Project #1
Predicting and managing API blend properties for batch and continuous manufacturing

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Problem Statement

- Developing new drug products can be difficult due to the extensive trial and error associated with formulation/process development
- Specifically, process development for high speed direct compression can be very time consuming, especially for cohesive APIs which are difficult to handle
  - Formulations with either high or very low drug loadings cannot be easily handled with direct compression tableting
- We propose to develop mechanistic and semi-empirical models that allow prediction of flow and other relevant bulk properties from material sparing measurements
- Such predictive framework along with dry coating toolbox can facilitate high-speed DC route for CM for a much wider range of drug loadings

Objectives

- Develop mechanistic/semi-empirical models to predict critical quality attributes of APIs and blends from powder properties, composition and processing.
  - Flowability
  - Bulk density
  - Agglomerate size
  - In long-term (for an extended project), blend uniformity and compactibility
- The model shall help determine the impact of dry coating on the API blend powders
  - Widening the scope of DC for high and very low drug loadings

Materials/Methods

- APIs
  - Acetaminophen (coarse and fine), Ibuprofen (various grades)
- Excipients
  - Microcrystalline Cellulose (various grades), Lactose (various grades)
- Flow enhancement agents (glidants)
  - Hydrophobic Nano Silica, Hydrophilic Nano silica
- Disintegrant
  - Crosprovidone
- Lubricant
  - Magnesium Stearate
- Processing devices
  - V-blender, Comil, Lab RAM
- Characterization methods
  - IGC for surface energy, FT4 powder tester, Rodos/Helos laser scattering, Accupyc 1330 Pycnomenter, etc

Model predictive approach

Particle scale properties (size, surface energy, surface roughness)

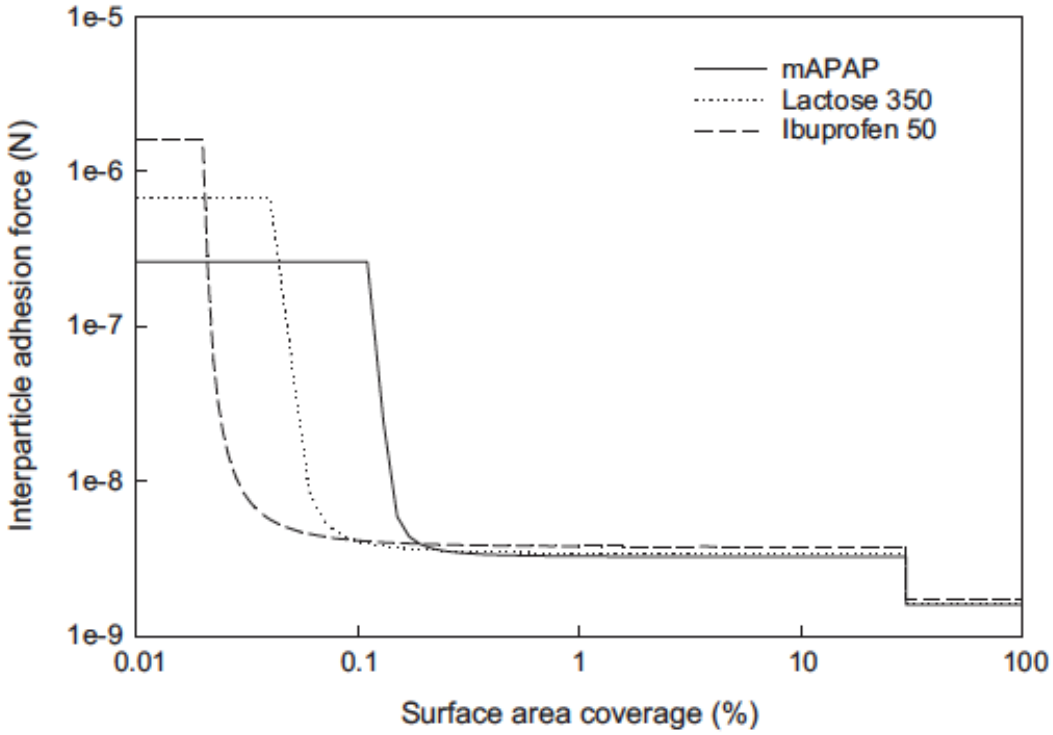
Bond number estimation

Blend properties prediction

$$Bo_g = \frac{F_{cohesion}}{W_g}$$

- Prediction of bulk density/porosity
- Prediction of FFC
- Prediction of agglomerate size

- Blend bulk density/porosity
- Blend FFC
- Blend CU
- Bonding/Tablet strength



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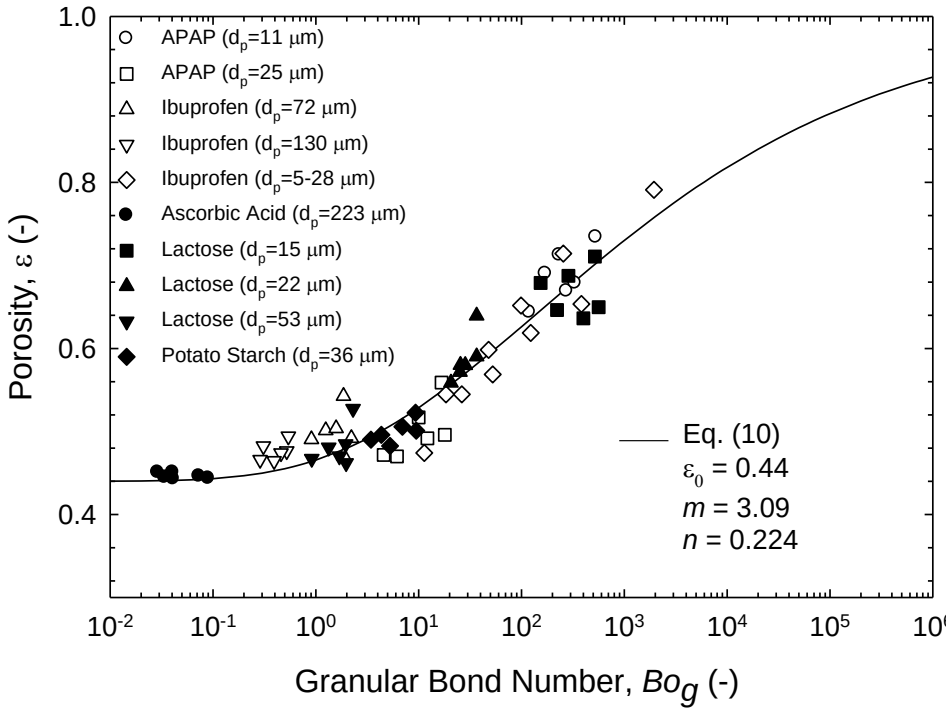
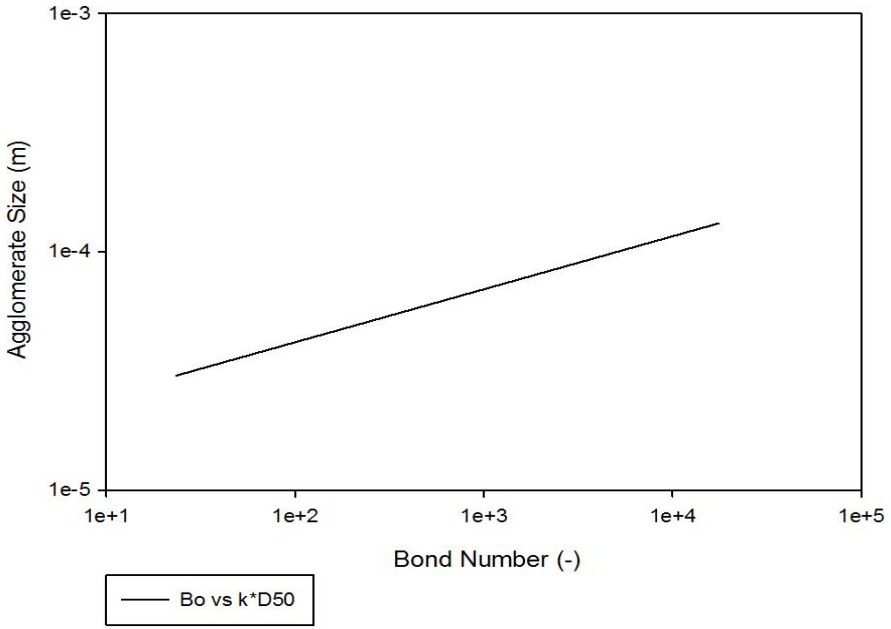
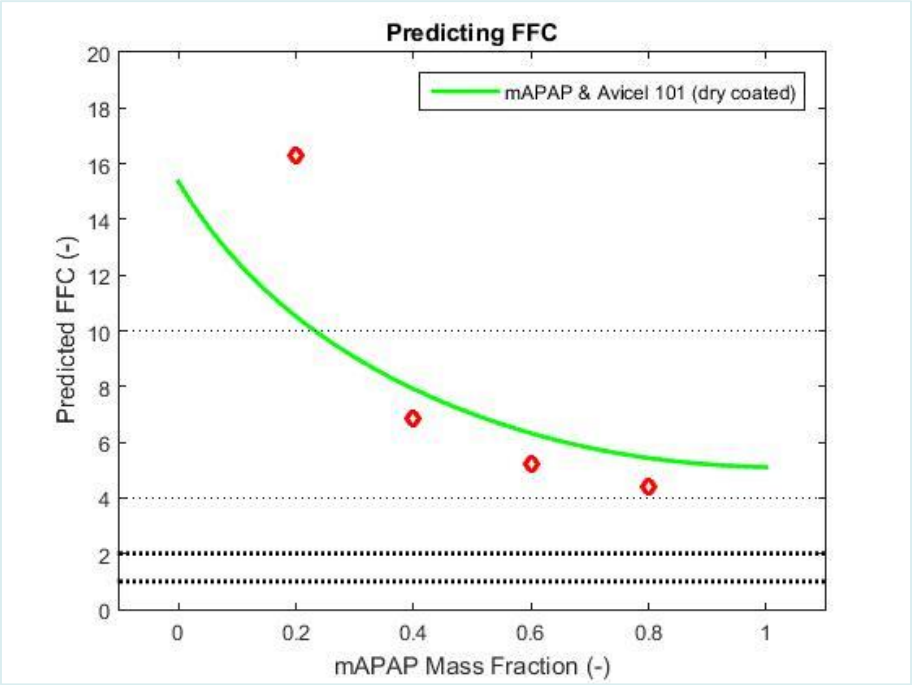
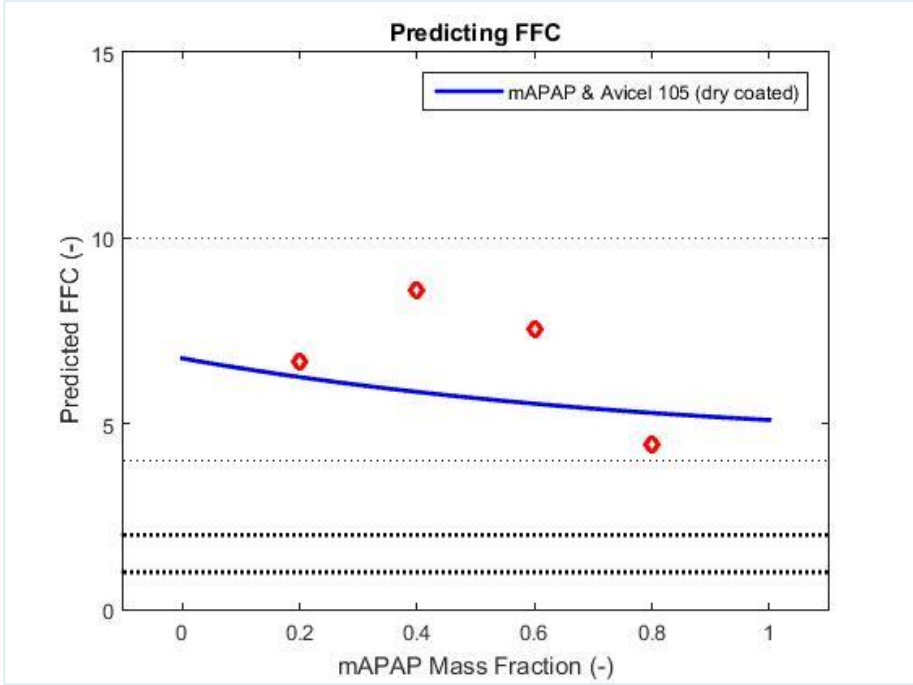


Agglomerate Size vs Bond Number



Proposed Work: Blend FFC prediction



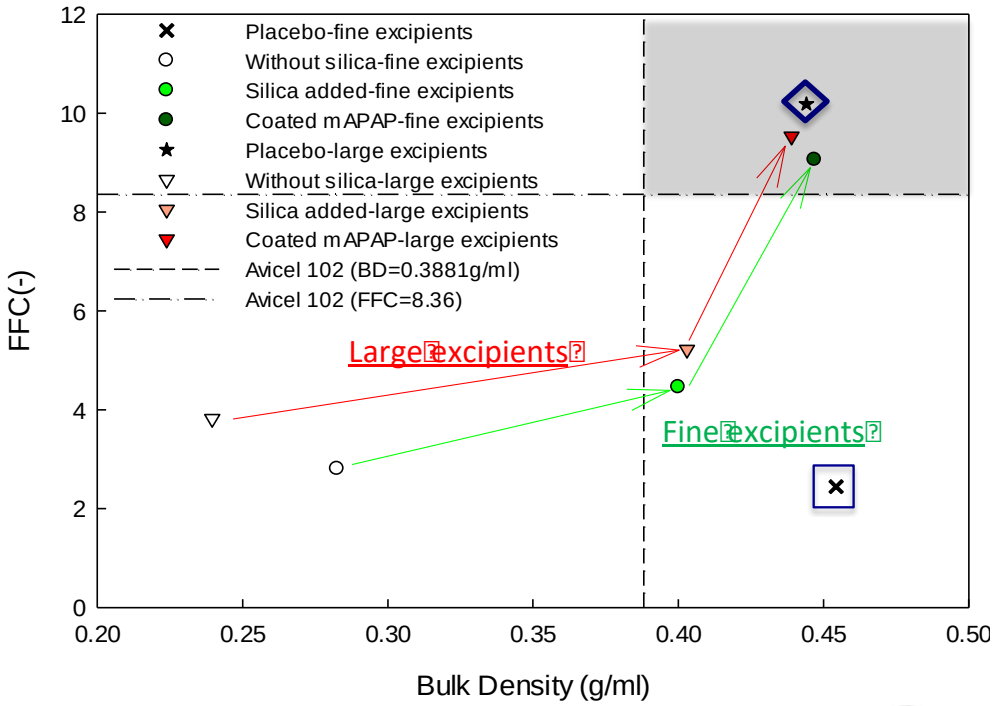


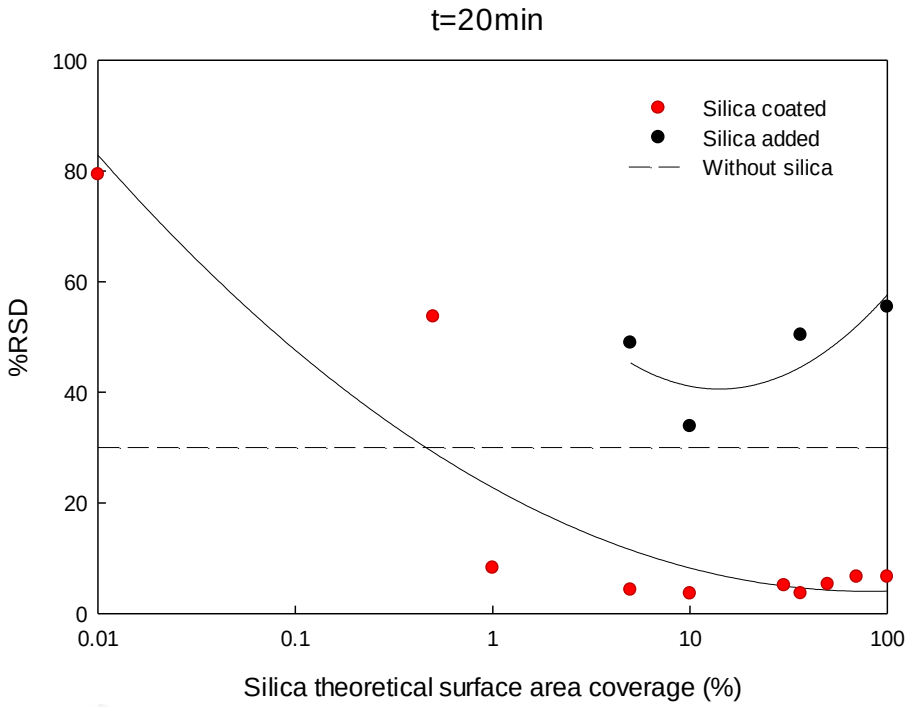
$$ff_{c,Mix} = \alpha\left(Bo_{g,Mix}\right)^{-\beta}$$

$$Bo_{g,Mix} = \left(\sum_{i=1}^{N}\sum_{j=1}^{N}\frac{w_{ij}}{Bo_{g,ij}}\right)^{-1}$$

- The current model does not account for the effect of size differences (ex – bimodal distribution) of blends.
- This phenomena is discussed in older literature but data has not been shown

Benefits: Direct compaction tableting at high drug loading and improved CU at low drug loading





Excellent FFC and bulk density for 60 wt % mAPAP (~10 micron) blends, ready for direct compaction

Acceptable CU for 5 wt % mAPAP (~10 micron) blends, due to dry coating of mAPAP

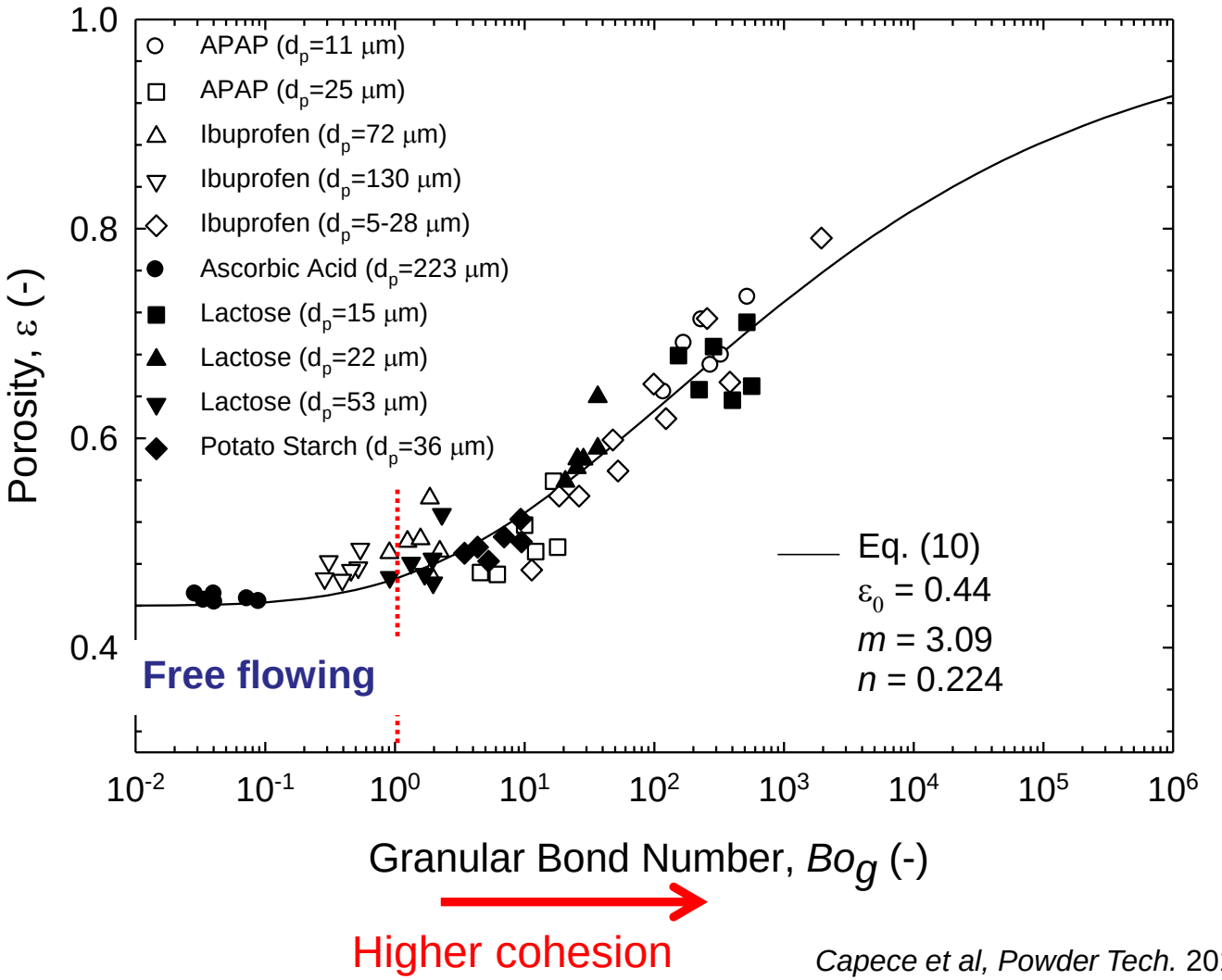
Anticipated Impact

- Reduce the amount of testing required in the formulation/process development stages
- Facilitate decision making regarding the need and degree of property enhancement of cohesive APIs necessary for using DC route at higher drug loadings
- Determination of the highest API loading for a given set of properties of the API manufactured via batch or continuous manufacturing (CM) with and without API dry coating
  - For future, predict the expected CU for tablets made in DC-CM
- For the target API loading, determine the API size and/or the need for dry coating for use in DC route for CM
- Overall, significantly reduce the development time needed by implementing a Quality by Design approach

Q & A?

Back-up slides

Properties modeling: Bond number vs. porosity of packed powders



- Bond number correlates very well with porosity for many materials and particle sizes
- Interparticle cohesion can be used to predict bulk powder behavior
- Our multi-asperity cohesion model (Chen et al., 2008) works very well

Capece et al, Powder Tech. 2014, 254 103-113.

Production Methods

Instrument	Purpose
LabRAM	Batch, Lab Scale Dry Coating
Comil	Continuous Cry Coating
V-blender	Blending

Characterization Methods

Instrument	Purpose
Rodos/Helos	Particle Size Distribution
Freeman Technology FT4	Flowability and Porosity
SEA IGC	Surface Energy
Accupyc 1330 Pycnomenter (not pictured)	Particle Density