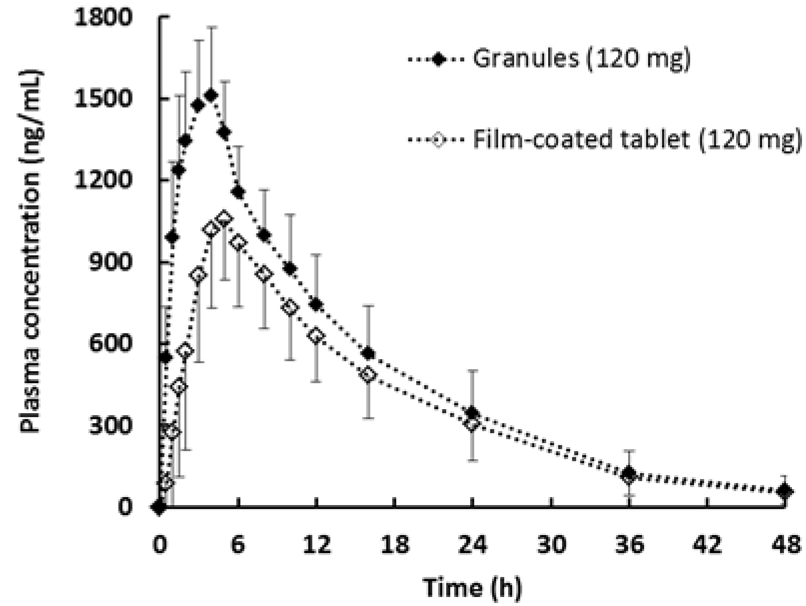
Parameter	Value
Molecular weight	445 g/mol
pKa	2.07 (b)
logD	1.86 (pH 7.4)
Solubility	Aqueous buffer pH 1-9: < 1 µg/mL FaSSIF: 10 µg/mL FeSSIF: 32 µg/mL
Permeability	High (P_{eff} 3.7×10^{-4} cm/s)
Physical state	Crystalline
Clinical formulations	Phase 1: IR **tablet** (dose strength 0.5 / 5 / 40 / 250 mg) Phase 2: IR **film-coated tablet** and IR **granules** in sachet (dose strength 120 mg)

Clinical pharmacokinetics
Overview

Tablet
(SAD)



Film-coated tablet / Granules
(120 mg)



- **Tablet** (Phase 1): dose proportional exposure for oral doses between 1.5 and 130 mg, less than dose proportional exposure for higher doses (C_{max} and AUC)
- **Granules** in sachet: similar exposure as tablet formulation
- **Film-coated tablet**: lower exposure compared to granules/Phase 1 tablet (AUC_{inf} -30%, C_{max} -35%)

Objectives

- To characterize the **mechanism of drug release and absorption** from immediate release formulations
- To understand the **root cause for different drug exposure** following administration of film-coated tablets and granules
- To develop an **in vitro-in vivo correlation** (IVIVC) model for future formulation development

Development of oral absorption model
Input parameters

Compound:

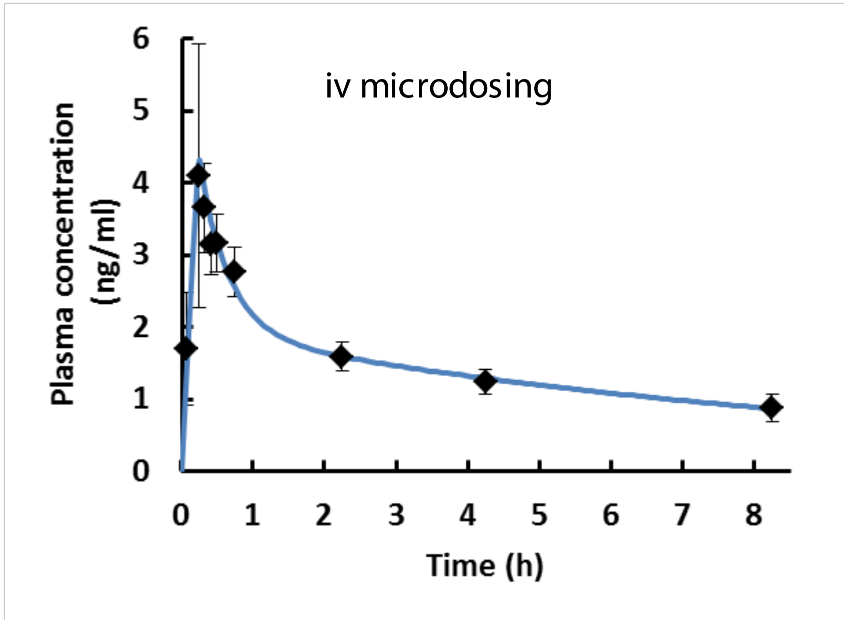
- Experimental physicochemical properties
- Formulation: IR tablet / IR suspension
- Dissolution model: Johnson

Gut Physiology:

- Human – Physiological – Fed (default)
- ASF model: Opt logD Model SA/V 6.1 (default)

Pharmacokinetics:

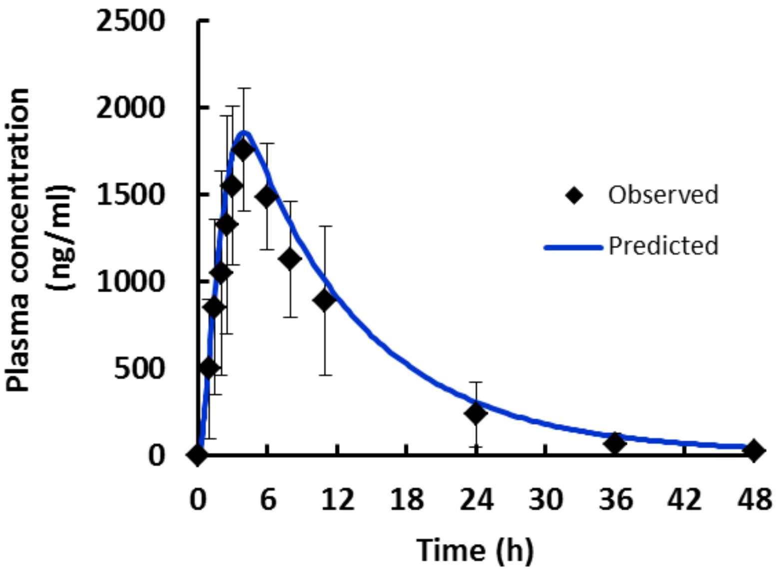
- Two-compartment PK
- Disposition PK: model fitting using iv microdosing data (PKPlus®)



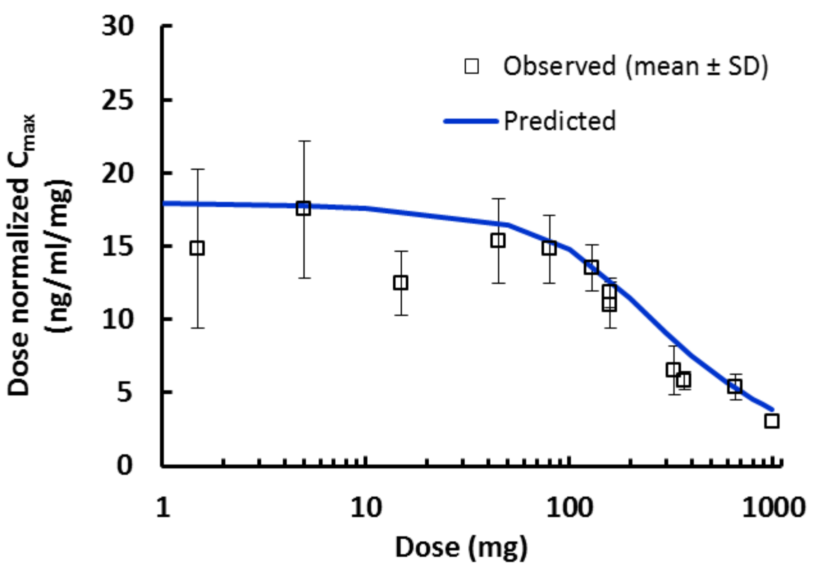
Model prediction for tablet formulation

Dose strengths: 0.5, 5, 40, and 250 mg

Single 160 mg dose



Dose-normalized C_{max}

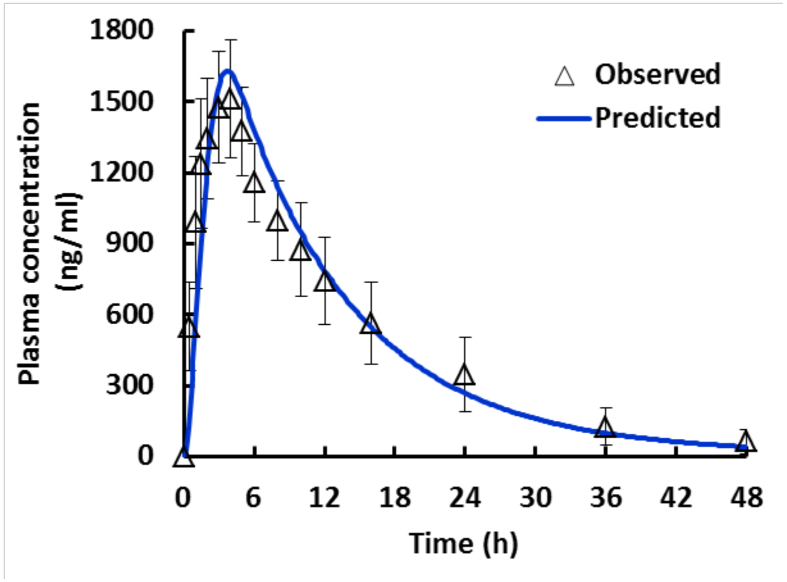


- Accurate prediction of oral exposure following administration of tablet formulations in the dose range from 1.5 to 1250 mg
- GastroPlus model captured dose-dependency in C_{max} and AUC

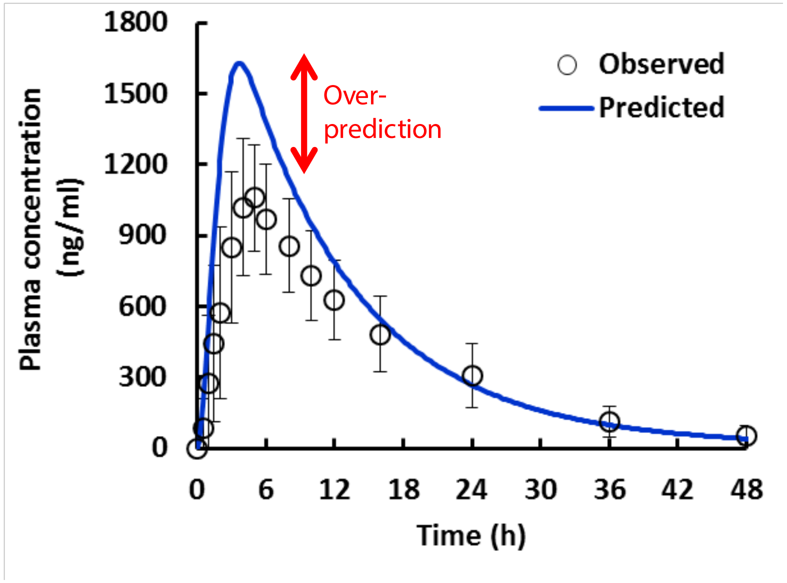
Model prediction for <u>granules</u> and <u>FCT</u>

Dose strength: 120 mg

120 mg Granules in sachet

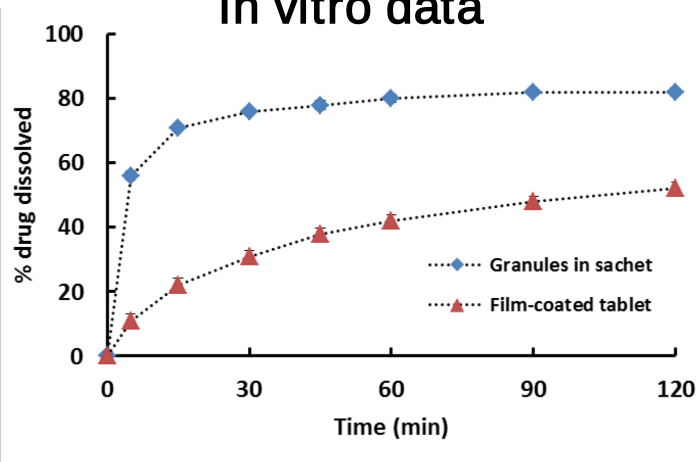


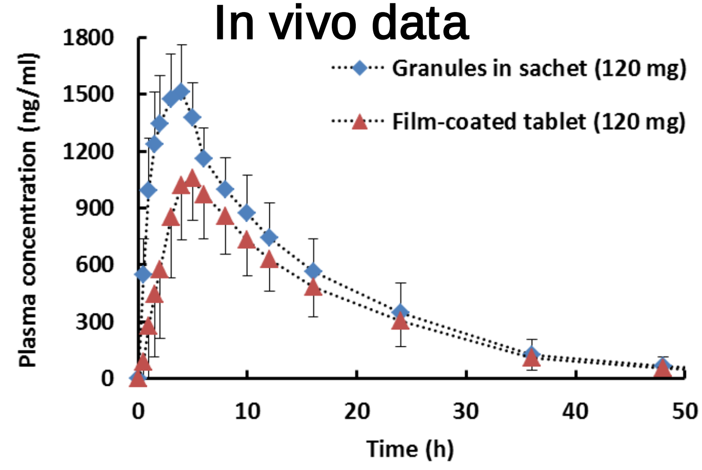
120 mg Film-coated tablet



- Accurate prediction of oral exposure for granules in sachet formulation
- However, exposure from film-coated tablet (same dose) was significantly overpredicted

IVIVC model development





In vitro dissolution method:

- USP 2 paddle apparatus (50 rpm)
- Medium: 900 mL FeSSIF pH 5.0, 37°C
- Formulation: equivalent to 40 mg API

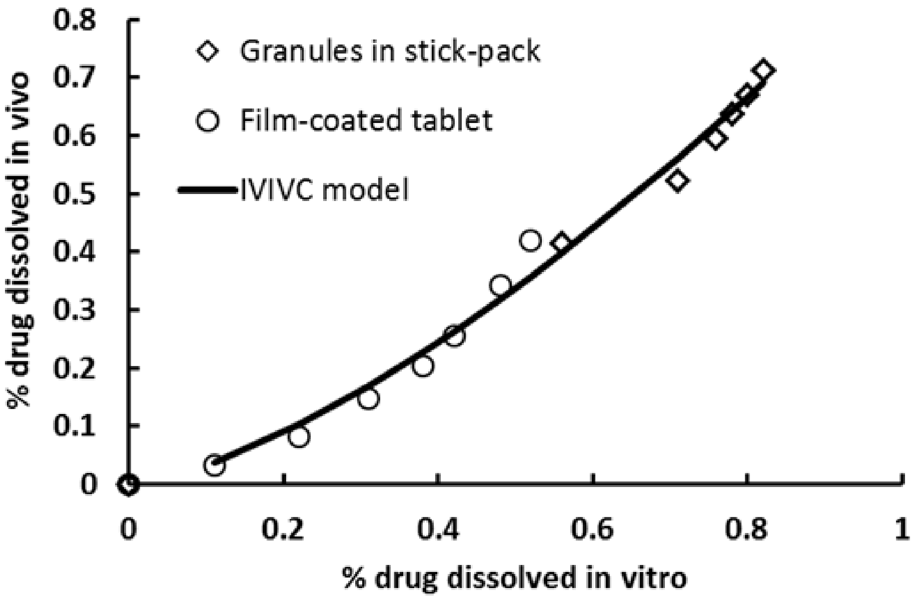
Deconvolution method:

- GastroPlus Mechanistic Absorption method
- For comparison: traditional deconvolution methods (numerical and Loo-Riegelmann)

Model development: in vitro and in vivo data using granules and film-coated tablet formulation (120 mg dose), fed state

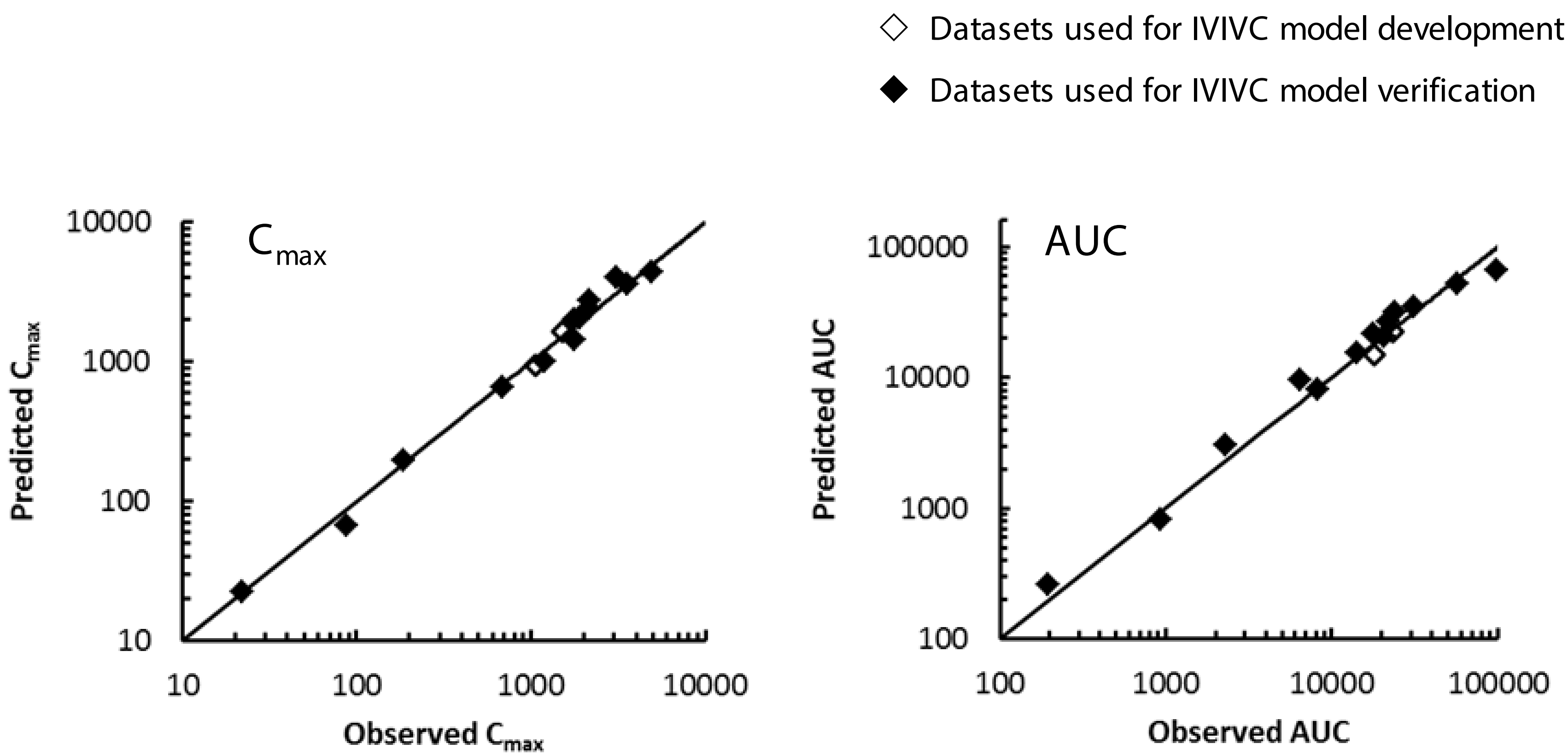
Model verification: in vitro and in vivo data using tablet formulation (dose strength 0.5, 5, 40, and 250 mg), dose range: 1.5-1250 mg, fed state

IVIVC model
Correlation



- The GastroPlus Mechanistic Absorption deconvolution method resulted in a very good correlation between in vitro and in vivo dissolution profiles
- Data sets used for model development: in vitro and in vivo data obtained from 120 mg granules in sachet and 120 mg film-coated tablet formulations

IVIVC model verification



- Good prediction of oral exposure from tablet formulation over the entire dose range from 1.5 to 1250 mg

Discussion

- The IVIVC model was predictive for oral drug exposure from IR formulations exhibiting different release rates (FCT, granules in sachet) over a large dose range, which made it suitable for guiding future formulation development

- Mechanistic absorption method was superior to traditional deconvolution methods (e.g., Loo-Riegelmann, numerical) mainly due to consideration of:
  - dissolution- and solubility-limited absorption (dose-dependent)
  - administration in fed state (e.g., prolonged gastric emptying)

- In vitro dissolution method did not provide real sink conditions, however, it captured the difference in release rate between formulations and resulted in an accurate IVIVC

Prediction of relative bioavailability between IR and OROS formulation of oxybutynin

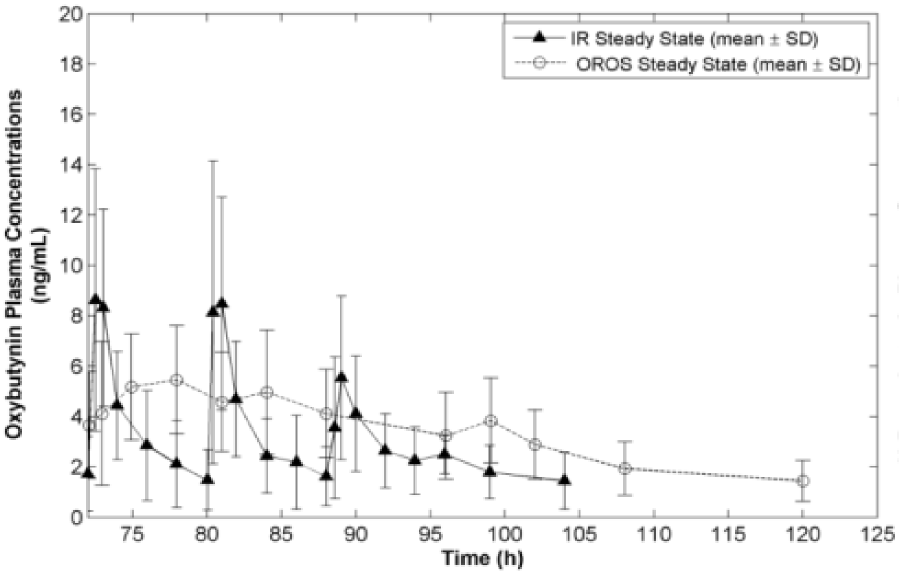
Andrés Olivares

Olivares-Morales A, Ghosh A, Aarons L, Rostami-Hodjegan A. Development of a Novel Simplified PBPK Absorption Model to Explain the Higher Relative Bioavailability of the OROS(R) Formulation of Oxybutynin. The AAPS journal. 2016;18(6):1532-49. doi: 10.1208/s12248-016-9965-3.

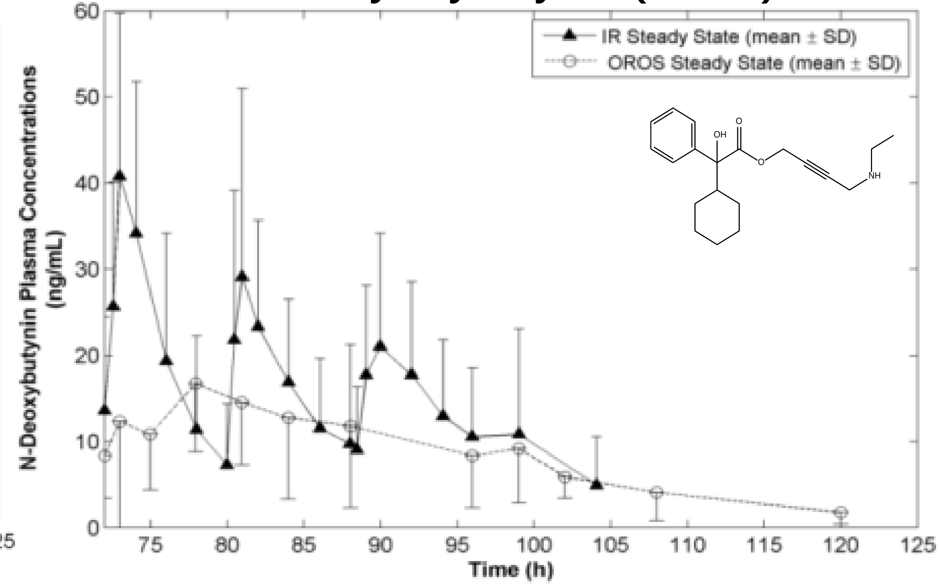
Oxybutynin's (OXY) OROS formulation

Higher bioavailability than its IR counterpart

Oxybutynin (OXY)



Desethyloxybutynin (DEOB)

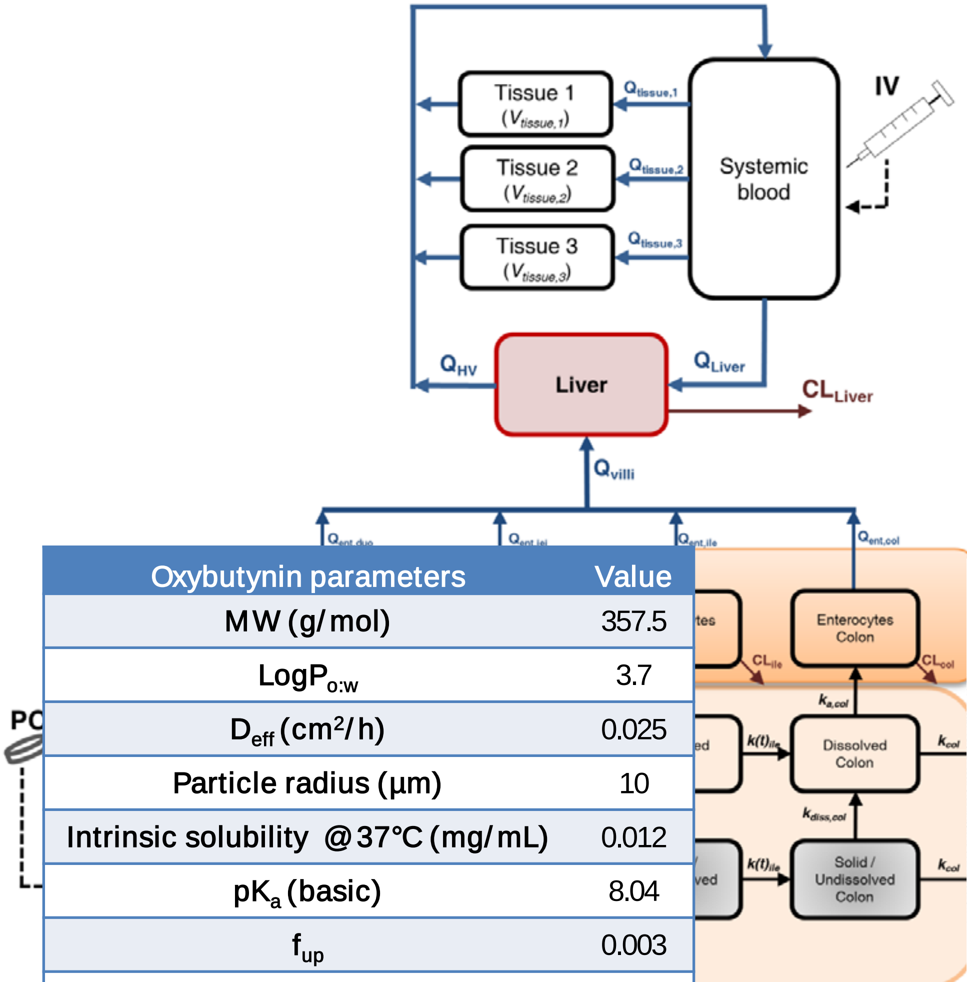


- BCS class 1, highly cleared, CYP3A substrate, low oral bioavailability
- OROS formulation vs. IR:
  - ✓ Parent exposure ~30-70% higher than IR
  - ✓ Exposure of the main metabolite decreased by ~30%
  - ✓ Improved safety profile (anti-muscarinic side effects), yet similar efficacy as the IR formulations

Gupta and Sathyan, 1999; Gupta et al. 1999; Sathyan et al. 2001

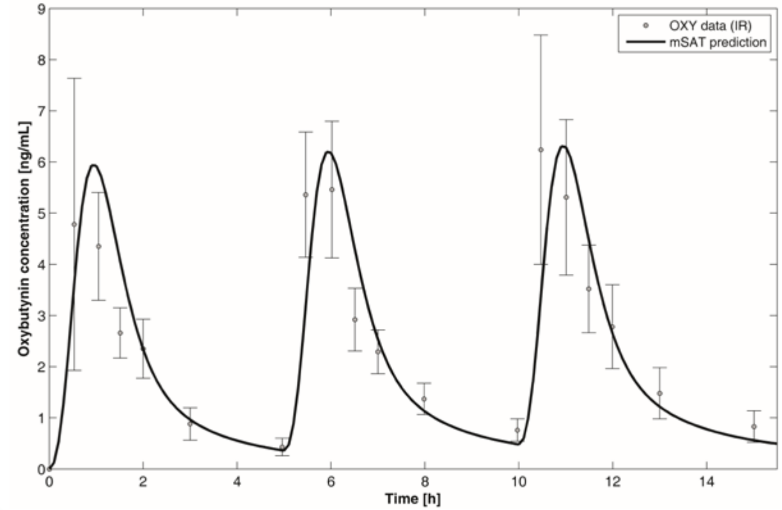
Mechanistic prediction of OXY's PK

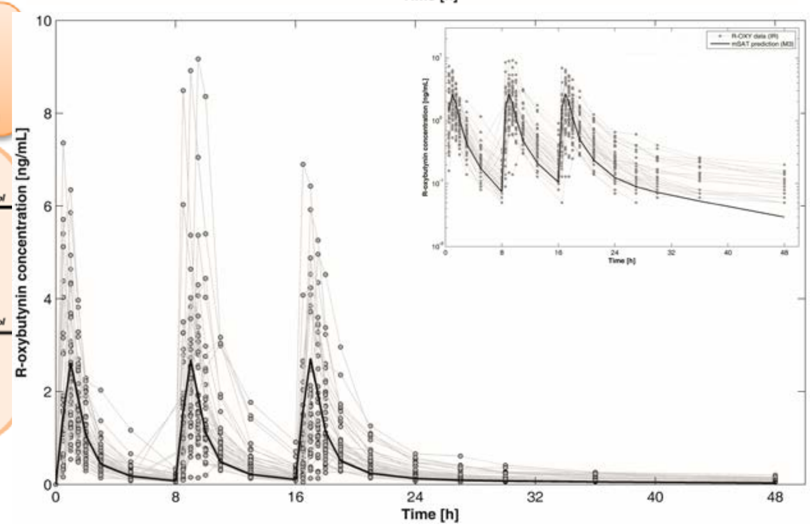
Bottom up PBPK predictions of IR formulation



Oxybutynin parameters	Value
MW (g/mol)	357.5
$LogP_{o:w}$	3.7
D_{eff} (cm^2/h)	0.025
Particle radius (µm)	10
Intrinsic solubility @37°C (mg/mL)	0.012
pK_a (basic)	8.04
f_{up}	0.003
Blood/ plasma ratio (BP)	0.69
P_{eff} (10^{-4} cm/s)	4.3

IR

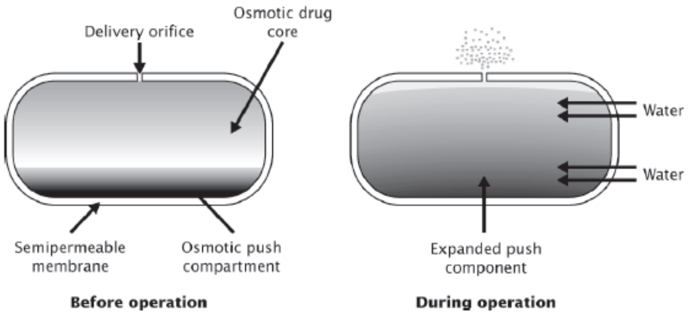


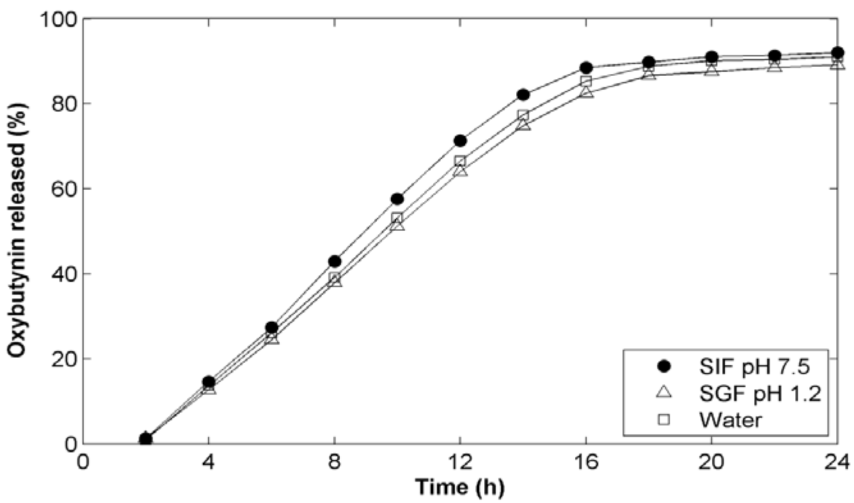


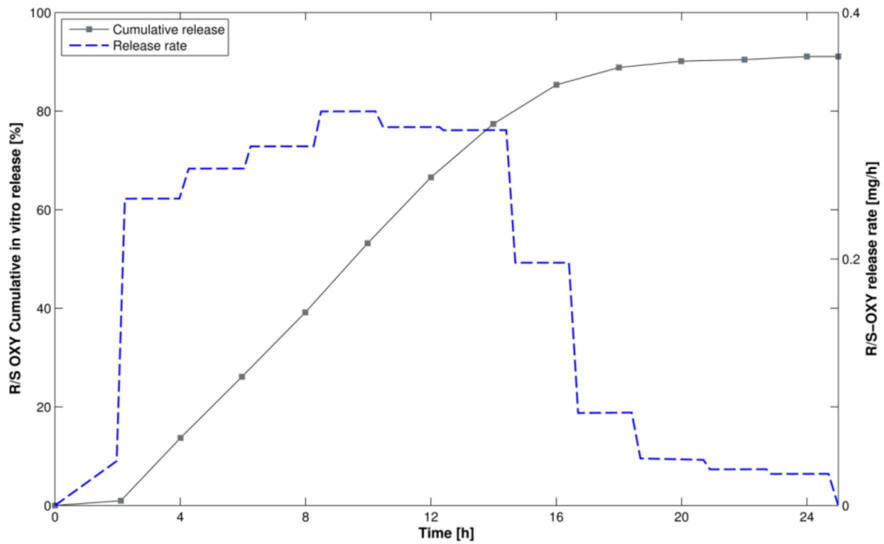
Observed data: Douchamps et al., 1988; Janssen clinical trail

Predicting OXY's OROS formulation
Integration of the in vitro release into the PBPK model

Osmotic [controlled] Release Oral [delivery] System

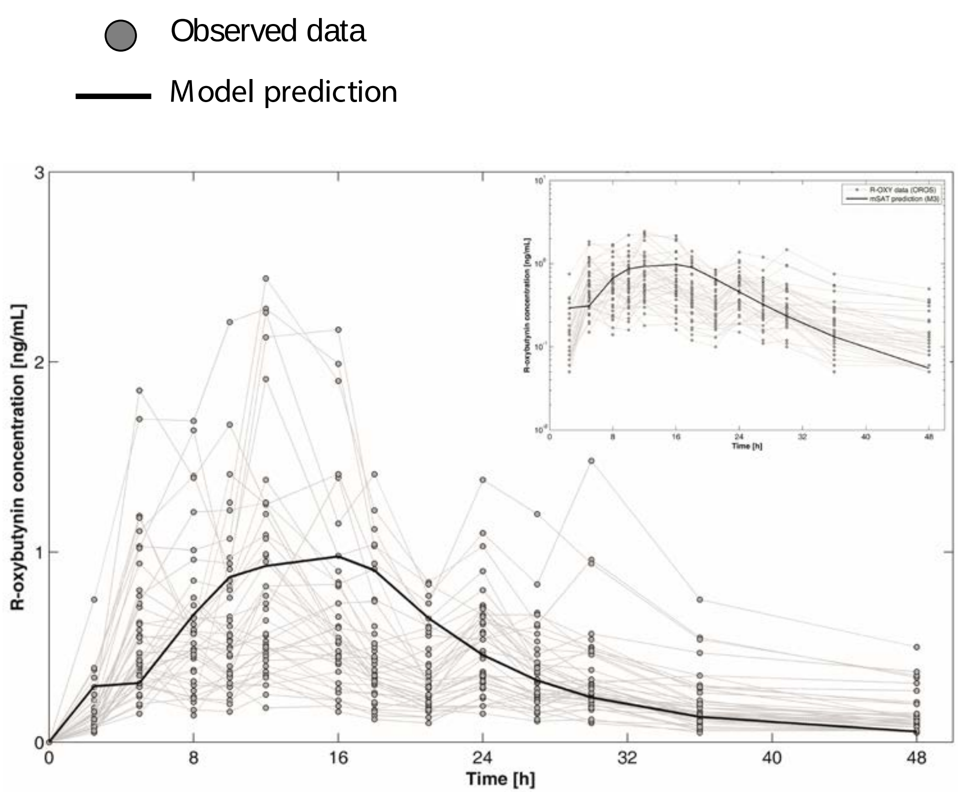


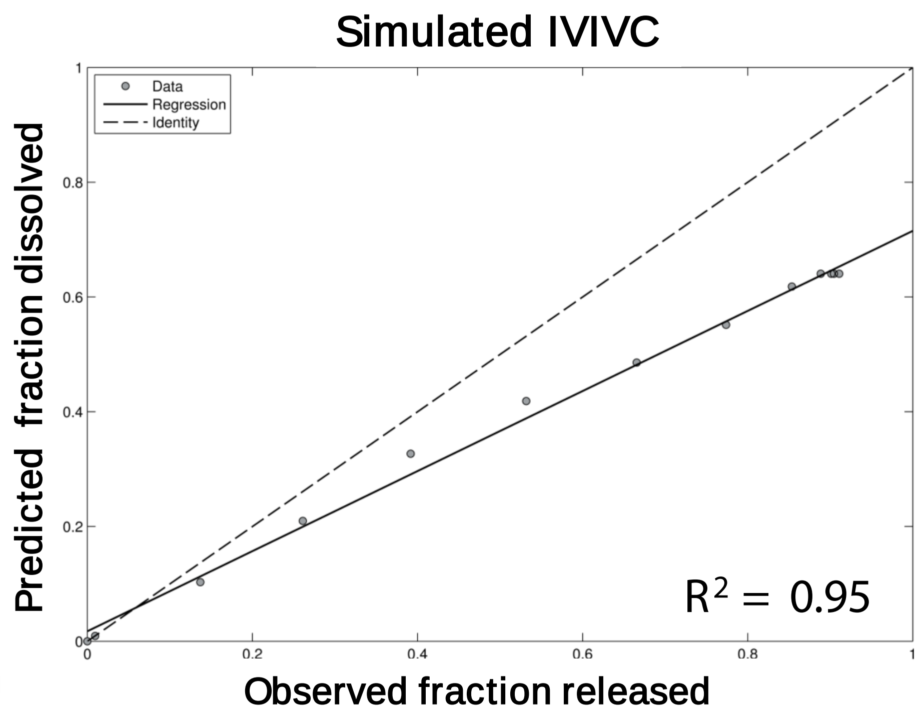




Conley et al, 2006; Sathyan et al., 2004; Pitsiu et al. 2001

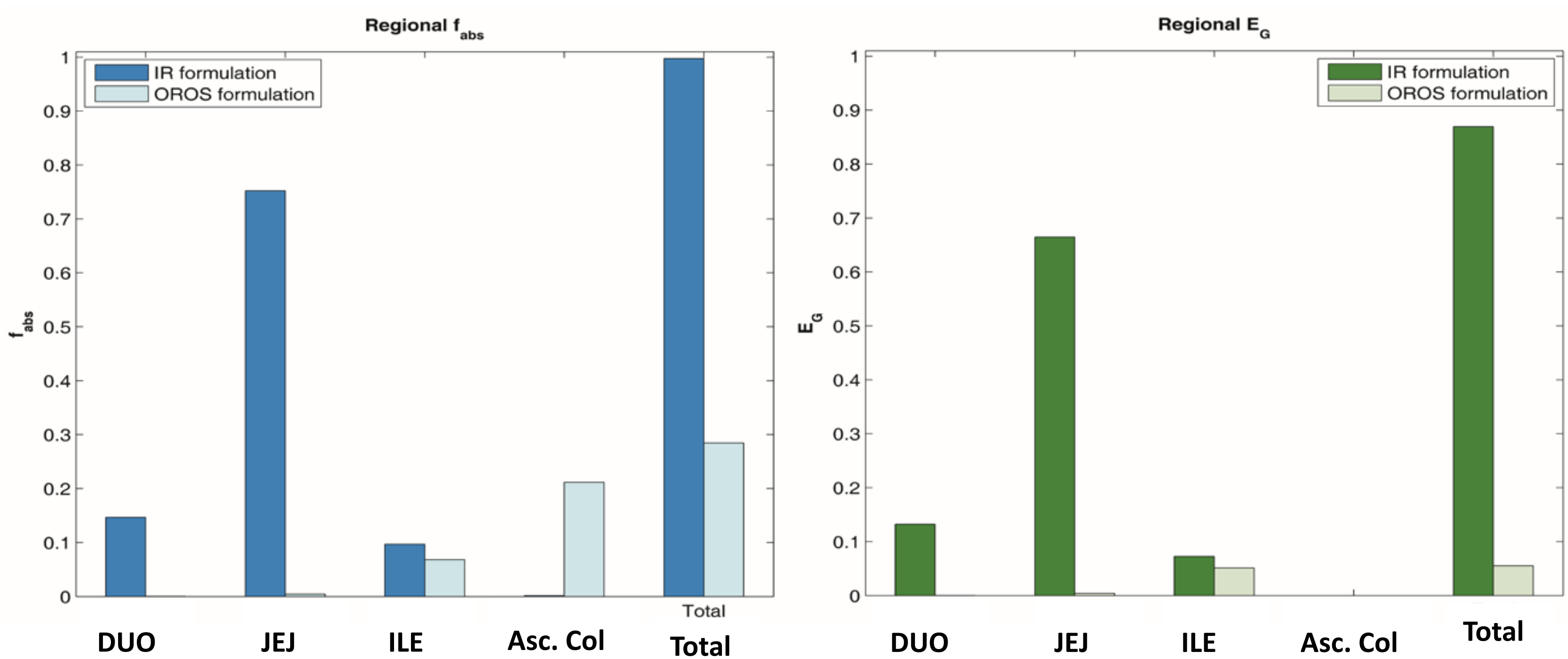
Predicting OXY's OROS formulation
Excellent IVIVC predicted for OROS formulation





Observed data kindly supplied by Janssen

Prediction of OXY's relative bioavailability
Intestinal interplay between absorption and metabolism



Formulation	$AUC_{0\text{-}t}$ (ng/mL/h) (obs.)	$AUC_{0\text{-}t}$ (ng/mL/h) (pred.)	F_{rel} (%) (obs.)	F_{rel} (%) (pred.)
IR (3x 5 mg)	21.7 ± 13.0	17.3	139 ± 44	**172**
OROS (10 mg)	18.6 ± 10.5	19.9	-	-

Discussion

- A PBPK approach predicted differences in oral bioavailability between OXY's IR and OROS were in good agreement with the observed data.
- In vitro release from the OROS tablet correlates very well with its in vivo dissolution.
- Major driver of higher bioavailability observed for oxybutynin OROS is the intestinal first-pass metabolism rather than the absorption differences between the two formulations. This particularly affects CYP3A4 substrates due to the uneven distribution of the CYP3A4 enzymes along the GI tract.

Overall discussion

- We showed three examples of the used mechanistic absorption/dissolution modelling provided further insights with respect to the key factors contributing to oral drug absorption and bioavailability.
- The use of the right *in vitro* experimental and modelling approaches such as mechanistic-deconvolution can guide clinical design and address team's questions related to formulation
- Validation of modelling approaches with external datasets are essential to generate confidence in the utility mechanistic modelling approach for addressing clinical questions.
- In our development projects this approach helped to define product specifications (i.e., particle size limits) under a QbD paradigm.

Acknowledgements

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Amin Rostami-Hodjegan

Janssen

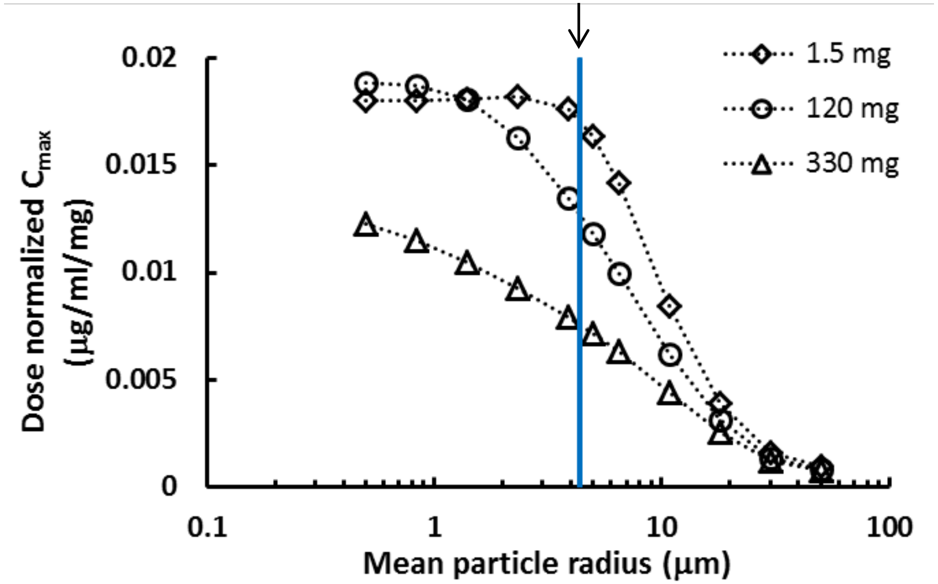
Avijit Ghosh

Doing now what patients need next

Parameter sensitivity analysis

Drug particle size

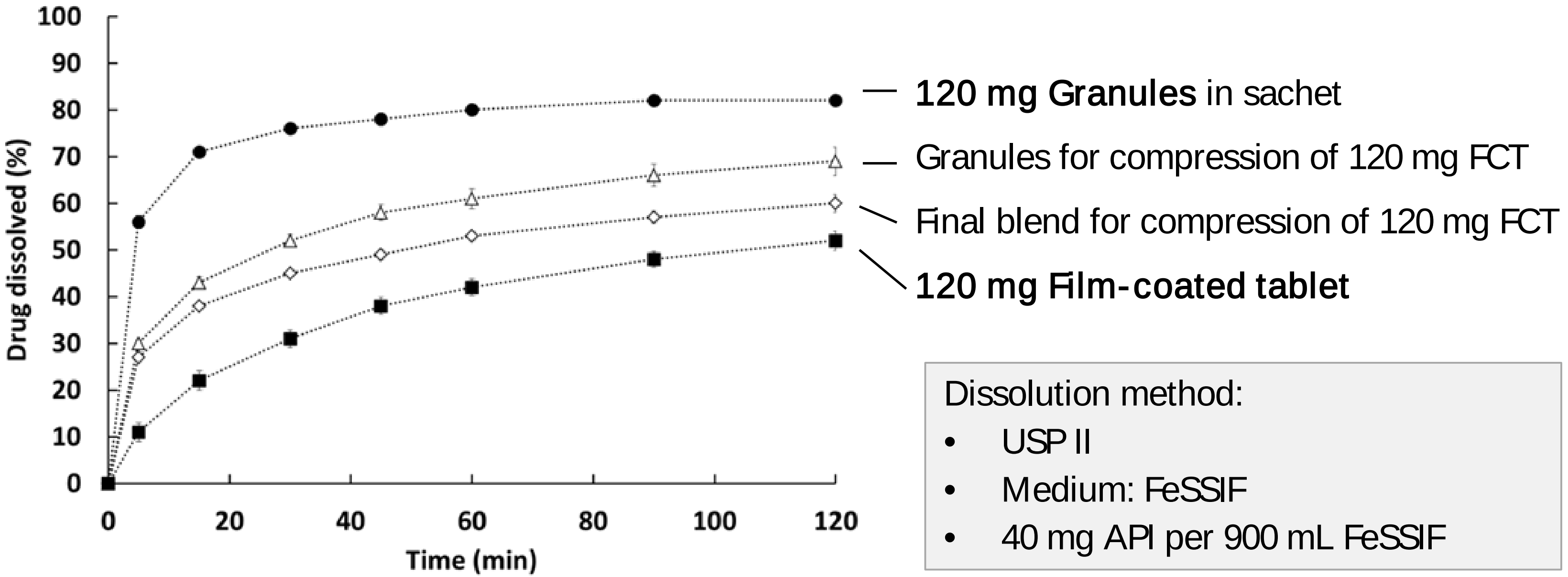
Mean drug particle radius of
API used in clinical formulations



- Drug particle radius has significant impact on C_{max}
- Mean drug particle radius of API used in clinical formulations is in a sensitive range with regard to its impact on C_{max}, especially for the 120 mg dose

In vitro dissolution profiles

Granules vs. film-coated tablets



Dissolution method:

- USP II
- Medium: FeSSIF
- 40 mg API per 900 mL FeSSIF

- Dissolution rate from granules in sachet >>> film-coated tablet
- Dissolution rate from granules in sachet >>> granules for compression of film-coated tablets
- Manufacturing process and formulation composition affect dissolution rate

Understanding differences in drug release

Comparison of clinical formulations

- Almost same manufacturing process and qualitative composition
- Comparatively high drug load in 120 mg FCT and 250 mg tablet formulation:

Formulation	Drug load (%)
0.5 mg tablet	0.07
5 mg tablet	0.70
40 mg tablet	5.30
250 mg tablet	**33.33**
120 mg granules in sachet	12.82
120 mg film-coated tablet	**25.81**

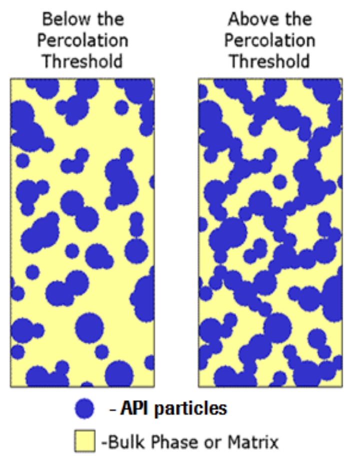
→ Potential exceedance of percolation threshold in the tablet matrix

Understanding differences in drug release

Percolation threshold

Isolated/individual clusters

within a continuous phase



Infinite/percolating cluster

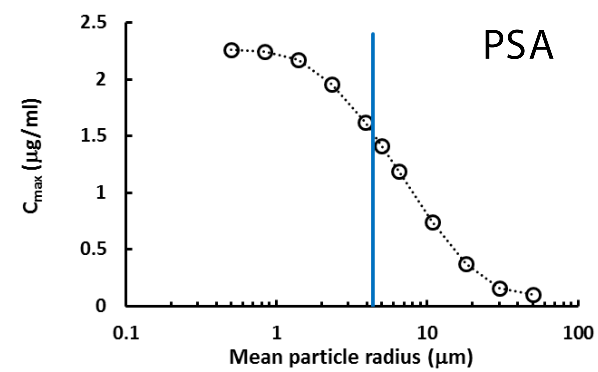
extends from one to the other side

Percolation threshold:

Critical drug concentration necessary to form a coherent network, which dominates the properties of the whole system

Figure source: http://www.tda.com/eMatls/composites.htm

- If the percolation threshold is exceeded, the API may not be released as single micronized particle, but as larger aggregate of multiple particles
- API surface area ↓ and dissolution rate ↓



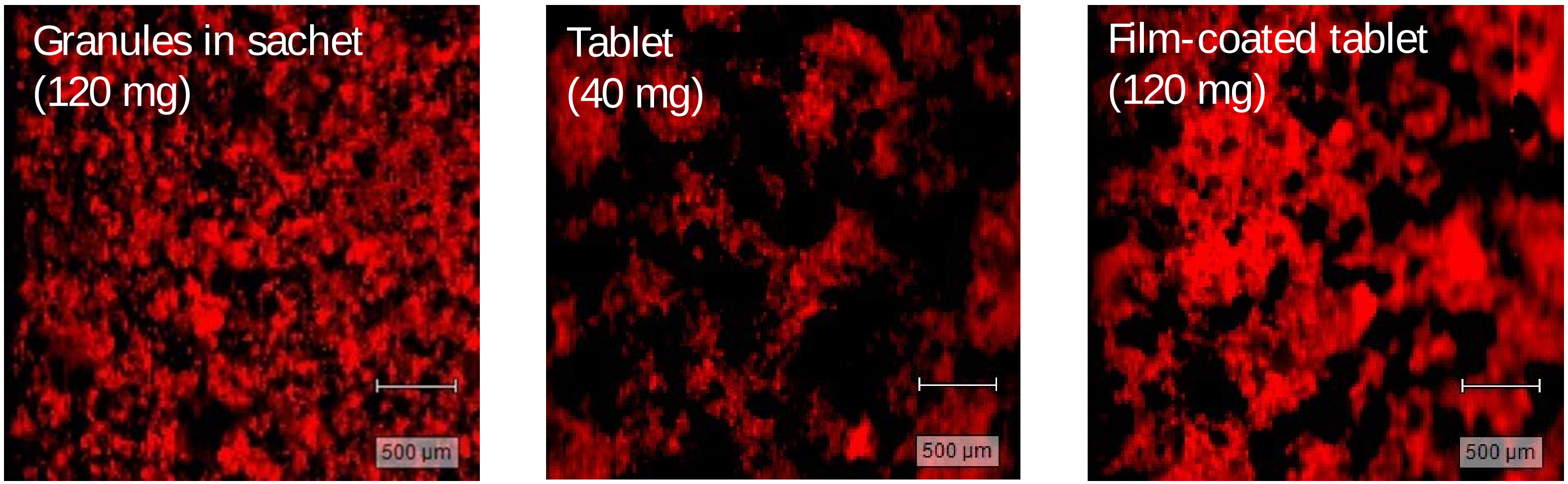
Raman imaging

Granules, tablet, film-coated tablet

<u>Raman Imaging:</u>

Red: drug substance

Black: formulation matrix



- All formulations exhibit regions with high drug particle density → cohesive properties of API
- Tablet compression increases cohesion of API particles
- 120 mg granules and 40 mg tablet formulation show API-rich regions which still include excipient particles
- 120 mg film-coated tablet shows large agglomerated clusters forming a coherent network in the tablet matrix

Doing now what patients need next