Evolution of Structure and Properties of Granules Containing Microcrystalline Cellulose and Polyvinylpyrrolidone During High-Shear Wet Granulation

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ABSTRACT: Granulation behavior of microcrystalline cellulose (MCC) in the presence of 2.5% polyvinylpyrrolidone (PVP) was systematically studied. Complex changes in flowability and tabletability of lubricated MCC granules are correlated to changes in intragranular porosity, morphology, surface smoothness, size distribution, and specific surface area (SSA). With 2.5% PVP, the use of 45% granulation water leads to 84% reduction in tablet tensile strength and 76% improvement in powder flow factor. The changes in powder performance are explained by granule densification and surface smoothing. The granulating water level corresponding to the onset of overgranulation, 45%, is significantly lower than the 70% water required for unlubricated MCC granules without PVP. At more than 45% water levels, MCC–PVP granules flow well but cannot be compressed into intact tablets. Such changes in powder performance correspond to the rapid growth into large and dense spheres with smooth surface. Compared with MCC alone, the onset of the phase of fast granule size enlargement occurs at a lower water level when 2.5% PVP is used. Although the use of 2.5% PVP hastens granule nucleation and growth rate, the mechanisms of overgranulation are the same, that is, size enlargement, granule densification, surface smoothing, and particle rounding in both systems. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:207–215, 2014
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INTRODUCTION

Prior to tableting, many pharmaceutical powders are processed by high-shear wet granulation (HSWG), where either water or a binder solution is sprayed unto a powder bed as it is vigorously agitated in a high-shear mixer to produce agglomerates. The main objectives of granulation are to: (1) improve powder flowability and increase bulk density to facilitate consistent die filling during high-speed tableting; (2) eliminate dust; (3) prevent segregation of powder blends; and (4) improve content uniformity.[1–3] However, the improvement in powder-handling properties is often associated with deteriorated tableting performance.[4–7] When tabletability deterioration is extreme, sufficiently strong tablets cannot be manufactured, a phenomeon known as "overgranulation."[8] To solve the problem of overgranulation effectively, a mechanistic understanding is highly desired. Microcrystalline cellulose (MCC), one of the most commonly used tablet excipients, has the problem of deteriorated tabletability when granulated either dry or wet.[7–9] Using the simplest system of MCC and water, it was recently shown that surface smoothing, particle rounding, reduced surface area, reduced granule porosity, and size enlargement during HSWG are responsible for the deteriorated tableting performance of MCC granules.[4–6,8] These changes in granule structure and properties lead to reduced total intergranular bonding area, hence loss of tablet strength.[10]

Although useful insights have been obtained from studying the simplest MCC and water system, the question of whether they are applicable to more complex systems remains open. Further tests of overgranulation mechanisms using more complex systems are of critical importance for solving real-world overgranulation problems. Among possible excipients used in a HSWG formulation, the polymeric binder is expected to have a significant impact on the development of granule structure[7] by influencing the granule nucleation and growth kinetics.[11,12] Therefore, we investigate a system containing MCC and polyvinylpyrrolidone (PVP), a common HSWG binder. In addition, we characterize granules after lubrication with 0.5% (wt %) magnesium stearate to ensure that knowledge derived from this work is more relevant to real pharmaceutical granules, which are invariably lubricated prior to tableting.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose, (Avicel PH101) was received from FMC Biopolymer (Philadelphia, Pennsylvania). PVP K30 was received from BASF (Geismar, Germany). Initial moisture content of the MCC was 4.24%. The amount of PVP was fixed at 2.5% of the weight of MCC for all batches. Water level during granulation was varied between 5% and 105% of the weight of

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MCC to prepare a total of 12 batches of granules. PVP binder solutions of different concentrations were prepared by dissolving PVP in distilled water corresponding to the desired water levels. A physical mixture of MCC and PVP (0% granulating water) was also prepared and characterized. Magnesium stearate was received from Mallinckrodt (St Louis, Missouri)

Methods

Each batch of granules, containing 100 g of MCC, was prepared using a custom-made laboratory scale high-shear granulator (1.7 L bowl volume, modified KitchenAid food processor, two impellers, 1750 rpm). Whenever possible, a binder solution was sprayed at approximately 30 g/min through a nozzle placed approximately 5 cm above the surface of moving powder bed. However, the binder solutions used for the 5% and 10% water levels were delivered drop wise from the nozzle tip because they were too viscous to be sprayed. Wet granules were massed for 10 min after all binder solution has been added. The wet-massing time was purposely prolonged to ensure uniform distribution of binder solution in the powder bed and reproducibility of the granulation process.[5] The wet granules were tray-dried for approximately 24 h at 40°C in an oven and then placed in a 32% relative humidity chamber for at least 48 h prior to further characterization. Water content in the granules ranged 3.7%–4.8% based on thermogravimetry measurements.

Powder compaction studies were conducted at room temperature and approximately 20% relative humidity. The physical mixture was prepared by mixing 100 g MCC and 2.5 g PVP in the granulator for 30 s. All samples were lubricated for 10 min with 0.5% magnesium stearate using a 1 quart (946 mL) twin shell dry blender (Patterson–Kelley, East Stroudsburg, Pennsylvania) before characterizing their particulate properties, tableting performance, and flowability.

Tableting performance was tested on a compaction simulator (Presster; Metropolitan Computing Company, East Hanover, New Jersey) to simulate 10-station Korsch XL100 tablet press using round flat-faced tooling (9.5 mm diameter). The dwell time was set at 20 ms, corresponding to a production speed of 61,600 tablets/h. Tablet dimensions were measured immediately after ejection. Tablet diametrical breaking force was determined using a texture analyzer (TA-XT2i; Texture Technologies Corporation, Scarsdale, New York) at a speed of 0.01 mm/s and 5 g trigger force. Tablet tensile strength was calculated from the breaking force and tablet dimensions.[13] True density of the MCC–PVP–magnesium stearate composite was obtained by fitting tablet density–compaction pressure data of the physical blend using the Sun method.[14] Powder tabletability (tablet tensile strength as a function of compaction pressure), compressibility (tablet porosity as a function of compaction pressure), and compactibility (tablet tensile strength as a function of porosity) were obtained.[15,16]

Powder flowability was measured in triplicate using a ring shear cell tester (RST-XS; Dietmar, Schulze, Wolfenbüttel, Germany). The powders were first presheared under a normal consolidation stress of 6 kPa. Shear tests were subsequetly performed under 0.23, 2, 3, 4, 5, and 0.23 kPa normal stresses to construct a yield locus. Unconfined yield strengths, f_c, and the corresponding major principal stresses, σ_n, were determined by drawing two Mohr's circles using standard procedures.[17] The flow factor, $ff = \sigma_n / f_c$ was subsequently calculated. A higher ff generally indicates better flow property. Avicel PH102 (FMC Biopolymer was also tested under the same experimental conditions) as a reference powder for adequate flowability.[18,19] Powder bulk density was calculated from the powder fill weight and volume of the shear cell.

To obtain qualitative information on particle shape, size, and surface properties, samples were sputter-coated with platinum (~50 Å coating thickness) and observed with a scanning electron microscope (SEM; Quanta 200F; FEI, Hillsboro, OR) operated at 10 kV. Particle size distributions were measured using a laser scattering particle size analyzer (Malvern Mastersizer 2000; Malvern Instruments Ltd., Worcestershire, UK). An inlet air pressure of 1 bar, a feed rate of 30%, and obscuration of 0.6%–6% were used for data collection. Granules produced with water levels of more than 65% contained particles larger than 2000 μm, which is too large for the laser scattering sizer to yield accurate size distribution information. In these cases, granule size was obtained from SEM images using the maximum Feret diameter (longest axis of a particle). Mercury intrusion porosimetry (MIP; Autopore IV 9500; Micromeritics, Norcross, Georgia) was used to measure the pore volume distibution of the materials. The incremental pore volumes were determined in the range of 5–33,000 psi. The pore diameter at a given pressure was computed using the Washbun equation.[20] Intragranular pore size cutoff points were determined by examining the pore size distribution data and SEM images for each powder, assuming intragranular pores are significantly smaller than intergranular pores.

The specific surface area (SSA) of samples was determined using Krypton adsorption over the partial pressure, P/P_o, range of 0.05–0.2, analyzed using the Brunauer, Emmet and Teller (BET) method[21] (ASAP 2020, Micromeritics, Norcross, Georgia).

Statistical software (Origin® 9.0; OriginLab Corporation, Northampton, Massachusetts) was used for all data fitting and statistical analyses. The best fitting function for each set of data was obtained using nonlinear regression by systematically varying the parameters until the residual sum of squares between the experimental data and predicted values reached a global minimum. Residuals plots were inspected to ensure the true global minimum was obtained for each set of data.[22] Nonlinear regression yielded both mean and standard errors for each parameter in the fitting function.

RESULTS

Particulate Properties

Table 1 summarizes the key observations on granules and their properties linked to powder flow and compaction behaviors essential for tablet manufacturing. SEM images provide qualitative information on granule shape, size, and surface features. In the physical mixture, comprised of MCC, PVP, and magnesium stearate particles, irregularly shaped porous MCC agglomerates with uneven surface can be observed (Fig. 1a). Granulation with 15% water leads to smoother MCC agglomerates and the generation of new agglomerates of small particles (Fig. 1b, arrowed). With increasing granulating water level, 25%–45%, the number of observable pores diminishes and fine surface projections on MCC have been completely eliminated (Figs. 1c–1e). Although the particles are more regular in shape, some agglomerates are also observed. At 45% water, these newly formed agglomerates appear larger than those at lower water