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Tailored Granule Properties Using 3D Printed Screw Geometries in Twin Screw Granulation

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ABSTRACT

Twin screw granulation is becoming increasingly relevant due to its compact size, continuous and robust mode of operation, customizable design, and flexible production capacity. This work describes the experimental study undertaken to understand the dependence of granule properties on the screw element design in a twin screw granulator. A CAD geometry analysis of the free volume in the granulator revealed that there is a direct quantitative correlation between the screw geometry and the maximum size and aspect ratio of the granules obtained using conveying elements. Conveying element geometries with different pitch lengths were 3D printed to generate cost-effective prototypes of the designs. Wet granulation experiments were performed using the 3D printed designs to test the hypothesis that the correlation between the granule shape and maximum granule size and the screw element geometry is predictable a priori. The

feasibility of 3D printing method for fabricating new screw element designs is examined. Quality-by-Design strategies and scale-up criteria for twin screw granulation are discussed.

Keywords: 3D printing, conveying elements, twin screw granulation, Quality-by-Design

1. Introduction

Continuous granulation has several advantages over the batch mode of operation, such as improved process efficiency and control, and higher material throughput [1]. ~~Commonly used industrial continuous granulators include high shear granulators, fluidized bed granulators, drum granulators, and twin screw granulators.~~ Twin screw granulators have a flexible design, short residence time, robust operation, and small equipment footprint~~, and capital cost~~ compared to the other continuous granulation methods and, hence, is of particular interest [2–4]. Twin screw granulation is different from the other continuous granulation methods due to 1) short residence times resulting in different rate dominating mechanisms, and 2) compartmental design resulting in nucleation separated from other granulation rate processes [5–8]. ~~In order to optimize the twin screw granulation operation for desired granule properties, it is essential to understand the key parameters affecting the critical quality attributes of granules.~~

~~The twin screw granulator primarily operates in the mechanical dispersion regime, relying largely on breakage of wet powder mass for effective liquid distribution. As a result, wet granule breakage is an important rate process in twin screw granulation.~~ Previous literature in twin screw granulation has shown that ~~G~~granule ~~breakage~~ properties ~~in a twin screw granulator is~~ are a strong function of the screw element type and geometry. ~~Literature reports focused on studying the different screw element designs have shown that granule properties are sensitive to the geometry of the screw elements.~~ Conveying elements ~~are shown to~~ give bimodal granule size distributions ~~and~~ with porous, elongated granules, ~~[8]. Conveying elements~~and are classified as low shear transport elements that ~~cause granule chipping and~~ mainly control the maximum granule size [8,9]. The maximum granule size in conveying elements is equal to the maximum diameter of a sphere that can fit in the region between the conveying element flights and the granulator barrel [9]. It was observed that as the pitch of the conveying elements decreases, there is an increase in the granule porosity and the mass fraction of fine and oversized granules [7]. In another report, increasing the pitch of conveying elements resulted in an increased mass fraction of medium sized granules (500-1180 µm), the granule aspect ratio, and the granule porosity [10].

~~The bimodal size distribution arises from the low shear behavior of conveying elements, resulting in large mass fraction of fines.~~ It is hypothesized that the distance between the flights of the conveying element significantly influences the extent of breakage in conveying elements, and the presence of conveying elements downstream of mixing elements reduces the fraction of oversized agglomerates [11–14]. Kneading elements are classified as high shear elements that result in dense, elongated granules with good mixing of the wet mass in the granulator [5,11]. The intermeshing region between the kneading discs is primarily responsible for breakage and liquid distribution [8,15]. ~~The reverse configurations show an improved liquid distribution compared to their forward counterparts [5].~~ Distributive mixing elements result in a more monomodal granule size distribution compared to the kneading and conveying elements, ~~[6–8].~~ ~~These elements cut and recombine the material to produce~~ and rounded granules that are more porous than kneading elements ~~[8]~~ [6–8]. The breakage mechanism in distributive mixing elements is shown to be granule crushing, and the maximum granule size in distributive mixing elements is also strongly governed by the screw element geometry [9].

Screw geometry also plays a significant role during scale-up of the twin screw granulator. The influence of Froude number, liquid to solid mass ratio, granulator scale, and powder feed number was studied on the granule size distribution, liquid distribution, and granule porosity using the distributive feed screw design [16]. Process parameters, represented by the Froude number and the powder feed number, had little to no influence on the granule properties [16]. In contrast, it was found that the granule d90 varied linearly with the screw diameter, indicating that the screw geometry directly affects the large granule sizes. Similar conclusions were obtained for a kneading and conveying element screw configuration at two different granulator scales, with a higher fraction of large granules observed in the large scale granulator [17]. Since screw element geometry has been shown to have a significant effect on granule properties during scale-up of the twin screw granulator, it is essential to study how the element geometry quantitatively affects the critical quality attributes of granules in order to develop effective ~~scaling~~ scale-up rules.

3D printing is also referred to as additive manufacturing, and involves the fabrication of a part by deposition of the material of construction as individual layers, instead of casting, forging, milling, or welding [18,19]. 3D printing provides the ability to manufacture complex geometries using a variety of materials such as polymers, metals, alloys, and ceramics [20,21]. It is suitable for fabricating customized products at a lower cost and reduced lead time, and is especially useful for rapid prototyping [18,19,22].

In this study, we have developed a quantitative correlation between the granule properties and the screw element geometry in conveying elements. We have also presented a proof-of-concept for 3D printing of screw elements as a cost-effective method for developing new screw element geometries.

2. Materials and Methods

2.1. Element Geometry Analysis and Conveying Element Designs

The dimensions of the open volume in conveying elements were determined using Computer Aided Drafting (CAD) files of the screw elements. The diameter of the largest sphere that could fit between the screw element and the barrel was used as an estimate of the largest granule size that could be produced by the element, and was determined from the CAD geometry. Three geometries of double-flighted conveying elements were considered based on the conveying element screw lead length to screw diameter ratio (L/D ratio): 0.5 L/D, 1 L/D, and 2 L/D. The CAD geometry of the 1 L/D conveying element was obtained from Thermo Fisher Scientific, as these screw elements were part of the EuroLab 16 mm twin screw granulator (Thermo Fisher Scientific, Karlsruhe, Germany) used in this work's experiments. The 0.5 L/D and 2 L/D conveying element designs and the barrel geometry were constructed as CAD files using the SolidWorks 2014 SP5.0 software. The conveying element designs with the dimensions and the sphere analysis are shown in Figure 1.

The 1 L/D conveying elements were obtained from Thermo Fisher Scientific, as part of the twin screw granulator, and were constructed of steel. The 0.5 L/D conveying elements were 3D printed using ABS Greyflex polymer and the 2 L/D conveying elements were 3D printed using the OP13 polymer. Both were produced in an EnvisionTEC Xtreme 3SP 3D printer. The 0.5 L/D conveying elements have a significantly smaller screw pitch compared to the 2 L/D conveying elements, and were fabricated using a softer and more flexible polymer to enable easier meshing of the twin screws. Since conveying elements do not cause significant breakage of the wet granular mass [9], the stress exerted on the wet granules is expected to be small for all three screw designs in this work. Furthermore, the surface finish of the 3D printed screw geometries was approximately 100 µm, which was set by the thickness of one printed polymer layer. Hence, differences in the material of construction or the surface finish of the screw elements is not expected to have a significant effect on the stress exerted on the wet granules or the flow of the wet granular material.

2.2. Materials

Multicomponent blends used for the granulation experiments consisted of 70% active pharmaceutical ingredient (API), 16.5% mannitol (Pearlitol 160C, Roquette Pharma, Lestrem, France), 5.4% microcrystalline cellulose (Avicel PH101, FMC Biopolymer, Wallingstown, Ireland), 5.1% sodium starch glycolate (Glycolys, Roquette Pharma, Lestrem, France), and 3% hydroxypropyl cellulose (Klucel, Ashland, Hopewell, USA). To assess the impact of changing formulation properties in conveying elements, three different APIs were considered for the 1 L/D conveying element experiments, namely, caffeine (BASF, Germany), micronized acetaminophen (micronized APAP) (Mallincrodt, Derbyshire, UK), and semifine acetaminophen (semifine APAP) (Mallincrodt, Derbyshire, UK). A high drug dose (70% API) was selected for the formulations as the APIs have significantly different properties, and the impact of changing the API properties are most easily observed for high drug dose formulations. Experiments for the 0.5 L/D and 2 L/D conveying elements were performed using the 70% caffeine blend. All the blend components were mixed in a Tote blender (Tote Systems, Fort Worth, USA, 5 L capacity, fill level ~ 2/3rd of total volume) at 16 RPM for 40 minutes, with a sieving step after the first 20 minutes using a 4 mm sieve to break large lumps. Deionized water with 0.1% w/w Nigrosin dye (Sigma Aldrich Corp., St. Louis, MO) was used as the granulating liquid for all the granulation experiments.

2.3. Raw Material Particle Size Distribution

The particle size distributions of the API and excipients were measured using wet dispersion laser diffraction in a Malvern Mastersizer 2000 Light Diffraction Particle Size Analyzer. A saturated solution in ethanol was used as dispersant for caffeine, and a saturated solution in water was used as a dispersant for micronized and semifine APAP. Saturated solutions in ethanol were used as dispersant for microcrystalline cellulose and mannitol. The particle size distribution of hydroxypropyl cellulose and sodium starch glycolate were not measured, as these materials tend to swell when wet. Three replicate measurements were performed on powder samples obtained from different locations in the bulk. Due to the presence of multiple components in the blend, each requiring a different dispersant, wet dispersion laser diffraction was not a suitable method for measuring the particle size distribution of the dry, un-granulated blends. Hence, sieve analysis was used to measure the size distribution of the un-granulated blends, as described in Section 2.5.

2.4. Granulation Experiments

The granulation experiments were conducted in a EuroLab 16 mm 25:1 length-to-diameter ratio twin screw granulator (Thermo Fisher Scientific, Karlsruhe, Germany). Figure 2 shows a sketch of the experimental set up. Experiments were conducted for double-flighted conveying elements, with 0.5, 1, and 2 L/D, respectively. The powder blend was fed into the twin screw granulator using a gravimetric feeder (Brabender Technologie, ON, Canada) with a feedback control loop. The feeder stabilization time was determined by the time required for the actual powder mass flow rate to match the set point, and was different for the three powders used. Stable feeder operation and steady state of the twin screw granulator was maintained during all granulation experiments by ensuring the actual powder mass flow rate was equal to the set point, and the screw torque was constant with time. All samples were collected after 120 s of granulator operation, as residence time studies for a 16 mm twin screw granulator have shown 60 s is sufficient time for the granulator to achieve steady state at the process conditions considered in this work [23,24]. A Masterflex peristaltic pump was used for feeding the liquid binder at different liquid flow rates to achieve the desired liquid to solid (L/S) mass ratio in the range of 0.15 to 0.30 in increments of 0.05. The experiments for 70% micronized APAP blends were performed at a powder mass flow rate of 3.5 kg/h and a screw speed of 800 RPM, due to the cohesive nature of the blend. All the other experiments were performed at a powder mass flow rate of 4 kg/h and a screw speed of 800 RPM, corresponding to a powder feed number of 0.011 (calculated as per [16]). Although the powder mass flow rate for the 70% micronized APAP blend experiments was different than the 70% semifine APAP and caffeine experiments, powder mass flow rate is shown to have little to no effect on the final granule properties [16]. Separate experiments were also performed for 70% micronized APAP blend at different powder mass flow rates to confirm this result. The product granules were tray dried at room conditions for 48 hours, before further characterization. Two replicate experiments were performed for the 1 L/D conveying elements. Since no significant variation was observed in the replicates, one experiment was performed for the 0.5 and 2 L/D conveying elements.

2.5. Granule/Blend Size Distribution

The size distributions of the dried granules and un-granulated blends were measured by sieve analysis using a $\sqrt{2}$ geometric series of sieves ranging from 63 μm to 8 mm. The mass based size distribution was normalized as,

$$f_i(ln\,x) = \frac{y_i}{ln(\bar{x}_{i+1}/\bar{x}_i)}, \qquad \text{Eq. (1)}$$

where y_i is the mass fraction in size interval i and $\bar{x}_i$ is the mean sieve size corresponding to interval i.

2.6. Liquid Distribution

The Nigrosin dye in the granulating liquid was used as the tracer for measurement of the amount of dye in each sieved granule fraction. The liquid distribution measurements were performed for the 70% micronized and semifine APAP granules at an L/S ratio of 0.15. Three granule samples of 1 g from each sieve cut were placed in a glass vial and mixed with 5 ml of deionized water. The mixture was sonicated for 1 h to ensure disintegration of the granules and dissolution of the dye in the aqueous phase. The suspension was poured in a 50 ml centrifuge tube and the vial was rinsed with 5 ml of deionized water, which was also added to the centrifuge tube. The samples were centrifuged for 10 minutes at 10,000 RPM using an Eppendorf Centrifuge 5804. Five milliliters of supernatant was withdrawn for dye concentration determination by UV-Vis spectroscopy analysis using a Cary UV Vis 300 spectrophotometer. The absorbance of the dye was measured at a wavelength of 574 nm and the dye concentration was determined using a calibration curve.

2.7. Granule Shape Characterization

Granule shape characterization was performed by image analysis. One hundred granules were randomly sampled from the size cuts of 2 to 2.36 mm, 2.8 to 3.35 mm, and 1.4 to 1.7 mm for 0.5, 1, and 2 L/D conveying elements, respectively for a midpoint L/S ratio of 0.25. Granule images were recorded using a 12 MP camera. Two dimensional granule image analyses were performed using the ImageJ 1.51h software. The scale of the image was set using a calibration standard in the image. Image cleaning was performed using the threshold function in ImageJ and the shape parameters were evaluated using the shape descriptor analysis tool.

3. Results and Discussion

3.1. Geometric Analysis and 3D Printing of Screw Elements

Figure 1 shows the CAD drawing of the double-flighted conveying elements with 0.5, 1, and 2 L/D enclosed in the barrel. Each element has a major diameter of 15.6 mm and minor diameter of 8.6 mm. The diameter of the conveying elements is slightly smaller than the barrel diameter of 16 mm, and the clearance allows for smooth rotation of the screws during operation. The pitch of the 0.5, 1, and 2 L/D conveying elements is 2.9 mm, 7.0 mm, and 14.8 mm, respectively. The space enclosed between the pitch of the screw, the barrel, and the depth of the screw is the maximum space for material in the conveying elements. Figure 1 shows that a granule in the conveying elements can follow two possible paths denoted by the arrows:

1) The granule can be conveyed along the axis of the barrel by the axial component of the flight velocity

2) The granule can follow a helical path along the flights of the conveying element.

In both cases, the granule encounters an unobstructed region of constant maximum size in the conveying element. Hence, it is expected that the granular material will have a maximum size related to the dimensions of this region. The maximum size in the screw elements was determined by evaluating the largest diameter of a sphere that can fit in this region. The maximum size in the 0.5 L/D conveying element was 2.9 mm, and in the 1 L/D and 2 L/D conveying elements was 3.49 mm. The maximum size in the 0.5 L/D conveying element was governed by the pitch of the screw. In contrast, the maximum size in the 1 and 2 L/D conveying elements was governed by the distance between the barrel wall and the depth of the screw thread. The predicted aspect ratio is determined from the ratio of the pitch length of the screw and the distance between the barrel and the depth of the screw thread from the CAD drawing. The predicted aspect ratio was calculated to be 1.2, 2.0, and 4.2 for 0.5, 1, and 2 L/D conveying elements, respectively,

$$Predicted\ aspect\ ratio = \frac{screw\ pitch\ length}{screw\ channel\ depth} \qquad \text{Eq. (2)}$$

The 0.5 and 2 L/D conveying element geometries were 3D printed using the materials described in Section 2.1. The CAD files obtained from the SolidWorks 2014 SP5.0 software are converted into the STL file type for printing in an EnvisionTEC 3SP printer. The high speed printing process allows for printing several copies of the screw elements within a few hours, without compromising the surface quality of the parts. ~~The twin screw granulator is a compact piece of equipment with a small free volume available for granulation; hence, it is essential to achieve high precision and good surface quality when 3D printing screw designs.~~ The thickness of one layer of printed polymer is approximately 100 μm and, consequently, the printer is capable of capturing and effectively printing small design features without surface stair-stepping on the inner or outer surfaces. The 3D printing method of fabrication using polymers is cost effective, as the screw elements cost at most $1 per piece. The images of the 3D printed elements (0.5, 2 L/D) and the original conveying element (1 L/D) after use in granulation experiments are shown in Figure 3. The screw elements were used for an operation period of 60 minutes and show ~~little to no~~no significant signs of wear after use. This result suggests that 3D printing is a fast, accurate, and cost effective method for fabricating new screw element geometries for testing.

~~The CAD geometry of a distributive mixing element (DME) was also constructed in the SolidWorks software using methods described elsewhere [9], and was considered for 3D printing using polymers. However, the geometry of the DMEs and the printing method requires having supports on the DME blade during printing. Under the current printer configuration, the supports penetrate into the DME blade, thus limiting the minimum blade thickness of the DME that can be printed without causing cracks in the part. Furthermore, the polymer 3D printed elements were likely to break due to pressure build-up in the granulator, during the wet granulation experiments. 3D printing of the distributive mixing screw elements using metals or polymers designed for printing automotive parts may be a possible solution to prevent the breakage of the parts during operation.~~

3.2. Raw Material Characterization

The volume frequency distributions of the API and excipients are shown in Figure 4, and the particle size distribution analysis is shown in Table 1. The average data from three replicates with a ± 95% confidence interval is shown in the table. Micronized APAP has the smallest average particle size among the three APIs whereas semifine APAP has the largest average particle size. Since the d90 of micronized APAP and caffeine is smaller than 100 µm, it is expected that a significant portion of the 70% micronized APAP and 70% caffeine blend is smaller than a mean sieve size of 100 µm. However, the sieve analysis of the dry, un-granulated blends (Figure 5) shows a smaller than expected mass of –100 µm particles for the 70% micronized APAP blend. The blend size distribution shows a shift to the larger particle sizes, with a considerable amount of +500 µm particles. This result indicates dry agglomeration of the 70% micronized APAP blend, which remains stable during sieving. The 70% caffeine blend shows the smallest extent of dry agglomeration and was used as the powder blend for understanding granulation in 3D printed elements, as described in Section 3.5.

Size distribution parameter (µm)	Micronized APAP	Semifine APAP	Caffeine	Mannitol	MCC
$d_{3,2}$ (Sauter mean diameter)	7.2 ± 0.7	23.2 ± 4.9	9.2 ± 3.1	54.3 ± 7.6	83.4 ± 0.4
$d_{4,3}$ (weighted average volume diameter)	23.6 ± 2.8	98.8 ± 16.0	40.3 ± 5.9	191.2 ± 22.3	28.8 ± 1.6
d10	5.4 ± 0.9	18.3 ± 2.5	11.0 ±7.6	38.9 ± 2.7	21.9 ± 0.2
d50 (median)	20.5 ± 2.7	71.9 ± 12.5	36.1 ± 4.0	140.8 ± 9.8	72.9 ± 1.3
d90	46.0 ± 5.0	210.9 ± 39.3	75.0 ± 7.7	422.3 ± 59.4	160.5 ± 2.9

Table 1: Particle size distribution analyses of APIs and excipients. Average from three replicates including a ± 95% confidence interval.

3.3. Granule Size Distribution in Conveying Elements

The granule size distributions for the 70% API blends at different L/S ratios in 1 L/D conveying elements are shown in Figure 6. The size distributions are bimodal in shape for all the blends. This behavior is typical of conveying elements [14,25]. The bimodal shape results from the low shearing behavior of conveying elements [9]. The liquid feed is introduced in the granulator through a drip nozzle at the nucleation zone (zone 2, in Figure 2). The nucleation zone, therefore, has a mixture of large nuclei and un-granulated powder blend, each amounting to the coarse and fine modes of the distribution, respectively. Since conveying elements mainly cause granule layering [5,13,14], the distribution remains primarily bimodal (Figure 6). As the L/S ratio increases, t~~T~~he amount of fines decreases ~~with an increase in the L/S ratio~~ due to increased availability of the granulating liquid, resulting in coalescence, which results in a smaller fraction of un-granulated fines [5,13]. This result is consistent with the observations in the literature [2]. The size distribution remains bimodal throughout the range of L/S ratios considered in this work. This observation is additional evidence to the conclusion that conveying elements ~~only~~ mainly cause wet granule layering and no significant liquid redistribution.

The first mode of the granule size distribution for the 70% micronized APAP granules is positioned at a larger mean sieve size compared to the 70% caffeine granules, despite micronized APAP having a smaller primary particle size compared to caffeine. It is interesting to note that the position of the first mode of the distribution for the 70% API blends corresponds closely to the modes of the dry blend size distributions measured using sieve analysis. This result suggests that the first mode in the granule size distribution mainly consists of dry agglomerates of the un-granulated blend, which remain intact during granulation and granule characterization. ~~This outcome is in accordance with the conclusion that conveying elements are low shearing transport elements that do not cause intense mixing.~~ The second mode of the distribution shows a sharp cut-off at a mean sieve size of 3.5 mm for the three blends at all L/S ratios considered. This ~~maximum granule size~~cut-off at a mean sieve size of 3.5 mm corresponds to the maximum sphere diameter obtained from the CAD geometry analysis described in Section 3.1. Hence, the maximum granule size depends strongly on the screw element geometry, which is not typical of any other granulator and could be used to tailor granule attributes. This analysis shows that the maximum granule size and the position of the first mode in conveying elements are predictable a priori.

3.4. Liquid Distribution in Conveying Elements

The liquid distribution across granule sizes was measured at the lowest L/S ratio (0.15) in 70% micronized and semifine APAP granules. The largest differences in the liquid distribution are evident at relatively low L/S ratio. Furthermore, it has been shown in the literature that the liquid distribution for conveying elements at L/S ratio of 0.15 is similar to L/S ratio of 0.2 [5,6]. Hence, the liquid distribution results for L/S ratio of 0.15 are shown in this work. Nigrosin dye was added to the granulating liquid as a tracer to quantify the liquid-to-solid mass ratio in all granule size cuts. Figure 7 shows the dye concentration, plotted as mass of dye per mass of granules, for all granule size fractions. The dye concentration represents the liquid-to-solid mass ratio of the granules in that size fraction. Since the liquid distribution results for the 70% micronized APAP (smallest particle size) and 70% semifine APAP (largest particle size) blends are similar, it was not necessary to include the caffeine results. The liquid distribution curve shows that there is little to no dye in the fines up to a 300 μm average sieve size, which also corresponds to the tail of the first mode of the granule size distributions (Figure 6). This result confirms that the first mode of the distribution is un-wet powder agglomerates and the outcome is in accordance with the conclusion that conveying elements do not cause redistribution of the granulating liquid.

3.5. Granulation Experiments with 3D Printed Elements and Granule Image Analysis

The granule size distributions of the granules from the 0.5, 1, and 2 L/D conveying elements for the 70% caffeine blend at all L/S ratios considered are shown in Figure 8. As expected, the granule size distributions from all of the conveying elements are bimodal due to the large mass fraction of un-wet powder dry agglomerates that constitute the fines region of the size distribution. The mass fraction of large granules increases with an increase in the L/S ratio for all three conveying elements, as coalescence is facilitated due to greater availability of the granulating liquid. This phenomenon has been commonly observed in the literature [5,25–27].

The first mode is positioned at a mean sieve size of 76.5 μm, which corresponds to the mode of the 70% caffeine dry blend sieve size distribution. Comparing the granule size distributions of the 0.5 and 1 L/D conveying elements, it is observed that the 1 L/D conveying elements result in a markedly larger amount of large granules compared to the 0.5 L/D conveying elements. It is also interesting to note that the 0.5 and 1 L/D conveying elements do not produce granules larger than 3.1 mm and 3.6 mm mean sieve size, respectively. These results agree with the geometric model proposed previously, where the maximum sizes in the 0.5 and 1 L/D conveying elements are 2.9 mm and 3.5 mm, respectively. The maximum size is referred to as the size of the largest granules that can be obtained from the screw elements. The size distribution of the 2 L/D conveying elements does not follow this trend. This behavior may be because the granules from these conveying elements were more elongated in shape and size measurements using sieve analysis depend upon the orientation of the granules as they pass through the mesh. It is also important to note that the elongated granules tend to be fragile and can break during sieving. Hence, the sieving size measurement of these granules can be misleading. Although the sieve analysis method of size distribution measurement will affect the results for all three types of conveying elements depending on the aspect ratio, the largest errors are expected for the 2 L/D conveying elements. This expectation is because the aspect ratio of the 2 L/D conveying elements are significantly larger than one, whereas the aspect ratio of granules from the 0.5 and 1 L/D conveying elements is close to one.

~~The second mode in the distributions is the mean sieve size corresponding to the maximum mass frequency of the larger granules whereas the first mode corresponds to the maximum mass frequency of the un-wet fines.~~ Image analysis was performed on the granules in the sieve cut corresponding to the ~~second mode~~mode at larger granule sizes of each distribution for an L/S ratio of 0.25 (midpoint L/S ratio). The largest mass fraction of granules are obtained in the size range of 2 to 2.36 mm, 2.8 to 3.35 mm, and 1.4 to 1.7 mm for the 0.5, 1, and 2 L/D conveying elements, respectively, and hence these size ranges are considered most practically relevant. Images of granules from 0.5, 1, and 2 L/D conveying elements are shown in Figure 9. It is evident from Figure 9 that the granule shape is a strong function of the screw pitch in the conveying elements. The 0.5 L/D conveying elements produce rounded granules. In contrast, the 2 L/D conveying elements produce highly elongated, thread-like granules. The aspect ratio (AR) distribution was measured as per the image analysis described in Section 2.7. The AR distribution is reported for granules of ~~mean sieve size 2.2 mm, 3.1 mm, and 1.6 mm~~in the size range of 2 to 2.36 mm, 2.8 to 3.35 mm, and 1.4 to 1.7 mm for 0.5, 1, and 2 L/D conveying elements, respectively, in Figure 10.

As mentioned in Section 3.1, the screw pitch of the 0.5, 1, and 2 L/D conveying elements is 2.9 mm, 7.0 mm, and 14.8 mm, respectively, whereas the distance between the barrel and the depth of the screw thread remains at 3.5 mm. The comparison of the experimentally measured AR and the one predicted from the CAD drawing is shown in Table 2. The experimentally measured AR is reported as the mean ± standard deviation of the distribution in Figure 9. The screw pitch to channel depth ratio calculated from the CAD geometry (equation 2) matches closely with the experimentally measured AR.

Screw Type	Experimentally measured AR	Screw pitch to channel depth ratio from CAD drawing
0.5 L/D	1.3 ± 0.2	1.2
1 L/D	1.8 ± 0.4	2.0
2 L/D	3.8 ± 1.9	4.2

Table 2: Aspect Ratio (AR) from experimental measurements and predicted from the CAD drawings.

Figure 11 shows the correlation between the AR measured from experiments and the CAD drawings of the conveying elements. The data follows a straight line through the origin with a slope of 0.9 confirming the geometric analysis of the conveying elements.

3.6.Tailored Granule Attributes and Scale-up Criteria

This work demonstrates the quantitative correlation between the granule size and shape, and the geometry of the conveying screw elements. This correlation is unique to twin screw granulators due to their small free volume and regime-separated operation, and can be used to develop Quality-by-Design strategies for continuous wet granulation. The maximum granule size and granule shape can be controlled by design by modifying the geometry of the screw elements appropriately. Conveying elements are ideal for layering and coating applications or trimming the granule shape and maximum size to achieve target requirements. In contrast, kneading and distributive mixing elements are designed for intense mixing of the powder and granulating liquid to obtain more monomodal granule size distributions and denser granules. Free volume analysis using CAD geometries aid in the understanding of the granule size and shape, and new screw element designs can be developed based on the process requirements. It is recommended that 3D printing of kneading, distributive mixing, or new screw element design prototypes utilize metals or polymers for automotive parts in order to increase element durability. ~~3D printing using polymers or metals is an effective method for fabrication of new screw element design prototypes.~~

There are two possibilities for scaling of the twin screw granulator as described in the literature: scaling up and scaling out. Scaling out refers to operating the granulator at increased screw speed and powder mass flow rate while maintaining powder feed number, to increase the production capacity. Scale-up refers to increasing the screw and barrel diameter of the granulator [16]. The strong dependence of granule properties on screw geometry suggests development of geometric scaling rules for twin screw granulation scale-up. ~~The twin screw granulator scale-up is most sensitive to screw diameter, with little effect of process parameters on the scaling [16].~~ We have shown that the channel depth strongly governs the maximum granule size. As a result, maintaining geometric similarity of conveying elements during scale up is likely to produce disparity in the d90 of the granule size distribution at different granulator scales, as observed in the literature [16]. To maintain similar granule size and shape, the ratio of the major diameter to minor diameter of the conveying element double flighted screw must be maintained and the channel depth should remain constant during scale-up. ~~These scale-up criteria result in maintaining equal free volume in the twin screw granulator, thereby increasing the powder feed number in the granulator if the large scale powder feed rate is high. It is possible that these may cause issues of powder jamming, backup of material in the granulator, and flooding in the granulator. Increasing the screw speed to maintain constant powder feed number is a possible solution to this challenge. Alternatively, maintaining equal material feed rate while extending processing time at large scale will also accomplish the same objective.~~

4. Conclusions

Conveying elements cause poor liquid distribution during the wet granulation operation, resulting in a bimodal granule size distribution. The first mode primarily consists of un-wet powder, and the position of the first mode corresponds to the mode of the dry blend sieve size distribution. The maximum granule size in conveying elements is dependent on the screw geometry and is equal to the maximum equivalent sphere diameter of the free volume in the screw channel, as assessed by CAD geometry analysis. The aspect ratio of the granules produced by conveying elements was approximately proportional to the ratio of the screw pitch to the distance between the barrel and the depth of the screw thread. The ability to 3D print the screw elements provides additional design flexibility and the advantage of prototype testing. As shown in this work, it is a convenient and cost effective method for testing design improvements in the twin screw granulator.

The direct quantitative correlation between the geometry of the screw elements and the size and shape of the granules produced by wet granulation is a step towards quality-by-design (QbD), effective scale-up criteria, and tailored granule characteristics. The breakage mechanism in the granulator and the resulting size distribution can be changed by choosing the type and design of the screw elements. This understanding is promising for designing new screw element geometries for improved control over granule properties.

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