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Distribution of a viscous binder during high shear granulation—Sensitivity to the method of delivery and its impact on product properties

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ABSTRACT

Binder distribution in the powder mass during high shear granulation is especially critical with the use of viscous liquid binders and with short processing times. A viscous liquid binder was delivered into the powder mass at two flow rates using three methods: pouring, pumping and spraying from a pressure pot. Binder content analyses at the scale of individual granules were conducted to investigate the impact of different delivery conditions on the homogeneity of binder distribution. There was clear evidence of non-uniformity of binder content among individual granules across all delivery conditions, particularly for the fast rates of delivery. Poorer reproducibility values of tablet thickness and disintegration time were observed when binder was poured but this may be overcome by pumping or spraying from the pressure pot. Greater homogeneity of binder distribution occurred with the slow rates of delivery and led to the earlier onset of granule growth and a consequent increase in granule size. Larger granule size and lower proportion of fines were in turn associated with increased granule bulk density and improvement of granule flow. In conclusion, delivery of a viscous binder at a slow rate either by pumping or via a pressure pot was most desirable during granulation.

1. Introduction

High shear wet granulation, a process by which agglomeration of powder particles occur in the presence of a liquid binder, is a major unit operation in the pharmaceutical industry (Giry et al., 2006). The distribution of the liquid binder in the powder mass occurs in three phases: (a) deposition of binder on the powder bed, (b) binder penetration due to wetting and/or solubilization of powder particles and (c) mechanical mixing by the impeller. The shearing forces imparted by the impeller are essential for the efficient distribution of binder (Knight et al., 1998), especially for viscous binders which penetrate and spread in the powder mass slowly (Seo et al., 2002). These forces allow for the reduction of binder droplet size and the intimate mechanical mixing of binder droplets and powder particles down to the particulate level.

There is no clear consensus on how a viscous binder should be added to the powder mass during granulation or how fast it should be added. Various methods have been employed and include rapid manual pouring of liquid onto the powder, continuous delivery by a pump, spraying of the liquid as fine droplets and the use of solid binders in melt granulation. The method of binder delivery determined the initial size of binder droplets and whether the immersion or distribution mechanism would predominate during nucleation (Johansen and Schafer, 2000; Schæfer and Mathiesen, 1996). Increasing the rate of binder delivery led to higher mean granule size as granules were formed earlier in the process (Smirani-Khayati et al., 2009) due to increased particle-droplet collision rate and speed of aggregation (Tan et al., 2006). On the contrary, granule size was not affected by the rate of binder delivery if there were no differences in droplet size (Hemati et al., 2003). It has also been suggested that regardless of the initial conditions for binder delivery, the size distribution of granules eventually reaches a dynamic steady state, during which agglomerate growth is the same as the attrition rate to yield a time-independent size distribution (Michaels et al., 2009). While most of the literature has focused on the impact of binder delivery conditions on the kinetics of granule growth (Knight et al., 1998; Scott et al., 2000), little is known about its influence on other granule or tablet properties.

It is postulated that the method and rate of binder delivery would influence binder distribution in the powder mass during

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granulation. Spraying of fine binder droplets is generally preferred over the pouring or melting-in method where liquid distribution would depend largely on mechanical energy supplied by the impeller (Knight et al., 1998; Litster et al., 2001). Homogenous binder distribution resulted in more consistent granule size, friability and strength (Smirani-Khayati et al., 2009). One common approach to assess binder distribution is by comparing binder contents in granules from different size fractions. However, heterogeneity of binder distribution among different size fractions persists even with prolonged wet massing times, as average binder content is widely reported to be higher in larger granules (Knight et al., 1998; Osborne et al., 2011; Reynolds et al., 2004; Scott et al., 2000). Hence, it may be difficult to identify the true impact of binder delivery conditions on binder distribution using this approach as the relation between larger granule size and higher binder content cannot be disregarded. An alternative approach by investigating the binder distribution in individual granules within the same size fraction (Reynolds et al., 2004) could potentially overcome the influence of binder content variation between granule size fractions. Considerable heterogeneity of binder distribution also exists among individual granules in all size fractions in the early stages of granulation but this difference is significantly narrowed for larger granules as granulation progresses (Reynolds et al., 2004; Smirani-Khayati et al., 2009). An increase in the wet massing time can in theory improve binder uniformity but drastic losses in compressibility due to over-granulation has been reported to occur within 10 min of wet massing (Shi et al., 2011). In order to reduce the processing time, the pharmaceutical industry typically conducts wet massing in high shear granulators for less than 5 min (Shi et al., 2011) with a slight excess of liquid binder (Michaels et al., 2009). With shorter time for binder distribution, binder delivery conditions are expected to have a greater impact on the homogeneity of binder distribution. This situation is of particular importance when low dose drugs are delivered to the granulations via the liquid binder.

The purpose of this study was to investigate the effects of different methods and rates of binder delivery on resultant granule and tablet properties. A powder mass comprising predominantly of paracetamol was granulated using a moderately viscous binder but with reasonable sprayability as the challenges in binder distribution are expected to be greater with binders of higher viscosity. The binder was delivered into the powder mass by 3 methods (poured in, pumped in and use of a pressure pot), each at 2 rates of delivery, constituting a total of 6 different binder delivery conditions. The impact of different binder delivery conditions on granule size, flow and strength as well as tablet thickness, hardness and disintegration was investigated. The homogeneity of binder distribution was evaluated by analyses of the binder content of individual granules in the same size fraction. With all other formulation and processing parameters being kept constant, it was of interest to determine how binder delivery conditions would impact on the homogeneity of binder distribution within the power mass and in turn, resultant granule and tablet properties.

2. Materials and methods

2.1. Materials

Paracetamol powder (Granules, India), with a median particle size of 40.2 μm and a span value of 2.71, and microcrystalline cellulose (MCC; Avicel® PH 101, FMC BioPolymer, Ireland) formed the powder mass for granulation. Pregelatinized starch (PGS; Starch 1500®, Colorcon, USA) and hydroxypropyl cellulose (HPC; Klucel™ EF, Ashland Aqualon Functional Ingredients, USA) were used in the preparation of the viscous liquid binder. Chlorpheniramine maleate (CPM; Panchsheel Organics, India) was dissolved in the liquid binder and functioned as a tracer substance in binder content analyses. Potassium dihydrogen phosphate (KH_2PO_4, Merck, Germany), ortho-phosphoric acid (H_3PO_4, Merck, Germany) and methanol (HPLC grade, Tedia, USA) were used in the preparation of the mobile phase for high performance liquid chromatography (HPLC).

Table 1
Formulation of granules.

Powder mass		Liquid binder	
Material	% (w/w)	Material	% (w/w)
Paracetamol	97.5	Pregelatinized starch	5.5
Microcrystalline cellulose	2.5	Hydroxypropyl cellulose	5.5
		Chlorpheniramine maleate	1.0
		Deionized water	88.0

2.2. Formulation for granulation experiments

Compositions of the powder formulation and liquid binder are presented in Table 1. The liquid binder was prepared by first dissolving CPM in approximately 120 g of deionized water and temperature raised to about 60 °C by adding hot water. HPC was slowly dispersed with stirring in the hot solution, followed by PGS. The dispersion was then made up to the desired weight with deionized water, stirred for an additional half hour and left at room temperature for at least 2 h to allow for cooling and complete hydration of HPC. The viscosity of the liquid binder, as measured on a rheometer (AR-G2, TA Instruments, USA) using the parallel plate method, was found to be 479 mPa s at 25 °C.

2.3. High shear wet granulation

Wet granulation was performed in a top-driven high shear granulator (Collette Ultima™ 10, GEA Process Engineering, Belgium) equipped with a 10 L mixing bowl. Paracetamol and MCC, amounting to a total of 1.7 kg, were dry mixed for 2 min at an impeller speed of 300 rpm. Wet massing began at the start of liquid binder delivery and lasted 5 min with the impeller and chopper speeds of 630 and 2700 rpm, respectively. The tip speed of the impeller during wet massing was 7.65 m/s. For each granulation experiment, 476 g of liquid binder, equivalent to 28% (w/w) of the powder mass, was used. Two rates of binder delivery, 'fast' and 'slow', for each of the 3 methods of delivery were investigated and they are described below.

(a) *Pour-in*: A funnel was placed in the liquid addition port and liquid binder was manually poured in to achieve the appropriate rates of binder delivery.
(b) *Pump-in*: Binder was delivered using a peristaltic pump (Masterflex® L/S, Cole-Parmer, USA) equipped with a silicone tube with an internal diameter of 10.5 mm. The pump speed was set at 600 and 45 rpm for the fast and slow rates of binder delivery, respectively.
(c) *Pressure pot*: Liquid binder was transferred to a pressurized pot and delivered into the powder mass via a spray nozzle. The pressure in the pot was set at 1.8 and 1.4 bar for the delivery of liquid binder at the fast and slow rates, respectively.

For each condition of binder delivery, granulation was conducted in triplicate. The actual duration of time required to deliver the binder during granulation was recorded and presented in Table 2.