The use of surrogates for dissolution testing for Immediate Release (IR) formulations, when is it feasible?

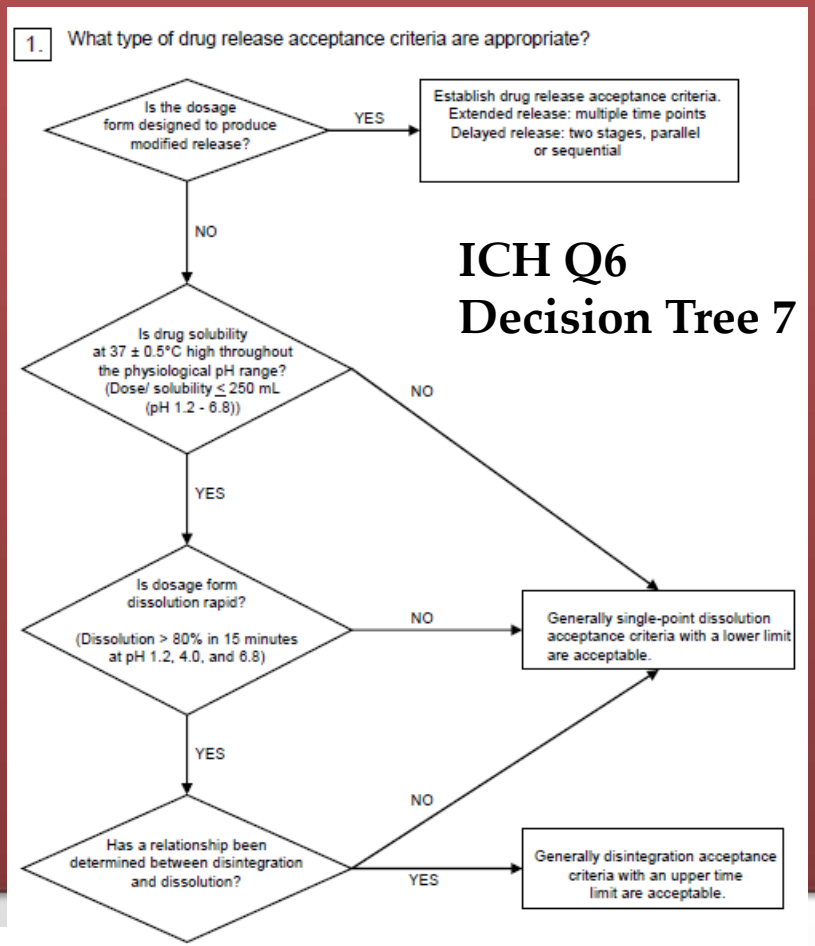
Limin Zhang (Bristol-Myers Squibb Company)
Andre Hermans (Merck & Co., Inc.)

2017 M-CERSI Workshop "Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development"

Outline

- Disintegration as surrogate measure for high solubility compounds (BCS I/III): FDA Dissolution draft guidance, ICH Q6
  - Case studies
- Surrogate testing for low solubility compounds (BCS II/IV):
  - General considerations
    - Understanding of dissolution mechanism, Properties that determine dissolution rate
  - Overview of potential surrogate measurements
  - Case Studies:
    - Case study 1/2: Use of dissolution modeling /software/ first principles:
    - Case study 3: Use mechanistic dissolution understanding to select surrogate testing
    - Case study 4: Multivariate dissolution modeling
    - Case study 5: NIR prediction of tablet dissolution
    - Case study 6: Use surrogate testing/modeling as input for in silico PBPK modeling to establish clinical relevant specification
- Benefits and potential applications for surrogate testing / dissolution modeling

Disintegration testing for high Solubility compounds (BCS I and III) - Regulatory View



ICH Q6
Decision Tree 7

FDA Draft Guidance for Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs:

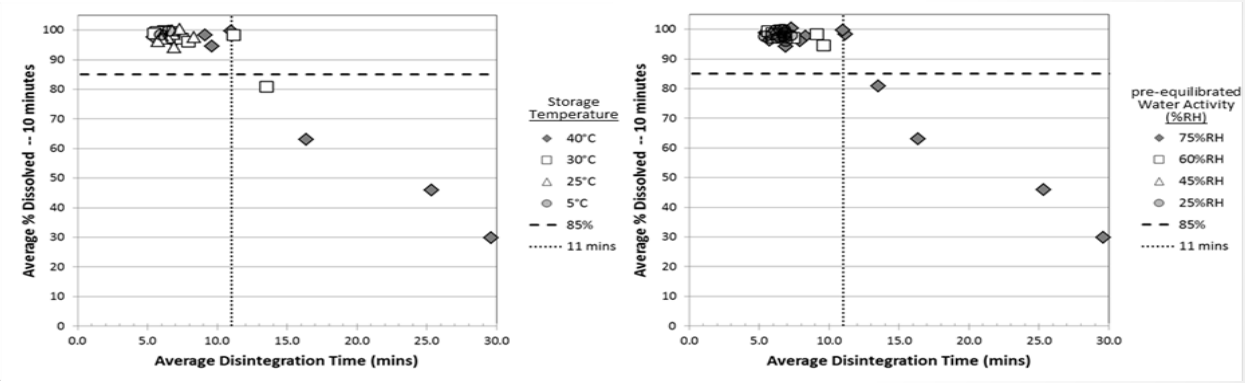
Section VI:

"For drug products in both BCS classes 1 and 3, USP disintegration testing can be used in lieu of the dissolution test if the product is shown to meet a dissolution specification of Q=80% in 15 minutes. For drug products that meet this criterion, the USP disintegration test, which requires the product to completely disintegrate within 5 minutes (via USP apparatus in 0.01M HCl), may serve as a surrogate for routine release and stability dissolution testing. However, the approved dissolution method should be retained as the primary method and the approved disintegration method as an alternate method. Note that to support post-approval changes for which dissolution testing would be typically be needed, you should use the approved dissolution method."

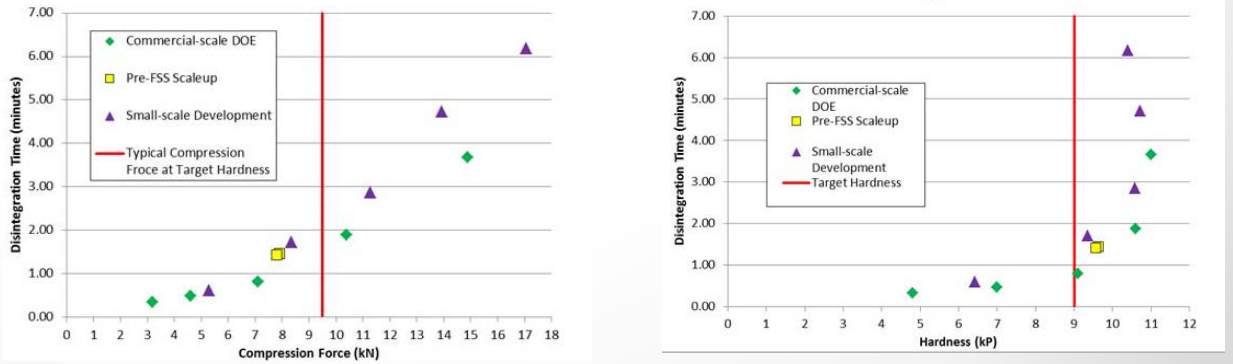
Example 1: Disintegration testing for BCS Class I compound

- Very rapid dissolution (>85% in 15 min)
- Relationship between Dissolution / Disintegration observed
- Disintegration is much more sensitive to process than dissolution. Will allow better tracking and trending of process performance

Disintegration / Dissolution relationship on stability

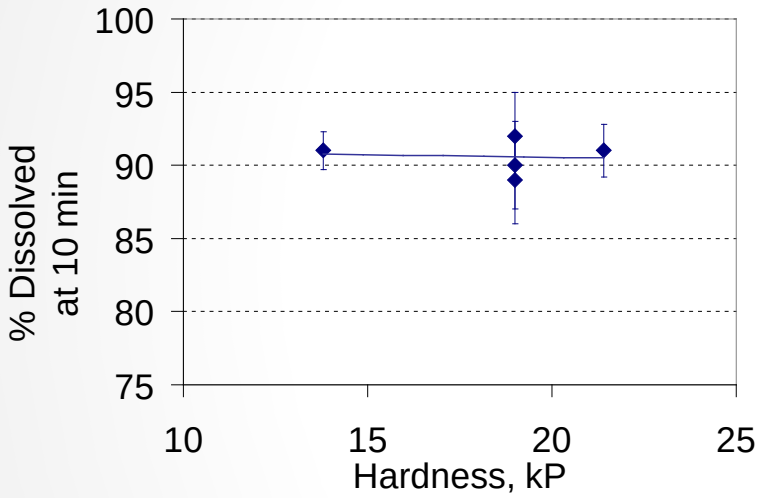


Disintegration Sensitivity to process factors

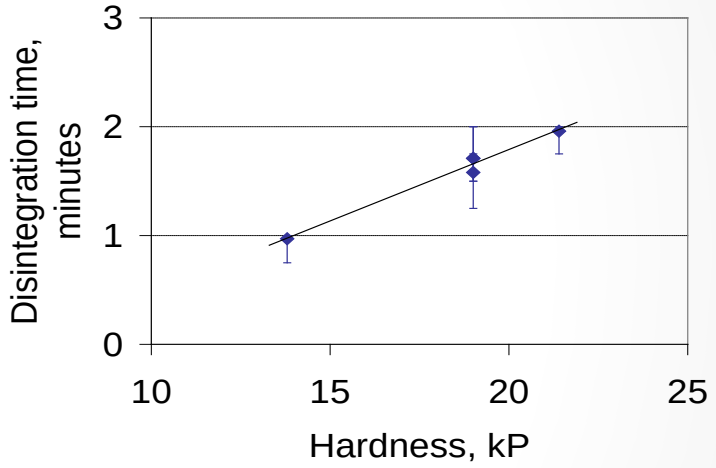


Example 2: for Disintegration testing for BCS Class I Commercial Product

Hardness-dissolution relationship



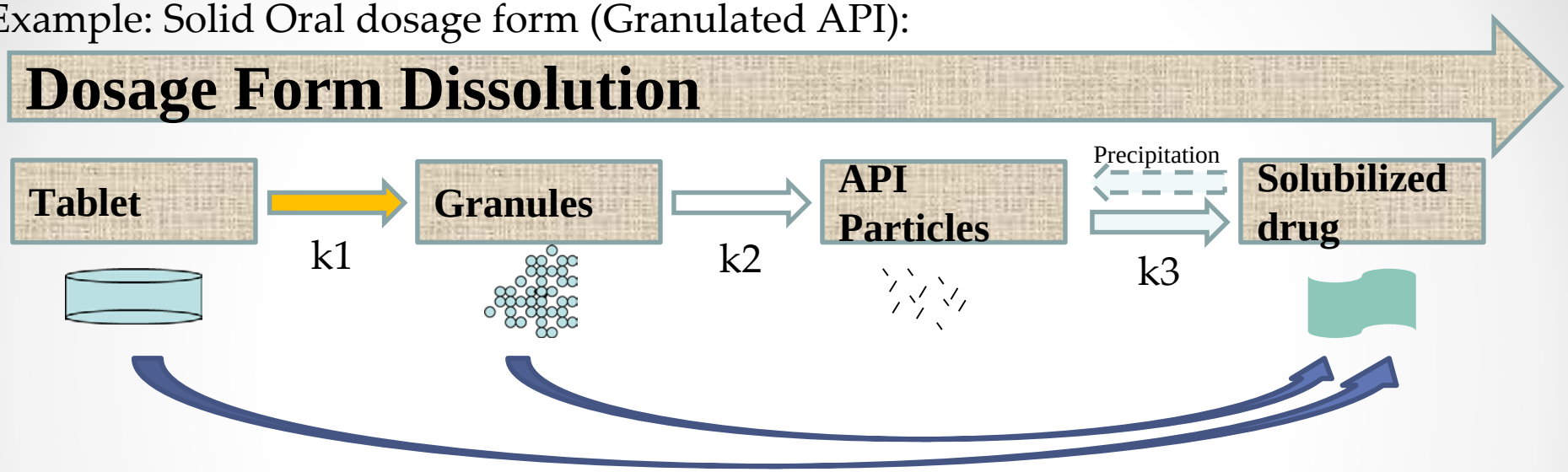
Hardness-disintegration relationship



- Initially disintegration was filed → More sensitive towards tablet hardness
- Post Launch disintegration testing was replaced by tablet hardness testing due to strong hardness-disintegration relationship (US only)

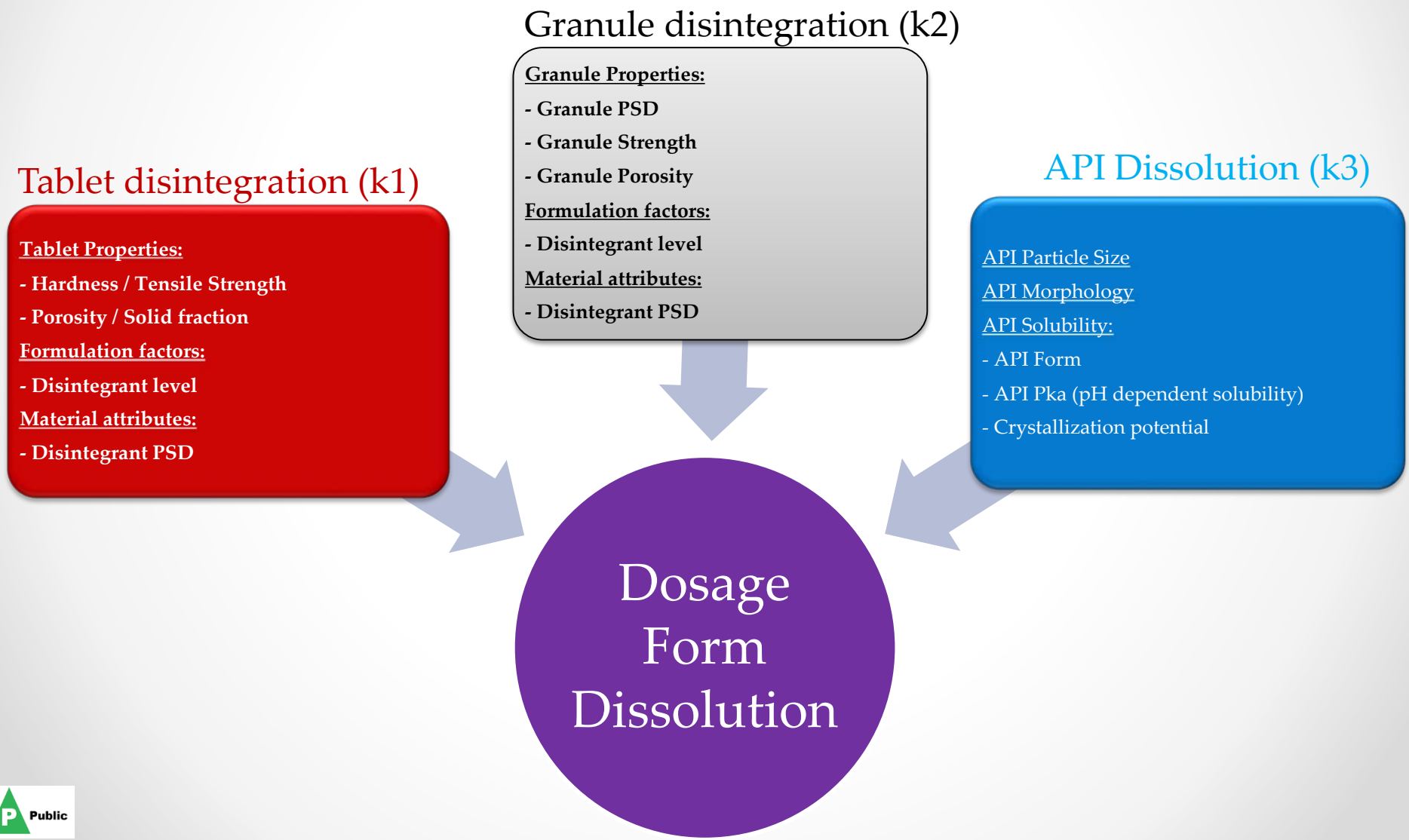
General approach to surrogate testing

Example: Solid Oral dosage form (Granulated API):



- Determine **rate limiting step** for the overall dosage form dissolution rate
  - For BCS 1/3: k3 is generally fast and not rate limiting
    - Therefore, k1 (disintegration is often good surrogate test for dissolution)
  - For BCS 2/4: More than one step could be rate limiting
- Determine properties that influence the dissolution rate for rate limiting step
  - Understand which critical process parameters (CPPs) and critical material attributes (CMAs) influence these properties
- Develop surrogate tests to measure these properties

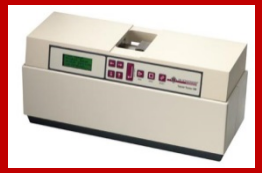
Properties that can influence dissolution rate (examples)



Type of surrogate measurement tools

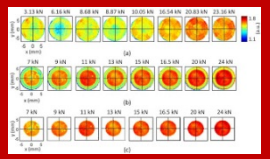
Tablet Disintegration

USP Disintegration apparatus

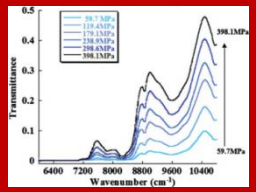


Tablet Hardness tester

Tablet dimensions (SA/Volume)



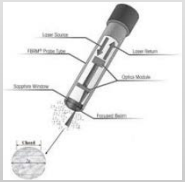
Terahertz Spectroscopy



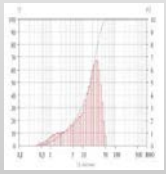
NIRS

Ultrasound / acoustic measurements

Granule Disintegration

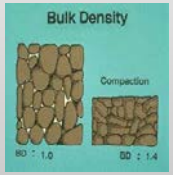


FBRM during dissolution



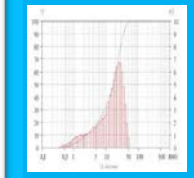
Particle size measurements

Pycnometry



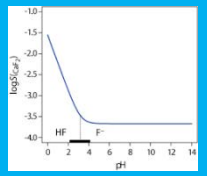
Bulk Density

API Dissolution

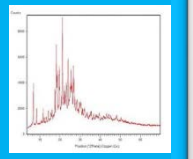


Particle size measurements

Microscopic techniques

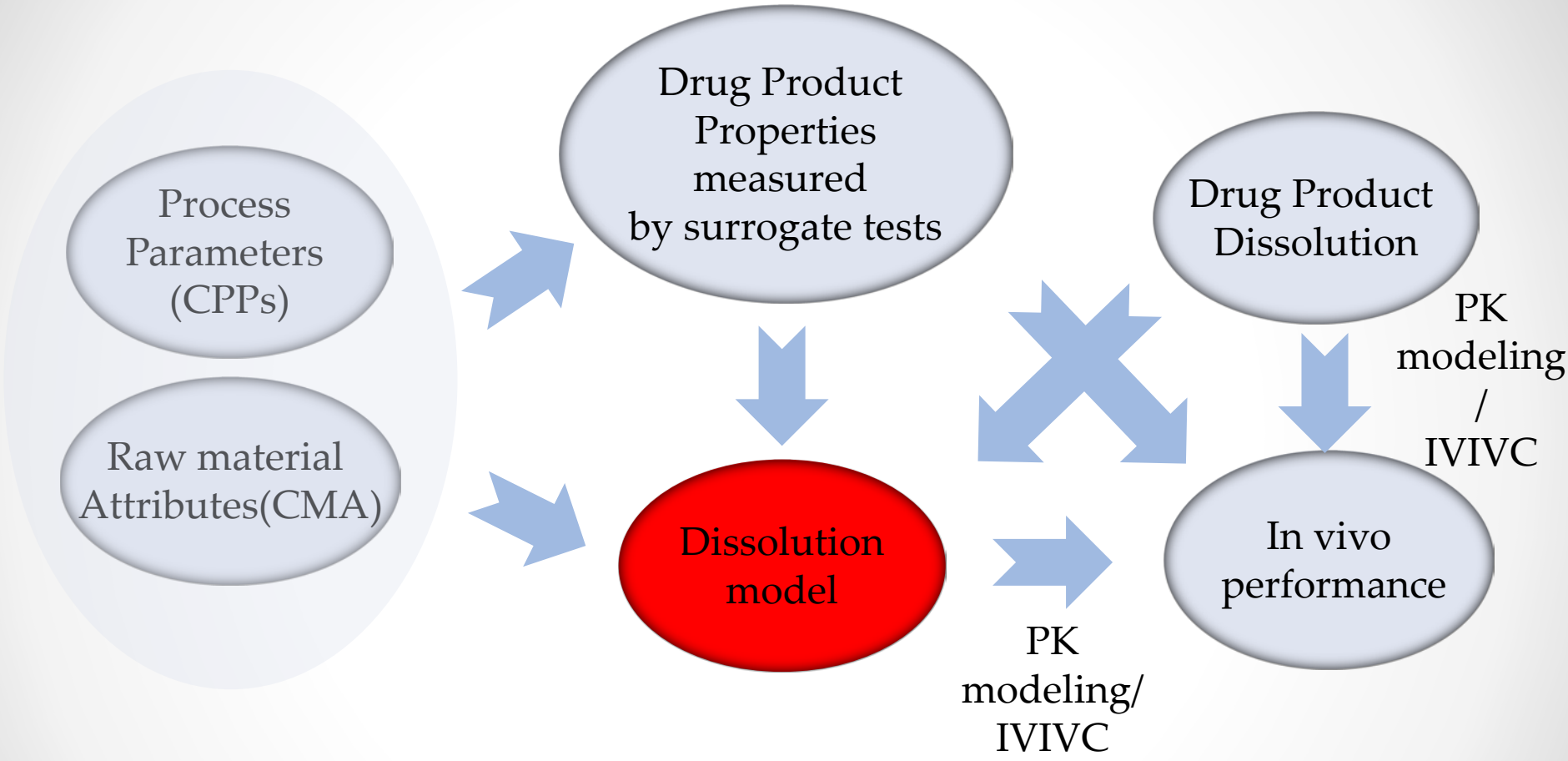


Solubility measurements



XRD (form control)

Building a dissolution model



Dissolution models can be build with multiple approaches (or combination of approaches):

- Based on first principles
- Empirical data / Correlations with surrogate measurements
- Multivariate Analysis

Case studies for low solubility compounds

- Case study 1 : Mechanistic in vitro dissolution simulation tool (DDD plus™) for in vitro dissolution experiments
- Case study 2: use modified Noyes-Whitney and Weibull equations for dissolution analysis
- Case Study 3: Build mechanistic dissolution understanding for enabled formulation based on tablet properties
- Case Study 4: Build dissolution understanding / model via multivariate approach
- Case Study 5: NIR prediction of tablet dissolution
- Case Study 6: Develop PBPK model and dissolution model to inform formulation design space

Case study 1: Mechanistic *in vitro* dissolution simulation tool (DDD plus™) for in vitro dissolution experiments

An advanced computer program that simulates the in-vitro disintegration and dissolution of oral solid dosage forms

Disintegrant effect

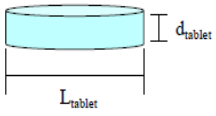
The effect of a disintegrant in the formulation is modeled using a fitted parameter (DE). DE increases the rate of disintegration for a tablet.

$$\frac{dM_{ND}}{dt} = -DE\left(\frac{\varepsilon}{\tau}\right)v\left(\frac{1}{d_{tablet}}\right)M_{ND}$$

$$DE = (k_{Disintegrant} * C_{ND}/M_U)$$

Optimizable

DE = disintegrant effect
$k_{Disintegrant}$ = optimizable constant
C_{ND} = non-disintegrated concentration of disintegrant
M_{ND} = mass of non-disintegrated drug
ε / τ = porosity / tortuosity ratio
v = fluid velocity
d_{tablet} = tablet diameter



The software simulates

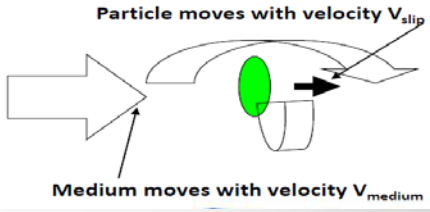
- particle size effect
- apparatus effects (vessel dimensions, mixing speed)
- medium effects (pH, ionic balance)

DDDPlus™ Mass Transfer model (assuming forced convection around a *spherical* particle):

Optimizable Calibration constant

$$\frac{dM_{U_i}}{dt} = -\left(\frac{3k\gamma}{\rho h_i}\right)\left[C_s - \frac{M_{D_t}}{V}\right]M_{U_i}$$

k = *f*(velocity, viscosity, diffusion coefficient, particle radius, particle density)
ρ = drug density
h_i = hydrodynamic boundary layer for bin i
Cs = solubility of drug
M_{Dt} = total mass of dissolved material
M_{Ui} = mass of undissolved (solid) material in bin i
V = volume of dissolution medium
i = particular bin
γ = calibration constant



Information provided by SimulationsPlus

Case study 1 example: Simulation of drug A dissolution

Drug A: a basic drug with two pKa

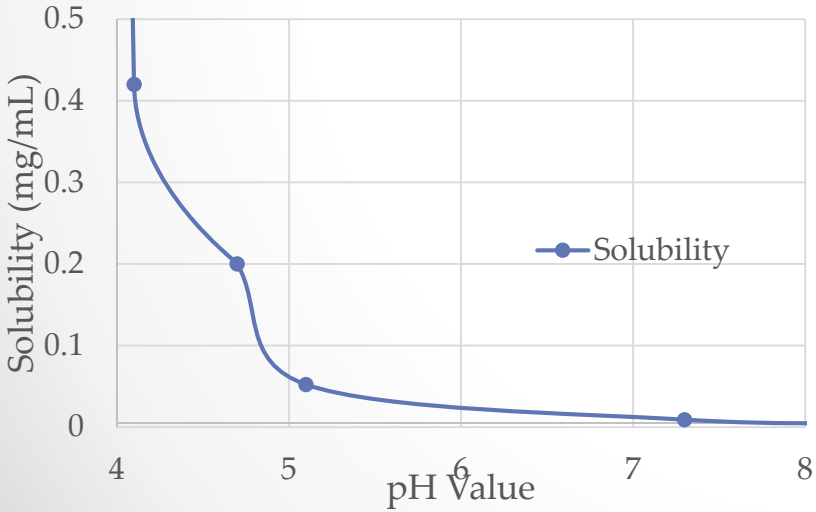
Form: salt

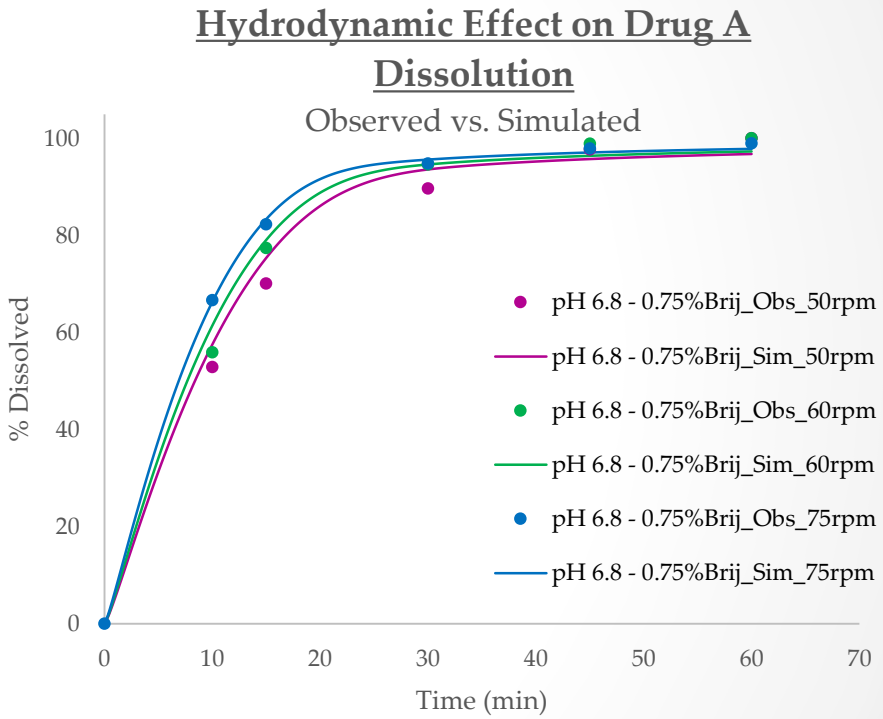
BCS Class: 2

Dosage: tablet, 60 mg (highest strength)

Conventional formulation

pH solubility plot:

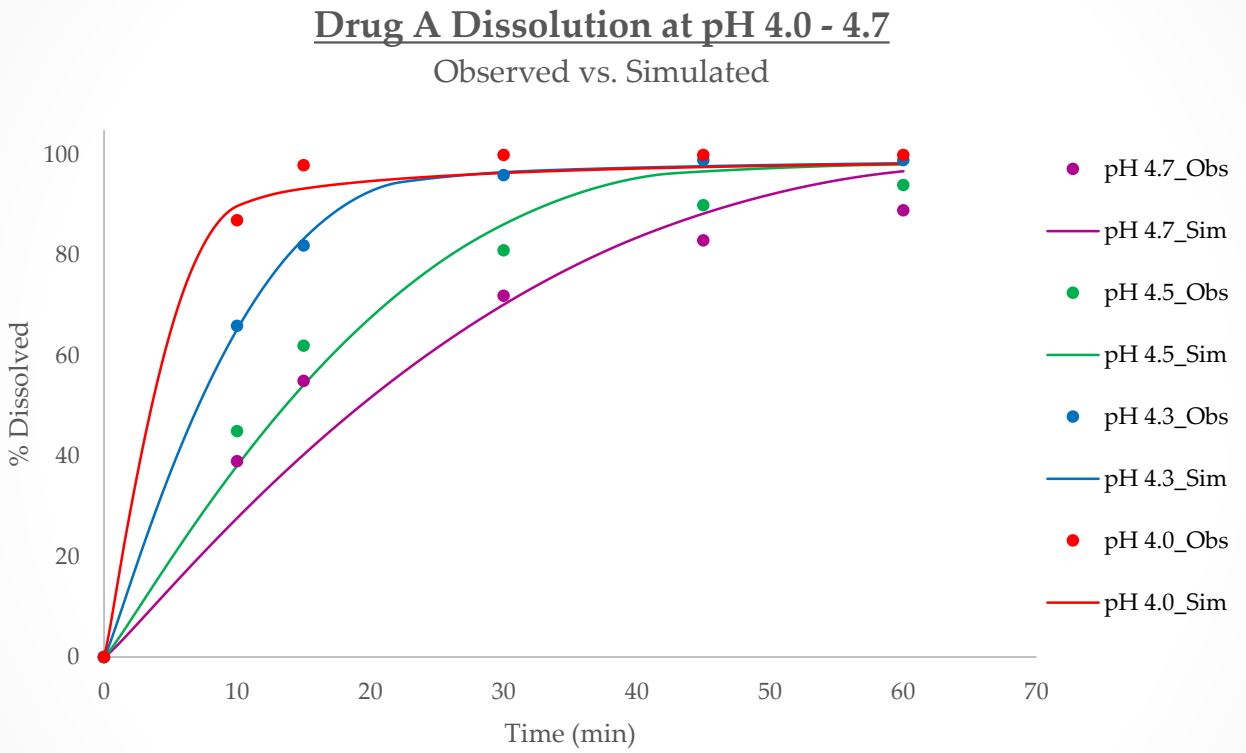




Public

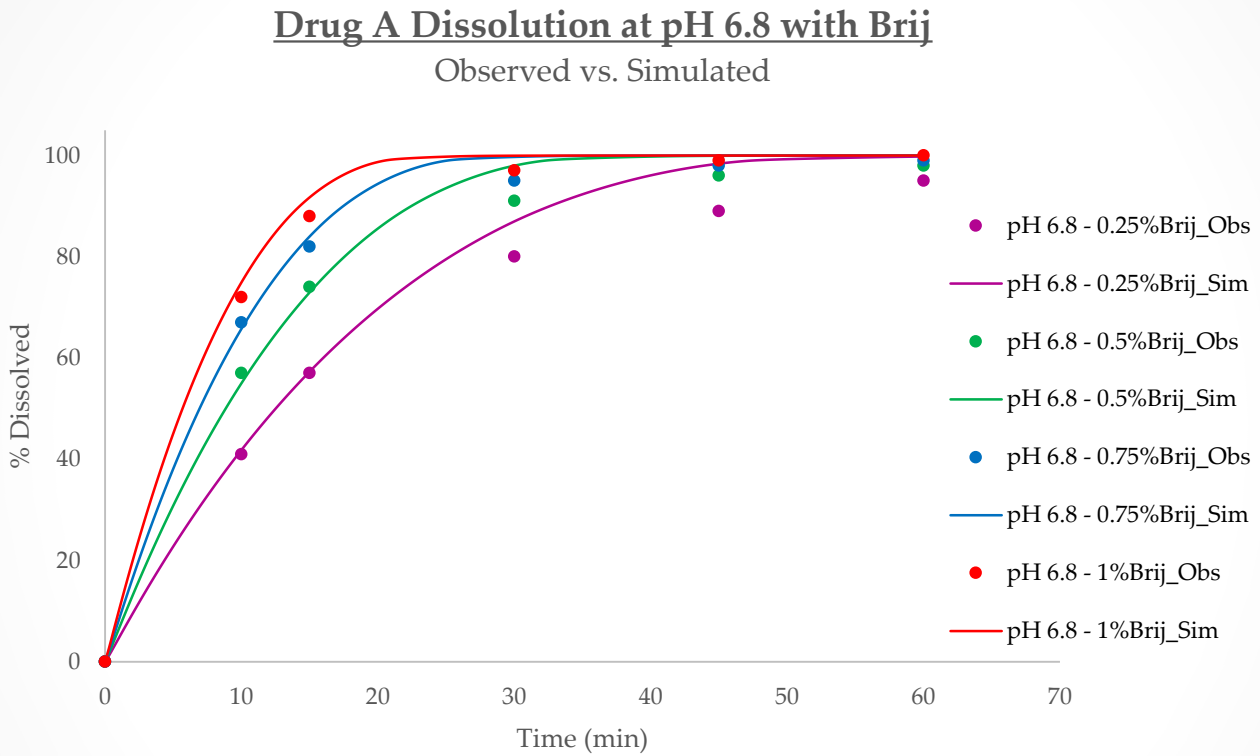
Z. Huang et al "Predictive Capability of DDD Plus for In-vitro Dissolution of Immediate Release Formulations" EAS 2016 Oral

Medium effect (pH) on drug A dissolution



Simulated dissolution rate was generated using calibration constants optimized by experimental data of pH 4.3 at 75 rpm

Medium effect (surfactant level) on drug A dissolution



Simulated dissolution rate was generated using calibration constants optimized by experimental data of pH 6.8 with 0.75% Brij at 75 rpm

Conclusion: DDD plus™ can be used for ranking order estimation, but it cannot replace dissolution testing in its current state.

Case study 2: Modified Noyes-Whitney and Weibull function for dissolution analysis

- Classic Noyes-Whitney Equation: cannot describe dissolution data deviated from first-order kinetics.

$$\frac{dC}{dt} = k(C_s - C)$$

- Modify the classic Noyes-Whitney Equation by multiple both sides with V/M_0 where Φ is the fraction of drug dose dissolved and q = M0/VCs is the dose/solubility ratio

$$\frac{d\Phi}{dt} = k\left(\frac{1}{q} - \Phi\right)$$

- Letting the dissolution rate coefficient be $k = k1t^{-h}$ and replacing in above Eq.

$$\frac{d\Phi}{dt} = k_1 t^{-h}\left(\frac{1}{q} - \Phi\right)$$

A. Dokoumetzidis *et al* "Analysis of Dissolution Data Using Modified Versions of Noyes–Whitney Equation and the Weibull Function" *Pharmaceutical Research*, Volume 23, No. 2, February 2006

Modified Noyes-Whitney and Weibull function for dissolution analysis

- Replacing $a = k1/(1 - h)$ and $b = 1 - h$, a modified version of the Weibull function can be derived.

$$\Phi = \begin{cases} \frac{1}{q}\left(1 - e^{-at^b}\right) & for\ t < T (\Phi < 1) \\ 1 & for\ t \geq T \end{cases}$$

- when q≥1 it describes a dissolution curve that reaches asymptotically the saturation level 1/q because only a portion of the drug dose is dissolved, and when q ≤ 1 it describes the entire dose is dissolved and plateau is reached at finite time.

To demonstrate the usefulness of the mathematical models, two model drugs were evaluated with the modified equation: one highly soluble, metoprolol, and one relatively insoluble, ibuprofen

Modified Noyes-Whitney and Weibull function for dissolution analysis

The following figure shows the metoprolol literature data (16) together with the fitted curves of modified Weibull and the simple Weibull. Modified Weibull fits better

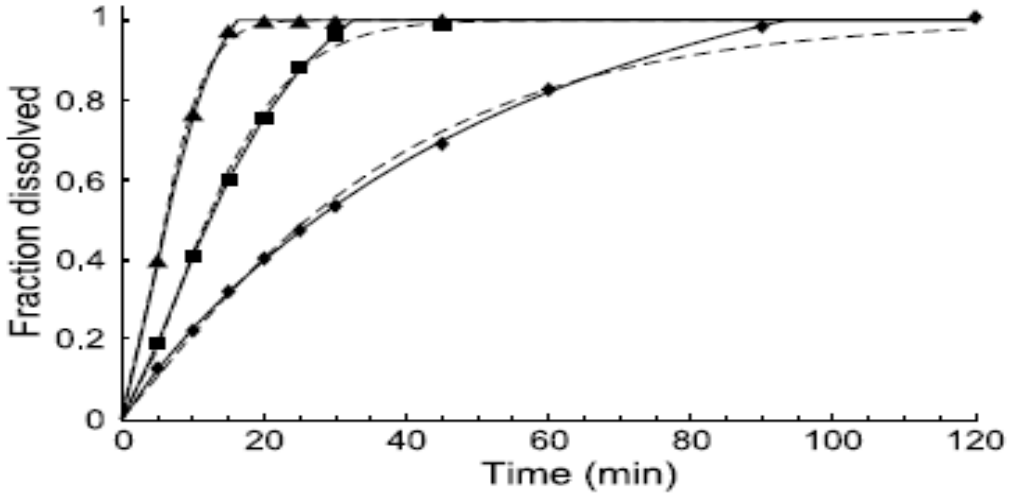


Fig. 3. Dissolution profiles from Polli *et al.* (16), fitted with the modified Weibull [Eq. (10)] (solid) and the simple Weibull [Eq. (3)] (dashed). Key according to Polli *et al.* notation: (▲) fast, (■) medium, (◆) slow.

Modified Noyes-Whitney and Weibull function for dissolution analysis

In the following figure, the dissolution curves of 50, 200, and 600 mg of ibuprofen are shown together with the fitted models.

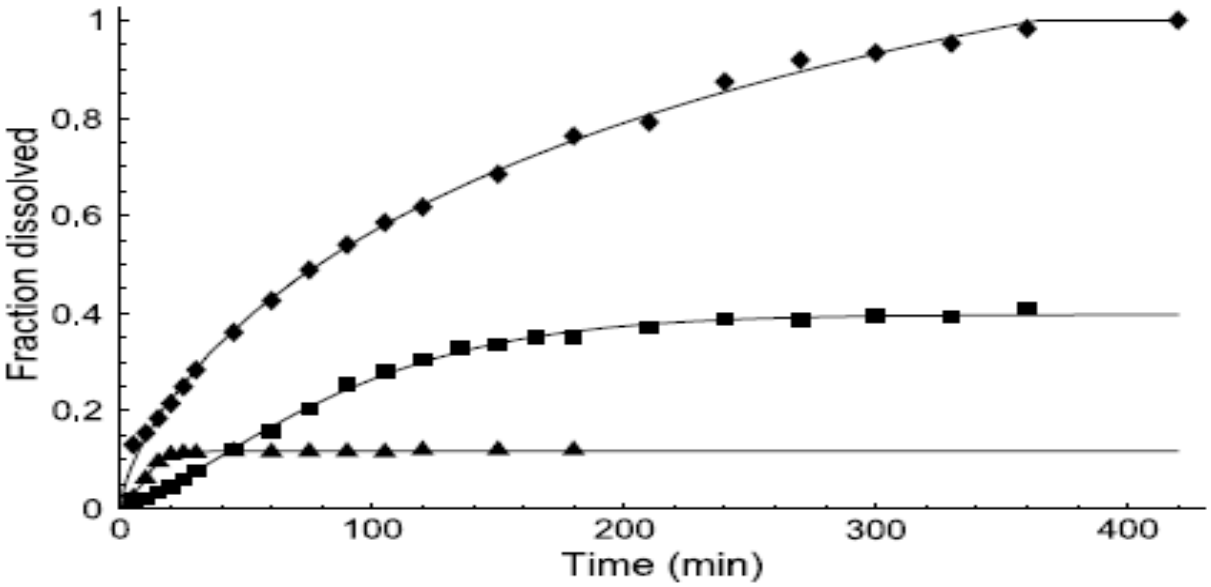


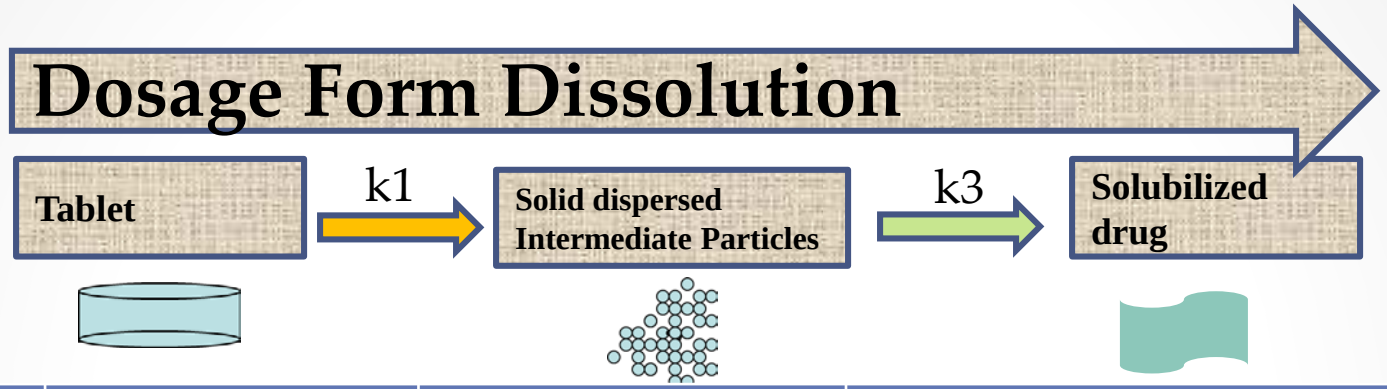
Fig. 4. Dissolution profiles of ibuprofen tablets, fitted with the modified Weibull [Eqs. (9) and (10)]. Key: (◆) 50 mg fitted with Eq. (10), (■) 200 mg fitted with Eq. (9), and (▲) 600 mg fitted with Eq. (9).

Modified Noyes-Whitney and Weibull function for dissolution analysis

Conclusion:

1. The modified equations fit better to a large range of datasets, especially for fast dissolution curves that reach complete dissolution.
2. The use of the branched equations gives better fittings and specific physical meaning to the parameters.

Case study 3: Amorphous solid dispersion



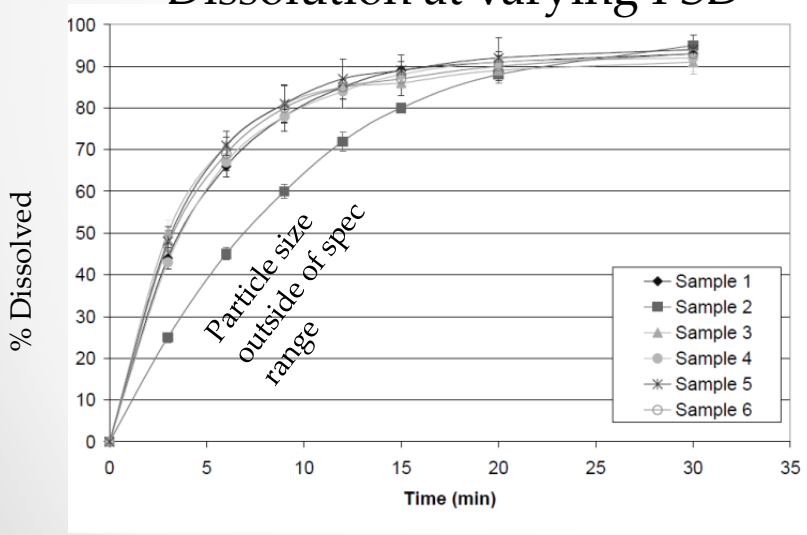
Dissolution step	Parameter controlling dissolution step	Impact on dissolution profile	Surrogate test		
k1 (Erosion / disintegration)	Tablet Hardness → Porosity	yes	Hardness tester	Disintegration	Solid fraction
	Tablet Moisture → Porosity	yes	Water Activity test		
	Tablet Shape	yes	Dimensional measurement		
k3 (Particle dissolution)	Particle size	Yes, but only at large PSD	Particle size measurement (sieve analysis)		
	Crystalline content	Yes, but no form conversion observed	XRD, Raman		

→ % Dissolved (t) = f(hardness) x f(moisture) x f(shape) x f(PSD) x f(API Form)

Case study 3: Amorphous solid dispersion Controlling Particle dissolution

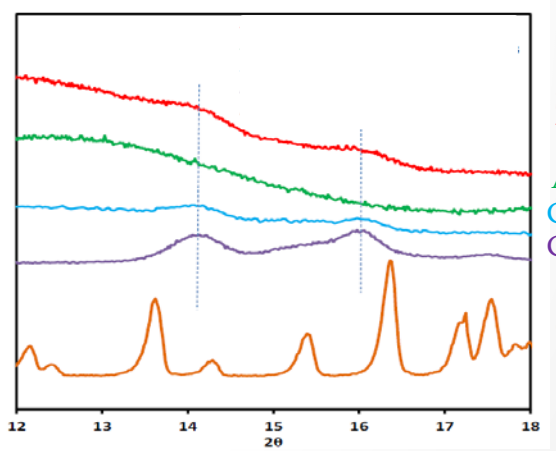
Dissolution step	Parameter controlling dissolution step	Impact on dissolution profile	Surrogate test
k3 (Particle dissolution)	Particle size	Yes, but only at large PSD	Particle size measurement
	Crystalline content	Yes, but no form conversion observed	XRD, Raman

Dissolution at varying PSD



→ No impact on dissolution within spec range

XRD to measure API form



→ No form conversion observed with existing manufacturing controls and on stability

→ k3 does not change with the established controls, Variations in k1 determine overall dissolution

Case study 3: Amorphous solid dispersion Understanding disintegration

- Tablets change dissolution rate and disintegration rate with changes in compression and water uptake on stability
- Dissolution-disintegration relationship could be established for each image separately

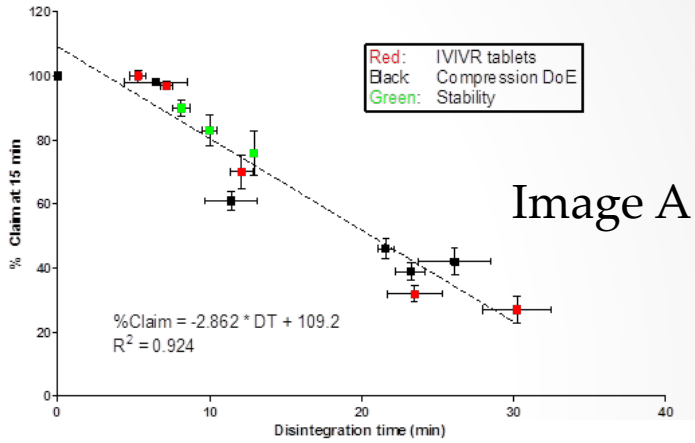
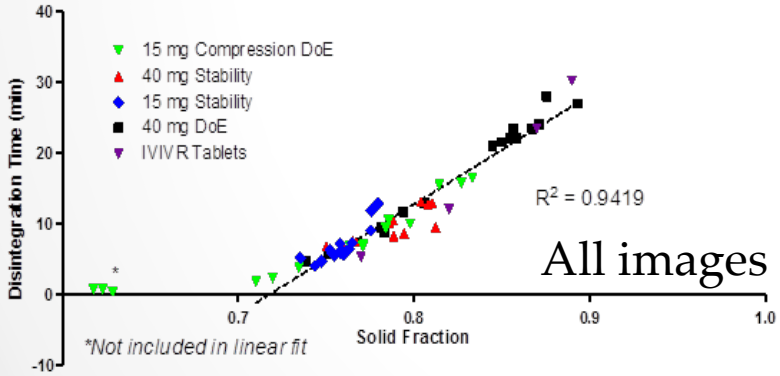
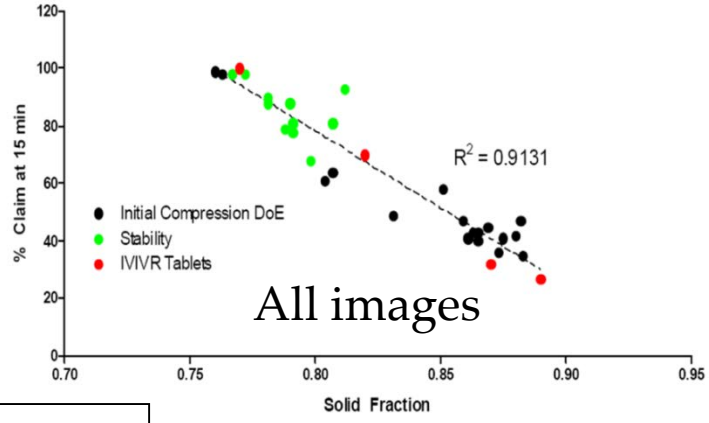


Image A



All images



All images

Solid Fraction is a measure of relative density of the tablet. 1 – Solid fraction assessment porosity in the tablet

$$SF = \frac{\frac{mass}{V_{apparent}}}{\rho_{true}}$$

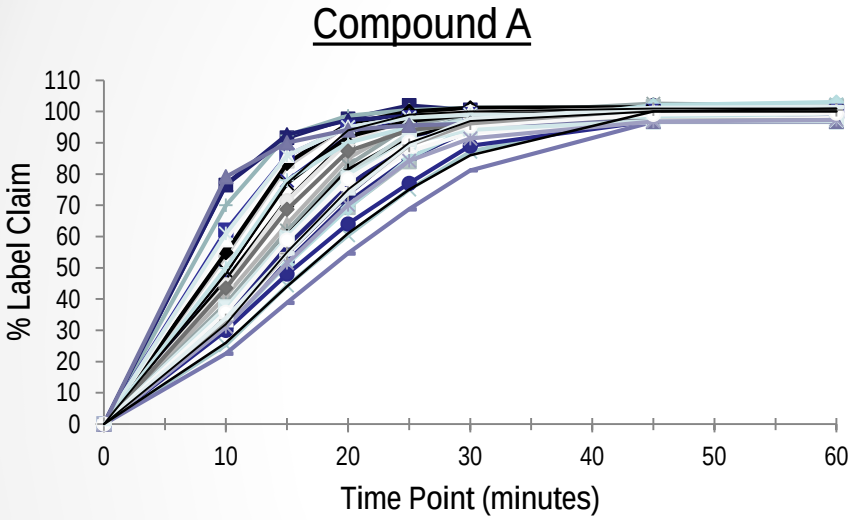
Solid fraction, good predictor of dissolution performance for all images

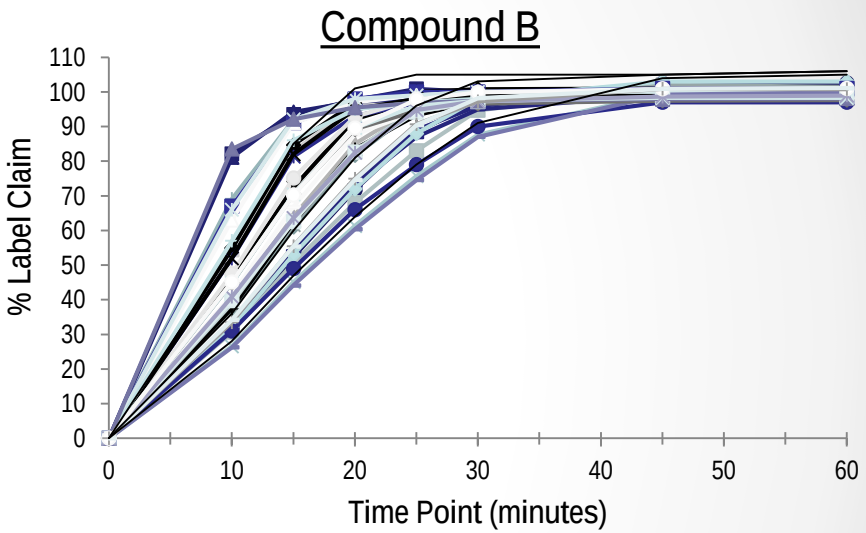
Case study 4: Multivariate dissolution model

- Fixed dose combination product:
  - Spray dried (amorphous) APIs followed by roller compaction
- Multiple Level DoE design to test impact on dissolution performance
  - Factor and level selection based on process experience and projected operating ranges
  - Factors studied:
    - Outlet temperature, Nozzle pressure compound A
    - Outlet temperature, Nozzle pressure compound B
    - RC Roll pressure
    - Tablet Hardness
    - Tablet Moisture

➡ Changes to all rates (k1, k2, k3) are included in the experimental design

Case study 4: Multivariate dissolution model



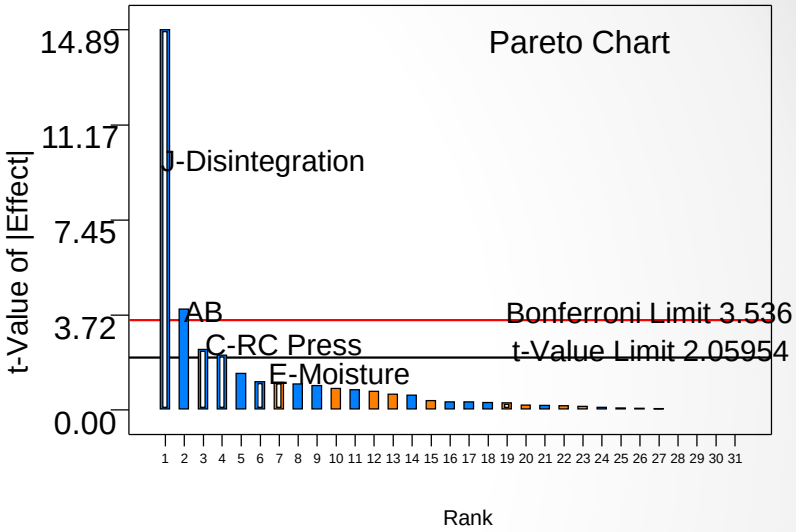


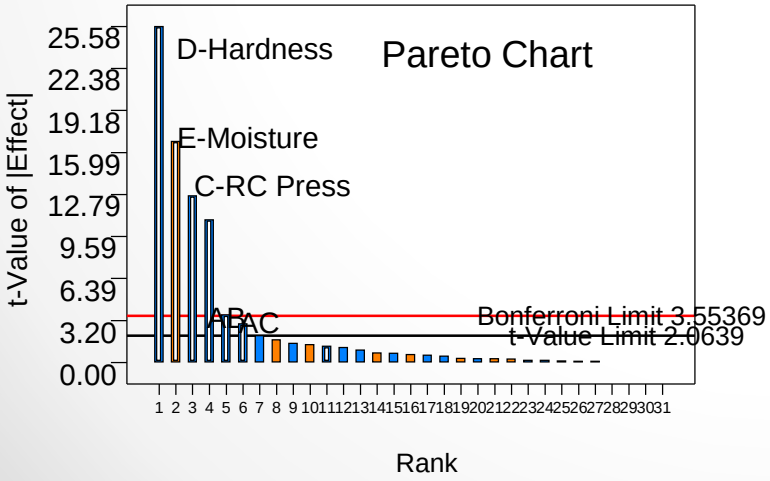
- Wide range of dissolution behavior was observed
- Dissolution behavior for both compound A and B was found to be similar
- Along with dissolution, other properties such as tablet hardness, tablet density and tablet disintegration time were measured

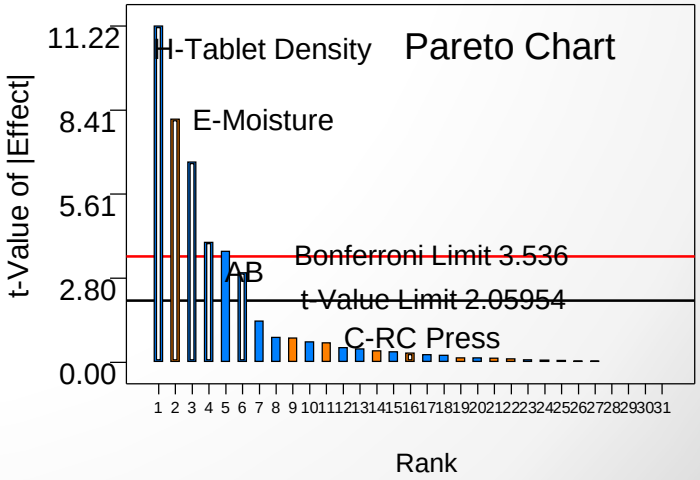
Case study 4: Multivariate dissolution model

Multivariate Analysis

- In assessing the predictive model from the 5-factor DoE, it was discovered that tablet density and disintegration have the ability to wash out other factors
- Tablet density can be predictive to both granulation and compression conditions
- Disintegration can be predictive to all factors

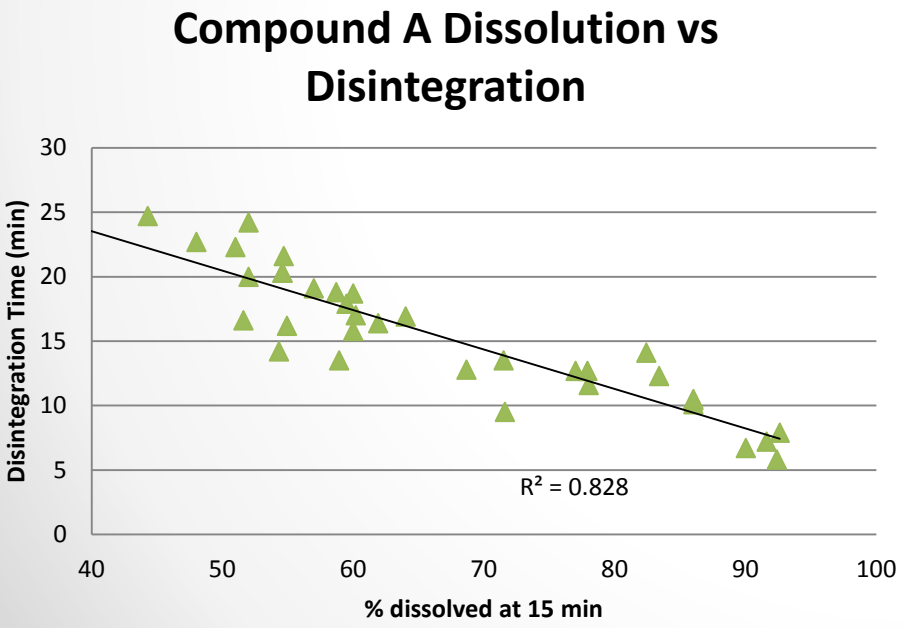


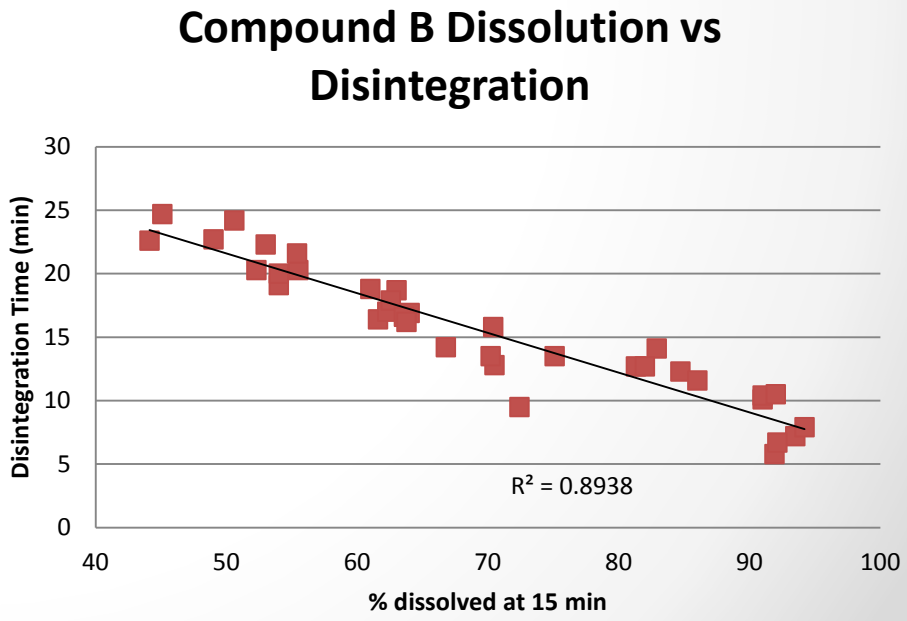




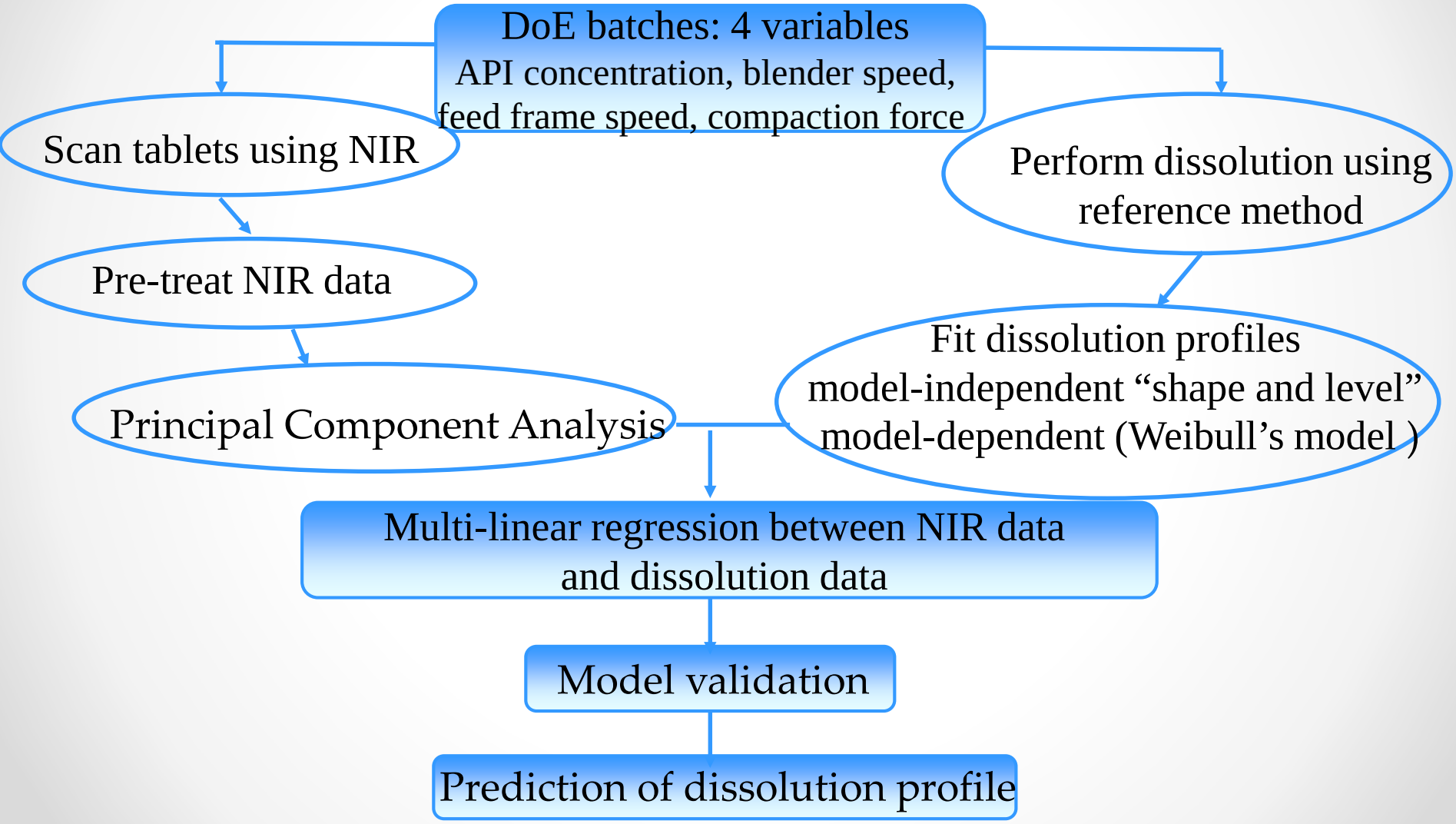
Case study 4: Multivariate dissolution model: Disintegration as a Quality Predictor

- Throughout program development, disintegration has been measured along with dissolution
- The correlation of disintegration with dissolution at 15 minutes is a highly linear correlation which has been reproduced in every batch thus far





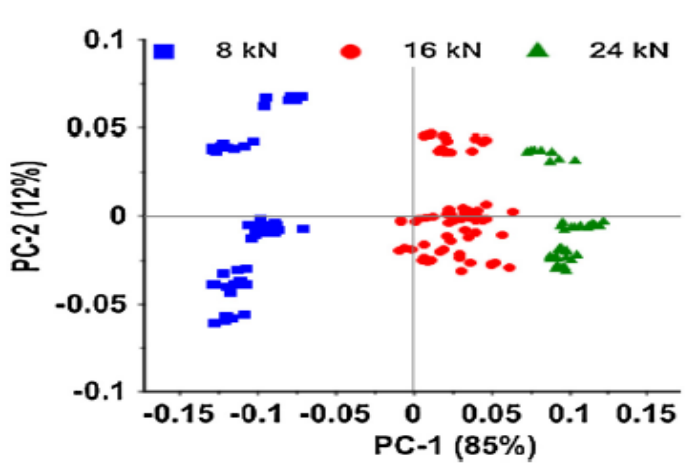
Case study 5: NIR prediction of tablet dissolution

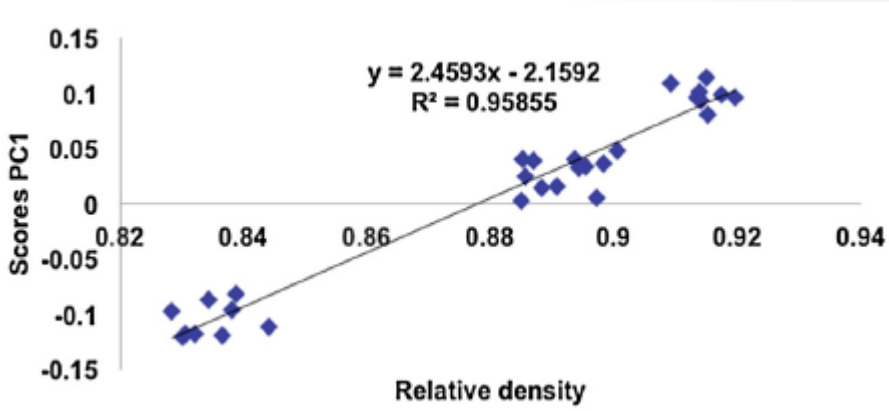


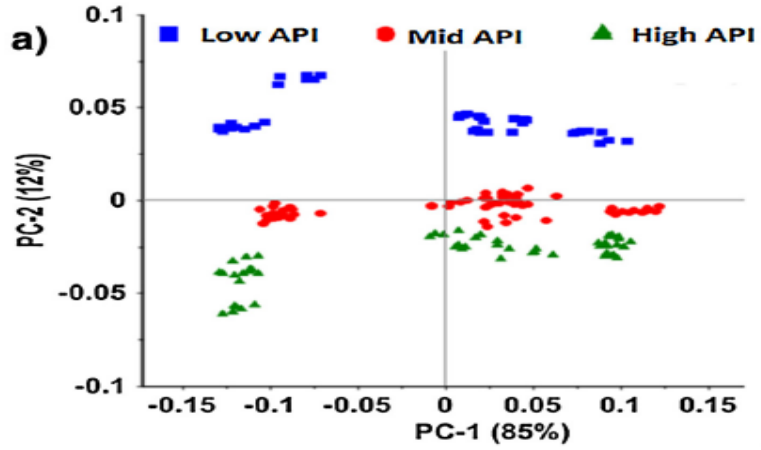
P. Parwar *et al* "Enabling real time release testing by NIR prediction of dissolution of tablets made by continuous direct compression (CDC) *International Journal of Pharmaceutics* 512 (2016) 96–107

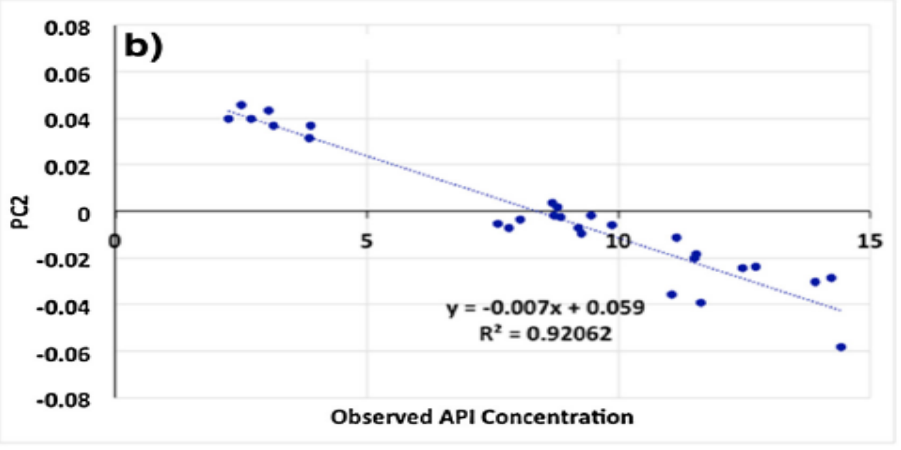
Multivariate analysis of NIR data

$$X = TP^T + E = Structure + Noise$$









Dissolution data fitting

1. Model independent approach (level-shape analysis)

$$\bar{y}_i = \sum y_{ij}/n$$

2. Model dependent approach (based on Weibull)

$$R_{ij} = y_{ij} - y_{..} - (y_{i.} - y_{..}) - \left(y_{.j} - y_{..}\right)$$

$$\%Dissolution = 100 * \{1 - exp^{(t)\wedge\beta/\alpha}\}$$

Multi-linear regression model

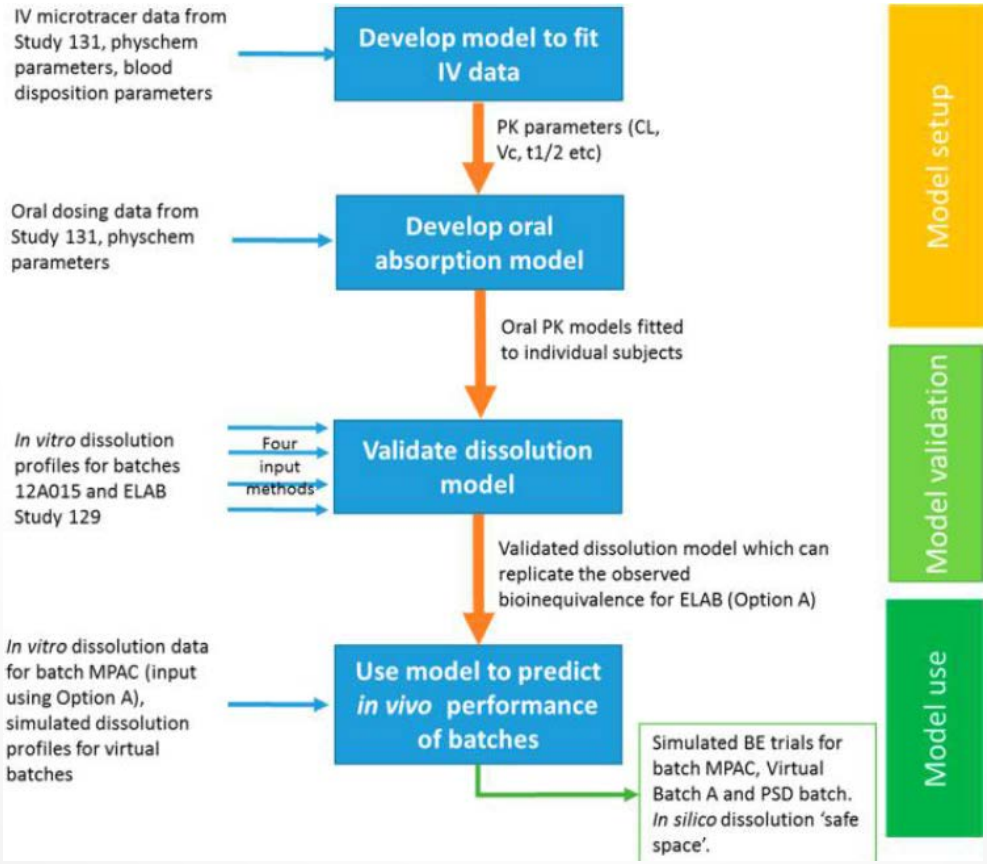
- Regression between the PCA scores and the parameters obtained from the model independent approach
  - Multi linear regression between level and shape parameters for dissolution profiles and the regressor variables (PC1, PC2 and PC3)
- Regression between the PCA scores and the parameters obtained from the model dependent approach
  - Multi linear regression between dissolution parameters (a and b) and the regressor variables (PC1, PC2 and PC3)

Conclusion:

The established multivariate linear regression model was able to predict the dissolution profile of individual tablets based on its NIR spectrum.

Case Study 6: Develop PBPK and dissolution model to inform formulation design space

X. Pepin *et al* "Justification of Drug Product Dissolution Rate and Drug Substance Particle Size Specifications Based on Absorption PBPK Modeling for Lesinurad Immediate Release Tablets" *Mol. Pharmaceutics* 2016, 13, 3256−3269



Benefits and potential applications for surrogate testing / dissolution modeling

- With robust understanding of drug product CPP, CMA and their impact to in vitro dissolution, a direct linkage between process parameters, raw material attributes, and dissolution can be established via surrogate methods
  - Enhance product understanding
  - Help with risk assessment process and offer some mitigation options
  - Increase speed in product development
  - Allow for developing a clinically relevant dissolution specification strategy
- Dissolution modeling and surrogate testing can be used to achieve real time release testing for dissolution
- Stability models can be developed for predicting dissolution performance during drug product stability
- Dissolution model (mechanistic or empirical) as input method for PBPK model to inform the bioequivalent formulation design space

Acknowledgements

- Zongyun Huang– DPST, Bristol Myers Squibb Co.
- David Good – DPST, Bristol Myers Squibb Co.
- Scott Jennings – DPST, Bristol Myers Squibb Co.
- Gina Thompson – Merck & Co., Inc.
- David Johnson – Merck & Co., Inc.
- Colleen Neu – Merck & Co., Inc.
- Jessica Miller – Merck & Co., Inc.