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Effect of Starting Material Particle Size on Its Agglomeration Behavior in High Shear Wet Granulation

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ABSTRACT

The effect of anhydrous lactose particle size distribution on its performance in the wet granulation process was evaluated. Three grades of anhydrous lactose were used in the study: "as is" manufacturer grade and 2 particle size fractions obtained by screening of the 60M lactose. Particle growth behavior of the 3 lactose grades was evaluated in a high shear mixer. Compactibility and porosity of the resulting granules were also evaluated. A uniaxial compression test on moist agglomerates of the 3 lactose grades was performed in an attempt to explain the mechanism of particle size effect observed in the high shear mixer. Particle growth of anhydrous lactose in the high shear mixer was inversely related to the particle size of the starting material. In addition, granulation manufactured using the grade with the smallest particle size was more porous and demonstrated enhanced compactibility compared with the other grades. Compacts with similar porosity and low liquid saturation demonstrated brittle behavior and their breakage strength was inversely related to lactose particle size in the uniaxial compression test, suggesting that material with smaller particle size may exhibit more pronounced nucleation behavior during wet granulation. On the other hand, compacts prepared at higher liquid saturation and similar compression force exhibited more plastic behavior and showed lower yield stress for the grade with smallest particle size. The lower yield stress of compacts prepared with this grade may indicate a higher coalescence tendency for its granules during wet granulation.

KEYWORDS: anhydrous lactose, particle size, high shear, wet granulation, granule growth.

INTRODUCTION

High shear wet granulation is a particle agglomeration process that is extensively used in the pharmaceutical industry. Particle size enlargement is attained by the addition of a liquid to the powder or a mixture of powders that are being mixed in a high shear mixer. Resulting particles, which are termed granules, usually have larger particle size and bulk density compared with the starting material. Granule particle size and characteristics, such as porosity and compactibility, are determined by the physical properties of the starting material and by process parameters employed during granulation.

Granule growth in high shear wet granulation is a dynamic process in which granules are continuously forming and breaking down.[1] Granule size achieved at a given set of experimental conditions depends on the relative rates of granule formation and breakdown. Granule growth in a high shear mixer proceeds initially by a nucleation mechanism. Liquid droplets are broken up and dispersed by the shear forces in the granulator and then proceed to wet the primary particle surface. Liquid bridge bondings are established between the surface wet particles, resulting in the formation of nuclei. Nucleation is the predominant granulation mechanism at low liquid concentration, and the rate of nucleation is proportional to the strength of the formed nuclei.[1,2] At the low liquid concentration characteristic of the nucleation stage, nuclei typically exhibit brittle behavior. Higher strength decreases the rate of nuclei breakdown, thus shifting the process toward larger nuclei size. As granulation continues, liquid saturation of the formed nuclei increases as a result of the continued addition of the binder liquid. Once granules reach a certain limiting liquid saturation, granules start to exhibit plastic behavior, and granule growth by coalescence becomes a predominant mechanism. Coalescence is the combining of 2 colliding granules to form a single larger granule, which results in rapid granule growth and therefore significant increase in granule growth rate. The probability of coalescence of 2 colliding granules increases as their ability to plastically deform under applied pressure increases. Plastic deformation of the colliding granules increases their area of contact, allowing for greater bonding and successful coalescence. Growth by coalescence is enhanced by factors that result in greater ability of granules to plastically deform upon application of stress and in the lower yield stress of the moist granules.[3-6] Thus, while lower breakage strength of brittle granules is expected to have a negative effect on granulation behavior, a lower yield strength for plastically deformable granules would result in more pronounced granule growth. Stress-strain behavior of moist granules is therefore thought to play an important role in granule growth by coalescence. Kristensen et al[7-9] used a uniaxial compression test to study stress-strain behavior of moist compacts. Granule growth by coalescence was inverse-

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ly related to the granule strength obtained in this test, suggesting the utility of this model in predicting coalescence behavior in wet granulation.[7-9]

Properties of the starting material, such as particle size, can affect strength and deformability of moist granules, and hence their behavior, in the high shear granulator at both the nucleation and coalescence stages. Despite the large number of reports on high shear wet granulation, very few reports address the effect of starting material particle size on the outcome from the high shear wet granulation process. Differences in granule structure and porosity, resulting from changes in starting material particle size, can also affect other characteristics of the granulation, such as compactibility. Granule growth was shown to be inversely related to starting material particle size for dicalcium phosphate,[9] while an opposite trend was reported for an investigational compound.[10] The purpose of this study is to enhance the understanding of the effect of particle size distribution on wet granulation behavior using anhydrous lactose as a model. In addition, a uniaxial compression test for moist compacts was performed in an attempt to explain the mechanism of the effect of particle size on granulation performance in the high shear mixer.

Materials and Methods

Materials

Anhydrous lactose, 60M grade, was obtained from Quest International (Irvine, CA). Three grades of anhydrous lactose were used in reported experiments: "as is" 60M grade (60M lactose); a particle size fraction ranging between 40 and 75 µm (Fraction I); and particle size fraction between 212 and 250 µm (Fraction II). Fractions I and II were obtained by screening of the 60M lactose through sieves with the appropriate mesh size.

Methods

Granulation Experiments in the High Shear Mixer

Granulation of the 3 fractions of anhydrous lactose was performed in a Collette Gral 10 high shear granulator (10-L bowl) (Niro Inc, Columbia, MD) using a batch size of 1.5 kg. Granulation of each lactose fraction was achieved using water as the granulating liquid. Water was added to the lactose in the granulator, with impeller speed maintained at the low setting and the chopper motor off, at a rate of 50 g/min using a peristaltic pump and a hydraulic nozzle. A wet granulation sample was obtained after 100 and 200 g of water were added to the granulator, and granulation was stopped after 300 g of water was added. Granulation samples were dried in a hot air convection oven at 60°C to a moisture content of ≤ 1%.

Physical Characterization of Granulation

Particle Size Distribution. Particle size distribution of the dried granulation was determined by mesh analysis using an Allen Bradley Sonic Sifter (Allen Bradley, Milwaukee, WI) equipped with a series of 6 screens and a pan. A ~10-g sample was tested with a pulse setting of "5," sift setting of "5," and a total sifting time of 5 minutes.

Porosity. Pore volume distribution of the granulation was determined by Mercury Intrusion Porosimetry (PoreSizer 9320, Micromeritics, Norcross, GA). A granulation fraction passed through 40-mesh screen and retained on 60-mesh screen was used for the porosity determination. Incremental pore volume was determined at different pressures ranging from 6 to 5000 psi, which corresponds to pore diameters from 30 to 0.03 µm.

Granulation Compactibility. Compression profiles were obtained for the 40- to 60-mesh granulation fraction. Compacts weighing 240 mg were compressed at different compression forces on the Instron model 5567 (Instron Corp, Canton, MA) using 11/32″ standard concave tooling set. A specific particle size was selected for the compression tests to eliminate any differences in compactibility that could be attributed to differences in granule size. Hence, differences in compactibility can be solely attributed to variation in granule internal structure and mechanical properties. After ejection from the die, hardness of the different compacts was determined as the force required to cause a tensile break of the compact in a diametrical compression test on the Instron.

Uniaxial Compression Test

Since mechanical properties of moist granules are expected to affect their growth behavior in the granulator, an attempt was made to study the stress-strain profile of moist agglomerates of the 3 lactose fractions. Due to the practical difficulties of studying the mechanical properties of an actual granule formed in the high shear granulator, stress-strain profiles were obtained for moist compacts of the 3 lactose samples instead. The moist compact simulates a wet granule, and the study of the mechanical behavior of wet compacts is expected to correlate with the performance of the wet agglomerates of the 3 lactose fractions in the high shear granulator.

The dry lactose sample was wetted to target moisture content by spraying with water and mixing very slowly with a glass rod to achieve uniform water distribution in the sample. A cylindrical mass was formed using a die and flat-faced punches, 1.27 cm in diameter, on the Instron. Wet compacts were compressed to either a target thickness (constant porosity experiment) or to a specified compression force (constant force experiment). For the constant porosity experiment, the Instron cross head was programmed to travel down at a speed of 5 mm/min until the target thickness of the compact with

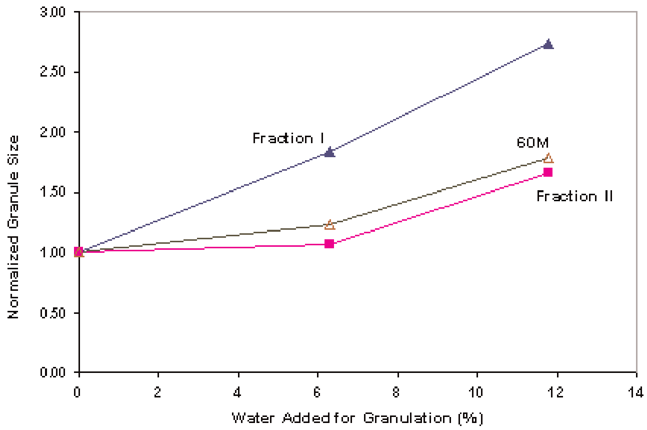

Figure 1. Effect of granulating water on granule growth of anhydrous lactose in the high shear granulator.

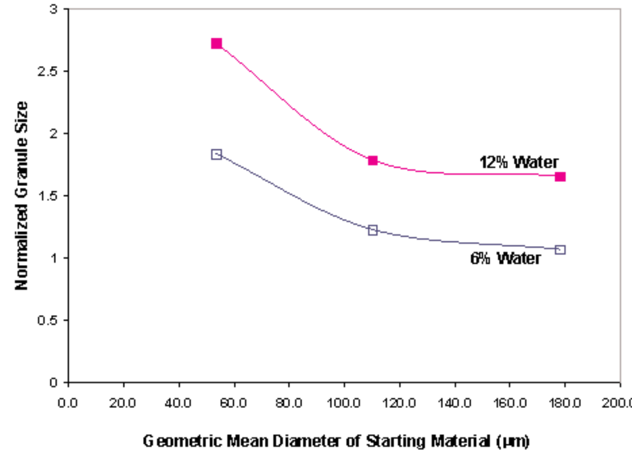

Figure 2. Effect of starting material particle size on granule growth of anhydrous lactose.

0.5 g of the solid was achieved. The thickness of the compact was chosen so that compacts with a porosity of 47% or 37% (on the dry basis) were obtained. For the constant compression force experiment, a weight of the moist sample equivalent to 1 g of the dry material was compressed using the target compression force of 700 N. In both experiments, the compact was removed from the die, and stress-strain profiles for the formed compact were then determined by loading the compact between the flat-faced platens of the Instron driven at a constant rate of 5 mm/min. The applied force and displacement were obtained and converted to the corresponding stress and strain values, respectively.

RESULTS AND DISCUSSION

Effect of Starting Material Particle Size on Granule Growth

Normalized granule size, obtained by dividing the geometric mean diameter of the granulation by the geometric particle size of the starting material, was used as a measure of particle growth in the granulator (Figure 1). Normalized granule size appeared to be inversely related to the starting material geometric mean particle size at a given water concentration (Figure 2). Small particle size lactose (Fraction I, geometric mean = 53.3 µm) showed more pronounced growth compared with the 60M lactose (geometric mean = 110.1 µm) and the large particle size lactose fraction (Fraction II, geometric mean = 178.0 µm). On the other hand, Fraction II showed slightly smaller normalized granule size than the 60M lactose, suggesting that the effect of starting material particle size may be less pronounced in this range. However, it is noteworthy that the 60M lactose has a wider particle size distribution than the other 2 particle size fractions, as indicated by its higher geometric SD (Table 1). The growth behavior of the 60M lactose in comparison to Fractions I and II may be a reflection of its wider particle size distribution and not just the difference in mean particle size.

Granulation Porosity and Compactibility

Granules prepared using Fraction I showed higher total pore volume compared with granules prepared using the large particle size lactose sample (Fraction II) (Table 2).

Hence, granulation porosity appeared to increase with the decrease in starting material particle size. The smaller particle size material thus showed lower densification tendency compared with larger particle size of the same material, since it produced more porous granules under the same experimental conditions. The lower porosity of the 60M sample compared with Fraction II may be attributed to its wider particle size distribution and the ability of the fine particles to fill in the voids between the larger particles.

Table 1. Granule Size Data for the Granulations Manufactured Using the Different Lactose Fractions

	Fraction I			Fraction II			60M Lactose		
Water Concentration (%)	**Geometric Mean Diameter (µm)**	**Normalized Granule Size**	**Geometric SD**	**Geometric Mean Diameter (µm)**	**Normalized Granule Size**	**Geometric SD**	**Geometric Mean Diameter (µm)**	**Normalized Granule Size**	**Geometric SD**
0	53.3	1	1.5	178.0	1	1.5	110.1	1	2.0
6	98.1	1.84	2.8	190.4	1.07	1.4	135.6	1.23	1.9
12	145.8	2.73	2.5	296.3	1.66	1.4	196.9	1.79	1.6

Table 2. Granule Pore Size Data Determined by Mercury Intrusion Porosimetry

Granulation	Total Pore Volume (mL/g)	Average Pore Diameter (µm)	Porosity (%)*
Fraction I	0.411	1.18	38.9
Fraction II	0.123	0.28	16.0
60M	0.072	0.33	10.1

*Calculated using true density value of 1.552 g/mL.[13]

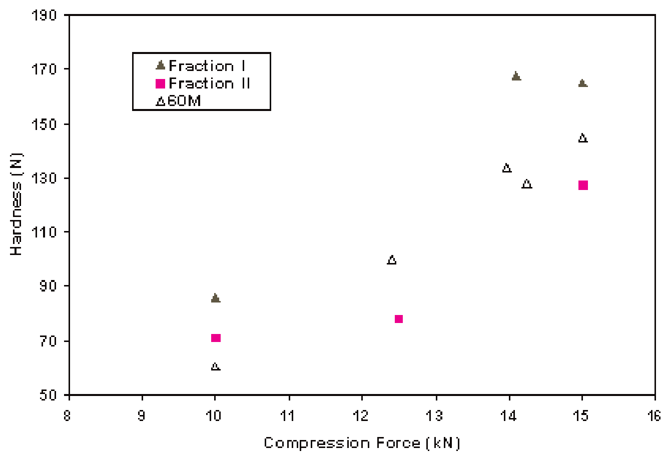

Figure 3. Compaction profiles of lactose granulation manufactured in the high granulator.

Granules manufactured using Fraction I were more compactable than those manufactured using Fraction II, as shown by the compression profiles for the 2 granulations (Figure 3). The more porous granules are expected to have lower strength and, as a result, would have higher fragmentation propensity under the applied compression force compared with the less porous granules.[10-12] Also, under the applied compression force, granules usually fragment along failure planes created between primary particles.[12] This, together with the higher granule porosity, would result in the formation of smaller fragments during compression of granules prepared using Fraction I. Consequently, a higher surface area available for bonding and smaller pore volume would be created during compression of those granules, resulting in a more compactable granulation.

Uniaxial Compression Experiments

Figure 4 shows representative stress-strain profiles of wet lactose compacts. Stress-strain profiles for all compacts show steady increase in strain as a function of the applied stress until a critical stress is reached. At the critical stress, a drop in the applied stress is observed, indicating breakage of a brittle compact (Figure 4A). To the contrary, a plastic compact maintains the critical stress at continuing strain (Figure 4B).

Constant Porosity Experiment

For all 3 lactose fractions, compression force required to achieve the specified compact porosity decreased as the water concentration increased (Figure 5). At the same water concentration, the force required to achieve the specified porosity was in the following order: Fraction I > Fraction II ≥ 60M lactose. The higher resistance of the smaller particle size material (Fraction I) to densification is in agreement with the higher porosity of the granules prepared in the high shear granulator using this fraction. Stress-strain profiles of the wet compacts showed breakage rather than yield at the critical stress for all the compacts at the 10% water concentration, indicating that compacts are still brittle at this liquid saturation condition. The liquid saturation corresponding to the 10% water concentration is probably more representative of the nucleation stage of granulation rather than the coales-

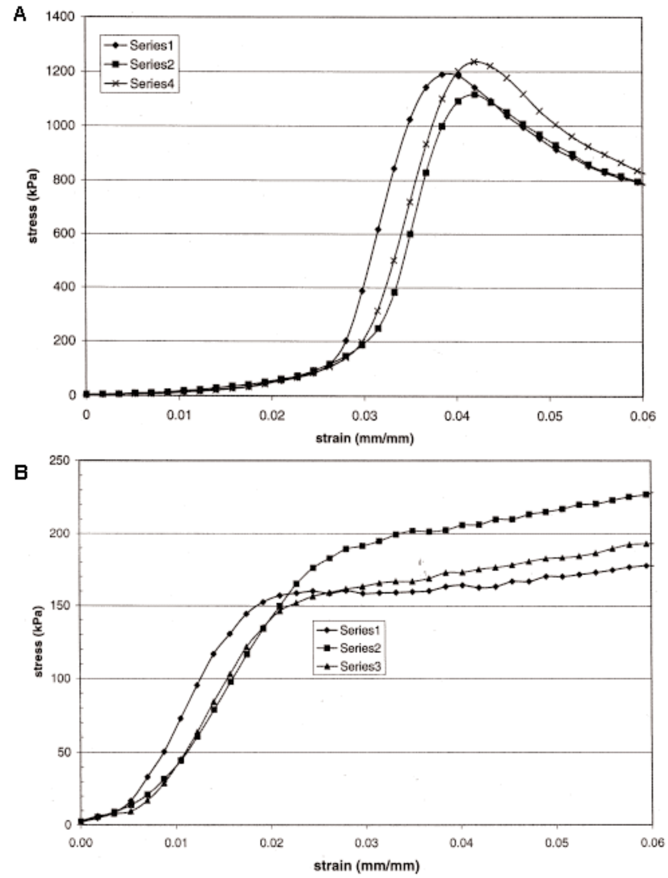

Figure 4. Representative stress-strain profiles (3 replicate samples) for lactose moist compacts. (A) Compact showing brittle behavior prepared using Fraction I and 10% water at 47% porosity. (B) Compact exhibiting plastic deformation prepared using 60M lactose and 20% water at 47% porosity.

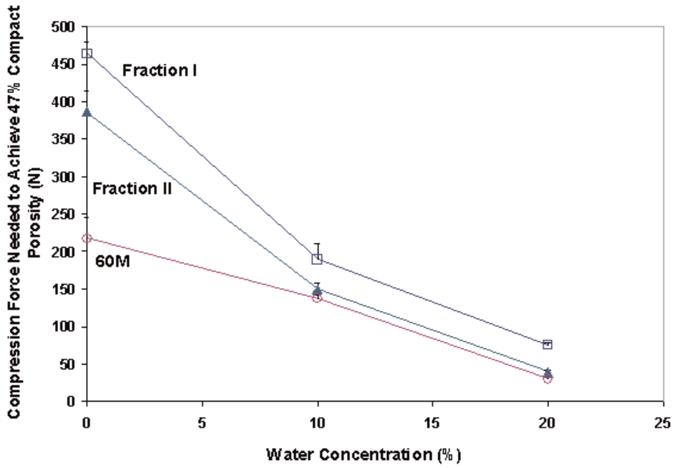

Figure 5. Effect of water content on compaction behavior of anhydrous lactose.

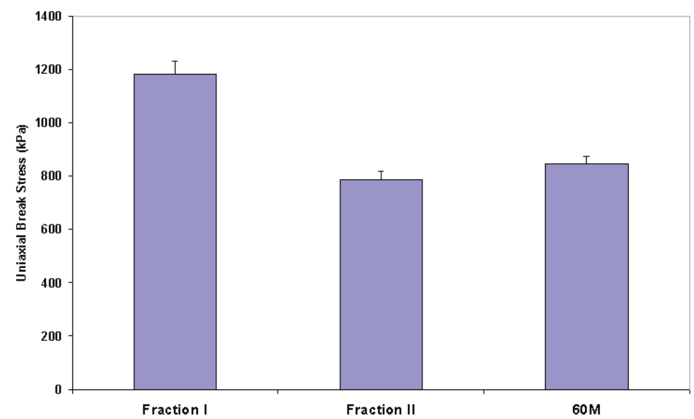

Figure 6. Strength of lactose compacts with 47% porosity and 10% water.

cence phase in which material usually exhibits plastic behavior. This is particularly true in this case in which the granulating liquid (water) has low viscosity, hence granule deformation would be essential for successful coalescence.[5] The breakage stress is higher for Fraction I than for the other 2 samples at 10% water concentration and 47% porosity, suggesting that this material may be capable of forming stronger nuclei and hence more pronounced nucleation phase (Figure 6). The higher strength of compacts prepared with smaller particle size material is attributed to the larger volume density of interparticle contacts.[6] Also, the viscous and capillary forces of the liquid bridge between particles increase as the particle size decreases as described by the following equation[2]:

$$F_{vis} + F_{cap} = 3\pi\mu U_0 a^2 / 4h + (\pi\gamma a) \sin^2 [\phi(C_0 + 2)] \quad (1)$$

where F_{vis} and F_{cap} are the viscous and capillary forces, respectively; a is particle radius; μ is liquid viscosity; U_0 is the relative velocity of the particles; *h* is half the interparticle distance; γ is the liquid surface tension; ϕ is the liquid bridge filling angle; and C_0 is the Laplace-Young pressure deficiency caused by the curvature of the free surface.

At the 20% water concentration, compacts prepared using Fraction I were still brittle at the 37% and 47% porosity as indicated by compact breakage at the critical stress. On the other hand, compacts prepared using the 60M lactose and Fraction II showed yield behavior rather than breakage at those liquid saturation conditions. The change from brittle to plastic behavior upon increase in water content is likely due to the lubricant effect of water, which disrupts interparticle-frictional forces at points of particle contact. The smaller particle size material has a larger surface area available for interparticle contact and hence requires more water to disrupt those contact points prior to the change of material behavior from brittle to plastic. As granule coalescence in the high shear granulator is usually enhanced significantly at the point where granule behavior starts to exhibit plastic deformation, these data suggest that 60M and Fraction II may reach the coalescence phase at a lower liquid saturation than the smaller particle size fraction. Compacts prepared with the 60M lactose showed lower yield stress at the 20% water concentration than those prepared using Fraction II (Figure 7).

Constant Force Experiments

Compacts prepared at the 700 N compression force showed the following order of porosity: Fraction I > 60M lactose > Fraction II (Figure 8). Compact porosity ranged between 27% and 30%, which is lower than the above constant porosity experiments. As seen above in the high shear and the constant porosity experiments, smaller particle size material demonstrated again that it is more resistant to densification. All compacts showed a yield behavior at the critical stress, indicating that all 3 lactose fractions exhibit plastic behavior at those experimental conditions. Experimental conditions for the constant force experiment more closely model material behavior during coalescence in a high shear mixer than the constant porosity experiments, as liquid saturation is sufficiently high for the material to exhibit plastic deformation behavior. Also, as coalescence usually occurs at a later stage in wet granulation, the constant force rather than constant porosity approach for compact preparation is more appropriate, where material would have had the opportunity to densify according to their inherent densification propensity. Yield stress of compacts in the uniaxial compression test is expected to be inversely related to the probability of plastic deformation of granules upon collision in the high shear mixer.[7-9] Plastic deformation of colliding granules has a paramount significance in determining whether the colliding granules would coalesce or bounce back, particularly when using low

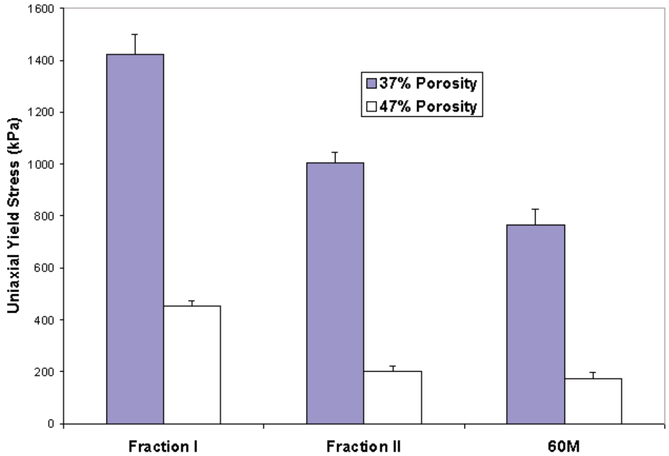

Figure 7. Strength of lactose compacts with 20% water.

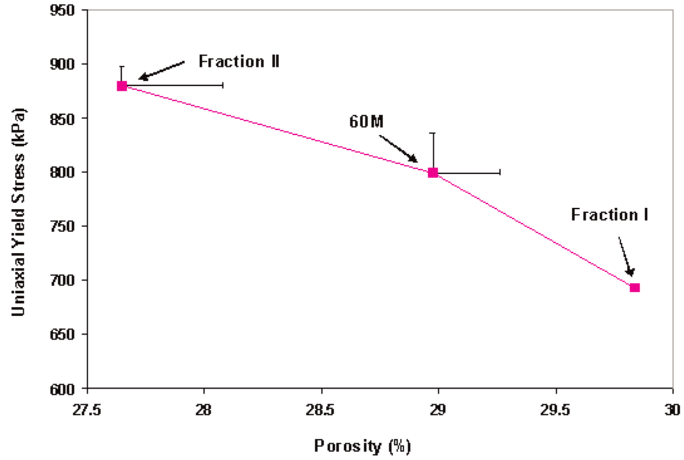

Figure 8. Yield stress and porosity of lactose compacts prepared using 20% water concentration and a compression force of 700 N.

viscosity granulating liquid.[5] Plastic deformation of granules subjected to a stress higher than their yield stress would result in enhanced surface area of contact during granule collision thus allowing for greater bonding. Surface deformation of granules would also squeeze the binder into the area of contact between the colliding granules, resulting in the formation of liquid bonds, and increase the probability of successful coalescence. In addition, plastic deformation aids in the dissipation of the kinetic energy of colliding granules, hence decreasing the energy available for the granules to bounce back. Yield stress of the compacts was in the following order: Fraction II > 60M lactose > Fraction I, suggesting that growth by coalescence would be more pronounced for the Fraction I granules compared with the other 2 lactose samples. Granule yield strength appears to increase with the increase in sample particle size. While granule strength is generally expected to be inversely related to particle size at constant porosity, differences in granule porosity in this case may be a more important factor in determining granule strength. It is noteworthy that yield stress of the compacts was in the reverse order of compact porosity, suggesting that material densification tendency may be an important factor in determining granule yield strength, and hence its deformability and coalescence behavior. The lower porosity of compacts prepared with larger particle size resulted in a higher strength for those compacts compared with the more porous compacts obtained with the smaller particle size sample. Those results highlight the importance of the effect of granule densification propensity on its mechanical properties and hence its growth behavior.

The effect of lactose particle size on granule growth behavior was similar to that previously observed for DPC 963.[10] The more detailed uniaxial compression experiments conducted in this study suggest that this behavior may be attributed to more pronounced nucleation and coalescence for the smaller particle size material. The apparent ability of the larger particle material to reach the coalescence stage prior to the smaller particle size material should be more favorable for granule growth. This, however, appears to be outweighed by the more robust nucleation and coalescence behavior of the later material resulting in more pronounced overall growth performance.

The effect of starting material particle size on lactose granule growth is opposite to that reported for dicalcium phosphate.[9] Both excipients are expected to have more robust nucleation for the smaller particle size material as suggested by higher agglomerate strength for the smaller particle size material at a given porosity. However, the different particle size effect on granule growth behavior may be attributed to a dissimilar effect on coalescence. Similar to lactose, larger particle size dicalcium phosphate was more easily densified compared with the smaller particle size fraction. Unlike lactose, the less porous agglomerate prepared with larger particle size material may not have higher strength than the more porous agglomerate obtained from the smaller particle size. The decreased porosity would tend to increase granule strength, while the concomitant increase in liquid saturation would exert an opposite effect as it disrupts interparticle frictional interaction. For cohesive materials like dicalcium phosphate,[1] the effect of increased liquid saturation and diminished interparticle friction is significant, possibly maintaining lower yield strength for the denser agglomerates prepared using the larger particle size material.

Conclusion

Granule growth and porosity of anydrous lactose granules during wet granulation were inversely related to lactose particle size. Uniaxial compression experiments suggest that the higher growth tendency of the smaller particle fraction could be attributed to more efficient nucleation and coalescence.

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