The role of fine particles on compaction and tensile strength of pharmaceutical powders

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ABSTRACT

The role of fine particles on compaction of powders and the resultant compact was studied experimentally. Samples of powders were prepared by successively removing fine particles from microcrystalline cellulose and lactose monohydrate powders. This method of preparing samples is unique compared to previous studies on particle size distribution, and allows for a better analysis of the role of fine particles. For each sample, the role of fine particles on the initial relative density of the materials during die filling, the compaction profile, the in-die elastic recovery during unloading of compaction force, and the tensile strength of the corresponding tablet was investigated. It was found that the initial relative density during the die filling process and early phase of compaction decreased as a portion of the fine particles was reduced. However, this difference in the relative density during the early stage disappeared at higher compaction forces. The peak compaction pressure, elastic recovery, and the compact's tensile strength remained the same regardless of the amount of fine particles, when plotted as a function of the relative density. These results indicate that the fine particles affect the initial packing, but not the compaction of these powders and the tensile strength of the compacts.

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1. Introduction

Powders and granular materials are the most commonly used materials in industrial processes and products. The characteristics of these materials are governed by the chemical and physical properties of the particles, the interaction among the particles, and additional external factors such as applied stresses and humidity. Among the physical properties, particle size distribution (PSD) is known to have a significant effect on the mechanical and kinematic properties of the powders. Some important effects of PSD include the efficiency of packing [1–4], mixing and segregation [5] and flow and handling [6,7] of powders. For powder compaction applications, the PSD may influence the mechanical strength [8–17] and drug release rate [18] of tablets. In principle, the smaller sized particles fill the void space between the large particles and increase the packing efficiency by increasing the solid fraction (also referred to as relative density) of the powder. For hard, spherical and mono dispersed system, a maximum relative density of 0.74 can be achieved for an arrangement of particles [19]. The presence of fine particles between large particles changes the structure of particle assembly and the mechanical interaction between the particles. While the fine particles assist in forming a higher density, they adversely affect

handling of powders [6,7,20]. Achieving higher densities and at the same time better handling of the powders with ease is desirable for high speed tablet manufacturing. Higher densities and better handling are both associated with the amount of fine particles present in the powders [21,22].

Extensive work has been conducted to identify the role of PSD on compaction and tensile strength of tablets [8–17]. Experiments of Sun and Himmelspach [12] showed that the tensile strength of compacted microcrystalline cellulose (MCC) powder decreases as the particle size increases. On the other hand, Mckenna and Mccafferty [8] and Herting and Kleinebudde [13] showed that the PSD has no effect on the tensile strength of compacted MCC powders. The experiments of Herting and Kleinebudde contain magnesium stereate (MgSt) as a lubricant while the experiments of Sun and Himmelspach [12] did not. The presence of MgSt was cited as a possible reason for the results of Herting and Kleinebudde [13]. However, Almaya and Aburub [17] reported that the PSD does not affect the tensile strength of MCC tablets in the absence of MgSt. These findings suggest the need for more rigorous investigation on the effect of PSD on the compaction process and the resultant tablet. From these studies, it is also known that particle size affects the tensile strength of compacts in different ways. For example, the tensile strength of starch compacts decreases as the particle size increases [17], while the PSD does not affect the tensile strength of sodium chloride and sucrose compacts [10]. Also, it is recognized that PSD and
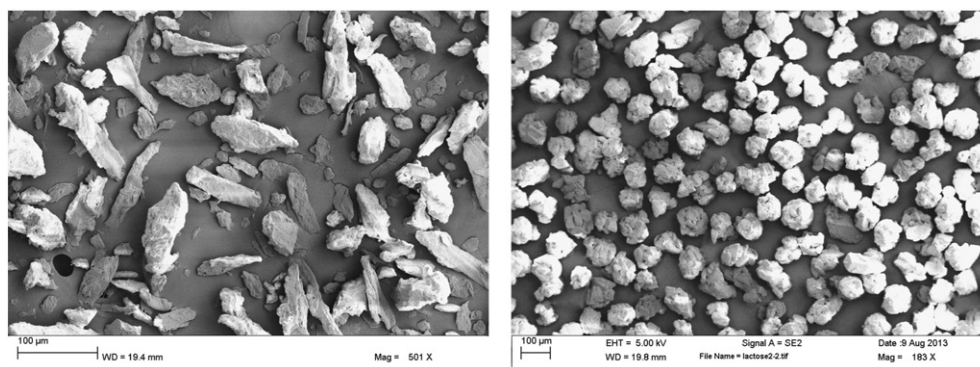
Fig. 1. Field Emission Scanning Electron Microscopy images of MCC-Avicel PH-102 (left) and lactose monohydrate (right). MCC particles have elongated shape and lactose particles have rounded shape.

humidity affect the tablet relaxation for some materials, such as sodium chloride, during short term storage after compaction, thereby affecting the tensile strength of the tablets as well [10].

Most of these studies are based on the comparisons of materials composed of narrow particle size distribution (i.e. solely fine particles or coarse particles). For example, results of Almaya and Aburub [17] are based on particle size of either fine (<74 μm) or coarse (180 μm–250 μm) particles. From these narrow particle size distributions, it is not clear how powders with a mixture of fine and coarse particles behave. Other studies on the effect of PSD on the compaction process and tensile strength properties of the compacts focused on particle sizes generated by dry granulation [13,14,23]. However, particles of the same material generated by granulation can have different true densities depending on the type of granulation process [24]. Therefore, it is difficult to identify the role of PSD and true density separately. All of these studies suggest that more research is required to clearly establish the effect of PSD on the tensile strength of tablets.

The primary goal of this work was to investigate the role of fine particles on the entire process of tablet compaction and on the mechanical strength of compacted powders. Several samples were prepared by removing selected portion of fine particles from the initial material, such that, for a given powder, each sample differed from the other by the smallest size of fine particle present. This preparation of powder samples by removing selected portion of the fine particles is unique compared to the other PSD preparation methods reported in the literature and allowed for a more precise investigation of the role of fine particles on the compaction process, that is, the initial die filling process, the evolution of the compaction pressure, the in-die elastic recovery of the compacted powders, and finally the tensile strength of compacts. For detailed comparison purposes, tablets of varying relative densities were made. Prior studies focused on the effect of PSD only on one or two of the above stages of the tablet compaction process. The current study, investigates processes that are affected by the presence of fine particles and the impact of fine particles on the tablet characteristics for two commonly used materials in pharmaceutical industry.

2. Materials and methods

Two commonly used pharmaceutical excipients: microcrystalline cellulose (MCC-Avicel PH-102, FMC Biopolymer, Newark, DE) and lactose monohydrate (Foremost Farms, Baraboo, WI), were used in this study. A Field Emission Scanning Electron Microscope (FESEM) was used to investigate the morphology of each material. The PSD was measured using a Beckman Coulter LS 13320 Laser Diffraction Particle Size Analyzer.

Four samples with different particle size distributions were prepared from each of the materials. The first samples for both materials had "as received" particle size distribution. The second, third and fourth samples were prepared by removing the fine particles which were

less than d_{20}, d_{50} and d_{75} sizes of the respective materials by mechanical sieving (about 100 g of powder was sieved for each sample). To achieve this, the powders on the lower pan were disposed off the pan at an interval of approximately 20 min. This procedure was repeated until the powder on the lower pan was a negligible amount. Particles less than d_{20} were removed from the second sample; particles less than d_{50} were removed from the third sample; and particles less than d_{75} were removed from the fourth sample by this procedure. The PSD of the samples was measured to determine if the desired distribution was achieved after the sieving operation.

The true density of MCC and lactose was measured using a AccuPyc Pycnometer (AccuPyc II 1340 V1.05 Unit 1 Serial No. 622) and helium as analysis gas. The samples were dried at 50 °C overnight before the density test. MgSt (Tyco Mallinckrodt, St. Louis, MO) was added as a lubricant to all samples at 0.25% w/w ratio. MgSt was mixed with samples of each material using a Resodyn Acoustic mixer (at a frequency of 70 Hz and duration of 2 min). Samples were stored in air tight plastic bags until used.

The samples were compacted using a Presster machine (The Metropolitan Computing Corporation of East Hanover, NJ) equipped with a 10 mm flat round face tooling at 200 mg press weight. At the start of the experiments and after about 20 tablets were compacted, the die wall was lubricated with MgSt using a cotton swab. A Kikusui Libra-2 tablet press was emulated at 16.4 rpm, which is the lowest compaction speed for this press. A low compaction speed was used to ensure that the compaction process is independent of the rate of material deformation. It has been known that the tableting speed
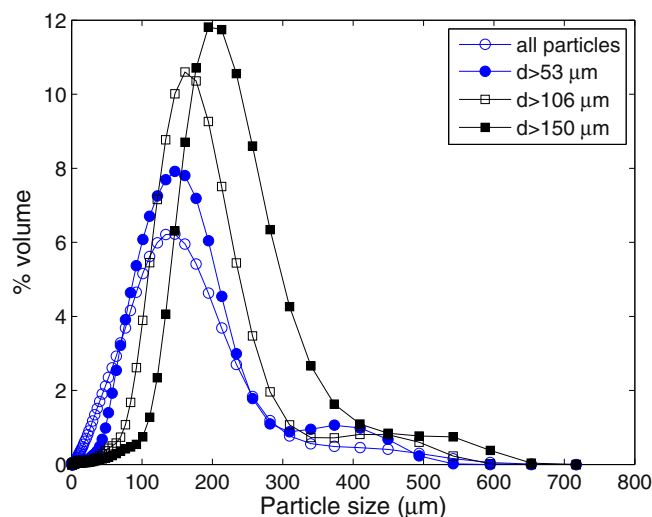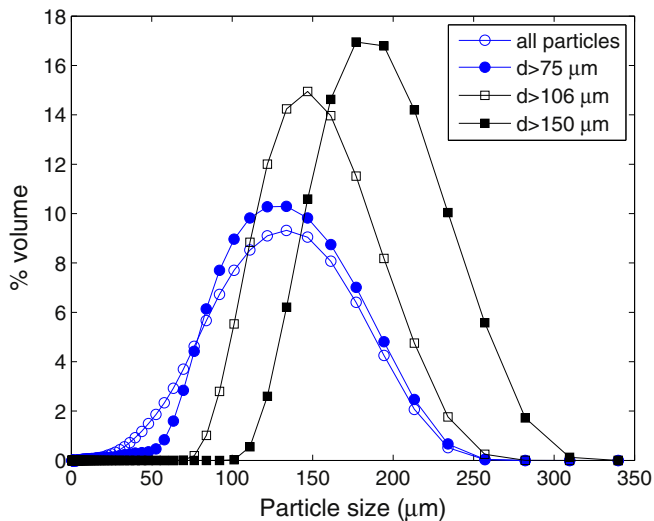

Fig. 2. Particle size distribution of MCC.

Fig. 3. Particle size distribution of lactose.

can affect the tabletability and compressibility of some materials such as MCC, starch, lactose, and dicalcium phosphate [25]. Compaction forces are measured by virtue of strain gauges placed on the pre-compression and compression roll pins. Since the forces on the upper and lower punches were almost the same, in these experiments the force on the upper punch was reported. No precompression force was applied for these experiments. Punch displacement was measured using a linear variable displacement transducer (LVDT; 250MHR, Schaevitz, USA) connected to each punch. For every machine setting five tablets were compressed.

After compaction, the dimensions of the tablets were measured using a caliper and the mass of the tablets was measured using a 0.1 mg precision scale. Diametrical breaking force of the tablets was measured using a hardness tester (Dr. Schleuniger Hardness Tablet Tester, Pharmatron). This test is also commonly referred to as diametrical compression test or Brazilian test. Prior studies have indicated that the time duration between tablet ejection and tensile strength testing can affect the tensile strength of tablets [10]. To avoid this variation in the tensile strength, all tablets were tested within two minutes after ejection. The tensile strength (σ_t) was computed from the measured breaking force F and dimensions of the tablets using the following equation:

$$\sigma_t = \frac{2F}{\pi Dt} \tag{1}$$

where D and t are the diameter and thickness of the tablets, respectively.

3. Results and discussion

Fig. 1 shows Field Emission Scanning Electron Microscope images of MCC and lactose. MCC particles have an elongated shape while the lactose particles are more rounded. PSD measured using Laser Diffraction Particle Size Analyzer is shown in Figs. 2 and 3 for all prepared samples of MCC and lactose powders, respectively. The PSD for "as received" MCC ranged from 0.23 to 750 μm, while the PSD for

"as received" lactose ranged from 2.3 to 230 μm. The cut off particle sizes (d_{20} for the second sample, d_{50} for the third sample, and d_{75} for the fourth sample) are shown in Table 1. As the exact sieve sizes of some of the cut off particle sizes are not available, the closest sieve size was used instead. A 75 μm sieve was used for the d_{20} size for lactose, and 105 and 150 μm sieves were used for the d_{50} and d_{75} sizes for both materials, respectively. It should be noted that it was not possible to remove the entire fine particles below the target sieve size. For each sample of both materials, about 10% by volume of the fine particles, which have a smaller size than the target sieve size, remained in the sample. Of those particles that passed through the sieve, some had sizes larger than the sieve size of the sieve. One of the reasons for this behavior may be the non-spherical shape of the particles, especially for noticeably elongated shape of MCC particles. The elongated particles may have a smaller size than the sieve size in one direction, but the effective diameter of these particles may be larger than the sieve size. The PSD of lubricated samples were similar to the pre-lubricated samples indicating that the lubricant and the mixing process did not affect the distribution.

Table 1 shows the average true density of the powders. For both MCC and lactose powders, the true density of the particles is similar regardless of the PSD. The true density of MCC in the current study is larger than the reported value by Sun [26]. Sun [26] has shown that
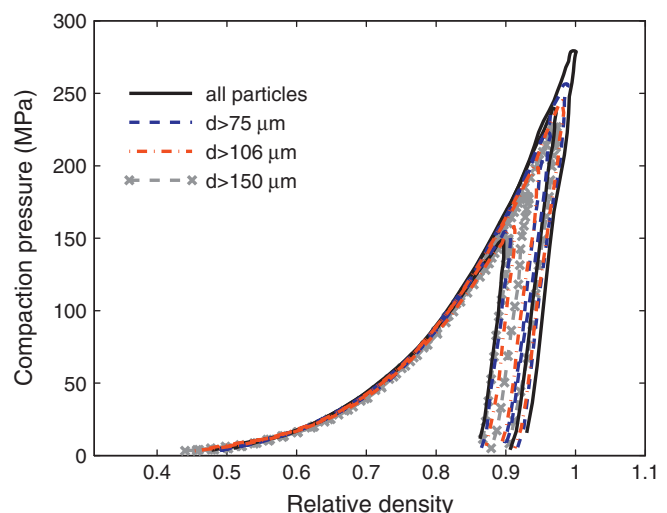
Table 1
Properties of MCC and lactose.

Powder	True density (g/cm³)	d_{20} (μm)	d_{50} (μm)	d_{75} (μm)
MCC	1.54	53	116	155
Lactose	1.53	73	114	142

Fig. 4. Compaction pressure vs. in-die relative density for MCC.

Fig. 5. Compaction pressure vs. in-die relative density for lactose.

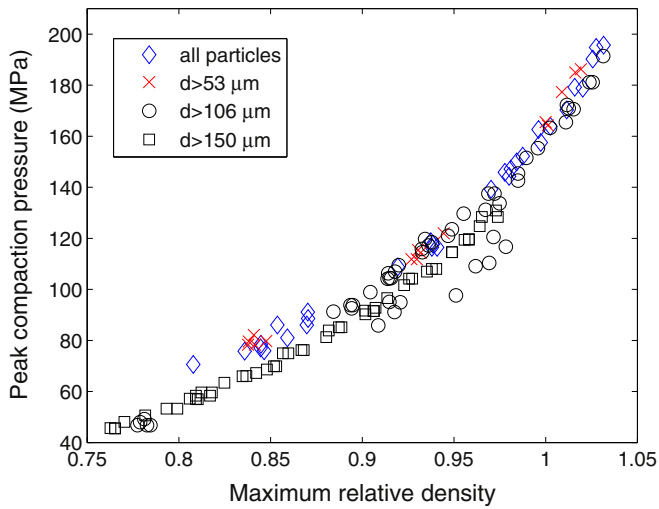**Fig. 6.** Peak compaction pressure vs. in-die maximum relative density for MCC.

Fig. 8. Elastic recovery vs. in-die maximum relative density for MCC.

the density measurements of MCC powders using a Helium Pycnometer may overestimate the true density, especially for powders with some moisture content. The loss on drying (LOD) values for the MCC and lactose powders are about 4.1% and 0.5%, respectively. The overestimation is related to the release of water from the powders, when exposed to a dry helium atmosphere [27]. Sun [27] has introduced a method that can be used to determine the true density of water content in powders based on regression of compaction pressure vs. tablet density. However, in the current study, the analysis and comparison of compaction behaviors of the powders and the tensile strength of the tablet are not affected by the value of the true density, because the true density was found to be independent of the PSD.

The tablet compaction process consists of loading and unloading of the compaction force. During the loading stage, the thickness of the powder decreased gradually, and at the end of the loading stage, the tablets have reached the smallest tablet thickness which corresponds to the maximum relative density. The applied compaction pressure is computed as $\frac{4P}{\pi D^2}$, where P is the compaction force. The relative density ρ of the tablets is computed from the dimensions and weight of the tablets as
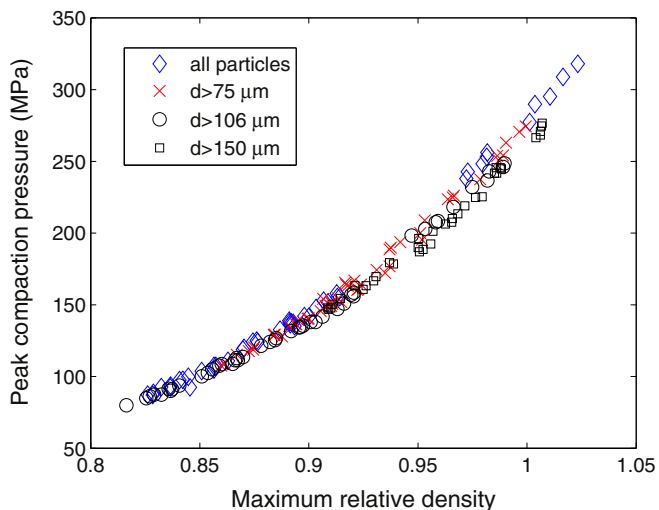
$$\rho = \frac{4m}{\pi D^2 t \rho_t} \qquad (2)$$

where ρ_t is the true density of the material, m is the mass of the tablet, and t is the thickness of the tablet. The relative density during compaction was computed by taking the gap between the upper and lower punches as the thickness. The maximum compaction force ranged from 5 kN to 20 kN, which corresponds to compaction pressures of 76 MPa and 254 MPa. The maximum relative density ranged from 0.82 to 1.0 for lactose, while the maximum relative density ranged from 0.76 to 1.0 for MCC.

During the unloading stage, some of the tablet deformation was recovered as the punches were removed from the tablets gradually. Figs. 4 and 5 show the compaction pressure vs. in-die relative density profile for each sample of MCC and lactose, respectively. Though the samples have different PSD, the curves follow similar loading and unloading paths. This clearly indicates that removing the fine particles (up to 150 μm) did not affect the loading and unloading path as a function of relative density. Figs. 6 and 7 show that, for both materials, the peak compaction pressure vs. the out-of-die relative density of tablets data follows the same trend. This indicates that the amount of fine particles has no effect on the compaction process. In other words, for all samples of the same material, equal magnitude of pressure is required to produce a tablet of a given relative density.
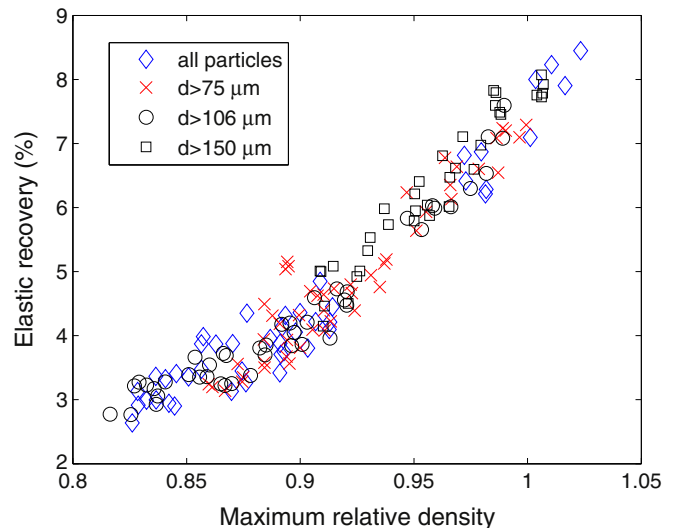

Fig. 7. Peak compaction pressure vs. in-die maximum relative density for lactose.
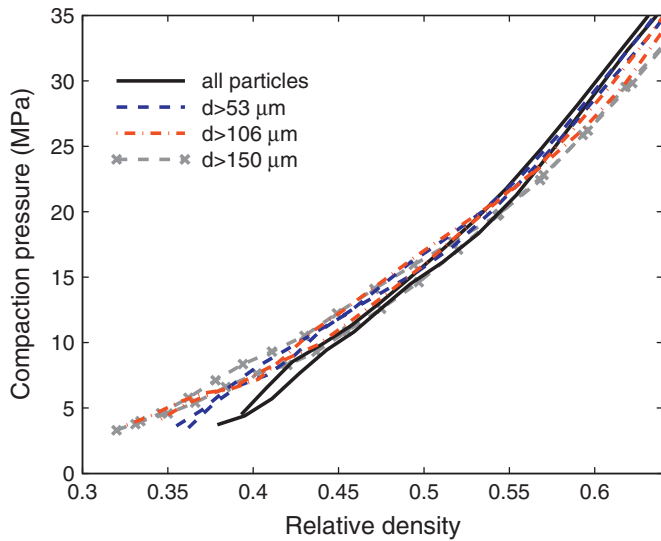

Fig. 9. Elastic recovery vs. in-die maximum relative density for lactose.

Fig. 10. Compaction pressure vs. in-die relative density for MCC.

Fig. 12. Initial relative density for samples of MCC. The error bar represents the standard deviation of the initial relative density.

During the initial compaction phase the particles undergo elastic and plastic deformations. When the compaction force is unloaded, the elastic deformation is recovered. The amount of elastic deformation recovered (elastic recovery) depends on the elastic properties of the particles and the bonding between the particles. The total elastic recovery (*ER*) can be expressed as

$$ER(\%) = \frac{\rho_m - \rho_f}{\rho_f} \times 100\%, \qquad (3)$$

where ρ_f and ρ_m are the final and the maximum relative densities during the unloading phase, respectively. The computation of ER is similar to the method used by Patel et al. [16], and Armstrong and Haines-Nutt [28], except that the relative density was used in the current research instead of the thickness of compacted powder. Figs. 8 and 9 show the total elastic recovery for MCC and lactose, respectively. The elastic recovery ranged from 3% to 9% for both lactose and MCC compacts. In general, the percentage of elastic recovery increases with ρ_m. In all cases, the amount of fine particles has no impact on the elastic recovery of the compacts.

Though the compaction pressure vs. the relative density curves are similar regardless of the amount of fine particles, the initial relative
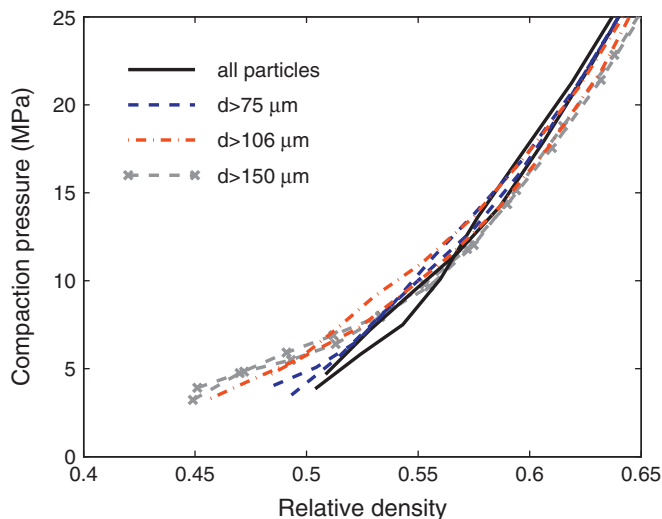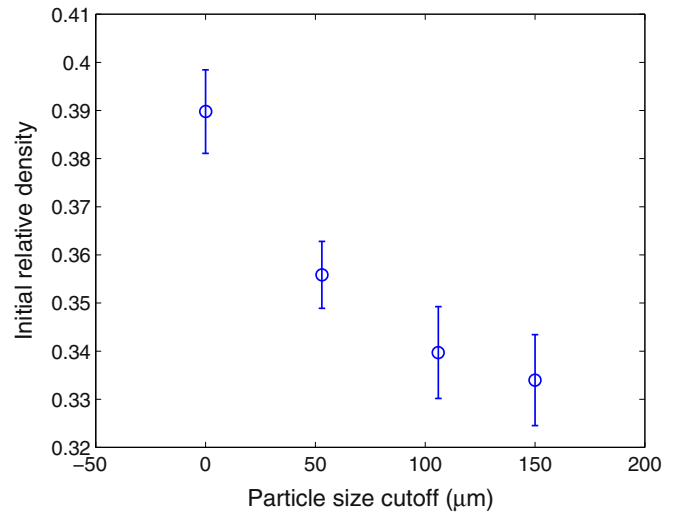
densities of the samples are different from each other. In this study, the initial relative density (also known as the critical relative density, which indicates jamming of powder bed) is defined as the relative density which corresponds to the application of a threshold compaction pressure, which was about 3 MPa. Figs. 10 and 11 show the compression pressure vs. in-die relative density profiles during the initial stages of compaction for MCC and lactose, respectively. The initial relative density corresponds to the first data points in these figures. In addition, Figs. 12 and 13 show the initial relative density for the four samples of both materials. The initial relative density ranged from 0.33 to 0.39 for MCC and from 0.46 to 0.51 for lactose. These values are much lower than the relative density of random loose packing of cohesionless, spherical particles of uniform PSD, which has a relative density of about 0.56 [29]. One possible reason for the lower density of the MCC and lactose powders may be the cohesive properties of the particles. In the presence of small particle sizes, typically ≤50 µm, inter-particle attractive forces become larger than particle weight, leading to the formation of stable arches that give rise to highly porous structures [20,30]. In addition to the cohesive properties of the particles, the shape of particles affects the packing of the powders. In gravitational depositions, particles with cylindrical shapes tend to form higher porosity (lower relative density) depositions than particles of
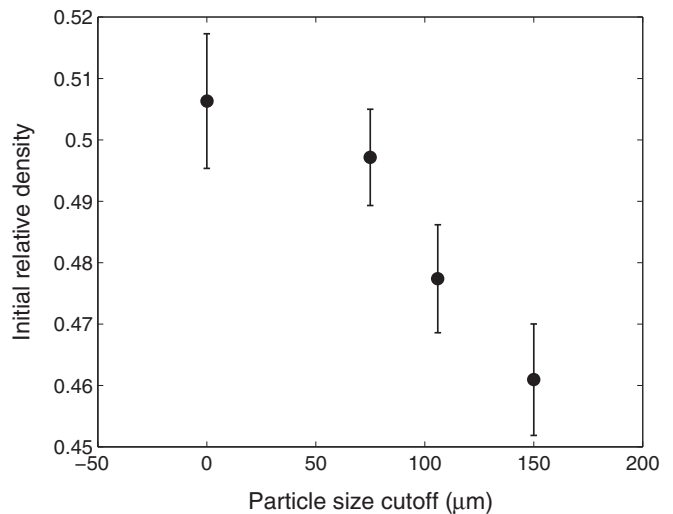

Fig. 11. Compaction pressure vs. in-die relative density for lactose.

Fig. 13. Initial relative density for samples of lactose. The error bar represents the standard deviation of the initial relative density.
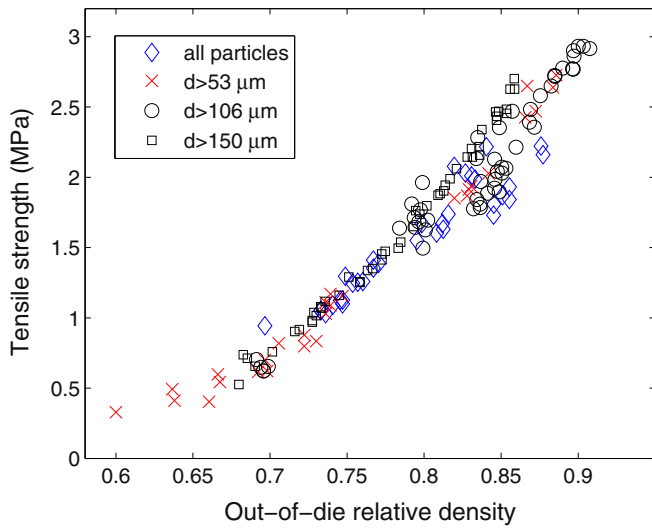
Fig. 14. Tensile strength vs. out-of-die relative density for MCC.

difference in the amount of fine particles of the samples. Moreover, beyond the relative density of 0.6, the particles deform as the compaction pressure is increased due to the limited available space for particles to move past each other easily. Beyond this point (relative density of 0.6), the difference in the compaction pressure vs. relative density plots disappears and the powder bed behaves more or less like a solid. Therefore, it is concluded that the amount of fine particles affects the particle rearrangement rather than the actual particle deformation.

After the unloading of the compaction load the tablets were ejected. The diameter D of the tablets expands slightly after ejection; the maximum measured D is 10.06 mm (which is about 0.6% expansion in D). The thickness t of the tablets was about 2 mm.

Figs. 15 and 14 show the tensile strength vs. the relative density after tablet ejection (out-of-die relative density) for MCC and lactose tablets, respectively. The tensile strength ranged from 0.5 to 3.5 MPa for both MCC and lactose tablets. The tensile strength increases with the relative density indicating that the tensile strength increases with maximum compaction pressure. In general, for a given relative density, the tensile strength of MCC tablets is greater than that of lactose tablets. For both materials, the tensile strength was not affected by the PSD, which is in agreement with the experimental results reported by Fichtner et al. [10], and Mckenna and Mccafferty [8], and previous Discrete Element Method simulation results [32–34]. However, the results of the current research particularly reveal that the amount of fine particles has no impact on the tensile strength of the MCC and lactose tablets.

The fact that the amount of fine particles does not affect the peak compaction pressure, the in-die elastic recovery, and the tensile strength of compacts have a significant implication on numerical modeling effort of powder compaction. Since particle mechanics simulations capable of describing compaction processes [35] require the representation of individual particles in the material, the computational efficiency is constrained by the number of particles in the system. State of the art discrete particle models are capable of modeling about a million particles. For example, a 500 mg of MCC-Avicel PH-102 powder consists of about 9 billion particles. The majority of these particles are fine particles of less than 1 μm size. On the other hand, if the particle sizes are greater than 100 μm, a 500 mg of MCC-Avicel PH-102 powder will have only about 500,000 particles. Based on the findings of this study, the compaction and tensile strength of tablets are not affected by the amount of fine particles. Therefore, it may be possible to develop computational modeling with fewer numbers of particles.

spherical shape [31]. As depicted in Figs. 12 and 13, the MCC samples (which have elongated particle shapes) have a lower initial relative density than that of the lactose samples (which have more rounded particles) (see Fig. 1).

For both materials, samples with the largest particle size cutoff have the lowest initial relative density. These results are consistent with prior findings on packing of granular mixtures [1–4]. The fine particles fill in the void space between the large particles and increase the relative density of the powder. However, even if the compaction pressure vs. relative density plot for the different samples starts at different points in the graph, the curves converge to a single curve beyond relative densities of 0.55–0.60. A relative density of 0.60 is slightly less than that of random close packing (RCP) of cohesionless, spherical particles, which is about 0.64 [19]. For relative densities below the RCP value, a significant rearrangement of particle positions occurs during the application of compaction pressure. In this regime, it is well known that the fine particles may adversely affect the ease of particle rearrangement [6,7,20]. Hence, the difference between the compaction pressure vs. relative density profiles during the initial die filling process and relative density of up to 0.6 for the different samples is due to the
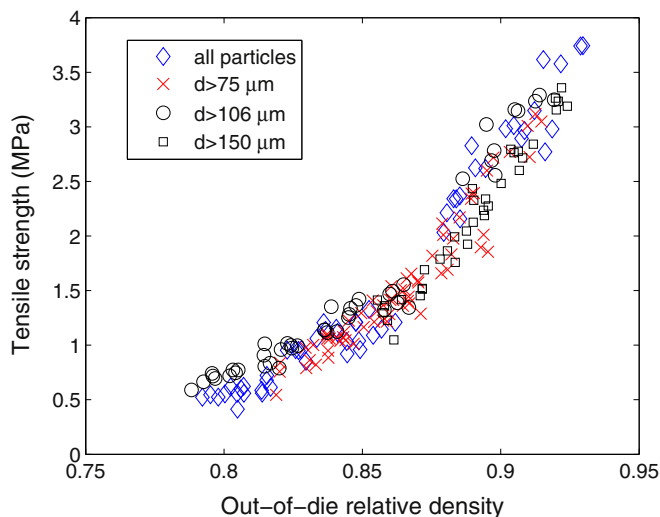
4. Conclusion

By removing portions of the fine particles successively, it was possible to investigate the role of fine particles on the compaction of MCC and lactose powders and tensile strength of the corresponding tablets. Removing the fine particles (up to 150 μm) affects the initial relative density (also known as critical density), such that, materials that contain more fine particles tend to have a larger initial relative density during die filling. The difference in the relative density persists during the early stages of compaction, up to a relative density of around 0.6. As the compaction of the powders continues beyond the relative density of 0.6, the difference in the compaction pressure vs. relative density profile becomes negligible.

The presence of fine particles did not affect the final mechanical characteristics of the tablets. The peak compaction pressure, elastic recovery and tensile strength remain the same regardless of the content of the fine particles, when plotted as a function of the relative density. These lead to the conclusion that the relative density is a primary metric for characterizing the powder compaction and tensile strength of tablets. In addition, the conclusions from this study have significant implications for numerical modeling efforts of powder compaction.

Fig. 15. Tensile strength vs. out-of-die relative density for lactose.

Acknowledgment

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