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

Carlota Mendez Torrecillas[1,2], Lee J. Gorringe [3], Nazer Rajoub [1,2], John Robertson [1,2], Richard G. Elkes [3], Dimitrios A. Lamprou[4], Gavin W. Halbert[1,2]**

[1] EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC), University of Strathclyde, Technology and Innovation Centre, 99 George Street, G1 1RD Glasgow, United Kingdom.

[2] Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS), University of Strathclyde, 161 Cathedral Street, G4 0RE Glasgow, United Kingdom.

[3] R&D Platform Technology & Science GSK ,David Jack Centre for R&D , Park Road, Ware, Hertfordshire, SG12 0DP, United Kingdom

[4] School of Pharmacy, Queen's University Belfast, 97 Lisburn Road, BT9 7BL,, United Kingdom

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Corresponding authors: Carlota Mendez Torrecillas and Gavin W. Halbert.

Corresponding authors email: carlota.mendez@strath.ac.uk and g.w.halbert@strath.ac.uk.

Corresponding authors phone number: +44 (0)141 548 2454

Corresponding authors address: Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS), University of Strathclyde, 161 Cathedral Street, G4 0RE Glasgow, United Kingdom.

ABSTRACT

The forces experienced by the particles inside a twin screw granulator (TSG) are one of the most difficult parameters to measure quantitatively. However, it is possible to perform accurately this measurement through the use of dye containing calibrated microencapsulated sensors (CAMES) whose rupture is directly dependant on their experienced shear stress. The current study measures the extent of local stresses in the transformation from powder to granules at different channel fills during TSG processing. Channel fill has shown good potential as a design tool, however, its validity for predicting particle size distributions has yet 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 value was not linear with the specific mechanical energy applied by the granulator. It was 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 the TSG increases exponentially after a certain channel fill a feature that requires to be considered in order to design safer, predictable and reliable granulation workspaces.

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

ABBREVIATIONS

B%	Percentage of broken sensors
CAMES	Calibrated Microencapsulated sensors
C_{eq}	Standardised concentration
C_i	Initial concentration
$C_{100\%}$	100% rupture of sensors concentration.
C_{stock}	Concentration of the stock solution
d10	Intercept 10 of the particle cumulative distribution
F	Powder feed rate (kg/hr)
L/S	Liquid-to-solid ratio
L/D	Length to Diameter ratio
m_i	Sample mass (g)
$\dot{m}$	Powder flowrate
n	Number of repetitions
N	Screws velocity
n_v	Volumetric efficiency of the conveyor
PSD	Particle Size Distribution
R2	Coefficient of determination
UV	Ultraviolet
V_F	Conveyor free volume

VMD	Volume mean diameter
SME	Specific Mechanical Energy
T	Torque
TSG	Twin-Screw Granulator
$\Delta\Phi$	Difference of channel fill
Φ	Channel fill fraction
σ_{CAMES}	Shear stress calculated by the calibrated CAMES

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

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.

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 referred as the total fraction occupied by powder and granules with respect to the full volume of the granulator (Gorringe et al., 2017; Lee et al., 2012). It depends on four factors: screw configuration, length to diameter ratio of the granulator, feed rate and screw velocity. The first two parameters are fixed properties during operation opposite to feed rate and screw velocity which are process variables (Seem et al., 2015). Both parameters have been extensively studied in the literature separately or combined where screw speed has been reported to have a minor influence on the granules properties compared with feed rate (Dhenge et al., 2011; Dhenge et al., 2010; Djuric and Kleinebudde, 2008; Keleb et al., 2004; Thompson and Sun, 2010). The screw velocity is inversely proportional to the channel fill obtaining higher channel fills for lower screw speeds. At the same time, increase in the feed rate, will increase the channel fill. Those two process variables together have a direct effect in the compaction forces applied to the wetted mass (Thompson and Sun, 2010). When the granulator is at low fill, there is a reduction in the compaction force and more friable and porous granules are therefore produced (Lee et al., 2012). Different equations for barrel fill have been defined having the use of feed rate and screw velocity in common (Gorringe et al., 2017, Osorio et al., 2017). On one side, Gorringe et al. used the fraction of the capacity of the twin screw granulator which facilitates the direct transfer to production lines from research phases. However, it does not take into account changes of screw configuration which limits the transfer to different assemblies (Gorringe et al., 2017). On the other side, Osorio et al. used the powder feed number to calculate this value where changes in configuration are considered. However, the calculation requires high technical knowledge of the equipment since parameters such as the cross-sectional area of the elements or net forward velocity of the powder need to be known (Osorio et al., 2017). Nevertheless, both studies have shown the capability of channel fill level 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 indicating how the increase of channel fill affects the process within the TSG. Some studies have already suggested there are inner variations due to the change in shape of the granules. High channel fills have been associated with more spherical products, whereas low channel fills have been reported to produce more elongated granules for the 16-mm TSG (Dhenge et al., 2011; Gorringe et al., 2017). However, Verstraeten et al. concluded that the process settings on a 25-mm TSG had minimum influence on the final shape of the granules whereby it is dictated by the restricted volume of the kneading elements compartment (Verstraeten et al., 2017). A considerable difference in some properties has also been reported for the same feed rates and screw speeds possessing different granulators or scale (Djuric et al., 2009; Osorio et al., 2017). Therefore, changes in granule morphology seem to indicate that changes in the local forces inside the granulator are dependent on both TSG scale and process settings. In any case, there are few examples of quantitative studies of the mechanical stresses in the screw elements. Traditionally, the stresses experienced by the granules in the TSG have been 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).

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

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

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.

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 11-mm 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.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Granulation

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

2.1.2 Mechanical stress measurement

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

2.2. Granulation experiments

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

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 (Φ) is calculated using equation 1 (Gorringe et al., 2017).

$$\Phi = \frac{\dot{\mathrm{m}}}{n_v\, \rho_B \left(V_F \frac{S_L}{L}\right) N}$$

Eq. 1

Where $\dot{m}$ is powder flowrate (kg/hr), n_v is volumetric efficiency of the screw to convey powder which is assumed 100%, ρ_B is the bulk density (kg/m^3), V_F is the conveyor free volume considered 25.04 cm^3 for this 11-mm TSG, S_L/L is the inverse of length to diameter ratio of the 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).

2.3 Offline granule size analysis

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, Germany). All the particle size distributions obtained were measured at 0.5 bar of primary pressure to avoid breakage of the granules during the analysis (MacLeod and Muller, 2012). The disperser conditions were optimised for each set of granules to obtain the optimal optical concentration of 0.5% during the particles measurement. All the particle size distributions (PSDs) were plotted in logarithmic scale of the volume mean diameter against the density distribution which were both calculated in accordance with ISO 13222-1:2014 (ISO 13322-1:2014, 2014). In order to compare if the PSDs are significantly equivalent, two methods were used depending on the number of experiments carried out for channel fill. For those cases under three experiments, F-test was used comparing the curves by the variance. This method 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 O'Brien homogeneity of variance assumption was used. This method will test if multiple data samples have equal variances, against the alternative that at least two of the data samples do not have equal variances (O'Brien, 1979; O'brien, 1981; The MathWorks Inc, 2013). This method was chosen because it does not take into account the shape of the population (Wang et al., 2017) as twin screw granulation produces polymodal PSDs shapes (Mendez Torrecillas et al., 2017). In addition, both methods were recommended when the length of the samples is smaller than 10 (Wang et al., 2017). All the analysis were performed using the software Matlab and Statistics Toolbox R2017a (The MathWorks, Inc., Natick, Massachusetts, United States) using each PSD as an individual level with a 0.05 significance level which is recommended for scientist data (Brandt and Brandt, 2014). The PSDs were compared also depending on the screw speed which will have a direct effect in the shear rate exerted on the powder mass (Lute et al., 2018). Three screw speeds were compared at three level of differences between channel fills (low: 0.108-0.147), medium (0.073-0.194) and high (0.046 -0.271).

2.4 Calibration of the microencapsulated stress sensors

2.4.1 UV calibration

To measure the microencapsulated stress sensor rupture a UV calibration relationship between absorbance and concentration, covering the possible range of rupture, was determined with ten systems, prepared gravimetrically (BP211D Analytical model, Sartorious, Surrey, United Kingdom), between 0-60 ppm by weight. A concentrated dye provided by the manufacturer (Automate™ Blue 8AHF, Keystone Inc, Chicago, USA) was weighted and solved in IPA obtaining three initial stock solutions of 115, 116 and 216 ppm. The concentrations were obtained to be gravimetrically within the measurement range of the weight scale. The dye was 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 specific volume of stock (V_{stock}) in IPA to reach a final total volume of 5 ml. The final 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).

2.4.2 Dye recovery from the granules

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

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.

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^{TM} SENSORS Lot 9-13-553, Mach I, Inc., Pennsylvania, USA). The rupture of the CAMES with <44 µm 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 ± 69.73 ppm_w for the fully broken CAMES.

The granules obtained from the TSG were dissolved in 4-10 ml of IPA, filtered and the absorbance was measured in the UV. The amount of IPA varied in order to optimise the washing of the filter. The concentration was calculated using the dye-IPA calibration. 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 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, Pensilvania, United States)..

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

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

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

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, σ_{CAMES} (kPa) is the shear stress calculated by the CAMES.

2.5 Relationship between shear forces and channel fill in granulation

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

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).

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

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.

3. RESULTS

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 parameter can be used to predict PSDs in the 11-mm TSG. In figure 4, six different channel fills were investigated showing high similarity between their density distributions along a channel fill line independent of the screw velocity. The equivalence between the shapes of the PSDs is remarkable at low (Φ=0.046 and Φ=0.073) and high (Φ=0.194 and Φ=0.271) channel fills where at low channel fills fines are more prevalent than at high channel fills. One 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) which could reduce the contact between powder and therefore, the granulation rate.

However, the middle channels show more discrepancies between them. In both cases (Φ=0.108 and Φ=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 concluded that at 0.05 level of tolerance, there were no significant differences between PSDs at the same channel fill (Table 3).

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

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 and L/S ratio and varying the screw velocity from 40 to 400 rpm (Table 1). In figure 6, the force required to both transport the powder with and without the addition of granulation fluid are presented. The torque necessary to move the powder when granulation takes place is nearly double than when powder is only transported. This phenomena can be associated with the changes of density due to the increased presence of formed granules and the resulting change in powder physical properties interacting with downstream elements. As well, the torque required at channel fills lower than 0.271 is relatively low in all the cases (<1.5 N.m) increasing slowly (green area). However, after that point, it increases sharply (red-coloured 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 screw speeds (Gorringe et al., 2017). Therefore, this change in trend could be an indication that after reaching a certain point, the material hold-up within the equipment increased sharply at small variations.

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

The specific mechanical energy spent in granulation was estimated subtracting the values of the SME used for transport of the dry powder from the values of SME used when liquid was added to the system. Although the transport of dry and wet powder has not the same efficiency, the SME does not take into account this difference since it is calculated as function of the total amount of material introduced in the equipment which is constant in this case. Figure 7a suggests that initially the specific mechanical energy value used for transport of the dry powder is higher than the one used for granulation until it equalises around a channel fill of 0.18. After that point energy used for granulation becomes predominant until the last channel fill value where transport became predominant again over granulation. The specific mechanical energy used in granulation does not vary as much as the one required from transport that varies from 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 granulation is almost constant.

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.

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 fills. In figure 9, three different levels of channel fill at two different sets of conditions each (Table 2) are presented. The local stress produced by the transport of the powder through the granulator without liquid addition was consistently in the range 360-490 kPa which corresponds for 55-70% of the total shear experienced by the formulation during granulation conditions. This result is consistent with the results obtained in figure 6 for no liquid addition where at channel fills up to 0.270, the torque required did not have great variations (0.49-0.68 N.m) and did not present a linear trend with channel fill. The breakage of the CAMES in this case is due only to the transport of the powder through the equipment since no liquid addition 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 channel fill range in figure 9. As the transport only data suggest this is not due to transport, this increase would be due only to granulation which is consequent with the increment in size observed in the PSDs in figure 4. However, with the variability obtained is not possible to confirm this trend and it is only possible to conclude that there is a significant increase in stress due to addition of water to give the granulation process.

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

4. CONCLUSIONS

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

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LIST OF FIGURES

Table 1. Summary of channel fill and shear stress relationship experiments with (w/) and 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

Table 2. Summary of experiments of channel fill at two different levels and shear stress 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

Table 3. Statistical analysis performed to the PSDs at different channel fill.

	F-test		Anova One-way-HOV			
Channel fill	**F**	**p-value**	**B-F statistic**	**df**	**p-value**	**Significantly 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

Table 4. Statistical analysis performed to the PSDs at different screw velocity.

		F-test		
Screw speed	**$\Delta\Phi$**	**F**	**p-value**	**Significantly different**
440 ± 6	**0.039**[1]	0.93	9.27E-1	No
300 ± 6	**0.039**[2]	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

REFERENCES

Bigio, D., Pappas, W., Brown II, H., Debebe, B., Dunham, W., 2011. Residence stress distributions in a twin screw extruder, SPE ANTEC Proceedings.

Brandt, S., Brandt, S., 2014. Data analysis, 4th ed. Springer.

Condo, A.C., Kosowski, B.M., 1991. Processing of materials using rupturable microcapsulates containing detection materials. Google Patents.

Dhenge, R.M., Cartwright, J.J., Doughty, D.G., Hounslow, M.J., Salman, A.D., 2011. Twin screw wet granulation: Effect of powder feed rate. Advanced Powder Technology 22, 162-166.

Dhenge, R.M., Cartwright, J.J., Hounslow, M.J., Salman, A.D., 2012. Twin screw wet granulation: Effects of properties of granulation liquid. Powder Technology 229, 126-136.

Dhenge, R.M., Fyles, R.S., Cartwright, J.J., Doughty, D.G., Hounslow, M.J., Salman, A.D., 2010. Twin screw wet granulation: Granule properties. Chemical Engineering Journal 164, 322-329.

Dhenge, R.M., Washino, K., Cartwright, J.J., Hounslow, M.J., Salman, A.D., 2013. Twin screw granulation using conveying screws: Effects of viscosity of granulation liquids and flow of powders. Powder Technology 238, 77-90.

Djuric, D., Kleinebudde, P., 2008. Impact of screw elements on continuous granulation with a twin-screw extruder. Journal of pharmaceutical sciences 97, 4934-4942.

Djuric, D., Van Melkebeke, B., Kleinebudde, P., Remon, J.P., Vervaet, C., 2009. Comparison of two twin-screw extruders for continuous granulation. European Journal of Pharmaceutics and Biopharmaceutics 71, 155-160.

Godavarti, S., Karwe, M.V., 1997. Determination of Specific Mechanical Energy Distribution on a Twin-Screw Extruder. Journal of Agricultural Engineering Research 67, 277-287.

Gorringe, L., Kee, G., Saleh, M., Fa, N., Elkes, R., 2017. Use of the channel fill level in defining a design space for twin screw wet granulation. International journal of pharmaceutics 519, 165-177.

ISO 13322-1:2014, 2014. Particle size analysis – Image analysis methods – Part 1: Static image analysis methods.

Keleb, E.I., Vermeire, A., Vervaet, C., Remon, J.P., 2002. Continuous twin screw extrusion for the wet granulation of lactose. International Journal of Pharmaceutics 239, 69-80.

Keleb, E.I., Vermeire, A., Vervaet, C., Remon, J.P., 2004. Twin screw granulation as a simple and efficient tool for continuous wet granulation. International Journal of Pharmaceutics 273, 183-194.

Lee, K.T., Ingram, A., Rowson, N.A., 2012. Twin screw wet granulation: The study of a continuous twin screw granulator using Positron Emission Particle Tracking (PEPT) technique. European Journal of Pharmaceutics and Biopharmaceutics 81, 666-673.

Lute, S.V., Dhenge, R.M., Salman, A.D., 2018. Twin Screw Granulation: An Investigation of the Effect of Barrel Fill Level. Pharmaceutics 10.

MacLeod, C.S., Muller, F.L., 2012. On the fracture of pharmaceutical needle-shaped crystals during pressure filtration: case studies and mechanistic understanding. Organic Process Research & Development 16, 425-434.

Mendez Torrecillas, C., Gavin Halbert, Dimitrios Lamprou, 2017. A novel methodology to study the polymodal particle size distributions produced during continuous wet granulation. International Journal of Pharmaceutics.

Mendez Torrecillas, C., Halbert, G., Lamprou, D., 2017. A novel methodology to study polymodal particle size distributions produced during continuous wet granulation.

Mundozah, A.L., Cartwright, J.J., Tridon, C.C., Hounslow, M.J., Salman, A.D., 2018. Hydrophobic/hydrophilic powders: Practical implications of screw element type on the reduction of fines in twin screw granulation. Powder Technology.

O'Brien, R.G., 1979. A General ANOVA Method for Robust Tests of Additive Models for Variances. Journal of the American Statistical Association 74, 877-880.

O'brien, R.G., 1981. A simple test for variance effects in experimental designs. Psychological Bulletin 89, 570.

Osorio, J.G., Sayin, R., Kalbag, A.V., Litster, J.D., Martinez-Marcos, L., Lamprou, D.A., Halbert, G.W., 2017. Scaling of continuous twin screw wet granulation. AIChE Journal 63, 921-932.

Pappas, W., Brown Ii, H., Fukuda, G., Adnew, R., Bigio, D., 2012. Variable strength stress bead analysis in a twin screw extruder. SPE ANTEC Tech. Papers.

Pradhan, S.U., Sen, M., Li, J., Litster, J.D., Wassgren, C.R., 2017. Granule breakage in twin screw granulation: Effect of material properties and screw element geometry. Powder Technology 315, 290-299.

Seem, T.C., Rowson, N.A., Ingram, A., Huang, Z., Yu, S., de Matas, M., Gabbott, I., Reynolds, G.K., 2015. Twin screw granulation—A literature review. Powder Technology 276, 89-102.

Silva, A.F., Vercruysse, J., Vervaet, C., Remon, J.P., Lopes, J.A., De Beer, T., Sarraguça, M.C., 2018. Process monitoring and evaluation of a continuous pharmaceutical twin-screw granulation and drying process using multivariate data analysis. European Journal of Pharmaceutics and Biopharmaceutics 128, 36-47.

The MathWorks Inc, 2013. Release, Matlab. Inc., Natick, Massachusetts, United States 488.

Thompson, M., 2014. Twin screw granulation-review of current progress. Drug development and industrial pharmacy, 1-9.

Thompson, M.R., Sun, J., 2010. Wet Granulation in a Twin-Screw Extruder: Implications of Screw Design. Journal of Pharmaceutical Sciences 99, 2090-2103.

Van Melkebeke, B., Vervaet, C., Remon, J.P., 2008. Validation of a continuous granulation process using a twin-screw extruder. International journal of pharmaceutics 356, 224-230.

Vercruysse, J., Burggraeve, A., Fonteyne, M., Cappuyns, P., Delaet, U., Van Assche, I., De Beer, T., Remon, J.P., Vervaet, C., 2015. Impact of screw configuration on the particle size distribution of granules produced by twin screw granulation. International journal of pharmaceutics 479, 171-180.

Verstraeten, M., Van Hauwermeiren, D., Lee, K., Turnbull, N., Wilsdon, D., am Ende, M., Doshi, P., Vervaet, C., Brouckaert, D., Mortier, S.T., 2017. In-depth experimental analysis of pharmaceutical twin-screw wet granulation in view of detailed process understanding. International journal of pharmaceutics 529, 678-693.

Wang, Y., Rodríguez de Gil, P., Chen, Y.-H., Kromrey, J.D., Kim, E.S., Pham, T., Nguyen, D., Romano, J.L., 2017. Comparing the performance of approaches for testing the homogeneity of variance assumption in one-factor ANOVA models. Educational and psychological measurement 77, 305-329.