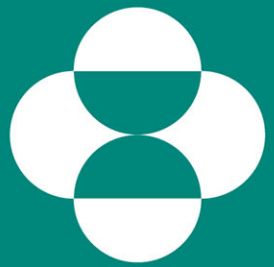
APPROACHES FOR ENTERING DISSOLUTION INTO THE ABSORPTION MODEL

REASONS FOR SELECTION, MODEL ASSUMPTIONS, AND PARAMETER ESTIMATION STRATEGIES

Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls Workshop, College Park, MD



MERCK

INVENTING FOR LIFE

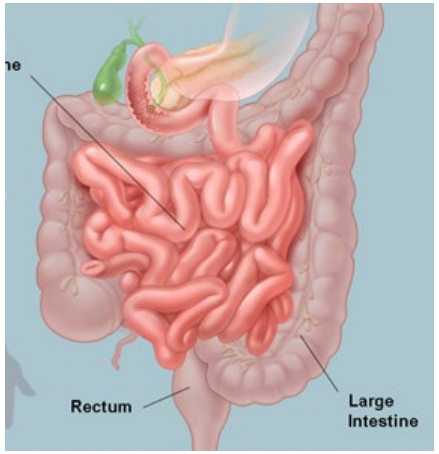
Filippos Kesisoglou, PhD, FAAPS
Biopharmaceutics and Specialty Dosage Forms, Pharmaceutical Sciences
Merck & Co., Inc., Kenilworth, NJ, USA

Outline

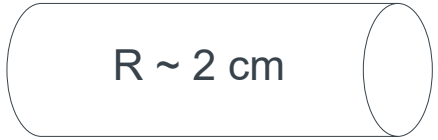
1. What are the approximations/assumptions needed
2. Importance of dissolution input for PPBM models
3. Approaches to incorporate dissolution data for IR drug products
   a. Approaches for IR products – Direct dissolution input, Empirical functions, “Semi-mechanistic” models
   b. Pros and cons for each approach
   c. Why it’s important to select dissolution model structure prior to validating the model - Can PK be really used to validate the dissolution model?
4. Approaches for ER products – towards IVIVCs
5. Summary

MERCK
INVENTING FOR LIFE

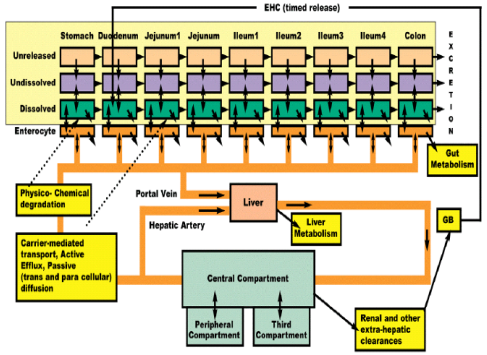
Level Setting on Approximations

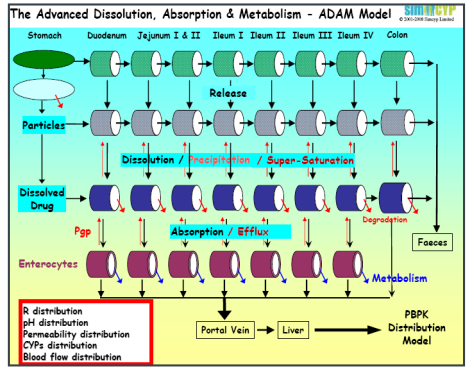


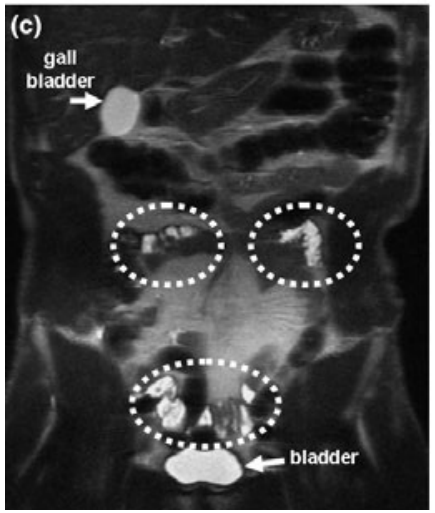
~



~







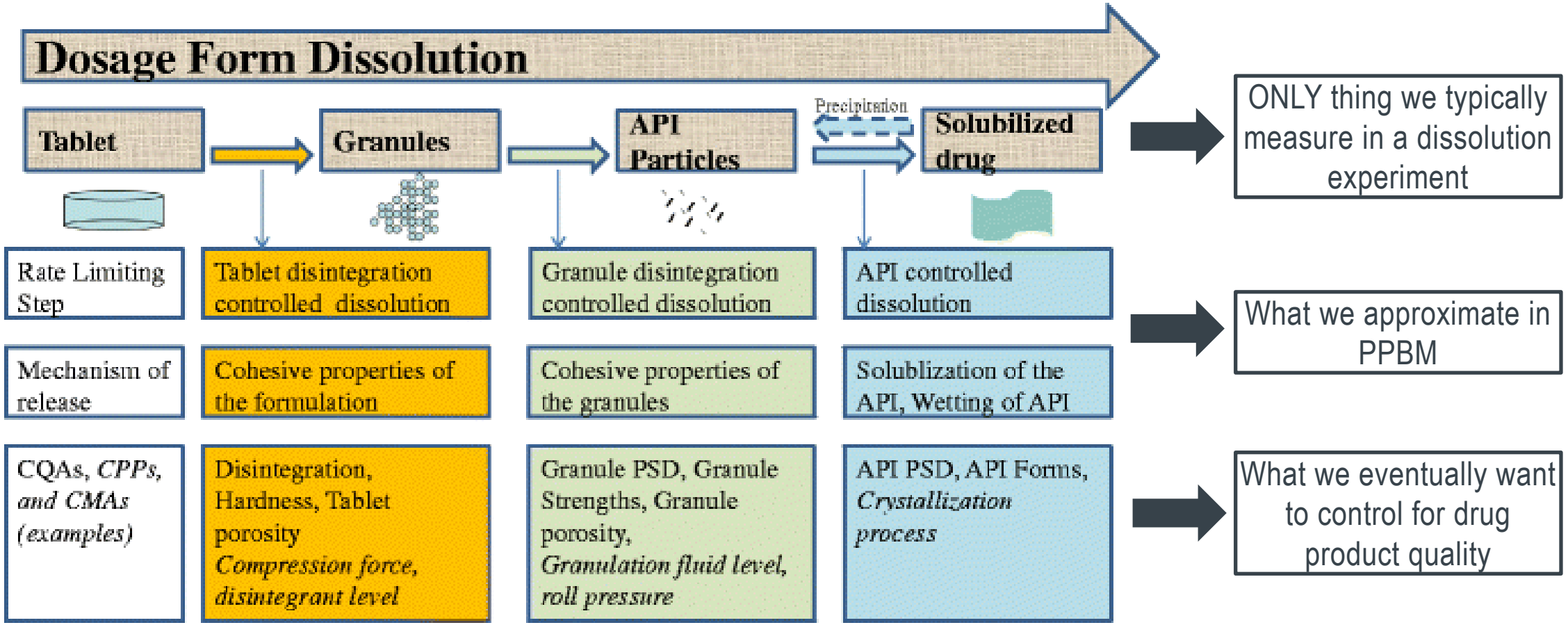
~

250 – 900 mL

~

MERCK
INVENTING FOR LIFE

Dissolution Can Be Rate Limited at Different Steps

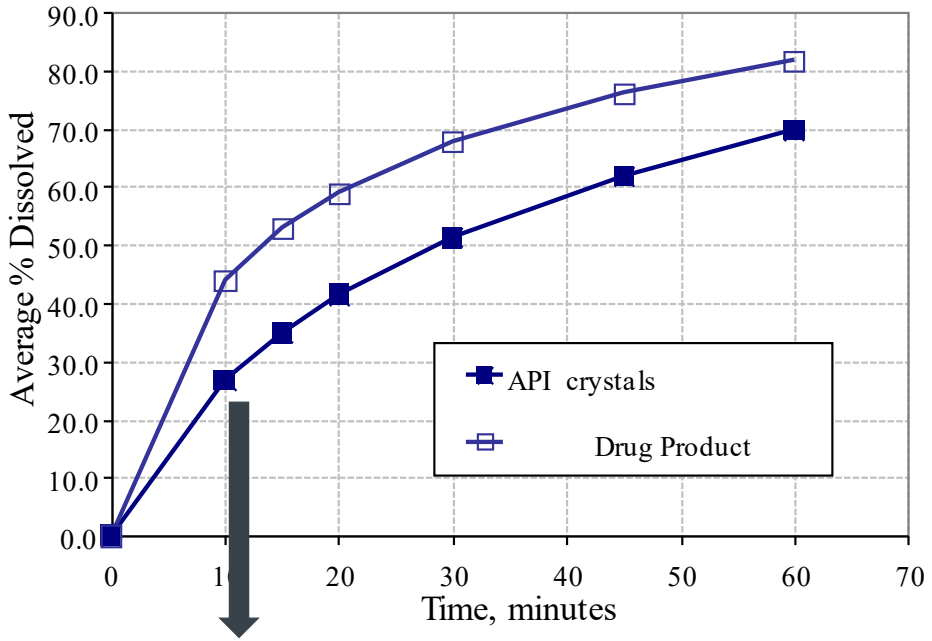


Hermans A, Abend AM, Kesisoglou F, Flanagan T, Cohen MJ, Diaz DA, Mao Y, Zhang L, Webster GK, Lin Y, Hahn DA, Coutant CA, Grady H. Approaches for Establishing Clinically Relevant Dissolution Specifications for Immediate Release Solid Oral Dosage Forms. AAPS J. 2017 Nov;19(6):1537-1549.

MERCK
INVENTING FOR LIFE

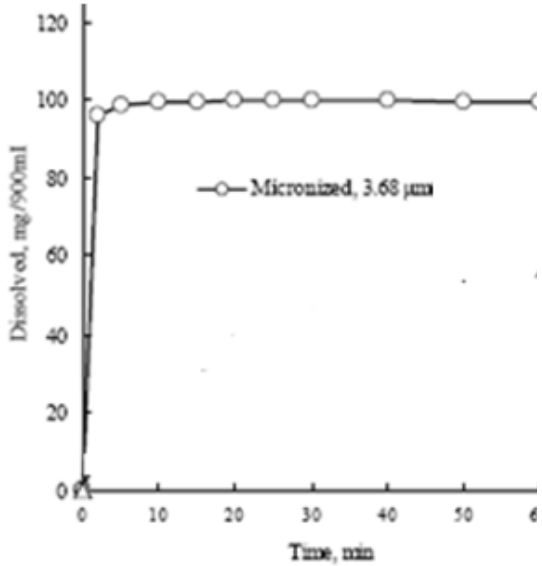
Primary API PSD Seldomly Reflects Formulation Dissolution

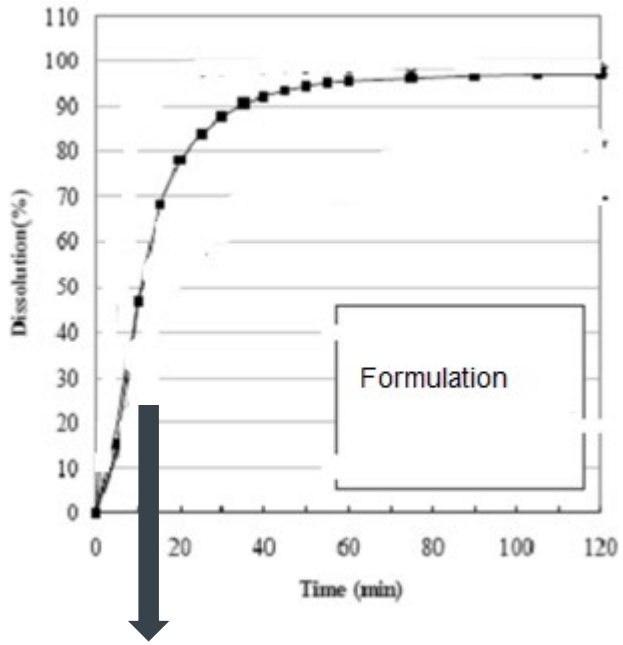
Solubility ~ 135 µg/mL across physiologic pH range
Formulation: API with “Standard” Excipients in Capsules



Crystal breakage during encapsulation results in faster dissolution profile

Solubility ~ 135 µg/mL across physiologic pH range
Formulation: API with “Standard” Excipients in Capsules





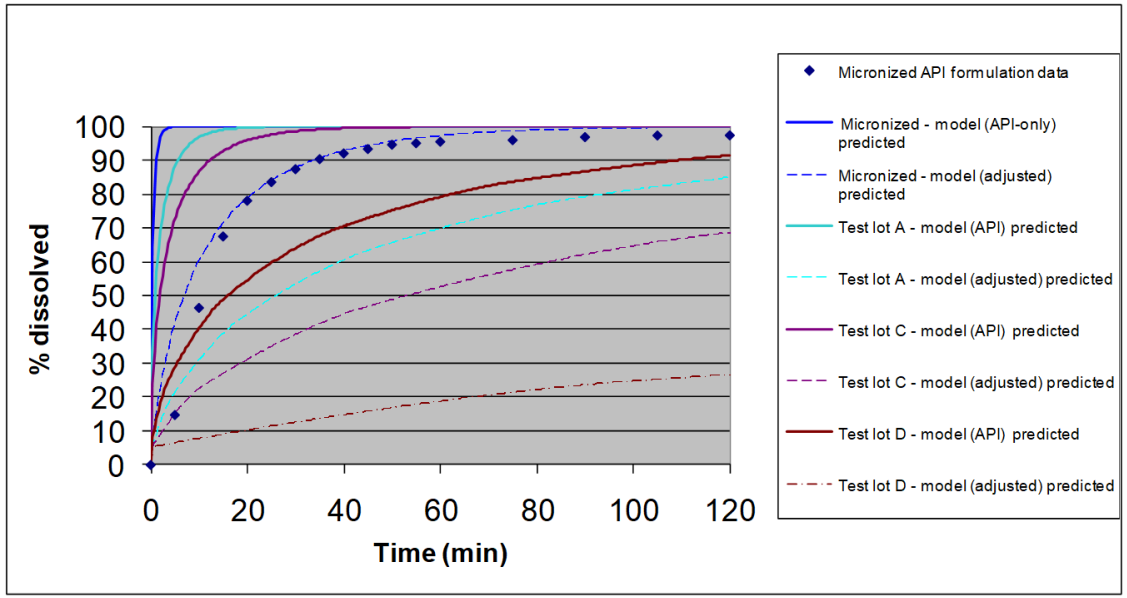
Tablet dissolution significantly slower than micronized API

While many publications use primary API PSD as input, for the most part it is not meaningful for PBBM applications for drug product quality

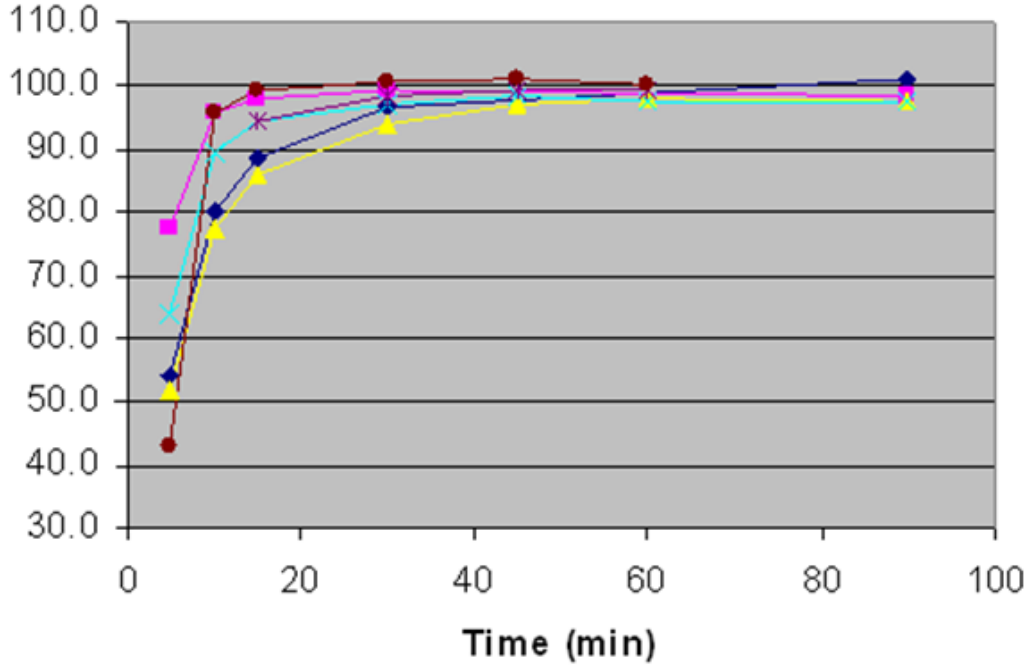
P. Rajniak, AIChE Annual Meeting, 2007
Kesisoglou F, IQPC BE-BA, 2011

MERCK
INVENTING FOR LIFE

Using Primary API PSD for Parameter Sensitivity Also May Not Be Meaningful



Model predicted dissolution as a function of increasing API PSD

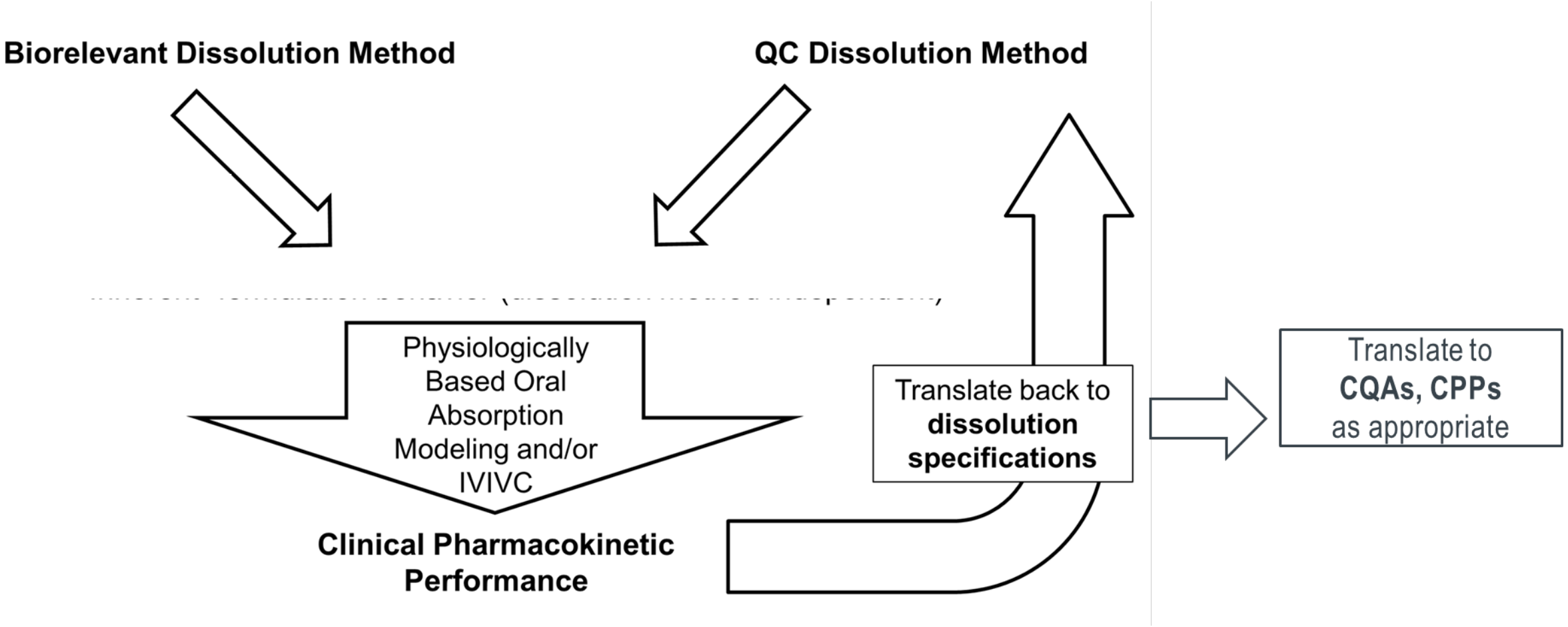


Observed tablet dissolution across API PSD

Current "First Principle" Models Cannot Fully Mechanistically Account for Formulated API

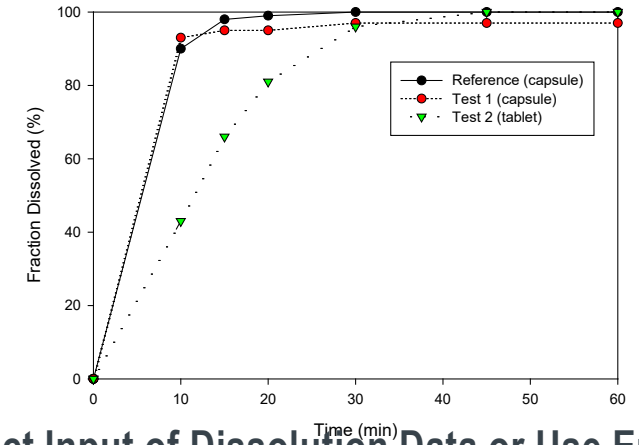
And that's OK !!! We just need to model around this

Input of Dissolution Data is Only Meaningful Way to Setup Models for Drug Product Quality

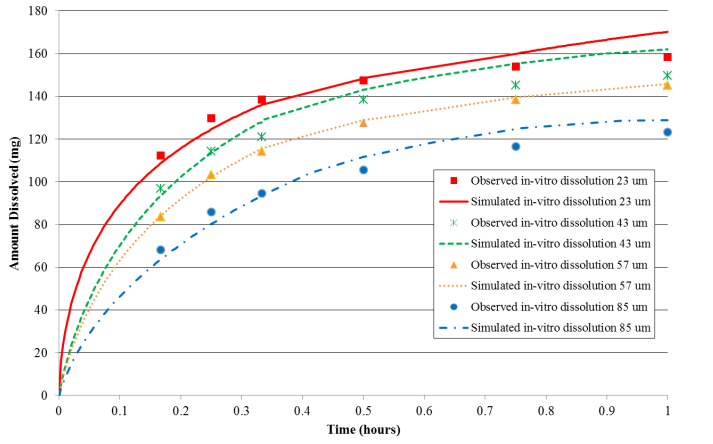


Kesisoglou F. The Role of Physiologically Based Oral Absorption Modelling in Formulation Development Under a Quality by Design Paradigm. J Pharm Sci. 2017 Apr;106(4):944-949.

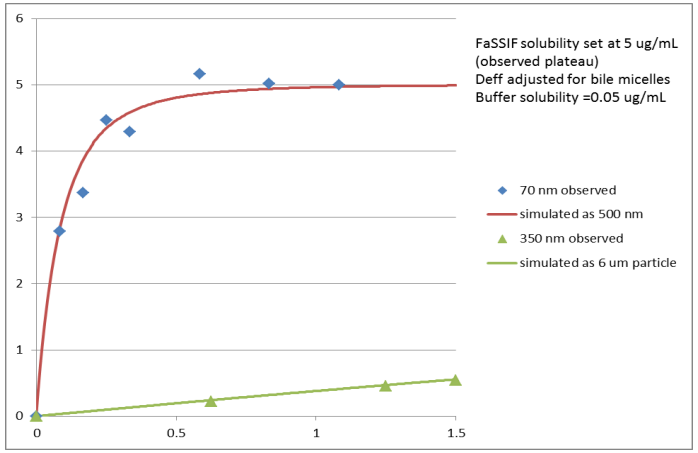
There Is No One-Size-Fits-All Approach to Entering Dissolution Data



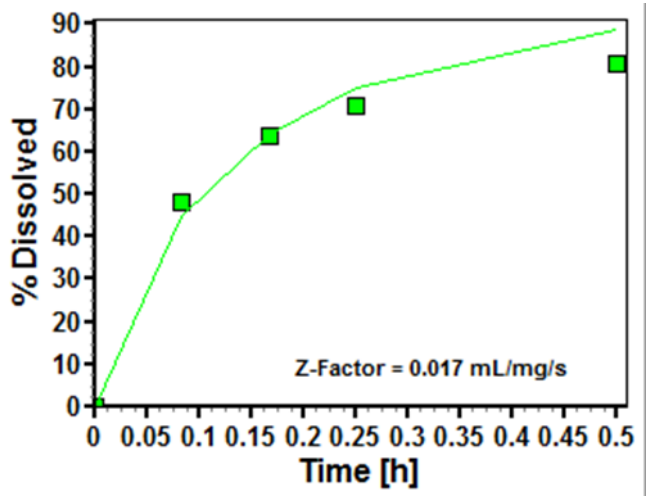
Direct Input of Dissolution Data or Use Empirical Function (i.e. 1-1 IVIVC)



Use API-PSD model incorporating a scaling correction factor



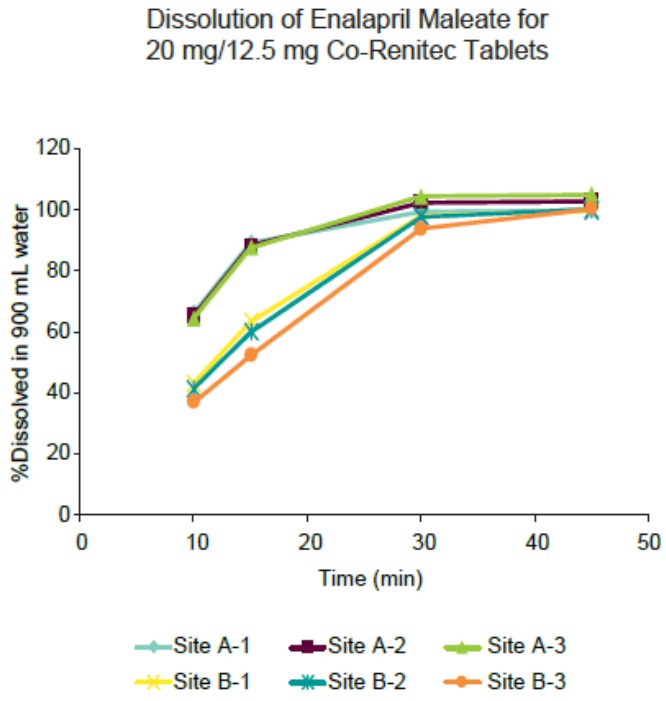
Estimate an "Effective" PSD from Dissolution Data



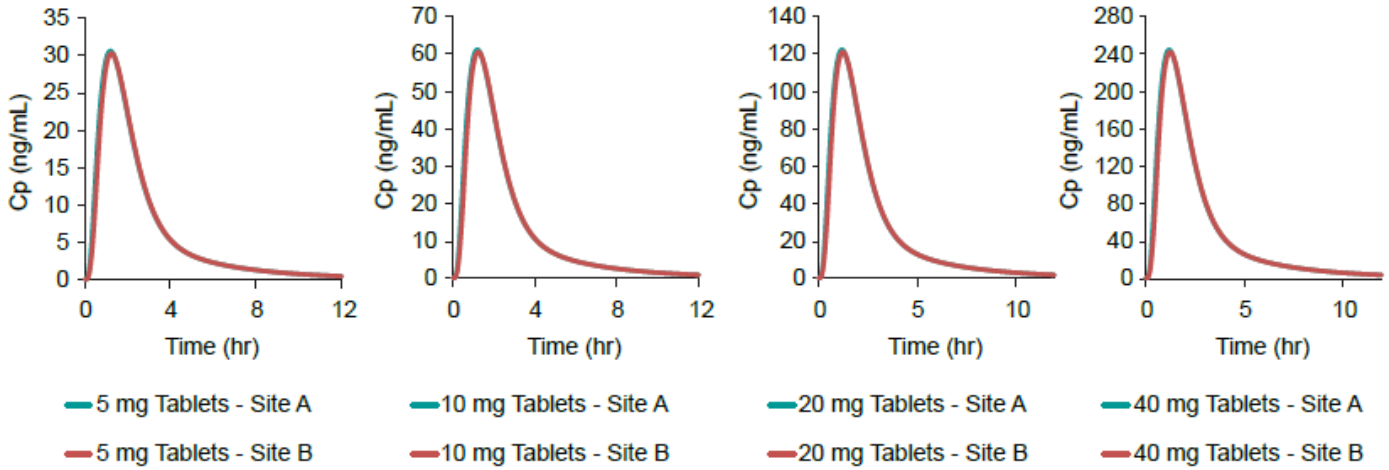
Use a composite dissolution parameter (z-factor)

MERCK
INVENTING FOR LIFE

Case Example: Direct Input for BE Projections for a BCS III API

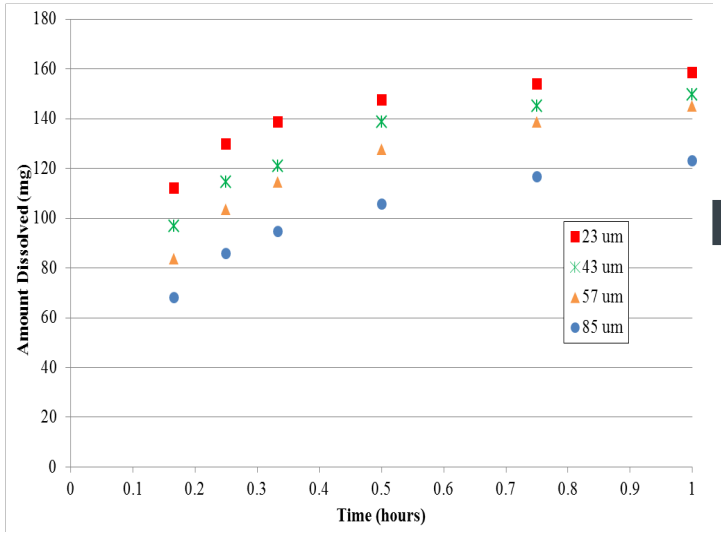


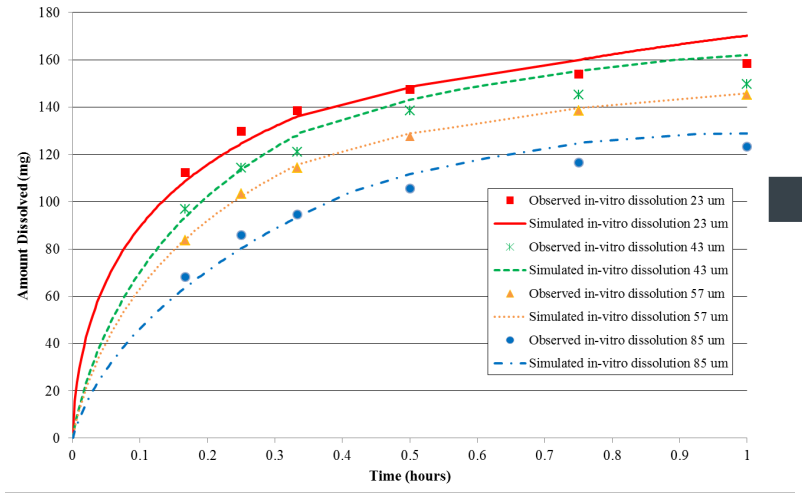
Note: F2 values of 34, 32, 28, 36, 33, 29, 36, 34, 29 in 3 versus 3 batches comparison between the formulations of these two sites.



Zhu W & Kesisoglou F, 4th FDA/PQRI Conference on Advancing Product Quality, 2019

Case Example: Dissolution Scalar(s) to Study API PSD PK Impact

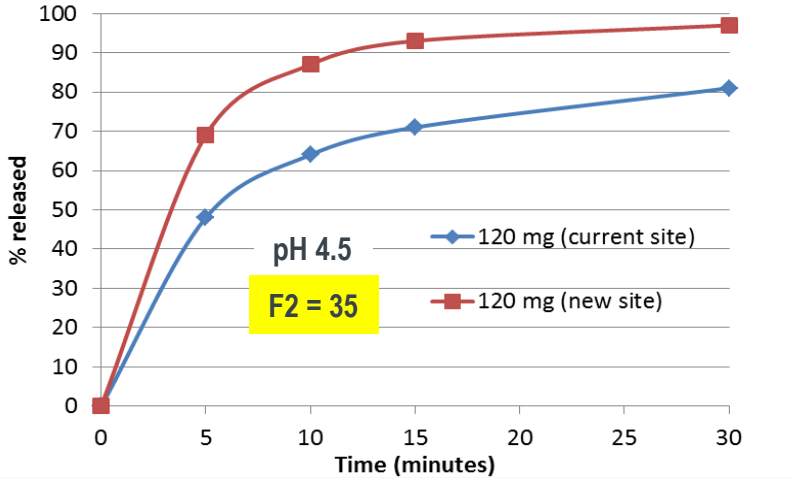


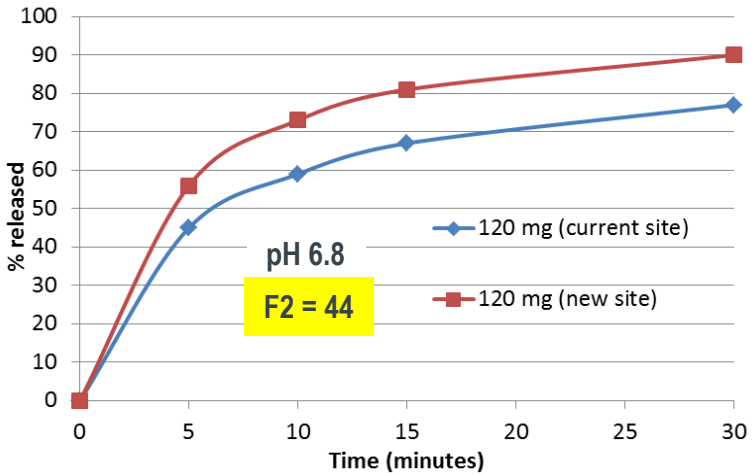


	200 mg			400 mg			800 mg		
	AUC (μg×h/mL)	C_{max} (μg/mL)	$C_{12\,h}$ (μg/mL)	AUC (μg×h/mL)	C_{max} (μg/mL)	$C_{12\,h}$ (μg/mL)	AUC (μg×h/mL)	C_{max} (μg/mL)	$C_{12\,h}$ (μg/mL)
Phase I suspension (35 μm)	2.12	0.87	0.011	6.26	1.49	0.018	9.32	2.79	0.026
23 μm	3.18 (1.5)	0.98 (1.1)	0.012 (1.1)	6.39 (1.0)	1.67 (1.1)	0.019 (1.1)	12.00 (1.3)	2.75 (0.9)	0.028 (1.1)
43 μm	2.91 (1.4)	0.90 (1.0)	0.011 (1.0)	5.76 (0.9)	1.54 (1.0)	0.019 (1.1)	10.40 (1.1)	2.39 (0.9)	0.028 (1.1)
57 μm	2.83 (1.3)	0.88 (1.0)	0.010 (0.9)	5.62 (0.9)	1.50 (1.0)	0.018 (1.0)	9.72 (1.0)	2.21 (0.8)	0.027 (1.0)
85 μm	2.32 (1.1)	0.76 (0.9)	0.010 (0.9)	4.97 (0.8)	1.25 (0.8)	0.016 (0.9)	7.29 (0.8)	1.64 (0.6)	0.025 (0.9)

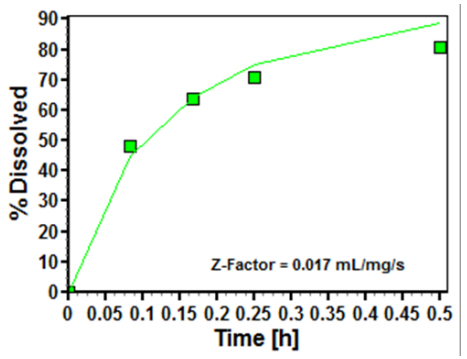
Kesisoglou F, Mitra A. Application of Absorption Modeling in Rational Design of Drug Product Under Quality-by-Design Paradigm. AAPS J. 2015 Sep;17(5):1224-36.

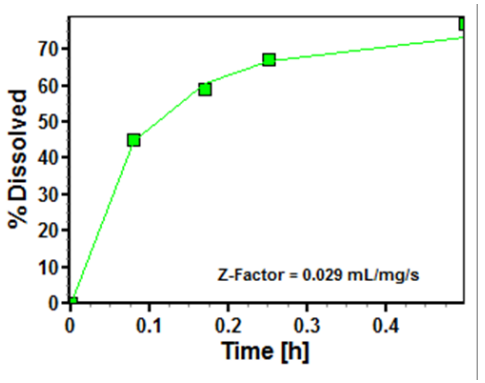
Case Example: Z-factor for a Site Change for a BCS II API





Observed Multimedia Dissolution Data (pH 2.0 Not Shown As Profiles Superimposable)





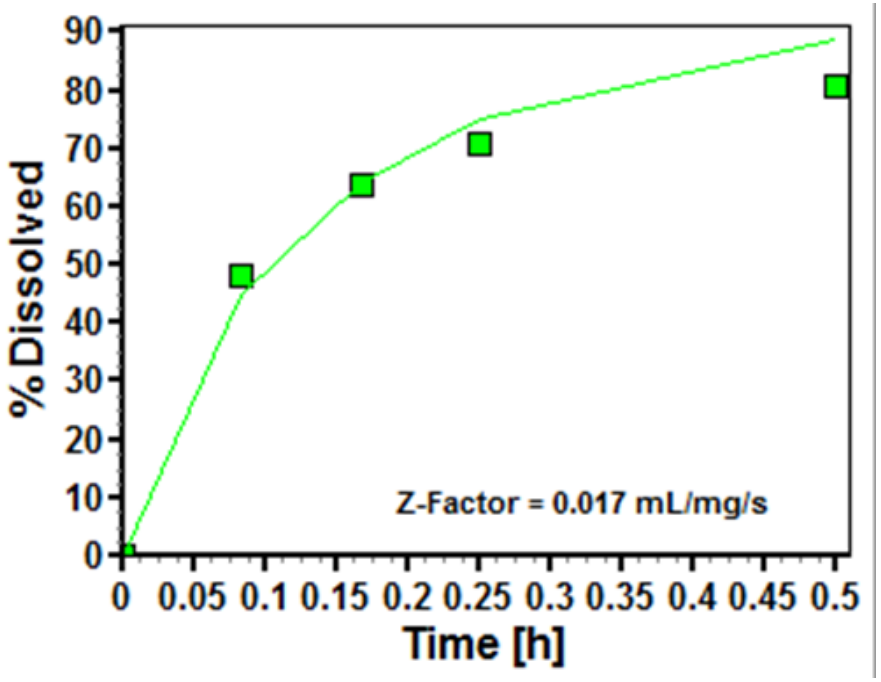
	$AUC_{0-120hr}$ (%CV)	C_{max} (%CV)	Relative $AUC_{0-120hr}$	Relative C_{max}
Dissolution in pH 4.5				
120 mg (current site)	34.4 (16.3%)	1.65 (15.3%)	--	--
120 mg (new site)	35.8 (15.3%)	1.82 (14.4%)	1.04	**1.10**
Dissolution in pH 6.8				
120 mg (current site)	30.8 (17.2%)	1.50 (18.6%)	--	--
120 mg (new site)	**34.1 (15.1%)**	**1.71 (19.1%)**	**1.11**	**1.14**

Similar Dissolution Fit and BE Predictions Obtained if a Scalar (Deff multiplier) is Used

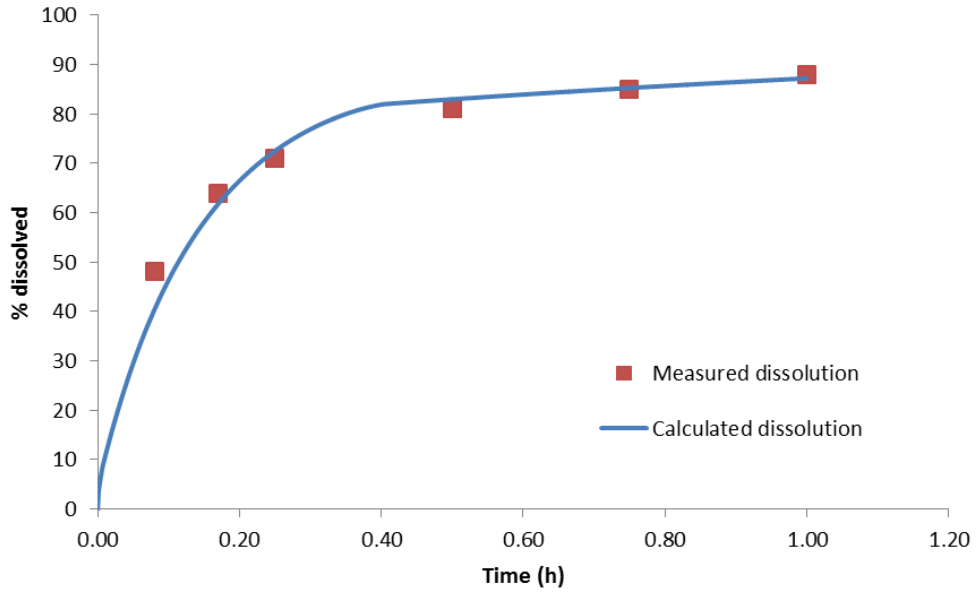
MERCK
INVENTING FOR LIFE

Mitra A, Kesisoglou F, Dogterom P. Application of absorption modeling to predict bioequivalence outcome of two batches of etoricoxib tablets. AAPS PharmSciTech. 2015 Feb;16(1):76-84.

“Effective” PSD Improves Fitting of Dissolution Profile



Z-factor Fit

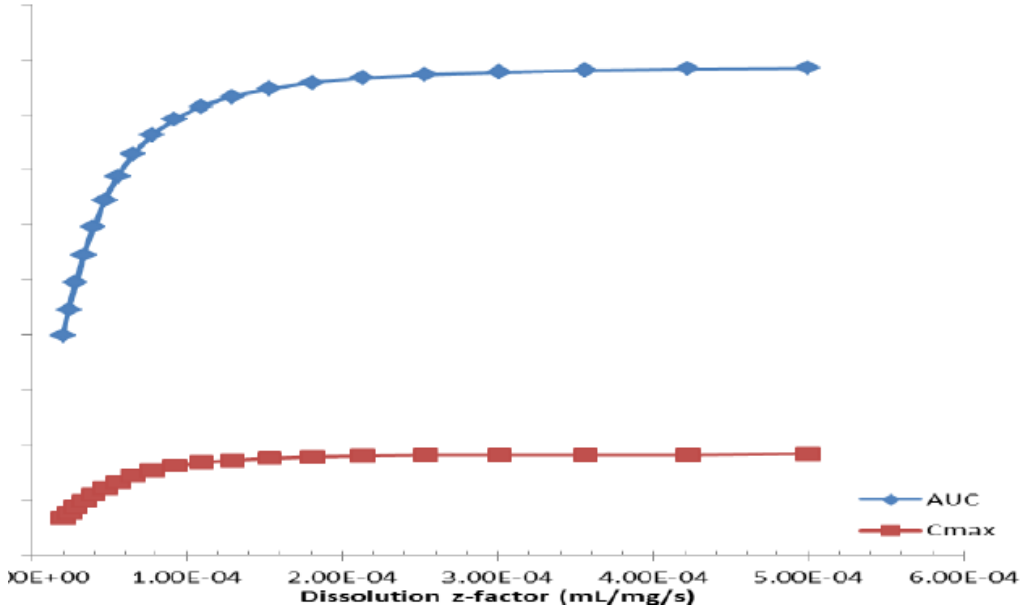


“Effective” PSD*

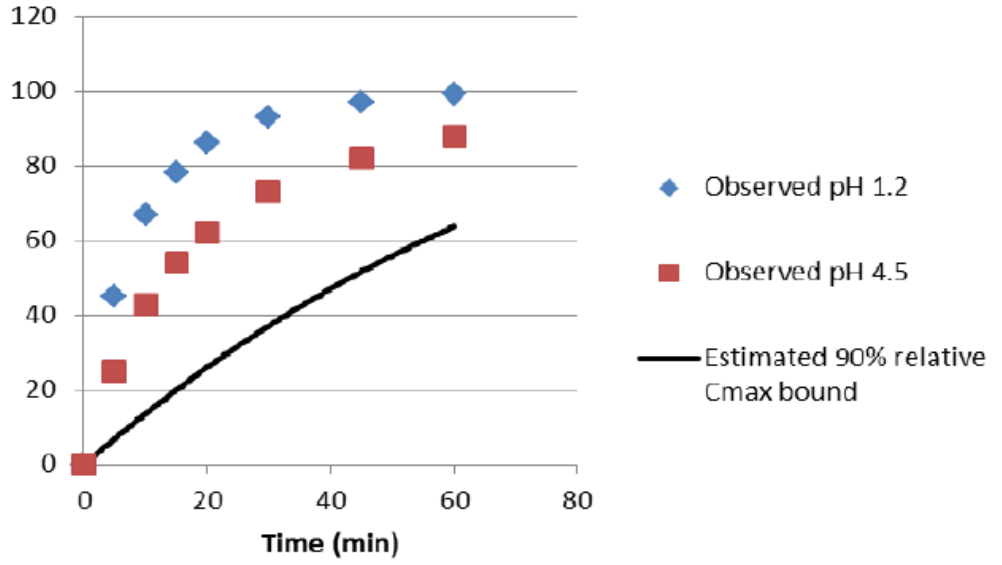
* Based on model by Pepin XJH, Sanderson NJ, Blanazs A, Grover S, Ingallinera TG, Mann JC. Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part I. Mechanistic modelling of drug product dissolution to derive a P-PSD for PBPK model input. Eur J Pharm Biopharm. 2019 Jul 12.

MERCK
INVENTING FOR LIFE

Case Example - Assessing Dissolution Safe Space for a Highly Soluble API



Sensitivity of AUC and Cmax to dissolution rate (z-factor)

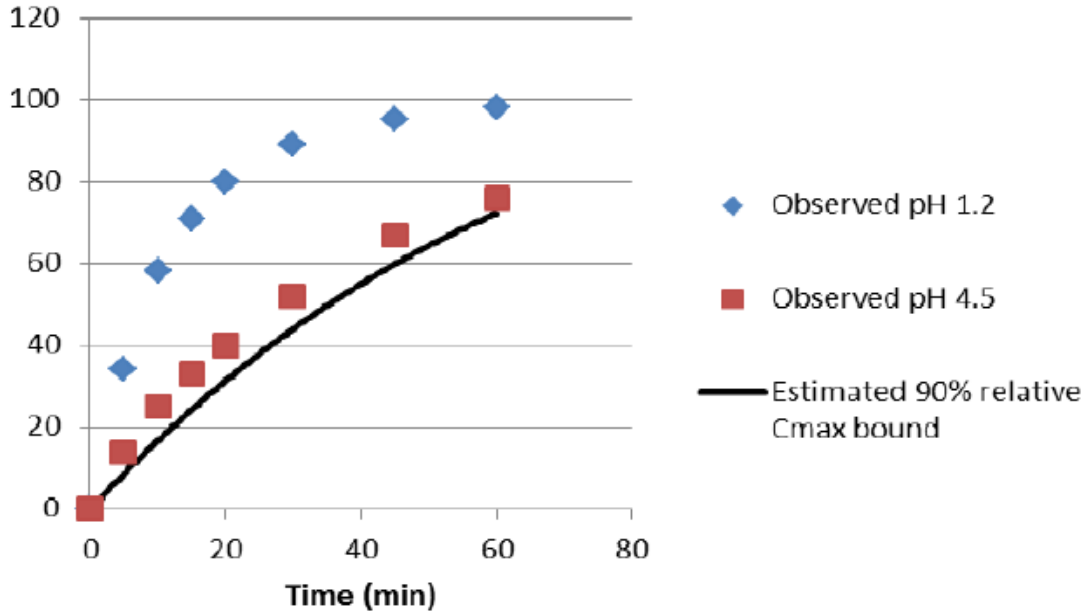


Estimated dissolution safe space

Z-factor allows for efficient exploration of "safe space"

MERCK
INVENTING FOR LIFE

Direct Input vs. Using a Dissolution Model May Not Be Very Different for Highly Soluble APIs



pH 4.5 Test	AUC ratio	Cmax ratio
Direct Input	0.99	0.93

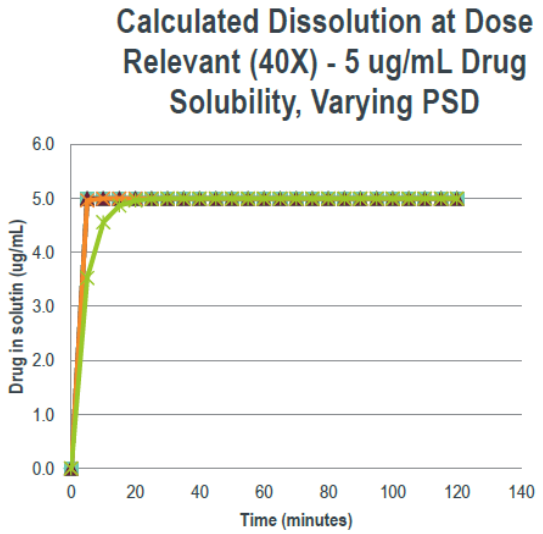
MERCK
INVENTING FOR LIFE

What Are the Pros/Cons of Each Input Method?

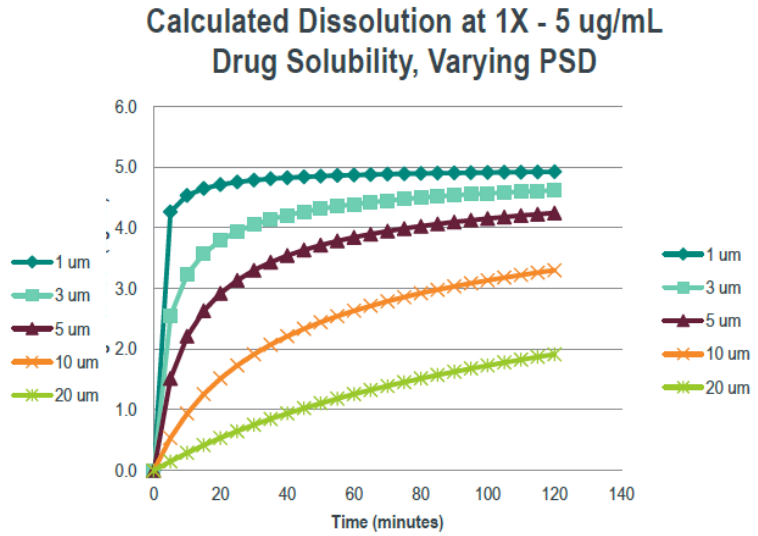
	Pros	Cons
Direct Input	No additional fitting required	Likely not physiologically meaningful with potential exception of BCS I/III
Empirical functions (e.g. Weibull)	Could be used for sensitivity analysis assuming 1:1 IVIVC	Likely not physiologically meaningful with potential exception of BCS I/III
API PSD with Single Correction Scalar	Can allow for linking back to API PSD for specifications if single scalar used across different API PSD profiles	Limited flexibility in fitting different shapes of dissolution profiles
Composite parameter (e.g. Z-factor)	Very flexible for parameter sensitivity analysis and to explore hypothetical dissolution space	Limited flexibility in fitting different shapes of dissolution profiles – often challenging to capture both rise and plateau of dissolution
Fit dissolution data to “effective” PSD	Very flexible to fit different shapes of dissolution profiles	Likely not a unique solution (not a major concern if used for BE projection of specific batch)

Use of Biorelevant Dissolution Data for BCS II/IV Compounds

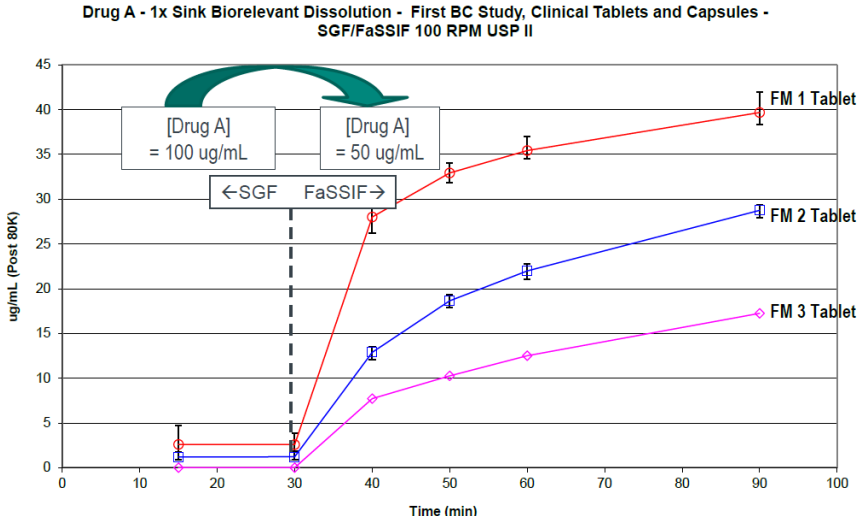
- There is no doubt that biorelevant solubilities are absolutely needed for PBBM
- However incorporation of biorelevant dissolution data may require additional experimentation
- For majority of BCS II/IV compounds, biorelevant dissolution is not adequate to capture behavior of full dosage form



Dosage Form Dissolution Only Reflects Behavior of Very Small Portion of Total Dose



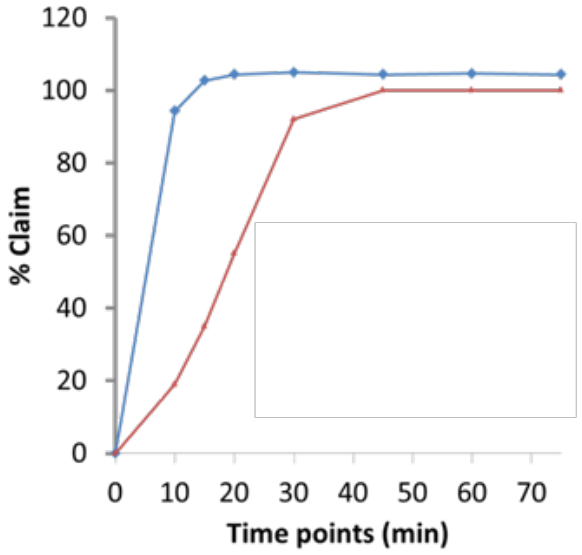
Additional experimentation needed to capture behavior of entire formulation

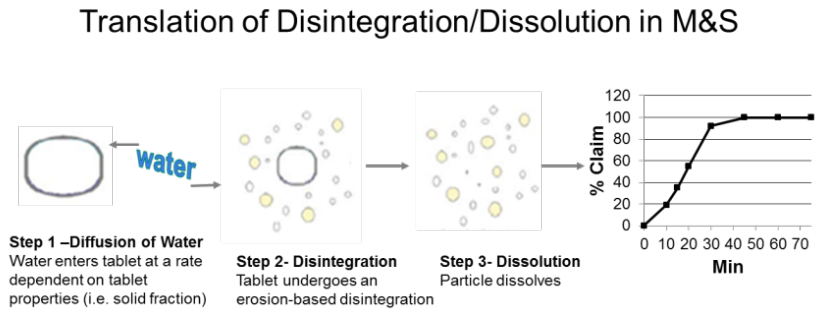


All three formulations are superimposable if full tablet is used. Human exposure is 6-fold different.

Kuiper J, Use of Biopredictive Methods during Early Formulation Screening, Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development MCERSI workshop, 2017

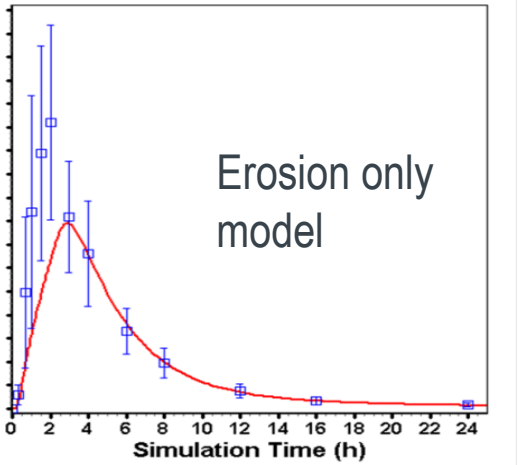
May Also Need to Account for Tablet Erosion

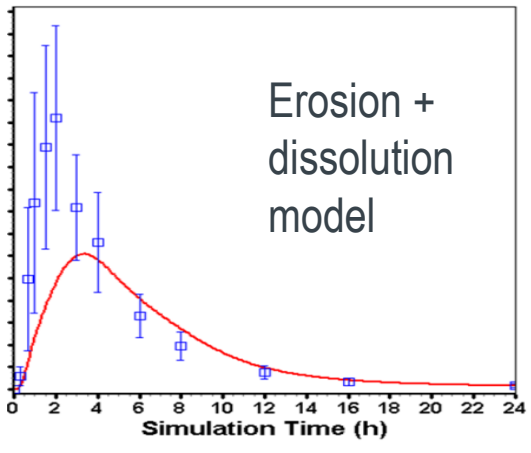




Model 1: Dissolution curve reflects erosion. At each point small particles (2um) generated that dissolve based on solubility

Model 2: Release of API particles is captured by erosion process (% eroded vs. time). Particles generated subsequently dissolve to give the resulting dissolution curve (probably more mechanistically correct model)

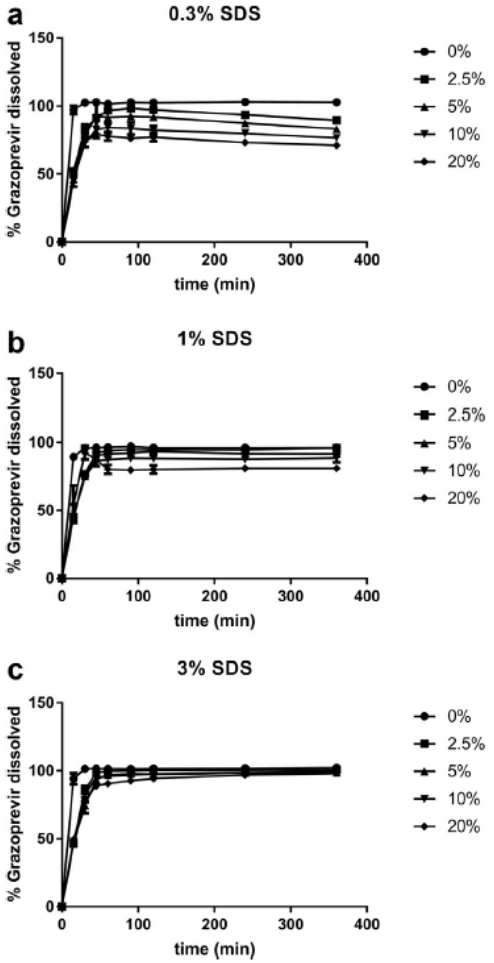




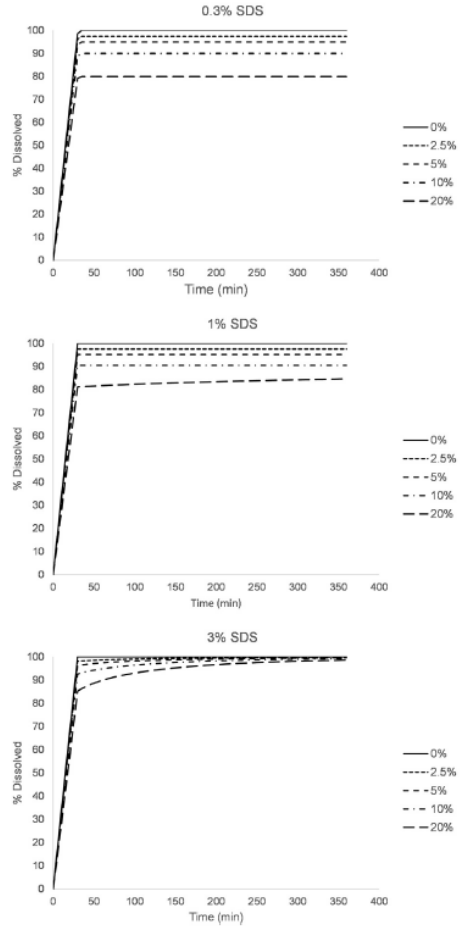
MERCK
INVENTING FOR LIFE

Dissolution Input to Study Multiple API Forms (e.g. crystallinity in ASDs)

- Dissolution modeling can capture dissolution behavior of some systems (IVIVE is still a challenge if if presence of crystals results in additional crystallization)
- Commercially software recently added more flexibility to interrogate this
- Best practices will need to evolve



Observed Dissolution



Simulated Dissolution

Hermans A, Kesisoglou F, Xu W, Dewitt K, Marota M, Colace T. Possibilities and Limiting Factors for the Use of Dissolution as a Quality Control Tool to Detect Presence of Crystallinity for Amorphous Solid Dispersions: An Experimental and Modeling Investigation. J Pharm Sci. 2019 Sep;108(9):3054-3062.

MERCK
INVENTING FOR LIFE

Agreement Between Simulated and Observed Data Doesn't "Validate" the Dissolution Model

BCS II Weak Acid (pKa 4.7)

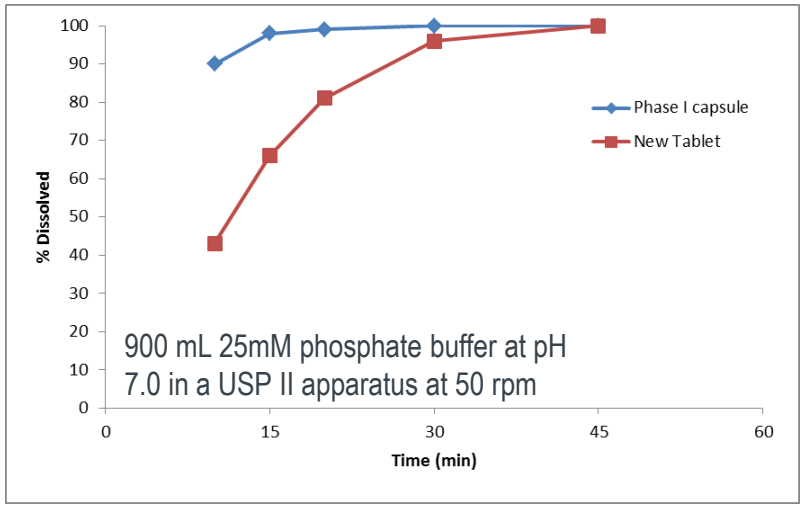
0.48 µg/mL @ pH 2.2, 0.92 mg/mL @ pH 7.8

Sodium salt solubility > 50 mg/mL (native pH 9.9)

Particle size of API < 10 µm

Linear PK in the dose range 2-300 mg

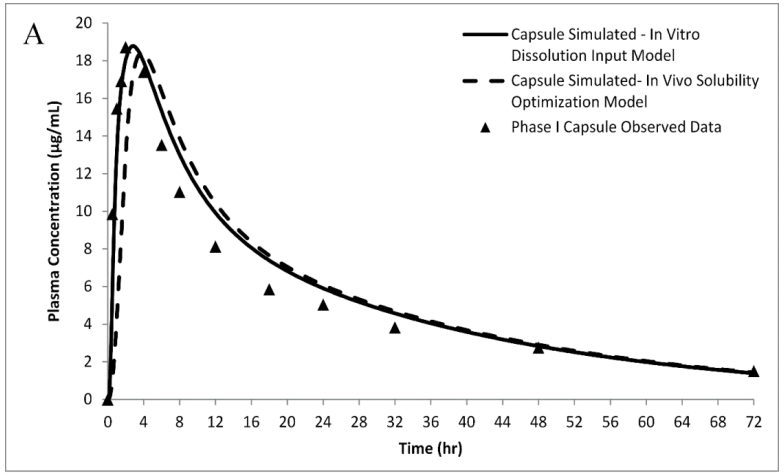
Capsule = 200 mg Free Acid, Tablet = 300 mg Na Salt

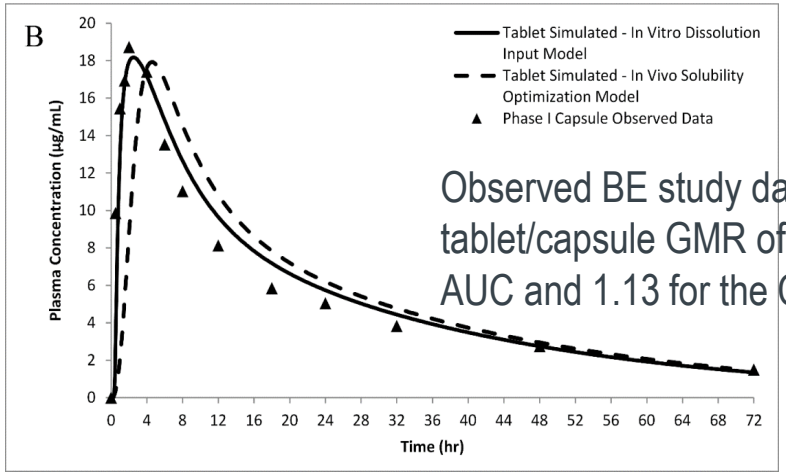


MODEL A: Direct Input Model – assumes 1:1 IVIVC; profile shifted by 15 min to capture lack of stomach solubility

MODEL B: In vivo solubility enhancement factor model – an in vivo solubility enhancement factor estimated based on fitting Phase I PK data for capsule (this may not represent a unique solution)

- To simulate tablets, dissolution fit to a hypothetical particle size (using the in vivo solubility value)





Observed BE study data: tablet/capsule GMR of 0.99 for AUC and 1.13 for the C_{max}

BOTH MODELS ARE SIGNIFICANT APPROXIMATIONS AND LIKELY NEITHER IS CORRECT – BOTH SUCCESSFULLY CAPTURE THE PK PROFILE

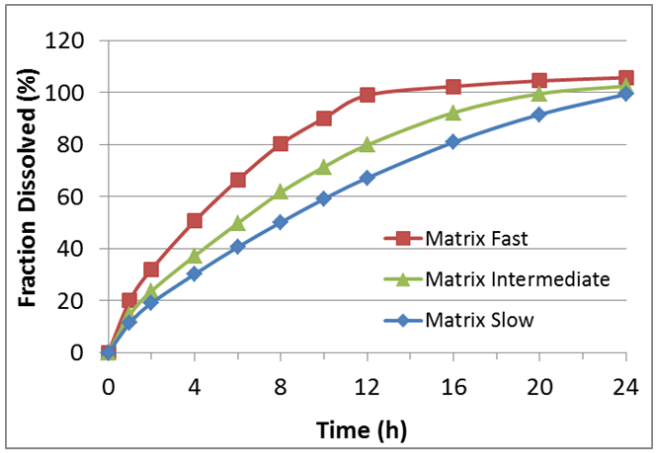
MERCK
INVENTING FOR LIFE

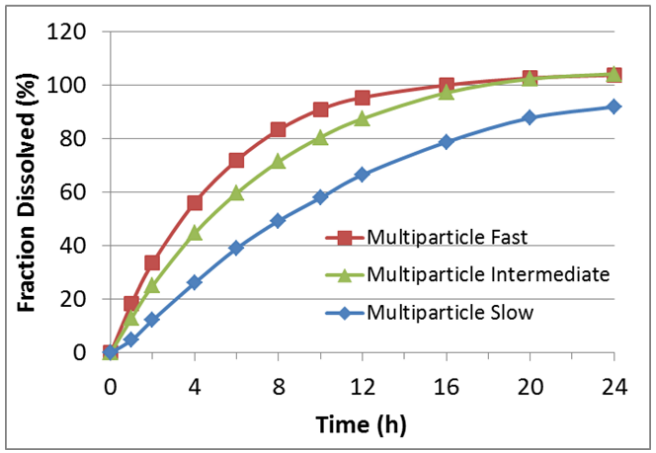
Kesisoglou F., DDF 2018, Berlin, Germany

How Should One Select Dissolution Model for PPBM Input for IR Products

- Based on Understanding of Rate Limiting Steps to Formulation Dissolution
- Based on Physiological Plausibility
  - Direct Input Likely Only Meaningful for BCS I/III Compounds
- Based on Best Fit of Dissolution Data
  - Important to Capture Dissolution Behavior of Entire Dosage Form
  - For Biorelevant Dissolution Data for BCS II/IV May Require Additional Experimentation
- NOT Retrospectively Based on “Validation” Against Clinical Data
  - For IR dosage forms, a large range of dissolution profiles would result in similar prediction

MR Formulations – PBBM Based IVIVC with Empirical Function for and ER formulation





High Soluble Compound, known to have regional absorption preclinically

- Fit Disso to Weibull
- Optimize Regional Permeability to Achieve an IVIVC
- Models Separately Established for Matrix and Multiparticulate Formulations
- Assess Prediction Errors

Formulations	C_{max} (ng/mL)			$AUC_{0\text{-last}}$ (ng*h/ml)		
	Observed	Predicted	PE(%)	Observed	Predicted	PE(%)
Matrix 8 hr	8.40	8.17	-2.7	81.01	74.72	-7.8
Matrix 12hr	4.69	5.36	14.3	70.14	60.45	-13.8
Matrix 16 hr	3.40	3.94	15.9	48.84	51.64	5.7
Matrix Average	NA	NA	**11.0**	NA	NA	**9.1**
Multiparticulate 8 hr	8.63	8.32	-3.6	92.12	87.67	-4.8
Multiparticulate 12 hr	5.52	6.15	11.4	70.11	77.41	10.4
Multiparticulate 16 hr	3.27	3.33	1.8	58.34	58.16	-0.31
Multiparticulate Average	NA	NA	**3.2**	NA	NA	**1.8**

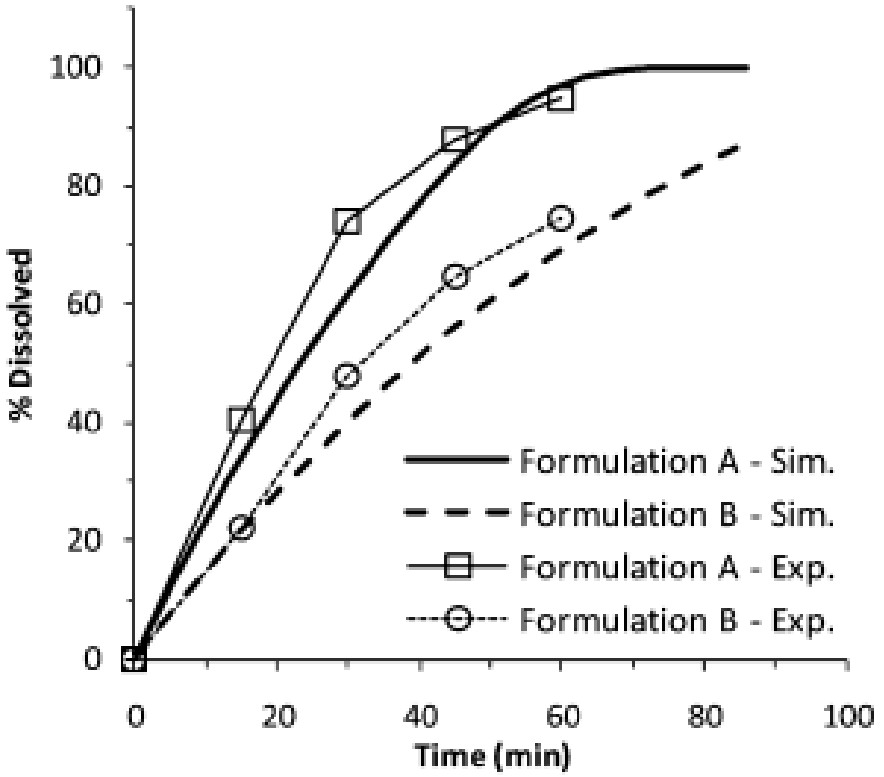
Generally Acceptable Prediction Errors

Kesisoglou F, Xia B, Agrawal NG. Comparison of Deconvolution-Based and Absorption Modeling IVIVC for Extended Release Formulations of a BCS III Drug Development Candidate. AAPS J. 2015 Nov;17(6):1492-500..

MERCK
INVENTING FOR LIFE

MR Formulations – PBBM Based on "Mechanistic" Model for DR system

BCS I compound
Enteric coated beads formulation to protect from stomach acid instability
Standard USP 2-stage acid-challenge dissolution method



$$-\frac{dX_s}{dt} = \frac{DS}{h}\left(C_s - \frac{X_d}{V}\right) \longrightarrow -\frac{dX_s}{dt} = \frac{3DX_0}{\rho f h(r_0^3 - r_c^3)}\left[\frac{X_s}{X_0}(r_0^3 - r_c^3) + r_c^3\right]^{2/3}\left(C_s - \frac{X_d}{V}\right)$$

Sperry DC, Thomas SJ, Lobo E. Dissolution modeling of bead formulations and predictions of bioequivalence for a highly soluble, highly permeable drug. Mol Pharm. 2010 Oct 4;7(5):1450-7.

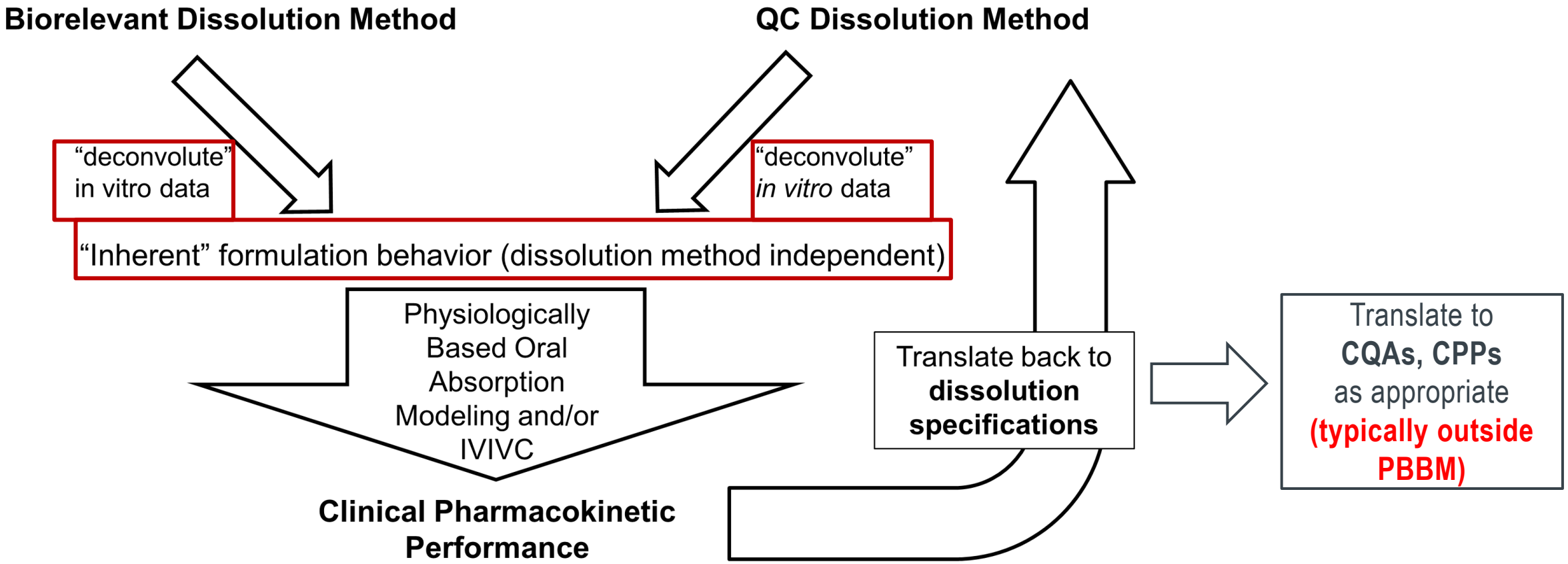
MERCK
INVENTING FOR LIFE

MR Formulations – PBBM Based IVIVC

- For most MR formulations (other than some osmotic systems) unlikely the IVIVC is really 1:1
- However unless very detailed measurements available clinically (e.g. local dosing at different areas) – identifiability issues will exist between dissolution and regional absorption
- Likely multiple combinations of dissolution/permeability can explain the data
- Thus generally OK to input release data using an empirical function

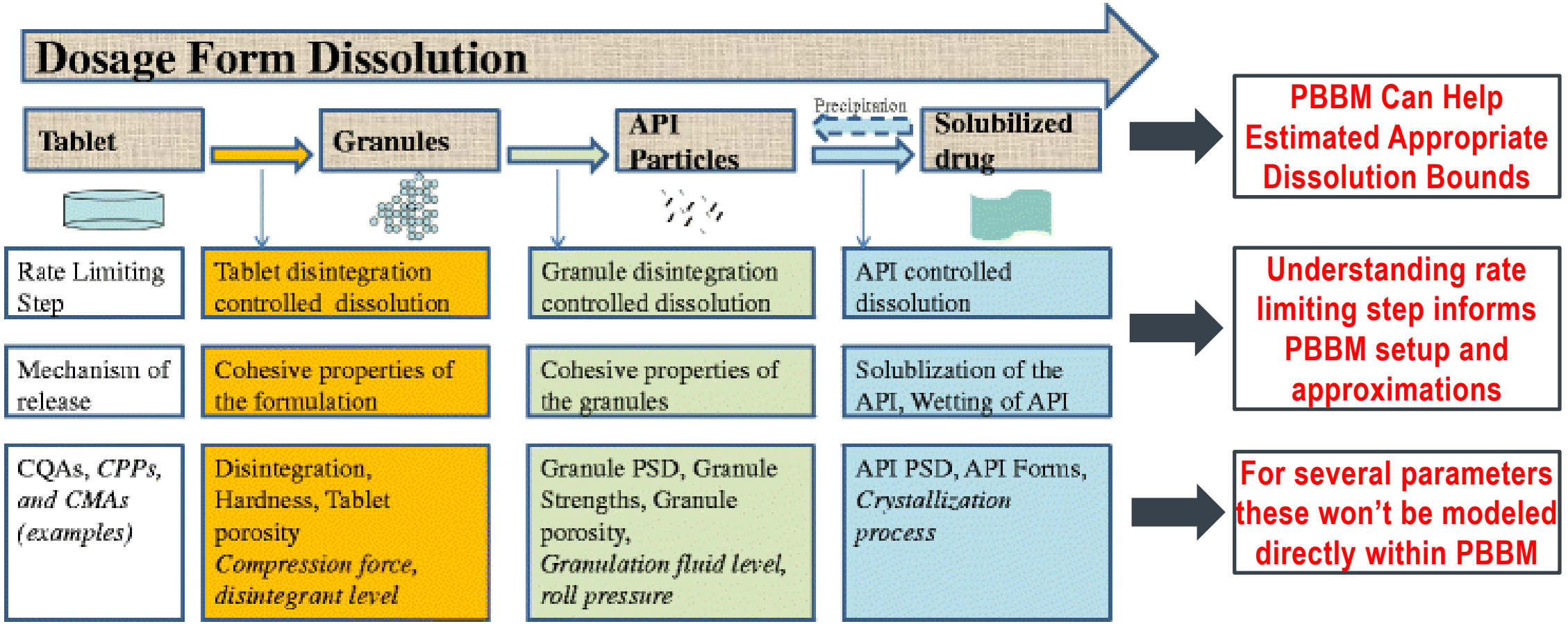
MERCK
INVENTING FOR LIFE

Input of Dissolution Data is Only Meaningful Way to Setup Models for Drug Product Quality



Kesisoglou F. The Role of Physiologically Based Oral Absorption Modelling in Formulation Development Under a Quality by Design Paradigm. J Pharm Sci. 2017 Apr;106(4):944-949.

Clinically Relevant Specifications



Hermans A, Abend AM, Kesisoglou F, Flanagan T, Cohen MJ, Diaz DA, Mao Y, Zhang L, Webster GK, Lin Y, Hahn DA, Coutant CA, Grady H. Approaches for Establishing Clinically Relevant Dissolution Specifications for Immediate Release Solid Oral Dosage Forms. AAPS J. 2017 Nov;19(6):1537-1549.

MERCK
INVENTING FOR LIFE

Summary

- Dissolution input in PPBM is the ONLY way to link to drug product quality
- There is no one-size-fits all approach to input of dissolution data
- Selection of input method should be based on understanding of formulation behavior – not on “validation” of model against clinical data
- With the potential exception of BCS I/III compounds, use of direct input and/or empirical functions should be avoided
- For MR formulations, use of empirical functions is appropriate

MERCK
INVENTING FOR LIFE

Acknowledgements

- Wei Zhu
- Jesse Kuiper
- Andre Hermans
- Multiple Merck Drug Product Development Teams

MERCK
INVENTING FOR LIFE