Experimental investigation of granule size and shape dynamics in twin-screw granulation

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Abstract

Twin-screw granulators (TSG), being promising in the context of continuous high shear wet granulation (HSWG), achieve mixing by a combination of screw configuration and process settings (e.g. feed rate, screw speed, etc.) producing a certain granule size and shape distribution (GSSD). However, the primary shaping mechanism behind this distribution is not well understood due to the opacity of the multiphase system. This study experimentally characterised the change in GSSD and dynamics along the TSG barrel length in order to understand the function of individual screw modules and process setting their interaction. Particle size analysis of granules collected at the outlet of the TSG suggested significant interaction between the process and equipment or screw configuration parameters to influencing the heterogeneity in GSSD. By characterisation of samples collected along the screw length a variant influence of screw modules at different process conditions was observed. At low liquid-to-solid ratio (L/S), the first kneading module played a more significant role in mixing, whereas the second kneading module was more involved in reshaping the

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granules. At high L/S and high throughput, aggregation took place mainly in the second kneading module changing the GSSD. Results from this study are important for better understanding of the key mechanisms of HSWG using TSG, essentially required for physical modelling, optimisation and control of the process. To our best knowledge it is the first time that such a study has been performed. The results obtained from this study will be used for the mechanistic modelling and further understanding of HSWG process in a TSG.
Keywords: twin-screw granulation, continuous processing, pharmaceutical production, shape analysis

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1. Introduction

Granulation is a process to enlarge powder particles, which can be advantageous for many reasons. The size enlargement results in gravity forces exceeding over the Van der Waals forces, thereby contributing to improvement in flow properties required for accurate dosing in further downstream processing. Especially in the pharmaceutical industry, where often highly potent drugs are processed, the amount of dust generated by powder handling is reduced by granulation, resulting in improved safety, which may otherwise cause health related problems for operators. Also, segregation (demixing) can be minimized along with the improved compression and dissolution characteristics of the granules. Therefore, wet granulation is an important process for particle enlargement during the formulation of solid dosage forms in the pharmaceutical industry [1]. Vervaet and Remon [3] reviewed the continuous granulation techniques extensively. The high shear twin-screw granulation system has received most attention in the last decades due to its inherent benefits of ease in continuous operation, operations integration possibility. [4]. The high shear wet granulation (HSWG) process in twin-screw granulator (TSG) process can be divided into several stages (Fig. 1). A number of different mechanisms, including growth, nucleation, aggregation, and breakage, which ultimately determine the characteristics of the produced granules, typically drive the dynamics of wet granulation. Although their sequence during granulation in TSG is still unclear in the literature, growth and breakage of granules are expected to occur simultaneously due to the inhomogeneous shear force distribution inside the TSG barrel [2]. For wet granulation many techniques and different types of equipment can be used. Recently, because of the many advantages

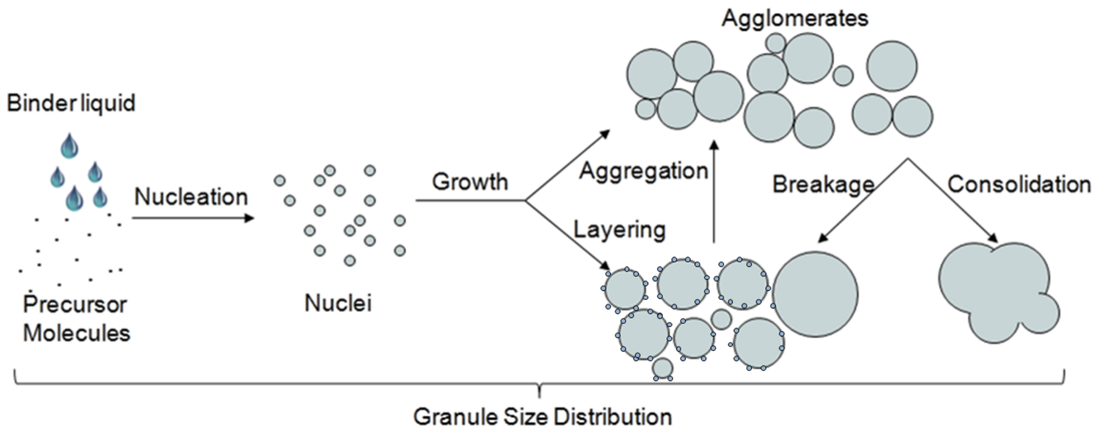


Figure 1: Wet granulation rate processes

of continuous processing, a trend towards continuous wet granulation is becoming more prevalent.

Normally in batch HSWG the granulation time is in the order of minutes, while in a TSG, it is limited to a few seconds [*ref to RTD article in communication*]. The short granulation time is, although desirable from the productivity point of view, challenging for micro to meso scale rate processes in HSWG (Fig. 1). The rate processes of wet granulation are required to occur during the short granulation time before the material leaves the TSG. Thus, beside a homogeneous distribution of granulation liquid and powder, the wet mixing in a TSG is also required to be achieved within the shortest mixing lengths and a minimum power input. To facilitate wet granulation, the TSG screw is composed of mainly two blocks (Fig. 2). The first and the larger component contains the inter-meshing conveying elements involved in transport of the dry and then the wetted powder. The second component are the mixing elements, which contain kneading discs staggered at a certain angle to cause restriction to the flow and hence provide the required mixing for wet granulation. These modules change the shear environment of the material being conveyed, which shape the final granule characteristic distribution, such as granule size and shape distribution (GSSD), moisture content and granule strength [5]. Besides, the functional role of the screw configuration, performance of a TSG is also related to the applied process parameters. Along with the screw speed and the screw configuration, the feeding rate of the powder and the granulation liquid which determine the liquid to solid ratio (L/S) and the fill ratio inside the barrel. Therefore, they can be independently chosen to achieve desired mixing levels of the powder and the granulation liquid, and influence the granulation yield at the outlet [6, 7].

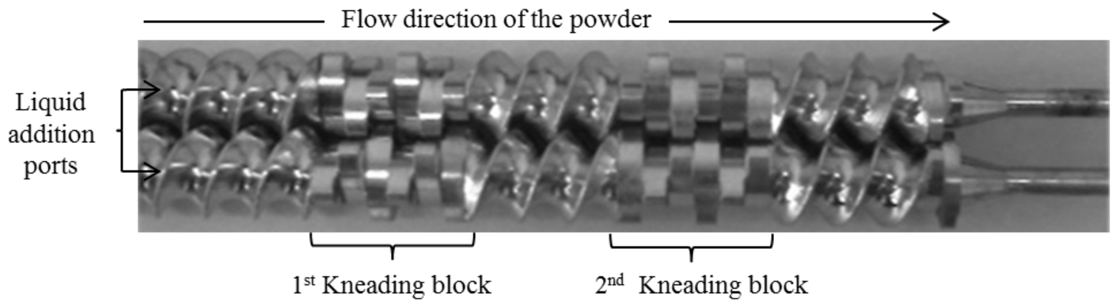


Figure 2: Screw configuration with 12 kneading discs (2 blocks) used in the twin screw granulator during the study.

However, there is very less understanding regarding the primary shaping mechanisms behind the particle size and shape distribution in the TSG during wet granulation, due to the opacity of the multiphase system [2, 8]. Most of the studies rely on the characterisation of the granules from the outlet of the TSG. Furthermore,the measured torque of the granulator drive is used as the steady state criterion in most studies using TSG. However, torque being a 0-dimensional measurement does not provides information to determine the role of change in process parameters together with role of individual screw element in the TSG.

This study extends the spatial dimension of the knowledge regarding HSWG using TSG to understand the dynamic change in characteristics of the material while progressing in the TSG barrel. The purpose of this study was to experimentally characterise the change in GSSD along the TSG barrel in order to understand the function of individual screw modules and their interaction with other process process parameters such as L/S, screw speed, filling degree in the TSG.

2. Materials and methods

2.1. Pharmaceutical model formulation

In this study, a premix of α-Lactose monohydrate (Pharmatose 200M, Caldic, Hemiksem, Belgium) and Polyvinylpyrrolidone (PVP) (Kollidon® 30, BASF, Ludwigshafen, Germany) was granulated with distilled water using the ConsiGma-1 continuous wet granulation system.

2.2. Continuous twin screw granulation

Granulation experiments were performed using a 25 mm diameter co-rotating TSG with option to open the barrel (Fig. 3), which is the granulation module of the ConsiGma-1 unit (GEA Pharma Systems, Collette™, Wommelgem, Belgium). The granulator screw had a length-to-diameter ratio

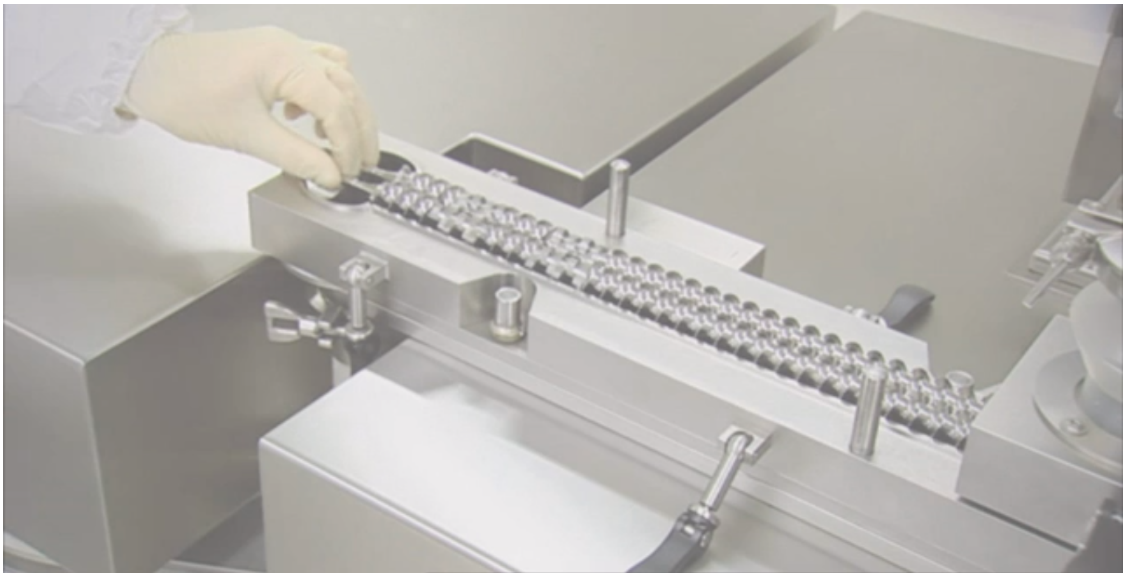


Figure 3: Twin-screw granulator from ConsiGma-1 unit (GEA Pharma Systems, Collette™, Wommelgem, Belgium) with option to open the barrel

of 20:1 (Fig. 2). The screw configurations up to 6 kneading discs (L = D/4 for each kneading discs) were composed of one kneading block. Whereas, in case of 12 kneading discs, two kneading blocks each consisting of 6 kneading discs at a stagger angle of 60° were used. Both kneading zones were separated by a conveying screw block (L = 1.5D). An extra conveying element (L = 1.5D) was implemented after the second kneading block together with 2 narrow kneading discs (L = D/6 for each kneading disc) in order to reduce the amount of oversized agglomerates, as reported by Van Melkebeke et al. [9]. The barrel jacket temperature was set at 25°C. The TSG barrel had a feed segment, where the powder entered the barrel and was transported through the conveying zone to the work segment, where the granulation liquid was added to the powder [6, 10] 2. During processing, the powder premix was gravimetrically fed into to granulator by using a twin screw feeder (Brabender, Duisburg, Germany). Distilled water as granulation liquid was pumped into the screw chamber by a peristaltic pump (Watson Marlow, Comwall, UK) using silicon tubings connected to 1.6 mm nozzles. The granulation liquid was added before the first kneading disc by dripping through two liquid feed ports, each port located on the central top of each screw in the barrel. The wetted, but not yet mixed powder was forced to follow a granulation track composed of the two co-rotating screws with a number of transport and mixing modules based screw configuration. As the wet powder progresses along the length of the granulator, the distribution of particle characteristic changes.

2.3. Experimental design and sample preparation

A full factorial experimental design was performed to evaluate the influence of number of kneading discs (2, 4, 6, 12), screw speed (500-900 rpm), powder feed rate (10-25 kg/h) and L/S (4.58-6.72% (w/w) based on wet mass) (Table 1). Three centerpoint experiments were performed as well, resulting in 32 + 3 = 35 experiments. For each run, samples were collected from different locations inside the barrel by opening the barrel after stopping the process running at steady state (Fig. 5). Sample location 1 was immediate before the first kneading block, sample location 2 on the first kneading block, sample location 3 was between first and second kneading block, sample location 4 and 5 were on the second kneading block and after. Irrespective of number of kneading block sample locations on the screw was kept same during the sampling. Sample location 6 was the regular outlet of the granulator, therefore large amount of granules was available for the study. The granules from all the experiments were oven dried at 40°C for 48 h and their GSSD was evaluated (see the responses in Table 1). The responses were evaluated with Modde 9.0 software (Umetrics, Umeå, Sweden).

2.4. Determination of torque

The TSG has an inbuilt torque gauge and the steady state criteria was decided based on the equilibration of the measured torque of the granulator. The torque values obtained after equilibration of the process were averaged to give the overall torque during each run. The drive motor torque values are an indication of the shear and compaction forces experienced by materials inside the barrel.

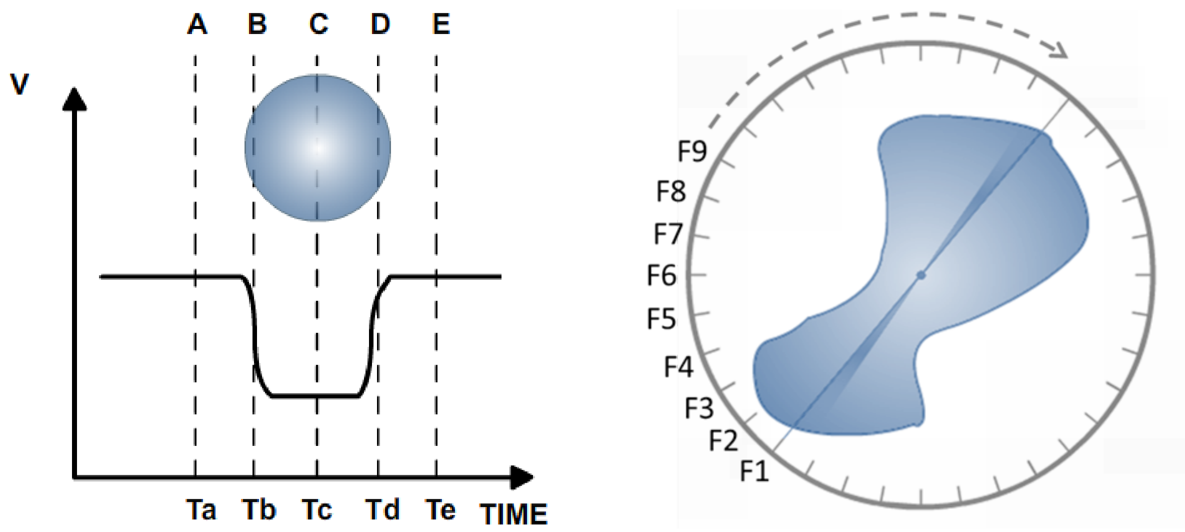
2.5. Characterisation of granules

2.5.1. Sieve test for particle size analysis

The granule size distribution (GSD) of the granule samples, collected at the outlet of the TSG during each design experiment, was determined using the sieve analysis method (Retsch VE 1000 sieve shaker (Haan, Germany)). The granules were placed on the shaker for 5 min at an amplitude of 2 mm using a series of sieves (150, 250, 500, 710, 1000, 1400 and 2000 µm). The amount of granules retained on each sieve was determined. All granule batches were measured in triplicate.

Table 1: Overview of experimental design runs: factor variables (number of kneading discs, screw speed, powder feed rate and liquid-solid ratio) and responses (Torque, F < 150 µm (defined as fines), 150 µm<F<1000 µm (interesting fraction for tabletting) and F>1000 µm (defined as oversized) granules).

Run Order	**Number of kneading discs (-)**	**Screw speed (RPM)**	**Powder feed rate (Kg/h)**	**L/S ratio (%)**	**Torque (N-m)**	**F<150 µm (g)**	**150-1000 µm (g)**	**F>1000 µm (g)**
1	2	500	10	4.58	1.38	35.00	47.70	27.60
2	2	500	10	6.72	0.92	22.30	49.40	48.70
3	2	500	25	4.58	1.30	36.20	38.30	39.80
4	2	500	25	6.72	1.24	26.10	43.50	51.90
5	2	900	10	4.58	1.25	37.90	50.00	17.40
6	2	900	10	6.72	1.44	23.60	52.70	42.90
7	2	900	25	4.58	1.55	39.90	42.80	27.00
8	2	900	25	6.72	1.54	26.00	48.30	37.70
9	4	500	10	4.58	1.53	40.70	45.20	24.60
10	4	500	10	6.72	1.73	22.60	46.40	53.50
11	4	500	25	4.58	2.02	45.80	38.20	30.10
12	4	500	25	6.72	2.16	29.40	42.40	53.00
13	4	900	10	4.58	2.00	43.10	48.60	18.40
14	4	900	10	6.72	1.89	25.70	50.50	51.60
15	4	900	25	4.58	1.98	45.90	43.30	21.60
16	4	900	25	6.72	1.46	30.70	46.00	45.30
17	6	500	10	4.58	2.59	38.30	52.30	20.00
18	6	500	10	6.72	2.97	28.50	45.10	47.10
19	6	500	25	4.58	2.27	42.50	45.20	24.20
20	6	500	25	6.72	2.28	33.60	43.40	41.50
21	6	900	10	4.58	3.06	42.80	49.50	18.70
22	6	900	10	6.72	3.07	29.00	50.80	44.90
23	6	900	25	4.58	2.09	43.90	47.70	17.80
24	6	900	25	6.72	2.46	32.60	50.80	36.00
25	12	500	10	4.58	2.92	43.20	49.00	20.80
26	12	500	10	6.72	3.06	23.80	48.10	50.40
27	12	500	25	4.58	2.40	45.40	43.80	23.30
28	12	500	25	6.72	4.70	16.10	50.30	64.20
29	12	900	10	4.58	1.95	40.70	49.60	24.40
30	12	900	10	6.72	2.60	22.20	53.00	50.70
31	12	900	25	4.58	2.02	45.10	45.70	22.70
32	12	900	25	6.72	1.86	26.20	45.10	56.10
CP 1	4	700	17.5	6	1.33	22.58	55.90	21.52
CP 2	4	700	17.5	6	1.32	18.52	53.03	28.45
CP 3	4	700	17.5	6	1.24	20.59	55.50	23.92



(a) (b)

Figure 4: (a) Principle of the laser obscuration time technique. The diameter of the particle is directly correlated to the duration of the obscuration (x-axis) and interaction signal generated by photodiode (y-axis). (b) The Ferret diameters is a parameter that provides information on the size (average Ferret diameter) and also give deep insight into a particles morphology (minimum Ferret and maximum Ferret) and which serves as a basis for the calculation of the aspect ratio.

The fractions <150, 150-1000 and >1000 µm were defined as the amount of fines, interesting fraction for tableting and oversized fraction, respectively.

2.5.2. Laser obscuration time technique for size and shape analysis of granules

The GSSD of the samples from sampling locations which were inside the TSG barrel (Fig. 5) were determined using a unique time domain measurement technique called Laser obscuration time (LOT) used by the EyeTech (Ankersmid B.V., Oosterhout, The Netherlands). In this setup, a rotating laser beam scans individual particles in the sample zone (Fig. 4a). As the particles are encountered, the laser beam is obscured and interaction signals are generated. These interaction signals are detected by a photodiode. Since the laser beam rotates with a constant speed, the duration of the obscuration (t) and the known rotation velocity of the laser beam (v) provides a direct measurement of each particle diameter (D) as:

$$D = v \times t \tag{1}$$

To ensure good data quality, a measurement confidence level of 95% was imposed for number and volume size distribution. Hence, the instrument continued scanning the sample until the

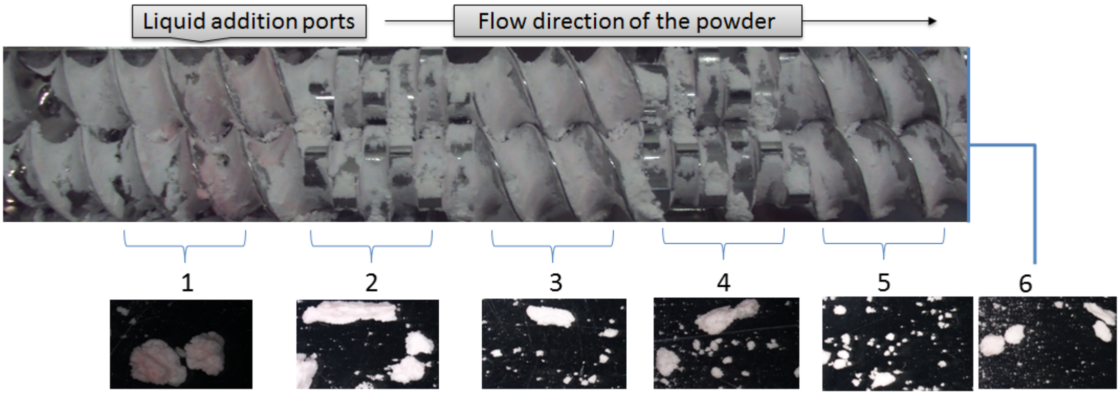


Figure 5: Sampling locations along the screw length: [1] before first kneading block, [2] on the first kneading block [3] between first and second kneading block, [4] on the second kneading block [5] after second kneading block, [6] outlet of the granulator

measured mean size of the granules was obtained within ±2.5% of the true mean. The average Feret diameter was used as size parameter that provides information on a diameter that is measured every 5 degrees, resulting in an average of total of 36 diameters for each granule (Fig. 4b, eq. 2). This size information also serves as a basis for the calculation of shape related parameters such as the aspect ratio, which measures the elongation in the granule and has been used in this study. It is a ratio of the length of the minor and the major diameter of the granule (eq. 3). Aspect ratio gives information about how far the particles are going away from the sphere model. Rod shape particles have aspect ratio less than 0.5 while an aspect ratio close to 1 indicates higher sphericity of the granules.

$$\text{Feret Diameter} = \frac{F_1 + F_2 + F_3 + F_4 .... F_{36}}{36} \tag{2}$$

$$\text{Aspect ratio} = \frac{\text{Minimum Feret Dimater}}{\text{Maximum Feret Dimater}} \tag{3}$$

The screw arrangement at sample locations 2 and 4 was changed based on the experimental design, which lead to deviation in granule characteristics at these locations purely due to the local and experimental run specific conditions. Therefore, they have not been used in this study and the samples from location 1, 3 and 5 in Fig. 5 were analysed for further study.

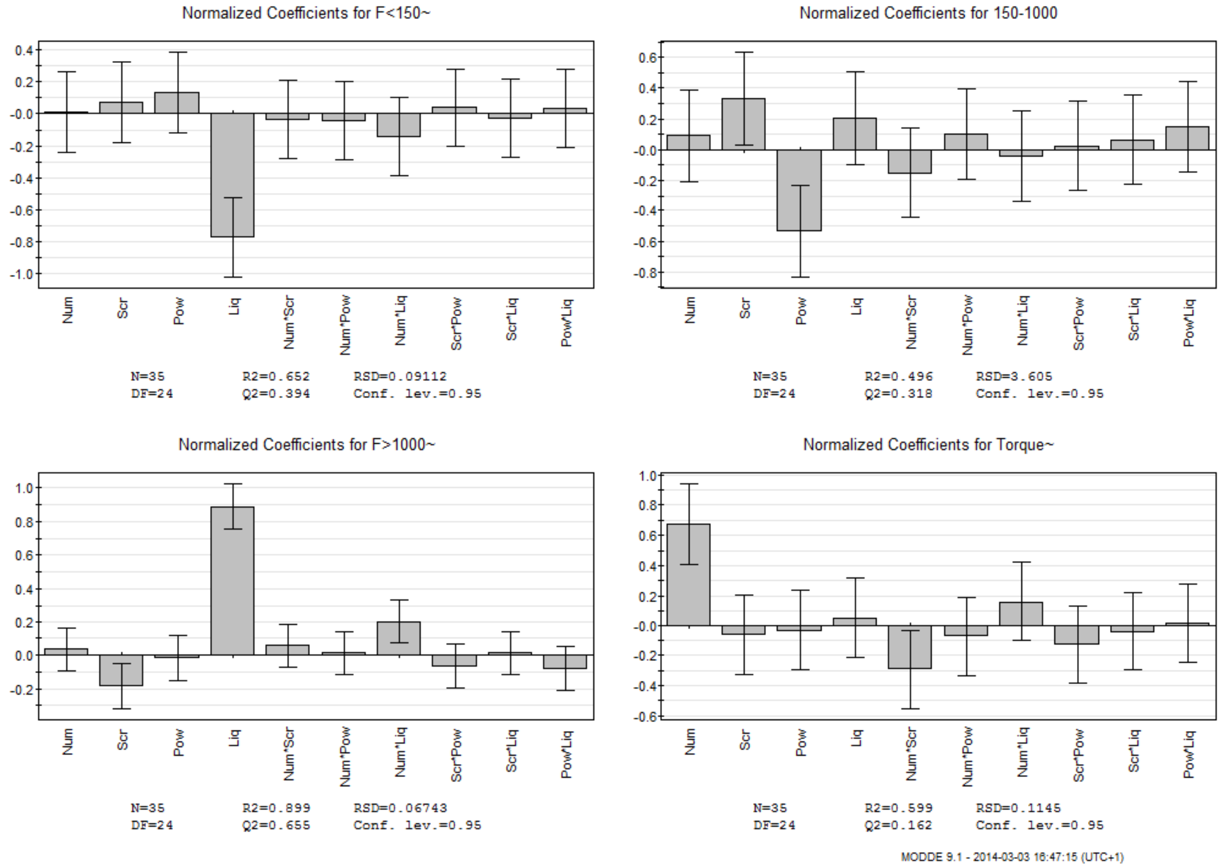


Figure 6: Coefficient plots of the partial least squares (PLS) models showed the mean responses of number of kneading discs (Num), screw speed (Scr)[500-900 rpm], powder feed rate (Pow)[10-25 kg/h] and liquid-solid ratio (Liq) [4.58-6.72 %] on the size fractions (F) defined as fines (F < 150 µm), interesting fraction for tabletting (150 µm< F< 1000 µm) and oversized granules(F>1000 µm) and the measured torque.

3. Results and discussion

This study examined the impact of four main factors of HSWG using TSG, which include the screw speed, number of kneading discs, powder feed rate and L/S during granulation.

3.1. Influence of process variables on granules from outlet

The sample collected at the outlet of the TSG (sample location 6 in Fig. 5) during each design experiment was analysed using the sieve test. This was to understand the response of the different factors namely screw speed, number of kneading discs, powder feed rate and L/S on the studied size fractions (F) of granules defined as fines (F < 150 µm), interesting fraction for tabletting (150 µm < F < 1000 µm) related to granulation yield, oversized granules (F > 1000 µm) and the measured torque (Nm) (Table 1). Since, several responses were measured, it was helpful to fit a model simultaneously representing the variation of all responses to the variation of the factors. Therefore, the partial least squares (PLS) method was employed which deals with many responses simultaneously, taking into their covariances into account (Fig. 6). The L/S had a significant effect on both the fines (16.10-45.87 % $<$ 150 µm) and oversize fraction (15.21-49.43 % $>$ 1000 µm) of the granules (Table 1). The fine fraction increased by reducing L/S, which can be understood by the fact that a less amount of powder was wetted at low L/S. On the other hand, the oversized fraction increased with increase in L/S and reduction in the screw speed. This can be explained by the increase in the amount of wetted powder at high L/S and the lack of proper sheared mixing due to low screw speed. Also, the conveying rate of the screw reduces with the reduction in the screw speed. This leads to increase in the residence time and accumulation of material inside the granulator barrel i.e. high fill ratio and hence less effective mixing in the TSG [*cite the RTD work*].

In case of the interesting fraction for the tabletting, the screw speed and powder feed rate were the most important factors which play an important role to obtain good yield (31.01-55.90%) (Fig. 6). An increased screw speed had a positive effect on this granule fraction as the high shear causes a homogeneous distribution of liquid in powder leading to a narrower granule size distribution. Also, for an effective mixing in the TSG, the fill ratio, which depends on the powder feed rate plays an important role [6]. While the increase in screw speed improved the interesting fraction yield, the increase in the powder feed rate caused a reduction in the yield, which shows that beyond a critical fill level, effective mixing is not possible inside the TSG barrel. This was also shown in our study to understand the mixing in the TSG [*cite the RTD work*].

The measured torque of granulator drive, which is related to the fill level and the shear mixing of material in the TSG, was found to be most affected by the number of kneading discs. An increase in the number of kneading discs caused a larger restriction to the flow of material and hence increased torque of the granulator drive. But this restrictive flow is directly related to the residence time of the powder and distributive mixing in the granulation essentially required for better granulation yield [8].

3.2. Influence of process variables on granules along the TSG length

The samples from location 1 (before the first kneading block), location 3 (after the first kneading block) and location 5 (after the second kneading block in screw configuration with 2 kneading blocks) were used to characterise the change in the GSSD along the TSG length (Fig. 5). For this purpose, the change in the number density of each size and shape class was compared. The average Feret diameter was used as a measure of granule size, whereas the shape characteristic of the granules from various locations in the TSG was determined using the aspect ratio as shape factor. In the primary comparison between the runs, it was found that granulation with 2 kneading discs did not generate consistent results (data not shown). We believe that 2 kneading discs in the screw configuration induce a very small fraction of screw channel restriction. Due to this, the primary response by the kneading block in terms of restriction to the flow was significantly asynchronous, thus generating less consistent results. Therefore, for further comparison only results from runs with 4, 6 and 12 kneading discs are presented. Furthermore, an increase in number of kneading discs from 4 to 6 showed the effect of change within the same kneading block, while an increase from 6 to 12 kneading discs showed the effect of adding a second kneading block in the TSG screw.

3.2.1. Effect of throughput

At low throughput of 10 kg/h, low L/S of 4.58 % (w/w) and low screw speed of 500 rpm, as the wetted powder conveyed from pre-kneading zone to the first kneading zone and further, the number density of the granules shifted towards the right, indicating an increase in the amount of larger granules (ID 1 in Fig. 7). The granules were observed to further enlarge at the increased number of kneading discs. Adding more kneading discs, remarkably, not only increased the number density of larger granules for the successive sample locations 3 and 5 which lie after the first kneading blocks and encounter the influence of kneading discs, but also for the sample location 1, which was before the kneading discs. Thus, it can be convincingly suggested that the significant amount of mixing and granulation occurs not only in the mixing section composed of kneading discs, but also in the previous section. This can also be explained by the fact that the material in mixing section flows more slowly than in the previous section and hence the built-up material in the flow restricted zone of the barrel is forced-mixed with the incoming materials. This difference became larger as the restriction to the flow was increased. Lee et al. have shown that the fill degree of 'non-kneading zone' of the granulator increases with an increase in the restriction to the flow [11]. Similar to the size distribution, the aspect ratio distribution of the granule samples moved to right indicating a reduction in elongation of the granules both for successive sample locations and increase in number of kneading discs (ID 1 in Fig. 8). Especially in case of 12 kneading discs, the

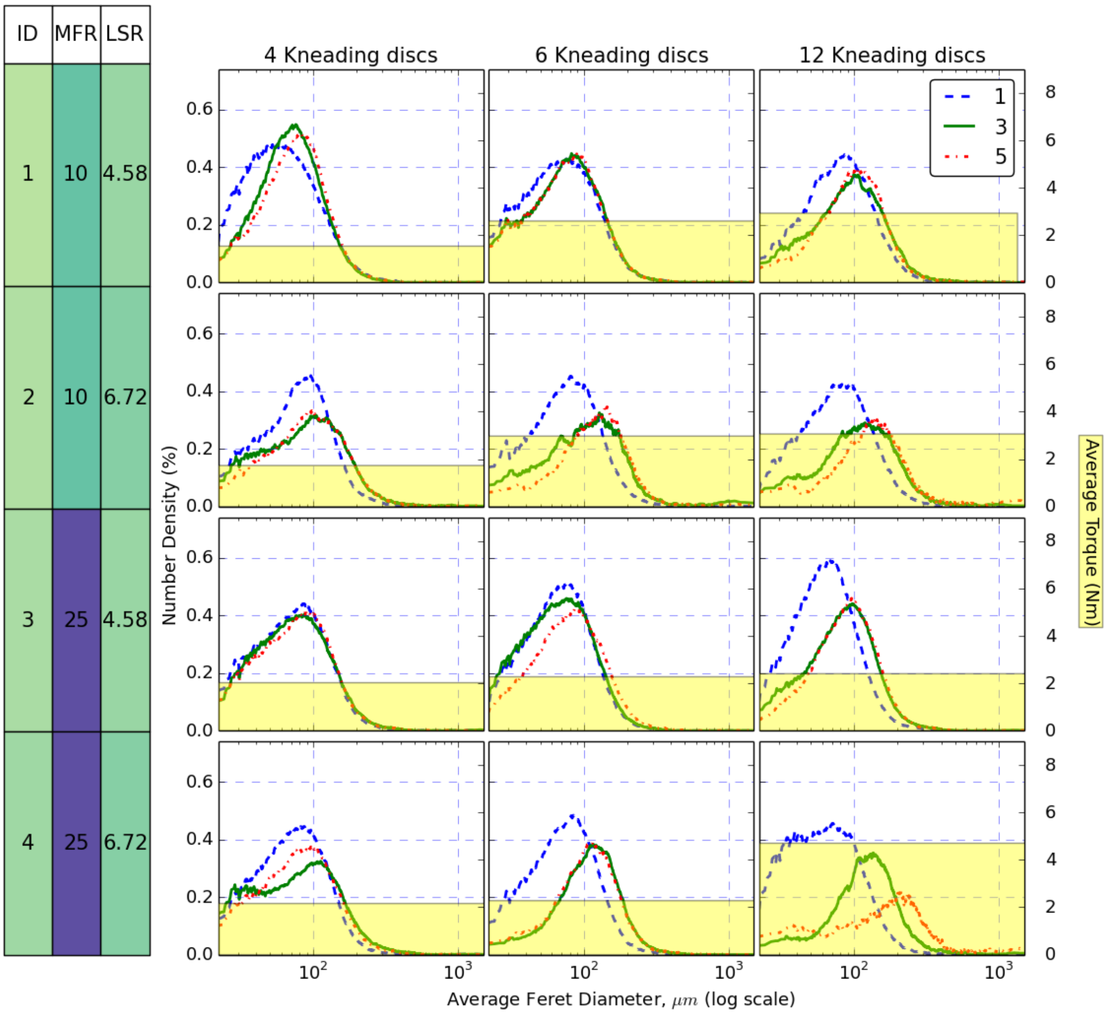


Figure 7: Number density of the granules (primary y-axis) having an average Feret diameter in the range of 20 to 1500 µm (log scale, shared x-axis) and torque level (secondary y-axis) at a different powder feed rate (10-25 kg/h), liquid to solid ratio (4.58-6.72% (w/w)) at low screw speed (500 rpm) [ID: experiment ID, MFR: throughput (kg/h), LSR: liquid-solid ratio (%)].

shape distribution became narrower indicating a more uniform granule shape. This spherification of granules together with an increase in size suggests that the granule enlargement processes in the TSG barrel are exhaustively coupled with granule reshaping processes such as consolidation and attrition. El Hagrasy et al. suggested that the increase in the number of kneading discs results in smearing of a progressively larger number of wet agglomerates from the conveying section [8]. The rotating tips of the kneading discs chop-off the edges of the elongated wet agglomerates formed during the conveying section, leading to more rounded granules. The wet surface exposed by this event was suggested to be picking up dry fines leading to growth of granules by the layering mechanism.

At low liquid to solid ratio (4.58 %) and low screw speed (500 rpm)

When increasing the throughput from 10 kg/h to 25 kg/h keeping the L/S at a lower level (4.58% (w/w)), the aggregation was very limited. Comparing the ID 1 and 3 plots in Fig. 7 shows only a minor increase in granules size for successive sample location, irrespective of number of kneading discs. This indicates a lack of granulation liquid to make strong bridges between powder particles in the agglomerates. There was a small reduction in the amount of fines for sample location 5 at 12 kneading discs condition suggesting some squeeze-out of the granulation liquid from the wetted powder leading to further granulation. Similar to the size distribution, the increase in throughput at this condition had no significant effect on the shape distribution (Fig. 8). Only at the higher number of kneading discs the elongation of the granules reduced with the progressive sample locations indicating a greater consolidation of granules. The chopping-off of the edges of the brittle and elongated granules in the second kneading block of the TSG might explain this observed phenomena [8].

At high liquid to solid ratio (6.72 %) and low screw speed (500 rpm)

At high L/S more granulation liquid was available to enhance the size enlargement rate processes such as wetting, nucleation and aggregation. Thus, the distributions from all the sample location had an inclination towards higher diameter (comparing ID 2 and 4 plots in Fig. 7). When comparing the 12 kneading discs configuration profile from sample locations 3 and 5, the second kneading block (ID 2 plot of Fig. 7) had a trivial influence on granulation reflected by no change in the GSD. However, due to an increase in throughput, a further granule size enlargement of location 5 sample

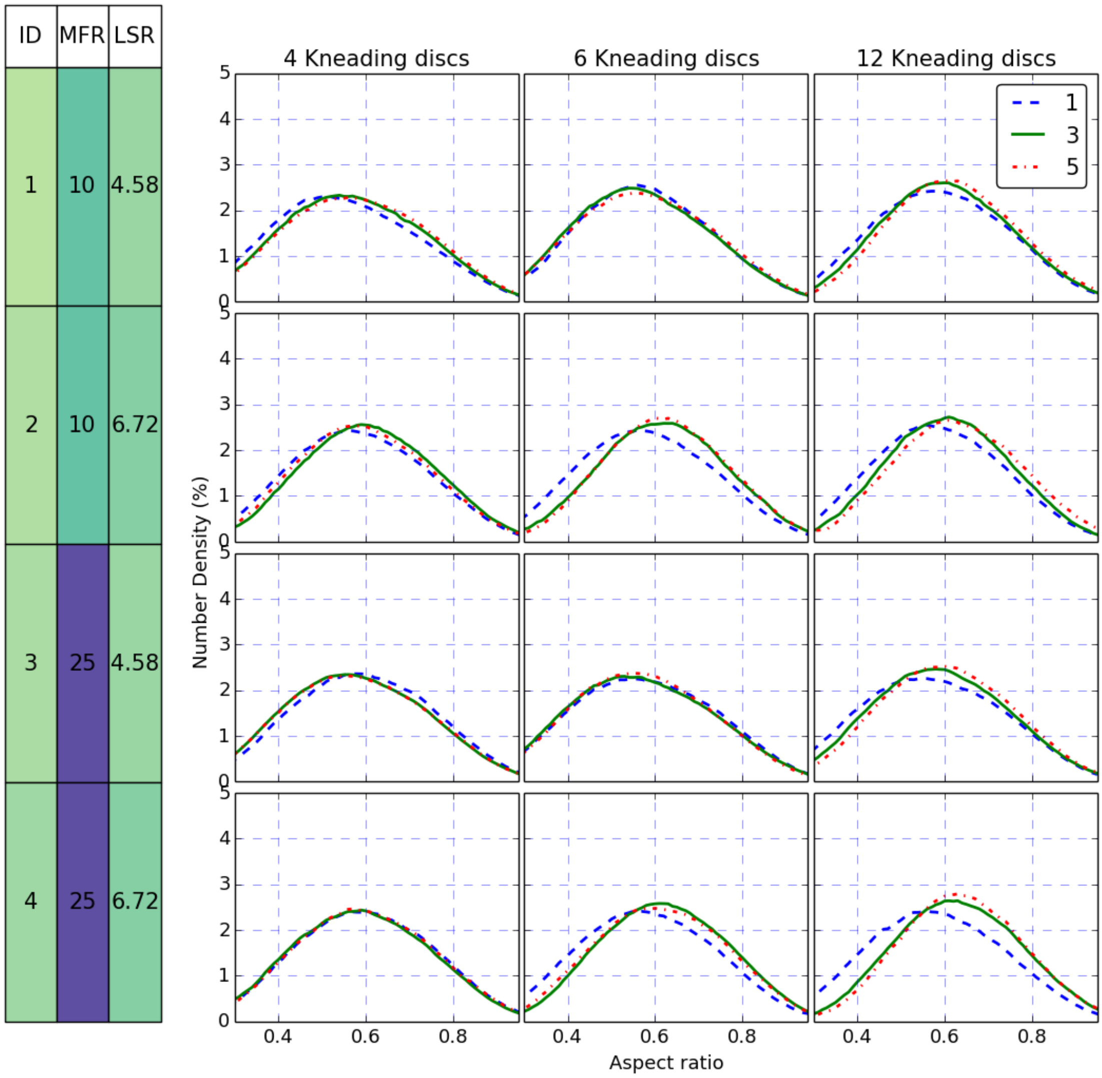


Figure 8: Number density of the granules (primary y-axis) having an aspect ratio in the range of 0.3 to 1 (shared x-axis) at a different powder feed rate (10-25 kg/h), liquid to solid ratio (4.58-6.72% (w/w)) at low screw speed (500 rpm) [ID: experiment ID, MFR: throughput (kg/h), LSR: liquid-solid ratio (%)].

was observed (ID 4 plot for 12 kneading discs in Fig. 7). This was possibly due to the abundance of unwetted powder in the granulator to agglomerate further, while the second kneading block squeezed-out the granulation liquid from the over-wetted granules formed in the preceding sections of the TSG screw. However, the size distribution at sample location 5 became much broader after introduction of second kneading block (2 kneading discs). This indicates that despite availability of granulation liquid, an inhomogeneous distribution of liquid over the material occurred due to poor shear-induced mixing at a screw speed of 500 rpm, resulting a broader GSD. A broad GSD might indicate an irregular shape, but this effect was less profound Along with the additional size transformation events leading to greater granule sizes, the increased throughput also affected the shape of the granules along the barrel length at high L/S. At a higher number of kneading discs, except for sample location 1, the aspect ratio profile significantly shifted towards the right and became narrower both for sample location 3 and 5 for the ID 2 and 4 plots in Fig. 8. This indicates an increase in sphericity and uniformity of granule shape while transfer of the material inside the granulator barrel in this condition. However, the higher fill ratio at increased throughput and sluggish flow of more wetted powder in the granulator barrel led to an almost doubled TSG drive torque (ID 4 plots in Fig. 7). This can be resolved by increasing the screw speed during granulation which increases the conveying rate and reduces the load on the screws.

At low liquid to solid ratio (4.58 %) and high screw speed (900 rpm)

High screw speed leads to a high level of shear induced mixing and shorter residence time of the processed materials inside the TSG. Whereas, an increase in throughput causes a higher torque required by the granulator drive. This increase in torque is attributed to the higher channel filling of the screws and the increased compaction, which in turn increases attrition of the wet mass between the screws and barrel wall [15]. Thus, an increased throughput at a low L/S would further contribute to the fragility of the granules and thus more susceptible to attrition and breakage. This presumption was found to be correct since the increased throughput for the 12 kneading block configuration showed a reduction in the larger granules after the second kneading block (location 3 and 5 profiles when comparing ID 1 and 3 plots for 12 kneading discs in Fig. 9). Beside the reduction in the granule size, the increased throughput did not affect the shape of granules and the profiles for the ID 1 and ID 3 plots in Fig. 10 corresponded the same pattern for equal number of kneading discs.

At high liquid to solid ratio (6.72 %) and high screw speed (900 rpm)

At higher L/S, the extra liquid causes an increase in the residence time of material in the granulator [14]. This additional time allows fines in the barrel of the granulator to adhere to granules, reducing levels of fines. Therefore, more uniform granulation occurs and a clear difference between the GSD profile from sample location 1,3 and 5 were observed when two kneading blocks were used (comparing ID 2 and ID 4 plots in Fig. 9). For the ID 4 plot at 12 kneading discs, the size distribution of sample location 3 was narrower than at sample location 5. The increased throughput only affected the shape of granules from location 1, where the granulation liquid was distributed to a larger amount of powder available at high throughput, thus having more uniform particle aspect ratio distribution for the ID 4 plots compared to ID 2 plots in Fig. 10. However, for sample location 3 and 5 the aspect ratio profile corresponded the same pattern for equal number of kneading discs.

3.2.2. Effect of liquid to solid ratio

At low throughput (10 kg/h) and low screw speed (500 rpm)

When the L/S in the TSG was increased from 4.58 % to 6.72 % at low throughput (10 kg/h) and at low screw speed (500 rpm), the degree of aggregation increased (comparing ID 1 and 2 in Fig. 7). More liquid at increased L/S enhanced wetting, nucleation and aggregation like granule enlargement rate processes [13]. With an increase in number of kneading discs the measured torque and shear mixing increased, leading to a reduction in the number density of smaller granules and an increase in the larger granules (ID 2 plot in the Fig. 7). Increasing number of kneading discs also induced a progressive mixing in the axial direction of the conveying section, leading to a shift of the GSD towards the higher granule size at sample locations 3 and 5 and their difference reduced. A narrower distribution was observed for the location 5 sample, as also reported by Dhenge et al. [14] and El Hagrasy et al. [12] in studies comparing samples collected at the granulator output only. However, an additional kneading block showed only a slight contribution to the aggregation when comparing the GSD profile from sample location 3 and 5 in ID 2 plots of Fig. 7. This was possibly due to the lack of sufficient unwetted powder in the granulator to agglomerate further.

The increase in L/S from 4.58 % to 6.72 % at low screw speed (500 rpm), translated into a decrease in the elongation (higher aspect ratio) of the granules for the screw configurations with 4 and 6 kneading discs (comparing ID 1 and 2 in Fig. 8). This outcome corresponds with results by

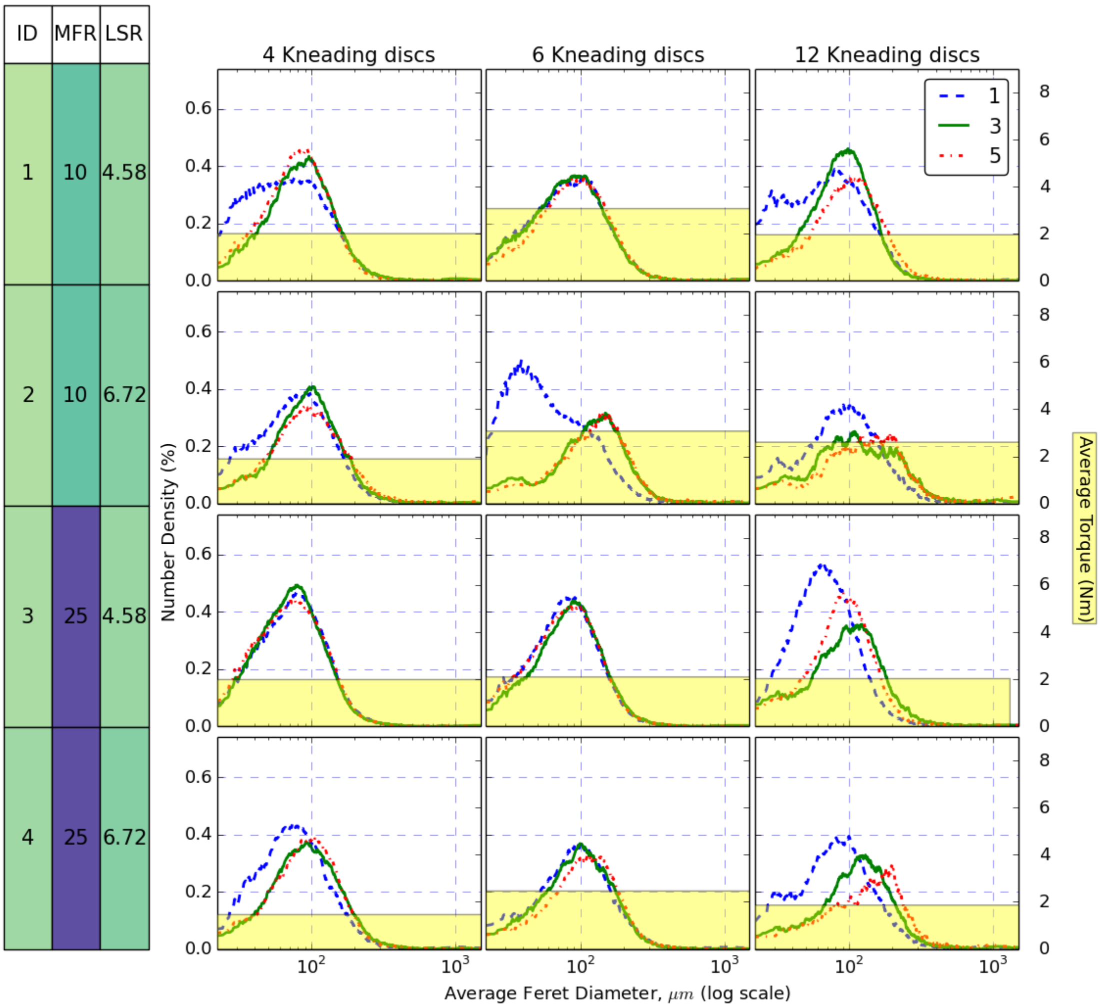


Figure 9: Number density of the granules (primary y-axis) having an average Feret diameter in the range of 20 to 1500 µm (log scale, shared x-axis) and torque level (secondary y-axis) at different powder feed rate (10-25 kg/h), liquid to solid ratio (4.58-6.72% (w/w)) at high screw speed (900 rpm) [ID: experiment ID, MFR: throughput (kg/h), LSR: liquid-solid ratio (%)].

Dhenge et al. where higher L/S produced more spherical granules [2]. For the successive sampling locations, an increase in the aspect ratio of the granules was observed for sample locations 3 and 5. However, there was no significant difference for increasing number of kneading discs configuration between ID 1 and 2 plots in Fig. 8) and the number density for smaller particle size remained same. This suggests that breakage was not the operative process, but the increase in consolidation caused a reduction in elongation of the granules. Altogether it can be asserted that the additional kneading block at this condition had minor contribution both in terms of granule enlargement and the spherification of granules.

At high throughput (25 kg/h) and low screw speed (500 rpm)

When the granulation was performed at high throughput (25 kg/h) and at low screw speed (500 rpm), the filling degree in the barrel increased and a larger amount of powder is available for granulation inside the barrel [15]. At this condition, when the L/S was increased (4.58 % to 6.72 %), an increased degree of aggregation was observed (comparing ID 3 and 4 plots in Fig. 7). However, the most remarkable change was observed for the screw configuration with 12 kneading discs when the number density profiles of the three sample locations was clearly segregated at the increased L/S condition. By the second kneading block in the TSG, due to the additional distributive mixing of the available unwetted material at high throughput and by the more available granulation liquid at increased L/S, an enhanced level of wetting, nucleation and aggregation rate processes was achieved. This also affected the shape of the granules along the length. Beside the shift of profile towards right in ID 4 compared to ID 3 plots of Fig. 8, indicating an increase in the aspect ratio of the granules at higher L/Salso the aspect ratio distributions became narrower, indicating an increased uniformity of granule shape. However the limiting factor in this condition is the torque of the TSG drive, which increased significantly due to high fill ratio and sluggish flow of wetted powder inside the granulator barrel.

At low throughput (10 kg/h) and high screw speed (900 rpm)

High screw speed increases the conveying rate and reduces the residence time of the wetted material [*cite the RTD paper*]. Thus at the low feed rate(10 kg/h) in this condition, the fill level in the TSG barrel is lowest. When the L/S was increased from 4.58 % to 6.72%, there was only a minor increase in granule size for the screw configuration with 4 kneading discs (comparing ID 1

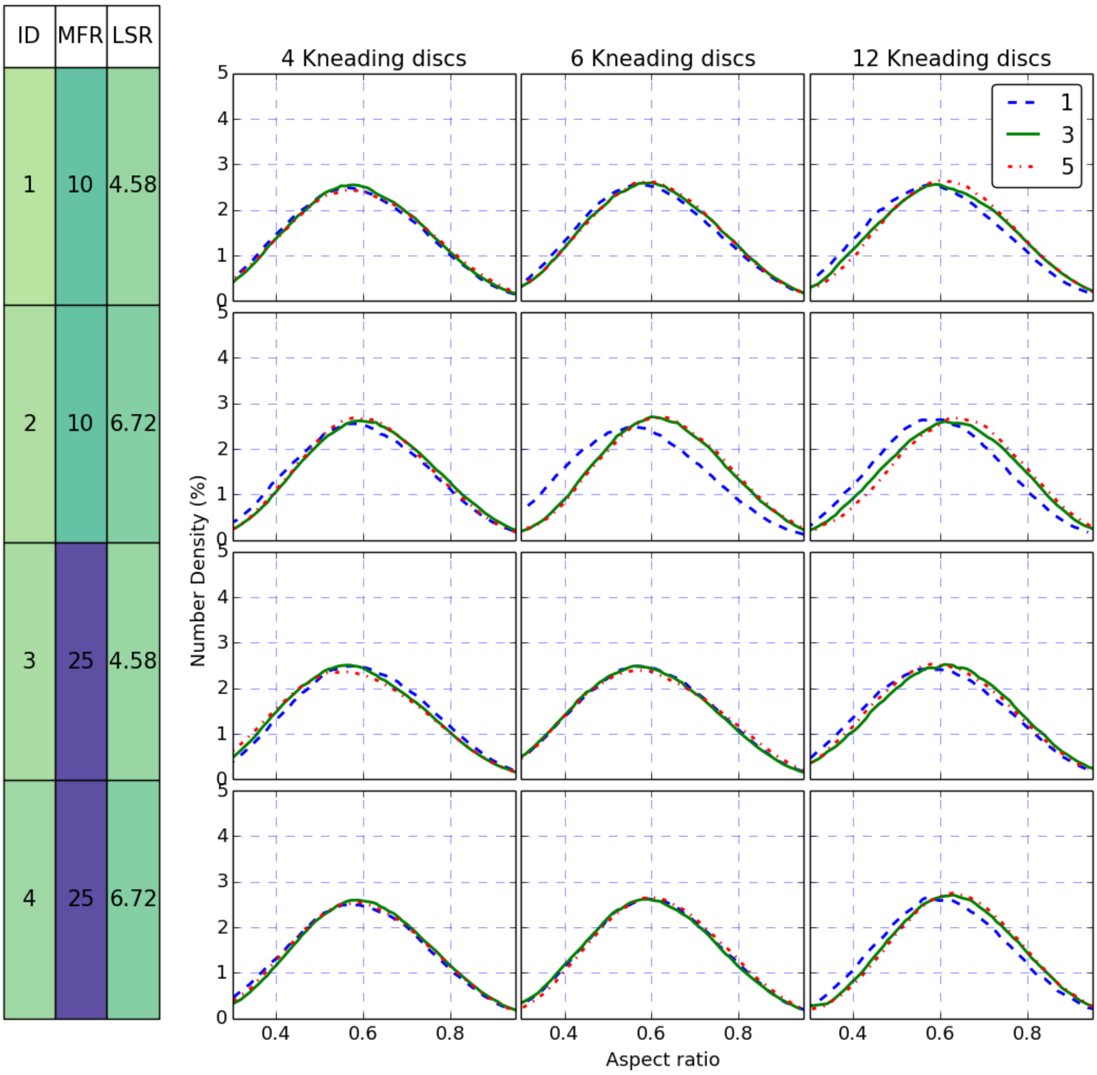


Figure 10: Number density of the granules (primary y-axis) having an aspect ratio in the range of 0.3 to 1 (shared x-axis) at different powder feed rate (10-25 kg/h), liquid to solid ratio (4.58-6.72% (w/w)) at low screw speed (900 rpm) [ID: experiment ID, MFR: throughput (kg/h), LSR: liquid-solid ratio (%)].

and 2 plots in Fig. 9). However, by increasing the number of kneading discs (6) and an additional kneading block (12 kneading discs) the aggregation level increased when increasing L/S, which was reflected by the shift in the distribution towards a higher diameter. Despite an increase in shear mixing due to higher screw speed (900 rpm), an additional kneading blocks showed a small contribution to the aggregation level when comparing the profiles from sample locations 3 and 5 in ID 2 plots of Fig. 9 which was also observed at low screw speed (Fig. 7). This may be due to the lack of unwetted powder in the granulator to support further agglomeration. The additional granulation liquid contributed to a more spherical shape for granules from successive samples of the TSG suggesting a higher level of consolidation of the granules. However, the shape distribution of samples before and after the second kneading block were similar. This indicated that at the very low fill level the second kneading block had a minor role in changing the shape of the granules.

At high throughput (25 kg/h) and high screw speed (900 rpm)

At high throughput, there is a large amount of powder available in the TSG barrel for granulation. But an increased L/S can only improve the agglomeration level when the mixing is increased. However, an increase in screw speed caused a reduction in the fill level and increase in the shear leading to an improved mixing. Especially at high screw speed the axial mixing inside the granulator increases significantly [*cite the RTD paper*]. Due to low restriction to the flow at a lower number of kneading discs, very less mixing of the powder and the granulation liquid consequent aggregation happened during transport of the material in the granulator barrel leading to minor difference between sample location 1, 3 and 5 (comparing ID 3 and 4 plots in Fig. 9). However, when the number of kneading discs was increased, the wetted powder was well mixed in lower filled barrel and hence agglomerated leading to increase in granule size. For the screw configuration with 12 kneading discs, most significant difference between all the three locations was observed, which can be attributed to the presence of an additional kneading block between sampling location 3 and 5 along with the one between sample location 1 and 3. The effective mixing and granulation at this condition also reflected in the shape dynamics when an increase in number of kneading discs only caused an increase in the density of high aspect ratio granules (comparing ID 3 and 4 plots in Fig. 10). From low to high number of kneading discs, for the location 1, 3 and 5 the aspect ratio distribution showed a close proximity. This indicated that shear induced consolidation occurred in the early stage of the granulation and the aggregation and the consolidation of the granules were happening on the same time.

3.2.3. Effect of combined change in throughput and liquid to solid ratio

At low screw speed (500 rpm)

When both throughput and the L/S were increased together from 10 to 25 kg/h and 4.58 to 6.72% (w/w) respectively, at low screw speed (comparing ID 1 and ID 4 plots in Fig. 7), not only the fill level in the barrel was increased, but also a greater amount of liquid became available to support the size enlargement rate processes. However, a greater shear is required to achieve the mixing of the wet powder in a highly filled TSG barrel and a subsequent more uniform granule size. Despite more granulation when comparing the profiles from ID 1 and 4 plots in Fig. 7, there was less difference between the GSD from sample location 1 and 2 in ID 4 plot of Fig. 7 due to the lack of mixing at a low number of kneading discs. However, a progressive mixing in axial direction occurred due to the shear induced during the conveying of the wet powder, hence changing the morphology in terms of reduction in smaller granules and an increase in the larger granules at sample location 3 and 5 in the ID 4 plot for 4 kneading discs in Fig. 7. But when the number of kneading discs was increased, the powder with higher moisture content in highly filled barrel agglomerated more. For the screw configuration with 12 kneading discs, a clear difference was observed between all the three sample locations. This can be attributed to an increased role of spatially separated kneading blocks and their presence between sampling location for this configuration, causing maximum possible mixing. However, the number density for the lower particle size also increased with spatial progress indicating that beyond the consolidation, breakage of the granules was also occurring as an important size reduction phenomena and had a competitive relationship with aggregation process in the second kneading block of the TSG at this condition.

The shape dynamics with increase in number of kneading discs at this condition also reflected greater need of mixing (comparing ID 1 and ID 4 plots in Fig. 8). At a low number of kneading discs, the aspect ratio or shape distribution of the location 1, 3 and 5 samples were similar. By increasing the number of kneading discs the shape distribution of the locations 1 and 3 samples became more distinct, while the difference between the sample locations 3 and 5 remained low. This was caused by an increase in the aspect ratio of the granules from sample location 3 and 5 with increasing in number of kneading discs. This shows that at increased shear first the particle shape changes through consolidation, only after which the breakage happens.

At high screw speed (900 rpm)

As discussed earlier, an increased mixing is required when the throughput and the L/S are high. The high shear and low fill level due to increased conveying rate at high screw speed can lead to a very efficient mixing in the TSG barrel in this process condition [6]. At high screw speed but four kneading discs the mixing of the wetted powder inside the TSG was mainly dispersive and therefore, there was very less difference between the profile for sample location 3 and 5 which were after the kneading discs(plot ID 4 in Fig. 9). With 6 kneading discs the restrictive forces stated playing a role, which resulted in formation of more stable GSD even before the material entered the first kneading block (plot ID 4 in Fig. 9). However, in lack of adequate distributive mixing of wetted powder, there was minor difference between sample location 3 and 5. When the second kneading block was added between sampling location 3 and 5 in the screw, the powder with high moisture content was distributively mixed and hence agglomerated furthermore (plot ID 4 in Fig. 9). This lead to size distribution profiles which were separated for all the three sample locations. Also, unlike the observations at low screw speed (ID 4 plot for 12 kneading discs in Fig. 7), the number density for the lower particle size did not increase with the spatial progress for high screw speed indicating that sufficient mixing occurred to support the aggregation process at location 5 in TSG barrel(ID 4 plot for 12 kneading discs in Fig. 8). Suitability of this condition also reflected in the shape dynamics as the increase in number of kneading discs only caused a minor increase in the aspect ratio distribution (comparing ID 1 and ID 4 plots in Fig. 10). At low to high number of kneading discs, for the location 1, 3 and 5 the aspect ratio distribution showed a proximity irrespective of throughput. This indicated that consolidation of the granules went well along with the aggregation during the conveying of the granules in the TSG barrel.

3.2.4. Effect of increase in screw speed

Beside the distributive mixing by the kneading discs, another important factor responsible for mixing is the screw speed causing the shear induced mixing. Increasing the screw speed increased the shear level, but reduced the mean residence time of the wet powder in the barrel. Hence, a competitory relationship exists between the shear mixing in the barrel and the residence time of the wetted powder both of which are desired to support granulation rate process. At low powder feed rate (10 kg/h) and L/S (4.58), when the screw speed was increased from 500 rpm (ID 1 plot of Fig. 7) to 900 rpm (ID 1 plot of Fig. 9), there was no significant shift in the GSDs. Only the measured torque level decreased. Although, an increase in screw speed reduced the fill level and improved mixing, there was no excess granulation liquid to create the possibility of more aggregation. Comparing the shape dynamics, the distribution of shape followed a consistent pattern due to a lower fill ratio and good mixing in the barrel. With the increasing number of kneading discs, there was an increase in the aspect ratio owing to an accumulated level of shear (ID 1 plots of Fig. 8 and 10).

At low powder feed rate (10 kg/h), but a high L/S (6.72%), an increased screw speed assisted early aggregation of the wetted powder, which is reflected by larger granules for all three sample locations irrespective of the number of kneading discs (comparing ID 2 plots of Fig. 7 and 9). The addition of more kneading discs further increased the agglomeration level. Furthermore, there was a successive reduction in the amount of fines by increasing the number of kneading discs. Also the aspect ratio of the granules in the shape distribution increased, indicating that the granules became more spherical at this condition as the number of kneading discs is increased. It can be assumed that increased shear caused a greater consolidation of granules and consequently an increased sphericity, while making squeezed-out liquid available to further granulate. This leads to the further shift of size distribution towards higher diameter.

However, when the feed rate was high (25 kg/h) and the L/S was low (4.58%), an increase in the screw speed resulted an early aggregation of the particles reflected by right shift in the size distribution of the granules for all the three locations with minimal number of kneading discs (comparing ID 3 plots in Fig. 7 and 8). Addition of more kneading discs to screw caused a reduction in the amount of fines in the screw configurations. However, for the configuration with 12 kneading discs there was a reduction in the number density of larger particle size at sample location 5 compared to sample location 3 indicating breakage of larger granules by second kneading block (ID 3 plot for 12 kneading discs in Fig. 7. This can be attributed to the lack of sufficient liquid in the granulation system to make strong bridges between the particles in the granules, which lead breakage upon excessive stress caused by high screw speed and high number of kneading discs. This lack of sufficient liquid in the granulation system to support the aggregation process was also reflected in the aspect ratio where due to lack of additional particle growth processes no significant change in the shape distribution was observed. The entire shape distribution at high shear remained the same as when low shear conditions were used.

The effect of an increase in screw speed at high levels of throughput and liquid solid ratio has been discussed in section 3.2.3. The major contribution of increasing the screw speed at high throughput and L/S is that the granulator torque is reduced, without affecting the granule size distribution. This allows operation at high throughput and is desirable from the productivity point of view at manufacturing scale.

4. Conclusions

This study showed that a balanced mixing is important to change the granule characteristics by aggregation and breakage mechanism along with the consolidation of the particles. The fill ratio in the barrel is an important factor both because its effects on the torque, and role in changing the size and shape of the particles. For high throughput operation, feed rate and screw speed should be increased simultaneously. But for the high agglomeration level, both throughput and liquid to solid ratio should be increased, otherwise it can be used to direct dominance of aggregation or breakage whenever required. A number of competing mechanisms, such as aggregation, consolidation and breakage occurred in the process. Although this study provided a detailed insight regarding the process, the experimental data produced no quantitative insight on which of these mechanisms were dominant. Unlike experimental results where only the collected data are available, models are transparent in the sense that any and all of the intermediate data can be observed after simulation. Therefore the results obtained from this study will be used for the mechanistic modelling of the process.

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References

[1] B. J. Ennis, Theory of Granulation: An Engineering Perspective, in: Handbook of Pharmaceutical Granulation Technology, 2010, pp. 6–58. doi:10.3109/9781616310035.002.

[2] R. M. Dhenge, J. J. Cartwright, M. J. Hounslow, A. D. Salman, Twin screw granulation: Steps in granule growth, Int. J. Pharm. 438 (1-2) (2012) 20–32. doi:10.1016/j.ijpharm.2012.08.049.

[3] C. Vervaet, J. P. Remon, Continuous granulation in the pharmaceutical industry, Chem. Eng. Sci. 60 (14) (2005) 3949–3957. doi:10.1016/j.ces.2005.02.028.

[4] A. Kumar, K. V. Gernaey, T. De Beer, I. Nopens, Model-based analysis of high shear wet granulation from batch to continuous processes in pharmaceutical production – a critical review, Eur. J. Pharm. Biopharm. 85 (3, Part B) (2013) 814 – 832. doi:10.1016/j.ejpb.2013.09.013.

[5] D. Djuric, B. Van Melkebeke, P. Kleinebudde, J. P. Remon, C. Vervaet, Comparison of two twin-screw extruders for continuous granulation, Eur. J. Pharm. Biopharm. 71 (1) (2009) 155–160.

[6] J. Vercruysse, D. Córdoba Díaz, E. Peeters, M. Fonteyne, U. Delaet, I. Van Assche, T. De Beer, J. P. Remon, C. Vervaet, Continuous twin screw granulation: Influence of process variables on granule and tablet quality, Eur. J. Pharm. Biopharm. 82 (1) (2012) 205–211. doi:10.1016/j.ejpb.2012.05.010.

[7] J. Vercruysse, M. Toiviainen, M. Fonteyne, N. Helkimo, J. Ketolainen, M. Juuti, U. Delaet, I. V. Assche, J. P. Remon, C. Vervaet, T. De Beer, Visualization and understanding of the granulation liquid mixing and distribution during continuous twin screw granulation using NIR chemical imaging, Eur. J. Pharm. Biopharm. (0) (2013) –. doi:10.1016/j.ejpb.2013.10.012.

[8] A. El Hagrasy, J. D. Litster, Granulation rate processes in the kneading elements of a twin screw granulator, AIChE J.

[9] B. Van Melkebeke, C. Vervaet, J. P. Remon, Validation of a continuous granulation process using a twin-screw extruder, Int. J. Pharm. 356 (1-2) (2008) 224–230. doi:10.1016/j.ijpharm.2008.01.012.

[10] M. Fonteyne, S. Soares, J. Vercruysse, E. Peeters, A. Burggraeve, C. Vervaet, J. P. Remon, N. Sandler, T. De Beer, Prediction of quality attributes of continuously produced granules using complementary pat tools, Eur. J. Pharm. Biopharm. 82 (2) (2012) 429–436. doi:10.1016/j.ejpb.2012.07.017.

[11] K. T. Lee, A. Ingram, N. A. Rowson, Twin screw wet granulation: the study of a continuous twin screw granulator using Positron Emission Particle Tracking (PEPT) technique., Eur. J. Pharm. Biopharm. 81 (3) (2012) 666–73. doi:10.1016/j.ejpb.2012.04.011.

[12] A. El Hagrasy, J. Hennenkamp, M. Burke, J. Cartwright, J. Litster, Twin screw wet granulation: Influence of formulation parameters on granule properties and growth behavior, Powder Technol. 238 (2013) 108–115. doi:10.1016/j.powtec.2012.04.035.

[13] J. Litster, B. Ennis, The science and engineering of granulation processes, Vol. 15, Springer, 2004.

[14] R. M. Dhenge, R. S. Fyles, J. J. Cartwright, D. G. Doughty, M. J. Hounslow, A. D. Salman, Twin screw wet granulation: Granule properties, Chem. Eng. J. 164 (2-3) (2010) 322–329, Pharmaceutical Granulation and Processing. doi:10.1016/j.cej.2010.05.023.

[15] R. M. Dhenge, J. J. Cartwright, D. G. Doughty, M. J. Hounslow, A. D. Salman, Twin screw wet granulation:

Effect of powder feed rate, Adv. Powder Technol. 22 (2) (2011) 162 – 166, special issue of the 6th World Congress on Particle Technology. doi:10.1016/j.apt.2010.09.004.