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

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17 **ABSTRACT**

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

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

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

31 1. Introduction

32 Continuous granulation has several advantages over the batch mode of operation, such as
33 improved process efficiency and control, and higher material throughput [1]. ~~Commonly used~~
34 ~~industrial continuous granulators include high shear granulators, fluidized bed granulators, drum~~
35 ~~granulators, and twin screw granulators.~~ Twin screw granulators have a flexible design, short
36 residence time, robust operation, and small equipment footprint, ~~and capital cost~~ compared to the
37 other continuous granulation methods and, hence, is of particular interest [2–4]. Twin screw
38 granulation is different from the other continuous granulation methods due to 1) short residence
39 times resulting in different rate dominating mechanisms, and 2) compartmental design resulting
40 in nucleation separated from other granulation rate processes [5–8]. ~~In order to optimize the twin~~
41 ~~screw granulation operation for desired granule properties, it is essential to understand the key~~
42 ~~parameters affecting the critical quality attributes of granules.~~
43 ~~The twin screw granulator primarily operates in the mechanical dispersion regime, relying~~
44 ~~largely on breakage of wet powder mass for effective liquid distribution. As a result, wet granule~~
45 ~~breakage is an important rate process in twin screw granulation.~~ ~~Previous literature in twin screw~~
46 ~~granulation has shown that Ggranule breakage properties in a twin screw granulator is are a~~
47 strong function of the screw element type and geometry. ~~Literature reports focused on studying~~
48 ~~the different screw element designs have shown that granule properties are sensitive to the~~
49 ~~geometry of the screw elements.~~ Conveying elements ~~are shown to~~ give bimodal granule size
50 distributions and with porous, elongated granules, [8]. ~~Conveying elements and~~ are classified as
51 low shear transport elements that ~~cause granule chipping and~~ mainly control the maximum
52 granule size [8,9]. The maximum granule size in conveying elements is equal to the maximum
53 diameter of a sphere that can fit in the region between the conveying element flights and the
54 granulator barrel [9]. It was observed that as the pitch of the conveying elements decreases, there
55 is an increase in the granule porosity and the mass fraction of fine and oversized granules [7]. In
56 another report, increasing the pitch of conveying elements resulted in an increased mass fraction
57 of medium sized granules (500-1180 μm), the granule aspect ratio, and the granule porosity [10].

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

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

84 3D printing is also referred to as additive manufacturing, and involves the fabrication of a part by
85 deposition of the material of construction as individual layers, instead of casting, forging,
86 milling, or welding [18,19]. 3D printing provides the ability to manufacture complex geometries
87 using a variety of materials such as polymers, metals, alloys, and ceramics [20,21]. It is suitable

88 for fabricating customized products at a lower cost and reduced lead time, and is especially
89 useful for rapid prototyping [18,19,22].

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

94 2. Materials and Methods

95 2.1. Element Geometry Analysis and Conveying Element Designs

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

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

118 layer. Hence, differences in the material of construction or the surface finish of the screw
119 elements is not expected to have a significant effect on the stress exerted on the wet granules or
120 the flow of the wet granular material.

121 2.2. Materials

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

139 2.3. Raw Material Particle Size Distribution

140 The particle size distributions of the API and excipients were measured using wet dispersion
141 laser diffraction in a Malvern Mastersizer 2000 Light Diffraction Particle Size Analyzer. A
142 saturated solution in ethanol was used as dispersant for caffeine, and a saturated solution in water
143 was used as a dispersant for micronized and semifine APAP. Saturated solutions in ethanol were
144 used as dispersant for microcrystalline cellulose and mannitol. The particle size distribution of
145 hydroxypropyl cellulose and sodium starch glycolate were not measured, as these materials tend
146 to swell when wet. Three replicate measurements were performed on powder samples obtained
147 from different locations in the bulk. Due to the presence of multiple components in the blend,

148 each requiring a different dispersant, wet dispersion laser diffraction was not a suitable method
149 for measuring the particle size distribution of the dry, un-granulated blends. Hence, sieve
150 analysis was used to measure the size distribution of the un-granulated blends, as described in
151 Section 2.5.

152 2.4. Granulation Experiments

153 The granulation experiments were conducted in a EuroLab 16 mm 25:1 length-to-diameter ratio
154 twin screw granulator (Thermo Fisher Scientific, Karlsruhe, Germany). Figure 2 shows a sketch
155 of the experimental set up. Experiments were conducted for double-flighted conveying elements,
156 with 0.5, 1, and 2 L/D, respectively. The powder blend was fed into the twin screw granulator
157 using a gravimetric feeder (Brabender Technologie, ON, Canada) with a feedback control loop.
158 The feeder stabilization time was determined by the time required for the actual powder mass
159 flow rate to match the set point, and was different for the three powders used. Stable feeder
160 operation and steady state of the twin screw granulator was maintained during all granulation
161 experiments by ensuring the actual powder mass flow rate was equal to the set point, and the
162 screw torque was constant with time. All samples were collected after 120 s of granulator
163 operation, as residence time studies for a 16 mm twin screw granulator have shown 60 s is
164 sufficient time for the granulator to achieve steady state at the process conditions considered in
165 this work [23,24]. A Masterflex peristaltic pump was used for feeding the liquid binder at
166 different liquid flow rates to achieve the desired liquid to solid (L/S) mass ratio in the range of
167 0.15 to 0.30 in increments of 0.05. The experiments for 70% micronized APAP blends were
168 performed at a powder mass flow rate of 3.5 kg/h and a screw speed of 800 RPM, due to the
169 cohesive nature of the blend. All the other experiments were performed at a powder mass flow
170 rate of 4 kg/h and a screw speed of 800 RPM, corresponding to a powder feed number of 0.011
171 (calculated as per [16]). Although the powder mass flow rate for the 70% micronized APAP
172 blend experiments was different than the 70% semifine APAP and caffeine experiments, powder
173 mass flow rate is shown to have little to no effect on the final granule properties [16]. Separate
174 experiments were also performed for 70% micronized APAP blend at different powder mass
175 flow rates to confirm this result. The product granules were tray dried at room conditions for 48
176 hours, before further characterization. Two replicate experiments were performed for the 1 L/D

177 conveying elements. Since no significant variation was observed in the replicates, one
178 experiment was performed for the 0.5 and 2 L/D conveying elements.

179 **2.5.Granule/Blend Size Distribution**

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

$$183 \quad f_i(\ln x) = \frac{y_i}{\ln(\bar{x}_{i+1}/\bar{x}_i)}, \quad \text{Eq. (1)}$$

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

186 **2.6.Liquid Distribution**

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

199 **2.7.Granule Shape Characterization**

200 Granule shape characterization was performed by image analysis. One hundred granules were
201 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,
202 1, and 2 L/D conveying elements, respectively for a midpoint L/S ratio of 0.25. Granule images
203 were recorded using a 12 MP camera. Two dimensional granule image analyses were performed
204 using the ImageJ 1.51h software. The scale of the image was set using a calibration standard in

205 the image. Image cleaning was performed using the threshold function in ImageJ and the shape
206 parameters were evaluated using the shape descriptor analysis tool.

207 **3. Results and Discussion**

208 **3.1. Geometric Analysis and 3D Printing of Screw Elements**

209 Figure 1 shows the CAD drawing of the double-flighted conveying elements with 0.5, 1, and 2
210 L/D enclosed in the barrel. Each element has a major diameter of 15.6 mm and minor diameter
211 of 8.6 mm. The diameter of the conveying elements is slightly smaller than the barrel diameter of
212 16 mm, and the clearance allows for smooth rotation of the screws during operation. The pitch of
213 the 0.5, 1, and 2 L/D conveying elements is 2.9 mm, 7.0 mm, and 14.8 mm, respectively. The
214 space enclosed between the pitch of the screw, the barrel, and the depth of the screw is the
215 maximum space for material in the conveying elements. Figure 1 shows that a granule in the
216 conveying elements can follow two possible paths denoted by the arrows:

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

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

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

$$232 \text{ Predicted aspect ratio} = \frac{\text{screw pitch length}}{\text{screw channel depth}} \quad \text{Eq. (2)}$$

233 The 0.5 and 2 L/D conveying element geometries were 3D printed using the materials described
234 in Section 2.1. The CAD files obtained from the SolidWorks 2014 SP5.0 software are converted
235 into the STL file type for printing in an EnvisionTEC 3SP printer. The high speed printing
236 process allows for printing several copies of the screw elements within a few hours, without
237 compromising the surface quality of the parts. ~~The twin screw granulator is a compact piece of
238 equipment with a small free volume available for granulation; hence, it is essential to achieve
239 high precision and good surface quality when 3D printing screw designs.~~ The thickness of one
240 layer of printed polymer is approximately 100 μm and, consequently, the printer is capable of
241 capturing and effectively printing small design features without surface stair-stepping on the
242 inner or outer surfaces. The 3D printing method of fabrication using polymers is cost effective,
243 as the screw elements cost at most \$1 per piece. The images of the 3D printed elements (0.5, 2
244 L/D) and the original conveying element (1 L/D) after use in granulation experiments are shown
245 in Figure 3. The screw elements were used for an operation period of 60 minutes and show ~~little~~
246 ~~to none~~ significant signs of wear after use. This result suggests that 3D printing is a fast,
247 accurate, and cost effective method for fabricating new screw element geometries for testing.

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

258 **3.2.Raw Material Characterization**

259 The volume frequency distributions of the API and excipients are shown in Figure 4, and the
260 particle size distribution analysis is shown in Table 1. The average data from three replicates
261 with a $\pm 95\%$ confidence interval is shown in the table. Micronized APAP has the smallest
262 average particle size among the three APIs whereas semifine APAP has the largest average

263 particle size. Since the d90 of micronized APAP and caffeine is smaller than 100 μm , it is
 264 expected that a significant portion of the 70% micronized APAP and 70% caffeine blend is
 265 smaller than a mean sieve size of 100 μm . However, the sieve analysis of the dry, un-granulated
 266 blends (Figure 5) shows a smaller than expected mass of $>100 \mu\text{m}$ particles for the 70%
 267 micronized APAP blend. The blend size distribution shows a shift to the larger particle sizes,
 268 with a considerable amount of $>500 \mu\text{m}$ particles. This result indicates dry agglomeration of the
 269 70% micronized APAP blend, which remains stable during sieving. The 70% caffeine blend
 270 shows the smallest extent of dry agglomeration and was used as the powder blend for
 271 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 \pm 0.7	23.2 \pm 4.9	9.2 \pm 3.1	54.3 \pm 7.6	83.4 \pm 0.4
d _{4,3} (weighted average volume diameter)	23.6 \pm 2.8	98.8 \pm 16.0	40.3 \pm 5.9	191.2 \pm 22.3	28.8 \pm 1.6
d10	5.4 \pm 0.9	18.3 \pm 2.5	11.0 \pm 7.6	38.9 \pm 2.7	21.9 \pm 0.2
d50 (median)	20.5 \pm 2.7	71.9 \pm 12.5	36.1 \pm 4.0	140.8 \pm 9.8	72.9 \pm 1.3
d90	46.0 \pm 5.0	210.9 \pm 39.3	75.0 \pm 7.7	422.3 \pm 59.4	160.5 \pm 2.9

272
 273 Table 1: Particle size distribution analyses of APIs and excipients. Average from three replicates
 274 including a $\pm 95\%$ confidence interval.

275 3.3.Granule Size Distribution in Conveying Elements

276 The granule size distributions for the 70% API blends at different L/S ratios in 1 L/D conveying
 277 elements are shown in Figure 6. The size distributions are bimodal in shape for all the blends.
 278 This behavior is typical of conveying elements [14,25]. The bimodal shape results from the low

279 shearing behavior of conveying elements [9]. The liquid feed is introduced in the granulator
280 through a drip nozzle at the nucleation zone (zone 2, in Figure 2). The nucleation zone, therefore,
281 has a mixture of large nuclei and un-granulated powder blend, each amounting to the coarse and
282 fine modes of the distribution, respectively. Since conveying elements mainly cause granule
283 layering [5,13,14], the distribution remains primarily bimodal (Figure 6). As the L/S ratio
284 increases, the amount of fines decreases with an increase in the L/S ratio due to increased
285 availability of the granulating liquid, resulting in coalescence, which results in a smaller fraction
286 of un-granulated fines [5,13]. This result is consistent with the observations in the literature [2].
287 The size distribution remains bimodal throughout the range of L/S ratios considered in this work.
288 This observation is additional evidence to the conclusion that conveying elements ~~only~~ mainly
289 cause wet granule layering and no significant liquid redistribution.

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

306 **3.4. Liquid Distribution in Conveying Elements**

307 The liquid distribution across granule sizes was measured at the lowest L/S ratio (0.15) in 70%
308 micronized and semifine APAP granules. The largest differences in the liquid distribution are

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

322 **3.5. Granulation Experiments with 3D Printed Elements and Granule Image Analysis**

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

330 The first mode is positioned at a mean sieve size of 76.5 μm , which corresponds to the mode of
331 the 70% caffeine dry blend sieve size distribution. Comparing the granule size distributions of
332 the 0.5 and 1 L/D conveying elements, it is observed that the 1 L/D conveying elements result in
333 a markedly larger amount of large granules compared to the 0.5 L/D conveying elements. It is
334 also interesting to note that the 0.5 and 1 L/D conveying elements do not produce granules larger
335 than 3.1 mm and 3.6 mm mean sieve size, respectively. These results agree with the geometric
336 model proposed previously, where the maximum sizes in the 0.5 and 1 L/D conveying elements
337 are 2.9 mm and 3.5 mm, respectively. The maximum size is referred to as the size of the largest
338 granules that can be obtained from the screw elements. The size distribution of the 2 L/D

339 conveying elements does not follow this trend. This behavior may be because the granules from
340 these conveying elements were more elongated in shape and size measurements using sieve
341 analysis depend upon the orientation of the granules as they pass through the mesh. It is also
342 important to note that the elongated granules tend to be fragile and can break during sieving.
343 Hence, the sieving size measurement of these granules can be misleading. Although the sieve
344 analysis method of size distribution measurement will affect the results for all three types of
345 conveying elements depending on the aspect ratio, the largest errors are expected for the 2 L/D
346 conveying elements. This expectation is because the aspect ratio of the 2 L/D conveying
347 elements are significantly larger than one, whereas the aspect ratio of granules from the 0.5 and 1
348 L/D conveying elements is close to one.

349 ~~The second mode in the distributions is the mean sieve size corresponding to the maximum mass~~
350 ~~frequency of the larger granules whereas the first mode corresponds to the maximum mass~~
351 ~~frequency of the un-wet fines.~~ Image analysis was performed on the granules in the sieve cut
352 corresponding to the ~~second mode~~ mode at larger granule sizes of each distribution for an L/S
353 ratio of 0.25 (midpoint L/S ratio). The largest mass fraction of granules are obtained in the size
354 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
355 elements, respectively, and hence these size ranges are considered most practically relevant.

356 Images of granules from 0.5, 1, and 2 L/D conveying elements are shown in Figure 9. It is
357 evident from Figure 9 that the granule shape is a strong function of the screw pitch in the
358 conveying elements. The 0.5 L/D conveying elements produce rounded granules. In contrast, the
359 2 L/D conveying elements produce highly elongated, thread-like granules. The aspect ratio (AR)
360 distribution was measured as per the image analysis described in Section 2.7. The AR
361 distribution is reported for granules of mean sieve size 2.2 mm, 3.1 mm, and 1.6 mm in the size
362 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
363 elements, respectively, in Figure 10.

364 As mentioned in Section 3.1, the screw pitch of the 0.5, 1, and 2 L/D conveying elements is 2.9
365 mm, 7.0 mm, and 14.8 mm, respectively, whereas the distance between the barrel and the depth
366 of the screw thread remains at 3.5 mm. The comparison of the experimentally measured AR and
367 the one predicted from the CAD drawing is shown in Table 2. The experimentally measured AR
368 is reported as the mean \pm standard deviation of the distribution in Figure 9. The screw pitch to

369 channel depth ratio calculated from the CAD geometry (equation 2) matches closely with the
370 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

371

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

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

377 **3.6.Tailored Granule Attributes and Scale-up Criteria**

378 This work demonstrates the quantitative correlation between the granule size and shape, and the
379 geometry of the conveying screw elements. This correlation is unique to twin screw granulators
380 due to their small free volume and regime-separated operation, and can be used to develop
381 Quality-by-Design strategies for continuous wet granulation. The maximum granule size and
382 granule shape can be controlled by design by modifying the geometry of the screw elements
383 appropriately. Conveying elements are ideal for layering and coating applications or trimming
384 the granule shape and maximum size to achieve target requirements. In contrast, kneading and
385 distributive mixing elements are designed for intense mixing of the powder and granulating
386 liquid to obtain more monomodal granule size distributions and denser granules. Free volume
387 analysis using CAD geometries aid in the understanding of the granule size and shape, and new
388 screw element designs can be developed based on the process requirements. **It is recommended**

389 **that 3D printing of kneading, distributive mixing, or new screw element design prototypes utilize**

390 ~~metals or polymers for automotive parts in order to increase element durability. 3D printing~~
391 ~~using polymers or metals is an effective method for fabrication of new screw element design~~
392 ~~prototypes.~~

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

412 **4. Conclusions**

413 Conveying elements cause poor liquid distribution during the wet granulation operation,
414 resulting in a bimodal granule size distribution. The first mode primarily consists of un-wet
415 powder, and the position of the first mode corresponds to the mode of the dry blend sieve size
416 distribution. The maximum granule size in conveying elements is dependent on the screw
417 geometry and is equal to the maximum equivalent sphere diameter of the free volume in the
418 screw channel, as assessed by CAD geometry analysis. The aspect ratio of the granules produced

419 by conveying elements was approximately proportional to the ratio of the screw pitch to the
420 distance between the barrel and the depth of the screw thread. The ability to 3D print the screw
421 elements provides additional design flexibility and the advantage of prototype testing. As shown
422 in this work, it is a convenient and cost effective method for testing design improvements in the
423 twin screw granulator.

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

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