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Pharmaceutical powder blends are multicomponent mixtures of excipients and the drug powder particles which have irregular shapes with equivalent diameters typically ranging from 40 microns to 300 microns. We consider idealizations of such systems with emphasis on the size dispersity in a pure excipient powder comprised of spherical particles. We study the characteristics of the particle packings generated through gravitational compaction followed by uniaxial compaction via Discrete Element Method simulations (Dutt et al., 2004 submitted). We present results for two common excipients: microcrystalline cellulose (MCC) and sucrose. For each excipient, we vary the degree of dispersity in the diameters of the particles. For insight into the geometrical characteristics of the particle packings, we calculate the coordination number, packing fraction, radial distribution functions and contact angle distributions for the various mixtures. The evolution of the force and stress distributions along with the stress-strain relations are calculated for each system. We discuss comparisons of these quantities for systems with different size dispersity and material properties. For MCC and sucrose mixtures with narrow size distributions (195-225 microns, 170-260 microns), the average packing fraction and coordination number prior to and after uniaxial compaction decreases with interparticle friction, in agreement with results for monodisperse spheres (Silbert et al., Phys. Rev. E (2002)).

## 1 INTRODUCTION

Particle packings of granular materials (Jaeger, Nagel & Behringer 1996) found in nature and industry are rarely comprised of monodisperse spherical particles; the particles will have different shapes and sizes. The spatial configurations of the particles along with the degree of the size polydispersity will affect the geometric aspects of the packing characteristics and its response to external loads which we call the "material response". It is of great importance to obtain insight into the influence of the size polydispersity on the resulting geometry and the material response of the particles packings to an externally applied strain; these issues are highly pertinent both in academia and industry, for example, the daily handling of large volumes of powders, in terms of transportation and processing, by the construction, food, cosmetic and

pharmaceutical industries, to name a few. More specifically, this approach can be utilized to study the packings of pharmaceutical powders (such as tablets (Alderborn & Nystrom 1996)); these are complex mixtures of the drug and the excipient particles which have a wide range of sizes, shapes and material properties. The focus of our studies are the effects of the size dispersity on the packings of excipient particles. For simplicity, we assume the particles to be spherical and, we look at packings of microcrystalline cellulose (MCC) and sucrose particles.

The paper is subdivided into the following sections: section 2 provides a description of the systems of our interest; section 3 describes the details of the numerical model and the numerical experiment; section 4 presents the results from our numerical experiments and section 5 summarizes the

## 2 POLY-DISPERSE SYSTEM OF INTERESTS

The geometric characteristics of a particle packing is strongly influenced by the degree of the size dispersity in the system such as the packing fraction, the average coordination number, the radial distribution function, the distribution of contacts and the contact angles. What is a bit intriguing is the effect of the size dispersity on the force distributions and the stress-strain response to an externally applied strain. Intuitively, an increase in the size dispersity would decelerate the stress buildup in packings with the caveat that one begins with identical values of the packing fraction for each sample explored. However, the effect on the force distributions by the size dispersity remains unclear. We address these various issues by examining unimodal agglomerates of MCC and sucrose with a mean particle diameter approximately equal to  $200\ \mu\text{m}$ . We approximate the MCC and sucrose particles to be spheres in order to remove the additional complexity of the shape of the particles. We study the effects of the size dispersity on the particle packings by introducing discrete components of varying concentrations in way so as to preserve the distribution of the particle sizes in the sample. For both MCC and sucrose, we have used the following four samples: a monodisperse sample S1 of particles with  $200\ \mu\text{m}$  diameter, a 2-component sample S2 with equal parts of particles with  $195\ \mu\text{m}$  and  $225\ \mu\text{m}$  diameters, a 4-component mixture S4 of particles with diameters given by  $170\ \mu\text{m}$ ,  $195\ \mu\text{m}$ ,  $225\ \mu\text{m}$  and  $260\ \mu\text{m}$  of concentration ratios 2:3:3:2 and a 6-component mixture S6 of particles with diameters given by  $150\ \mu\text{m}$ ,  $170\ \mu\text{m}$ ,  $195\ \mu\text{m}$ ,  $225\ \mu\text{m}$ ,  $260\ \mu\text{m}$  and  $295\ \mu\text{m}$  of concentration ratios 3:6:8:8:6:3. Each sample contains a total of 1800 particles with the same mean size. We present results for MCC particles, unless specified otherwise.

## 3 NUMERICAL MODEL

We have used 3D Discrete Element Method (DEM) simulations to carry out our numerical experiments. The particles are non-rigid and can undergo small deformations on contact with other particles. The degree of deformation at a contact will determine the contact force experienced by the two particles forming the contact. We have used the Hertz-Kuwabara-Kono contact force model to represent the normal forces and a linear damped harmonic oscillator model to represent the tangential contact forces. The material properties such as the Young's modulus and the Poisson ratio are used to determine the contact force parameters (Schafer, Dippel & Wolf 1996). The Young's moduli and the Poisson ratios for MCC and Sucrose

are  $9.08 \times 10^9\ \text{Pa}$  and  $2.70 \times 10^{10}\ \text{Pa}$ , and 0.3 and 0.25, respectively (Alderborn & Nystrom 1996). Interparticle substrate friction has been accounted for by including Coulomb's friction criteria (Aastrom, Herrman & Timonen 2000); thereby, adding two more control parameters: the coefficient of kinetic friction  $\mu_k$  and the coefficient of static friction  $\mu_{stat}$ . All the simulations are performed in two stages: the particles are allowed to settle under gravity followed by constant strain uniaxial compaction at  $1\ \text{mm/s}$ . Both phases of the simulations are carried out for a preset interval of time. Further details of the interparticle forces and the numerical simulation can be found in (Dutt, Hancock, Bentham & Elliott 2005).

## 4 RESULTS

We have used various quantitative measures to characterize the geometric aspects of the packings obtained via gravity compaction (GC) and uniaxial compaction (UC), as mentioned earlier. Numerical experiments have been repeated, using the various samples, under identical external conditions (i.e., the duration of the GC and the UC phases), for different values of the interparticle substrate friction (for simplicity, we have taken  $\mu_k = \mu_{stat}$ ). Substrate friction serves to quench the kinematics at the interparticle contacts; as a consequence, the values of the packing fraction and the coordination numbers for a mechanically stable agglomerate of particles are found to decrease with increasing friction. These trends have been observed for packings of monodisperse spheres (Silbert, Ertas, Grest, Halsey & Levine 2002). We have found similar behavior for all the samples after the GC and the UC phases, independent of the degree of polydispersity; in addition, our results show the packing fraction and the coordination number to decrease nonlinearly with increasing substrate friction, in agreement with (Silbert, Ertas, Grest, Halsey & Levine 2002). Intuitively, during the GC phase, a stable value of the packing fraction is attained in a decreasing interval of time (from the commencement of the simulation) with increasing values of friction for all the monodisperse and multi-component mixtures studied. A comparison of the distribution of contacts for the various mixtures after the GC and the UC phases is provided in Fig. 1. These are results from numerical experiments using the same value of substrate friction ( $\mu_k = \mu_{stat} = 0.1$ ). After settling under gravity for the same interval of time, the contact distribution favors lower average number of contacts and a greater spread with increasing size dispersity. As expected, the contact distribution shifts in favor of a higher average number of contacts after the UC phase, for all the samples, maintaining the trends displayed after the GC phase, as a function of the

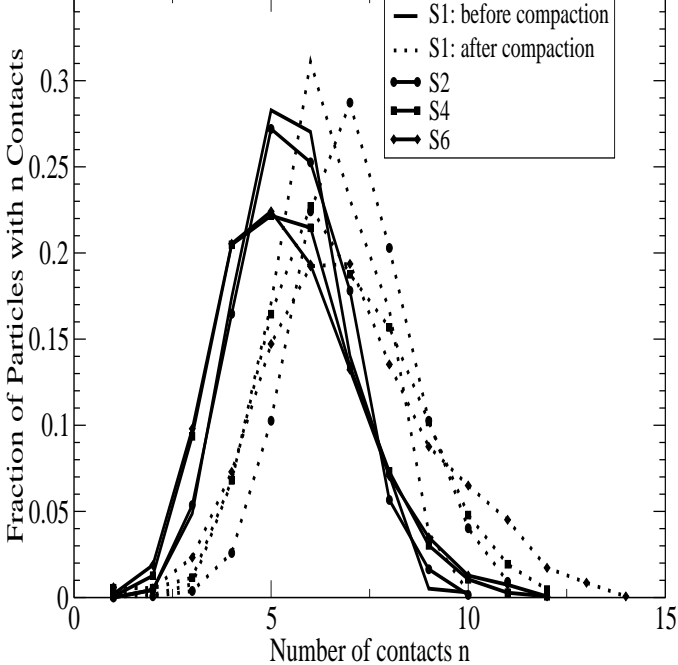


Figure 1. Fraction of particles  $N(n)$  with a given number of contacts  $n$  after settling under gravity (the solid curves) and on completion of the UC phase (dotted curves), for samples S1, S2, S4 and S6.

size dispersity. The increasing range of the average number of contacts with the size dispersity can be understood as follows: a system of particles, beginning with random positions and settling under gravity, will generate voids which may not be large enough to accommodate the particles, thereby resulting in mechanically static but unstable packings. As the width of the size range of the particle agglomerates increases, the voids generated via the GC phase of the particles will be able to accommodate an increasing fraction of the particles, resulting in static packings with increased mechanical stability, with the contact distribution shifting in favor of higher average number of contacts. Due to the relatively narrow difference in the size ranges between the various samples studied, increasing the size dispersity tends to spread out the distribution without significantly affecting the coordination number.

Insight into the packing structure can be obtained via the radial distribution function (RDF) which can indicate the degree of mixing, keeping in mind the concentrations of the individual components. In the case of sample S1, the RDF will also highlight the presence of crystallization or close packing. Fig. 2 shows the RDFs for the four samples after the GC and UC phases. The RDF of the monodisperse agglomerate shows an expected increase in the close-packing after completion of the UC phase due to the increase in the amplitude of the second peak (Clarke & Jonsson 1993). For the multicomponent mixtures, the first few amplitudes arise from the different contacts; the relative heights of the amplitudes indicate the degree of mixing, keeping in mind the concentra-

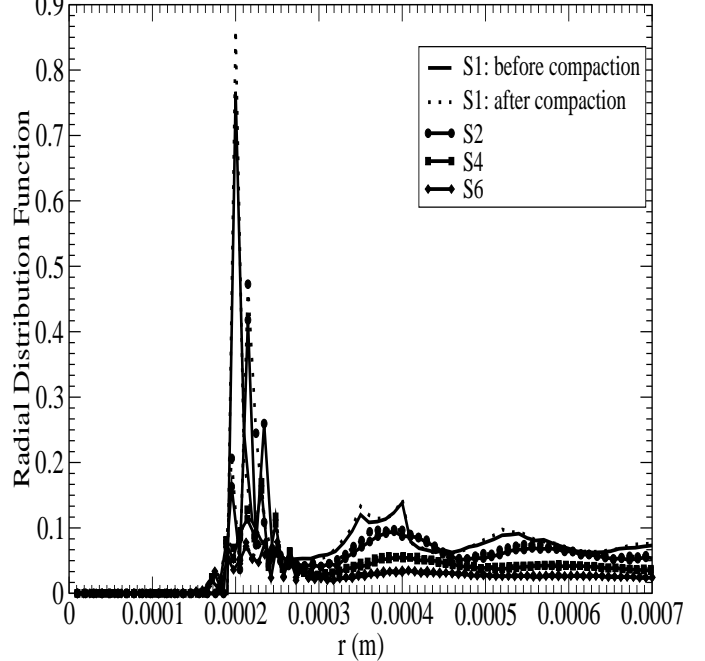


Figure 2. Radial distribution functions after settling under gravity (solid line) and on completion of the uniaxial compaction phase (dotted lines), for the various samples.

tions of the various components. The difference between the RDFs after the GC and the UC phases decreases with increasing size dispersity; however, longer intervals of the UC phase will introduce noticeable changes in the RDFs. In addition to the RDF calculations, the distribution of contact angles can be used to study the internal structure of the dense particle packings. The contact angles are calculated by taking the projection of the contact vector on the coordinate axes. Our results indicate no significant differences between the polar and the azimuthal angle distributions for the various samples. Our results for the azimuthal angle distributions have been summarized in Fig. 3. However, after the UC phase, the azimuthal angle distribution shifts in the favor of higher azimuthal angles, implying the reorientation of the contact vector so that the participating particles are attaining greater mechanical stability.

We have also explored the distribution of the normal contact forces before and after the UC phase, and the stress response to an externally applied strain, as a function of the size dispersity. The motivation behind this line of query is to look at the influence of the contact network and the packing fraction on the force and stress response of the particle agglomerate. Fig. 4 shows the normal contact force distribution  $P(f_n)$  before and after the UC phase, for the various MCC and Sucrose samples. Each normal contact force  $F_n$  has been normalized by the average normal contact force  $\langle F_n \rangle$  ( $f_n = F_n / \langle F_n \rangle$ ) for each set of results. Before the UC phase, the distribution of the large contact force ( $f_n > 1$ ) follow an exponential functional form ( $P(f_n) \propto \exp(-\beta f_n)$ ) due to

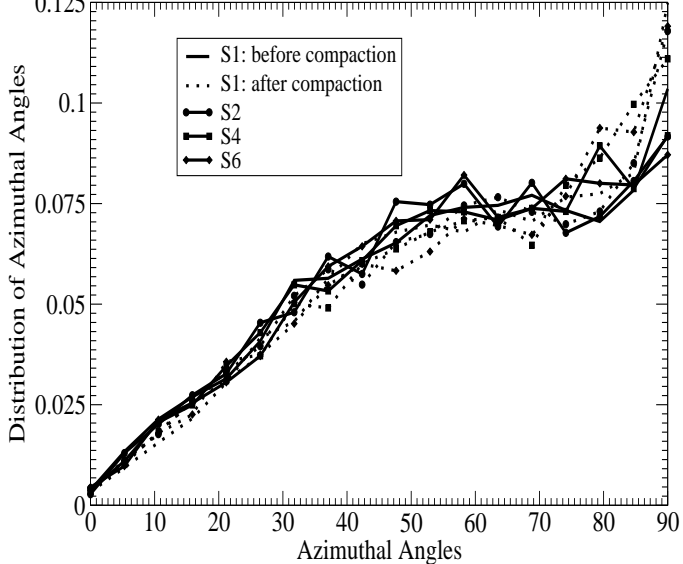


Figure 3. Azimuthal angle distribution after settling under gravity (solid line) and on completion of the UC phase (dotted lines), for the various samples.

the small number of contacts which bear the large contact forces. After the UC phase, the normal contact force distribution evolves to a Gaussian functional force ( $P(f_n) \propto \exp(-\alpha f_n^2)$ ) indicating a more even distribution of the load throughout the contact network (Liu, Nagel, Schecter, Majumdar, Narayan & Witten 1995)-(Thornton & Anthony 1998). For the weak contact forces ( $f_n < 1$ ), we find the results to agree with existing studies which have shown the distribution of the weak contact forces to adhere to a power law. We find similar observations for the tangential contact forces.

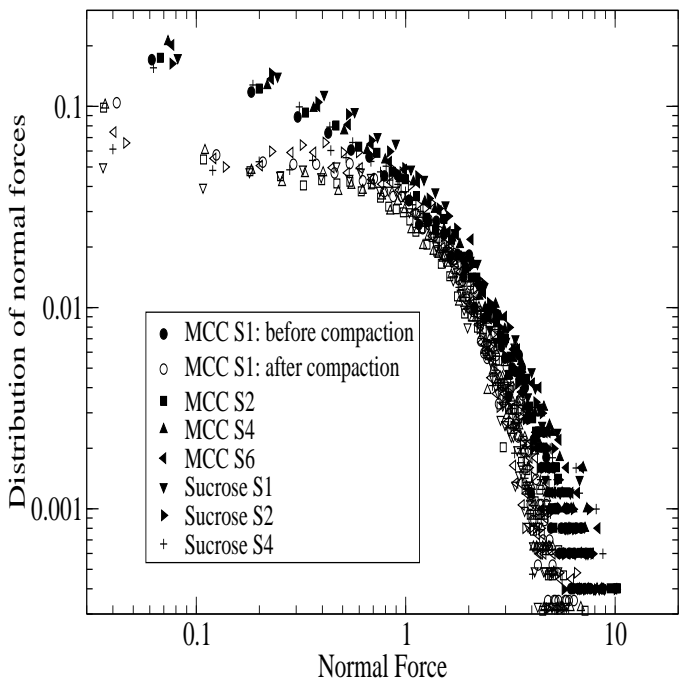


Figure 4. Normal contact force distribution  $P(f_n)$  ( $f_n = F_n / \langle F_n \rangle$ ) for the various MCC and Sucrose samples, before and after the UC phase.

initial packing fraction, the size distribution of the particles and the material properties. We have found the increasing size dispersity to decelerate the stress buildup in the particle agglomerate. This trend is however influenced by the initial packing fraction (before the commencement of the UC phase) which may account for the aberration in the behavior as demonstrated by the bidisperse mixture.

## 5 DISCUSSIONS

We find our studies for both MCC and sucrose particle packings to indicate that increasing the size dispersity introduces a larger spread in the contact number distribution while maintaining the same mean number of contacts. Also, the RDF calculations for the packings, prior to and after the UC phase, show decreasing differences between the two calculations with increasing size dispersity, indicating an increasing scope for further compaction. Otherwise, our studies have yielded expected trends in the behavior in terms of the interparticle friction and the particle size dispersity. The latter is a consequence of the narrow size dispersity of our samples; this is an issue we will address next. We will continue to address queries concerning the various aspects of the force distributions and the stress response to an external strain. We will be publishing further details of our findings elsewhere.

We would like to acknowledge Pfizer for providing funding support.

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