IFPRI Gift Project # 130A

Selection of Flow Aids: Model-based Prediction of Flow Properties Enhancements

PI: Rajesh (Raj) Davé

Siddharth Tripathi, Sangah Kim, Zhixing Lin

New Jersey Institute of Technology, Newark (USA)

Outline

- Review tasks and deliverables
- Equipment (characterization and processing) and leveraged resources
- Technical topics to be covered –
  - Modeling
    - Contact models - review
    - Additive compatibility/suitability and how to select (*not presented; in the backup slides*)
    - Advances needed, validation and model improvements (work in progress)
  - Experimental
    - Materials - mostly fine powders, pharma related, hydrophobic and hydrophilic silicas as flow aids
    - Characterization examples: FFC, agglomeration, dissolution
- IFPRI member interactions, manuscripts
  - Collaborations and input invited on powder materials, characterization and processing

- Tasks (0-36 months)
  - Task 1: Literature search for relevant models
  - Task 2: Development of models
  - Task 3: Database of material properties
  - Task 4: Test/validate particle- contact models
  - Task 5: Dry coating of selected materials; mixer type
  - Task 6: Characterization to assess enhancements
  - Task 7: Test/validate bulk-scale models

- Deliverables (0-24 months; ***these deliverables on track***)
  - D1: A report on currently available predictive models for designing dry coated powders ***[To be included in the annual report]***
  - D2: A database of host materials with comprehensive property measurements ***[To be included in the annual report]***
  - D3: Model(s) for determining the suitability between host and guest particles. ***[Interim update to be included in the annual report]***
  - D4: Model(s) for estimating the ideal amount of guest particles. ***[Interim update to be included in the annual report]***
  - D5: Model(s) for computing the particle adhesion.
  - D6: An interim report on the new models and their validation with available data.

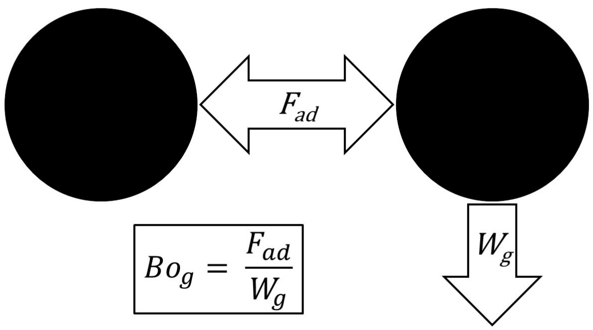
Deliverables	Year 1				Year 2				Year 3			
	Q1-Y1	Q2-Y1	Q3-Y1	Q4-Y1	Q1-Y2	Q2-Y2	Q3-Y2	Q4-Y3	Q1-Y3	Q2-Y3	Q3-Y3	Q4-Y4
Task 1				✓ D1								
Task 2								D6				D12
Task 3				✓ D2								
Task 4								D5				
Task 5							D3, D4					
Task 6										D9		
Task 7										D7, D8	D10	D11

Equipment and leveraged resources

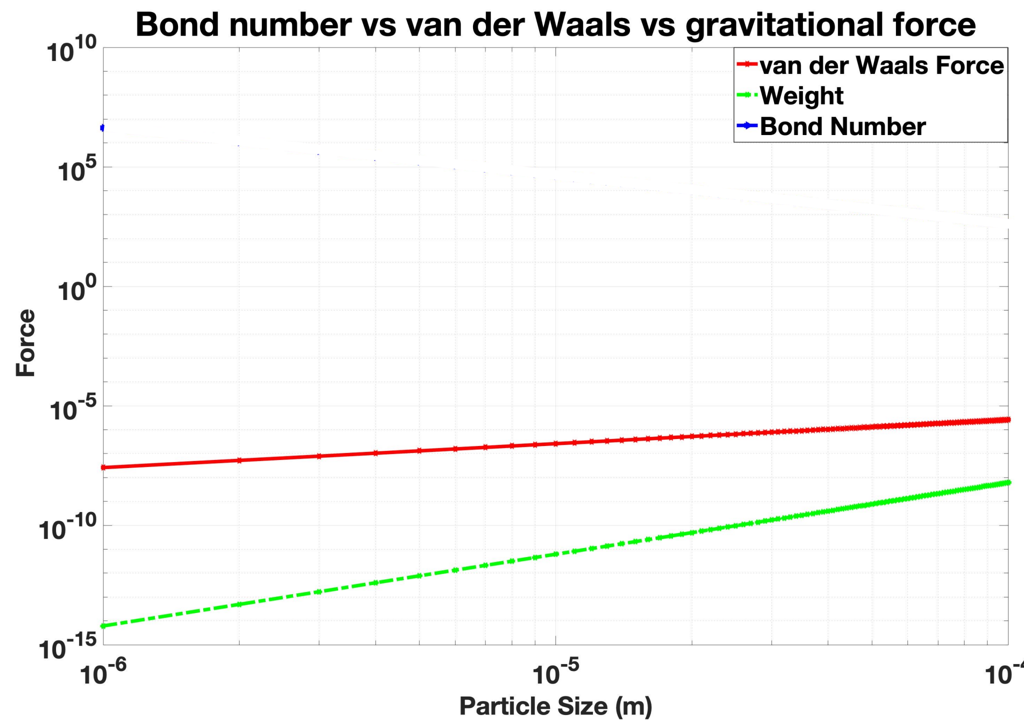
- Processing
  - LabRAM and V-blender as benchmarking batch-operated devices
  - Conical mill (comil) as a continuous, industry relevant device
- Particle Size Measurements, including agglomeration
  - Qualitative: SEM imaging, optical microscopy
  - Quantitative: Sympatec Rodos/Helos, Gradis/QicPic, Coulter LS 13 320 (liquid-dispersion) as needed
- Particle shape, morphology, surface roughness
  - Qualitative: SEM imaging
  - Quantitative planned: Rodos/QicPic, find collaborators for using AFM, possible use of ImageJ Pro usage
- Surface Energy Measurements; Inverse Gas Chromatography – Surface Energy Analyzer from SMS
  - Specific Surface Area: BET
- Powder testing and flowability measurements
  - FT4
    - Flow Function Coefficient, Bulk Density
    - Pending: BFE, Cohesion, Unconfined Yield Strength
  - Several other testers available at NJIT – Flodex, Hosokawa powder tester, etc
    - Collaborated with Granutools for use of GranuPack; further collaborations planned
- Leveraged resources
  - NSF funded synergistic projects
  - Partial TA support for graduate students

Modeling: Review of available models

Cohesion of fine powders



- The ratio of Force of adhesion to weight of particles, termed as "Bond Number" signifies the cohesiveness of powders.



$$F_{ad} = \frac{A * D}{24 * z_o^2}$$

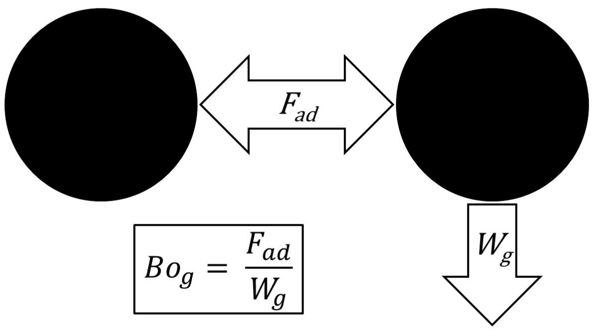
$A = 10^{(-19)}$ J

Z_o = 0.4nm

$$W_g = \frac{\pi}{6} * \rho_p * D_p^3$$

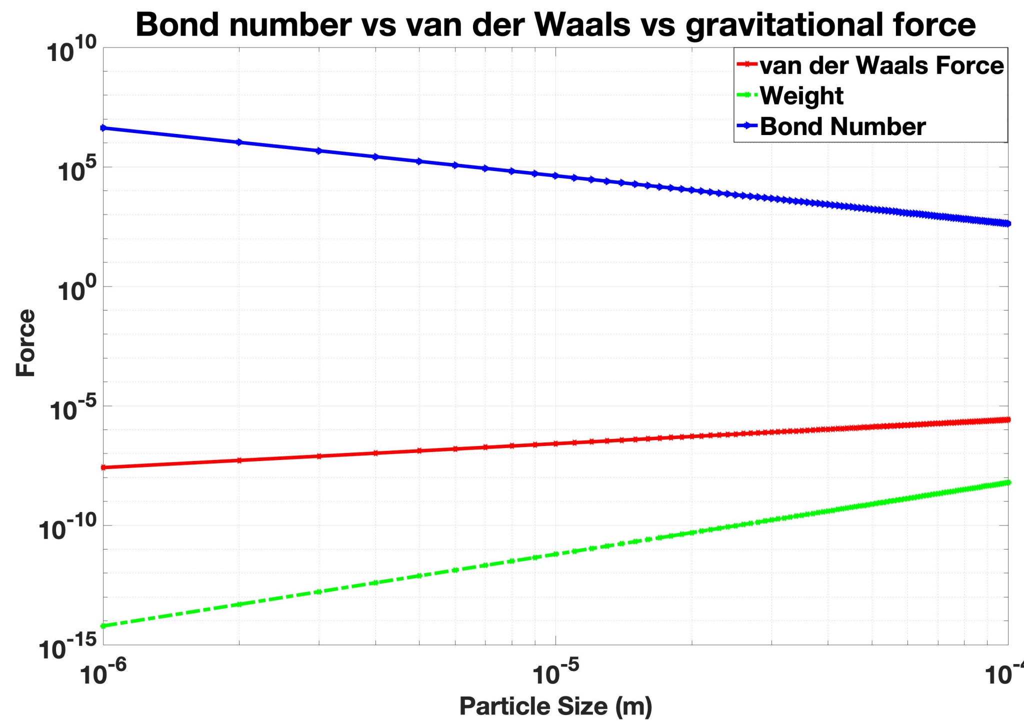
$$B_{og} = \frac{F_{ad}}{w_g}$$

Bond number (dimensionless ratio)



- The ratio of Force of adhesion to weight of particles, termed as “Bond Number” signifies the cohesiveness of powders.

- B_{og}<=1 Free Flowing
- B_{og}>>1 Cohesive



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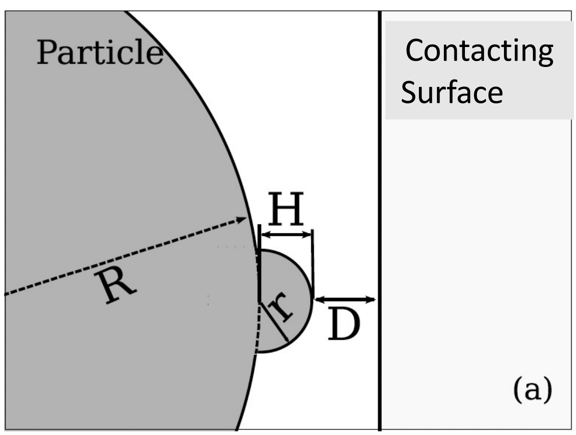
Rumpf model: Preliminary explanation of how dry coating reduces cohesion

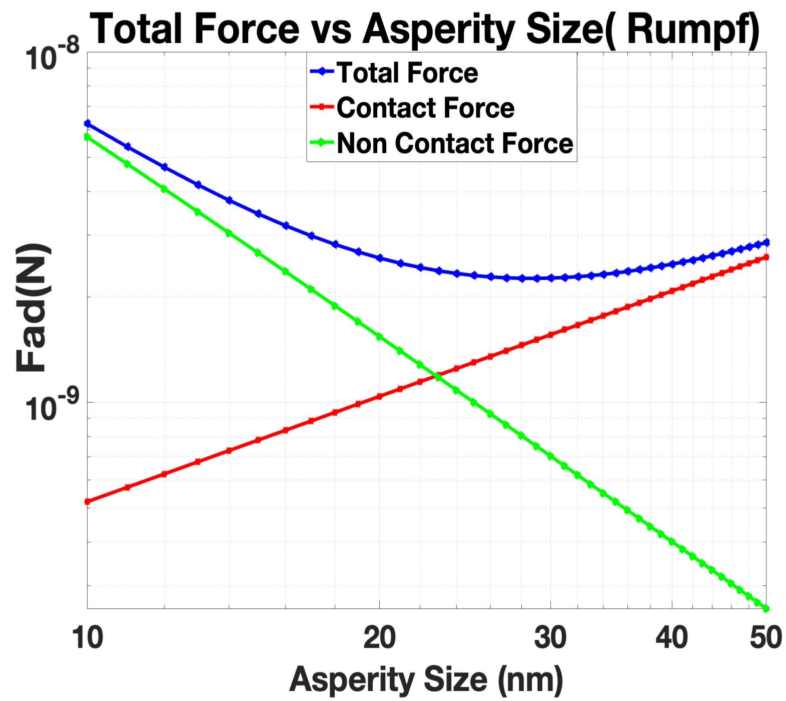
The classical Rumpf theory assumes that the asperity of the rough surface is a single hemispherical element

Particle surface (non-contact)

Asperity-surface (contact)

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





- Contact-term: contact force for asperities bigger than 10 nm dominates as asperity size increases
- Noncontact term: dominates when asperities are very small ~ about a few nanometers or even zero

Unfortunately, this is only a single asperity model

1-D analysis concerning the effect of size of asperities

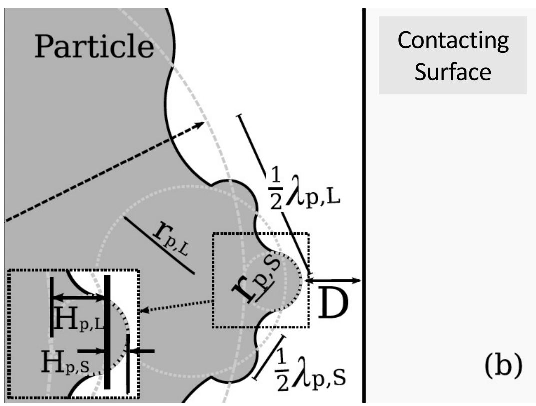
Extension(s) of Rumpf model for rough surfaces

Rabinovitch (Florida) model

Particle surface (non-contact)

Asperity surface (contact)

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

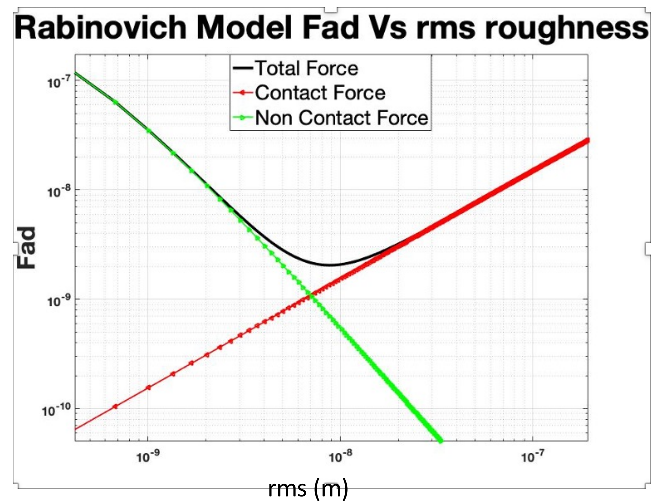


$$r_{i,J} = \frac{\lambda_{i,J}^2}{32k_1 rms_{i,J}}$$

$$H_{i,j} = k_1 rms_{i,J}$$

Parameters from AFM

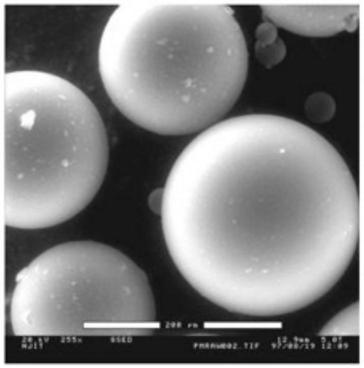
k_1= 1.817



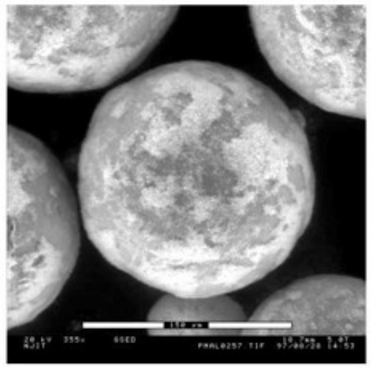
- Still only a single asperity model - one dimensional, only concerns with the effect of size of asperities
- Size and spacing between them related by rms value measured using AFM
- Other recent models marginally extend this one; e.g., Colorado replaced the flat surface (wafer) with a rough one – yet a single asperity model

These models do not explain the role of silica coverage – (surface area coverage - SAC)

Single asperity models cannot account for the flow aid impact accounting for the amount and process intensity/time

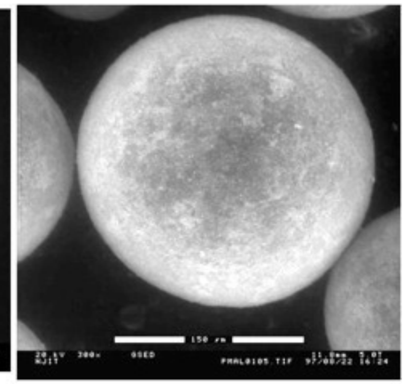


PMMA uncoated

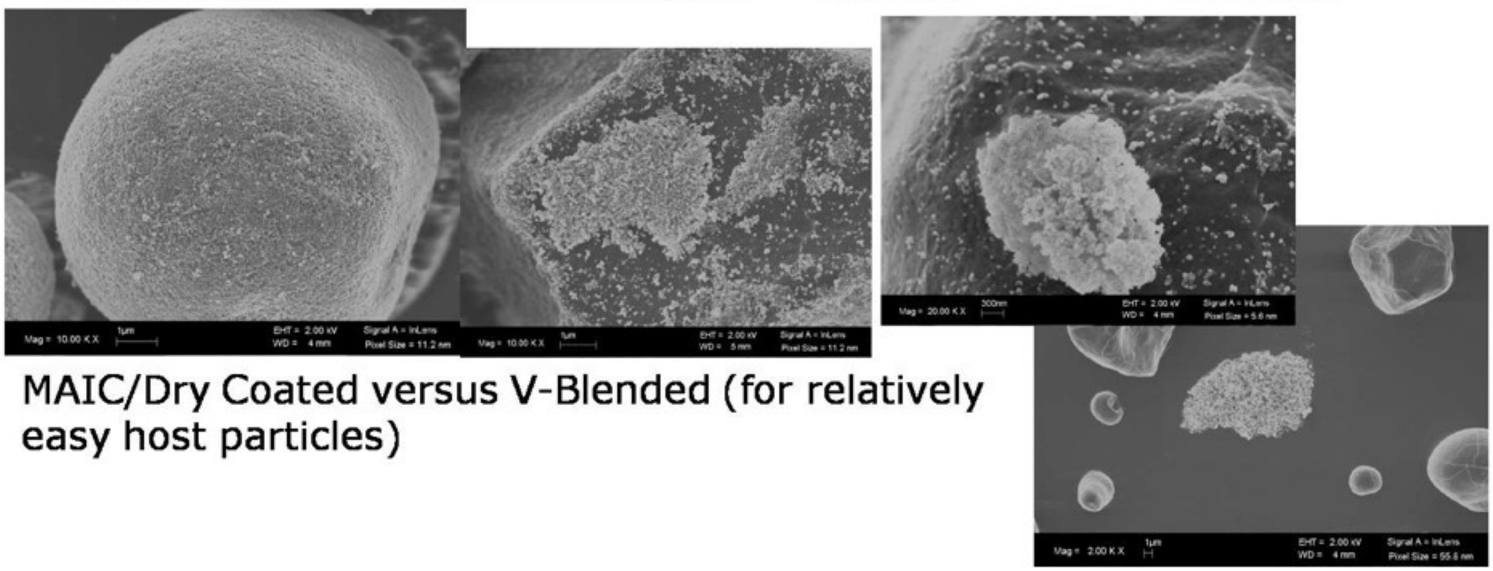


Processed 2.5 minutes

5 minutes



10 minutes

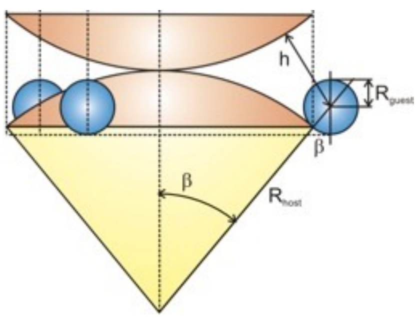


MAIC/Dry Coated versus V-Blended (for relatively easy host particles)

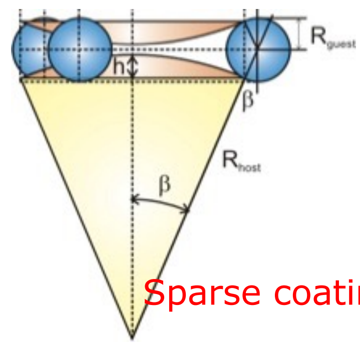
Model accounting for the spatial distribution of asperities (or rough surfaces)

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

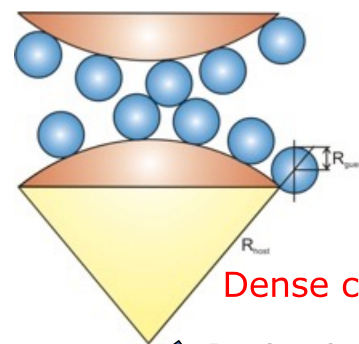


Guest-Host



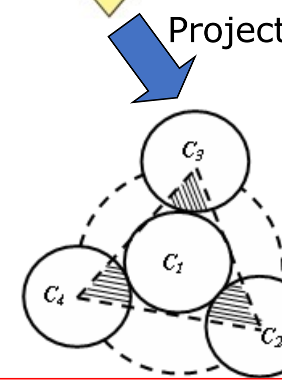
Sparse coating

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

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

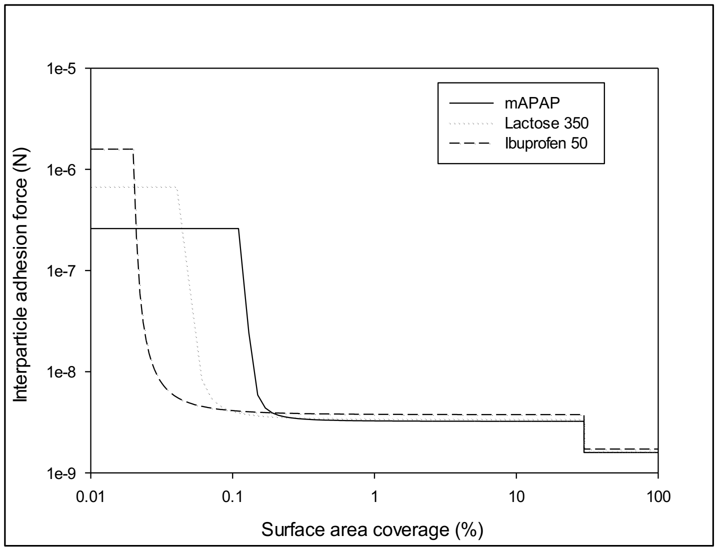
R972+Cornstarch

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

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

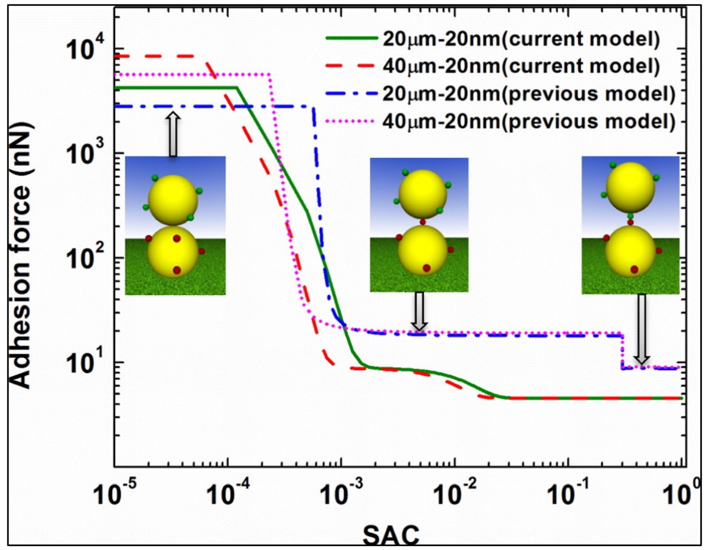
Deterministic and probabilistic models for spatial distribution of asperities

Chen et al. AICHE J (2008)



- The effect of surface area coverage (SAC) on interparticle force
- ~30% SAC enough for G-G contact
- We will provide improved recommendations for the targeted theoretical SAC

Deng et al. Powd. Tech (2017)



- Probability (Monte Carlo) based simulations for computing interparticle force
- Gradual transitions between H-H, H-G and G-G contacts and corresponding adhesion forces reduction

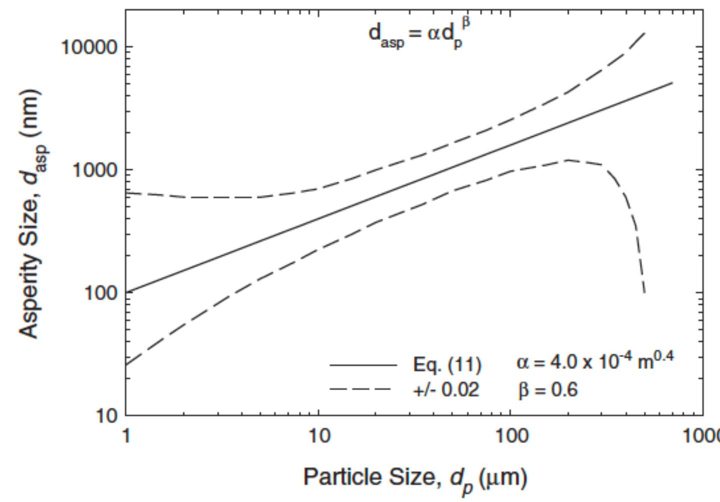
- Two orders of magnitude reduction predicted, while considering multi asperity contacts.
- SAC term to relate distribution of guest on Host particle
- SAC can be controlled and hence force reduction can be tailored
- Dry coating can be modelled, Mechanistic understanding of adhesive force reduction via dry coating

Modeling: Advances needed and work in progress

Contact model assumptions, limitations, challenges

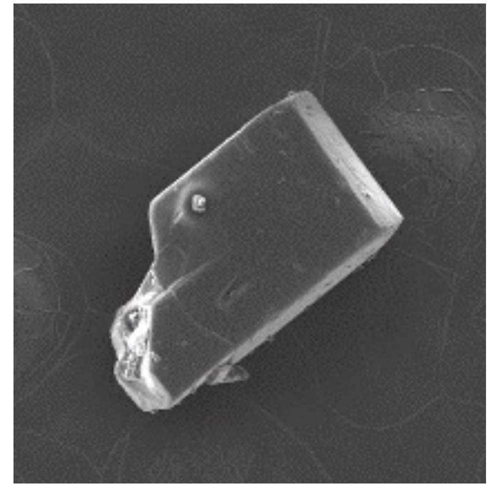
- All classic models and derivatives are single asperity models
  - Yang et al 2005: such models provide good first order estimates of cohesion reduction ~ d/D, or d/D_{asp}
  - Estimating D_{asp} remains a challenge, despite Massimilla/Donsi (200 nm) and Aibing Yu (f(D) – figure on right) recommendations
- A major limitation of single-asperity models: Not able to account for the true impact of flow aid amount and distribution
- Chen et al 2008: Extended single-asperity to multi-asperity to remove single-asperity limitation
  - Limitations: Ideal particle sizes and shapes
    - Mono-sized spherical particles – both host and guest
    - Uniform surface chemistry
    - Monolayer uniform coating of guest (No agglomeration of guests; uniform distribution)
  - Strengths: Predicts highest cohesion reduction at SAC > 30 % based on multi-asperity or guest-guest contact
    - Helps select the flow additive size and its amount
    - Has performed very well for prediction of the extent of adhesion force reduction a variety of ***real*** powders
- Challenges: Addressing limitations
  - Particle shape, surface roughness, asperity size, guest agglomeration, actual SAC (including accurate estimation of host surface area)
  - Effect of process intensity and time (later phase of the project)

Prof. Aibing Yu recommendation

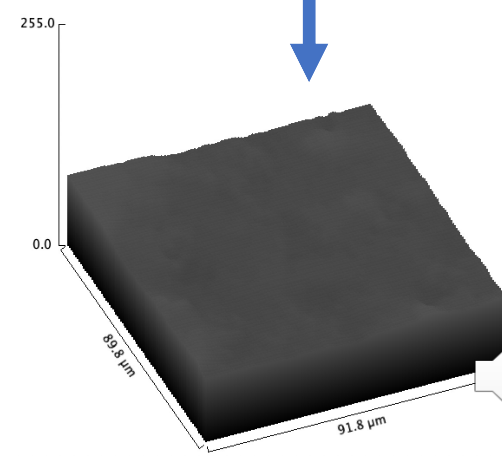


Particle shape and surface roughness effects

- Particle shape – aspect ratio
  - Aspect ratios (D_{major}/D_{minor}) under ~5 do not have significant effect on contact forces
    - Equivalent to increased surface energy (*Deng et al, Granular Matter, 2013*)
    - Dry coating would greatly improve flowability
  - Much greater aspect ratios (needles) reduce flow due to cohesion and interlocking
    - Flow aid (and dry coating) could help reduce cohesion but unlikely to tackle interlocking
- Surface roughness – very smooth or macro-rough particles are more cohesive
  - Acetaminophen – more cohesive due to smooth surface (defies 200 nm asperity size assumption); yet dry coating is more effective
  - Griseofulvin – less cohesive due to macro-roughness (also defies 200 nm assumption); but dry coating is less effective
  - Model under development to explain these effects
  - Accurate estimation of surface roughness remains a tedious/challenging task
    - AFM or SEM based image analysis



Smooth particle - acetaminophen



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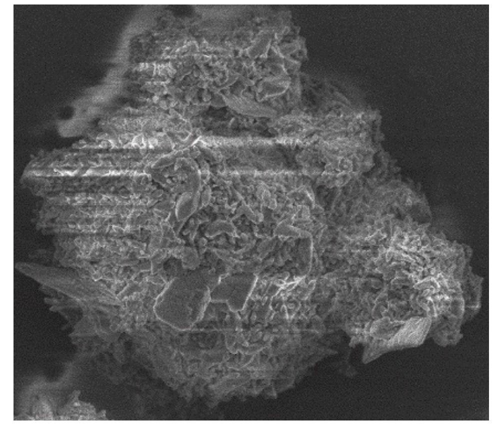
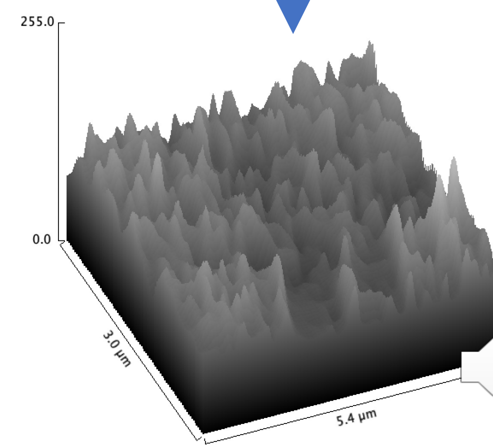
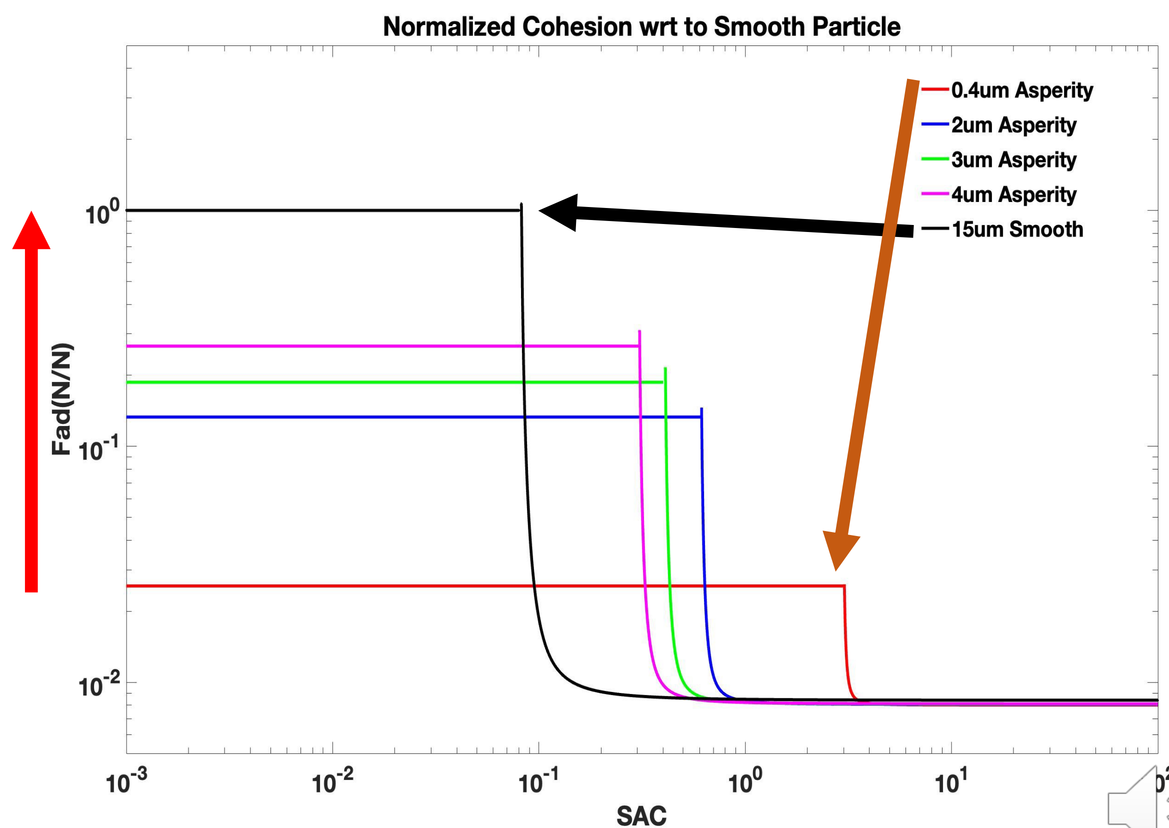


Macro rough particle - griseofulvin



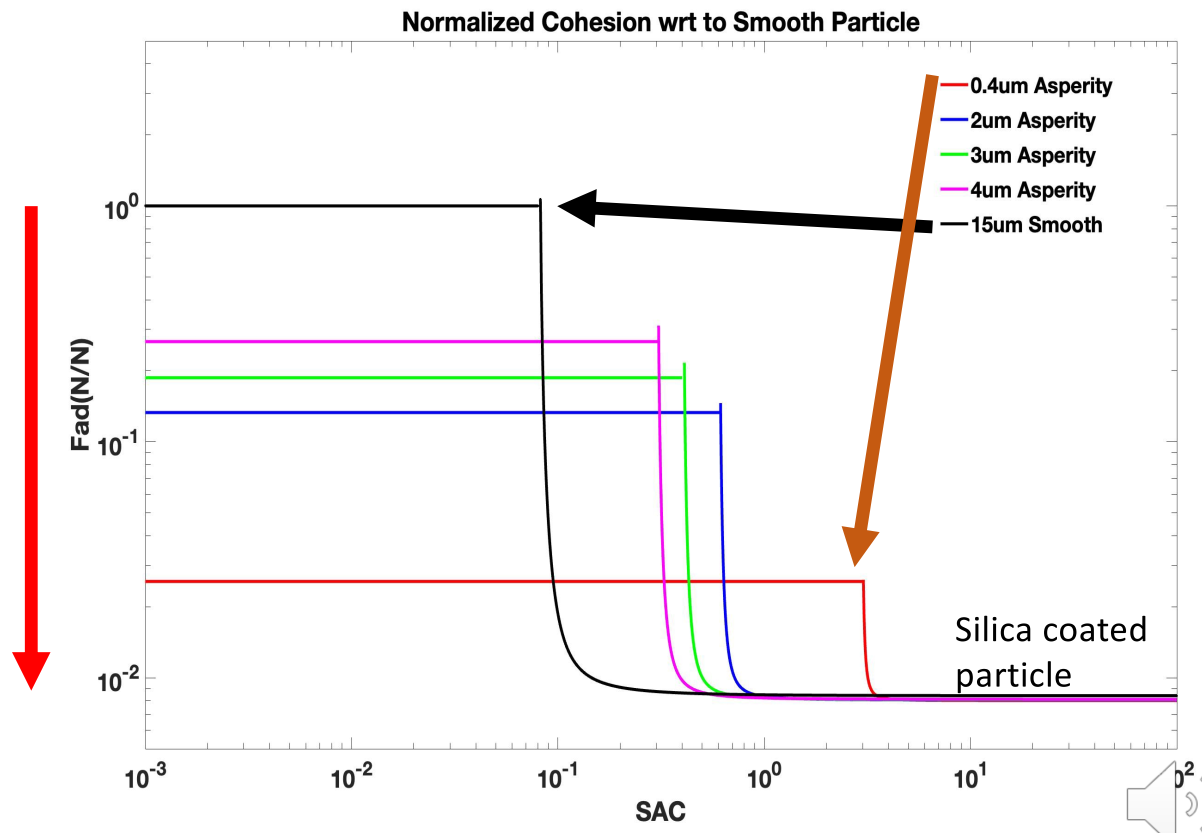
Particle surface roughness effect:
Normalized cohesion for comparison (Uncoated)

Over-estimation of cohesiveness if smooth particle is macro rough



Particle surface roughness effect: Normalized cohesion for comparison (coated)

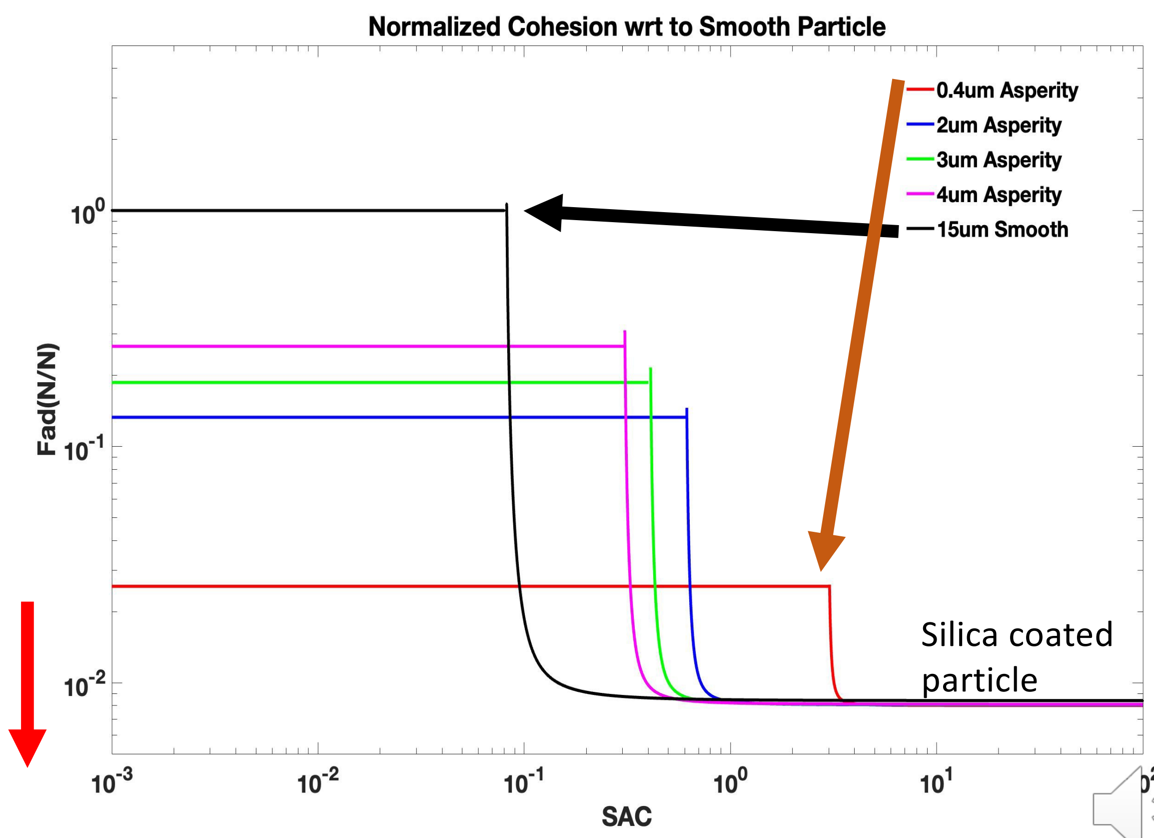
~ 2 order magnitude cohesion reduction after dry coating for smooth particle



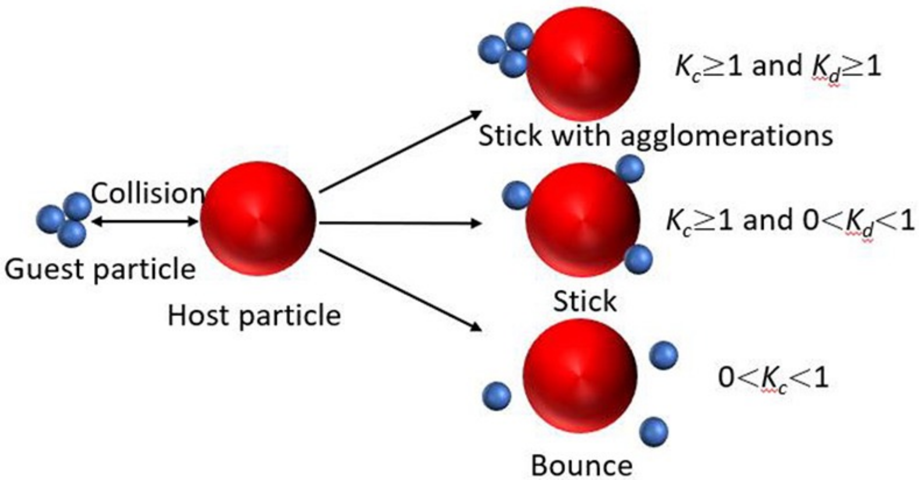
Particle surface roughness effect:
Normalized cohesion for comparison (coated)

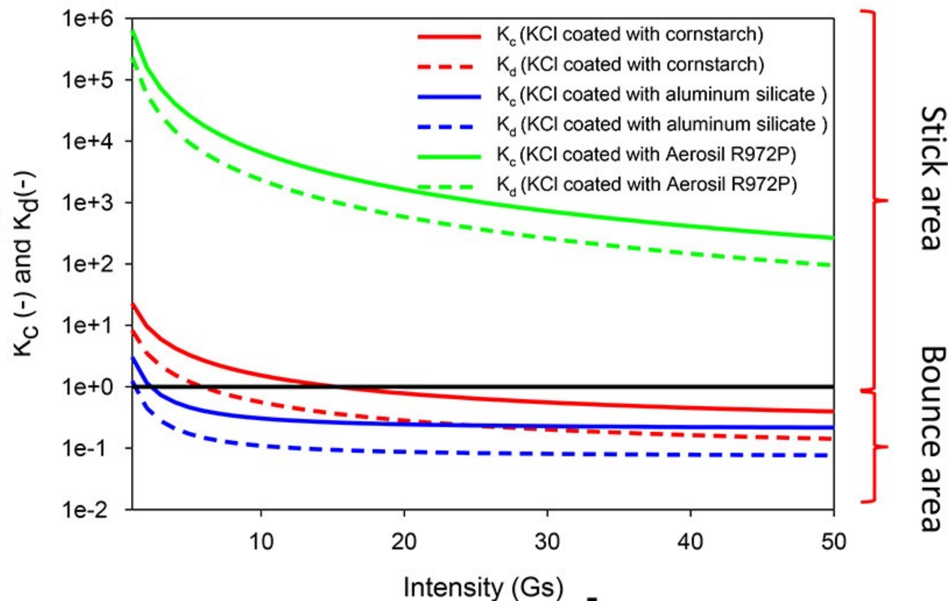
~ 1 order magnitude cohesion reduction after dry coating for rough particle

Initial asperity sizes determines the level of enhancements after silica coating



Effect of process intensity: Fumed silica should work well for dry coating





K_c and K_d predict dry coating performance

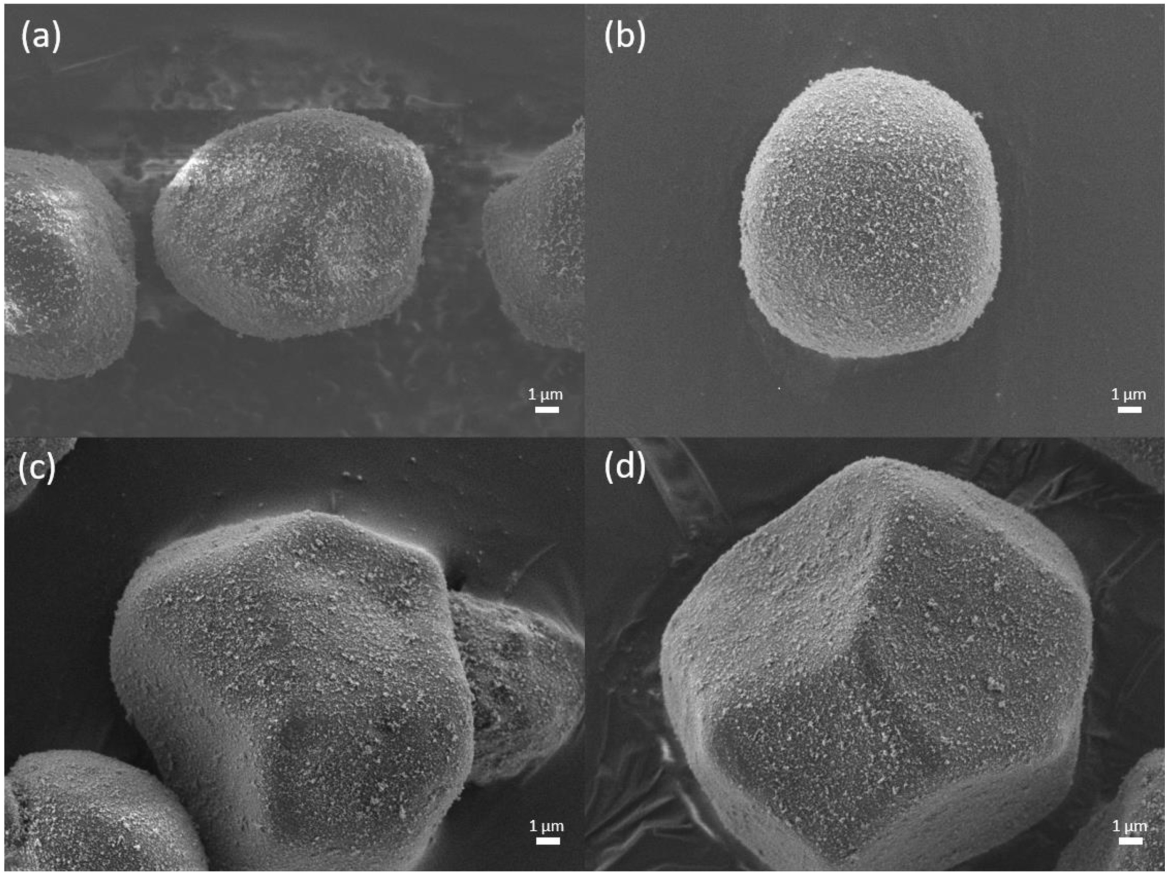
Micro guests detach

Nano guests attach, but form agglomerates

Please refer to Zheng et al. Powd. Tech. (2020) for details

Effect of process intensity: Fumed silica works well for dry coating

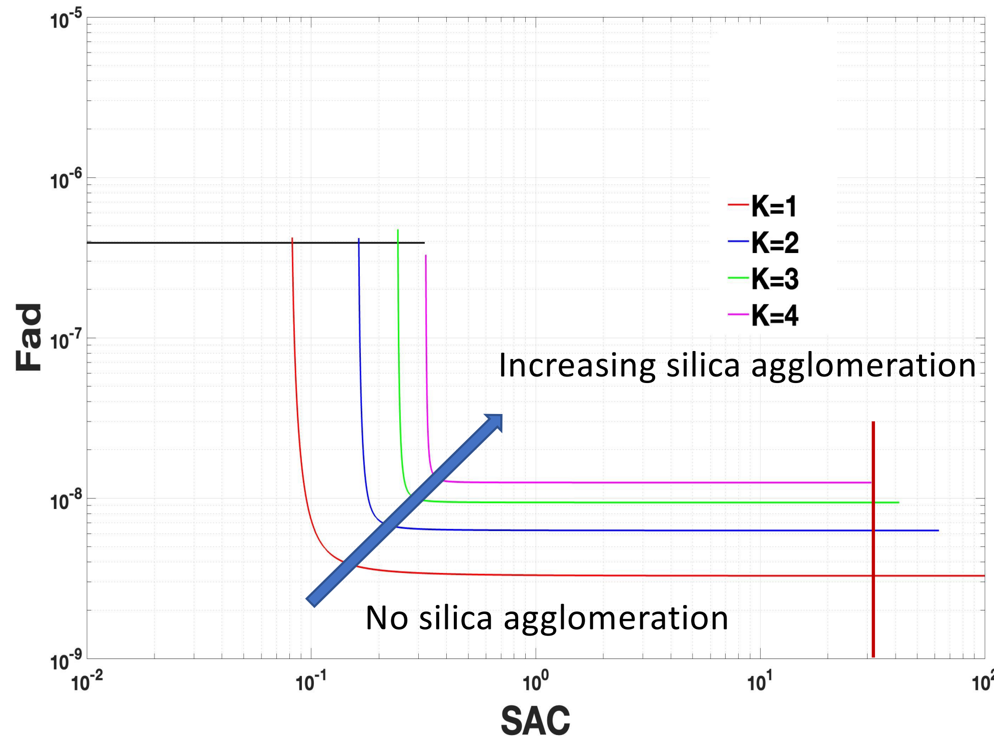
- Nano-sized flow aids, e.g., fumed silica are most suitable for dry coating
- Tend to attach onto the surface of host particles at all process intensities
  - Achieving good dry coating quality
  - The silica particles could form agglomerates at higher silica amounts and process intensities



SEM images of cornstarch coated with Aerosil R972 processed at: (a) 30 Gs, (b) 50 Gs, (c) 70 Gs, (d) 90 Gs.

Effect of guest (silica) agglomeration: Reduced effectiveness for cohesion reduction

- Preliminary model accounts for silica agglomeration: Reduced effectiveness due to two negative/adverse effects
  - The effective surface area coverage (SAC) reduces because of agglomeration
  - The effective asperity size gets enlarged
- The reduction in cohesive force shifts from two orders to one order of magnitude if the agglomeration ratio (K) is 3 or greater
- Further, the assumption of Guest-Guest contact regime may not be satisfied



Experimental

Example materials used

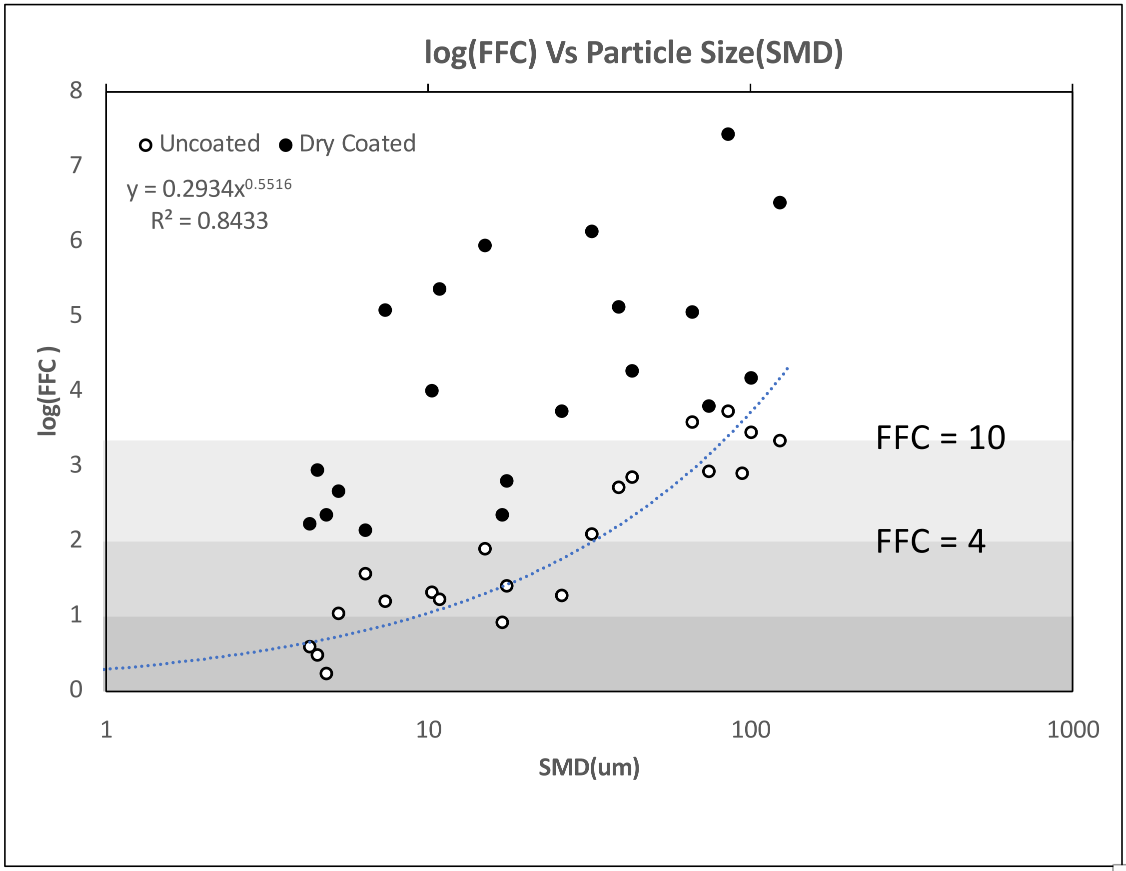
Material	d_{50} (µm)	$d_{3,2}$ (µm)	γ_d (J/m^2)
micronized Acetaminophen (mAPAP)	7.31	4.82	46.38
coarse Acetaminophen (cAPAP)	23.25	17.54	40.86
Ibuprofen 50 (Ibu50)	52.76	32.20	38.92
Ascorbic Acid (AA)	224.28	123.35	41.00
Fenofibrate (FNB)	6.82	4.52	39.50
Griseofulvin (GF)	10.56	6.37	39.70
Itraconazole (ITZ)	10.03	5.26	36.40
Metformin (MTFN)	162.00	94.30	43.70
Theophylline (THPY)	137.00	74.30	44.80

Material	d_{50} (µm)	$d_{3,2}$ (µm)	γ_d (J/m^2)
Cornstarch (CS)	14.37	15.00	32.34
Granulac 200 (Gran200)	27.94	10.27	34.37
Granulac 230 (Gran230)	21.98	7.36	34.37
Lactose 120 (Lac120)	93.87	38.93	37.46
Sorbolac 400 (Sorb400)	8.69	4.29	43.44
Pharmatose 350 (Pharm350)	28.25	26.00	41.82
Pharmatose 450 (Pharm450)	19.19	17.00	44.69
Pharmatose DCL11 (DCL11)	115.37	85.18	39.48
Avicel 101 (Av101)	64.24	42.94	42.33
Avicel 102 (Av102)	116.59	65.97	56.05
Avicel 105 (Av105)	18.97	10.84	47.80
Avicel 200 (Av200)	185.89	100.43	47.11
Pharmacel 101 (Pharm101)	51.40	24.30	51.98

Flowability: FFC (log-base 2) before and after dry coating

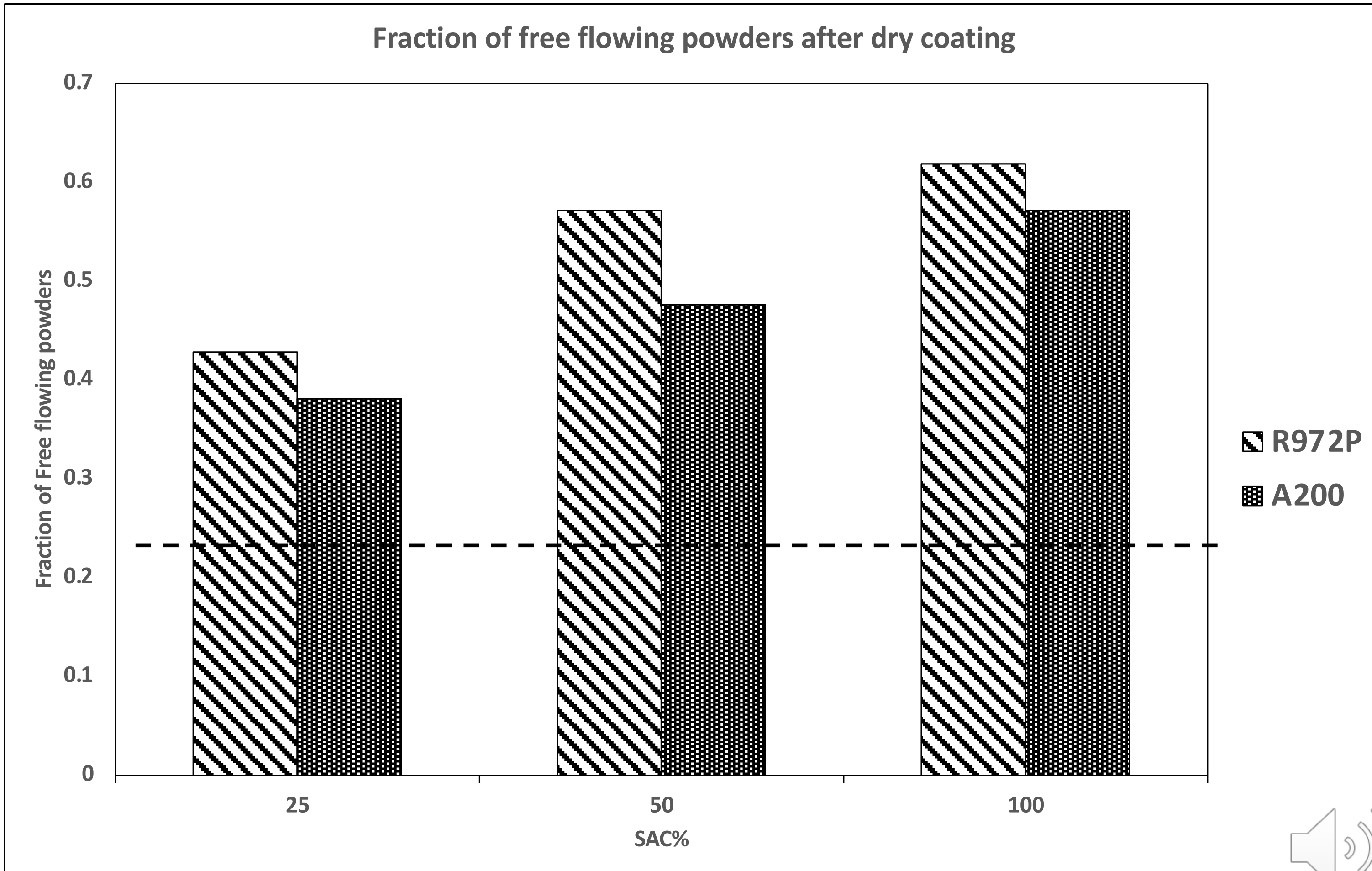
- Flowability remarkably improves after Dry coating
- At least one flow regime improvement after dry coating
- Only 4 powders > 85 microns were free flowing prior to coating

FFC Value	Flow Classification
1 – 2	Very Cohesive
2 – 4	Cohesive
4 – 10	Easy Flowing
> 10	Free Flowing



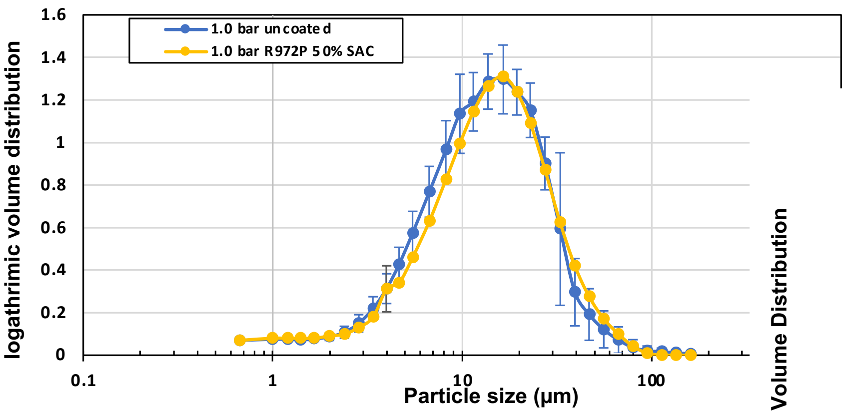
Extent of flow enhancement after dry coating: A full length paper available by 7/22

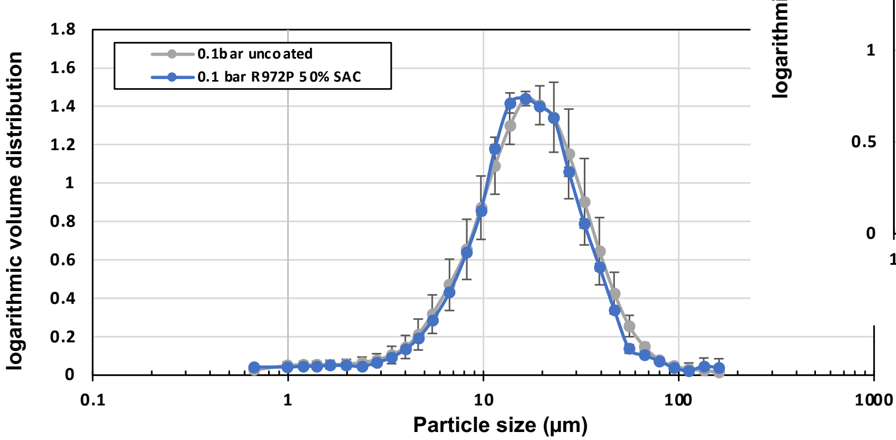
- Both R972P and A200 lead to significant flow improvements at various SAC levels
- Almost 60 % free flowing for 50 or greater SAC %

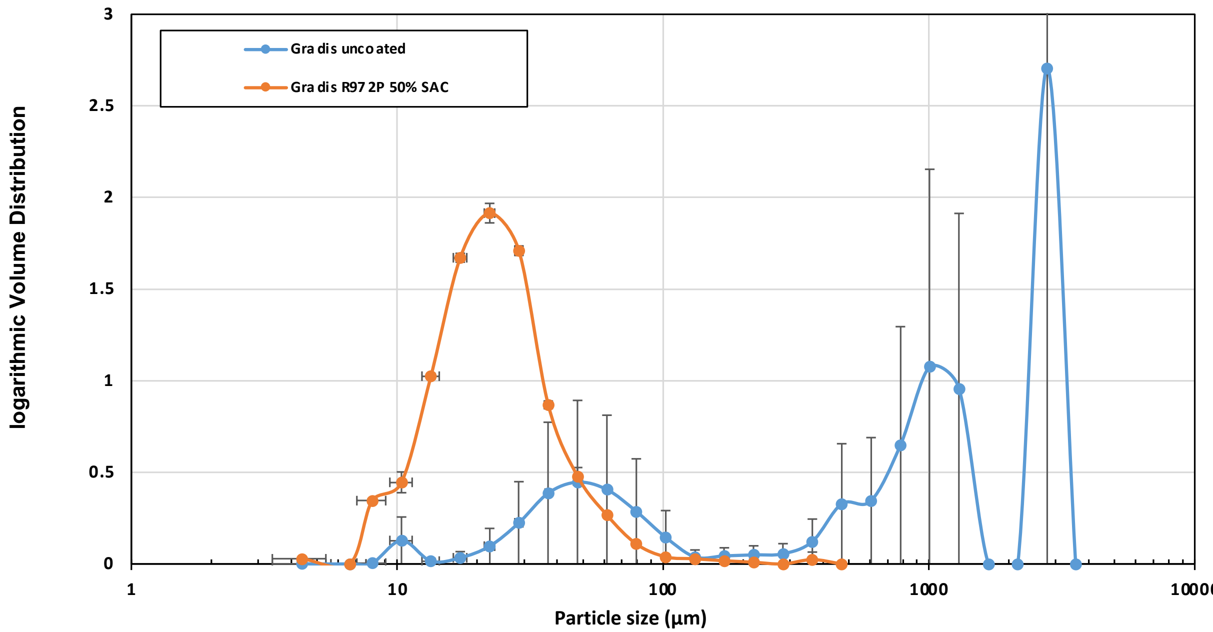


Agglomeration: Assessment, dissolution, and potential as a flow indicator

Milled ibuprofen – dry PSD assessment – nominal milled size 10 microns

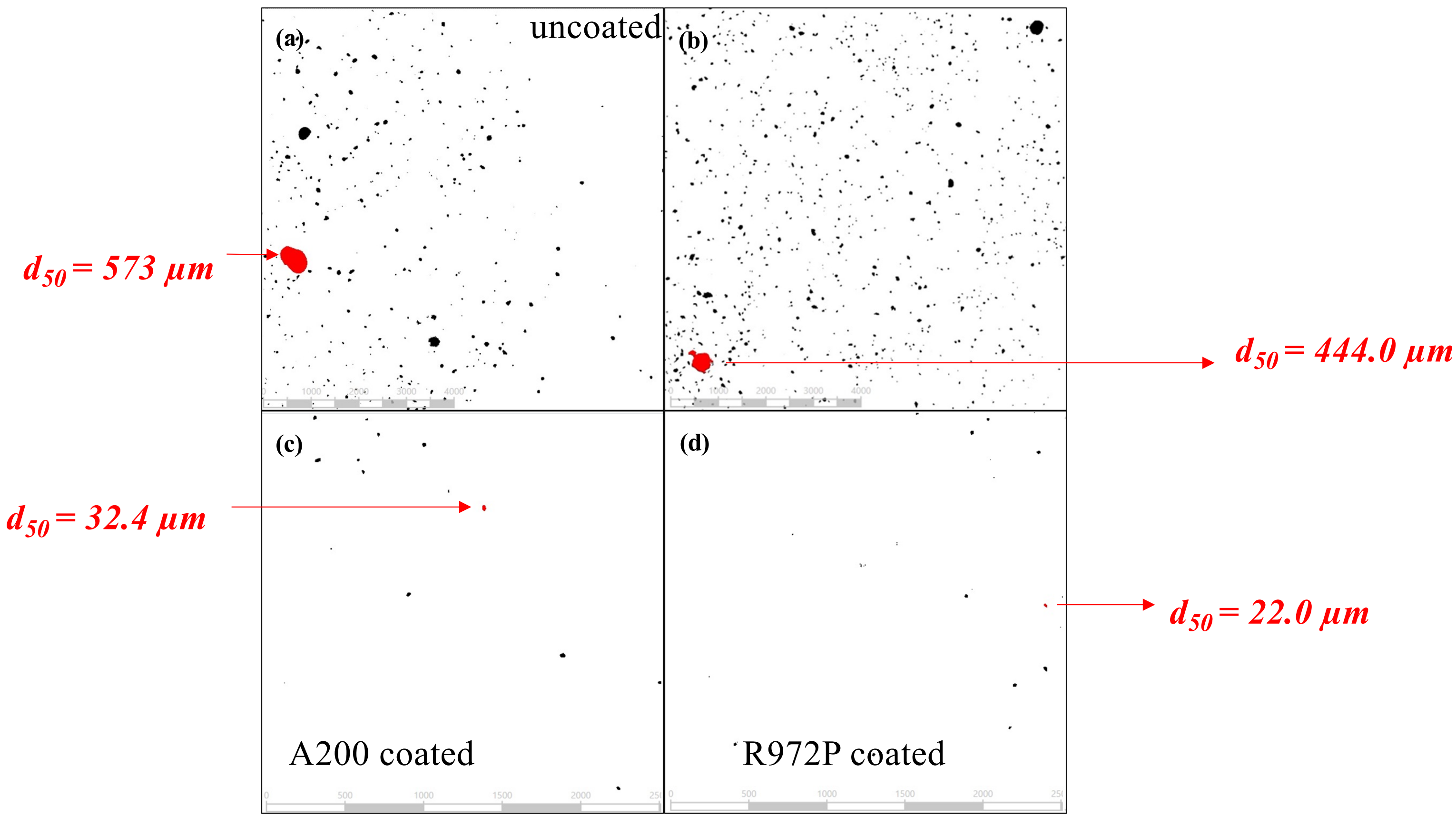


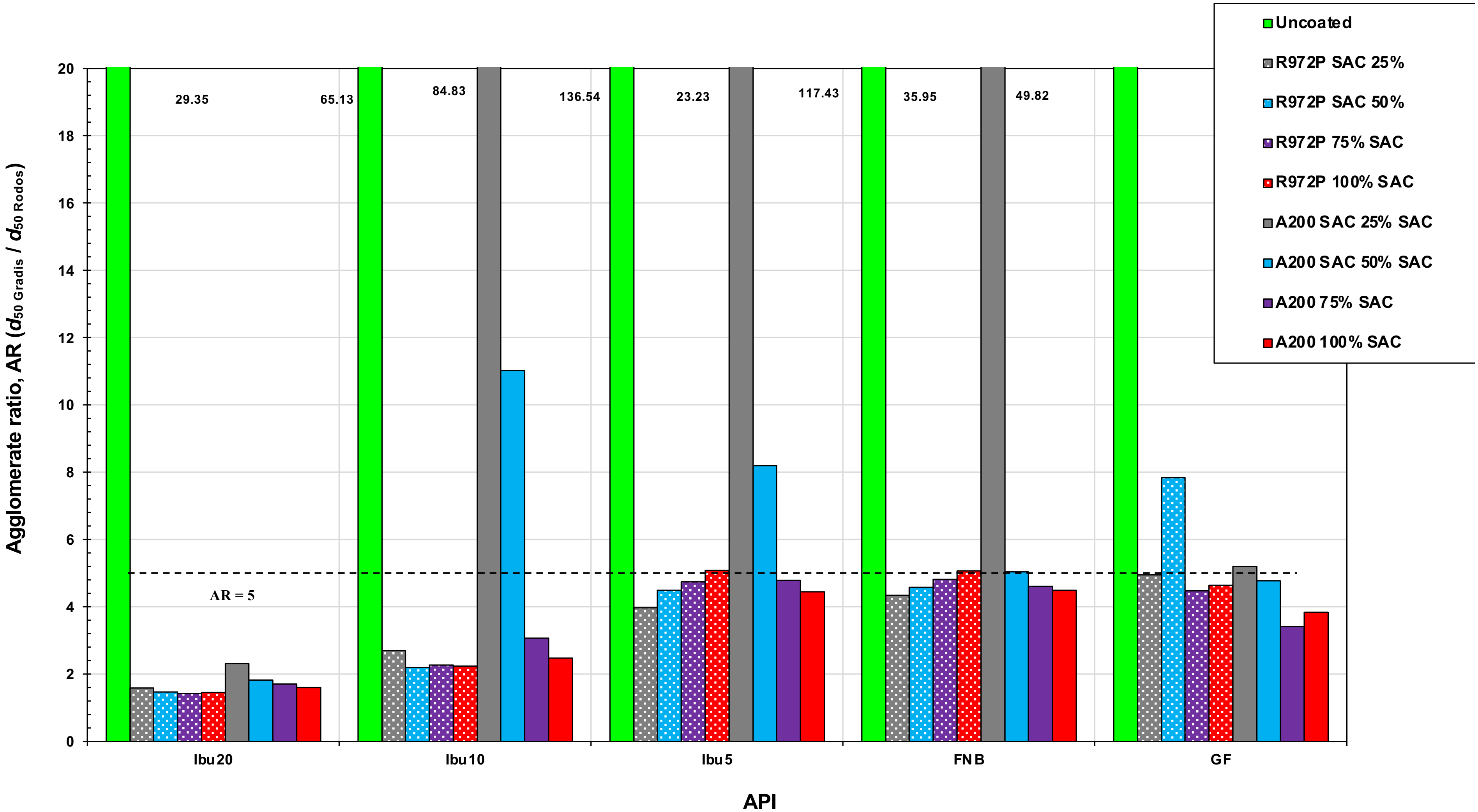




Images using Gradis/QicPic

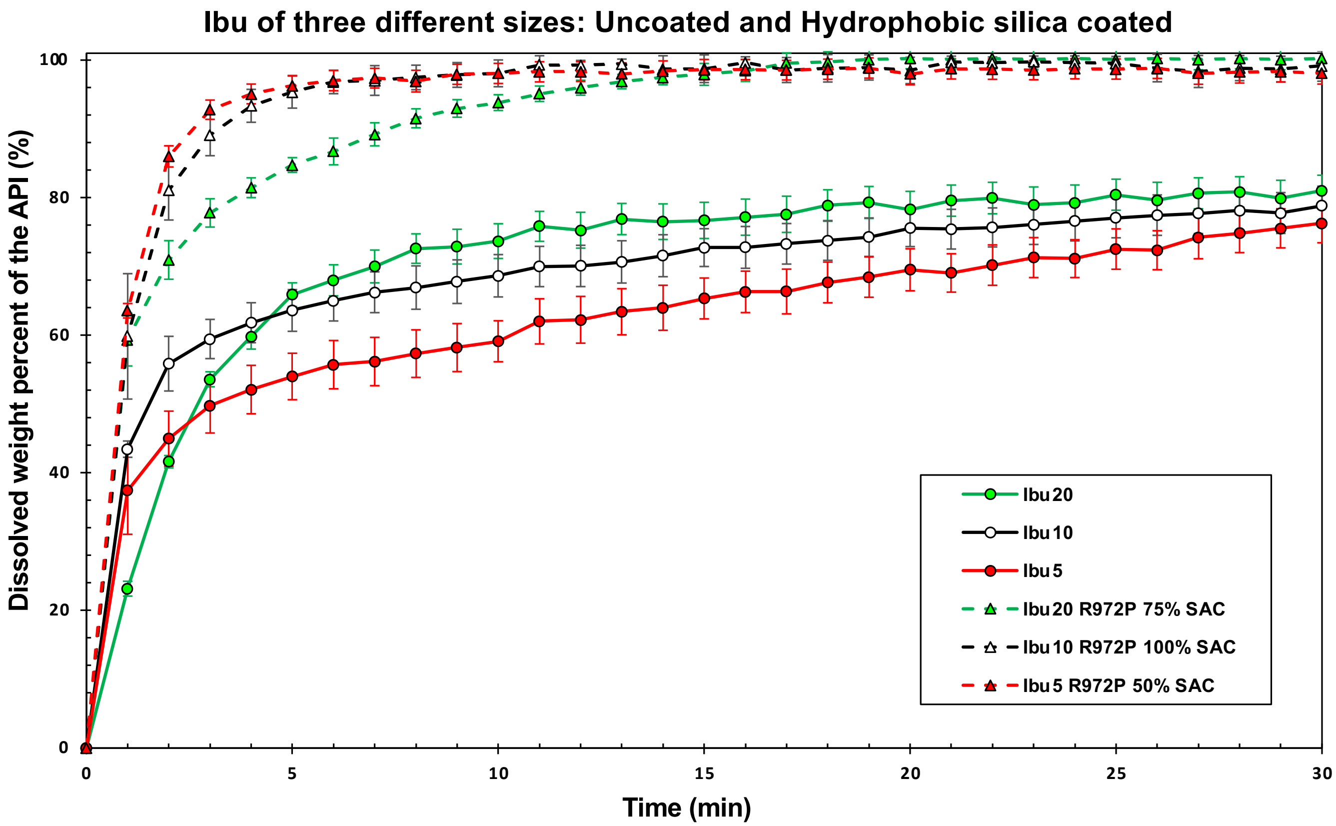
Milled ibuprofen – nominal milled size 10 microns



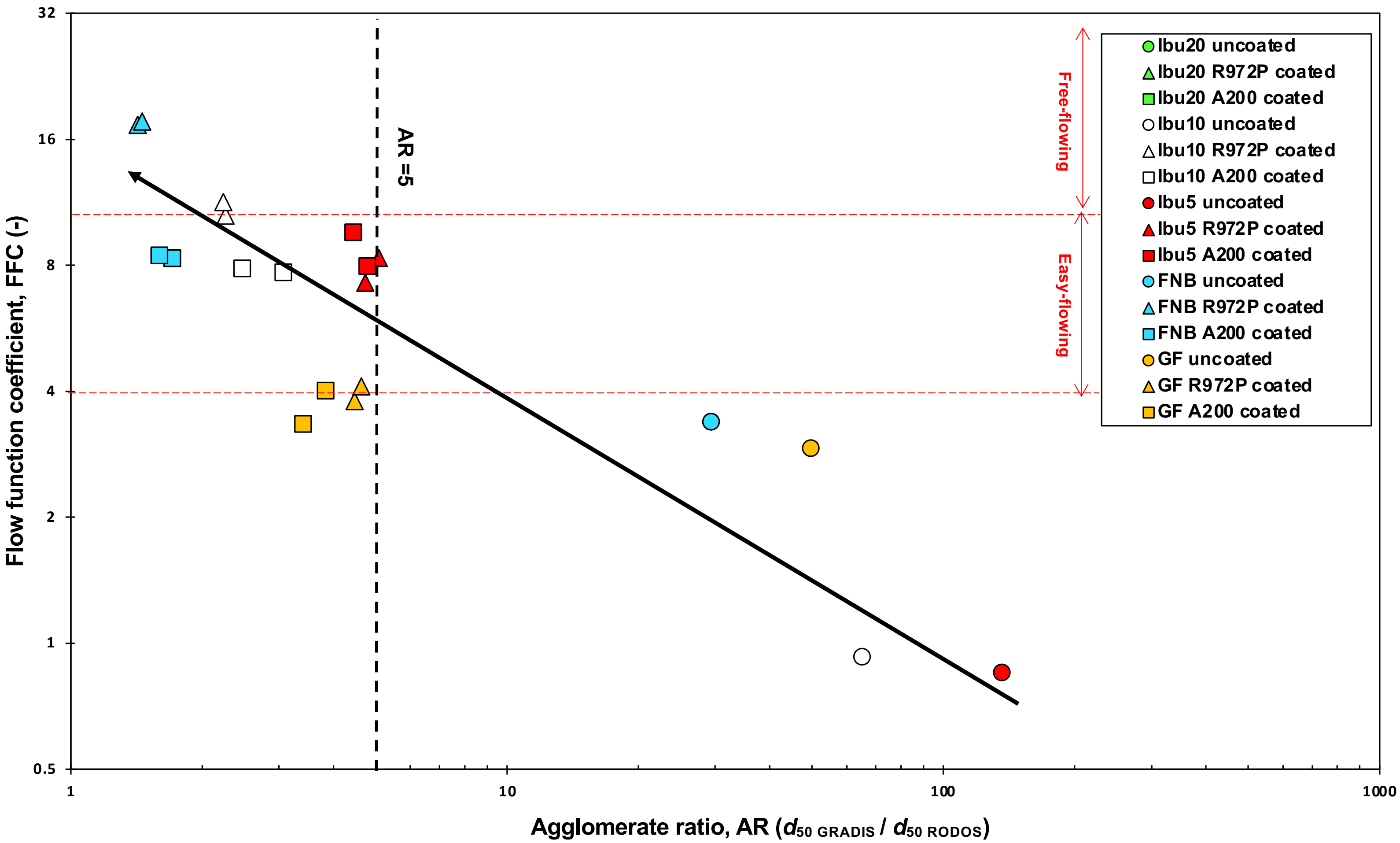


Agglomerate ratio, AR ($d_{50\ Gradis}$ / $d_{50\ Rodos}$)
0
2
4
6
8
10
12
14
16
18
20
29.35
65.13
84.83
136.54
23.23
117.43
35.95
49.82
AR = 5
Ibu20
Ibu10
Ibu5
FNB
GF
API
Uncoated
R972P SAC 25%
R972P SAC 50%
R972P 75% SAC
R972P 100% SAC
A200 SAC 25% SAC
A200 SAC 50% SAC
A200 75% SAC
A200 100% SAC

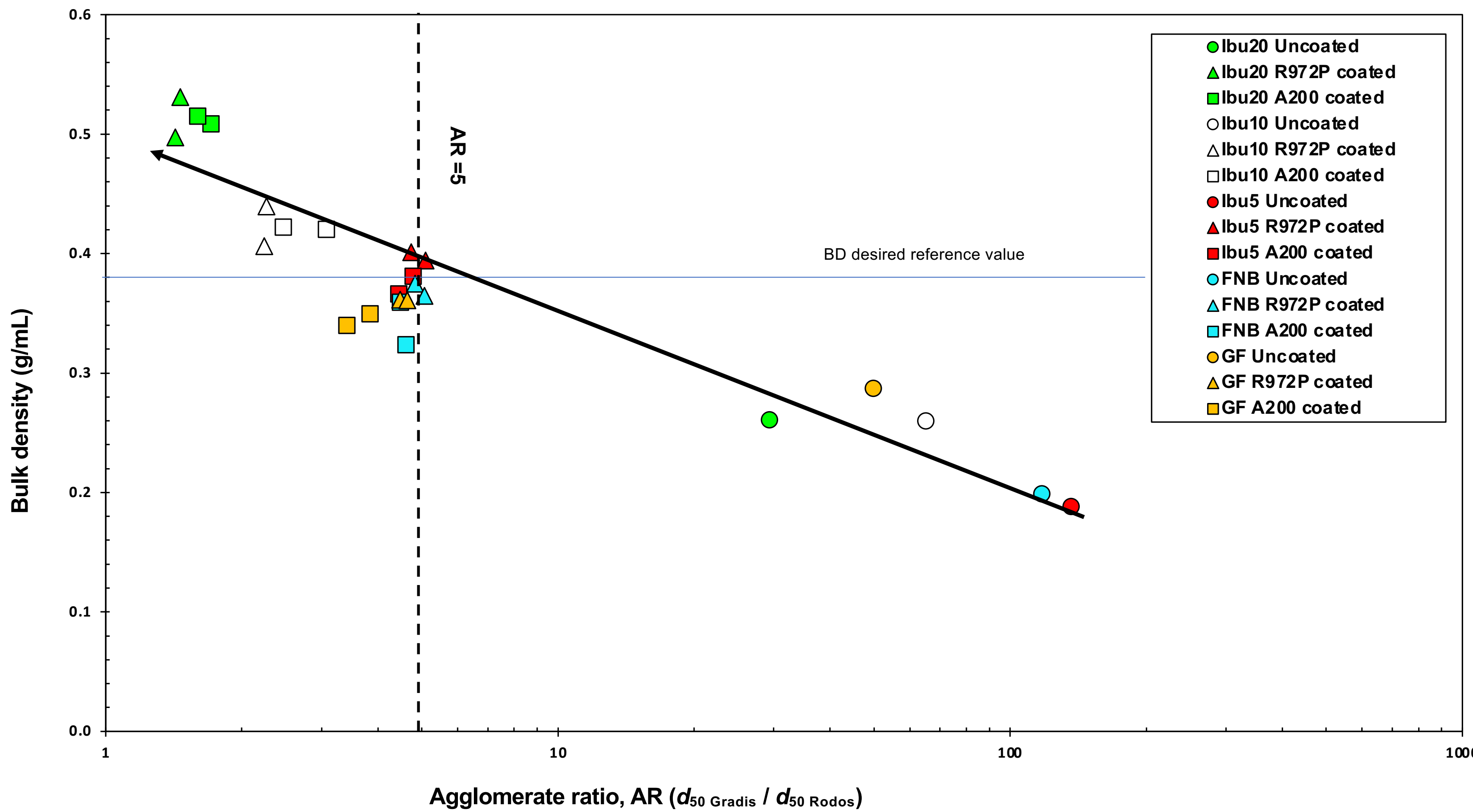
Ibu5, Ibu10, Ibu20 dry coated with hydrophobic R972P: dissolution enhancement



Possible relation between Agglomerate Ratio (AR) and the FFC values



Possible relation between Agglomerate Ratio (AR) and the bulk density



Ongoing work, IFPRI member interactions, papers/manuscripts

- Work in progress
  - New or extended models: guest-host compatibility, guest amount, contact models to account for surface roughness and particle shape, models to link particle scale to bulk scale properties
  - Characterization: Assessing surface roughness via SEM imaging, more accurately measure powder surface area and powder agglomeration, complete set of bulk property characterization for the database
- IFPRI member interactions
  - Ongoing meetings with IFPRI Project Liaisons, additional members welcome
  - Seeking input on test/surrogate materials, specialized characterization, processing equipment
  - Planning tutorials and a workshop – early Spring 2023
- Papers and manuscripts
  - Published/Accepted
    - *International Journal of Pharmaceutics*, 606, 120853, 2021.
    - *AIChE Journal*, 68 (4), e17603, April 2022.
    - *Pharmaceutical Research*, submitted March 2022, accepted May 2022.
  - In preparation (targeted submission during 2022)
    - Blend uniformity enhancements for low active-loaded blends synergist effect of minute amount of silica in a blend
    - Flow enhancements of ~20 different fine powders
    - Perspective article on contact models – challenges and opportunities
    - The impact of powder surface macro-roughness on cohesion and powder bulk properties

Thank you

Backup slides

- Surface energy and host-guest compatibility
- SEM images after coating

Evonik silica (Measured in 2021 and 2022) ** Fresh batch	Dispersive SE (mJ/m2)	Polar SE (mJ/m2)
R972P	37.7	5.1
A200	48.7	4.7

Evonik silica (Measured around 2016 - 2018)	Dispersive SE (mJ/m2)	Polar SE (mJ/m2)
R972P	36.4	2
A200	42.8	21

Experimental results from NJIT group using SMS IGC/SEA but at different time points.

Xihan et al. 2013

Table 2. Surface Energy of as Received Host Material (Ibuprofen 50), Guest Materials, and Uncoated 5 µm Ibuprofen

	LW Dispersion Component of Surface Energy (mJ/m^2)	Lewis Acid–Base Component of Surface Energy (mJ/m^2)
Ibuprofen 50	29.9	5.50
UC-IBU-5	54.4	4.70
Silica M5P	36.5	21.2
Silica TS530	34.1	2.00

Table I. Glidant Material Properties

Maxx and Sunkara 2018

Glidant	Nominal size, d_g (nm)	Dispersive surface energy, γ_d (mJ/m^2)	Total Surface energy, γ (mJ/m^2)	Surface Property
Cab-O-Sil M5P	20	48.41	51.83	Hydrophilic
Aerosil R972	16	22.17	24.65	Hydrophobic
Aerosil 200	12	35.39	37.64	Hydrophilic

Maxx	disp	polarity	
R972P	22.17	2.48	24.65
A200	35.39	2.25	37.64

Table 1
Key particle and material properties of as received powders.

Materials	Particle size d_{50} (µm)	True density (g/cm^3)	*Dispersive surface energy (mJ/m^2)
Aerosil 200	0.012	2.2	42.8
R972P	0.020	2.65	36.4
Avicel PH-102	122	1.56	47.43
Avicel PH-101	66	1.56	46.35
Avicel PH-105	20	1.56	47.66
Prosolv 50	51	1.54	n/a
Prosolv 90	93	1.54	n/a

* Dispersive surface energy of selected materials are from (Rajesh Dave, 2017), n/a: not available.

Chen et al. 2018 & Dave 2017 (Patent application)

Reported results from the publicly available research resources

Surface energy measurements for APIs including milled ones (hosts) and nano-silica (guests) and their compatibility assessment through *coating quality index*

(Previous data for silica SE values)

API and silica	Dispersive SE (mJ/m2)	Polar SE (mJ/m2)	$\left\|{}^{B/A}\lambda - {}^{A/B}\lambda\right\|$ For R972P	Expected coating quality with R972P	$\left\|{}^{B/A}\lambda - {}^{A/B}\lambda\right\|$ For A200	Expected coating quality with A200
R972P	36.4	2	-	-	-	-
A200	42.8	21	-	-	-	-
Ibu20	50.1	5.9	35.2	Good	16.0	Good
Ibu10	47.3	8.1	34.0	Good	17.2	Good
Ibu5	83.7	24.6	139.8	Good	88.6	Good
FNB (milled)	44.0	6.3	23.6	Good	27.6	Good
GF (As received)	40.5	4.5	13.1	Good	38.1	Good

Surface energy measurements for APIs including milled ones (hosts) and nano-silica (guests) and their compatibility assessment through *coating quality index*

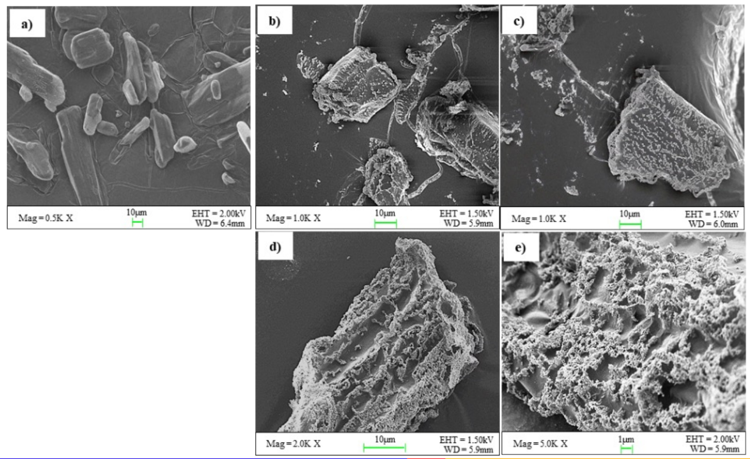
(Recent data for silica SE values)

API and silica	Dispersive SE (mJ/m2)	Polar SE (mJ/m2)	$\left|{}^{B/A}\lambda - {}^{A/B}\lambda\right|$ For R972P	Expected coating quality with R972P	$\left|{}^{B/A}\lambda - {}^{A/B}\lambda\right|$ For A200	Expected coating quality with A200
R972P	37.7	5.1	-	-	-	-
A200	48.7	4.7	-	-	-	-
Ibu20	50.1	5.9	26.4	Very good	5.2	Mediocre
Ibu10	47.3	8.1	25.2	Very good	4.0	Poor
Ibu5	83.7	24.6	131.0	Very good	109.8	Very good
FNB (milled)	44.0	6.3	14.8	Very good	6.3	Mediocre
GF (As received)	40.5	4.5	4.3	Poor	16.8	Very good

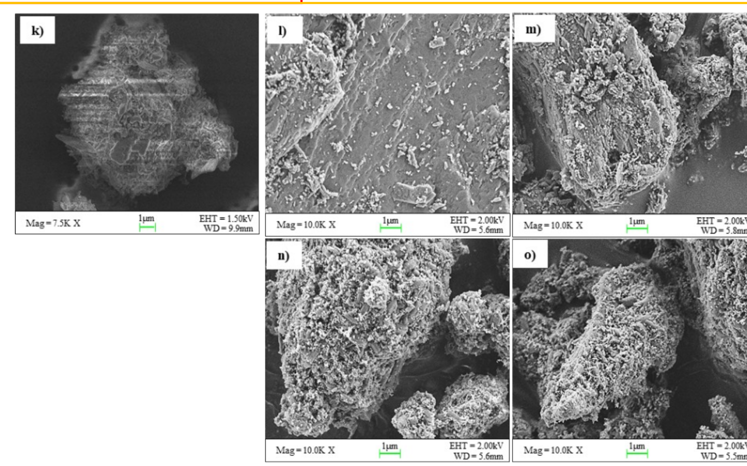
	Coating quality index					
Data from 2021 - 2022	SE Differential FNB R972P	14.8	Good	SE Differential FNB A200	6.3	Mediocre
	SE Differential GF R972P	4.3	Poor	SE Differential GF A200	16.8	Good
	SE Differential Ibu20 R972P	26.4	Good	SE Differential Ibu20 A200	5.2	Mediocre
	SE Differential Ibu10 R972P	25.2	Good	SE Differential Ibu10 A200	4.0	Poor
	SE Differential Ibu5 R972P	131.0	good	SE Differential Ibu5 A200	109.8	good
Data from 2016 – 2018	SE Differential FNB R972P	23.6	Good	SE Differential FNB R972P	27.2	Good
	SE Differential GF R972P	13.1	Good	SE Differential GF R972P	37.7	Good
	SE Differential Ibu20 R972P	35.2	good	SE Differential Ibu20 R972P	15.6	good
	SE Differential Ibu10 R972P	34.0	Good	SE Differential Ibu10 R972P	16.8	Good
	SE Differential Ibu5 R972P	139.8	good	SE Differential Ibu5 R972P	89.0	good

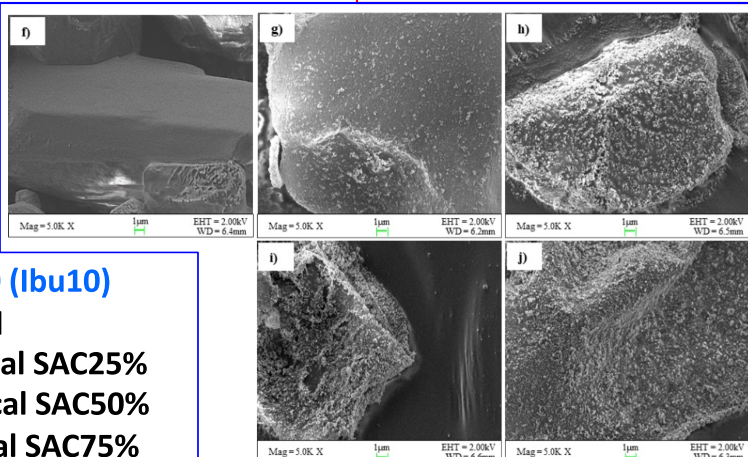
SEM images before and after the coating

Ibuprofen20 (Ibu20)
(a) Uncoated
(b) theoretical SAC25%
(c) theoretical SAC50%
(d) theoretical SAC75%
(e) theoretical SAC100%.



Griseofulvin (GF)
(k) Uncoated
(l) theoretical SAC25%
(m) theoretical SAC50%
(n) theoretical SAC75%
(o) theoretical SAC100%.





Ibuprofen10 (Ibu10)
(f) Uncoated
(g) theoretical SAC25%
(h) theoretical SAC50%
(i) theoretical SAC75%
(j) theoretical SAC100%.