When Mechanistic IVIVC Falls Short: The Case for IVIVR in Oral Drug Delivery

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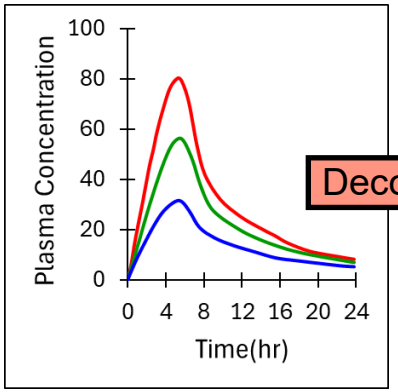
NEXT-GENERATION DELIVERY INNOVATIONS

Introduction

- Traditional IVIVC
- Utilizing IVIVR and PBBM
  - Benefits
  - Dissolution modeling
- Case Studies
  - IVIVR and z-factor dissolution
  - Product specific particle size distribution (PPSD) safe space

Mechanistic IVIVC

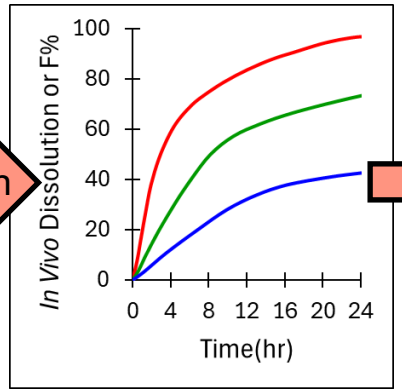
PK Data



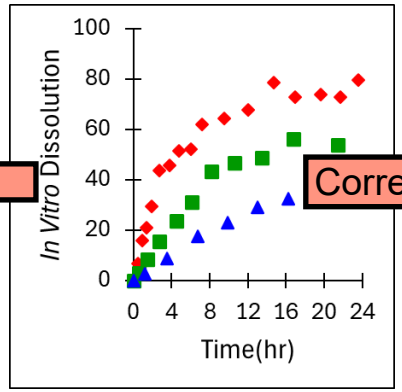
IV Data

Deconvolution

In Vivo Dissolution or F%

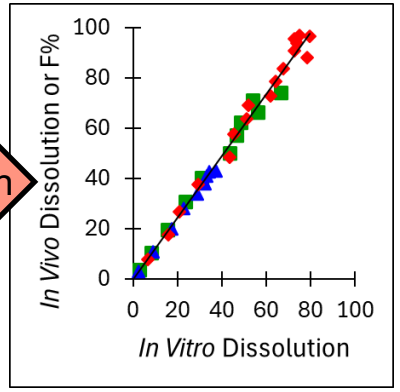


In Vitro Dissolution



Correlation

IVIVC



Things to consider:

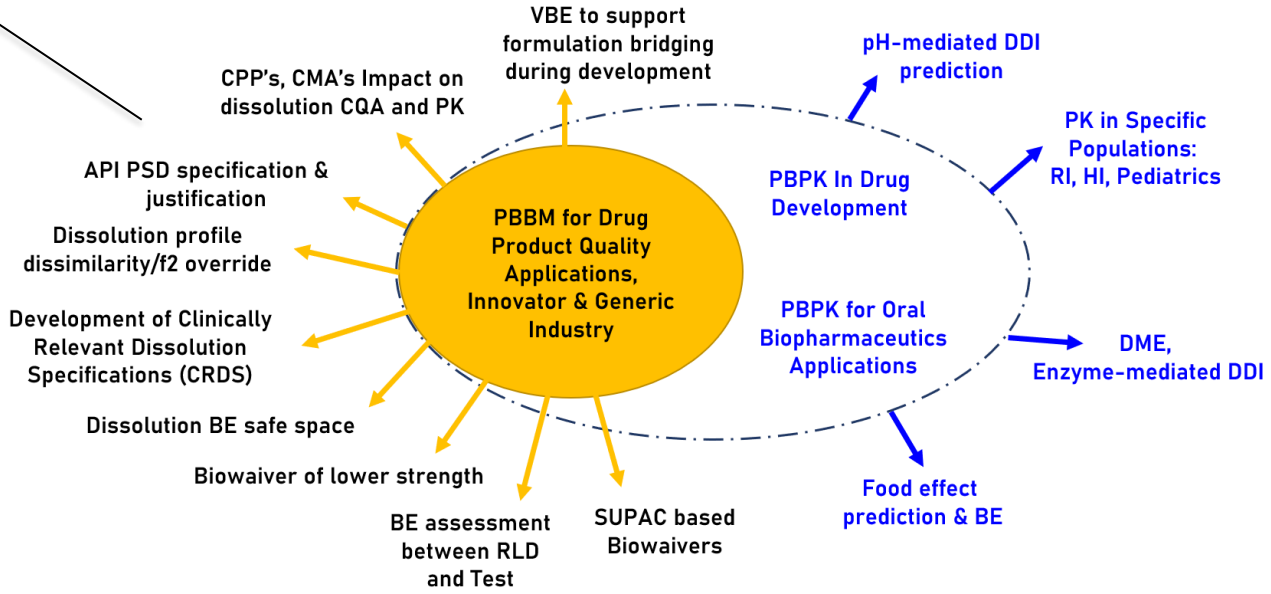
- Internal (fitted data) and external (new data) validation
  - Internal criteria: mean absolute PE ≤ 10%, individual absolute PE≤ 15%
  - External criteria: PE ≤ 10% (10<PE<20% further studies required, PE> 20%, inadequate)
- A good approach for ER formulations but… IR formulations can present challenges with these methods, especially BCS Class II

BCS Classification and IVIVC

Class	Solubility	Permeability	Absorption rate control	IVIVC
I	High	High	Gastric emptying	Possible, if ***dissolution is rate limiting*** step
II	Low	High	Dissolution	Possible, if *in vitro* & *in vivo* dissolution are similar
III	High	Low	Permeability	Limited, since ***absorption is rate limiting*** step
IV	Low	Low	Case by case	Not expected (unless dissolution is identified as limiting step)

The case for IVIVR: Physiologically-Based Biopharmaceutics Models

A regulatory tool!
Can be used to waive human evaluations



API: Active pharmaceutical ingredient, BE: Bioequivalence, CMA: Critical material attribute, CPP: Critical process parameter, CRDS: Clinically relevant dissolution specifications, DDI: Drug-Drug interactions, DME: Distribution, metabolism and excretion, HI: Hepatic impairment, PBPK: Physiologically-Based Pharmacokinetics, PSD: particle size distribution, RI: Renal impairment, RLD: reference listed drug, SUPAC: Scale-up and post-approval changes, VBE: Virtual bioequivalence

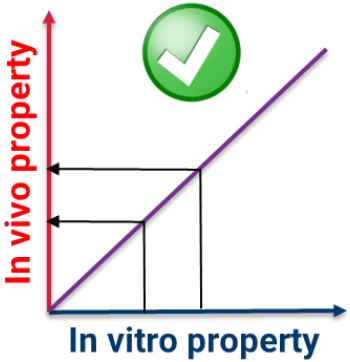
Benefits of PBBM

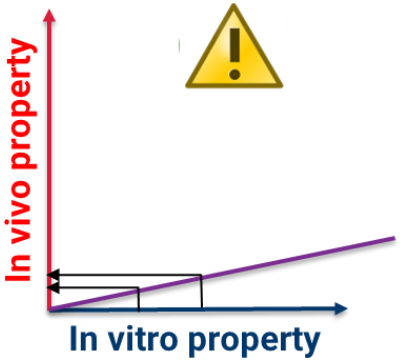
Mechanistic understanding → increase product value	Limitations to drug absorption (solubility, permeability, dissolution rate…) → guide formulators for 1st time right or LCM, Acceptable content of excipients,
Clinically relevant design spaces	Edge of failure for Critical Material Attributes and Critical Process Parameters
Justify drug product specifications	Enables the establishment of CRDPS
Support PACs	At submission, only a limited # of batches are manufactured. Product and process performance my deviate from initially filed specifications
Regulatory flexibility	Change in specifications: Flexibility granted within the safe space
Biowaivers	Reduction of unnecessary human testing. Best use of clinical resources combined with modelling and simulation

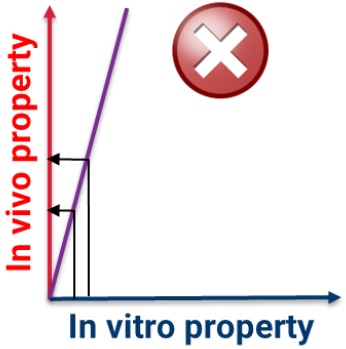
Dissolution modeling for PBBMs

Discrimination level of methods

Discrimination: changes in product in vitro performance are shown when CMA and or CPP are varied
Rank order: Changes in product in vitro performance align with in vivo behaviour







Right level : changes of in vitro properties translate to in vivo performance

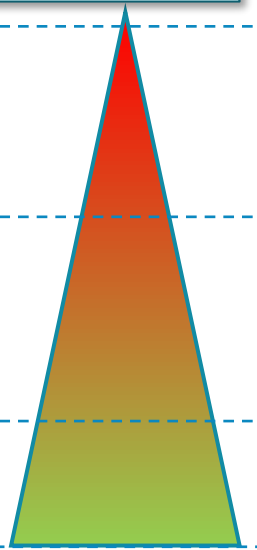
Over discriminative: large changes in vitro translate to smaller changes in vivo

Under discriminative: small changes in vitro translate to larger changes in vivo

Both these methods may be clinically relevant and biopredictive

NEXT-GENERATION DELIVERY INNOVATIONS

Dissolution Integration: How Methods Compare

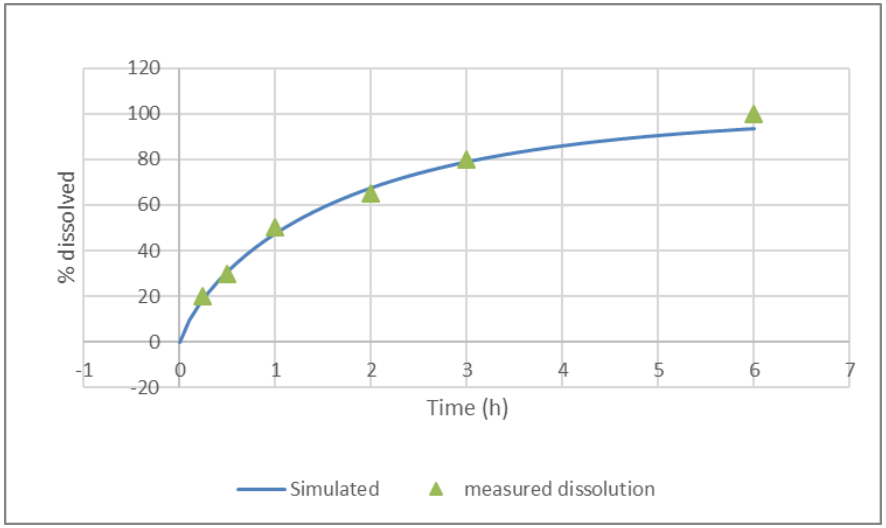


	Assumptions/conditions of use
Less Mechanistic	
Direct input Weibull fit	Solubility/dose/volume is not limiting dissolution, hydrodynamics in vitro is not impacting release Formulation controls release (e.g. MR or eroding formulations)
Z-factor vs pH Fixed z-factor	Z-factor should not depend on pH, Check inputs if it does. Could mask issue with pH-dependent wettability. Cannot use with surfactants since lumped factor
P-PSD	A DP batch specific 1-10 bin PSD which represents the DS particles available for dissolution after product disintegration
More mechanistic	

MR: Modified release, P-PSD: Product Particle size distribution

Weibull Equation

>V9.7 : up to three phase-Weibull



Max % dissolved	100
Lag time (h)	0
A parameter	1.54986
b parameter	0.799337
t1/2diss (min)	66
t80%diss (min)	188

$$P\%(t) = P_{max} \times \left(1 - \exp\left(-\frac{(t - t_{lag})^b}{A}\right)\right)$$

Simple to fit to dissolution data
With 3 phases all profiles matched
Fill missing points

Is not mechanistic.
Imposes release over time

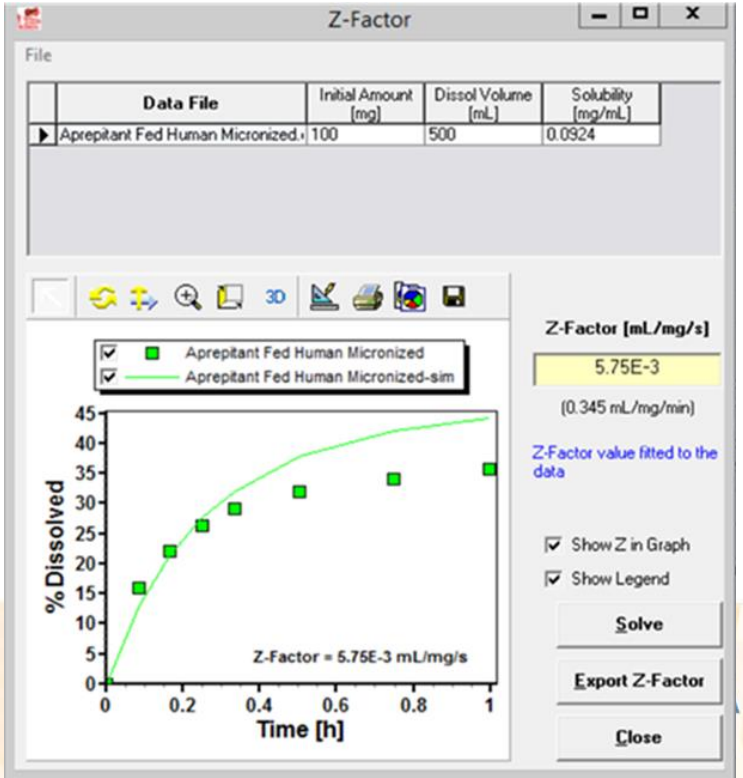
Z-factor Takano

Takano, R., et al. (2006). "Oral absorption of poorly water-soluble drugs: computer simulation of fraction absorbed in humans from a miniscale dissolution test." Pharm Res 23(6): 1144-1156.

$$\frac{dX_{d,vitro}(t)}{dt} = \frac{3D}{\rho h r_0} \times X_{0,s,vitro} \times \left(\frac{X_{s,vitro}(t)}{X_{0,s,vitro}}\right)^{2/3} \times \left(C_s - \frac{X_{d,vitro}(t)}{V_{vitro}}\right)$$

$$z = \frac{3D}{\rho h r_0}$$

$$= z \times X_{0,s,vitro} \times \left(X_{s,vitro} \times \left(\frac{X_{s,vitro}(t)}{X_{0,s,vitro}}\right)^{2/3} \times \left(C_s - \frac{X_{d,vitro}(t)}{V_{vitro}}\right)\right)$$



Z groups particle size, diffusion and thickness of UWL and drug density.

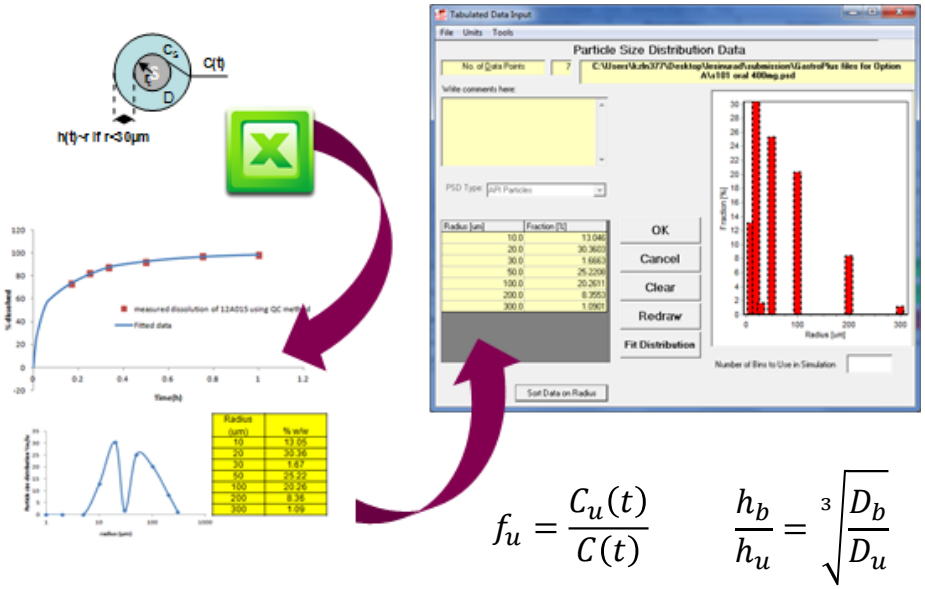
Simple to fit to dissolution data
Mechanistic (dose, pH, volume)

May not match all profiles (multimodal)

Cannot differentiate diffusion of micelles from free drug
Cannot integrate hydrodynamics over time
Particle size constant (OK for early stages)

NEXT-GENERATION DELIVERY INNOVATIONS

P-PSD (classic)



$$f_u = \frac{C_u(t)}{C(t)} \qquad \frac{h_b}{h_u} = \sqrt[3]{\frac{D_b}{D_u}}$$

$$\frac{dm_{solid}}{dt} = -A(t) \times \left(f_u \times \frac{D_u}{h_u(t)} + \frac{1-f_u}{f_u} \times \frac{D_b}{h_b(t)} \right) \times \left(C_{S,u} - C_u(t) \right)$$

1- Use of one dissolution data to extract the P-PSD

2- Verification that P-PSD is predictive of other dissolution conditions for same batch

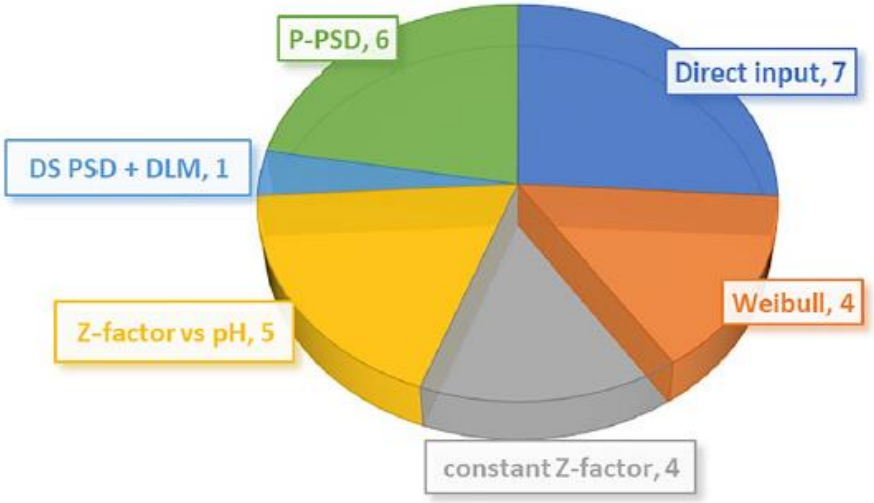
3- Use of P-PSD as input in PBPK model

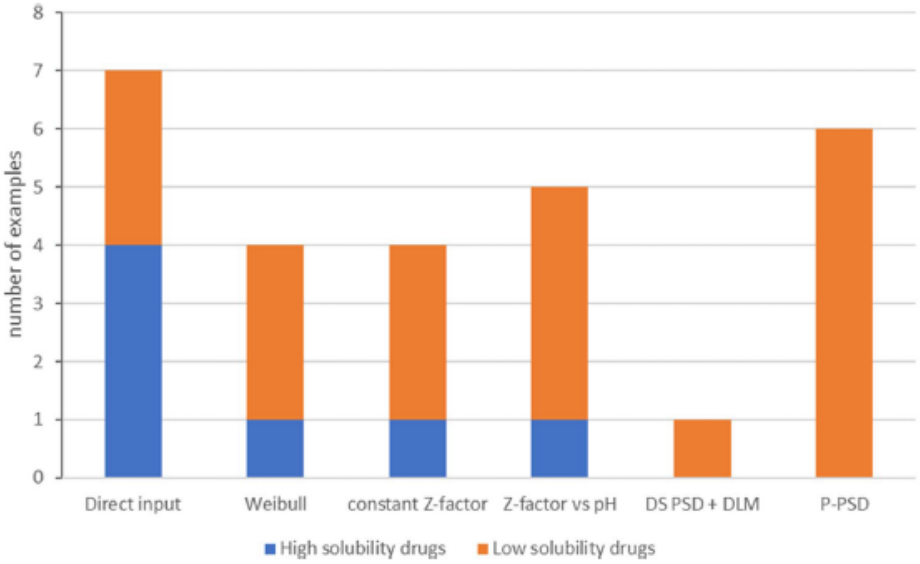
Simple to fit to dissolution data
Mechanistic (dose, pH, volume, surfactant)

Classic model comprises hydrodynamics with Johnson assumption

A: Pepin, X.J.H., et al., Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part I. Mechanistic modelling of drug product dissolution to derive a P-PSD for PBPK model input. European Journal of Pharmaceutics and Biopharmaceutics, 2019. 142: p. 421-434.

IR Dissolution Integration: Literature





(1) Anand, O.; Pepin, X. J. H.; Kolhatkar, V.; Seo, P. The Use of Physiologically Based Pharmacokinetic Analyses—in Biopharmaceutics Applications - Regulatory and Industry Perspectives. *Pharmaceutical Research 2022. DOI: 10.1007/s11095-022-03280-4.*

DLM: Diffusion layer model (Simcyp)

Case Studies
Z-Factor IVIVR

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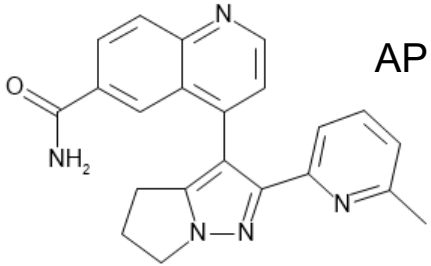
NEXT-GENERATION DELIVERY INNOVATIONS

Galunisertib PBBM Model



AP = ADMET Predictor V 9.5

- TGF-b inhibitor for liver carcinoma
- PK data in rat and human available in literature
- Partition coefficient calculated with Lukacova method
  - LogP adjusted to 2.15 to calculate Kp for both human and rat

[2] Fitted HLM clearance was used to generate Vmax with predicted Km. The fitted value for solution was adjusted for the non-crossover population tested for solid dosage forms

Property	Value	Ref
LogP	1.85	[1]
pKa	-0.68,2.05[1],4.2 (Base) 11.01 (Acid)	AP 9.5 [1] Exp. Fit
Exp Sol. (mg/mL)	0.05 @ pH 7.5	Exp
Solubility Factor	302	Exp. Fit
FaSSIF Sol. (mg/mL) FeSSIF Sol. (mg/mL)	0.05 0.12	Exp. Exp
Human Peff (10^{4}*cm/s)	4.8	Fit
Blood:plasma concentration ratio (R_{bp})	0.8 (human) 1.21 (rat)	AP AP
Plasma protein binding (Fup)	9.5% (human) 9.22% (rat)	AP AP
Diff Coef.	0.68	AP
Metabolism (3A4) **PBBM Model Built based on Solution Data**		
Vss L	50.2 L	NCA
Km (mg/mL) CL HLM (uL/min/mg prot) Vmax Gut (mg/s) Vmax PBPK (mg/s/mg enzyme)	79.69 51 - 65[2] 4.533 – 5.778 0.011 - 0.014	AP Fit Solution[2]

Galunisertib In Vitro Dissolution Data

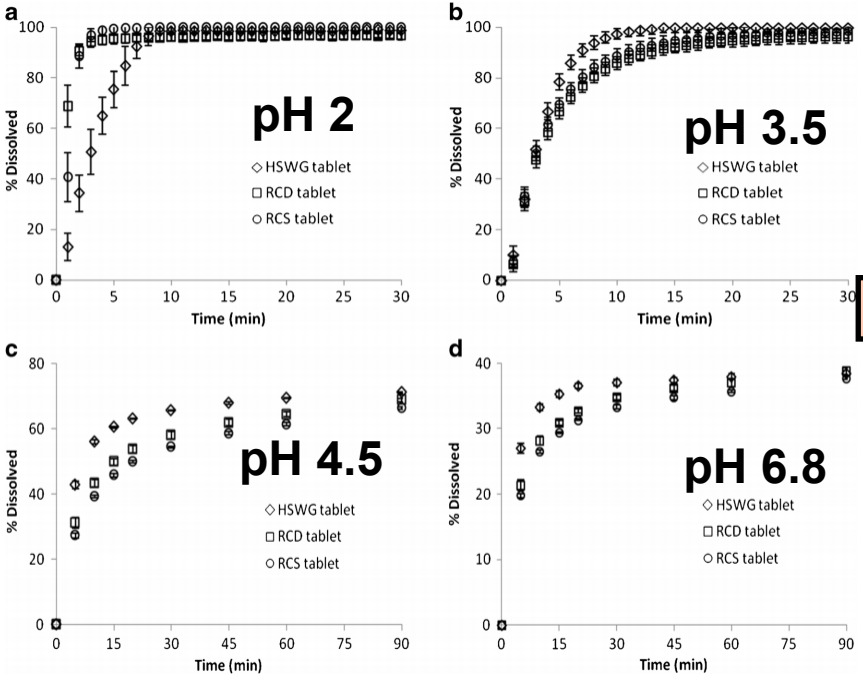
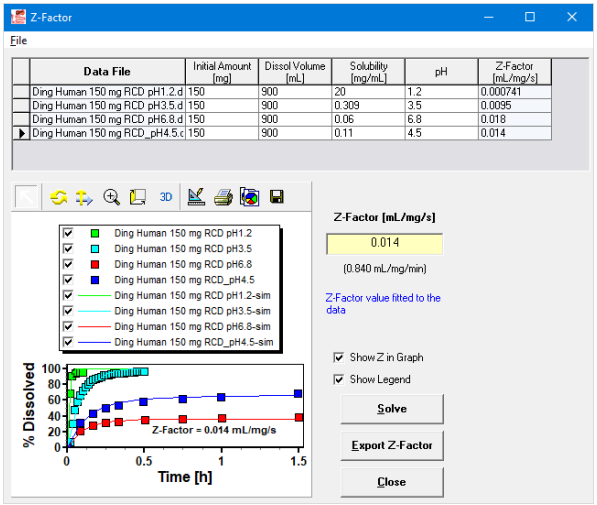


Fig. 3. *In vitro* dissolution profiles of galunisertib tablets. **a** In 0.01 N HCl at pH 2. **b** In citrate phosphate buffer at pH 3.5. **c** In acetate phosphate buffer at pH 4.5. **d** In phosphate buffer at pH 6.8

Ding, et al, AAPS Journal, 2015, 17(6), pg. 1395-1406

Fit

Fitting the Z-Factor Dissolution

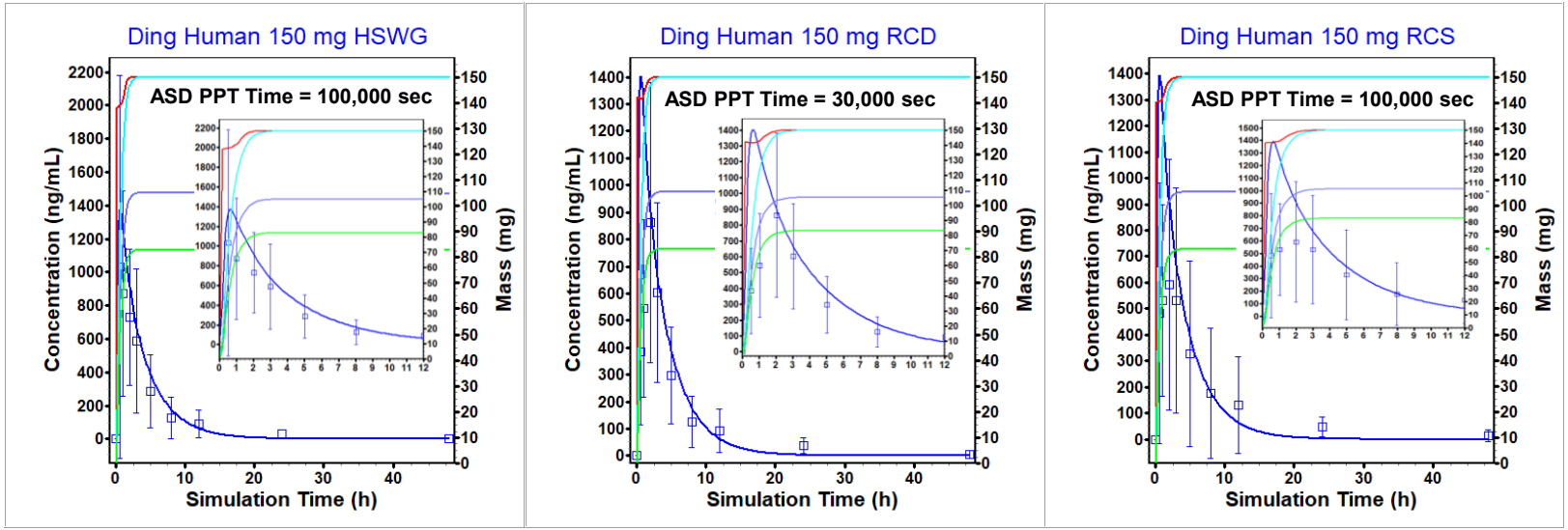


pH	HSWG mL/mg/s	RCD mL/mg/s	RCS mL/mg/s
1.2	0.000165	0.000741	0.000468
3.5	0.012	0.0095	0.01
4.5	0.022	0.018	0.016
6.8	0.029	0.014	0.012

HSWG – High Shear Wet Granulated
RCD – Roller compacted conventional milling
RCS – Roller compacted slurry milled

NEXT-GENERATION DELIVERY INNOVATIONS

Does USP2 In Vitro Dissolution Predict In Vivo PK?

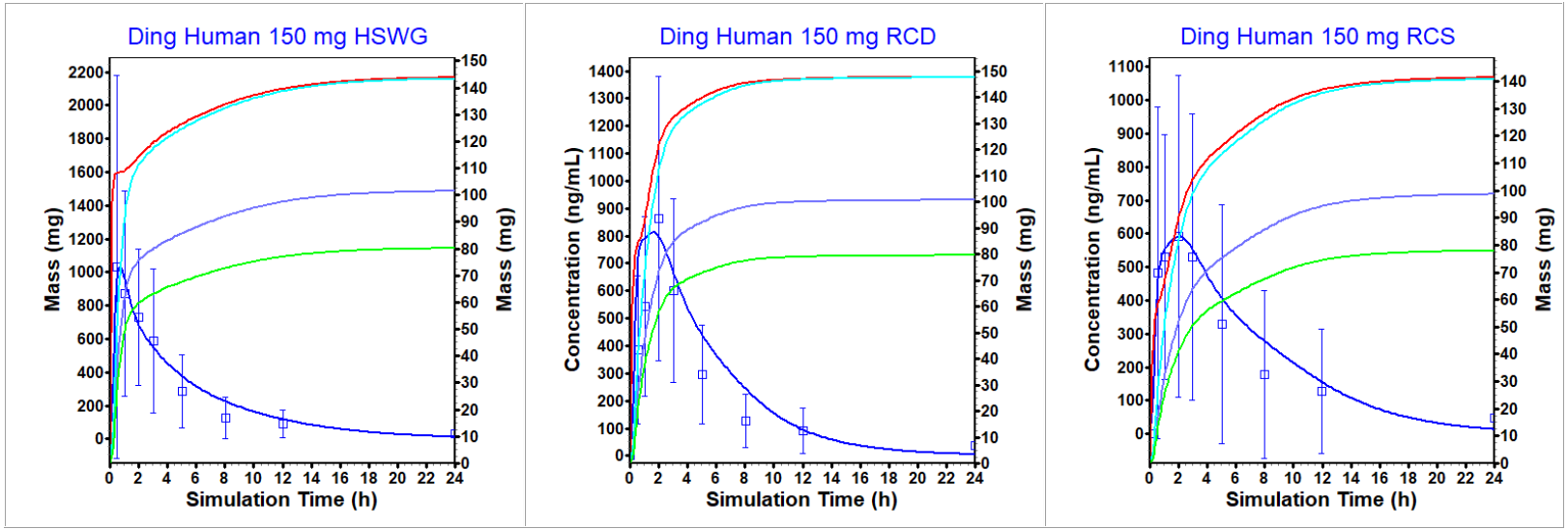


- Using Z-Factor as a function of pH based on USP2 *in vitro* data, the dissolution *in vivo* is overpredicted.
- While there is *in vitro* differentiation – the resulting rates predict no *in vivo* differences (over discriminative)

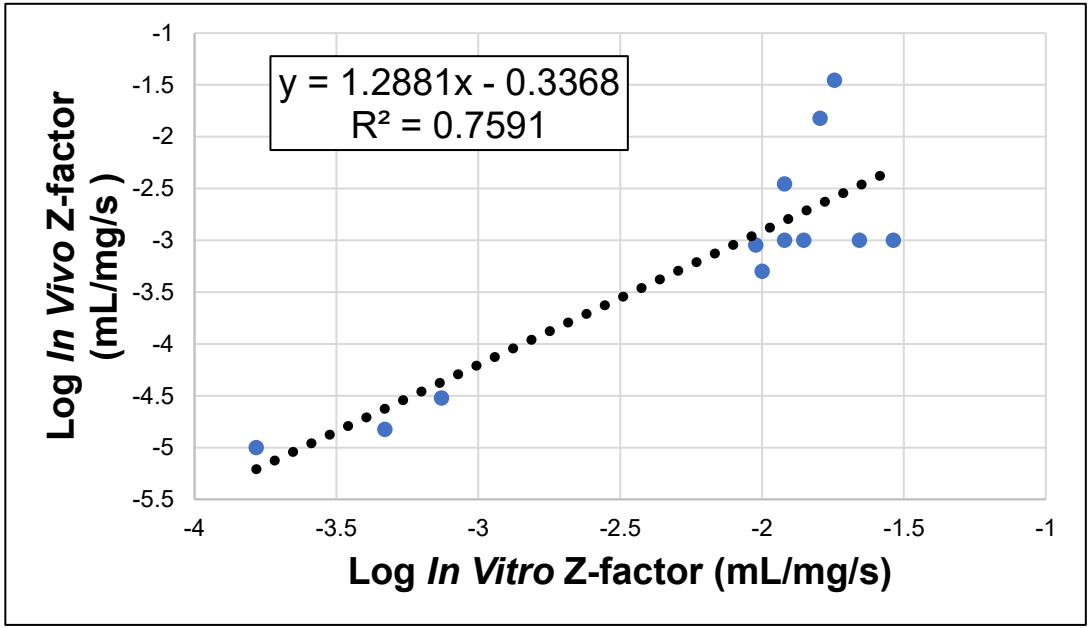
ASD = Artificial Stomach Duodenum Dissolution Test

In Vivo Z-factor Dissolution Fit

- *In vivo* dissolution was calculated by optimizing z-factor values at the same pH's as the *in vitro* data
- *In vivo* dissolution is much slower in general than *in vitro*.

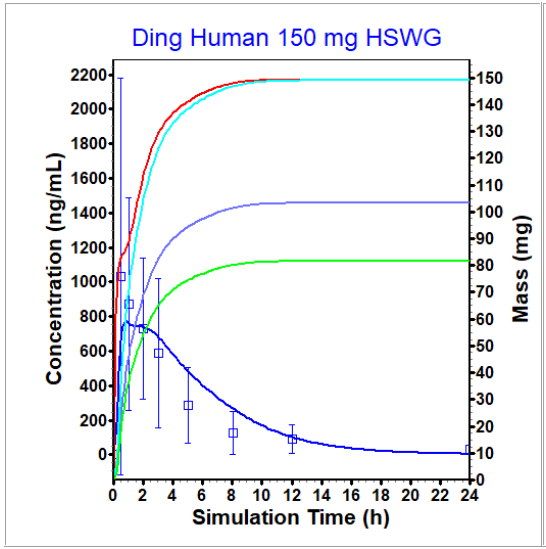


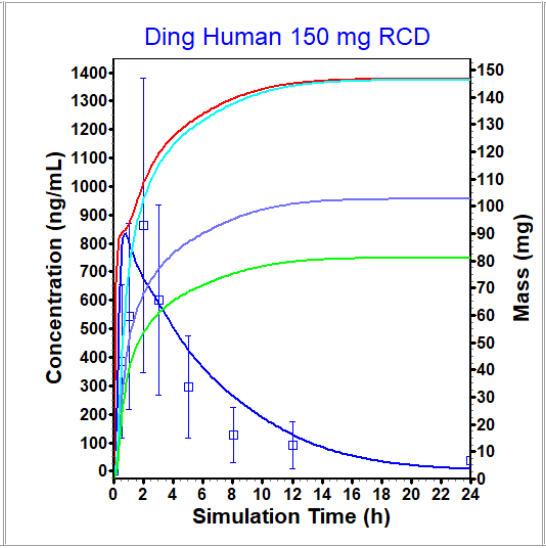
Z-Factor Based IVIVR

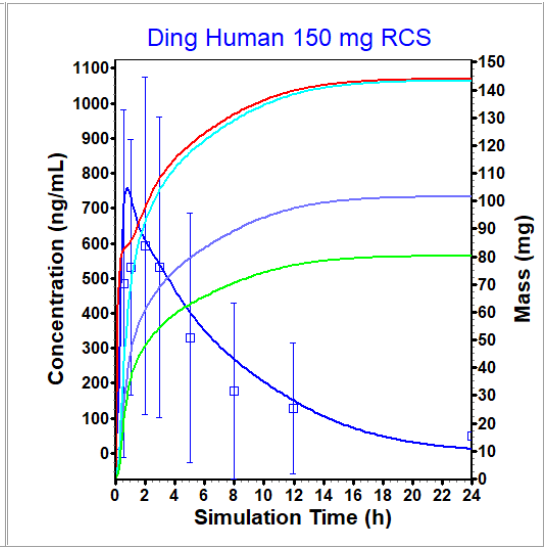


- An IVIVR could be built by using fitted *in vivo* Z-factor values at each pH vs. the *in vitro values*.

Z-factor IVIVR Internal Validation







- This certainly improves the predictions based on the over discriminative *in vitro* method.
- This method has been used successfully in other client projects to describe *in vivo* dissolution of IR products.

	Cmax Error	AUC Error
HSWG	-25.16	0.67
RCD	-3.08	4.90
RCS	27.83	-4.96
Mean	18.69	3.51

Case Study
PPSD and Safe Space

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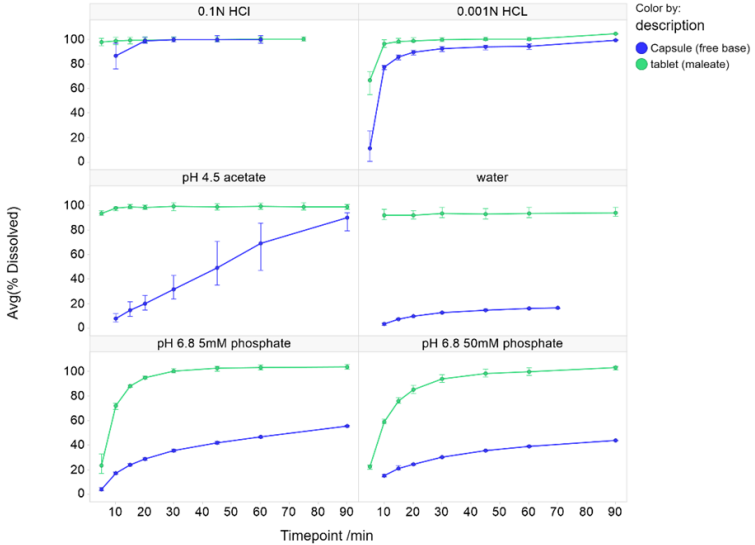
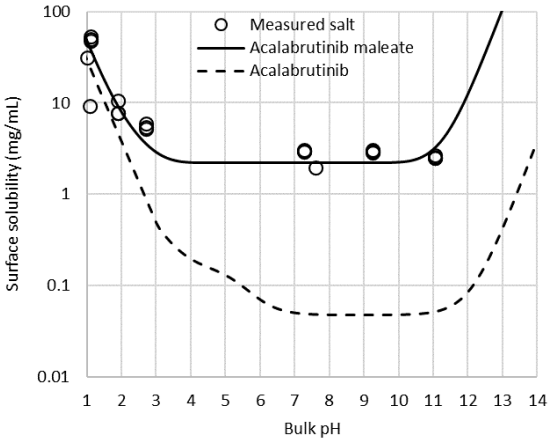
Acalabrutinib Maleate Tablet (AMT)

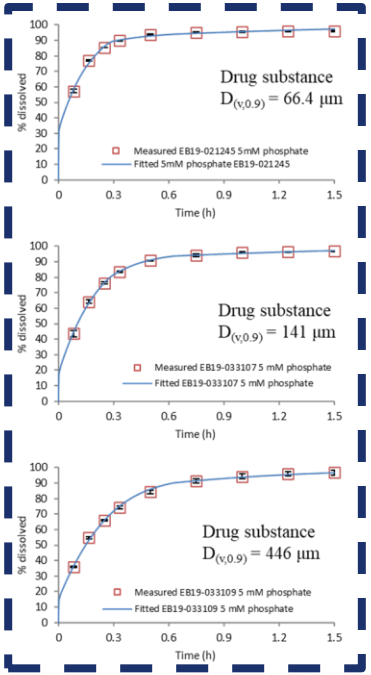
- Project information
  - Acalabrutinib free base is associated with label restriction for patients undergoing acid reducing agent (ARA) treatment
  - 20-40% hematological cancer patients are estimated to take ARAs
  - Acalabrutinib maleate increases surface solubility compared to the free base leading to faster and complete dissolution in all media
- Model purpose
  - Justify proposed dissolution specification for AMT



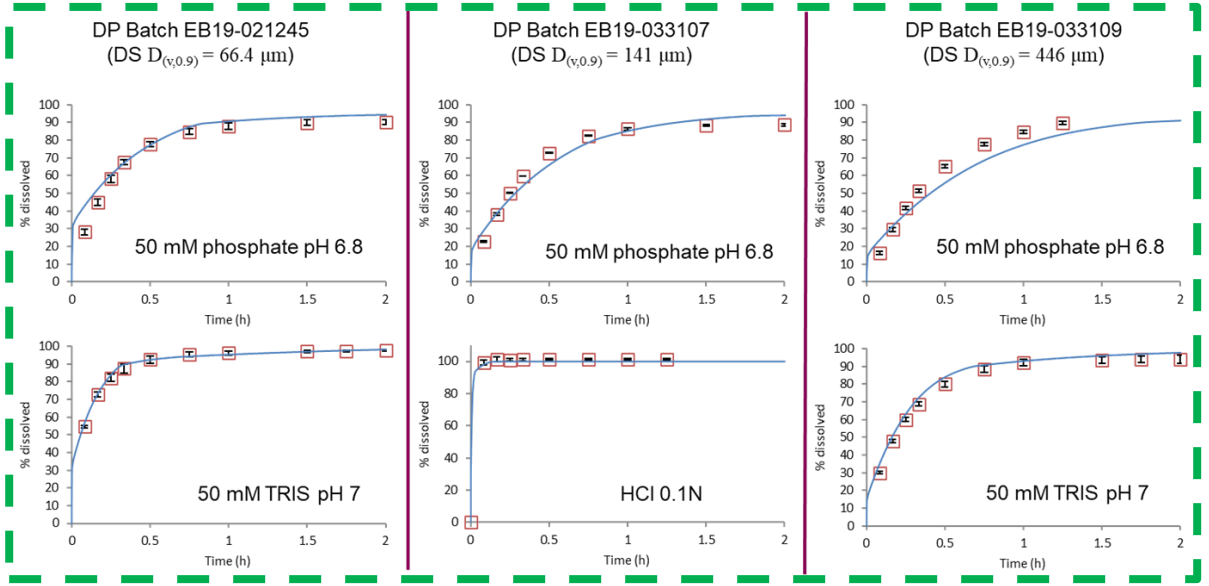


AMT : P-PSD Fitting of Dissolution

1-QC dissolution method + P-PSD extraction



2-P-PSD verification: dissolution prediction in other media

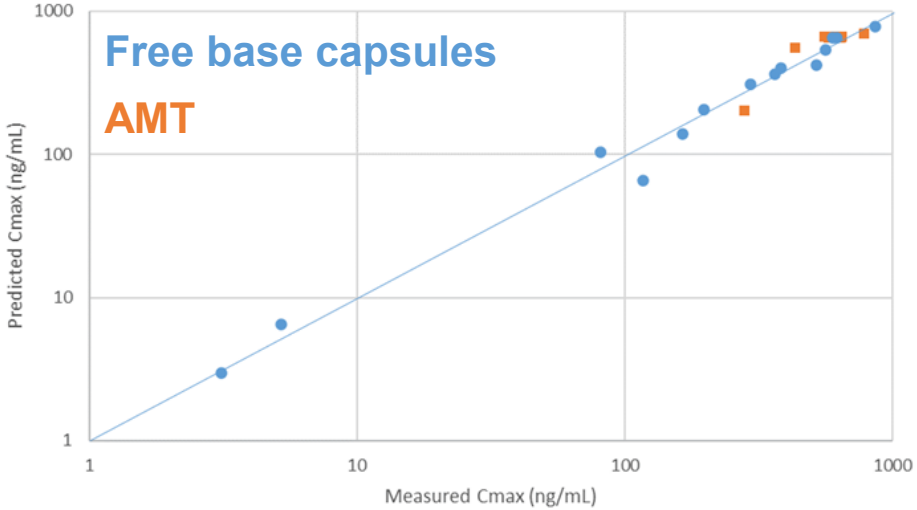


AFE=1.02, AAFE= 1.06

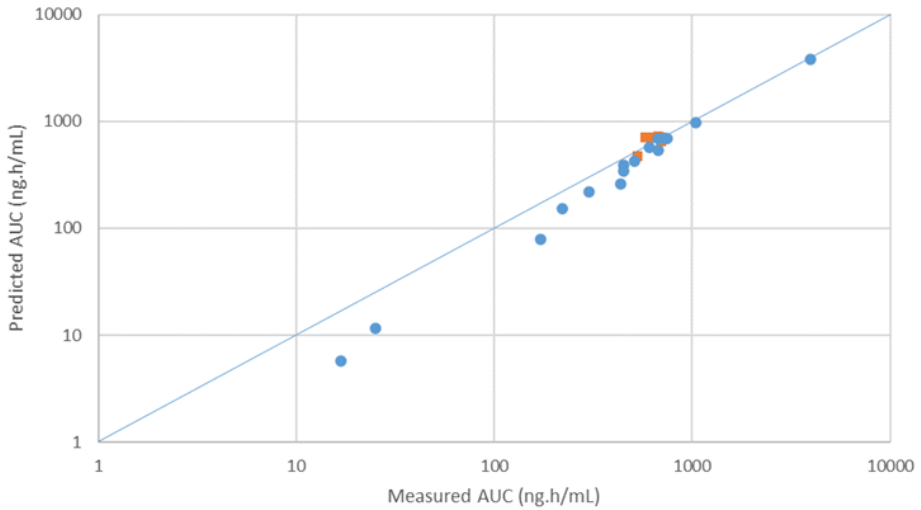
Absolute error P-PSD = 6% vs z-factor = 12%
P-PSD chosen

AMT : PBBM Validation

AFE = 1.01, AAPE = 6.7%



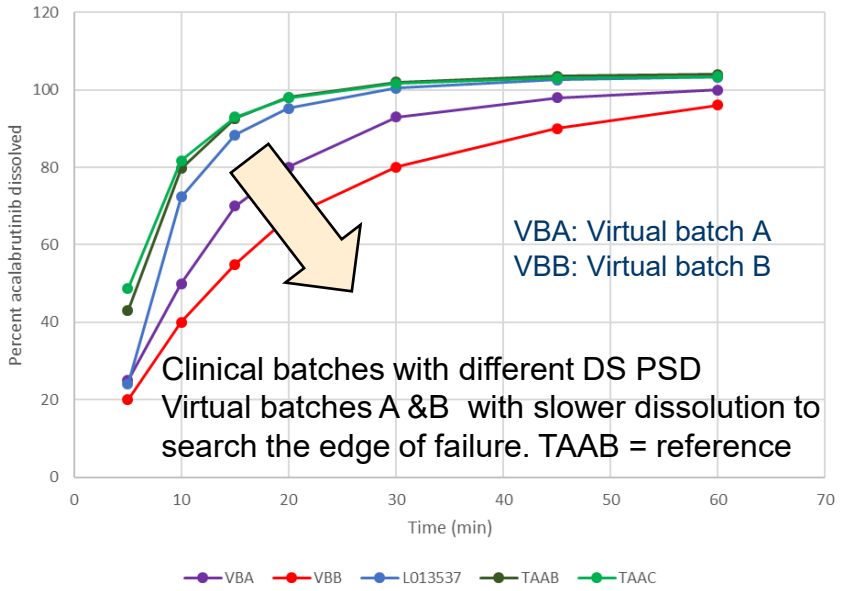
AFE = 1.05, AAPE = 8.5%



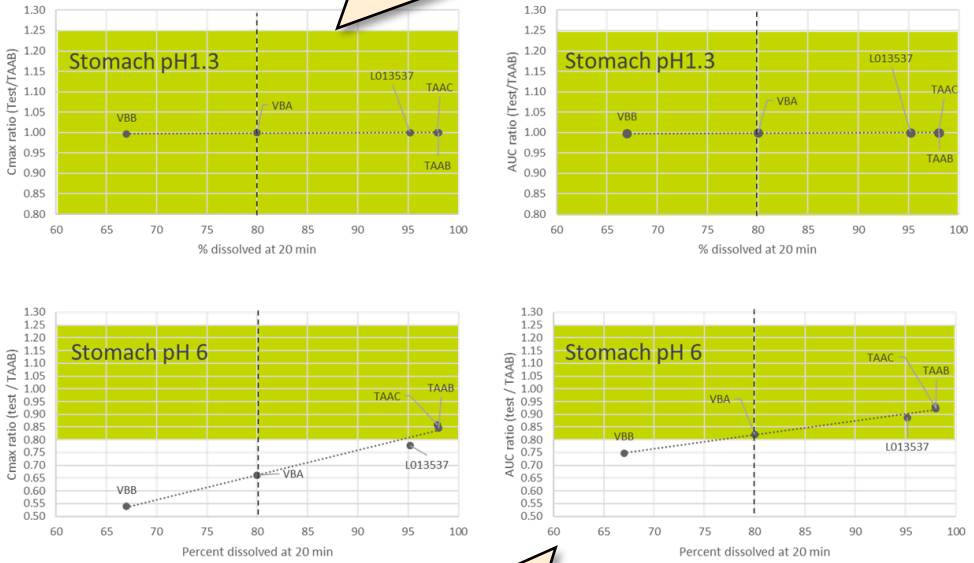
Acceptable model prediction performance across studies with no adjustment of the disposition parameters

AMT : PBBM Use

In vitro dissolution with QC method

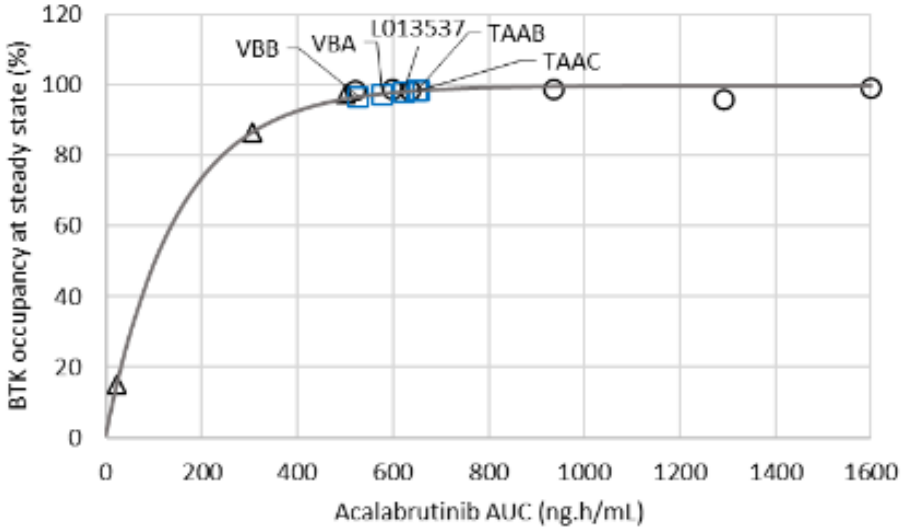


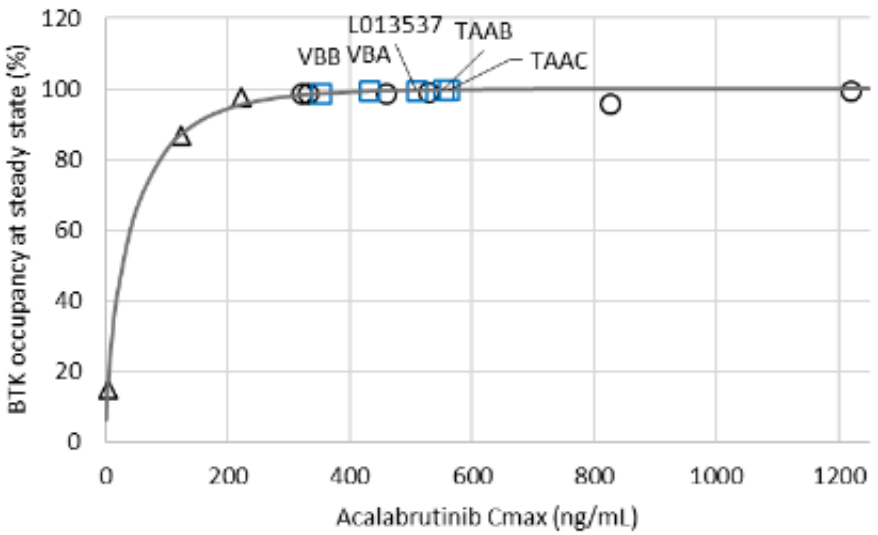
VBA and VBB bioequivalent to reference in acidic stomach conditions



VBA and VBB with PPI not BE to reference (in acidic conditions)

AMT : PBBM + PKPD Model

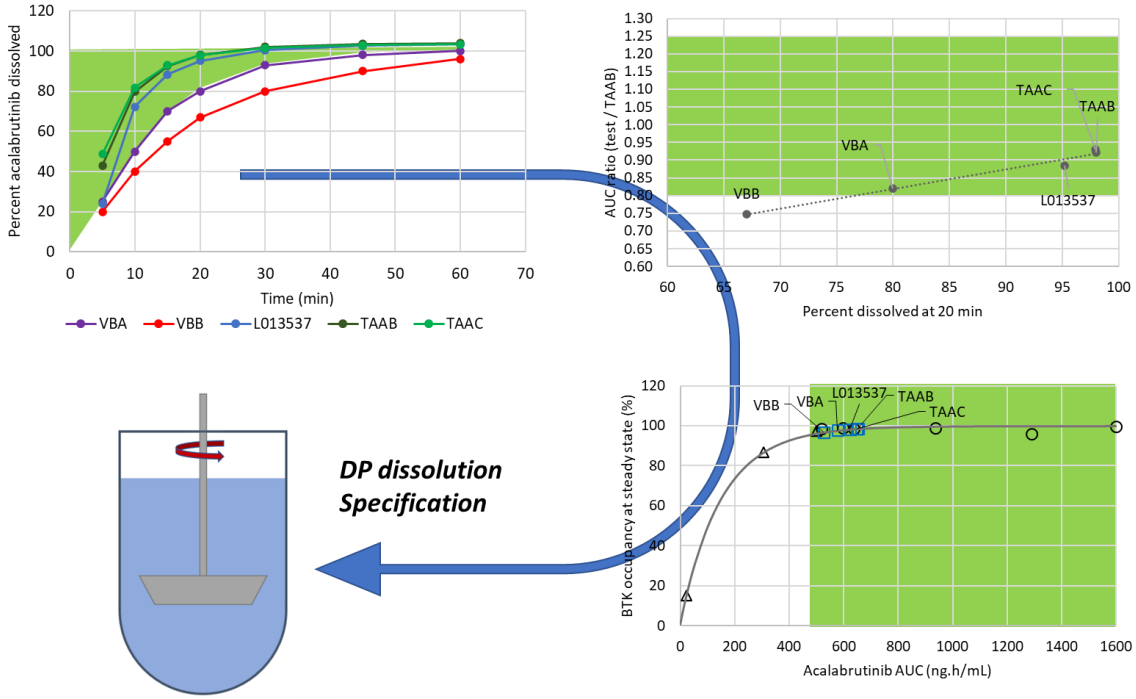




BTK-occupancy vs AUC or vs Cmax, show that exposure to VBA or VBB in neutral stomach conditions are anticipated to be safe and effective : Similar target engagement compared to pivotal efficacy study

Acalabrutinib Maleate Tablet: Conclusions

- VBA was used to delineate dissolution safe space identified using PBBM and PKPD



Q=80% 20-30 minutes is anticipated to be safe and effective for 100 mg AMT
Oral solution extemporaneously prepared from tablet was administered in the clinic and proved BE to the tablet (upper bound of safe space)

Summary

- Traditional IVIVC is robust for ER formulations where dissolution is rate limiting.
- Traditional IVIVC is difficult with respect to IR formulations especially BCS Class II
- PBBM is an answer and focuses on drug substance and drug product quality
- Useful understanding of critical product and drug attributes along the development
- Integration of dissolution and choice of dissolution method is key
- PBBM : safe space definition for a quality attributes applicable to IR and MR formulations
- PBBM is an element of the review of the entirety of data
- PBBM template exists to support reporting of model and background information