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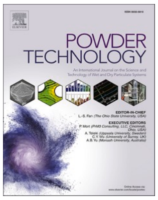


Pre-nucleation in high-shear wet granulation

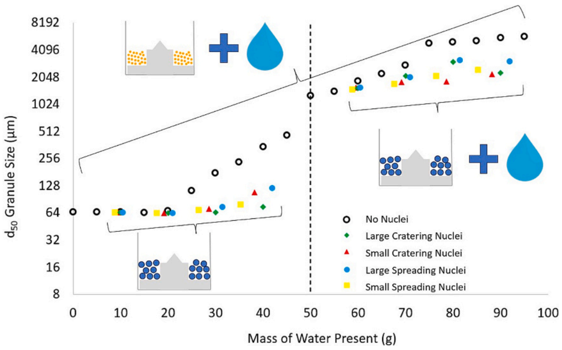
Diana S. Kumar [a], Sarang Oka [b], Heather N. Emady [a,*]

[a] School for Engineering of Matter, Transport, and Energy, Arizona State University, 501 E Tyler Mall, Tempe, AZ 85287, USA
[b] Hovione, Drug Product Continuous Manufacturing, 40 Lake Dr, East Windsor, NJ 08520, USA

HIGHLIGHTS

- High-shearing of pre-nucleated granules alone does not yield promising product.
- Activating pre-nucleated granules with liquid addition can yield improved results.
- Pre-nucleated granulation results deviate from traditional mixer granulator results.
- Liquid to solid ratio differences do not account for the observed trends.
- Partial granulation rate process separation was achieved.

GRAPHICAL ABSTRACT



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ABSTRACT

Wet granulation is broken down into three rate processes that are often inseparable from each other, hindering characterization of the relationship between operating conditions and product properties. Single-drop granulation is a form of drop-controlled nucleation intended to isolate the Wetting & Nucleation rate process. In this work, 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 were 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. A clear and consistent trend of deviation from traditional granulation results is observed. Liquid to solid ratio is ruled out as a sole cause for the deviation, indicating that pre-nucleation may have applications in granular material production with respect to liquid dosing in granules, granule size control, and efficient material usage.

1. Introduction

Granulation is the process of agglomerating small particles into larger pellets to increase the size of the bulk distribution. Wet granulation is one such process 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 bulk 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

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* Corresponding author.
E-mail address: heather.emady@asu.edu (H.N. Emady).

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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 achieve. 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 operations 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 and binder drop velocity, along with the physiochemical properties of the liquid and powder, 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 to solid ratio, and compression strength. The breakage and strength of these single-dropped granules have also been explored in a breakage-only mixer granulator [13–15].

Single-drop granulation is hypothesized to influence a narrower bulk distribution and provide better control over the size of the granular product. In this study, we explore the effect of pre-nucleating granules via single-drop granulation prior to charging them to a high-shear mixer granulator and evaluate the impact for potential applications. 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

2.1. 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 (1 atm), 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.

2.2. Particle characterization

A particle size distribution for raw (as-received) MCC was obtained through optical microscopy (Malvern Morphologi G3SE). A sample of 5 mm^3 was dispersed with the built-in Sample Dispersion Unit, which is appropriate for dispersing particles between 1 μm and 1 mm in size. The d_{10}, d_{50}, d_{90}, and d_{43} volume mean particle size 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 min at a rate of 250 taps per minute to obtain the tapped density. Particle porosity was measured with a Micromeritics Accupyc II 1340 Helium Pycnometer.

Table 1
Powder properties for raw microcrystalline cellulose. Values reported are averages with standard deviations over three trials.

Bulk property	Value
d_{43} Volume Mean Particle Size (μm)	80 ± 30
d_{10} (μm)	36 ± 3
d_{50} (μm)	79 ± 7
d_{90} (μm)	120 ± 20
Particle Porosity (%)	79.839 ± 0.006
Bulk Density (kg/m^3)	340 ± 10
Tapped Density (kg/m^3)	510 ± 10

2.3. Granule product characterization

Granulated material was analyzed for mass-based particle size distribution (PSD) with a RO-TAP RX-29 sieve shaker (Model B, W.S. Tyler). Sieve trays with mesh sizes of 4000, 2000, 1000, 500, 250, 125, and 0 μm were used to obtain the size distributions along a log-2 scale. 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 these bins; however, this categorization is needed 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 Eq. (1):

$$Width = \frac{d_{90} - d_{10}}{d_{50}} \tag{1}$$

2.4. 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 by hand with a syringe. Half-inch, Fisher Scientific stainless-steel needle tips were used to control drop size, with 30-gauge needle tips producing drop diameters of 2.24 ± 0.03 mm, and 14-gauge needle tips producing drop diameters of 4.0 ± 0.2 mm, each measured over 10 drops with a high-speed camera. 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 hand sieved out of the petri dish to eliminate the raw powder and then charged to the granulator. Having been generated prior to insertion into the granulator, these granules are considered pre-nucleated. Unfortunately, the fragility of these granules prevents them from being dried or machine sieved. Attempting to do so with these materials has only led to a complete disintegration of the granule, so the pre-nucleated granules were not dried prior to being charged to the mixer granulator.

Ten sample granules of each formation mechanism and size were evaluated experimentally to determine their properties. A high-speed camera was used to observe the drop penetration time and the granule formation mechanism [7,11,12]. These granules were also analyzed 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.

Average liquid to solid ratio was measured for each granule type 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 to solid ratio of the granules. Larger granules tended to have a higher liquid to solid ratio than smaller granules.

2.5. *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 based on the work of Oka et al. [1] with the same powder material and a similar granulator size. Liquid addition, when applicable, was maintained at 10 g/min to preserve nucleation in the drop-controlled regime. The liquid was generated by hand with a syringe and a 14-gauge stainless-steel needle tip 5 cm above the bed in the form of single drops. Liquid drop size was measured with a high-speed camera (Photron Fastcam Mini) prior to granulation experiments. Drop diameters of 4.0 ± 0.2 mm were measured over 10 drops.

2.6. *Experimental procedure*

An experimental schedule for the pre-nucleation trials can be found in the top portion of Table 3. The naming convention used is % Pre-Nucleated Powder - % Raw Powder - % Additional Liquid - Pre-Nucleated Granule Type (L/H for low or high drop heights and 14/30 for 14-gauge or 30-gauge needle tips). % Pre-Nucleated 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. As such, batches without liquid addition during mixing will have a nonzero liquid to solid ratio. To maintain sieving mass consistency, 50 g of powder was used in each experiment. To achieve this, the liquid to solid ratios in Table 2 were used to find the mass of each granule type necessary to obtain this dry-basis mass of 50 g of powder. Furthermore, 50 g of liquid addition during mixing is considered the base case of 100% Additional Liquid, making a liquid to solid ratio of 1.0. Where applicable, the required quantity of raw powder was charged to the granulator first. Then, the required quantity of pre-nucleated 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 min 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 min.

Upon completion of the wet-massing process, each granulated product was poured onto a baking tray, and dried in an oven for 24 h at 60 °C. After drying, each batch was charged to a sieve shaker and agitated for a total of 5 min to obtain the resulting granule size distribution. Despite drying for 24 h, some over-granulated material failed to dry completely. This may have led to a skewing of the mass-based PSD toward the over-granulated bin.

Each type of pre-nucleated granule was tested under eight conditions. Four trials were performed without the addition of further liquid, and four trials were performed with the addition of 50 g of further liquid. The fraction of the charge that was pre-nucleated granular material as opposed to raw powder was varied from 25% to 100%. These experiments were conducted for the purpose of identifying appropriate uses for pre-nucleated material and for better insight into the stages of granulation. Experiments with a small fraction of pre-nucleated granules and a large fraction of raw powder are representative of the early stages of granulation and were expected to exhibit much more layered growth than coalescence. Experiments with large fractions of pre-nucleated granules are representative of the later stages of granulation and were expected to have more coalescence interactions than layering. Additionally, these experiments allowed for the progression of deviation of pre-nucleated material from traditional granulation practices to be more closely explored. Experiments with liquid addition during mixing were performed to identify whether overhead liquid addition served as a necessary catalyst in the high-shear wet granulation process. The type of pre-nucleated granule was varied between trials to evaluate any influence from initial formation mechanism or granule size.

Liquid to solid ratio is known to have a significant influence on the wet granulation process. Due to the presence of liquid in the pre-nucleated material, additional experiments were conducted with only raw powder, varying the mass of liquid added to each batch, for better comparison. The experimental schedule for these additional trials can be found in the bottom portion of Table 3.

3. Results

3.1. *No liquid addition during mixing*

Fig. 1 shows the granule PSDs from the experiments in which there was no liquid added during mixing. Fig. 1a-d each show the PSD results for a separate type of pre-nucleated granule, and each figure shows the 5 fractions of pre-nucleated material used experimentally. It can be seen from the plots 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 pre-nucleated granules. The base case in blue (hollow circle), representing raw powder with no granulation (0−100−0), is the basis for comparison with the pre-nucleated granule experiments (on these plots, this line is difficult to see due to the great similarity of some trials). The experiments with 25% (25–75–0) and 50% (50–50–0) of the charge being pre-nucleated material do not appear to have granulated at all, as these PSDs

Table 2

Pre-nucleated, single-dropped, granule properties. Values reported are averages with standard deviations over 10 trials.

Drop height (cm)	Liquid drop needle gauge	Formation mechanism	Granule projected area diameter (mm)	Granule height (mm)	Drop penetration time (s)	Liquid to solid ratio (m_{liquid}/m_{solid})
1	30	Spreading	5.2 ± 0.2	3.3 ± 0.2	0.047 ± 0.003	0.67
1	14	Spreading	10.1 ± 0.6	4.9 ± 0.4	0.081 ± 0.002	0.77
20	30	Crater Formation	5.4 ± 0.1	3.3 ± 0.3	0.024 ± 0.002	0.73
20	14	Crater Formation	9.6 ± 0.4	4.8 ± 0.6	0.051 ± 0.004	0.75

Table 3
Overall experimental schedule, including nomenclatures and varied parameters. The top portion is for the pre-nucleation experiments, and the bottom portion is for the added liquid experiments. The naming convention used is % Pre-Nucleated Powder - % Raw Powder - % Additional Liquid - Pre-Nucleated Granule Type (L/H for low or high drop heights and 14/30 for 14-gauge or 30-gauge needle tips).

Designation	Pre-nucleated powder mass (g)	Raw powder mass (g)	Additional liquid mass (g)	Granule formation mechanism	Batch liquid to solid ratio (m_{liquid}/m_{solid})
25-75-0 H30	12.5	37.5	0	Crater Formation	0.19
25-75-0 L30	12.5	37.5	0	Spreading	0.18
25-75-0 H14	12.5	37.5	0	Crater Formation	0.20
25-75-0 L14	12.5	37.5	0	Spreading	0.21
50-50-0 H30	25	25	0	Crater Formation	0.38
50-50-0 L30	25	25	0	Spreading	0.35
50-50-0 H14	25	25	0	Crater Formation	0.40
50-50-0 L14	25	25	0	Spreading	0.42
75-25-0 H30	37.5	12.5	0	Crater Formation	0.57
75-25-0 L30	37.5	12.5	0	Spreading	0.53
75-25-0 H14	37.5	12.5	0	Crater Formation	0.60
75-25-0 L14	37.5	12.5	0	Spreading	0.63
100-0-0 H30	50	0	0	Crater Formation	0.76
100-0-0 L30	50	0	0	Spreading	0.71
100-0-0 H14	50	0	0	Crater Formation	0.80
100-0-0 L14	50	0	0	Spreading	0.84
25-75-100 H30	12.5	37.5	50	Crater Formation	1.19
25-75-100 L30	12.5	37.5	50	Spreading	1.18
25-75-100 H14	12.5	37.5	50	Crater Formation	1.20
25-75-100 L14	12.5	37.5	50	Spreading	1.21
50-50-100 H30	25	25	50	Crater Formation	1.38
50-50-100 L30	25	25	50	Spreading	1.35
50-50-100 H14	25	25	50	Crater Formation	1.40
50-50-100 L14	25	25	50	Spreading	1.42
75-25-100 H30	37.5	12.5	50	Crater Formation	1.57
75-25-100 L30	37.5	12.5	50	Spreading	1.53
75-25-100 H14	37.5	12.5	50	Crater Formation	1.60
75-25-100 L14	37.5	12.5	50	Spreading	1.63
100-0-100 H30	50	0	50	Crater Formation	1.76
100-0-100 L30	50	0	50	Spreading	1.71
100-0-100 H14	50	0	50	Crater Formation	1.80
100-0-100 L14	50	0	50	Spreading	1.84
0-100-0	0	50	0	N/A	0.00
0-100-10	0	50	5	N/A	0.10
0-100-20	0	50	10	N/A	0.20
0-100-30	0	50	15	N/A	0.30
0-100-40	0	50	20	N/A	0.40
0-100-50	0	50	25	N/A	0.50
0-100-60	0	50	30	N/A	0.60
0-100-70	0	50	35	N/A	0.70
0-100-80	0	50	40	N/A	0.80
0-100-90	0	50	45	N/A	0.90
0-100-100	0	50	50	N/A	1.00
0-100-110	0	50	55	N/A	1.10
0-100-120	0	50	60	N/A	1.20
0-100-130	0	50	65	N/A	1.30
0-100-140	0	50	70	N/A	1.40
0-100-150	0	50	75	N/A	1.50
0-100-160	0	50	80	N/A	1.60
0-100-170	0	50	85	N/A	1.70
0-100-180	0	50	90	N/A	1.80
0-100-190	0	50	95	N/A	1.90

match the raw powder very closely. The experiments with 75% (75–25–0) and 100% (100−0−0) of the charge being pre-nucleated material have a slight increase in the granule sizes, as seen by the slight rightward shift of the PSDs. The shift is much more prevalent in the experiments with higher fractions of pre-nucleated material.

3.2. *Liquid addition during mixing*

Fig. 2 shows the PSDs from the experiments in which there was 50 g of additional liquid fed to the granulator during mixing to impose traditional high-shear granulation conditions onto the pre-nucleated granule batches. Similar to Fig. 1, Fig. 2a-d each show the PSD results for a separate type of pre-nucleated granule, and each figure shows the 5 fractions of pre-nucleated material used experimentally. In these trials, additional liquid was dripped in from above with the syringe, producing distinct droplets to keep granules in the single-drop regime. The PSDs are now more heavily weighted at larger size fractions for all scenarios when compared to the scenarios without liquid addition. Regardless of the charge composition or granule formation mechanism used to produce the pre-nucleated material, a significant amount of granular product was produced. The base case in blue (hollow circle), with no pre-nucleated material (0−100−100), depicts traditional high-shear granulation and is the basis for comparison to experiments with pre-nucleated granular material. Similar to the experiments without additional liquid, the size distribution shifts toward the larger granules as a larger fraction of the granulator charge consists of pre-nucleated material. There are no clear distinctions in the PSDs between the different types of pre-nucleated granules used. It is clear that liquid addition during mixing greatly facilitated the production of granules. It is also clear that each PSD is influenced by the ratio of pre-nucleated material to raw powder charged to the granulator prior to granulation, with a higher fraction of pre-nucleated material producing larger granules.

3.3. *Liquid to solid ratio in traditional granulation*

Fig. 3 shows the PSDs of experiments in which traditional high-shear wet granulation conditions occurred. No pre-nucleated material was used in these experiments, and the quantity of liquid added was instead varied between trials. Fig. 3a-d show 20 liquid quantities ranging from 0 g to 95 g of water, in increments of 5 g, split evenly in an increasing fashion across the four plots for clarity. Trials with 100 g of water or

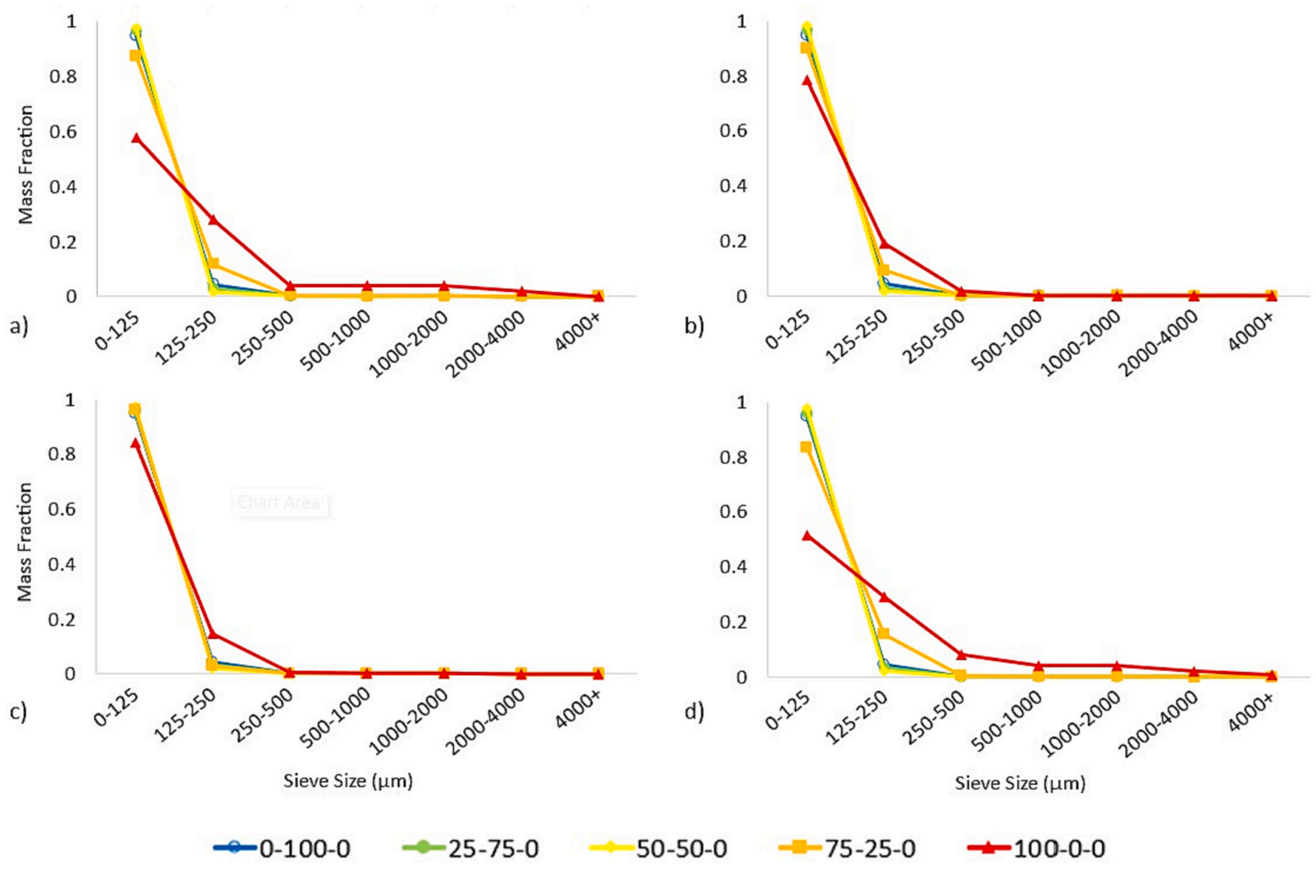

Fig. 1. Sieved particle size distributions for the post-mixing material in which there was no liquid addition during mixing and pre-nucleated granules were: a) small Crater Formation granules (H30), b) small Spreading granules (L30), c) large Crater Formation granules (H14), and d) large Spreading granules (L14). Each plot contains five PSDs, each representing one of the five ratios of pre-nucleated material to raw powder that was charged to the granulator. Cooler colors represent a lower fraction of pre-nucleated material. The blue, hollow circle, lines represent the base case: a trial with no pre-nucleated material. The solid shape warmer colors represent a higher fraction of pre-nucleated material, with the red triangle lines depicting cases with only pre-nucleated material. The legend is given as % Pre-Nucleated Powder - % Raw Powder - % Additional Liquid. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

higher resulted in a slurry and were discarded. The PSDs in Fig. 3a show primarily ungranulated material, while the PSDs in Fig. 3d show primarily over-granulated material. Granular product was obtained for liquid quantities between 25 g (0–100–50) at a liquid to solid ratio of 0.5 and 70 g (0–100–140) at a liquid to solid ratio of 1.40.

3.4. Granule size distribution quantitative analysis

The top portion of Table 4 shows the quantitative statistics for the pre-nucleated material experiment PSDs. Interpolated granule d_{10}, d_{50}, d_{90}, width, and yield values are shown. Liquid to solid ratio is included again for easier comparison. The statistics for the trials in which 25% (25–75–0 XX) and 50% (50–50–0 XX) of the charge to the granulator was pre-nucleated material with no additional liquid look nearly identical to the statistics for the trial representing the original fines (0–100–0), regardless of formation mechanism. For the four 75% (75–25–0 XX) and four 100% (100–0–0 XX) pre-nucleated material 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 liquid addition during mixing produced size distributions made up of granules that were larger than the base granulation case (0–100–100) with no pre-nucleated material. They are also all larger than the trials without additional liquid, as measured by the d_{10}, d_{50}, and d_{90}. The size distribution width was the narrowest for the traditional granulation trial (0–100–100) than any trial with pre-nucleated material.

The bottom portion of Table 4 shows the quantitative statistics for the liquid quantity experiment PSDs. The first increase in granule sizes occurs at 0.5 liquid to solid ratio, or 25 g of liquid (0–100–50). Granule size, width, and yield increase with liquid to solid ratio until 1.0 liquid to solid ratio, or 50 g of liquid (0–100–100), is achieved. Beyond this point, granule size continues to increase, but width and yield decrease as the over-granulated fraction increases.

Fig. 4 graphically shows the quantitative statistics as a function of the total liquid quantity in each granulation batch. Types of pre-nucleated material are shown in color with solid shape data points and trials without pre-nucleated material are shown in hollow black circles. The d_{10}, d_{50}, and d_{90} all increase steadily with liquid quantity for all trials. It can be clearly seen that a larger fraction of pre-nucleated material leads to a larger deviation from the traditional granulation results. Trials with pre-nucleated material show a smaller PSD width and lower yield than traditional granulation of the same liquid content when mixing-stage liquid addition does not occur. When mixing-stage liquid addition does occur, however, the trials with pre-nucleated material show a larger PSD width and higher yield than traditional granulation of the same liquid content.

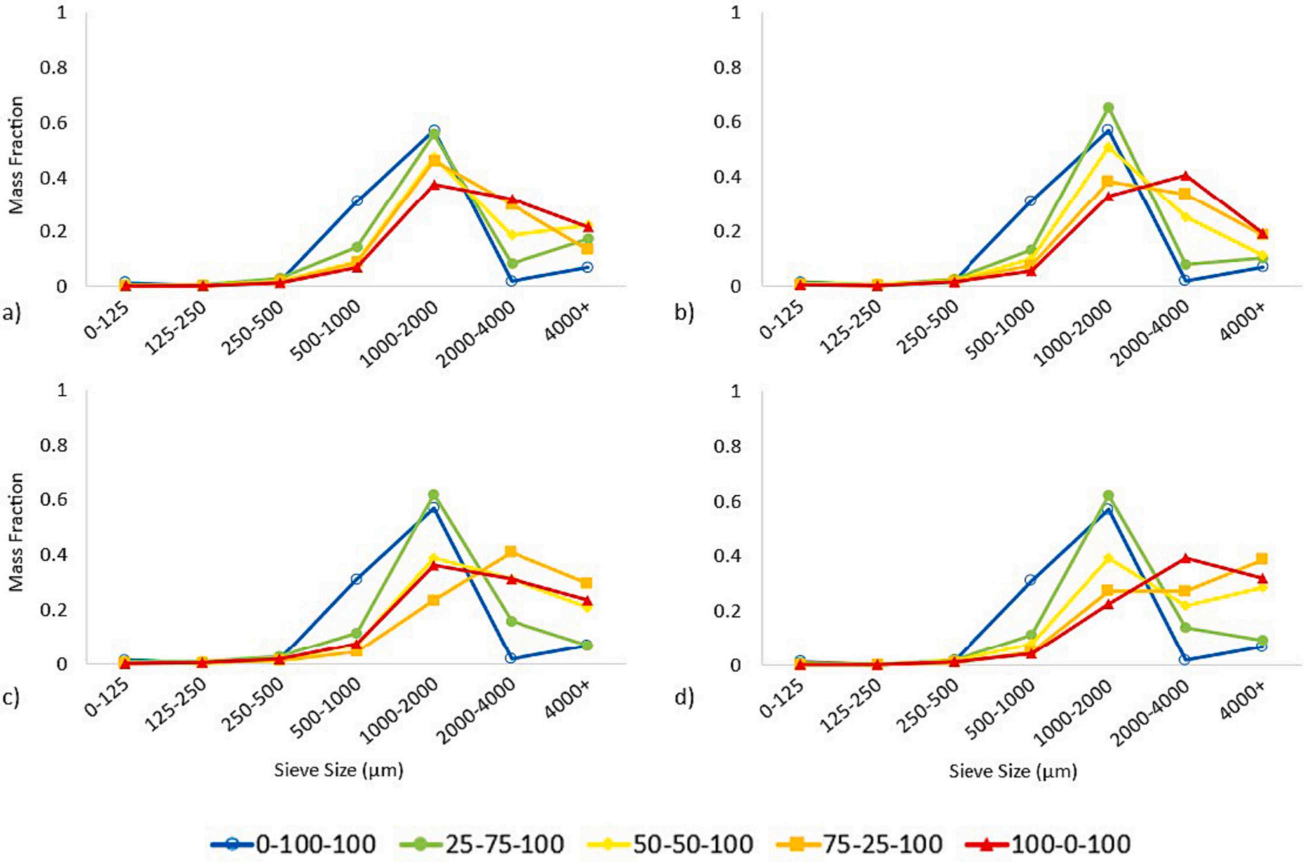

Fig. 2. Sieved particle size distributions for the post-mixing material in which there was 50 g of liquid addition during mixing and pre-nucleated granules were: a) small Crater Formation granules (H30), b) small Spreading granules (L30), c) large Crater Formation granules (H14), and d) large Spreading granules (L14). Each plot contains five PSDs, each representing one of the five ratios of pre-nucleated material to raw powder that was charged to the granulator. Cooler colors represent a lower fraction of pre-nucleated material. The blue, hollow circle, lines represent the base case: a trial with no pre-nucleated material. The solid shape warmer colors represent a higher fraction of pre-nucleated material, with the red triangle lines depicting cases with only pre-nucleated material. The legend is given as % Pre-Nucleated Powder - % Raw Powder - % Additional Liquid. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

4.1. *Effect of pre-nucleated granular material*

The results of the granule size distributions clearly show that the presence of pre-nucleated granules in the granulator charge have a consistent influence on the resulting PSD. It is notable that the pre-nucleated granules are approximately 5–10 mm in diameter, but none of the PSDs in Fig. 1 have granules that large. The lack of large granular product and presence of a high fraction of fines indicate that the pre-nucleated granules are broken down significantly to near fines as soon as agitation begins, likely due to pre-nucleated granules being very frail. The pre-nucleated granule PSDs in Fig. 1 remain practically identical to the baseline until the pre-nucleated granules consist of 75% (75–25–0) or 100% (100–0–0) of the charge composition, which could indicate that the liquid brought in by the pre-nucleated granules is not sufficient to cross the threshold for growth to occur in the 25% (25–75–0) or 50% (50–50–0) cases. This idea is supported by Fig. 4a-c, which show that neither traditional granulation trials nor pre-nucleated material trials exhibited any deviation from fines until at least 20 g of liquid (0.4 liquid to solid ratio) was present in the charge. Due to the sieve bin limitations, it is possible that growth occurred within the fines bin for these trials, but could not be quantified with the equipment used. The lack of growth at low fractions of pre-nucleated material could also indicate that the pre-nucleated granule pieces are better suited to coalesce without the presence of fines.

The four plots in Fig. 2 show each of the four pre-nucleated granule types under conditions in which 50 g of liquid addition occurs during mixing. Unlike the trials in Fig. 1, any fraction of pre-nucleated material charged to the granulator resulted in a shift of the PSD toward larger granule sizes, with a larger fraction of pre-nucleated granules leading to a larger size shift. The PSDs appear to broaden with the addition of pre-nucleated granules; however, due to the limitations of large bins available, a full distribution is not obtained and cannot be fully characterized. This directly opposes the hypothesis that single-dropped granules will narrow the granule size distribution. These trials with liquid addition during mixing resulted in a higher yield than the trials without liquid addition during mixing.

There is a clear trend across all of these trials that a larger fraction of pre-nucleated granules produces larger-sized granules. In examining the batch yields, the trials without additional liquid all had a yield less than 0.5, and the trials with additional liquid all had a yield higher than 0.6. This indicates that pre-nucleated material performs better under granulation conditions in which there is further liquid addition during agitation, rather than having pre-nucleation function as the only wetting process. It is hypothesized that some of the yield values may be smaller than the true values due in part to the classification of the largest bin as over-granulated material, which was excluded from the yield. Due to the trend that granule size increases with pre-nucleated material fraction, material in the largest bin may just be large granules, rather than over-granulated material.

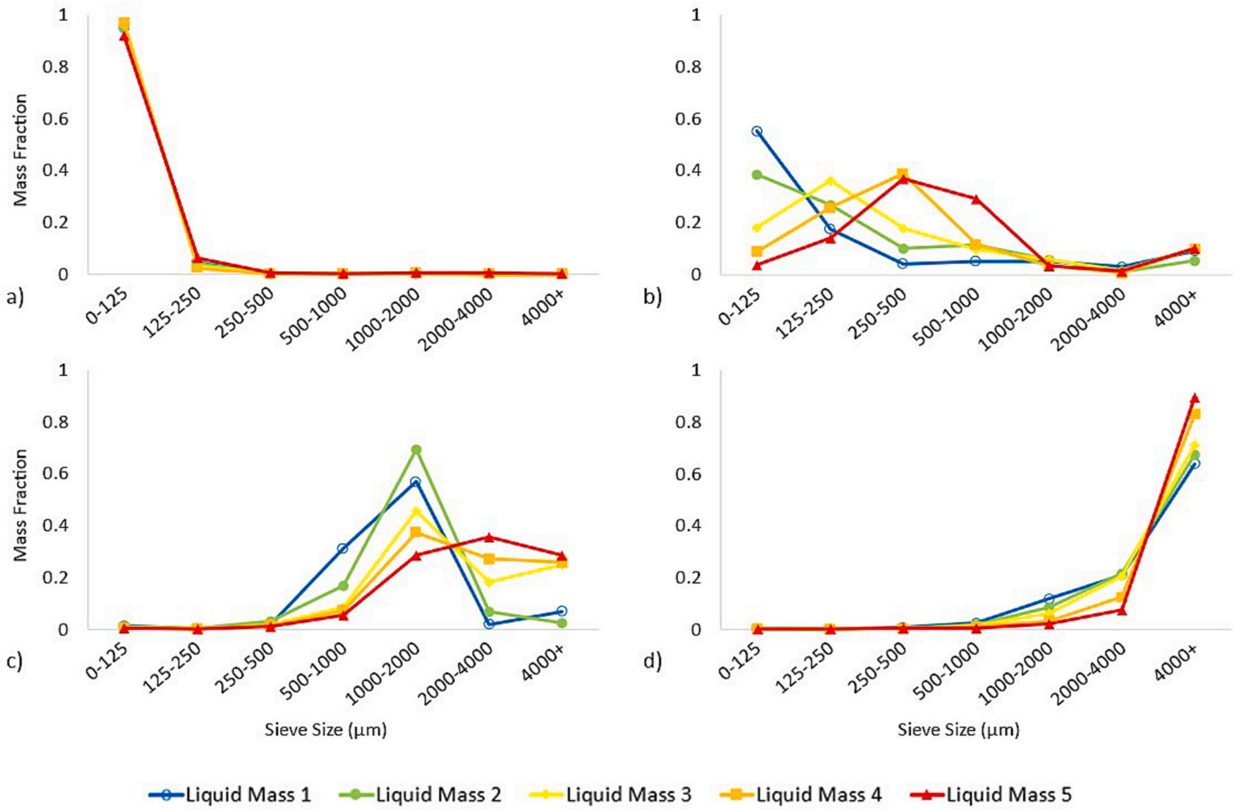

Fig. 3. Sieved particle size distributions for the post-mixing material in which the amount of liquid addition during mixing was varied from 0 g to 95 g in increments of 5 g, and no pre-nucleated material was used. The plots show five liquid addition masses ranging from: a) 0–20 g, b) 25–45 g, c) 50–70 g, and d) 75–95 g. On each plot, Liquid Mass 1 is the smallest amount of liquid and Liquid Mass 5 is the largest amount of liquid.

4.2. Pre-nucleation granule size and formation mechanism effects

While the presence of pre-nucleated material in a batch had a clear impact on the resulting granular product, the pre-nucleated granule sizes, liquid to solid ratios, and formation mechanisms had no dominant impact on the resulting batch PSDs. It was hypothesized that the size or formation mechanism for the pre-nucleated granules might provide varied macro-scale internal structures, which would lend advantages for certain types of pre-nucleated material during the agitation process. This hypothesis is not supported by the data collected, as it is likely that the high-shearing process disrupted any potential macro-scale internal structures for the pre-nucleated material.

4.3. 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. Pre-nucleated granules were generated under four different conditions that led to significant differences in the resulting material. Two liquid drop sizes resulted in large and small granules, while two liquid drop heights resulted in Spreading and Crater Formation granules. All physiochemical properties and wetting conditions were identical except the size and velocity of the impacting 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. Each set of pre-nucleated granules had a very narrow size distribution, 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 pre-nucleated granules had no agitation or shear upon formation to promote consolidation or densification, leaving them extremely frail. The breakage retained some bulk properties of the original pre-nucleated granules, like density and liquid to solid ratio, but due to the pseudo-stochastic 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 batches with pre-nucleated material in Fig. 1 did not result in 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 into 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 prior to being charged to the mixer granulator. 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

Table 4
Quantitative statistics for the granule size distributions of each experiment. The top portion is for the pre-nucleation experiments, and the bottom portion is for the added liquid experiments. The naming convention used is % Pre-Nucleated Powder - % Raw Powder - % Additional Liquid - Pre-Nucleated Granule Type (L/H for low or high drop heights and 14/30 for 14-gauge or 30-gauge needle tips).

Designation	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	Width	Yield	Batch liquid to solid ratio (m_{liquid}/m_{solid})
25-75-0 H30	13	65	117	1.60	0.03	0.19
25-75-0 L30	13	65	116	1.60	0.03	0.18
25-75-0 H14	13	65	117	1.60	0.04	0.20
25-75-0 L14	13	65	117	1.60	0.04	0.21
25-75-100 H30	709	1565	5711	3.20	0.82	1.19
25-75-100 L30	730	1504	4000	2.17	0.89	1.18
25-75-100 H14	769	1558	3595	1.81	0.93	1.20
25-75-100 L14	796	1570	3891	1.97	0.90	1.21
50-50-0 H30	13	64	115	1.60	0.02	0.38
50-50-0 L30	13	64	114	1.60	0.02	0.35
50-50-0 H14	13	64	116	1.60	0.03	0.40
50-50-0 L14	13	64	115	1.60	0.02	0.42
50-50-100 H30	905	1807	6203	2.93	0.77	1.38
50-50-100 L30	865	1732	4420	2.05	0.88	1.35
50-50-100 H14	1022	2130	6092	2.38	0.79	1.40
50-50-100 L14	1000	2061	6605	2.72	0.71	1.42
75-25-0 H30	14	71	152	1.93	0.13	0.57
75-25-0 L30	14	69	122	1.56	0.10	0.53
75-25-0 H14	13	65	117	1.60	0.04	0.60
75-25-0 L14	15	75	176	2.16	0.16	0.63
75-25-100 H30	956	1853	5000	2.18	0.86	1.57
75-25-100 L30	1010	2127	5847	2.27	0.81	1.53
75-25-100 H14	1167	3004	6647	1.82	0.70	1.60
75-25-100 L14	1131	3184	6971	1.83	0.61	1.63
100-0-0 H30	22	108	498	4.40	0.42	0.76
100-0-0 L30	16	79	198	2.29	0.21	0.71
100-0-0 H14	15	74	174	2.15	0.16	0.80
100-0-0 L14	24	121	616	4.88	0.48	0.84
100-0-100 H30	1026	2224	6151	2.30	0.78	1.76
100-0-100 L30	1077	2481	5924	1.95	0.80	1.71
100-0-100 H14	1018	2292	6293	2.30	0.76	1.80
100-0-100 L14	1192	3094	6756	1.80	0.68	1.84
0-100-0	13	66	119	1.60	0.05	0.00
0-100-10	13	66	118	1.60	0.05	0.10
0-100-20	13	65	117	1.60	0.04	0.20
0-100-30	13	65	116	1.60	0.03	0.30
0-100-40	14	68	122	1.60	0.08	0.40
0-100-50	23	113	3520	30.92	0.35	0.50
0-100-60	32	178	1429	7.84	0.56	0.60
0-100-70	68	234	4044	16.96	0.72	0.70
0-100-80	130	348	4057	11.29	0.81	0.80
0-100-90	179	465	4114	8.46	0.86	0.90
0-100-100	610	1276	1978	1.07	0.92	1.00
0-100-110	664	1414	1991	0.94	0.96	1.10
0-100-120	921	1846	6386	2.96	0.74	1.20
0-100-130	1011	2223	6452	2.45	0.74	1.30
0-100-140	1093	2793	6602	1.97	0.71	1.40
0-100-150	1558	4865	7373	1.20	0.36	1.50
0-100-160	1878	5037	7407	1.10	0.32	1.60
0-100-170	2156	5182	7436	1.02	0.29	1.70
0-100-180	2855	5587	7517	0.83	0.17	1.80
0-100-190	3833	5762	7552	0.65	0.10	1.90

with fresh powder. The wetting in these scenarios with additional liquid are very similar to traditional granulation, with the primary difference being that the batches with pre-nucleated granules have liquid content to begin with, but this type of re-wetting 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.

4.4. 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 that 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 pre-nucleated granules, some trials were conducted that contained only pre-nucleated granules, while others were conducted with a mixture of pre-nucleated granules and fines. Since agitation was kept constant across trials, consolidation was expected to be present, facilitating the growth mechanisms.

Trials that contained only pre-nucleated granules were expected to grow primarily via coalescence due to the lack of fines to facilitate layered growth. The presence of breakage may generate some fines, but, in the ideal case, this is considered negligible. The trials that contained a mixture of pre-nucleated granules and fines were expected to experience layered growth as well as coalescence. Layered growth was expected to be nearly exclusive in the trials with low amounts of pre-nucleated 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 pre-nucleated 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 pre-nucleated granules present produced larger granules than the trials with fewer pre-nucleated 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. Fig. 5 shows three granules that were produced in the same batch (100–0–100 L14) with only pre-nucleated 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

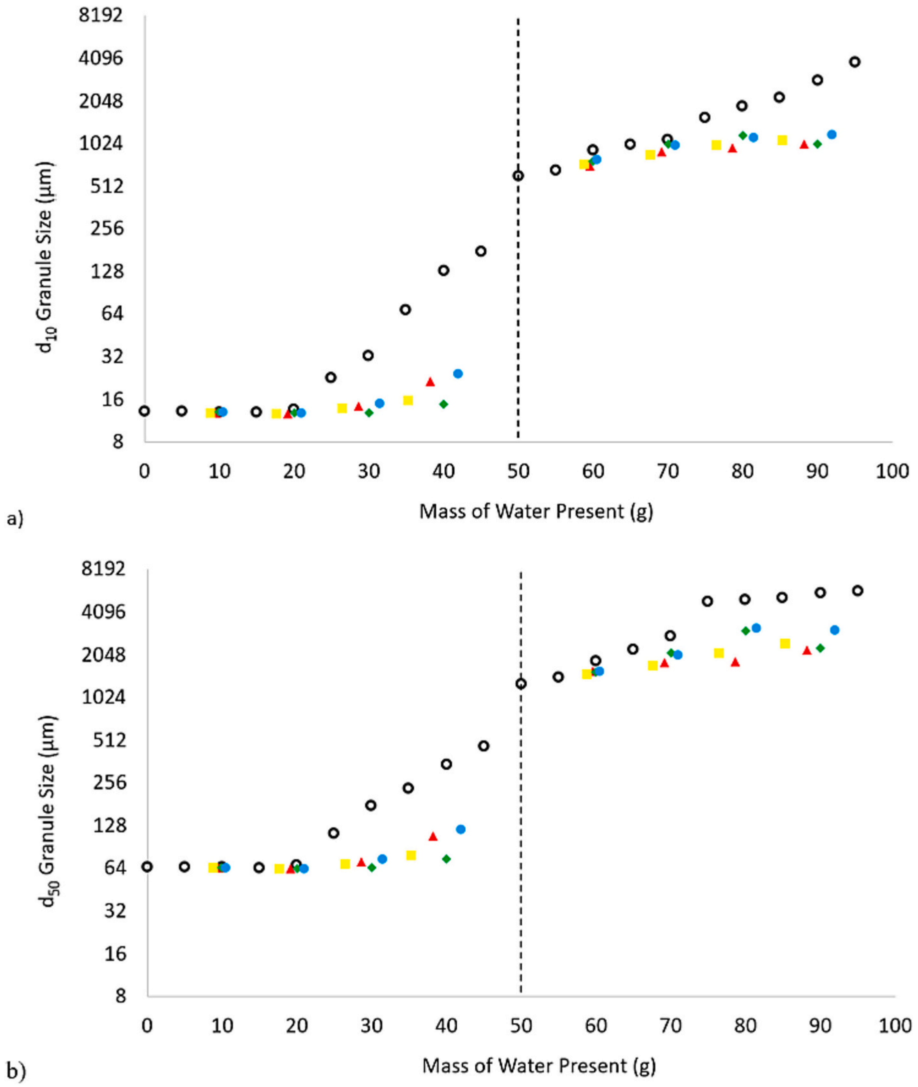

Fig. 4. a) d_{10}, b) d_{50}, c) d_{90}, d) granule size distribution width, and e) batch yield for all experiments. Graphs are shown on the basis of total water mass present in the system. Trials with any fraction of pre-nucleated material are shown in solid color shapes and trials without pre-nucleated material are shown in hollow black circles. The pre-nucleated material percentage resets down to 0% after the 50 g marker. At smaller water masses, the pre-nucleated trials are those without liquid addition, and at larger water masses, the pre-nucleated trials are those with liquid addition.

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 PSDs.

4.5. 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 assumes 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.

4.6. Liquid to solid ratio

A primary confounding factor that needed to be 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 [16–19]. Pre-nucleated material contains a significant amount of liquid within it, as shown by the liquid to solid ratio in Table 2. With higher fractions of pre-nucleated material, the overall system contains more liquid, as shown by the liquid to solid ratios in Tables 3 and 4. This means that the pre-

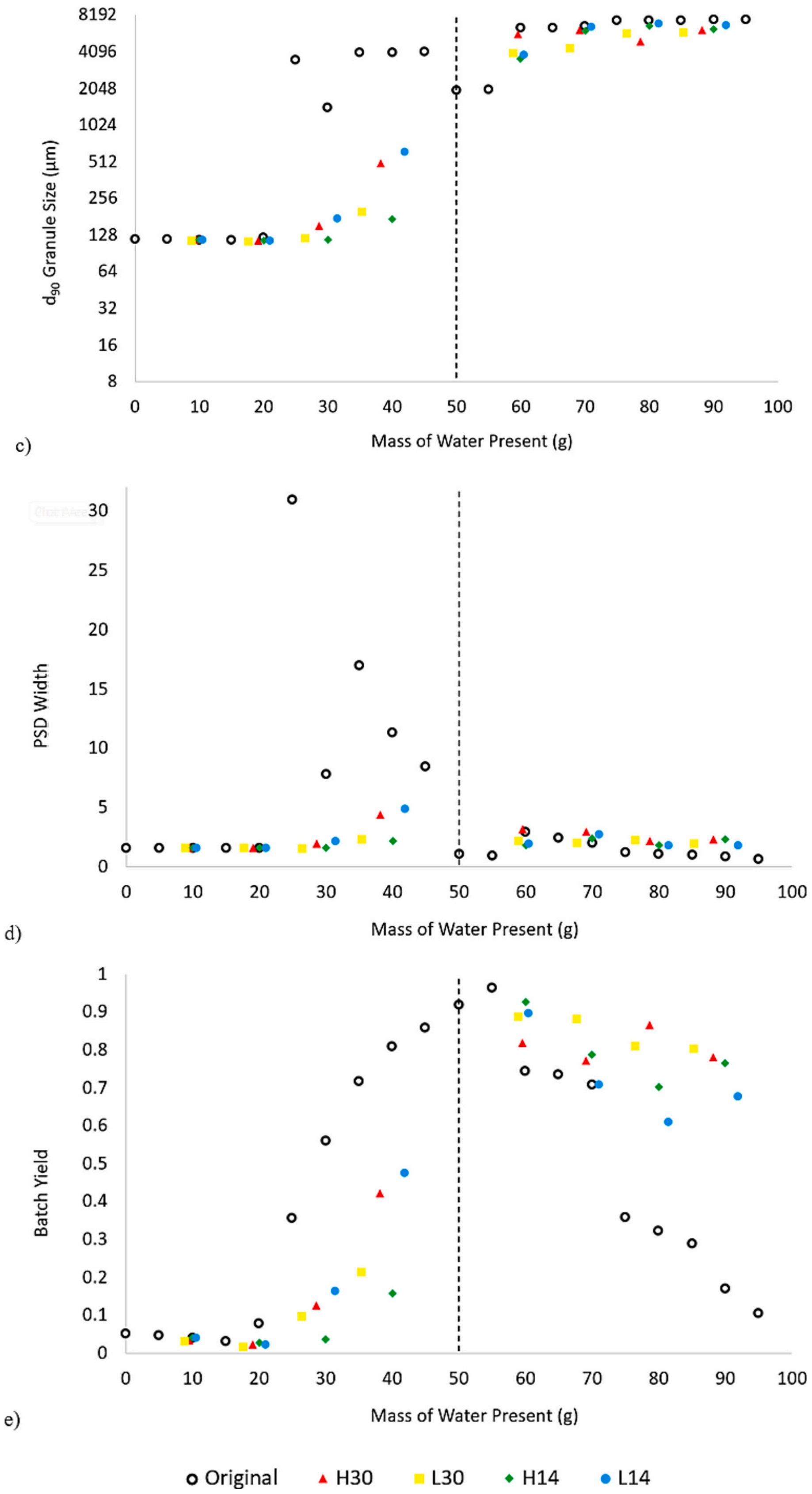

Fig. 4. (*continued*).

Fig. 5. Three granules from the 100–0–100 batch of large 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.

nucleation experiments conducted have a broad range of liquid to solid ratios, ranging from 0.0 all the way to nearly 1.8. To evaluate this alternative explanation for the effectiveness of pre-nucleated material, a direct comparison to traditional granulation trials with varied liquid contents was necessary. Since the pre-nucleation experiments spread across a wide range of liquid to solid ratios, twenty liquid quantities were added in the form of traditional wet granulation for comparison, seen in Fig. 3. As mentioned before, Fig. 3a shows that negligible PSD growth occurs for liquid to solid ratios less than 0.4, and Fig. 3d shows that over-granulation dominates for batches with a liquid to solid ratio greater than 1.5. Fig. 4 shows the characteristic statistics for comparison on the basis of total liquid quantity. The left half of Fig. 4 shows the comparison of pre-nucleation trials without liquid addition during mixing to the corresponding liquid quantities in traditional granulation. With increasing liquid content in the pre-nucleation batches corresponding to a higher fraction of pre-nucleated material, this also results in a larger deviation from the traditional granulation's liquid quantity trials. A larger fraction of pre-nucleated material, and corresponding larger liquid content, shows a larger deviation from the traditional granulation statistics. The right half of Fig. 4 shows the comparison of pre-nucleation trials with liquid addition during mixing to the corresponding liquid quantities in traditional granulation. These pre-nucleation trials had 50 g of liquid addition as well as the liquid in the pre-nucleated material. In comparing these trials to the corresponding traditional granulation trials, the same trend is observed: a larger fraction of pre-nucleated material leads to a larger deviation from the traditional granulation results.

While the higher liquid quantity present in pre-nucleated material corresponds to some larger growth in the PSD, it does not represent the full extent of behavior of batches with pre-nucleated material. Fig. 4a-c clearly show that the presence of pre-nucleated material leads to a clear and consistent deviation from the results that would be obtained if the phenomena were solely due to the excess liquid content. From these plots, it is evident that there is more at play than just liquid to solid ratio confounding. The trials containing pre-nucleated granules consistently show that they maintain smaller particle sizes when compared to traditional granulation of the same liquid amount. This could indicate that the presence of pre-nucleated granules increases the liquid carrying content of the granulation batch. This might be significant in the pharmaceutical industry for charging granules with higher doses of liquid-bound medicine. Additionally, in examining the d_{50} plot in Fig. 4b, it is clear that the batches with pre-nucleated granules are much slower to reach total over-granulation. When traditional granulation transitioned from growth into over-granulation, the batches with pre-nucleated granules at similar liquid to solid ratios continued to be in the growth regime. The distribution of PSD widths in Fig. 4d show little deviation between traditional granulation techniques and pre-nucleation. At larger liquid contents, the pre-nucleated batches are shown to have slightly wider PSDs than the traditional granulation batches; however, the narrowness of the traditional granulation batches is likely due to the excessive over-granulation that is occurring. This data does not support the hypothesis that pre-nucleation of granules will produce a narrower PSD. The plot of yields in Fig. 4e shows that the pre-nucleated granule batches lag behind the trend of the traditional granulation batches. The yield is slower to increase at lower liquid contents; however, it is also slower to decrease at higher liquid contents. This aligns with the hypothesis that the presence of pre-nucleated granules increases the liquid carrying capacity of the granulation batch. The pre-nucleated granule batches require more liquid to break away from the fines bin; however, as they reach high liquid contents, they are much slower to become over-granulated. It is hypothesized that the liquid distribution and re-wetting in the system are the causes for the deviations, and further experimentation is necessary to explore these hypotheses.

4.7. *Implications and applications*

The goal of this work has been to utilize rate process separation to better understand the high-shear wet granulation process and explore the potential uses of pre-nucleated granules. Several results with implications on the study of high-shear wet granulation have been observed. Fig. 4d and Table 4 demonstrate that all of the batches containing pre-nucleated granules resulted in a larger PSD width than the batches without pre-nucleated granules. This directly opposes the theory that single drop granulation will influence a narrower granule size distribution. Fig. 1 provides some insight into this, demonstrating the fragility of pre-nucleated granules compared to the high-sheared granular product. While the pre-nucleated granules should have been 5–10 mm in size, the granule size distributions in Fig. 1 are nearly that of fines, indicating that the pre-nucleated granules were completely broken up after 2 min of wet massing. This implies that single drop nuclei, even when added via traditional liquid addition, will experience breakage on a near-immediate timescale upon being formed.

Another significant result from this work is that there may be a minimum liquid to solid ratio necessary for the size enlargement rate processes to outcompete the destructive rate processes. Fig. 4a-c demonstrate that negligible size enlargement occurs with a liquid to solid ratio lower than 0.4, regardless of liquid addition mechanism. These figures also demonstrate that batches with pre-nucleated granules experience size enlargement driven by liquid content at a slower rate than batches with traditional granulation. This opens the door to the use of pre-nucleation to obtain granules with a higher liquid content without increasing the granule size, including for the purpose of minimizing overgranulation.

The higher liquid loading capability brought about by the use of pre-nucleation has a practical application in the manufacturing of higher dosage tablets in which the active pharmaceutical ingredient (API) is liquid bound. A liquid carrier that is fully saturated with API would be able to achieve a higher dose without having to sacrifice an ideal granule size or utilizing a more expensive liquid carrier. Pre-nucleation can also improve material usage efficiency. Fig. 4e demonstrated that in all scenarios where pre-nucleation was coupled with traditional liquid addition, the batch yield was higher than the corresponding trials in which the same amount of liquid was added via traditional overhead means. Primarily due to the decrease in overgranulation, more material was retained for use, reducing the amount of waste material and increasing the product yield. Lastly, the use of pre-nucleated granules offers an additional mechanism through which to control granule properties. As demonstrated in Fig. 4a-c, the rate of size enlargement corresponding to an increase in liquid content is much smaller for pre-nucleated granule batches than traditional granulation batches, which allows for much more precise control over the product granule size and larger margin of error in a production plant.

5. Conclusions

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 batch material that is composed of pre-nucleated material. Charging a larger fraction of pre-nucleated granules to the granulator results in larger granule sizes. It is also concluded that the different pre-nucleation types failed to show a direct influence on the resulting granular PSD. Future work will include in-depth characterization of these granular results for desirable qualities such as tabletability, compaction characteristics, drug loading capability, and porosities. Furthermore, the poor performance of pre-nucleated material without additional liquid reflects the difficulty in isolating the granulation rate processes. Liquid addition during mixing reintroduces the Wetting & Nucleation rate process, and the trials without liquid addition during mixing demonstrate poor Consolidation & Growth behavior. Lastly, liquid to solid ratio is clearly eliminated as the sole cause for the behavior shown in these experiments, though it is likely to lend a contributing influence. In conclusion, pre-nucleation has been demonstrated to produce a measurably different result from traditional granulation processes and shows potential for use as an additional control factor in granular material production. This study on pre-nucleation has furthered our understanding of the drop-controlled nucleation regime as well as the identification of a critical liquid to solid ratio needed for size enlargement to occur. Pre-nucleation has also been identified to have potential applications with respect to liquid dosing in granules, granule size control, and efficient material usage.

CRediT authorship contribution statement

Diana S. Kumar: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sarang Oka:** Methodology, Validation, Writing – review & editing. **Heather N. Emady:** Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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