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The effect of the binder size and viscosity on agglomerate growth in fluidised hot melt granulation

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ABSTRACT

Fluidised hot melt granulation (FHMG) is a novel granulation technique for processing pharmaceutical powders. Several process and formulation parameters have been shown to significantly influence granulation characteristics within FHMG. In this study we have investigated the effect of the binder properties (binder particle size and binder viscosity) on agglomerate growth mechanisms within FHMG. Low-melting point co-polymers of polyoxyethylene–polyoxypropylene (Lutrol® F68 Poloxamer 188 and Lutrol® F127 Poloxamer 407) were used as meltable binders for FHMG, while standard ballotini beads were used as model fillers for this process. Standard sieve analysis was used to determine the size distribution of granules whereas we utilised fluorescence microscopy to investigate the distribution of binder within granules. This provided further insight into the growth mechanisms during FHMG. Binder particle size and viscosity were found to affect the onset time of granulation. Agglomerate growth achieved equilibrium within short time-scales and was shown to proceed by two competing processes, breakage of formed granules and re-agglomeration of fractured granules. Breakage was affected by the initial material properties (binder size and viscosity). When using binder with a small particle size (<250 μm), agglomerate growth via a distribution mechanism dominated. Increasing the binder particle size shifted the granulation mechanism such that agglomerates were formed predominantly via immersion. A critical ratio between binder diameter and filler has been calculated and this value may be useful for predicting or controlling granulation growth processes.

1. Introduction

Due to the poor flowability, compressibility and compactibility of many drugs, particle size enlargement processes have been developed to reduce the potential difficulties during solid dosage form manufacture. There are many granulation techniques that have been used in the pharmaceutical industry. However, new granulation techniques are still being investigated and developed in order to overcome some of the inherent limitations of conventional processes.

Melt granulation (MG) is a process by which pharmaceutical powders are agglomerated using low-melting point pharmaceutical materials as meltable binders. The meltable binders are added to the system either as a molten liquid or a solid that melts during the process. The system provides heat continuously to maintain the molten state of the binder thus facilitating granulation. The system is subsequently cooled to solidify the binder and harden the granular structure [1]. Over the last decade, MG has received increasing attention because aqueous or organic solvents are not required which negates the problems associated with in-process hydrolysis and solvent removal [2]. The most commonly used equipment for melt granulation is a high-shear mixer [3,4], in which the process temperature is raised above the melting point of the binder either by using a heating jacket or by the shear forces generated from the high speed of the impeller blades [5]. The factors affecting agglomerate formation and growth mechanisms in high-shear mixers have been investigated theoretically. It has been previously reported that agglomerate formation occurs either via a distribution or immersion mechanism or by a combination of both [1] Growth mechanisms have been shown to be affected by binder droplet size, liquid saturation of agglomerates, impeller speed and particle size/wettability and binder viscosity.

In addition to shear granulators, fluid beds have been developed for melt granulation purposes. The use of a fluid bed conveniently combines granulation, drying and coating into a single unit operation. A number of articles have also been published describing the kinetics of fluidised bed melt granulation (FBMG) [6–9]. During this process, a binder spray nozzle system is used to spray molten binder onto fluidised fillers. Upon wetting, the particles initially bind together by liquid bridges, which subsequently solidify to

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form solid bridges [8]. The binder spray rate, fluid bed temperature, binder type, binder viscosity and droplet size have been shown to significantly affect the granulation process [6].

Fluidised hot melt granulation (FHMG) is novel melt granulation process in which granules are produced by mixing low-melting point solid binders with other excipients and drug directly in a fluid bed of hot air. In comparison to FBMG, FHMG has no spray nozzle system, making it a more simple and rapid technique for producing granules with high levels of fluidity and compressibility [10]. Although FHMG has been investigated as a novel technique for manufacturing pharmaceutical granules [11,12], only a small number of articles have investigated the kinetics and mechanism of granule growth [13]. Previous work by our group has shown that the binder concentration and binder/filler particle size may affect the size distribution and shape characteristics of the granules [14]. Moreover, it has been found that agglomeration occurs very rapidly. In this study, we have extended our investigations to examine the effect of binder size and viscosity with regard to onset of granulation, the size distribution of the granules and agglomerate growth mechanisms within FHMG.

2. Materials and methods

2.1. Materials

Standard ballotini (glass) beads (JENCONS-PLS, Leighton Buzzard, UK) with a size range of 150–250 μm were used as an inert model filler. Low-melting point polymers – Poloxamer 188 and Poloxamer 407 (BASF ChemTrade, GmbH, Burgbernheim, Germany) – were used as meltable binders. Poloxamer 188 and Poloxamer 407 were sieved respectively using laboratory test sieves (Retsch GmbH&Co KG, Germany) into different size fractions (45–90, 125–250, 250–500, 500–710 and 710–1000 μm) that were used during FHMG. Sulphamerazine (Sigma, UK) was used as the fluorescent additive when conducting fluorescence microscopy.

2.2. Viscosity analysis

The apparent viscosity of molten binder (Poloxamer 188 and Poloxamer 407) across the shear stress range from 0.5 and 50 Pa was determined at 65 ± 1 °C using a rotational rheometer (AR2000 Advanced Rheometer, UK). A stepped flow mode in conjunction with 6 cm parallel plate geometry and a fixed gap of 1000 μm was used in all analyses. The solid samples were loaded onto the lower stationary plate of the rheometer, allowing the sample to melt and equilibrate for 5 min before testing. Each sample was measured in triplicate and the viscosity of the samples was determined from the flow rheogram as the ratio of shearing stress to shear rate.

2.3. Fluidised hot melt granulation

A laboratory fluid bed dryer (Mark II, Sherwood Scientific Ltd, Cambridge, UK) consisting of a granulation container with a fine mesh nylon gauze air distributor, stainless steel support gauze on the bottom and a filter bag at the top was used for granulation. The heating temperature for the inlet air was maintained at 65 ± 1 °C, and the airflow rate was maintained between 1.5 and 2.0 m s^{-1}. The binder content for each experiment was fixed at 6% (w/w), which has been determined as a suitable value in previously published work by our group [14]. In order to control the air temperature and investigate granulation time sufficiently and accurately, two fluid bed systems were used. The materials were first pre-mixed and put into a pre-heated fluid bed for a defined granulation time (5 s, 15 s, 30 s, 45 s, 1 min, or 3 min, separately), and then quickly transferred to a fluid bed with cooled air which solidified the binder and prevented further granulation. The cooling airflow rate was 1.5–2.0 m s^{-1} and the cooling time for each granulation experiment was 2 min.

2.4. Size distribution analysis

The size distribution of the agglomerates was determined using a sieve stack. The product of each batch was placed onto a series of six ASTM standard sieves (Retsch GmbH&Co KG, Germany) with the range from 125 to 2000 μm. The sieve stack was vibrated using a COPLEY Scientific AS 200 Control 'g' sieve shaker (Nottingham, UK). The amplitude of vibration was set up at 0.5 mm, and sieving time was 5 min.

2.5. Breakage investigations

In order to investigate the effect of binder/filler properties on the breakage and re-aggregation in FHMG, a series of breakage experiments were conducted. A defined mass (50.0 g) of granules with a particle size range between 1000 and 2000 μm, which were produced by different binder/filler systems, were individually poured into the pre-heated fluid bed to re-fluidise for 1 min, then cooled immediately with cold air for 2 min. The percentage mass of broken granules (size below 1000 μm) was subsequently determined.

2.6. Microscopic determination of granulation mechanism

Microscopic images were collected using a Nikon ECLIPSS TE300 microscope with a Nikon Digital Camera DXM1200 (Nikon, Japan) controlled by Lucia G software. A fluorescent additive (sulphamerazine) was combined within the meltable binder in order to investigate binder distribution characteristics within granules, and thus make it possible to understand in more detail granule growth processes during FHMG.

2.7. Statistical analysis

Where necessary, statistical significance was determined using parametric hypothesis testing for multiple samples (analysis of variance). Post hoc comparisons of the means of individual factors were performed using Fisher's PLSD test. In all analyses, at least five replicates were recorded and in all cases, $P < 0.05$ denoted significance.

3. Results and discussion

3.1. The effect of binder viscosity on agglomerate growth within FHMG

Poloxamers are a group of non-ionic triblock co-polymers of polyoxyethylene–polyoxypropylene–polyoxyethylene (PEO–PPO–PEO) that are commercially available under the trade names Lutrol® or Pluronic®. Alteration of the architecture of this triblock structure through changes in molecular weight and the relative size of each particular block has led to the widespread application of these polymers within the pharmaceutical industry. In this study, we have used two different poloxamers, 407 and 188, that differ in their percentage of PEO and the molecular weight of the repeating PPO unit. Poloxamer 407 contains 70% PEO and has a PPO repeat unit with a molecular weight of 4000 Da whereas Poloxamer 188 contains 80% PEO and a PPO repeat unit with a typical molecular weight of 1750 Da. Rheological analysis of the two molten poloxamers confirmed an almost Newtonian flow response. The shearing stress/shearing rate data was fitted to the Ostwald-de-Walde model to determine the flow index and the consistency. A flow index close to unity is indicative of a Newtonian

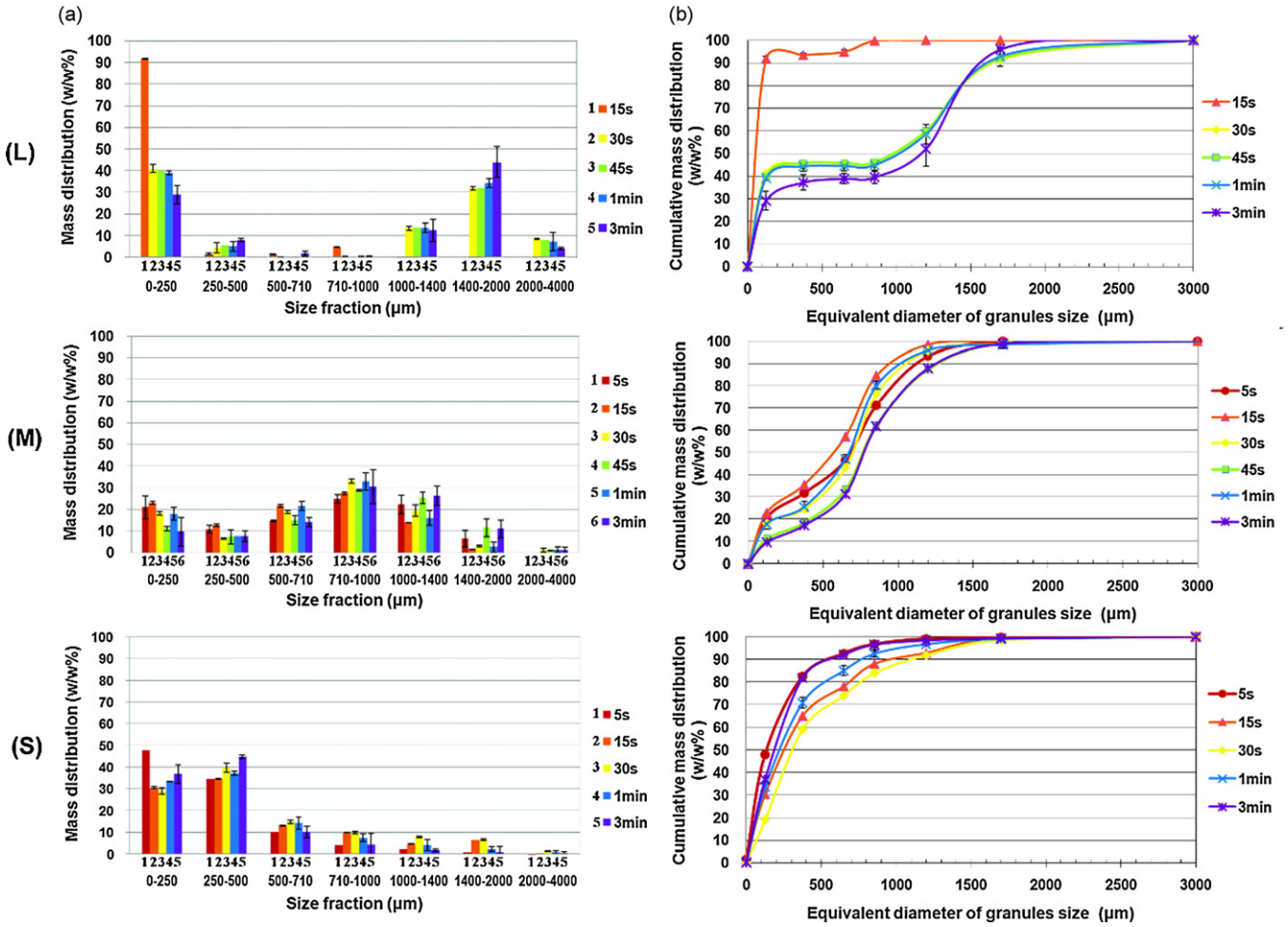

Fig. 1. (a) Size distributions of the granules produced by FHMG for various granulation times; (b) Cumulative particle size distribution of the granules produced by FHMG for various granulation times. (L) binder size = 710–1000μm; (M) binder size = 125–250μm; (S) binder size = 45–90μm (Filler type: Standard ballotini beads; Binder type: Poloxamer 188).

response whereas the consistency is a measure of the apparent viscosity at a shear rate of $1\,s^{-1}$. Poloxamer 188 had a flow index of 0.97 ± 0.03 and a consistency of $1.71 \pm 0.10\,Pa\,s^n$ whereas as Poloxamer 407 had a flow index of 0.98 ± 0.01 and a consistency of $7.20 \pm 0.48\,Pa\,s^n$. As expected, due to molecular weight differences, the consistency of Poloxamer 407 at 65 °C (granulation processing temperature) was significantly higher than that of Poloxamer 188.

Fig. 1a and b illustrates the size distribution and cumulative size distribution of the granules produced using the lower viscosity binder, Poloxamer 188, and standard ballotini beads at different granulation times, whereas Fig. 2a and b shows the results obtained when using Poloxamer 407 (higher molten viscosity). In both figures data is shown for three different binder size fractions, namely L (710–1000 μm), M (125–250 μm) and S (45–90 μm). In addition to yielding information on the size distribution of granules [21], the information presented in Figs. 1 and 2 may also be used to determine the onset of granulation (the time when the un-granulated fractions decrease significantly) and the effective granulation time (the time needed for the granulation to reach a stage wherein there is limited change to the mean particle size).

Previously we have shown that the mean particle diameter of granules in a defined system does not change significantly after approximately 2.5 min, suggesting granule growth within FHMG occurs very rapidly [2]. For these reasons, we aimed to further our understanding of FHMG by using granulation times ranging from 5 s to 3 min to determine the onset of granulation and the time required for effective agglomerate growth.

As shown by the data presented in Figs. 1 and 2, the onset time of granulation in each binder system (L, M and S) was dependent upon the viscosity of the binder. For the granulation system utilising the large binder particle size (710–1000 μm), the use of a higher viscosity binder resulted in a reduction in the onset of granulation. For example, the onset of granulation decreased from 15 to 5 s when Poloxamer 407 was used in place of Poloxamer 188. Conversely, when the binder particle size was reduced as in the case of M (125–250 μm) and S (45–90 μm) systems, the use of a higher viscosity Poloxamer 407 increased the onset of granulation.

The opposing results obtained for the larger binder particle size (L – 750–1000 μm) may be attributed to the concurrent processes operating during granulation. Firstly, binder consistency has a conflicting effect on melt granulation by promoting agglomerate growth through coalescence [15], but additionally counteracting agglomerate growth by decreasing the deformability of agglomerates, hence decreasing binder distribution [23,24]. Therefore in systems where growth is highly dependent upon distribution of the binder (discussed further in Section 3.4) the process may be retarded through the use of a higher melt viscosity binder. This is what is observed for the M and S systems wherein the increase in the time required before the onset of granulation may be attributed to slower effective binder distribution when using Poloxamer 407. However, when using a larger binder size, as observed in this study when using a binder with a particle size range from 710 to 1000 μm, the agglomerate growth is not as dependent upon binder distribution but more reliant on the contact/collision of filler particles with

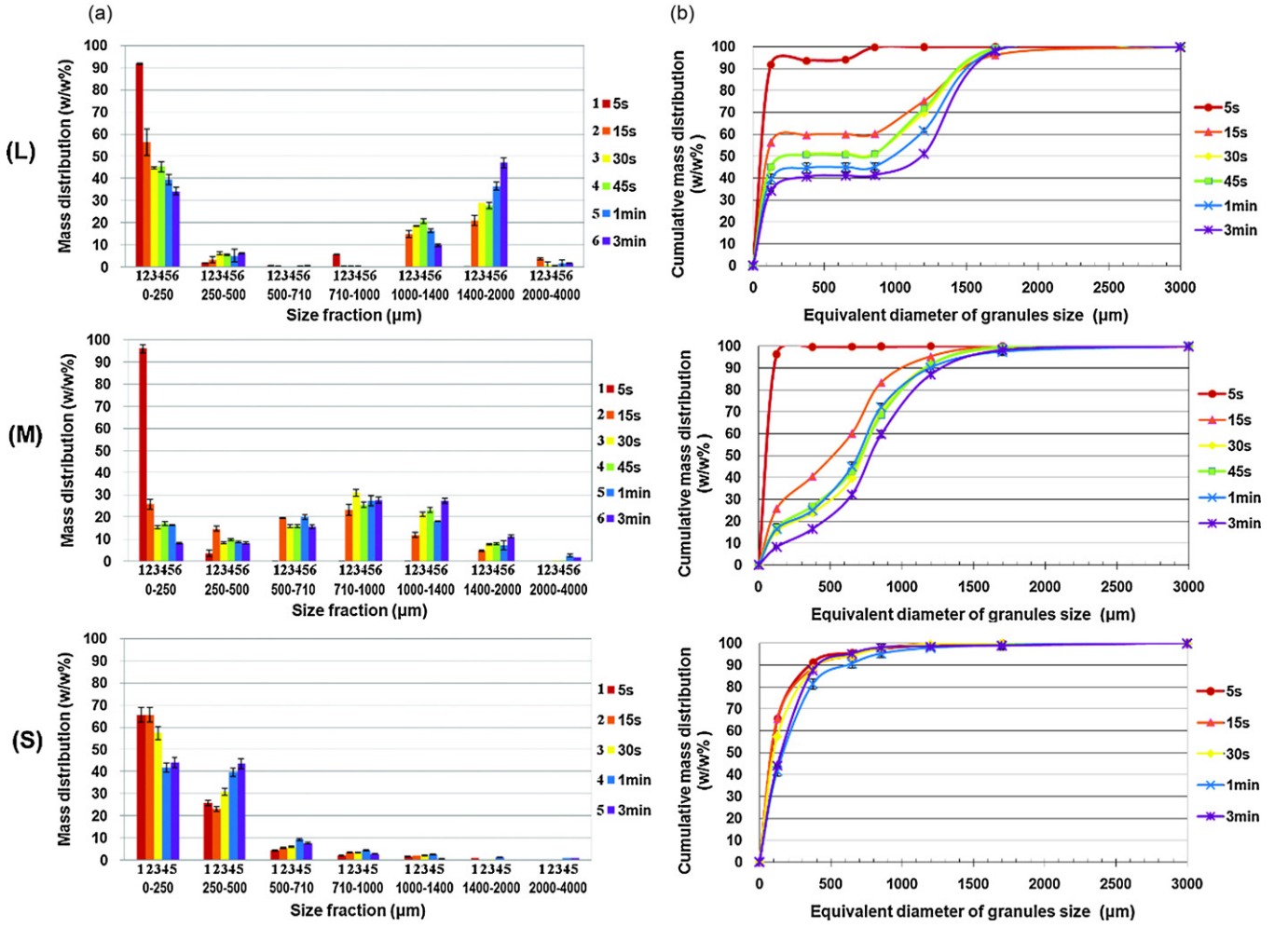

Fig. 2. Size distributions of the granules produced by FHMG for various granulation times; (b) Cumulative particle size distribution of the granules produced by FHMG for various granulation times. (L) binder size = 710–1000 μm; (M) binder size = 125–250 μm; (S) binder size = 45–90 μm (Filler type: Standard ballotini beads; Binder type: Poloxamer 407)

the surface of binder. Again this may be attributed to the different mechanism of granule growth within a large binder particle size system (Section 3.4). In this case, binder distribution and the rate of dispersion have less effect on the onset of granulation. Interestingly, in such a system, a larger binder particle size and a higher viscosity, promotes the successful attachment of filler particles to surface of the binder, thus leading to a faster onset of granulation.

Although the onset of granulation significantly influenced the viscosity of molten binder, the size distribution of the final granules remained unchanged. It can be observed from Figs. 1a and 2a that the size distribution was similar irrespective of the viscosity of the molten binder. In this respect, the particle size of the initial binder was the principal factor affecting the size distribution of the granules.

3.2. The effect of binder particle size on agglomerate growth within FHMG

In order to investigate the effects of binder particle size on the size distribution of granules and onset time of effective granulation, three representative types of binder size were used for FHMG: Type (L) having a diameter range from 710 to 1000 μm, which was approximately 4-fold larger than the filler (150–250 μm); Type (M) having a diameter range from 125 to 250 μm, which was similar to the filler; and Type (S) having a diameter range from 45 to 90 μm, which was approximately 2.5-fold smaller than the filler.

Granules produced using a binder with a large particle size (710–1000 μm) or indeed a small particle size (45–90 μm) had a narrow size distribution. The L-system produced granules with a particle size concentrated between 1000 to 2000 μm, whereas for the small size binder (L) granules had a size fraction concentrated in the size range from 250 to 500 μm. The system, (M), that had a binder and filler particle size that were similar produced a broader size distribution ranging from 250 to 2000 μm (Figs. 1a and 2a). Another interesting difference between the two systems was the relative amount of un-granulated fractions. In systems wherein the binder was larger than the filler (L) or vice versa (S) a significant percent of un-granulated material was observed after the maximum 3 min granulation period. This could be attributed to a combination of segregation within the fluid bed and also in the (S) system to the inherent difficulty with distribution of the small binder across the surface of the filler, increasing the possibility of unsuccessful collision between particles. This may result in the formation of weak bonds between the filler particles leading to increased breakage.

Furthermore, increasing the binder particle size significantly increased the onset time for granulation (Figs. 1b and 2b). For example, when using Poloxamer 188 changing the binder particle size from 710–1000 μm (L) to 45–90 μm (S) decreased the onset time of granulation from 15 s to less than 5 s. The difference in the time required for the onset of granulation may be partially explained through consideration of heat transfer from the hot air stream to the fluidised particles. In this system, the rate of heating ($-\delta Q/\delta T$),

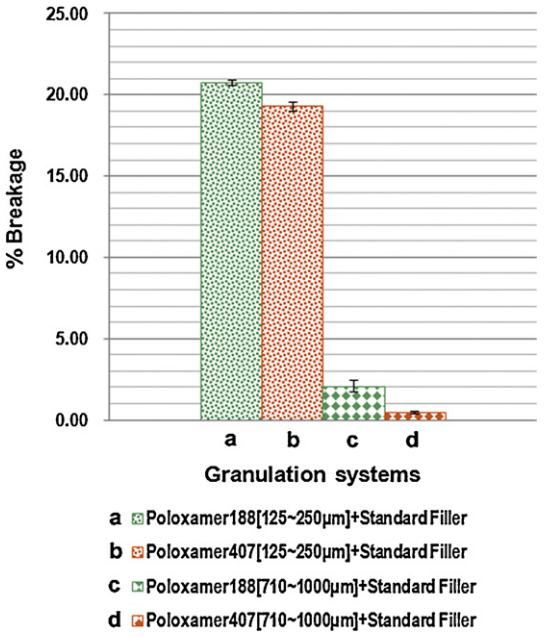

Fig. 3. Effects of binder particle size and viscosity on the breakage characteristics of granules during FHMG process.

is dependent upon the heat transfer coefficient (h), solid surface area (A) and the temperature difference between the solid surface (binder and particles) and the surrounding environment (hot air stream). The relationship between these components is shown in Eq. (1) [22].

$$-\frac{dQ}{dt} = h \cdot A(T_{env} - T_0) \quad (1)$$

'T_0' is the temperature of the solid surface and 'T_{env}' is the temperature of the hot air stream.

Given that T_{env}, T_o and h are all constant, the only factor affecting the rate of heating is the solid surface area (A), which is related to the initial binder particle size. In these studies each granulation system contained the same mass of binder and the true density value of binders was constant. For these reasons, a binder with a larger particle size and subsequently a smaller surface area would take more time to melt due to the slower heat transfer rate from the hot air stream. This resulted in a delayed onset time for binder deformation and hence delayed onset of granulation.

3.3. Breakage investigations

In order to fully understand growth and breakage processes with FHMG, a number of breakage experiments were conducted as described in Section 2.5. Interestingly, breakage of granules was significantly higher when a binder with a smaller particle size was used. Moreover, decreasing the viscosity of the binder significantly increased the percentage of breakage. As shown in Fig. 3, the percentage breakage of granules produced using a larger binder (710–1000 μm) was less than 7% for each system whereas the percentage breakage of the granules produced using a median binder (125–250 μm) exceeded 19%. This effect may be attributed to the different structure of the granules, which may be further explained by the different agglomerate growth mechanisms within the separate granulation experiments (Section 3.4). Granules produced using a larger binder, were more spherical in shape and had a more closely packed structure (Figs. 5 and 6). This larger binder size resulted in granules that had filler particles concentrated around the larger binder. Similar results have been previously shown for systems in which the binder particle size exceeds the filler particle size [24]. The obvious embedding of filler particles into a larger binder droplet appear to have resulted in a more physically stable granule and hence a reduced percentage breakage during these studies.

Additionally, binder viscosity was shown to affect the breakage characteristics of the granules. As previously reported, agglomerate growth depends on the deformation of agglomerates [16]. With a lower binder viscosity, granules are structurally less resistant to deformation due to the lower consistency of the molten binder. Consequently, such granules are more susceptible to breakage [21]. A higher viscosity binder imparts a greater resistance to deformation, due to the increased consistency of the molten binder. This added mechanical strength and increased elastic character increases the resistance to breakage [17]. Interestingly, binder particle size and had a more significant effect upon granule strength and hence breakage than binder consistency.

3.4. Agglomerate growth mechanisms within FHMG

It has been previously reported that there are two differing nucleation and growth mechanisms during melt granulation, namely, distribution and immersion (Schæfer et al., 2001). A distribution mechanism is most often characterised by distribution of a liquid binder on to the surface of filler particles followed subsequently by coalescence of wetted particles. Conversely, an immersion mechanism is more typically characterised by attachment and subsequent immersion of primary particles at the surface of a binder droplet to form granules [18] Agglomerate nuclei and growth mechanisms within FHMG may be assumed to be similar to melt granulation processes. In the present study, agglomerate growth in systems utilising binders with a small and median particle size were shown to occur via a distribution mechanism, whereas those systems utilising a large binder particle size occurred via an immersion mechanism.

Fig. 4 illustrates the main agglomerate nuclei and growth processes proposed when utilising binders of varying particle size. As shown in Fig. 4 (L) using a large binder particle should result in a smaller filler particle first attaching to the surface of the larger binder particle followed by immersion inside the binder resulting in an immersion mechanism. The particles on the outermost layer are pushed further into the granule as a result of the collision with growing granules and initial particles. As the immersion process continues more filler particles are layered on the surface of the binder and embedded until no more molten binder can migrate from the inside of the growing agglomerate to the surface. At this stage, collisions would be unsuccessful in that filler particles would no longer adhere to the surface. Conversely, Fig. 4 (M) and (S) provides an example of a distribution mechanism within FHMG. In this mechanism, binder and filler particles are distributed randomly within the fluid bed and are fused together due to melting of the binder. In such systems, molten binder is freely available on the surface of the initial filler particles, making further coalescence possible. As the granulation proceeds, the successive collision between binder and filler depletes active binder (molten binder on the surface of the agglomerates) and thus coalescence stops.

To further understand binder distribution within the granules and to support the proposed agglomerate growth mechanisms for FHMG, binders were combined with a fluorescent additive and these modified binders were used during granulation (Fig. 5). The shape and size of the initial binder, filler particles and formed granules were analyzed under regular light, and UV light. The use of a modified fluorescent binder facilitated our understanding of binder and filler distribution in the agglomerates. As shown in Fig. 5, there are distinct difference between the filler and the binder. These differences translate to the agglomerate formed during granulation and the images of a granule under UV/green light provide clear

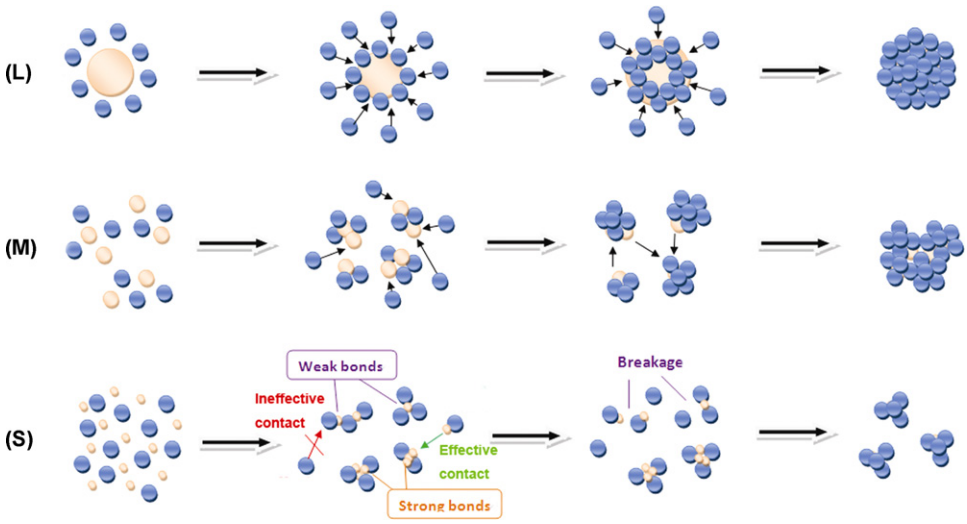

Fig. 4. Proposed agglomerate growth mechanisms within FHMG using: (L) binder size = 710–1000 μm; (M) binder size = 125–250 μm; (S) binder size = 45–90 μm.

information on the distribution of binder both within, and on the surface of the binder.

Images of granules produced using a large (710–1000 μm) and median (125–250 μm) binder particle size are shown in Fig. 6. Binder distribution was not uniform throughout granules produced via a distribution mechanism. Some sections of the granule contained higher binder concentrations than others. This may be attributed to the random agglomeration of binder and filler particles at the beginning of the process. Furthermore, the heterogeneous distribution of binder may also be attributed to the breakage and re-agglomeration with other granules thus forms highly concentrated regions of poloxamer. As shown in Fig. 6b, granules produced using a large binder particle size were formed via an immersion mechanism. Granules were very spherical in

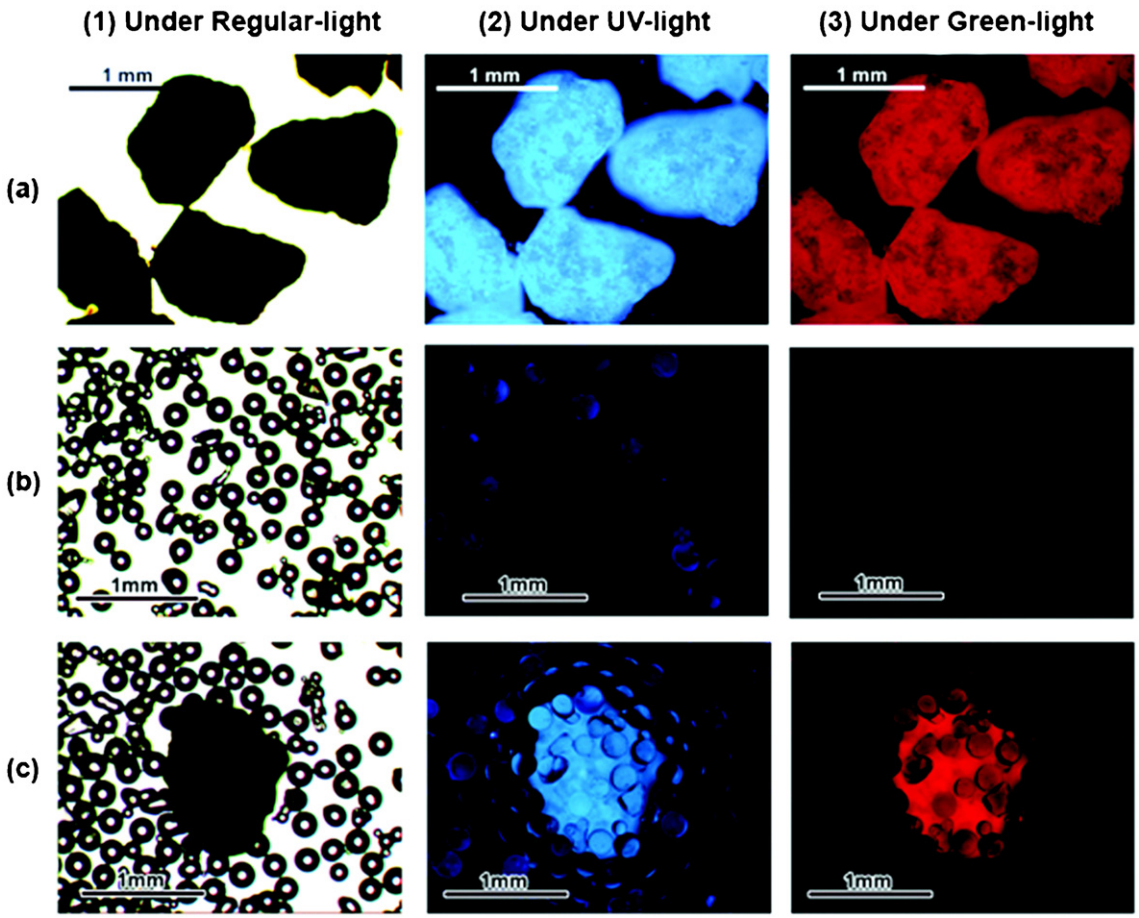

Fig. 5. Microscopic images of fluorescence binder and model filler at x40 magnification: (a) Fluorescence binder (poloxamer 188 with sulphamerazine, size: 710–1000 μm); (b) Model filler (ballotini beads, size: 125–250 μm); (c) A single binder particle on the top of the spread of ballotini beads. (1) Images under regular light; (2) Images under UV-light; (3) Images under Green-light. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

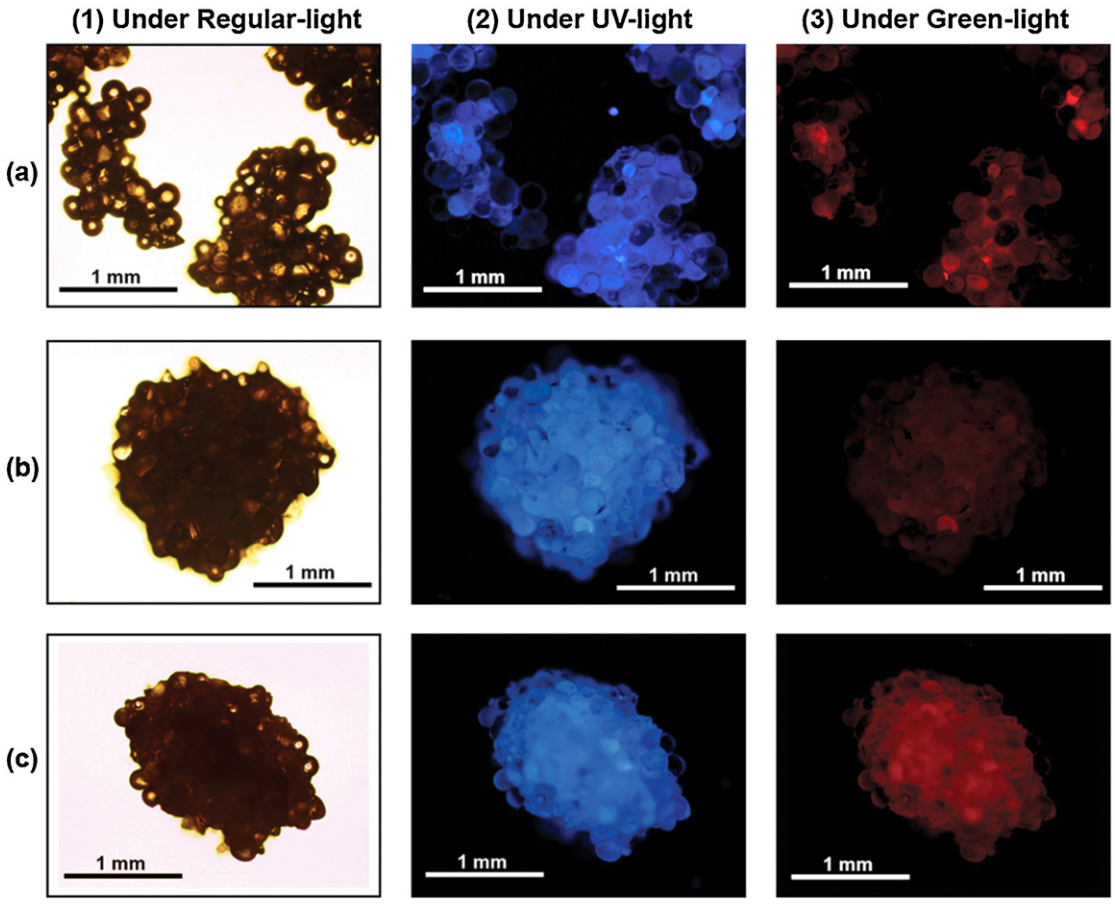

Fig. 6. Fluorescence microscopic images of granules produced by different agglomerate grow mechanisms. (a) Granule particle produced by median size binder system (distribution mechanism); (b) Granule particle produced by large size binder system (immersion mechanism); (c) Cross-section of the granule particle produced by large size binder system (immersion mechanism). (1) Images under regular light; (2) Images under UV-light; (3) Images under Green-light (Filler type: Standard ballotini beads; Binder type: Poloxamer 188). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

nature and binder distribution was more homogeneous. This supports the theory previously reported by Schæfer and Mathiesen [24] that suggests an immersion mechanism results in a higher binder concentration within the agglomerate and a size fraction that corresponds to the size of initial molten binder droplets. A further observation was that the increased concentration of binder within the granule and the more significant sphericity increased made the granule more robust. This resulted in less breakage (Fig. 3) and a more narrow size distribution (Figs. 1a and 2a). The high percentage of breakage recorded for granules produced by a distribution mechanism is likely to cause re-distribution of binder within the granules leading to an active re-agglomeration process, and hence result in a more broad size distribution. Additionally, the higher concentration of binder within granules produced by immersion mechanism may also explain why a larger amount of un-granulated material (Figs. 1a and 2a) was obtained within large binder systems (immersion) in comparison to systems granulated using a median particle size binder (distribution).

As shown in Fig. 6 (3) binder was retained on the surface of granules that were formed via a distribution mechanism, suggesting there were still 'active' regions making further agglomeration possible. Conversely, here was no observable binder distributed on the surface of granules produced via an immersion mechanism, indicating that further agglomeration and coalition would be less likely. This may further explain the higher percentage of un-granulated fractions in the system using a larger binder particle size. Within an immersion process, granules are formed by the growth of single binder particles, so every single granule contains a higher concentration of binder compared with the same size granule produced via distribution mechanisms [24]. However, this high concentration of binder is trapped inside the granule by the outside layer of filler particles on the granule surface, preventing further growth and coalescence. Conversely, a distribution process results in a random distribution of binder between filler particles and the higher percentage breakage observed for these granules (Fig. 3) promotes re-distribution of binder within the un-granulated fractions and thus facilitates the generation of 'active' sites and further agglomeration.

Fig. 6c depicts the cross-section of a granule produced using a binder with a large particle size and hence proceeding via an immersion mechanism. Comparison of Fig. 6c (3) and b (3), illustrates that there was limited binder spread on the surface of the granule and a high binder concentration inside the granule. In this study we suggest that immersion involves layering of filler particles on the outside of binder cores followed by immersion of particles. This is subsequently followed by attachment of a new layer of filler particles on to the outside surface of the cores followed by immersion. This continues until no further binder can migrate from the inside to the surface of the granules, and thus filler particles may no longer attach to the surface, preventing granulation (Fig. 4 (L)). Granule growth is thus dependent upon the initial particle size of the meltable binder and the immersion level of the filler [21].

Due to the difficulty in observing granule formation in the fluid bed, an opposite process of granule formation (granule disintegration) was monitored using modified dissolution experiments. By observing the dissolution mechanisms of granules, we aimed to fur-

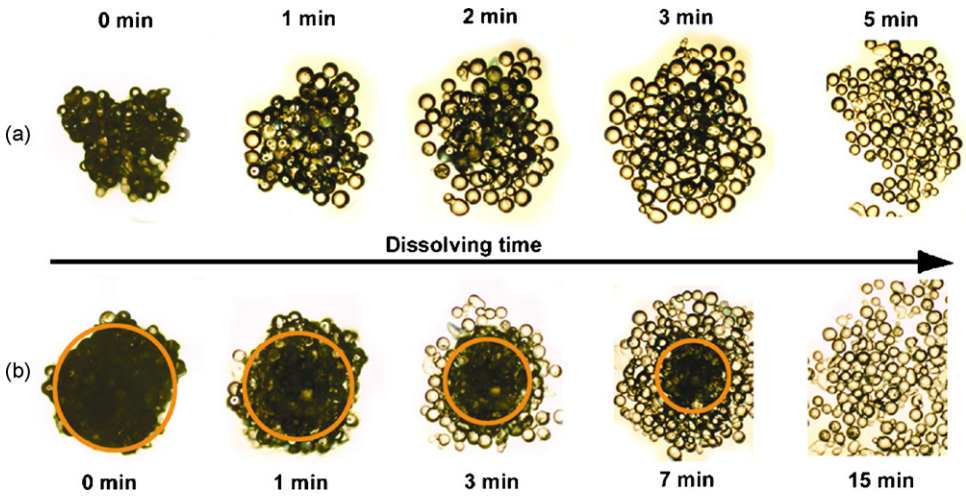

Fig. 7. Microscopic images of granules following addition of water at defined time points. (a) Granules have been produced via a distribution mechanism; (b) Granules have been produced via an immersion mechanism.

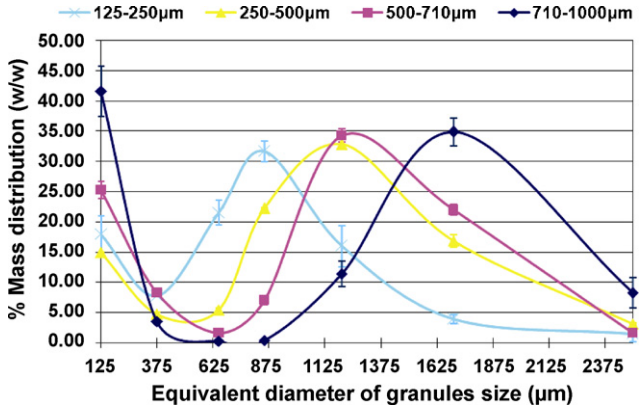

Fig. 8. Size distribution curves of granules produced by different particles size of binder. (Filler type: Standard ballotini beads; Binder type: Poloxamer 188).

ther understand and examine the agglomerate growth mechanisms in FHMG. Dissolution experiments were performed by dissolving granules of a similar size that had been formed by either via a distribution or an immersion mechanism. In these experiments dissolution buffer was added to the granules and images were captured using a microscope. It is evident that the dissolution time of granules formed via an immersion mechanism was much longer than a granule produced via a distribution mechanism (Fig. 7). As observed this may be attributed to the higher binder concentration inside the granule formed via immersion and the compact and layered structure of these granules. Dissolution proceeded from the outer surface of the agglomerate. As dissolution fluid moved from outer to inner layers, more filler particles in the inner regions of the granule were subsequently released. Conversely, dissolution of granules formed via a distribution mechanism, was rapid and evenly distributed throughout the granule.

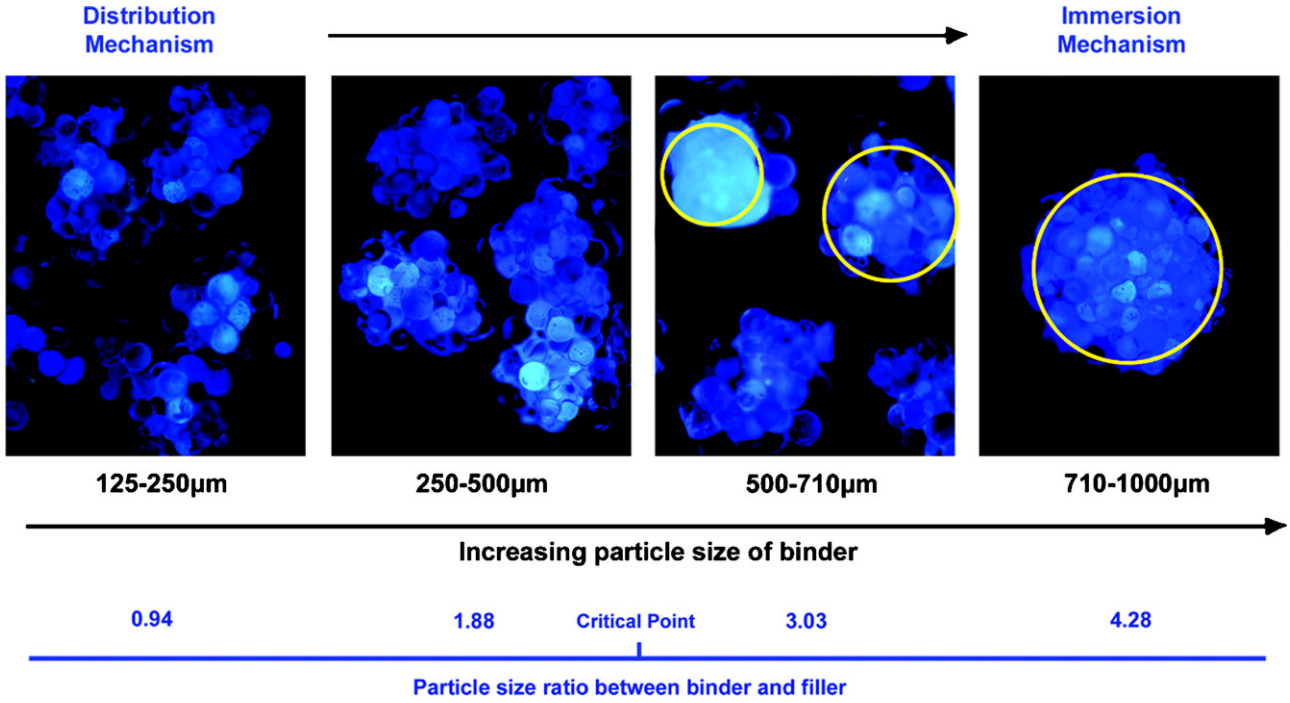

Fig. 9. Fluorescence microscopic images of granules produced by different particles size of binder. (Filler type: Standard ballotini beads; Binder type: Poloxamer 188).

Given the initial results of this study confirming binder particle size was the most significant factor affecting agglomerate growth mechanisms within FHMG, further investigations were designed to extend our understanding of the effects of binder size on size distribution and growth mechanisms within FHMG.

Fig. 8 illustrates the size distribution curves of granulation systems produced using different sizes of binder (125–1000 μm). Increasing the binder size resulted in a significant increase in the average granule size from 855 to 1700 μm. Interestingly, granulation systems using a binder particle size ranging from 250 to 500 or 500 to 710 μm, did not exhibit a significant difference in the average granule size. As shown in Fig. 9 an increase in binder particle size results in a change in the granulation mechanism from distribution to immersion. From the shape of the granules, the predominant growth mechanism for the system using a binder particle size ranging from 125 to 250 μm was distribution, whereas the growth mechanism for the system containing a binder particle size ranging from 710 to 1000 μm was immersion. However, from the shape of the granules it was difficult to ascertain the appropriate growth mechanism for those systems containing a binder particle size from 250 to 500 and 500 to 710 μm. Although the growth mechanism for the 250–500 μm system is more likely to be distribution and the growth process for the binder size (500–710 μm) is most likely to occur via an immersion mechanism, the growth mechanisms within both systems are most probably a combination of both. In previous work reported by our group, the filler particle size was shown to affect the agglomerate growth mechanism [14] whereas in this study we suggest that the particle size ratio between binder and filler may be a more effective factor to define the growth mechanism within FHMG. Definition of a critical ratio between the particle size of binder and filler may be indicative of a critical point of conversion between the two (distribution and immersion) mechanisms. In this work, when the binder particle size increased from (125–250 μm) to (710–1000 μm), the average particle size ratio between binder and particle changed from 0.94 to 4.28. It has been observed that agglomerate growth mechanisms changed from a distribution to an immersion process when binder particle size increased from (250–500 μm) to (500–710 μm), indicating the critical ratio of average particle size of binder and filler may lie within the range from 1.88 to 3.03 for the Poloxamer 188 and standard ballotini systems in our study. This theory may also be extended to fluid bed melt granulation (FBMG) systems wherein it has been previously reported that a distribution mechanism is promoted by a low ratio between droplet size and particle size, whereas immersion is promoted by a high ratio [19]. In the study conducted by Abberger et al. [19] using lactose and PEG3000, a distribution mechanism was observed when using a 30 μm PEG droplet and lactose with a particle size of 164 μm (binder/filler size ratio = 0.18), whereas an immersion mechanism was confirmed when using a 90 μm PEG droplet and lactose particles with an average size of 32 μm (binder/filler size ratio = 2.81). When the ratio was between 0.18 and 2.81, the distribution and immersion happened simultaneously.

In conclusion, a critical ratio between binder and filler particles may be a very useful parameter to understand nucleation and agglomerate growth within melt granulation systems and may help to design and control the granulation process. However, the precise value of the critical ratio needs to be further investigated.

4. Conclusion

Agglomerate growth mechanisms in fluidised hot melt granulation (FHMG) were investigated using low-melting point co-polymers of polyoxyethylene–polyoxypropylene (Poloxamer 188 and Poloxamer 407) as meltable binders, and standard ballotini beads as model fillers.

Binder properties such as the binder particle size and viscosity were determined to influence the size distribution, onset of effective granulation and breakage characteristics of the granules. The onset of granulation was delayed by a larger binder particle size. Increasing the viscosity and the binder particle size significantly increased the time required to achieve equilibrium. Increased breakage of the granules was observed when a smaller binder size and binder of lower viscosity was used.

Fluorescence microscopy was successfully used as an effective tool to provide detailed information on binder distribution within the granules and facilitated confirmation of agglomerate growth mechanisms during FHMG. Within the several parameters investigated in this study, the particle size of binder was determined as the most significant factor affecting the growth mechanism in FHMG. It can be concluded that the particle size ratio between binder and filler is an effective factor affecting the growth mechanism. Furthermore, there should be a critical ratio between the particle size of binder and filler, which could indicate the critical point of the conversion between distribution and immersion mechanisms. This ratio between the particle size of the binder and filler may be very useful in understanding the granulation process.

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