

Model-guided flow enhancements of fine pharmaceutical powders via dry particle coating: linking particle-scale with bulk-scale through granular Bond number

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Abstract: Dry coating of fine pharmaceutical powders with nano-sized flow aids has been shown to enhance their bulk properties and processability, greatly facilitating direct compression tablet manufacturing. Here, a model-based understanding of cohesion reduction due to dry coating is presented to provide industrial adoption guidelines. It is shown that, unlike existing single-asperity contact models, our multi-asperity particle contact model explains the effect of the amount of silica, the predominant role of the particle surface roughness, and insufficient flowability enhancements through conventional blending. Our model, coupled with two other models, is used for the determination of the amount and type of guest particles. These models provide an estimate of reduced cohesion as a function of particle size, particle density, asperity size, surface area coverage, and dispersive surface energy. Cohesion is nondimensionalized by using the granular Bond number with the hope of linking the particle scale properties with bulk-scale properties such as flowability, bulk density, and powder agglomeration. Experimental results show that when done properly, dry coating led to significant bulk property enhancements such that 10 μ m powders attained flowability, fluidizability, and dispersibility as good as 100 μ m powders; qualitatively agreeing with the model-predicted dramatic reduction in Bond number.

1 Introduction

Predicting and tailoring powder behavior is essential in industries that involve powder-based processes, particularly in the pharmaceutical industry. A priori determination of how pharmaceutical powders will flow, pack, or agglomerate is critical, as these bulk properties significantly influence several operations such as transport, feeding, mixing, die-filling, and tablet compaction [2]. The current industry trend toward using finer particle sizes to enhance pharmacokinetics leads to further challenges associated with cohesive powders, which typically exhibit poor flow and packing behavior. This, in turn, increases difficulties in handling and processing these materials, highlighting the importance of understanding the highly cohesive nature of many pharmaceutical powders.

Particle size is widely recognized as the most influential factor at the particle scale affecting the properties of bulk powders [1, 3]. However, significant knowledge gaps remain regarding the impact of various particle-scale properties on predicting bulk property prediction, especially when powders are dry-coated for surface modification. Dry coating results in a tailored particle morphology without altering the particle size, which can lead to dramatically reduced cohesion [4, 5]. Therefore industry reliance on

particle size alone is inadequate leading to trial-and-error and suboptimal design of formulations [1].

This paper addresses the challenges of predicting bulk powder properties and their enhancements after dry coating based on particle-scale measurements. This is done by correlating dimensionless cohesion, represented by granular Bond Number as the ratio of adhesive to body forces, to bulk properties. Mechanistic predictive particle-contact models are used that account for particle size, surface roughness, surface energy, and true density. The presented results should facilitate industrial design of formulations and make decisions regarding whether to consider employing dry coating processes for enhanced product design.

2 Theoretical

For dry, uncharged pharmaceutical powders, van der Waals (vdW) forces dominate interparticle interactions. These forces are approximately 10 times stronger than electrostatic forces, while capillary forces remain negligible in the absence of moisture. The vdW forces arise from dipole-induced attractions between molecules constituting the particles. The granular Bond number (Bog) quantifies cohesiveness:

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$$Bog = \frac{F_{cohesion}}{W_g} \quad (1)$$

Where $F_{cohesion}$ represents the cohesive force between particles, estimated using contact models employing several particle scale properties, and W_g represents the particle weight, estimated employing particle size (volume estimation) and true density. This explains why coarser particles generally flow better than fine particles despite experiencing stronger absolute cohesion forces. Our previous papers have validated the link between the Bond number and various properties of bulk powder, such as the minimum fluidization bubbling velocity, bulk density, angle of repose, and flow function coefficient.

The multi-asperity contact model for estimating van der Waals forces in dry-coated particle systems represent a significant advancement over single-asperity models. It considers the distribution of roughness and the effect of surface area coverage (SAC) of guest particles on host particles.

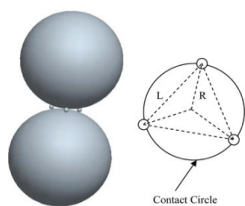


Figure 1. Schematic of Multi asperity model

The adhesion of uncoated particles as given by:

$$F_{cohesion} = \frac{AD}{12z_0^2} \quad (2)$$

reduces with surface area coverage (SAC) at nano roughness,

$$SAC = \frac{N \times \frac{\pi d^2}{4}}{4\pi \left(\frac{d_{asp} + D}{d_{asp}}\right)^2} \times 100\% \quad (3)$$

correspondingly, the weight percent of the guest particles is:

$$Wt \% = \frac{(Nd^3 \rho_D)}{(D^3 \rho_D) + (Nd^3 \rho_{dasp})} 100\% \quad (4)$$

The adhesive force between two coated particles becomes:

$$F_{ad} = \frac{Adasp}{4z_0^2} + \frac{A}{24 \left(\left(1 + \frac{dasp}{D} \right)^2 \frac{1.21dasp^2}{SAC \cdot D^2} - 1 \right)^2} * D \quad (5)$$

This model reveals three distinct adhesion regimes with increasing SAC:

1. Host-host contact (as-received particles adhesion, Eq. 2)
2. Host-guest contact (adhesion with changing SAC, Eq. 5)
3. Guest-guest contact (dry coated particle, above 30%SAC, Eq. 6)

Above 30% SAC threshold, the contact is between guest-guest and force equation becomes:

$$F_{cohesion} = \frac{A}{12z_0^2} \left(\frac{D}{2(H_0/z_0)^2} + \frac{3daspD}{dasp+d_p} \right) \dots \dots \dots (6)$$

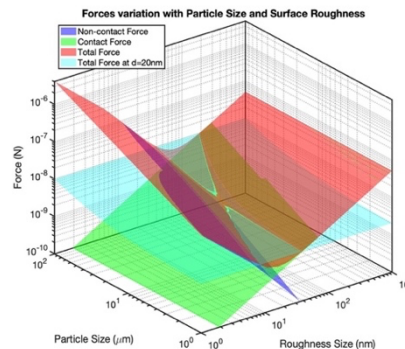


Figure 2. Force visualizations as function of particle size and roughness sizes

Here, N = number of guest particles per host particle, d = guest particle diameter, D = host particle diameter, ρ_{dasp} = guest particle density, ρ_D = host particle density, A = Hamaker constant, z_0 = equilibrium separation distance (0.4 nm) [6]. d_{asp} is size of roughness, the size of guest material for dry coating, H_0 represents the total separation distance between the host particles of size D , which includes the molecular separation distance z_0 (0.4 nm) plus the effect of asperities as $H_0 = z_0 + d_{asp}/2$. In Eqs. 5 and 6, the non-contact force is represented by the first term and the contact force is represented by the second term in each case. Figure 2 illustrates the interplay between particle size, surface roughness, and adhesion forces as per Eq. 6 for the case $30\% < SAC < 100\%$. The plot reveals that nanoscale roughness (1-100 nm) creates a distinct "valley" of minimum adhesion, explaining why nanomaterials are particularly effective as flow aids. The non-contact force, 2nd term in Eq. 6 (blue plane), decreases with roughness but increases with particle size, while the contact force, 1st term in Eq. 6 (green plane), increases with both parameters. Notably, the turquoise plane representing dry-coated particles with 20nm silica demonstrates how dry coating normalizes adhesion forces regardless of initial particle morphology. The multi-asperity model thus provides a theoretical foundation for rationally designing dry coating processes with appropriate guest particle to host particle size and weight ratio.

3 Materials and Methods

A variety of pharmaceutical powders, including active pharmaceutical ingredients (APIs) and excipients (fillers, binders, inhalation-grade materials), are tested for property improvement via dry coating using two silica types: A200 and R972P, properties are provided in references [1, 7].

Particle size distribution was measured using Sympatec Helos/Rodos laser diffraction at 1.0 bar. True density was determined with AccuPyc 1330 helium pycnometry and Surface energy was assessed using IGC.

Powder flowability was evaluated using an FT4 rheometer. Other bulk property measurements include

agglomerate ratios and conditioned bulk density etc.

Samples were dry-coated in a LabRAM acoustic mixer (60Hz, 70G) for 5 minutes to distribute nano-silica uniformly on host particles, creating engineered surface roughness.

4 Results and Discussion

4.1 Bulk Property Enhancements

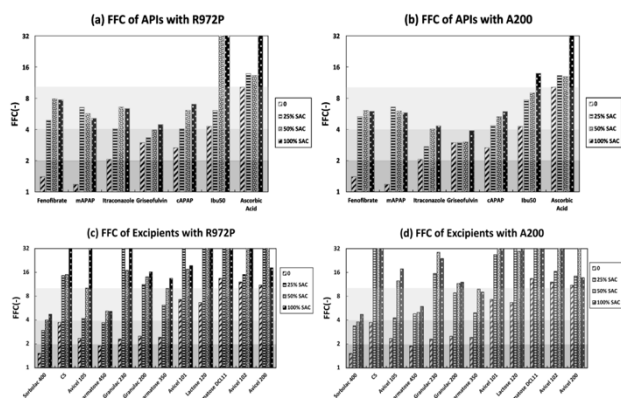


Figure 3. Flow function coefficient (FFC) as a function of surface area coverage (SAC) of (a) host active pharmaceutical ingredients (APIs) by hydrophobic R972P nano-silica, (b) host APIs by hydrophilic A200 nano-silica, (c) host excipients by R972P, and (d) host excipients with A200

The Surface Area Coverage (SAC) approach for dry coating pharmaceutical powders demonstrated consistent effectiveness across diverse materials. Experimental results (Figure 3) showed that 50% SAC generally provides optimal flow improvement for both APIs and excipients, regardless of silica type (hydrophobic or hydrophilic).

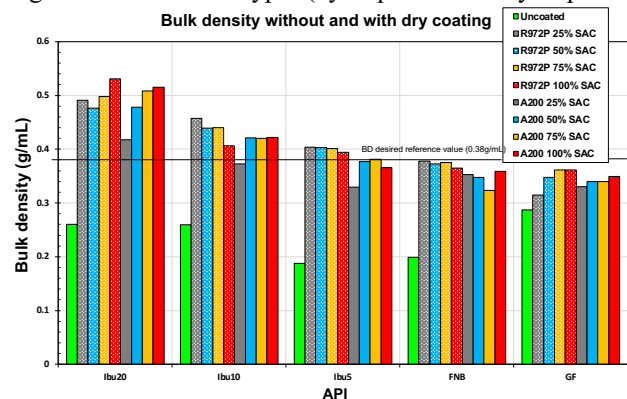


Figure 4. Bulk density improvement by dry coating [8]

This aligns with theoretical models predicting guest-guest contact at approximately 30% SAC. The 50% SAC threshold typically corresponds to less than 1 wt% silica for most powders, suggesting higher amounts are rarely necessary. This approach offers a more reliable method for determining optimal coating amounts than traditional weight percentage methods, providing consistent and

efficient strategies for improving powder flowability in pharmaceutical formulations.

Figure 4 illustrates the enhancements in bulk density for various pharmaceutical materials after dry coating with silica at different surface area coverages. The uncoated materials (represented by blue bars) display consistently lower bulk densities than their coated versions. Both hydrophobic (R972P) and hydrophilic (A200) silica effectively improve bulk density beyond the reference value of 0.38 g/mL, which is requisite for direct compression tableting. All materials exhibit pronounced enhancements, indicating that engineered surface roughness achieved via dry coating reduces cohesion, allowing for improved particle packing, while at the same time facilitates the particle separation or dilation needed at incipient flow. Thus dry coating promotes both packing and flowability, thus powder processability for pharmaceutical manufacturing.

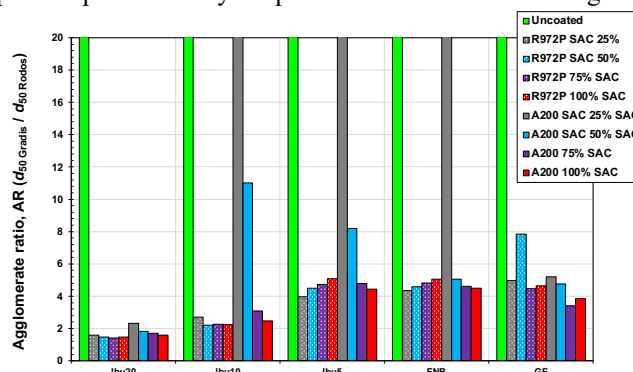


Figure 5. Agglomerate ratio (AR) of as-received and dry-coated materials [8]

Figure 5 illustrates that dry coating effectively reduces cohesion and minimizes agglomeration in various pharmaceutical APIs. The Agglomerate Ratio (AR)—the ratio of agglomerate size (d_{50} from Gradis/QicPic no dispersion pressure) to primary particle size (d_{50} from Rodos/Helos, under dispersion pressure)—serves as an indicator of agglomeration. Uncoated materials (green bars) show very high AR values (exceeding 20), showing severe agglomeration. However, even a modest 25% SAC in dry coating significantly lowers agglomeration

4.2 Surface Morphology Analysis

The SEM images confirm the altered morphology resulting from the dry coating of nano silica onto the host surface. This modified morphology leads to a significant reduction in cohesion and enhanced bulk properties.

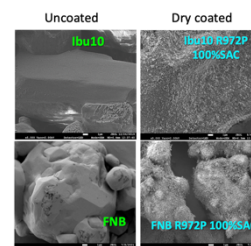


Figure 6. Example SEM images

4.3 Prediction of Bulk flowability via Bond Number

Figure 7 illustrates how correlating particle size results in an inability to capture properties before and after dry coating. While uncoated powders show a correlation between particle size and Flow Function

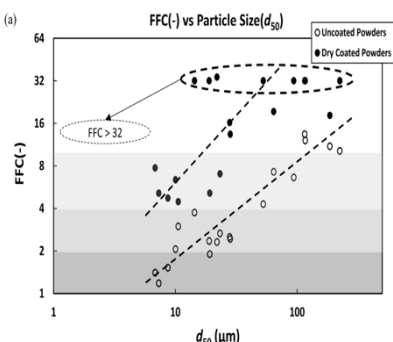


Figure 7. FFC plotted against median particle size [1]

Coefficient (FFC), dry-coated powders with identical particle sizes exhibit dramatically improved flowability. The clear separation between trend lines for uncoated and dry-coated materials demonstrates that surface properties significantly influence bulk behavior.

When the Bond Number is calculated by estimating adhesion from Eq. 5, substituting $d_{asp} = 0$ for as-received particles and d_{asp} as the size of the coating materials, adhesion is estimated both before and after dry coating. Then, when substituted into Eq. 1, the Bond Number is calculated for both the pre-coating and post-coating conditions. Analysis of calculated Bond Number (Bog) as a flowability predictor shows strong correlations with experimental FFC values across various materials, following power-law trends. By incorporating particle size, density, asperity scale, and surface energy, Bog provides a

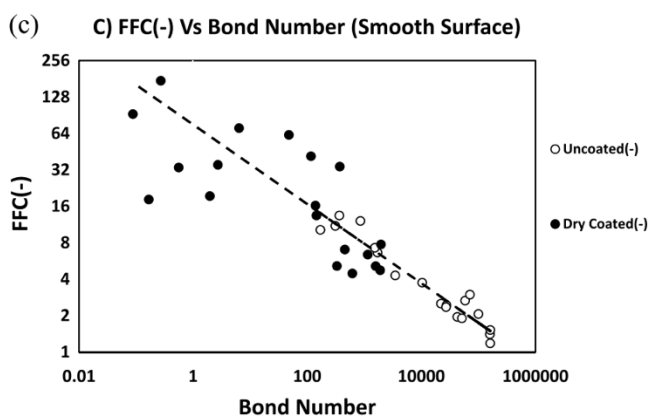


Figure 8. Flowability of coated and uncoated powders captured using Bond Number [1]

comprehensive basis for flowability prediction, validating dry coating as an effective technique for enhancing pharmaceutical powder properties.

5 Conclusions

The multi-asperity model discussed is shown to provide reliable reduction in cohesion and hence guidelines for proper selection of dry coating parameters, the guest particle types and their concentrations. Granular Bond number can be used to link the particle-scale with bulk-scale properties. Further, engineered surface roughness due to dry coating of nano-sized guests markedly diminishes cohesion in fine pharmaceutical powders, enhancing their bulk properties such as flowability, bulk density, and reduced agglomeration. These enhancements help improve pharmaceutical product performance, leading to better content uniformity, consistent die filling, and superior tablet quality. In summary, the proposed model-based approach is expected to reduce reliance on traditional trial-and-error techniques for rational formulation design.

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