PRE-NUCLEATION IN HIGH-SHEAR WET GRANULATION

Diana S. Kumar[1], Sarang Oka[2] & Heather N. Emady[1]

1 School for Engineering of Matter, Transport, and Energy, Arizona State University, 501 E Tyler Mall, Tempe, AZ 85287, USA
2 Hovione, Drug Product Continuous Manufacturing, 40 Lake Dr, East Windsor, NJ 08520, USA
heather.emady@asu.edu

ABSTRACT

Wet granulation can be broken down into three rate processes: Wetting & Nucleation, Consolidation & Growth, and Breakage & Attrition. These stages are often inseparable from each other, which hinders the characterization of the relationship between operating conditions and product properties in wet granulation processes. Single-drop granulation is a form of drop-controlled nucleation intended to isolate the Wetting & Nucleation rate process by allowing a single droplet to form a single granule upon impacting a static powder bed. Single-dropped granules (pre-nucleated granules) were charged to a mixer granulator under varied conditions to observe how the individual rate processes and resulting granulated product are affected by various pre-nucleation conditions. Batches with larger fractions of pre-nucleated granules tended to produce a larger granule size than batches with few or no pre-nucleated granules. Pre-nucleated granules on their own failed to produce a reasonable granular product, but performed well under conditions with standard liquid addition. A difference in granular product can also be identified between the formation mechanisms utilized to produce the pre-nucleated granules.

KEYWORDS

High-Shear Granulation, Wet Granulation, Single-Drop Granulation, Nucleation

1. INTRODUTION

Granulation is the process of agglomerating small particles into larger pellets to increase the size of the bulk distribution. Wet granulation is one in which the agglomeration is caused by the introduction of a liquid binder that bridges between particles, pulling them together. Granulation can have many different objectives such as improving the flow properties, compression characteristics, or mixture uniformity [1-3]. Each of these would benefit from the development of tools and techniques to better control, predict, and eventually design the resulting granule properties. While physical properties such as density, porosity, mixture uniformity, compression pressure, and surface roughness are important, the granule size, size distribution, and shape tend to be the most commonly desired properties to control. Since wet granulation often takes place in some form of agitator such as shear mixers, fluidized beds, tumbling drums, or similar devices, three rate processes occur simultaneously: Wetting & Nucleation, Consolidation & Growth, and Breakage & Attrition [4].

These overlapping processes make a narrow product distribution difficult to design. Particle separation or homogenization often takes place after the granulation process with sieving, milling, or tableting [5]. Better control of the rate processes would minimize the need for post-granulation processes and improve the yield of each batch. In an effort to isolate the Wetting & Nucleation rate process, single-drop granulation has been explored as the wet granulation process in which one liquid droplet impacts a powder bed and generates a single nucleus [2,6-10]. It has been found that the experimental conditions such as powder bed porosity, binder drop velocity, and physiochemical properties affect the formation mechanism of the nucleated granule [8,11,12]. Three primary

formation mechanisms have been identified to be Tunneling, Spreading, and Crater Formation. According to Emady et. al [11], "Tunneling occurs in loose, cohesive powder beds, where aggregates are sucked into the drop that then tunnels into the bed. For coarser powders, granules are formed by Spreading at a low impact velocity, and Crater Formation at a high impact velocity. With Spreading, the drop spreads across the powder bed surface with very shallow capillary penetration. In Crater Formation, the drop impact forms a crater in the powder bed, deforming elastically while picking up particles from the crater, and then penetrates into the bed by capillary action." Each formation mechanism results in its own single-dropped granules of common size and shape. Single-dropped granules have been shown to have varied content uniformity for heterogeneous powder beds [2] and they may have other varying properties such as porosity, density, liquid content, and compression strength. This is the first study, to our knowledge, to apply the single-drop granulation technique to a traditional high-shear wet granulation process.

2. MATERIALS AND METHODS

Materials Used

The powder beds were made from Microcrystalline Cellulose (MCC) powder (Avicel PH-101, FMC BioPolymer, Philadelphia, PA). The liquid binder used was Deionized (DI) Water. All experiments were conducted at room temperature (21°C), atmospheric pressure (1atm), and room humidity (30% RH). These materials were chosen due to the minimal safety concerns and the widespread use of each material across many industries.

Particle Characterization

A particle size distribution for raw (as-received) MCC was obtained through optical microscopy (Malvern Morphologi G3SE). The sample of 5 mm^3 was dispersed with the built-in Sample Dispersion Unit, which is appropriate for particles between 1 μm and 1 mm. The d10, d50, d90, and mean particle sizes can be found in Table 1. The size measured is the particle projected area diameter, and the statistics provided are volume transformed by the measurement device for comparison to mass-based size distributions like sieving. The bulk density of MCC was found by sieving the raw powder through a 600 μm mesh sieve tray into a graduated cylinder to a volume of 100 mL. The mass of the powder added was then used to calculate the bulk density. The graduated cylinder was then tapped in a SOTAX Tapped Density Tester. An amplitude of 15 mm was used for 10 minutes at a rate of 250 taps per minute to obtain the tapped density.

Table 1. Bulk Powder Properties for Microcrystalline Cellulose. Values reported are averages with standard deviations over three trials.

Bulk Property	**Value**
D_{43} mean particle size (μm)	80 ± 30
d_{10} (μm)	36 ± 3
d_{50} (μm)	79 ± 7
d_{90} (μm)	120 ± 20
Bulk Density (kg/m^3)	340 ± 10
Tapped Density (kg/m^3)	510 ± 10
Percent Porosity (%)	79.839 ± 0.006

Sieve Shaker

Granulated material was analysed for mass-based particle size distribution (PSD) with a RO-TAP RX-29 sieve shaker (Model B, W.S. Tyler) [13]. Sieve trays with mesh sizes of 4000, 2000, 1000, 500, 250, 125, and 0 µm were used to obtain the size distributions. Particles between 0 and 125 µm were considered fines, and granules in the 4000+ µm bin were considered over-granulated. It was recognized that this may not perfectly align with the produced material in each case, as there may be true granules present in this bin; however, this categorization is necessary for calculation of yield and was deemed a necessary approximation. Yield is considered to be the mass fraction of granules that are not in the fines or over-granulated bins divided by the total mass of powder used in the experiment. The d_{10}, d_{50}, and d_{90} values can then be linearly interpolated from the PSD. A theoretical 8000 µm tray with no granules is used in some cases to extrapolate data at the largest size. The width of the PSD is thus defined in Equation 1:

$$Width = \frac{d_{90} - d_{10}}{d_{50}}$$

Eq (1)

Operating Conditions

The KG5 mixer granulator from Key International consists of a 1.0 L stainless steel cylindrical bowl. The container is equipped with an impellor consisting of three 7 cm blades angled at 60 degrees. The container is also equipped with a removable chopper, which was not used for any of the experiments conducted in this study. The lid has an opening for liquid addition at a radius of 5.75 cm from the center of the impellor. The impellor was maintained at 300 rpm for all experiments. Liquid addition, when applicable, was maintained at 10 g/min. The liquid was generated with a syringe and a 14 gauge stainless steel needle tip 5 cm above the bed in the form of drops. Liquid drop size was measured with a high-speed camera prior to granulation experiments. Drop diameters of 3.95 ± 0.17 mm were measured over 10 drops.

Nuclei Generation

Single-drop nuclei were produced in a petri dish before addition to the mixer granulator. The petri dish was filled by pouring raw powder into the dish, and a flat surface was created by sliding a ruler across the top of the petri dish to remove excess powder. DI water was dropped onto the petri dish with a syringe, and half-inch, 14 gauge, Fisher Scientific stainless steel needle tips were used to control drop size. Drop heights of 1 cm and 20 cm above the bed were used to achieve the low and high drop impact velocities, respectively. The granules were then sieved out of the petri dish to eliminate the raw powder and then charged to the granulator.

Ten sample granules of each formation mechanism were evaluated experimentally to determine their properties. A high-speed camera (Photron Fastcam Mini) was used to observe the drop penetration time and the formation mechanism [7,11,12]. These granules were also analysed for size and shape properties using the prism method, in which three dimensions of a granule are visible by use of a 45 degree mirror, and image analysis software, ImageJ. The granule properties are shown in Table 2.

Granule liquid content was measured so that a constant amount of solid material could be charged to the mixer granulator in each experiment. A petri dish full of flat-surfaced powder was massed, then a large number of granules were produced by liquid addition. The petri dish was massed again and the difference in mass was the mass of liquid added to the granules. The granules were then removed from the powder bed and the powder bed was massed once again. Comparing the final mass to the initial mass reveals the amount of powder used to form the granules. The ratio of liquid mass to solid

mass is characterized as the liquid content of the granules. The Crater Formation granules are smaller and more saturated with liquid than the Spreading granules.

Table 2. Pre-Nucleated, Single-Dropped, Granule Properties. Values reported are averages with standard deviations over three trials.

Drop Height	Formation Mechanism	Projected Area Diameter (mm)	Granule Height (mm)	Drop Penetration Time (s)	Liquid Content (m_{liquid}/m_{solid})
1 cm	Spreading	10.1 ± 0.6	4.9 ± 0.4	0.079 ± 0.002	0.70 ± 0.02
20 cm	Crater Formation	9.6 ± 0.4	4.8 ± 0.6	0.051 ± 0.004	0.77 ± 0.02

Experimental Procedure

An experimental schedule can be found in Table 3. Naming convention is Percent Single Drop - Percent Raw Powder - Percent Additional Liquid – Granule drop height (L – low or H – high). Mass of Single-Drop Powder is the mass of powder in the single-drop granules used, not the mass of the overall granules since the single-drop granules have a considerable amount of liquid within them. To maintain sieving mass consistency, 50 g of powder was used in each experiment. Where applicable, the required quantity of raw powder was first charged to the granulator. Then, the required quantity of single-dropped granules was charged to the granulator on top of the raw powder. This order was maintained to mimic the traditional formation of granules by overhead liquid addition; however, it is noted that pre-nucleated granules have the ability to be charged to the granulator at different locations to establish varied initial conditions. Once the powder was added to the mixer granulator, if additional liquid was required, 5 minutes of granulation began at an impellor speed of 300 rpm and a liquid addition rate of 10 g/min. After this step, all experiments were wet-massed at the same impellor speed of 300 rpm for 2 minutes.

Upon completion of the wet-massing process, each granulated product was poured onto a baking tray, and dried in an oven for 8 hours at 60°C. After drying, each batch was charged to a sieve shaker and agitated for a total of 5 minutes to obtain the resulting granule size distribution.

Table 3. Experimental schedule, including nomenclatures and varied parameters

Experiment Code	Mass of Single-Drop Powder (g)	Mass of Raw Powder (g)	Mass of Additional Liquid (g)	Single-drop Granule Type
0 – 100 – 0	0	50	0	N/A
0 – 100 – 100	0	50	50	N/A
25 – 75 – 0 L	12.5	37.5	0	Spreading (Low)
50 – 50 – 0 L	25	25	0	Spreading (Low)
75 – 25 – 0 L	37.5	12.5	0	Spreading (Low)
100 – 0 – 0 L	50	0	0	Spreading (Low)
25 – 75 – 100 L	12.5	37.5	50	Spreading (Low)
50 – 50 – 100 L	25	25	50	Spreading (Low)
75 – 25 – 100 L	37.5	12.5	50	Spreading (Low)
100 – 0 – 100 L	50	0	50	Spreading (Low)
25 – 75 – 0 H	12.5	37.5	0	Crater Formation (High)
50 – 50 – 0 H	25	25	0	Crater Formation (High)
75 – 25 – 0 H	37.5	12.5	0	Crater Formation (High)
100 – 0 – 0 H	50	0	0	Crater Formation (High)
25 – 75 – 100 H	12.5	37.5	50	Crater Formation (High)
50 – 50 – 100 H	25	25	50	Crater Formation (High)
75 – 25 – 100 H	37.5	12.5	50	Crater Formation (High)
100 – 0 – 100 H	50	0	50	Crater Formation (High)

3. RESULTS

No Additional Liquid

Figure 1 shows the granule particle size distribution (PSD) from the experiments in which there was no additional liquid in the granulator. Figure 1a shows the trials in which Spreading granules were used and Figure 1b shows the trials in which Crater Formation granules were used. Only single-dropped granules were charged to the mixer with varied amounts of raw powder. It can be seen that the PSDs are more heavily weighted at the smaller size fractions for all scenarios in which there was no additional liquid, regardless of the granule formation mechanism used to produce the single-drop granules. The experiment with 0% single drops is meant to represent the raw powder with no granulation, and can be considered to be the baseline scenario. The experiments with 25% and 50% of the charge being single-dropped granules do not appear to have granulated at all, as these PSDs match the raw powder very closely. The experiments with 75% and 100% of the charge being single-dropped granules have a slight increase in the granule sizes. The shift is much more prevalent in the experiment in which the single-dropped granules were produced with the Crater Formation granule formation mechanism as opposed to the Spreading granule formation mechanism.

a) b)

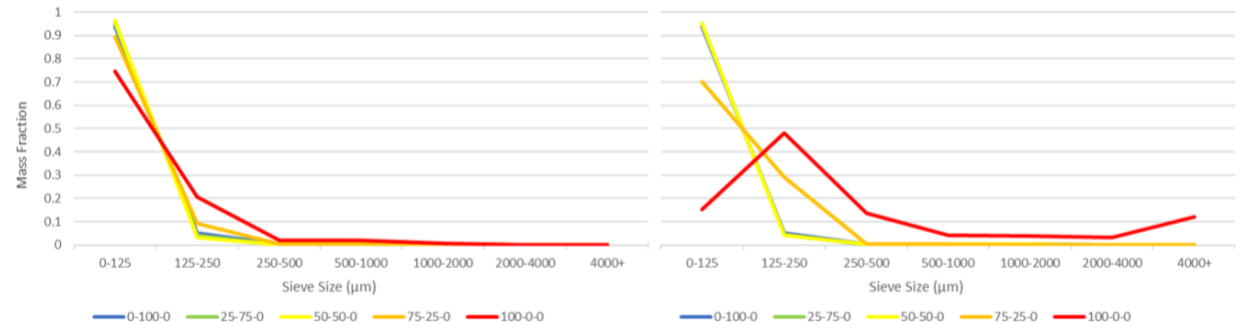

Figure 1. Sieved particle size distribution (PSD) for the post-mixing material in which there was no liquid addition and single-dropped granules were produced via the: a) Spreading granule formation mechanism and b) Crater Formation granule formation mechanism.

Additional Liquid

Figure 2 shows the granule particle size distribution (PSD) from the experiments in which there was 50 g of additional liquid fed to the granulator. Figure 2a shows the trials in which Spreading granules were used and Figure 2b shows the trials in which Crater Formation granules were used. Single-dropped granules were charged to the mixer with varied amounts of raw powder, and then additional liquid was dripped in from above with the syringe, producing distinct droplets. It can be seen that the PSDs are now more heavily weighted at the larger size fractions for all scenarios as compared to the scenarios without additional liquid. Regardless of the granule formation mechanism used to produce the single drops, a significant amount of granules were produced. The experiment with 0% single drops is meant to represent the raw powder with regular granulation, and can be considered to be the standard result from this mixer granulator. The size distribution shifts toward the larger granules as more raw material is composed of single-dropped granules. There is no clear distinction between the formation mechanisms of the single-dropped granules; however, it seems that the over-granulated size fraction is more heavily weighted for the Crater Formation granules rather than the Spreading granules. It is clear that the addition of liquid facilitated the production of granules and that size distribution is influenced by the percentage of single-dropped granules present in the batch prior to granulation.

a) b)

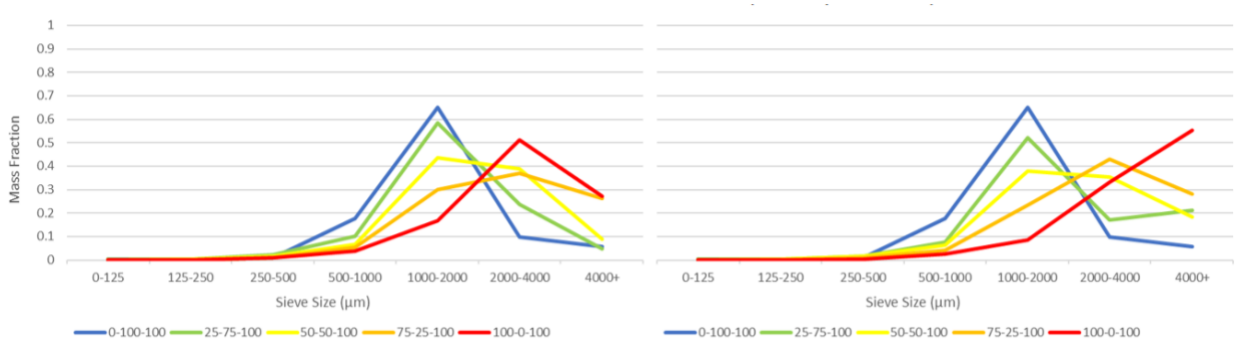

Figure 2. Sieved particle size distribution (PSD) for the post-mixing material in which there was 50 g of liquid addition and single-dropped granules were produced with the: a) Spreading granule formation mechanism and b) Crater Formation granule formation mechanism.

Size Distribution Quantitative Analysis

Table 4 shows the quantitative statistics for the granule particle size distributions. Interpolated d_{10}, d_{50}, d_{90}, yield, and width values are shown. The statistics for the trials in which 25% and 50% of the charge to the granulator was single-dropped granules with no additional liquid look nearly identical to the statistics for the trial representing the original fines, regardless of formation mechanism. For the 75% and 100% single-dropped granule trials with no additional liquid, a noticeable increase in the sizes of the characteristic statistics can be seen, along with an increase in the granule yield and distribution width, regardless of formation mechanism. All trials with additional liquid produced size distributions made up of granules that were larger than the base granulation case with no single-dropped granules and larger than the trials without additional liquid, as measured by the d_{10}, d_{50}, and d_{90}. The size distribution width was narrowest for the traditional granulation trial. Granules produced in the trials with Crater Formation single-dropped granules were slightly larger than the granules produced in the trials with Spreading single-dropped granules. The Crater Formation granules also led to a greater yield than the Spreading granules.

Table 4. Granule Yield and Statistics

Experiment Code	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)	Granule Yield	Width
0 – 100 – 0	13	66	120	0.06	1.60
0 – 100 – 100	736	1471	3144	0.94	1.25
25 – 75 – 0 L	13	66	118	0.05	1.60
50 – 50 – 0 L	13	65	117	0.05	1.60
75 – 25 – 0 L	14	70	132	0.30	1.69
100 – 0 – 0 L	17	84	218	0.73	2.40
25 – 75 – 100 L	849	1632	3554	0.78	1.66
50 – 50 – 100 L	1035	1950	3939	0.82	1.49
75 – 25 – 100 L	1116	2722	6481	0.72	1.97
100 – 0 – 100 L	1305	3108	6527	0.45	1.68
25 – 75 – 0 H	13	66	118	0.05	1.60
50 – 50 – 0 H	13	66	118	0.04	1.60
75 – 25 – 0 H	18	89	211	0.11	2.16
100 – 0 – 0 H	82	216	4658	0.25	21.22
25 – 75 – 100 H	1006	3547	6115	0.95	1.64
50 – 50 – 100 H	1039	2206	5799	0.91	1.44
75 – 25 – 100 H	1196	2985	6582	0.74	2.16
100 – 0 – 100 H	1818	4380	7276	0.73	1.80

4. DISCUSSION

The results of the sieved granule size distribution show that the presence of single-dropped granules can provide a consistent influence on the high-shear wet granulation process. In all cases studied, the presence of single-dropped granules totalling at least 75% of the charged powder increased the overall granule sizes compared to the traditional granulation trial as seen by the characteristic statistics in Table 4. In all cases, the granules produced are much smaller than the sizes of the original single-dropped granules, which is due to the single-dropped granules being very frail. The d_{50} of all trials are less than 5 mm in diameter, while the single dropped granules have a mean diameter of around 10 mm, indicating that the initial single-dropped granules were broken up when initially charged to the granulator. Additional liquid seems to have had a dominating effect on the production of viable granules, as seen by the yield calculations. With the exception of the Spreading

100% single-drop trials, the yields without additional liquid were all 0.30 or below and the yields with additional liquid were all 0.70 and above. It is hypothesized that these exceptions may be due in part to the classification of the largest bin as over-granulated material, which was excluded from the yield, even though the trend with increasing single-dropped granule percentage indicates that much of the material in that bin may just be large granules rather than over-granulated material. In looking at the Crater Formation 100% single-drop trial, it is notable that the width is much larger than any of the other trials, however examination of the PSD reveals that this is due to the formation of a bimodal distribution.

Formation Mechanism Differences

The single-dropped granules formed by Crater Formation increased the high-shear granule sizes more than the single-dropped granules formed by Spreading as seen by the d_{10}, d_{50}, and d_{90} being larger for each Crater Formation trial when compared to its respective Spreading trial. The single-dropped granules formed by Crater Formation had a higher liquid content, despite being smaller than the single-dropped granules formed by Spreading, which may be due to the higher impact velocity needed to produce Crater Formation granules. The more compact and liquid saturated Crater Formation granules, upon being broken up by the impellor, broke into pieces with the aforementioned properties that were more suitable to form nuclei for high-shear granules. With denser nuclei that had more liquid available to bridge with new powder, the Crater Formation granule pieces were less likely to experience further breakage and were more likely to encourage growth, which led to the larger high-shear granule sizes that were experimentally observed.

Wetting & Nucleation

Wetting & Nucleation is the rate process in which a liquid binder is introduced to a powder bulk to initiate a growth process. Nucleation occurs when a liquid droplet impacts raw powder and undergoes capillary penetration to form a granular center. Wetting is the broader addition of liquid to a powder bulk, which can be a precursor to nucleation, but may also be a catalyst for the Consolidation & Growth rate process. A primary purpose of this study was to explore the viability of nucleating granules prior to being charged to a mixer granulator. Single-dropped granules were generated with two different formation mechanisms, Spreading and Crater Formation, which led to significant differences in the resulting granulated material. All physiochemical properties and wetting conditions were identical except the impact velocity of the liquid droplet. Spreading granules were more disk-like, as the low velocity droplet spread out upon impact before penetrating the bed due to capillary forces. Crater Formation granules had a rounder, mushroom cap, shape as the high velocity droplet created a crater in the powder bed and dragged free particles into the droplet along the way. This dragging at high velocity produced a smaller, more compact, granule that contained a higher fraction of liquid than the low velocity counterpart. Both sets of pre-nucleated granules had very narrow size distributions, compared to the resulting size distribution from the mixer granulator. It was predicted that the narrow initial size distribution would contribute to a narrower size distribution from the mixer granulator; however, the breakage that occurred immediately in the granulator is likely the source of the broadening of the PSD. This breakage happened immediately in the mixer since the single-dropped granules had no agitation or shear to promote consolidation or densification, leaving them extremely frail. The breakage retained some bulk properties of the original single-dropped granules, like density and liquid content, but due to the pseudo-random nature of breakage, the pieces were varied in size. This means that, in reality, the breakage pieces became the actual nuclei in the high-shear mixer.

Since the single-dropped granules did not produce a reasonable granular product, with or without the presence of fines, additional liquid was introduced to the mixer granulator. While this greatly improved the granular product obtained, it added further complexity to the process, since additional wetting and potentially nucleation occurred. The trials without fines experienced a form of wetting in

which existing nuclei or granules came into contact with a liquid droplet and were either engulfed by the droplet to create a large external liquid layer or were agglomerated by the droplet to other existing nuclei or granules. This additional agglomeration can be considered as forming new nuclei at a larger scale with these existing nuclei or granules playing the role of the fresh powder being agglomerated. This process occurs in traditional granulation as well, but is exaggerated in this scenario due to the pre-nucleation that occurred. The trials with fines present in the mixer experienced this, as well as fresh nucleation occurring when the liquid droplets added by syringe came into contact with fresh powder. These scenarios with additional liquid are very similar to traditional granulation, with the primary difference being that this occurs immediately in the presence of pre-nucleated granules, but would occur later in traditional granulation as the presence of granules and moisture in the mixer are initially built up. In these experiments, the presence of the pre-nucleated granules led to an increase in size of the resulting granular material.

Consolidation & Growth

Consolidation & Growth is the rate process associated with size enlargement in a wet granulation process. Consolidation is the compaction of a granule to increase the density and allow the formation of a small liquid layer around the granule. This occurs through agitation which rearranges and compacts the particles that make up each granule, squeezing the excess liquid to the surface where it can be used for growth. Two primary forms of growth are coalescence, in which similarly sized granules collide and stick together to form a larger granule, and layered growth, in which fines are collected by the external liquid layer of a larger granule, creating a slow and uniform increase in granule size. In exploring the potential applications of single-dropped granules, some trials were conducted that contained only single-dropped granules, while others were conducted with a mixture of single-dropped granules and fines. Since agitation was kept constant across trials, consolidation was expected to be present, facilitating the growth mechanisms. Consolidation is expected to be easier for the Crater Formation granules rather than the Spreading granules due to the higher liquid content that makes it easier to form an external liquid layer. This trend is reflected in that the resulting granule sizes for the Crater Formation trials are all larger than their respective Spreading trials.

Trials that contained only single-dropped granules were expected to grow via coalescence exclusively due to the lack of fines to facilitate layered growth. The trials that contained a mixture of single-dropped granules and fines were expected to experience layered growth as well. Layered growth was expected to be nearly exclusive in the trials with low amounts of single-dropped granules, since fines would be plentiful and the probability of granule-granule collisions would be significantly reduced, minimizing the occurrence of coalescence. Thus, higher fractions of single-dropped granules should result in the dominance of coalescence over layered growth and produce a PSD that grows at a faster rate than a layered growth dominating scenario. In agreement with these expectations, trials with larger fractions of single-dropped granules present produced larger granules than the trials with fewer single-dropped granules.

Without constant liquid addition, it was hypothesized that the granules might consolidate and grow in a more predictable manner than in traditional granulation; however, significantly less growth was observed when no liquid was added than in the traditional granulation trial. This prompted the further liquid addition to the pre-nucleated bulk, which succeeded in encouraging further Consolidation & Growth of the granules. This additional wetting of the granular bulk greatly reduced the agitation necessary for consolidation and the formation of an external liquid layer. In all trials with liquid addition, the resulting granule sizes were larger than their counterparts without liquid addition, as demonstrated by the statistics in Table 4. Yield greatly increased in these trials; however, a confounding factor is that in the experiments with fines, this liquid addition introduced nucleation back into the granulation process. Additional nucleation also led to an increase in the yield within these trials. While this inhibits the effort to segregate the rate processes for individual analysis and

characterization, it does demonstrate that a traditional granulation process with some presence of pre-nucleated granules in the charged powder can have a significant, controllable, influence on the resulting granule sizes.

Furthermore, this broad, segregating, view may not paint a clear story. Figure 3 shows three granules that were produced in the same batch (100 – 0 – 100 L) with only single-dropped granules and additional liquid. Despite the lack of fines and the expected domination of coalescence, the right granule seems to have been formed by coalescence, the middle granule seems to have been formed by layered growth, and the left granule appears to be a remnant of caking that did not break up upon drying. The presence of all three of these phenomena indicate that the segregation efforts that this study attempted to impose may not have been as strict as theorized. It is possible that the middle granule is simply the result of consolidation rather than layered growth, or that attrition in the granulator creates enough fines to support layered growth. Further exploration into the formation of each type of granule is necessary to fully understand these phenomena. Lastly, it is possible that caking, among other factors, may be skewing the mass fraction of the over-granulated bin, reducing the accuracy of the produced PSD's.

Figure 3. Three granules from the 100 – 0 – 100 batch of Spreading formation mechanism that all ended up in the 4000+ µm sieve tray. They appear greatly varied in shape and growth mechanism. The left granule appears to have been formed by caking, the middle granule appears to exhibit layered growth, and the right granule seems to demonstrate coalescence.

Breakage & Attrition

Breakage & Attrition is the rate process associated with size reduction in a wet granulation process. Breakage is considered to be the splitting of a granule into two or more pieces, the opposite of coalescence. Attrition is considered to be the loss of fines from the outer layer of a granule, the opposite of layered growth. Both forms of size reduction are caused by agitation, which primarily takes the form of collisions between granules and either fixed points within the equipment, moving components of the equipment, or other granules within the mixer. No chopper or baffles were used in these experiments, wet-massing time was kept constant, and an impellor speed of 300 rpm with a radius of 7 cm (2.2 m/s tip speed) was used in all trials. Analysis of these experiments assume a constant amount of Breakage & Attrition across all trials since agitation was kept constant. Particle-particle collisions are the exception since particles of differing sizes will contribute proportional momentum to collisions, and the particle sizes varied with time and across trials. The effects of these differences are neglected for the purposes of this analysis.

Liquid to Solid Ratio

A primary confounding factor that is not accounted for in these experiments is the Liquid to Solid ratio, which is known to have a large effect on the high-shear wet granulation process [14-16]. The particle size distributions clearly trend towards larger granules in the scenarios with larger amounts of liquid in the system. Single-dropped granules contain a significant amount of liquid within them, as shown by the liquid content in Table 2. With higher fractions of single-dropped granules, the overall system contains more liquid. This means that the experiments conducted have a broad range of Liquid to Solid ratios, ranging from 0% all the way to nearly 180%. This provides an alternative

explanation for some of the trends that appear in the particle size distributions. It also may provide an explanation for the differences between granule formation types as the Crater Formation granules carried more liquid than the Spreading granules. It does not seem to provide a full picture; however, since the largest fraction of single-dropped granules contains nearly 80% liquid content and the standard granulation experiment with no single-dropped granules contains 100% liquid content. The enormous difference between the two trials cannot fully be explained by the system's liquid content. Unfortunately, the fragility of the single-dropped granules prevents them from being dried. Attempting to do so with these materials has only led to a complete disintegration of the single-dropped granule. As such, this is a confounding factor that will be explored in future work.

5. CONCLUSION

The results of this study indicate that pre-nucleated granules can be used to influence the high-shear wet granulation process. Methods in which pre-nucleated granules could be used were explored, and it was found that pre-nucleated granules are poor candidates to be sheared with the intent to produce a high yield of granular material. Additional liquid can be used to activate the pre-nucleated granules, and clear trends in the resulting granule sizes are shown to be directly correlated to the fraction of charged material that is composed of single-dropped granules. Charging a larger fraction of single-dropped granules to the granulator results in larger granule sizes. It is also concluded that the granule formation mechanism used to generate the pre-nucleated granules has an influence on the particle size distribution as well. Crater Formation single-dropped granules produced consistently larger granule sizes than Spreading single-dropped granules. This difference is largely attributed to the compaction and liquid content differences between the formation mechanisms. Lastly, the poor performance of single-dropped granules without additional liquid reflects the difficulty in isolating the rate processes. Additional liquid reintroduces the Wetting & Nucleation rate process, and the trials without additional liquid demonstrate poor Consolidation & Growth. Liquid to solid ratio is offered as an alternate explanation to some of the trends observed in this study and requires future investigation.

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