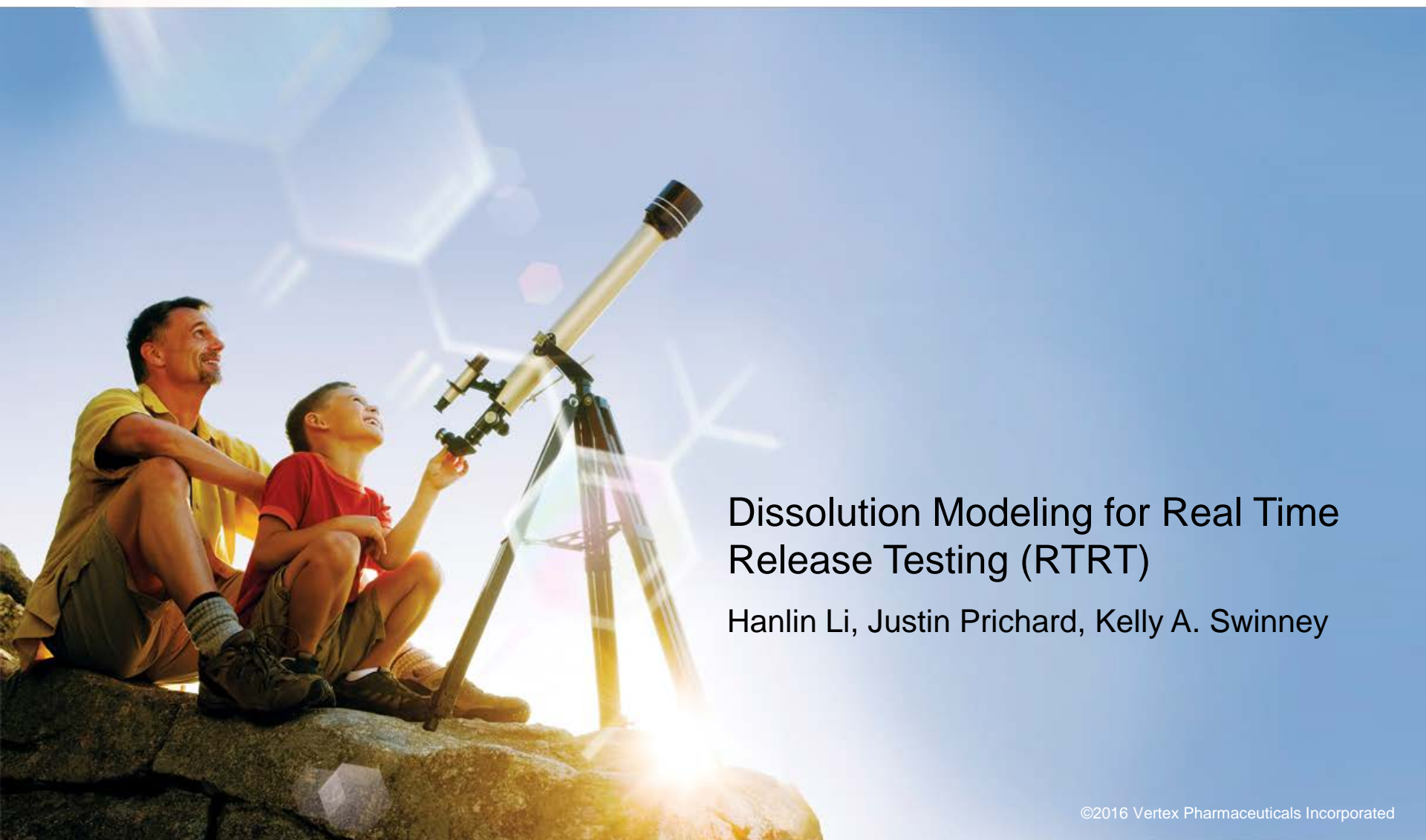




THE SCIENCE *of* POSSIBILITY



Dissolution Modeling for Real Time
Release Testing (RTRT)

Hanlin Li, Justin Prichard, Kelly A. Swinney

Outline

- Introduction to continuous manufacturing and RTRT at Vertex
- RTRT for dissolution – model development approach
- Case Study



Vertex Business Drivers for Continuous Manufacturing



Early finalization of formulation/process on commercial scale



“Data rich” QbD commercial design space



High quality, consistent product

Vertex's Continuous Manufacturing Rig

Powder In



Day 1 AM

Multi-product Line

- Smaller scale equipment
- All unit ops in one facility



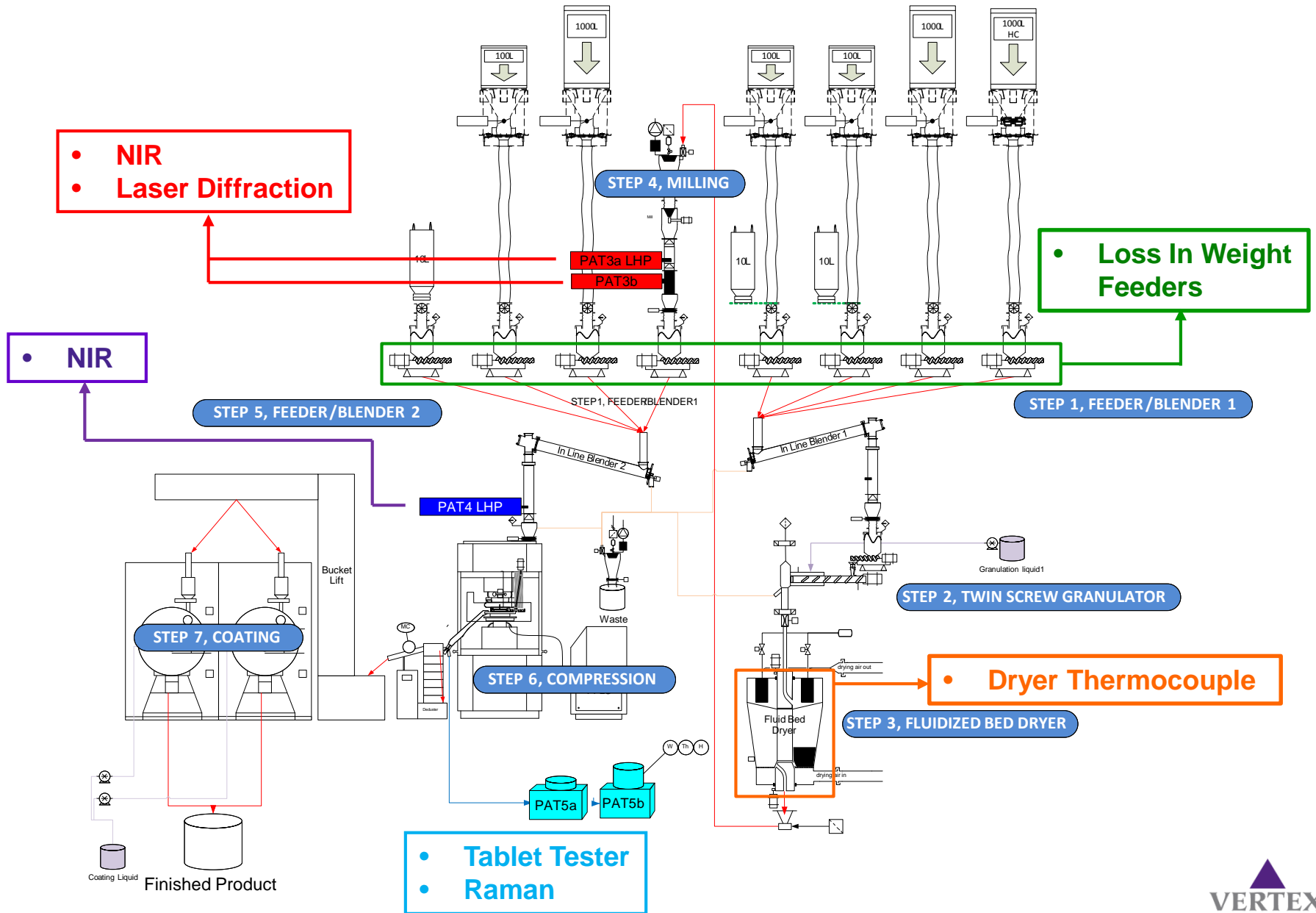
Day 1 AM



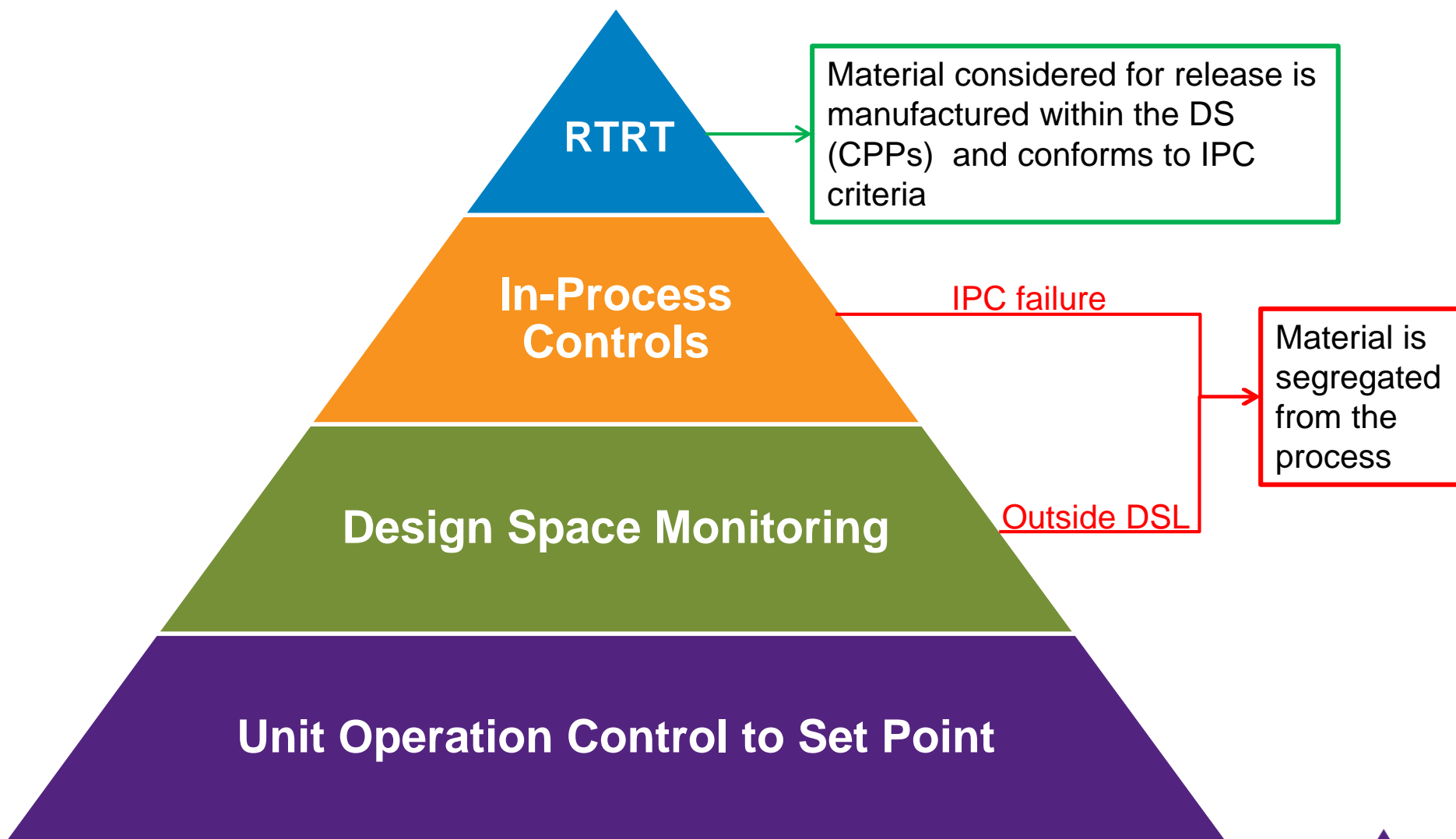
Coated Tablets Out

PAT Automated Control Strategy => IPCs + RTRT

PAT Locations Available for IPC and RTRT Measurements



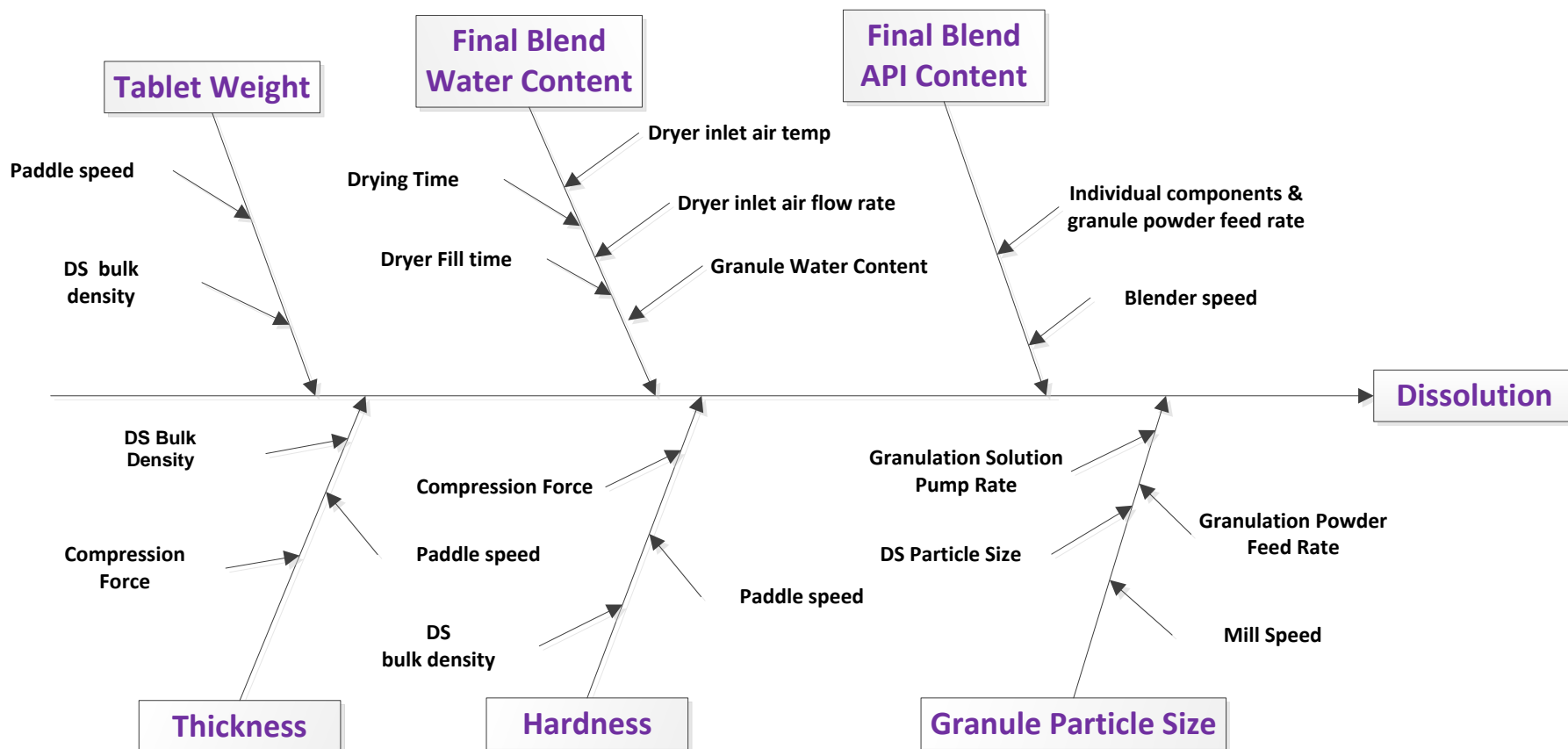
CM Control Strategy Building Blocks



Example of RTRT for Continuous Manufacturing

Critical Quality Attribute	PAT Technology	RTRT Method	Material
Identification	Raman	Confirm presence of API	Core Tablet
Assay	NIR	API Content	Final Blend
	Weight	Tablet Weight	Core Tablet
Dissolution	Laser Diffraction	Granule Particle Size	Milled Granules
	NIR	API Content, Water Content	Final Blend
	WTH	Tablet Weight, Hardness, Thickness	Core Tablet
Water Content	NIR	Water Content	Final Blend
Content Uniformity	NIR	Variance in API Content	Final Blend
	Weight	Variance in Tablet weight	Core Tablet
Physical Form	Raman	API physical form	Core Tablet

RTRT for Dissolution



- The inputs are based on knowledge of the process and factors influencing dissolution performance at the time of batch release.

Dissolution Model Development Approach

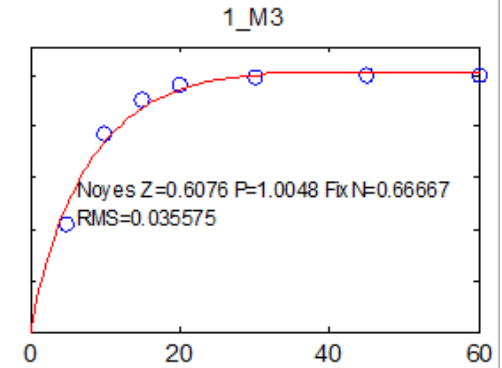
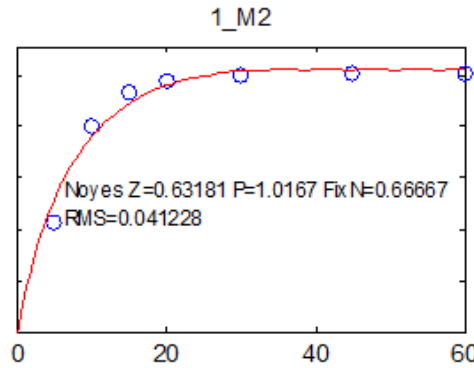
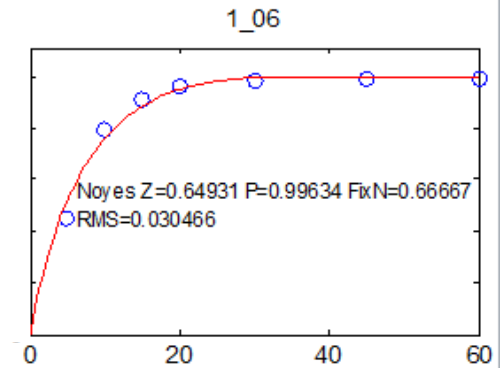
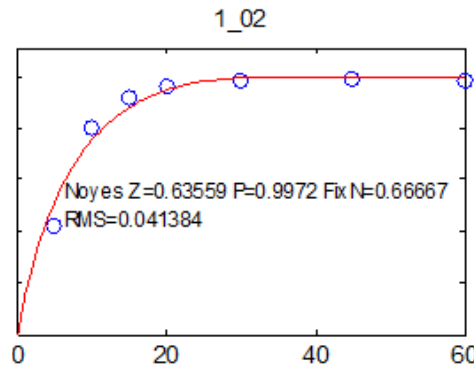
1. Determine the dissolution rate from the reference dissolution profiles
2. Model Z using measured attribute data
 - Core Tablet (PAT 5 - Kraemer): Hardness, Thickness, Weight
 - Final Blend (PAT 4 - NIR): water content, API content
 - Granules (PAT 3b – Malvern): particle size distribution
3. For routine use, Z is predicted and used to predict the a dissolution profile



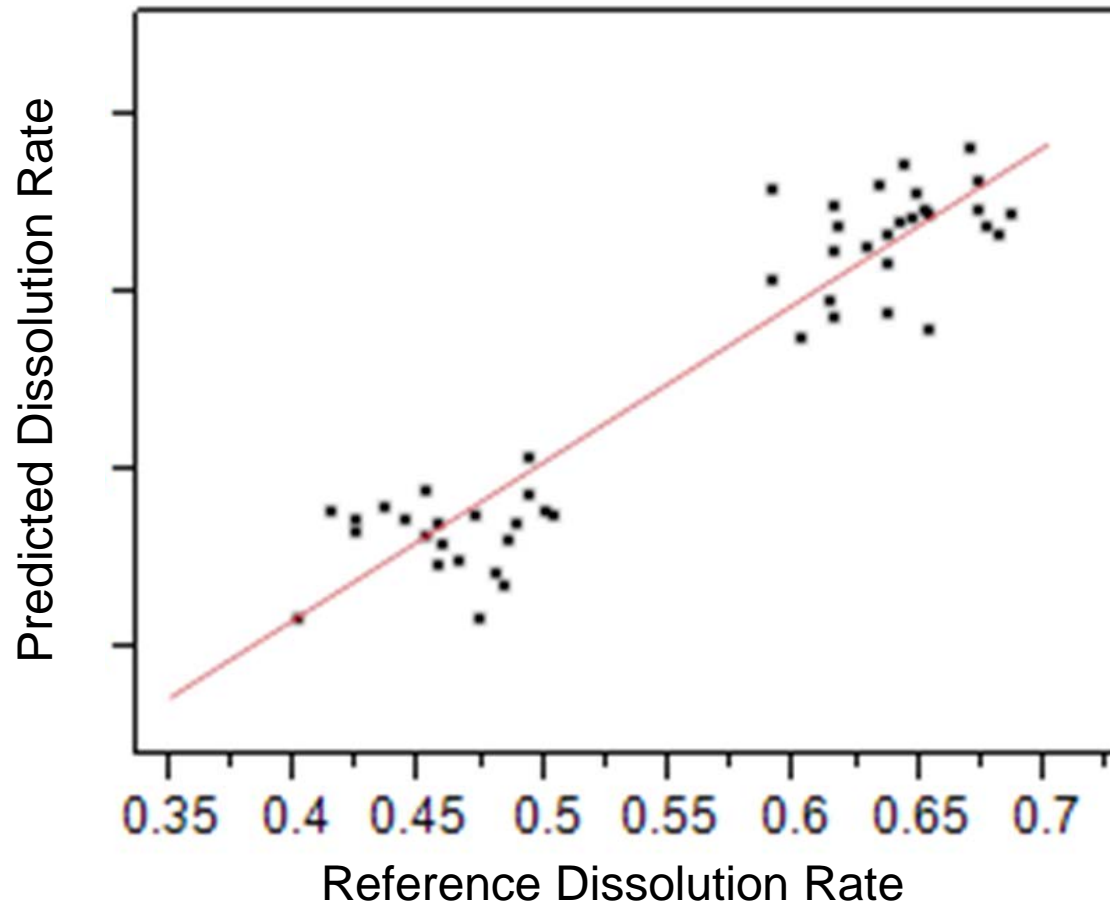
Step 1: Determine the dissolution rate from the reference dissolution profiles

$$\frac{dLC}{dt} = z(p - LC)^n \left(S - \frac{Dose}{Vol} LC \right)$$

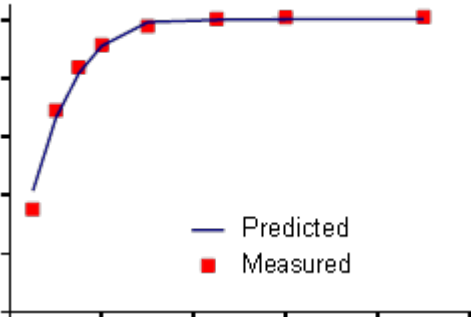
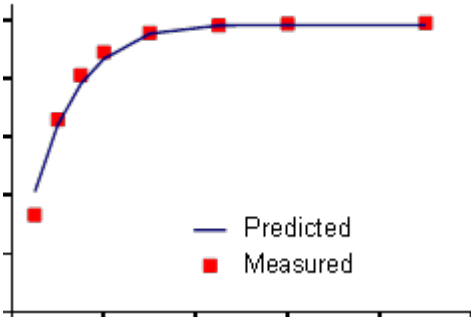
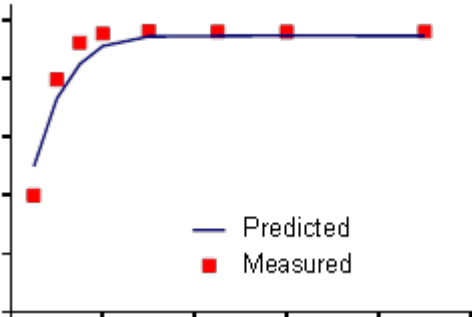
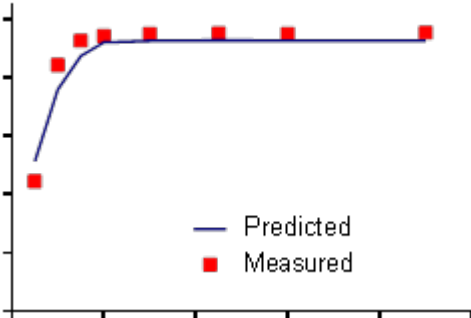
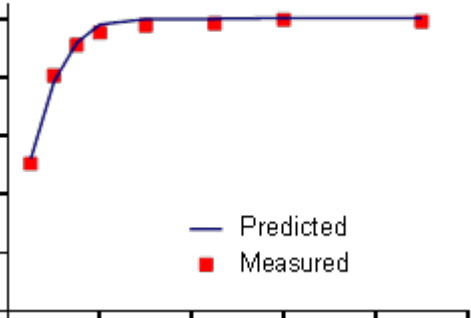
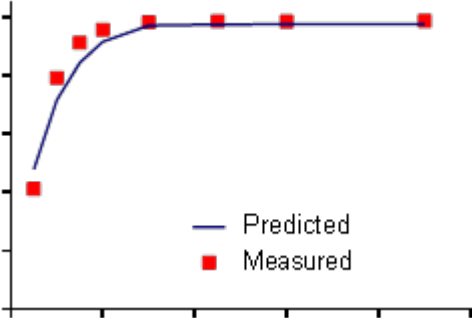
- LC: dissolution % at time t
- Dose: dose
- Fixed parameters
 - n: shape factor
 - Vol: volume
 - S: solubility
- Parameters to be fitted:
 - z: rate (scale) factor
 - p: plateau



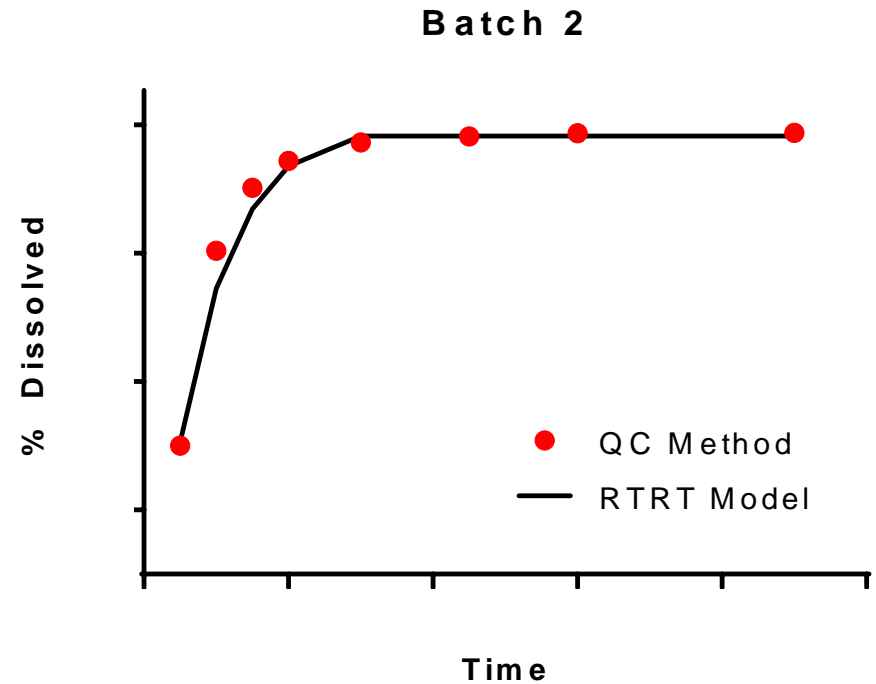
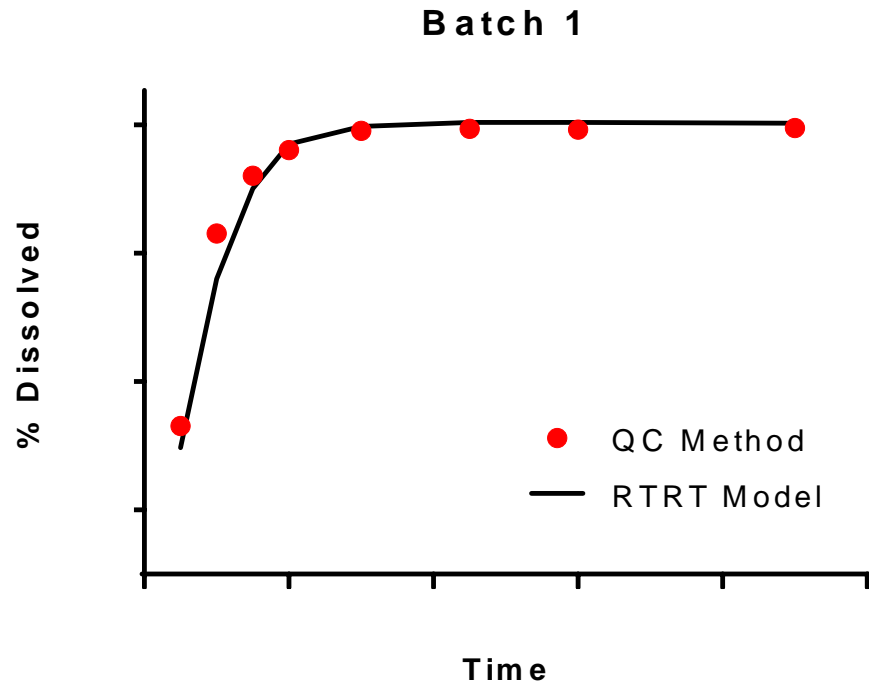
Step 2: Model dissolution rate using measured attribute data



Reconstruct Dissolution Curve using Predicted Dissolution Rate



RTRT Dissolution Model: Case Study

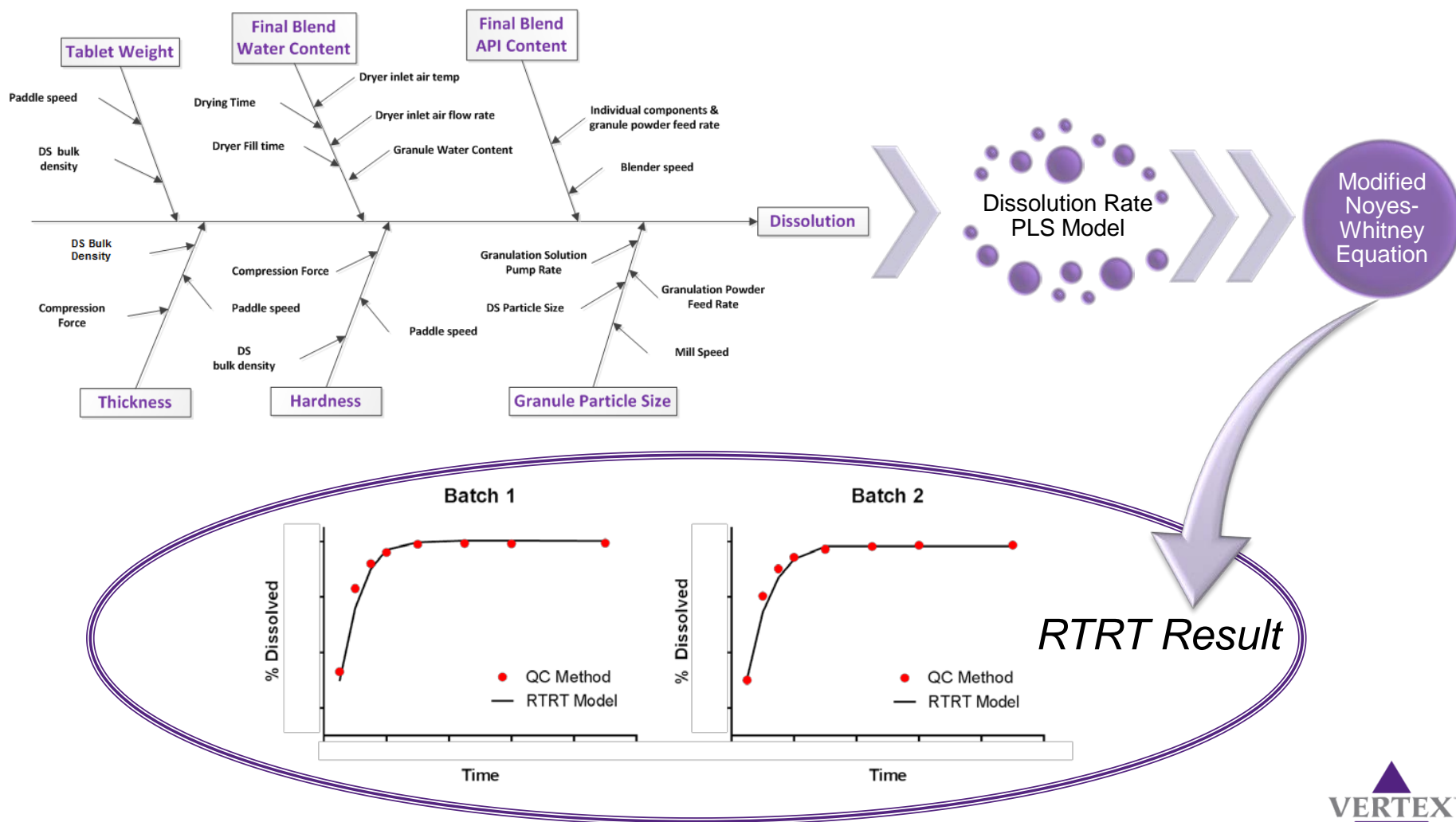


USP <1092>: Absolute difference not more than 5% for time points > 85% released



In Summary

Process knowledge and identified factors influencing dissolution performance used to develop RTRT dissolution method



Acknowledgements

- Vertex Team
 - Pharmaceutical and Preclinical Science
 - Technical Operations
 - Supply Chain Management
 - Quality
 - CMC Regulatory
 - Facilities
 - Global Information Systems
- Equipment Manufacturers
- Our CMOs, Suppliers, and Research Collaborators
- Regulatory Agencies (FDA, EMA, MHRA, etc)

