Model-based reduction of cohesion through dry coating

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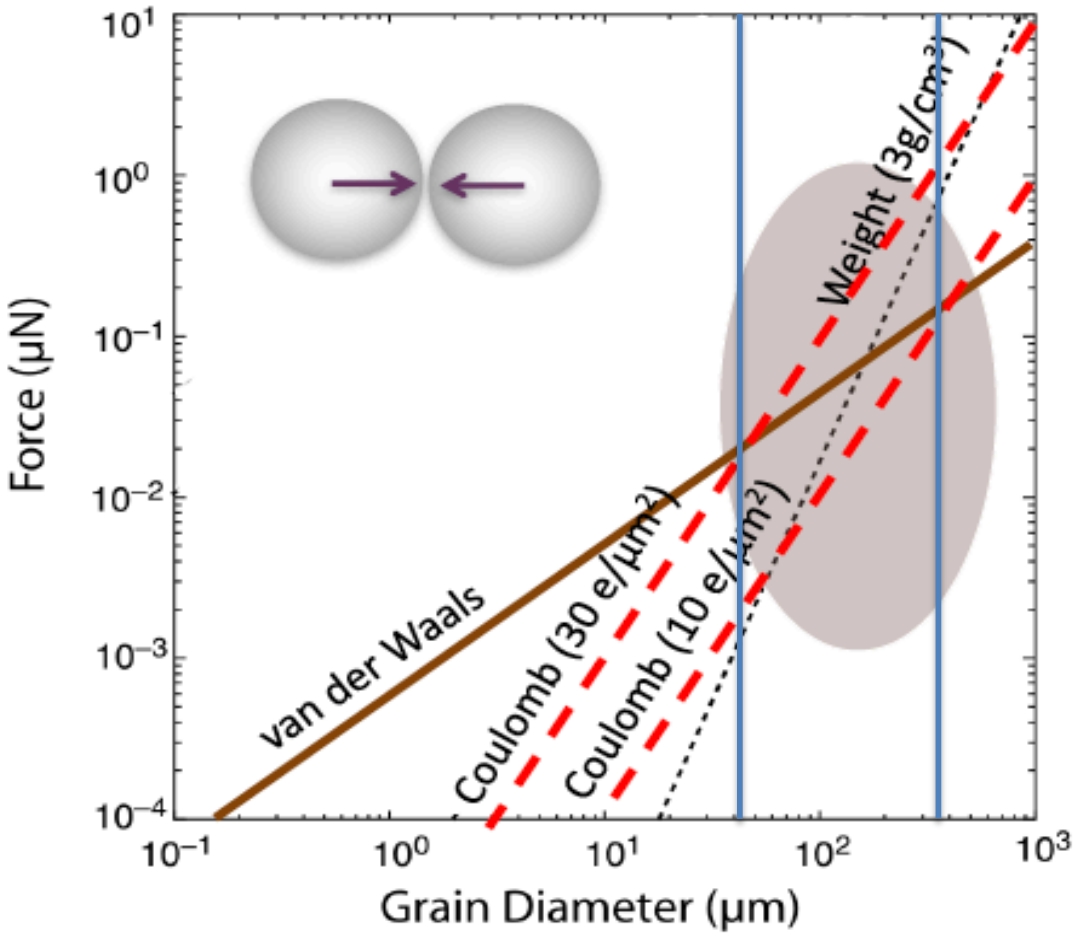
Take home message (intended)

- I am not married to dry coating!
  - However: For fine dry powders (~ 100 μm or less) cohesion could be greatly and predictably reduced by dry coating with nano-additives
    - van der Waals (vdW) may be the dominating adhesion force
  - Dry coating alters surfaces hence the powder behavior can be changed dramatically
- A lot is known; but also many unanswered questions
  - Known (to a reasonable level):
    - vdW is a function of surface chemistry (surface energy) and contact radius (surface roughness)
      - Dry coating with nano-particles can impact both
    - How to dry coat using multitude of devices; **silica does not "drop-off" but may transfer to other surfaces**
    - Type and amount of additives to select for a given host
    - Decision making regarding dry coating based on regime maps of desired properties
      - Which powder tests to use
    - First order linking of particle and bulk-scale through at least one scaling parameter
- Significant improvements in desired properties for many practical applications
  - Improved: Bulk density, flowability (FFC), dispersion, fluidization, content uniformity, potential for direct compression, dissolution, rheology of slurries
    - For a phama needles-shaped API with aspect ratio > 10 had FFC of 2.1 increased to 3.15 – 4.10 depending on the quality of dry coating
  - Reduced: agglomeration, heterogeneity for milled materials, electrostatic tendency, sintering (delayed sintering), solid bridging
  - Potential for better mixing and reduced segregation by using finer constituents
  - Creating ordered mixtures with process and materials properties understanding
- Misc:
  - Dry coating must be done well (process intensity and process/residence time);
  - Assessment of agglomeration is nontrivial; we should not ignore those for fine powders
  - Assessment of surface asperities is a potential challenge

Relative magnitude of attractive forces vs. Particle Size



- dry grains, freely flowing
- no liquid bridges
- vd Waals-type forces include all short-ranged (nm) adhesion

Note: 30 e/μm² corresponds to one extra electronic charge per ≈30,000 surface atoms

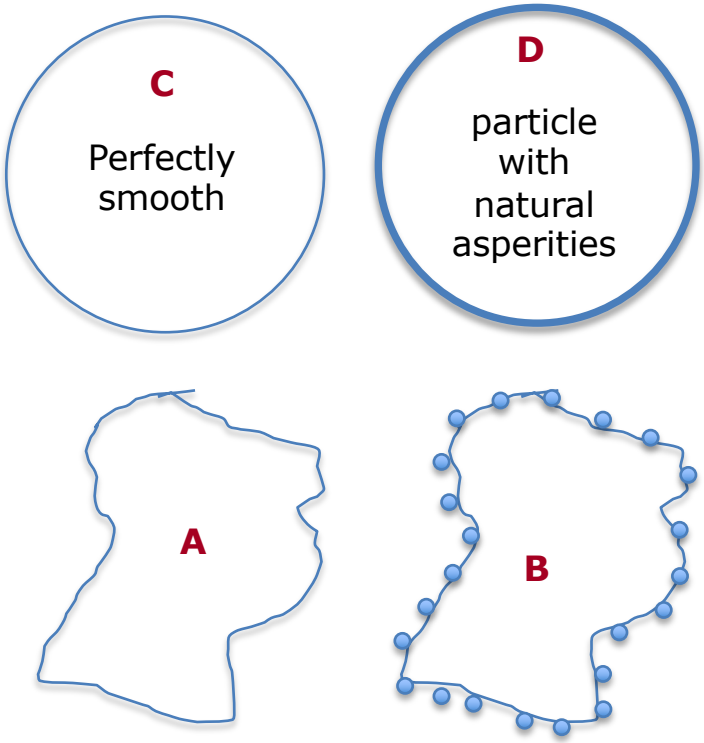
Courtesy of Prof. Heinrich Jaeger

Cohesion

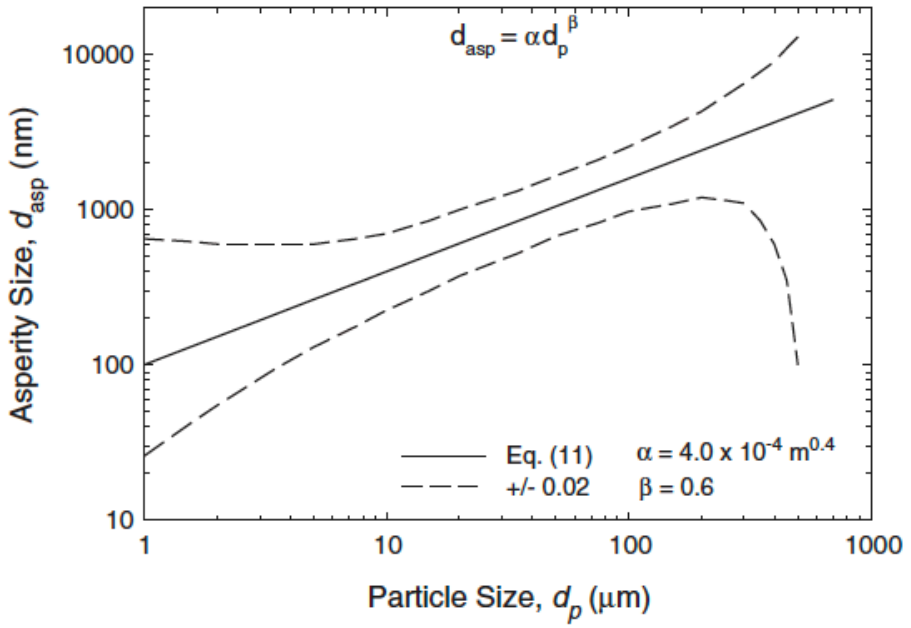
- “A powder can be free-flowing if the particles do not stick together or cohesive if the particles cling to one another to form aggregates. The likelihood of cohesion increases with decreasing size of the powder particles; particles below 100 µm have generally been found to be cohesive” (J. Bridgewater)
  - Van der Waals
  - Electrostatics
  - Liquid bridges
  - Jamming (usually low cohesion) or interlocking (aspect ratio effect)
  - Sintering and solid bridging?
- Influenced by?
  - Size, also state of agglomeration (MAIC could reduce/unify agglomerate size)
  - Surface roughness
  - Shape
  - Moisture/humidity, storage time, etc

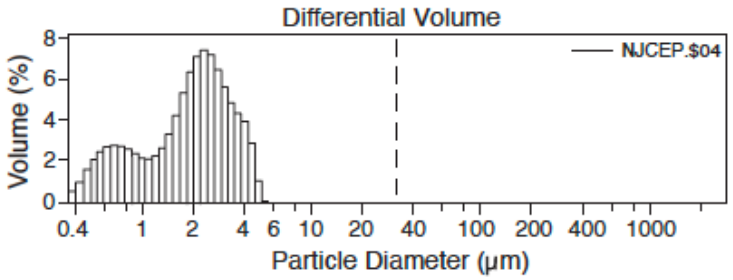
J. Bridgewater, Fundamental powder mixing mechanisms. Powder Technol. 15:215-236 (1976)

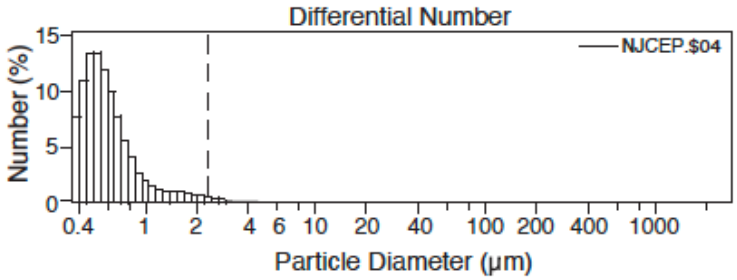
Which is the most and least "cohesive"



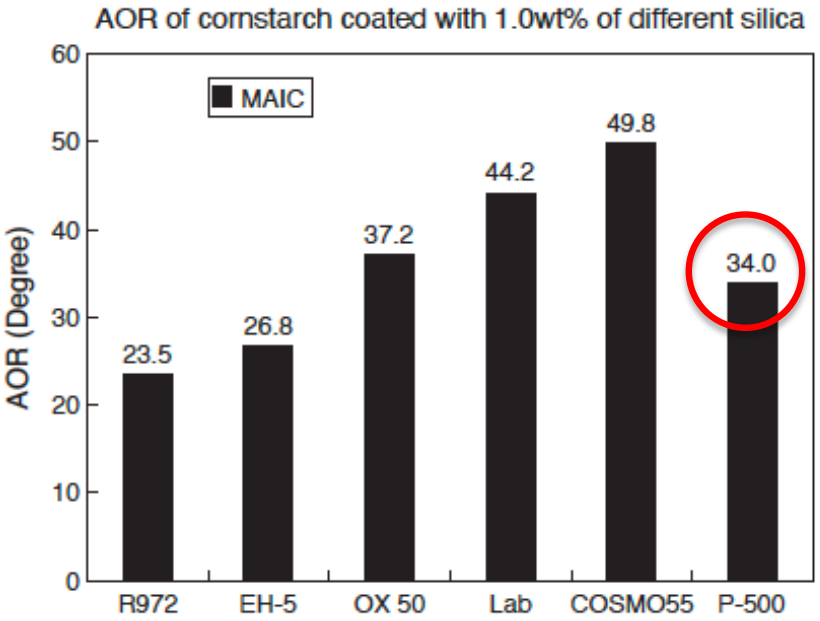
About "natural asperities" (Massimilla and Donsi proposed 200 nm diameter)







Smaller asperities impact may be dominating



Prediction of bulk properties from particle scale properties: A scaling parameter?

Bond Number:

$$B_{og} = \frac{F_{adhesive}}{W_g}$$

- B<=1 Free Flowing
- B>>1 Cohesive

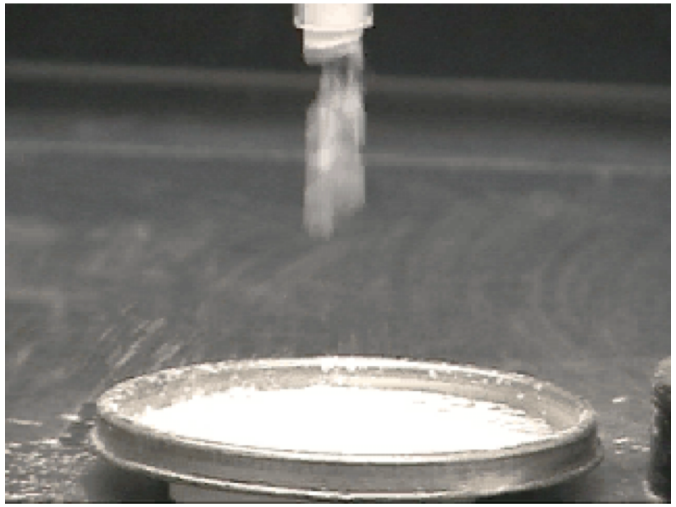
To Improve the Flow:

- **Reduce adhesive force**
  - Surface Roughness
  - Surface Free Energy
  - Hardness
  - Elastic Modules
- **Increase particle weight**
  - Density
  - Particle Size
  - "g"

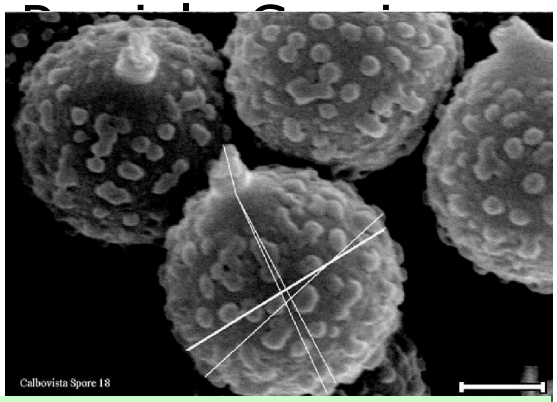
We have ways to estimate the Bond number from particle scale measurements

Surface Engineering

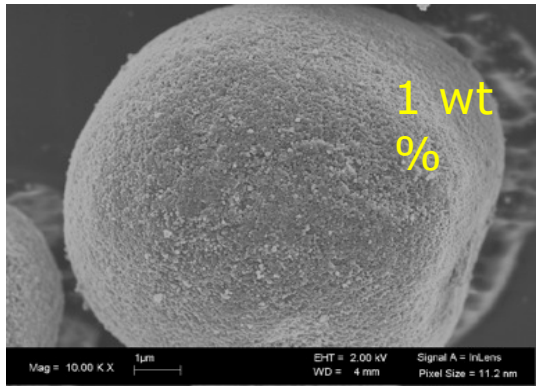
Fine micronized particles desirable in industry due to high surface area. However, they are **cohesive**, leading to severely hampered processibility; e.g., flowability, fluidization and dispersion



Solution: Taking cues from Nature - Surface Engineering via



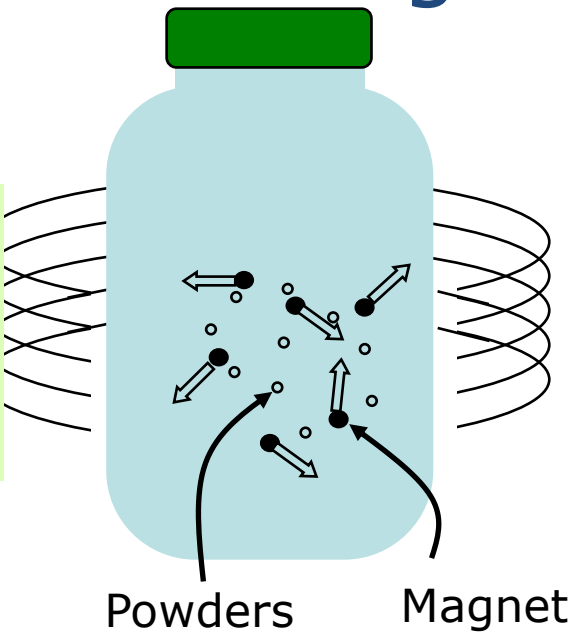
Powder Tech. 2005



Batch processes: Blending & coating devices

Magnetically Assisted Impaction Coating (MAIC)

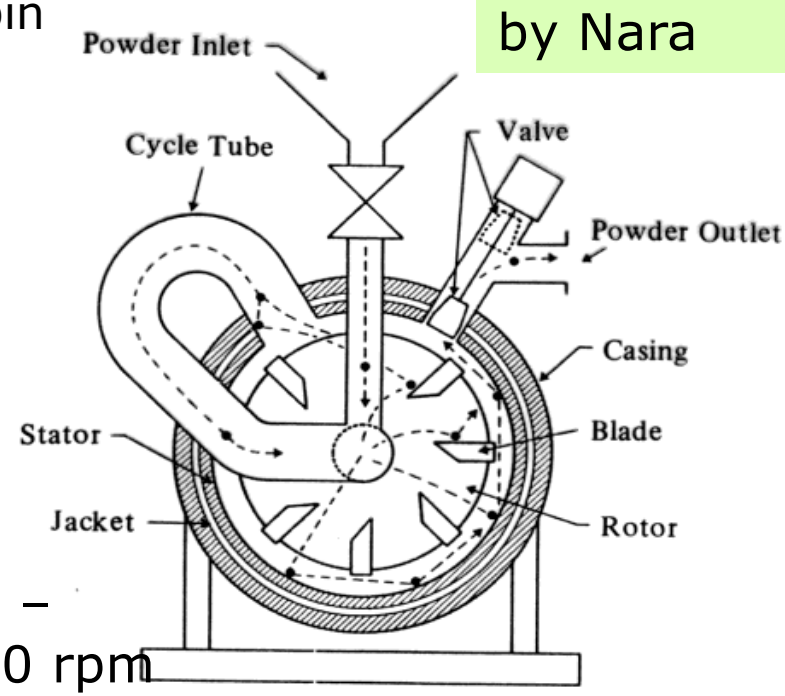
10 min



Oscillating Electromagnetic Field, causes magnets to spin at up to 1000 Hz

2-5 min

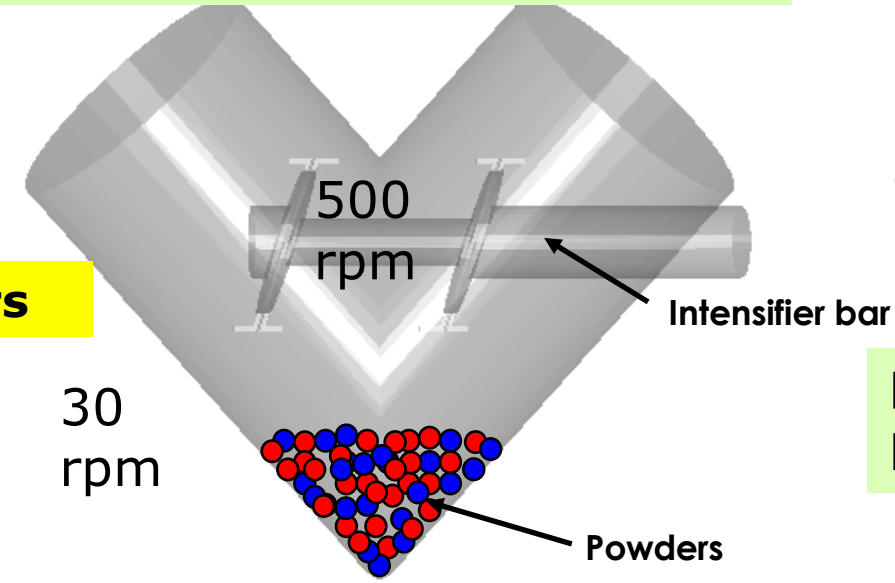
Hybridizer by Nara



5000 – 15000 rpm

V-Blender with Intensifier bar

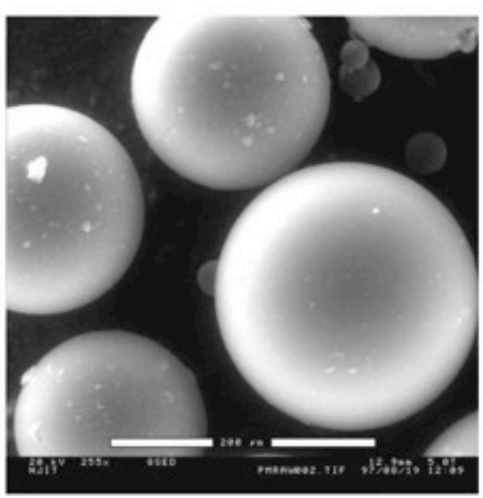
1 to 3 hrs



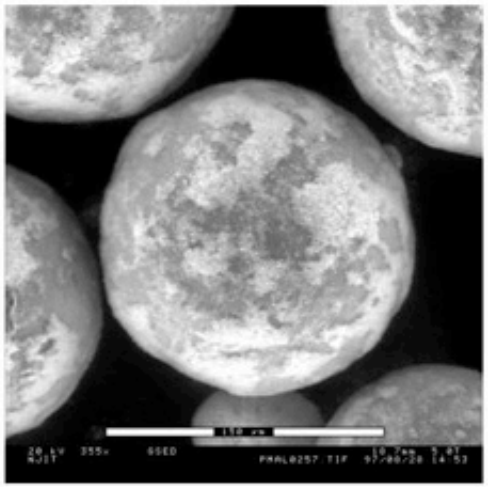
Not Shown, Mechanofusion by Hosokawa Micron

~10 min

Surface Coating Process: Why "Blending" does not work or works inconsistently

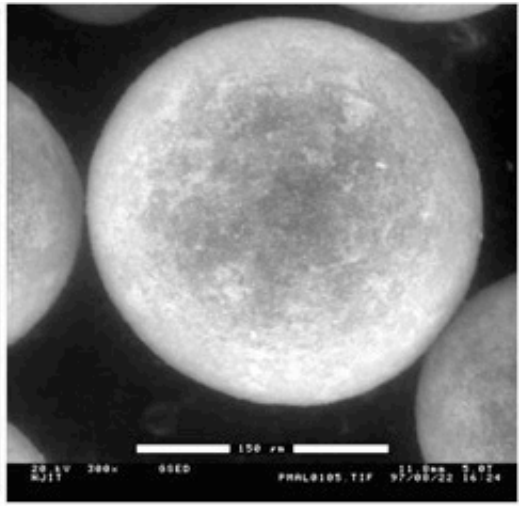


PMMA uncoated

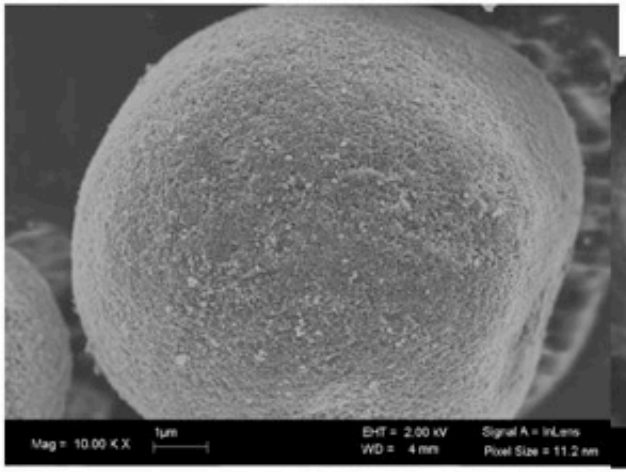


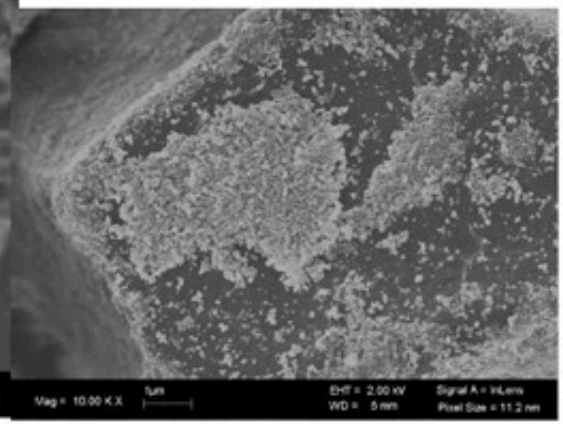
Processed 2.5 minutes

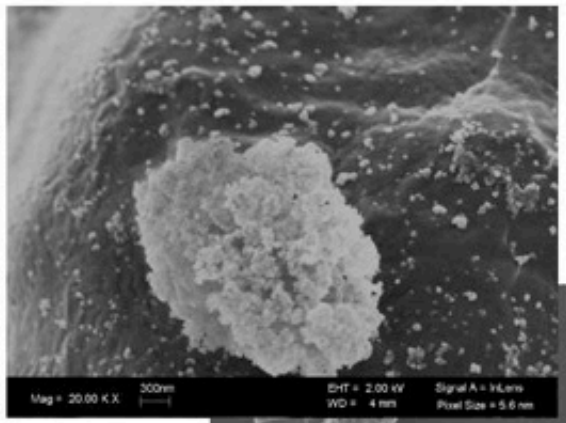
5 minutes

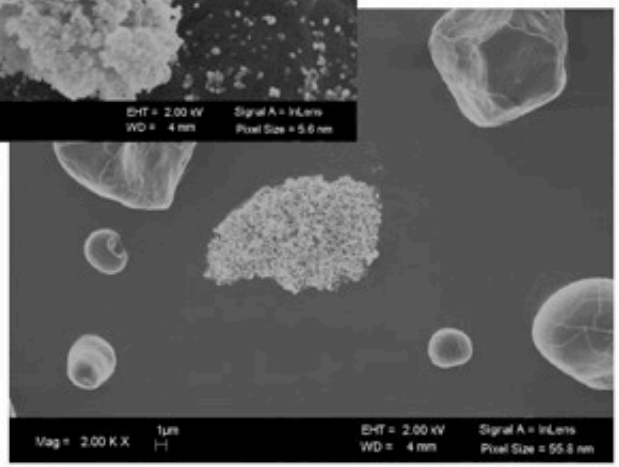


10 minutes





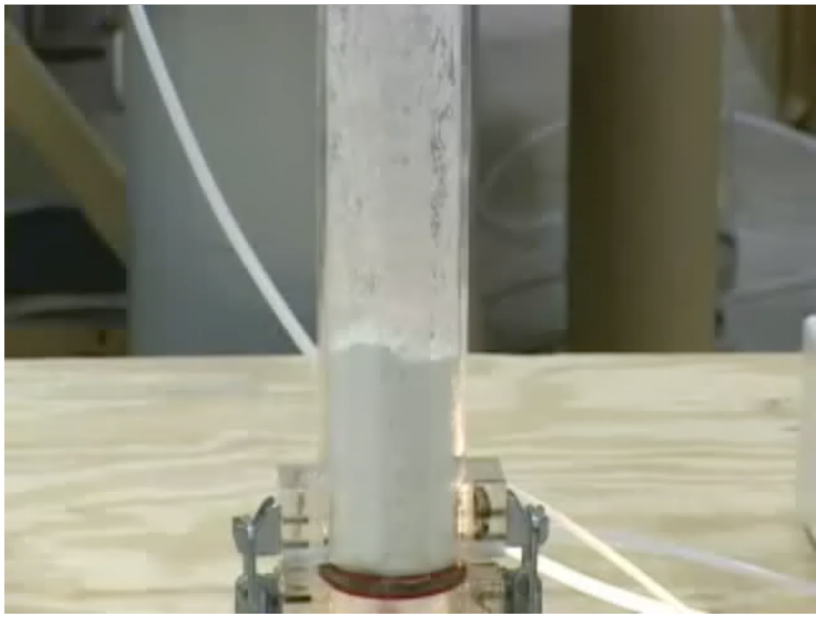


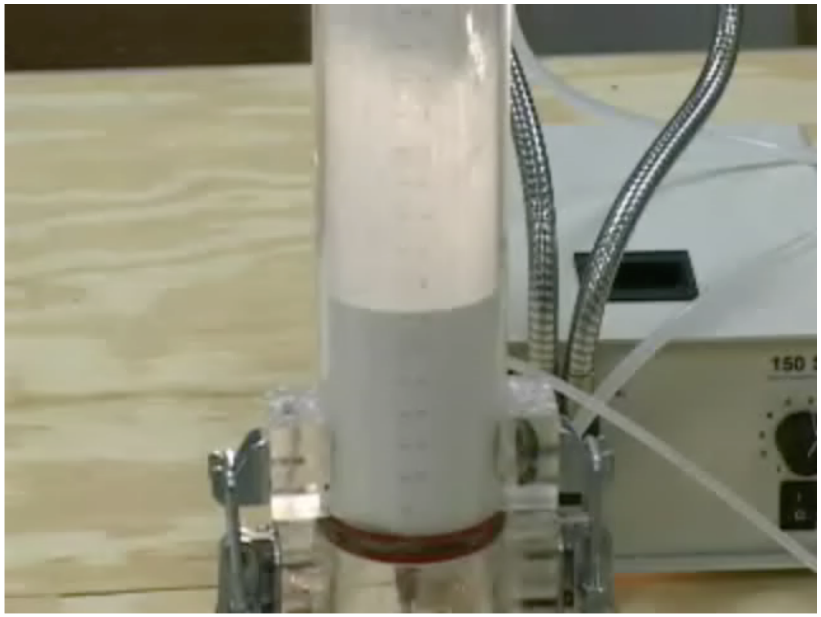


MAIC/Dry Coated versus V-Blended (for relatively easy host particles)

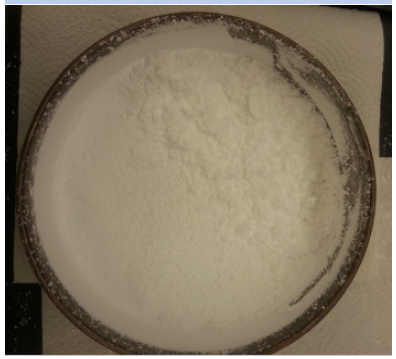
Critical Powder Properties:
Pushing the Boundary through Nano-scale roughness

- ***Packing density*** – 50 -100 % increase
- ***Fluidization and coating*** – reduced the size from 100 μm to 10 μm
- ***Dispersion*** – 5 μm behaving like 100 μm
- ***Agglomeration*** – reduced by ~ 10 times
- ***Content uniformity*** – from fail to pass





1.7mm---500μm	<45μm

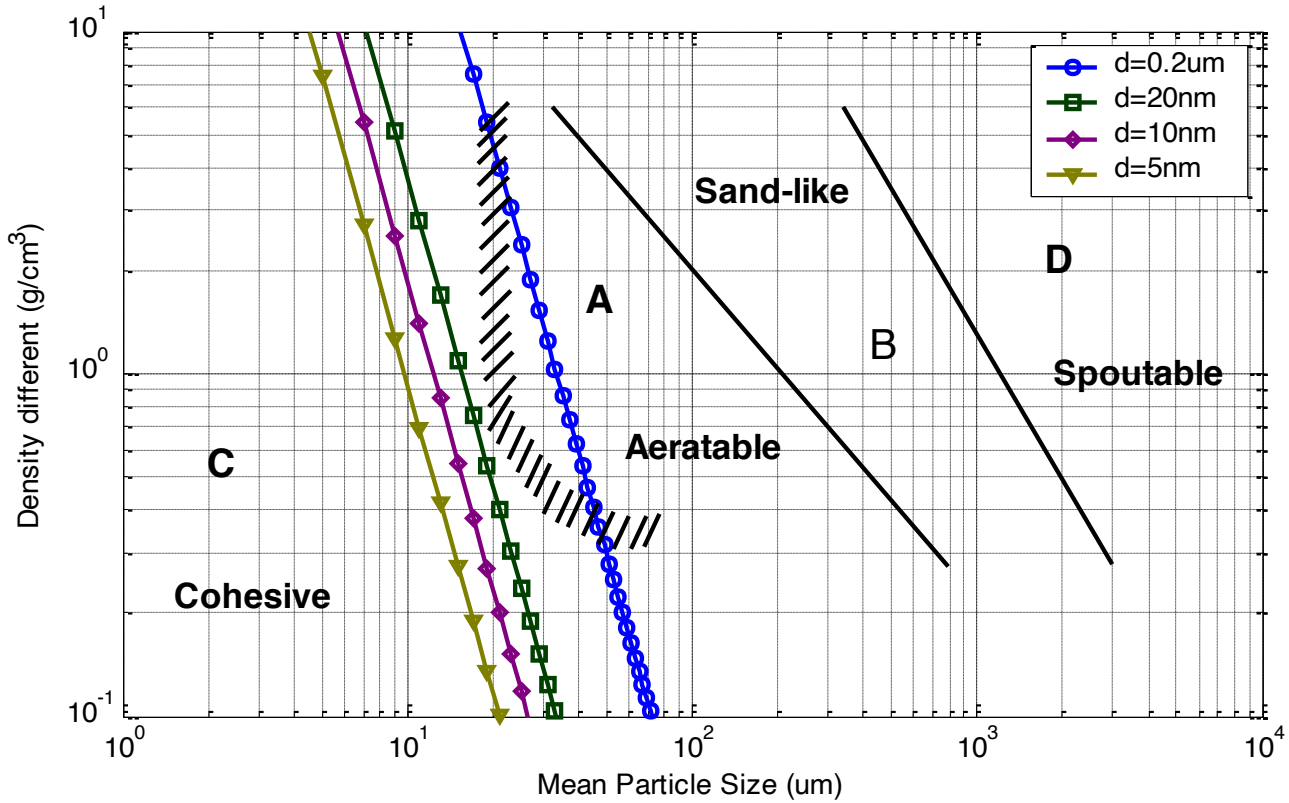


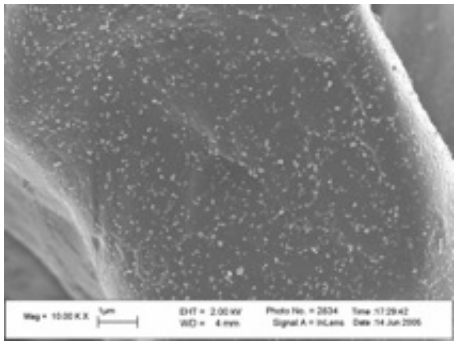
Eur. J. Pharm. Sci. 2017

AIChE J. 2008

Fluidization of "Class C" powders: Manipulating Geldart's Phase Diagram

- Based on the reduction in cohesion due to dry coating of nano-sized particles
  - Change the scale of surface asperity "l" by nano-coating





$$A = 10^{-19}\ \text{J},$$
$$l = 0.2\ \mu\text{m},$$
$$\delta = 0.4\ \text{nm},$$
$$\varepsilon = 0.5$$

$$\frac{\pi d_p^{\,3}}{6}(\rho_p - \rho_f)g(\varepsilon^{-4.8} - \varepsilon) = \frac{Al}{24\delta^2}$$

This chart should use non-dimensional coordinates

$l = d/2d_p$

d is the size of the coated guest particle

New Approaches:
Scalable Dry-coating Devices

Host size: 15 – 200 micron

Modified Comil

Continuous surface modification; capable of adding/coating nano-particles, amino acids, MgSt, and surfactants

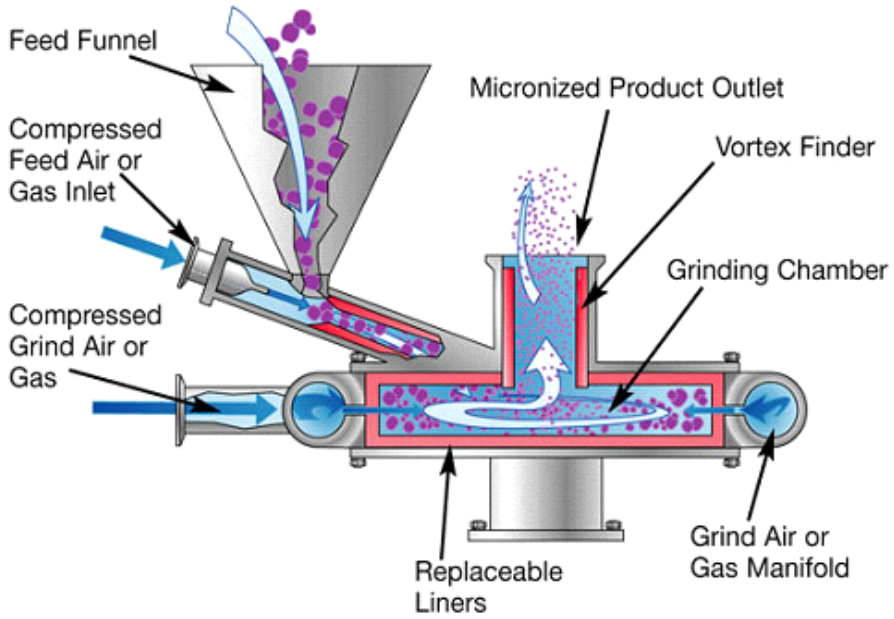
Tested at lab and pilot scale at Pfizer

Vibratory Mixer

A material sparing batch device; capable of coating nano-particles, amino acids, MgSt, and surfactants

Tested at lab scale at Pfizer

Host size: 2 – 30 micron



Fluid Energy Mill

Continuous size reduction and coating, co-grinding with surface modification; capable of coating nano-particles, amino acids, MgSt, surfactants, waxes, lipids, and liquids

Tested at pilot and production scale at Army/Holston Plant for RDX

Powder testing: Big Picture

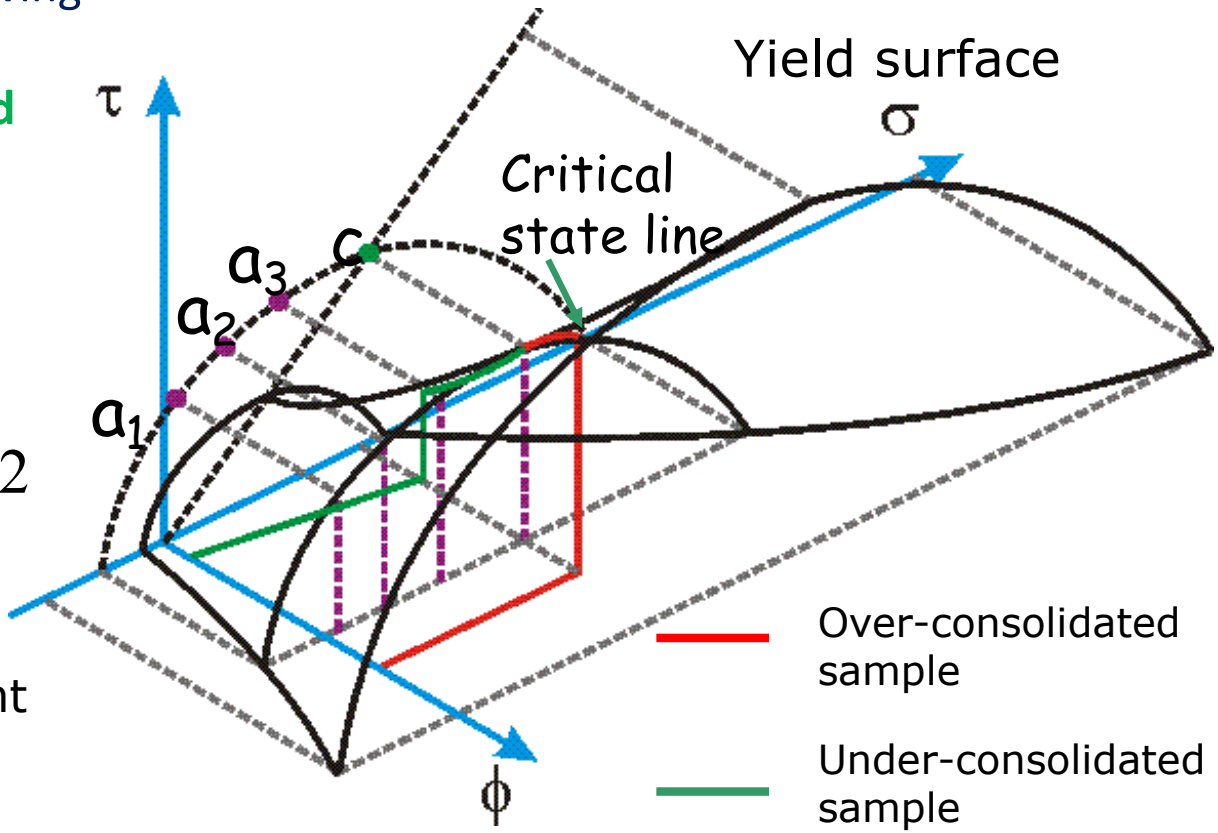
The state of the powder requires knowing three inter-related variables:
Consolidation stress, shear stress, and solid fraction

There could be a fourth, often ignored variable, **agglomeration**!

$$N = k^D \quad Bo \approx k^{D+2}$$

Bo- Bond Number, a ratio of cohesion force to particle weight (F_c/mg)

k - the ratio of agglomerate to particle size

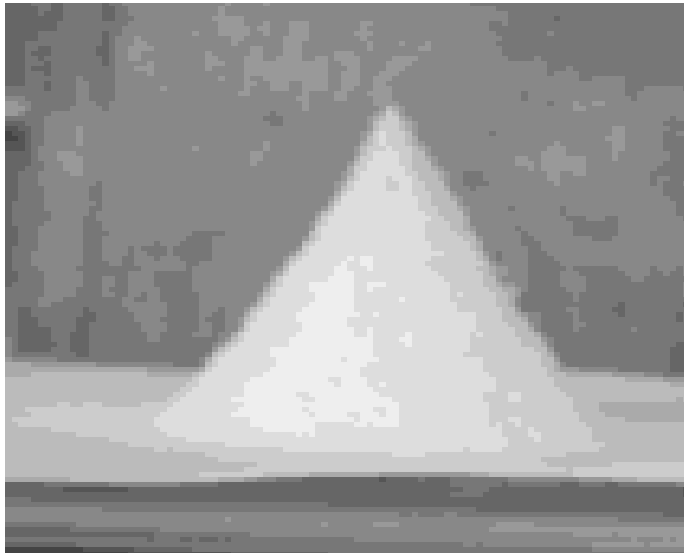


Courtesy Miguel Sanchez-Quintanilla

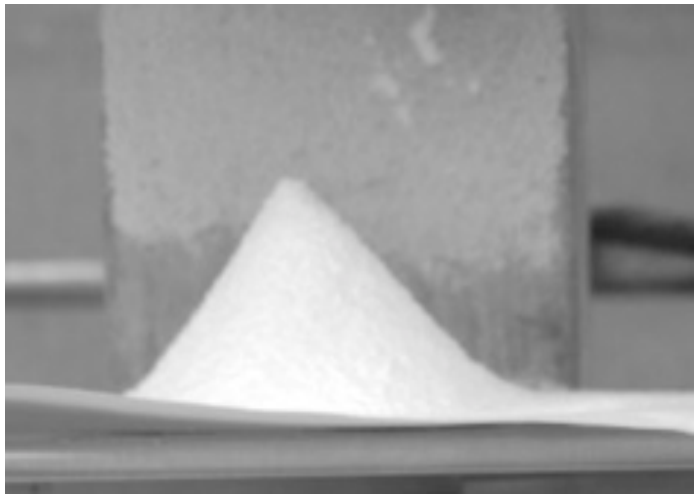
Goal of most powder testing methods is to find a "piece" of the yield surface; best to match testing to your flow situation. Not valid for collisional systems where **dynamic testing** needed.

Examples: AoR, Housner ratio, Flodex/critical orifice, or dilation in a tumbler may relate to a single point or a very small line on the yield surface (*the state of consolidation cannot be varied*)

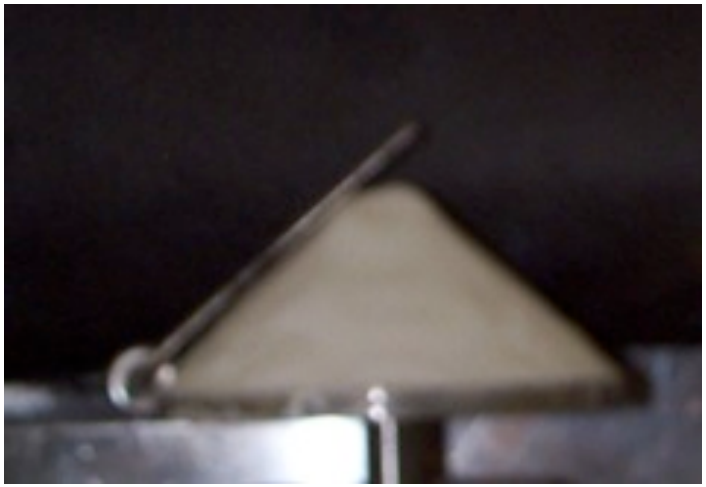
Powder piles obtained using MAPF and Hosokawa



Uniform nano-agglomerates through external agitations helped their fluidization



Piles using MAPF



Piles using Hosakawa Micron Tester

Pharma powders flow poorly: Size, FFC, bulk density

FFC Value	Flowability
< 2	Not Flowing
2-4	Cohesive
4-10	Easy Flowing
> 10	Free Flowing

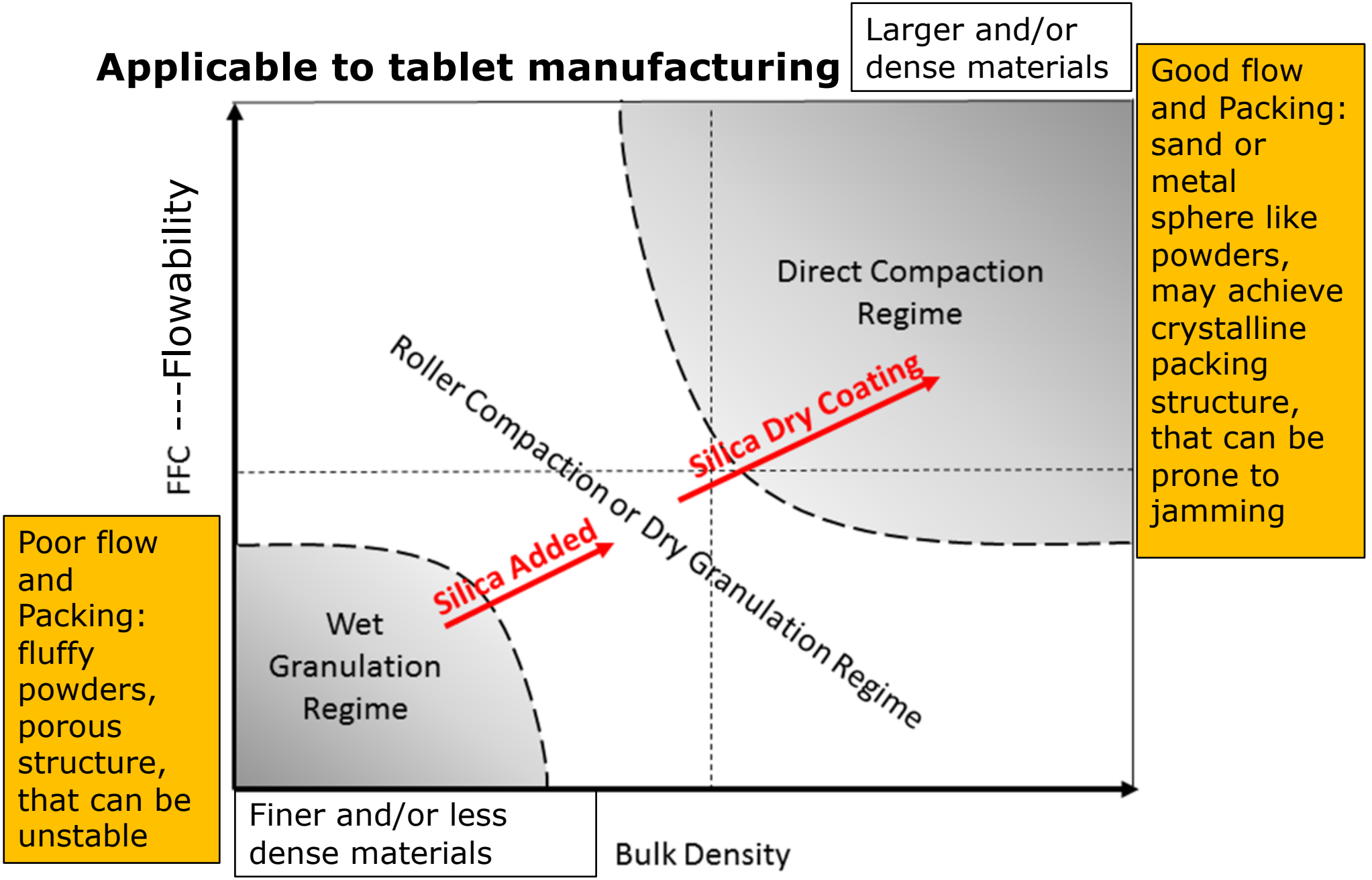
- For ease of tablet manufacturing, granulation should be avoided
- For direct compression tableting, blend **bulk density > 0.4** and **FFC > 7** recommended
- Using fancy excipient does not help!

Material	Particle size – d50 (µm)	Bulk density (g/ml)	FFC
Micronized APAP	10	0.197	1.67
Coarse APAP	30	0.343	1.89
Ibuprofen 50 US	61	0.404	4.28
Ibuprofen 90 US	102	0.483	4.07
Ascorbic Acid	215	0.905	5.47
Avicel 101 AR	66	0.325	4.3
Avicel 102 AR	122	0.325	6.95
Avicel 105 AR	19	0.357	2.49
Avicel 200 AR	~ 200	0.335	10.3
Lactose 350	26	0.415	2.9
Lactose 450	17	0.406	2.8
Pharmatose DCL11	108	0.648	15.1
Prosolv 90 HD	112	0.5	14.6

Bulk Density and FFC of mAPAP+Prosolv blends		
Drug load	Bulk Density	FFC
10 %	0.486	8.93
30 %	0.406	3.43
60 %	0.282	1.71

Powder Processibility Map: Bulk density & Flowability

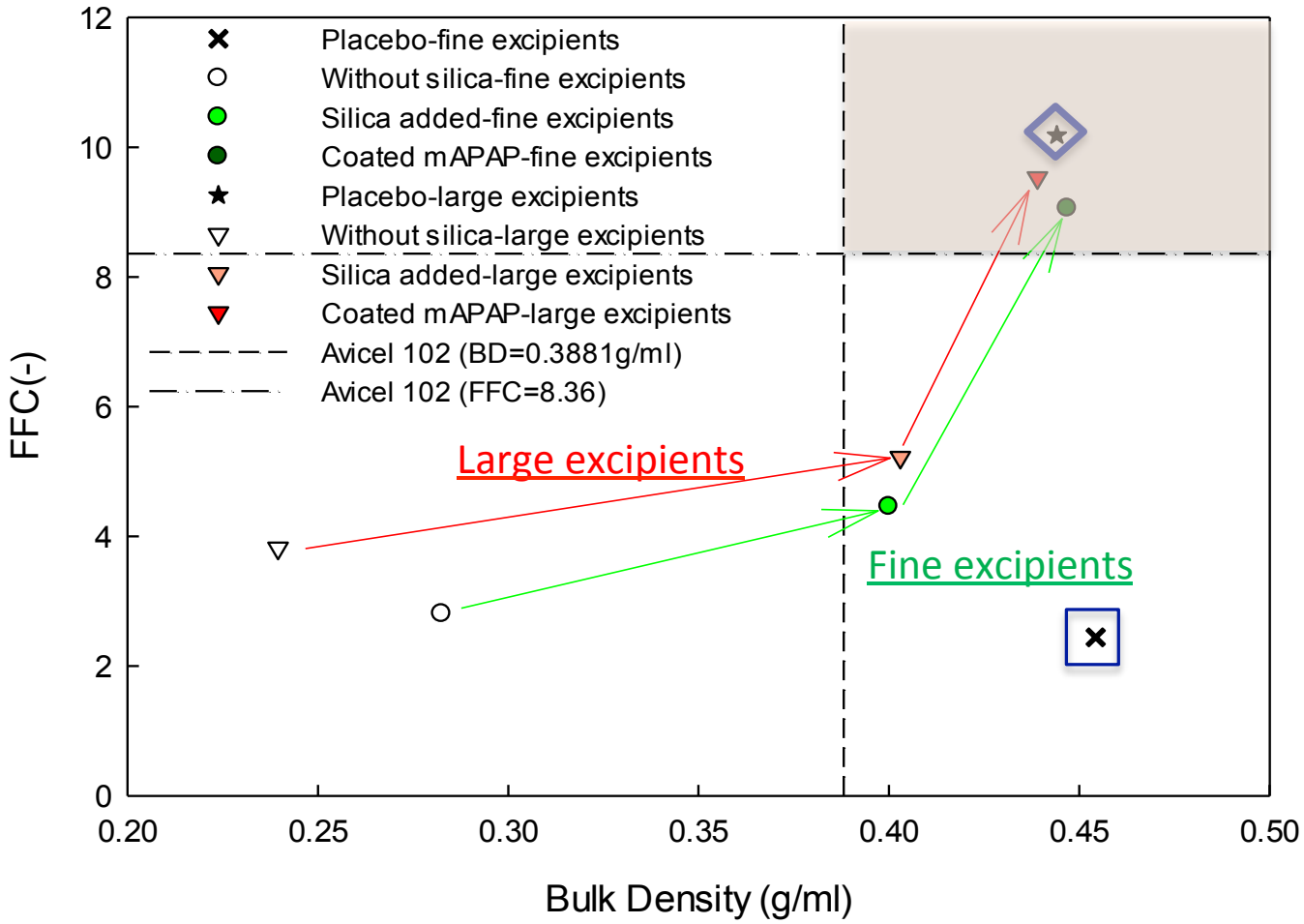
Applicable to tablet manufacturing



Int. J Pharm. 2018

Dashed lines are typical properties of Avicel PH 102

Case study: Fine dry coated API (mAPAP ~ 10 μm) blends could be direct compressed at high (60 %) drug loading



- Greatly improved flow and packing density
- Higher drug loading (60 wt %)
- Direct tablet compression
- Reduced cost, improved quality
  - **No granulation required**!

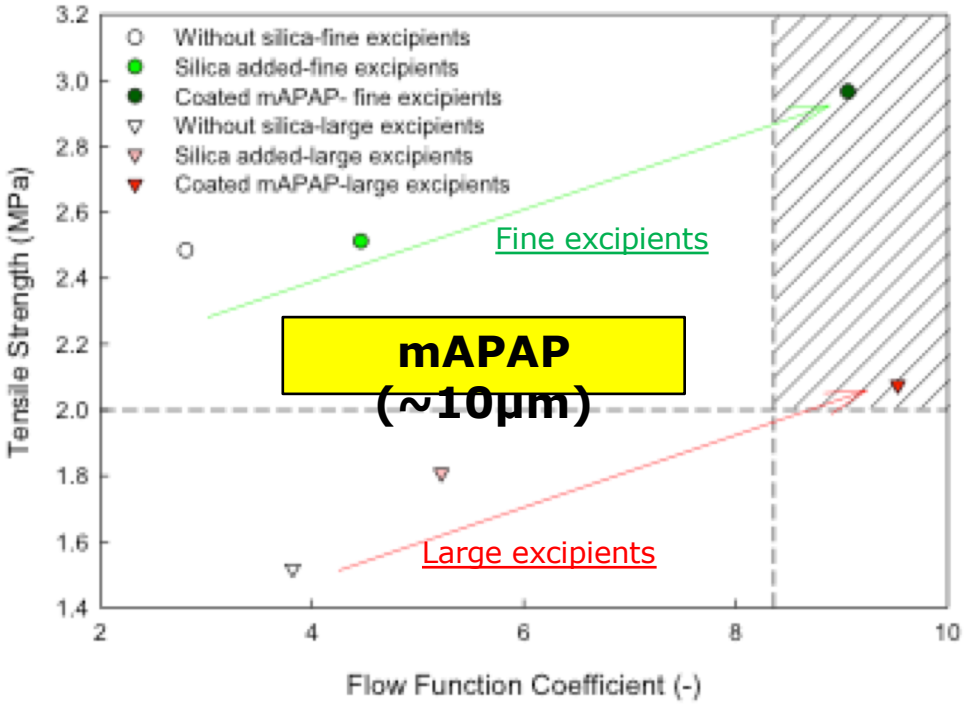
Dry coating fine drug powder eliminates the need for fancy excipients and greatly improves robustness of blend formulation

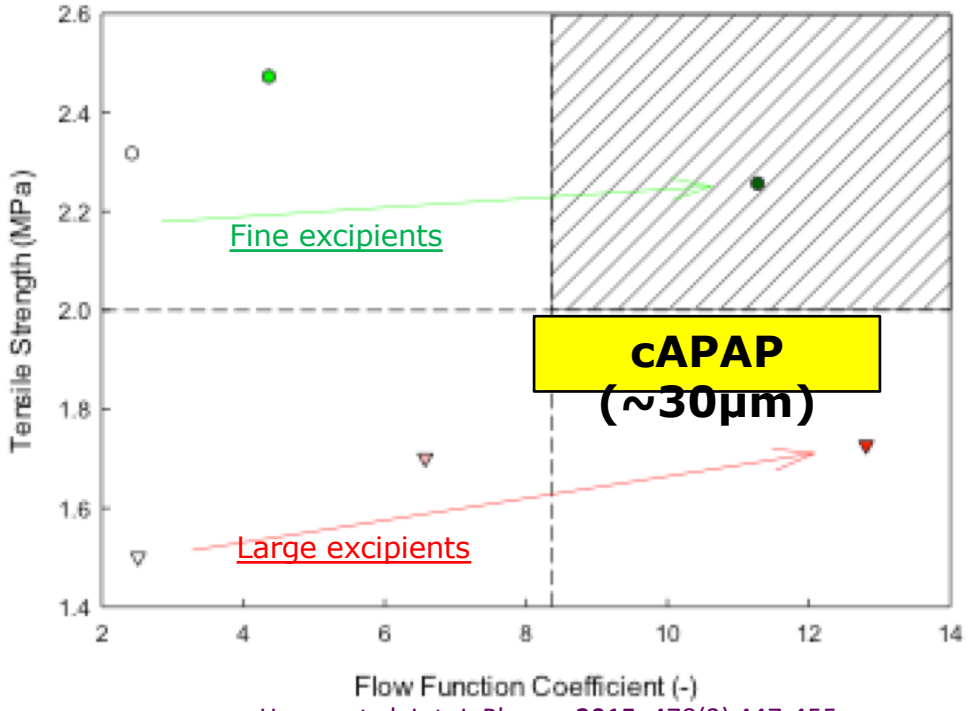
Int. J. Pharm. 2015

Case study: Tablet strength

Dry coating fine API in high drug loading (60% (w/w)) blend improves tablet strength

Excipients		Type
Avicel 105	Pharmatose 450	Fine (~20µm)
Avicel 102	Pharmatose DCL11	Large (~120µm)





Huang et al, Int. J. Pharm. **2015,** 478(2) 447-455.

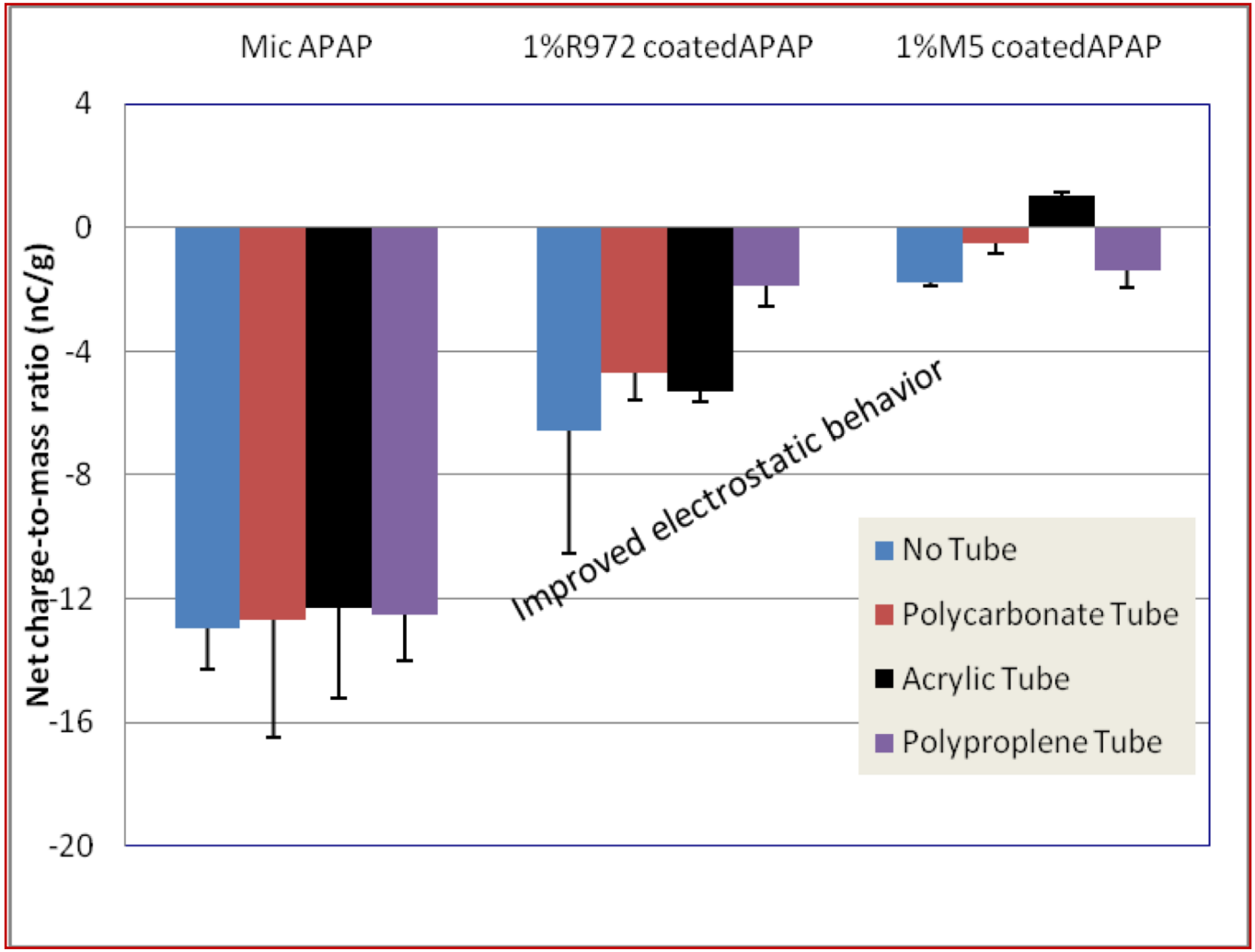
- **Dry coating cohesive API improves both flowability and tablet tensile strength**
- **Fine excipients obtain higher tablet tensile strength**

Int. J. Pharm. 2015

Case Study: Electrostatic behavior of micronized Acetaminophen (Mic APAP)

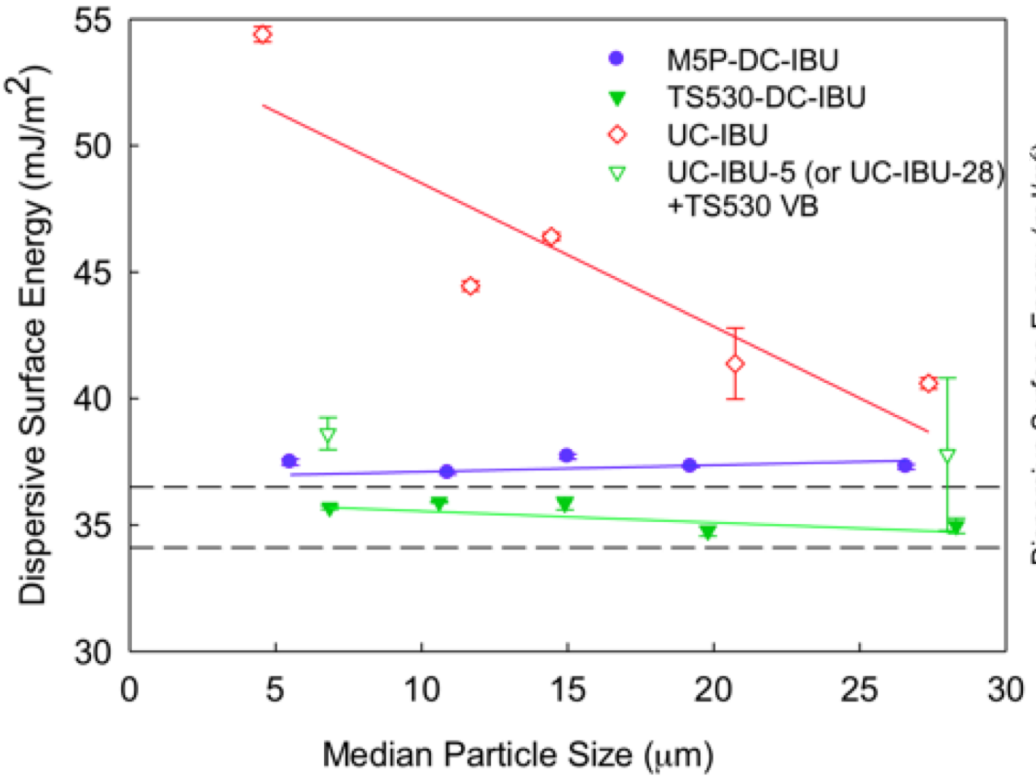
Energetic discharges during processing may prove hazardous

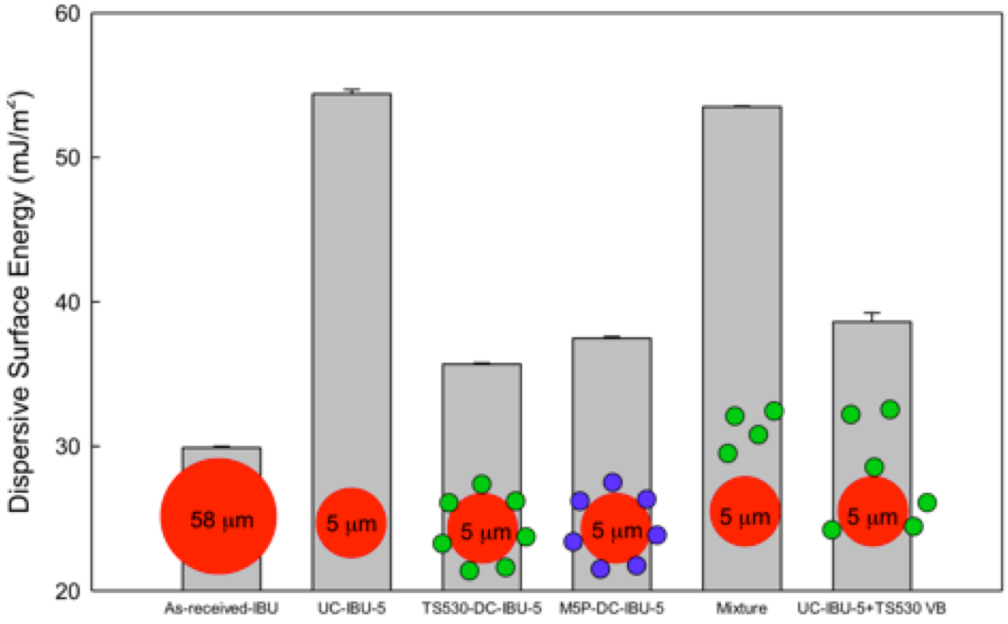
RH 60%, 23^{0}C



J. Pharm. Sci. 2015

Case study: Surface energy to explain positive impact of dry coating during micronization/milling



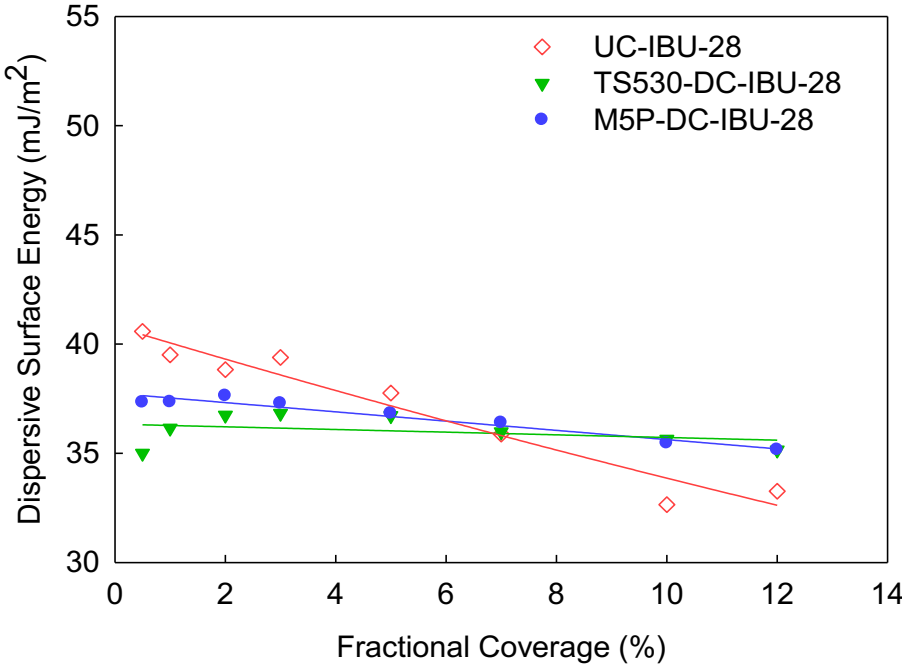


- Results (at fixed probe coverage) represent the highest surface energy sites
- As micronization intensity grows, surface energy increases; however, for dry coated powders, it does not due to passivation of active sites by silica particles

Int. J. Pharm 2011, Int. J. Pharm 2013, J of Pharm Sci 2013

Dry coating reduces surface energy heterogeinity after milling due to passivation

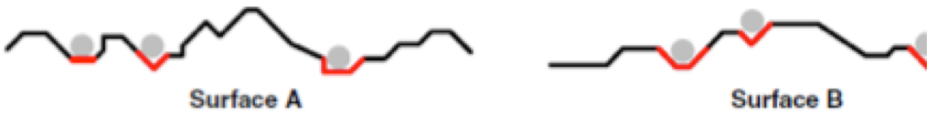
0.5 % -12% surface coverage



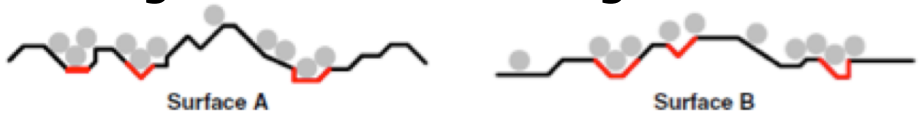
Fractional coverage: how much surface area of the powders being tested; different amount of solvent probe is injected in the IGC

Reduced the heterogeneity of milled powders

Low surface coverage

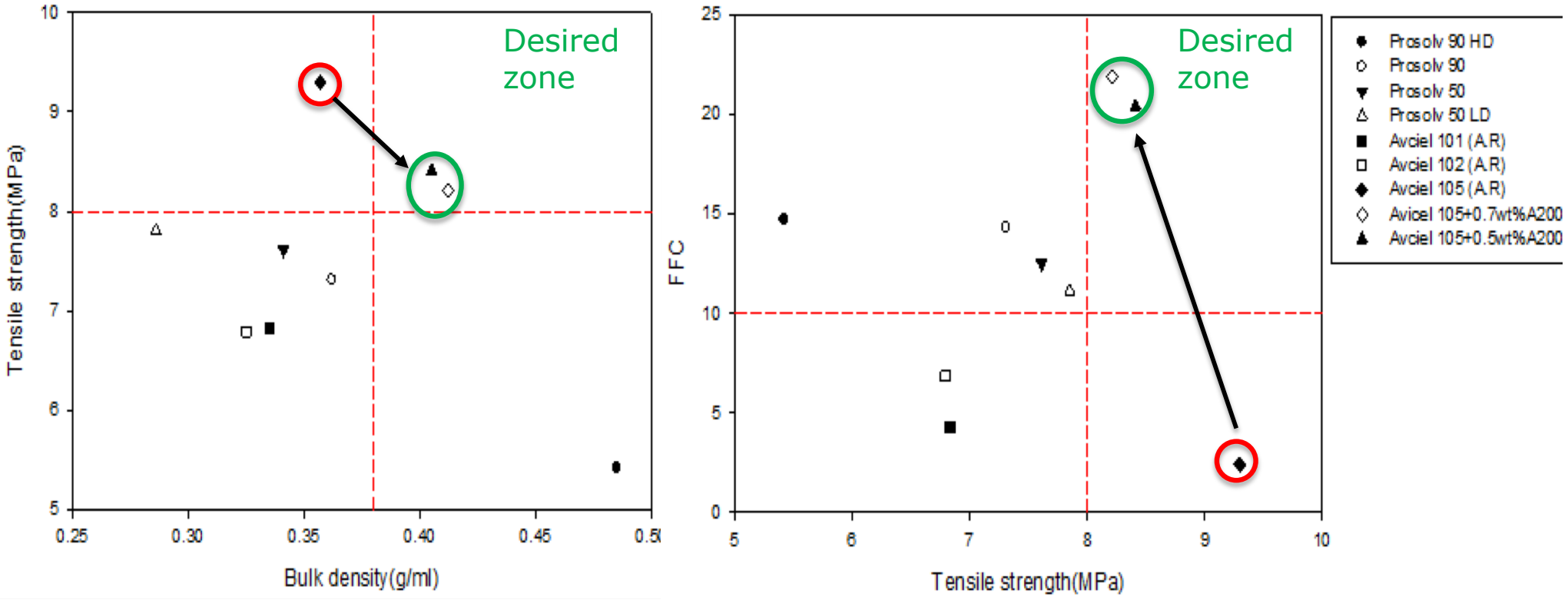


High surface coverage



Int. J. Pharm 2011, Int. J. Pharm 2013, J of Pharm Sci 2013

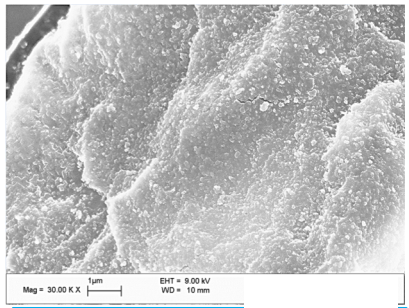
Case Study: Engineered Fine Excipients



Compared with commercial excipients, the surface engineered excipients exhibit better performance in bulk density, flowability as well as compaction shown in these phase maps

Int. J. Pharm 2018a

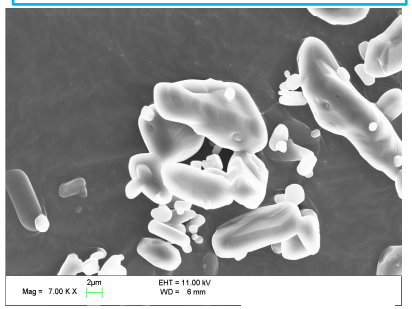
Binary blends of finer dry coated MCC (Avicel PH105 – 20 microns) has better performance towards direct compaction



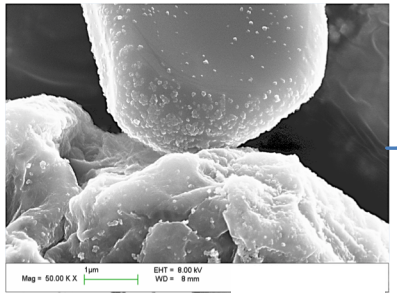
Engineered ex

+

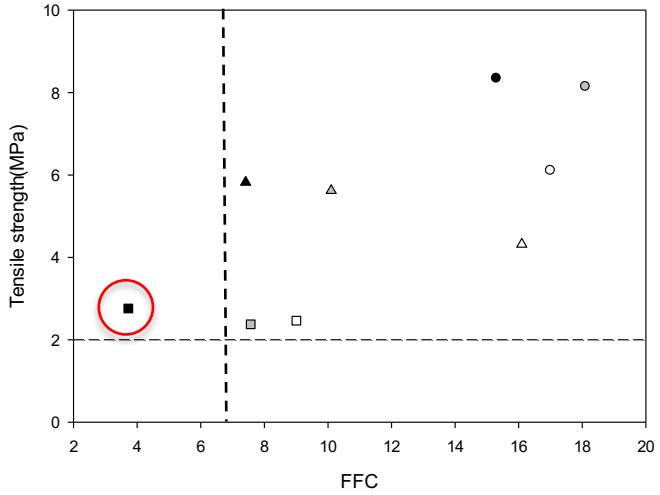
cohesive poorly-compactable API



Binary blends at low, medium, and high drug loadings

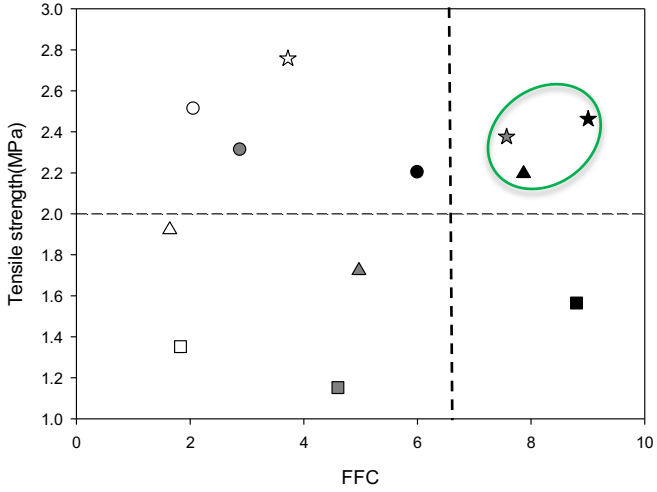


Blend Direct Compaction Processability



10 %, 30 %, 60 % drug loading

Blend Direct Compaction Processability for all Excipients at 60 % drug loading

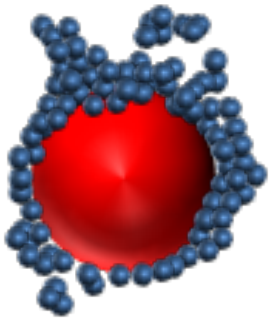


60 % drug loading; DC Avicel PH 105 compared with Prosolv 50 and Prosolv 90

APIs:
mAPAP – 10 microns
cAPAP – 30 microns
Ibuprofen – 50 microns

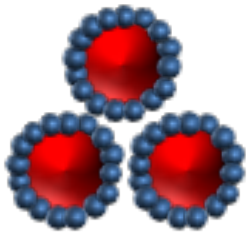
Int. J. Pharm 2019

Engineered Excipients in Fine Size Ranges

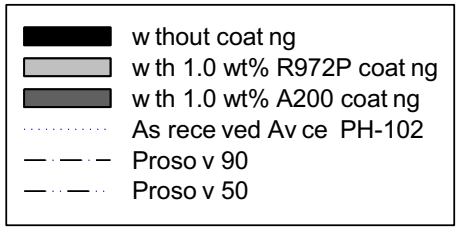


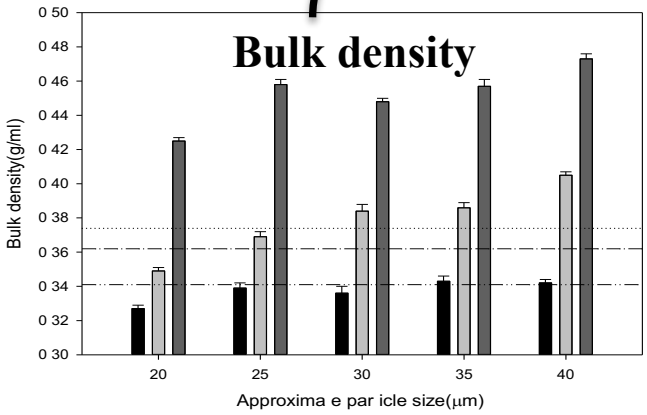
Pre-Blend (Avicel 102 + nano-silica – A200 or R972P)

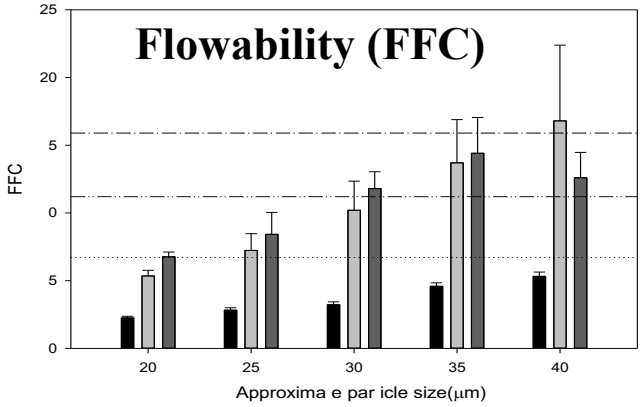
Simultaneous milling and surface coating with fluid energy mill (FEM)

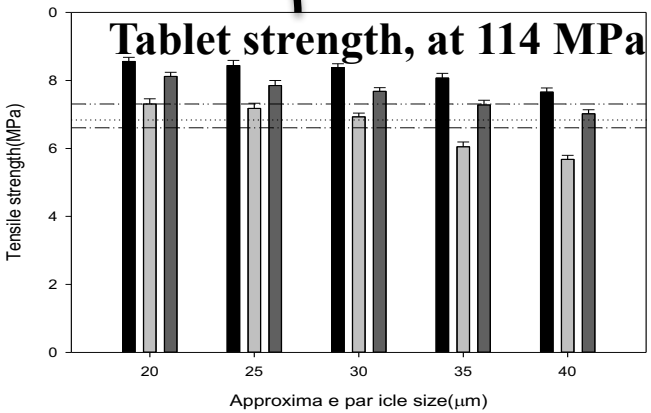


Milled-dry coated fine excipients (20 - 40 µm) compared favorably to commercial silicified excipients



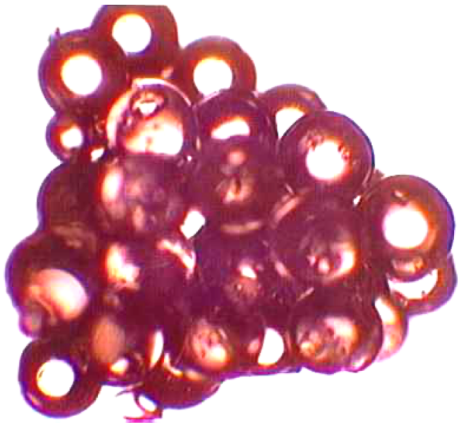


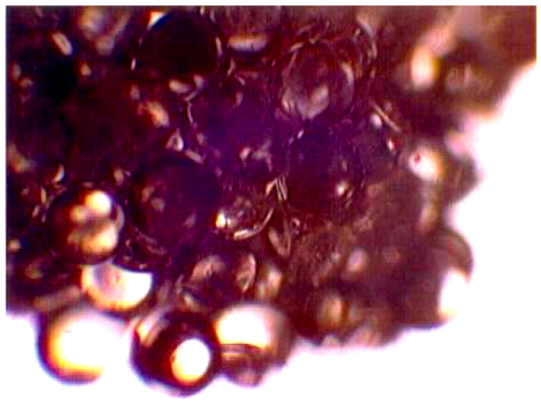




Int. J. Pharm 2018b

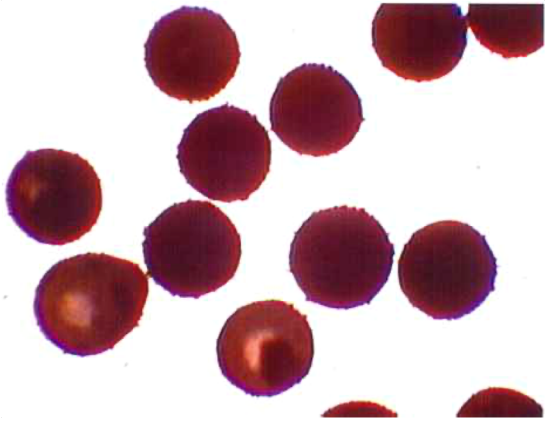
What about sintering and solid bridges?

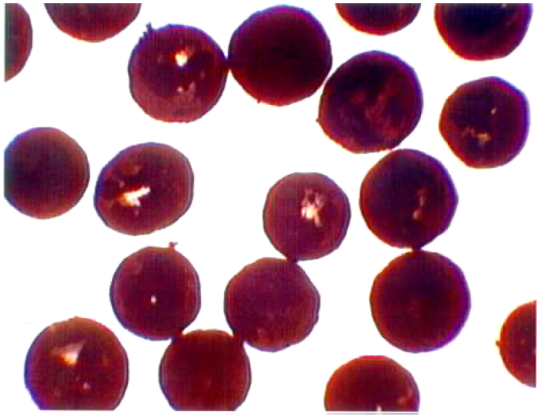


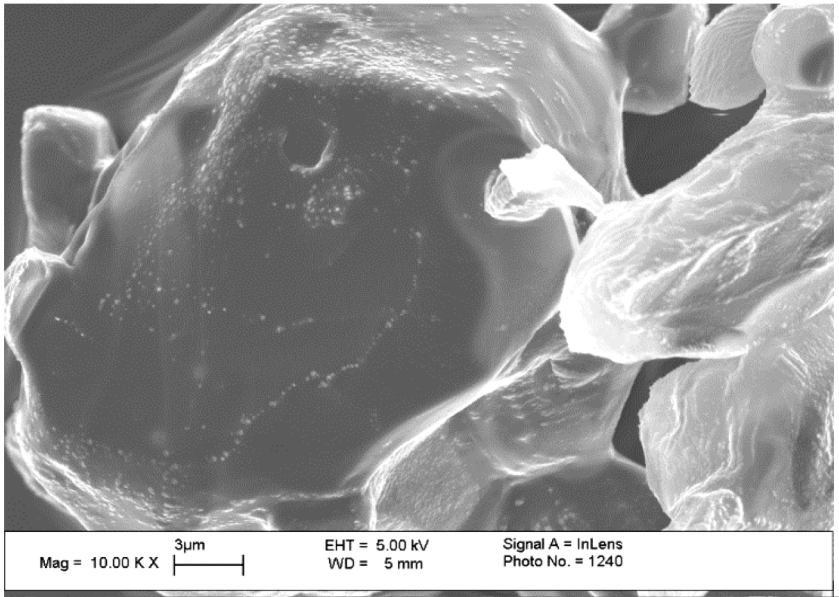


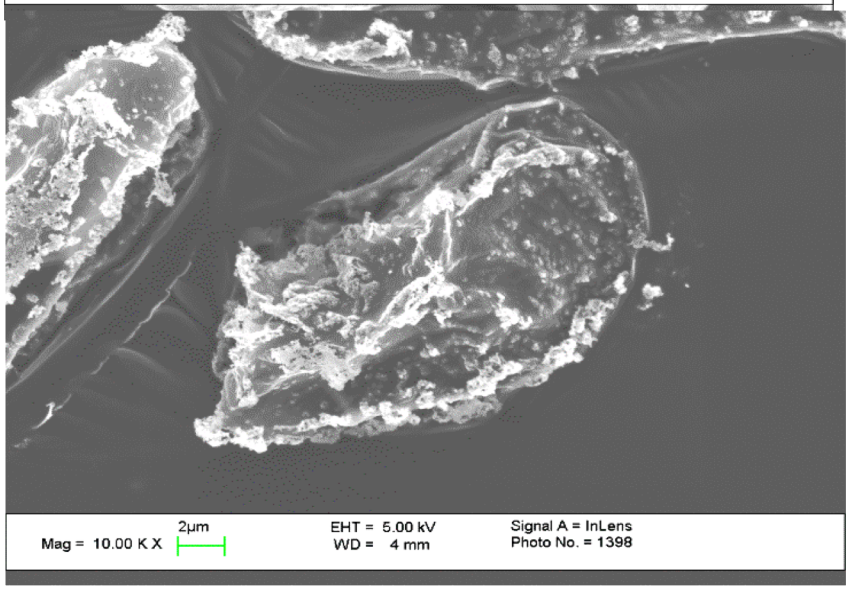
600°C 700°C

Coated by sub-micron silicon carbide - ~2 % wt.

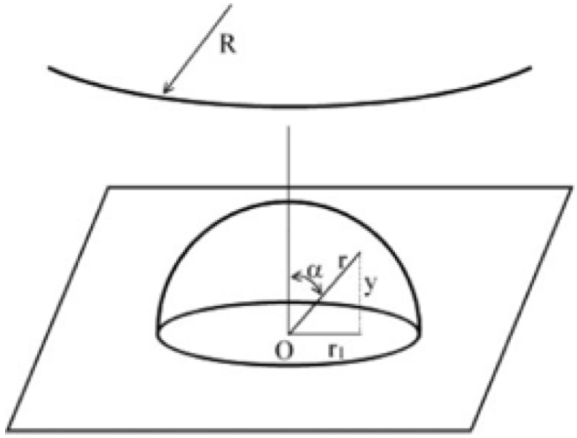








How does dry coating reduce cohesion?
Nano-rough surfaces: Handling asperities

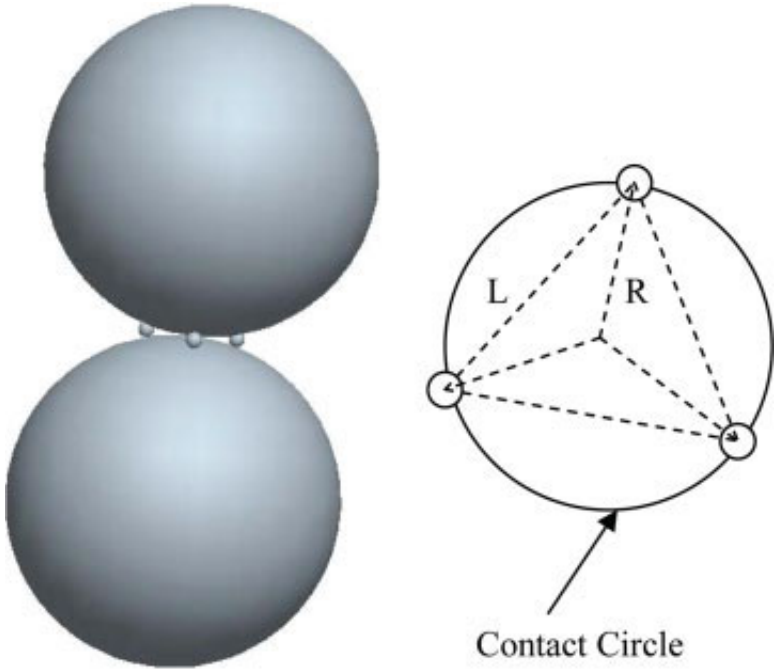


$$F_{ad} = \frac{A}{12z_0^2}\left[\frac{dD}{d+D} + \frac{D}{(1+d/2z_0)^2}\right]$$

Rumpf Model – Single asperity

Rabinovich Model (U. of Florida) – Modified Rumpf – Still single asperity

$$F_{ad} = \frac{AD}{12z_0}\left[\frac{1}{1+D/(2\times 1.48rms)} + \frac{1}{(1+2\times 1.48rms/2z_0)^2}\right]$$



NJCEP/NJIT Model – Multiple asperity model

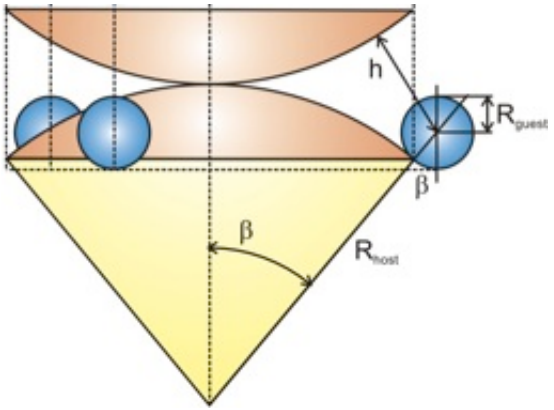
$$F_{ad} = \frac{Ad}{4z_0^2} + \frac{A}{24\left(\sqrt{\left(1+\frac{d}{D}\right)^2} - \frac{1.21}{SAC}\left(\frac{d}{D}\right)^2 - 1\right)^2 D}$$

Powder Tech. 2005, 2010 *AIChE J. 2008*

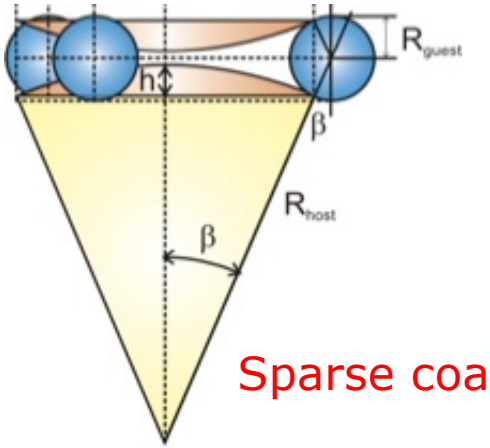
Contacts due to dry particle coating

In order to model the interparticle force, one must consider the nature of contact between two cohesive powders: *Three contact types exist, and are determined by the Surface Area Coverage (SAC) of guest particles*

Host-Host

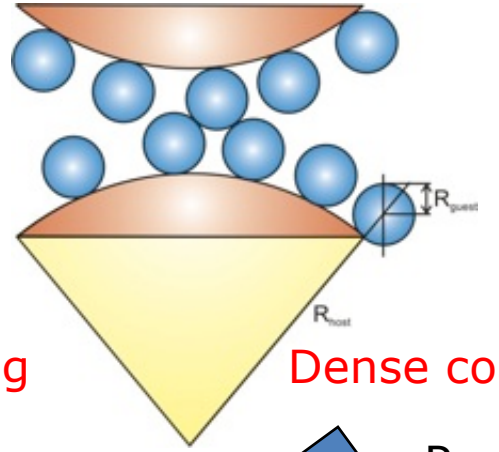


Guest-Host



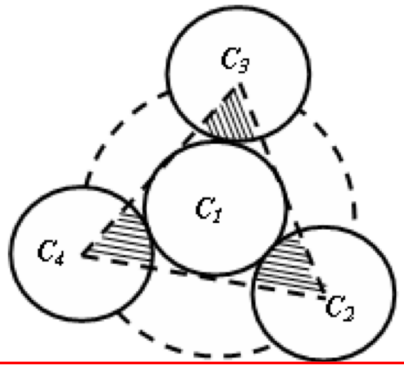
Sparse coating

Guest-Guest



Dense coating

Projection



Transition between contacts

$$SAC_{guest-host} = \frac{1.21}{1+2\left(d_a / d_g\right)} \times 100\%$$

d_a Asperity size on host particle surface

d_g Guest particle size

Distance *L* between host particles is Zero

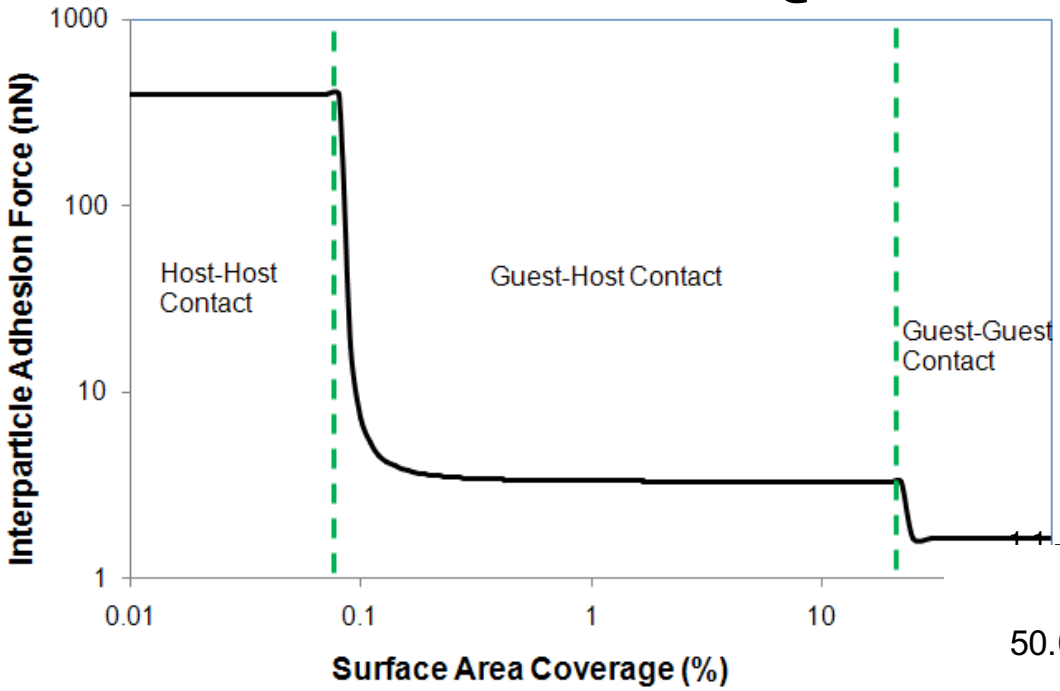
$$SAC_{guest-guest} = 30\%$$

R972+Cornstarch

$$SAC_{guest-host} \approx 0.96\%\left(0.01 wt\%\right)$$

$$SAC_{guest-guest} \approx 30\%\left(0.22 wt\%\right)$$

Surface Area Coverage based Adhesion Model and Qualitative Validation



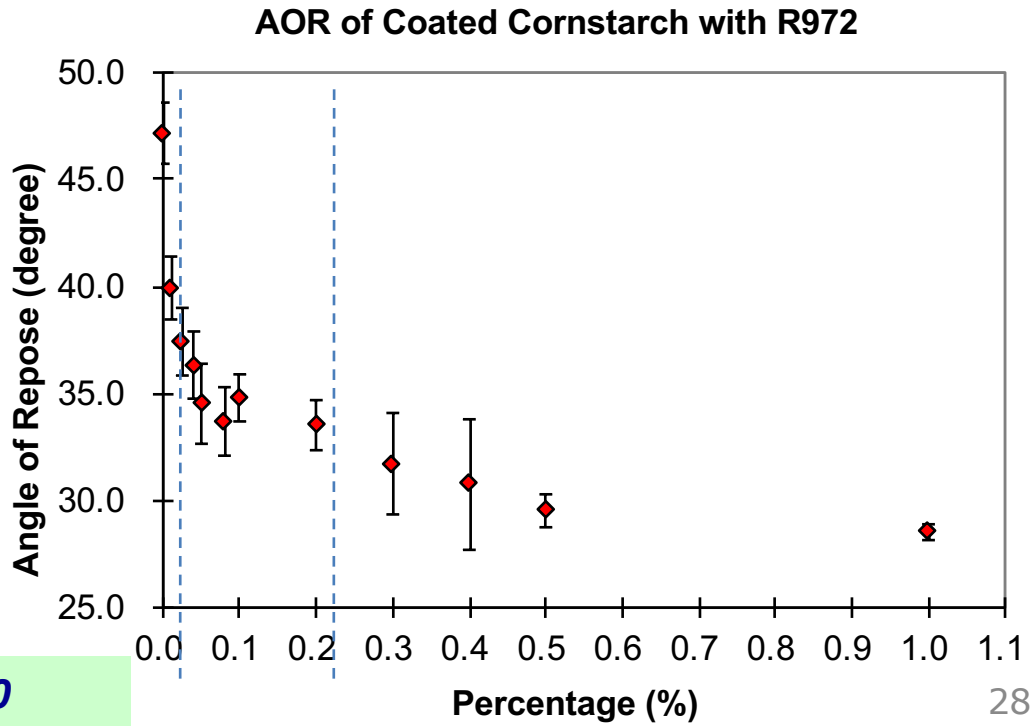
Contact Mode/SAC significantly affects the inter-particle force and fluidization behavior

The trend of minimum fluidization velocity (and AoR) agrees well with the trend of interpretable adhesion force under the effect of SAC

$$A = 10^{-19} J \quad z_0 = 0.4nm \quad d = 20nm \quad D = 15\mu m$$

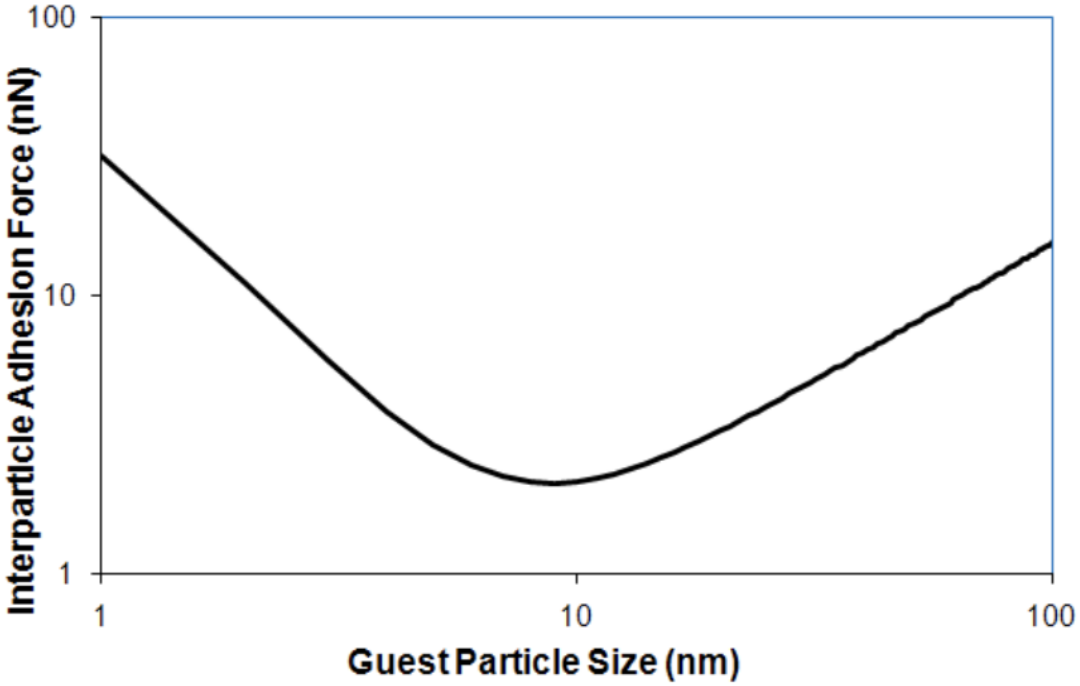
$$F_{ad} = \frac{Ad}{4z_0^{\,2}} + \frac{A}{24\left(\sqrt{\left(1+\frac{d}{D}\right)^2 - \frac{1.21}{SAC}\left(\frac{d}{D}\right)^2} - 1\right)^2 D}$$

Two additional contact models have been developed to relax assumptions such, uniform guest size and coating, no consolidation, etc



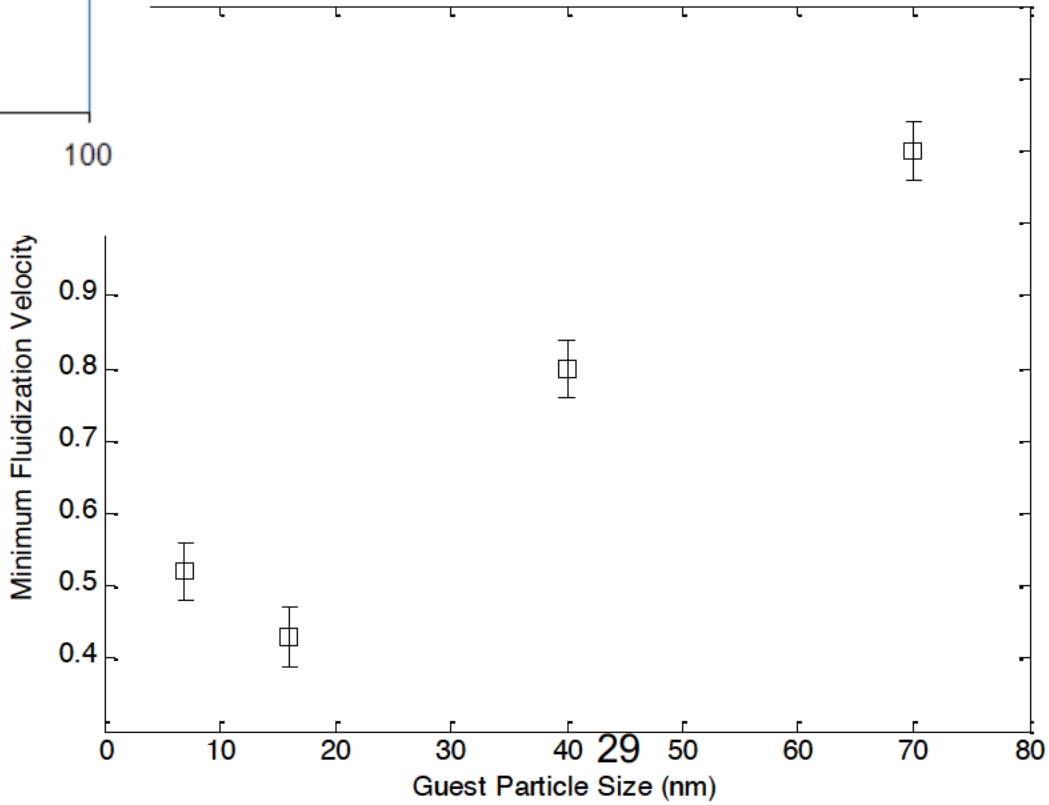
AIChE J. 2008 *Phys Rev E 2009; Coll & Surf A 2010*

Model Verification- Influence of Surface Asperity



An ***optimal*** guest particle size leads to the minimum interparticle adhesion force (left)

The trend of minimum fluidization velocity (below) also agrees with the trend of interparticle adhesion force under the effect of guest particle size



$A = 10^{-19} J$

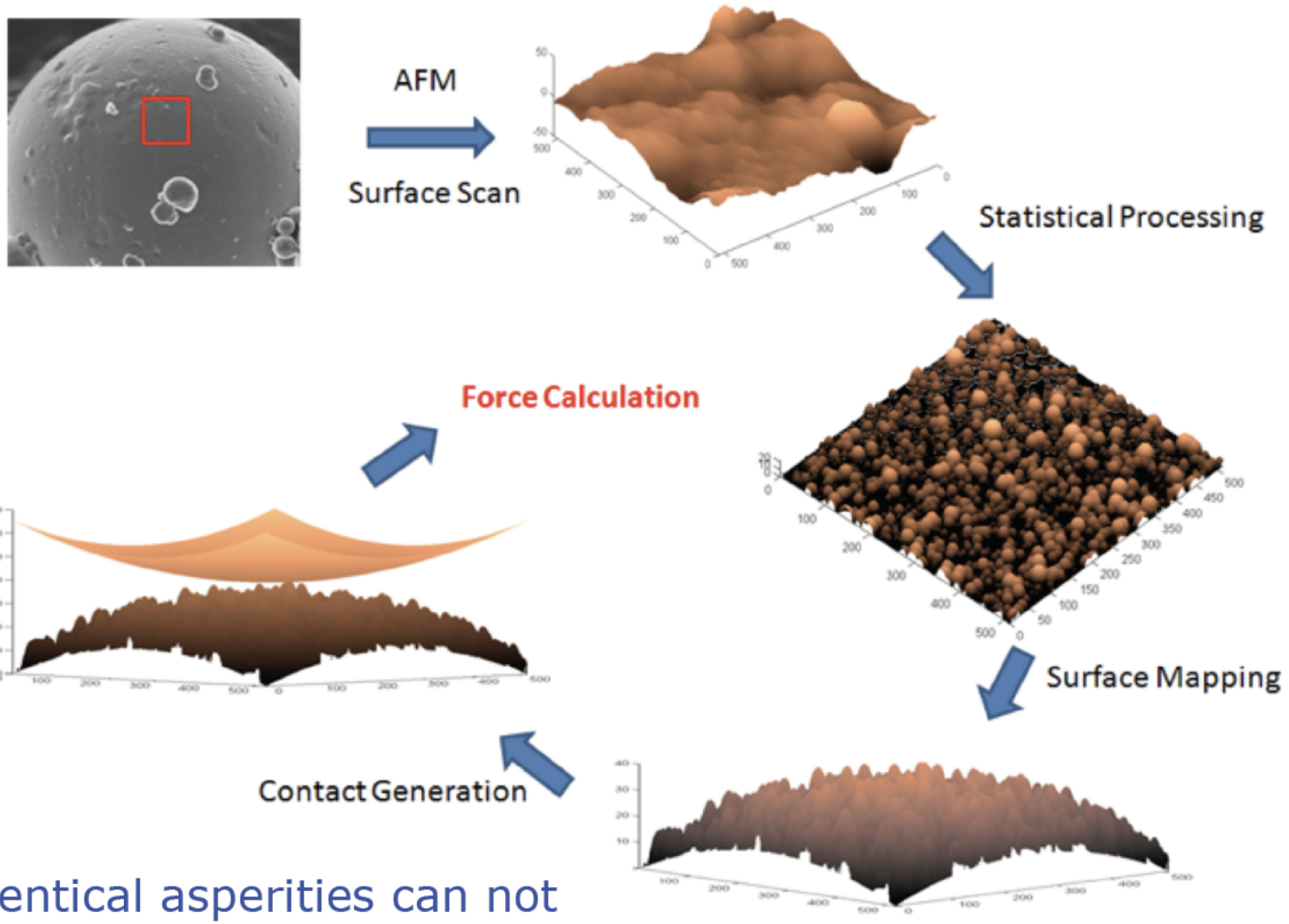
$z_0 = 0.4nm$

$D = 15\mu m$

$SAC = 100\%$

AIChE J. 2008

Advanced Pull-off Force Model: Accounting for Non-uniform Size & Spacing of Asperities, and Normal Stress (JKR/DMT type models used)

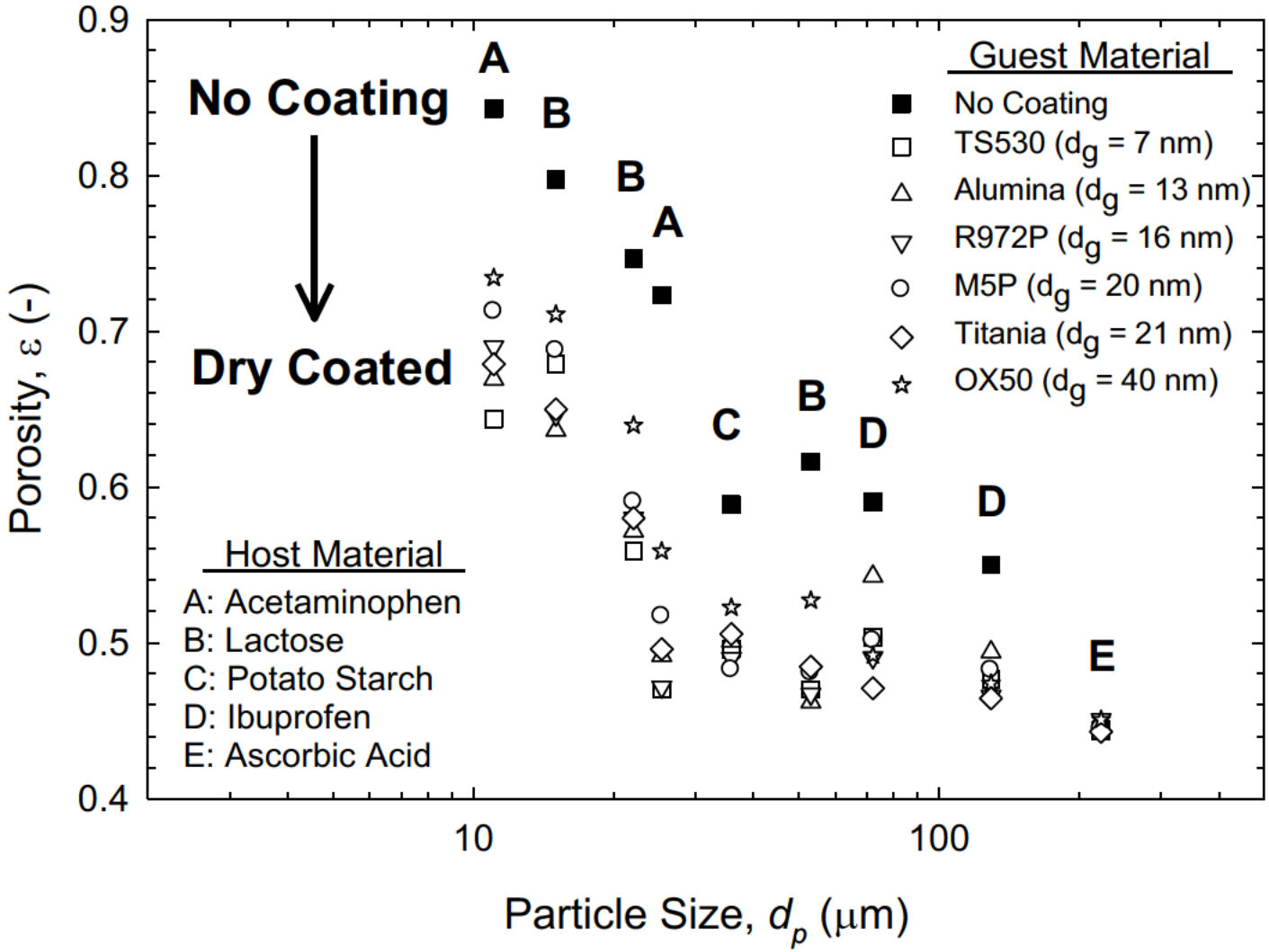


Identical asperities can not be used to represent arbitrarily rough surface

Particle surface is not perfectly smooth

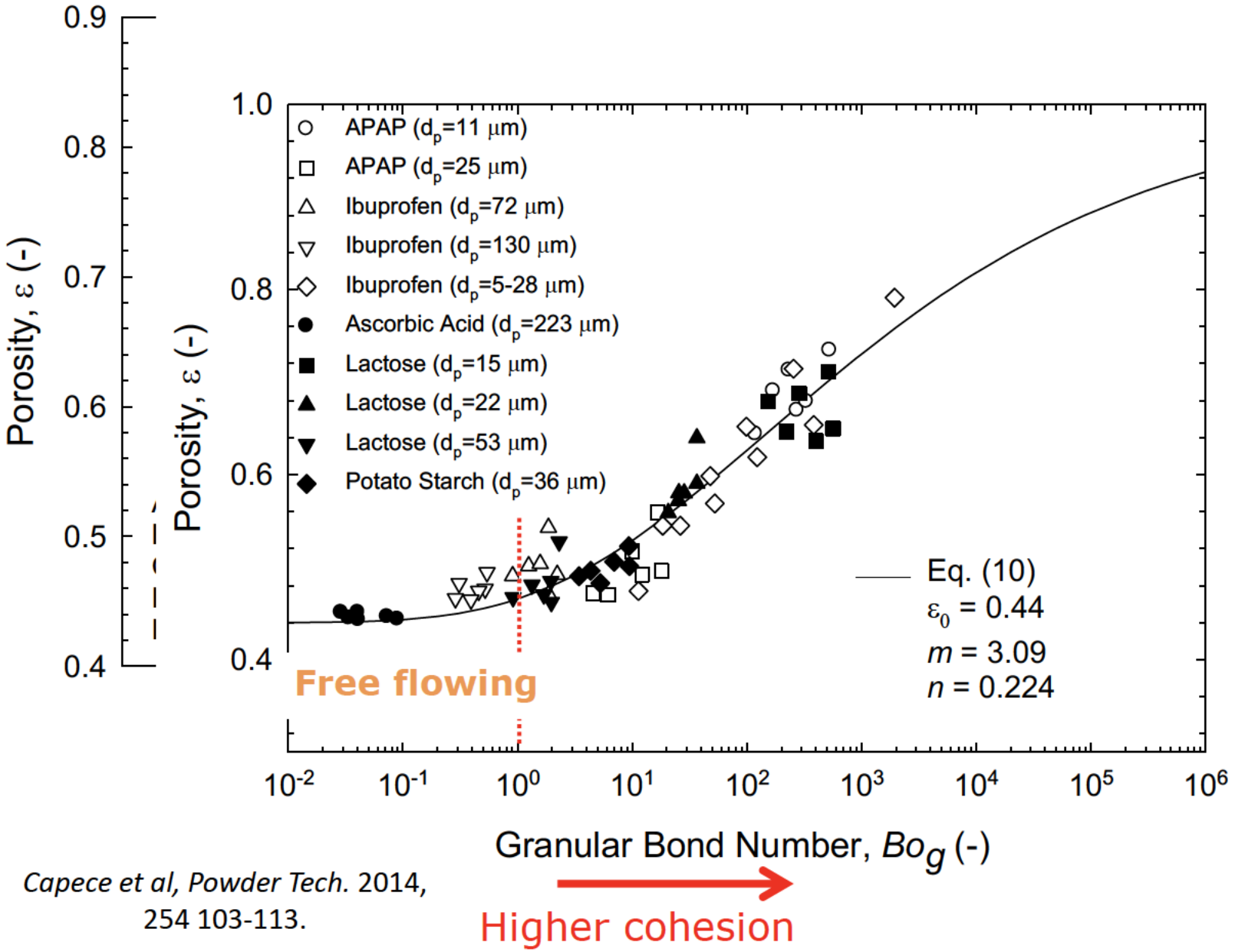
Phys Rev E 2009; Coll & Surf A 2010

Linking particle and bulk scales : Particle size vs. porosity of packed powders



- Porosity may not directly correlate with particle size as different surface roughness is imparted.
- Dry coating improves porosity by decreasing interparticle cohesion
- 25 μm particles can achieve porosity near 0.44 (minimum porosity for free flowing powders)

Linking particle and bulk scales: Bond number vs. porosity of packed powders



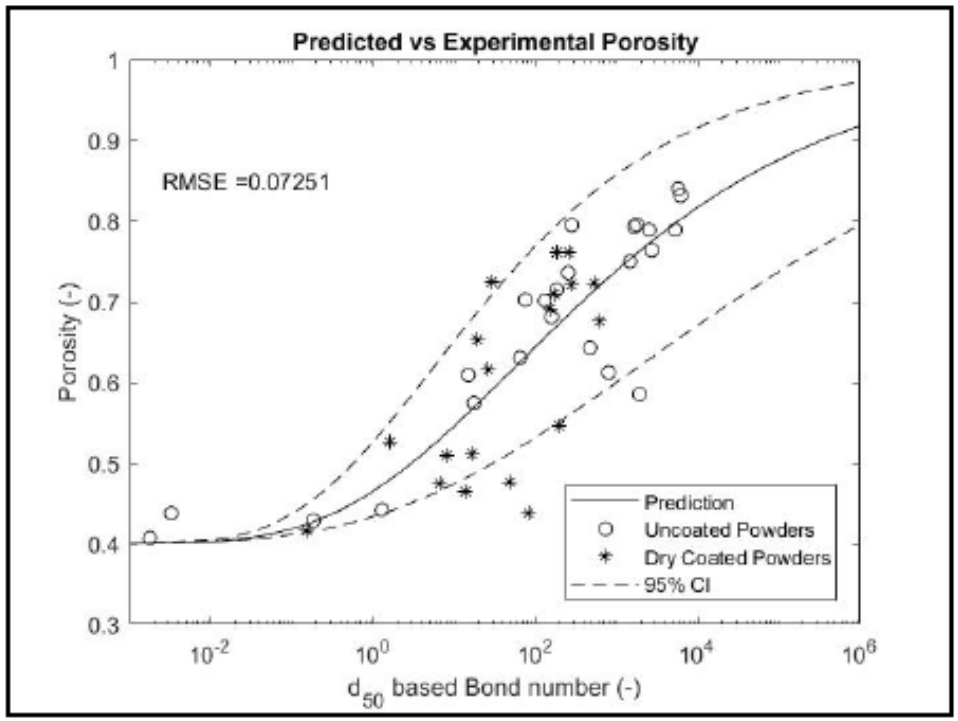
Bond number correlates very well with porosity for many materials and particle sizes

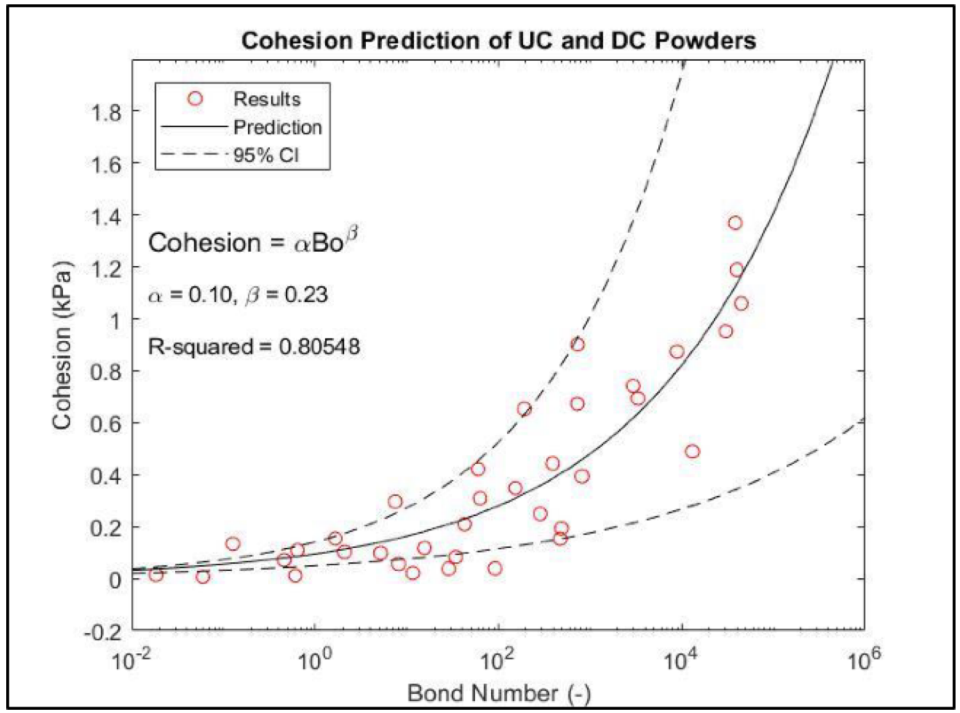
Interparticle cohesion can be used to predict bulk powder behavior

Our multi-asperity cohesion model (Chen et al., 2008) works very well

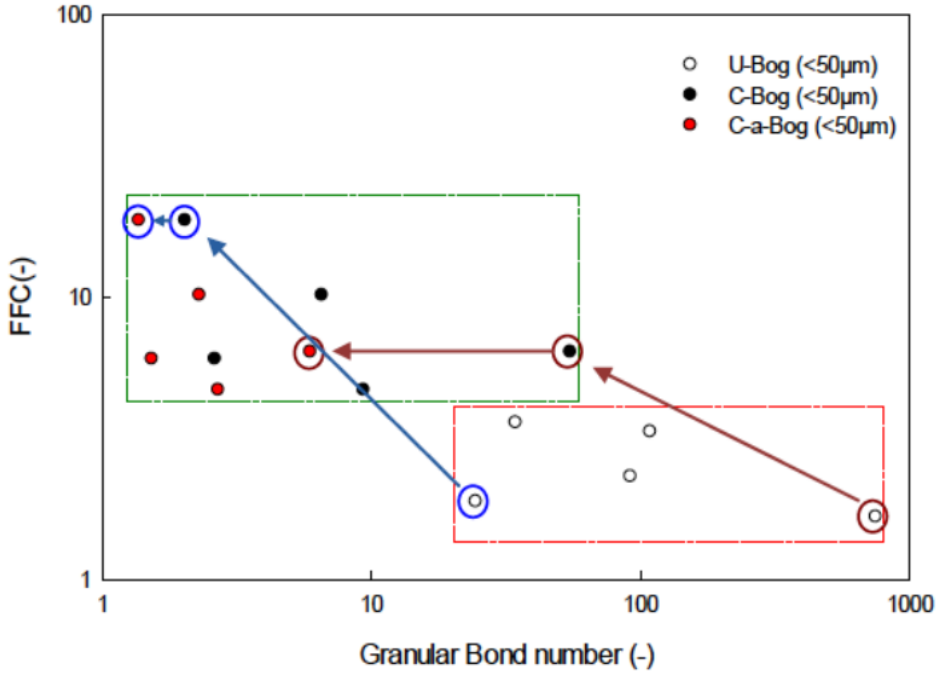
Capece et al, Powder Tech. 2014, 254 103-113.

Predicting solid fraction and flow (cohesion) of different pharma powders based on the Bond Number



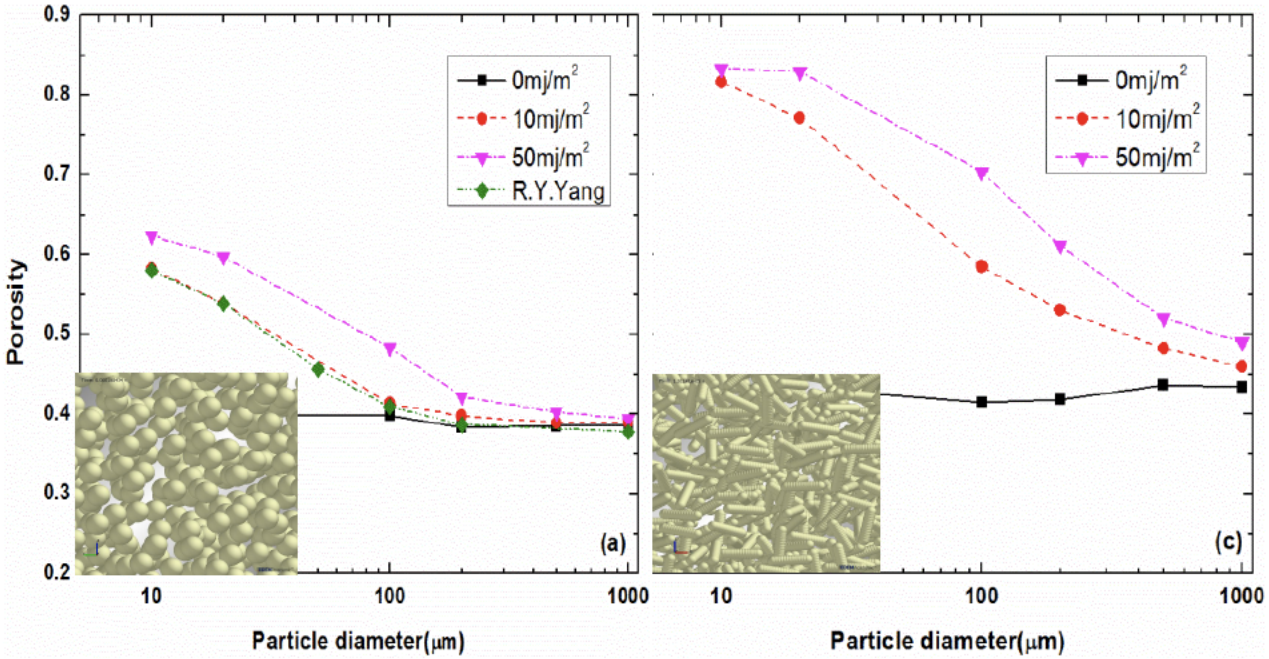


A few thoughts



Acknowledging that fine powders agglomerate hence aggregate Bond number may need to be used

Could we "lump" aspect ratio effect in to cohesion?



Closing remarks

- Surface modification allows for reducing the influence of poor intrinsic flowability of fine powders
  - Cohesion reduction could be about an order of magnitude – usually regardless of the particle shape etc (d/D)
- Particle contact modeling provides design guidelines for the flow and other related properties improvement
  - Two tunable parameters for reducing or “adjusting” cohesion
    - Particle design based on nano-rough contact geometry and contact “surface energy”
  - Granular Bond number is a useful scaling parameter
    - What size should be used as a basis? How to capture entire PSD?
    - How to handle blends (Bond number geometric averaging could help but not enough)?
- Questions and future work (incomplete list):
  - Coating/mixing device modeling and scale-up
  - Improve and validate flow, bulk density, agglomeration prediction models, including for blends
  - Asperity size estimation
  - Material sparing powder flow characterization and prediction
  - Predicting agglomerate sizes as a function of mixing/process conditions
    - Experimental evaluation of agglomerate sizes in blends is a challenge
  - Review papers as well as a perspective papers are needed
  - Role of friction etc

Acknowledgments

- Contributors:
  - Students: M. Azad, L. Beach, M. Capece, L. Chen, Y. Chen, X. Han, Z. Huang, L. Jallo, K. Kunnath, J. Scicolone, D. To, K. Zheng
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