Continuous manufacturing: Interaction Effects Between Formulation Composition And Process Parameters on Product Properties

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ENGINEERING RESEARCH CENTER FOR

STRUCTURED **O**RGANIC **P**ARTICULATE **S**YSTEMS

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C-SOPS: Broad strokes

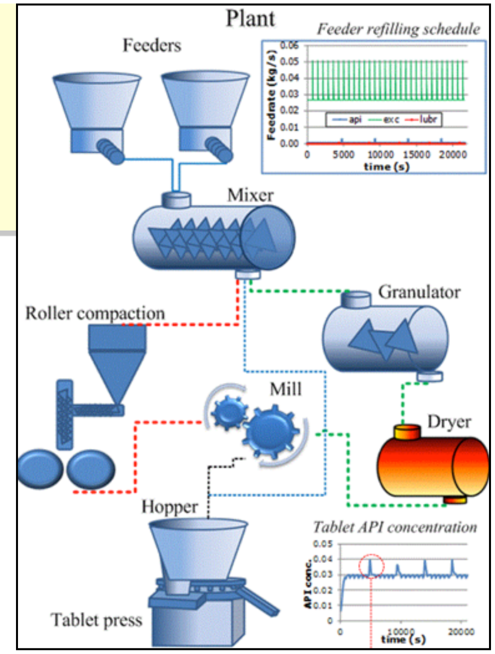
- Focus: pharmaceutical product and process design
- Team: 40 faculty, 80 students and postdocs, 120 industrial mentors
- Participants: Rutgers (lead), Purdue, NJIT, Univ. of Puerto Rico
- 35 member companies (pharmaceuticals, equipment, instrumentation, software, process control)
- Very close collaboration with FDA (scientific support for regulations, training for reviewers and inspectors)
- Budget:
  - *NSF ($4,000,000/yr)*
  - *University cash match (~$1,000,000/yr.)*
  - *Member companies (cash~$1,000,000, in-kind~$500,000/yr.)*
  - *Associated cash projects (~$4,000,000/yr.)*

C-SOPS Convergent Technology Development Model

- Projects are conducted and managed by teams of academics and industrial members
- Industrial participants include:
  - *End users of technology,*
  - *Suppliers of technology components,*
  - *Technology integrators,*
  - *Commercialization partners*
- **End user need** (voice of the customer) is established at the very beginning and revalidated throughout project
- **Built-in commercialization mechanism** (commercialization partner is identified early and included in the development)
- Students learn in this environment by
  - *Internships in industry*
  - *Working with industrial scientists in residence*
  - *Discussing with industrial mentors on a monthly basis*

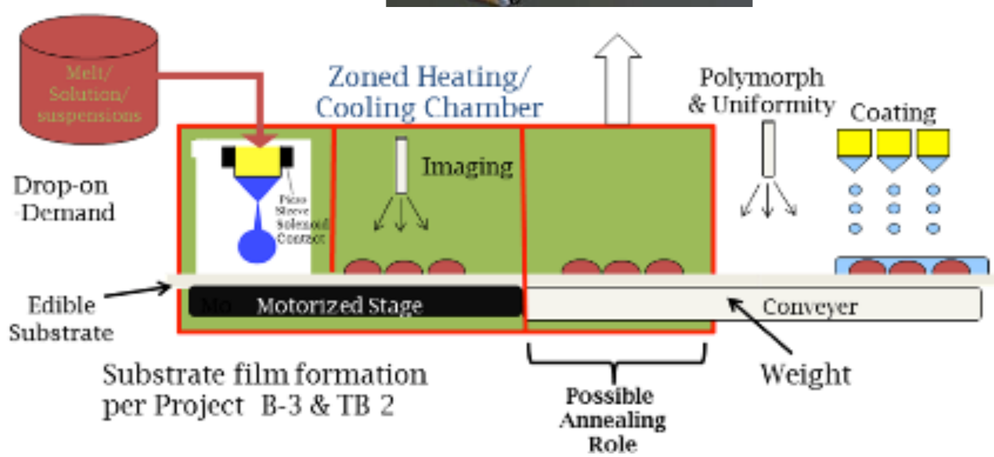
Main Technology Initiatives

- Continuous Manufacturing of tablets and capsules (Rutgers lead)
  - *Faster development*
  - *Lower cost*
  - *Improved quality*



- Thin films containing drug nanoparticles (NJIT lead)
  - *Poorly soluble drugs*
  - *Pediatric and elderly formulations*
  - *Adjustable dose (for personalized medicine)*

- Microdosing-based manufacturing (Purdue lead)
  - *Multidrug therapies*
  - *Diagnostics*
  - *Personalized medicine*
  - *Point of need manufacturing*

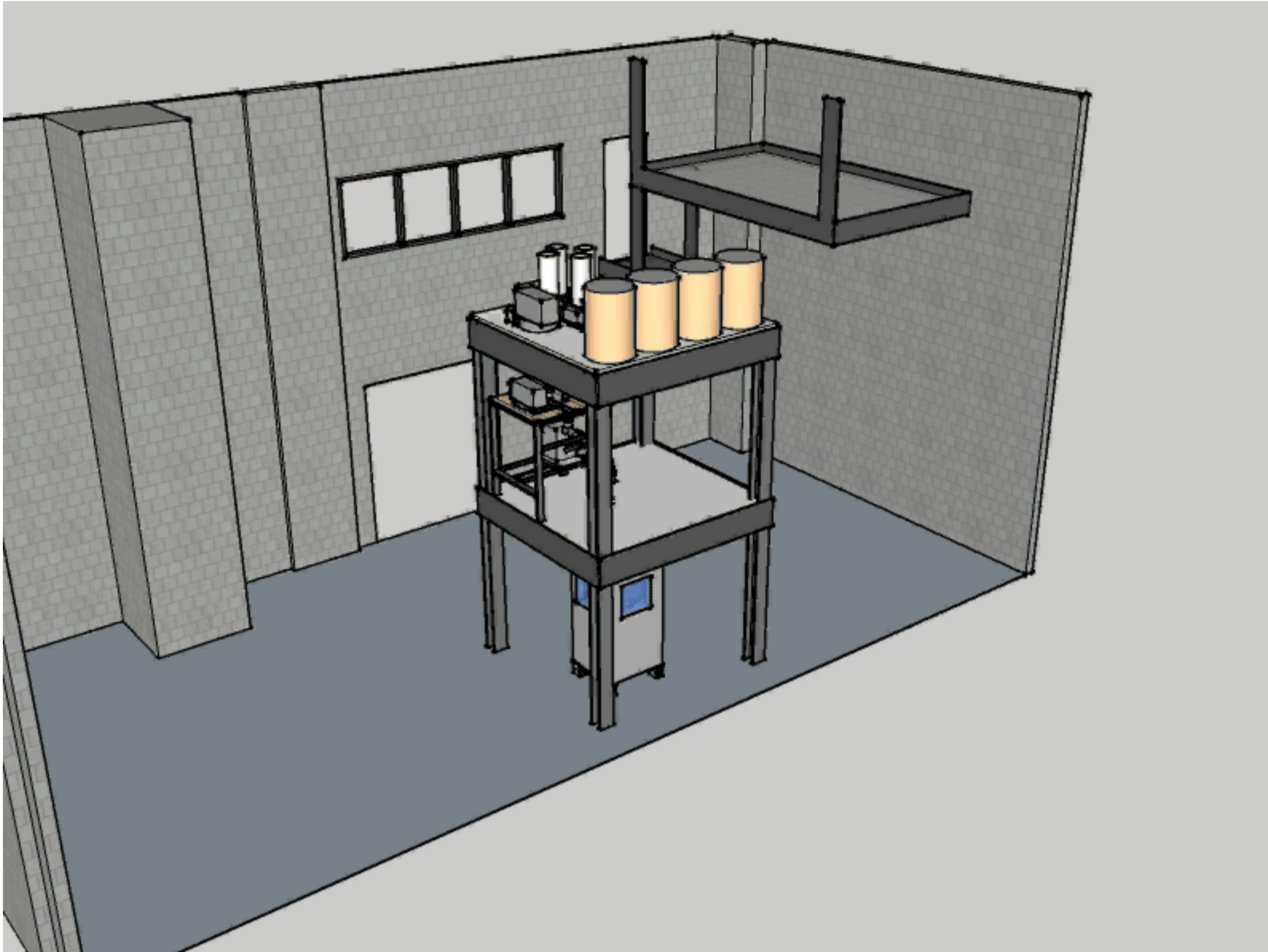


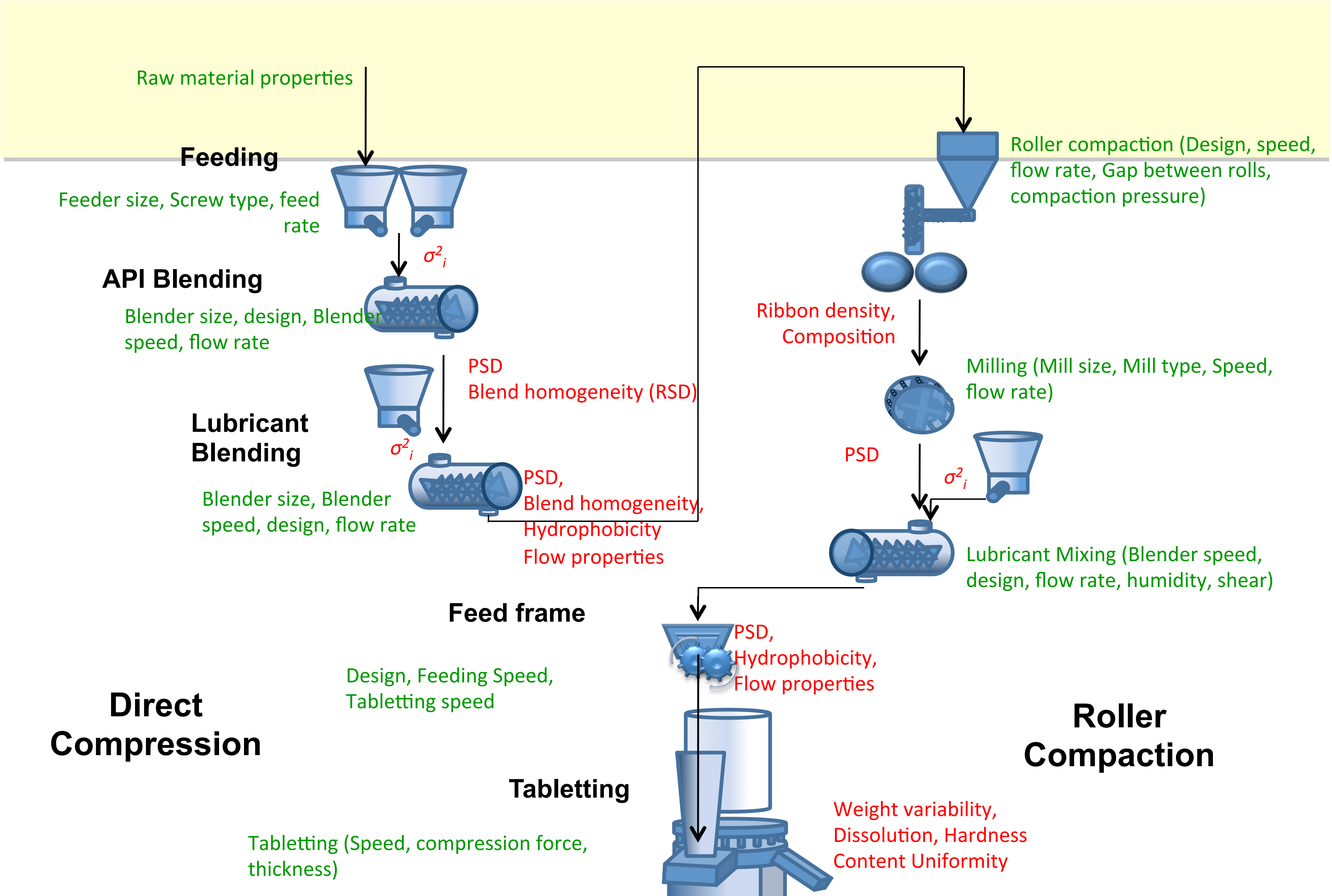
Continuous Manufacturing Case Study

- 2004 – Rutgers forms continuous manufacturing consortium (Pfizer, Merck, GEA, Apotex)
- 2006 – C-SOPS funded – continuous manufacturing consortium becomes TB1
- 2008 – Proof of concept achieved
- 2009 – NSF Translational Research Funds received ($1.8 million)
- October 2010 – J&J approaches C-SOPS seeking support to develop "INSPIRE^2"
- Feb 2011 – J&J funding for C-SOPS (~ $400K) approved
- Sept 2011 – capital funding for INSPIRE^2 ($15 million) approved
- Jan 2012 – C-SOPS in negotiations with 4 other companies

Why Continuous Manufacturing?

- Smaller equipment
- No scale up
- No wasted batches
- Better quality control
- Meaningful PAT
- More uniform processing
- Faster development
- Controllable agglomeration
- Controllable segregation?




Raw material properties
Feeding
Feeder size, Screw type, feed rate
σ^2_i
API Blending
Blender size, design, Blender speed, flow rate
PSD
Blend homogeneity (RSD)
Lubricant Blending
σ^2_i
Blender size, Blender speed, design, flow rate
PSD,
Blend homogeneity,
Hydrophobicity
Flow properties
Roller compaction (Design, speed, flow rate, Gap between rolls, compaction pressure)
Ribbon density,
Composition
Milling (Mill size, Mill type, Speed, flow rate)
PSD
σ^2_i
Lubricant Mixing (Blender speed, design, flow rate, humidity, shear)
Feed frame
Design, Feeding Speed,
Tabletting speed
PSD,
Hydrophobicity,
Flow properties
Direct Compression
Roller Compaction
Tabletting
Tabletting (Speed, compression force, thickness)
Weight variability,
Dissolution, Hardness
Content Uniformity
Throughput?
Tablet size
Compression speed
Composition

QbD Approach

- CQAs – Critical responses
- CPPs – Critical inputs
- Pivotal IPPs (segmentation of the parametric space)
- PAT
- DOE methods
- Mechanistic models
- Validation, Optimization

Challenging dynamics

- Scenario 1: detect “bad powder”
  - *Divert powder to scrap, continue running on internal capacity?*
  - *Continue running normally and divert tablets?*
- Scenario 2: high RSD
  - *Speed-up blender? This decreases hold-up and temporarily increases flow rate*
  - *Need surge capacity upstream of blender, or temporary speed up of TP*
  - *Slow down blender? Opposite dynamics*

Modeling and Configuration

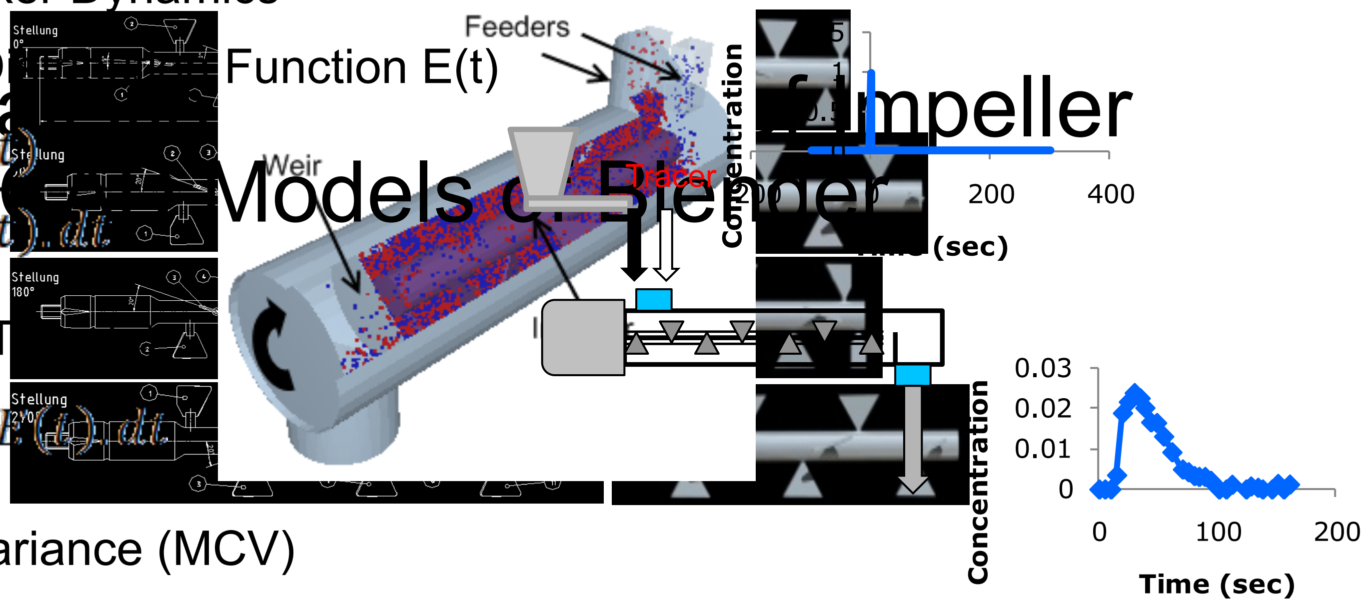
Understanding Mixer Dynamics

Residence Time Di… Function E(t)

$$E(t) = \frac{c(t)}{\int_0^\infty c(t).dt}$$

Mean Residence T…

$$\tau = \int_0^\infty t.E(t).dt$$



Mean Centered Variance (MCV)

$$\sigma_\tau^2 = \frac{\int_0^\infty (t-\tau)^2.E(t).dt}{\tau^2}$$

Effect of Process and Device Parameters

Number of Blade Passes $N_p = \omega * \tau$

Material properties

- In continuous pharmaceutical manufacturing, powder is subjected to different unit operations including feeding, continuous mixing, "pumping" (feed-frames) and compaction.
- Various amounts of strain are applied on the powder as it undergoes different unit operations, affecting micromixing and material properties.
- Cohesive flow properties of excipients and active ingredients can cause large variability in ingredient flow rates.
- Variability in composition can cause processing issues, content uniformity problems, drug dissolution variability, etc.
- PAT and closed loop control are **required**

Approach

- Case Study 1: Bench-top study of formulation and process variables
  - Apply controlled amount of strain to various formulations.
  - Study the effects of composition, strain and mixing order on powder and tablet
    - Powder Flow, Homogeneity, Electrostatics, Hydrophobicity
    - Tablet Hardness, Microstructure, Dissolution.
- Case Study 2: Strain in continuous process
  - Continuous feeders and mixers
  - Lubrication
  - Effect of feed frame

Case Study 1

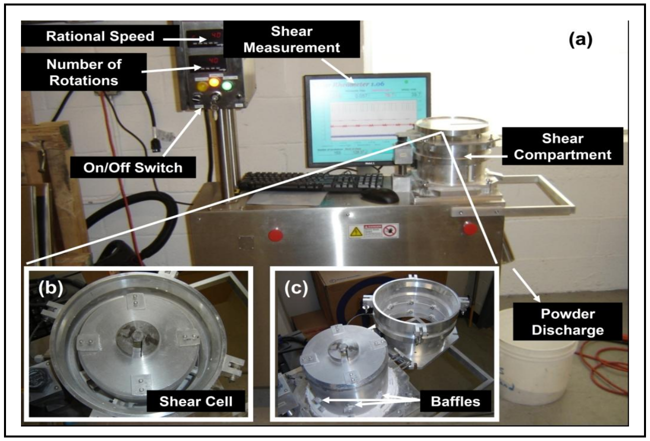
- Step 1 – Prepare multiple formulations varying mixing order
- Step 2 – Strain the powders in a controlled shear environment.
- Step 3 – Measure powder properties: powder flow properties, electrical properties, hydrophobicity.
- Step 4 – Prepare tablets and test the tablet dissolution.
- Step 5 – Characterize the tablets using SEM X-ray EDS, Line Scan Analysis (X-ray EDS), XRD of powders and tablets.

Materials

- The following formulations were prepared.
  1. 9% Mic.Acetaminophen + 44.5% Avicel 102 + 44.5% Pharmatose.
  2. 9% Mic.Acetaminophen + 44.5% Avicel 102 + 44.5% Pharmatose **+ 1% MgSt.**
  3. 9% Mic.Acetaminophen + 44.5% Avicel 102 + 44.5% Pharmatose **+ 1% Cab-O-Sil.**
  4. 9% Mic.Acetaminophen + 44.5% Avicel 102 + 44.5% Pharmatose **+ 1% MgSt + 1% Cab-O-Sil.**

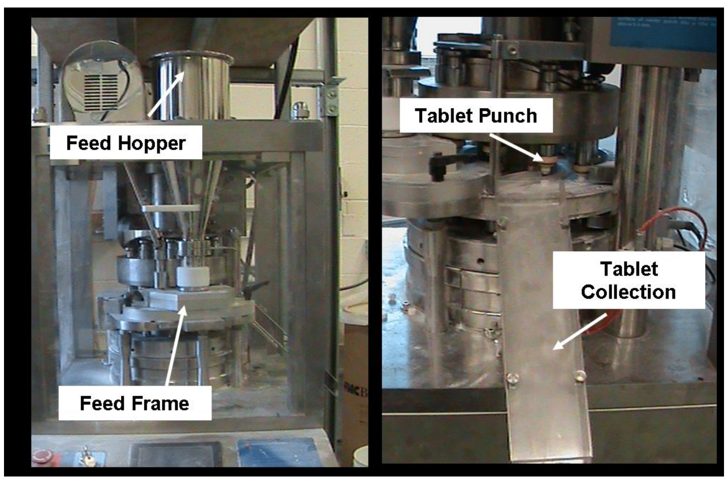
Methods

Controlled Shear Environment



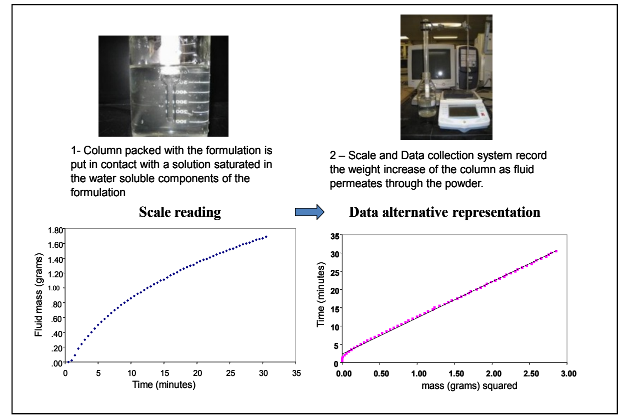
Formualtions prepared were sheared at shear rate of 80 rpm and shear strain of 40 rev, 160 rev and 640 rev.

Rotary Tablet Press



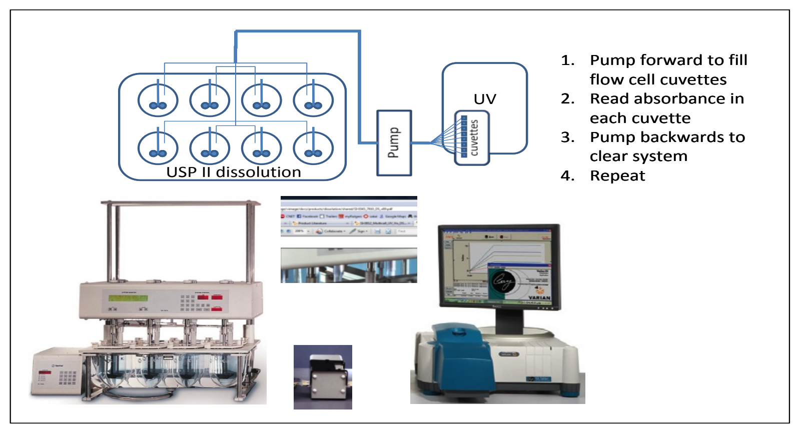
Powders were compressed into tablets at a compression force of 12 kN.

Hydrophobicity



Hydrophobicity was measured from the slope of the squared mass verses time.

Dissolution



A modified USP method was used for dissolution testing of acetaminophen tablets.

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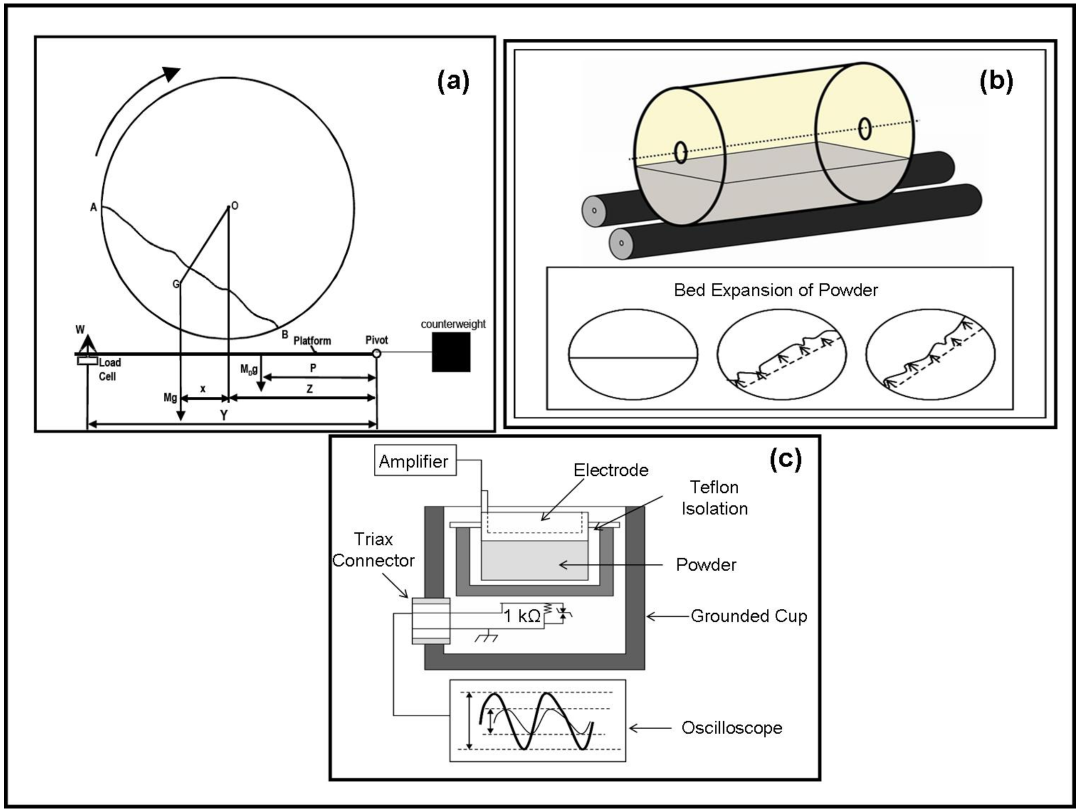
Methods (Contd..)

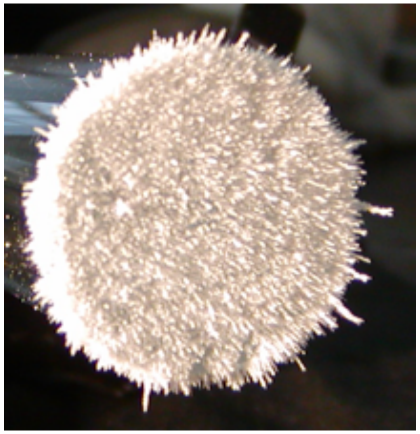


Laboratory equipment for the measurement of flow and electrical properties of pharmaceutical powders (a) Gravitational Displacement Rheometer (GDR) to measure flow index (Alexander et al., 2006) (b) Dilation rollers with cylinder filled to 40% powder for measuring bed expansion (c) Impedance measurement using oscilloscope, faraday cup and amplifier.

Charging and Granular Flow

- Adhesion
  - *Grains stick to surfaces*
    - *Coating*
  - *Grains stick to one another*
    - *Agglomeration*
  - *Nonuniform flow*
  - *Unpredictable behavior*
  - *Poor mixing*
- Repulsion
  - *From charged surfaces*
  - *From other grains*
  - *May lead to segregation*

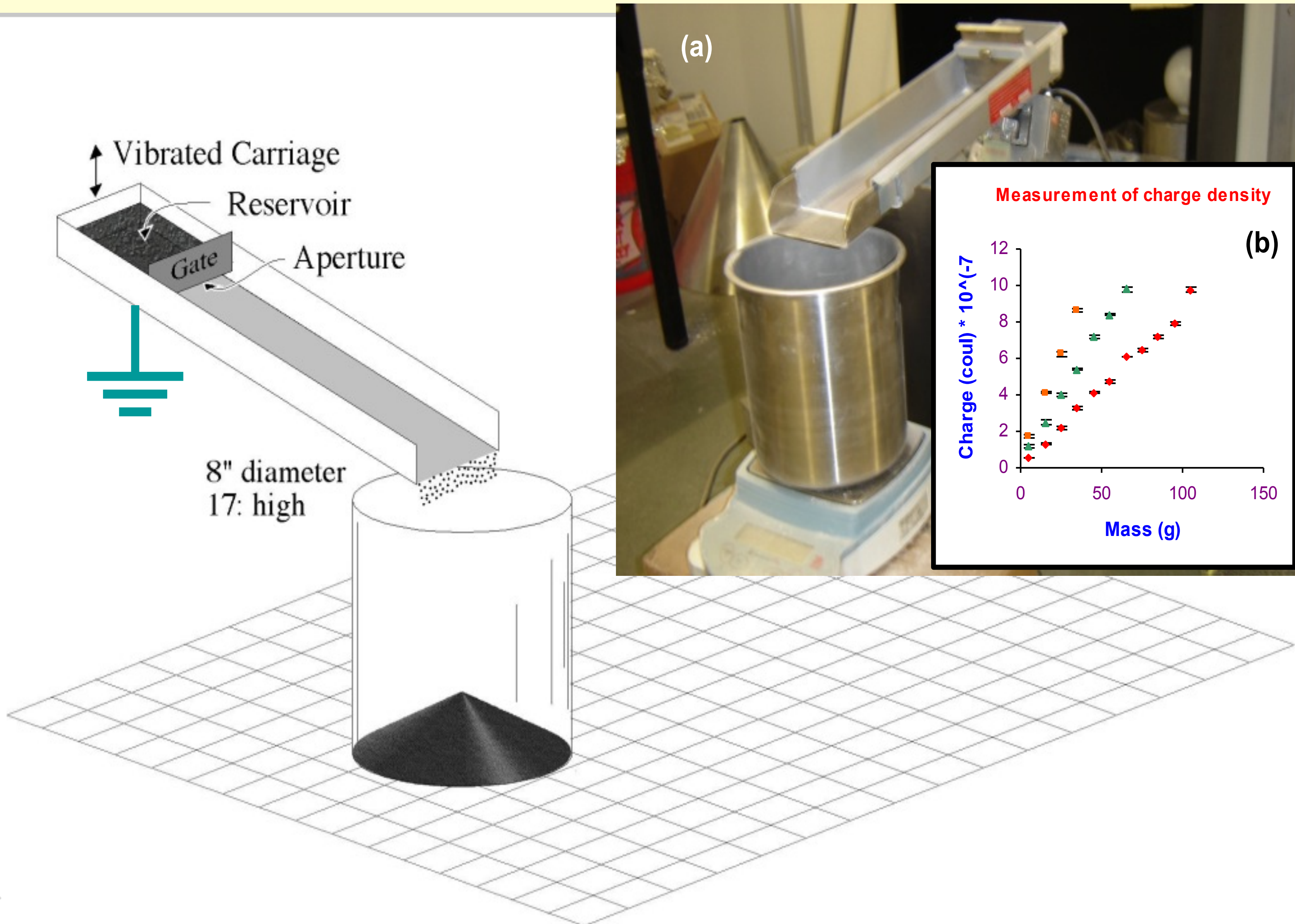
Sand adhered to a hopper



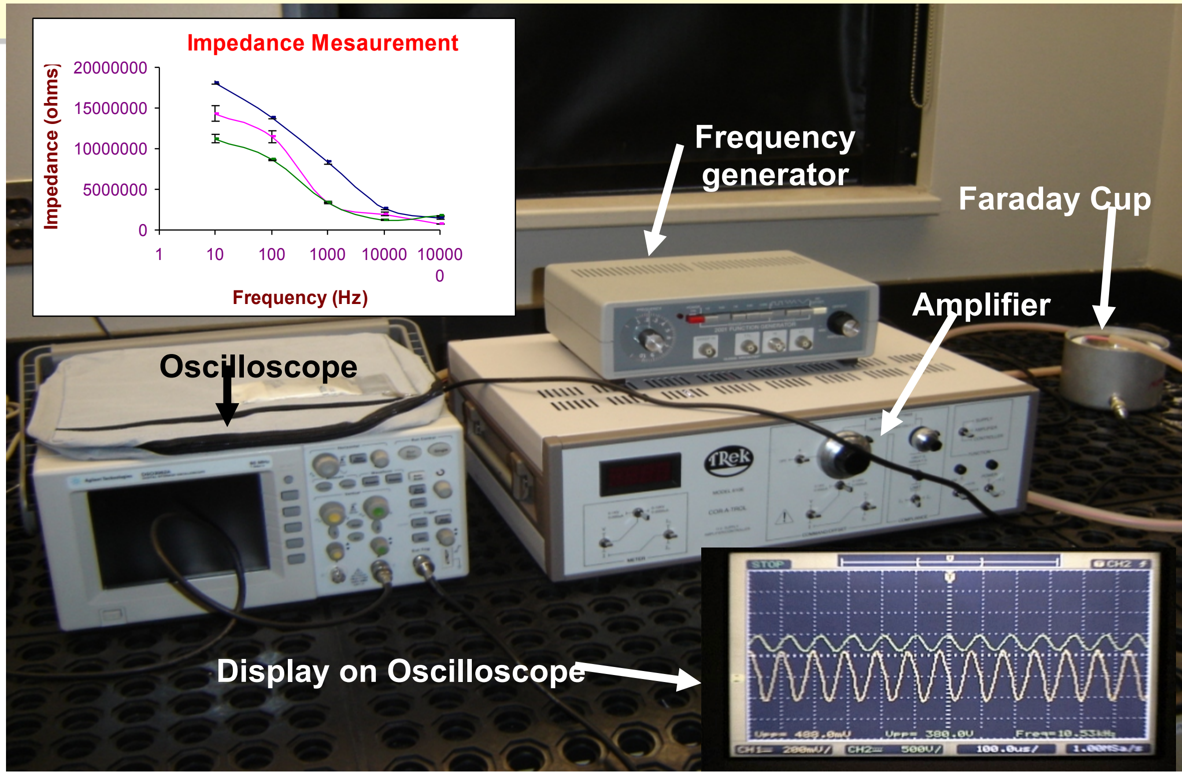
Cellulose adhered to a charged rod

Marche et al., Electrostatic instabilities, charging and agglomeration in flowing granular materials, 2008.

Measurement of Charge Density



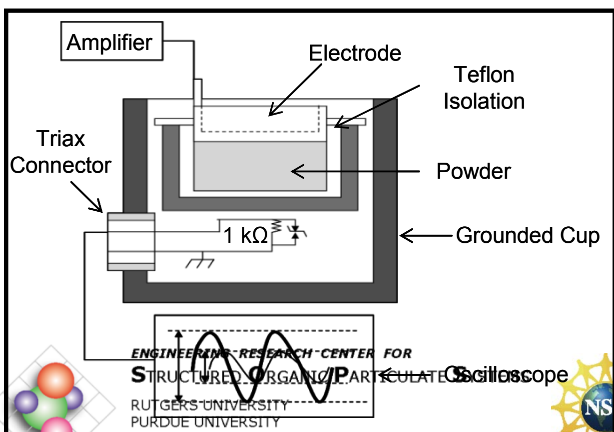
Impedance Measurement

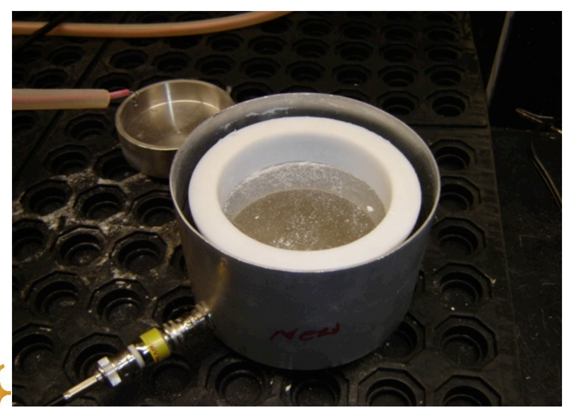


The Model 610E high voltage (HV) supply amplifier controller supplied by Trek Inc was used for voltage supply.

A frequency meter ranging from 10 Hz to 100k Hz was used to supply frequency to the amplifier which in turn supplied voltage depending upon the supplied frequency.

The powder was kept in the Faraday cup and HV out from the amplifier was connected to the Faraday cup, which supplied voltage to the powder through the cup.





Changes in impedance are directly related to the variation in the conductivity of the powder bed.

This can be due to a change in composition (blend effect), a change in density, or a change in microstructure.

Triboelectrc Charge

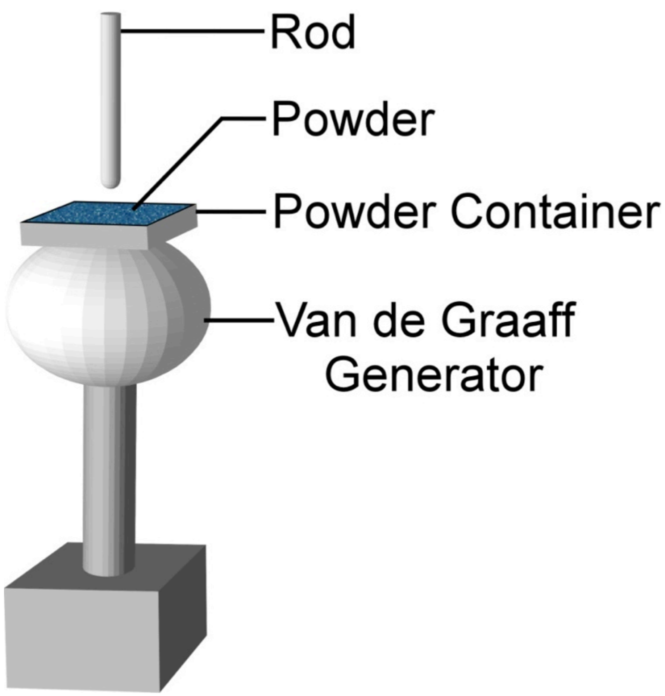
Triboelectric Demixing at Hopper Discharge

- Can we measure intrinsic properties that predict this?

Marche et al., Electrostatic instabilities, charging and agglomeration in flowing granular materials, 2008.

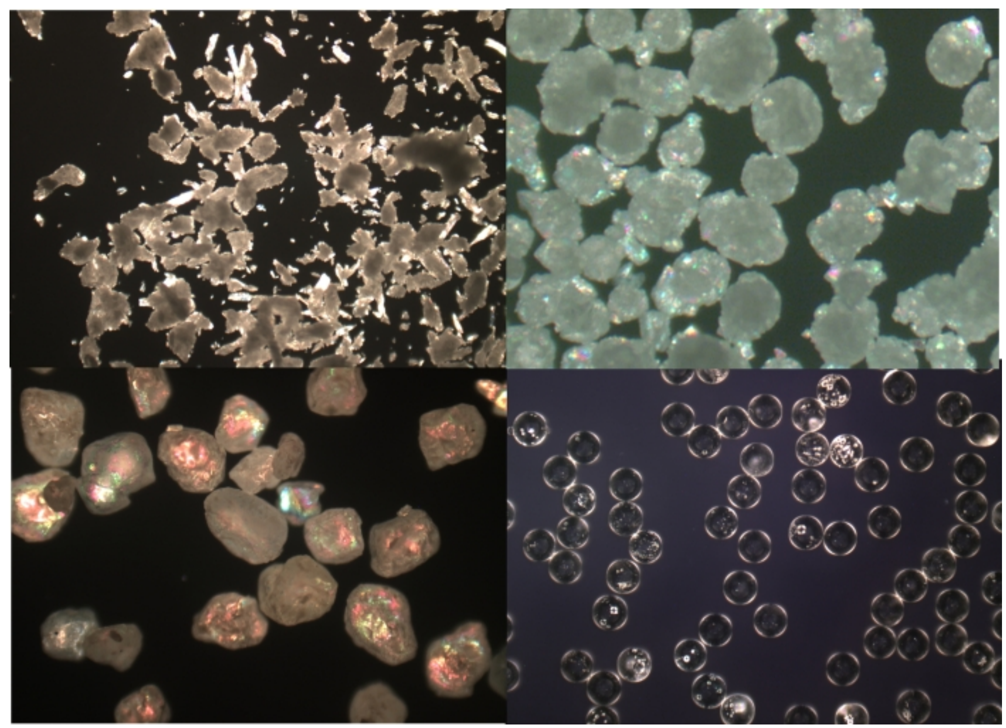
Nonuniform Electric Fields

- Experiments
  - *High voltage produced with Van de Graaff generator*



Microcrystalline Cellulose

Lactose



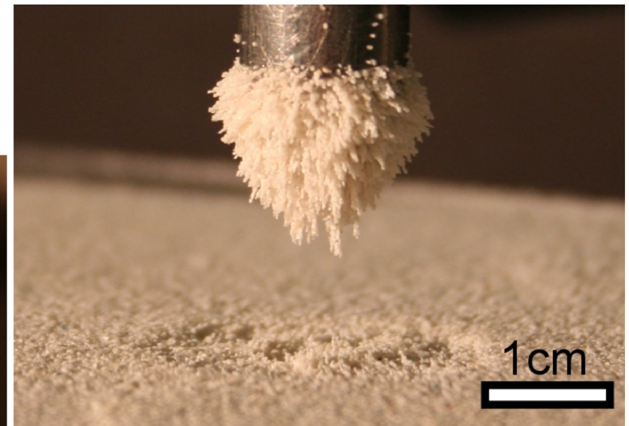
White Sand

150µm glass beads

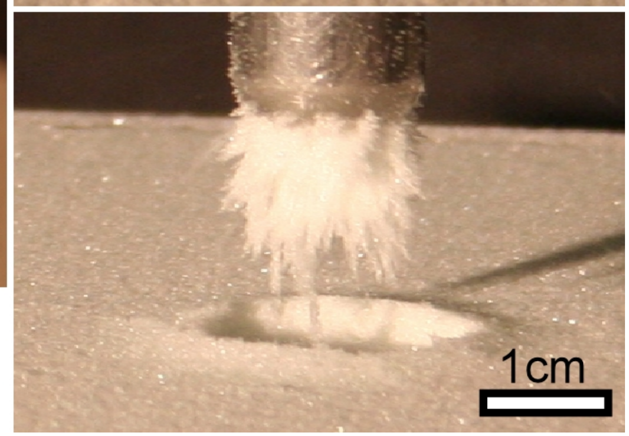
Marche et al., Electrostatic instabilities, charging and agglomeration in flowing granular materials, 2008.

Adhesion

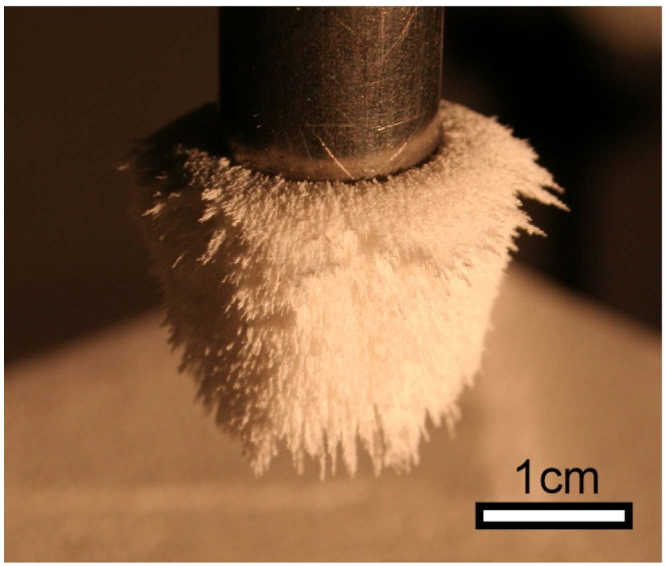
- Materials adhere to a grounded rod in E-field



White Sand



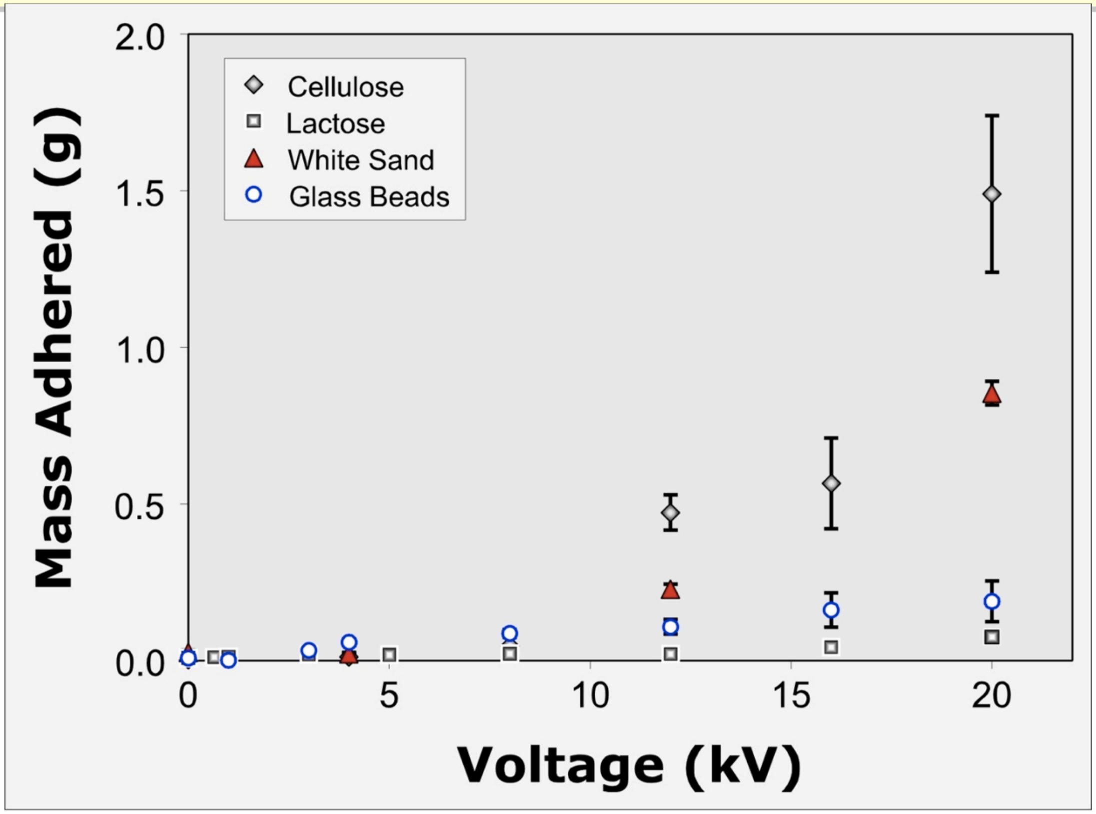
Glass Beads



Cellulose

Cellulose, sand and 150μm glass beads adhered to a grounded metal rod above the VDG generator at 20kV. Almost no material adheres to the rod when the VDG's voltage is 0. (Marche et al., Electrostatic instabilities, charging and agglomeration in flowing granular materials, 2008)

Adhesion and E-field Strength



The mass of material adhered to a grounded rod as a function of the voltage of the VDG. As the voltage increases so does the strength of the electric field allowing more material to adhere to the rod.

(Mareche et al., Electrostatic instabilities, charging and agglomeration in flowing granular materials, 2008).

Effect of Shear Rate, Strain, and Blend Composition on Electric Properties

Impedance

$Y_{ijk} = \mu + B_i + R_j + BR_{ij} + S_k + BS_{ik} + RS_{jk} + \varepsilon_{ijk}$

B_i=Blend effect

R_j=Shear Rate effect

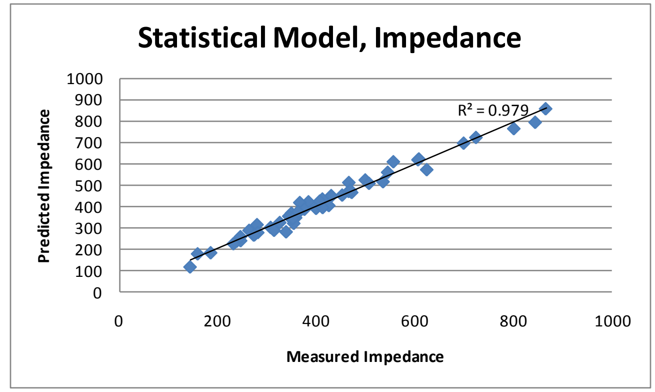
BR_{ij}=Blend-Shear Rate interaction

S_k=Strain Effect

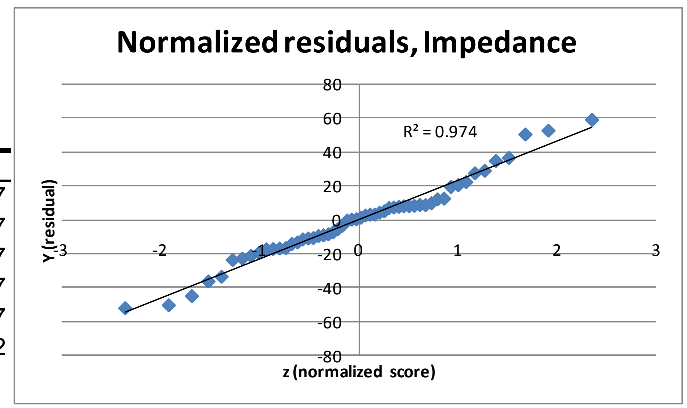
BS_{ik}=Blend-Strain interaction

RS_{jk}=Shear Rate-Strain Interaction

ε_{ijk} = Residual Error



Comparison between predicted and observed values for impedance. The factors blend, shear rate, and strain, and their two-way interactions account for 98% of all the variability in the data set.



Test of normality for residuals of the observed impedance measurements. The residuals are normally distributed, displaying a R^2 of .97 when compared to a normal distribution.

Main ANOVA Impedance

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
blend	532243.2	5	106448.6	72.63467	3.95828E-12	2.710889837
shear rate	13574.93	2	6787.466	4.631391	0.022240458	3.492828477
strain	18228.16	2	9114.082	6.218946	0.007939147	3.492828477
blend*shear rate	208431.4	10	20843.14	14.22221	5.0522E-07	2.347877567
Blend*strain	599390.2	10	59939.02	40.89907	4.08381E-11	2.347877567
shear rate*strain	5610.956	4	1402.739	0.957152	0.452281797	2.866081402
Error	29310.7	20	1465.535			
Total	1406790	53				

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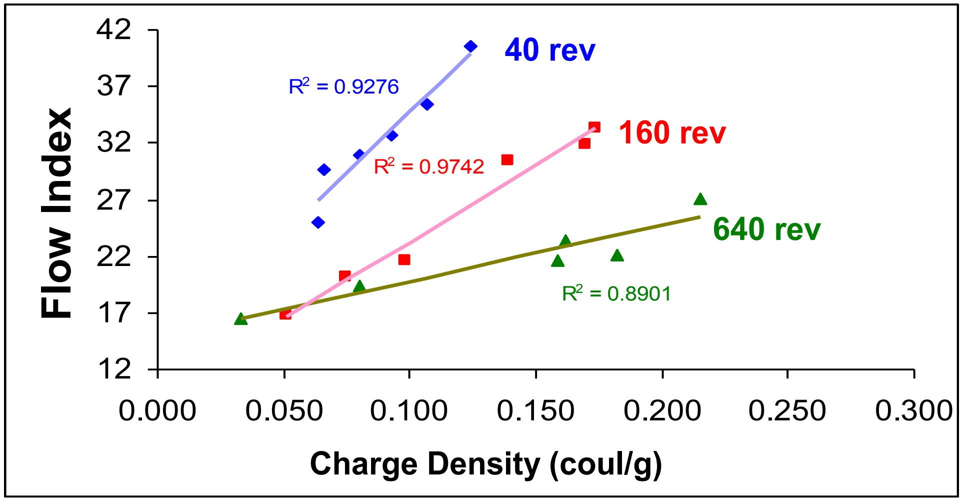
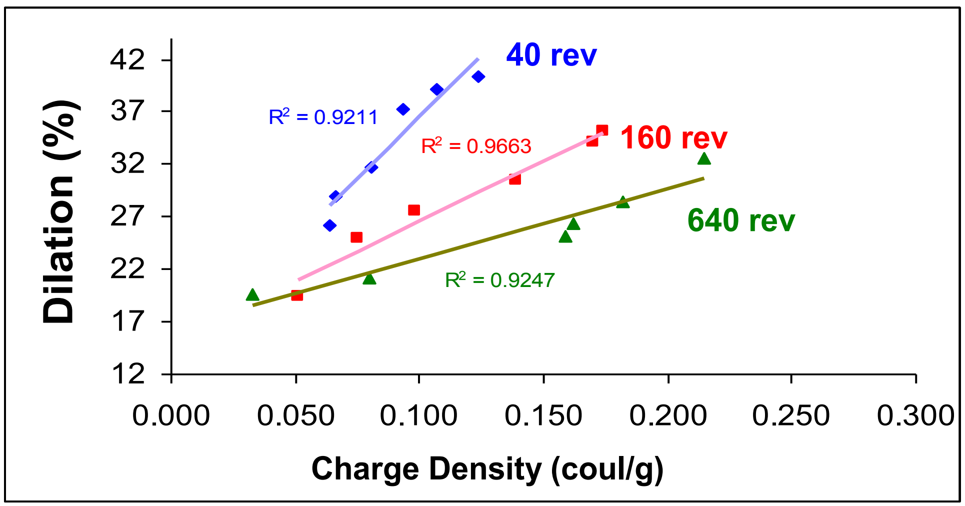
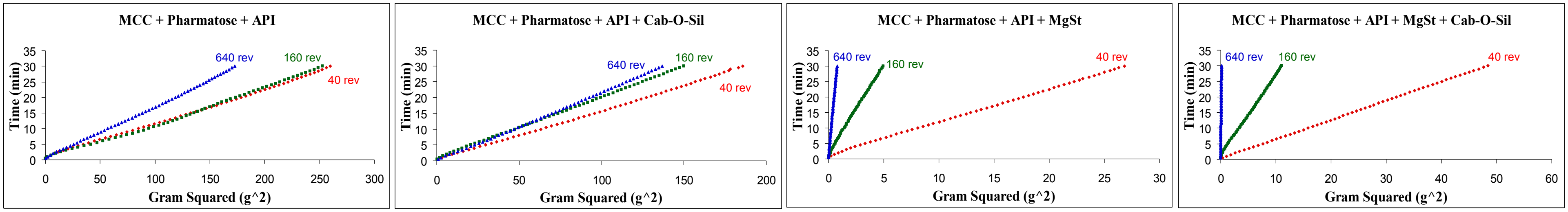
Effect of Composition And Strain on Flow Properties: An Electric Connection

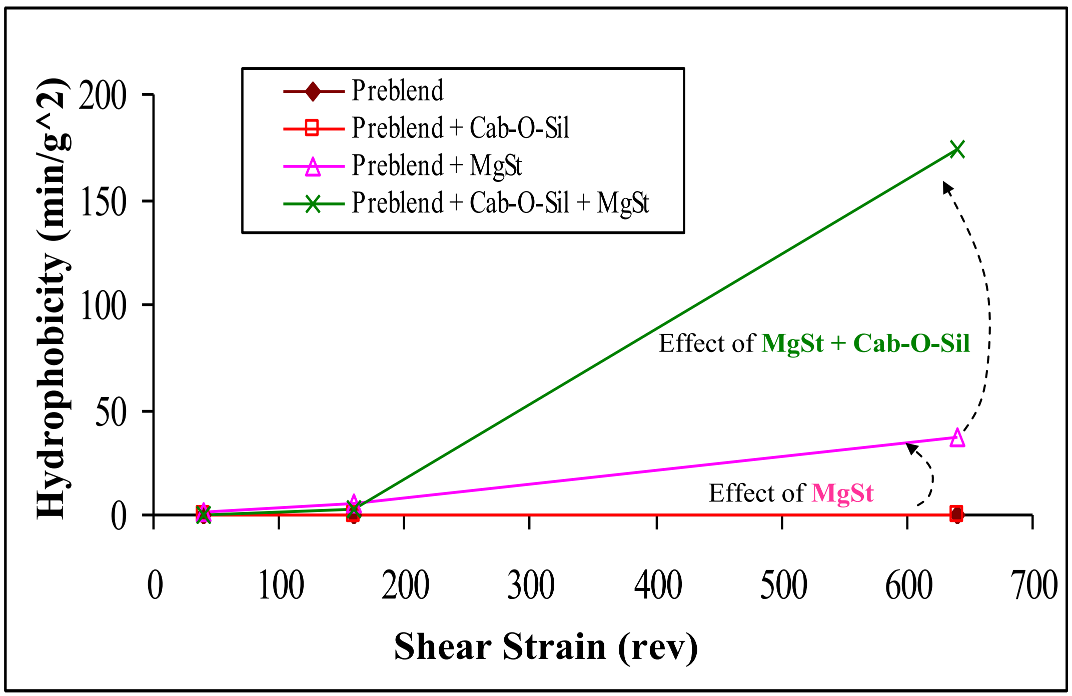




(a) Flow index and (b) dilation correlate to charge acquisition for different shear treatments. Flow index and dilation increased with charge acquisition indicating worsening of powder flow with charge accumulation.

(Shear – Hydrophobicity)



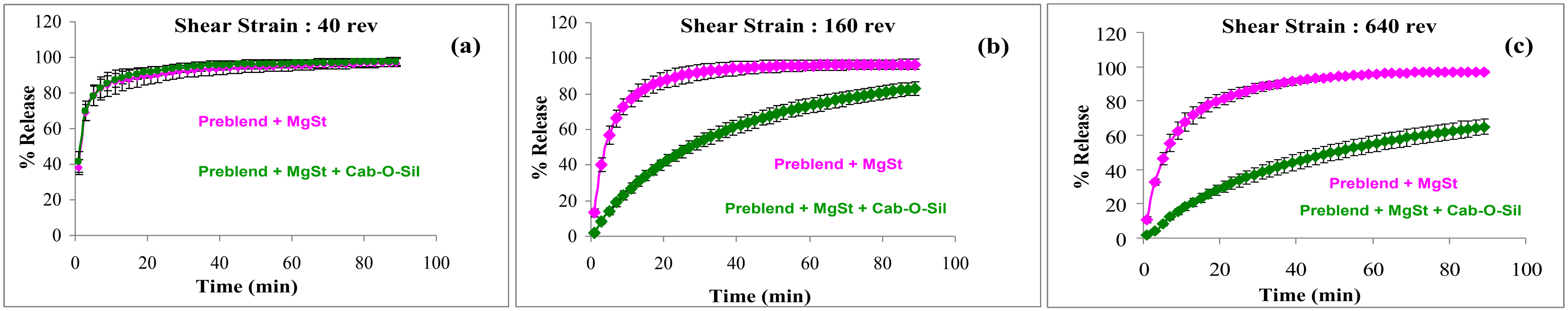


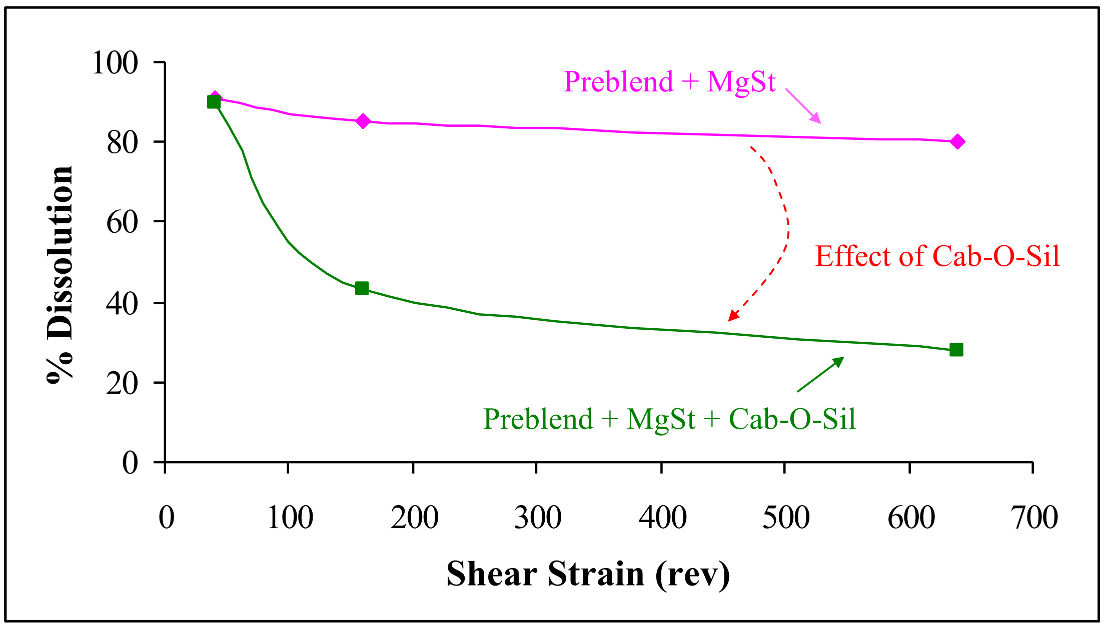
Cab-O-Sil alone had a minimum effect on powder hydrophobicity.

Hydrophobicity slightly increased with an addition of MgSt alone.

Interestingly, hydrophobicity was found to be sharply increased with an addition of both MgSt and Cab-O-Sil to the powder blend.

Shear - Dissolution





Drug release rate decreased with an increase in shear strain for the blends with both MgSt + Cab-O-Sil.

The effect is intensely dependent on strain

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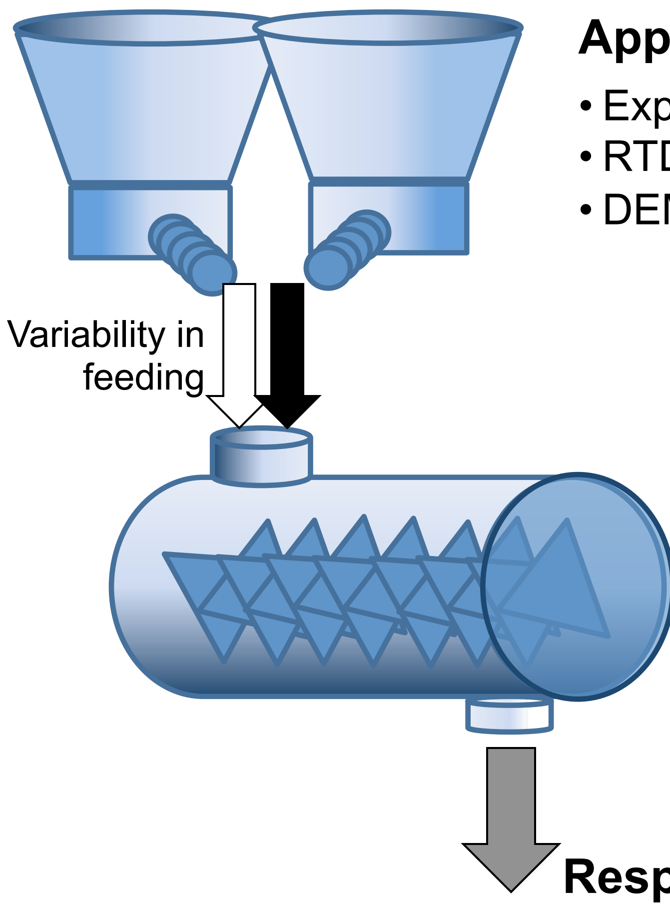
NSF

Case Study 2

Raw material properties
- Particle size distribution
- Flow properties
- Electrostatic behavior

Process parameters
- Flow rates
- Impeller speed

Design parameters
- Impeller blade configuration
- Weir design
- Mixer design



Approach
- Experimental characterization
- RTD modeling
- DEM modeling

Responses
- Blend uniformity (RSD)
- Flow properties
- Hydrophobicity

Case Study 2

Experimental Set-up & Continuous Mixer

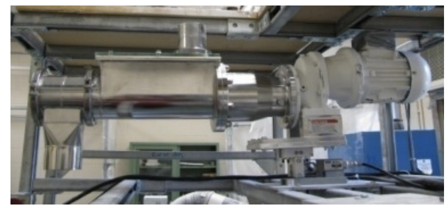
Experimental set-up

(a)

Gericke continuous mixer integrated with Schenck AccuRate LIW feeders

(b)

Mixer

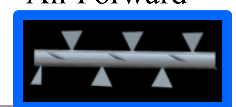


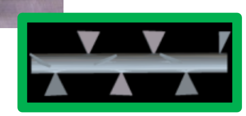
Impeller Design

Length - 12 inch
Diameter – 4 inch

12 triangular blades

All Forward



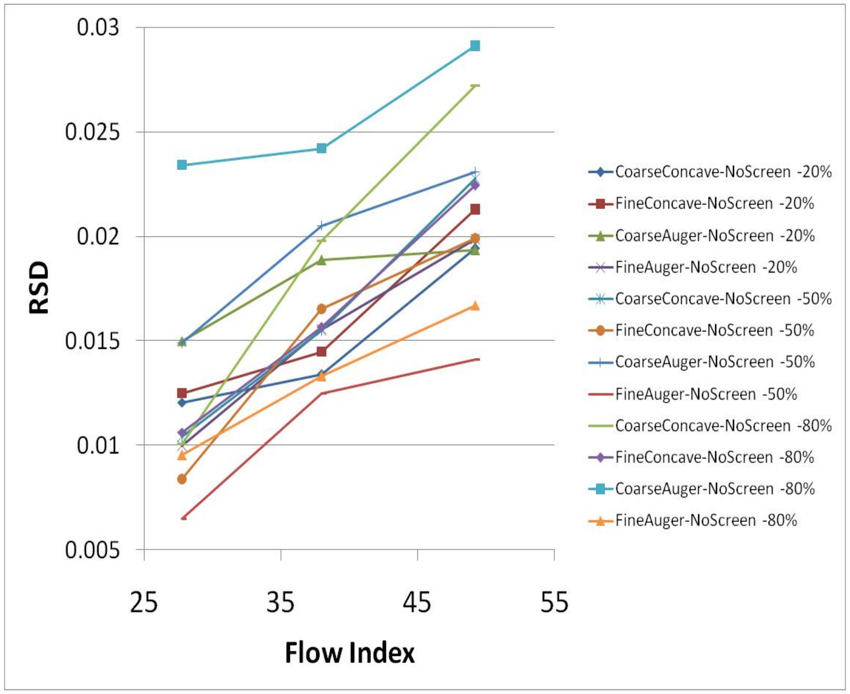


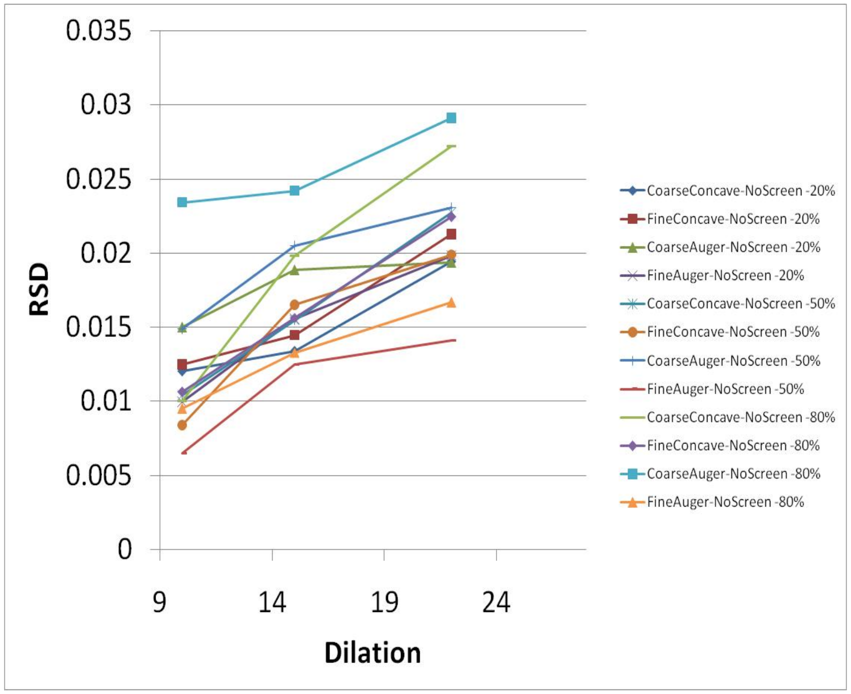
Alternate

Weir

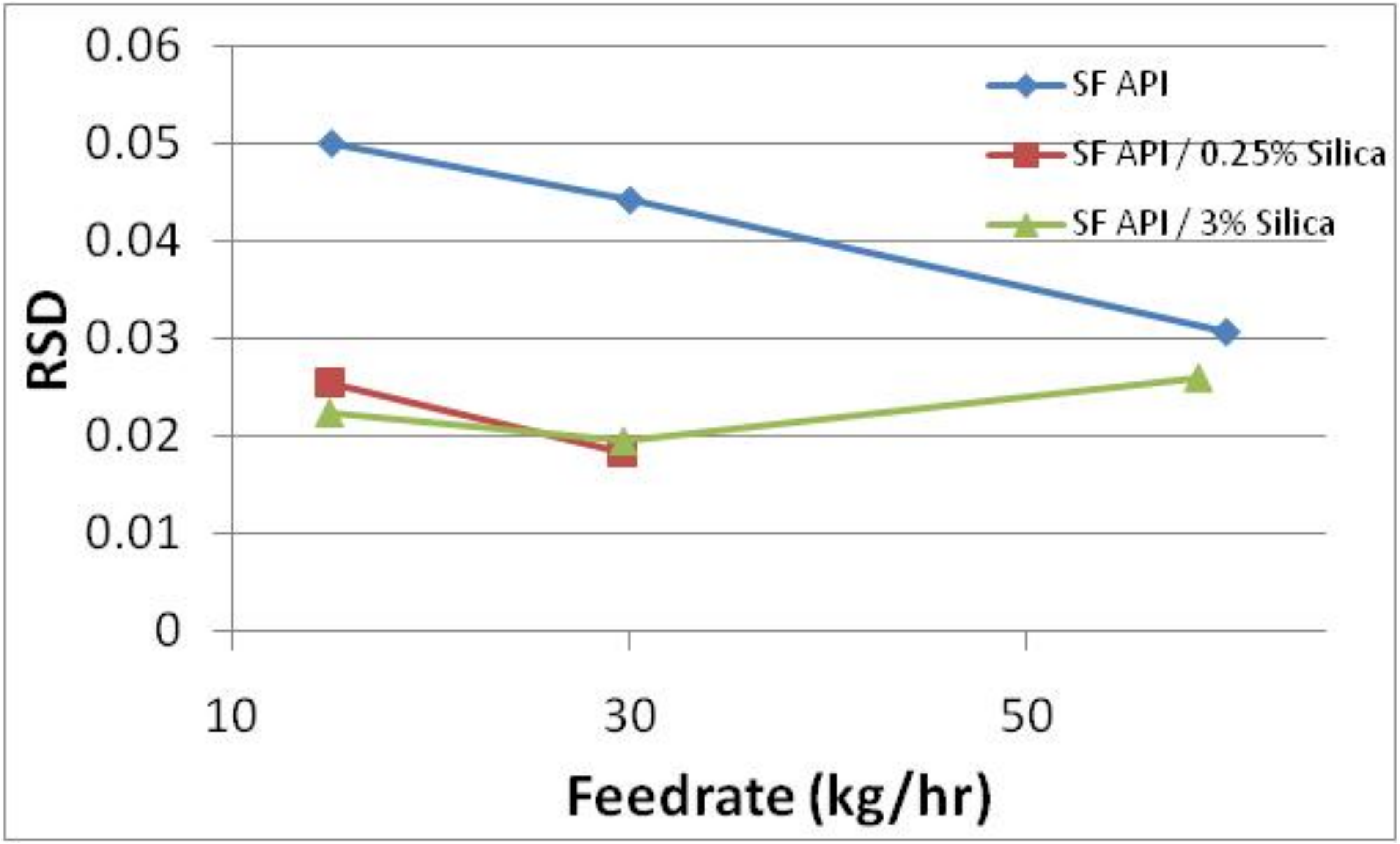
Working system

RSD vs. Flow Properties (KT35 Feeder)





Feeding blends of Acetaminophen/SiO2 (with KT35 feeder)

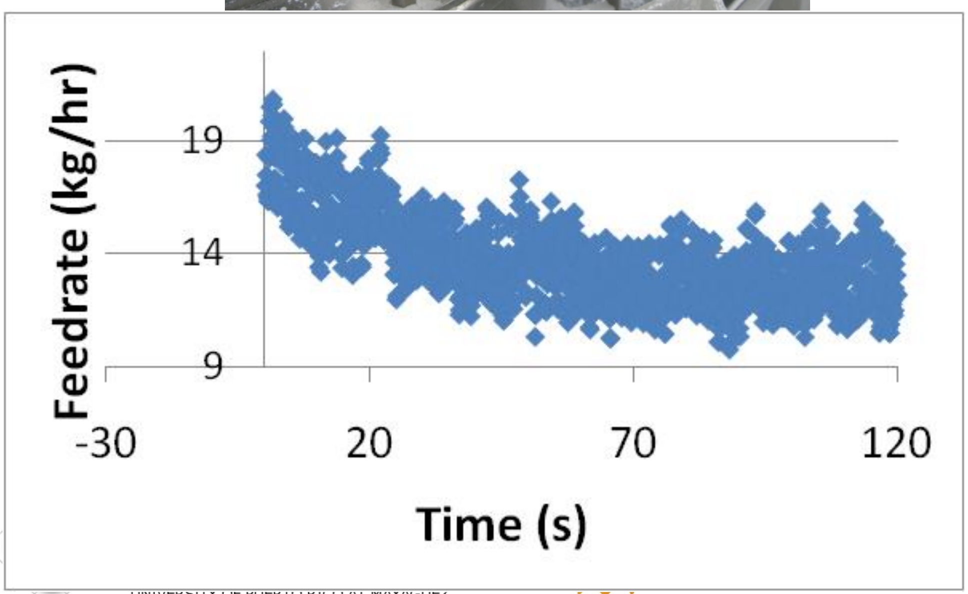


"Rat holing" and bridging

Agitation and hopper flow also affect screw filling consistency.

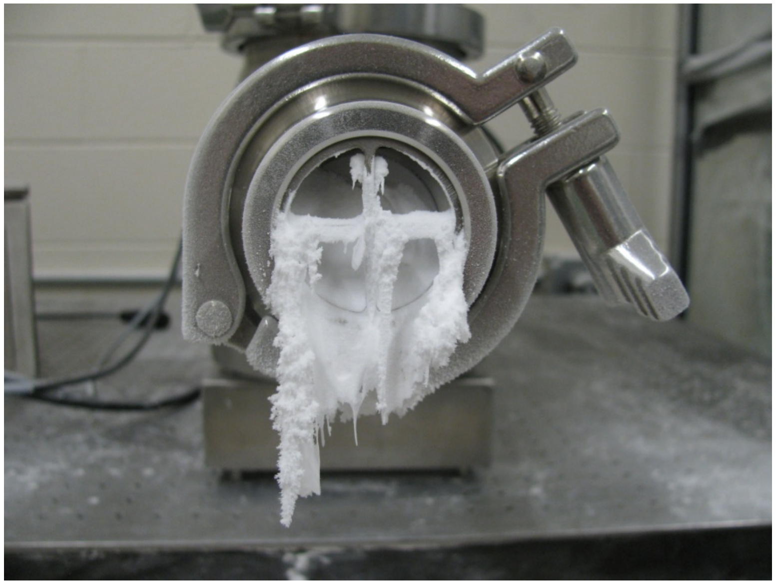
Screw Coating and "sticky" powders

Coating of the screws reduces the space available material that can be fed and reduces the capacity of the feeder.



Electrostatics in Feeders

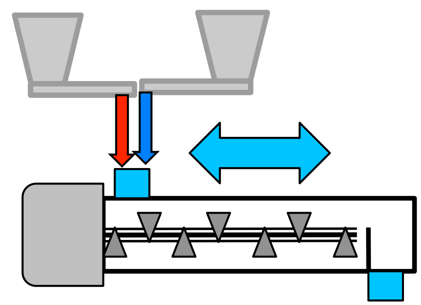
"Bearding" can cause flowrate inconsistency caused by chunks of material breaking off intermittently.



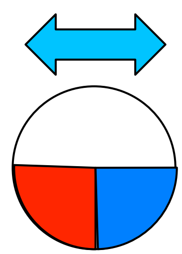

Examine bulk powder flow behavior in the continuous mixer

- **Rationale**
  - *Convection, shear and dispersion govern powder mixing processes*

Axial mixing required to compensate the incoming feed rate variability → RTD



Radial mixing required for mixing the initially unmixed powders → Total Shear



Methodology

– *RTD measurement*
  - *Residence time distribution function*

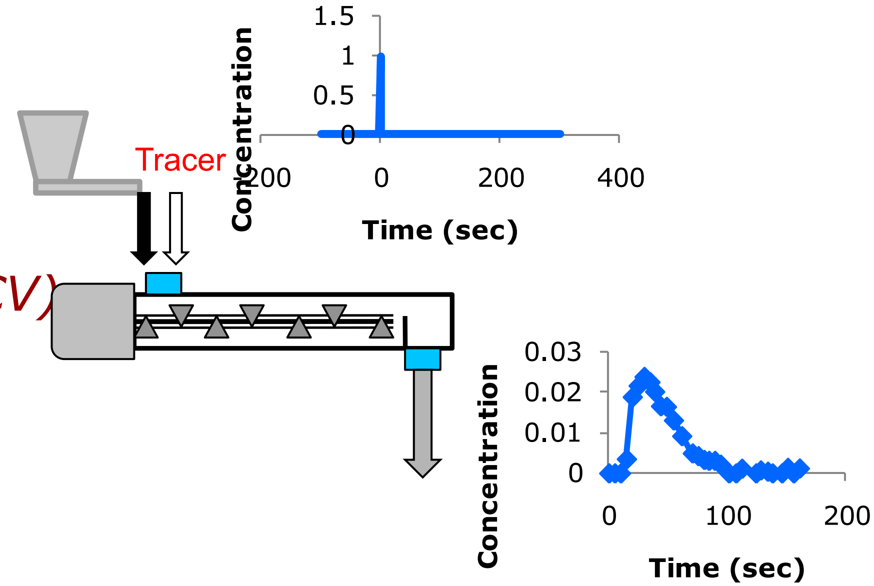
$$E(t) = \frac{c(t)}{\int_0^\infty c(t).dt}$$

  - *Mean Residence time (MRT)*

$$\tau = \int_0^\infty t.E(t).dt$$

  - *Mean Centered Variance (MCV)*

$$\sigma_\tau^2 = \frac{\int_0^\infty (t-\tau)^2.E(t).dt}{\tau^2}$$



- *Total Shear(# Blade passes)*

$$\#\,\text{Blade passes} = \text{Shear rate (Rev/sec)} \times \text{Residence Time (sec)}$$

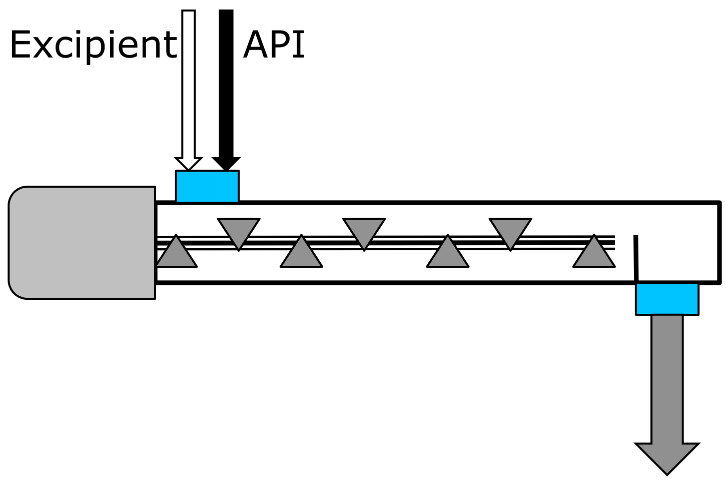
Results

Effects of process parameters

Case Study

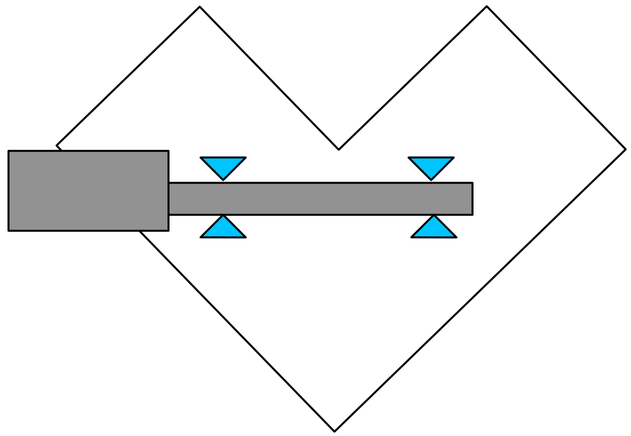
EQUAL # blade passes

Continuous blending



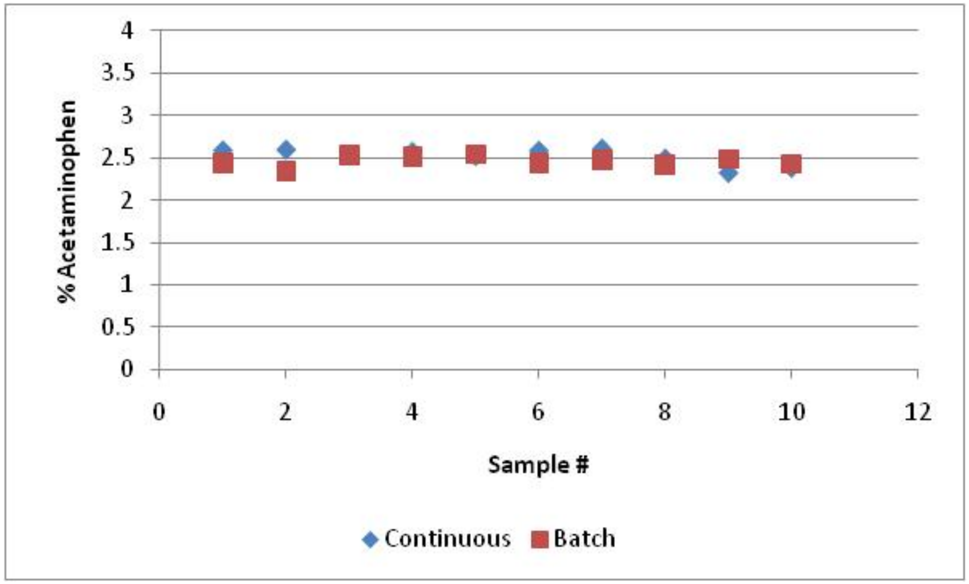
•Volume: 1 Liter
•Total feed rate = 30 kg/hr
•Blender RPM = 100, alternate blade
•RTD measurement: 90 blade passes

Batch blending



•V blender (3.74 Liter)
•65% Fill level
•Number of revolutions (45) = ½ Blade passes in the continuous blender = 90 passes
•RPM =15 (3 min blending time)

Blending Performance (RSD)



$$F = \frac{RSD_1^2}{RSD_2^2}$$

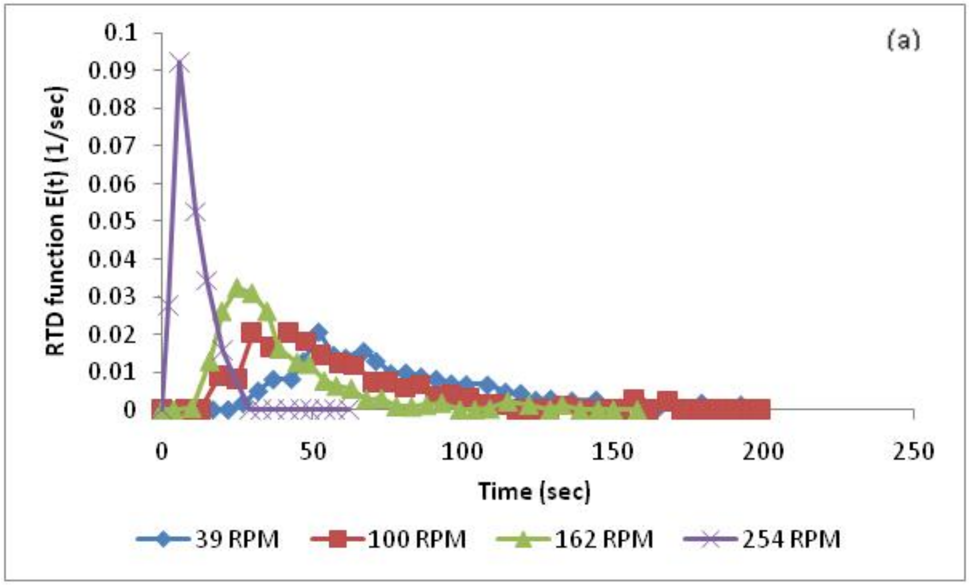
	UV analysis of 10 Samples		
	Std Dev	Mean	RSD
Continuous	0.09	2.52	3.76
Batch	0.05	2.47	2.11

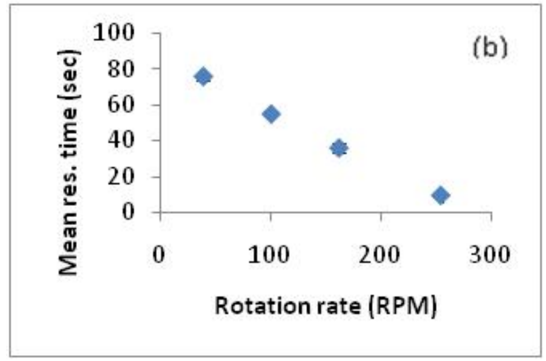
p=0.11, Statistically no significant difference between the batch and continuous runs

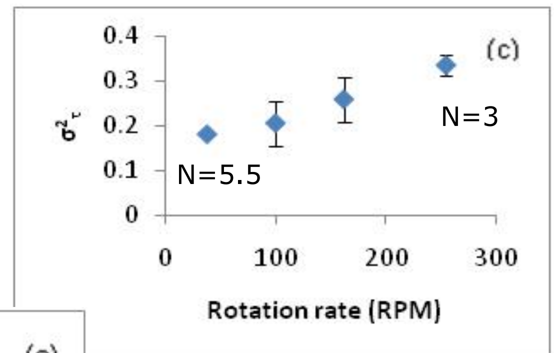
Tabletting performance

	Continuous	**Batch**
Hardness	183.23	177.47
Weight (g)	0.427	0.426
Weight variability (% RSD)	0.423	0.436

Effect of Rotation rate on RTD





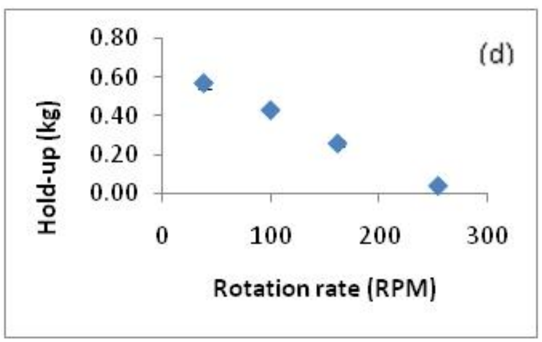


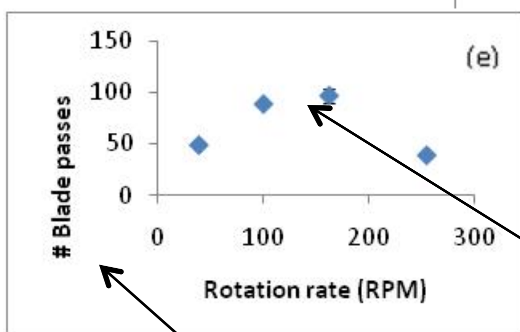
$\sigma_\tau^2 = 1$

Ideal CSTR

$\sigma_\tau^2 = 0$

Ideal PFR

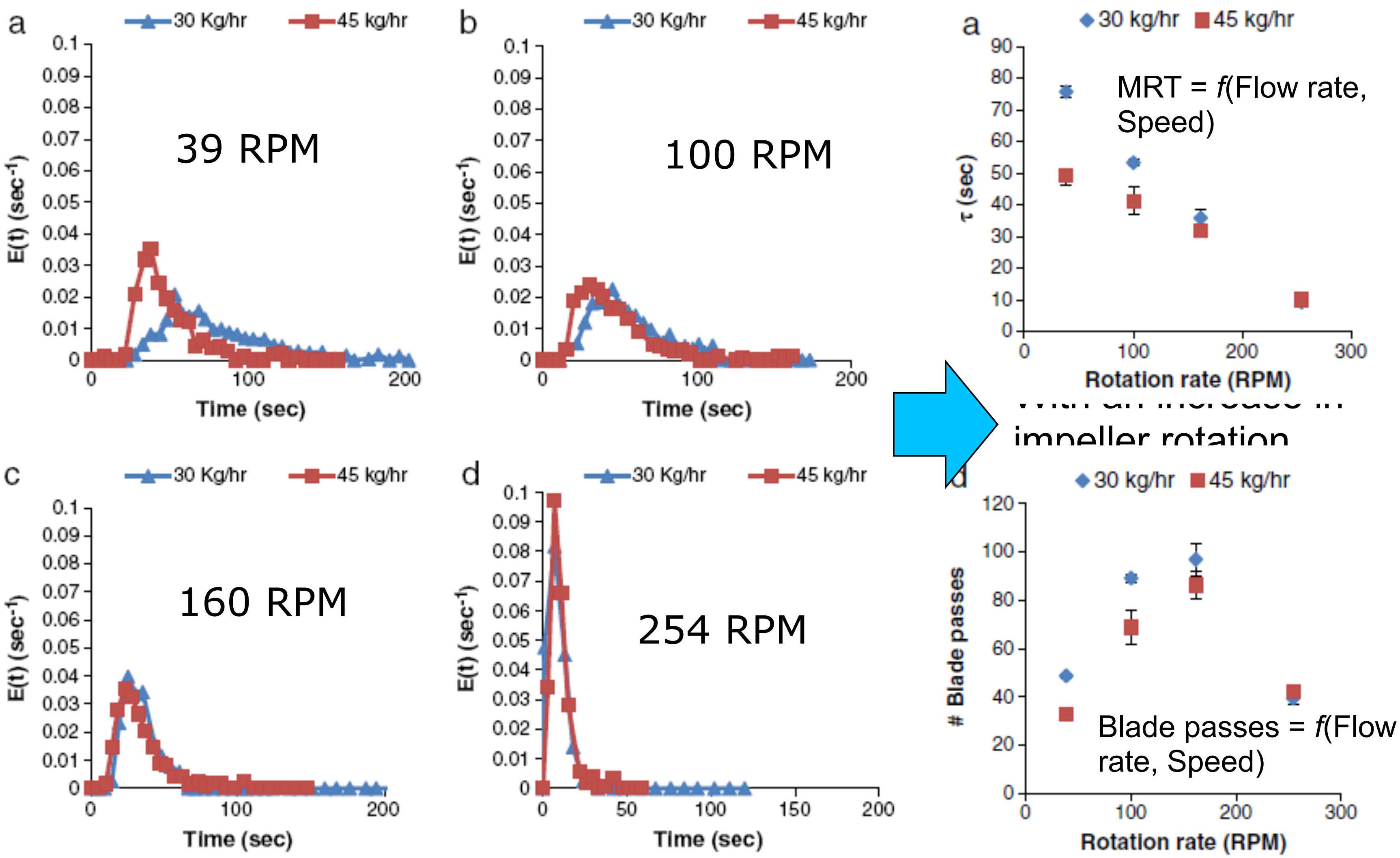




- Increase in RPM decreases MRT
- Increase in RPM increases MCV
- Strain is maximum at intermediate rotation rates

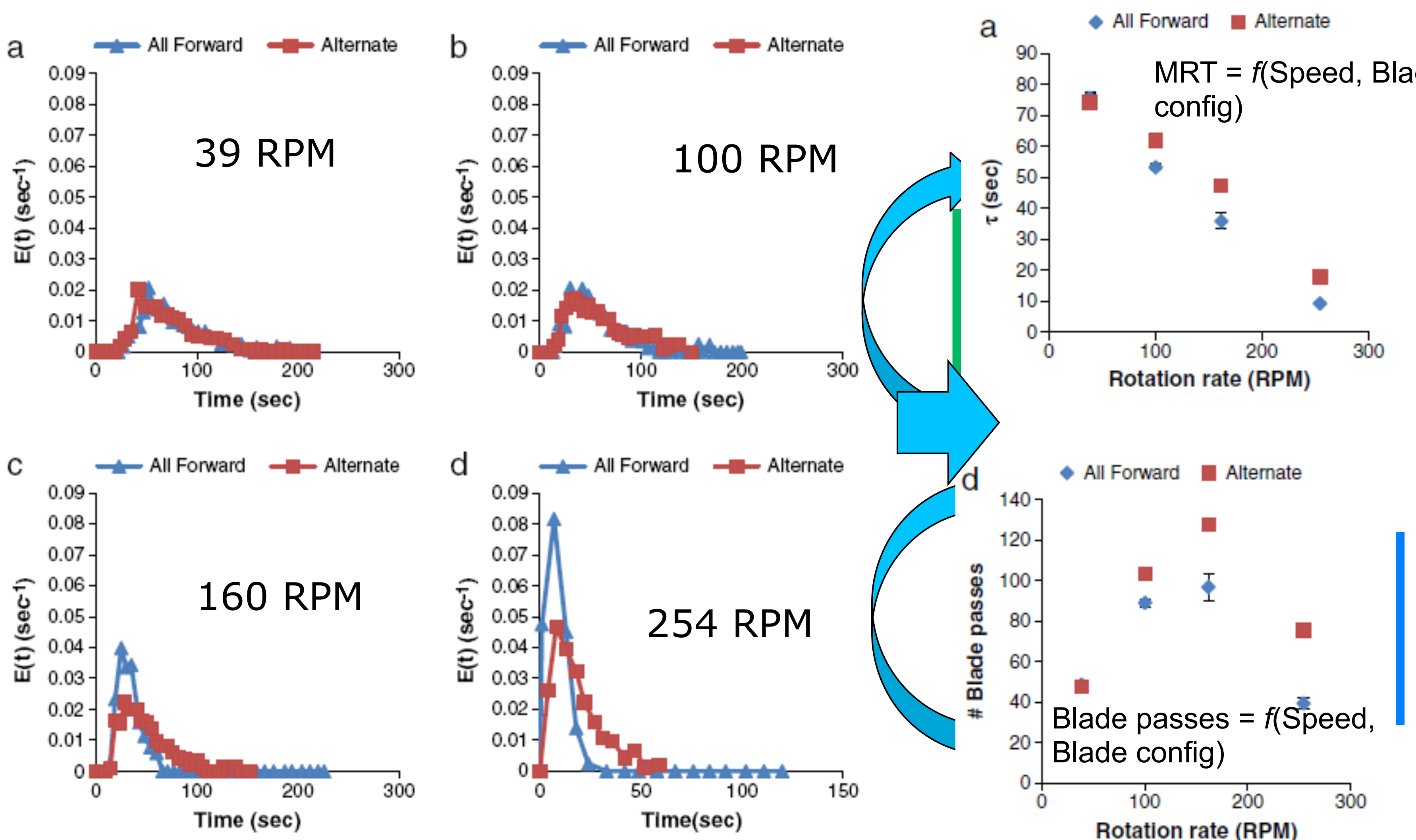
$$Strain = Shear\ rate(RPM) \times Mean\ Residence\ time$$

Effect of Flow rate on RTD

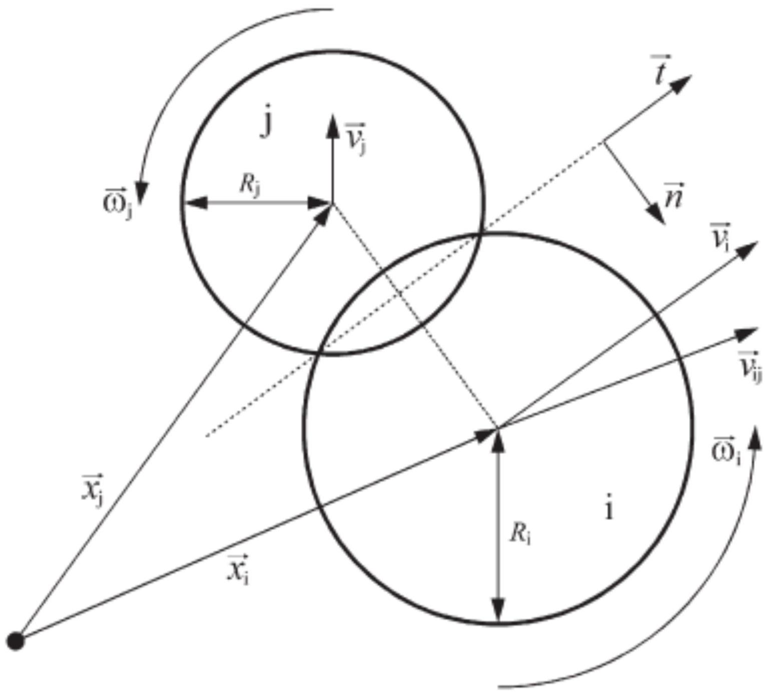


Effects of design parameters

Effect of Blade configuration on RTD



Discrete Element Modeling (DEM)



Total Force on Particles

$$F_{Total} = \sum F_{contact} + \sum F_{body}$$

Particle motion

Linear $$m_i \ddot{x}_i = \sum_j \left[F_{ij}^n + F_{ij}^t \right] + \sum_k F_{body}$$

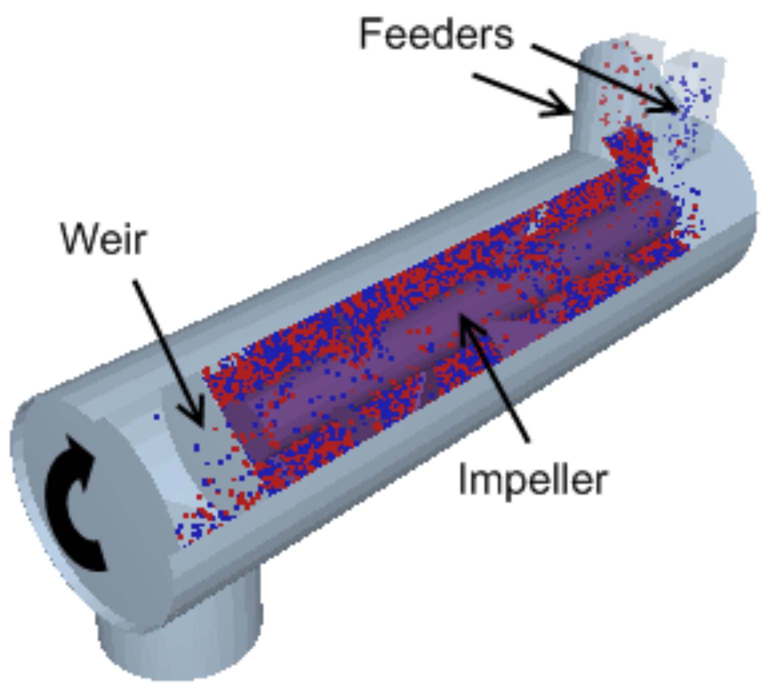
Angular $$I_i \ddot{\theta}_i = \sum_j \left[R_i \times F_{ij}^t \right] + \sum_l \tau_{body}$$

Contact model used: Hertz-Mindlin

Y. Tsuji, T. Tanaka, T. Ishida, Lagrangian numerical simulation of plug flow of cohesionless particles in a horizontal pipe, Powder Technol 71 (1992) 239-250.

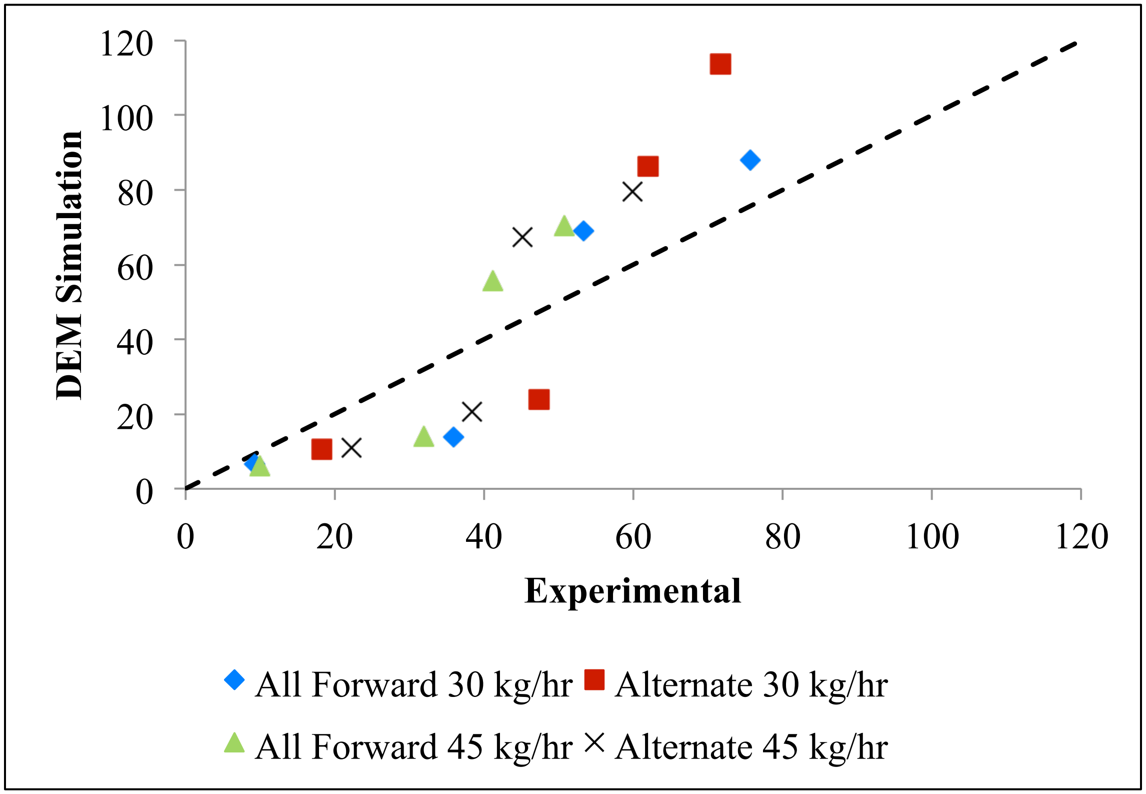
Simulation set-up

Particle Properties	Shear Modulus: 2e+06 N/m^2 Poisson's Ratio: 0.25 Density: 1500 Kg/m^3 Diameter: 2 mm Normal Size distribution with S.D. = 0.2 (Truncated at lower limit of 70% and a higher limit of 130%)
Particle-Particle Interactions	Coefficient of Static Friction : 0.5 Coefficient of Rolling friction : 0.01 Coefficient of Restitution: 0.1
Blender Walls	Material: Glass Shear Modulus: 26 GPa Density: 2200 Kg/m^3 Poisson's Ratio: 0.25
Blades	Material: Steel Shear Modulus: 80 GPa Density: 7800 Kg/m^3 Poisson's Ratio: 0.29
Particle-Blade Interactions	Coefficient of Static friction: 0.5 Coefficient of Rolling friction: 0.01 Coefficient of Restitution: 0.2
Particle-Wall Interactions	Coefficient of Static friction: 0.5 Coefficient of Rolling friction: 0.01 Coefficient of Restitution: 0.1



Simulation program: EDEM™ by *DEM Solutions*

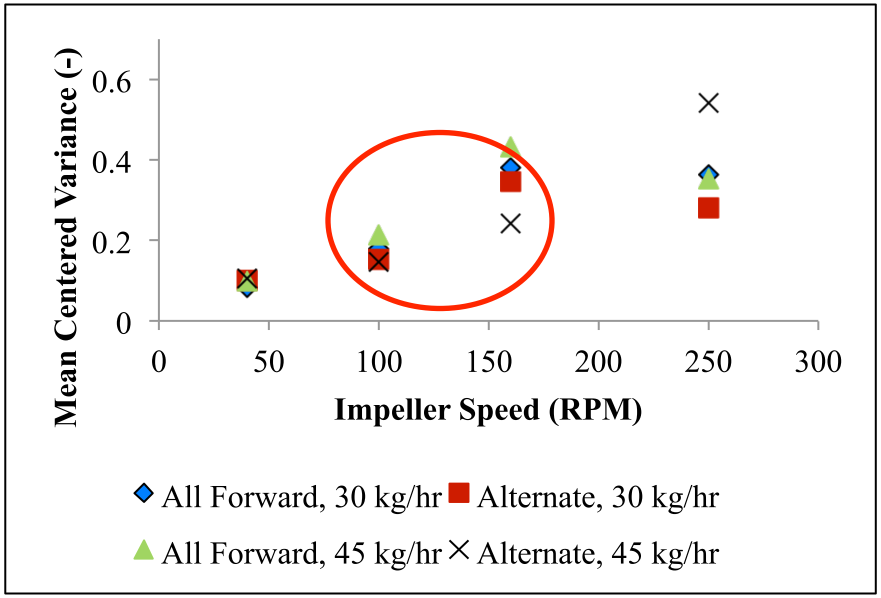
DEM simulations vs. Experiments (Mean Residence Time)



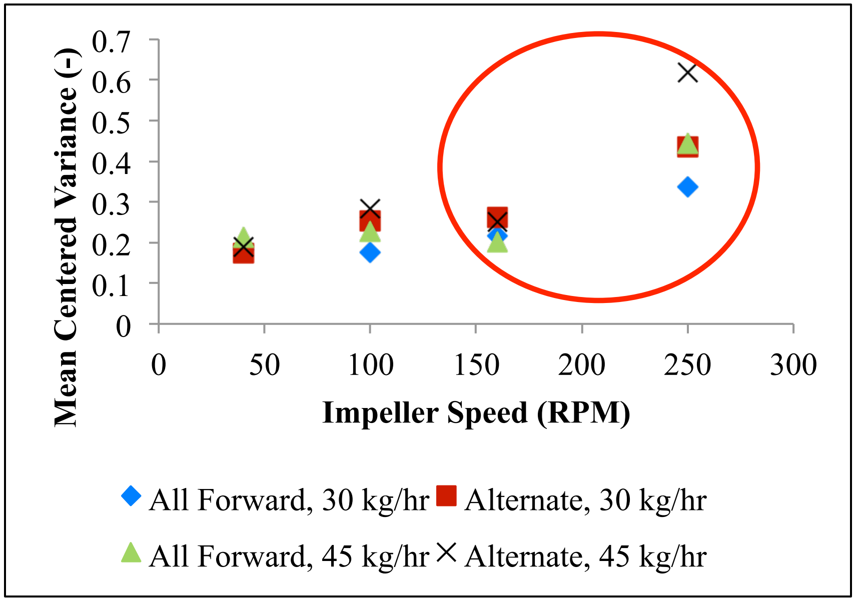
- Qualitative trends are captured reasonably well in DEM simulations
- Fluidization occurs at lower a impeller speed in DEM simulations
- # particles in DEM simulations (10^4)<< Experimental scenarios (10^{13})

DEM simulations vs. Experiments (Mean Centered Variance)

DEM Simulations



Experimental



In both cases

- MCV values are higher under fluidized conditions
- Lack of a correlation between MCV, and flow rate, blade pattern

Effects of material properties

RTD modeling

Axial dispersion model

$$\frac{\partial c}{\partial t} + u\frac{\partial c}{\partial z} = D\frac{\partial^2 c}{\partial^2 z}$$

$$\theta = (t - t_0)/\tau, \xi = z/l$$

$$C(\xi,\theta) = \frac{C_0 Pe^{1/2}}{(4\pi\theta)^{1/2}} e^{-\frac{Pe(\xi-\theta)^2}{4\theta}}$$

← Analytical solution

Axial dispersion coefficient →

$$D = \frac{u.l}{Pe}$$

Peclet number

Concentration vs. time data fitting using MATLAB least square fitting algorithm to estimate ***Pe*,*t_0*,*C_0*,*τ***

Y. Gao[1], A. Vanarase[1](Shared First Authorship), F. Muzzio, M. Ierapetritou, Characterizing continuous powder mixing using residence time distribution, Chemical Engineering Science 66 (2011) 417-425.

Effect material properties on powder flow behavior

Input variables:

Material properties

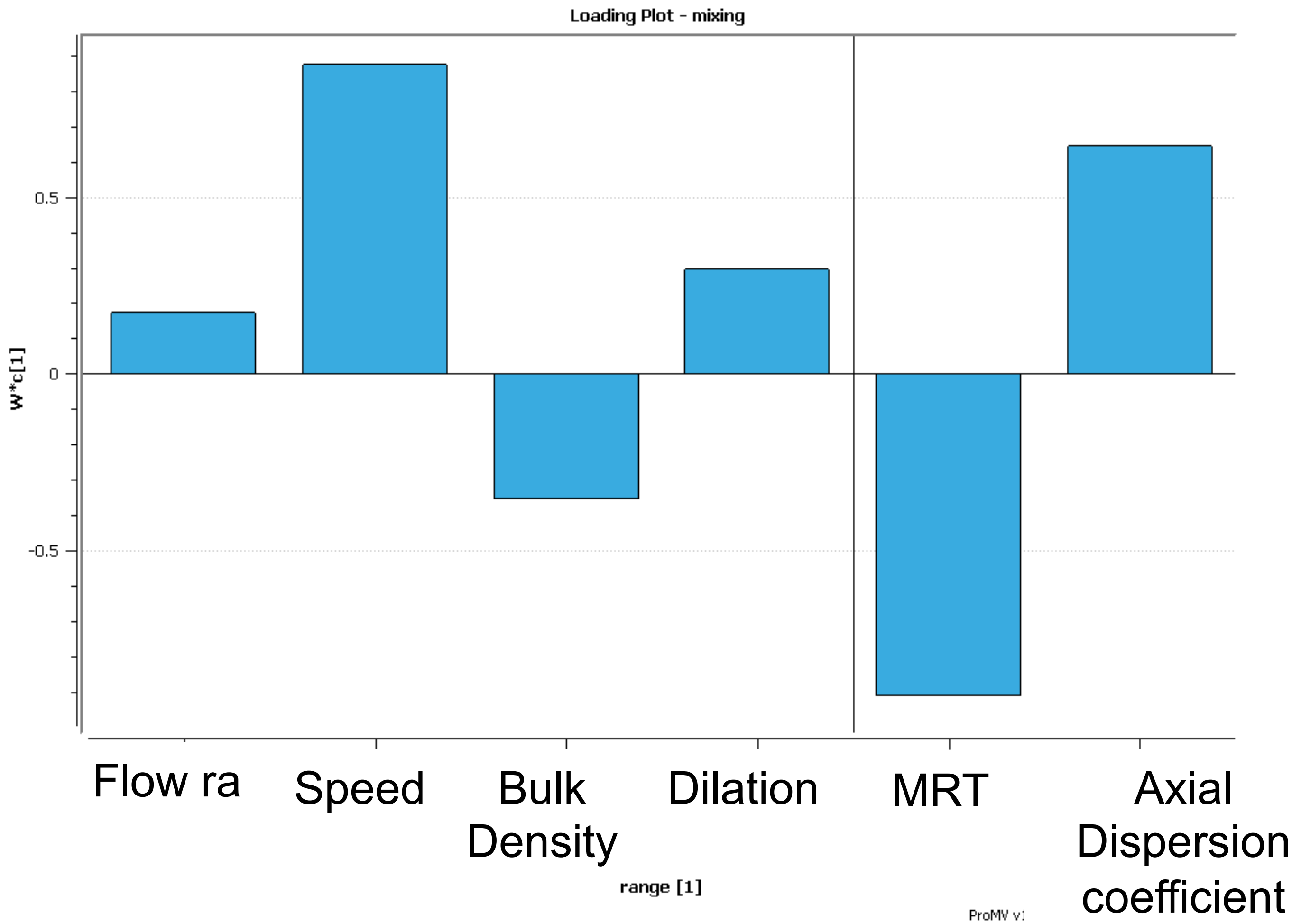
Material	Bulk Density	Carr Index	% Dilation	d50
Avicel101	0.3343	22.25	48.67	90
Avicel200	0.38	10.97561	16.2	234.1
Fast Flo Lactose	0.5926	9.67	22.05	120.01
CaHPO4	0.7688	15.27	29.47	186.2

Process parameters

- Impeller speed (40,100,160,250 RPM)
- Flow rate (30 kg/h,45 kg/h)

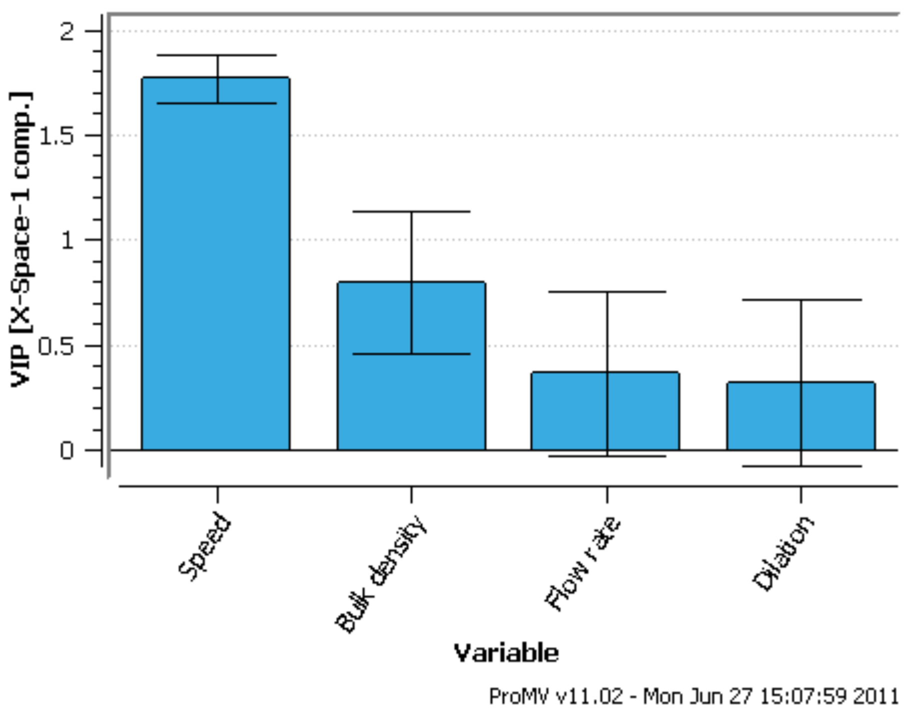
Output variables: RTD → Model fitting → Residence time, Axial dispersion coefficient

PLS Analysis

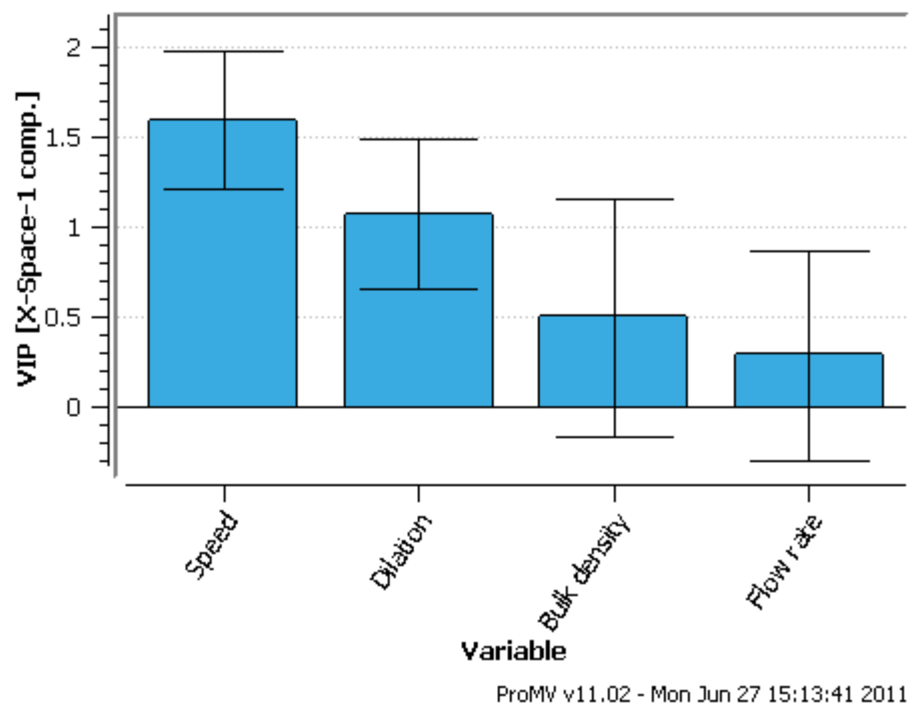


Variable Importance Plots (VIP)

Mean Residence Time



Axial Dispersion coefficient

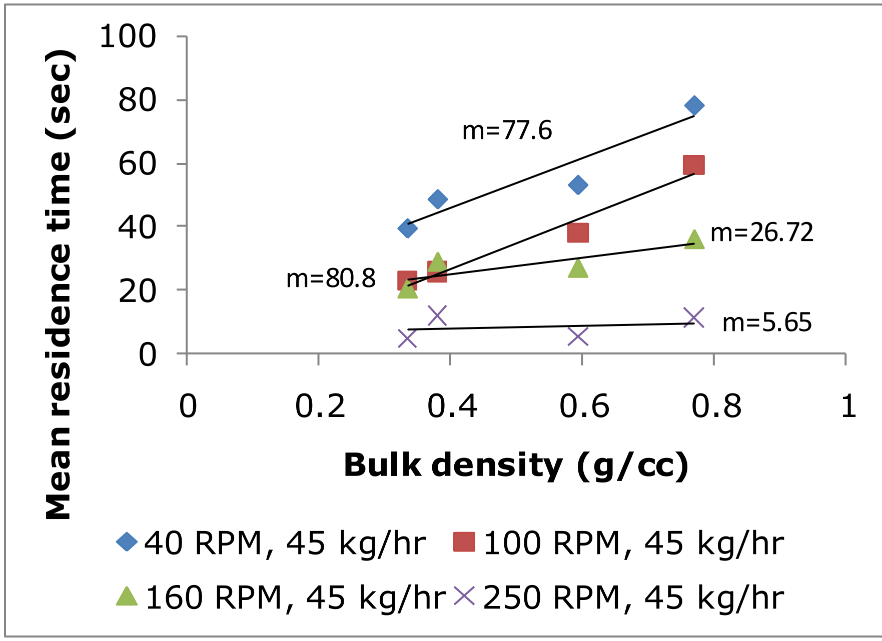


MRT: Impeller speed and Bulk density are the most important variables

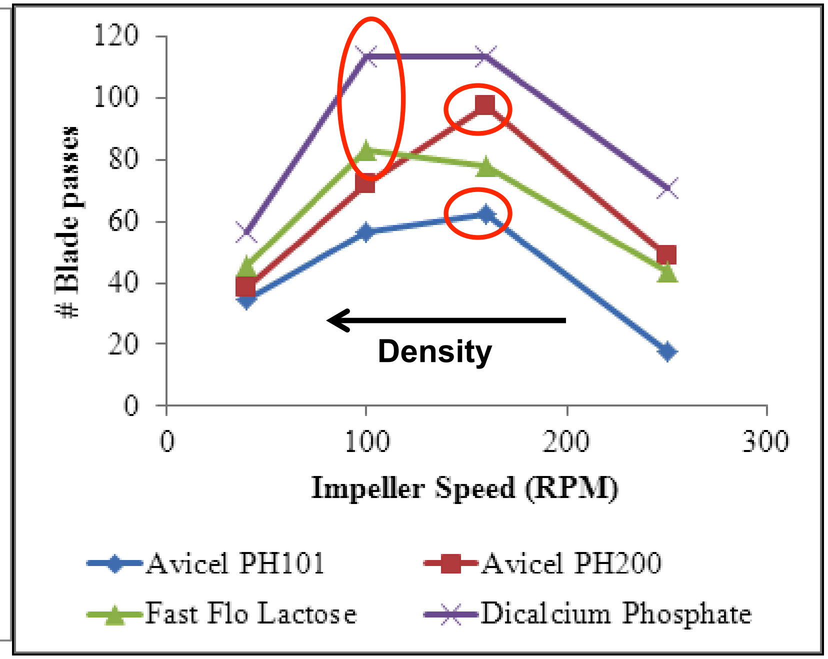
Axial Dispersion Coefficient: Impeller speed and Cohesion are the most important variables

Effect material properties on powder flow behavior

Mean Residence Time



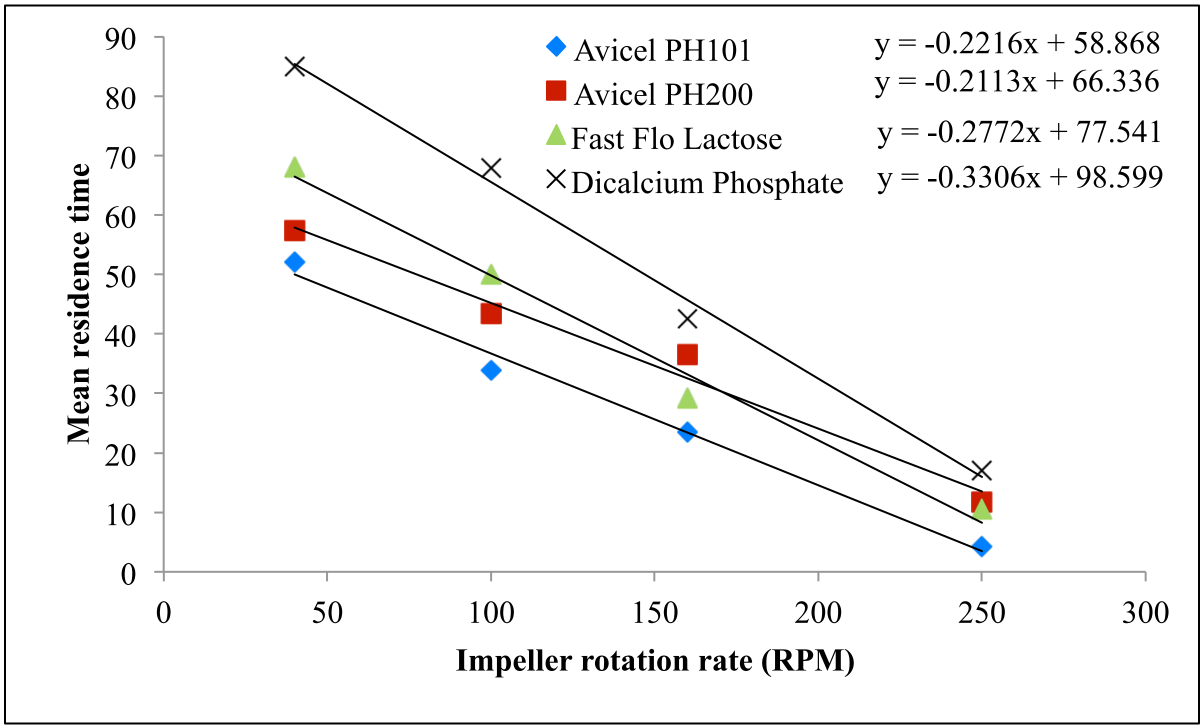
Blade passes



- Increase in bulk density leads to increase in the mean residence time
- The optimal impeller speed is lower for powders with higher bulk densities

Correlations between RTD parameters and process variables

Mean Residence Time

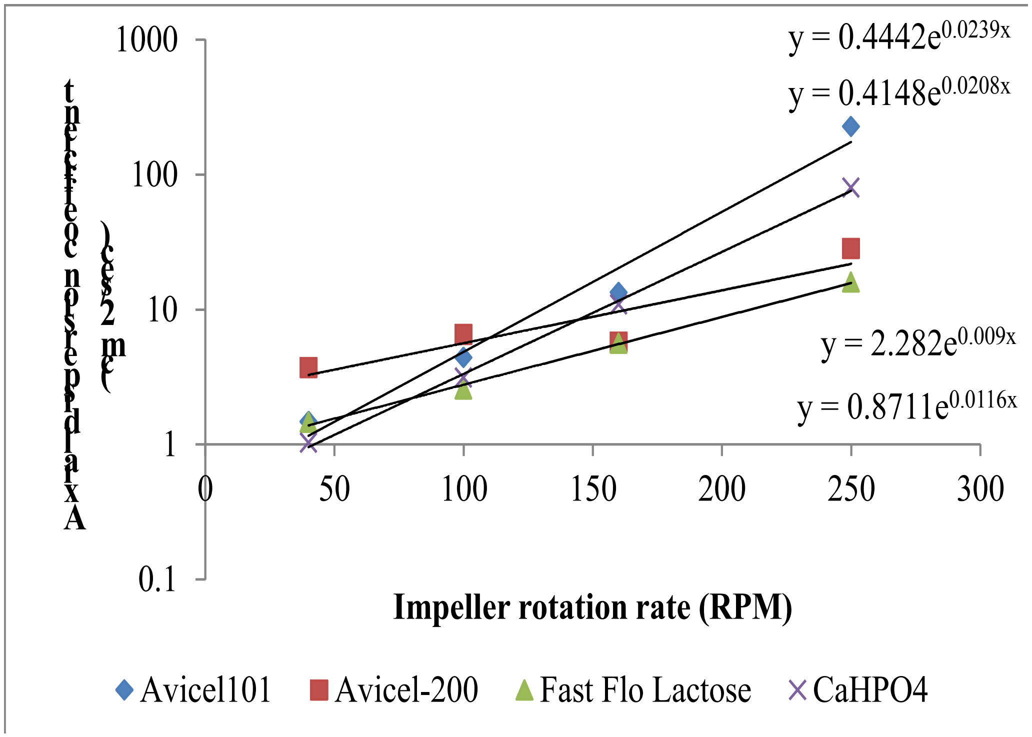


$$MRT = a_2 + b_2 . N$$

Correlations between RTD parameters and process variables (Cont.)

Axial dispersion coefficient

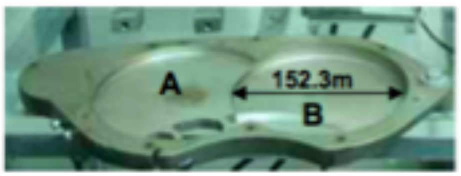
$$D = \frac{L^2}{Pe.\tau}$$

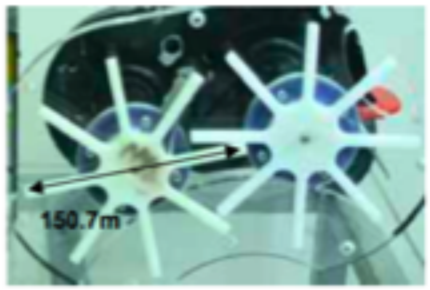


$$D_z = a_1 e^{b_1 N}$$

Beta Press Feed Frame Effect of Tablet Properties

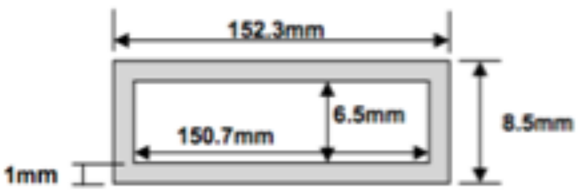
Rafael Mendez-Roman, Carlos Velazquez and Fernando Muzzio

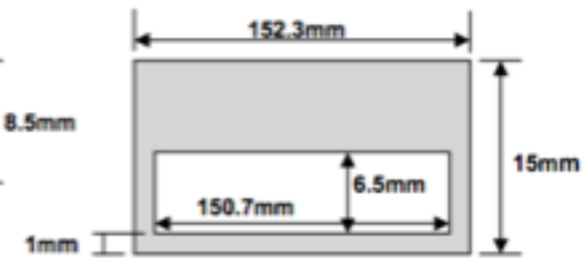


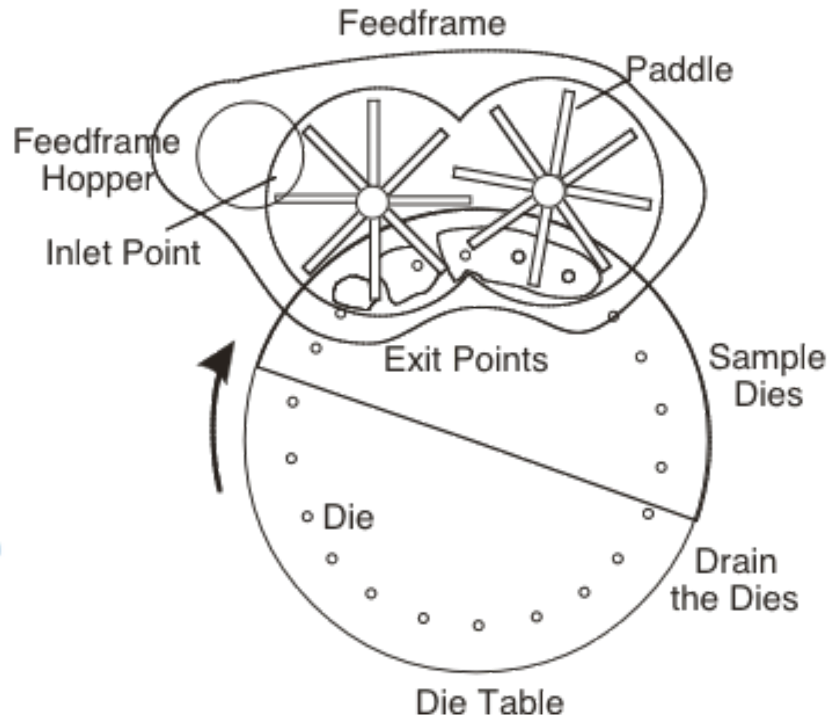


A

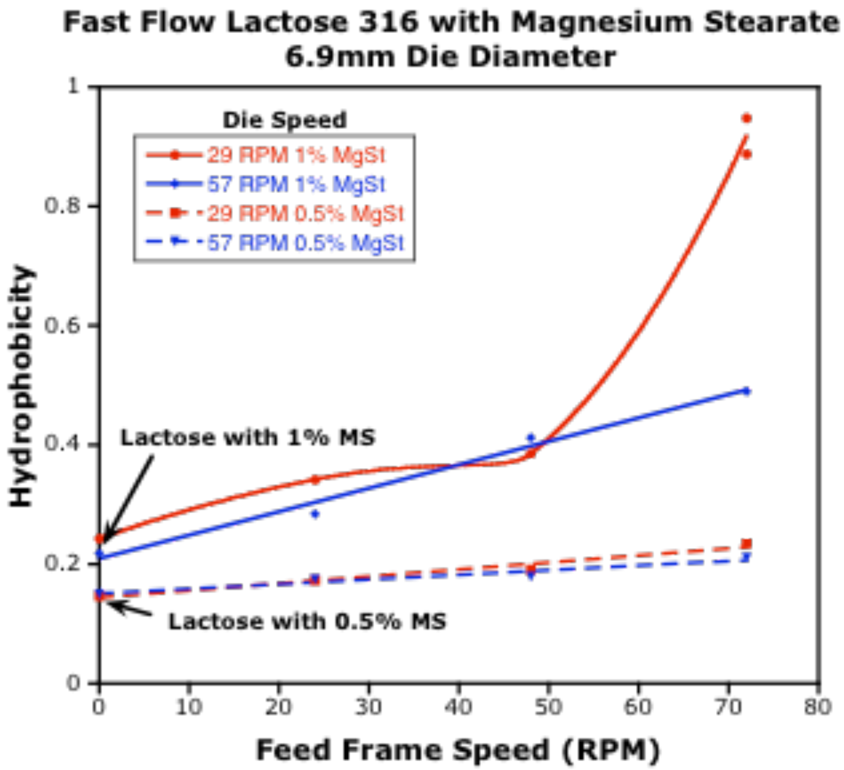
B

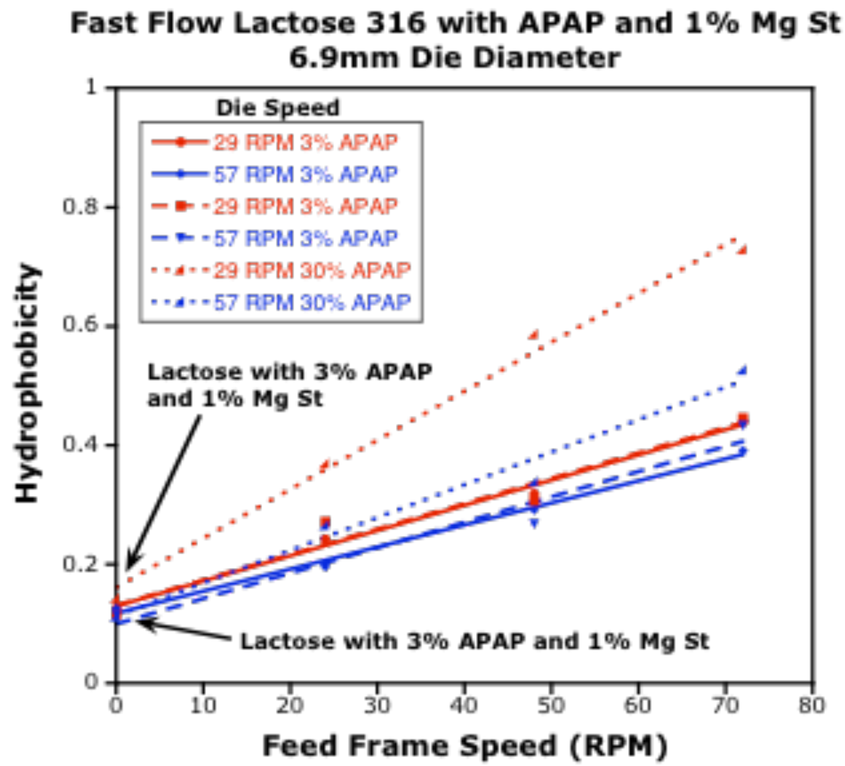






Effect of the Feed Frame Speed on the Hydrophobicity





The hydrophobicity increases with the feed frame speed

ENGINEERING RESEARCH CENTER FOR
STRUCTURED ORGANIC PARTICULATE SYSTEMS
RUTGERS UNIVERSITY
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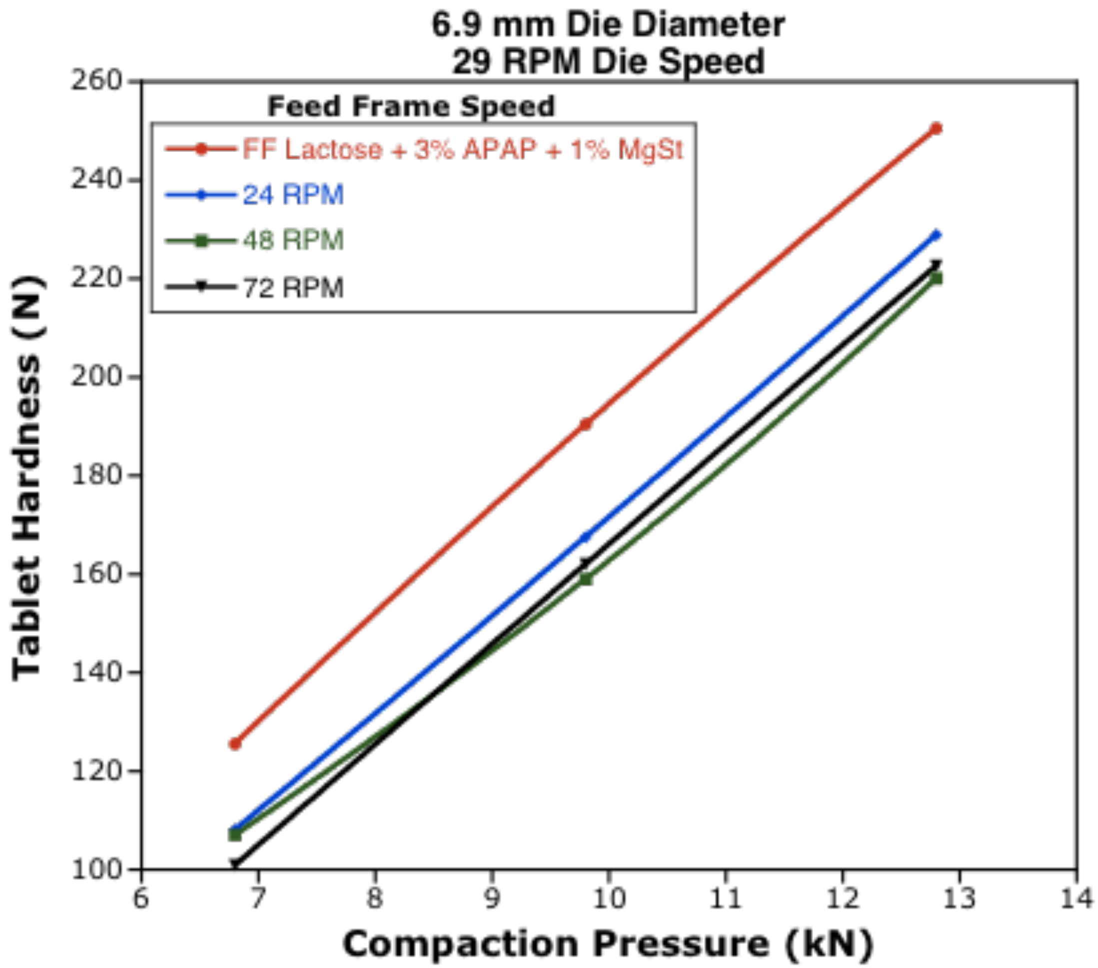
NEW JERSEY INSTITUTE OF TECHNOLOGY
UNIVERSITY OF PUERTO RICO AT MAYAGÜEZ

Tablet Compaction

- Tablets were prepared from untreated and treated blends of 3% APAP, 1% MgSt and 96% fast flow lactose at three different compression pressures: 6.8, 9.8, and 12.8 kN.
- The treated blend was exposed in the feed frame to three different shear strain conditions by using the following conditions:
  - Die disc speed: 29 RPM and
  - Feed frame speed: 24, 48, and 72 RPM
- The tablets were prepared in a Presster Model 252 with a IPT-B tooling type by Metropolitan Computing Corporation simulating the roller conditions of a Fette PT 2090 IC 36 stations with a setup speed of 104400 TPH (tablets per hour) [48.3 RPM or 1.038m/sec turret speed] and a die diameter of 10 mm.

Tablet hardness for untreated and treated material inside the feed frame



Conclusions

- Formulation / Product development
  - *Strain and mixing order of blend components have a significant effect on blend homogeneity, powder flow, electrostatics, tablet microstructure, and drug release rate.*
- Feeders
  - *Feed rate variability correlates to powder cohesion*

Conclusions

- Mixers
  - *For low dosage APAP, intermediate rotation rates show best mixing performance.*
  - *Continuous mixing process was characterized using RTD measurement methodology.*
  - *Increase in rotation rate decreases MRT, increase MCV.*
  - *Intermediate rotation rates exert maximum number of blade passes.*

Conclusions

- Lubrication
  - *Mixing and lubrication can be done in single mixer*
  - *Overlubrication risk is small*

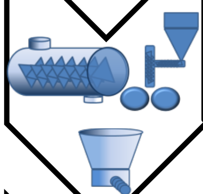
- Feeders/Mixers
  - *Method has been developed for integrated design*
  - *Mixers can filter out most high frequency noise but low frequency noise is a problem*

- Feed Frames
  - *Can cause major increase in hydrophobicity*
  - *Can decrease tablet hardness*

Dynamic flowsheet modeling

- A critical tool for the preliminary design step for any chemical process
- Define:
  - *Each equipment (i.e. heat exchangers, distillation columns, OR.. feeders, mixers, granulators etc.)*
  - *Material properties*
  - *How the equipment is interconnected*
- Reduced-order models:
  - *In fluid-based systems: mass & energy balances + rate equations to estimate flows, temperatures, pressures of streams*
  - *In solids-based systems: mass & energy balances, population balances & empirical correlations to estimate flows, PSD, bulk density, RSD**……?***
- Material properties of powder mixtures is still area of undergoing research
- How are the processes connected?

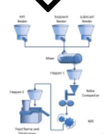
Steps towards final goal



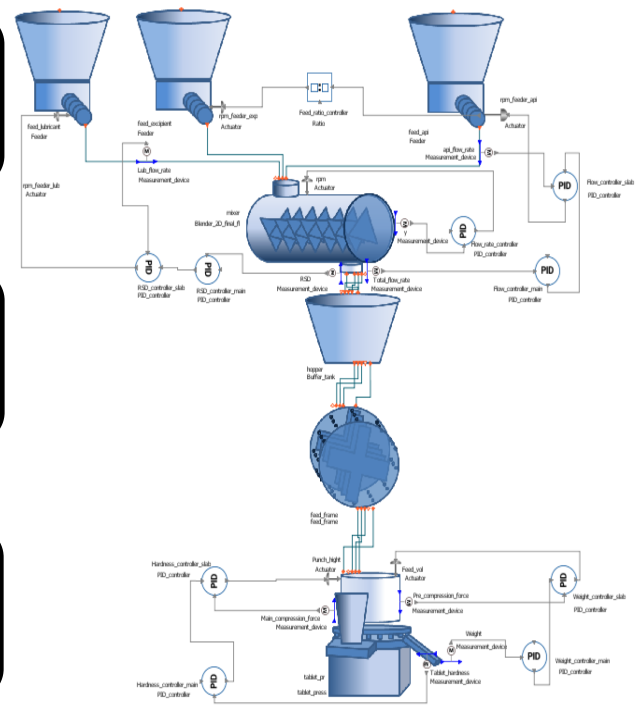
- Populate unit operation model library

DEM, FEM models

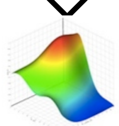
Model reduction techniques



- Integration of unit operations to form different operation scenarios
  (direct compaction, dry granulation, wet granulation)



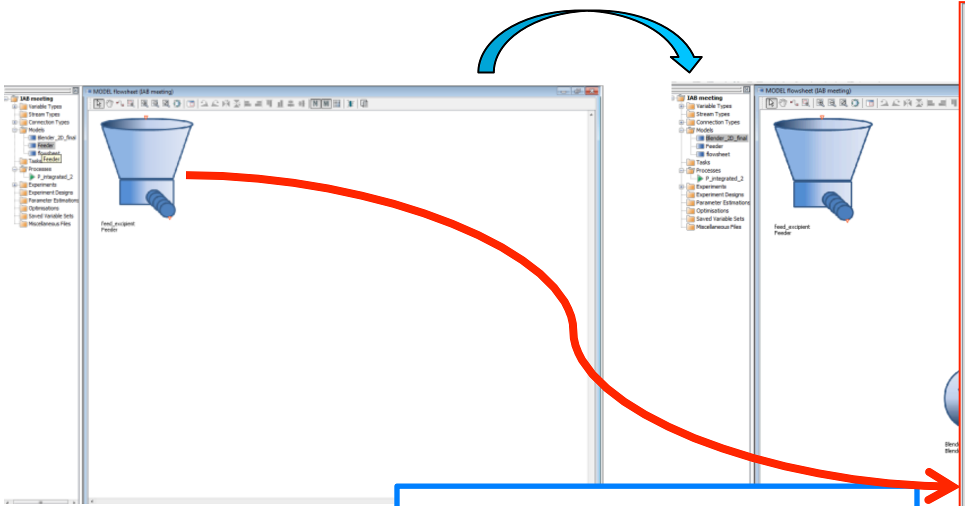
- Integration of control strategies



- Sensitivity analysis and steady-state or dynamic optimization

Modeling software (gPROMS)

- Once the model library is populated, it is simple to form a flowsheet through ‘**drag-and-drop’** procedure

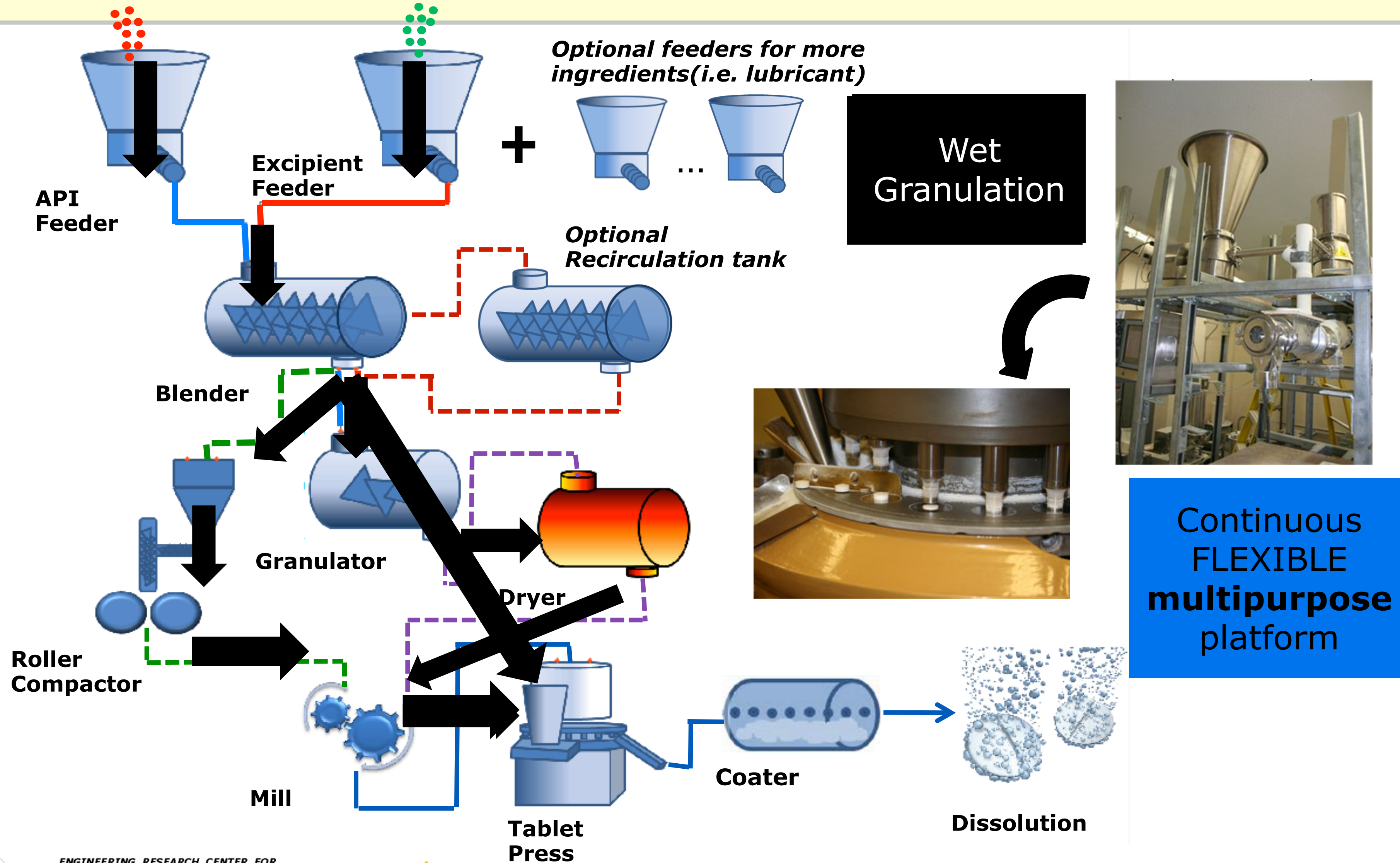


Add all processes

- A code is behind each process

```
SET
 Axial  := [cFDM, 2, no_axial_elements];
 Radial := [cFDM, 2, no_radial_elements];

EQUATION
   # axial velocity
   vl = rpm*drum_rad;
   Ff("Excipient")=0.8*vl;
   Ff("Api")=0.8*vl;
   Fb("Excipient")=0.2*vl;
   Fb("Api")=0.1*vl;

   FOR r :=0 TO BlenderRadius DO
     Fr("Excipient",r)=7*vl;
     Fr("Api",r)=5.5*vl;
   end

   # auxillary vectors
   FOR i IN Components DO
      FOR z := 0 TO BlenderLength DO
           F_at_rplus(i,z,0:BlenderRadius|-)  = F(i,z,0|+:BlenderRadius);
           F_at_rplus(i,z,BlenderRadius)      = F(i,z,BlenderRadius);
           F_at_rminus(i,z,0|+:BlenderRadius) = F(i,z,0:BlenderRadius|-);
           F_at_rminus(i,z,0)                 = F(i,z,0);
      END
   END

FOR i IN Components DO
      FOR r := 0 TO BlenderRadius DO
           F_at_zplus(i,0:BlenderLength|-,r)  = F(i,0|+:BlenderLength,r);
           F_at_zplus(i,BlenderLength,r)      = F(i,BlenderLength,r);
           F_at_zminus(i,0|+:BlenderLength,r) = F(i,0:BlenderLength|-,r);
           F_at_zminus(i,0,r)                 = F(i,0,r);
      END
END

   # Blender Inlet
   FOR i IN Components DO
       FOR r :=0|+ TO BlenderRadius|- DO
              $F(i,0,r) = -Ff(i)*F(i,0,r)
                          +Fb(i)*F(i,0|+,r)
                           +Fr(i,r)*(1*F_at_rplus(i,0,r)-2*F(i,0,r)+1*F_at_rminus(i,0,r)) ;

       END
   END
```

Final flowsheet model- multipurpose



Challenges

- Integration of models of different detail
  - *Population balance models*
  - *Data-driven models*
  - *First-principle models*
- Quantitative model validation
  - *Need for experimental data*
- Non-existence of universal set or critical material properties tracked throughout processes.
  - *Models for different unit operations take into account different properties thus integration is challenging*
- Handling of distributed parameters, due to particle size distributions
  - *Handled by chosen software→ gPROMs*