Mapping of Regimes for the Key Processes in Wet Granulation: Foam vs. Spray

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The evaluation of foam and spray granulation mechanisms and their performances in achieving uniform liquid distribution in a high-shear mixer-granulator is presented. A regime map is presented to describe the granulation mechanisms for the foam and spray systems. Foam and spray granulation are shown to successfully create granules of well-distributed moisture at the end of wet massing despite there was a deviation from the theoretical moisture content at the end of binder addition. In the wetting and nucleation regime, spray granulation involves drop penetration nucleation outside of the drop-controlled regime, whereas foam granulation operates favorably in the mechanical dispersion regime. For foam granulation, mechanical dispersion produces more uniform granule-size distributions below the overwetting limit. Spray granulation exhibits steady granule growth, whereas foam granulation shows induction granule growth followed by rapid granule growth. The regime map provides a basis to customize formulations and compare the different foam and spray granulation mechanisms. © 2013 American Institute of Chemical Engineers *AIChE J*, 59: 2328–2338, 2013
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Introduction

Spray granulation

Wet granulation process is generally considered to involve three sets of rate processes—wetting and nucleation, consolidation and growth, and breakage and attrition.[1] The first stage of wet granulation is wetting and nucleation, where the liquid binder first comes into contact with the powder bed, forming liquid bridges between the particles to hold them together into initial particle agglomerates (also called nuclei). Wetting commences by penetration (due to capillary action) or dispersion (due to mechanical mixing) of the liquid binder through the powder bed, causing nucleation of the particles into nuclei. The initial nuclei are often small and loose agglomerates.[1] These small and loose agglomerates enter the consolidation and growth stage as the nuclei collides with each other during granulation. This often results in the densification of granules, which also leads to the growth in granule size. For systems where insufficient liquid is added, consolidation and growth will not occur due to the low degree of liquid saturation of the granules, and the granule size is purely determined by the wetting and nucleation conditions.[1] During the granulation process, the granules also break and cause reduction in granule size due to impact or compaction in the granulator or during subsequent product handling.[1]

The success of forming granules of uniform properties (size, content, etc.) often depends on the distribution of fluid binder within the powder as the fluid first comes into contact with the surface of a powder bed. As represented by a large number of efforts attempted to improve the distribution of liquid binder throughout a moving powder bed,[2–4] ensuring uniform wetting and nucleation during wet granulation is a recognized need in the pharmaceutical industry to achieve uniform granule-size distributions. A monomodal, narrow granule-size distribution has often been reported to be a consequence of uniform wetting and nucleation.[3,5–8] Ensuring a controlled wetting and nucleation generally gives rise to controlled granule growth and breakage, which eventually leads to the formation of homogeneous granules. For poor wetting and nucleation, the granules will be immersed with uneven liquid binder content, with the large granules associated with more liquid binder than the smaller granules. Continued granulation will lead to uneven granule growth, as large granules continue to grow steadily due to higher saturation, whereas small, low saturation granules remain in the nucleation stage or display crumb behavior. The small granules may display little or no granule growth, but this induction stage will end, and rapid coalesce growth will occur as soon as the granules become sufficiently surface wetted. For systems that become overwetted, the granules will turn into a slurry.[1]

Since a decade ago, work has been directed to produce regime maps that describe and enable prediction of nuclei granule formation.[9–14] The key formulation properties and process parameters that control the granulation rate processes have been well-established, and in some cases, regime maps are becoming available for granulation process design and control. These maps illustrate the behavior of nuclei granule formation based on the system parameters (formulation properties and process parameters) that dictate the operating regime in any particular system.

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Foam granulation

Great progress has been made in understanding and controlling wet granulation mechanisms, but the development has been focussed on the "spray" processes. It is well-understood what happens when the spray droplets of binder hit the powder bed, forming the first nuclei, and later the nuclei grow or break into larger or smaller granules. This process of nuclei granules formation can now be achieved by foam granulation, where aqueous foamed binder is added on to the powder to enable nuclei granules formation.

Foam granulation technology was first introduced in 2004 for manufacturing pharmaceutical granules and tablets.[15] Keary and Sheskey[15] reported the discovery of foam granulation for pharmaceutical wet granulation processes and carried out a series of laboratory-scale and pilot-scale experiments to investigate the effects of foam granulation on binder distribution, control of binder addition, processing time, tablet properties, and drug dissolution.[15] The authors claimed that foam granulation offers many processing advantages, including improved binder dispersion and wetting throughout the powder, less binder and water required, a reduction in drying and manufacturing time, and simpler binder addition without the need for nozzles while maintaining similar granule and tablet properties compared to spray granulation. Sheskey et al.[16] also demonstrated that the foam granulation allows formulations to be easily scaled as a result of fewer scaling issues and the process control was good even at high application rates. For both a controlled-release (CR) and an immediate-release (IR) formulation, the granule and tablet properties were acceptable and the drug dissolution was on-target.[15,16]

Subsequently, additional work has also been reported to refine the technology. Sheskey et al.[17,18] investigated the use of aqueous foamed binders in delivering low-dose and water-sensitive drugs onto powders during wet granulation of CR and IR tablet formulations using high-shear mixers and fluid beds. Sheskey et al.[17,18] claimed that the foamed binders break quickly and dispersed uniformly within the powders, which effectively distributed low levels of drug throughout the powder bed of the CR and IR tablet formulation during both high-shear and fluid-bed granulation. More recently, Cantor et al.[19] evaluated the performance of conventional wet granulation and foam granulation in delivering high-drug load formulations which are brittle, viscoelastic, and ductile in characteristics. Cantor et al.[19] found that foam granulation significantly enhanced the plasticity of a granulation containing a brittle drug but produced a material with mixer deformation behavior for formulation containing a ductile drug. For viscoelastic materials, foam granulation did not enhance the plasticity of the formulation as well as conventional wet granulation process.[19]

Fundamental studies on foam granulation have also been carried out to investigate how foamed binder interacts with the powder particles to form nuclei granules on static powder beds as well as in a high-shear mixer-granulator.[20–23] Tan et al.[20] found that the foam addition method required less liquid binder to nucleate the same number of grams of powder, indicating improved nucleation efficiency compared to the drop addition method. Tan and Hapgood[21] showed that foam granulation was able to create a more uniform nuclei-size distribution when the powders were nucleated with a low amount of binders using a high-shear mixer-granulator. The studies focused on wetting and nucleation, where granule growth and breakage were not taken into account.[21] Additionally, Tan and Hapgood[21–23] indicated that foam-induced nucleation and granulation processes involve both liquid penetration and mechanical dispersion mechanisms and demonstrated the critical importance of the nucleation and binder distribution in determining the granule-size distributions for foam granulation processes.

This work proposes a regime map to describe and map out the key processes in foam and spray granulation. The performance of foam and spray granulation in producing homogenous granules with uniform moisture content is also investigated.

Table 1. Powder and Liquid Binder Properties

Powder/Liquid Binder	Grade	Viscosity (mPa s)	Average Particle Size (μm)
Microcrystalline cellulose	PH 101	–	50
Lactose monohydrate	100 mesh	–	150
	200 mesh	–	75
4% HPMC	E5PLV	19.1	–

Experimental

Materials

The powders used were lactose (100 mesh, Wyndale, New Zealand) and microcrystalline cellulose (MCC; Avicel PH101, Sigma Aldrich, Australia). Both powders are commonly used as excipients in the pharmaceutical industry. The liquid binder used was 4% Hydroxypropyl Methylcellulose (HPMC) (Methocel E5PLV, Dow Wolff Cellulosics, USA). A small quantity of food dye (Queens Fine Food Ltd., Australia) was dissolved in the binder solution for visual observation during the experiments. Table 1 indicates the powder and liquid binder properties, which were obtained from vendor specifications.

Methods

Granulation experiments were carried out in a 5-L laboratory-scale high-shear mixer-granulator (KG-5, Key International). To introduce the 4% HPMC binder solution as an aqueous foam, a custom built foam generator[22,23] was used. The foam generator passes air and liquid at independently controlled flow rates through a packed bed to produce a stream of foam with the desired air to liquid ratio. The outlet of the flexible tubing containing the freshly formed flowing foam was placed in the nozzle port of the granulator lid. The granulator was also equipped with a digital readout of impeller power consumption during granulation. The overhead chopper was not used during the experiments.

One kilogram of powder (composition as given in Table 1) was added to the mixer and dry-mixed before liquid binder addition. For foam granulation, the liquid binder was delivered at a flow rate of 0.1 L/min and mixed with air supplied at a flow rate of 0.5 L/min or 1.0 L/min, which generated aqueous foams with air volume fractions of 83 and 91%, respectively. The air volume fraction is described as the "foam quality" (FQ). For spray granulation, a single flat nozzle (TP650017) connected to a 5 -L spray pot (Spraying Systems, Wheaton, USA) was positioned through the nozzle port to allow the spraying of the HPMC binder solution at a matching flow rate of 1.0 L/min. Liquid addition was carried out for a designated period until the liquid binder reached the

Table 2. Operating Conditions for Granulation Experiments

Powder Formulation	Liquid Binder	FQ (%)	Impeller Speed (rpm)
100-mesh lactose and microcrystalline cellulose	4% HPMC	0	295
		83	295
		91	295
		0	515
		83	515
		91	515
100-mesh lactose		0	295
		83	295
		91	295

desired amount (20–60%). The impeller was set to a constant speed for a given formulation. Table 2 summarizes the operating conditions for the granulation experiments.

To measure the moisture content as a function of granule size, wet granule sieving was performed. Wet granule samples were removed from the granulator and immediately frozen using liquid nitrogen.[24,25] The frozen granules were quickly hand sieved into five size fractions using a small stack of sieves (2 mm, 1 mm, 500 μm, 250 μm, and pan). The moisture content of each size fraction was determined by quickly weighing the wet granule fractions (after the liquid nitrogen had evaporated) and reweighing after drying overnight at 50°C in a fan-forced oven.[24,25]

The average moisture content of the granules was also checked from the mass of the wet granules obtained after sampling and the loss in weight after drying. Dry granule sieving was performed after drying in a fan-forced oven at 50°C overnight. Sieving was carried out using a mechanical dry sieve shaker (Retsch A200, Australia) in an ordered set of sieves: pan, 25 μm, 32 μm, 45 μm, 63 μm, 90 μm, 125 μm, 180 μm, 250 μm, 425 μm, 630 μm, 850 μm, 1 mm, 2 mm, and 4 mm. The weight mean diameter, d_m was determined as

$$d_m = \frac{\sum_i M_i d_i}{\sum_i M_i} \quad (1)$$

where M_i is the particle mass fraction of sieve size interval i, d_i is the mean diameter of sieve size interval i in microns.

Power consumption values during granulation of two different formulations, a 100-mesh lactose powder and MCC mixture, and a 100-mesh lactose powder were recorded. The power consumption profiles were used to monitor the progress of granulation, where appropriate, by linking with the granule-size distributions to compare foam and spray granulation.

Results

Granule-size distribution

Figure 1 shows the granule-size distributions for foam granulation (91% FQ and 83% FQ) and spray granulation (0% FQ) at 295-rpm impeller speed. Figure 2 shows similar data at a higher impeller speed (515 rpm). The granule fractions were defined into three classes—fine particle whose size is less than 180 μm, intermediate granule which having size between 180 and 1000 μm, and the coarse agglomerate whose size is larger than 1000 μm.

In all cases, increasing the liquid binder level increases the average granule size and the spread of granule-size distribution, in which the peak of the granule-size distribution shows a steady monotonic increase from around 125 to 4000 μm.

On the basis of the evolution of granule-size distribution, the granulation can be defined into stages of (I) wetting and nucleation, (II) growth, (III) overwetting, and (IV) caking in corresponding to the liquid binder level. Here, we also compare the granule-size distribution as a function of FQ in response to the changes of granulation from one stage to another.

Wetting. At 20% liquid to solid ratio, the initial granule-size distributions are almost identical for both foam granulation (91% FQ and 83% FQ) and spray granulation (0% FQ). The granule-size distributions are monomodal, and contained mainly ungranulated particles. The added liquid only gives rise to a slightly increased cohesion of the mass due to the excellent water-absorption property of MCC.[26] This stage is classified as wetting.

Nucleation. At 30% liquid to solid ratio, nuclei begin to form. The granule-size distributions show a peak at around the 125-μm size fraction, with a small increase in the

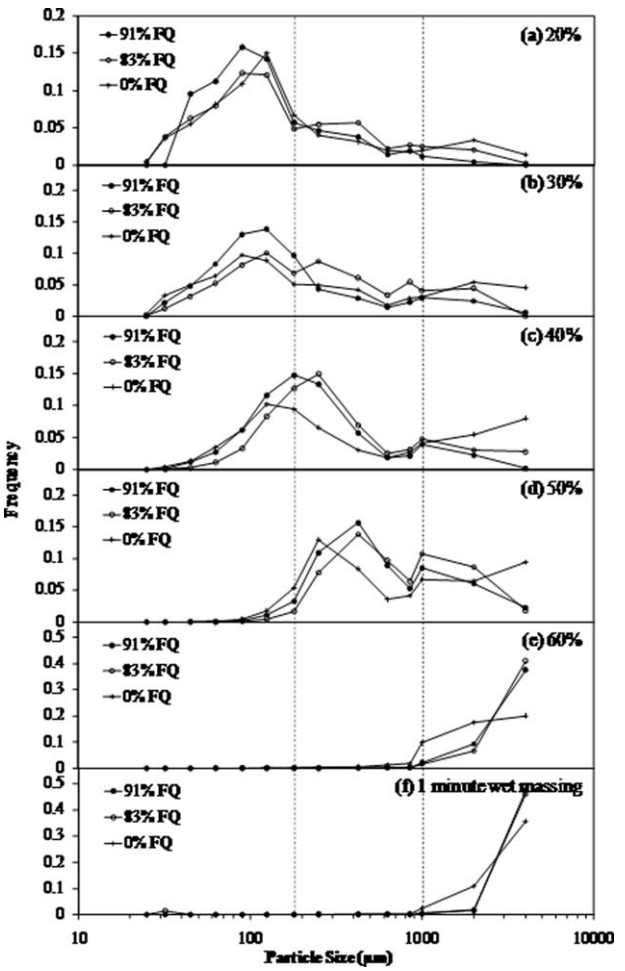

Figure 1. Granule-size distribution as a function of FQ after (a) 20 (b) 30 (c) 40 (d) 50, and (e) 60% foam addition and (f) after 1-min wet massing—4% HPMC, 100-mesh lactose, and MCC formulation, 295 rpm.

The dotted lines divide the granule size (x) into fine (x<180 μm), intermediate (180<x>1000 μm), and coarse (x>1000 μm) fractions.

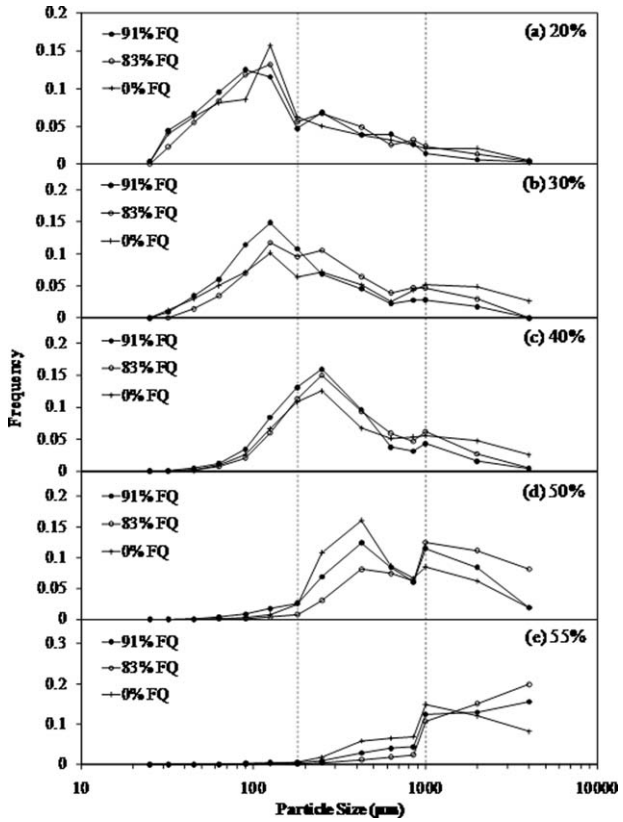

Figure 2. Granule-size distribution as a function of FQ after (a) 20 (b) 30 (c) 40 (d) 50, and (e) 55% foam addition—4% HPMC, 100-mesh lactose, and MCC formulation, 515 rpm.

The dotted lines divide the granule size (x) into fine (x<180 μm), intermediate (180<x>1000 μm) and coarse (x>1000 μm) fractions.

intermediate and coarse fractions. This is most likely due to nucleation. With spray, the granule-size distribution shows the largest fraction of coarse nuclei compared to foam. This nucleation effect is more pronounced for spray granulation, followed by foam granulation at 83% FQ and 91% FQ.

Growth. At 40% liquid to solid ratio, the granule-size distributions show an increase in the peak from 125 to 250-μm size fraction. With spray, the coarse nuclei continue to grow into coarser granules, producing the broadest granule-size distribution. Foam granulation at 83% FQ also creates a broader granule-size distribution compared to 91% FQ.

Overwetting. At 50% liquid to solid ratio, the granule-size distributions are bimodal and show a large increase in the fraction of coarse granules. In all cases, the bimodal granule-size distributions show two peaks around the 425 and 1000-μm size fraction, suggesting that the granulation becomes unstable as a result of uneven granule growth.

In both cases of 295- and 515-rpm impeller speed, foam granulation with 83% FQ resulted in a broader granule-size distribution compared to 91% FQ. For spray granulation at 295 rpm, the granule-size distribution is generally less uniform, with the granules distributed on the lower end of fine size (~125 μm) and the upper end of coarse size (~4 mm). The distribution of granules was improved by increasing the impeller speed to 515 rpm, where the granules were evenly distributed with fewer coarse granules. It is noted that for foam granulation at 515-rpm impeller speed, the granule-size distributions are actually skewed toward larger sizes compared to 295-rpm impeller speed (see Figures 1d and 2d).

Caking. For liquid binder levels larger than 55%, most fine and intermediate fractions disappeared, and there was a tremendous increase in the fraction of coarse granules. The coarse granules grew further into larger agglomerates after the batches were wet massed. In all cases, the granule-size distributions were concentrated around the 4-mm size fraction after 1 min of wet massing.

Weight mean diameter

Figures 3 and 4 show the progression of the granule weight mean diameter and the mass percentage of fines (previously defined as granules smaller than 180 μm). For both foam (91% FQ and 83% FQ) and spray (0% FQ) granulation, it is clear that increasing the liquid binder level increases the granulation extent which also increases the average granule size. The same trends were observed for both low impeller (295 rpm) and high impeller (515 rpm) settings. The results at 295 rpm are shown in Figure 3, whereas those at 515 rpm are shown in Figure 4.

In both Figures 3 and 4, the changes in the granule weight mean diameter corresponded well with the evolution of granulation stage. As granulation proceeds from wetting and nucleation to growth, and continues on to reach overwetting

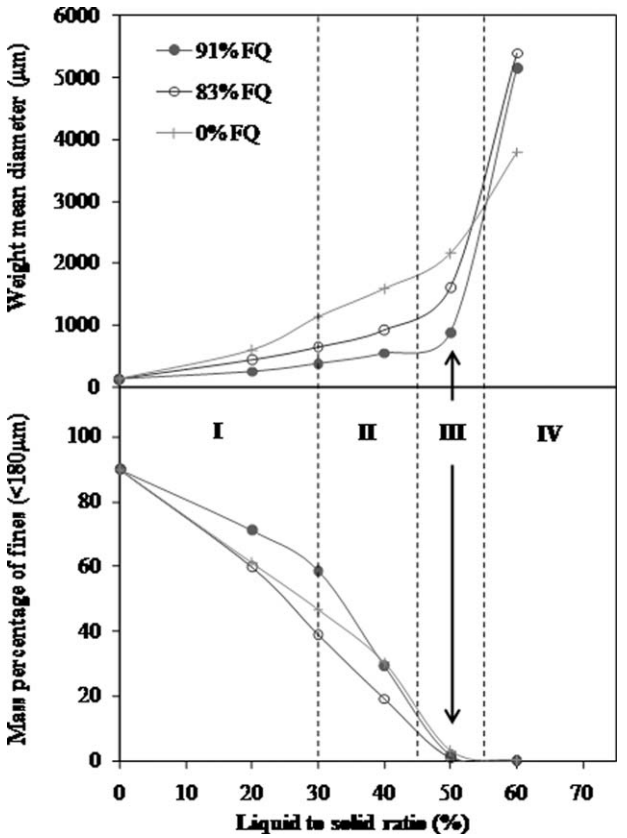

Figure 3. Weight mean diameter as a function of liquid binder level at 295-rpm impeller speed for foam (91% FQ and 83% FQ) and spray (0% FQ) granulation—4% HPMC, 100-mesh lactose and MCC formulation.

The dotted lines divide the granulation into (I) wetting and nucleation, (II) growth, (III) overwetting, and (IV) cake.

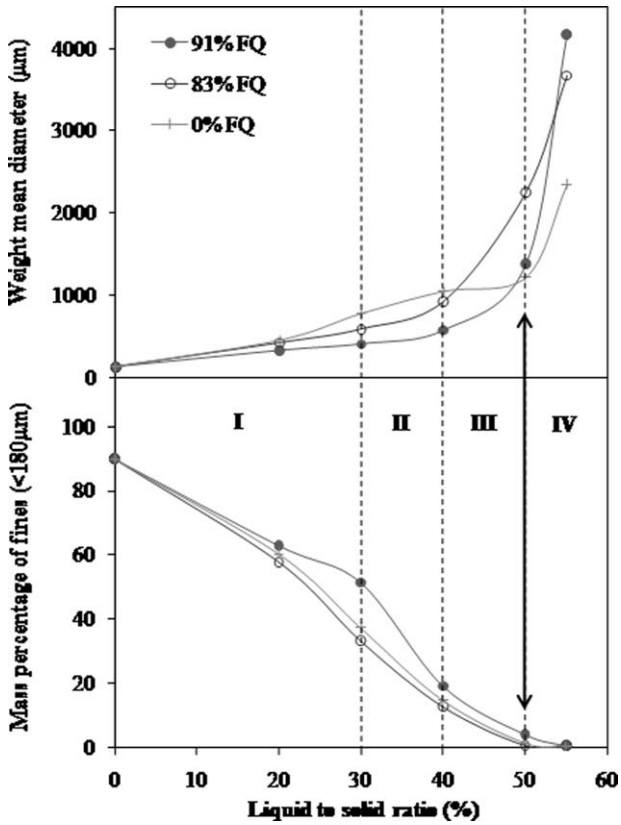

Figure 4. Weight mean diameter as a function of liquid binder level at 515-rpm impeller speed for foam (91% FQ and 83% FQ) and spray (0% FQ) granulation—4% HPMC, 100-mesh lactose, and MCC formulation.

The dotted lines divide the granulation into (I) wetting and nucleation, (II) growth, (III) overwetting, and (IV) cake.

and caking, the weight mean diameter shows a corresponding size increase. The liquid binder level required to cause the increase of granule weight mean diameter (also to promote the transition between the granulation phases) decreases with increasing the impeller speed.

Both Figures 3 and 4 indicate that foam granulation and spray granulation display different granule growth behaviors. Spray granulation tends to produce steady granule growth, where the granules show a steady increase in the weight mean diameter as granulation proceeds. For foam granulation, induction growth behavior was observed. The granule weight mean diameter shows a small increase initially, which is then followed by a substantial increase. Note that the increase in granule weight mean diameter decreases with increasing FQ, which indicates that increasing the FQ facilitates induction growth behavior.

From Figures 3 and 4, it is seen that the fraction of fine granules in all the foam and spray granulation batches has a profound effect on the granule growth behavior. As indicated by the marked arrow, the disappearance of the fine granules coincides with the end of the granule induction growth stage (or the onset of rapid granule growth). It seems that the presence of the fine particles in the granulation batches controls the granule induction growth period. When the fine granules have disappeared, granule induction growth behavior ceases. This behavior was also shown by Wauters et al.[25] in the granulation of copper concentrate (chalcopyrite) in a rotating drum granulator. The finding implies that the induction period can be shortened by removing the fines, which is similar to the effect of increasing the liquid binder level.[1]

Moisture distribution

The performance of foam and spray granulation in achieving uniform liquid distribution was studied by evaluating the wet and dry granule-size distributions and the moisture distribution as a function of granule size for foam and spray granulation.

Wet and Dry Granule-Size Distributions. Figure 5 shows the wet and dry granule-size distributions after liquid binder addition and 2 min of wet massing for foam granulation (91% FQ and 83% FQ) and spray granulation (0% FQ). All of the granule-size distributions at the end of liquid binder addition were relatively wide. Both wet and dry granule-size distributions show a large fraction of granules greater than 1 mm.

More specifically, spray granulation has generated the largest fraction of granules greater than 2 mm at the end of binder addition. The granule-size distribution immediately after spray delivery of liquid binder is the widest, followed by foam binder addition with 83% FQ and then 91% FQ. This trend is indicated by both the wet and dry granule-size distributions, despite that the granule-size distributions are slightly different. The minor differences in the wet and dry granule-size distributions after sieving are probably due to the difference in the strength of wet and dry granules as a result of the nitrogen freezing and drying processes, and/or sampling variations.

After 2 min of wet massing, the granule-size distributions became monomodal. The granule size is concentrated around the 500–1000-μm size fraction. This shows that wet massing has led to the breakage of the coarse granules into smaller fractions for both foam and spray granulation. The overall granule-size distributions are practically similar, although the size distribution of granules for foam granulation is slightly skewed toward larger sizes compared to spray granulation.

Moisture Content in Granules. Figure 6 shows the distribution of moisture content after 50% liquid binder addition as a function of granule size class for foam granulation (91% FQ and 83% FQ) and spray granulation (0% FQ). In all cases, it was found that the moisture was concentrated mainly in the large granules. The finer fractions were associated with relatively less moisture.

The moisture content in the foam bounded granules was slightly more homogeneously distributed compared to spray bounded granules. For fractions greater than 1000 μm, the moisture content in the 91% FQ granules had the smallest deviation from the theoretical moisture content (as shown by the dashed line). The moisture distribution is generally more uniform in the granules formed at 91% FQ compared to 83% FQ and 0% FQ.

Figure 7 shows the distribution of moisture content after 2 min of wet massing as a function of granule size class for foam granulation (91% FQ and 83% FQ) and spray granulation (0% FQ).

At the end of wet massing, it is seen that the moisture distribution in the granules was improved, with now around 5% deviations from the theoretical moisture content (as shown by the dashed line). For both foam and spray-bounded granules, the moisture content in the granules was distributed

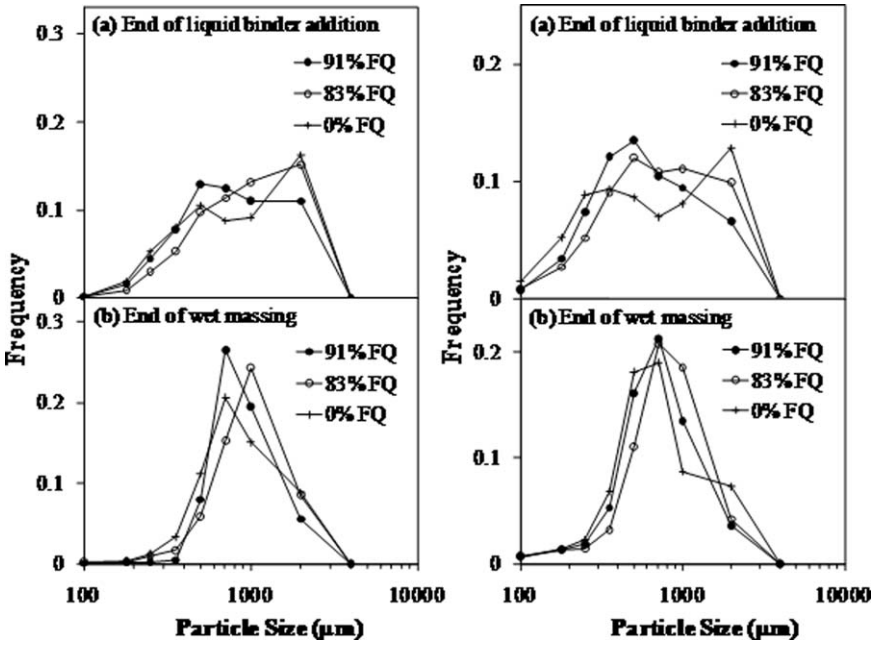

Figure 5. Wet (left) and dry (right) granule-size distributions after (a) liquid binder addition (b) 2 min of wet massing for foam (91% FQ and 83% FQ) and spray (0% FQ) granulation—4% HPMC, 100-mesh lactose, and MCC formulation, 50% L:S, 515 rpm.

among the 500–1000-μm granule-size fraction. The fine fractions (smaller than 500 μm) were associated with less moisture than the larger granules. It is expected that the smaller granules are less saturated, solely in terms of satisfying the mass balance. The <250-μm fraction has low-moisture content as the fraction is mostly the ungranulated powder which does not contain internal pores (because they are not granules). Note that some moisture evaporation during the wet massing phase may also have contributed to the lower-average moisture content values for each batch.

Power consumption profile

Figure 8 shows the power consumption during foam granulation (91% FQ and 83% FQ) and spray granulation (0% FQ) relative to the power consumption during the dry mix for a 1:1 mass ratio of lactose and MCC mixture. The power consumption profiles obtained are very similar to the classical power consumption curves,[27–29] as shown in Figure 9. Note that our granulation was ceased before phase V, that is, before a slurry was formed.

The impeller power consumption curves are divided into dry mixing, liquid binder addition, and wet-massing stages. For both foam and spray granulation, the power consumption profiles show similar trends—starting with a constant value during the dry mixing stage, rising steeply with liquid binder addition, and leveling off into a plateau where power consumption becomes stable. No significant difference was observed between the three batches, except spray granulation showed a lower rise in the power consumption value at around 240 s.

During the dry mixing stage, the power consumption value was constant. As liquid binder addition began, the added

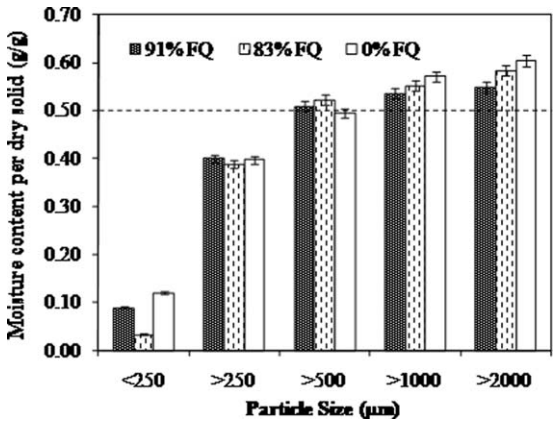

Figure 6. Moisture content after 50% liquid binder addition as a function of granule-size class for foam (91% FQ and 83% FQ) and spray (0% FQ) granulation—4% HPMC, 100-mesh lactose, and MCC formulation, 515 rpm.

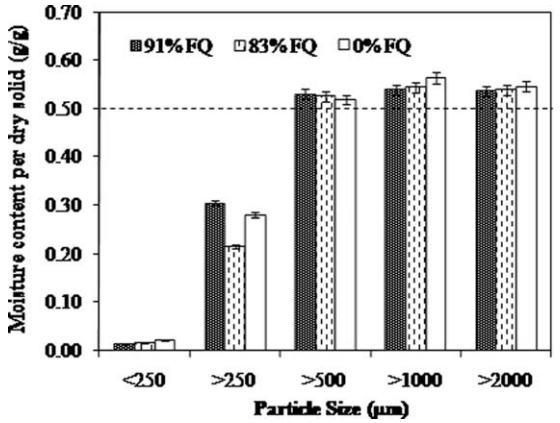

Figure 7. Moisture content after 2 min of wet massing as a function of granule-size class for foam (91% FQ and 83% FQ) and spray (0% FQ) granulation—4% HPMC, 100-mesh lactose, and MCC formulation, 515 rpm.

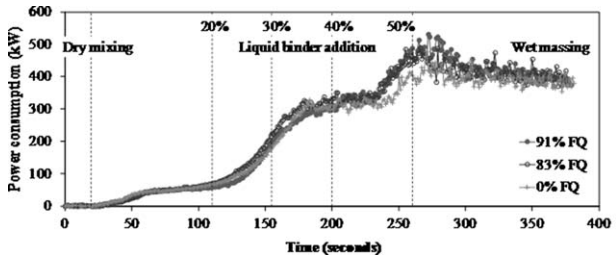

Figure 8. Power consumption profiles during foam (91% FQ and 83% FQ) and spray (0% FQ) granulation—4% HPMC, 100-mesh lactose, and MCC formulation, 515 rpm.

The processes started with dry mixing, followed by liquid binder addition, and ended with wet massing.

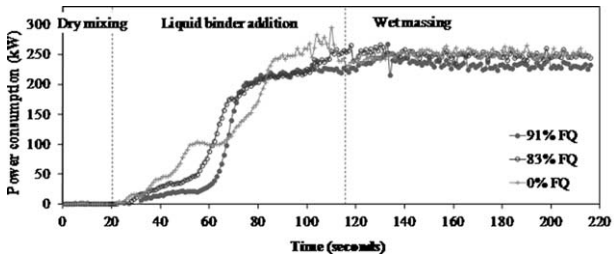

Figure 10. Power consumption profiles during foam (91% FQ and 83% FQ) and spray (0% FQ) granulation—4% HPMC, 100-mesh lactose, 295 rpm.

The processes started with dry mixing, followed by liquid binder addition, and ended with wet massing.

fluid gave rise to a slightly increased cohesion of the mass which also caused a small increase in the power consumption value. A decrease in the slope is observed. This is interpreted as the result of lubrication of the powder mass, which reduces the strength of the bulk and consequently the stress on the impeller.

As liquid binder addition continued, an abrupt increase in the power consumption value occurred at around 130 s. The increase in the power consumption value at liquid binder level greater than 30% signals the start of the formation of liquid bridges between the primary particles, where nuclei begin to form. Until the liquid binder level was raised to about 35–40%, the power consumption curves began to level off. It has been reported that the optimal amount of granulating liquid is located at this plateau phase of liquid binder addition.[27,28,30–32] As indicated by Figures 1 and 2, the corresponding granule-size distribution is shown to be more or less well-defined at this granulation stage.

A further addition of liquid binder produced a second rapid rise in the power consumption as a result of the combined effects of the increased granule size and moist cohesion (due to increased liquid content). Liquid binder addition was ceased at 260 s, which was then followed by wet massing. The power consumption showed a slight increase at the start of wet massing, suggesting that there was continuous dispersion of the additional fluid. The slight drop in the power consumption and the following leveling off indicates that there was no free fluid left to be mixed during the final minute of wet massing. This consumption profile indicates that the granulation with a liquid binder level $\geq$50% corresponds to the "irreversible overwetting" phase (phase IV shown in Figure 9), where the granules have reached the transition from funicular to capillary state.[27,28,33,34] As shown by Figures 1 and 2, the corresponding granule-size distributions support this trend.

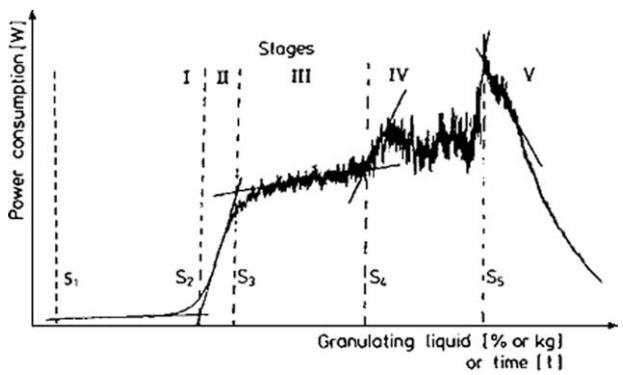

Figure 9. Division of a power consumption curve according to Leuenberger et al.[27–29]

Figure 10 shows the power consumption during foam granulation (91% FQ and 83% FQ) and spray granulation (0% FQ) of pure 100-mesh lactose powder. The power consumption profiles show similar transition stages to the previous formulation shown in Figure 8. The initial dry mixing period gives rise to a constant power consumption, followed by a steady increase in power consumption due to liquid binder addition. It is seen that foam granulation with 91% FQ and 83% FQ and spray granulation (0% FQ) produced different rates of power consumption value rise. Spray granulation incurs the fastest rate of power rise followed by foam granulation at 83% FQ and then 91% FQ. Foamed binder addition involves some lag time between binder addition and ramp-up to final power consumption as agglomeration builds over time, and this lag time increases as FQ increases; whereas spray binder addition causes a shorter lag time and faster agglomeration behavior. The power consumption passes through a local maxima when the liquid binder is added as a spray, suggesting nonuniform liquid binder distribution and uncontrolled granule growth.

At a critical liquid binder level, the power consumption shows a sudden rapid increase. For spray granulation, the power consumption did not increase during spray binder addition between 50 and 65 s, which is likely due to the lubrication effect of the powder mass. However, this pattern is not recognized in either case of foam granulation for the pure lactose power formulation.

For foam granulation at 83% FQ and 91% FQ, the power consumption enters the plateau phase at about 90 s. At this stage, foamed binder addition did not cause a significant increase in the power consumption, suggesting that the added foam was well-incorporated into the powder mix. The power consumption stayed relatively stable until the end of wet massing. In contrast, a continued increase of the power is observed for spray binder addition. The plateau phase begins at about 120 s during the wet massing phase. This difference in the power consumption profiles between foam and spray granulation possibly suggests that foamed binder is easier to disperse than spray binder. Considering the optimal amount of liquid binder lies in the plateau phase of liquid binder addition,[27] the result also implies that foam granulation requires a lower amount of liquid binder compared to spray granulation for a 100-mesh lactose powder formulation.

For the 100-mesh lactose and MCC mixture, foam and spray granulation show relatively small differences in the power consumption profiles, probably due to the water-absorption property of MCC. The powder is able to absorb the liquid binder into its porous configuration before becoming saturated, thus delaying its capacity to form liquid bridges, and holding up the changes of power consumption in response to liquid binder addition. For 100-mesh lactose powder that is readily wettable, apparent differences in the power consumption are observed between foam and spray granulation. The differences in the power consumption suggest that foam and spray granulation exhibit different granulation behavior, which will be discussed in the following section.

Discussion

Both foam and spray granulation promote granule formation through the use of a liquid binder. Spraying produces small droplets of liquid binder, whereas foaming generates small bubbles of gas contained within the liquid binder. Both processes differ in the nature of liquid binder addition, but they are generally carried out in an effort to enhance the distribution of binding fluid. Poor distribution of binding fluid usually results in uncontrolled granule nucleation and growth, which can lead to the formation of inhomogeneous granules with broad-size distributions. It is, therefore, important to understand the mechanisms controlling foam granulation, and to establish the interrelationships between liquid distribution, granule nucleation and growth, and granule-size distribution.

Foam vs. spray

Wetting and Nucleation. It is well-known that uneven initial distributions of liquid during granulation will cause some sections of powder to receive more liquid binder than others, leading to the formation of large, highly saturated nuclei as well as relatively small, unsaturated nuclei. The large, saturated nuclei continue to grow further into larger granules as granulation proceeds. The end result is a broad final granule-size distribution.[1] This granulation behavior is indicated by the granule-size distributions presented in Figures 1 and 2. Granulation starting with a broad initial nuclei-size distribution eventually also leads to a broad final granule-size distribution.

During the wetting and nucleation stage, it is commonly recognized that the spray droplets of binder penetrate the powder mass to create nuclei if the penetration time is small.[9] Drop penetration controlled nucleation is the ideal nucleation mechanism for spray granulation.[9] In industrial practice, it is common for the drop penetration time to be too long to fall within the drop-controlled regime [9,35,36] and liquid distribution occurs instead via mechanical dispersion. The resultant nuclei-size distribution is often bimodal due to initially uneven nucleation, where some particles are nucleated into larger nuclei while others sections of powder remain dry and un-nucleated.

In foams, the foam can also drain into the powder[21,22] to form nuclei. However, this can be undesirable for foam granulation, as liquid dispersion was most efficient when the FQ was high and/or the powder agitation was vigorous, leading to nucleation via mechanical dispersion.[21,22] In foams, the drainage rate becomes more pronounced as the FQ decreases or the liquid viscosity decreases, leading to higher localized saturation. Liquid-penetration controlled nucleation using lower quality foams produces an equivalent effect to spray-induced nucleation at long drop penetration times, and leads to the formation of broad granule-size distributions.

In this work, further evidence to support the proposed mechanisms controlling foam granulation is given by the power consumption profiles. From the pure lactose granulation, Figure 10 showed that the power consumption profile during spray binder delivery had the fastest rate of power consumption rise, followed by foam binder delivery at 81% FQ, and then 91% FQ during the initial granulation stage. As granulation proceeded, the power consumption for spray binder delivery continued to increase nonmonotonically, whereas the power consumption for foam binder delivery stayed relatively stable but reached the plateau phase earlier. Note that this behavior of power consumption change was not observed in the granulation of the lactose and MCC mixture due to the water absorption property of MCC.

It is clear that the power consumption increases with increasing liquid binder content, which also signifies the increase in the saturation of the powder mass or the formation of nuclei granules.[27,37,38] The earlier onset of power consumption rise during initial spray binder delivery is likely to indicate an increase in the powder saturation and the amount of nuclei formed. The spray droplets penetrate as a continuous phase, which likely create a more saturated powder mass (and form more initial granules). This means that spray granulation tends to involve early liquid penetration wetting and nucleation. However, with foam granulation, the delay in the power consumption rise suggests that nucleation by liquid penetration wetting is relatively insignificant in this case. Note that the power consumption value rise also delays with increasing the FQ for foam granulation, indicating that early liquid penetration and nucleation effects are insignificant for higher foam qualities. This was seen in the case of pure lactose formulation (see Figure 10). This behavior was also observed in our previous studies.[21–23,39]

In addition, it is probable that the foam-induced nuclei were so weak initially that any nuclei formed were mechanically dispersed into fines. Spray-induced nuclei are presumably more saturated and stronger due to localized drop penetration. It should be noted that nucleation by the drop penetration mechanism in this case mostly falls out of the drop-controlled regime,[9] where the penetration in fact involves coalescence of multiple drops. This is supported by the granule-size distributions presented in Figures 1 and 2, which show broad initial granule-size distributions with un-nucleated fines and larger nuclei ($>$1mm). At the wetting and nucleation stage, the relatively large nuclei are mostly attributed to slow-to-disperse big clumps being formed by uneven drop penetration. The granule-size distributions are generally less uniform compared to foam binder addition.

Drop-controlled nucleation is the ideal regime to obtain narrow nuclei-size distributions for spray granulation,[9] but operating in this regime is often difficult. Particularly at the production scale, there is a large potential for high-shear spray granulation to operate outside of the drop-controlled regime,[35,36] which means that the granulation process generally relies on mechanical mixing. From our previous work,[21] we have seen how foam can be efficiently dispersed by mechanical mixing, and a narrower nuclei-size distribution with fewer lumps can be obtained. In this case, foam granulation appears

as a superior alternative by showing strong performance in creating rapid dispersion and efficient particle coverage. Given that most full-scale spray granulation processes operate in the mechanical dispersion regime, switching to foam granulation would improve liquid distribution and reduce the formation of large granules while maintaining the same solution flow rate and overall granulation time.

Growth Behavior. After wetting and nucleation, the nuclei compact and grow during the subsequent granulation, where the nuclei enter the induction growth stage. It is clear that large granules are associated with more moisture than the small granules, which is also shown in Figures 6 and 7. As mentioned earlier, the large, wet granules continue to become surface-wet during the compaction. Relatively small, dry nuclei will layer onto those surface-wet nuclei, creating large granules with the relatively small nuclei granules remaining visible on the outer layer of the large granules. Only until all small, dry nuclei have disappeared will further granulation then cause the large nuclei granules to coalesce with each other, entering the rapid growth stage. This behavior is indicated by Figures 3 and 4, which show that the disappearance of fine granules coincides with the end of the induction stage. In other words, rapid granule growth begins as soon as all of the fine granules have been picked up by the larger granules. This behavior was indicated by Wauters et al.[25] in drum granulation.

When the granules enter the growth stage, foam granulation appears to cause extensive growth, forming more large granules compared to spray granulation. This is indicated by the final granule-size distributions presented in Figures 1 and 2. This trend of granule-size distribution changes suggests that foamed binder may initially inhibit nucleation or growth, but once the liquid is there, the foamed binder will promote rapid granule growth. In other words, foam granulation tends to exhibit induction growth behavior initially, and rapid growth behavior later. This behavior of foam granulation is also supported by the weight mean diameter data shown in Figures 3 and 4, which show a small increase initially followed by a rapid increase of the average granule size later on. Note that the increase of the weight mean diameter increases with decreasing FQ and increasing impeller speed, indicating that the induction growth effect tends to diminish at these conditions. In comparison, our results also show that spray granulation tends to display steady growth in this case.

Moisture distribution

The study evaluating the performance of foam and spray granulation in delivering homogeneous granules shows that the moisture distribution in the large granules deviates the most at the end of spray binder addition, followed by foam binder addition at 83% FQ, and then 91% FQ. There are two possible reasons for this result, which can be attributed to the different wetting and nucleation mechanisms involved in foam granulation and spray granulation

1. Spray granulation was operated outside of the drop-controlled regime[9]: The nuclei granules were created from an uneven drop distribution. Due to localized (multiple) drop penetration, coarse, highly saturated nuclei granules were created. This is supported by the wet and dry granule-size distributions at the end of spray binder addition, which show a large fraction of coarse granules. The coarse granules are more saturated, whereas the fine granules are associated with a lower-moisture content (see Figures 5 and 6). The fine nuclei were possibly the ungranulated particles or fragments broken from the coarse granules due to attrition.

2. Foam granulation was operated in the mechanical dispersion regime: Localized liquid penetration is relatively less significant, which is likely to have created fine, less saturated nuclei granules due to mechanical dispersion. However, foam binder addition at a low FQ can still cause nucleation by the foam drainage mechanism forming coarse, saturated nuclei granules. This is supported by the wet and dry granule-size distributions and the moisture distribution in granules at the end of foam binder addition, where foam binder addition at 83% FQ has created a larger fraction of coarse granules associated with more moisture compared to 91% FQ (see Figures 5 and 6).

For both foam and spray granulation, the granule moisture distributions were improved at the end of wet massing, despite the slight deviations from the theoretical moisture content. This improvement in moisture distribution is clearly due to the effect of further mixing. The wet and dry granule-size distributions show that the coarse granules are redispersed into finer granules at the end of wet massing, resulting in unimodal granule-size distributions (see Figure 5). It is likely that the moisture was also mechanically redistributed (see Figure 7).

The performance of foam and spray granulation in delivering homogeneous granules was shown to successfully create granules of reasonably well-distributed moisture at the end of the granulation process. This study demonstrates the successful use of mechanical mixing in redispersing the granules and improving the moisture distribution, although the granulation may initially operate outside of the ideal operating regime.

A foam granulation regime map

Iveson's growth regime map[10,11] shows the different classes of granule growth behavior based on two parameters: the typical amount of granule deformation during impact and the liquid saturation of the granules. The map was shown to be useful in predicting the granule growth behavior, but measuring the Stokes deformation number, St_{def} (the vertical axis in Iveson's growth regime map) and the maximum liquid pore saturation, $S_{\max}$ (the abscissa in Iveson's growth regime map) is often difficult in practice.[10,11] The two dimensionless groups require information on the fundamental properties such as granule deformability, dynamic yield stress, characteristic porosity which are time-dependent characteristics,[10,11] and this information is often not practically available in most industrial granulation processes.

Here, we propose a regime map based on Iveson's growth regime map[10,11] to describe the granulation behavior of the foam and spray systems as mentioned above. The map, as shown in Figure 11, summarizes the granulation behavior for the systems as a function of impeller speed, FQ, and liquid to solid ratio. The regime map is relatively more practical as it is plotted in terms of the granulating condition—impeller speed, liquid to solid ratio, and FQ which can be easily determined. The map shows the regimes of operation for the key stages of granulation: (I) wetting and nucleation, (II) growth—induction, steady, and rapid growth, (III) overwetting, and (IV) caking.

At low liquid binder levels, the mass behaves as an essentially dry powder. The added liquid binder causes wetting-only behavior as the liquid binder is mainly absorbed into

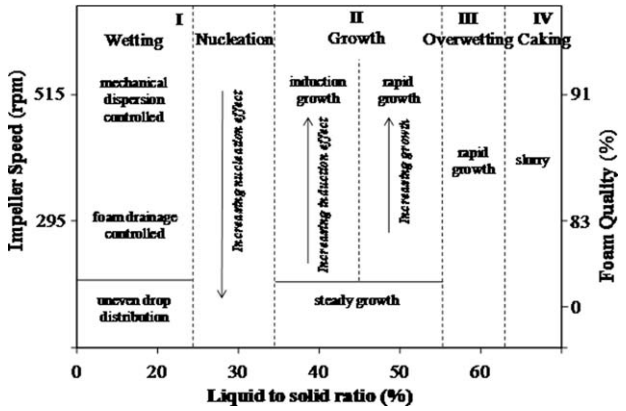

Figure 11. Regime map for the granulation systems—foam vs. spray.

The dotted lines divide the granulation into (I) wetting and nucleation, (II) growth, (III) overwetting, and (IV) caking.

the MCC powder. At slightly higher liquid binder levels, nucleation occurs. Two wetting and nucleation mechanisms for foam granulation have been defined—drainage-controlled nucleation, and mechanical dispersion-controlled nucleation.[21–23] For foam granulation, decreasing the FQ from 91% to 83% FQ enhances nucleation due via drainage-controlled nucleation, where particles are nucleated nonuniformly in a manner similar to drop penetration of a spray droplet. Increasing the FQ to 91% FQ shifts the wetting and nucleation to mechanical-dispersion controlled, where the nucleation due to localized liquid penetration is low and the liquid is mechanically dispersed throughout the powder, producing a more uniform saturation distribution. For spray granulation (0% FQ), liquid penetration is the predominant mechanism.[40,41] This has led to a more pronounced nucleation of large nuclei for spray-induced wetting and nucleation operated outside of the drop-controlled nucleation regime.

Increasing the liquid binder level shifts the granulation from nucleation to granule growth. Spray granulation tends to exhibit steady granule growth, whereas foam granulation shows induction granule growth followed by rapid granule growth. In the induction regime for foam granulation, increasing the impeller speed and/or increasing the FQ will increase the induction effect. In the rapid growth regime for foam granulation, increasing the impeller speed and/or decreasing the FQ aids granule consolidation or coalescence due to large liquid amounts and more liquid bridges, which reduce the induction effect and promote a more rapid growth (provided breakage does not occur).

At very high liquid binder levels, both foam and spray granulation enter the rapid granule growth regime. The fine and intermediate granules disappear as they layer onto the larger granules, forming overwetted granules. When excess liquid binder is added, the systems eventually form a slurry regardless of the granulation conditions.

The regime map for the granulation systems provides an understanding of the interacting effects between impeller speed, FQ, and liquid binder level on the granulation transition phases involved in foam and spray granulation. The control strategy for a granulation system should depend on the regime in which that system lies.

If a granulation system lies in the wetting/nucleation regime, it will never grow rapidly provided its induction time is never exceeded. The granule-size distribution shall be controlled by the wetting and nucleation conditions—"foam drainage" or "mechanical dispersion" controlled.[21–23] Decreasing the FQ will promote nucleation but too low of a FQ is generally undesired if highly saturated and coarse nuclei are created by "foam drainage" controlled wetting and nucleation. "Mechanical dispersion" controlled wetting and nucleation would be the ideal operating regime provided the system lies below a critical liquid content that any mechanical impact will not aid granule coalescence and the formation oversized agglomerates.

In the granule growth regime, decreasing the FQ reduces the induction growth effect. This is often undesirable, as it may shift from the induction region to the rapid growth region. The effect is similar with increasing the liquid binder level, where rapid growth occurs when excessive liquid binder is added. Although mechanical dispersion is the ideal operating mode for foam granulation, care must be taken that impeller speed is not excessive, as increasing the impeller speed in the granule growth regime will promote rapid growth and a slurry can be formed.

The regime map defines the transition of granulation stages as a function of material and process properties. As there is insufficient published experimental data on foam granulation available at present to be plotted on the regime map, further foam granulation studies on a wider range of formulations and mixers are required to confirm that the regime map boundaries and its generally applicability to pharmaceutical foam granulation. With the exception of FQ, the regime map axes are currently dimensional—further experiments and analysis will be required to convert the axes to nondimensional parameters such as saturation and applied shear. However, the map is usable as is although the liquid level will need to be adjusted for each formulation. The fully validated regime map will be useful in tailoring the key material and process parameters for a targeted approach to foam granulation processes.

Conclusions

In this study, foam granulation was compared with spray granulation in a high-shear mixer-granulator. Granule-size distributions and power consumption during granulation were studied as a function of impeller speed, FQ, and liquid to solid ratio. The moisture distribution in foam-bound granules and spray-bound granules after liquid binder addition and wet massing were also evaluated.

The moisture distribution in the granules showed a deviation from the theoretical moisture content at the end of the liquid binder addition. Spray binder addition shows the largest deviation, followed foam granulation at 83% FQ, and then 91% FQ. For both foam and spray granulation, wet massing successfully redispersed the coarse granules and improved the moisture distribution in the granules. This study demonstrates the successful use of mechanical mixing in redispersing the granules and improving the moisture distribution.

A regime map is presented by plotting impeller speed, FQ, and liquid to solid ratio to illustrate the granulation behavior for the systems investigated. Spray granulation tends to involve drop penetration nucleation outside of the drop-controlled regime,[9] whereas foam granulation operates favorably in the mechanical dispersion regime. For spray-induced nucleation, the initial granule-size distributions showed a larger fraction of coarse nuclei as a result of uneven drop penetration and

nucleation effects. For foam granulation, mechanical dispersion produced more uniform granule-size distributions for liquid binder levels below the overwetting limit. The opposite was observed when the granulation entered the rapid growth regime. In the growth regime, spray-bounded granules showed steady granule growth, whereas foam bounded granules tended to exhibit induction granule growth, followed by rapid granule growth behavior. For foam granulation, decreasing the FQ reduces the induction growth effect and promotes rapid granule growth.

The regime map should provide a basis to customize formulations and compare the different granulation behaviors for foam granulation process.

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