Dry Coating Approaches to Enhance Powder Properties

Raimundo Ho, Process R&D

Maxx Capece, Drug Product Development

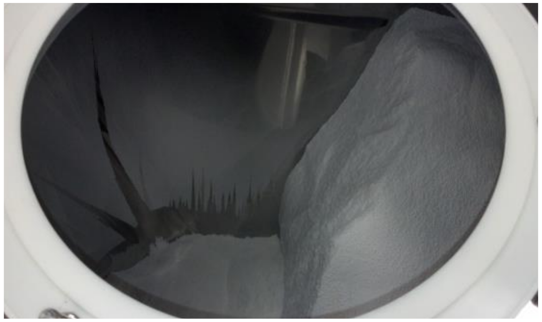
July 13, 2022

Presented at the FDA and M-CERSI Workshop ‘Co-Processed API’

abbvie

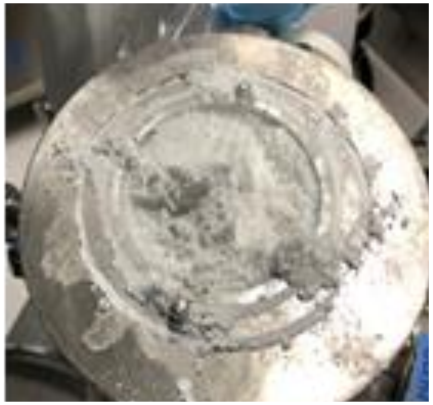
Challenges with Poor Physical Properties

Good powder flowability is essential to pharmaceutical processes



Powder flowability affects:

- Mixing/blending
- Segregation
- Feeding/transfer/hopper flow
- Coating
- Fluidization
- Capsule filling
- Die filling/tableting



Consequences of poor powder flowability:

- Unacceptable DP content uniformity
- Variable tablet/capsule weights
- Variable potency
- Complicates manufacturing
- Reduces manufacturing efficiency (addition of granulation steps)
- Complicates product/process development

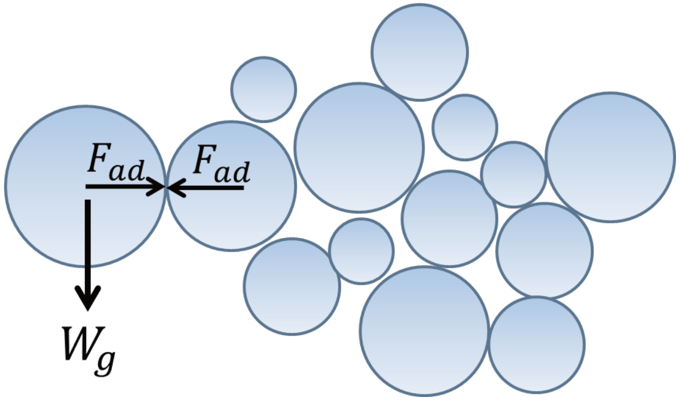
Concept of Granular Bond Number

Inter-particle cohesion parameter (Granular Bond Number):

$$Bo_g = \frac{F_{\text{cohesion}}}{F_{\text{non-cohesive}}}$$

Nase et al., Powder Tech. 116 (2001) 214-223.

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



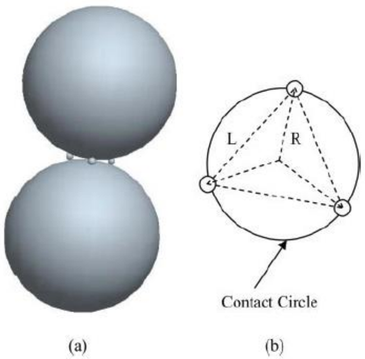
$Bo_g \gg 1$
Cohesive

$Bo_g < 1$
Non-cohesive/Free Flowing

Adhesion Force Model

Adhesive force between two particles:

$$F_{ad} = \frac{A}{16\pi}\left(\frac{1}{l_0^2}\frac{d_p}{2} + \frac{3}{z_0^2}\frac{d_p d_{asp}}{d_p + d_{asp}}\right)$$



Chen et al., AIChE Journal 54 (2008) 104-121.

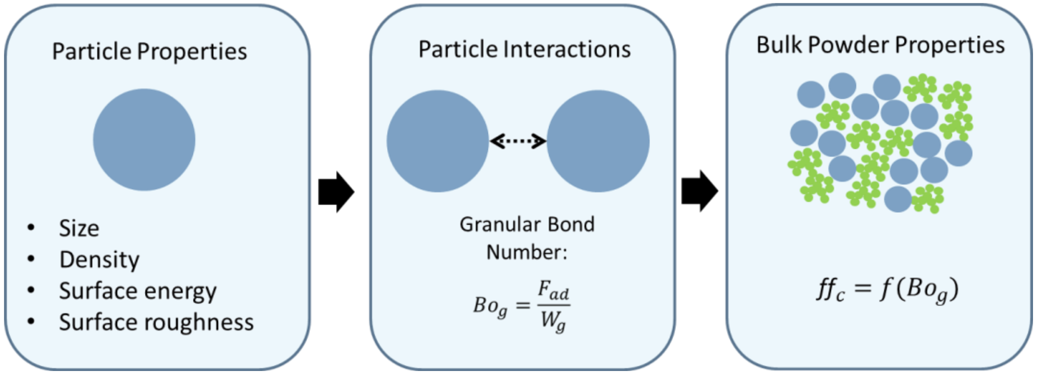
Particle Property	Effect on F_{ad} with increase in property
Particle size, d_p	↑
Hamaker constant, A	↑
Asperity size/Surface roughness, d_{asp}	↑
Separation distance, l_0	↓

Frenkel equation

$$A = 24\pi D_0^2 \gamma_d$$

From inverse GC

Modeling Powder Flowability from Material Properties

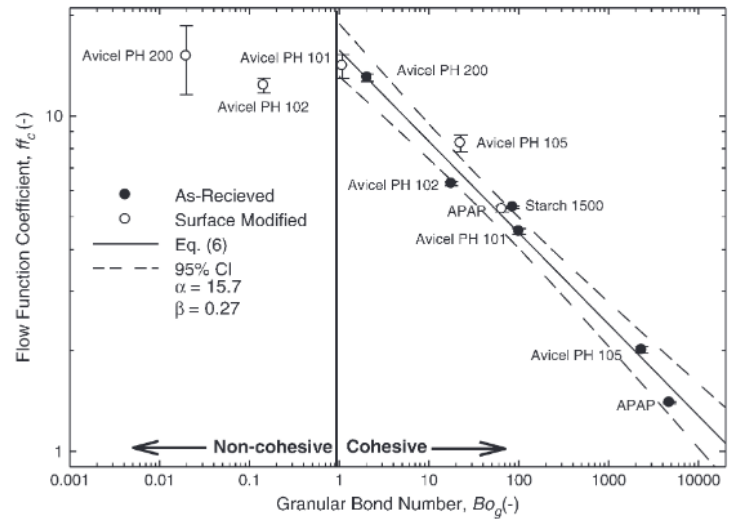


ff_c - B_{og} relationship:
Single component

$$ff_c = \alpha\left(\frac{1}{Bo_g}\right)^{\beta}$$

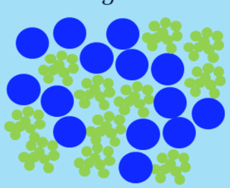
ff_c - B_{og} relationship:
Powder blend

$$ff_{c,Mix} = \alpha\left(\frac{1}{Bo_{g,Mix}}\right)^{\beta}$$

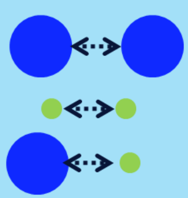


Bond number of a multicomponent mixture

$Bo_{g.Mix}$



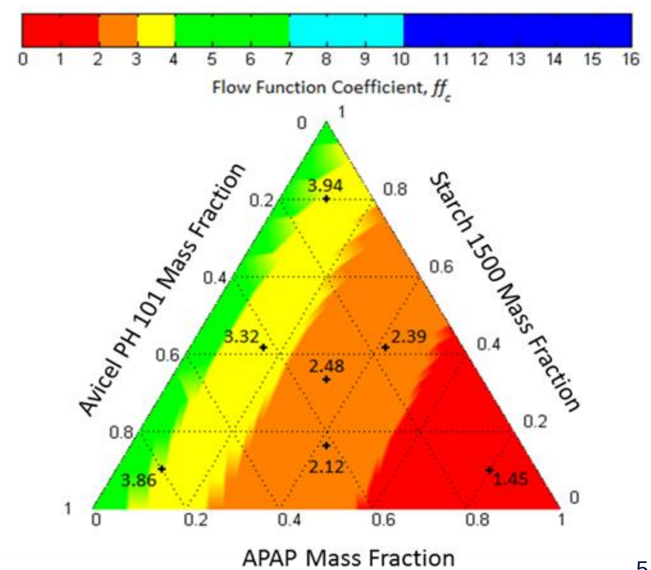
$Bo_{g.ij}$



Weighted harmonic mean:

$$\frac{1}{Bo_{g,Mix}} = \sum_{i=1}^{N}\sum_{j=1}^{N}\frac{w_{ij}}{Bo_{g.ij}}$$

$$w_{ij} = f_{SA,i} f_{SA,j}$$



Capece, M., Ho, R., Strong, J., & Gao, P. (2015). Prediction of powder flow performance using a multi-component granular Bond number. Powder Technology, 286, 561-571.

Co-processing Routes

	1	2	3	4
Route	**Crystallization and/or Precipitation of API and/or Nonactive Component(s)**	Additive Mediated Crystallization of API	Carrier Particles	Nonactive Component Addition During API Isolation
Mechanisms	» Agglomeration » Heteronucleation » Surface coating » Dispersion of API in polymer matrix	» Relative growth-rate modification of crystal faces by adsorption of additive » Modification of nucleation kinetics	» Adsorption » Confinement	» Surface coating » API/nonactive component ordered mixtures
Physical State of API	» Crystalline » Amorphous	» Crystalline	» Crystalline » Amorphous » Gel/Oil » Liquid	» Crystalline » Amorphous

Courtesy of the IQ Co-processed API Working Group

abbvie

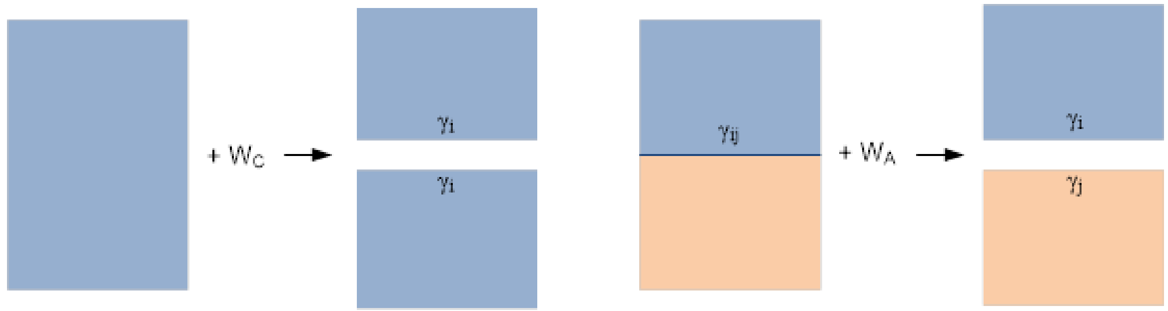
Nonactive Component Addition During API Isolation via Nano Dry Coating

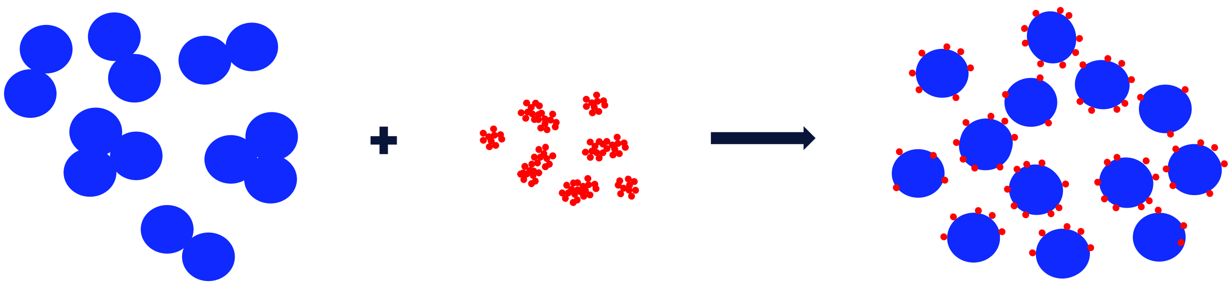
- Nonactive component(s) added during isolation or milling steps:
  - Modified surface charge, reduced cohesiveness
  - Reduced risk of amorphous formation by mechanical activation
  - Avoiding need for batch pre-processing steps in continuous drug manufacturing processes by incorporation of this step into common API unit operations

- **Dry Coating Literatures**

  - J. Yang et al. **Dry particle coating for improving the flowability of cohesive powders**. *Powder Technology* (2005) 158:21-33
  - Luo, Y.; Zhu, J.; Ma, Y.; Zhang, H. **Dry coating, a novel coating technology for solid pharmaceutical dosage forms**. *Int. J. Pharm.* (2008) 358:16−22.
  - Q. Zhou et al. **Improving powder flow properties of a cohesive lactose monohydrate powder by intensive mechanical dry coating**. *J Pharm Sci* (2010) 99:969-981.
  - S. Chattoraj et al. **Profoundly improving flow properties of a cohesive cellulose powder by surface coating with nano-silica through comilling**. *J Pharm Sci* (2011) 100:4943-4952.
  - M. Mullarney et al. **Applying dry powder coatings using a resonant acoustic mixer to improve powder flow and bulk density.** Pharmaceutical Technology (2011):94-102.

Interparticle Adhesion/Cohesion





i = glidant
j = API

$$W_C = \gamma_i(dA + dA) = 2\gamma_i dA \qquad W_C = \gamma_j(dA + dA) = 2\gamma_j dA \qquad W_A = (\gamma_i + \gamma_j - \gamma_{ij})dA$$

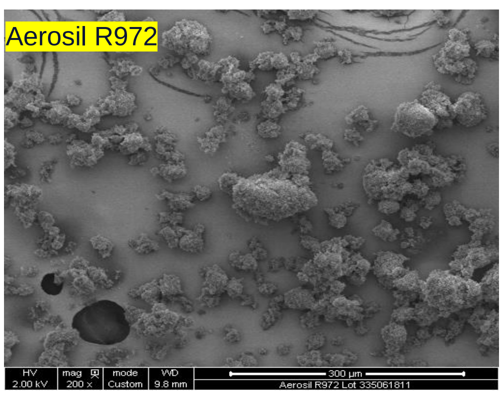
- Glidant-Glidant $\quad E_C = 2\gamma_i dA = 2\gamma_i S_i w_i m \qquad SA_i = S_i w_i m$
- API-AP $\quad E_C = 2\gamma_j S_j w_j m$
- Glidant-API $\quad E_A = E_D + E_{AB}$
- **Thermodynamic Energy of Dispersion**

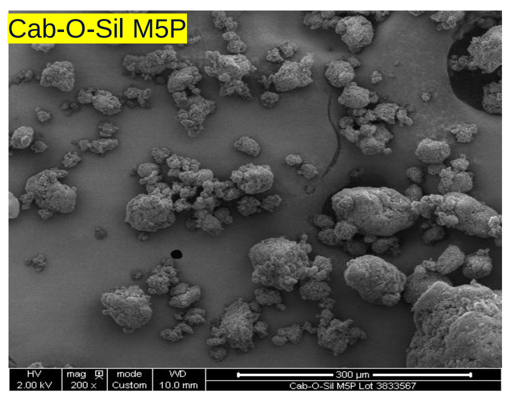
$$E_{Dispersion} = E_{API-API} + E_{Glidant-Glidant} - E_{API-Glidant}$$

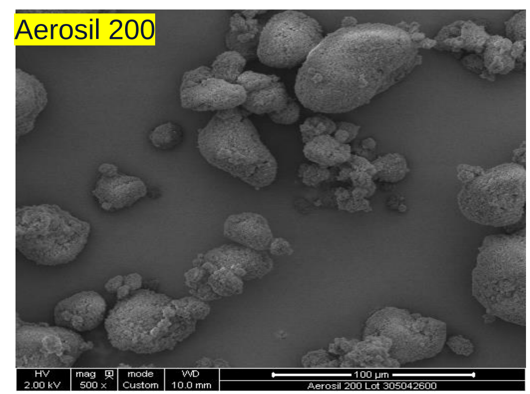
Physical Properties of Glidant: Colloidal Silicon Dioxide

Colloidal silicon dioxide - widely used glidant with small particle size, large surface area and different surface treatments to improve flow properties of dry powders

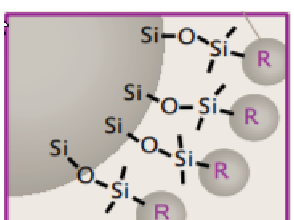
Glidant Type	Measured SSA (Vendor SSA) (m^2/g)	Average Particle Size (nm)	γd (mJ/m^2)	γab (mJ/m^2)	γt (mJ/m^2)	Hydrophilicity	Surface Chemistry
Aerosil 200	167 (175)	12	42.2	9.3	51.5	0.18	Hydrophilic
Cab-O-Sil MP5	215 (193)	14	32.8	6.6	39.4	0.17	Hydrophilic
Aerosil R972	98 (110)	16	37.1	3.6	40.7	0.09	Hydrophobic



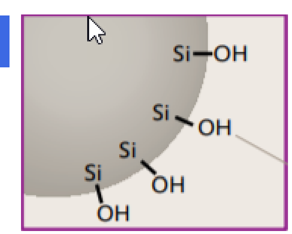




Dimethylsilane groups



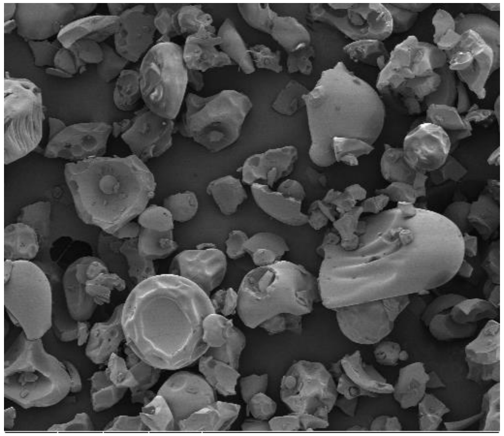
Silanol groups

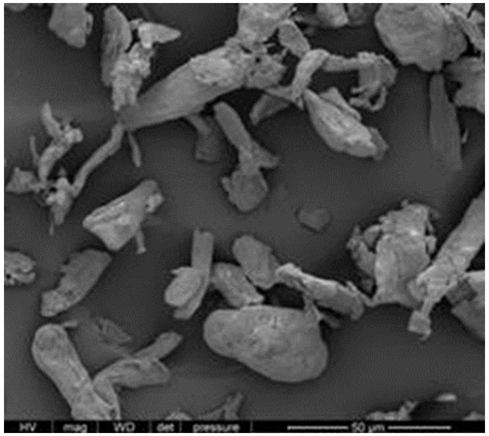


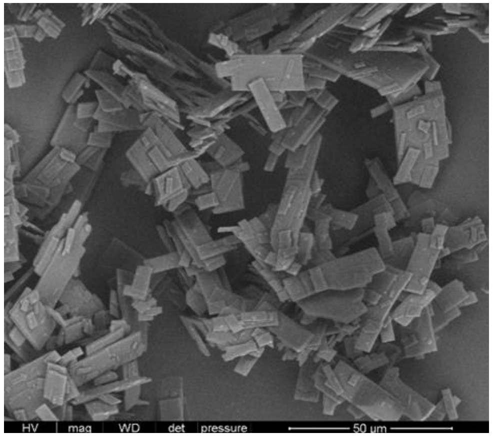
abbvie

Physical Properties of Model Host Compounds

Material	Measured SSA (m^2/g)	Average Particle Size (µm)	γd (mJ/m^2)	γab (mJ/m^2)	γt (mJ/m^2)	Hydrophilicity	Surface Chemistry
Compound 1	0.31	~100	73.7	25.3	98.9	0.26	Hydrophilic
Compound 2	1.86	~20	46.7	5.9	52.6	0.11	Hydrophobic
Compound 3	0.67	~40	41.4	4.3	45.6	0.09	Hydrophobic

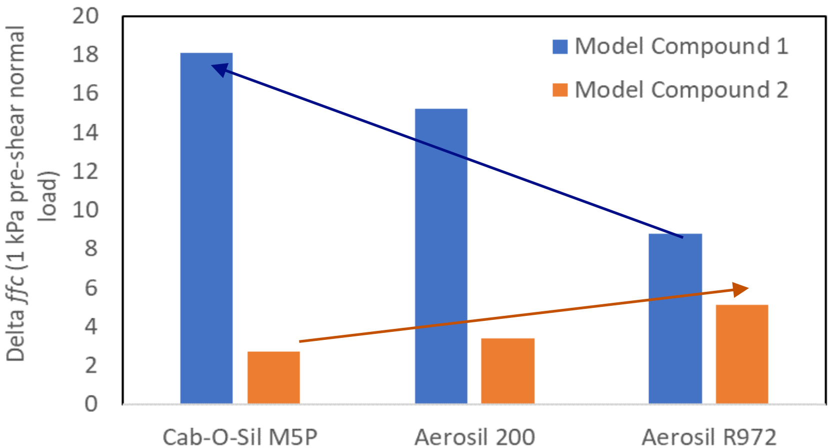






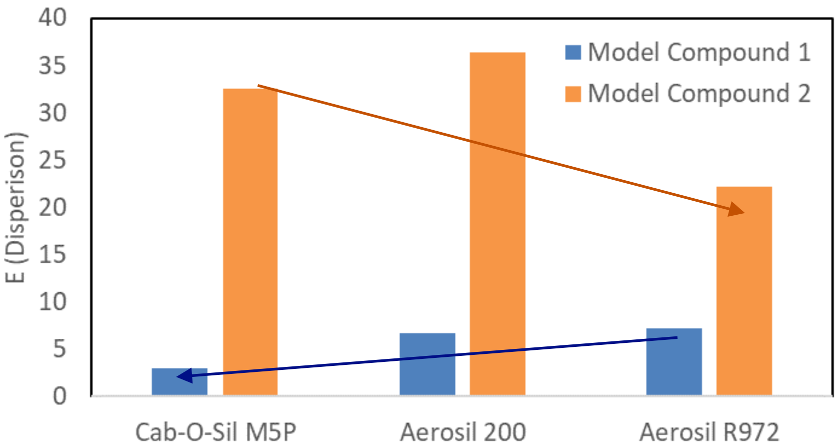
Nanocoating Enhancement:
Effect of Glidant Type for Different Host Particles Surface Chemistry

Flowability Enhancement



Hydrophilic Hydrophobic

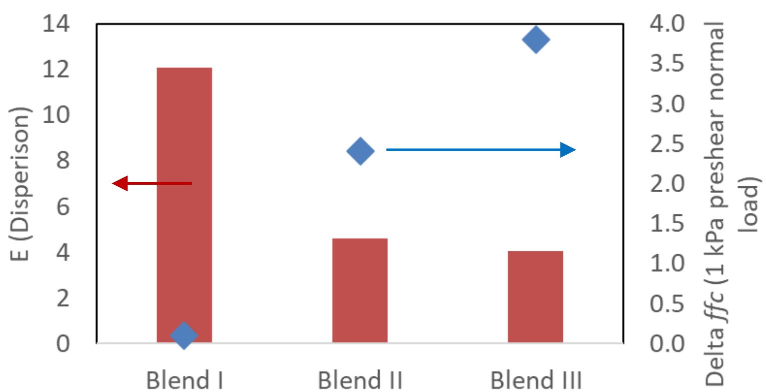
Cohesion-Adhesion Balance

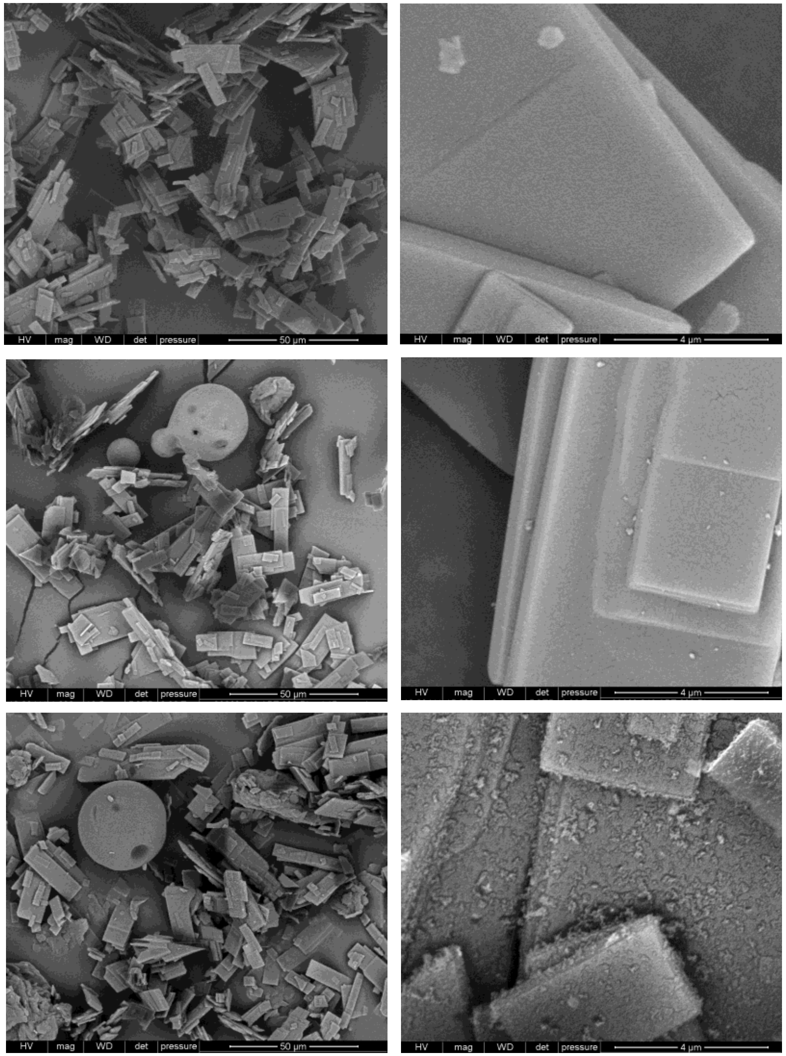


The effectiveness of glidant type is dependent on balance of cohesion/adhesion of the mixture.

Nanocoating Enhancement:
Effect of Glidant Type on 40% DL Blends (Compound 3)

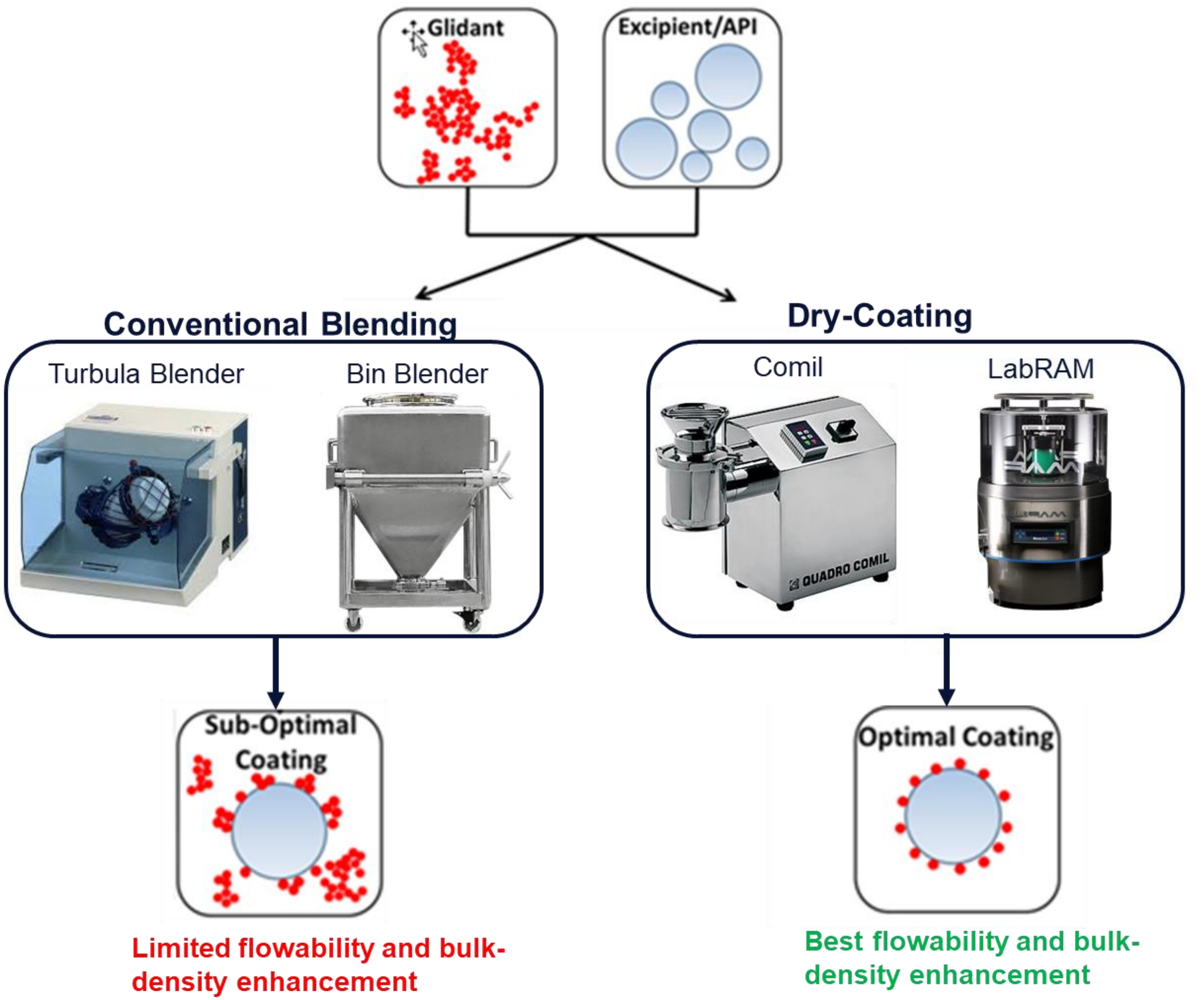
Function	% (w/w)		
	Blend I	**Blend II**	**Blend III**
Active	40.00	40.00	40.00
Filler	15.50	15.50	15.50
Filler	15.25	15.25	15.25
Binder	15.00	15.00	15.00
Filler	7.00	7.00	7.00
Disintegrant	5.00	5.00	5.00
Glidant	**0.60 (M5P)**	N/A	N/A
Glidant	N/A	**0.60 (R972)**	**1.00 (R972)**
Lubricant	**1.65**	**1.65**	**1.25**
	100.00	100.00	100.00





abbvie

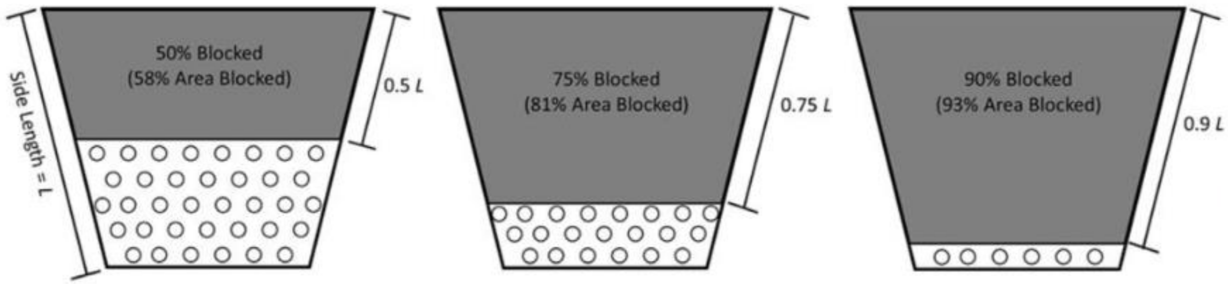
Lab-Scale Feasibility Studies



- Optimal coating is determined by thermodynamic factors (adhesion/cohesion).
- Dry-coating processes incorporate glidants more effectively than conventional blending and produce powders with enhanced flowability and bulk density.
- Dry-coating can be developed using the Comil. LabRAM can be used as a material sparing approach to demonstrate feasibility to benchmark performance.

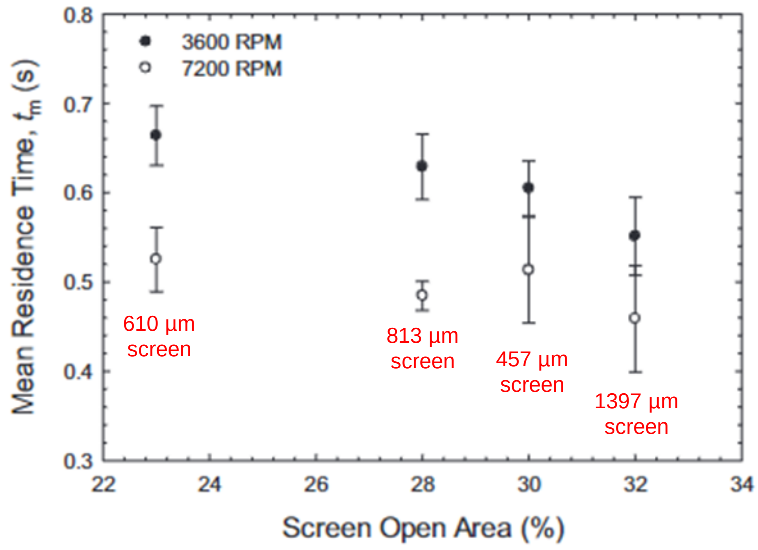
Scale-Up Considerations: Drying Coating Comil Process

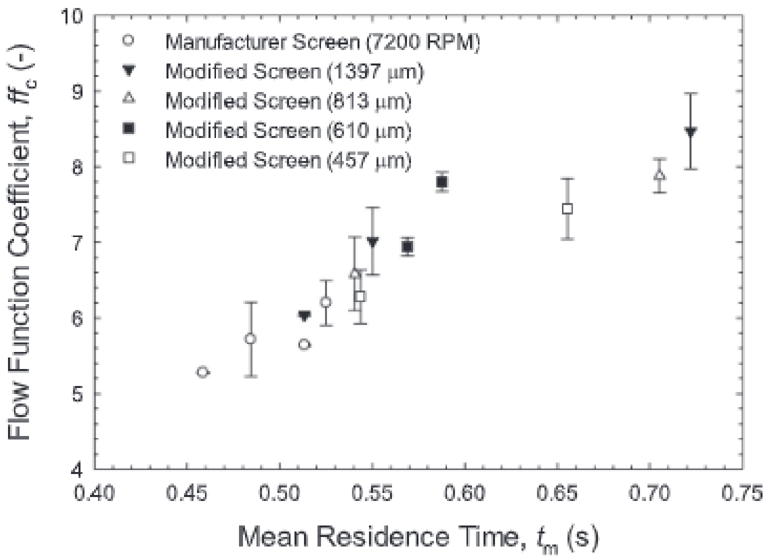
'Single-pass' conical screen milling approach to incorporate glidant



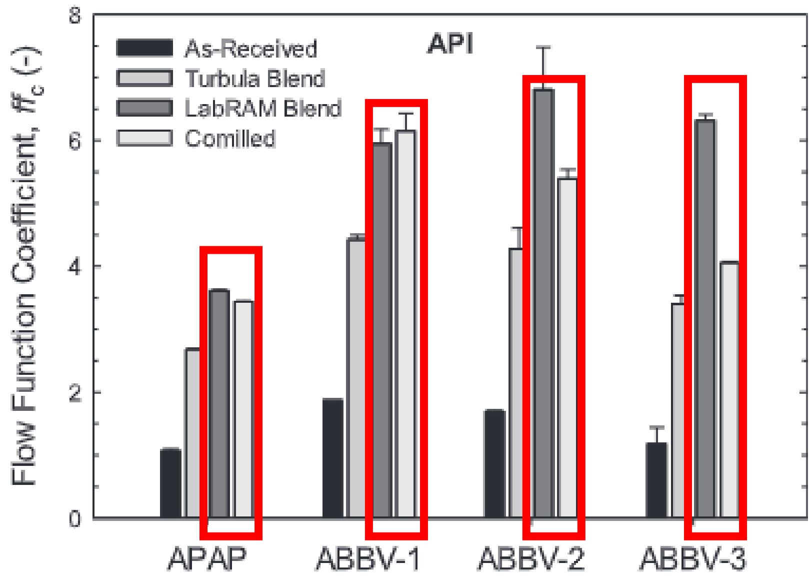
Mean residence time

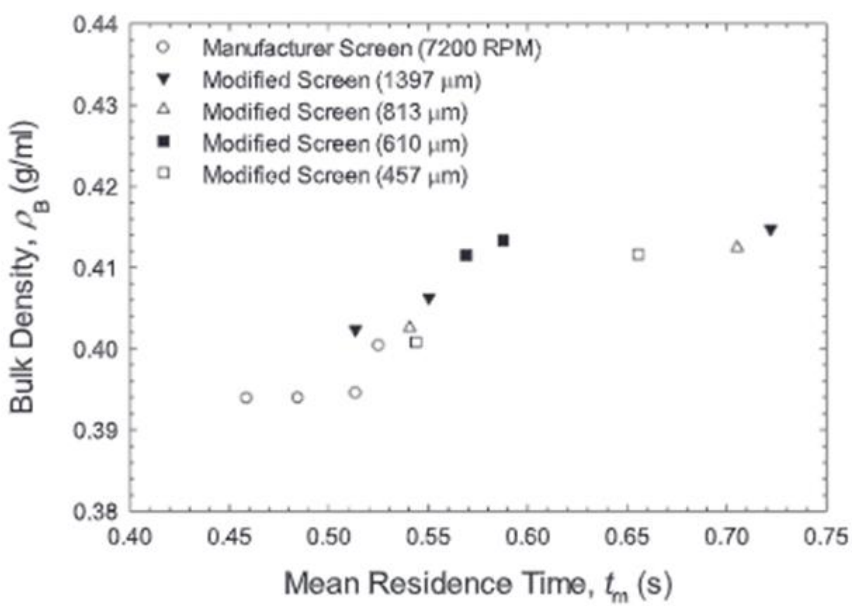
$$t_m = \frac{m_H}{\dot{m}}$$

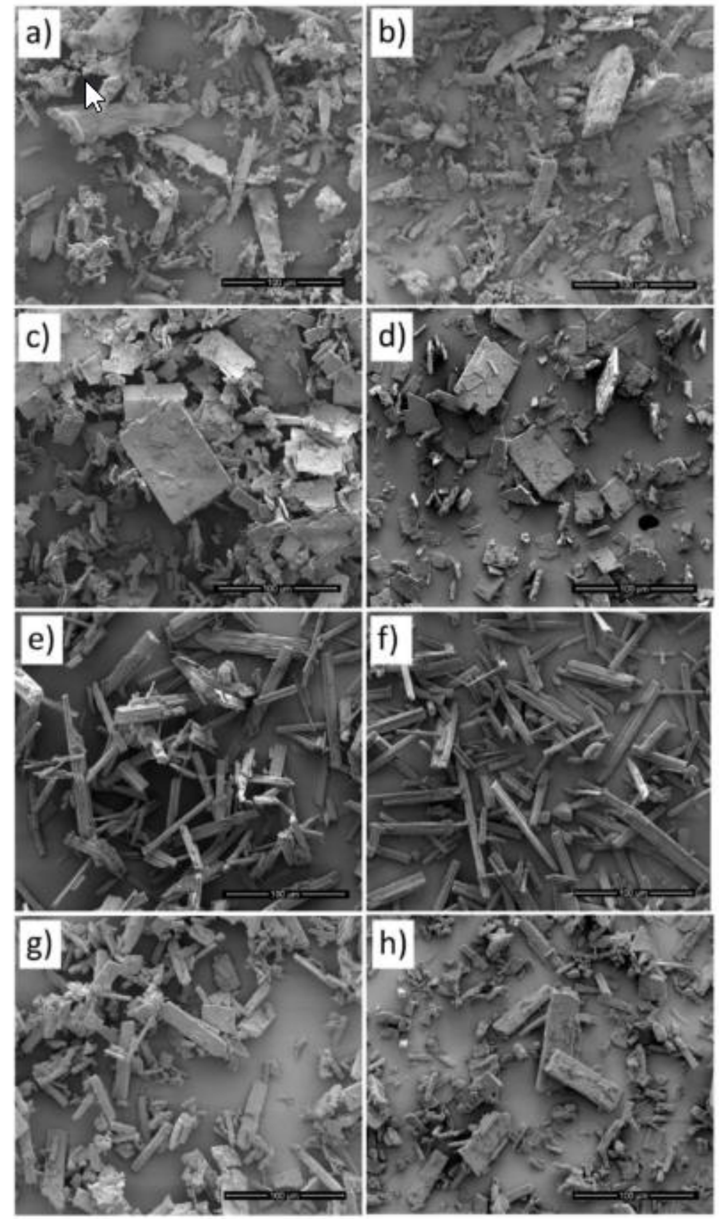




Capece, M., Borchardt C., Jayaraman a. (2021). Improving the effectiveness of the Comil as a dry-coating process: Enabling direct compaction for high drug loading formulations. Powder Technology, 379, 617-629.


API
As-Received
Turbula Blend
LabRAM Blend
Comilled
Flow Function Coefficient, ff_c (-)
0
2
4
6
8
APAP
ABBV-1
ABBV-2
ABBV-3


Manufacturer Screen (7200 RPM)
Modified Screen (1397 μm)
Modified Screen (813 μm)
Modified Screen (610 μm)
Modified Screen (457 μm)
Bulk Density, ρ_B (g/ml)
0.38
0.39
0.40
0.41
0.42
0.43
0.44
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
Mean Residence Time, t_m (s)


a)
b)
c)
d)
e)
f)
g)
h)

Summary

- Powder flowability of multicomponent mixtures can be modeled via their material properties via granular Bond number.
- For nanocoating applications, interparticle adhesion/cohesion forces are dominant mechanism.
- Significant improvement in blend powder properties (e.g. flowability, bulk density) can be achieved by:
    - fundamentally understanding the surface properties (chemistry) of the API and excipients, and their potential interfacial interactions;
    - the glidant type and properties have significant role (and often underappreciated) in enhancing blend bulk properties by achieving right balance of adhesion versus cohesion;
    - combining efficient mixing process (e.g. dry coating by effective Comil unit operation) that can fully maximize the role of the glidant.
- The addition of nonactive component (i.e. glidant) during the API milling steps via nano dry coating has to potential as a co-processed API approach to
    - modify API surface properties, reduce cohesiveness;
    - enable high DL direction compression formulations;
    - avoid need for batch pre-processing steps in continuous drug manufacturing processes by incorporation of this step into common API unit operations.

abbvie