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THE STATE UNIVERSITY OF NEW JERSEY

Advanced Pharmaceutical Manufacturing as an Enabler of QbD and Science-based Regulation Solid Dose Case Study

May 9, 2017

Presented by
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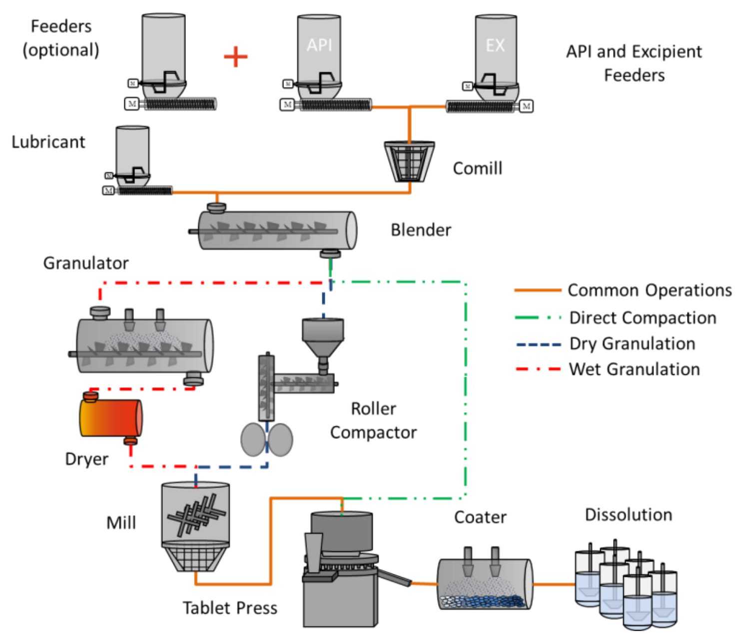
Advanced Pharmaceutical Development

The goal is to model pharmaceutical processes *in silico* and use these tools for optimization

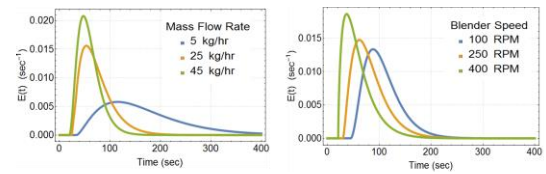
Material Properties

e.g., Flow, Bulk Density, Angle of Repose

Integrated Process Model "Flowsheets"

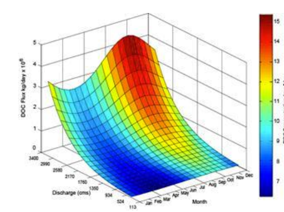


Predictive Modeling



Reduced Order Model

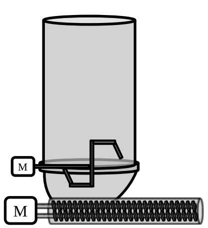
$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i<j}\sum \beta_{ij} x_i x_j + \varepsilon$$



Optimization

$$\min f(x)$$
$$st. \quad h(x) = 0$$
$$g(x) £ 0$$

Unit Ops Models



e.g., Feeders

$$y = f(x,a,t,m,n)$$

$$\frac{dy}{dt} = g(x,a,t,m,n)$$

Operating Parameters & Design

The Design Chain

How does the process create a structure?

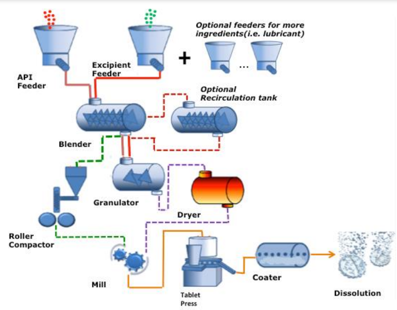
How do material properties affect the structure?

How does the structure determine performance?

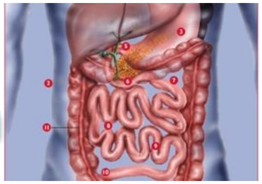
In vitro performance

Bulk Ingredient

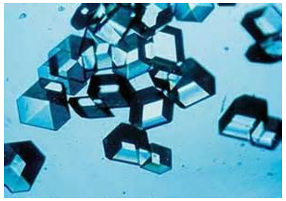
Product



Process



In vivo performance



Crystal

A Strategy for Minimizing time and materials Maximizing process understanding

(as defined as part of the collaboration with Janssen)

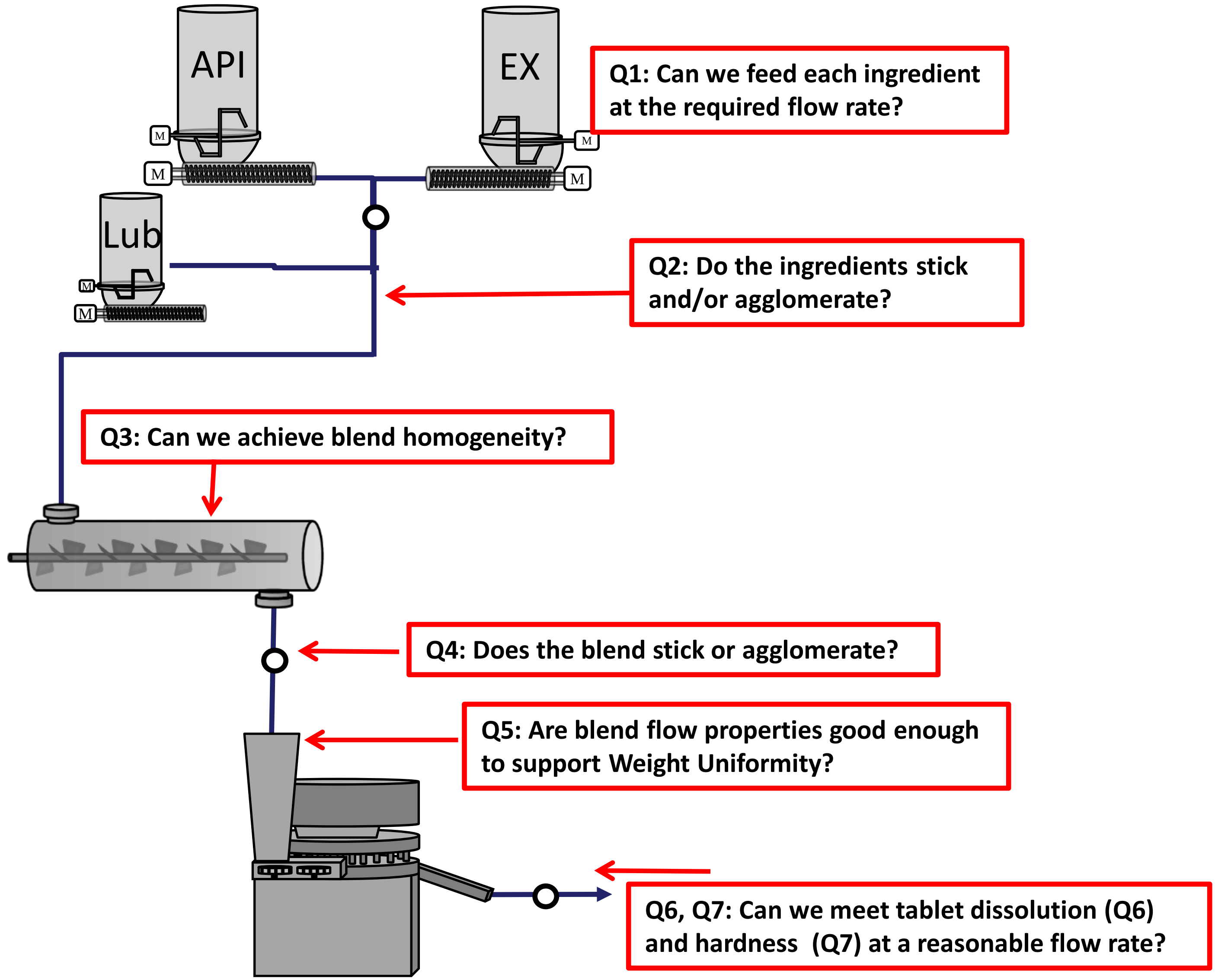
- Identify system failure modes
- Define measurements and metrics to predict impact of failure modes for a given formulation
- Build material property data base and predictive models for new materials and surrogates in unit ops
- Use relevant failure mode knowledge to define DOEs and select PAT and control
- Perform integrated formulation and process optimization

Critical Questions in DCCM

(as defined as part of the Collaboration with Janssen)

Improving API processability

Minimizing amounts of API needed in development



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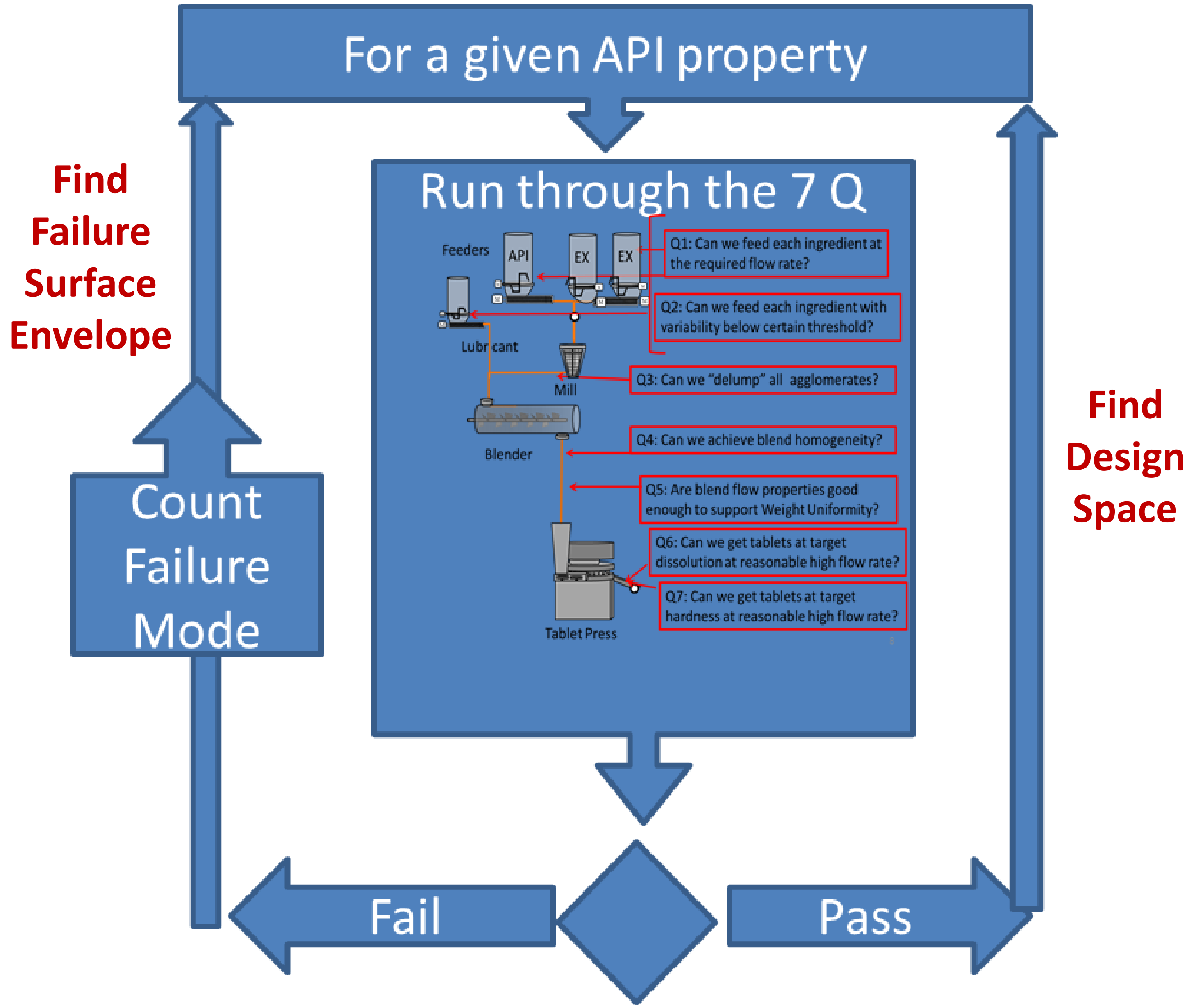
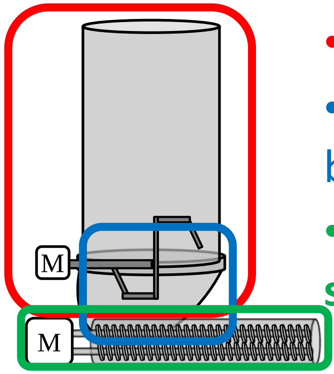
Strategy



What can go wrong in a Feeder?



- **Hopper**
- Flow aid system – bridge breaker
- **Conveying system – screws**

- Clogging – Obstructions:
  - **Cohesion, Electrostatic** (Surface Energy?, PSD?)
- Fluctuations
  - **Compressibility.**
- Refill
- Low Flow Rate is more challenging

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Approach

Manufacturability (Next steps)

Feeder Characterization

- Q1: Can we feed each ingredient at the required flow rate?
- Q2: Can we feed each ingredient with variability below certain threshold?

Blender Characterization

- Q3: Does the blend stick/or agglomerate?
- Q4: Can we achieve blend homogeneity?
- Q5: Are blend flow properties good enough to support weight uniformity?

Tablet Characterization

- Q6: Can we get tablets at target dissolution at reasonable high flow rate?
- Q7: Can we get tablets at target hardness at reasonable high flow rate?

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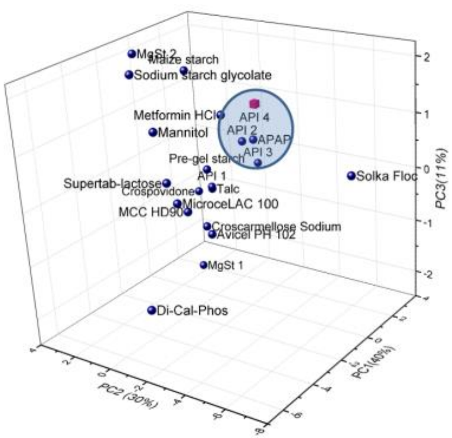
Characterization Techniques

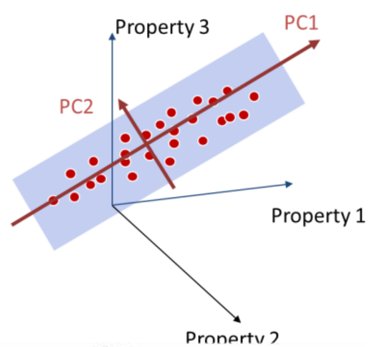
- Particle size distribution
  - *d10, d50, d90*
- Shear cell test
  - *Cohesion, Unconfined Yield Strength, Major Principal Stress, Flow Function Coefficient, and Angle of Internal Friction at initial consolidation stresses of 3kPa, 6kPa, 9kPa, and 15kPa*
- Compressibility test
  - *Conditioned bulk density, Compressibility index*
- Permeability test
  - *Pressure drop*
- Stability/ Variable Flow Rate test
  - *Basic Flow Energy, Stability Index, Specific Energy, Flow Rate Index*
- Electrostatics
  - *Impedance, dry impedance*

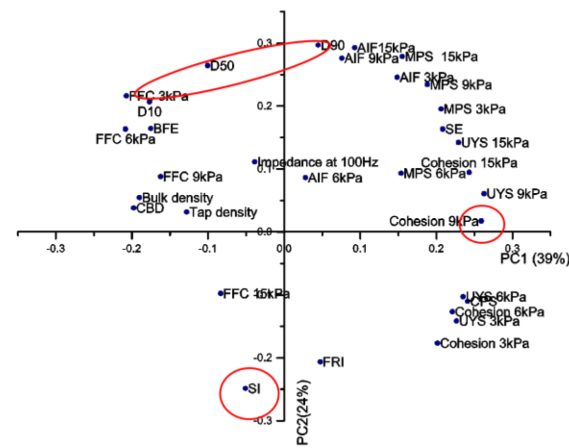
Define the design space

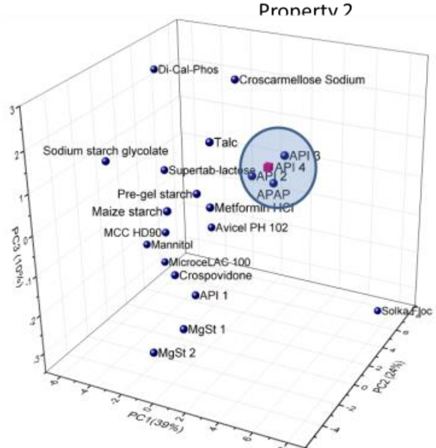
- 10-15 measurement techniques with 35-50 measured parameters
- Only 3-5 can explain more than 85% of variability

Full model.
Characterization time: 11hs







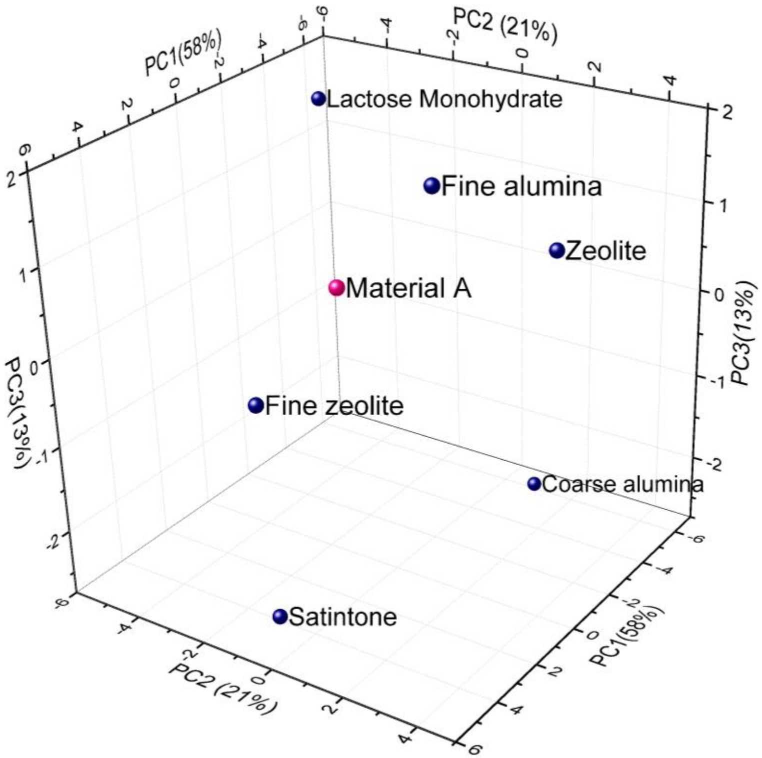


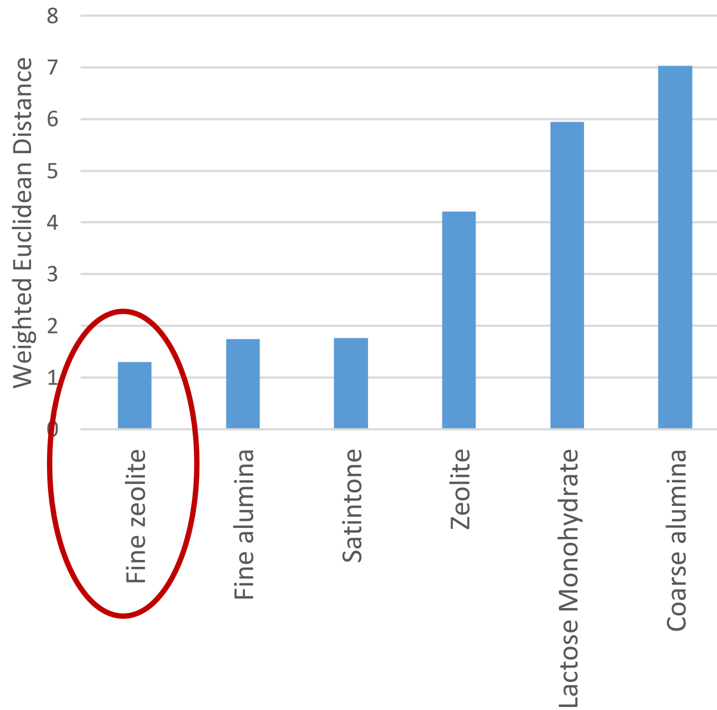
Reduced model.
Characterization time: **3hs**

Predicting feeding performance from material flow properties

- For a given new material, can we compare it to existing materials in the library?
- Once a new material is included in the material library, can we predict its feeder performance?
- Can we predict the optimal screw choice for a given new material?

Similarity scores of the new material





Material similarity can be quantified by calculating weighted Euclidean distance. Smaller distance corresponds to higher similarity.

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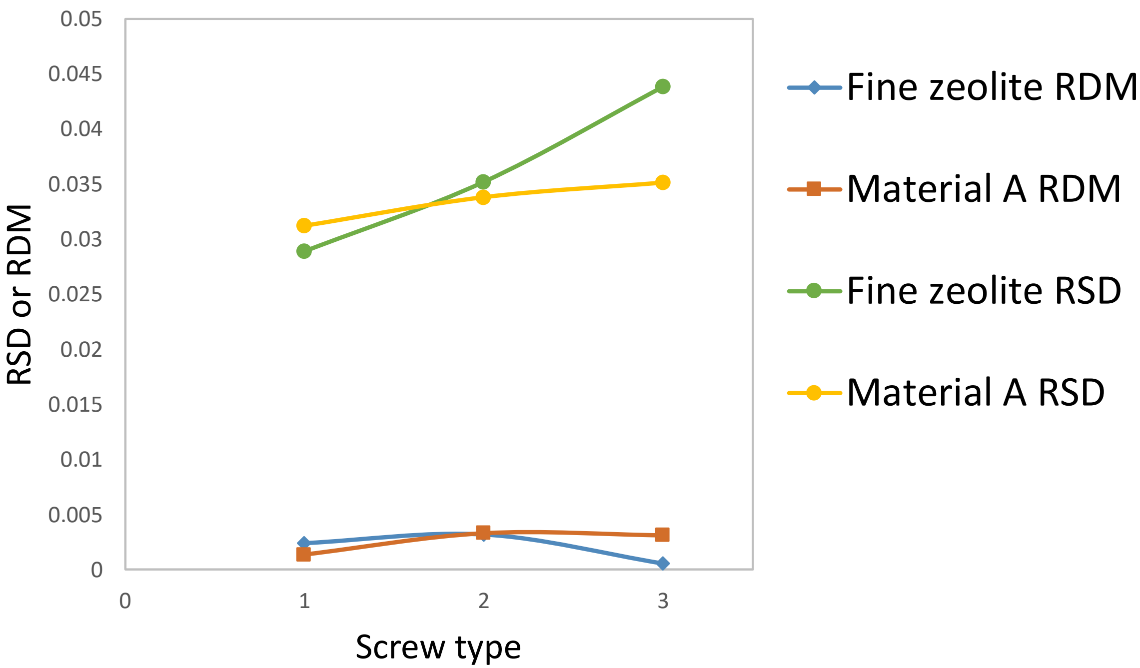
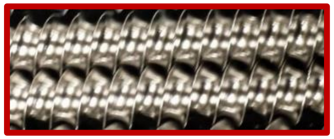
Prediction using similarity scores



screw type 1
fine concave screw



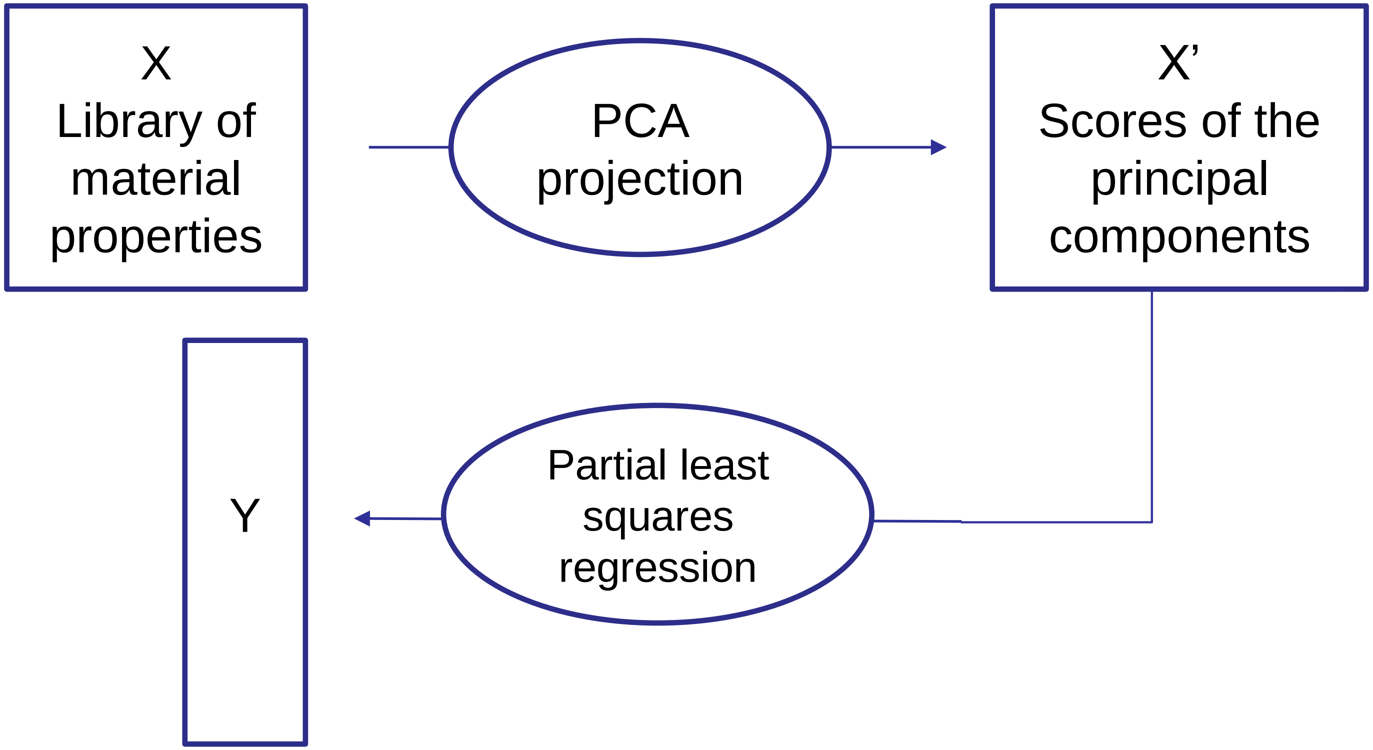
screw type 2
fine auger screw

screw type 3
coarse concave screw

- Receive new material
- Characterize new material properties
- Perform PCA with existing materials
- Calculate weighted Euclidean distance
- Rank similarity between materials
- Predict the optimal feeder screw based similar materials

Prediction using PLS regression

Alternatively, when material with matching flow properties is difficult to find, a partial least squares (PLS) regression can be used. A PLS regression model relates material flow properties directly to feeder performance, quantified by RSD and RDM.

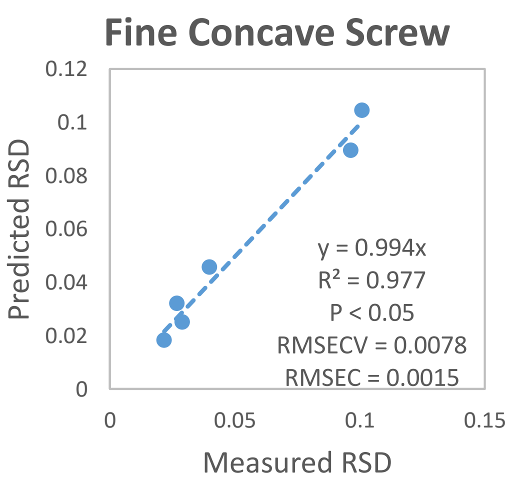


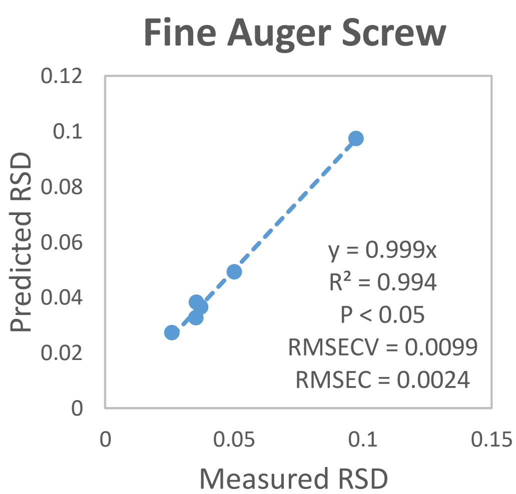
Predicting feeding performance

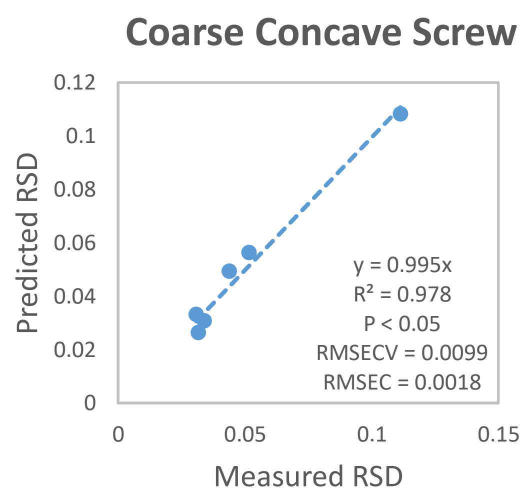
- PLS regression helps to answer:

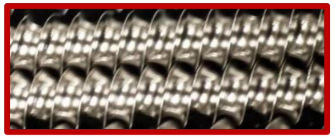
1. For a new material with given properties, can we predict RSD or RDM for a certain screw?

2. For a new material, what is the optimal screw selection?









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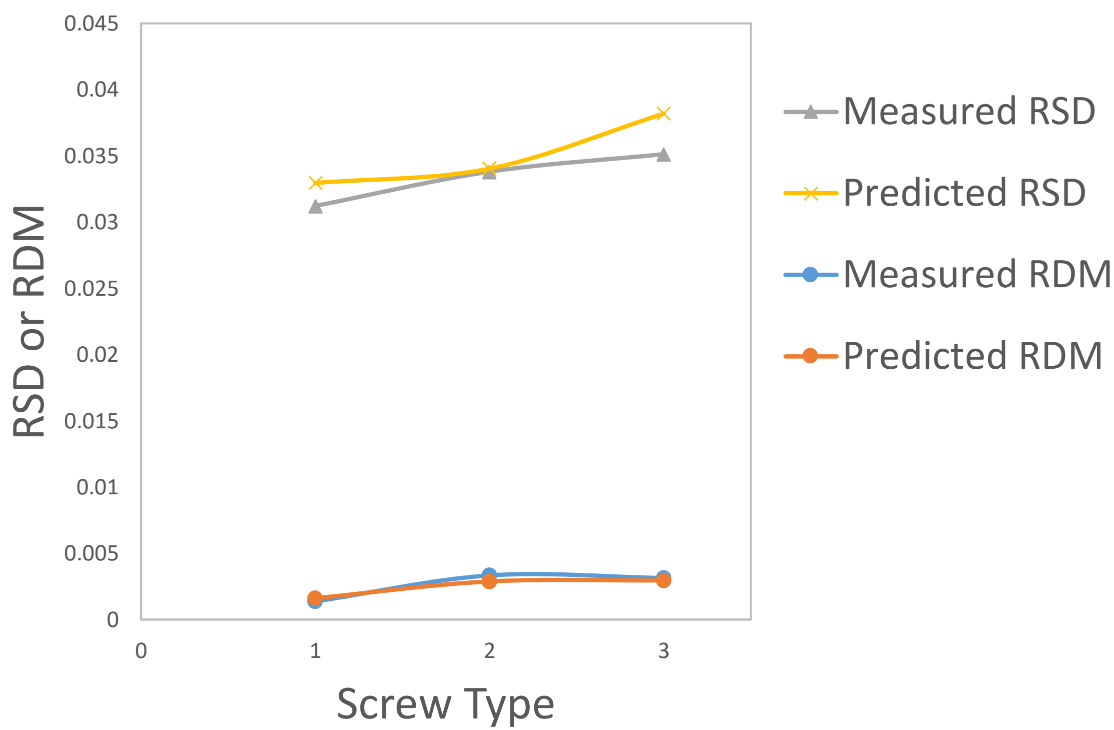
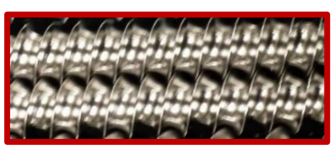
Prediction using PLSR models



screw type 1
fine concave screw



screw type 2
fine auger screw

screw type 3
coarse concave screw

Receive new material

↓

Characterize new material properties

↓

Project data to PLSR models to predict feeder performance

↓

Select optimal screw based on model prediction

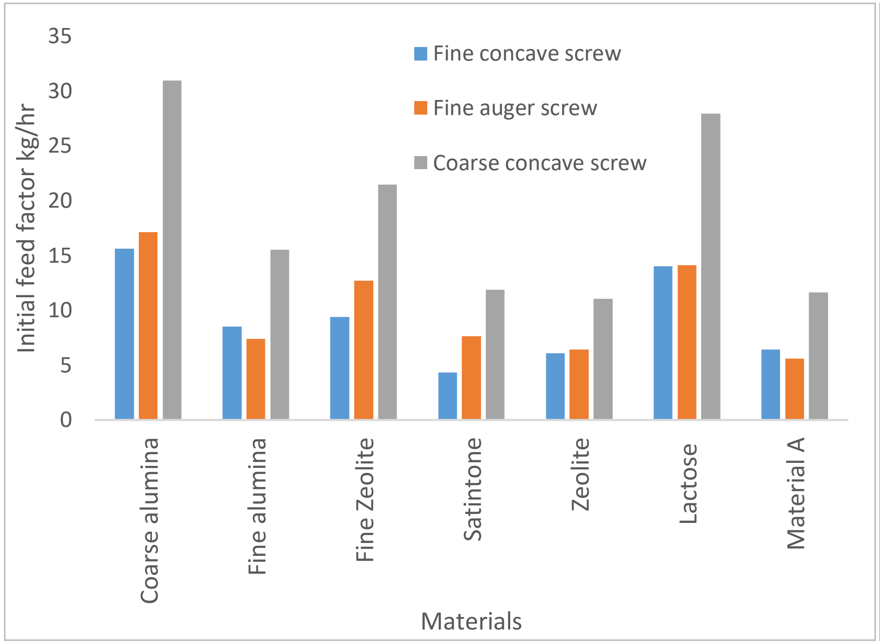
↓

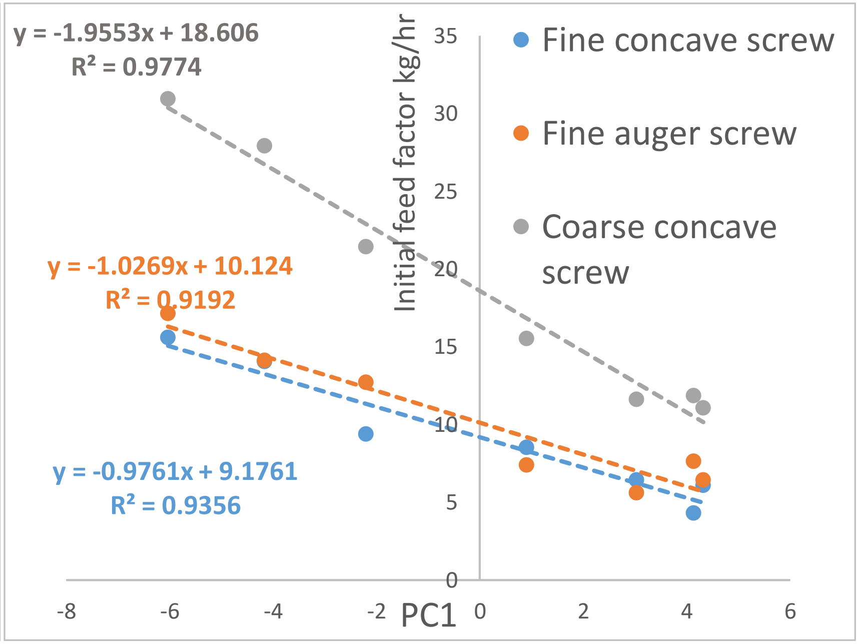
Run confirmatory feeder experiment

↓

Add confirmatory data and update model knowledge

Predicting feed factor from material properties





- Initial feed factor reflects maximal feeding capacity for a material.
- Results show that using scores of the first principal component, the initial feed factor can be predicted based on the linear correlation.
- The feed factor using different screws can also be predicted.

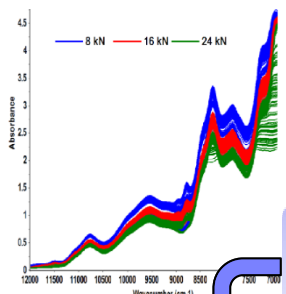
General dissolution prediction methodology

Identify dissolution mechanism

Define target conditions

Experimental design around the targeted drug conditions

Analyze tablets with NIR

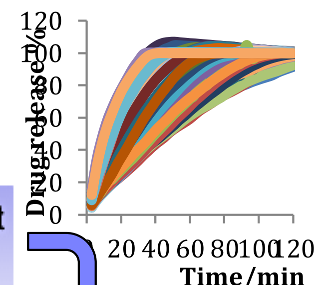


Scores (PC1, PC2, PC-3)

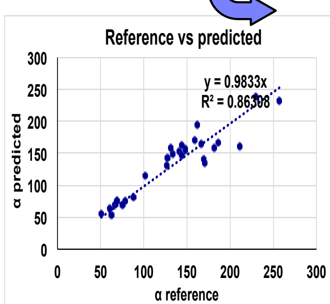
Extract dissolution information

Model dependent approach (alpha beta)

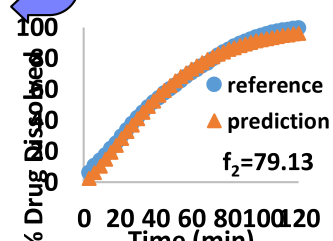
Model Independent approach (shape level)



Multilinear regression



Predict dissolution profile of tablets at targeted time point in CM



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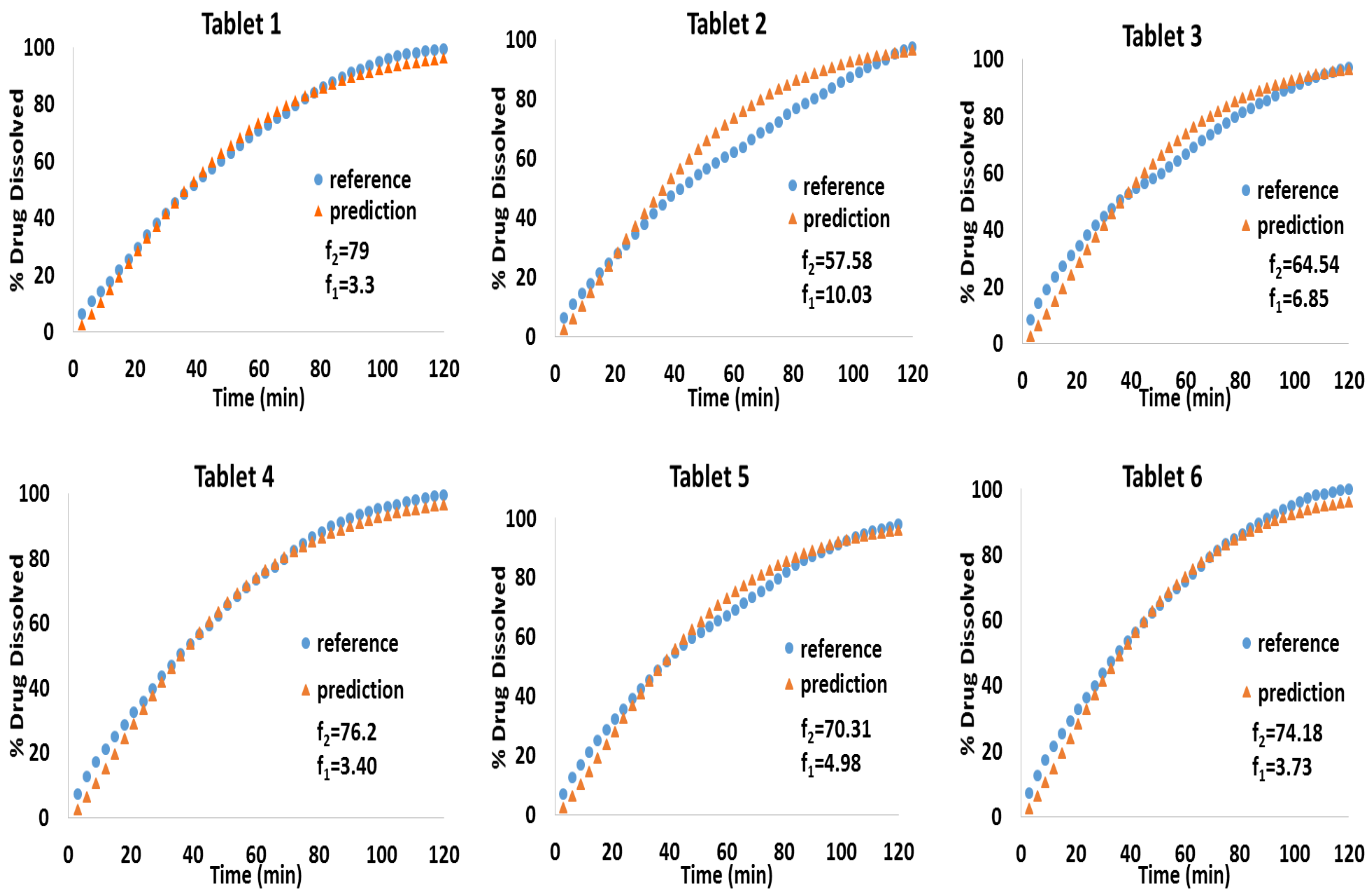
Capability of predict individual tablet dissolution profile: Model-dependent approach



Reference: *dissolution profiles*
Predicted: *NIR PCs*

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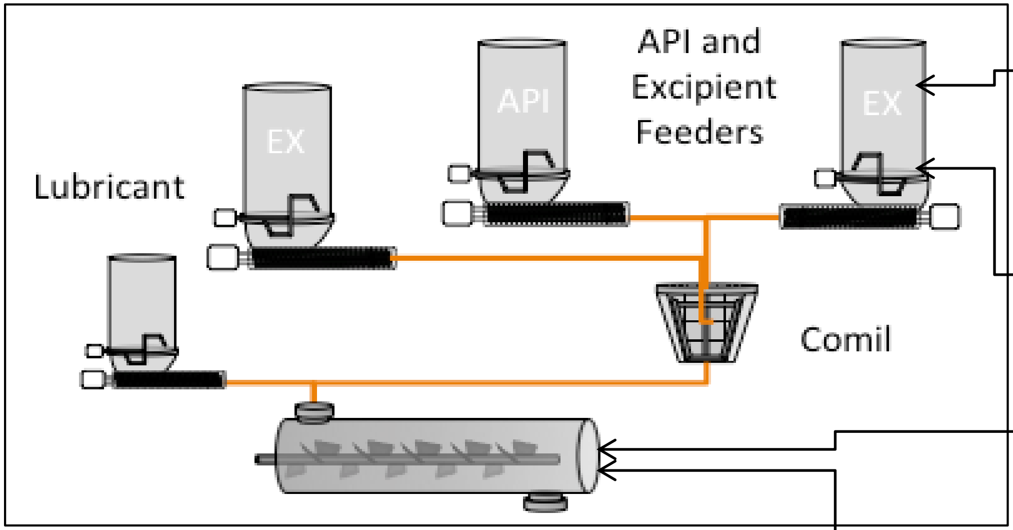
Module 1 – feeders and blenders



Q1: can we feed each ingredient at the required flow rate?

Q2: do the ingredients stick and/or agglomerate?

Q3: can we achieve blend homogeneity?

Q4: does the blend stick or agglomerate?

Feeder, Mill, Blender: Inputs and Outputs

Unit Op	Inputs	Processing Parameters	Responses	Output Material Properties
Feeder $^{(i)}$	**RM Cohesion $^{(i)}$ [Coh1^{i}]** **RM Compressibility $^{(i)}$ [Cps1^{i}]** **RM Surface Energy $^{(i)}$ [SE1^{i}]** **RM Electrostatic $^{(i)}$ [E1^{i}]** **RM PSD $^{(i)}$ [PSD1^{i}]** **RM Bulk Density $^{(i)}$ [BD1^{i}]**	RPM Impeller (RPM1) RPM Screw (RPM2) Refill Rate (RR) Hopper Size/geometry (HSG) Screw type (ST)	**Feeder Flow Rate (FFR)** = f [Coh1, Cps1, SE1, E1, RPM1, RPM2,FR, HSG, ST] **Feeder Flow Rate Variability** (σ_{FFR}) = f[Coh1, Cps1, SE1, E1, RPM1, RPM2,FR, HSG, ST]	**Cohesion 2 (Coh2)** = f[Coh1, Cps1, SE1, E1, RPM1, RPM2,FR, HSG, ST] **Powder Bulk Density2 (DB2)** = f [Coh1, Cps1, SE1, E1, RPM1, RPM2,FR, HSG, ST]
Mill	**Coh2 $^{(i)}$** **σFFR2$^{(i)}$** **Composition (PSD, $^{(i)}$ [C%]** **Bulk Density2 $^{(i)}$ [BD2^{i}]** **Hip: Density has no effect beyond what's captured by cohesion**	RPM Blade (RPM3) Mill Screen (MS) Screw type (ST) Spacers Geometry (SG)	Mill Holdup	**Blend Homogeneity 3 (BH3)** = f[Coh2, σFFR2, RPM3, FR5, C%, MSSG, ST] **Agglomeration 3 (Ag3) =** f[Coh2, σFFR2, RPM3, FR5, HSG, ST, C%] **Cohesion 3 (Coh3)** = f[Coh2, σFFR2, RPM3, FR5, HSG, ST, C%] **Density 3 (D3)** = f [Coh2, σFFR2, RPM3, FR5, HSG, ST, C%]
Blender	Blend Homogeneity 3 [BH3] Agglomeration 3 [Ag3] **Composition [C%]** Cohesion 3 [Coh3] Bulk Density 3 [BD3] Mill Holdup	RPM Blade (RPM4) Blender Geometry (BG) Screw type/ Blade pattern (STBP)	Holdup (investigate composition in blender) Blender Residence Time (BRT) Dispersion Coefficient (BDC) Blade Passes (BBP)	**Lubricity4 (L4)** =f[FR5, Ag3, RPM4, BG, STBP, C%] **Compatibility (Cpt4)** = f[L4, FR5, Ag3, RPM4, BG, STBP, C%, PSD3 (i)] **Cohesion 4 (Coh4)** = f[Coh3, L4, RPM4, FR5, Ag3, HSG, ST, C%] **Agglomeration 4 (Ag4)** = f [RPM4, FR5, Ag3, HSG, ST, C%] **Blend Homogeneity 4 (BH4)** =f[BH3, RPM4, FR5, Ag3, HSG, ST, C%] **Bulk Density 4 (BD4)** =f [BD3, L4, RPM4, FR5, Coh3, HSG, ST, C%]

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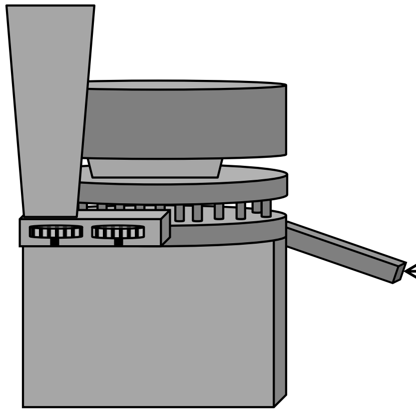
Feed Frame and Tablet Press

Module 1

Q5: are blend/granule flow properties good enough to achieve desired weight uniformity?



Q6: will tablet weight and hardness be adversely affected by the CM process?

Q7: will tablet dissolution be adversely affected by the CM process?

Feed Frame and Tablet Press: Inputs and Outputs

Unit Op	Inputs	Processing Parameters	Responses	Product Properties
Tablet Press and Feed Frame	Lubricity [L4]	RPM Feed Frame (RPM5)	Compaction Force (CF)	**Tablet Thickness (TH5)** = f[FR, L4, RPM5, **CH, ThG, FC, C%, FFG, TT, #S, PC**]
	Compactibility [Cpt4]	RPM Turret (RPM6 = Flow Rate (FR))	Ejection Force (EF)	**Weight Variability (WV5)** = f[L4, FR, Ag4, RPM5, Coh4, BH4, BD4, CH, **C%, FFG, TT, #S, PC]**
	Composition [C%]	Chute Height (CH)	Dwell Time (DT)	**Tablet Density (porosity) 5 (TD5)** = f [Coh4, L4, RPM4, FR, Ag3, **PSD(i), C%**]
	Cohesion 4 [Coh4]	Thickness Gap (ThG)		**Content Uniformity 5 (CU5)** = f[BH4, RPM5, Ag4, WV5, **C%, FFG, TT, #S, PC**]
		Fill Cam [FC]		**Hardness 5 (H5)** = f[Cpt4, RPM5, FR, L4, WV5, **C%, FFG, TT, #S, PC**]
		Feed Frame Geometry (FFG)		**Dissolution 5 (Diss5)** = [Cpt4, RPM5, FR, L4, WV5, **C%, FFG, TT, #S, PC**]
	Agglomeration 4 [Ag4]	Tablet Tooling (TT)		
	Blend Homogeneity 4 [BH4]	# stations (#S)		
	Bulk Density 4 [BD4]	Pre Compression (PC)		

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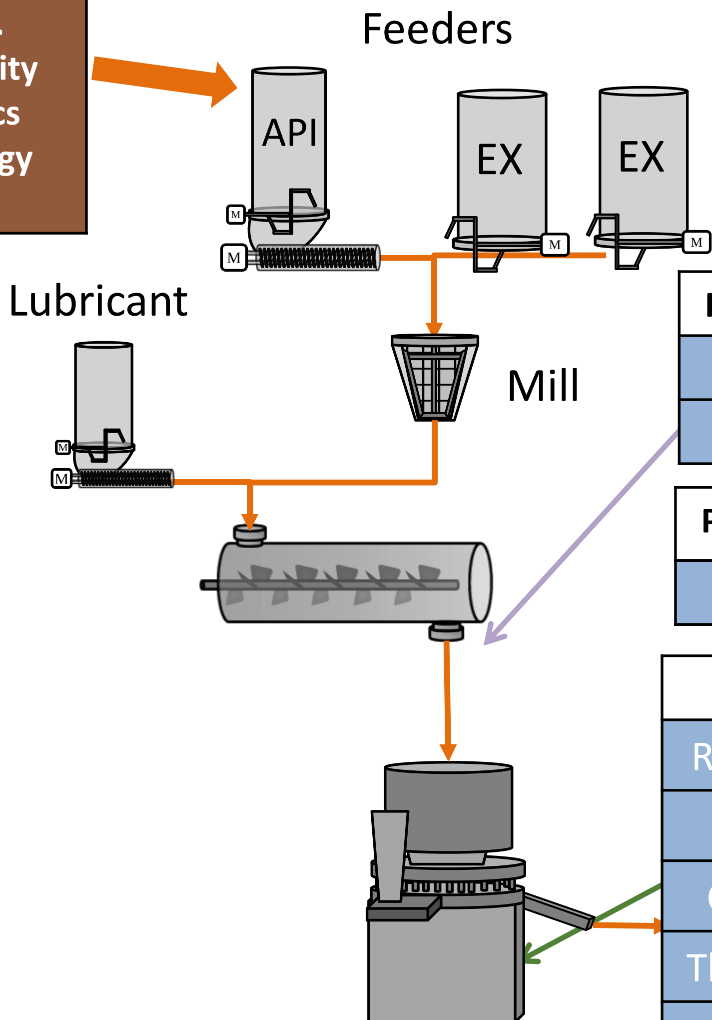
Material Properties-Process Parameters Interrelation

Raw Material Properties (RMP)

- Cohesion1.
- Compressibility
- Electrostatics
- Surface Energy
- PSD



Process Parameters

- RPM2 (Mill)
- Screen Size

Process Parameters

- RPM3 (Blender)

Process Parameters

- RPM5 (Feed Frame)
- RPM6 (flow Rate)
- Chute Height (CH)
- Thickness Gap (ThG)
- Pre Compaction (PC)
- Fill Cam [FC]

Lubricated Blend

Intermediate Material Properties (IMP)

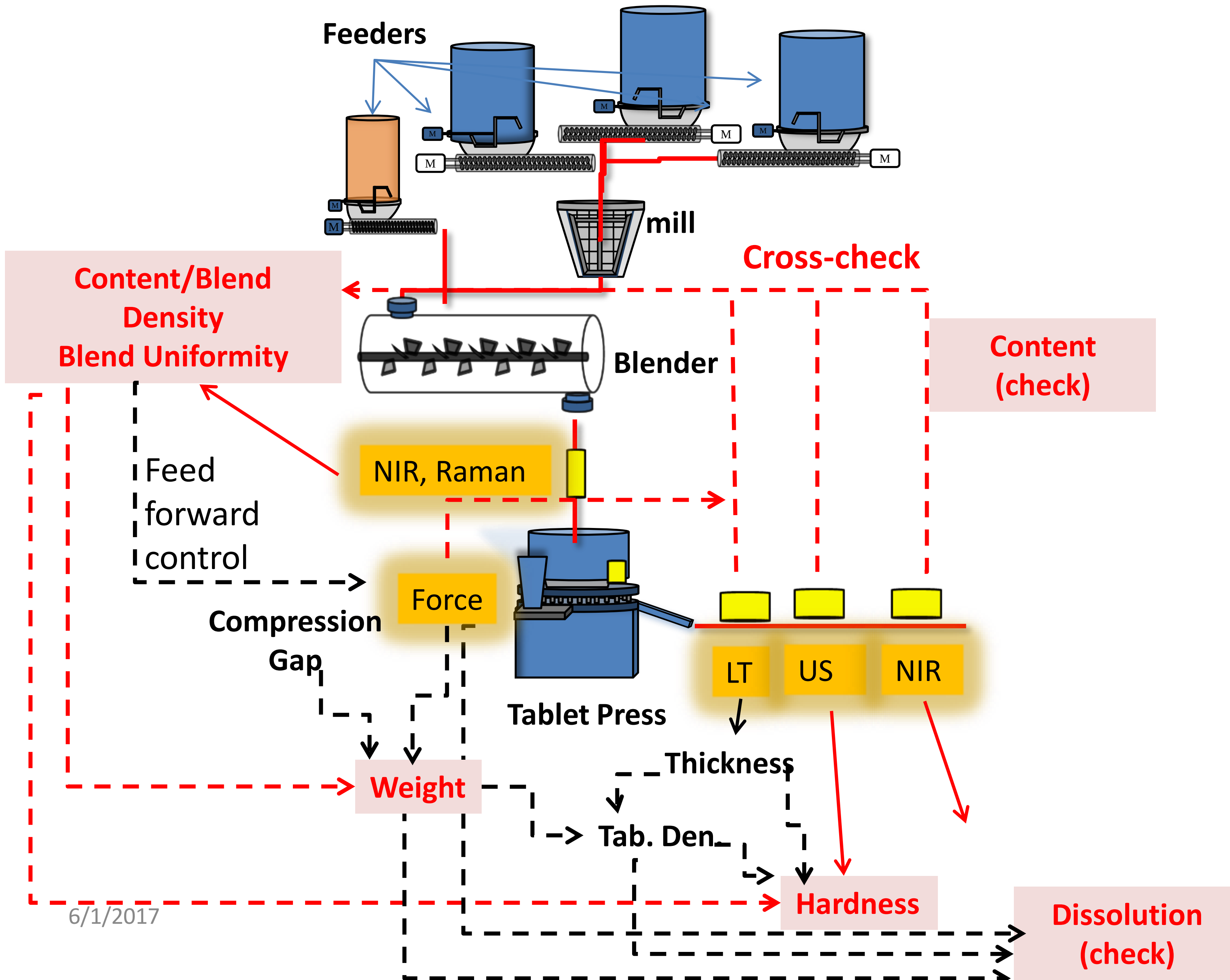
- Lubricity4
- Compactability4.
- Cohesion4
- Agglomeration4
- Blend Homogeneity4
- Bulk Density4

Product

Product Material Properties (RMP)

- Thickness
- Weight Variability
- Density (porosity)
- Content Uniformity
- Hardness
- Dissolution

General RTR Sensing Approach



Conclusions

- Process Engineering toolbox quickly reaching maturity
- Real Time Quality Assurance, Closed Loop Control, RTR are all feasible
- Solid dose CM is just the beginning – same toolbox applies, with moderate effort, to
  - API CM
  - Biologicals CM
  - Precision Manufacturing
- Non-destructive testing (dissolution predictions) potentially leads to new methods for understanding in vivo behavior
- Open Issue: What do we do with all this data?