International Journal of Pharmaceutics 478 (2015) 439–446

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Controlling granule size through breakage in a novel reverse-phase wet granulation process; the effect of impeller speed and binder liquid viscosity

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

ARTICLE INFO

Article history:
Received 3 September 2014
Received in revised form 19 November 2014
Accepted 28 November 2014
Available online 2 December 2014

Keywords:
Wet granulation
Reverse-phase granulation
Intragranular porosity
GeoPyc
Impeller speed
Modified capillary number

ABSTRACT

The feasibility of a novel reverse-phase wet granulation process has been established previously highlighting several potential advantages over the conventional wet granulation process and making recommendations for further development of the approach. The feasibility study showed that in the reverse-phase process granule formation proceeds via a controlled breakage mechanism. Consequently, the aim of the present study was to investigate the effect of impeller speeds and binder liquid viscosity on the size distribution and intragranular porosity of granules using this novel process. Impeller tip speed was found to have different effects on the granules produced by a conventional as opposed to a reverse-phase granulation process. For the conventional process, an increase in impeller speed from 1.57 to 3.14 $m\,s^{-1}$ had minimal effect on granule size distribution. However, a further increase in impeller tip speed to 3.93 and 4.71 $m\,s^{-1}$ resulted in a decrease in intragranular porosity and a corresponding increase in mean granule size. In contrast when the reverse-phase process was used, an increase in impeller speed from 1.57 to 4.71 $m\,s^{-1}$ resulted in increased granule breakage and a decrease in the mean granule size. This was postulated to be due to the fact that the granulation process begins with fully saturated pores. Under these conditions further consolidation of granules at increased impeller tip speeds is limited and rebound or breakage occurs. Based on these results and analysis of the modified capillary number the conventional process appears to be driven by viscous forces whereas the reverse-phase process appears to be driven by capillary forces. Additionally, in the reverse-phase process a critical impeller speed, represented by the equilibrium between centrifugal and gravitational forces, appears to represent the point above which breakage of large wet agglomerates and mechanical dispersion of binder liquid take place. In contrast the conventional process appears to be difficult to control due to variations in granule consolidation, which depends upon experimental variables. Such variations meant increased impeller tip speed both decreased and increased granule size. The reverse-phase process appears to offer simple control over granule porosity and size through manipulation of the impeller speed and further evaluation of the approach is warranted.

1. Introduction

The feasibility of employing a novel reverse-phase wet granulation process has previously been reported (Wade et al., 2014a). The reverse-phase process involves the controlled addition of the powder formulation into the agitated binder liquid to create wetted powder particles which favour granule formation. Addition of further powder reduces the liquid saturation of the granules, with the desired particle size being obtained through controlled breakage. Proposed advantages of the reverse-phase process over the conventional wet granulation approach include a reduced risk of uncontrolled granule growth and batch loss, and the elimination of variables associated with binder liquid addition. Additionally, the reverse-phase process has the potential for simpler process control where it is hypothesised that the reverse-phase granulation process can be controlled by a few simple variables; binder liquid quantity, binder liquid viscosity and impeller speed, to reach the desired granule properties.

The effects of binder liquid quantity and binder liquid viscosity at a constant impeller tip speed have been reported previously (Wade et al., 2014a). An increase in binder liquid quantity was reported to significantly increase granule mass mean diameter and

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

http://dx.doi.org/10.1016/j.ijpharm.2014.11.067
0378-5173/

decrease intragranular porosity for both the conventional and reverse-phase granulations processes with the reverse-phase process generally producing 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 conditions. For both granulation processes the binder liquid viscosity was found to have no effect on granule mass mean diameter and intragranular porosity. Controlled breakage was proposed to be the predominant granule formation mechanisms in the reverse-phase process, therefore the effect of impeller speeds on the process are of particular interest, especially since impeller speed is known to affect granule consolidation (Saleh et al., 2005), growth (Knight et al., 2000) and breakage (Liu and Litster, 2009) in the conventional granulation process.

An increase in impeller speed, when using the conventional granulation process, has been reported to increase granule consolidation and growth, but also increase granule breakage in high shear granulators, depending upon the formulation and process variables. Knight et al. (2000) found that as impeller speed in a high shear mixer increased there was an initial increase in granule size, followed by a subsequent reduction. At low impeller speeds the granules had high sphericity, while those at high impeller speeds had a more irregular shape, indicative of breakage phenomena. Saleh et al. (2005) studied the combined effects of liquid content and impeller speed on the granulation of alumina powder with aqueous PEG binders and reported that increasing liquid content and/or increasing impeller speed resulted in a decrease in granule porosity and an increase in pore saturation. The effect of impeller speed on granule size distribution of a gabapentin tablet formulation was found to be complex (Litster and Kayrak-Talay, 2011), due to the balance between the increase in growth but also the increase in breakage, making a priori prediction difficult without quantitative knowledge of the growth and breakage regimes.

Increasing impeller speed will increase the frequency and energy of impacts resulting in reduced granule porosity, and therefore increased liquid saturation (Ennis et al., 1991; Ouchiyama and Tanaka, 1980; Iveson and Litster, 1998a). An investigation of the breakage of glass ballotini and lactose particles found that the rate of breakage was influenced by liquid saturation, binder liquid viscosity, binder liquid surface tension, and primary powder particle size (Liu and Litster, 2009). The calculated Stokes deformation number, St_{def}, gave a good prediction of the breakage probability for each formulation and a boundary St_{def} value of 0.2 was proposed. The increase in impeller speed was thought to promote a shift from nucleation to steady or induction growth; and from steady growth to crumb behaviour. Such an observation could explain the apparently contrasting reports that increased impeller speed can both increase granule growth and increase granule breakage.

The breakage mechanism is considered very important in wet granulation processes as it is thought to influence, and potentially control, the final granule size distribution (Liu and Litster, 2009). Iveson et al. (2001) discussed the relevance of granule consolidation in breakage, indicating that an increase in impeller speed will increase the collision velocity between granules. If the increase in collision energy is greater than the dissipation capacity of the system then colliding granules will rebound, which reduces the probability of granule coalescence and growth. Therefore the effect of impeller speed on granule consolidation, and porosity, should be considered along with the resultant granule particle size, in order to gain further insight into this phenomenon. Hoornaert et al. (1998) reported an increase in the rate of granule consolidation with increasing impeller speed, whereas in contrast Eliasen et al. (1998) reported a decrease in granule consolidation. The effects of impeller speed appear to depend upon the formulation and equipment variables selected and therefore warrant further study for the specific system in question.

Due to the fundamental differences between the reverse-phase and conventional granulation processes: i.e., the reverse-phase process starts from a condition characterized by a high liquid saturation and the conventional process starts from a low liquid saturation condition; it is proposed that an increase in impeller speed will have different effects. It is hypothesised that in the reverse-phase granulation process breakage of large moist agglomerates will control the final granule size, and that an increase in impeller speed will result in a greater extent of breakage and a reduced granule size. In contrast it may be suggested that use of the conventional granulation process will cause an increase in consolidation with increasing impeller speed, reducing the porosity of the powder mass, resulting in an increase in S_{max}, and a corresponding increase in granule size. There is the potential that for the conventional process, at elevated impeller speed, the impact energy may not be able to be dissipated and granules may either rebound resulting in a minimal growth, or break resulting in a granule size decrease.

Accordingly, the aim of this study was to compare the effects of binder liquid viscosity and impeller speed on the size and porosity of the granules prepared using the reverse-phase and conventional methods of granulation.

2. Materials and methods

2.1. Materials

Poly(vinyl pyrrolidone) (PVP) (Plasdone K29/32) was obtained from ISP Pharmaceuticals, Covington, Kentucky, USA. DryFlo® displacement medium was supplied by Micromeritics, Norcross, Georgia, USA. Pharmaceutical grade hydroxyapatite (HA) (TRI-CAL WG™, tricalcium phosphate anhydrous granular) was obtained from Innophos Ltd., Chicago Heights, Illinois, U.S.A. for which micromeritic and compaction properties have been reported previously (Wade et al., 2013).

2.2. Granulation process

Aqueous granulation binder liquid was prepared by dissolving 10 or 20% w/w PVP in water with agitation. Following dissolution of the PVP, the solution was held without agitation for at least 12 h to allow deaeration. Binder liquid surface tension, density, viscosity and contact angle with HA powder for both 10 and 20% w/w PVP have previously been reported (Wade et al., 2014a). Granules were prepared in a high shear granulator fitted with a 1 L stainless steel bowl (P1-6, Diosna Dierks & Sohne GmbH, Osnabruck, Germany).

For the reverse-phase granulation process the total volume of binder liquid was added directly to the granulator bowl. Separate experiments were performed employing 200 mL of 10 or 20% w/w aqueous PVP binder liquid and impeller speeds of 1.57–4.71 $m\,s^{-1}$. Dry HA powder (600 g) was added to the moving liquid using a vibratory feeder with a controlled feed rate of approximately 5 $g\,s^{-1}$ (Syntron F-T0, FMC Technologies Inc., Tupelo, Mississippi, U.S.A.). Wet massing was performed for 10 s following complete addition of the HA powder.

Granules were also prepared by the conventional process where 600 g of dry HA powder was added to the granulator bowl. PVP binder (10 or 20% w/w) was sprayed onto the moving powder bed at a rate of approximately 2.17 $g\,s^{-1}$ through a 65° VeeJet nozzle (SS-650033, Spraying Systems, Wheaton, Illinois, USA) using a pressurised vessel set to 3 bar. Separate experiments were performed employing 200 mL of 10 or 20% w/w aqueous PVP binder liquid and impeller speeds of 1.57–4.71 $m\,s^{-1}$. Wet massing was performed for 10 s following complete addition of the binder liquid.