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Prediction of powder flow performance using a multi-component granular Bond number

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ABSTRACT

In order to improve fundamental understanding of powder flow behavior which is essential to the success of many pharmaceutical processes, this study investigates the relationship between particle-scale interactions dominated by the cohesive van der Waals force and the flow function coefficient. This study finds that the granular Bond number, defined as the ratio of the inter-particle cohesion force to particle weight, correlates well to the flow function coefficient, a metric used to assess powder flow performance and defined as the ratio of consolidation stress to unconfined yield strength. The inter-particle cohesion force was calculated by the so-called multi-asperity model which is a modification of the well-known Rumpf equation. As a major novelty, a granular Bond number is defined for multi-component mixtures (i.e. powder blends) and used to predict the flow function coefficient of binary, ternary, and quinary mixtures of a model API, acetaminophen, and two common pharmaceutical excipients, microcrystalline cellulose and pregelatinized starch. Surface modification via dry-coating was also used to alter the inter-particle force and more thoroughly investigate the effect of particle interactions on powder flow performance. Since the multi-component granular Bond number takes into account particle properties and particle interactions of all components in the powder blend, this novel approach shows good predictability for powder mixtures. Although the flow function coefficient alone is not a stringent prediction of powder flow, the modeling effort put forth in this study can be used to better guide formulation development.

1. Introduction

Particulate processes remain exceedingly difficult to model, design, and control despite the industrial importance of powders and other granular materials [1]. The difficulties associated with particulate processes arise from the fact that powders often exhibit complex and diverse bulk-scale behaviors which lack the proper fundamental understanding. While bulk-scale behavior originates from contact and non-contact interactions among particles and their interaction with a medium such as a gas or liquid, particle-scale interactions are difficult to resolve. Additionally, constitutive relationships derived from first-principles relating bulk-scale behavior, particle-scale interactions, and particle properties are generally unattainable.

These scientific deficiencies are particularly problematic in the pharmaceutical industry in which tablets and capsules comprise the majority of pharmaceutical products. The success of even the most basic operations such as powder flow into a die cavity cannot be predicted with much certainty [2]. While powder flowability is critical to the success of tableting, it is also an important factor in many other pharmaceutical processes such as mixing/blending, coating, and capsule filling [2–4]. A poorly flowing powder can result in unacceptable content uniformity, variable tablet/capsule weights, or prevent manufacturing altogether for an otherwise acceptable formulation [2–5]. Since active pharmaceutical ingredients (APIs) are often characterized as cohesive and poorly flowing, ensuring adequate flowability requires significant development work in the formulation of solid dosage forms. Due to the variable physiochemical properties of each API, solid dosage formulation remains highly empirical as well as a material and time consuming process. Needless to say, greater fundamental understanding of bulk powder behavior such as flowability is required to achieve more robust formulation development.

Given that adequate powder flowability is essential to formulation development, there has been much effort devoted to this topic with most studies focused on elucidating the effect of particle size distribution [6–8], particle shape [9–12], or moisture [13,14]. These studies may be most useful for understanding the flow of coarse non-cohesive particles, but they omit the underlying mechanisms responsible for the flow behavior of fine (~100 μm and smaller) cohesive particles [15,16]. Fine, dry, and uncharged powders, which represent many APIs and pharmaceutical excipients, are dominated by the inter-particle cohesive force known as the van der Waals force [17]. Because the van der Waals force can be orders of magnitude greater than particle weight,

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the ratio of which is known as the granular Bond number, fine powders are usually characterized as cohesive and poorly flowing. Since the granular Bond number can be approximated from measureable particle properties, it may be possible to explain and predict powder flow behavior on a more fundamental basis.

To better guide formulation development, this study investigates the relationship between particle-scale interactions dominated by the cohesive van der Waals force and powder flow performance. A model API, acetaminophen, and two common pharmaceutical excipients, microcrystalline cellulose and pregelatinized starch, are investigated individually and in mixtures. Dry-coating, a process which modifies the surface properties of particles and alters particle interactions, was also utilized to more systematically investigate the effect of inter-particle force on flow performance. This study finds that the granular Bond number, a parameter which quantifies inter-particle cohesion, correlates well with the flow function coefficient, a metric commonly used to evaluate the unconfined yield strength of powders and assess flow performance. As a major novelty, a granular Bond number for multi-component mixtures (i.e. powder blends) is formulated and successfully used to predict the flow function coefficient of two, three, and five component powder blends. Accordingly, the model put forth in this study can be used to determine the effect of particle properties on powder flow performance of individual materials or to predict the flow performance of powder blends as quantified by the flow function coefficient.

2. Theoretical preliminary

In order to provide a more fundamental description of bulk-scale powder behavior, particle-scale interactions must be considered. For two particles in close contact, their interaction is controlled by capillary, electrostatic, and van der Waals (vdW) forces [17,18]. In the absence of condensed moisture capillary forces are irrelevant, and electrostatic forces are known to be of secondary importance and about 10 times weaker than the vdW force under typical experimental conditions [18]. Thus, discussion is restricted to vdW force which is expected to be the dominate force for fine, dry, uncharged powders.

The vdW force originates from the dipole-induced attraction between two particles' constituent molecules. The magnitude of this force depends on the properties of the particles in contact. These properties mainly include particle size, geometry, surface roughness, surface energy, and mechanical properties such as hardness and elasticity. For fine particles, generally ~100 μm and smaller, the vdW force can cause severe agglomeration resulting in non-ideal powder properties such as poor flowability [17]. Such powders are termed “cohesive”.

In order to account for the vdW force between two particles, many cohesion force models have been proposed taking into account different particle geometries, modes of contact, and particle deformation behavior [17–20]. The expression for cohesion force shown in Eq. (1) is a modification of the well-known Rumpf model [21].

$$F_{cohesion} = \frac{A}{12 z_0^2}\left(\frac{d_p}{2(H_0/z_0)^2} + \frac{3 d_{asp} d_p}{d_{asp} + d_p}\right) \tag{1}$$

The so-called “multi-asperity” model of Eq. (1) gives the cohesion force $F_{cohesion}$ between two spherical particles (or adhesion force for dissimilar particles) of diameter d_p with rough surfaces characterized by asperities of diameter d_{asp}. The first term within the parentheses on the r.h.s. of Eq. (1) accounts for the non-contact force between the two particles separated by distance H_0 whereas the second term accounts for the contact force between the particle and the asperities. The contribution of the non-contact force is typically small and can be neglected unless separation distance is about 20 nm or less. The Hamaker constant A is a material property and can be calculated based on the material's surface energy. The equilibrium separation distance z_0 is assumed to be 0.4 nm. The separation distance H_0 can be approximated by Eq. (2) for asperities assumed to be half-spheres, but it can be more precisely determined if the spatial and size distributions of the asperities are known [22].

$$H_0 = z_0 + d_{asp}/2 \tag{2}$$

The multi-asperity model was chosen here since it has been shown to predict fluidization behavior of cohesive powders which indicates that it can offer an accurate determination of the vdW force to predict bulk-scale powder behavior [21]. It has also been used to explain the effects of inter-particle cohesion on powder bed porosity [23]. Since it is generally known that powders that pack well also flow well, the multi-asperity model is also used in the following to elucidate the effect of inter-particle cohesion on powder flow performance.

While the cohesion force between two particles can be determined from Eq. (1), a multitude of other body and surface forces must be considered in relation to the vdW force to determine a particle's overall cohesiveness. The force of gravity, a competing force to the vdW force, is most relevant for typical particulate processes although centrifugal or hydrodynamic drag forces may also become applicable depending on the process. The importance of this concept is exemplified by the fact that two coarse particles experience a larger cohesion force than two fine particles yet are also better flowing. Hence, a dimensionless parameter known as the granular Bond number, defined as the ratio of cohesive forces to non-cohesive forces, is used to quantify inter-particle cohesion [17]. The granular Bond number, hereafter referred to as “Bond number”, shown in Eq. (3) is most relevant for simple powder flow.

$$Bo_g = \frac{F_{cohesion}}{W_g} \tag{3}$$

As shown in Eq. (3), the Bond number quantifies inter-particle cohesion as the ratio of cohesion force (or adhesion force for dissimilar particles) to the particle weight due to gravity. Particles with higher cohesion forces relative to their weight ($Bo_g > 1$) are considered cohesive whereas particles with lower cohesion forces relative to their weight ($Bo_g < 1$) are consider non-cohesive. This explains why coarse particles can have a higher cohesive force than fine particles but typically have acceptable flow behavior.

It should be advised that the Bond number strictly quantifies inter-particle cohesion. The behavior of particle assemblies (i.e. powders) is far more complex, but it is expected that inter-particle cohesiveness should dictate, in a fundamental way, bulk-scale behavior such as powder flow performance. In fact, the Bond number of Eq. (3) has been shown to correlate with bulk-scale powder properties such as minimum fluidization bubbling velocity [22], bulk density [23,24], angle of repose [25], and the flow function coefficient [26]. The latter two are used as metrics to quantify powder flowability and motivated the current work. While these two previous studies [25,26] have very clearly shown the relationship between the Bond number and either angle of repose or the flow function coefficient, this study will expand on these concepts and formulate a practical methodology to relate interparticle cohesiveness to powder flow performance. The utility of the Bond number to explain bulk powder behavior could be further enhanced if it could also be applied to multi-component mixtures (i.e. powder blends). Since all previous investigations [22–26] of inter-particle cohesiveness and bulk powder behavior have restricted study to single component powders, two important questions arise: 1) Can the Bond number be extended to explain the behavior of powder blends? This possibility is of course dependent on the second question which at present has not been addressed in literature. 2) How is the Bond number of a powder blend calculated? To explain and predict powder flow performance under a more fundamental basis, these questions are addressed through investigation of single- and multi-component mixtures in the following sections.