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Scaling of Continuous Twin Screw Wet Granulation

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Abstract

Scaling rules were developed and tested for a continuous twin screw wet granulation process using three scales (11mm, 16mm and 24mm barrel diameter) of twin screw granulators (TSG). The distributive feed screw (DFS) configuration used produced high porosity granules (50-60%) with broad bimodal size distributions, especially in the 16mm and 24mm TSGs. Three dimensionless numbers, Froude number (*Fr*), liquid-to-solid ratio (*LSR*), and powder feed number (*PFN*), were identified and their effect on granule size distribution, porosity and liquid distribution tested. Granule size increased with increasing *LSR* as expected. However, *Fr* and *PFN* had no significant effect on d_{10} or d_{50} and only a small effect on d_{90}. In contrast, granulator scale had a strong effect on granule size distribution, with d_{90} increasing almost linearly with barrel diameter. This is consistent with breakage of large granules being a dominant mechanism and directly controlled by the geometry of the screw.

Keywords: twin screw granulation, continuous manufacturing, powders, scaling

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Introduction

Powder processing is critical in many industries including catalysts, pharmaceuticals, agrochemicals and minerals. In the pharmaceutical industry more than 75% of the final products are in solid dosage forms.[1] The high quality required in pharmaceutical products calls for the understanding of their manufacturing processes and their impact on intermediate and final product properties.[2] In the past several years, there have been advances in process understanding, along with the expansion of continuous manufacturing, in the pharmaceutical industry driven by several initiatives by regulatory agencies and pharmaceutical companies.[3,4]

There are three common manufacturing routes for pharmaceutical solid dosage forms - direct compression, dry granulation and wet granulation. For continuous wet granulation, twin screw wet granulation (TSG) has emerged as an alternative to batch granulation. In general, some of the advantages of continuous processing over batch processing include reduced equipment size, reduced development time using a smaller amount of the active pharmaceutical ingredient (API), increased controllability and ability to integrate process analytical tools (PAT).[5,6] In comparison to batch granulation, TSG provides the optimum throughput necessary in pharmaceutical manufacturing, is flexible in design and has been shown to have regime-separated granulation rate processes, i.e. wetting and nucleation, breakage and attrition, and layering and consolidation, along the length of the TSG.[7,8]

One of the advantages of continuous processing as a whole is that it might require limited scale-up since the amount of processed material can be increased by simply augmenting the total throughput (powder flow rate) and/or extending the processing time at one scale. While this is true, the reality is that different scales of continuous processing equipment exist and are needed. Different equipment scales are used depending on total throughput of the processed material as well as the stage of development: early development, clinical trials or commercial scale manufacturing. While several researchers have studied the influence of TSG processing parameters (powder flow rate, liquid flow rate and screw speed) on granule properties (size distribution, shape, porosity and strength), their findings are applicable only to the equipment scale on which the experiments were conducted. This could potentially lead to difficulties during scale up if the granule attributes are not preserved.[9,10] Djuric *et al.* compared two twin screw granulator scales (19mm and 27mm) using a full factorial design by varying the total powder flow rate and screw rotation rate. Although these studies considered the Froude number and the screw speed, neither parameter was held constant during scale up.[11] Nevertheless, the main results showed that a higher percentage of fines (granules < 125 μm) was obtained in the small scale granulator (D = 19mm) while a higher percentage of over-sized granules (> 3150 μm) was obtained in the large scale granulator (D = 27mm). To the best of our knowledge, this is the only published work comparing different TSG scales.

In addition, the powder flow rate, often used as a scaling parameter, has been shown to have an influence on granule attributes.[12] The powder flow rate largely determines the fill level of the powder inside the TSG barrel. Higher powder flow rates lead to greater compaction and densification of the powder in the TSG barrel, affecting the size, shape, strength and porosity of the granules.[10,12,13] Djuric *et al.* showed that the median granule size (d_{50}) increased with increasing total powder flow rate, especially for the larger granulator. In a different study, Dhenge *et al.* found the effect of flow rate to be the opposite, where the granule size decreased with increasing flow rate.[10] The differences in results could be due to the different screw configurations used in the studies. On the other hand, several studies have shown the screw speed to have only minor effects on the granule properties.[12,13] At a given powder feed rate, screw speed affects the residence time and fill level in the granulator. Dhenge *et al.* found more compaction of the granules at low screw speeds, resulting in smoother and more spherical granules.[5]

One of the advantages of TSG is the flexibility in design, including a wide range of possible screw elements and screw configurations to be used. Most screw elements and configurations used in TSG have been adopted from hot melt extrusion, which was the original purpose of a twin screw machine. With this in mind, the effects of screw elements (e.g. conveying elements, kneading elements, distributive mixing elements, and distributive feed screw) and screw configurations on granule properties have been studied by several researchers. Conveying elements (CEs) have been shown to yield bi-modal granule size distributions and highly porous granules.[8,14,15] Kneading elements (KEs), depending on their orientation, can behave similarly to CEs (offset angles of 30° and 60° in the forward direction), or very differently (offset angle of 90°) by forcing the material against the direction of the flow leading to less fines in the granulation as well as highly dense, elongated-shaped granules.[7,16,17] Distributive mixing elements (DMEs) were shown to yield highly porous granules and mono-modal granule size distributions with a large fraction of the granules between 100 to 1000 µm.[18] The distributive feed screw (DFS) has been studied relatively less than other screw elements.[8] We recently reported the effect of DFS on granule properties in an 11-mm TSG.[16] The DFS behave similarly to CEs, yielding bimodal granule size distributions and highly porous granules at the process parameters used. The DFS had not been characterized for the 16mm and 24mm TSGs used in these studies.

The main objective of this work was to identify the key dimensionless groups that control granule properties and develop a model to map the operating space of three geometrically similar twin screw granulators: 11mm, 16mm, and 24mm diameter. While the process parameters themselves are scale dependent, these dimensionless groups are scale independent. Consequently, three dimensionless groups for scaling were identified and tested. These were the liquid to solid ratio (*LSR*), Froude number (*Fr*), and the powder feed number (*PFN*). A distributive feed screw (DFS), otherwise known as combing elements[8], was used as part of the screw configuration in all three TSG scales. A wet granulated immediate release formulation was used to test the dimensionless groups in this article. The work applies specifically to wet granulation systems, rather than hot melt extrusion. Granulation properties, namely granule size distribution (GSD) and metrics (d_{10}, d_{50}, and d_{90}), granule porosity, and liquid distribution as a function of scaling (processing) parameters were compared for all three TSG scales in this study.

Developing potential scaling rules using dimensional analysis

Consider the process parameters that are available to vary when scaling a twin screw granulation process: $D, \omega, L, g, \dot{m}_p, \dot{m}_l, \rho_b, F_1, F_2, \ldots$, where D is the barrel diameter, ω is the angular velocity of the shaft, L is the barrel length after wetting addition of liquid, $\dot{m}_p$ *and* $\dot{m}_l$ are the mass flow rates of the powder and liquid respectively, ρ_b is the bulk density of the powder and $F_1, F_2, \ldots$ are a series of geometric ratios that describe the geometry of the individual screw elements and the screw configuration.

The granule attributes of interest are parameters of the granule size distribution (d_{10}, d_{50}, d_{90}, etc.), the granule porosity (ε) and the liquid distribution (*LD*). In general, we can write:

$$d_{50} = f_1(D, \omega, L, g, \dot{m}_p, \dot{m}_l, \rho_b, F_1, F_2, \ldots) \quad [1]$$

$$\varepsilon = f_2(D, \omega, L, g, \dot{m}_p, \dot{m}_l, \rho_b, F_1, F_2, \ldots) \quad [2]$$

and so on. Applying the principles of dimensional analysis, these functions in terms of controlling dimensionless groups can be reframed:

$$\frac{d_{50}}{D} = g_1\left(LSR, PFN, Fr, \frac{L}{D}, F_1, F_2, \dots\right) \qquad [3]$$

$$\varepsilon = g_2\left(LSR, PFN, Fr, \frac{L}{D}, F_1, F_2, \dots\right) \qquad [4]$$

where LSR is the liquid to solid ratio:

$$LSR = \frac{\dot{m}_l}{\dot{m}_p} \qquad [5]$$

PFN is the powder feed number:

$$PFN = \frac{\dot{m}_p}{\rho_b \omega D^3} \qquad [6]$$

and Fr is the Froude number:

$$Fr = \frac{D\omega^2}{2g} \qquad [7]$$

Note that formulation properties in this analysis have been neglected on the assumption that these will not be changed during scale up. Further, if scale up will be undertaken by keeping important geometric ratios similar (length to diameter ratio - L/D - for the whole TSG and for each screw element used, and the relative size of the cut out sections in the DFS), eqns. 3 and 4 can be simplified to:

$$d_{50} = D . g_1(LSR, PFN, Fr) \qquad [3a]$$

$$\varepsilon = g_2(LSR, PFN, Fr) \qquad [4a]$$

Note that this analysis suggests that parameters of the particle size distribution may be a function of scale (TSG barrel diameter) as well as LSR, PFN and Fr. While this analysis is performed purely on the basis of dimensional analysis, the physical significance of the different dimensionless groups can be also investigated. The liquid to solid ratio (*LSR*) is always a critical parameter in wet granulation. At low *LSR*, the granule size distribution is developed through a combination of nucleation, breakage and powder layering with the fines to lump ratio directly related to *LSR*. At higher *LSR*, coalescence and extruded granules are observed.[19,20]

The powder feed number (*PFN*) is proportional to the ratio of volumetric feed rate to the turnover of volume in the shaft due to the screw rotation. It is therefore related to the fill level in a particular screw element. For any element, the rate of volume turnover is:

$$\dot{V} = F_1 D^2 (\frac{\omega}{2\pi}) L_{elem} \quad [8]$$

where L_{elem} is the length an element pushes material forward during one screw rotation, and F_1 is a geometric ratio related to the fraction of free cross sectional area of the barrel after accounting for the shaft and screw element:

$$F_1 = \frac{A_{elem}}{D^2} \quad [9]$$

where A_{elem} is free the cross-sectional area of the element perpendicular to the barrel length calculated from the CAD file for the element used. The length to diameter ratio of an element is also a known geometric ratio:

$$F_2 = \frac{L_{elem}}{D} \quad [10]$$

The net forward velocity of powder (v_p) will be lower than the screw flight due to slip of the powder against the screw element surface as well as back mixing. We define:

$$F_3 = \frac{2\pi v_p}{\omega L_{elem}} \quad [11]$$

Thus the fractional fill level in a screw element is:

$$\phi = \frac{\dot{m}_p/\rho_b}{F_1F_2F_3\omega D^3} = \frac{1}{F_1F_2F_3}PFN \qquad [12]$$

For example, for the simple conveying elements used in this study, $F_1 = 0.45$ and $F_2 = 1$. If we estimate $F_3 = 0.5$, for the center point conditions used in this paper, $PFN = 0.0130$ and $\phi \approx 0.36$. Note that F_3 may vary with powder flow rate and therefore *PFN*. If F_3 is independent of *PFN* it implies that powder residence time is independent of flow rate.

The Froude number (*Fr*) is important for high shear mixer granulators where the balance between gravity and centripetal force establishes the flow field in the granulator. It is unclear whether *Fr* will have a significant effect on powder flow in the confined barrel of the TSG. Note that the screw element diameter should be used as the diameter *D* in the above analysis. In practice, however, the clearance between the screw elements and the barrel wall is small, approximately 2.6% of the barrel diameter. For simplicity, we used the barrel diameter for the diameter dimension *D* in this paper.

Materials and Methods

Materials and Equipment

A placebo formulation composed of α-lactose monohydrate (73.5% w/w), microcrystalline cellulose (20% w/w), hydroxypropylmethyl cellulose (5% w/w) and croscarmellose sodium (1.5% w/w) was used in this study. This is the same formulation used in studies of rate processes in the 16mm twin screw granulator.[17,18] Size parameters of the blend components and blend are given in Table 1. For the 11mm TSG experiments, the dry blend was pre-mixed using a Turbula® T2F mixer (Glen Mills Inc., New Jersey, USA) in batches of 500 g for 20 min at 46 RPM. For the 16mm TSG experiments, a Plough mixer (Processall Inc., Cincinnati, OH, USA) was used to blend the dry materials in batches of 1000 g for 5 min at the impeller speed of 200 RPM. For the 24mm TSG experiments, a 30-L BV030 tote blender (Pharmatech, Warwickshire, UK) was used to pre-mix the dry formulation in batches of 8000 g for 15 min at 12 RPM. The batches of formulation used for experiments at each scale were prepared using available blenders at the locations where each twin screw granulator was located. Standard rotation rates and total blending times were used for each blender to obtain uniform blends.

The pre-mixed formulation was fed into twin screw granulators of three different sizes. These were the Process 11mm (with a ratio of 40 to 1 of the total granulator length (L_{TSG}) to the granulator diameter (D)), EuroLab 16mm TSG (25:1 L_{TSG}:D), and Pharma 24mm (40:1 L_{TSG}:D) (Thermo Fisher Scientific, Karlsruhe, Germany). Pictures of the distributive feed screw (DFS) and the screw configuration used in these experiments are shown in Figure 1. All screw elements were supplied by Thermo Fisher Scientific as well.

A Brabender DDSR20 volumetric feeder (Brabender-Technologie, Germany) was used for the 11-mm TSG experiments. A gravimetric calibration for the placebo blend used was created yielding a linear correlation (R^2=0.9997) between the powder mass flow rate and the controller input. Gravimetric Brabender feeders, FW18 and FW40, were used to feed the formulation into the 16mm and 24mm TSGs, respectively. The granulating liquid was composed of 0.1% (w/w) aqueous solution of nigrosin black dye. Granulation liquid was fed into the granulators at different feed rates to achieve liquid to solid ratios (*LSR*) of 0.15, 0.20, 0.25 and 0.30. For the 11mm (Thermo Fisher Scientific, Karlsruhe, Germany) and 16mm (Cole Parmer, Vernon Hills, IL, USA) TSGs, peristaltic pumps were used. For the 24mm TSG, a loss-in-weight Thermo liquid feeder with a Watson Marlow pump head (Wilmington, MA, USA) was used. The powder feeders and liquid feeders (pumps) were calibrated before each experimental run every day. In this case, a fairly free-flowing blend was used with water as the granulating liquid. For the 11mm TSG experiments, the powder feeder yielded a variability (relative standard deviation - RSD) of 9.67% for the low flow rates (~1 kg/hr) and 1.3% for the high flow rates (~5 kg/hr). One representative sample for each experiment run in all three TSGs was taken and analyzed for moisture content using a moisture analyzer (Mettler Toledo Deluxe Halogen). Ultimately, the measured *LSR* was quantified and plotted against the theoretical *LSR* values. The difference between the measured *LSR* and the theoretical *LSR* was considered. For sake of brevity, these figures were omitted from the manuscript. In summary, the measured *LSR* was close to the theoretical *LSR* and the difference between the measured *LSR* and theoretical *LSR* was within acceptable limits due to the intrinsic nature when feeding powders and the additional variability added when using a peristaltic pump to feed the granulating liquid. The differences between the measured *LSR* and the theoretical *LSR* were between ~1% to 16% and ~0.5% to 20% for the 11mm TSG and 16mm TSG, respectively. Although this analysis was not performed for the 24mm TSG, we hypothesize that feeding at higher feed rates both for powder and liquid will yield similar or better *LSR* values (with less variability in feeding leading to a lower difference between the measured and theoretical *LSR* values).

For the 24mm TSG, the liquid feed stream coming from the pump is split into two streams after it reaches the inlet port in the TSG. This is different in the 11mm and 16mm TSG, where only one liquid stream is fed into the granulators. The rate of wetting changes when two droplets (24mm TSG) rather than one droplet (11mm and 16mm TSGs) wet (penetrate) the powder bed. The location of where the droplet falls might also have an influence on the size and quantity of granules formed. In the 24mm TSG, two droplets fall, one onto the center of each shaft, while in the 11mm and 16 mm TSGs, only one droplet falls in the mid-section of the two shafts. This might have an influence on the final properties of the granules and would need to be further investigated.

The powder was fed into the third to last zone and the liquid was fed into the second to last zone of each TSG. Figure 2 shows the inlet positions of the powder feed (Zone 3) and liquid feed (Zone 2). Three conveying elements (CEs) were placed downstream of the DFS used and before the TSG outlet. The 11mm and 24mm TSGs have 8 zones, while the 16mm TSG has only 6 zones. The 11mm and 24mm TSGs are geometrically identical to each other having an L:D of 40:1, while the 16mm TSG has an L:D of 25:1. This means that the powder will go through 1.5 CEs more in the 11mm and 24mm TSG than in the 16mm TSG after liquid addition before reaching the DFS.

The processing parameters in all three twin screw granulators were based on the three dimensionless groups defined in equations 5-7. Four *LSR* values (0.15, 0.20, 0.25, and 0.30), three *Fr* values (1.43, 3.22, and 5.73) and three *PFN* values (7.77×10^{-3}, 1.30×10^{-2}, and 1.81×10^{-2}) were studied. The *LSR* values were chosen based on results from previous studies in the 16mm TSG. These studies showed that the granule properties were most sensitive using these *LSR* values.[17,21] In addition, the *Fr* and *PFN* values were calculated based on the standard operating conditions for the 16mm TSG. Typical rotation rates and powder flow rates in the 16mm TSG are 200-800 RPM and 1-12 kg/hr, respectively. A full factorial experimental design was used. The screw rotation rates and powder flow rates used for each TSG scale are summarized in Table 2. Due to equipment limitations, some experiments in the 16mm TSG, indicated by N/A, were not completed.

Granule characterization

Granules collected for each experiment were spread on a tray and dried at room temperature for 48 hours. The dry granules were split using a rotary cone sample divider (Laborette 27, Fritsch GmbH, Idar-Oberstein, Germany). The granule size distribution (GSD) was measured by sieve analysis using sieves from 63 μm to 8 mm following a √2 series. The normalized mass frequency with respect to the logarithm of the particle size was plotted as shown in equation 13.[22]

$$f_i(ln x) = \frac{y_i}{\ln({}^{x_i}/_{x_{i-1}})} \quad [13]$$

where y_i is the mass fraction in size interval i and x_i is the upper limit of the size interval i.

The true density of the granules was first measured using a helium pycnometer (AccuPyc, Micromeritics, Germany), followed by envelope density measurement using a Geopyc (Micromeritics, Germany). Granules in the size fraction 1.0-1.4 mm were used for all granule density measurements. The granule porosity (ε) was then calculated using equation 14.

$$\varepsilon = 1 - \frac{\rho_g}{\rho_s} \quad [14]$$

where ρ_g and ρ_s are the envelope and true density of the granules, respectively.

The method used in analyzing the liquid distribution (*LD*) has been reported in El Hagrasy and Litster.[17] In brief, granule samples from each sieve fraction were dissolved in water, sonicated for one hour, followed by further dilution and centrifugation for 17 minutes at 400 RPM. The concentration of nigrosin dye in the supernatant was measured using UV/Vis spectrophotometry at λ=574 nm.

Results and Discussion

The main effects of scaling (processing) parameters (*LSR*, *Fr* and *PFN*) and TSG scale on granule size distributions (GSDs), granule size parameters (d_{10}, d_{50} and d_{90}), granule porosity (ε) and liquid distribution (*LD*) are presented and discussed for selected experiments in this section. Selected combinations of *LSR* values, *Fr* values and *PFN* values were chosen to demonstrate the overall behavior. In addition, the main effects of the parameters on the granule size metrics (d_{10}, d_{50} and d_{90}) over the full range of conditions studied are summarized.

Granule Size Distribution

GSDs obtained from the 16mm twin screw granulator (TSG) for $Fr = 3.22$ and $PFN = 1.30\text{x}10^{-2}$ as a function of *LSR* are shown in Figure 3. The granule size increased with increasing *LSR*. Bimodal GSDs were obtained in most cases using the distributive feed screw (DFS) configuration, especially at low values of *LSR*. Larger lumps leading to more and larger granules (≥1 mm) were obtained at high values of *LSR*. Hence, as the *LSR* increased, the amount of fines (<125 μm) decreased significantly with minor changes in the fraction of intermediate size granules (>125 μm & <1mm). We expect that the nuclei saturation will not vary with *LSR* but rather more nuclei will be formed with increasing *LSR*. The amount of layering that occurs in the granulator will be a function of *LSR*. Previous work by El Hagrasy has shown that granule porosity decreased a with increasing *LSR*, which may be due to greater consolidation at higher *LSR*.[17] Therefore, product granule saturation may increase with *LSR*. The major granulation rate processes for the DFS configuration were drop nucleation and layering of fines with limited breakage of lumps. This behavior was seen for all values of *Fr* and *PFN* studied. Although high values of *LSR* yielded monomodal GSDs, most of the granules are too large for downstream pharmaceutical processing. For most processing conditions, the largest sized granules were less than 3000 μm in size indicating breakage of larger lumps, which is consistent with findings of El Hagrasy and Sayin using different screw configurations in the same TSG scale.[17,18]

The effect of *Fr* on GSD at *PFN*=$1.30\text{x}10^{-2}$ and *LSR* values of 0.20 and 0.30 in the 16mm TSG are plotted in Figure 4. Varying *Fr* did not have a significant effect on GSD. These results are consistent for all values of *PFN* and *LSR* used at all scales. GSDs for all three values of *PFN* used at *Fr* = 3.22 and *LSR* values of 0.20 and 0.30 in the 16mm TSG are shown in Figure 5. There are only small differences in GSD caused by variations in the *PFN* when using the DFS configuration. These results are consistent for all values of *Fr*, *LSR* and TSG scales used. Minor changes in GSD indicate there may be slightly more breakage of large lumps at low *Fr* and low *PFN*, leading to more layering and reduction in fines.

The effect of TSG scale (or screw diameter - *D*) was analyzed and is summarized in Figure 6, which shows the results for *Fr* = 3.22 at *PFN* = $1.30\text{x}10^{-2}$ at *LSR* values of 0.20 and 0.30. Bimodal GSDs were common from the 16mm and 24mm TSGs, especially at low values of *LSR*. Nearly monomodal distributions were obtained for the 11mm TSG. Better, more uniform GSDs were achieved for the 11mm TSG with less large granules than in the other two TSG scales. Overall, more large granules were obtained for the 24mm TSG than for the 16mm TSG. In most cases, a larger fraction of fines was generated in the 16mm than in the 24mm TSG. Results suggest that breakage of large granules and lumps is dependent on the scale of geometry of the screw elements. As scale increases, the size of a granule that can leave the granulator without breaking also increases. Note, however, that the granulating liquid is fed into the 24mm TSG differently than for the two smaller scales. The liquid feed is split into two streams, each on top of each screw, in the 24mm TSG. This may have a confounding effect on the results.

The granule size parameters d_{10}, d_{50}, and d_{90} are plotted as a function of *LSR*, *Fr and PFN* in Figures 7 and 8. As expected, d_{10}, d_{50}, and d_{90} increase with increasing *LSR*.[17,18] However, Figure 7 shows that *Fr* only had a small effect on any of the GSD properties when compared to the effect of *LSR*. This was true for all other combination of parameters used. This is consistent with the limited studies on the literature which showed rotation rate did not have large effects on the granule properties.[12,13] Nevertheless, for this set of data d_{50} and d_{90} increased and d_{10} decreased a little with increasing *Fr* especially at high values of *LSR*. Figure 8 shows the effect of *PFN* on GSD properties. Although there is no significant impact of *PFN* on d_{10} and d_{50}, d_{90} does increase with increasing *PFN*. Thus, increasing *Fr* and *PFN* leads to slightly broader GSDs. This may be due to changes in the powder flow patterns down the TSG as these dimensionless groups change, causing less efficient breakage on large granules.

The effect of TSG scale on d_{10}, d_{50}, and d_{90} as a function of *LSR* is shown in Figure 9. The mean values of d_{10}, d_{50}, and d_{90} were calculated from the results of the three *Fr* values for *PFN*=1.30×10^{-2}. The TSG barrel diameter has a dramatic impact on the size of large granules (lumps) in the product. d_{90} increases approximately linearly with scale, with d_{50} also increasing monotonically as scale increases. The effect of TSG scale on d_{90} was greater than the effect of *LSR*. This is likely due to more efficient breakage at the 11mm scale and supports the hypothesis that breakage is controlled by the geometry in the confined twin screw. For geometrically similar screw elements, the size of the gap through which a granule can flow without breakage was observed to scale directly with the barrel diameter. There is not as clear a trend for d_{10} with TSG scale. While d_{10} is greater for the 24mm TSG, values for the 11mm and the 16mm TSGs are similar with the 11mm TSG giving slightly higher d_{10} values. This probably reflects a complex balance between generation of fines by breakage and/or attrition and layering of fines onto wet granule surfaces.

Statistical analysis was performed to elucidate the main effects, interactions, and levels of significance of the scaling (processing) parameters on the particle size. A summary of analysis of variance (ANOVA) showing the *p-values* for the full data set for the effect of TSG scale, *LSR*, *PFN*, and *Fr* on d_{10}, d_{50}, and d_{90} are given in Table 3. At *p-value* = 0.05*,* only TSG scale (barrel diameter) and *LSR* have a statistically significant effect on d_{10} and d_{50}. All four parameters do have a statistically significant effect on d_{90}. For d_{90}, two of the interactions, *TSG*LSR and TSG*PFN* are also significant. The coarse end of the GSD is much more sensitive to changes in operating conditions than the fines.

Granule Porosity and Liquid Distribution

The porosity of granules with sizes between 1.0 mm and 1.4 mm was measured. The granule porosity as a function of *LSR,* TSG scale *FR* and *PFN* is shown in Figure 10 and statistical analysis is shown in Table 4. Granule porosity decreases with increasing *LSR*. In all cases this change was statistically significant (*p-value* < 0.05). The TSG scale, *Fr* and *PFN* did not generate a clear trend in the measured porosity. Note that granule porosity for the DFS configuration was always high, in the range of 50 - 60%.

Due to the time consuming nature of the analysis, liquid distribution was only measured at *LSR* = 0.15 (where liquid distribution is expected to be the poorest) and at *Fr* = 5.73 and *PFN* = 7.77×10^{-3}. Liquid distribution results are presented in Figure 11 for the three TSG scales. The almost vertical lines (high slopes) are representative of a large variability in the liquid distribution with each sieve size cut. This means that the mixing and liquid distribution obtained with the DFS screw configuration were poor. The similar slopes of the distributions also suggest that there is no significant effect of TSG scale on the efficiency of mixing and liquid distribution, at least over the range of parameters used in this study.

4.3 Implications for TSG Design and Scaling

The DFS configuration was chosen for this scaling study due to industrial interest, the screw designs were available at all three TSG scales used, and there was relatively little published data on this configuration. This configuration yields bimodal size distributions with relatively poor liquid distributions, especially at 16mm and 24mm barrel diameters. Previous studies have shown that efficient breakage of large granules (lumps) formed in the liquid addition section is a key to achieving monomodal size distribution and good liquid distribution.[17,18] The DFS elements look superficially similar to Distributive Mixing Elements (DMEs) which give efficient breakage of large granules. However, the DFS elements are cut out conveying elements with the same spiral configuration as conveying elements. Thus, relatively large lumps can be conveyed along the barrel without being broken by the DFS. A combination of DFS and CE, as used in this study, is not likely to be the optimum configuration for controlling granule size distribution. On the other hand, like DME configurations, the DFS configuration does produce consistently high porosity (low density) granules which could be an advantage for downstream compressibility of the granules to form tablets.

With regard to developing simple and reliable scaling rules, this study is a “good news, bad news” story. First the good news: For the formulation studied, a striking feature of this study is how little effect basic process parameters, powder flow rate and screw speed, and their dimensionless counterparts *PFN* and *Fr* have on the granule properties, indicating the robust nature of TSG. Further studies will be needed to understand the effect of formulation properties in TSG. Contrast this with previous studies, which have shown that the screw configuration (type and arrangement of screw elements) has a very large impact on granule properties.[15–18] Thus, a very wide range of production rates can be achieved with relatively little effect on granule properties through *scaling out*, i.e., operating the same TSG for longer campaign times, and at increased screw speed and powder feed rate. To increase production rate from the same screw, we recommend increasing the screw speed to maintain *PFN* constant, although moderate changes in *PFN* are also likely to be acceptable. *LSR* should be kept constant in design by increasing the liquid feed in proportion to the powder feed and then used as a fine tuning parameter during operation. This scaling out approach means that the same granulator may possibly be used for all phases of clinical trials and even in full scale production for some pharmaceutical products.

In contrast, *scaling up* by changing the barrel diameter does have a strong impact on the size of large granules and the spread of the granule size distribution. This is consistent with breakage (the dominant rate process) being controlled by geometry of the TSG. To traverse the TSG, unbroken, weak granules must be small enough to pass through gaps between elements that intermesh on the two shafts. For geometrically similar screw elements, the size of the gap through which a granule can flow without breakage was observed to scale directly with the barrel diameter and the size of the lumps (d_{90}) will also increase approximately linearly. This increase is predictable using an appropriate mechanistically based model of the TSG, but is unavoidable. It is not possible to achieve the same GSD in the large scale TSG as in the small scale if the granulators are geometrically similar, and this will have implications for downstream drying, milling and tableting. It may be possible to redesign the key screw element, DFS in this case, so that the absolute gap size remains invariant during scale up. This would improve our ability to scale up the process without changing the granule size distribution, as well as other granule attributes.

Sometimes granule porosity (density), rather than granule size, may be the key property of interest. Here, the news is better. The granule porosity is insensitive to most process changes except *LSR* and is also scale independent. In the TSG, granules undergo relatively little densification, particularly for this screw configuration. Granule density will change little when either scaling out or up. Contrast this with high shear wet granulation (HSWG), where granule densification coupled with coalescence can dominate the granule properties. It is very difficult to scale HSWG and maintain constant granule porosity.

Conclusions

Three dimensionless groups for scaling were identified and tested: the liquid to solid ratio (*LSR*), Froude number (*Fr*) and the powder feed number (*PFN*). These dimensionless groups were studied in three different geometrically-similar TSG scales (11mm, 16mm and 24mm) using a distributive feed screw (DFS) as part of the screw configuration for an immediate release formulation. The DFS configuration yielded bimodal granule size distributions (GSDs) with poor liquid distribution. GSDs and metrics were strongly dependent on *LSR*. The granule size increased with increasing *LSR*. However, *Fr* and *PFN* had only a minor, but statistically significant, effect on the larger lumps (d_{90}) of GSDs with no significant effect on d_{10} or d_{50}. In contrast, d_{90} was strongly dependent on TSG scale with the size of lumps increasing approximately linearly with barrel diameter. More efficient breakage of large lumps occurred with decreasing TSG scale. This fits with our mechanistic understanding that with the current liquid feeding method, breakage is the most important rate process, determining the final properties of granules, and the size of granules broken is set by geometry (i.e. gap size). Gap size is proportional to scale (screw diameter). Nevertheless, the TSG scale did not have an effect on the granule porosity for the DFS configuration.

When operating at one scale, but increasing the powder flow rate, we recommend increasing the liquid flowrate to maintain *LSR* constant and increasing the screw speed to keep *PFN* constant. This strategy was effective for DFS elements over all conditions studied. When increasing TSG scale, expect more and larger lumps to be produced. Reducing *LSR* reduces the amount of lumps. However, do not expect to exactly match the GSD by this strategy. In general, as scale increases, the GSD is broader and more likely to be bimodal.

Acknowledgements

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References

1. Mahato RI, Narang AS. Pharmaceutical Dosage Forms and Drug Delivery (2nd edition). Boca Raton: CRC Press, 2011.
2. Wu H, Tawakkul M, White M, Khan MA. Quality-by-Design (QbD). An integrated multivariate approach for the component quantification in powder blends. Int J Pharm. 2009;372:39-48.

3. ICH. Pharmaceutical Development - Q8 (R2), 2009. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf.

4. FDA. Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, 2004. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf.

5. Dhenge RM, Fyles RS, Cartwright JJ, Doughty DG, Hounslow MJ, Salman AD. Twin screw wet granulation: Granule properties. Chem Eng J. 2010;164:322-329.

6. Vervaet C, Remon JP. Continuous granulation in the pharmaceutical industry. Chem Eng Sci. 2005;60:3949-3957.

7. Djuric D, Kleinebudde P. Continuous granulation with a twin-screw extruder: Impact of material throughput. Pharm Dev Technol. 2010;15:518-525.

8. Djuric D, Kleinebudde P. Impact of screw elements on continuous granulation with a twin-screw extruder. J Pharm Sci. 2008;97:4934-4942.

9. Vercruysse J, Córdoba Díaz D, Peeters E, Fonteyne M, Delaet U, Van Assche I, De Beer T, Remon JP, Vervaet C. Continuous twin screw granulation: Influence of process variables on granule and tablet quality. Eur J Pharm Biopharm. 2012;82:205-211.

10. Dhenge RM, Cartwright JJ, Doughty DG, Hounslow MJ, Salman AD. Twin screw wet granulation: Effect of powder feed rate. Adv Powder Technol. 2011;22:162-166.

11. Djuric D, Van Melkebeke B, Kleinebudde P, Remon JP, Vervaet C. Comparison of two

twin-screw extruders for continuous granulation. Eur J Pharm Biopharm. 2009;71:155-160.

12. Seem TC, Rowson NA, Ingram A, Tim Chan Seem T, Rowson NA, Ingram A, Huang Z, Yu S, de Matas M, Gabbott I, Reynolds GK. Twin screw granulation — A literature review. Powder Technol. 2015;276:89-102.

13. Thompson MR. Twin screw granulation – review of current progress. Drug Dev Ind Pharm. 2015;41:1223-1231.

14. Thompson MR, Sun J. Wet granulation in a twin-screw extruder: Implications of screw design. J Pharm Sci. 2010;99:2090-2103.

15. Dhenge RM, Washino K, Cartwright JJ, Hounslow MJ, Salman AD. Twin screw granulation using conveying screws: Effects of viscosity of granulation liquids and flow of powders. Powder Technol. 2013;238:77-90.

16. Sayin R, Martinez-Marcos L, Osorio JG, Cruise P, Jones I, Haltbert, GW, Lamprou, DA, Litster JD. Investigation of an 11 mm diameter twin screw granulator: Screw element performance and in-line monitoring via image analysis. Int J Pharm. 2015;496:24-32.

17. El Hagrasy AS, Litster JD. Granulation rate processes in the kneading elements of a twin screw granulator. AIChE J. 2013;59(11):4100-4115.

18. Sayin R, El Hagrasy AS, Litster JD. Distributive mixing elements: Towards improved granule attributes from a twin screw granulation process. Chem Eng Sci. 2015;125:165-175.

19. Benali M, Gerbaud V, Hemati M. Effect of operating conditions and physico–chemical

properties on the wet granulation kinetics in high shear mixer. Powder Technol. 2009;190:160-169.

20. Shanmugam S. Granulation techniques and technologies: recent progresses. Bioimpacts. 2015;5:55-63.

21. Hagrasy AS El, Hennenkamp JR, Burke MD, Cartwright JJ, Litster JD. Twin screw wet granulation: Influence of formulation parameters on granule properties and growth behavior. Powder Technol. 2013;238:108-115.

22. Allen T. Particle size analysis by sieving. In: Allen T. Particle size measurement. Amsterdam: Elsevier, 2003:208-250.

Figure 1 – Picture of (left) distributive feed screw (DFS) and (right) screw configuration with conveying elements (CEs) used. The pitch length of the conveying elements (CEs) and the DFS element is 0.5D.

Figure 2 – Schematic of screw configuration and powder and liquid inlet positions

Figure 3 – Effect of *LSR* on granule size distribution. Other parameters: 16mm TSG, *Fr* = 3.22 and *PFN*=$1.30\text{x}10^{-2}$

Figure 4 – Effect of *Fr* on granule size distribution for (A) *LSR* = 0.20 and (B) *LSR* = 0.30. Other parameters: 16mm TSG and *PFN* = $1.30\text{x}10^{-2}$

Figure 5 – Effect of *PFN* on granule size distribution for (A) *LSR* = 0.20 and (B) *LSR* = 0.30. Other parameters: 16mm TSG and *Fr* = 3.22

Figure 6 – Effect of TSG scale (barrel diameter) on granule size distribution for (A) *LSR* = 0.20 and (B) *LSR* = 0.30. Other parameters: *Fr* = 3.22 and *PFN* = $1.30\text{x}10^{-2}$

Figure 7 – Effect of *LSR* and *Fr* on (A) d_{10}, (B) d_{50}, and (C) d_{90}. Other parameters: 16mm TSG and *PFN*=$1.30\text{x}10^{-2}$

Figure 8 – Effect of *LSR* and *PFN* on (A) d_{10}, (B) d_{50}, and (C) d_{90}. Particle size analysis for 16mm TSG and *Fr* = 3.22

Figure 9 – Effect of TSG scale (barrel diameter) and *LSR* and on (A) d_{10}, (B) d_{50}, and (C) d_{90}. Other parameters: Mean values of *Fr* at *PFN*=$1.30\text{x}10^{-2}$

Figure 10 – Effect of (A) *LSR* and TSG scale (barrel diameter) on granule porosity (ε) for *Fr* = 3.22 and *PFN* = $1.30\text{x}10^{-2}$; (B) *LSR* and *Fr* on ε for 16mm TSG and *PFN* = $1.30\text{x}10^{-2}$; and (C) *LSR* and *PFN* on ε for 16mm TSG and *Fr* = 3.22

Figure 11 – Effect of TSG scale (barrel diameter) on liquid distribution (LD) for *LSR* = 0.15 at *Fr* = 5.73 and *PFN* = $7.77\text{x}10^{-3}$

Figure 1 – Picture of (left) distributive feed screw (DFS) and (right) screw configuration with conveying elements (CEs) used. The pitch length of the conveying elements (CEs) and the DFS element is 0.5D.
Figure 1

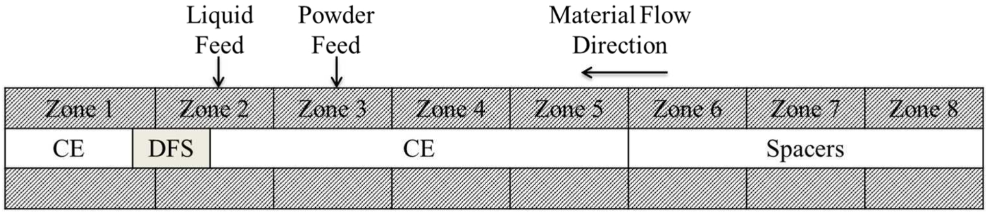


Figure 2 – Schematic of screw configuration and powder and liquid inlet positions
Figure 2

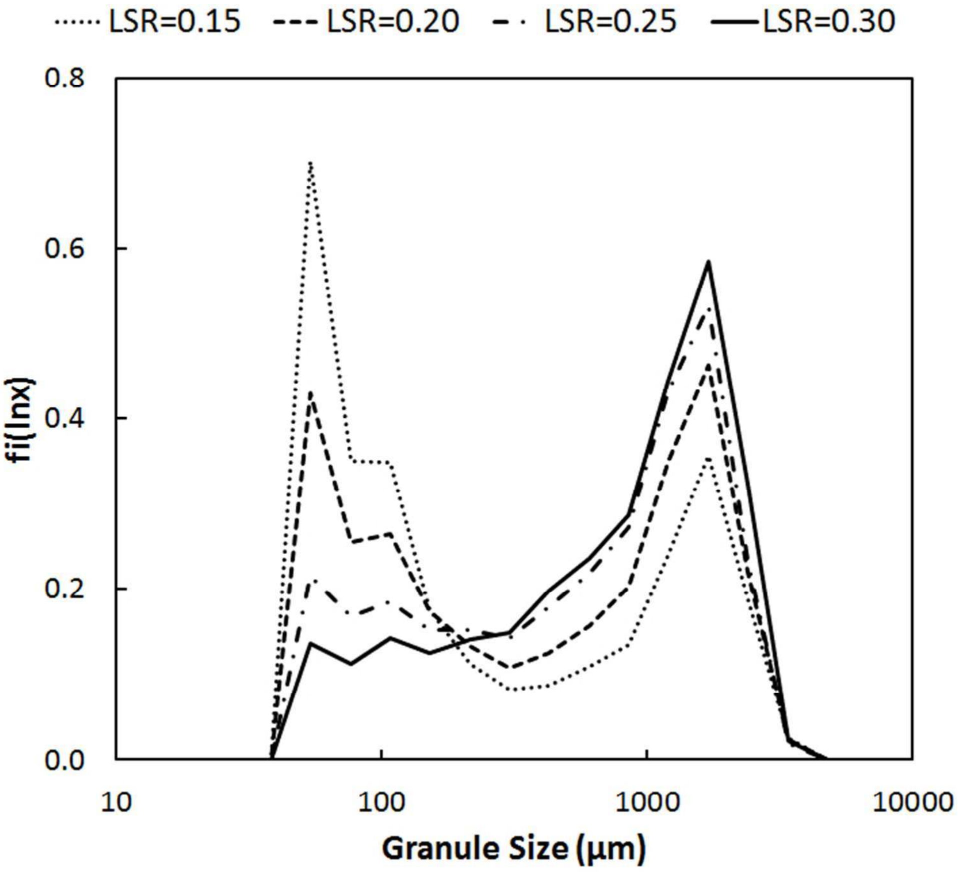


Figure 3 – Effect of *LSR* on granule size distribution. Other parameters: 16mm TSG, *Fr* = 3.22 and *PFN*=1.30x10^{-2}
Figure 3

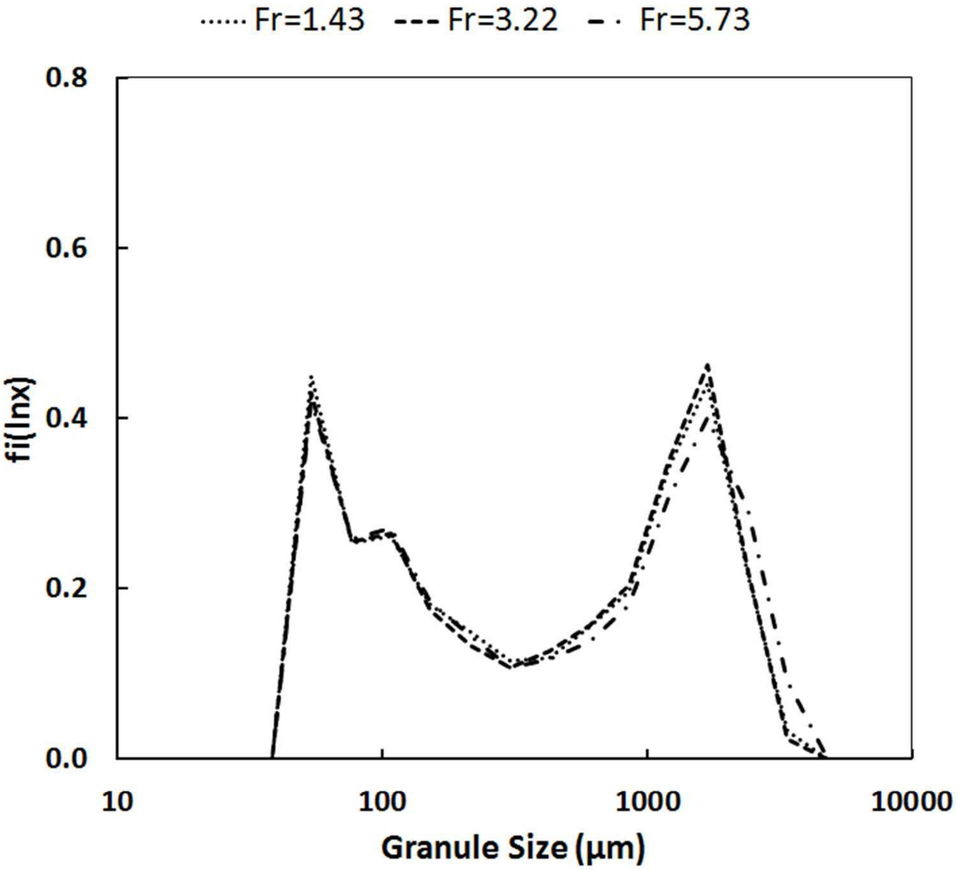


Figure 4A
Figure 4

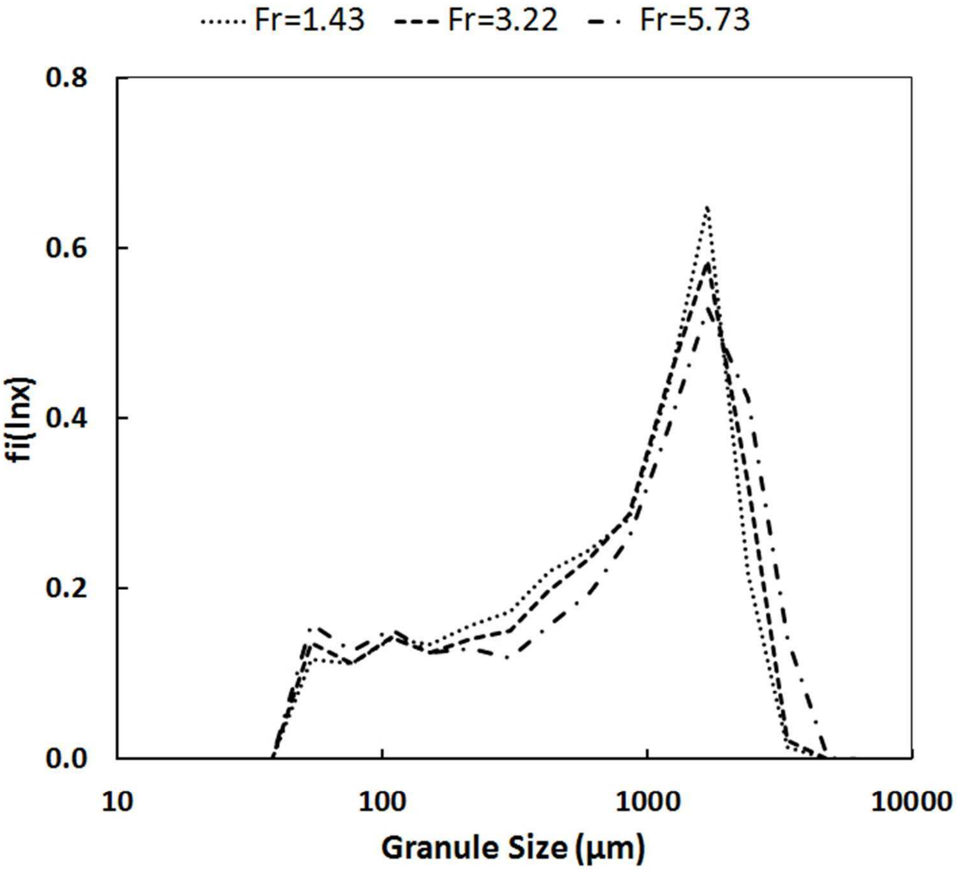
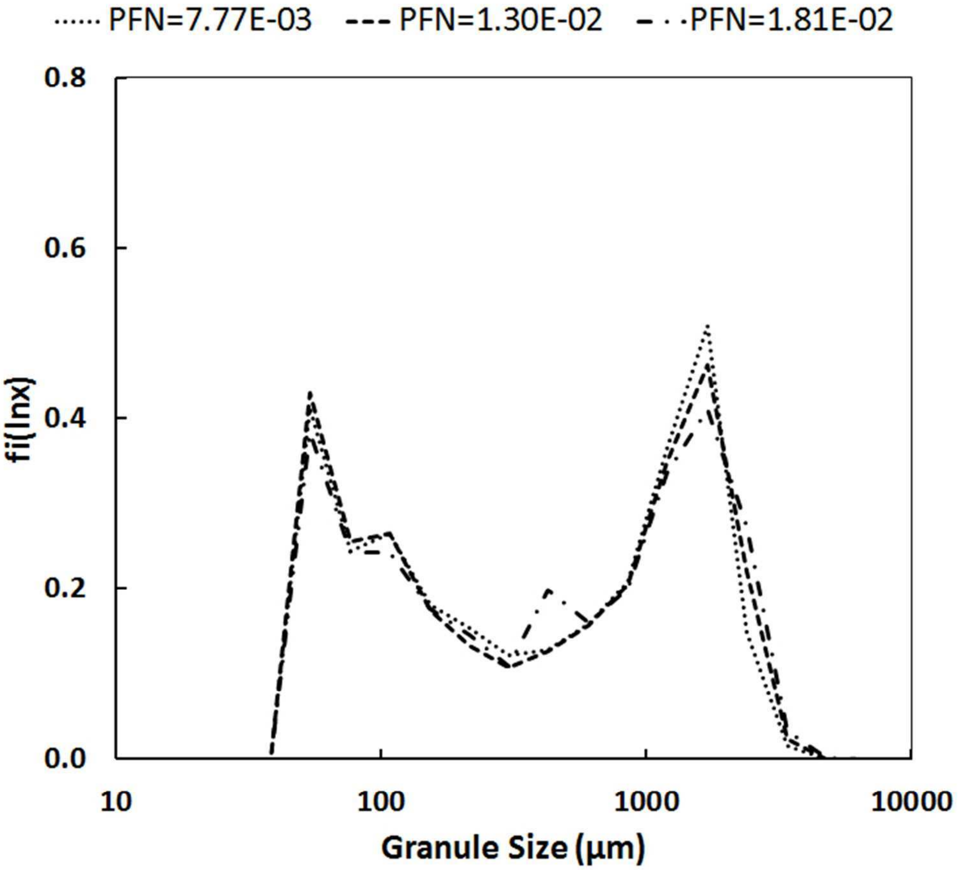


Figure 4B┼ ┼ Figure 4 – Effect of *Fr* on granule size distribution for (A) *LSR* = 0.20 and (B) *LSR* = 0.30. Other parameters: 16mm TSG and *PFN* = 1.30x10^{-2}
Figure 4



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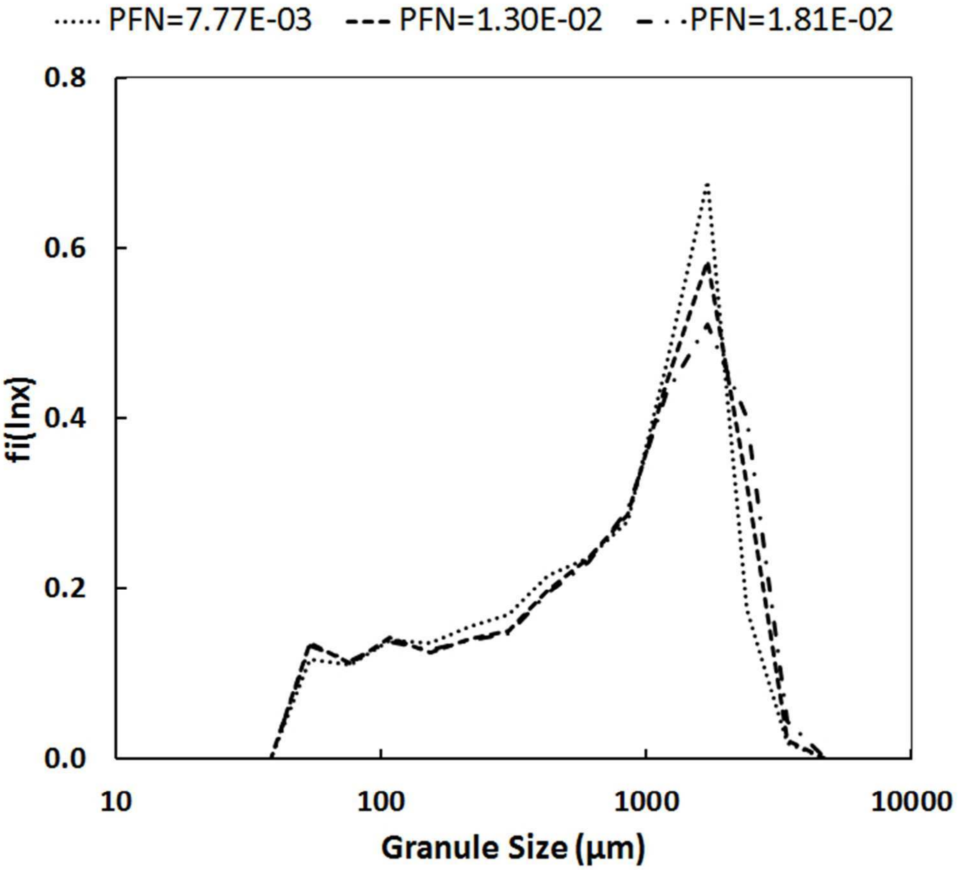
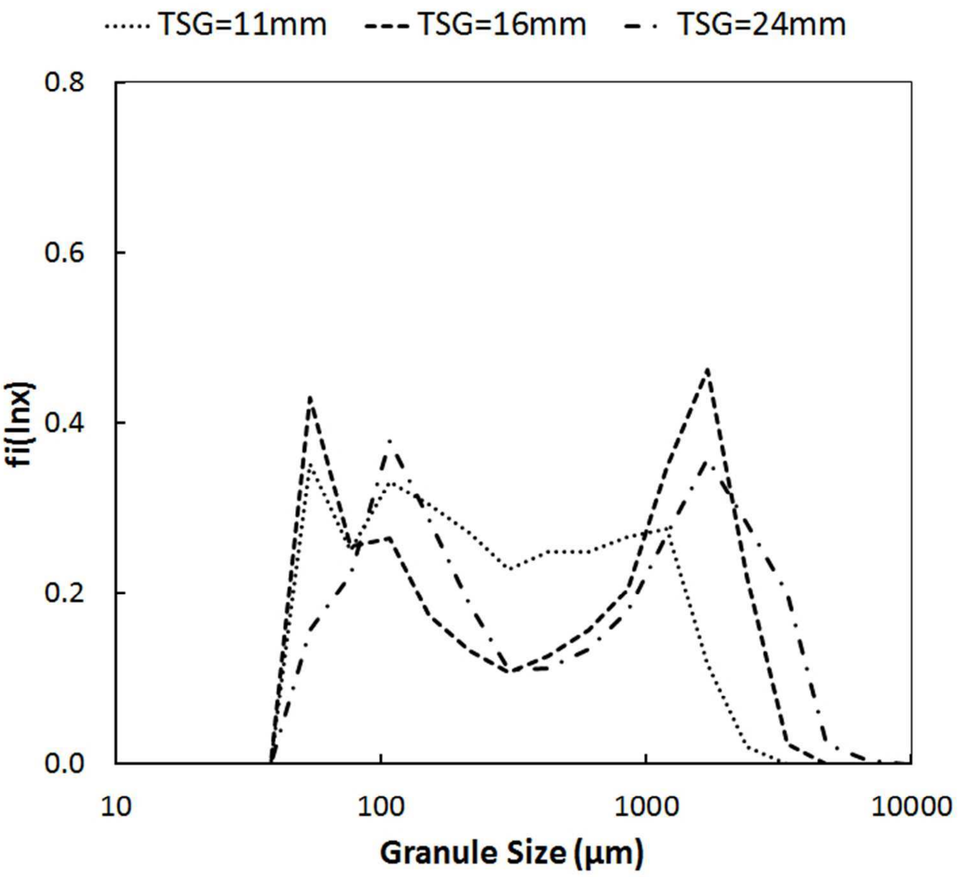


Figure 5B

Figure 5 – Effect of *PFN* on granule size distribution for (A) *LSR* = 0.20 and (B) *LSR* = 0.30. Other parameters: 16mm TSG and *Fr* = 3.22
Figure 5



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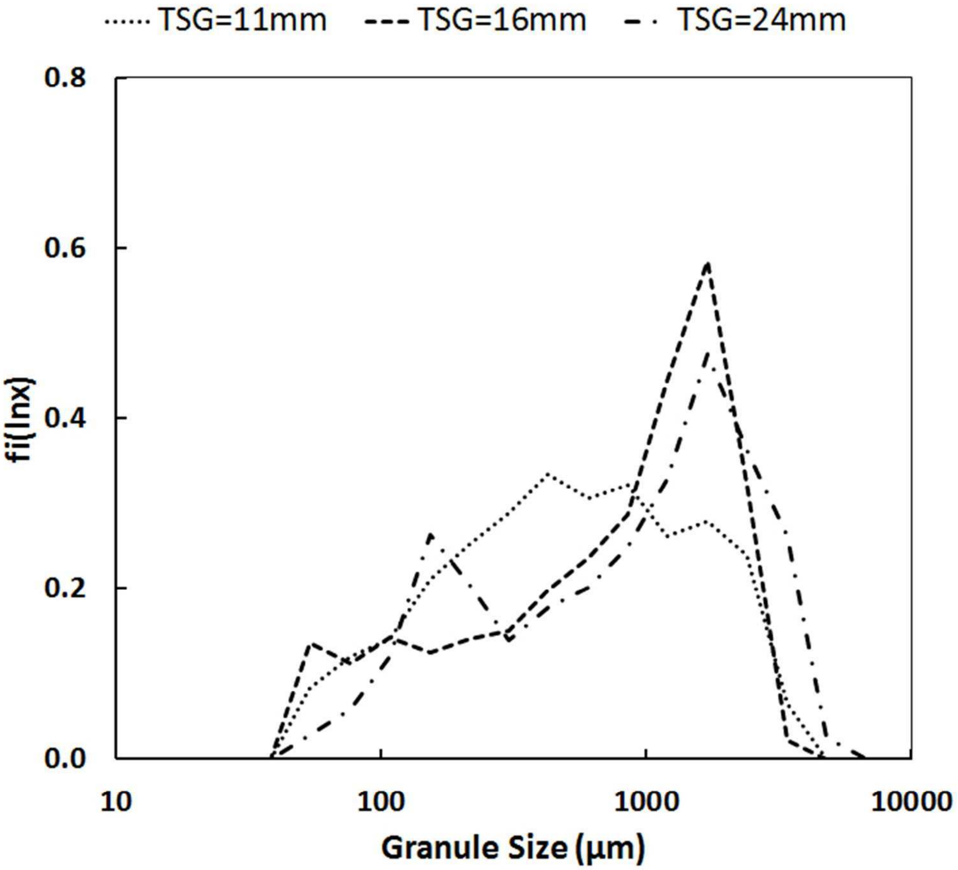

Figure 6B

Figure 6 – Effect of TSG scale (barrel diameter) on granule size distribution for (A) *LSR* = 0.20 and (B) *LS*R = 0.30. Other parameters: *Fr* = 3.22 and *PFN* = 1.30x10-^{2}
Figure 6

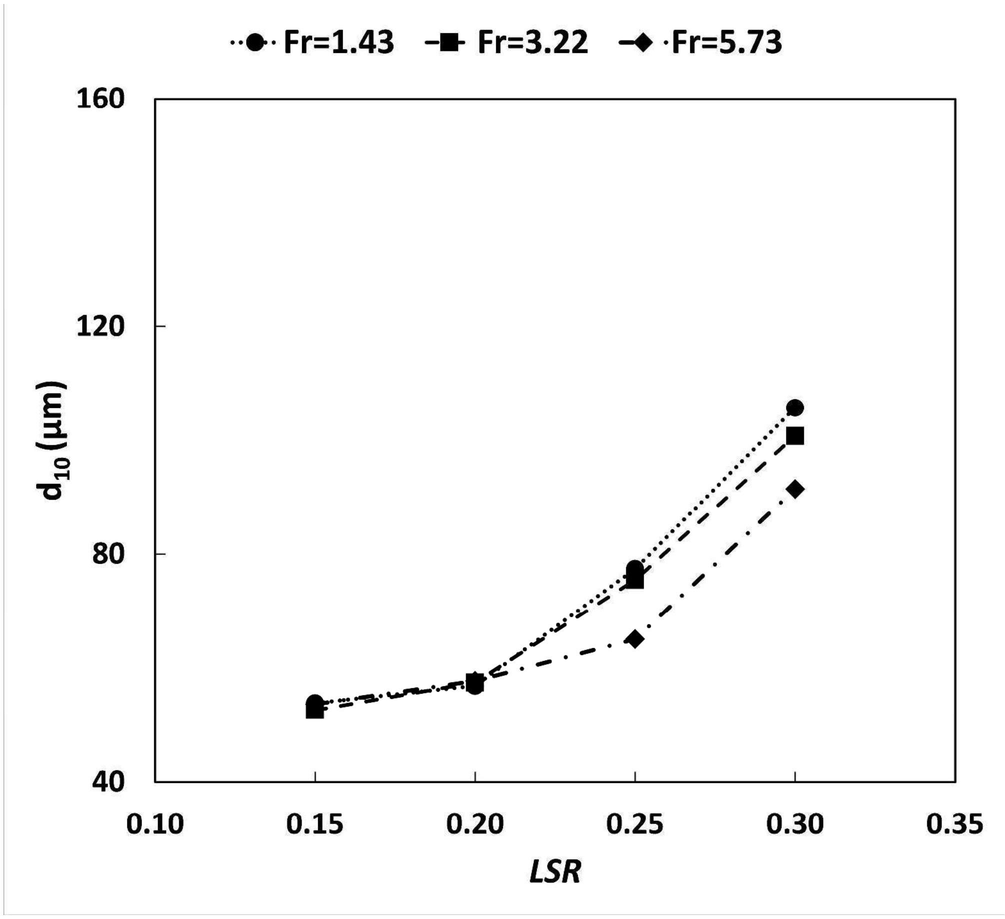

Figure 7A
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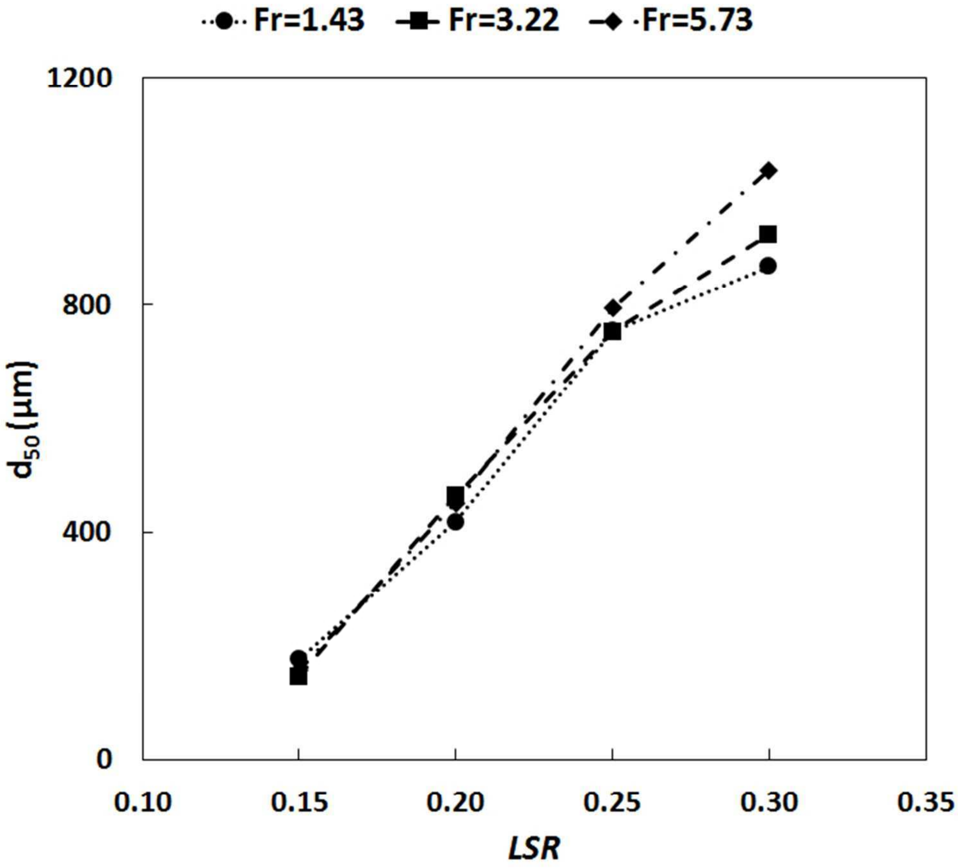

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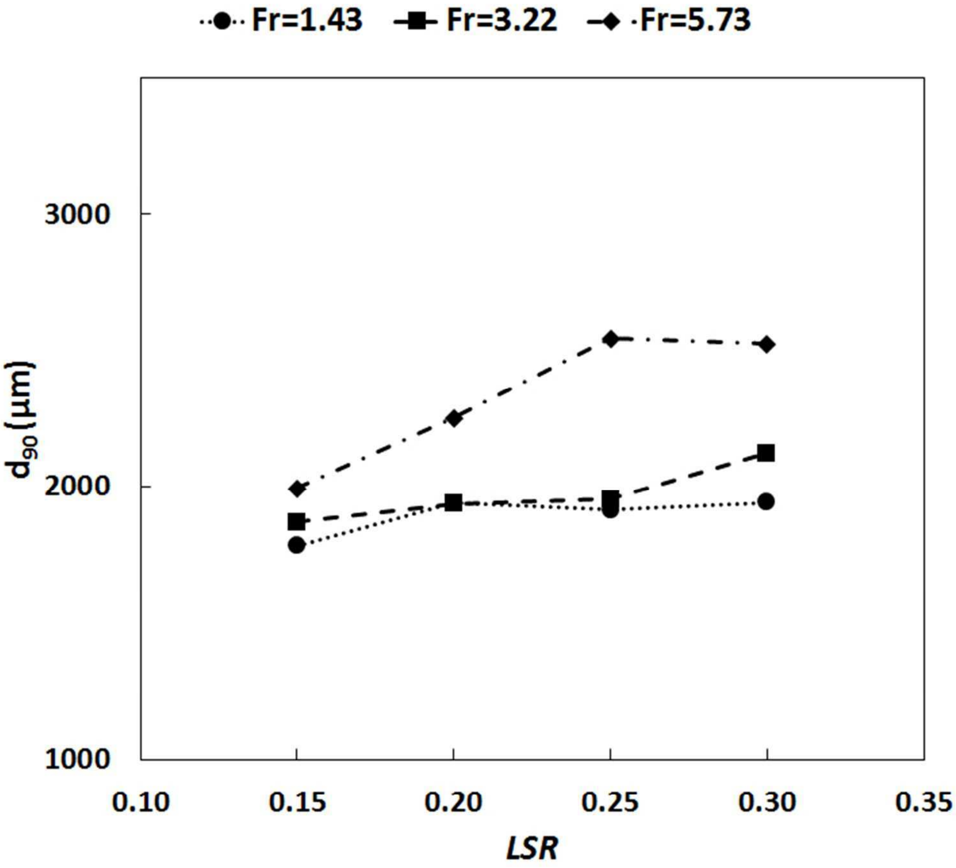

Figure 7C

Figure 7 – Effect of *LSR* and *Fr* on (A) d_{10}, (B) d_{50}, and (C) d_{90}. Other parameters: 16mm TSG and *PFN*=1.30x10^{-2}
Figure 7

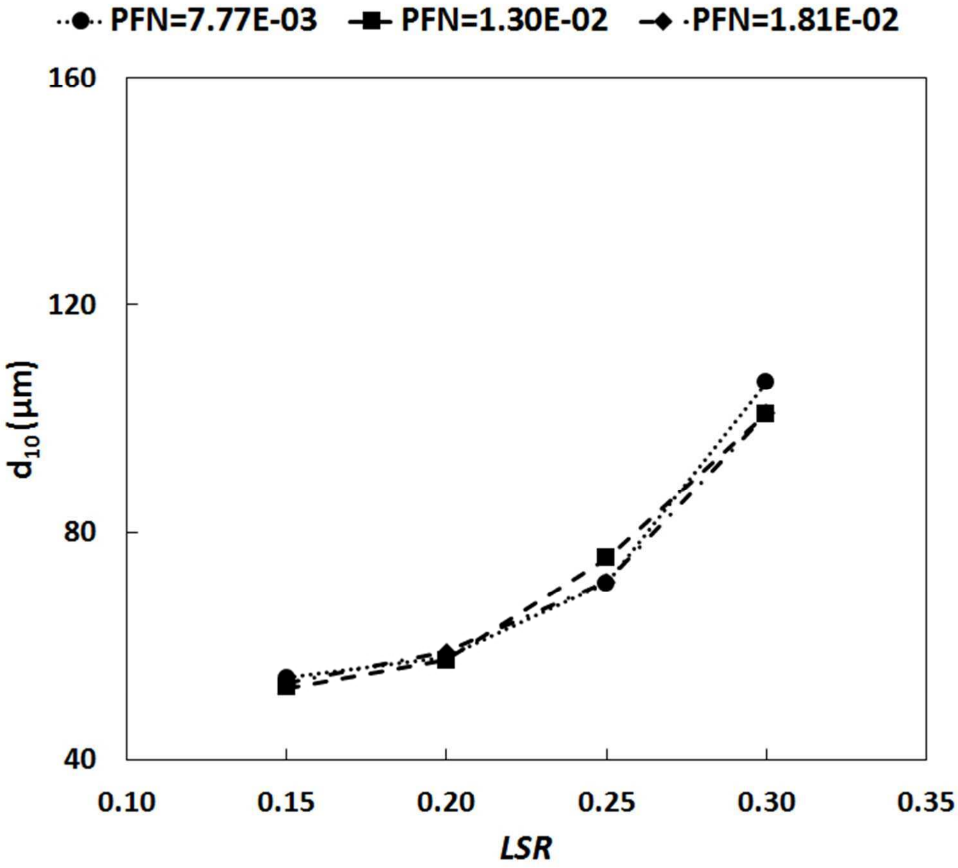

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Figure 8

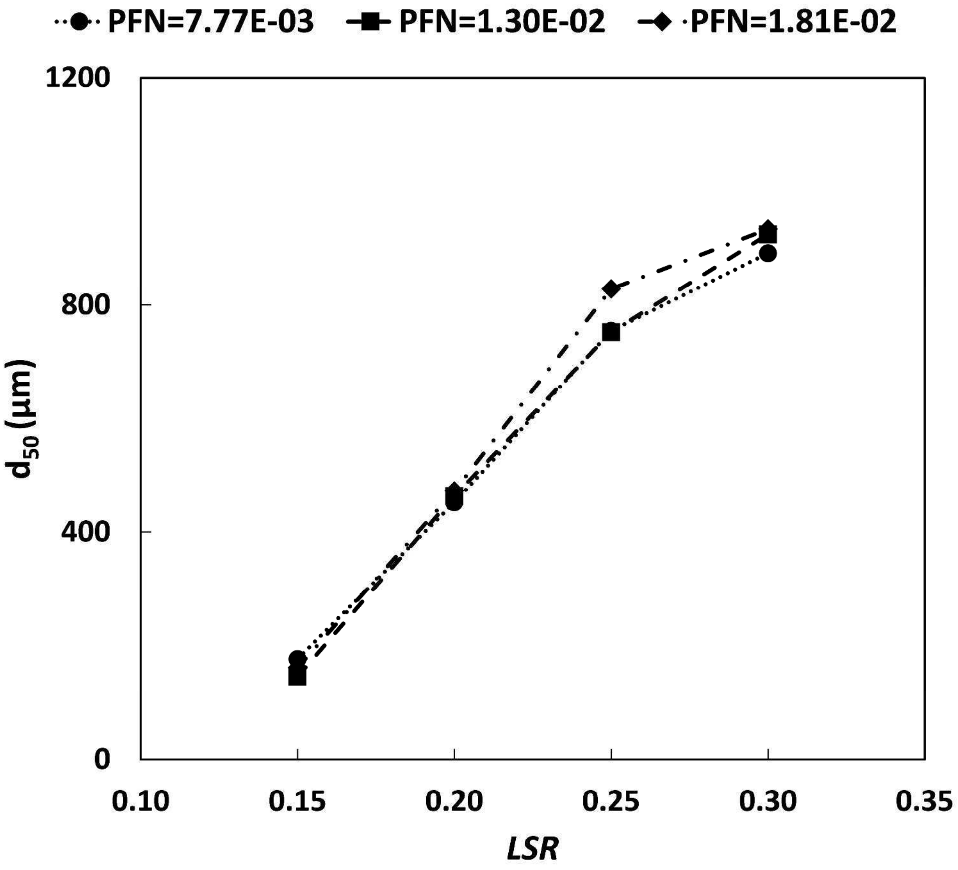

Figure 8B
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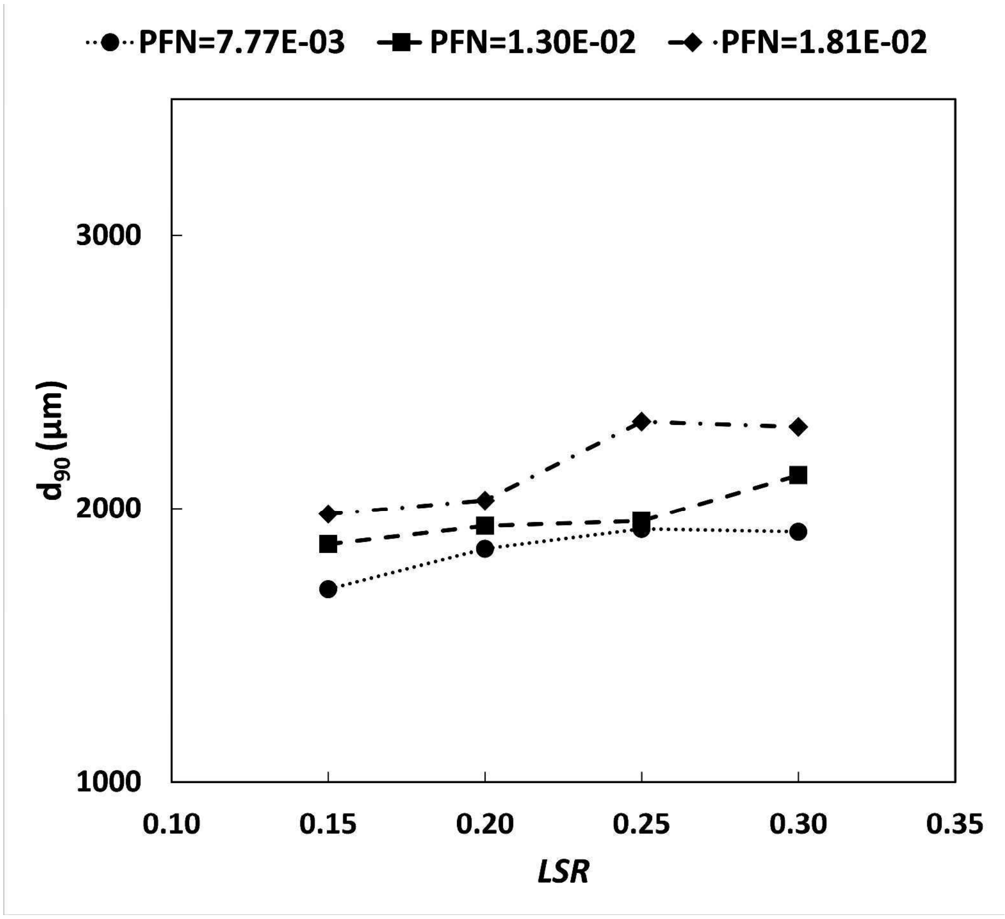

Figure 8C

Figure 8 – Effect of *LSR* and *PFN* on (A) d_{10}, (B) d_{50}, and (C) d_{90}. Particle size analysis for 16mm TSG and *Fr* = 3.22.

Figure 8

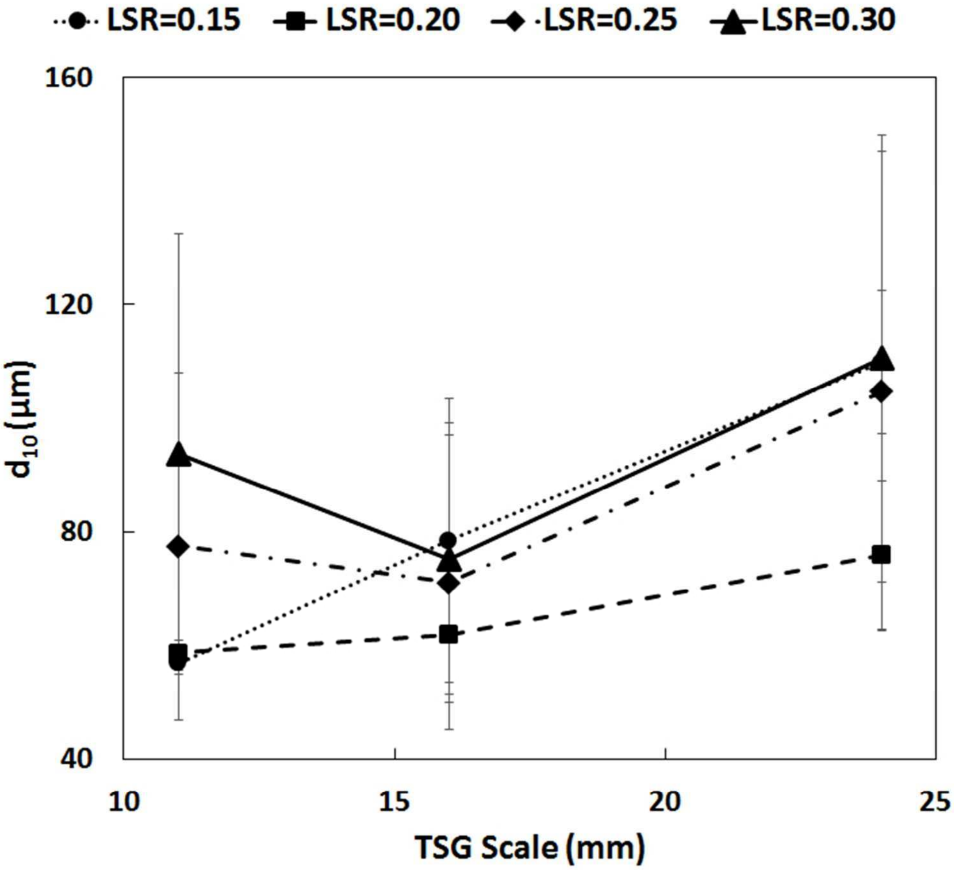

Figure 9A
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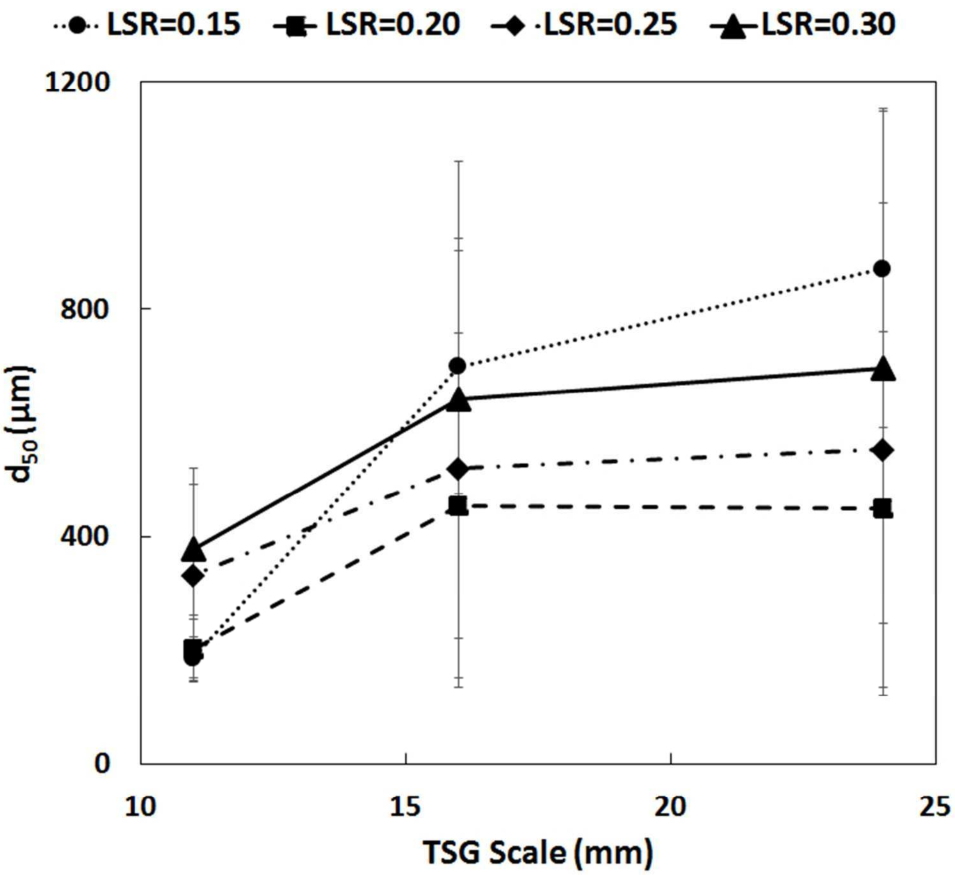

Figure 9B
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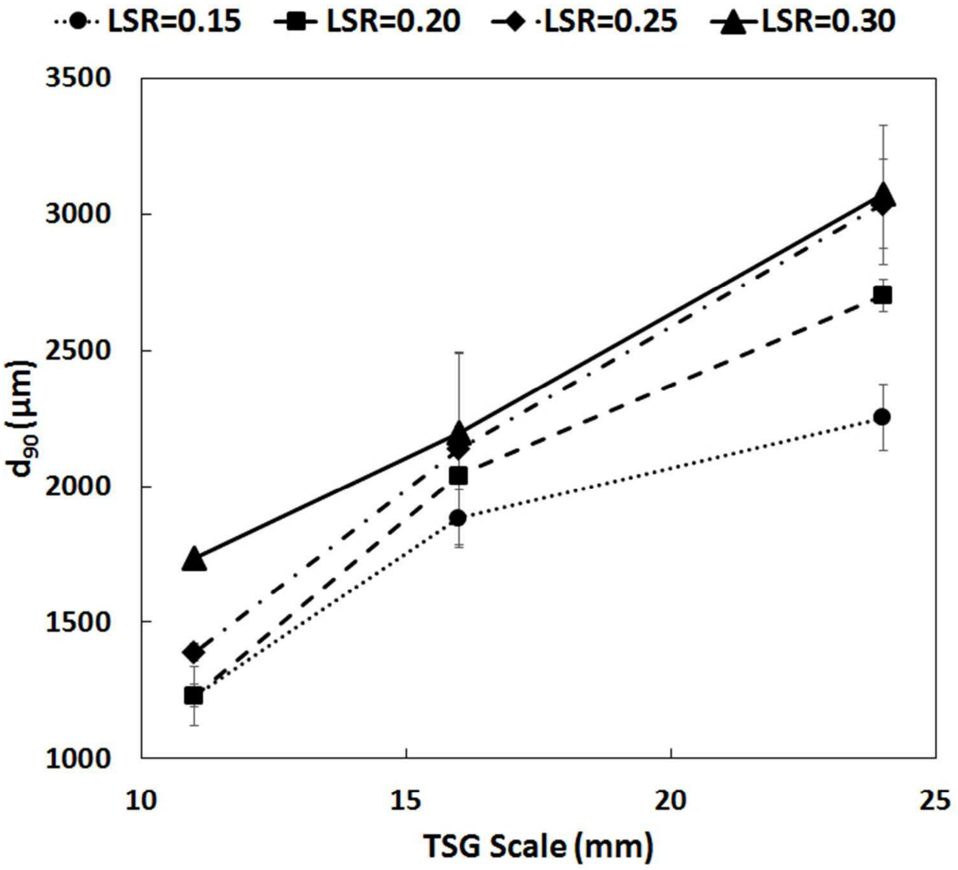

Figure 9C┼ Figure 9 – Effect of TSG scale (barrel diameter) and *LSR* and on (A) d_{10}, (B) d_{50}, and (C) d_{90}.
Other parameters: Mean values of *Fr* at *PFN*=$1.30\text{x}10^{-2}$
Figure 9

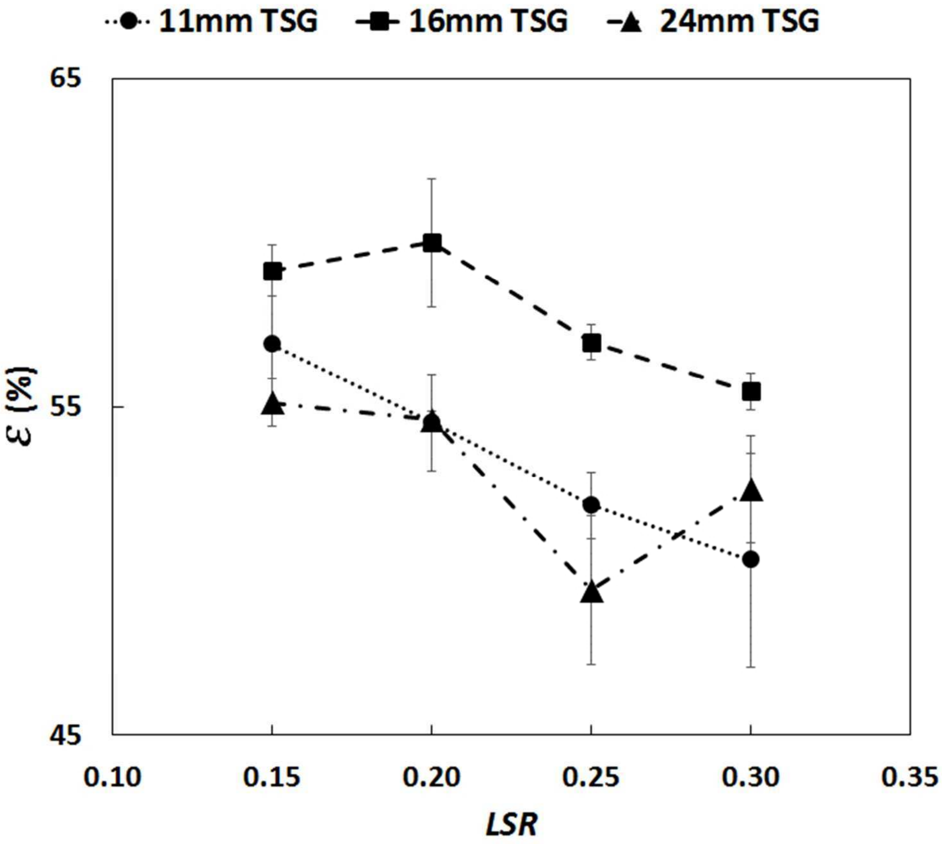

Figure 10A
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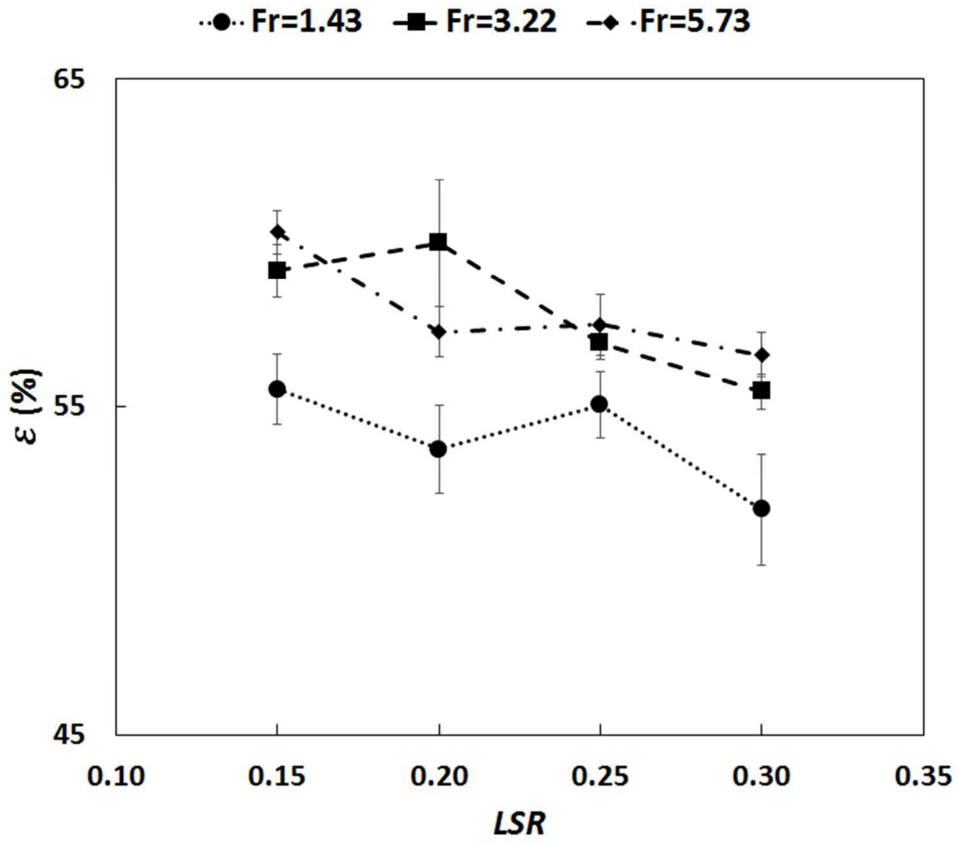

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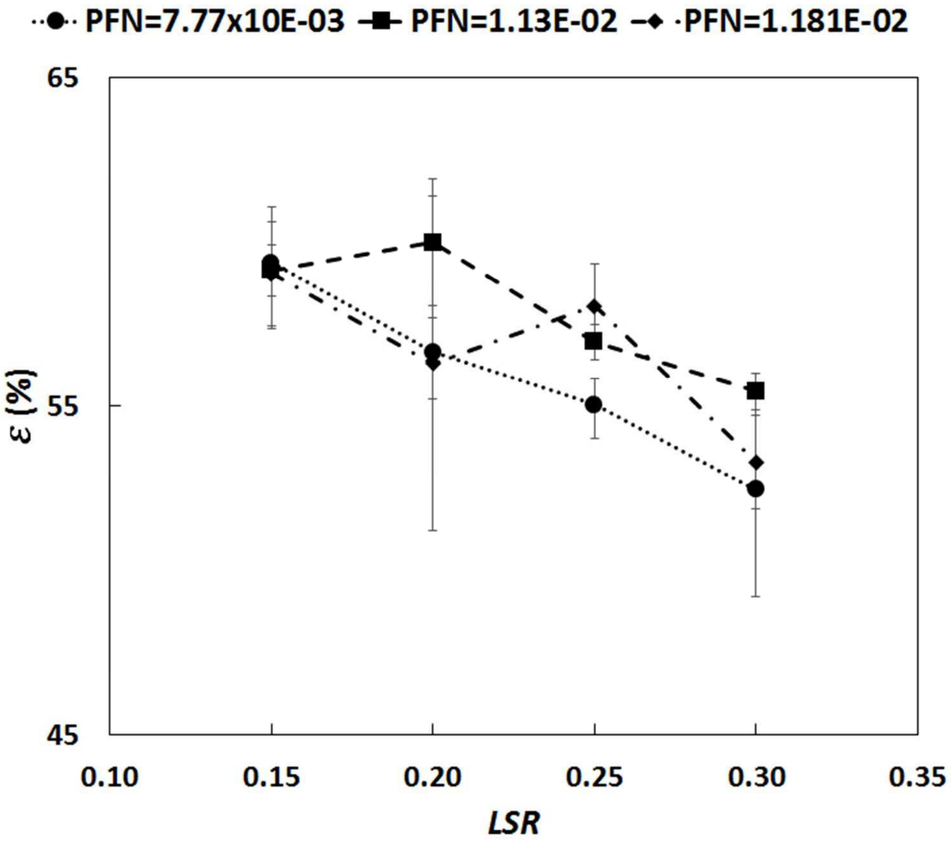

Figure 10C

Figure 10 - Effect of (A) *LSR* and TSG scale (barrel diameter) on granule porosity (*ε*) for *Fr* = 3.22 and *PFN* = $1.30\text{x}10^{-2}$; (B) *LSR* and *Fr* on *ε* for 16mm TSG and *PFN* = $1.30\text{x}10^{-2}$; and (C) *LSR* and *PFN* on *ε* for 16mm TSG and *Fr* = 3.22
Figure 10

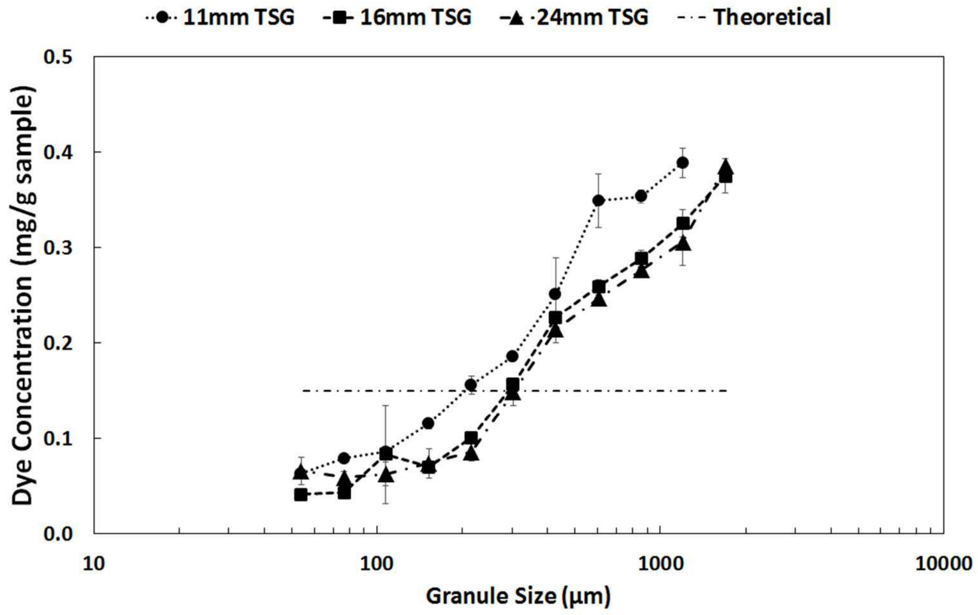

Figure 11 – Effect of TSG scale (barrel diameter) on liquid distribution (LD) for LSR = 0.15 at Fr = 5.73 and *PFN* = 7.77×10^{-3}

Figure 11

Material	Grade	Supplier	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)
α-lactose monohydrate	Pharmatose 200M	DFE Pharma	6.2	40.6	111.4
Microcrystalline cellulose	Avicel PH101	FMC BioPolymer	20.9	51.8	107.2
Hypromellose 2910	Pharmacoat 603	ShinEtsu	34.2	83.5	165.4
Croscarmellose sodium	Ac-Di-Sol	FMC BioPolymer	18.3	44.6	116
Initial blend	-		54.4	88.4	122.8

Table 1 – Particle size of raw material

	Fr	Rotation Rate (min^{-1})	*PFN*	Flow Rate (kg hr^{-1})
D = 11 mm	1.43	482	7.77E-03	0.94
			1.30E-02	1.57
			1.81E-02	2.19
	3.22	723	7.77E-03	1.41
			1.30E-02	2.35
			1.81E-02	3.29
	5.73	964	7.77E-03	1.88
			1.30E-02	3.14
			1.81E-02	4.39
D = 16 mm	1.43	400	7.77E-03	2.40
			1.30E-02	4.00
			1.81E-02	5.60
	3.22	600	7.77E-03	3.60
			1.30E-02	6.00
			1.81E-02	8.40
	5.73	800	7.77E-03	4.80
			1.30E-02	8.00
			1.81E-02 (N/A)	11.20 (N/A)
D = 24 mm	1.43	327	7.77E-03	6.61
			1.30E-02	11.02
			1.81E-02	15.43
	3.22	490	7.77E-03	9.92
			1.30E-02	16.53
			1.81E-02	23.15
	5.73	653	7.77E-03	13.23
			1.30E-02	22.05
			1.81E-02	30.86

Table 2. Process parameters used for each TSG scale (D) based on dimensionless groups *Fr* and *PFN*

	d_{10}	d_{50}	d_{90}
	p-values		
TSG	**0.000**	**0.000**	**0.000**
LSR	**0.000**	**0.000**	**0.000**
PFN	0.898	0.652	**0.000**
Fr	0.155	0.927	**0.001**
TSG**LSR*	0.186	**0.000**	**0.000**
TSG**PFN*	0.523	0.577	**0.007**
TSG**Fr*	0.085	0.608	0.127
*LSR*PFN*	0.724	0.793	0.526
*LSR*Fr*	0.676	0.730	0.583
*PFN*Fr*	0.133	0.058	**0.003**
R^2. R^2_{adj}	72.13%, 54.32%	96.47%, 94.21%	97.14%, 95.31%

Table 3. Summary of statistical analysis showing the *p-values* from the analysis of variance (ANOVA) of d_{10}, d_{50} and d_{90} for all scaling parameters used and their second order interactions

	Fr=3.22, *PFN*=1.30X10^{-2}
	p-values
TSG	0.003
LSR	0.012
R^2. R^2_{adj}	91.00%, 83.50%
	TSG=16mm, *PFN*=1.30X10^{-2}
	p-values
Fr	0.005
LSR	0.041
R^2. R^2_{adj}	88.42%, 78.77%
	TSG=16mm, *Fr*=3.22
	p-values
PFN	0.160
LSR	0.010
R^2. R^2_{adj}	85.20%, 72.87%

Table 4 –Summary of statistical analysis on porosity showing the *p-values* as a function of scaling parameters for data in Figure 11.

Responses to Editor and Reviewers

Manuscript ID: AIChE-16-18004

Title: Scaling of Continuous Twin Screw Wet Granulation

Authors: Juan G. Osorio, Ridade Sayin, Arjun V. Kalbag, Laura Martinez-Marcos, Dimitrios A. Lamprou, Gavin W. Halbert and James D. Litster

First, we would like to thank the editor and the reviewers for his/her valuable comments and input. Editor's comments on formatting are noted below followed by a revision of reviewers' comments. Changes due to reviewers' comments are highlighted in the manuscript in red as the font color.

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Response: SI units are used throughout the manuscript

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Literature cited should be listed in numerical order in the order in which they are cited in the text and referenced in the text with a superscript number without brackets. Give the complete information, including names of all authors, titles of the article and periodicals or books, numbers of pages and volumes, and publication years. Authors should use the AMA style to format their references. Examples follow:

Journal:

1. Cohn KH, Ornstein DL, Wang F. The significance of allelic deletions and aneuploidy in colorectal carcinoma: results of a 5-year follow-up study. Cancer. 1997;79:233-244.

Book:

1. Givan AL. Flow cytometry: first principles (2nd edition). New York: John Wiley & Sons, Inc., 2001.

Book Chapter:

1. Luketich JD, Ginsberg RJ. Diagnosis and staging of lung cancer. In: Johnson BE, Johnson DH. Lung cancer. New York: Wiley-Liss, Inc., 1995:161-73.

Response to Reviews – Reviewer 1

Manuscript ID: AIChE-16-18004

Title: Scaling of Continuous Twin Screw Wet Granulation

Authors: Juan G. Osorio, Ridade Sayin, Arjun V. Kalbag, Laura Martinez-Marcos, Dimitrios A. Lamprou, Gavin W. Halbert and James D. Litster

First, we would like to thank Reviewer #1 for his/her valuable comments and input. Reviewer's comments are addressed below and changes to the manuscript were made and are noted in red as the font color.

Reviewer 1 comments and responses below:

This is a timely and significant manuscript which should be published with minor revisions. I don't think this work addresses the fullness of scale up issues but I also don't think it should. I think it is just a start of the discussion. That said, I feel the authors need to better define the scope of their work so newcomers to the field are not inclined to quote this work for inappropriate systems. I will expand on this below.

SPECIFIC COMMENTS

1. The main objective paragraph should provide some information on how broadly the authors expect the current state of these dimensionless groups to be applied. For example, the validation of this work was done for wet granulation of a typical immediate release formulation in a screw with one compacting element. Are the authors implying the same groups are universal to controlled release, hot melt granulation, etc or should these groups be restricted to systems closely resembling the validated process for now?

Response: We have revised the main objective paragraph to include that these studies were performed for an immediate release formulation. The main objective paragraph also makes reference that this work is specific for twin screw wet granulation as described below.

Text already in Introduction: p.5, lines 53-56 and p.6, lines 3-4.

Added text to the manuscript: p.6, lines 15-20.

Added text to the manuscript: p.20, lines 39-42.

2. While I may not personally subscribe to all of the chosen dimensionless numbers used in this analysis, I don’t think my choices are relevant to this review either. It is evidence that the field has many rich discussions yet to come. That said, I think it is contingent upon the authors to explain their choices as well as their selection of processing parameters. For example, I was particularly interested to see that screw speed was selected as a parameter though it is often considered only a minor or negligible contributor. There will need to be a representative factor of the shear stresses on these particles but I question if screw speed is providing that. Having an explanation for all of the selected parameters will allow greater discussion in the literature later.

Response: The selection of processing parameters is explained in detail in the “Developing potential scaling rules using dimensionless analysis” section in pages 6-9. Specific to the screw speed, in this case, the Froude number, the text below was already included as part of the manuscript.

Text already in manuscript: p.9, lines 20-25

Added text to the manuscript: p.4, lines 55-56 and p.5, lines 3-9.

3. The authors are cautioned on their accretions that these extruders are geometrically scaled just because they are made by the same manufacturer. The 16mm and 24mm may be geometrically scaled (well reasonably close based on their diameter ratios) but that would be highly unlikely of the 11mm. The shafts would break too rapidly if that were the case. Quoting diameter ratio would be advised in the experimental section but this comment is more meant as a means to explain deviations in the results and discussion section.

Response: The overall dimensions of screw elements do scale with the barrel diameter. For example, the screw elements have an L:D ratio of 1 at all three granulator scales. However, the reviewer is correct that in detail, some of the geometry may not scale exactly. We have modified the manuscript in several places with qualifying statements to reflect this. See our response to reviewer 2 questions below:

Reviewer 2-1. Section 2 **-** Line 2: Is this L indicating the post wetting granulator length?

Response: Yes, *L* is the post wetting granulator length. This has been clarified in the symbol definition in the first paragraph of the “Developing the scaling rules using dimensionless analysis” section in pages 6-9.

Reviewer 2-3. ‘By keeping the TSGs geometrically similar’: What does keeping TSGs geometrically similar means? TSGs contain unit elements of screws with features like channel depth, clearance from barrel, kneading discs thickness, etc... Is geometric scaling of these features done? Is that approach justified?

Response: As the reviewer points out, our statement here is too loose. We made the following change to the manuscript in the paragraph following eqn.7, p.7, lines 39-44.

Reviewer 2-4. 'Turnover of volume in the shaft': Only here authors acknowledge the fact that they are working with "turnover of volume in the shaft due to the screw rotation", but throughout the manuscript the authors choose to ignore that clearance which is geometrically scaling if it remains unacknowledged.

Response: This was ignored on purpose. The study was performed on scaling the processing parameters not the geometric parameters. This is useful to be able to use equipment which is readily/commercially available in industrial settings as well as what manufacturers already produce. This work should raise awareness of this point and the previous point made in this review. No changes were made to the manuscript.

Reviewer 2-9 - 'This means that the powder will go through 1.5 CEs more in the 11mm and 24mm TSG than in the 16mm TSG after liquid addition before reaching the DFS.' Are these geometrical differences accounted to have a meaningful comparison?

Response: In the context of this study, we believe this unavoidable difference in geometry has a small effect. No changes were made to the manuscript.

Reviewer 2-10. Can it be explained why Fr and PFN had little effect on GSD? Is that suggesting to select a wider experimental domain? Material throughput normally has strong impact on GSD.

Response: We hypothesize that the resilience of the GSD to changes in operating conditions is due to the mechanisms controlling GSD development. These are largely geometrically controlled breakage of large wet granules and some powder layering. These processes are insensitive to screw speed and hold up. We think the reviewer is correct that if the *PFN* was increased sufficiently, different behavior would be observed where extrusion and/or jamming may occur. We have observed this with other screw element configurations that are not part of this study.

Different studies, referenced in the Introduction, have shown different effect of powder flow rate on the granule properties, specifically size. In our case, with the screw configuration used, the *PFN* at one scale did not generate much effect on the particle size. On the other hand, we are finalizing a manuscript using other screw configurations which show that for there is a larger effect of *PFN* and *Fr* on granule size, therefore it is dependent on the scale and the screw configuration.

Reviewer 2-11 - Statement "Results suggest that breakage of large granules and lumps is dependent on geometry of the screw elements." is that geometry or scale of geometry? Moreover, isn't that suggesting that the applied scaling principle is incorrect?

Response: Yes, it is the scale of geometry of the screw elements to which we refer. This clarification was made in the manuscript in p.15, line 45. Please see responses to comments #3, #4 and #10 as well.

4. Considering the different feeders being used in this study, the accuracy and precision of each to hold setpoint should be quoted. Similarly, the accuracy and precision of each pump should be provided.

Response: For the 11mm TSG experiments, a volumetric feeder was used. The calibration was performed using the controller input to determine the mass flow rate. This yielded a linear function for our fairly free-flowing powder blend used in all experiments. For the powder feeder, the standard deviation of the feed rate was low, as indicated by the error bars. The relative standard deviation of the feed rate was 9.67% for the low flow rates (~1 kg/hr) and 1.3% for the high flow rates (~5 kg/hr). Intrinsically, there will be more variability at low powder flow rates than high powder flow rates.

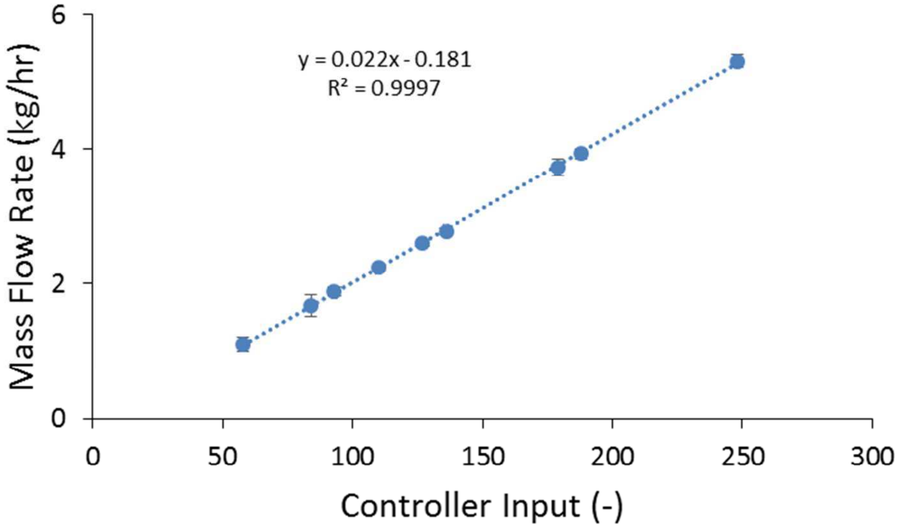

Figure showing volumetric feeder calibration for the powder feeder used for the 11-mm TSG experiments

For the 11mm TSG experiments, the liquid feeder pump was calibrated every day before running experiments. Unfortunately, we did not save the calibration information. Nevertheless, we took one representative sample for each experiment ran in the 11mm TSG. For each sample, the moisture content, and ultimately, the measured liquid to solid ratio (*LSR*) was analyzed and quantified using a moisture analyzer. This information is shown in the figure below. Each data point belongs to one experiment. The overall average is within the theoretical *LSR* and the difference between the measured *LSR* and theoretical *LSR* (shown in the second figure below) is within acceptable limits due the nature when feeding powders and the additional variability added when using a peristaltic pump to feed the granulating liquid, in this case water. Further samples would have to have been analyzed to get a mean value and variability for each single experiment.

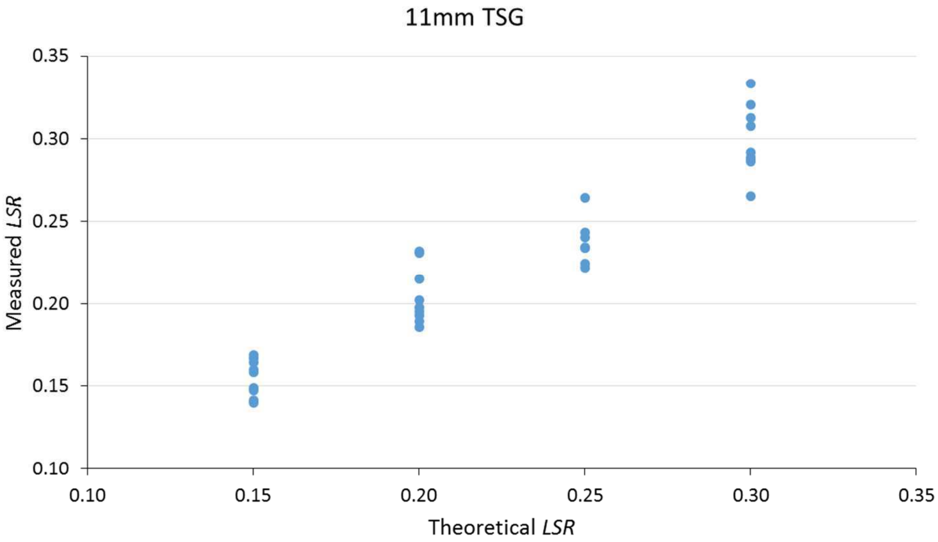

Figure showing measured *LSR* and theoretical *LSR* for the 11mm TSG experiments

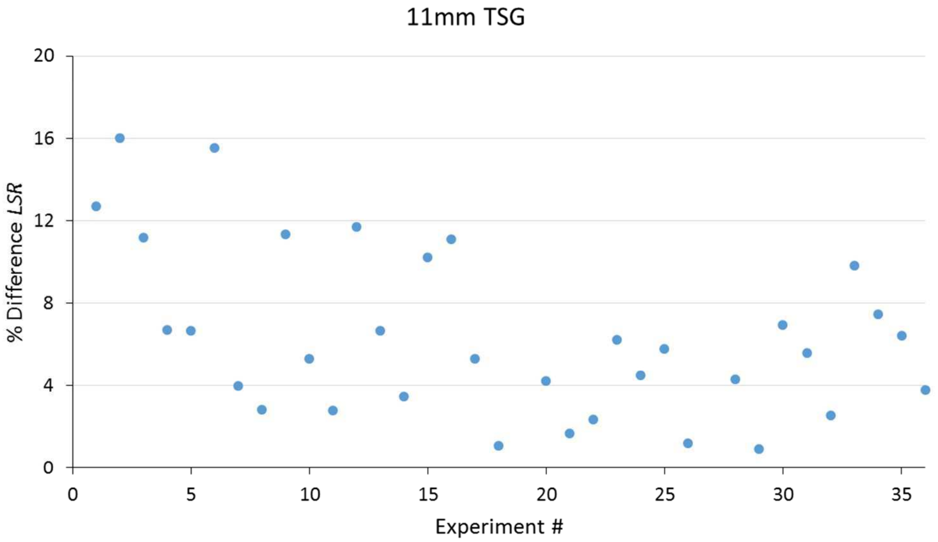

Figure showing the difference between measured *LSR* and theoretical *LSR* for the 11mm TSG experiments

The same analysis was performed for the 16mm TSG experiments. A sample was taken for each experimental run to measure their moisture content, and ultimately, the measured *LSR*. This information is shown in the figure below. Each data point belongs to one experiment. The overall average is within the theoretical *LSR* and the difference between the measured *LSR* and theoretical *LSR* (shown in the second figure below) is within acceptable limits due the nature when feeding powders and the additional variability added when using a peristaltic pump to feed the granulating liquid. This analysis was not performed for the 24mm TSG, we hypothesize that feeding at higher feed rates both for powder and liquid will yield similar or better *LSR* values (with less variability and difference between the measured and theoretical *LSR* values). In addition, both the

powder and liquid feeders used for the 16mm and 24 mm TSG experiments were also calibrated every day before running the experiments.

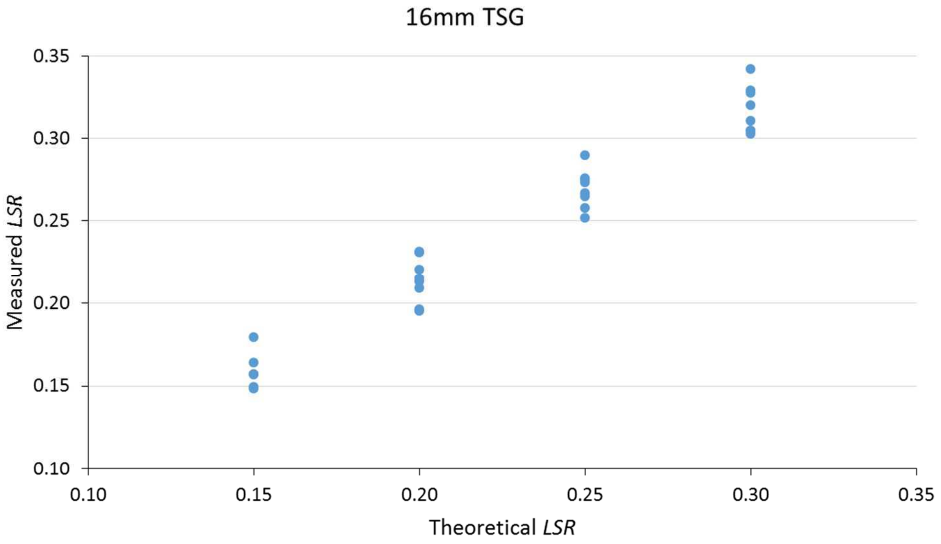

Figure showing measured LSR and theoretical *LSR* for the 16mm TSG experiments

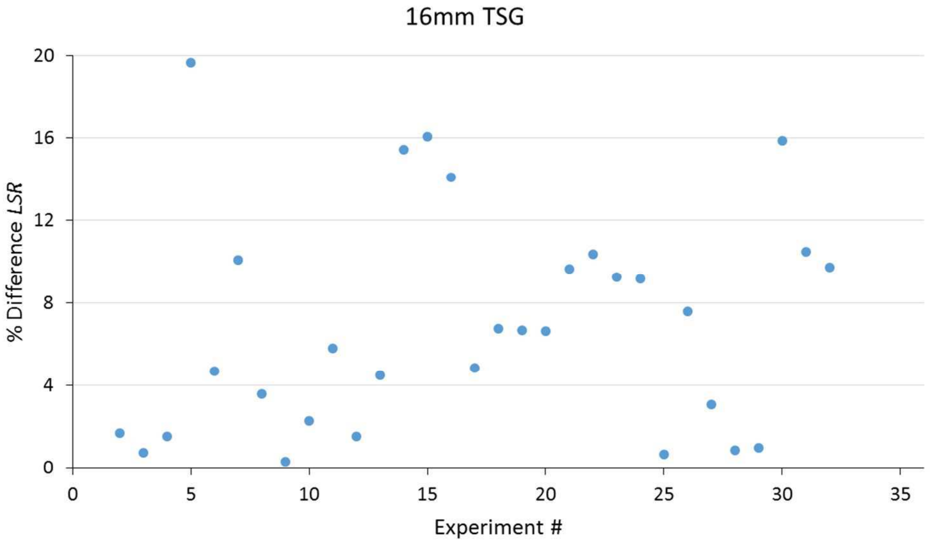

Figure showing the difference between measured LSR and theoretical *LSR* for the 16mm TSG experiments

Added text to the manuscript, p.10, line 57 and p.11, lines 3-41

5. The authors have highlighted the split liquid stream with the 24mm but not clarified how that made the process different with respect to granulation.

Response: Added text to the manuscript: p.11 lines 49-57 and p.12, lines 3-8.

6. Pg 12. How does the state of saturation vary with the selected L/S ratios?

Response: Added text to the manuscript: p.14, lines 36-45.

7. I would like to see more discussion in the text on Figures 7 and 8. These are the first real comparisons made of scaling factors in the manuscript and the authors are glossing over important details. In general, Fr does not look like a good scaling factor for particle size – decent for d50 but poor for the breadth indicators of d90 and d10. PFN seems much better relative to LSR. Though even for PFN, d90 seems poorly correlated. To be honest, the fact that d90 isn't captured well doesn't surprise me with the selected geometric parameters – but I think the authors should be giving much deeper discussion here.

Response: The statistical analysis of all the data (see Table 3 in p.51 in manuscript) shows that there is no statistical difference of either *PFN* or *Fr* on d_{10} and d_{50} over the full data set. For this reason, we are reluctant to speculate too much on the modest effects of these parameters seen on the subset of the full data given in Figures 7 and 8. Note that there is a detailed discussion of mechanisms and implications in the Results and Discussion section for which we have made some modifications as described in p.16, lines 15-27.

8. Figure 9 – caption could be improved to clearly indicate that all three extruders were involved.

Response:

The following text was modified for captions containing TSG scale: "Figure 9 – Effect of TSG scale (barrel diameter) and *LSR* and on (A) d_{10}, (B) d_{50}, and (C) d_{90}. Other parameters: Mean values of *Fr* at *PFN*=1.30x10^{-2}"

"(barrel diameter)" was added to the text in Figures 6, 10 and 11 caption as well to clarify this.

9. I question whether the x-axis of Figure 9 is really appropriate for comparison. Diameter alone is really not a scaling factor. Depending on the dominant mechanisms – i.e. stress, residence time, etc, it is usually D^2 or D^3. I wonder if the authors have reviewed scaling theory in extruders? I can direct you to the book "Polymer Extrusion" by Chris Rauwendaal for some interesting discussion. There is also a more appropriate book by James L. White on twin screws but the name eludes me.

Response: The dimensionless analysis in Eqn. 3 suggests that dxx may be proportional to D if other dimensionless groups are held constant. The actual scaling factors (*LSR*, *PFN*, and *Fr*) are constant in all three TSG scales used in this Figure and others for comparison

purposes. In the discussion, we hypothesize that d_{90} is controlled by the largest gap that a granule can pass through unbroken, which is proportional to the barrel diameter *D*. Therefore, we believe that plotting d_{90} vs *D* gives a good way to test this hypothesis.

Added text to the manuscript in p.16, lines 47-49.

10. In fact, Figure 9 and 11a don't seem consistent with the theme of this paper which is on scaling factors. There aren't any in either. The authors seem to be wandering off topic. I have also have concerns about the limited evidence provided by Figure 12 in terms of scaling but think the data is still valuable. Perhaps the authors could at least attempt to identify which parameter, LSR, Fr, or PFN was most influential for liquid distribution? Otherwise the figure and the results for Figure 12 seem unhelpful to the present paper.

Response: We respectfully disagree that there are no scaling factors in Figure 9 and 11. Figure 9 was just explained in the previous response. Regarding Figure 11, the authors want to show the effect of scaling parameters (*LSR*, *PFN* and *Fr*) on the granule porosity and determine if there was an effect of TSG scale (barrel diameter) on the granule porosity as well. The authors did not fully show/characterize the effect of *PFN* and *Fr* on the liquid distribution in this study. Also, the liquid distribution was only performed for the low *LSR (0.15)* as changes in liquid distribution are most evident at the lowest liquid to solid ratio. Given that we had established that some particle size parameters were scale dependent, even when *LSR*, *Fr* and *PFN* were held constant, we believe it is still valuable to publish the more limited data on liquid distribution to show that it is insensitive to TSG diameter. A qualifying statement has been added to the manuscript in p.18, line 6.

11. PG 13. "the size of gap through which a granule can flow without breakage scales directly with the barrel diameter." In the broadest sense this is true but it is not technically correct. The diameter ratio and the diameter determine the gap. Twin screw extrusion has advanced considerably over the last two decades, going from a diameter ratio of 1.55 to 1.7. Different suppliers give different ratios based on the torque requirements of the extruder (which are little for TSG) and in-house design knowledge. I am simply pointing out that your statement is out of step with extrusion technology.

Response: For the DFS element used in this study, the maximum distance between the teeth in the DFS did indeed scale directly with barrel diameter. Note that this is not the ratio between the barrel diameter and the shaft diameter. To avoid confusion, we have rephrased the sentence as described on p.19, lines 37-42.

12. I don't think Figure 10 is necessary.

Response: This figure has been removed since these effects are shown in previous figures.

Response to Reviews – Reviewer 2
Manuscript ID: AIChE-16-18004

Title: Scaling of Continuous Twin Screw Wet Granulation

Authors: Juan G. Osorio, Ridade Sayin, Arjun V. Kalbag, Laura Martinez-Marcos, Dimitrios A. Lamprou, Gavin W. Halbert and James D. Litster

First, we would like to thank Reviewer # 2 for his/her valuable comments and input. Reviewer's comments are addressed below and changes to the manuscript were made and are noted in red as the font color.

Reviewer 2 comments and responses below:

Section 2:

1. Line 2: Is this L indicating the post wetting granulator length?

Response: Yes, *L* is the post wetting granulator length. This has been clarified in the symbol definition in the first paragraph of the "Developing potential scaling rules using dimensionless analysis" section in p.6, line 37.

2. Formula Froude number: D cannot be barrel diameter, but should be screw/impeller diameter if being used to calculate the Fr number. This will be in principle incorrect as inertial forces are driven by the diameter of the screws. In the high shear environment of the twin-screw granulator, the clearance between screw and barrel is a very important factor which cannot be ignored. This should be corrected.

Response: The reviewer is correct. In practice, however, the clearance between the screw elements and the barrel wall is small, approximately 2.6% of the barrel diameter. For simplicity, we used the barrel diameter D. To highlight this approximation, the text in p.9, lines 25-35 has been added at the end of the section of developing scaling rules.

3. 'By keeping the TSGs geometrically similar': What does keeping TSGs geometrically similar means? TSGs contain unit elements of screws with features like channel depth, clearance from barrel, kneading discs thickness, etc... Is geometric scaling of these features done? Is that approach justified?

Response: As the reviewer points out, our statement here is too loose. We made changes to the manuscript in the paragraph following eqn.7, p.7, lines 39-44.

4. 'Turnover of volume in the shaft': Only here authors acknowledge the fact that they are working with "turnover of volume in the shaft due to the screw rotation", but throughout the manuscript the authors choose to ignore that clearance which is geometrically scaling if it remains unacknowledged.

Response: This was ignored on purpose. The study was performed on scaling the processing parameters not the geometric parameters. This is useful to be able to use equipment which is readily/commercially available in industrial settings as well as what manufacturers already produce. This work should raise awareness of this point and the previous point made in this review. No changes were made to the manuscript.

5. Calculation F1: What is Aelem; is it area of different screw elements? If so, how was it computed? Please provide the procedure.

Response: Text in p.8, lines 38-41 was added to the manuscript.

Section 3.1:

6. Please provide grade of HPMC used in this study

Response: The grade of HPMC was added and its supplier corrected in Table 1.

7. ‘For the 24mm TSG, the liquid feed stream coming from the pump is split into two streams after it reaches the inlet port in the TSG. This is different in the 11mm and 16mm TSG, where only one liquid stream is fed into the granulators.’ => What is the expected impact of this?

Response: Text in p.11, lines 49-57 and p.12, lines 3-9 was added to the manuscript.

Figure 2

8. zone 4-8 in the screws seem to have no role, why are these appointed as different zones?

Response: The zone numbers correspond to manufacturer descriptions and are commonly used by practitioners. Therefore, we included them in the figure to avoid confusion and emphasize we did not use the full length of the TSG in our experiments.

9. 'This means that the powder will go through 1.5 CEs more in the 11mm and 24mm TSG than in the 16mm TSG after liquid addition before reaching the DFS.' Are these geometrical differences accounted to have a meaningful comparison?

Response: In the context of this study, we believe this unavoidable difference in geometry has a small effect. No changes were made to the manuscript.

Section 4.1.

10. Can it be explained why Fr and PFN had little effect on GSD? Is that suggesting to select a wider experimental domain? Material throughput normally has strong impact on GSD.

Response: We hypothesize that the resilience of the GSD to changes in operating conditions is due to the mechanisms controlling GSD development. These are largely geometrically controlled breakage of large wet granules and some powder layering. These processes are insensitive to screw speed and hold up. We think the reviewer is correct that if the *PFN* was increased sufficiently, different behavior would be observed where extrusion and/or jamming may occur. We have observed this with other screw element configurations that are not part of this study.

Different studies, referenced in the Introduction, have shown different effect of powder flow rate on the granule properties, specifically size. In our case, with the screw configuration used, the *PFN* at one scale did not generate much effect on the particle size. On the other hand, we are finalizing a manuscript using other screw configurations which show that for there is a larger effect of *PFN* and *Fr* on granule size, therefore it is dependent on the scale and the screw configuration.

11. Statement "Results suggest that breakage of large granules and lumps is dependent on geometry of the screw elements." is that geometry or scale of geometry? Moreover, isn't that suggesting that the applied scaling principle is incorrect?

Response: Yes, it is the scale of geometry of the screw elements to which we refer. This clarification was made in the manuscript in p.15, line 45. Please see responses to comments #3, #4 and #10 as well.

Section 4.3.:

12. Statement 'a striking feature of this study is how little effect the basic process parameters, powder flow rate and screw speed, and their dimensionless counterparts PFN and Fr have on the granule properties, indicating the robust nature of TSG. => Isn't it too early to claim this with a single formulation study? It could be that this specific formulation is less sensitive compared to other formulations.

Response: This is reasonable criticism. Text in p.18, lines 48-58 was modified in the manuscript.