Enabling Real Time Release testing (RTRt) with NIR-based prediction of dissolution for Tablets made by Continuous Direct Compression (CDC)

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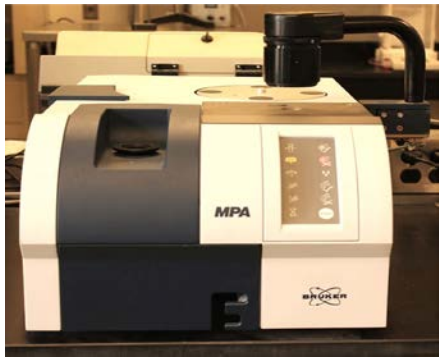
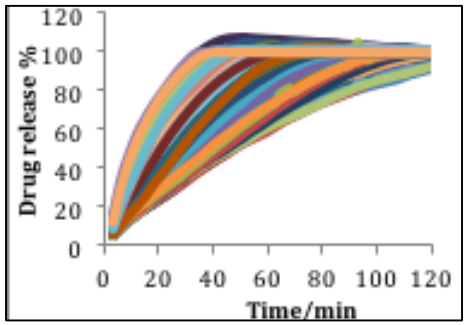
Methodology

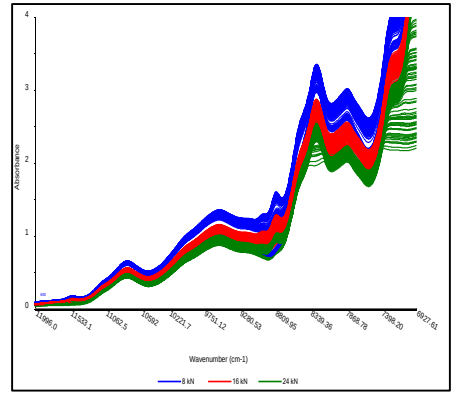


Tablets: Define Target Conditions

Design of Experiment

Variation in *Process Parameters* ←→ Tablet *Dissolution*





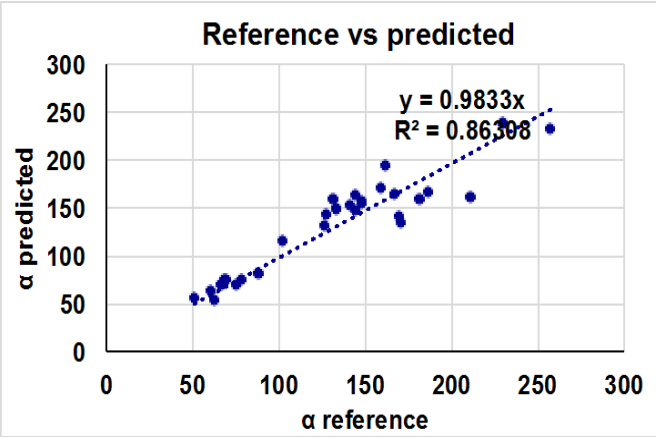
Dissolution Data

NIR Data

Model Based Fitting Parameters

Model Independent

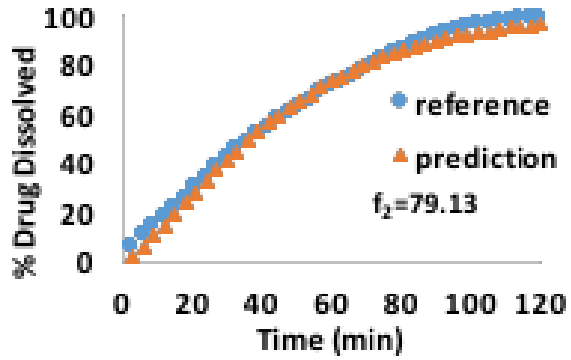
Principal Component Analysis



Dissolution Model

Multiple Linear Regression

Dissolution Validation



Case study: Tablet Specifications

Formulation:

Active Ingredient: Semi-fine Acetaminophen (APAP) 9%

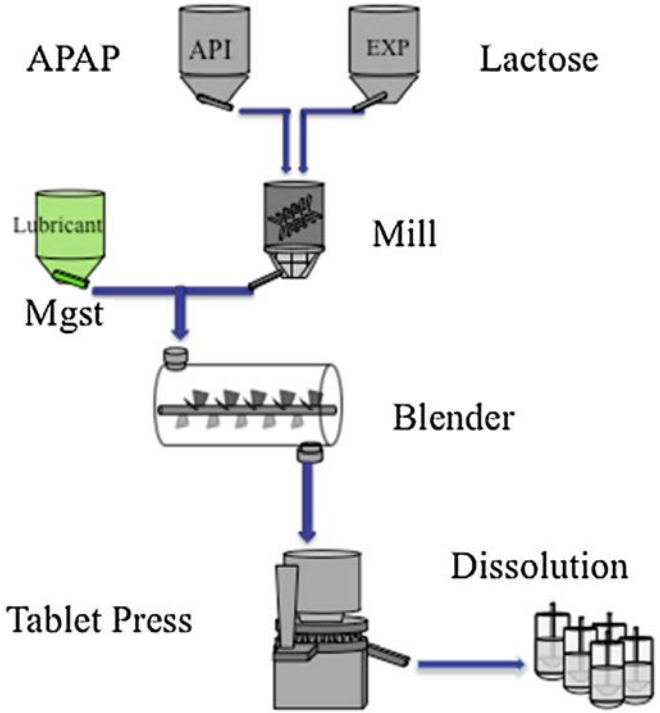
Excipients: (Binder) Lactose Monohydrate 90%;

(Lubricant) Magnesium Stearate (MgSt) 1%.

Variable

Case study: Manufacturing Process

Continuous Manufacturing Pilot Plant @ Rutgers



Feeders

K-Tron KT20- Acetaminophen

K-Tron KT35- Lactose Monohydrate

K-Tron MT12- Magnesium Stearate

20 kg/h

Fixed

Quadro S197 comil

Delump active and excipient

Glatt GCG 70 blender

24 blades

200 rpm

Variable

Kikusui Libra2 tablet press

36-station

Type B flat tooling;

10 mm diameter

24 kN &
20 rpm

Variable

Experimental Design

Target Product Specification

API Target: 9% APAP

Force (*Hardness*): 24 kN (300MPa)

Blender speed: 200 rpm **Feed Frame speed:** 25 rpm

Throughput: 20 kg/hour Tablet weight: 350 mg

DOE: 4 Variables & 3 Levels

	API	Force	Blender	Feed Frame
Low	5%	8 kN	150 rpm	20 rpm
Target	9%	16 kN	200 rpm	25 rpm
High	13%	24 kN	250 rpm	30 rpm

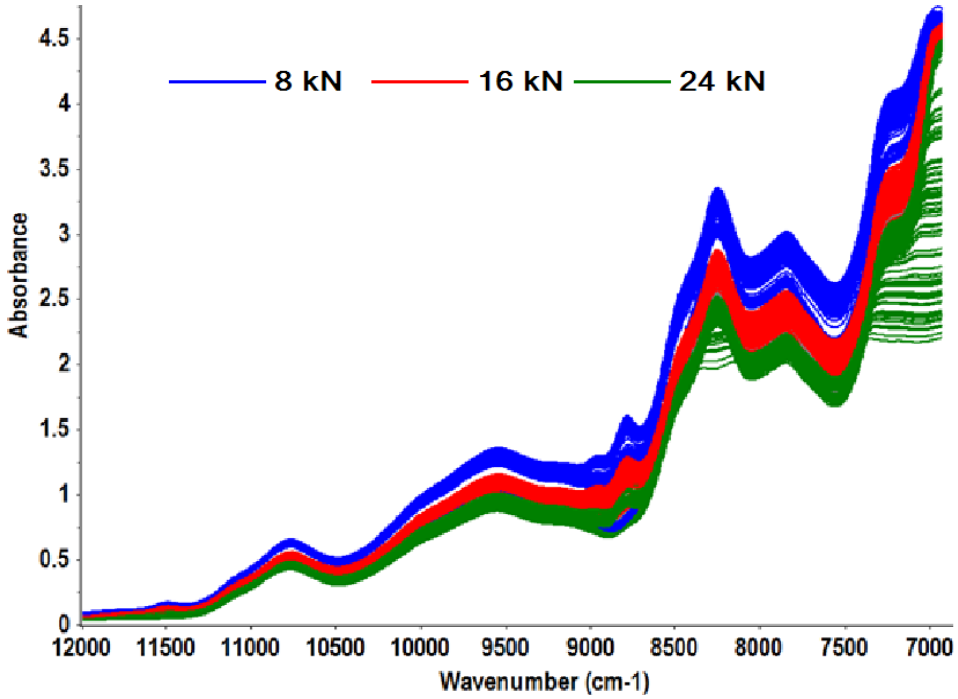
Fractional Factorial Design

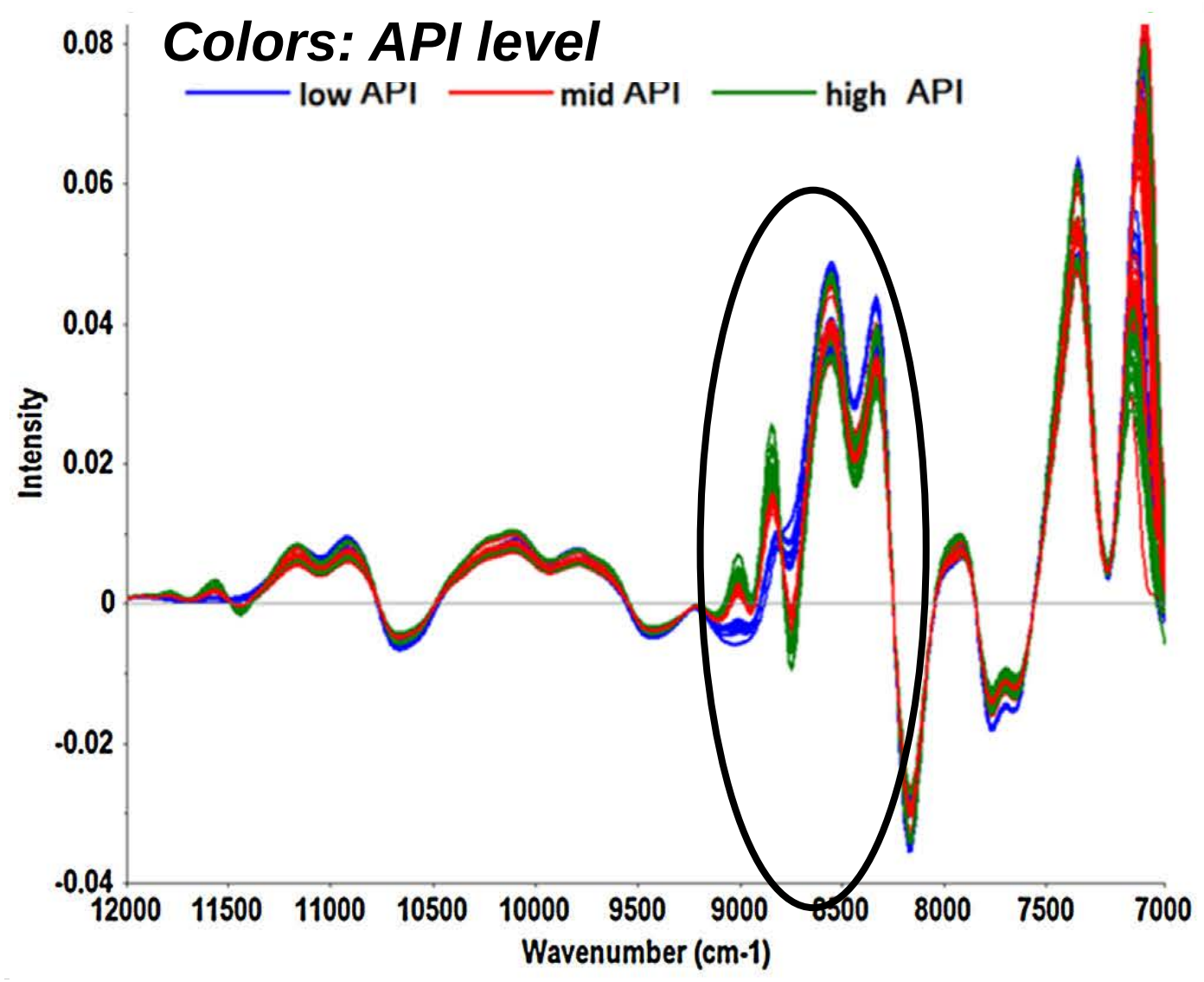
3^{4-1} design + 3 center points = 30 conditions

6 tablets / condition

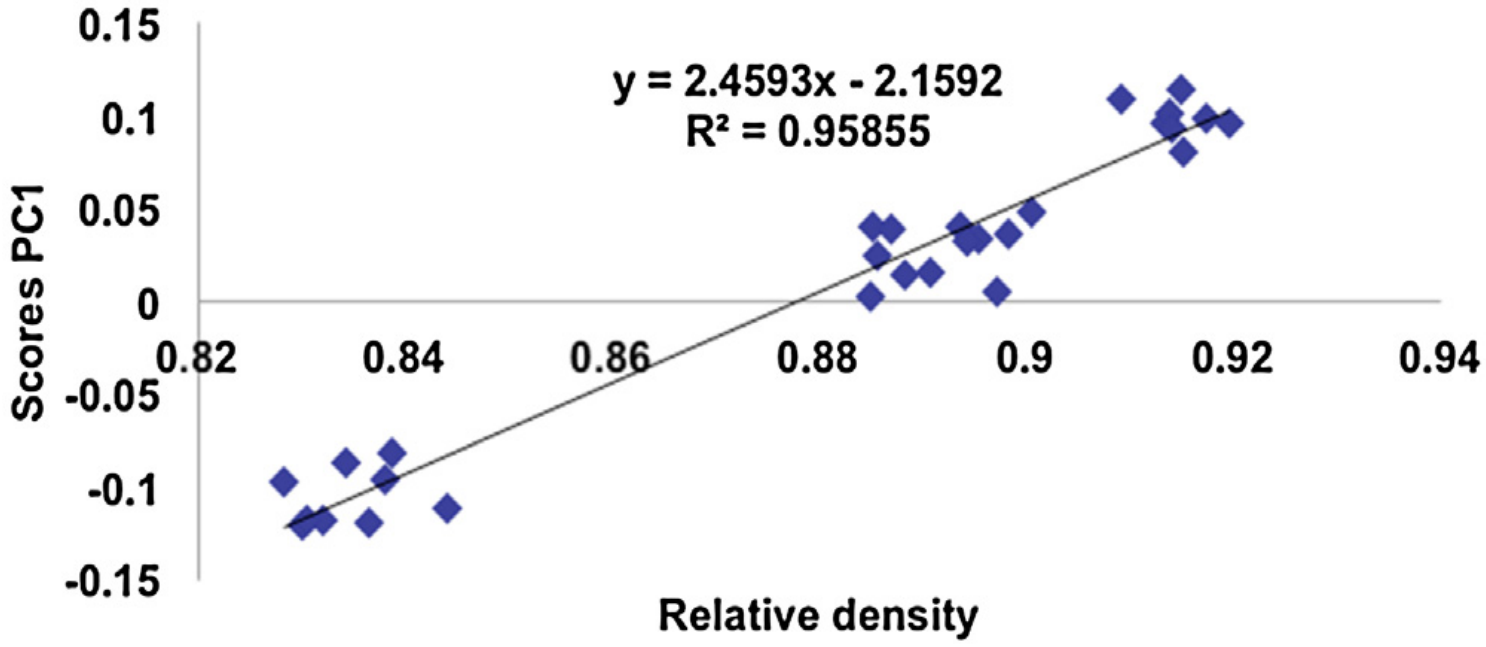
Near Infra-Red Transmission Spectra Measurements

Bruker MPA; OPUS 6.5 Software



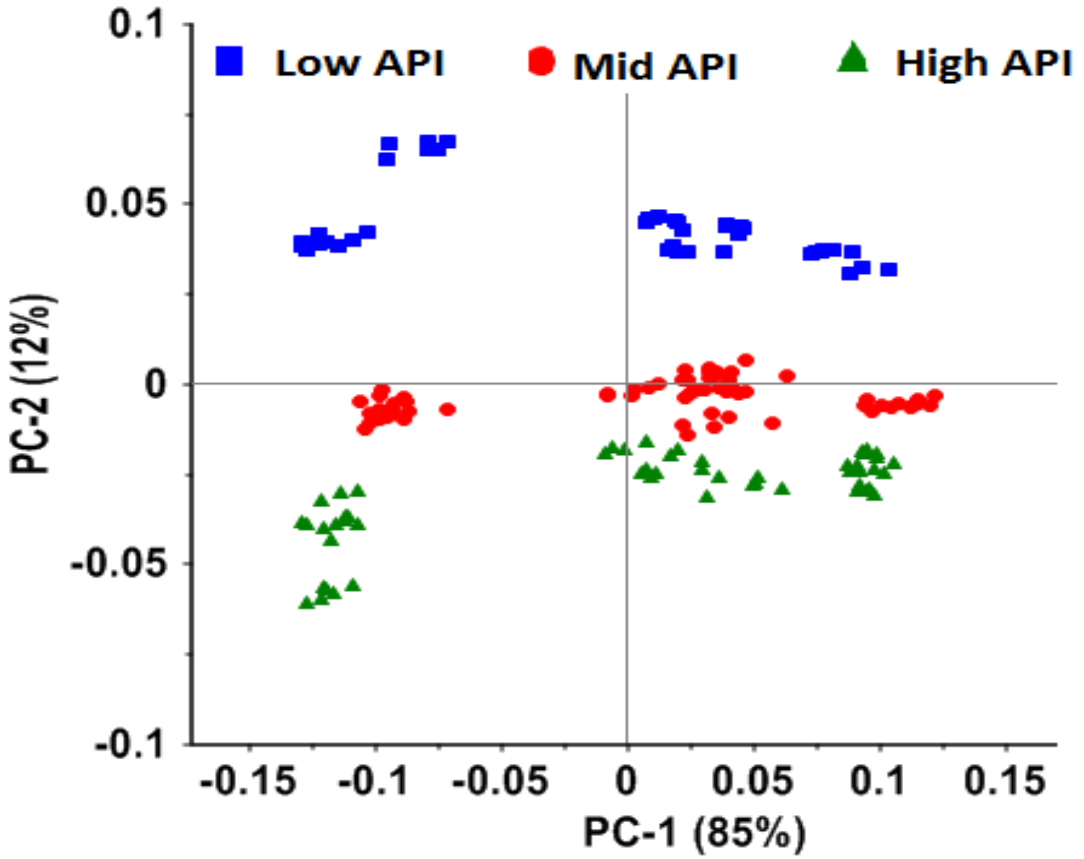


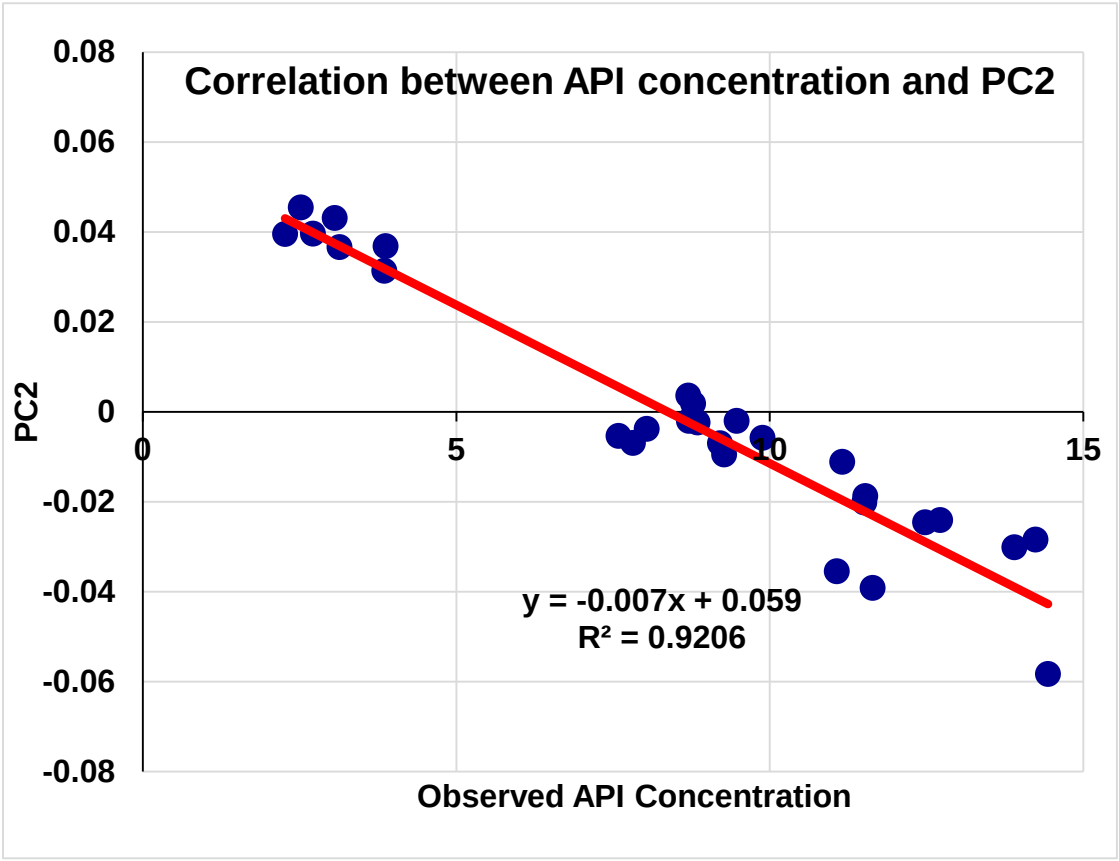
NIR: Principal Component Analysis



PC1 Clearly correlated with relative density
→ Compaction Force

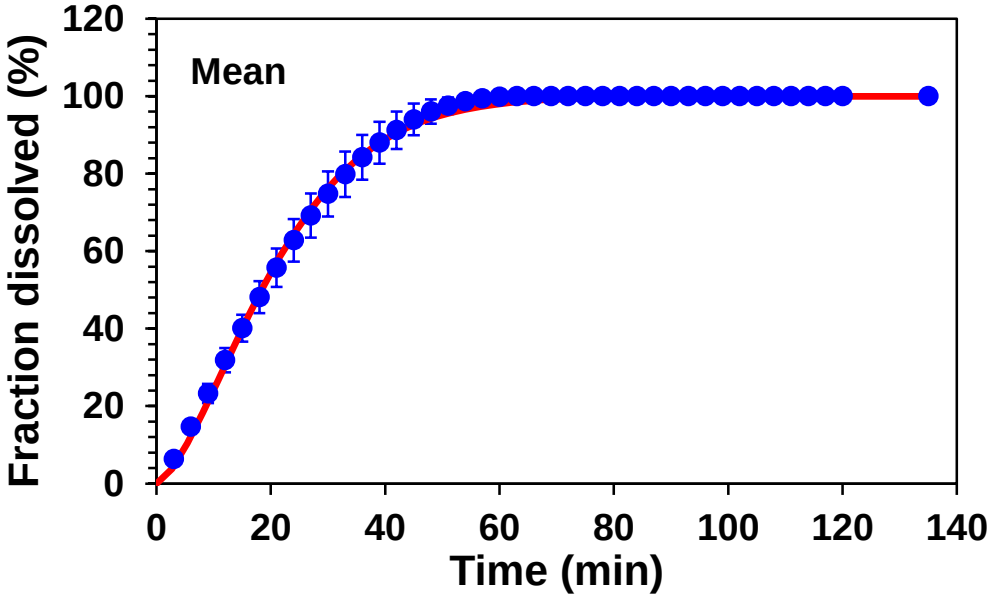
NIR: Principal Component Analysis





PC2 Clearly correlated with API concentration

Dissolution Measurements and Model Fitting



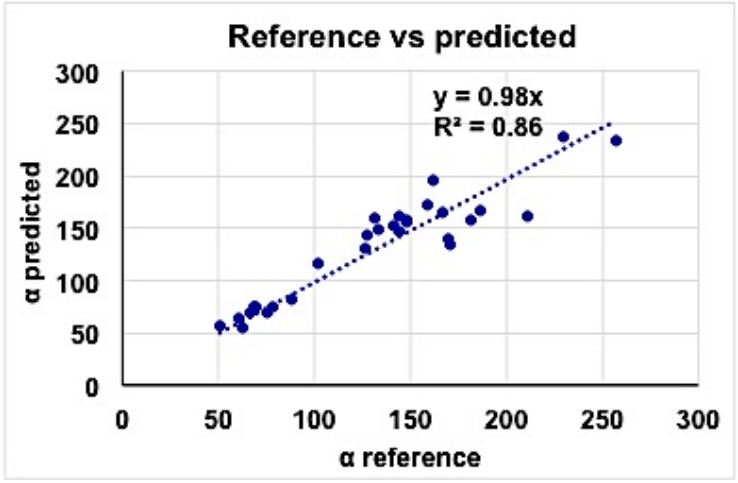
Weibull Model

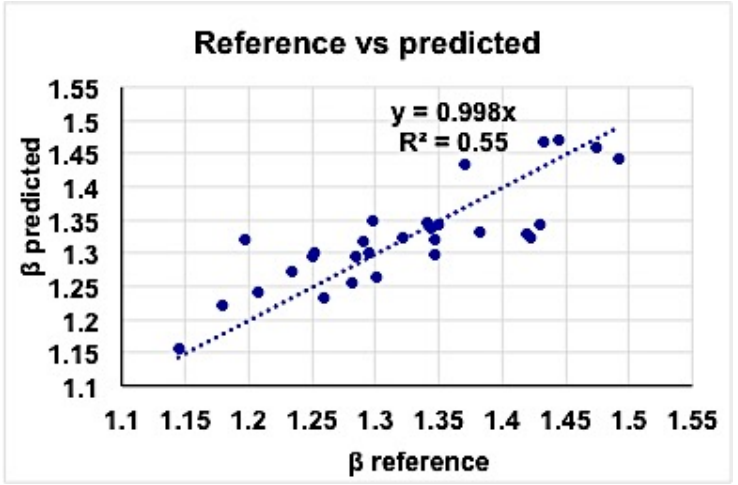
$$f(t) = 100\left\{1 - e^{-\frac{t^{\beta}}{\alpha}}\right\}$$

Parameters α y β

Multilinear Regression

3 *Regressor* Variables: PC1, PC2, PC3 → 2 *Response* Variables: α y β

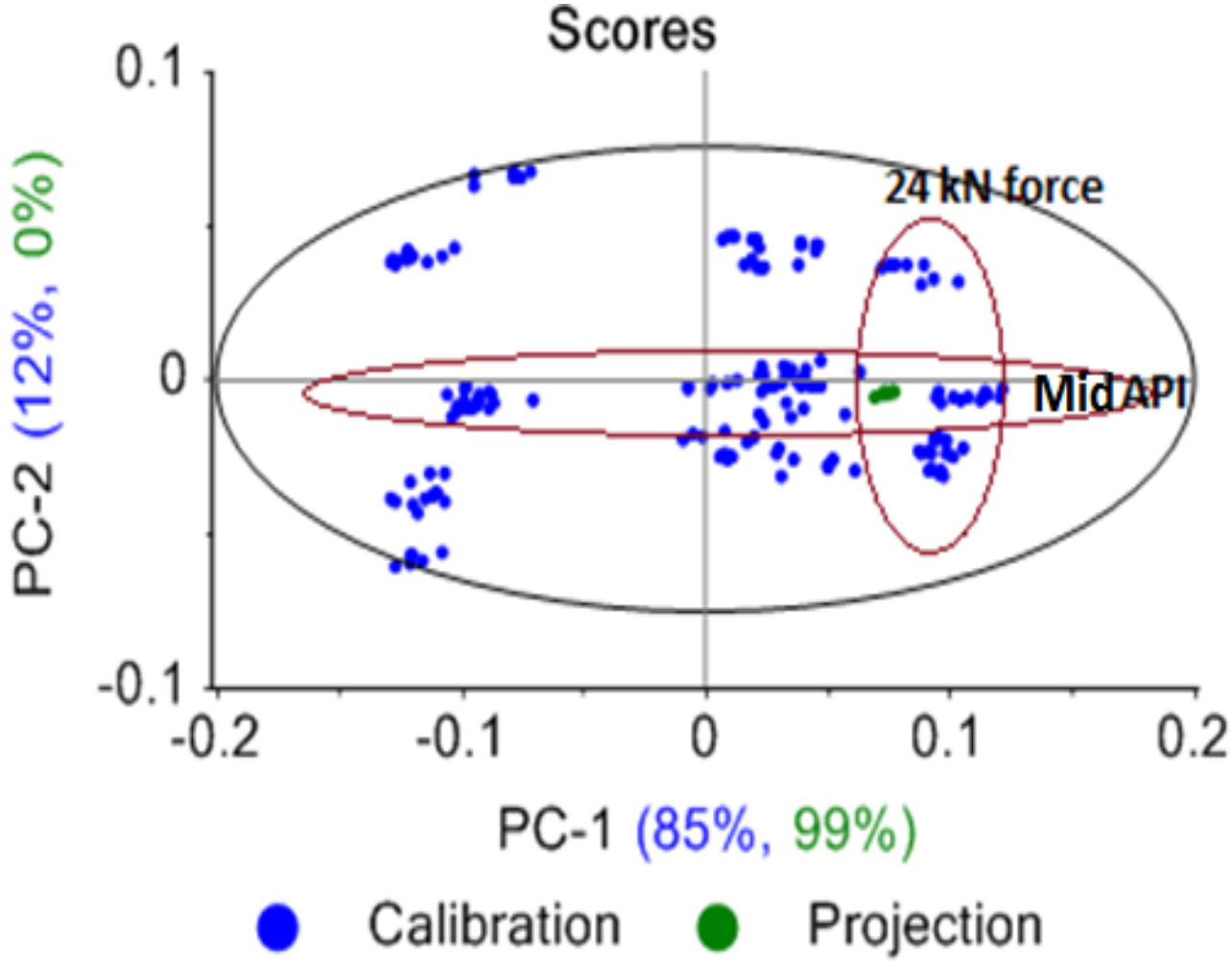




Predictive Dissolution Model Validation Tablets: PCA Scores

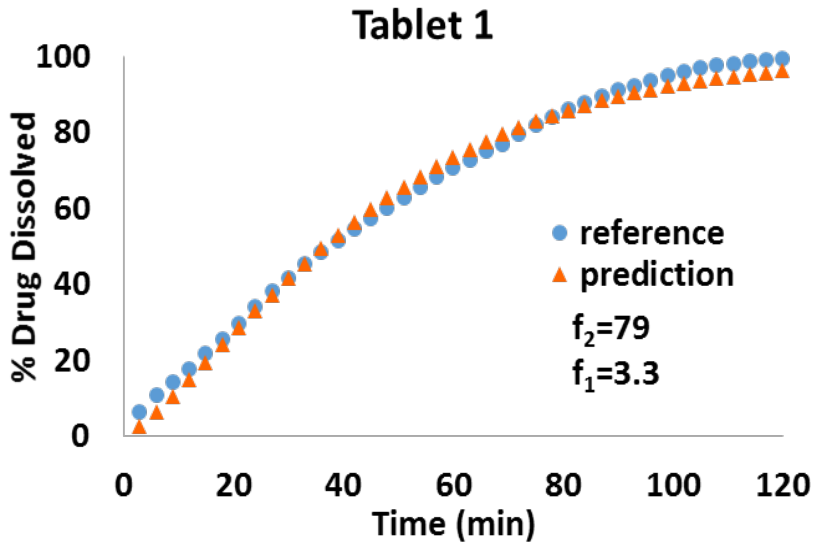
Independent Validation Set
Continuous line

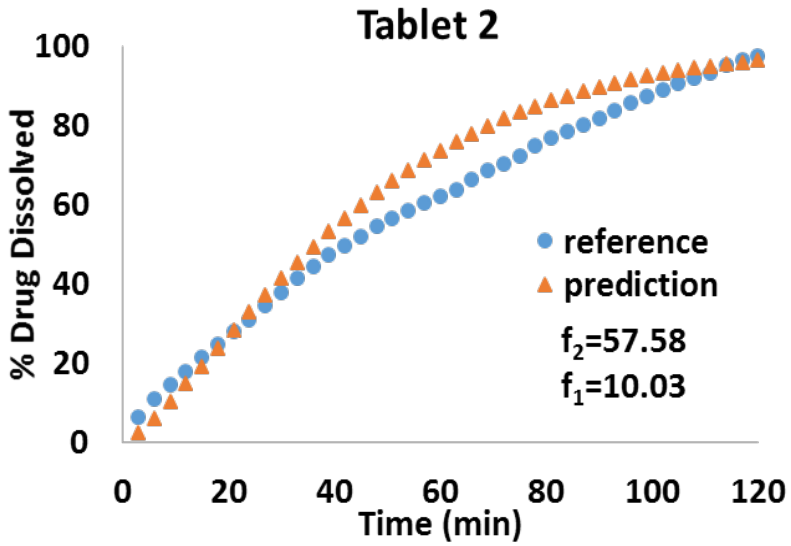
- Target condition:
  - *9% API*
  - *24 kN compaction force*
  - *Blender speed 200 rpm*
  - *feed frame 25 rpm*
- 6 tablets-350 mg
- Flow rate: 20 kg/hr

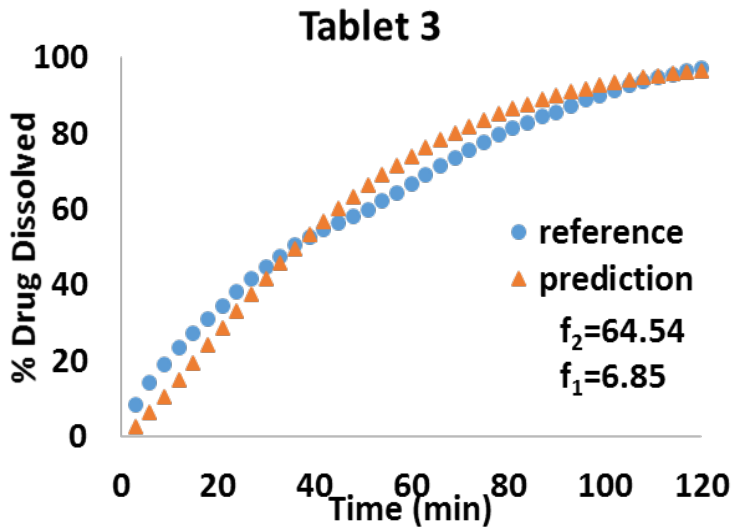


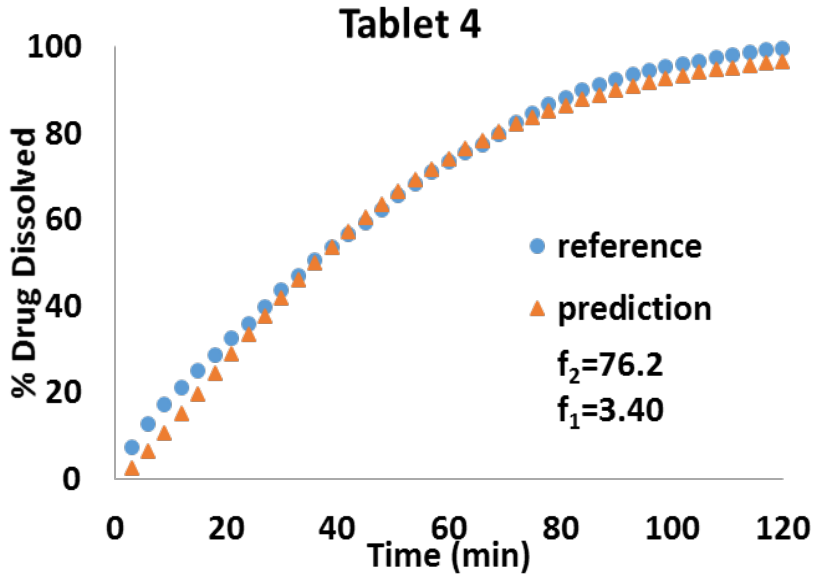
Predictive Dissolution Model

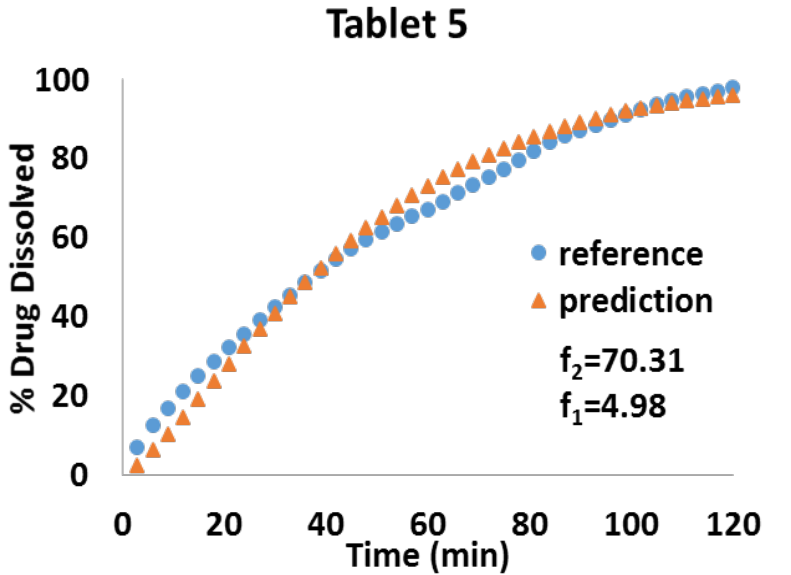
Validation: Predicted vs Measured dissolution profiles

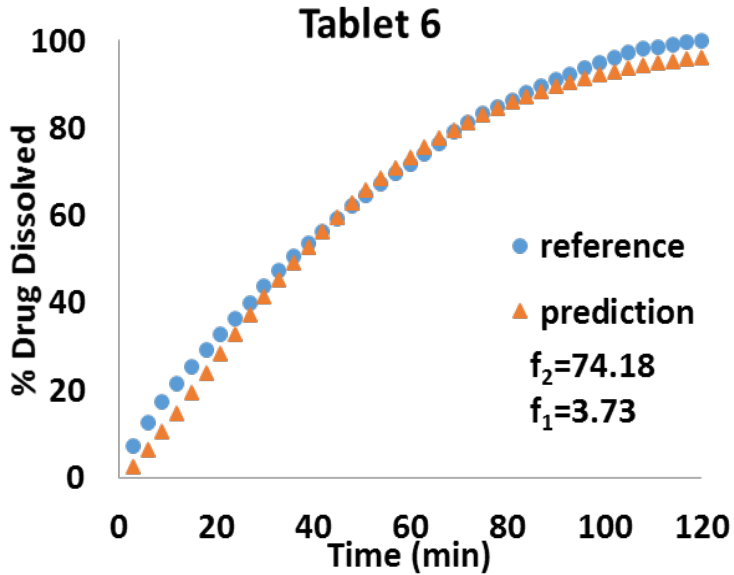












Conclusion

- Demonstrated **Real-time release testing** possibilities in continuous manufacturing platform.
- Non-destructive (NIR) prediction of tablet dissolution.
- General methodology based on statistical analysis applicable to other dissolution problems.

Further challenges

- One type of formulation examined
  - Dissolution depended on API, tablet porosity and shear
- Study other (complex) formulations
  - Controlled, extended, delayed release

Acknowledgements

- NSF- Engineering Research Center