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The evolution of granule fracture strength as a function of impeller tip speed and granule size for a novel reverse-phase wet granulation process

J.B. Wade [a,*], G.P. Martin [b], D.F. Long [a]

[a] Technical Services/Manufacturing Science Division, Eli Lilly & Company, Indianapolis, IN 46285, USA
[b] King's College London, Institute of Pharmaceutical Science, London SE1 9NH, UK

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ABSTRACT

The feasibility of a novel reverse-phase wet granulation process has been established previously and several potential advantages over the conventional process have been highlighted (Wade et al., 2014a,b, b). Due to fundamental differences in the growth mechanism and granule consolidation behaviour between the two processes the reverse-phase approach generally formed granules with a greater mass mean diameter and a lower intragranular porosity than those formed by the conventional granulation process under the same liquid saturation and impeller tip speed conditions. The lower intragranular porosity was hypothesised to result in an increase in the granule strength and subsequent decrease in tablet tensile strength. Consequently, the aim of this study was to compare the effect of impeller tip speed and granule size on the strength and compaction properties of granules prepared using both the reverse-phase and conventional granulation processes. For the conventional granulation process an increase in the impeller tip speed from 1.57 to 4.71 m s^{-1} (200–600 RPM) resulted in an increase in the mean granule strength ($p < 0.05$) for all granule size fractions and as the granule size fraction increased from 425–600 to 2000–3350 μm the mean fracture strength decreased ($p < 0.05$). For the reverse-phase process an increase in impeller tip speed had no effect ($p > 0.05$) on mean granule strength whereas, like the conventional process, an increase in granule size fraction from 425–600 to 2000–3350 μm resulted in a decrease ($p < 0.05$) in the mean fracture strength. No correlation was found between mean granule fracture strength and the tablet tensile strength ($p > 0.05$) for either granulation approach. These data support the rejection of the original hypothesis which stated that an increase in granule strength may result in a decrease in the tablet tensile strength. The similar tablet tensile strength observed between the conventional and reverse-phase granulation processes indicated that while mechanistic differences exist in the formation of the granules, which resulted in significant granule-scale fracture strength differences, the granule compaction properties at pharmaceutically relevant tableting pressures were unaffected.

1. Introduction

In this work, a novel reverse-phase granulation process is investigated. The reverse-phase granulation process proceeds by the controlled addition of the powder components of the formulation into the binder liquid, with mixing. Powder is added throughout the course of the process and the fraction of granular void space filled with binder liquid, termed liquid saturation (S_{max}), is steadily reduced. Upon complete addition of the powder formulation the desired granule size is obtained through a controlled breakage process. The reduction in S_{max} as the process proceeds effectively moves the process away from a point of over-wetting and uncontrolled granule growth. This is opposite to the conventional granulation approach where binder liquid is added to the powder formulation to increase S_{max} with granule growth ideally occurring as a result of controlled coalescence. The reverse-phase process presents a number of potential advantages.

First, the wetting and nucleation mechanisms in conventional granulation processes can be difficult to control. Drop penetration time is affected by powder bed porosity and effective pore size and depends upon agitation intensity and primary particle size (Hapgood et al., 2002). Dimensionless spray flux optimums are affected by binder liquid addition factors such as droplet size, spray area and powder flux (Litster et al., 2001). Control of granule

* Corresponding author. Tel.: +1 317 651 5427.
E-mail address: wade_jonathan@lilly.com (J.B. Wade).

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nucleation can be challenging at the small scale and often not feasible at the commercial scale (Plank et al., 2003). The reverse-phase process follows an immersion mechanism therefore drop penetration time and dimensionless spray flux are not relevant. Instead binder liquid is dispersed by a breakage mechanism which is controlled by the binder liquid quantity and the impeller tip speed (Wade et al., 2014a,b,b).

Second, the conventional granulation process proceeds as liquid coverage of powder particles approaches a calculated S_{max} value to promote consolidation and coalescence. However, the process must be terminated immediately prior to uncontrolled growth which is typically associated with achievement of complete coverage of the powder surface. Commercially the binder liquid contains binding agents dissolved or dispersed in a fixed quantity of water, which is added to the powder formulation in its entirety. Determining the desired volume of binder liquid to be added requires knowledge of several, typically, uncontrolled variables such as primary powder particle size, powder flow patterns and collision energy. An appropriate process endpoint criteria must also be established for the process. Insufficient control of any of these variables can result in elevated S_{max} values, uncontrolled granule growth and batch loss.

The novel reverse-phase wet granulation process has been investigated previously. The effects of S_{max} and binder liquid viscosity on the physical properties of hydroxyapatite granules produced by the reverse-phase process have been reported (Wade et al., 2014a). At S_{max} up to ~1 the reverse-phase granules have greater size and lower intragranular porosity than conventionally prepared granules. At $S_{max} > 1.1$ the conventional process underwent uncontrolled growth and granule size increased significantly as a result of decreased intragranular porosity whereas granule growth continued steadily for the reverse-phase process. The reverse-phase process was concluded to proceed by an advantageous steady growth mechanism whereas the conventional process proceeded by an induction growth mechanism.

The effect of impeller tip speed on the reverse-phase granulation of hydroxyapatite has also been reported (Wade et al., 2014b). For the reverse-phase process an increase in impeller speed from 1.57 to 4.71 m s^{-1} resulted in decreased mean granule size due to increased breakage. In contrast for the conventional process an increase in impeller speed from 1.57 to 3.14 m s^{-1} had minimal effect on the granule size distribution, however further increase in impeller tip speed to 3.93 and 4.71 m s^{-1} resulted in granule densification and a corresponding increase in mean granule size. The reverse-phase granulation process was proposed to begin with fully saturated pores therefore as impeller tip speed is increased further granule consolidation is limited and rebound or breakage occur. Analysis using the modified capillary number concluded that the reverse-phase process was driven by capillary forces whereas the conventional process was driven by viscous forces. Further, for the reverse-phase process a critical impeller speed represented the threshold above which breakage of large wet agglomerates and mechanical dispersion of binder liquid occured. In contrast, the conventional process was found to be difficult to control due to variations in granule consolidation as impeller tip speed was varied.

The reverse-phase process has been shown to be feasible and potential advantages relative to the conventional process have been demonstrated. However, in general the use of the reverse-phase process was found to produce granules with a greater mass mean diameter and lower intragranular porosity when compared to those generated using the conventional granulation process under the same liquid saturation and impeller tip speed conditions (Wade et al., 2014a,b,b). Given the differences in growth mechanism and consolidation behaviour there is the potential for the reverse-phase process to result in granules with greater strength and potentially inferior compaction properties which may negate the potential advantages of the approach.

This hypothesis is supported by studies on microcrystalline cellulose granules prepared with an aqueous binder liquid (Carvajal and Macias, 2012). As microcrystalline cellulose granule porosity decreased the granule strength increased according to an exponential relationship. When compressed it was found that as granule strength increased the tablet tensile strength decreased, again according to an exponential relationship.

A similar relationship was reported when studying the effect of different drying techniques on the mechanical properties of extruded MCC pellets prepared with 60/40 water/ethanol (Bashaiwoldu et al., 2004). Fractions of a common batch of MCC pellets were dried using either a fluid bed dryer, fan assisted hot air oven, freeze dryer or desiccator at room temperature with dried silica-gel resulting in pellets. The resultant pellets were characterised for porosity and single pellet tensile strength and also compacted into tablets of constant solid fraction. An inverse relationship between pellet porosity and individual pellet tensile strength was observed where an increase in porosity from 13.8% to 31.6% resulted in an individual pellet tensile strength decrease from 6.96 to 1.96 MPa. Tablet tensile strength had a positive relationship with pellet porosity and increased from ~0.02 to 0.55 MPa over the porosity range studied. The authors propose that the increase in porosity resulted in weakening of inter-particulate links and therefore decreased strength.

Finally, two related studies characterised the effect of impeller speed on the structure and mechanical properties of calcium carbonate granules prepared with 65% (w/w) aqueous PEG4000 binder liquid. First the effects of impeller blade angle, impeller tip speed and granulator scale on granule crushing strength were investigated (Rahmanian et al., 2008). An increase in the blade angle from horizontal to 45° resulted in a greater extent of granule densification and an increase in granule crushing strength. Similarly an increase in impeller tip speed across granulator scales of 1, 5 and 250 L resulted in an increase in granule strength. Second the effects of impeller speed on granule structure was evaluated using X-ray microtomography (Ghadiri et al., 2009). A phase volume model was applied to quantify granule porosity and individual granule strength was determined. As impeller speed was increased from 230 to 350 RPM the granule porosity decreased from 38.6% to 16.7% and the corresponding granule crushing strength increased from 0.24 N to 2.30 N. In both cases the increased granule strength was proposed to be due to the more intensive mixing and greater degree of granule compaction at higher impeller tip speeds resulting in less porous granules.

In the context of the present study, it has been shown that the reverse-phase process results in granules of lower intragranular porosity than granules produced using the conventional granulation process. These less porous granules are proposed to have a greater strength and may therefore be expected to result in tablets with a lower tensile strength at a constant tablet solid fraction. Consequently, since impeller tip speed has been shown to affect granule consolidation and growth for both the reverse-phase (Wade et al., 2014b) and conventional granulation processes (Knight et al., 2000; Saleh et al., 2005) the aim of this study was to compare the effect of impeller tip speed and granule size on the strength and compaction properties of granules prepared using both the reverse-phase and conventional granulation processes.

2. Materials and methods

2.1. Materials

Poly(vinyl pyrrolidone) (PVP) (Plasdone K29/32) was obtained from ISP Pharmaceuticals, Covington, Kentucky, USA.