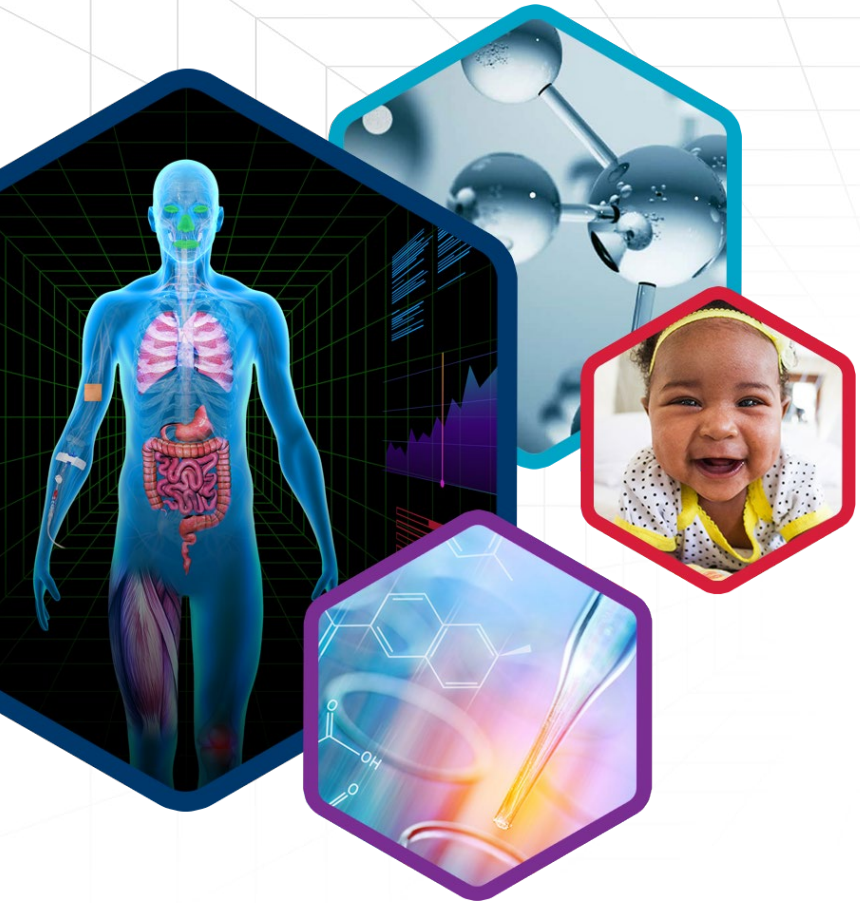


SimulationsPlus

Cognigen | DILIsym Services | Lixoft

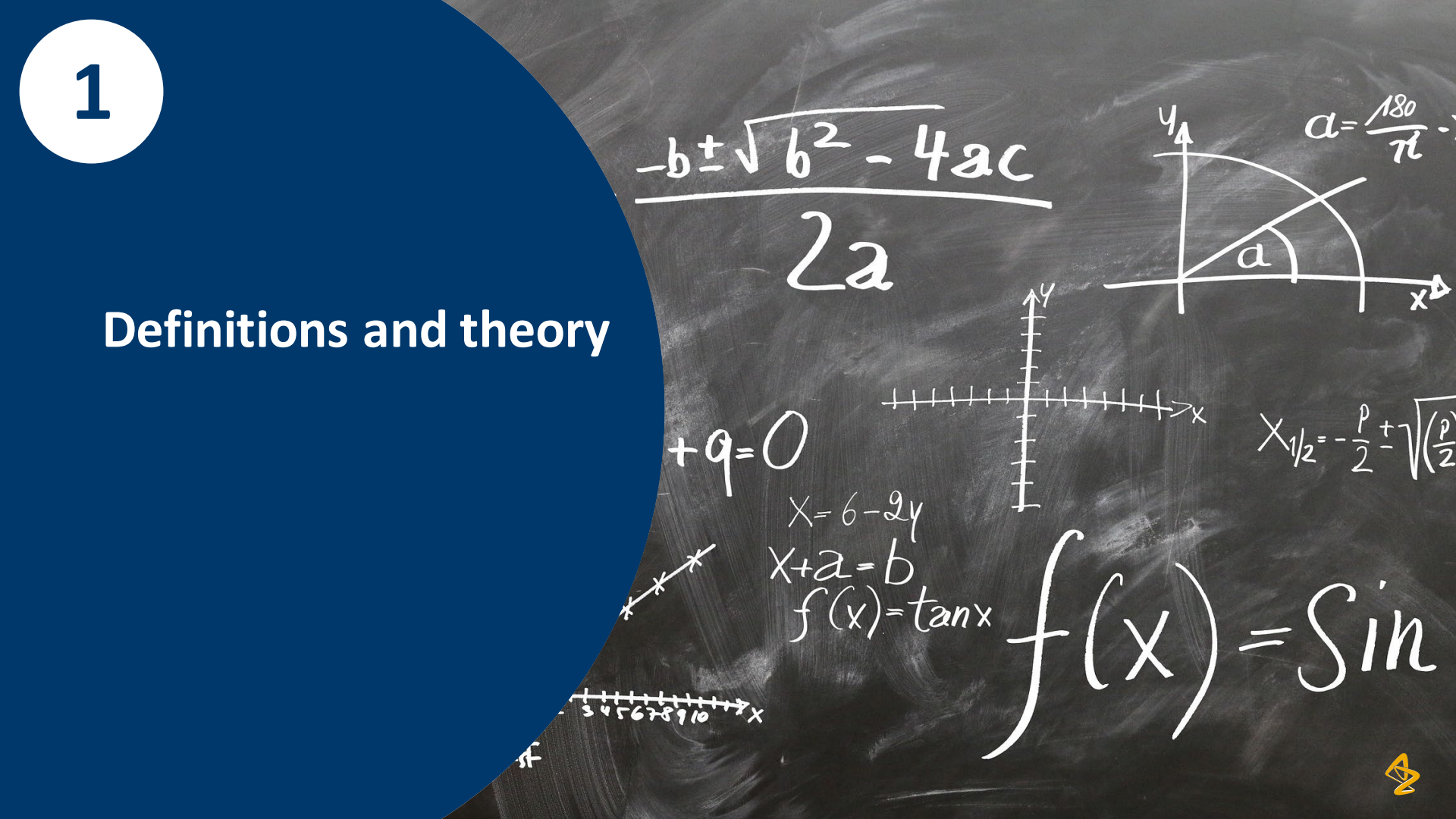
Approaches to establishing Bioequivalence safe space for orally administered drug products: Applications & case studies

Xavier Pepin

24 May 2022

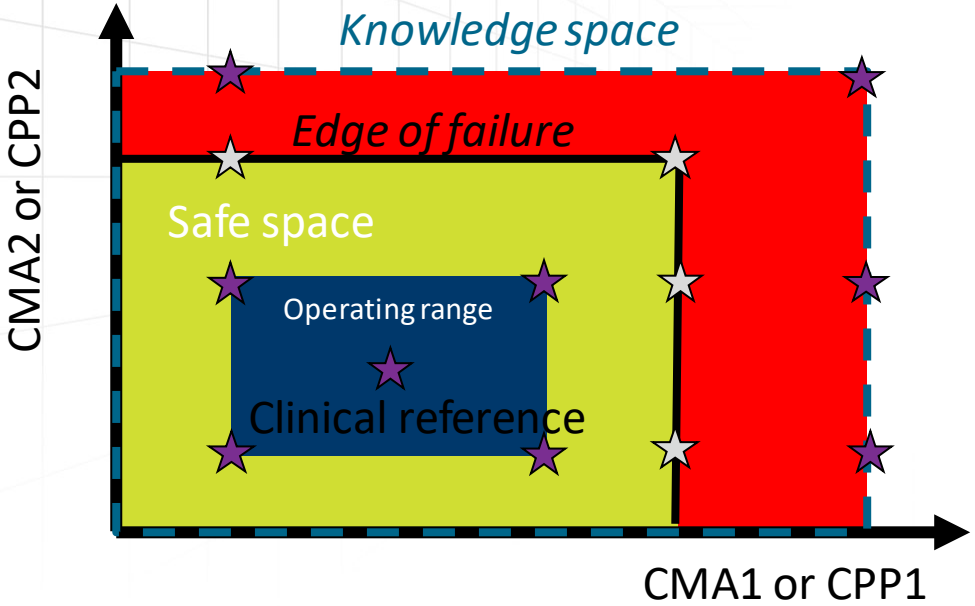
1

Definitions and theory



Definition of safe space

Range of quality attributes for a drug product where all the batches manufactured are anticipated to be bioequivalent to one another



Knowledge space: Range of product QAs tested in the clinic

Operating range: Range of product QAs normally used for routine batch production

Clinical reference: DP Batch(es) used for pivotal studies

Edge of failure: Max QAs beyond which batches are not BE to clinical reference

Critical Biopharmaceutics Attribute (CBA): QA (CMA or CPP) which impacts exposure

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

PBBM does not remove the need for clinical trials but allows to optimize the clinical resources/timing, increase mechanistic understanding and allows informed decision making

How to establish an in vitro in vivo link

Positive efficacy readout
High value or high risk compound

IR product with rapid dissolution is rapid >80% in 15 min

In vitro package convincing

BCS I or III

MR product envisaged

BCS II or IV

Waive BE requirements using BCS based biowaiver guidance

Develop formulation variants n=3 with different release profiles

Prototype dissolution using Preclinical method(s)

Clinical study with variants:
in vivo human evaluation with IV microdosing, markers of gastric emptying, pH probe in stomach.

If variants BE, safe space = clinical knowledge space

Present safe space to authorities

Extract in vivo absorption profiles from PBPK modelling

Use PBBM for QbD, safe space, specs justification (dissolution and DS PSD), virtual BE, support changes within safe space

Clinically relevant dissolution methods development

Use vitro and vivo data + refined PK-PD or PK-Tox to maximize therapeutic index, define best commercial formulation or LCM opportunities through PBPK

How to integrate dissolution

MR :

Direct input

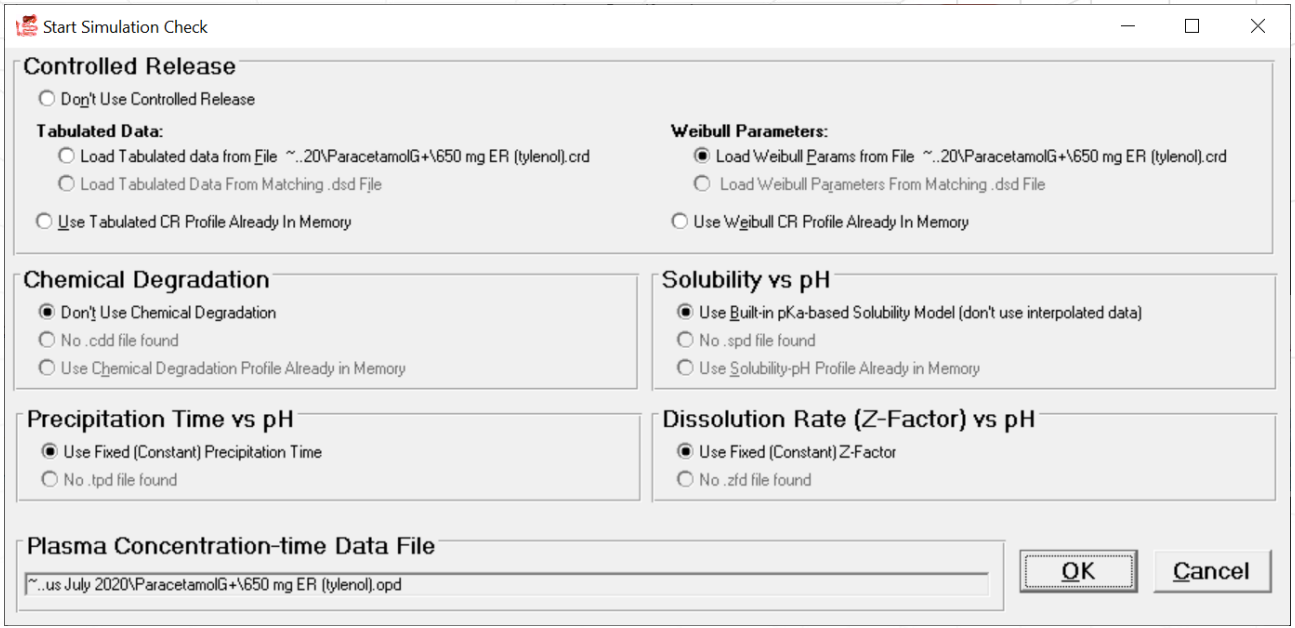
Weibull

IR :

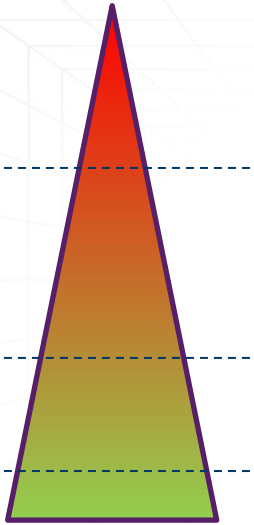
Weibull

Tabulated Z-factor

Johnson…etc

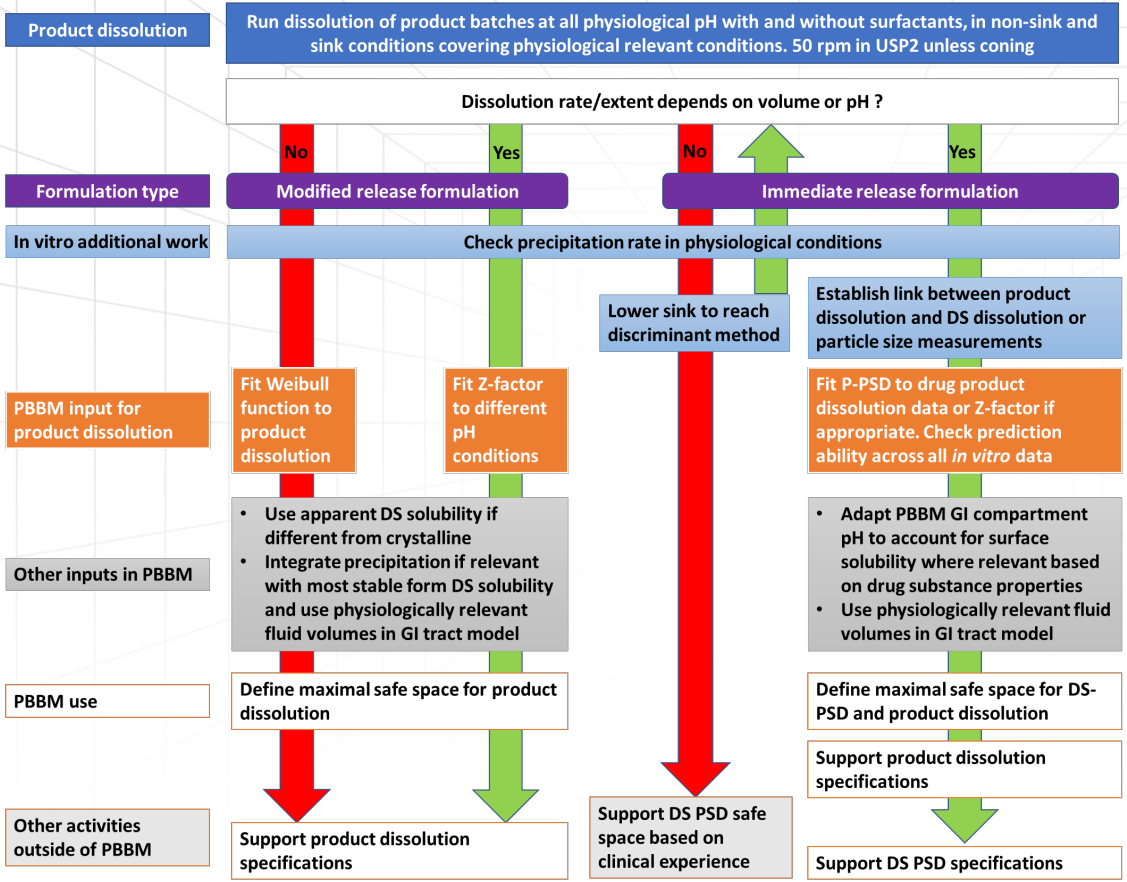


Dissolution integration: How methods compare



	Assumptions/conditions of use
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
DLM scalar fitted to DS PSD	All DS particles are equal to the scalar (sphericity, aggregation, wettability, attrition during process, excipient effects…)
P-PSD	A DP batch specific 1-10 bin PSD which represents the DS particles available for dissolution after product disintegration

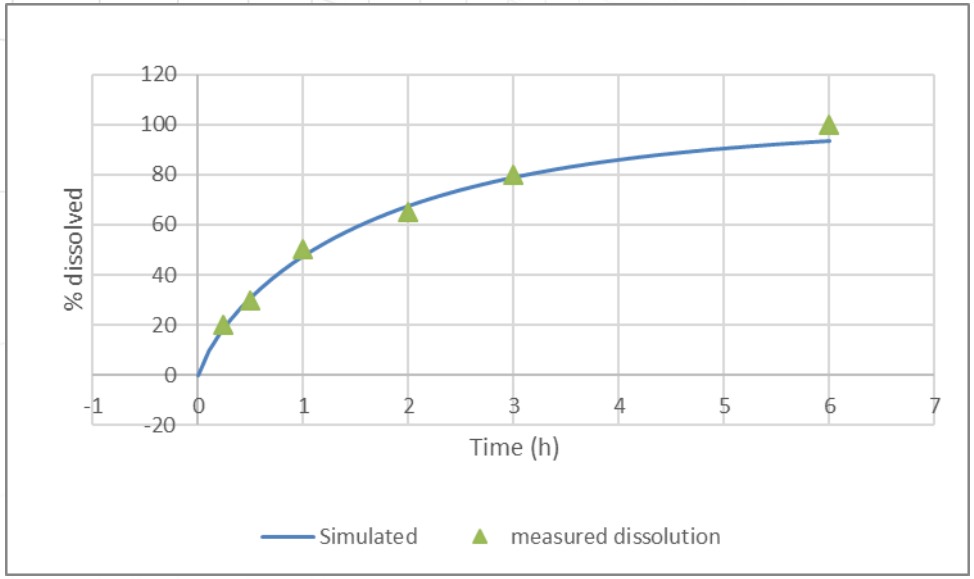
Strategy for integration of dissolution in PBBM



Weibull equation

>V9.7 : up to three phase-Weibull

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



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

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

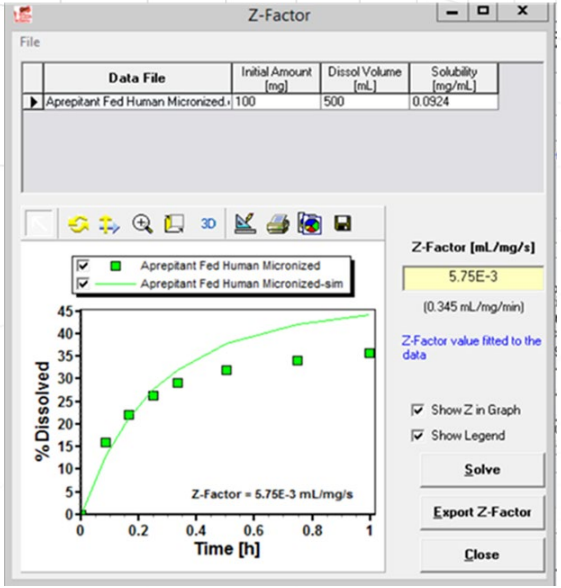
Is not mechanistic.
Imposes release over time

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.

$$\frac{dX_{d,vitro}(t)}{dt} = \frac{3D}{\rho hr_0} \times X_{0,s,vitro} \times \left(\frac{X_{s,vitro}(t)}{X_{0,s,vitro}}\right)^{2/3} \times \left(C_s - \frac{X_{d,vitro}(t)}{V_{vitro}}\right)$$

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



$$z = \frac{3D}{\rho hr_0}$$

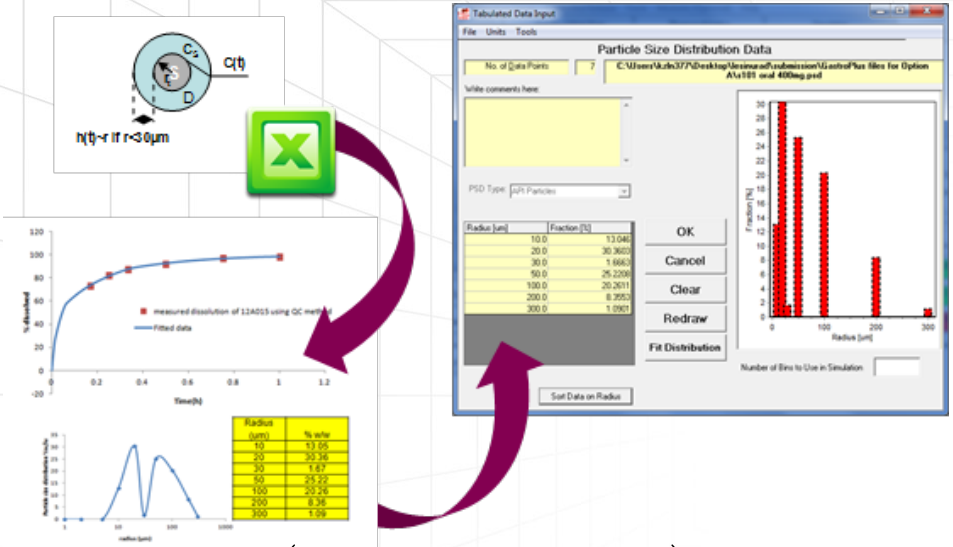
Z groups particle size, diffusion and thickness of UWL and drug density.

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)

P-PSD [a]



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

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

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

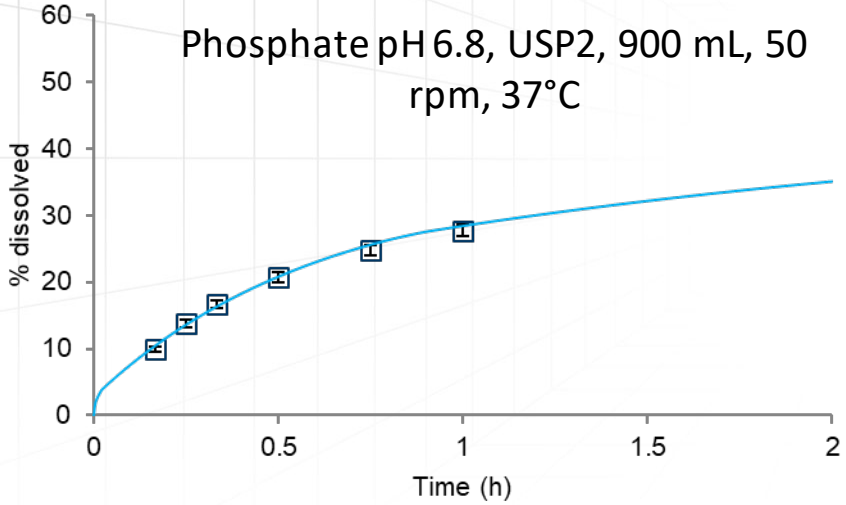
Simple to fit to dissolution data
Mechanistic (dose, pH, volume, surfactant)

Basic model comprises hydrodynamics with Johnson assumption

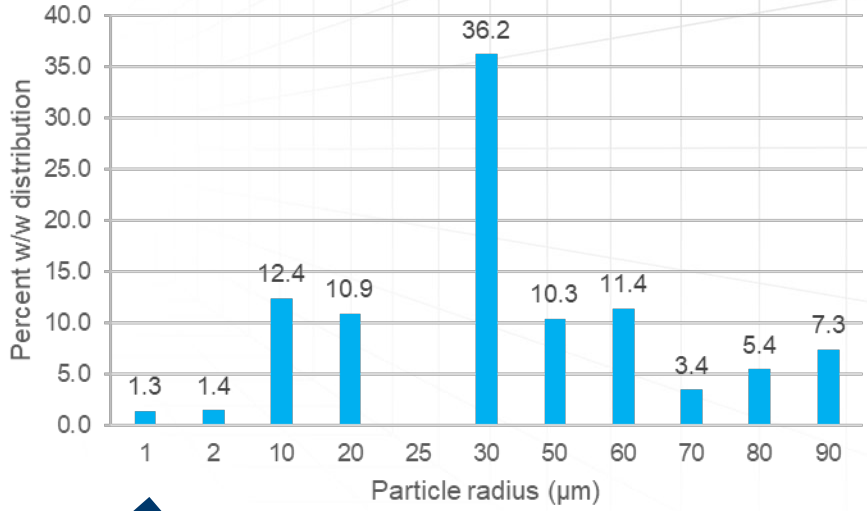
a: https://doi.org/10.1016/j.ejpb.2019.07.014

Example for P-PSD extraction

Step 1 : 100 mg acalabrutinib capsule batch W027180

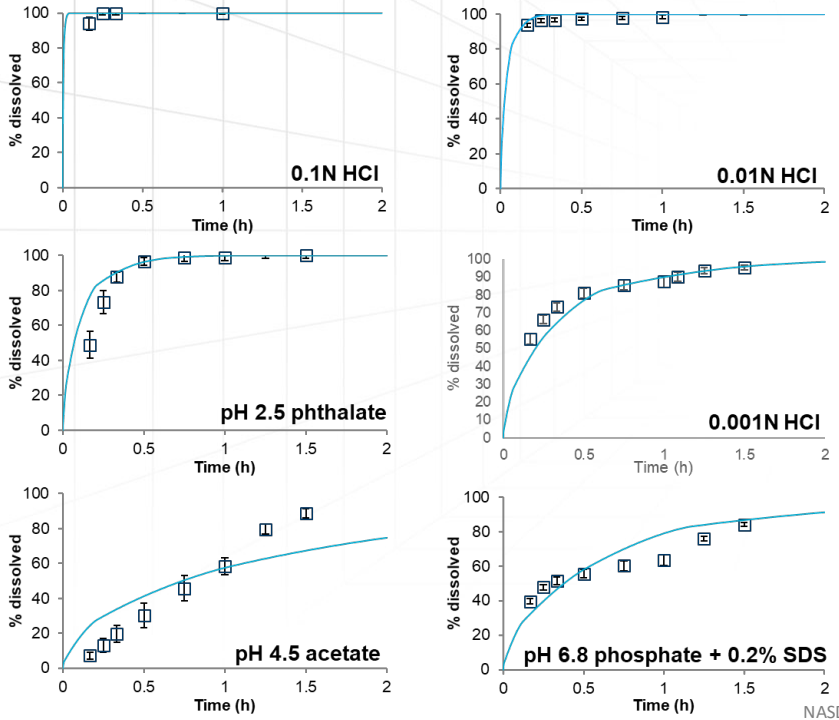


P-PSD for batch W027180



Example for P-PSD verification

Step 2 : Predicting other conditions for 100 mg acalabrutinib capsule batch W027180



P-PSD able to reproduce the observed dissolution rates in other conditions of pH with and without surfactant

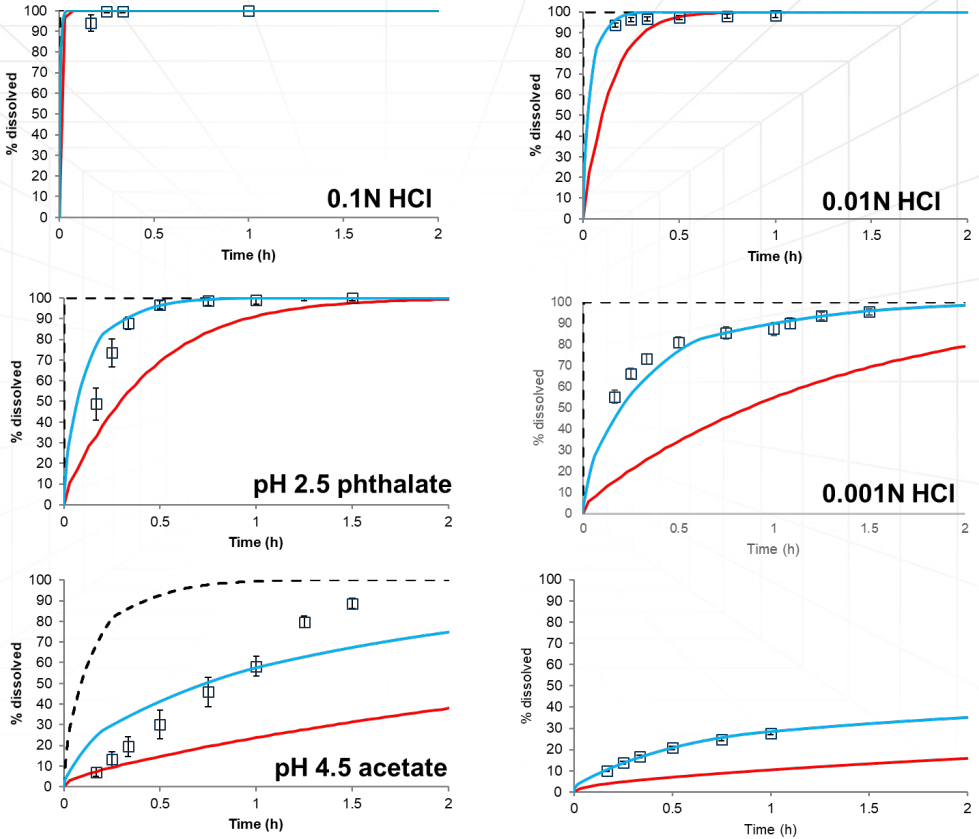
Use of surface pH
Different UWL thicknesses (if micelles)

Other alternatives to predict dissolution (DS-PSD or bulk solubility)

DS-PSD underestimates dissolution

Bulk solubility and P-PSD overestimates dissolution

Surface solubility and P-PSD is the way forward !



100 mg capsule batch W027180

Why do we need P-PSD
Could we use DS PSD instead ?

DS-PSD : laser diffraction (or other methods)

DS is an intermediate to the product

Product manufacturing process → attrition [a] = ↗surface or consolidation = ↘surface

Real particle shape is not spherical and can be aggregated = surface underestimated

Poor wettability → Laser will overestimate dissolution rate and extent

P-PSD

Integrates excipients, process parameters, wettability issues

Is based on the product that we give to patients.

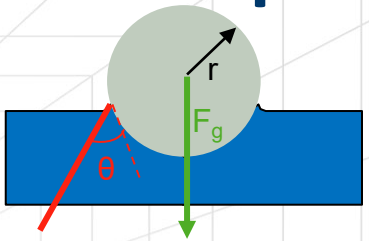
Is extracted from dissolution : link to in vitro performance (integrates hydrodynamics using same hypotheses than in silico tools)

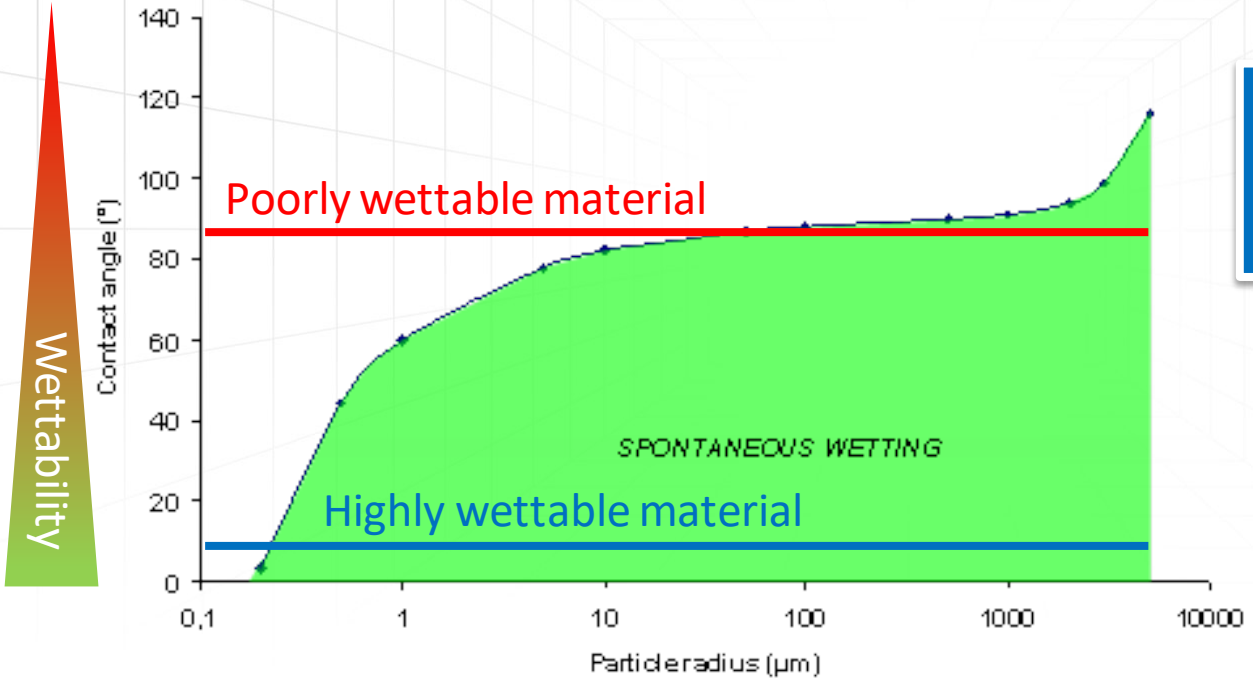
Provides a size distribution using spherical morphology : adapted to in silico models

a: https://europe.compactionsimulation.com/effect-of-fragmentation-on-dissolution/

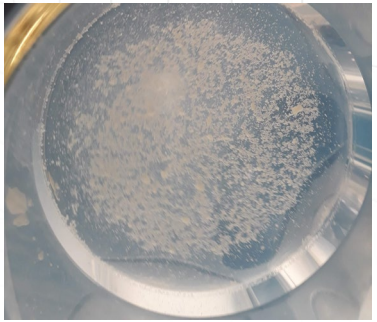
Wettability of drugs : not all particles are equal !

Limiting contact angle for spherical particle spontaneous wetting due to gravitation. ρS = 1.2 g/mL, ρL = 1 g/mL, ηL = 1 mPa.s

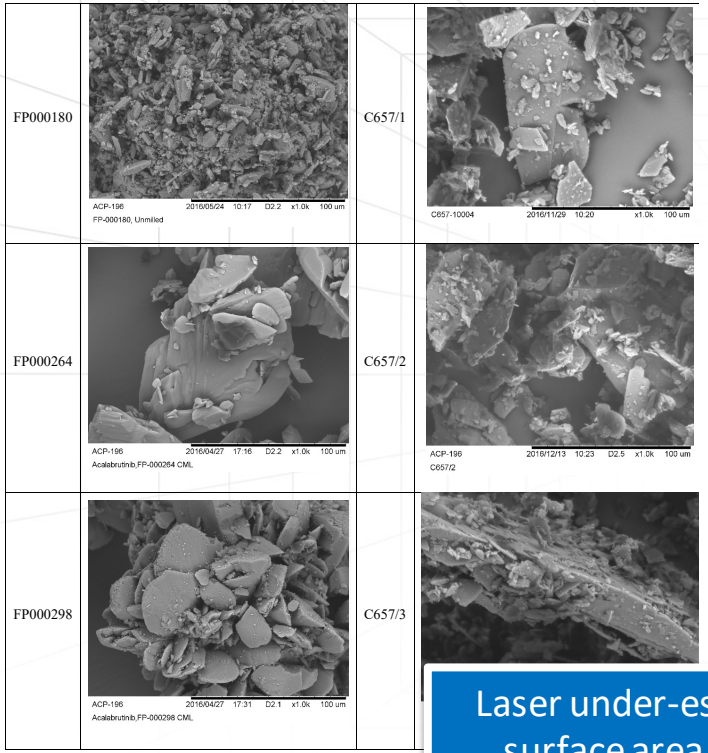


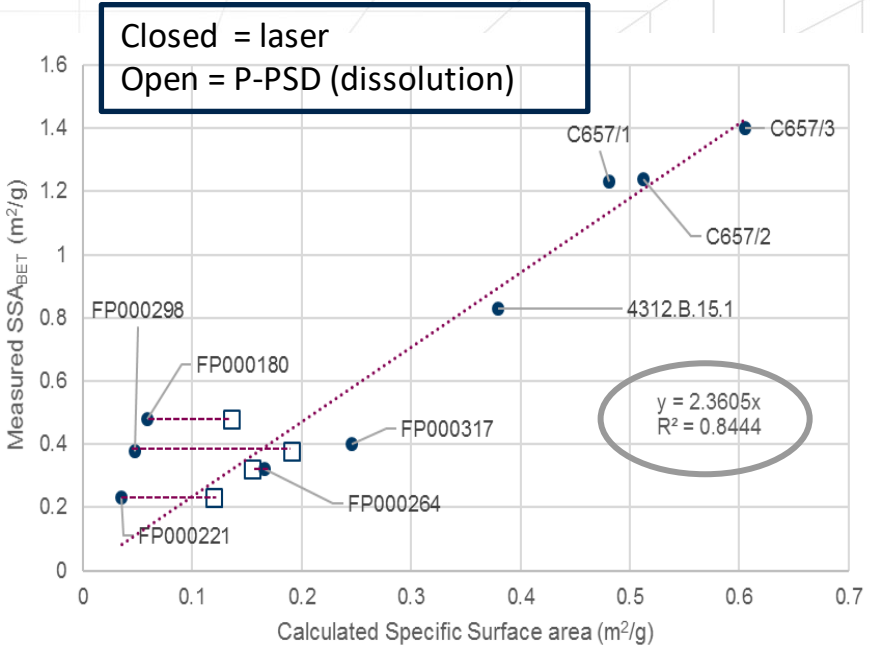


Size of particles determines spontaneous wetting
Small particles wet less easily than large particles



Issue of DS morphology and aggregation





Laser under-estimates surface area esp. if particles are aggregated

Dissolution of DP reveals "more" surface than laser diffraction on DS

P-PSD with hydrodynamics

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

Same base model and equation
h (Thickness of UWL) depends on agitation

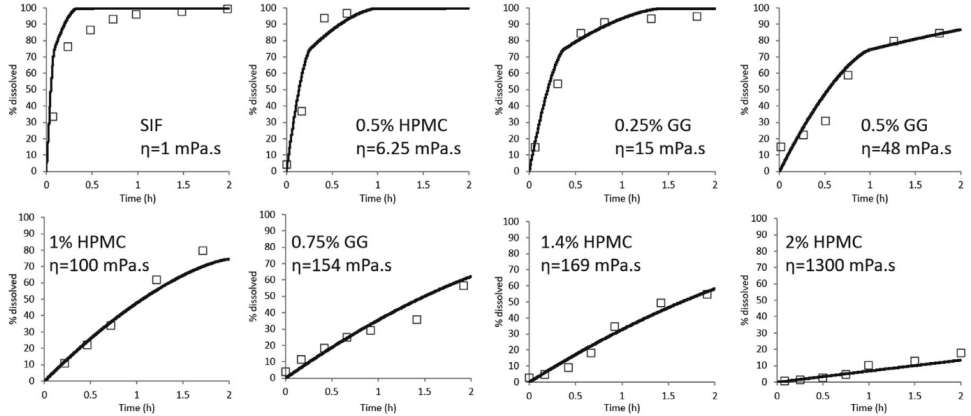


Figure 9. Trospium chloride (Spasmex®) immediate release tablet dissolution in viscous media, fitted (for 1% HPMC) and predicted for all other conditions with a single P-PSD with the HD model. Labels show medium apparent viscosity (mPa.s). Footnotes to Figure 9: GG = Guar Gum, HMPC= Hydroxypropyl methyl cellulose, SIF = Simulated Intestinal Fluid. Symbols represent measured percent dissolved, solid lines represent simulations.

$$h = \frac{2r}{Sh} \qquad Sh = 2 + 0.6 Re_p^{1/2} Sc^{1/3} \qquad Sc = \frac{\vartheta}{D}$$

$$Re_p = \frac{2r \times v_{fl,av}}{\vartheta} \quad if \ K \geq 1$$

$$Re_p = \frac{(2r)^{4/3} \times \varepsilon^{1/3}}{\vartheta} \quad if \ K < 1$$

$$Er_p = \left(6\pi\eta r v_{fl,av} + \frac{4}{3}\pi r^3 (\rho_s - \rho_L) g \right) \times 2r$$

$$Ec_p = \frac{2}{3}\pi r^3 \rho_s v_{fl,av}^2$$

$$K = \frac{Ec_p}{Er_p}$$

$$\frac{h_b}{h_u} = \sqrt[3]{\frac{D_b}{D_u}}$$

Unique P-PSD can predict data in different agitation or in media with different viscosities

a: https://jpharmsci.org/article/S0022-3549(21)00549-9/fulltext

P-PSD with coning

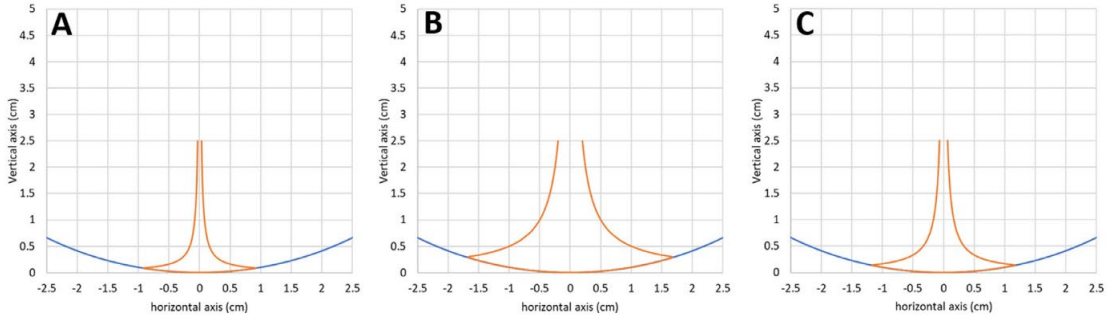
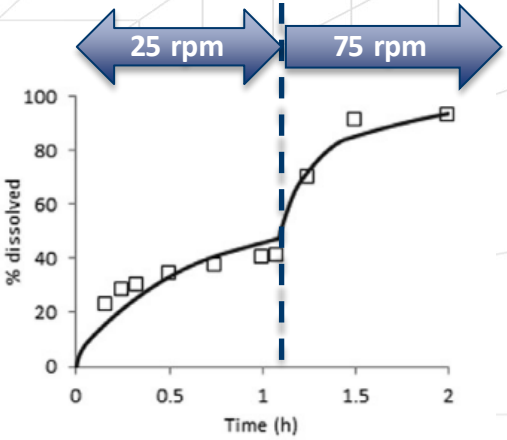


Figure 3. Vertical section of sedimentation spaces (orange lines) for simulations A (ω=50rpm, r=20μm), B (ω=50rpm, r=50μm), and C (ω=150rpm, r=50μm), in USP2 apparatus.



Equation utilizes excipient amount and properties to predict sedimentation or DS properties to predict sedimentation in the absence of excipients

Model able to predict the impact of coning on dissolution as a function of agitation in USP2

2

Case studies

1) Priadel® 200 mg
2) BMS-663068

Priadel 200 mg: Post approval justification for a dissolution specification change

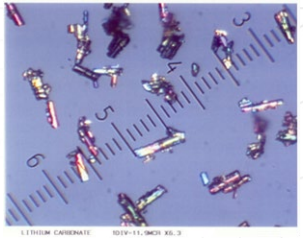
- ***Lithium carbonate 200 mg –Priadel ®***
  - Issues of dissolution testing at end of product shelf life
  - Formulation with magnesium stearate, maturation process during storage
  - Old data in the dossier
  - Current large specifications for dissolution with no issue of safety
    Approx. 3 batches per year were destroyed (since not meeting dissolution specs) + complex management of batches at the plant

- ***Question to be answered by PBBM***
  - Can dissolution specifications be changed to avoid product losses without impacting drug efficacy and safety ?

Ref: Heimbach T, Suarez-Sharp S, Kakhi M, Holmstock N, Olivares-Morales A, Pepin X, Sjögren E, Tsakalozou E, Seo P, Li M, Zhang X, Lin H-P, Montague T, Mitra A, Morris D, Patel N, Kesisoglou F. Dissolution and Translational Modeling Strategies Toward Establishing an In Vitro-In Vivo Link—a Workshop Summary Report. The AAPS Journal. 2019;21(2).

Biopharmaceutical properties of Li^{2+}

- Lithium carbonate $Li_2CO_3 \rightarrow 2Li^+ + CO_3^{2-}$



D50 30-50µm

- Solubility
- In water at 37°C = 12 mg/mL

$$CO_3^{2-} + 2H^+ \rightarrow H_2CO_3$$

$$H_2CO_3 + H^+ \rightarrow H_3O^+ + \overset{\uparrow}{CO_2}$$

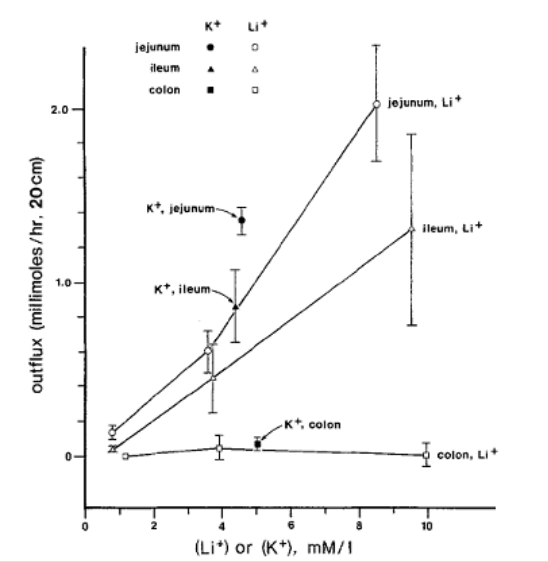
- Dissolution not pH dependent . Existence of CO_2 bubbles which can reduce dissolution rate (isolation of the tablet)

Need to increase HCL molarity to 0.025M to buffer carbonates

Biopharmaceutical properties of Li^{2+}

- Permeability
- Was measured in man 40 years ago !

J.M Diamond et al. J. Membrane Biol. 72, 153-159 (1983)



$$\frac{dM}{dt} = SP_{eff}C$$

Fluxes transformed in Peff using radii from ICRP89 & lengths perfused in vivo

	Flux/Concentration (cm3/h)[a]	radius cm	length cm	Peff x 10^4 cm/s
Jejunum	228.7	1.38	20	3.66
Ileum	134.5	0.98	20	3.03
Colon	14.7	2.41	20	0.13

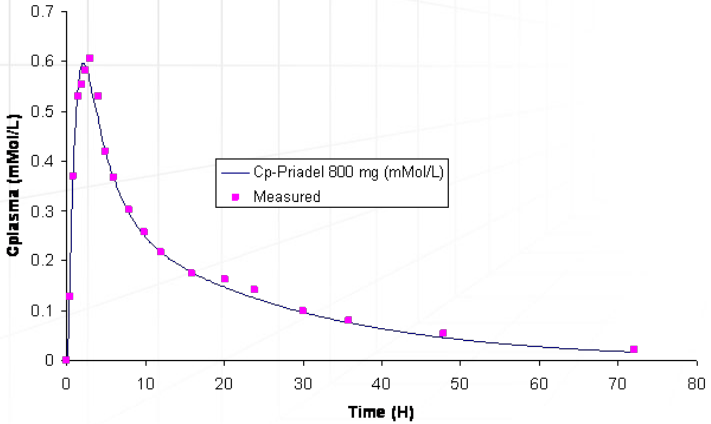
Good solubility and good permeability except in the colon

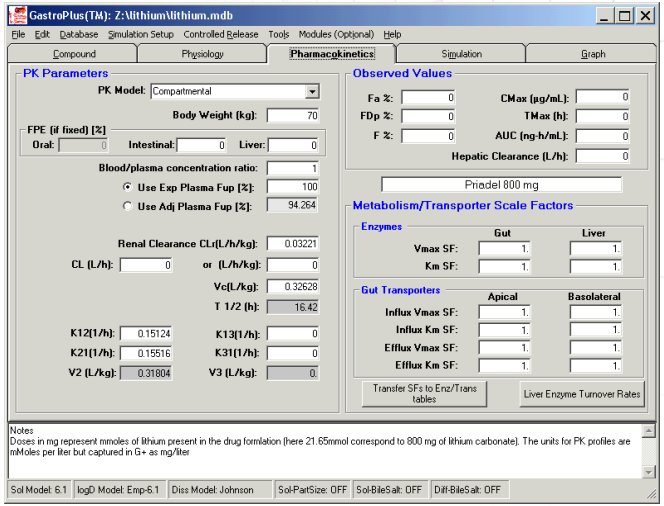
http://www.icrp.org/publication.asp?id=ICRP%20Publication%20110

GastroPlus model setup

Priadel 2 x 400 mg profile used to set up the PK model

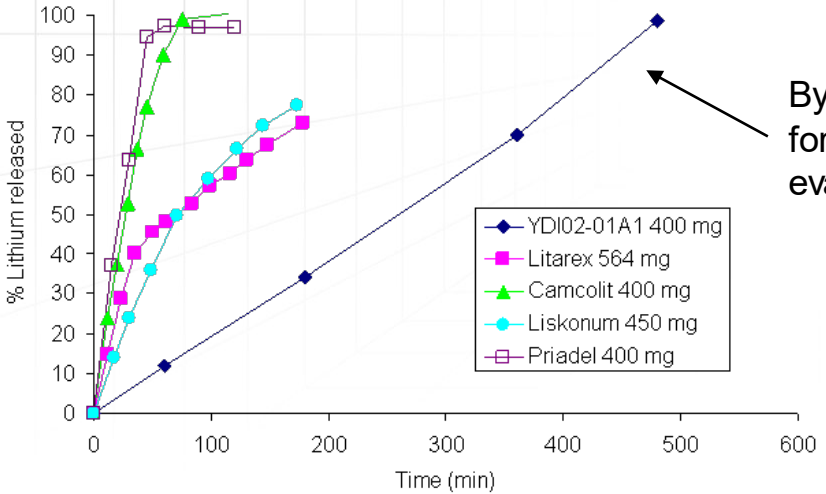
- GastroPlus™ V7, ASF model 6.1, Human fasted physiology
- Lithium is excreted by the kidneys with no metabolism
- Fit of Vd, k12, k21 & CLR to observed PK profile





GastroPlus model validation

Direct IVIVC: Dissolution data integrated with a Weibull function
All 5 formulations below were tested in the clinic
Some are IR with one MR : Assumption for BCS1 = In vitro dissolution is representative of in vivo dissolution

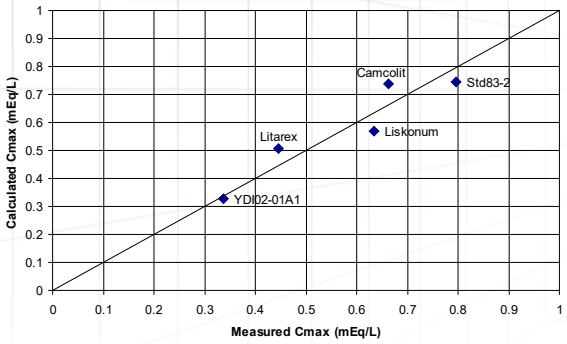


By chance a slow release formulation of lithium that was evaluated in human in 2001 !

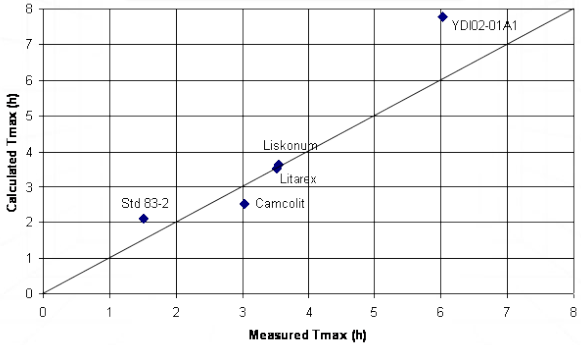
GastroPlus model validation

Prediction errors were below 10% for AUC and C_{max}, assumption for CRD is verified

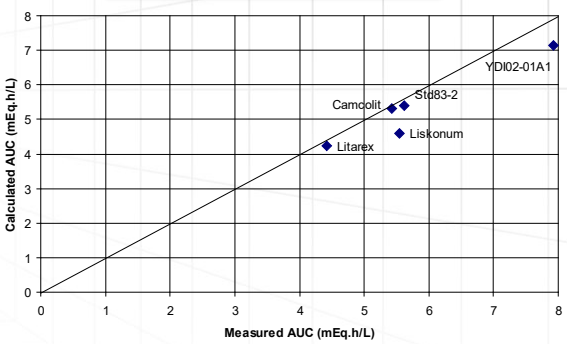
9% error on Cmax



18% error on tmax

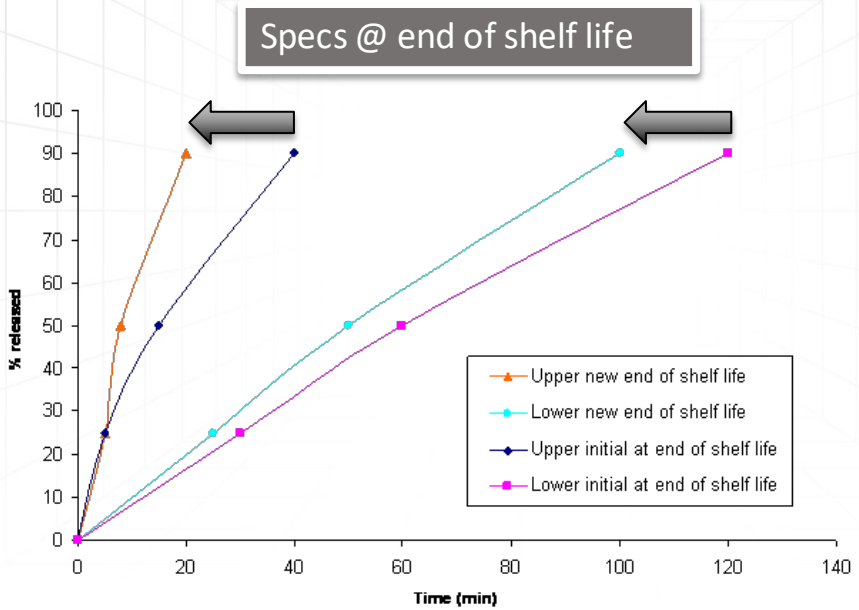


7% error on AUC



GastroPlus model use

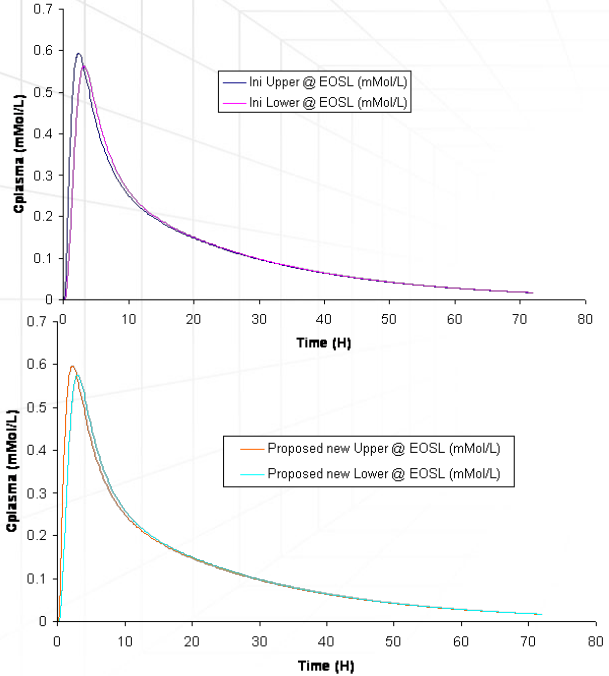
Evaluation of old and new proposed specifications



Virtual batches dissolving at the specifications were used in the model

GastroPlus model results

Evaluation of old and new proposed specifications at end of shelf life



With new proposed specs, DP at end of shelf life are bioequivalent to one another and ratios are closer to 1

PK parameter	Upper/lower	Lower/upper
AUC ratio	1.01	0.99
C_{max} ratio	1.05	0.95
T_{max} ratio	0.73	1.36

PK parameter	Upper/lower	Lower/upper
AUC ratio	1.01	0.99
C_{max} ratio	1.04	0.96
T_{max} ratio	0.75	1.33

New proposed specs, are more restrictive !

Priadel 200 mg conclusion

Variation dossiers submitted to UK and Irish authorities
Positive reply in spring 2012

Safeguarding public health

MHRA

Ms H McKenzie
AVENTIS PHARMA LIMITED
ONE ONSLOW STREET
GUILDFORD
SURREY
GU1 4SY
UNITED KINGDOM

29/06/2012

Dear McKenzie,

APPROVAL

Our Reference:	PL 04425/0322 - 0024
Your Reference:	04425
Product:	Priadel 200
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Standard
EU Procedure Number (if applicable):	
Reason:	To update the limits of dissolution test at shelf life specification to limits outside the approved range. Additionally, a minor change is made to the finished product dissolution test procedure.

The Licensing Authority agrees to the above submission(s), including any replacement and amendment pages of the original that were provided with your written request.

The approval date is 29/06/2012.

Please retain this letter with the formal documents relating to the Marketing Authorisation/Registration as evidence of approval.

All Marketing Authorisations/Registrations are subject to standard provisions contained in current medicines regulations, full details of which are published on the MHRA website:
http://medicines.mhra.gov.uk/ourwork/licensingmeds/licensingmeds.htm

Yours sincerely,

MHRA

Medicines and Healthcare products Regulatory Agency
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An executive agency of the Department of Health

PL 04425/0322 - 0024

Approval - Page 1 of 1

No batch is discarded

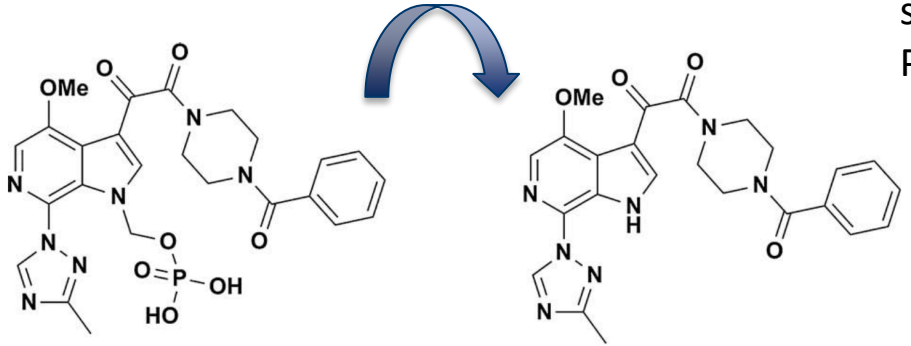
Easier production, storage, release management

BMS-663068 - Guide formulation design

Drug name	BMS-663068 (highly soluble HIV-1 attachment inhibitor phosphate ester prodrug)
Literature references	I. Brown J, Chien C, Timmins P, Dennis A, Doll W, Sandefer E, Page R, Nettles RE, Zhu L, Grasela D. Compartmental absorption modeling and site of absorption studies to determine feasibility of an extended-release formulation of an HIV-1 attachment inhibitor phosphate ester prodrug. Journal of Pharmaceutical Sciences. 2013;102(6):1742-1751. II. Stillhart C, Pepin X, Tistaert C, Good D, Van Den Bergh A, Parrott N, Kesisoglou F. PBPK Absorption Modeling: Establishing the In Vitro–In Vivo Link—Industry Perspective. The AAPS Journal. 2019;21(2)
Purpose of the model	Define the target quality attributes of an MR formulation to reach the desired PK profile
BCS class	3
Compound nature	crystalline
pKa values (A or B)	NR
Log P or log D at pH	1.7 at pH 6.5
Clinical reference	MR matrix tablets
Variants	IR and several MR matrix formulations
Dose or dose range (mg)	600 mg
Change to default absorption model	ASF and transit time were fitted to individual subjects using site of absorption study
Dissolution method (s) used	USP type 1 apparatus, 100 rpm, pH 6.8 phosphate buffer
Integration of dissolution in PBBM	Data fitted with Weibull
Model outcome	PBBM was refined and used to design commercial formulation based on CBAs

Mechanism of absorption

Alkaline phosphatase (epithelial surface)



Pro-drug

BMS-663068

BMS-626529

Active moiety, short half life, solubility limitation to absorption

P_{eff} = 1.34 10^{-4} cm/s

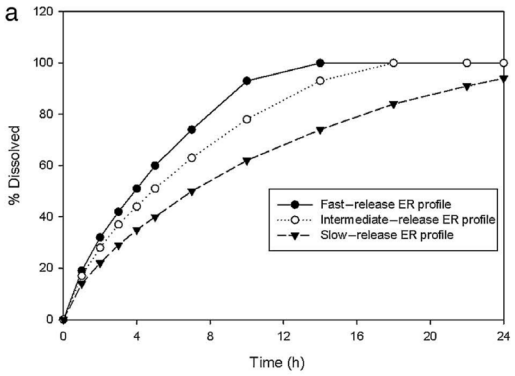
Lower GI tract absorption ?

Human GI tract absorption study
Parameterize the ASF in GastroPlus

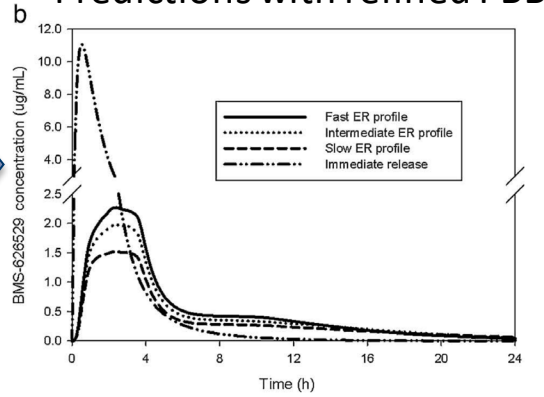
Feasibility of an ER formulation (600 mg pro-drug) to extend duration of action (C_{trough}) and limit C_{max}

Initial IVIVC study

In vitro



Predictions with refined PBBM



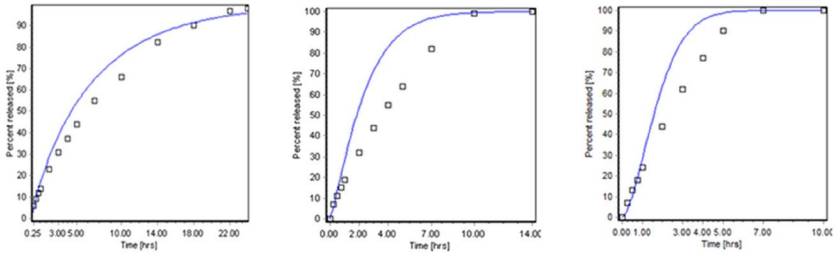
Initial IVIVC : Discrepancy between in vivo and in vitro dissolution → large difference in profiles & release mechanisms. Used to identify CBA for target matrix tablets : Surface to volume ratio and drug to polymer ratio

Table 4. Model-Predicted (Pred.) Versus Observed (Obs.) Parameters Following Delivery of 600 mg BMS-663068 as Fast-, Intermediate-, and Slow-Releasing Extended-Release Tablets

		Extended-Release Tablet Formulation		
Pharmacokinetic Parameter		Fast	Intermediate	Slow
C_{max} (μg/mL)[a]	Pred. (n = 8)	2.20 (28)	1.92 (28)	1.48 (28)
	Obs. (n = 15)	5.21 (29)	4.41 (31)	1.81 (56)
$AUC_{(0-T)}$ (μg h/mL)[a]	Pred. (n = 8)	12.68 (24)	11.33 (23)	9.12 (22)
	Obs. (n = 15)	21.41 (34)	18.96 (29)	9.42 (50)
C_{12} (μg/mL)[a]	Pred. (n = 8)	0.31 (40)	0.27 (42)	0.21 (42)
	Obs. (n = 15)	0.13 (54)	0.16 (84)	0.09 (69)

[a]Geometric mean (CV%)

In vitro — In vivo

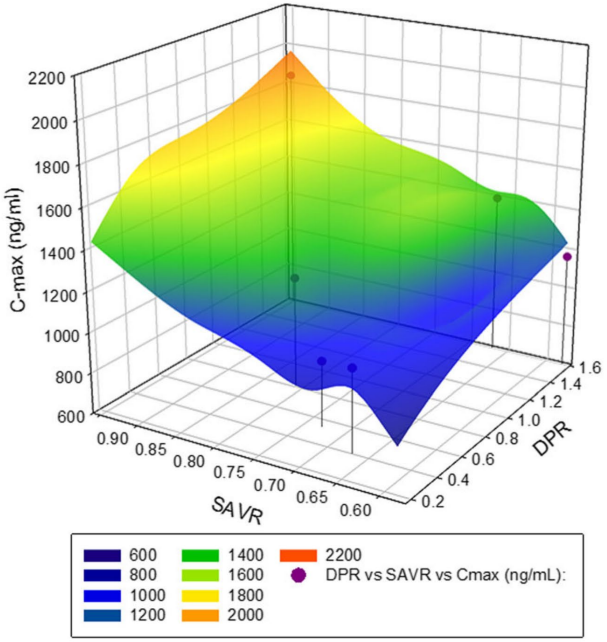


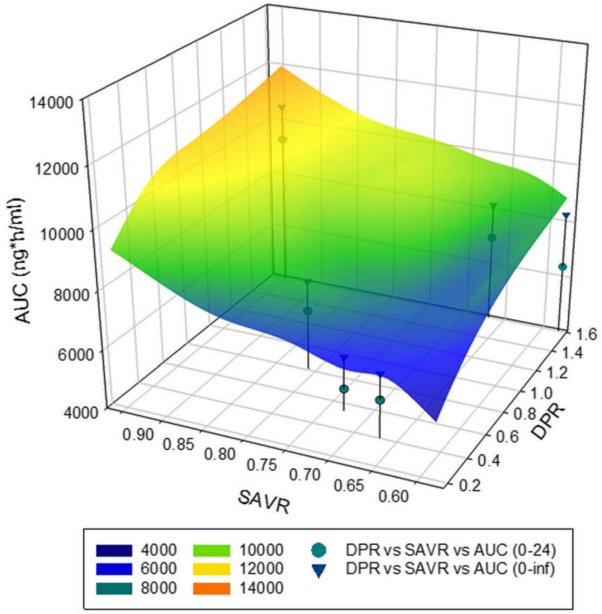
Definitive IVIVC study

New formulation variants centered around the commercial tablet
2 CBAs : Surface to volume ratio and drug to polymer ratio

Simulation with GastroPlus *

Just in time manufacture for adaptative clinical trial





* In vitro clinically relevant methodology or refined PBBM

BMS-663068 : PBBM Conclusions

- PBBM allowed integration of site of absorption study to refine absorption prediction along the GI tract (model set-up)
- PBBM allowed to gain a mechanistic understanding of the in vivo release mechanisms and difference with in vitro release
  - → optimization of the in vitro release to be clinically relevant
  - → Understanding of the drug product CBAs
- Once the link between in vitro and in vivo is established, PBBM can be used to define formulation design space (s) and verified with just in time manufacture for adaptative clinical trials
- Data has been used to set and justify release specifications which are within a safe space for the product

Take home messages

- PBBM can be used alongside more classical IVIVC to determine safe space
- Drug product dissolution can be integrated in a mechanistic way or not (time based)
- Link between in vitro performance (dissolution) and in vivo PK establishes the clinical relevance of the dissolution method
- PBBM allows to gain understanding of the failure modes of the formulation
- PBBM use can span multiple usages from specification justification to post approval changes.
- The safe space establishment is integral to enabling these changes
  - Sensitivity analysis, Virtual BE main tools to define limits

Thanks