

# The impact of channel fill level on internal forces during continuous twin screw wet granulation

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## 1 The impact of channel fill level on internal forces during continuous twin

## 2 screw wet granulation.

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#### 23 ABSTRACT

The forces experienced by the particles inside a twin screw granulator (TSG) are one of the 24 most difficult parameters to measure quantitatively. However, it is possible to perform 25 accurately this measurement through the use of dye containing calibrated microencapsulated 26 sensors (CAMES) whose rupture is directly dependant on their experienced shear stress. The 27 current study measures the extent of local stresses in the transformation from powder to 28 granules at different channel fills during TSG processing. Channel fill has shown good 29 potential as a design tool, however, its validity for predicting particle size distributions has yet 30 31 to be demonstrated in an 11-mm TSG. The results of this study showed that the particles within the twin screw granulator experienced stresses in the range of 350-1000 kPa and this 32 value was not linear with the specific mechanical energy applied by the granulator. It was 33 34 observed that the majority of these stresses were produced by material transport processes rather than the granulation in itself. In addition it was determined that the torque required by 35 the TSG increases exponentially after a certain channel fill a feature that requires to be 36 considered in order to design safer, predictable and reliable granulation workspaces. 37

Keywords: Twin screw granulation, Design space, Stress, Channel fill level, Particle size
distribution, Continuous wet granulation

# 40 **ABBREVIATIONS**

41	В%	Percentage of broken sensors
42	CAMES	Calibrated Microencapsulated sensors
43	$C_{eq}$	Standardised concentration
44	Ci	Initial concentration
45	C100%	100% rupture of sensors concentration.
46	$C_{stock}$	Concentration of the stock solution
47	d10	Intercept 10 of the particle cumulative distribution
48	F	Powder feed rate (kg/hr)
49	L/S	Liquid-to-solid ratio
50	L/D	Length to Diameter ratio
51	mi	Sample mass (g)
52	ṁ	Powder flowrate
53	n	Number of repetitions
54	Ν	Screws velocity
55	nv	Volumetric efficiency of the conveyor
56	PSD	Particle Size Distribution
57	R2	Coefficient of determination
58	UV	Ultraviolet
59	$V_{\rm F}$	Conveyor free volume

60	VMD	Volume mean diameter
61	SME	Specific Mechanical Energy
62	Т	Torque
63	TSG	Twin-Screw Granulator
64	$\Delta \Phi$	Difference of channel fill
65	Φ	Channel fill fraction
66	σ <sub>CAMES</sub>	Shear stress calculated by the calibrated CAMES

### 68 **1. INTRODUCTION**

Granulation is a common industrial operation for particle size enlargement, which traditionally has been performed in batch based operations. Continuous granulation processes which offer advantages such as improved quality, rapid API sparing development and greater flexibility have driven interest to shift towards continuous operation. Continuous granulation not only offers the probability of enhanced product quality it also simplifies and reduces risk in the development process by using the same equipment in both development and production processes (Keleb et al., 2002; Van Melkebeke et al., 2008).

One of the common equipment items evaluated to perform continuous granulation are the twin 76 screw granulators (TSGs) (Mundozah et al., 2018; Silva et al., 2018). The advantage of this 77 equipment is the flexibility offered from the high number of possible working environments 78 achieved by changing different sections of the screw assembly, different segment geometries 79 or feed port locations (Dhenge et al., 2011; Djuric and Kleinebudde, 2008). Even within a 80 constant screw and barrel configuration, a wide range of different outputs can be obtained by 81 varying conditions such as feed rate or liquid/solid ratio (Mendez Torrecillas et al., 2017; 82 Thompson, 2014). However, the current state of art of this technology leads to a high 83 84 experimental burden that does not yet allow the full realisation of the anticipated acceleration and active pharmaceutical ingredient (API) savings in pharmaceutical development process. 85

The establishment of a flexible design space based on scale independent approaches would have value in setting process control strategies as well as being advantageous during the product lifecycle when the throughput of the process can be varied on demand. This requires an increased knowledge of the granule properties as function of the process parameters. Also, it is required to determine the acceptable working limits and conditions of the TSG equipment.

91 Previous studies have shown the capability of channel fill level as a main parameter to establish the design space (Gorringe et al., 2017; Lute et al., 2018; Osorio et al., 2017). This is normally 92 referred as the total fraction occupied by powder and granules with respect to the full volume 93 of the granulator (Gorringe et al., 2017; Lee et al., 2012). It depends on four factors: screw 94 configuration, length to diameter ratio of the granulator, feed rate and screw velocity. The 95 first two parameters are fixed properties during operation opposite to feed rate and screw 96 velocity which are process variables (Seem et al., 2015). Both parameters have been 97 extensively studied in the literature separately or combined where screw speed has been 98 reported to have a minor influence on the granules properties compared with feed rate (Dhenge 99 et al., 2011; Dhenge et al., 2010; Djuric and Kleinebudde, 2008; Keleb et al., 2004; Thompson 100 and Sun, 2010). The screw velocity is inversely proportional to the channel fill obtaining 101 higher channel fills for lower screw speeds. At the same time, increase in the feed rate, will 102 increase the channel fill. Those two process variables together have a direct effect in the 103 compaction forces applied to the wetted mass (Thompson and Sun, 2010). When the 104 granulator is at low fill, there is a reduction in the compaction force and more friable and porous 105 granules are therefore produced (Lee et al., 2012). Different equations for barrel fill have 106 been defined having the use of feed rate and screw velocity in common (Gorringe et al., 2017, 107 Osorio et al., 2017). On one side, Gorringe et al. used the fraction of the capacity of the twin 108 screw granulator which facilitates the direct transfer to production lines from research phases. 109 However, it does not take into account changes of screw configuration which limits the transfer 110 to different assemblies (Gorringe et al., 2017). On the other side, Osorio et al. used the powder 111 feed number to calculate this value where changes in configuration are considered. However, 112 the calculation requires high technical knowledge of the equipment since parameters such as 113 the cross-sectional area of the elements or net forward velocity of the powder need to be known 114 (Osorio et al., 2017). Nevertheless, both studies have shown the capability of channel fill level 115

as a main parameter to establish the design space. Channel fill fraction correlates strongly
with the granule attributes within same scale obtaining very similar granule size distributions
for runs at the same fraction at the same TSG scale (Gorringe et al., 2017, Lute et al., 2018,
Osorio et al., 2017).

Despite the potential of channel fill as a design tool, there is not an extensive knowledge base 120 indicating how the increase of channel fill affects the process within the TSG. Some studies 121 have already suggested there are inner variations due to the change in shape of the granules. 122 High channel fills have been associated with more spherical products, whereas low channel 123 fills have been reported to produce more elongated granules for the 16-mm TSG (Dhenge et 124 al., 2011; Gorringe et al., 2017). However, Verstraeten et al. concluded that the process 125 settings on a 25-mm TSG had minimum influence on the final shape of the granules whereby 126 it is dictated by the restricted volume of the kneading elements compartment (Verstraeten et 127 al., 2017). A considerable difference in some properties has also been reported for the same 128 feed rates and screw speeds possessing different granulators or scale (Djuric et al., 2009; Osorio 129 et al., 2017). Therefore, changes in granule morphology seem to indicate that changes in the 130 local forces inside the granulator are dependent on both TSG scale and process settings. In 131 any case, there are few examples of quantitative studies of the mechanical stresses in the screw 132 Traditionally, the stresses experienced by the granules in the TSG have been elements. 133 134 calculated at a global level as direct function of the torque applied by the granulator (Dhenge et al., 2012) or as function of the screw speed (Lute et al., 2018). 135

Pradhan et al. measured the breakage at different type of screw elements with pellets of ballotini glass beads mixed with liquid binder of known dynamic yield strength (up to 160 Kpa) and size. It was concluded that the breakage of the pellets was dependent on the available gap size of the screw elements. When pellets were larger than the available gap size, they appeared completely broken. Whereas, those smaller than the gap size were dependent upon their

dynamic yield strength. For the 16mm-TSG, they determined that the maximum size of 141 granule which will remain unbroken was 3.49 mm for conveyor elements and 3.18 mm for 142 distributive mixing elements. In addition, pellets under the limit showed a constant breakage 143 probability of 20% which is independent of their yield strength (Pradhan et al., 2017). Other 144 studies for the same scale measured the total stress indirectly depending on the torque and the 145 volume of solid where the suggested stress acting on the material varied between 73 and 106 146 kPa (Dhenge et al., 2012). Although those results are not directly comparable due to change 147 of scale, screw configuration and formulation, they give an indication of the order of magnitude 148 149 of the stresses experienced by the granules.

The local stress applied to the granules can be measured directly by the use of 150 microencapsulated sensor particles (CAMES), calibrated to rupture at specific critical stress 151 levels releasing a dye which can be measured spectrophotometrically. Therefore, it is possible 152 to have an accurate measurement of the total stresses exposed to a sample during its production. 153 These stress sensitive beads have already been used before in continuous extrusion obtaining 154 insight into the stress history of a hot melt extruder (Bigio et al., 2011; Pappas et al., 2012). 155 CAMES are sized equivalent to the powder input so they provide information at the correct 156 scale of scrutiny. This size characteristic will provide a more representative value than 157 previous attempts where the sensors were not at the same scale as the powder and therefore 158 experienced the inherent restrictions within channel of TSG. 159

Due to changes of density during the granulation, this study will compare the results depending on the total force applied by the granulator for unit of mass. This parameter is known as specific mechanical energy (SME) (Dhenge et al., 2013; Vercruysse et al., 2015) and it will provide an insight into global energy input /torque and help to understand the forces and loads acting on particles and how these change.

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In addition to the local mechanical stresses and channel fill, it is necessary to understand the relationship between channel fill fraction and torque used by the equipment. Increasing the transported amount of powder along the equipment would have a direct influence in the torque required. This study attempts to verify the applicability of the channel fill fraction to the 11mm TSG as well as the transferability of the CAMES measurement from extrusion to granulation. In addition, it will establish the relationship between the stress experienced by the granules at different channel fills and torque requirements.

#### **173 2. MATERIALS AND METHODS**

#### 174 2.1 Materials

#### 175 **2.1.1 Granulation**

The powder formulation contained 73.5% w/w lactose monohydrate (PubChem CID: 104938, 176 Pharmatose 200,DFE Pharma, IMCD UK Ltd, Sutton, Surrey, United Kingdom), 20% w/w 177 microcrystalline cellulose (PubChem CID: 14055602, Avicel PH101, Sigma-Aldrich Company 178 Ltd., Dorset, England), 5% w/w hypromellose (PubChem CID: 57503849, Pharmacoat 603, 179 Shin-Etsu Chemical Co. Ltd, Wiesbaden, Germany) and 1.5% w/w croscarmellose sodium 180 (PubChem CID: 6328154, Ac-Di-Sol, Danisco, Copenhagen, Denmark). The formulation was 181 blended in batches of 5 kg in a 15L blender bin for 10 minutes at 17 rpm in a Agiblend AB015 182 (Pharmatech, Coleshill, United Kingdom). Granulating liquid was distilled water (EMD 183 Millipore<sup>™</sup> Pure Water Reservoirs, Millipore SAS, Mosheim, France) which was maintained 184 at a liquid-to-solid ratio of 0.175 in weight. The volumetric mean diameter of the formulation 185 was 71.54 µm with a homogeneity factor of the PSD (Mendez Torrecillas, 2017) of 69.9%. 186

#### 187 2.1.2 Mechanical stress measurement

In order to measure the local mechanical stress, microencapsulated chemical sensors 188 (CAMES<sup>TM</sup>, Mach I, Inc., Pennsylvania, USA) were used. These microcapsules (diameter < 189 44 µm) contain an organic UV detectable blue dye in xylene encapsulated in a polymeric 190 sphere with rupture determined by the applied shear stresses (Condo and Kosowski, 1991). In 191 this case, the rupture and shear stress are related linearly in a range of 231.75 to 1224.25 kPa 192 (0-100% breakage). The blue dye is an anthraquinone (Automate<sup>™</sup> Blue 8AHF, Keystone 193 Inc, Chicago, USA) which is fully soluble in IPA (2-Propanol,  $\geq$ 99.8%, HiPerSolv 194 195 CHROMANORM® for HPLC, VWR International Limited, Lutterworth, United Kingdom)

with  $\lambda$ max of 645.77 nm. The sensors were added to 125 g batches of the formulation in a proportion of 0.53% w/w and mixed in 5 l blender at 3 rpm for 40 min.

### **198 2.2. Granulation experiments**

The experiments were carried out using a Thermofisher Pharma 11-mm Twin Screw 199 Granulator (Process 11, 40:1 L/D, Thermo Fisher Scientific, Karlsruhe, Germany) operating a 200 constant temperature of 20°C with a cooler thermostat (Eco RE630, LAUDA DR. R. WOBSER 201 GMBH & CO. KG, Lauda-Königshofen, Germany). The TSG was fed via a gravimetric feeder 202 (Brabender Gravimetric feeder DDW-MT, Brabender Technologie Gmbh & Co. Kg Duisburg, 203 Germany) and the liquid added by a syringe pump to remain a constant Liquid-to-solid ratio 204 of 0.175 (Harvard Syringe Pump, Harvard Apparatus UK, Cambridge, United Kingdom). The 205 screw configuration consisted of 1 set of 9×0.25D bilobe kneading element (60° forward), 1 × 206 207 0.25D distributive mixing element (DME), 3×1D distributive feed screws (DFS) and the rest conveyors. Samples for analysis were taken when steady state was reached after 2.5 minutes 208 which was over twice the maximum mean residence time. The residence time was calculated 209 for all the conditions dividing the material hold-up of the equipment by the feed rate (Gorringe 210 et al., 2017). Afterwards, the samples were dried for 2 h in an oven (Memmert UNB100, 211 Memmert GmbH + Co. KG, Schwabach, Germany) at 60 °C. This conditions ensured a final 212 moisture under 1% in weight 213

The channel fill for the 11-mm TSG was studied using the summary of experiments which can be found in figure 1 where the points of measurements are represented. The channel fill ( $\Phi$ ) is calculated using equation 1 (Gorringe et al., 2017).

217 
$$\Phi = \frac{\dot{m}}{n_{\nu} \rho_B \left( V_F \frac{S_L}{L} \right) N}$$

218

Eq. 1

219 Where  $\dot{m}$  is powder flowrate (kg/hr),  $n_v$  is volumetric efficiency of the screw to convey powder 220 which is assumed 100%,  $\rho_B$  is the bulk density (kg/m<sup>3</sup>), V<sub>F</sub> is the conveyor free volume 221 considered 25.04 cm<sup>3</sup> for this 11-mm TSG, S<sub>L</sub>/L is the inverse of length to diameter ratio of the 222 TSG, i.e. inverse of 40:1 for the 11-mm TSG and N is the screws velocity (rpm).

Channel fill fraction was calculated based in bulk density since the liquid will be absorbed into the voids of bulk powder. Although, the profile of the parameter is difficult to determine experimentally due to changes within the granulator, mean bulk density can be assumed constant for a given liquid to solid ratio, screw configuration and formulation (Gorringe et al., 2017).

#### 228 2.3 Offline granule size analysis

229 The analysis of the granule size distribution was performed using the QICPIC/RODOS L with vibratory feeder VIBRI/L (Sympatec GmbH System-Partikel-Technik, Clausthal-Zellerfeld, 230 Germany). All the particle size distributions obtained were measured at 0.5 bar of primary 231 pressure to avoid breakage of the granules during the analysis (MacLeod and Muller, 2012). 232 The disperser conditions were optimised for each set of granules to obtain the optimal optical 233 concentration of 0.5% during the particles measurement. All the particle size distributions 234 (PSDs) were plotted in logarithmic scale of the volume mean diameter against the density 235 distribution which were both calculated in accordance with ISO 13222-1:2014 (ISO 13322-236 1:2014, 2014). In order to compare if the PSDs are significantly equivalent, two methods were 237 used depending on the number of experiments carried out for channel fill. For those cases 238 under three experiments, F-test was used comparing the curves by the variance. This method 239 240 tests the null hypothesis if the variances of two populations are equal (Brandt and Brandt, 2014; The MathWorks Inc, 2013). When three or more experiments were carried out, Anova with 241 O'Brien homogeneity of variance assumption was used. This method will test if multiple data 242

samples have equal variances, against the alternative that at least two of the data samples do 243 not have equal variances (O'Brien, 1979; O'brien, 1981; The MathWorks Inc, 2013). This 244 method was chosen because it does not take into account the shape of the population (Wang et 245 al., 2017) as twin screw granulation produces polymodal PSDs shapes (Mendez Torrecillas et 246 al., 2017). In addition, both methods were recommended when the length of the samples is 247 smaller than 10 (Wang et al., 2017). All the analysis were performed using the software Matlab 248 and Statistics Toolbox R2017a (The MathWorks, Inc., Natick, Massachusetts, United States) 249 using each PSD as an individual level with a 0.05 significance level which is recommended for 250 scientist data (Brandt and Brandt, 2014). The PSDs were compared also depending on the 251 screw speed which will have a direct effect in the shear rate exerted on the powder mass (Lute 252 et al., 2018). Three screw speeds were compared at three level of differences between channel 253 fills (low: 0.108-0.147), medium (0.073-0.194) and high (0.046 -0.271). 254

#### 255 2.4 Calibration of the microencapsulated stress sensors

#### 256 **2.4.1 UV calibration**

To measure the microencapsulated stress sensor rupture a UV calibration relationship between 257 absorbance and concentration, covering the possible range of rupture, was determined with ten 258 systems, prepared gravimetrically (BP211D Analytical model, Sartorious, Surrey, United 259 Kingdom), between 0-60 ppm by weight. A concentrated dye provided by the manufacturer 260 (Automate<sup>™</sup> Blue 8AHF, Keystone Inc, Chicago, USA) was weighted and solved in IPA 261 obtaining three initial stock solutions of 115, 116 and 216 ppm. The concentrations were 262 obtained to be gravimetrically within the measurement range of the weight scale. The dye was 263 264 fully soluble in IPA and it was found to be fully mixed after 10 manual rotations. The subsequent solutions with concentrations between 0-60 ppmw were prepared by dissolving a 265 specific volume of stock (V<sub>stock</sub>) in IPA to reach a final total volume of 5 ml. The final 266

concentrations were recalculated depending on the exactly weight added in order to increase the accuracy of the calibration. The absorbance was analysed in a UV Spectrometer (Carl Zeiss MCS600, Oberkochen, Germany) with offline cell holder attachment (Fibre-coupled cuvette holder of 10 mm cuvettes with UV Fiber Optics, Hellma GmbH & Co, Müllheim, Germany). The calibration was repeated three times with an acceptance criteria of coefficient of regression ( $R^2$ ) over 0.999 (figure 2).

## 273 2.4.2 Dye recovery from the granules

The study of a possible interference of the formulation in the measurement of released dye was 274 investigated. The recovery of dye from both the blend and individual components of the blend 275 was determined by adding 10 ml of a 60 ppm by weight dye-IPA solutions. The solutions 276 were mixed with the blend and each of the individual components. Filtration was performed 277 using a sample processing manifold (Biotage® VacMaster<sup>™</sup> 10, Biotage, Uppsala, Sweden) 278 using syringe isolute single fritter reservoir filter 70 ml 5µm (Biotage, Uppsala, Sweden) with 279 smaller pore diameter than the d10 of the individual components particle size. Afterwards, 280 monitored vacuum was applied by a vacuum controller (BUCHI<sup>™</sup> V-850, BÜCHI 281 Labortechnik AG, Flawil, Switzerland). The dye solution recovered was analysed measuring 282 the absorbance at the same wavelength of the UV calibration (645.77 nm). 283

After filtration dye recovery was between 98-101% which is inside of the variance range of the UV spectrometer and let us concluded that released dye can be fully recovered from the materials.

## 287 2.4.3 Breakage of the microencapsulated stress sensors

The shear stress which produces sensor rupture is calibrated for each lot by the manufacturer and the relationship between the shear stress and the percentage of rupture was shown to be linear (CAMES<sup>TM</sup> SENSORS Lot 9-13-553, Mach I, Inc., Pennsylvania, USA). The rupture

of the CAMES with <44  $\mu$ m was qualitatively confirmed by the use of shear cell rotor-stator integrated with a microscopic stage (Leica Microsystems (UK) Ltd, Milton Keynes, United Kingdom). The stage was adjusted to a gap distance between the rotor and stator discs to match the mean size of the sensors and spinning speeds range of 0.01 to 5 rad / sec. In figure 3, the shear stress over the sensors was increased by the increment of the velocity of the rotor. As it was expected, the CAMES break at the increase of shear stress.

In addition to determine quantitatively the absorbance of 100% sensor rupture the sensors were mixed with the blend in 0.53% w/w proportion and compressed in a manual hydraulic press (Specac Ltd., Orpington, United Kingdom) with a die of 0.8 cm applying a force over 7000 kPa, which is higher than the maximum value indicated by the manufacturer. The fully broken capsules and the released dye were dissolved in IPA, filtered and their absorbance was analysed in UV. Five samples from different batches were analysed providing a concentration of 547.38  $\pm$  69.73 ppm<sub>w</sub> for the fully broken CAMES.

The granules obtained from the TSG were dissolved in 4-10 ml of IPA, filtered and the 304 absorbance was measured in the UV. The amount of IPA varied in order to optimise the 305 washing of the filter. The concentration was calculated using the dye-IPA calibration. 306 307 Concentrations were standardised using equation 2 depending on the exact amount of IPA and filtered solid. Afterwards, standardised concentration was divided by the concentration given 308 309 from a 100% rupture according to equation 3. From that value is possible to calculate the shear stress using equation 4 which was provided by the manufacturer (MACH I Inc, 310 Pensilvania, United States).. 311

312 
$$C_{eq} = C_i * \frac{1}{m_i} * \frac{1}{V_i}$$
 Eq. 2

313 
$$B = \frac{C_e}{C_{100\%}}$$
 Eq.3

$$\sigma_{CAMES}(kPa) = 9.925 * B(\%) + 231.75$$
 Eq. 4

Where  $C_{eq}$  is the standardised concentration (ppm),  $C_i$  is the concentration calculated from the absorbance (ppm),  $m_i$  is the mass of the sample (g),  $V_i$  is the volume of the sample (ml), B is the percentage of broken sensors (%),  $C_{100\%}$  is the concentration when 100% of the sensors are broken,  $\sigma_{CAMES}$  (kPa) is the shear stress calculated by the CAMES.

## 319 **2.5** Relationship between shear forces and channel fill in granulation

Eight replicate granulations with CAMES and ten replicate granulations without them were 320 carried out in the 11-mm TSG with a constant feed rate and L/S ratio but by varying the screw 321 velocity between 40-400 rpm (Table 1) in order to vary the torque as calculated by the 322 equipment software. In addition, the same conditions were reproduced without liquid addition 323 to study the effect of the granulation process on the torque. The results were compared with 324 both torque and specific mechanical energy for the granulations without the CAMES. 325 Formulation experiments were conducted thrice whereas a single repetition was carried out for 326 CAMES plus formulation. In addition, three different conditions at the same high channel fill 327 were studied to investigate the variability of the specific mechanical energy at same channel 328 fill. 329

In addition, the granulations with CAMES were used to compare the specific mechanical energy with total shear forces experienced by the granules. Samples of 0.5 g after reaching steady state were taken and analysed by the method explained in the previous section. The specific mechanical energy of the granulation was calculated by applying equation 5. (Dhenge et al., 2013; Godavarti and Karwe, 1997).

$$SME = \frac{2*\pi*T*N}{F}$$
 Eq.5

- 336 Where SME is the specific mechanical energy (kJ/kg), T is the motor torque of the TSG (N.m),
- N is the screws velocity (rpm) and F is the feed rate of the powder (kg/hr).

To study the relationship between local stress and channel fill, three channel fills were selected (low: 0.073, medium: 0.146 and high: 0.270) at two different velocities: 150 and 400 rpm (Table 2). In order to isolate the impact of granulation from the conveyor transport of the powder, samples of 2 grams were taken for each run at the solid feeder exit and compared with the granules at the end of the twin screw granulator before and after the binder addition.

343 **3. RESULTS** 

## 344 3.1 Demonstration of 11-mm TSG channel fill scalability

The potential of using channel fill to scale up feed rate was investigated verifying if this 345 parameter can be used to predict PSDs in the 11-mm TSG. In figure 4, six different channel 346 fills were investigated showing high similarity between their density distributions along a 347 channel fill line independent of the screw velocity. The equivalence between the shapes of 348 the PSDs is remarkable at low ( $\Phi$ =0.046 and  $\Phi$ =0.073) and high ( $\Phi$ =0.194 and  $\Phi$ =0.271) 349 channel fills where at low channel fills fines are more prevalent than at high channel fills. One 350 351 explanation for this behaviour is that the mean residence time and material hold-up increased for the same feed rate as function of the channel fill (Gorringe et al., 2017; Lee et al., 2012) 352 which could reduce the contact between powder and therefore, the granulation rate. 353

However, the middle channels show more discrepancies between them. In both cases ( $\Phi$ =0.108 and  $\Phi$ =0.147), two of the conditions presented very similar shapes and one of them was different. In order to compare statistically if the curves were significantly different, F-test and one way Anova with O'Brien homogeneity of variance assumption were performed depending on the number of experiments carried out for channel fill. In all the cases, it was

359 concluded that at 0.05 level of tolerance, there were no significant differences between PSDs360 at the same channel fill (Table 3).

In figure 5, the PSDs were compared depending on the screw speed at three levels of difference 361 of channel fill ( $\Delta \Phi$ ): low (0.039), medium (0.121) and high (0.225). In this case, it is possible 362 to observe that PSDs appeared significantly different at high level of difference of channel fill 363 but this difference was not that significant when  $\Delta \Phi$  was small. F-test statistical analysis was 364 carried out (Table 4) for the PSDs and it confirmed that at low channel fill differences, the 365 variation of channel fill is not significant. However as  $\Delta \Phi$  increases, the difference in the 366 PSDs increases too reaching a point at high levels of channel fills where the PSDs are not 367 statically equivalent anymore. This suggests the inadequacy of using screw velocity as a 368 design tool for predict PSDs this formulation. 369

#### 370 **3.2 Relationship between channels fill and torque**

The channel fill effect on the torque required was studied at a constant feed rate of 0.5 kg/hr 371 and L/S ratio and varying the screw velocity from 40 to 400 rpm (Table 1). In figure 6, the 372 force required to both transport the powder with and without the addition of granulation fluid 373 The torque necessary to move the powder when granulation takes place is 374 are presented. nearly double than when powder is only transported. This phenomena can be associated with 375 the changes of density due to the increased presence of formed granules and the resulting 376 change in powder physical properties interacting with downstream elements. As well, the 377 torque required at channel fills lower than 0.271 is relatively low in all the cases (<1.5 N.m) 378 increasing slowly (green area). However, after that point, it increases sharply (red-coloured 379 380 area). Gorringe et al. demonstrated that the material hold-up and the mean residence time inside the granulator are linear functions of the channel fill and increases considerably at low 381 screw speeds (Gorringe et al., 2017). Therefore, this change in trend could be an indication 382

that after reaching a certain point, the material hold-up within the equipment increased sharplyat small variations.

For instance, in this region, a variation of 20 rpm screw speed (±33.33%) at 60 rpm (40-80 385 rpm) will change the channel fill between 0.240 and 0.479 (equation 1) which will suddenly 386 increase the torque from 1.8 to 3.2 N.m which supposes at 77.8% change. At the same time, 387 a small variation of feed rate would produce the channel fill to fluctuate significantly. For 388 instance, a deviation of 0.05 kg/hr at 0.5 kg/hr and 60 rpm would produce a change of channel 389 fill between 0.288 and 0.352 (equation 1) which will make increase the torque around a 30.4%. 390 This can be seen as a limit of the equipment behaviour where there is a substantial change in 391 the slope of the curve. 392

The specific mechanical energy spent in granulation was estimated subtracting the values of 393 the SME used for transport of the dry powder from the values of SME used when liquid was 394 added to the system. Although the transport of dry and wet powder has not the same efficiency, 395 the SME does not take into account this difference since it is calculated as function of the total 396 amount of material introduced in the equipment which is constant in this case. 397 Figure 7a suggests that initially the specific mechanical energy value used for transport of the dry powder 398 is higher than the one used for granulation until it equalises around a channel fill of 0.18. After 399 that point energy used for granulation becomes predominant until the last channel fill value 400 where transport became predominant again over granulation. The specific mechanical energy 401 used in granulation does not vary as much as the one required from transport that varies from 402 403 206 to 36.8 kJ/kg. Furthermore, comparing figure 7a and 7b shows that after 0.27 channel fill, although the torque required increases dramatically, the specific mechanic energy used in 404 granulation is almost constant. 405

In addition, the specific mechanical energy was studied at channel fill of 0.27 produced by three different conditions (figure 8). It was found that this value was not constant depending on the channel fill and it varied highly depending on the torque requirements. However, the large size of the error bars seems to indicate that the specific mechanical energy has not a constant value along the same conditions of feed rate and screw velocity. The range variation of this parameter reduces highly its potential as process design parameter.

## 412 **3.3** Effect of the increase of channel fill and torque in the shear stress.

The CAMES were used to measure the stress experienced by the powder at different channel 413 fills. In figure 9, three different levels of channel fill at two different sets of conditions each 414 (Table 2) are presented. The local stress produced by the transport of the powder through the 415 granulator without liquid addition was consistently in the range 360-490 kPa which 416 corresponds for 55-70% of the total shear experienced by the formulation during granulation 417 conditions. This result is consistent with the results obtained in figure 6 for no liquid addition 418 where at channel fills up to 0.270, the torque required did not have great variations (0.49-0.68419 N.m) and did not present a linear trend with channel fill. The breakage of the CAMES in this 420 case is due only to the transport of the powder through the equipment since no liquid addition 421 422 was done at that point. In addition, figure 9 suggests that the local stress experienced in the combined granulation and transport process increases when channel fill increases within 423 channel fill range in figure 9. As the transport only data suggest this is not due to transport, 424 this increase would be due only to granulation which is consequent with the increment in size 425 observed in the PSDs in figure 4. However, with the variability obtained is not possible to 426 confirm this trend and it is only possible to conclude that there is a significant increase in stress 427 due to addition of water to give the granulation process. 428

Granulation using a constant feed rate of 0.5 kg/hr and L/S=0.175 and varying the screws velocity between 40-400 rpm (Table 1) are presented in figure 10 with the local stress plotted against the channel fill with the specific mechanical energy as labels. Interestingly the results suggest that granules experience higher local stresses at a specific range of channel fills and this is not directly related to overall SME input. The points with highest local stresses align to transition to exponential torque rise with increased granulation energy but prior to fully filled barrel.

Nonetheless, it is possible to conclude that all the formulation or powder introduced into the 436 twin screw granulator experienced a total stress between 360 and 1000 kPa. Direct 437 comparisons with the literature is not possible due to the change of scale and formulation. 438 However, these values are significantly higher than those found in literature (under 160 kPa). 439 Further exploration to understand the internal forces of the granules will be required to identify 440 if this disagreement could be due to the lack of size equivalence between formulation and 441 sensors (Pradhan et al., 2017), underestimation of some internal forces experienced by the 442 granules from global estimates (Dhenge et al., 2011) or a direct relationship to change in scale 443 and screw configuration. 444

445

#### 447 **4. CONCLUSIONS**

The applicability of channel fill as a parameter to inform PSD, local stress (via CAMES) and 448 torque was studied. Channel fill fraction used previously for the 16-mm TSG as design tool 449 was shown to be a good predictor of granule PSD shape on 11-mm TSG with superior design 450 potential than the SME and the screw speed. Consequently, the channel fill can be used to 451 scale up and down productions remaining a constant channel fill and configuration. Also, it 452 could increment the functionality of the equipment in environments with high variability in 453 production. In addition, the applicability of the CAMES microparticles in granulation was 454 demonstrated offering a novel way to measure TSG internal stress at a particle scale of scrutiny. 455 It was verified that during granulation, the powder experienced total stresses in a 360-1000 kPa 456 range which was relatively higher than it was expected. A potential local maxima in local 457 stress was observed that doesn't align to high SME input but instead with torque transition 458 caused by channel fill. As well as the same channel fills, the stress experienced by the granules 459 was similar confirming the expectation that granules would have similar morphological 460 properties. Transport of the granules without liquid addition suggested that up to 70% of the 461 total breakage of the CAMES and up to 86% of the required torque may not be created by 462 granulation process. Furthermore, it was found that the twin screw granulator does not present 463 a linear relationship between channel fill and torque increasing sharply after a certain point and 464 becoming sensitive to small variations in speed and or fill. Understanding this interplay of 465 local and global behaviour can be critical in both implementation and control of the technology. 466

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480 5 rad/sec

- 481 Figure 4. PSDs depending on the channel fill
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- 491 mechanical energy).
- 492

493	Table 1.	Summary	of	channel	fill	and	shear	stress	relationship	experiments	with	(w/)	and
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494 without (w/o) CAMES.

Screws velocity (rpm)	Feed rate (kg/hr)	L/S	Φ	CAMES
400	0.5	0.175	0.068	w/ and w/o
350	0.5	0.175	0.078	w/ and w/o
300	0.5	0.175	0.091	w/o
250	0.5	0.175	0.110	w/ and w/o
200	0.4	0.175	0.137	w/o
150	0.5	0.175	0.183	w/ and w/o
100	0.5	0.175	0.274	w/ and w/o
80	0.5	0.175	0.342	w/ and w/o
60	0.5	0.175	0.457	w/ and w/o
40	0.5	0.175	0.685	w/ and w/o

495

497	Table 2.Summary	of experiments	of	channel	fill	at t	two	different	levels	and	shear	stress
498	relationship.											

Φ	Screws velocity (rpm)	Feed rate (kg/hr)	L/S
0.073	150	0.2	0.175
0.073	400	0.53	0.175
0.146	150	0.4	0.175
0.146	400	1.06	0.175
0.270	150	0.74	0.175
0.270	400	1.98	0.175

	F	-test	Anova C	)ne-way-H	OV	
Channel	F	р-	<b>B-F statistic</b>	df	p-	Significantly
fill		value			value	different
0.046	0.749	0.693	-	-	-	No
0.073	0.755	0.700	-	-	-	No
0.108	-	-	0.491	7	0.827	No
0.147	-	-	0.855	7	0.560	No
0.194	1.396	0.608	-	-	-	No
0.271	-	-	1.3	8	0.304	No

500 Tal	ole 3.	Statistical	analysis	performed	to the	PSDs at	different	channel fi	11.
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501

503	Table 4.	Statistical	analysis	performed t	o the PS	Ds at d	ifferent	screw v	elocity.
			~ 1						2

		F	-test	
Screw speed	ΔΦ	F	p-value	Significantly different
440 ± 6	0.0391	0.93	9.27E-1	No
300 ± 6	0.039 <sup>2</sup>	0.67	6.05E-1	No
440 ± 6	0.121	2.40	2.71E-1	No
196 ± 6	0.225	34.52	4.57E-6	Yes

504

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