



The development of a growth regime map for a novel reverse-phase wet granulation process



Jonathan B. Wade^{a,*}, Gary P. Martin^b, David 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 May 2016

Received in revised form 19 August 2016

Accepted 24 August 2016

Available online 26 August 2016

Keywords:

Wet granulation

Reverse-phase granulation

Growth regime map

Stokes deformation number

Intragranular porosity

ABSTRACT

The feasibility of a novel reverse-phase wet granulation process has been established and potential advantages identified. Granule growth in the reverse-phase process proceeds via a steady state growth mechanism controlled by capillary forces, whereas granule growth in the conventional process proceeds via an induction growth regime controlled by viscous forces. The resultant reverse-phase granules generally have greater mass mean diameter and lower intragranular porosity when compared to conventional granules prepared under the same liquid saturation and impeller speed conditions indicating the two processes may be operating under different growth regimes. Given the observed differences in growth mechanism and consolidation behaviour of the reverse-phase and conventional granules the applicability of the current conventional granulation regime map is unclear. The aim of the present study was therefore to construct and evaluate a growth regime map, which depicts the regime as a function of liquid saturation and Stokes deformation number, for the reverse-phase granulation process. Stokes deformation number was shown to be a good predictor of both granule mass mean diameter and intragranular porosity over a wide range of process conditions. The data presented support the hypothesis that reverse-phase granules have a greater amount of surface liquid present which can dissipate collision energy and resist granule rebound resulting in the greater granule growth observed. As a result the reverse-phase granulation process results in a greater degree of granule consolidation than that produced using the conventional granulation process. Stokes deformation number was capable of differentiating these differences in the granulation process.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

The wet granulation growth regime map for conventionally formed granules depicts the granulation regime for a given granulation system to be a function of granule liquid saturation, S_{\max} , and Stokes deformation number, St_{def} (Iveson and Litster, 1998a; Iveson et al., 2001). Several general themes are immediately identified from the growth regime map. An increase in binder liquid amount will increase the liquid saturation and move the system from dry to nucleation to induction or steady growth, and potentially the slurry condition. An increase in impeller speed or binder viscosity will increase the St_{def} , and potentially S_{\max} , and therefore move the system from nucleation or induction to steady growth to the crumb or slurry regimes.

The regime map boundaries are not “validated”, however some experimental data have been reported previously. The boundary between nucleation and steady or induction growth behaviour depends upon the binder amount required to reach critical pore saturation and the consolidation behaviour of the wet granules. Published results suggest at $S_{\max} < 0.7$ insufficient liquid is present to achieve coalescence and only nuclei form (Kayrak-Talay et al., 2013). An S_{\max} between 0.8–0.9 generally results in a steady growth regime (Iveson et al., 2001; Butensky and Hyman, 1971; Sherington, 1968). Whereas, induction growth systems are those which are so strong they do not deform sufficiently to coalesce without the presence of free liquid at the granule surfaces, i.e. $S_{\max} > 1$. The boundary between steady growth and induction growth has been reported in the range of St_{def} 0.001–0.003 (Iveson et al., 2001). Since an increase in the liquid saturation reduces the induction time it stands to reason that at high liquid saturations the difference between steady growth and induction growth disappears and both systems exhibit rapid growth. The boundary

* Corresponding author.

E-mail address: wade_jonathan@lilly.com (J.B. Wade).

between steady and crumb growth has been reported as St_{def} of 0.1 (Iveson et al., 2001) and ~ 0.2 (Tardos et al., 1997).

The feasibility of a novel reverse-phase wet granulation process has been established (Wade et al., 2014a). The reverse-phase process involves the inversion of the conventional granulation process such that the powder formulation is added to the agitated binder liquid in a controlled fashion to create wetted powder particles which favour granule formation. Further powder is then added to reduce the liquid saturation of the system and the desired granule size is obtained through controlled breakage (Wade et al., 2014b). Advantages of the reverse-phase process when compared to the conventional process include lower risk of uncontrolled granule growth and elimination of variables associated with binder liquid addition (Wade et al., 2014a). Additionally, the reverse-phase process has the potential for simpler process control with binder liquid quantity, binder liquid viscosity and impeller speed reported as the major variables associated with engineering the desired granule properties (Wade et al., 2014a; Wade et al., 2014b; Wade et al., 2015).

Granule growth in the reverse-phase process has been shown to proceed via a steady state growth mechanism controlled by capillary forces, whereas granule growth in the conventional process proceeds via an induction growth regime controlled by viscous forces (Wade et al., 2014b). The resultant reverse-phase granules generally have greater mass mean diameter and lower intragranular porosity when compared to conventional granules prepared under the same liquid saturation and impeller speed conditions (Wade et al., 2014a; Wade et al., 2014b) indicating the two processes may be operating under different growth regimes. Given the observed differences in growth mechanism and consolidation behaviour of the reverse-phase and conventional granules the applicability of the current conventional granulation regime map is unclear. The aim of the present study was therefore to construct and evaluate a growth regime map for the reverse-phase granulation process.

2. Materials and methods

2.1. Materials

Poly (vinyl pyrrolidone) (PVP) (Plasdone K29/32) was obtained from ISP Pharmaceuticals, Covington, Kentucky, USA. DryFlo[®] displacement media was obtained from Micromeritics, Norcross, Georgia, USA. Pharmaceutical grade hydroxyapatite (HA) (TRI-CAL WGTM, tricalcium phosphate anhydrous granular) was obtained from Innophos Ltd., Chicago Heights, Illinois, USA and the methods for determination of micromeritic 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. Following dissolution of the PVP, the solution was held without agitation for at least 12 h to allow deaeration. Methods for the measurement of binder liquid surface tension, density, viscosity and contact angle with HA powder 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 50, 100, 150, 200 and 250 mL of the 10 or 20% w/w aqueous PVP binder liquid and impeller speeds of 200–600 RPM (1.57–4.71 m s⁻¹). The binder liquid was mixed for 30 s using an impeller speed of 400 RPM (3.14 m s⁻¹) and chopper speed of 1000 RPM (0.89 m s⁻¹).

Following mixing 600 g of dry HA powder was added to the moving liquid using a vibratory feeder with a feed rate of approximately 5 g s⁻¹ (Syntron F-T0, FMC Technologies Inc., Tupelo, Mississippi, USA). 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 and mixed for 30 s using an impeller speed of 400 RPM (3.14 m s⁻¹) and chopper speed of 1000 RPM (0.89 m s⁻¹). Following mixing the 10 or 20% w/w PVP binder liquid was sprayed at a spray rate of approximately 2.17 g s⁻¹ onto the moving powder bed through a 65° VeeJet nozzle (SS-650033, Spraying Systems, Wheaton, Illinois, USA) at 3 bar pressure. Separate experiments were performed employing 50, 100, 150, 200 and 250 mL of the 10 or 20% w/w aqueous PVP binder liquid and impeller speeds of 200–600 RPM (1.57–4.71 m s⁻¹). Wet massing was performed for 10 s following complete addition of the binder liquid.

The resultant granules were dried as a thin layer in a hot air convection oven (Lindberg/Blue, SPX Thermal Solutions, Rochester, New York, USA) at 60 °C to a moisture content of $\leq 1.2\%$, as measured by loss on drying at 105 °C (Computrac MAX2000-XL, Arizona Instruments, Chandler, Arizona, USA).

2.3. Granule physical characterisation

Granule size analysis was performed by sieve analysis. Approximately 100 g of dried granules (n=4) were placed onto tared 8 inch diameter ASTM certified screens (pan, 75, 150, 250, 425, 600, 850, 1000, 1700, 2000, 3350, 4750 and 8000 μm). The sieve stack was then mounted on a single intensity sieve tester (RoTap RX-29, W.S. Tyler, Mentor, Ohio, USA) and the granules sieved. Preliminary work indicated that sieving times of 5, 10 and 15 min showed no differences in the granule mass retained on each sieve therefore a sieving time of 5 min was selected. After sieving 13 size fractions were collected and the mass mean diameter, d_{pm} , was determined using Eq. (1):

$$d_{pm} = \frac{(\sum f_i \times d_{pi})}{\sum f_{i-n}} \quad (1)$$

where f_i is the mass fraction of size interval i , d_{pi} is the mean diameter of size interval i (μm).

The envelope density of granule samples (n=4) was determined by a powder pycnometry method (GeoPyc[®] 1360, Micromeritics, Norcross, Georgia, USA). The apparatus uses displacement theory to determine the sample volume which is then used to calculate the envelope density of the accurately weighed granule sample. The method employed has been described in detail previously (Wade et al., 2014c).

2.4. Measurement of powder surface velocity

In the present study the surface velocity of the powder bed was used as a surrogate for the representative collision velocity experienced between two particles in the granulator. Surface velocity was measured using a high-speed camera (TroubleShooter TS1000ME, Fastec Imaging, San Diego, USA) fitted with a wide angle lens. The high-speed camera was mounted on a tripod such that the camera was facing directly downwards and focussing on the granulation process through a safety interlocked PerspexTM cover. Two 1000 W halogen spotlights were used to illuminate the focal area. Video footage of the powder bed was recorded at 500 frames s⁻¹ during the 10 s wet massing period of each experiment. The diameter of the granulator bowl (12.00 cm) was used as a reference feature to calibrate the distance measurements.

Download English Version:

<https://daneshyari.com/en/article/2500779>

Download Persian Version:

<https://daneshyari.com/article/2500779>

[Daneshyari.com](https://daneshyari.com)