J-STAR RESEARCH, Inc

ENABLING TECHNOLOGY

Dry Particle Coating for the Enhancement of Flowability and Bulk Density

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Enabling Technology

II. Dry Particle Coating for the Enhancement of Flowability and Bulk Density

Purposes

Many active pharmaceutical ingredients (API) exhibit deficient bulk powder properties such as poor flowability, low bulk density, high cohesion, etc. These deficiencies may cause some major issues for the performance of downstream processing including the blending, content uniformity, and tablet making.

One of the methods for the improvements of the bulk powder properties is via the dry powder coating. This study is providing this coating technology.

Materials and Methods

The mechanism of the dry powder coating can be illustrated in Figure 1, in which the host particles (API) are coated with the guest particles (such as SiO_2) via mechanical forces. This coating can effectively increase the spacing between the host particles and the apparent surface roughness; hence it reduces the cohesive forces between the hosting particles, resulting in significant benefit to pharmaceutical powder processing because the easy transport of large bulk quantities of powder through unit operations is essential to manufacture solid dosage forms such as capsules and tablets.

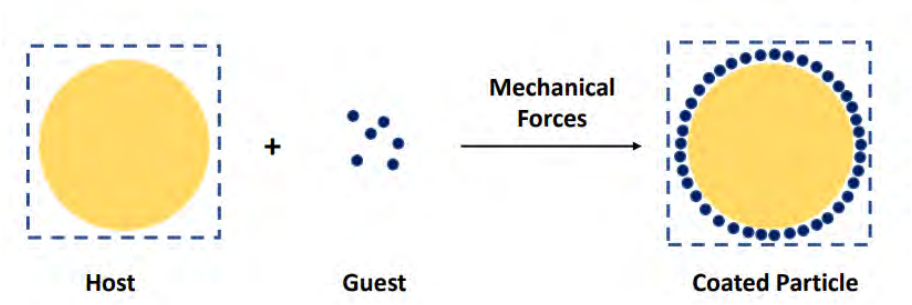


Fig. 1. Illustration of dry coating mechanism

The mechanical forces for the dry coating come from the shear and the collisions between the host particles and the guest particles during mixing. Four different coating devices to provide the mechanical forces are used in this study and they are listed in Table I.

Table I
Coating devices for dry powder coating

Coating Devices	Batch Mode	Continuous Mode
Comil (Quadro, Engineering, Canada)	v	yes
Pharma RAM II (Resodyne AcousticMixer, USA)	v	yes
Sturtevent Micronizer® jet mill (Sturtevant, Inc, USA)	v	yes
High shear granulator (Waring LB10G Blender, USA)	v	no

All four above-mentioned coating devices are available at J-Star. A simple description of each device in terms of the setup and the coating principle is provided here. The material (guest) used for this coating study is hydrophobic silica R972P from Evonik, with the particle size less than 50 nm (0.05 µm). The material (host) used in this study include corn starch (excipient) and ibuprophen (API) with the particle size around 120µm.

Comil

The setup and the illustration of comil coating are described in Figures 2a and 2b, respectively. As shown in Fig. 2b, when powders including the host particles (API) and the guest particles (SiO_2) after blending are charged to the mill, they are retained and mixed in the middle of the conical vessel. The rotation of the impeller generates centrifugal forces pushing the mixed particles toward the screen. As the particles are trapped between the screen and impeller edge (shear zone), significant shear forces are conveyed to deagglomerate the silicon dioxide particles. After this deagglomeration, the nano-sized silicon dioxide particles break down and preferentially attach to the larger host particle (API) (1).

Fig. 2a. Setup of comil

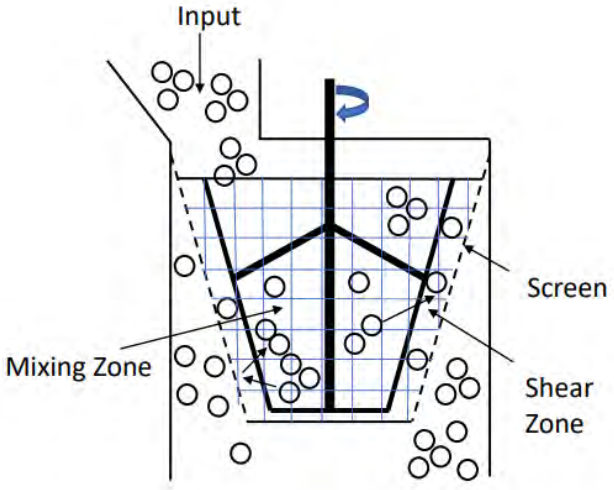


Fig. 2b. Illustration of comil mixing and shear zones

This coating process requires the selection of screen and impeller and some operating conditions such as operating speed and the powder feeding rate that are specific to the powder as to maximize dispersion and enable throughput without screen blinding.

Some premixing between the host particles and the guest particles using V blender prior to the comil operation is recommended to ensure a homogeneous coating. The comil can be operated in either a batch mode or a continuous mode as shown in Table I (1, 2)

Resonant Acoustic Mixer

The setup of the acoustic mixer (Pharma RAM II) and the illustration of the coating mechanism of the acoustic mixer are provided in Figures 3a and 3b, respectively.

The RAM II mixer exploits low frequency, high intensity, acoustic energy to rapidly fluidize and disperse as much as 1,000g (1 Kg) of a variety of materials. The RAM mixer uses acoustic energy to mix the desired media in the vessel through an oscillating boundary as shown in Fig. 3b, which accelerates the mixing vessel by as much as 100 times the acceleration of gravity (100

G). As the result of this oscillation, a propagation of mechanical energy through a system of plates, weights and springs under the oscillating boundary creates a longitudinal acoustic pressure wave in the mixing vessel, as shown in Fig. 3b. The frequency of the driver is optimized by the control system so that the system operates at resonance. By operating at resonance, the acoustic energy is absorbed by the media (3).

Fig. 3a. Pharma RAM II

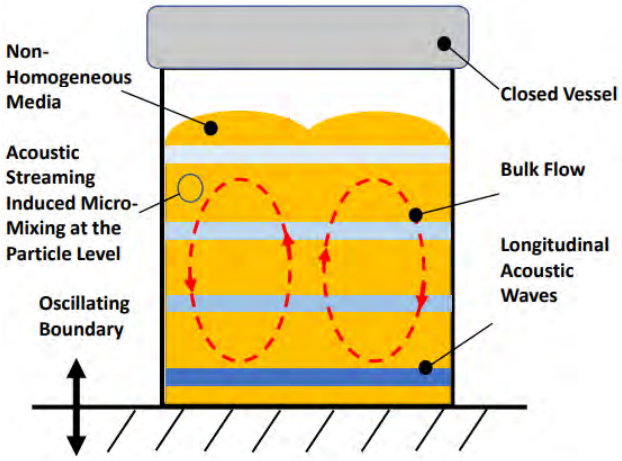


Fig. 3b. RAM mixing mechanism

The particle trajectory of the bulk powder in the vessel as the result of the longitudinal acoustic pressure wave can be illustrated by using two circular motions and micro mixing at the particle level (4) as shown in Fig. 3b. The efficient mixing is accomplished by creating a homogeneous shear zone throughout the vessel without the aid of mixing media or impeller. At a high acceleration, a significant shear strain within the bulk powder can be induced in a very short time. The high degrees of shear disperse fine particles and make them adhere to the surfaces of lager host particles to accomplish the coating process. This coating process is typically completed in less than 10 minutes (4).

The RAM mixing system can be operated in a batch mode and the capacity is up to 420 Kg. It can also be operated in a continuous mode. It should be noted that the mixing vessel for the RAM system is a closed system and there is no metal part in the vessel. Hence no contamination of the pharmaceutical product occurs from the RAM mixing process. In addition, the particle size distribution of the product before vs. after the RAM mixing typically remains the same.

Jet Mill

The setup and the illustration of the mixing mechanism in the Sturtevent Micronizer® jet mill are presented in Figures 4 a, 4b and 4c, respectively

The Sturtevant Micronizer® jet mill used in this study is classified as Fluid Energy Mill (FEM) because the reduction of the particles is accomplished by compressed fluid (air or nitrogen). Jet mills have no moving parts, thereby eliminating contamination due to contact with external grinding media (5). As shown in Figure 4b, the compound particles are fed to the funnel and then

sucked into the grinding chamber through the venturi region by the feed air. The shape of the grinding chamber looks like a pancake as shown in Fig. 4b.

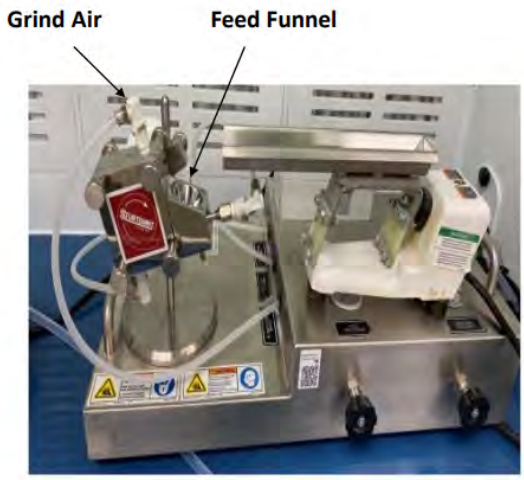


Fig. 4a. Sturtevant Micronizer® jet mill

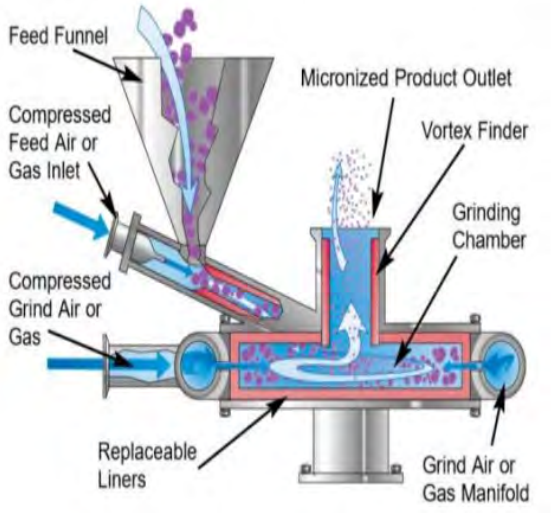


Fig. 4b. Flow pattern in Sturtevant Micronizer® jet mill (Sturtevant Inc.)

After the particles are sucked into the grinding chamber, they are moving in the vortex trajectory as shown in Fig. 4b and 4c. Larger particles are moving at higher velocities along the peripheral wall. High pressure grind air (nitrogen) is injected in the grinding chamber through the specially design nozzle placed at regular distance to accelerate the particles to cause the particle-particle collisions and the particle-wall collisions resulting in the reduction of particle size. The smaller particles after the collisions are moving at lower velocities and hence are subjected to a lower centrifugal force. When the drag force is higher than the centrifugal force, the fine particles (micronized product) are dragged to the outlet and collected in a bag. In the meantime, the heavier oversized particles are held in the grinding chamber by centrifugal force until micronized to a desired size by optimizing the grinding pressures and feed rates.

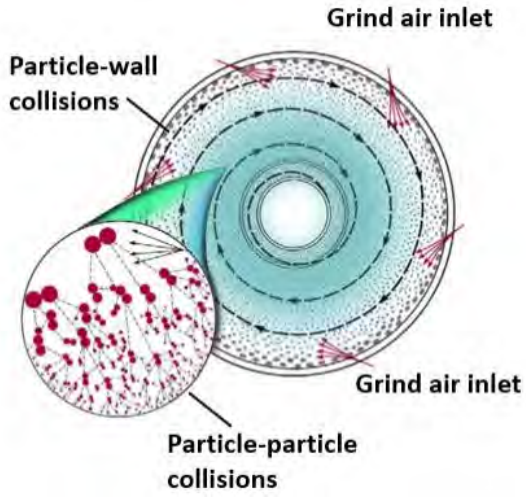


Fig. 4c. Collisions in the grinding chamber (Sturtevant Inc.)

The coating process in the jet mill occurs when the host particles are colliding with the guest particles. However, when the guest particle size is significantly smaller than the host particle size, the guest particles are subjected to lower centrifugal forces and hence are concentrated at

the center of the grinding chamber. Consequently, the chances of the guest particles to collide with the host particles become less.

High Shear Granulator

The setup of the high shear granulator (mixer) and the illustration of the flow pattern are presented in Figures 5a and 5b, respectively.

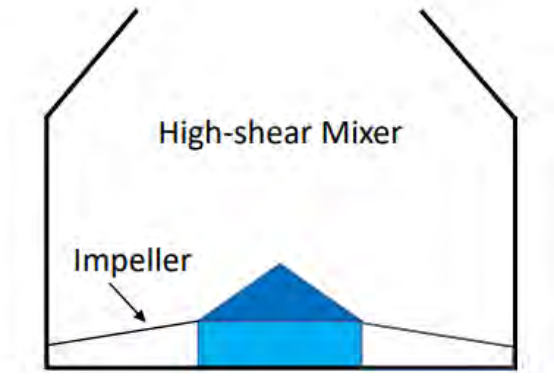


Fig. 5a. Schematic of a high-shear mixer

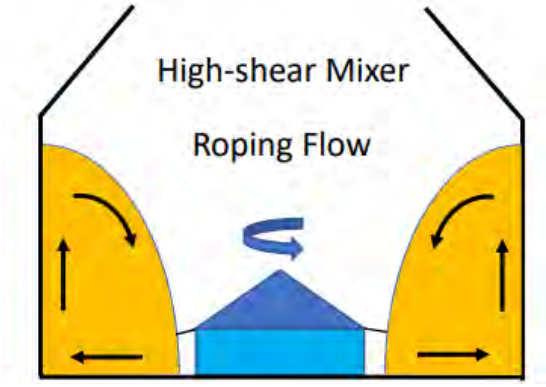


Fig. 5b. Roping flow for the high-shear mixer

Dry powder coating was carried out in a high-shear mixer (Waring LB10G Blender). The schematic of the mixer is presented in Figure 5a. Both the host and the guest particles were charged to the mixer and the tip speed of the blade was set at 10 m/sec, a standared high speed for a high shear granulation (6) for two to four minutes. At such a high speed, "roping" behavor was observed (7), as shown in Figure 5b. Particles from the bottom of the bed were forced up the vessel wall and then tumbled down the angled bed surface to the center of the bowl.

As the impeller rotates, both the host and guest particles are subjected to the force from the impeller and travel at both radial and vertical directions at different velocities, resulting in particle-particle collisions. Consequently, the guest particles adhere to the host particles due to the collusions to accomplish the coating process.

Flowability and Bulk Density Measurement

The flowability and the bulk density of the powders are measured by using FT4, a powder rheometer (8). The relationship between the value of the flow function coefficient and the flowability (9) is listed in Table II.

Table II

The flow function coefficient value and the flowability

Flow Function Coefficient (FFC) Value	Flowability
FFC <1	Not flowing
1< FFC <2	Very cohesive
2 < FFC <4	Cohesive
4 < FFC < 10	Easy-flowing
10 < FFC	Free-flowing

Results and Discussions

It has been demonstrated that both the packing and the flow of cohesive API particles can be significantly improved after they are coated with nano-silica by dry coating techniques. The objective of these improvements is to ensure that the tablets can be made from the coated API via direct compression since it is the most efficient method for tableting. Recently, quantitative improvements in terms of the bulk density and FFC value (10) have been proposed to carve an area suitable for direct compression in bulk density and FFC value map. This area, a sweet spot, includes all the API candidates when the bulk density of the coated API is greater than 0.4 g/cc and the FFC value of the coated API is higher than 7. Clearly the demarcations of this proposal need further work. In this study, the map of the bulk density vs. FFC value is used to evaluate the effectiveness of the dry coating of two candidates, corn starch (excipient) and Ibuprofen (API) with four different coating techniques: comil, LabRAM mixer, jet mill and a high shear granulator.

Corn Starch and Silica System

The corn starch with a particle size (D50) around 16 μm (Excipient handbook) was used as the host, designated as A1 in Table III. It has bulk density of 0.47 g/cc and FFC value of 3.07, classified as cohesive material as shown in Table II. It was coated with 1 % silica (R972P) via four different methods: LabRAM (A2), comil (A3), a high shear granulator (A4) and Jet Mill (A5). The operating condition of each method is listed in Table III. The results of the coating from those four methods are listed in Table III and Figures 6a and 6b.

Table III
Effectiveness of dry coating of corn starch with 1% silica

Materials	Material and Operating Conditions	Bulk Density, g/cc	SD*	FFC Value	SD*
A1	Raw Corn Starch	0.47	0.01	3.07	0.33
A2	LabRAM, 90G, operating time: 1min	0.75	0.01	26.60	10.65
A3	Comil, 2000 RPM, feed rate: 20g/min	0.76	0.01	18.30	2.65
A4	High Shear granulator (blender), tip speed: 10m/s, 2 min duration	0.75	0.01	24.25	6.58
A5	jet mill, grind air pressure: 40 psi, feed rate: 20 g/min	0.70	0.01	27.20	4.24

* SD: standard deviation

The coated corn starch via all four coating methods, designated as A2 to A5, exhibits a significantly improvement in both bulk density and flowability, as illustrated in Table III. Since both LabRAM and comil have been established for dry coating in the literature, the results from these two methods are examined first. Fig. 6 shows that the uncoated corn starch A1 is located in the bulk density and FFC value map outside of the area for the easy-flowing and high density area, a sweet spot. In contrast, the coated corn starch, A2 and A3, coated by LabRAM and

comill, respectively, are within the sweet spot. Furthermore, the FFC value for both A2 and A3 are higher than 10; hence, they are classified as free flowing material.

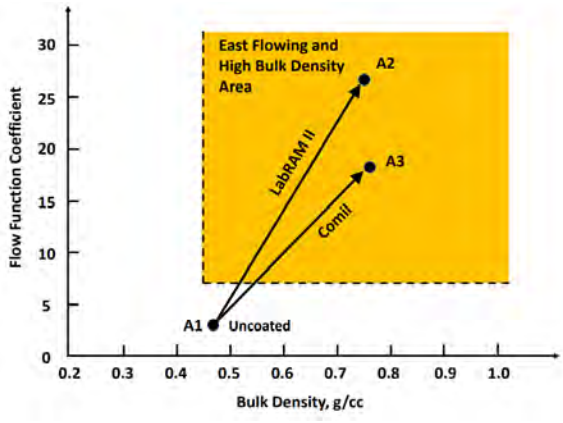
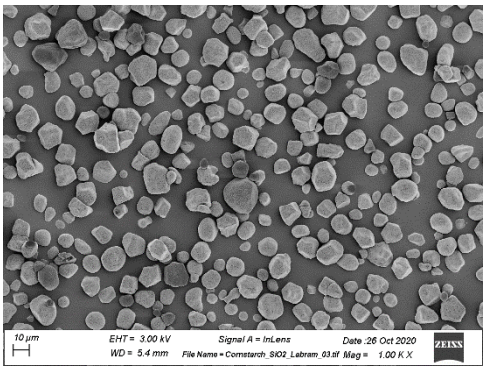
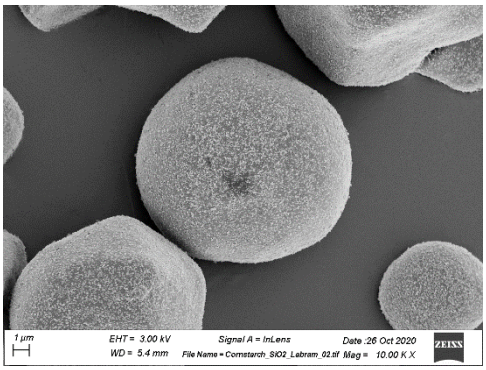


Fig. 6. A map of bulk density vs. FFC value for uncoated and coated corn starch particles

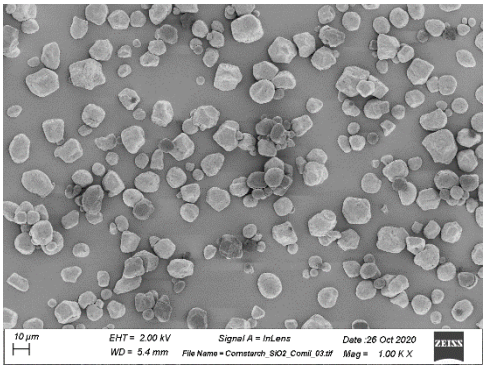
The coated corn starch by LabRAM (A2) exhibits a higher value of FFC than that by Comil (A3) as shown in Figure 6. This difference in FFC value is caused by the quality of coating illustrated in Figure 7 (b) vs. 7(d); The density of SiO_2 particles coated on corn starch by LabRAM is much higher than than by Comil. It should be noted that there is no size reducton of corn starch by using either LabRAM or Comil, as shown in Figure 7(a) and Figure 7(c)

(a) (b)





(c) (d)



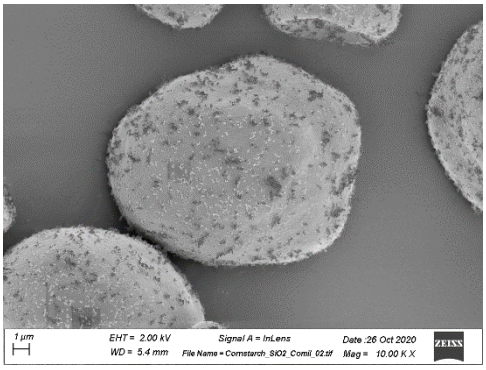


Fig. 7 (a) & (b) SEM images of Corn starch coated with SiO_2 by LabRAM;
(c) & (d) SEM images of corn starch coated with SiO_2 by Comil

It is very interesting to note that the coated corn starch by a high-shear granulator (A4) and a jet mill (A-5), two methods less commonly used for dry coating, are also located in the sweet spotas shown in Fig. 8. In addition, they are also classified as free flowing material because the FFC values are high than 10.

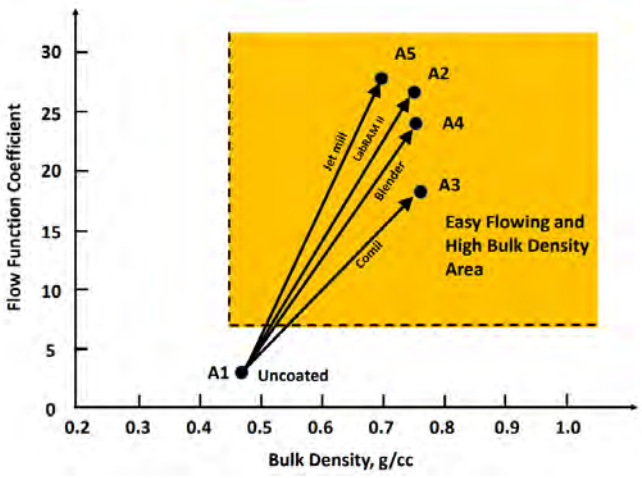


Fig. 8. A map of bulk density vs. FFC value for uncoated and coated corn starch particles

Ibuprophen and Silica System

The Ibuprophen (API) with a particle size (D50) around 120 µm was used as the host, designated as B1 in Table IV. It has bulk density of 0.34 g/cc and FFC value of 4.77, classified as easy flowing material as shown in Table II. It was coated with 1 % silica (R972P) via four different methods: LabRAM (B2), comil (B3), a high shear granulator (B4) and jet mill (B5). The operating condition of each method is listed in Table IV.

Table IV
Effectiveness of dry coating of Ibuprofen with 1% silica

Materials	Material and Operating Conditions	Bulk Density, g/cc	SD*	FFC	SD*
B1	Raw Ibuprofen	0.34	0.01	4.77	0.08
B2	LabRAM, 90G, operating time: 1 min	0.53	0.01	20.30	2.47
B3	Comil, 2000 RPM, feed rate: 20g/min	0.48	0.01	14.80	4.67
B4	High Shear granulator (Blender), tip speed: 10m/s, 2 min duration	0.49	0.01	9.82	3.94
B5	jet mill, grind air pressure: 40 psi, feed rate: 20 g/min	0.27	0.01	1.16	0.07

* SD: standard deviation

Fig. 9 shows the results of the change in bulk density and the flow performance of uncoated host prticles (ibuprophen) (B1), RAM dry coated powders (B2) and comil dry coated powders (B3). It is noted that the increase of the bulk density is accompanied with the improvement of the flow performance. Due to this increase in bulk density and the improvement in flow performace, the coated ibuprophen is located in an area suitable for making tablets via direct compression.

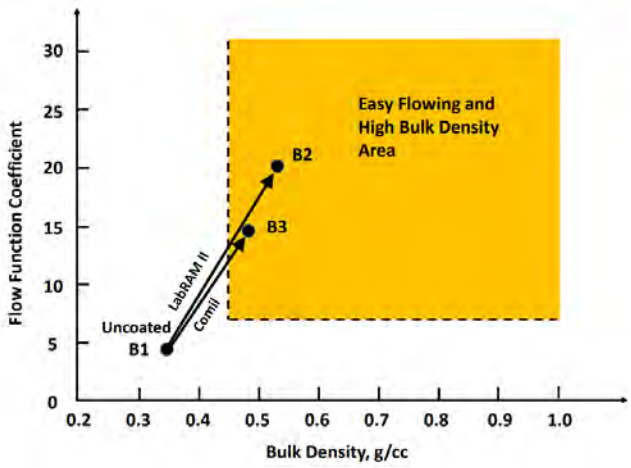


Fig. 9. A map of bulk density vs. FFC value for uncoated and coated ibuprophen particles

Figure 9 shows that the coated ibuprophen particles via the RAM technique exhibit a higher bulk density and FFC value than that via comil. This probably is due to a higher shear strain (90 G) imparted to the bulk powder system in RAM unit. The SEM images of coated ibuprophen are presented in Figure 10 (a) and (b) showing a uniform coating and a size change.

It should be also noted that RAM can use a small quanity of API for screening purpose in the early stage of drug product development. Both comil and RAM can be operated in both batch mode and continuous mode.

(a) (b)

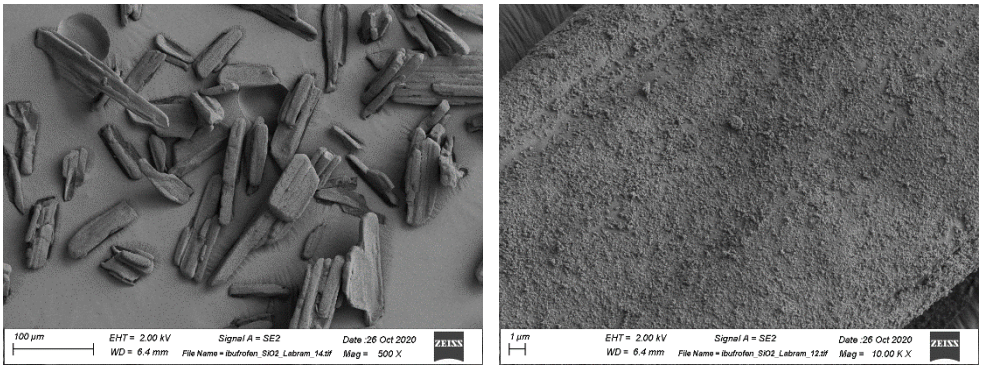


Fig. 10. (a)&(b) SEM images of Ibuprophen coated with SiO_2 by LabRAM

The coating of the ibuprofen was also carried out by using a high shear granulator (Blender) and a jet mill. The results of this coating are compared with those from comil and LabRAM and presented in Fig. 11.

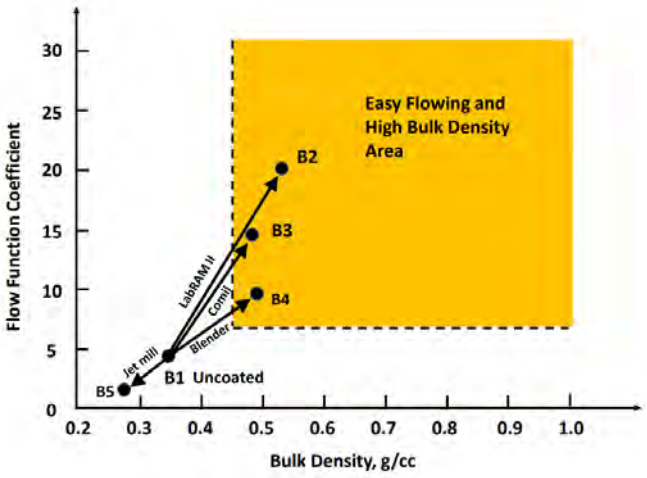


Fig. 11. A map of bulk density vs. FFC value for uncoated and coated ibuprophen particles

Fig. 11 shows that both the bulk density and the flow performance of ibuprophen particles are improved from the coating by the blender. These improvements make the coated ibuprophen by a blender sutible for the direct compression to make tablets.

Both the bulk density and the FFC value for ibuprophen were reduced from the coating by a jet mill, as shown in Fig. 11. This reduction is caused by two reasons. First, as a high grind pressure 40 psi was used for the jet mill, as shown in Table IV, the particle size of the host ibuprophen was reduced from 120 µm to a few µm, resulting in significant increase in surface area and cohesive force among the fine particles; Consequently, there is a huge decrease in bulk density and flowability. Similar results were obtained by other researchers (5). Second, due to the difference in particle size between the host (120 µm) and the guest (50 nm), the residence time is longer for the host (ibuprophen) than for the guest (silica), resulting in a decrease of chances for particle-to-particle collisions and for coating. A clear evidence of the size reduction of ibuprophen and poor coating by jet mill is illustrated in Figure 12 (a) and (b).

(a) (b)

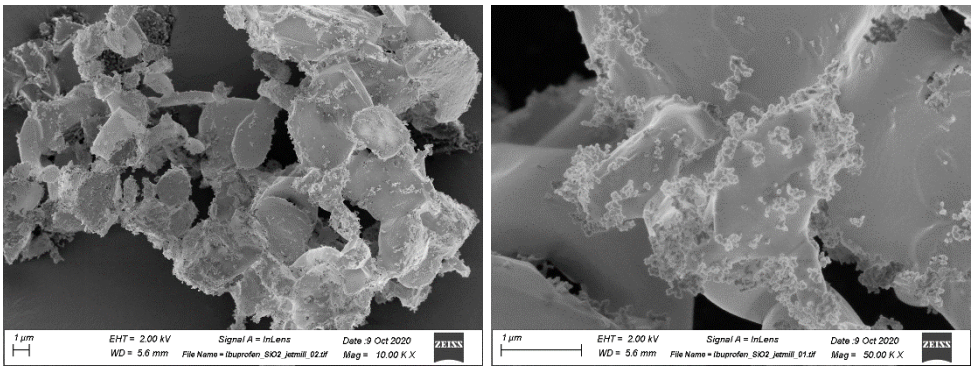


Fig. 12 (a)&(b) SEM images of Ibuprophen coated with SiO_2 by jet mill

Conclusions

The mechanism of the dry particle coating and a short description of four coating techniques including comil, LabRAM, a high shear granulator and a jet mill are provided. A suitable area (a sweet spot) in the map of the bulk density vs. FFC value is identified in which the bulk density is higher than 0.45 g/cc and the value of FFC is higher than 7; API candidates with the bulk density and FFC value are located in this sweet spot can be made into tablets via the direct compression. It has been demonstrated that all four coating techniques can be used to bing a cohesive materail like corn starch with low bulk density and FFC value into this sweet spot. It also shows that three coating tchniques except a jet mill can bring a low bulk density material such as ibuprophen into this sweet spot.

References

1. Matthew P. Mullarney, Lauren E. Beach, Rajesh N. Davé, Beth A. Langdon, Mark Polizzi and Daniel O. Blackwood, "Applying dry powder coatings to pharmaceutical powders using a comil for improving powder flow and bulk density," Powder Technology, vol. 212, 397–402, October 2011.
2. Z. Huang, J. V. Scicolone, L. Gurumurthy, R. N. Davé, "Flow and Bulk Density Enhancements of Pharmaceutical Powders using a Conical Screen Mill: A Continuous Dry Coating Device," Chemical Engineering Science, Vol 125, p209–224, March 2015.
3. Matthew P. Mullarney, Beth A. Langdon, and Mark A. Polizzi, "Applying Dry Powder Coatings Using a resonant acoustic mixer to improve powder flow and bulk density", Pharmaceutical Technology, October 2011.
4. Juan G. Osorio and F. J. Muzzio, "Evaluation of resonant acoustic mixing performance" Powder Technology, 278 (2015) 46-56.
5. Xi Han, Chinmay Ghoroi, Daniel To; Yuhua Chen, Rajesh N. Davé, "Simultaneous micronization and surface modification for improvement of flow and dissolution of drug particles," International Journal of Pharmaceutics, 415, 185– 195, August 2011.
6. R. Plank, B. Diehl, H. Grinstead, J. Zega, "Qualifying liquid coverage and powder flus in high-shear granulation" Powder Technol. 134(2003) 223-224.
7. J. D. Litster, K. P. Hapgood, J. N. Michaels, A. Sims,M. Roberts, S.K. Kameneni, "Scale-up of mixer granulators for effective liquid distribution" Powder Technol. 124 (2002) 272-280
8. Freeman, R., 2007. Measuring the flow properties of consolidated, conditioned and aerated powders – a comparative study using a powder rheometer and a rotational shear cell. Powder Technol. 174, 25–33.
9. Schulze, D., 2008. Powders and Bulk Solids. Springer.
10. Kuriakose Kunnath, Zhonghui Huang, Liang Chen, Kai Zheng, Rajesh Davé, "Improved properties of fine active pharmaceutical ingredient powder blends and tablets at high drug loading via dry particle coating," International Journal of Pharmaceutics, 543(1-2), pp. 288-299, 2018.