A Formulation Strategy for Solving the Overgranulation Problem in High Shear Wet Granulation

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ABSTRACT: Granules prepared by the high shear wet granulation (HSWG) process commonly exhibit the problem of overgranulation, a phenomenon characterized by a severe loss of the ability to form adequately strong tablet. We hypothesize that the incorporation of brittle excipients promotes brittle fracture of granules during compaction, thereby improving tablet mechanical strength by increasing bonding area. On this basis, we have examined the effectiveness of incorporating a brittle excipient into a plastic matrix in addressing the overgranulation problem. A complete loss of tabletability is observed for plastic microcrystalline cellulose (MCC) when $\geq$55% of granulating water was used. The incorporation of a brittle excipient, either lactose or dibasic calcium phosphate (Dical) into the MCC matrix leads to improved tabletability in a concentration-dependent manner, with higher amount of brittle excipient being more effective. For each mixture, tablet tensile strength goes through a minimum as the granulating water increases, for example, 1.4 MPa for the mixture containing 80% of lactose and 2.1 MPa for the mixture containing 80% Dical. These results, along with scanning electron microscope evidence, show that the addition of brittle excipients to an otherwise plastic powder is an effective formulation strategy to address the overgranulation problem in HSWG. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2434–2440, 2014

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INTRODUCTION

The tabletability of wet granulated pharmaceutical powders is routinely observed to be reduced when compared with the virgin powder.[1–5] In extreme cases, a granulated powder does not form intact tablets,[6] let alone forming tablets with adequate mechanical strength, in the pharmaceutically relevant compaction pressure range of 50–400 MPa. This phenomenon of severe loss of powder tabletability is known as overgranulation.[7] It has also been observed that drug release rate may be slowed down after wet granulation.[8] Consequently, the term "overgranulation" may also be used to describe the situation when the drug release rate is unacceptably low after granulation.

Recent work has shown that plastic microcrystalline cellulose (MCC) undergoes size enlargement, densification, shape rounding, and surface smoothing during high shear wet granulation.[5] These changes in particle properties limit the formation of sufficient interparticulate bonding area, over which intermolecular-attractive forces are significant.[9] For example, the overgranulated MCC granules are hard and resistant to deformation.[7] They likely undergo a significant degree of reversible elastic deformation during compression, a behavior observed in MCC pellets.[4] When it occurs, the extensive elastic recovery of granules during decompression decreases the total bonding area among granules. Consequently, the tablet is mechanically weak.[9]

As high levels of plastic excipients, including MCC and other polymers, are routinely used in tablet formulations intended for wet granulation, it is reasonable to expect that the overgranulation problem of formulated powders during wet granulation has an origin similar to that observed in MCC, that is, insufficient bonding area. If so, an effective strategy for overcoming the overgranulation problem would be to increase bonding area in a tablet. Consistent with this concept, size reduction by milling has been used to salvage overgranulated powders.[2,7] This size reduction strategy, although effective, is not ideal because it is merely reactive to a manufacturing crisis and it requires additional processing steps. An ideal strategy for solving this problem is to eliminate it by designing the formulation in such a way that the powder mixture is inherently resistant to overgranulation.

Insight for developing such a formulation strategy to address the overgranulation problem may be gained by considering parallel work in dry granulation that is also faced with a similar situation of loss of tabletability. It has been shown that size enlargement in dry granulated powders deteriorates powder tabletability of plastic materials.[10] However, brittle materials exhibit little or no sensitivity to granule size enlargement.[11] These observations agree with the mechanism of reduced area of bonding in a tablet that leads to the lower tablet mechanical strength. Larger granules of plastic materials have smaller area that can form interparticulate bonding in tablet because they do not fracture when compressed. This naturally leads to reduced tabletability. On the contrary, brittle granules undergo extensive fragmentation when compressed to generate new lubricant-free surfaces that are available for bonding. Therefore, the large original granule size exerts little negative impact on tablet strength of brittle materials.

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On the basis of this understanding, we hypothesize that the incorporation of a brittle excipient into an otherwise plastic matrix for the HSWG process promotes fragmentation of large granules during compaction. The fragmentation subsequently minimizes the negative effect of large granule size on available bonding area to alleviate or even eliminate the overgranulation problem. We test this hypothesis using binary mixtures of MCC with each of the two brittle excipients, lactose and dibasic calcium phosphate (Dical). Although both lactose and Dical are brittle, they represent different types of materials because lactose is water soluble, whereas Dical is not.[12] Some of lactose is dissolved during the wet granulation process, which crystallizes out during subsequent water removal by drying. On the contrary, the solution-mediated redistribution of brittle excipient during granulation process is not expected for Dical because of its extremely low solubility in water. This may cause structural differences and affect fragmentation propensity of resultant granules.

MATERIALS AND METHODS

Materials

Materials used in this study were provided by respective commercial suppliers as following: MCC (Avicel PH101; FMC Biopolymer, Philadelphia, Pennsylvania), polyvinylpyrrollidone (PVP; Kollidon K30; BASF, Geismar, Germany), lactose monohydrate (Foremost Farms, Baraboo, Wisconsin), anhydrous Dical (Anhydrous Emcopress; JRS Pharma, Cedar Rapids, Iowa), and magnesium stearate, (Mallinckrodt, St Louis, Missouri). A fixed amount of PVP, 2.5% (wt %) of the powder mixtures, was dissolved in varying amounts of water to form polymer solutions, which were sprayed during the wet granulation process. For each mixture, the amount of water ranged from 5% to the maximum amount possible without forming a paste. Physical mixtures of MCC–PVP–lactose or MCC–PVP–Dical (0% granulating water) were prepared as a control.

The use of PVP as a binder during granulation process and magnesium stearate as a lubricant prior to compaction make this work more relevant to the common HSWG process during pharmaceutical manufacturing. Hence, the knowledge derived from this work can be applied to solve overgranulation problems with more confidence.

Methods

Powder mixtures, 100 g per batch, at various ratios of MCC–lactose (20%, 40%, 50%, 60%, and 80% lactose) and MCC–Dical (40%, 60%, and 80% Dical) were first mixed in a laboratory scale high shear granulator (1.7 L bowl volume, modified KitchenAid food processor, two impellers, 1750 rpm) for 30 s before spraying an appropriate PVP binder solution at a rate of approximately 30 g/min through a nozzle placed approximately 5–8 cm above the moving powder. The materials were massed for 10 min after all binder solution has been added. The prolonged massing is intended to maximize the chance of overgranulation to challenge the effectiveness of the proposed formulation strategy. 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 compaction. The physical mixtures were prepared by mixing MCC and lactose (or Dical) at predetermined ratios with 2.5 g PVP in the granulator for 30 s. Before compaction, all samples were mixed with 0.5% magnesium stearate for 10 min using a 1-quart (946 mL) twin shell blender (Patterson-Kelley, East Stroudsburg, Pennsylvania) operated at 25 rpm.

Powder compaction studies were conducted at room temperature and approximately 20% relative humidity. Granules were compressed on a compaction simulator (Presster; Metropolitan Computing Company, East Hanover, New Jersey) to simulate a 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 diametral 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] Tabletability plot (tensile strength as a function of compaction pressure) was obtained.[14,15] All data fitting and statistical analyses were carried out using commercial software (Origin® 9.0; OriginLab Corporation, Northampton, Massachusetts). Tabletability profiles were fitted to polynomial functions of appropriate order, from second to fifth, for the best fitting. Resultant functions were subsequently used to obtain the tablet tensile strengths at compaction pressures of 100, 200, and 300 MPa. Unless specified, tablet tensile strength reported in the following sections refers to tablet compressed at 300 MPa.

Tablet fracture surfaces after the diametral compression test for breaking force were sputter coated with platinum (~50 Å coating thickness) and examined with a Scanning Electron Microscope (SEM; JEOL 6500F, Tokyo, Japan) operated at 5 kV, to obtain qualitative information on granule deformation behavior. Granules were also sputter coated with platinum (~50 Å coating thickness) and observed with a SEM(Quanta 200F; FEI, Hillsboro, Oregon) operated at 10 kV.

RESULTS

Granule size generally increases with increasing level of granulating water or brittle excipient concentration.[6,16] To define the appropriate range of the granulating water, we first determine the water-holding capacity of each powder by recording the maximum amount of water that can be added to the powder while being granulated in the granulator without forming a paste or thick slurry (Fig. 1). Water is added to the powder bed at 5% or 10% increments until the first sign of suspension formation is observed, the corresponding water level is recorded as the paste-forming water level (red line in Fig. 1). The water level immediately before the last water addition that leads to paste formation is taken as the water-holding capacity (black line in Fig. 1). The formation of a thick slurry, which is essentially a dispersion of solid particles in the granulating liquid,[17] indicates that the maximum amount of liquid to produce agglomerates has been exceeded. The water-holding capacity of powder without forming a slurry decreases in the following order: MCC (135%) > Dical (45%) > lactose (15%). The water-holding capacities of the mixtures range between those of the pure powders as expected. Similar observations have been made previously, where a higher MCC concentration in the starting powder required a higher amount of water to produce desired pellets or granules.[16,18,19]