Understanding In Vitro Dissolution and Clinical Performance for High-Risk IR Products

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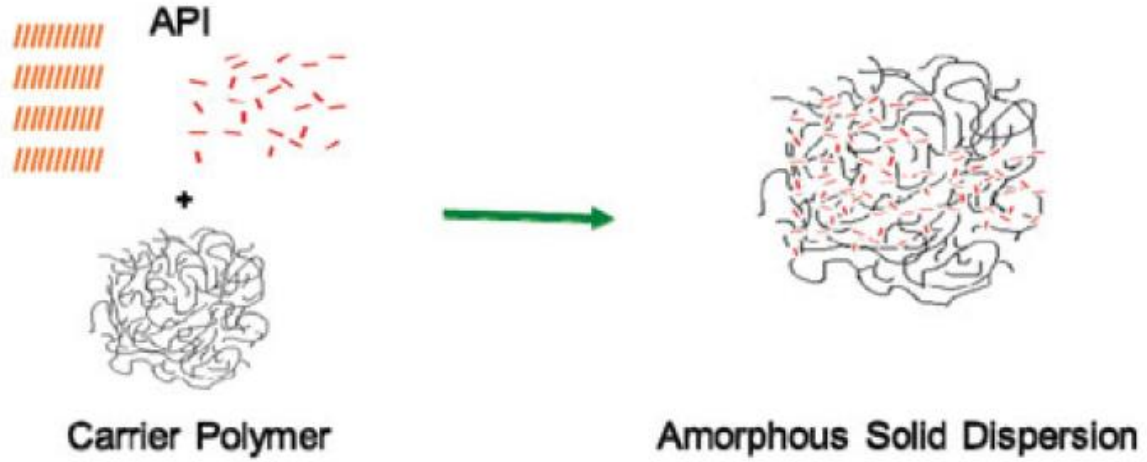
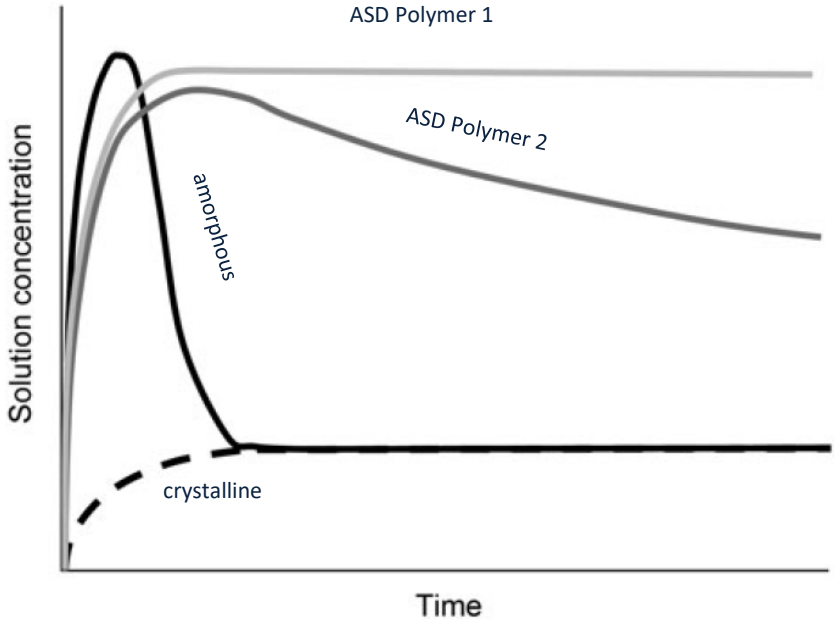
Outline

- High risk IR formulations such as amorphous solid dispersions
- Dissolution to understand critical attributes for ASDs:
  - Develop a QC method based on the sink concept
  - Residual crystallinity
  - Compression sensitivities

Amorphous Solid Dispersion Formulations





Shah et al, "Amorphous Solid Dispersions, Theory and Practice", 2014.

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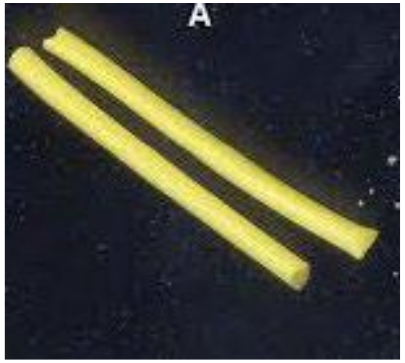
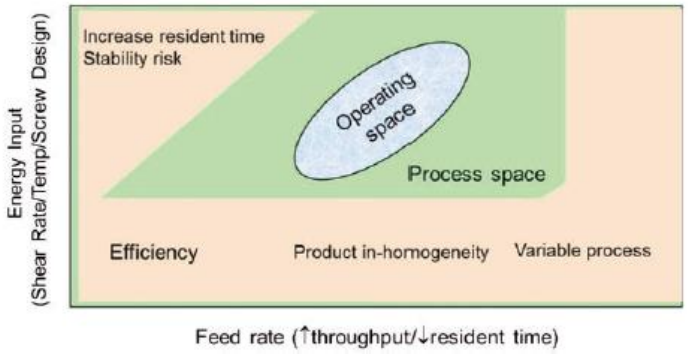
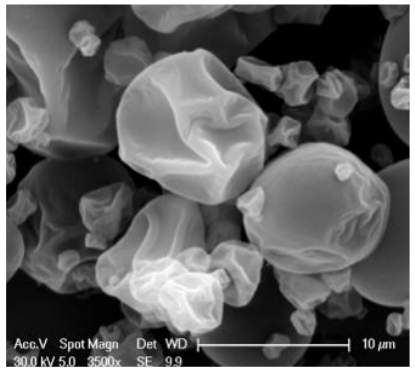
Amorphous Solid Dispersion Formulations

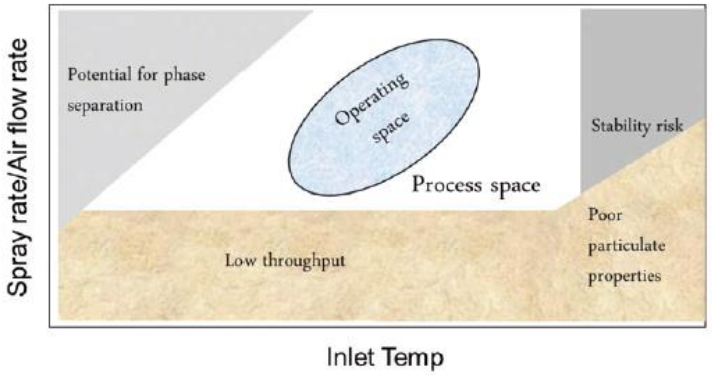
Hot-Melt Extrusion



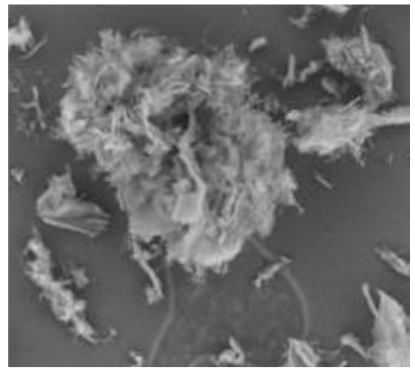


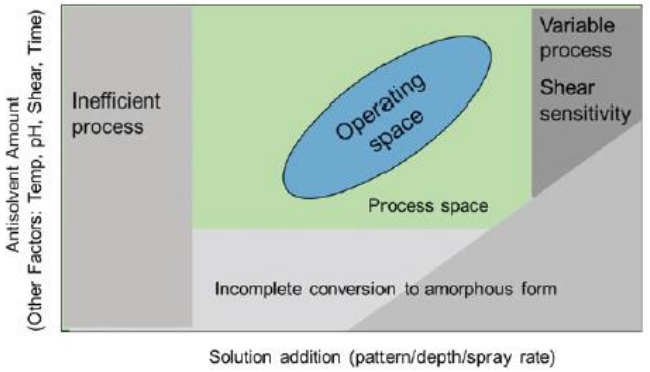
Spray-Drying Dispersion





Co-Solvent Precipitate





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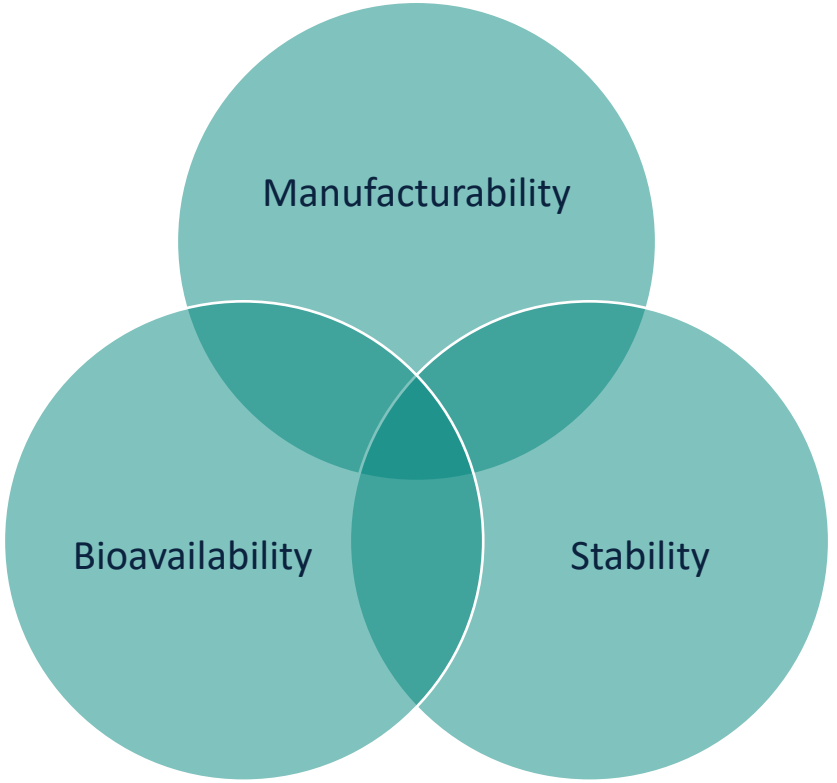
Amorphous Solid Dispersion Formulations

A control strategy aims to maintain the drug product in the amorphous state throughout the intended shelf-life of the product by:

- **Ensuring robustness of the manufacturing process to provide consistently amorphous material.**
  - **ASD particle size/morphology**
  - **Granulation process**
  - **Tableting**
- **Moisture control strategy to avoid crystalline content**
  - **Environmental control during the manufacturing**
  - **Packaged product**
  - **During in-use**
- **Impact on CQAs – Dissolution**
  - **Impact of CPPs**
  - **CMAs**
  - **Crystallinity content**
  - **Clinical experience**



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Amorphous Solid Dispersion Formulations

Sink Conditions

Having a volume of medium (V) at least three times the volume required to form a saturated solution (V_{sat}) of the drug substance; that is, $V/V_{sat} \geq 3$

V/V_{sat} ratio is too large

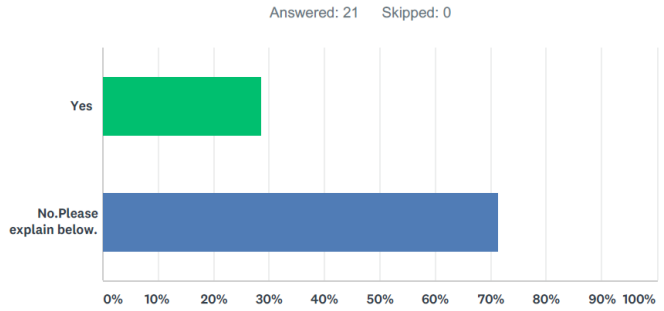
V/V_{sat} <3

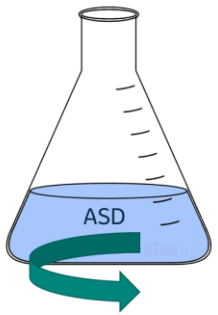
Dissolution test may not detect critical changes in the formulation and manufacturing process

May be acceptable if it is appropriately justified

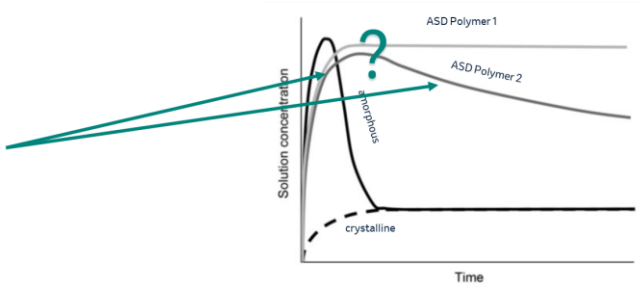
Sink condition is a good starting point for Dissolution method development

Q5 For dissolution methods used for amorphous drug formulations, do you define solubility and sink conditions based on crystalline drug solubility?

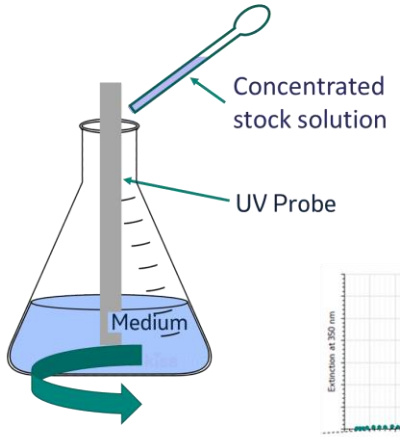


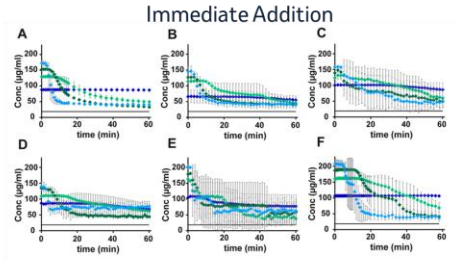


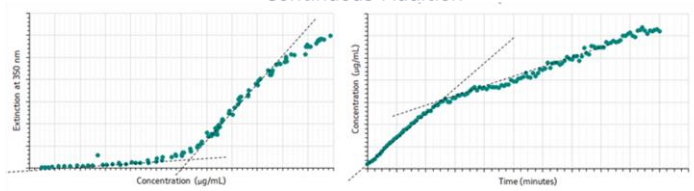
Measurement:
Sampling for dissolution



Two processes:
- Dissolution of ASD
- Precipitation of Drug







Hermans, A., Milsmann, J., Li, H. et al. Challenges and Strategies for Solubility Measurements and Dissolution Method Development for Amorphous Solid Dispersion Formulations. AAPS J 25, 11 (2023)

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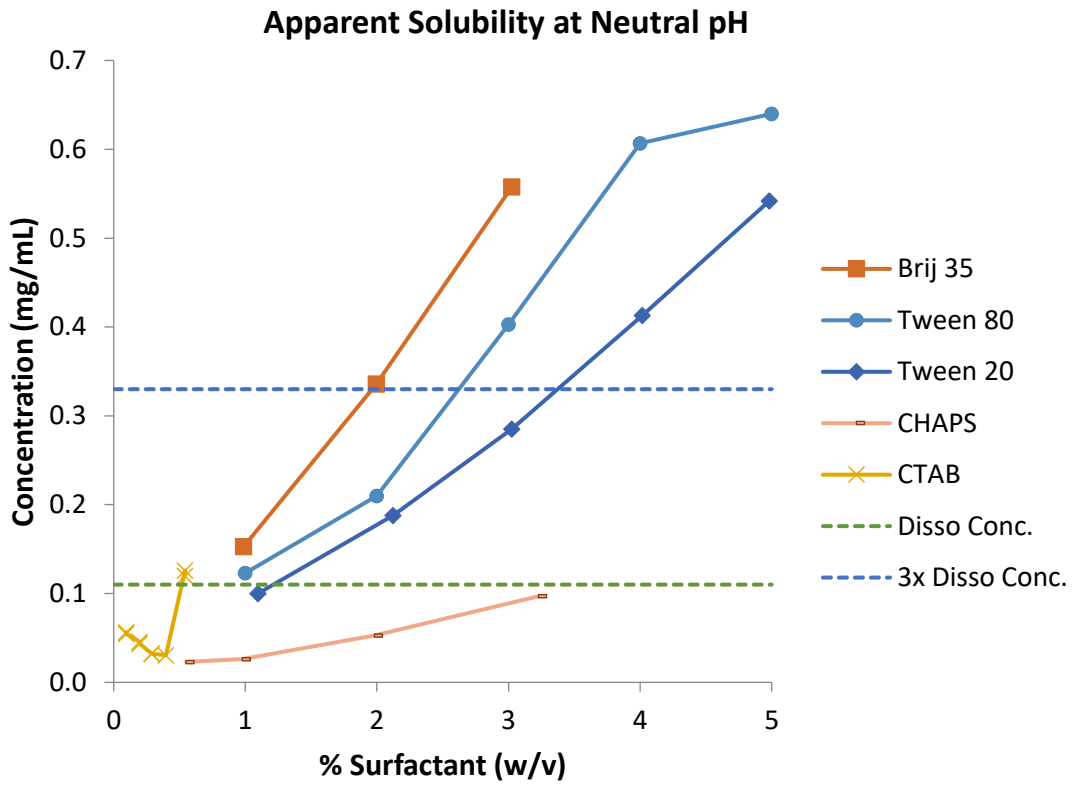
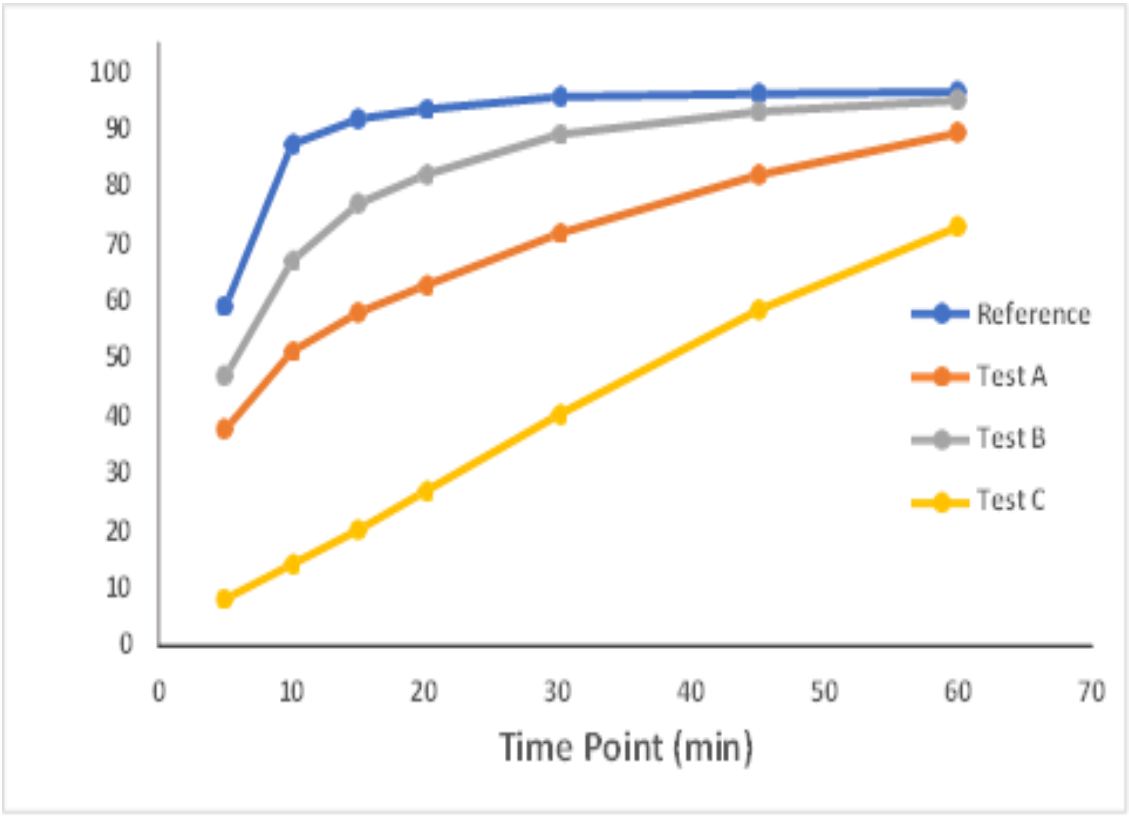
Case Study 1: QC method based on the sink concept

- Selection of surfactant for amorphous solid dispersion-based tablet
- Slower dissolution with low hardness and sensitivity to the moisture content of tablets



Media with 3% Tween 80



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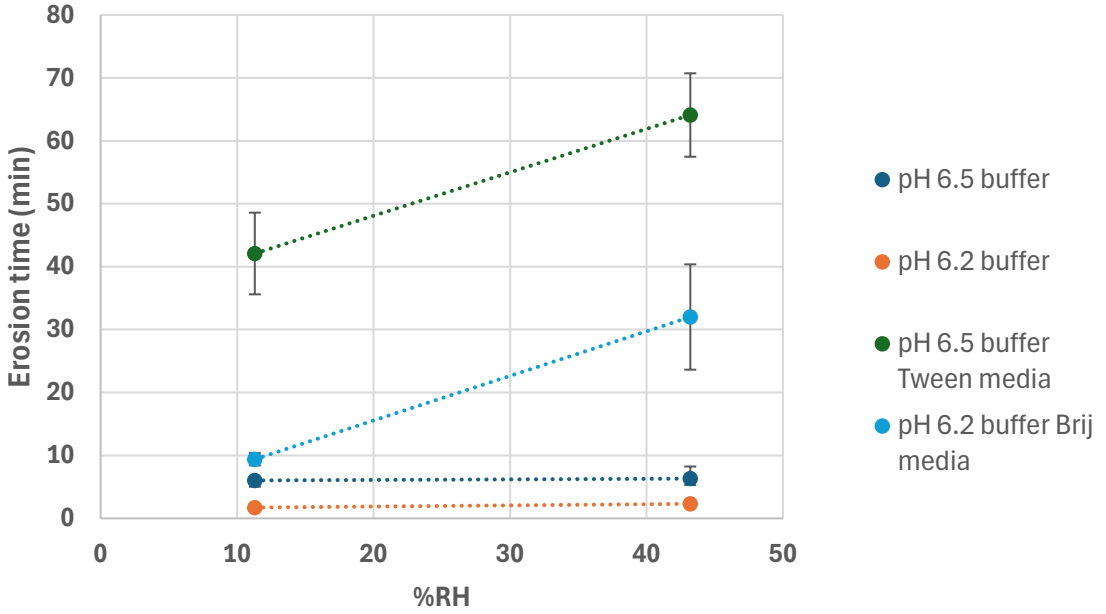

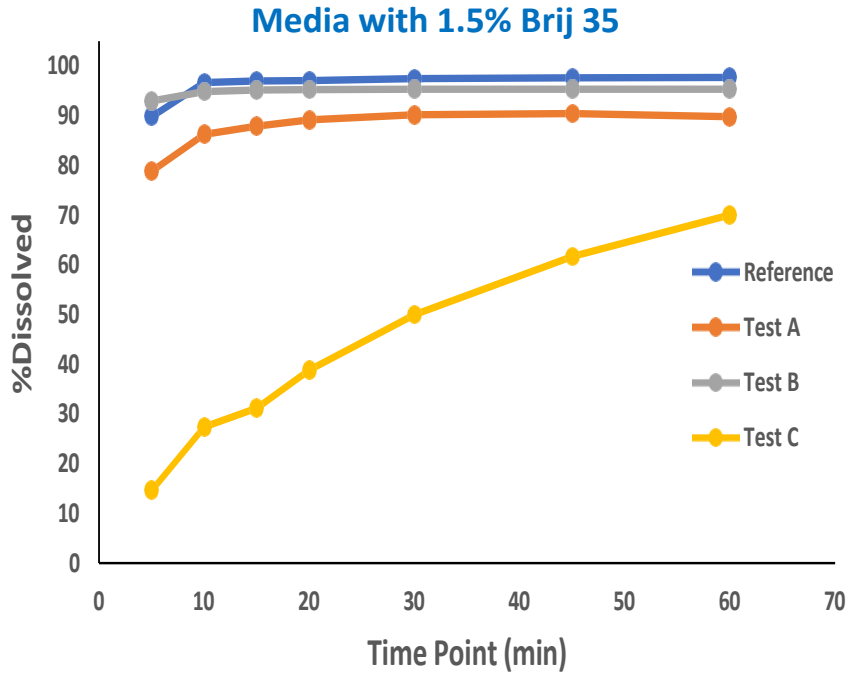

Treatment Comparison	Test A/Reference	Test B/Reference	Test C/Reference
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
AUC0-∞	1.01 (0.92, 1.10)	1.05 (0.97, 1.14)	0.96 (0.85, 1.08)
Cmax	1.07 (0.92, 1.24)	1.08 (0.96, 1.21)	0.78 (0.66, 0.93)

- The dissolution method is selected based on the clinical relevance
- The clinical relevance study helped select the dissolution specification

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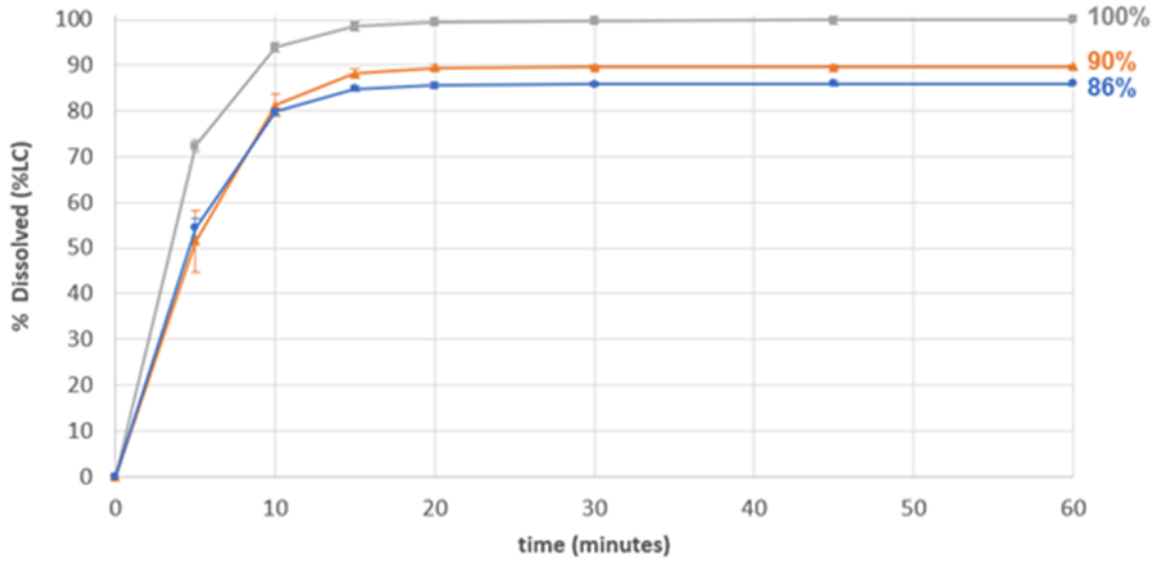
Case Study 2: Understanding the clinical relevance of API form changes

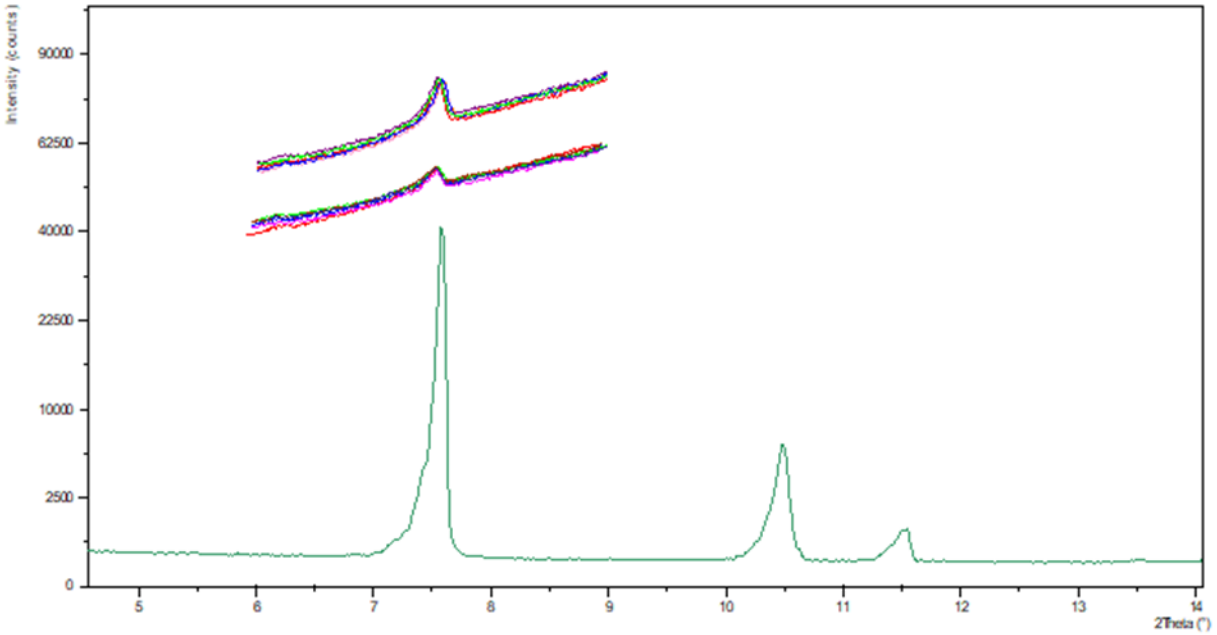
- Crystalline content in the drug product triggers a reduction in dissolution rate and a lower extent of dissolution, suggesting potential PK impact

Impact of Crystallinity on Dissolution



Conditions: USP II (Paddle), 50 rpm; 50 mM potassium phosphate buffer and 68 mM potassium chloride, pH 6.5, 900 mL; Infinity spin after 45 min. Error bars show standard deviation

Spiked Crystallinity in Drug Product



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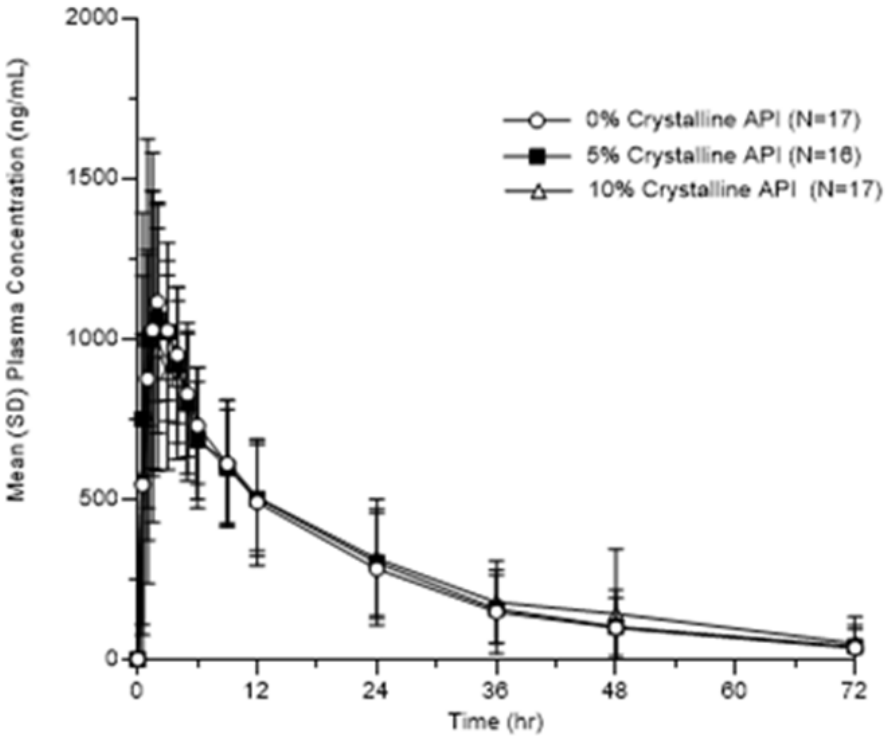
Case Study 2: Understanding the clinical relevance API form changes



Parameters	0% Crystalline API (Reference)	5% Crystalline API (Test 1)	10% Crystalline API (T2)
Cmax (ng/mL)	1220 (25.8)	1180 (38.6)	1130 (38.5)
AUC0-inf (h*ng/mL)	17700 (51.2)	19100 (60.1)	18800 (53.6)
Cmax Ratio	--	0.985 (32.9)	0.959 (30.6)
AUC0-inf Ratio	--	1.04 (15.7)	1.01 (9.5)

- Although dissolution performance was impacted, there was no significant impact on C_{max} or AUC up to 10% crystallinity.

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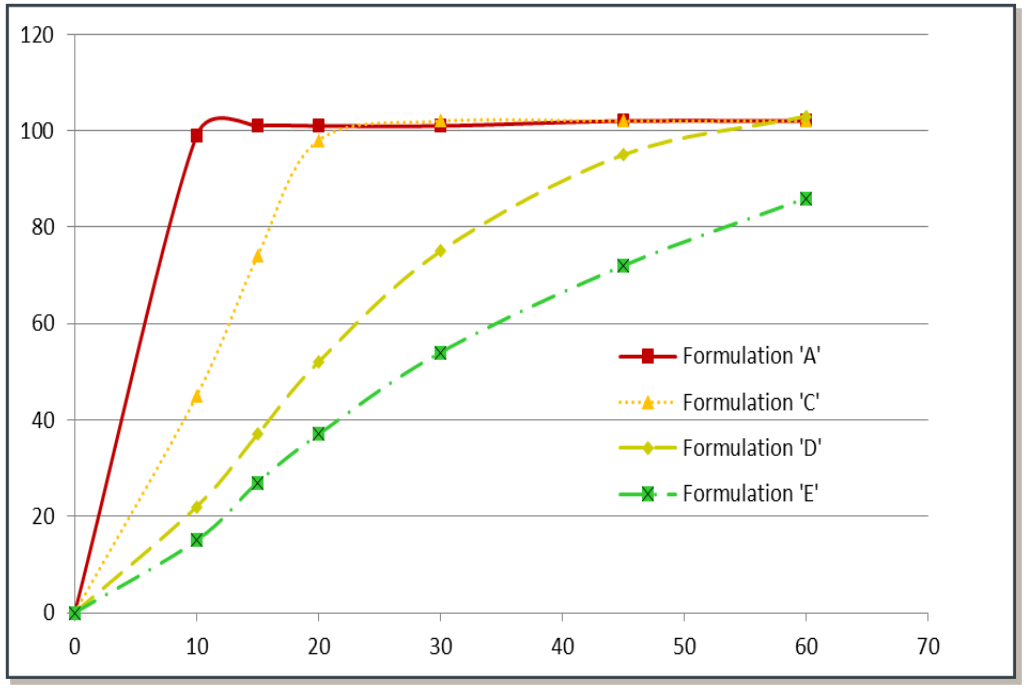
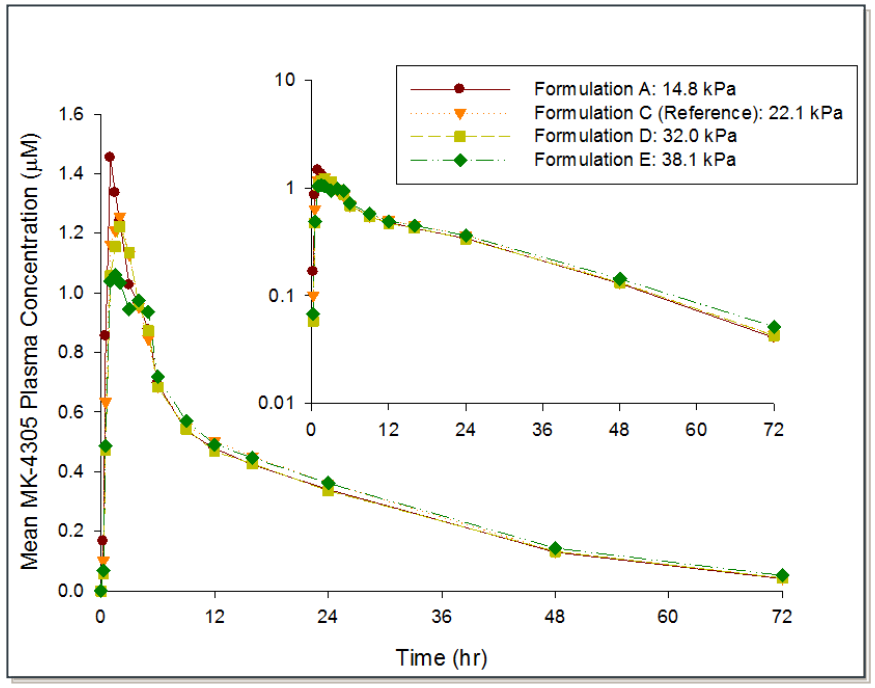
Case Study 3: Understanding the manufacturing process and moisture control strategy

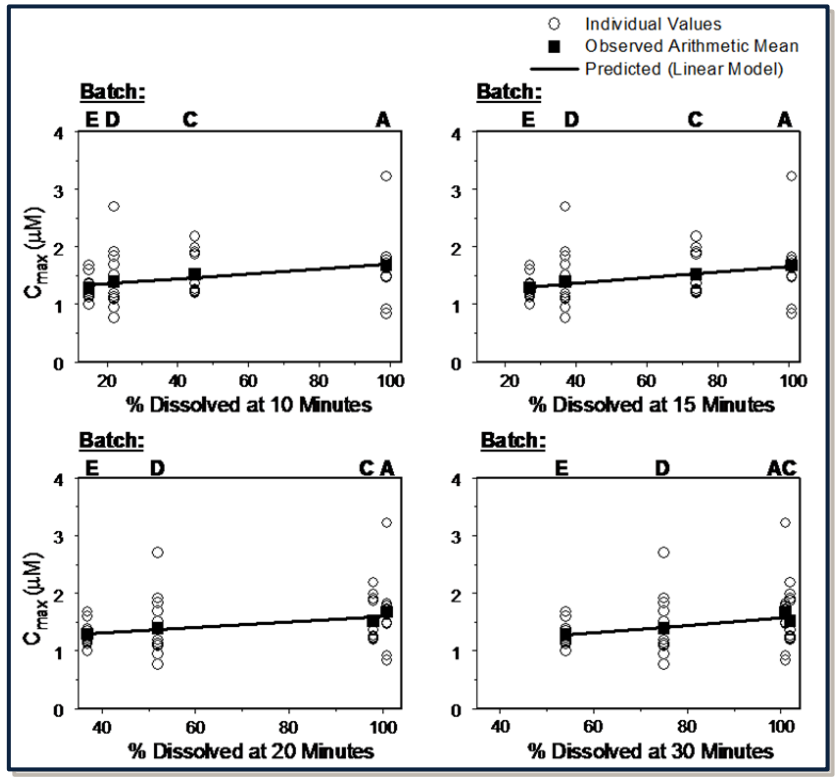
- The dissolution mechanism is erosion-based disintegration of the tablet cores
- Hardness and moisture content of tablets have been determined to have significant effects on the erosion rate





Case Study 3: Understanding the manufacturing process and moisture control strategy

Level C IVIVC

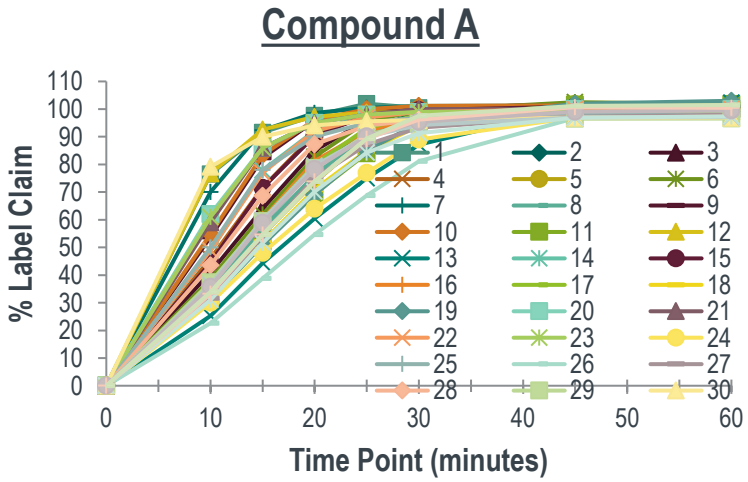


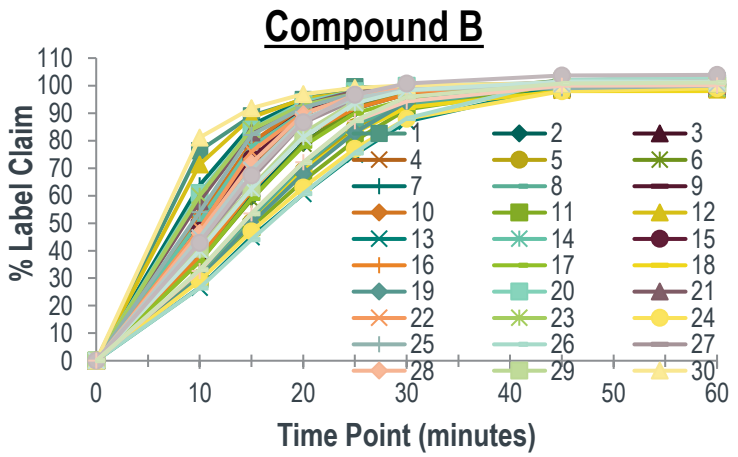
Dissolution time point	lower dissolution range (% Claim)	upper dissolution range (% Claim)
10 min	10.3%	79.9%
15 min	42.2%	100%
20 min	64.9%	100%
30 min	77.8%	100%
45 min	86.0%	100%

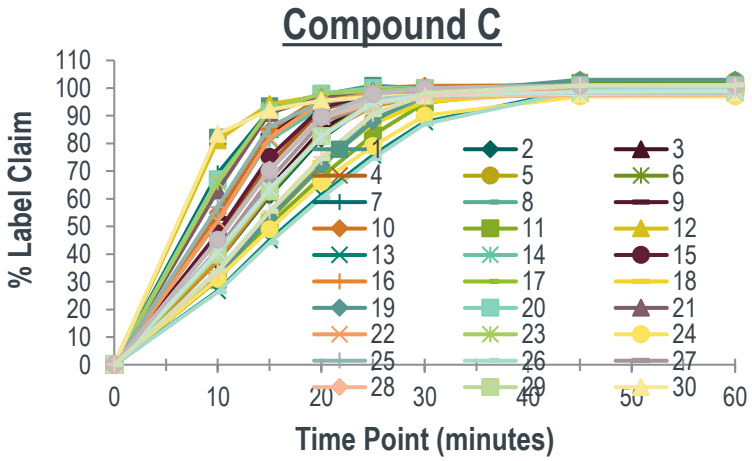
- Setting in process controls
- Setting environmental and package controls for moisture
- Dissolution Specification Setting based on lower acceptable range for IVIVC model (supportive)
- Use the IVIVC model to predict in vivo performance for future BE studies

Case Study 4: Understanding the manufacturing process and moisture control strategy

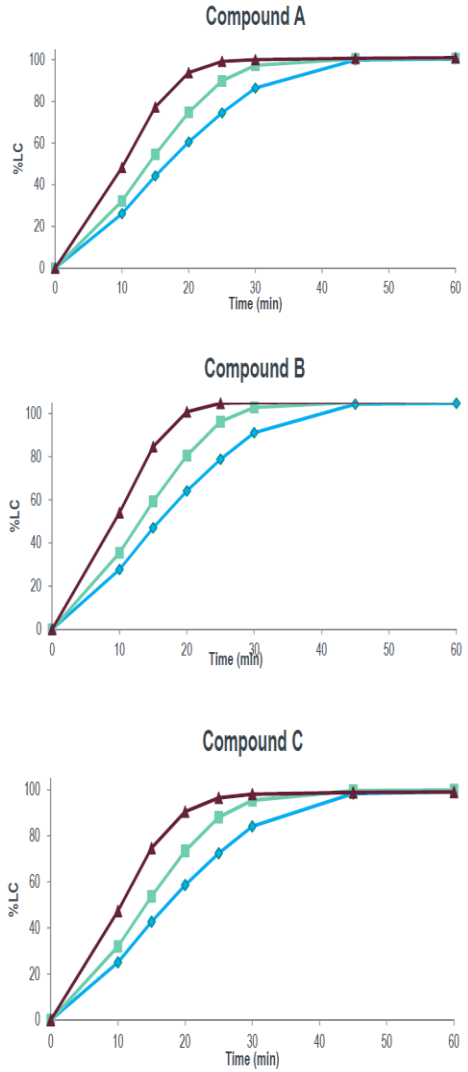
- Compound A and B: Amorphous Solid dispersion, Compound C: Crystalline, High Solubility
- DoE based on risk assessment around 5 main factors that influence dissolution:
  - Spray Dry conditions for A and B, Roll Compaction Force, Tablet Hardness, Tablet Moisture



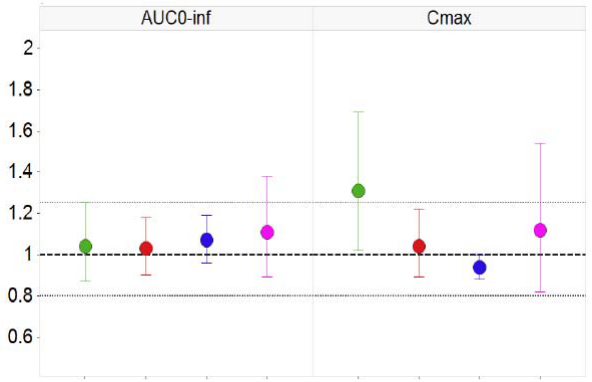




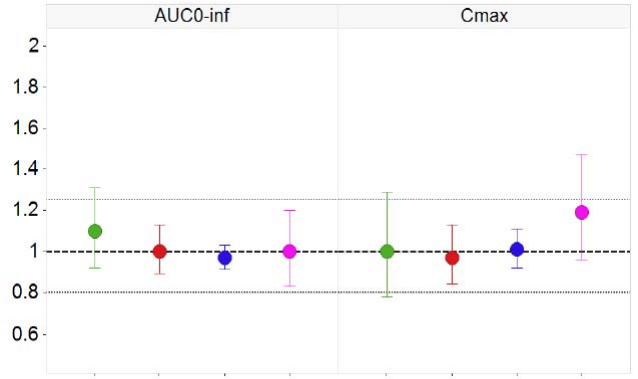
Case Study 4: Understanding the manufacturing process and moisture control strategy

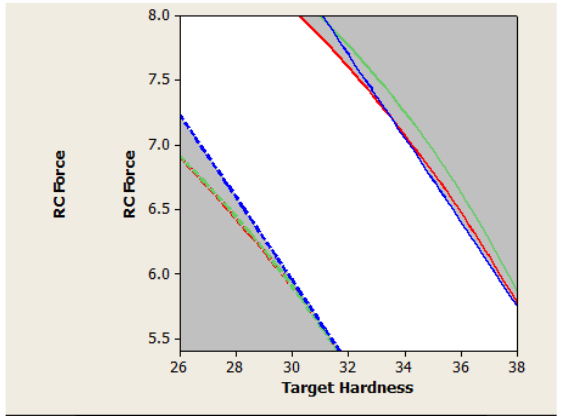


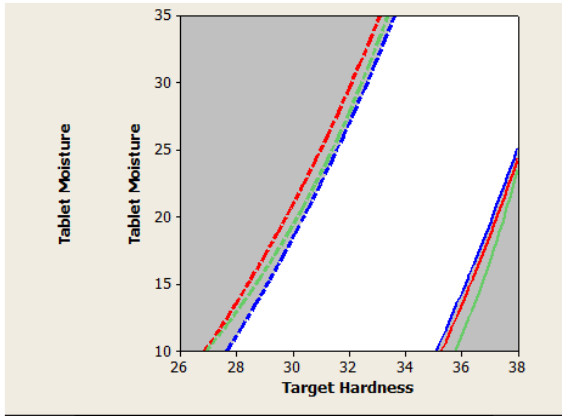
Fast vs Target



Slow vs Target







- Dissolution modeling can establish a direct linkage between CPPs, CMA, and in-vivo performance, enabling a clinically relevant control strategy

Acknowledgements

- Merck & Co., Inc., Rahway, NJ, USA
  - Andre Hermans
  - Filippos Kesisoglou
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