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Twin screw wet granulation: Granule properties

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ABSTRACT

Granulation is an important particle size enlargement process, used in many applications. Granulation has, for many years, been a batch process because of a greater knowledge base. However, the technique of using a twin screw granulator has been found to be very effective at granulating and is an attractive proposition for manufacturing processes because it can be operated continuously. The acceptability of the granules produced varies depending on a number of different parameters. The effect on the properties of granules caused by varying the screw speed, powder feed rate and the ratio of liquid to solid were investigated.

This work focuses on the effect that process variables have on the properties of granules and shows that all three-process variables (screw speed, powder feed rate and liquid to solid ratio) had varying influences on residence time and torque, which in turn affected the distribution of size, strength, shape and structure of the granules. For all three-process variables, it was found that by varying the process variables mentioned above resulted in changes to the average particle size distribution. The granules that were produced, however, were irregular, non-spherically shaped granules.

The properties of the granules produced by changing each variable in turn were tested and compared in order to determine the optimal conditions for agglomeration using a twin screw granulator, for the used formulation. The ideal conditions will produce to meet the predefined target criteria of mechanically strong and consistent granules, which is important for reliable process operation.

1. Introduction

Granulation is a process of agglomerating smaller particles together into larger, semi-permanent aggregates in which original particles can still be distinguished [1]. It is a size enlargement of particles, which is typically required to improve flow, compaction or homogeneity of a downstream blend of materials in the production of solid oral dosage forms. Granulation can either be a dry or wet process and the granules that are formed can be categorized into either dry or wet depending on the type of bonding between primary particles. In dry granulation powder particles are compressed under high pressure and then subsequently milled through a screen to form granules. This can either be achieved by converting the powder into a slug or squeezing it between two narrowly separated, heavy rollers, more commonly known as roller compaction [2]. In wet granulation, granules are formed by the addition of a liquid media onto a powder bed which is under the influence of an impeller (in high-shear granulator) or air (in fluidised bed granulator). The agitation imparted into the system along with the wetting of the components within the formulation results in the coalescence or consolidation of the primary powder particles to produce wet granules. Generally the liquid binder is sprayed or poured over an agitated bed of powder particles which proceed to grow in size as particles bind to one another in a process termed agglomeration.

Granulation can be either a batch or continuous process. Continuous granulation offers several commercial and technical advantages over batch granulation:

1. Reduced number of scale-up steps compared to batch.
2. Fully automatable.
3. More amenable to uni and multivariate control strategies (PAT).
4. Lower associated API costs.
5. Reduced development time required to produce acceptable product.
6. Higher throughput of material than traditional batch granulation techniques.
7. Smaller equipment footprint.

The main financial drivers for R&D are related to the speed of development and the reduction in the required quantities of

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Active Pharmaceutical Ingredients (API's) in order to quickly map an experimental design space. As stated above, continuous processing also removes several scales of development as teams move from lab scale equipment through to commercial scale installations.

There are various different methods of continuous granulation that can be used, as well as different types of equipment, process parameters can be altered to change the properties of the granules that are produced. Continuous granulation deals with at least two process steps: homogeneous blending and subsequent agglomeration of the powder feed material. Further process steps such as drying would need to be added to achieve a viable commercial production facility [3]. Continuous granulation is currently used for the production of pharmaceutical granules. Vervaet and Remon [4] gave an overview of some of the current continuous processing methodologies. The different approaches of granulation outlined in their work covered fluidised bed agglomeration, spray drying, semi continuous high-shear granulation, roller compaction and extrusion.

Co-rotating twin screw granulation has recently gained popularity within the pharmaceutical industry. Some papers indicate the potential of extrusion as a continuous wet granulation technique [5]. Previous research works have been carried out on how some granule properties are affected by varying the powder feed rate, liquid content, screw speed [5–7] and screw configuration [8]. There are also some reports on influence of these parameters on residence time of food materials in twin screw extruder [9,10].

However the influence of these parameters on properties of granules has not been fully explained on the basis of residence time and torque. The research work presented here examines the effect of varying the powder feed rate, liquid to solid ratio and the screw speed using a co-rotating twin screw granulator on the residence time and average torque and relationship of these two with properties of granules such as size, shape, structure, flow and strength.

2. Materials and methods

2.1. Preparation of granules

All the experiments were performed on a co-rotating twin screw granulator (Euro lab 16 TSG, Thermo Fisher Scientific, Stone, United Kingdom) having a length to diameter ratio of 25:1, using a screw configuration as in Fig. 1. The formulation under consideration consisted of following excipients (brand name, particle size and content in total formulation is mentioned in brackets), α-lactose monohydrate (Lactochem, 55 μm, 73.5%), microcrystalline cellulose (Avicel PH 101, 57 μm, 20%), crosscarmellose sodium (Ac-Di-Sol, 58 μm, 1.5%) and hydroxypropyl cellulose i.e. HPC (Klucel, 66 μm, 5%). Water was used as the granulation liquid and was pumped into the granulator using a peristaltic pump (Watson Marlow, U.K.). HPC was used as binder. All the excipients were premixed in high-shear mixer (Romaco Roto Junior) and transferred to a gravimetric, loss-in-weight twin screw feeder (K-Tron Soder, Switzerland) in parts (25 kg in total). During all the experiments the barrel of the granulator was set at a constant temperature of 25 °C. Granules (batch size 1 kg) were collected after 2 min once the system was allowed to equilibrate. The screw configuration was kept constant for all the experiments, as it is in Fig. 1; the elements for this configuration are listed in Table 1.

Table 1
Screw elements used in Fig. 1.

Screw element code	Screw element name	Ratio of length to diameter
FS	Feed screw	$L = D$
LPFS	Long pitch feed screw	$L = 2D$
F60°	Mixing element at 60° pitch	$L = D/4$
DFS	Discharge feed screw	$L = D$

Granulation was carried out at different powder feed rates, liquid to solid ratios and screw speeds whilst keeping two of the three parameters constant. To study the effect of powder feed rate on granule properties, pre-blended powder was added at 2, 3.5 and 5 kg/h. The screw speed and the fractions of granulation liquid (water) were kept constant. When studying the effect of the liquid to solid ratio (liquid fraction or L/S) on granular properties, the granulation liquid (water) was pumped into the granulator so that there was 0.25, 0.3 or 0.4 fraction of liquid present. The speed of the screw and powder feed rate remained constant. The effect of screw speed of 250, 400 and 550 rpm were used to investigate what effect screw speed had on the properties of the granules produced at a constant powder feed rate and liquid to solid ratio.

2.2. Measurement of average residence time and torque

Residence times for each of the conditions were measured to determine how long the material had to granulate inside the granulator. The residence times were measured by injecting about 0.2 mL of 0.5% blue dye (Patent Blue V Sodium Salt) solution at the powder inlet, with the powder and timing how long it took for the colour to appear at the barrel end. The equipment has an in-built torque measurement sensor which measures the torque and displays directly on the control panel after every 5 s. The torque values displayed after equilibration of the process were averaged to give overall torque in the particular batch. The torque values were considered as an indication of extent of shear and compaction forces experienced by powder inside the barrel.

2.3. Drying and size analysis of granules

The granules from all the experiments were oven dried at 40 °C for 48 h and their shape, size distribution, flow property and strength was evaluated. Samples of the granulated material were analysed using QICPIC particle size analyser with WINDOX 5.4.1.0 software (Sympatec U.K.).

2.4. Shape and surface characterisation of granules

Granules were collectively studied for their shape, size and surface characteristics using Zeiss stereo microscope (Zeiss U.K.). The

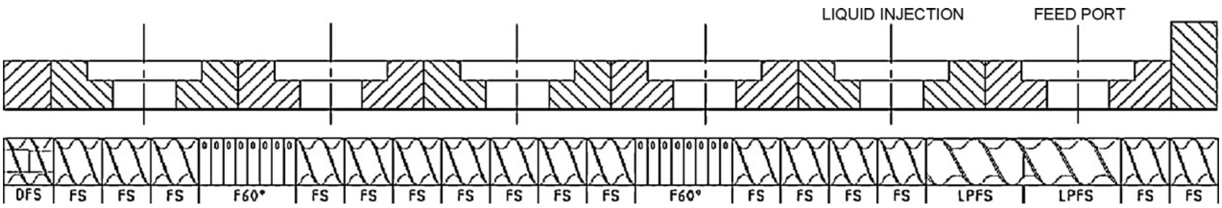

Fig. 1. Configuration of the co-rotating screws (screw elements in Table 1).

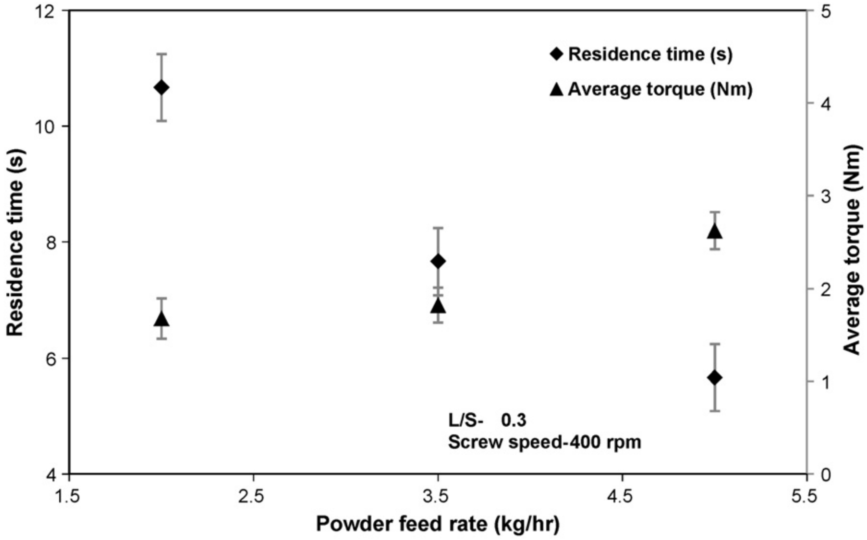

Fig. 2. Residence time and average torque produced at powder feed rates of 2, 3.5 and 5 kg/h.

microscope provided images that illustrated the surface characteristics of the granules that include the roughness, shape and size.

2.5. Determination of flowability (angle of repose) of granules

The static angle of repose for each sample batch was determined using a glass conical funnel, with an outlet diameter of 0.5 cm, fixed on a metal stand. The funnel was fixed at a height of 6 cm above the base. A digital camera was positioned exactly in front of the funnel to take images. The funnel was closed and 100 g of granules was poured in. Once the outlet was opened, the granules flowed out to form a cone on the base. The images were captured using a camera and then fed to the computer software 'Image J' for determining the static angle of repose. The procedure was repeated five times for each sample and an average was calculated. The experimental values then compared to the range of repose angles prescribed by United State Pharmacopoeia [11] and the flow property was described accordingly.

2.6. Estimation of strength of granules

Granules (100 g) were placed on a sieve shaker (Retsch Technology, Germany) with sieves of 300 and 600 μm for 3 min, at amplitude of 2 mm to obtain specific size class for strength analysis. The reason behind selecting this size range was to compare the different batches of granules avoiding an effect of varying sizes of granules. The strength of granules was determined out using Zwick/Roell Z 0.5 materials testing machine with a PC for real time data logging and analysis. The granules were placed in a die with a 10 mm diameter and component height of 10 mm and compressed at a test speed of 5 mm/min, with an upper force limit of 450 N. The test was repeated 10 times in order to get accurate data from the analysis. The die and punch was cleaned each time to ensure that no material from previous measurements affected results. The average strength of granules was then calculated using Adam's equation (1) [12].

$$\ln\ P = \ln\left[\frac{\tau}{\alpha}\right] + \alpha\varepsilon_n + \ln(1 - e^{-\alpha\varepsilon_n}) \qquad (1)$$

where P is the applied pressure, τ is the average agglomerate strength (also known as Adam's strength parameter), α is a constant rated to friction and ε_n is the natural strain. τ and α were obtained by fitting the data into Eq. (1) as natural logarithms of the applied pressure and as a function of the natural strain, by non-linear regression.

3. Results and discussion

3.1. Influence of powder feed rate

Fig. 2 shows influence of powder feed rate on residence time of the material inside the barrel and torque produced during granulation. It was observed that the residence time decreases significantly with increase powder feed rate. At low powder feed rate there was less powder inside the barrel hence the degree of channel filling was low. This also means that there was low throughput force for powder hence the powder resided for longer time inside the barrel. Further to this, the residence time was shorter for high powder feed rates. The high powder feed rate led to higher degree channel filling of screws creating high throughput force which may have resulted in plug flow of powder. The shortest residence time was noted at powder feed rate of 5 kg/h. This may be due to very high throughput force which conveyed the powder quickly.

Fig. 2 also shows the average torque produced during the granulation of powder material at varying powder feed rates. Varying feed rate had different loads of powder mass and different degrees

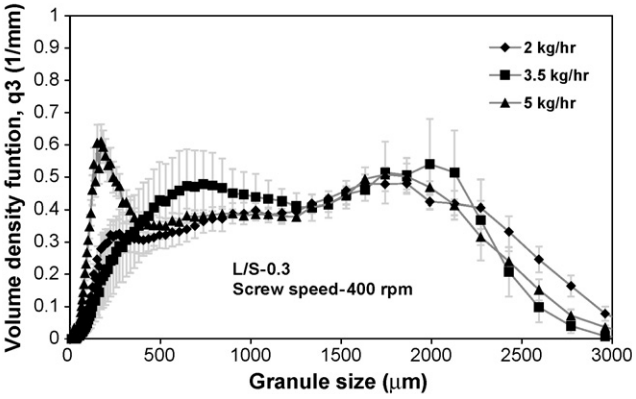

Fig. 3. Size distributions for changing powder feed rates.

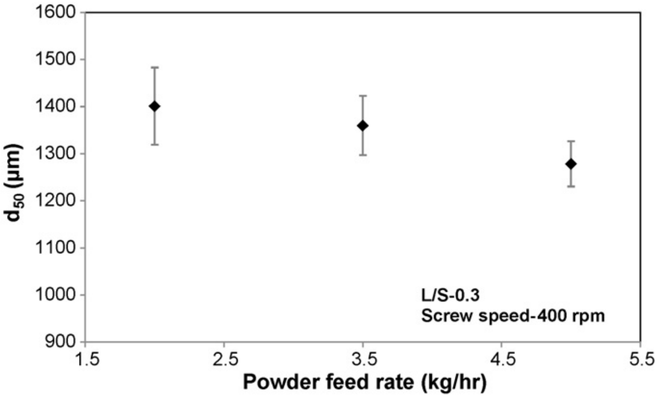

Fig. 4. d_{50} values for changing powder feed rates.

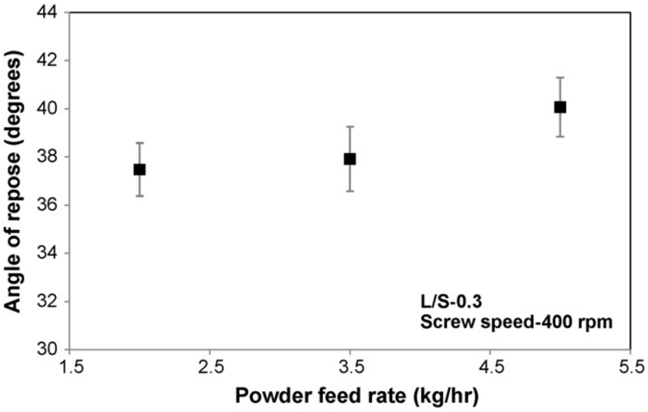

Fig. 6. Angles of repose for three powder feed rates indicating flowability.

of barrel filling which produced variation in force required to rotate the screws at the predefined rotational speed. Hence the torque was different at every condition. The torque values were considered as an indication of extent of compaction of powder inside the barrel. At low powder feed rate the barrel was not filled completely hence the screws had less conveying load on them and low torque was produced. As the powder feed rate was raised to 5 kg/h the sharp rise in the torque value took place indicating increase in conveying load on screws which further reflected the increase in compaction force experienced by the powder mass. The similar trends of residence time and torque were observed when granulation was carried out at L/S of 0.25, screw speed of 250 rpm and L/S of 0.4, screw speed of 550 rpm at powder feed rate of 2, 3.5 and 5 kg/h, respectively (data not shown here).

The influence of residence time was clearly observed on size distribution of granules. The size distributions for all powder feed rates were bimodal (Fig. 3). A bimodal distribution of granule size indicates the presence of both a high percentage of both small and large size granules. Fig. 3 also shows that 5 kg/h had more small size granules than were produced at a powder flow rate of 2 kg/h. The percentage of smaller granules was fairly similar between the 2 and 3.5 kg/h powder feed rates.

At low powder feed rate the residence time became long but torque decreased which resulted in restricted packing of primary particles in the granules in production of large and porous granules. This resulted in increase in average granule size, d_{50} (Fig. 4). The reverse effect was observed at high powder feed rate due to high torque produced during the process. Although there was a general trend for a reduction in granule size with increasing powder feed rates, the agglomerates that were produced were still fairly large; the smallest mean particle diameter was given at 5 kg/h and is over 1300 μm. The majority of granules produced at low powder flow rates were found to be elongated. Increasing powder feed rates produced fewer elongated granules and had a corresponding rise in spherical granules. At a powder feed rate of 3.5 and 5 kg/h, the proportion of elongated agglomerates was found to decrease slightly whilst the sphericity found to be increased (Fig. 5a and b).

The improved sphericity of granule may be due to increased barrel filling at high powder feed rate which led to increase in shearing forces from barrel on to the powder mass and became more spherical. Analysis of repose angles showed the flowability of the granules. Angles of repose of all three powder feed rates marginally differed from each other and granules were found to flow fairly (Fig. 6).

The strength of the granules produced increased as the powder feed rate was increased (Fig. 7). The increasing strength of the granules was caused by the increasing degrees of channel filling at higher powder feed rates. High powder feed rates compact the powder inside the granulator barrel. When powder compaction inside the granulator is increased, the granules that form interact more with the ungranulated material in the barrel. This interaction between the powder and the surface of the granules causes the powder to efficiently pack over the granule surface and around each other. The surface of the granules begin to pack the powder more effectively at higher powder feed rates, interlocking the primary particles onto the surface of the granules. The better the interlocking of the primary particles onto the structure of the granules, the

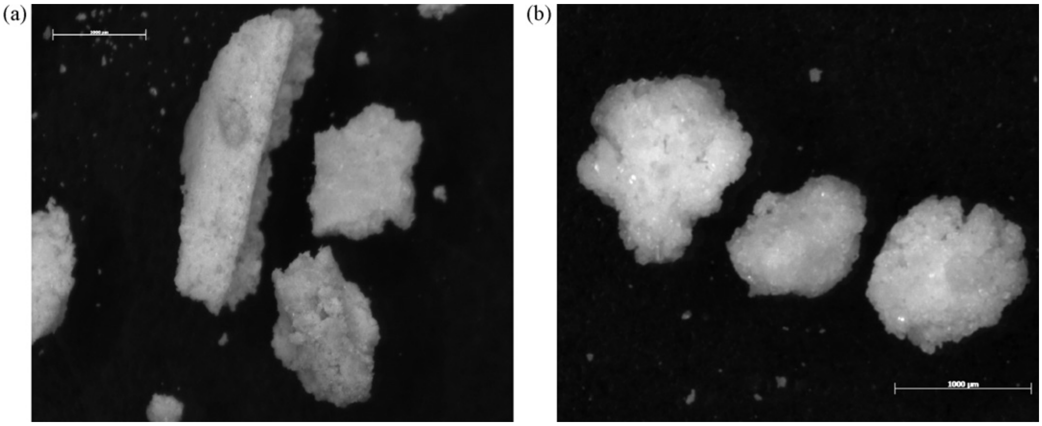

Fig. 5. (a) Granules produce using a powder feed rate of 2 kg/h, scale bar is for 1000 μm. (b) Granules produce using a powder feed rate of 5 kg/h, scale bar is for 1000 μm.

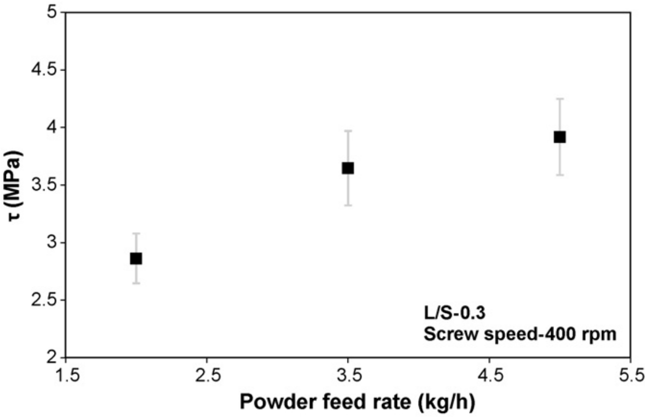

Fig. 7. Granules strength for changing powder feed rates.

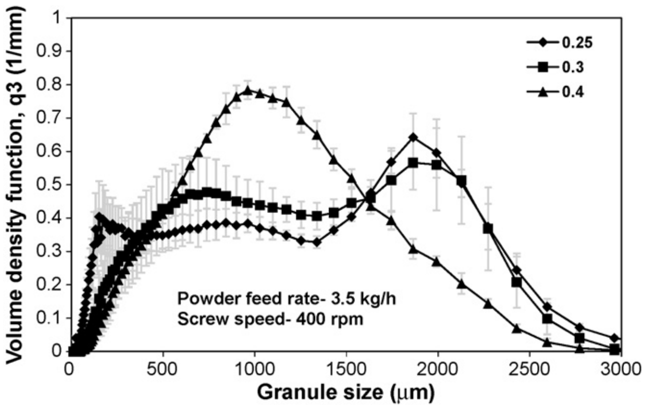

Fig. 9. Size distributions for three L/S.

stronger the granule becomes. This result agrees with Fu et al. [13] who found that in a batch high-shear mixer if granulations are left for a long time, the strength still increases. The reason was that with more time, the interlocking primary particles can rearrange themselves on the surface of the granules.

3.2. Influence of liquid to solid ratio (L/S)

Fig. 8 shows influence of liquid to solid ratio on residence time of the powder material inside the barrel and torque produced during granulation. It was observed that the residence time and torque increased with increase in L/S. The residence time and torque followed similar trends when granulation was carried out at powder feed rate of 2 kg/h, screw speed of 250 rpm and powder feed rate of 5 kg/h screw speed of 550 rpm at L/S of 0.25, 0.3 and 0.4, respectively (data not shown here). The increase in residence time and torque was due to change in mass and consistency of the material. As the liquid in the barrel increased the powder became wet and behaved like paste. The pasty powder took longer time to flow in the barrel and for the same reason it increased the torque values. Analysis of the granules, produced using varying liquid fractions, was carried out to determine what effect the changing liquid amount had on the physical granule properties.

Fig. 9 shows the size distribution of the three fractions of liquid, from this it can be seen that at L/S of 0.4, a monomodal distribution occurred indicating an even distribution of granule sizes with a peak around the 1000 μm mark confirmed by d_{50} results in Fig. 10.

The two lower fractions of liquid created a bimodal size distribution. The two bimodal distributions show that there were mixed proportions of small and large granules in these samples compared to an even distribution of sizes, demonstrated by the monomodal distribution at L/S of 0.4. The oversized agglomerates reduced with an increase in the fraction of liquid. At higher L/S, the extra liquid caused an increase in the residence time of material in the granulator (Fig. 8).

The additional time allowed fines in the barrel of the granulator to adhere to granules, reducing levels of fines. The effect of increasing fraction of liquid on the size of the granules was found to reduce the d_{50} average particle size. The smallest d_{50} particle diameter was produced at L/S of 0.4 (Fig. 10). The reason that the mean granule diameter was larger at lower L/S was due to the more elongated shaped granules that were produced at lower fractions of liquid (Fig. 11a), which distorted the data. At low fractions of liquid, the granules that were produced had a rougher surface (Fig. 11a) and were more elongated compared to the smoother more spherically shaped granules (Fig. 11b) that were created at higher liquid fraction.

The granules that were produced at lower liquid fractions contained less liquid and therefore formed fewer liquid bridges with the powders. At higher fractions of liquid, more liquid bridges formed and the granules took a more spherical shape (Fig. 11b), with the some fines interlocking into the gaps around the surface. Although there is evidence of a smooth surface at lower liquid fraction it is more pronounced at a L/S of 0.4. The values of angle of repose were found to decrease with increase in L/S (Fig. 12). This was due to differences in granule size, structure and shape for the three different conditions.

At low liquid fractions, the elongated, rough surfaced and oversized agglomerates were produced. This raised the repose angle

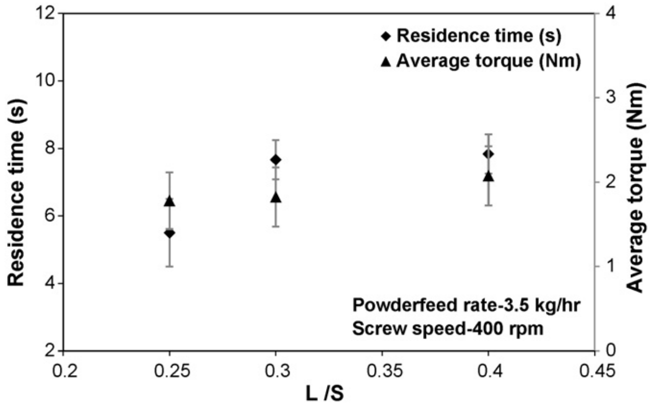

Fig. 8. Residence time and average torque produced at L/S of 0.25, 0.3 and 0.4.

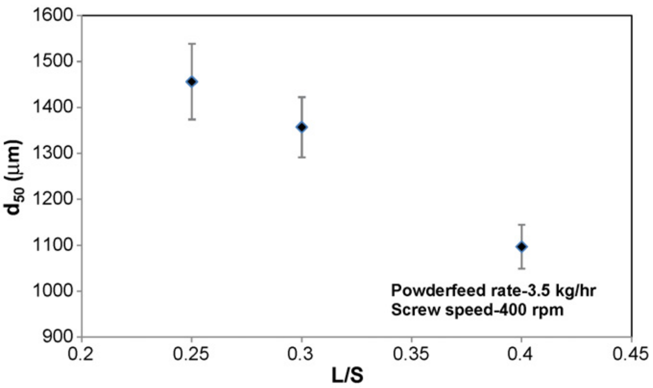

Fig. 10. d_{50} values for changing L/S.

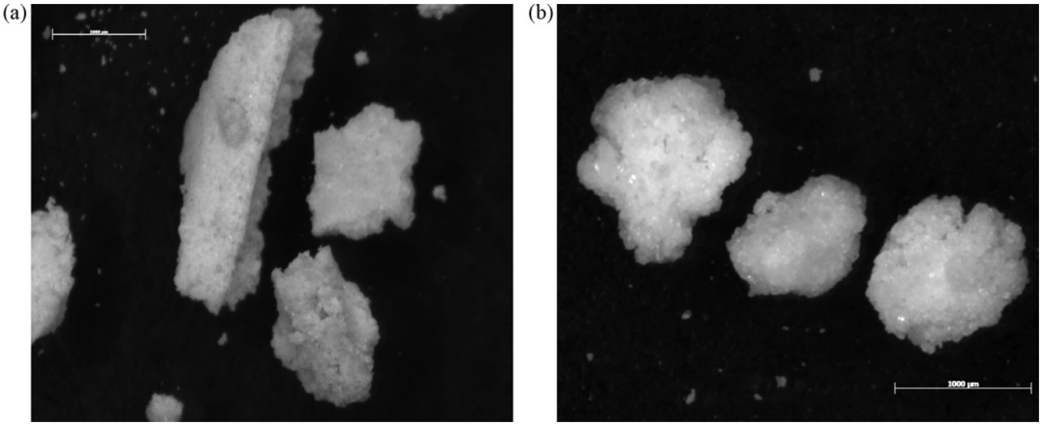

Fig. 11. (a) Rough elongated granules produced at L/S of 0.25. (b) Rounder, smoother granules produced at L/S of 0.4.

whereas at higher L/S, the more spherically shaped, smooth and moderately oversized granules improved the flow. However, in all three cases granules were found to flow fairly.

The mechanism of granulation affected the strength of the granules, with strength found to increase with an increase in the liquid fraction (Fig. 13). The stronger granules were produced at high L/S because the liquids were able to interact more with the powder. With an increased availability of liquid binder to the powders, this created more liquid bridges due to the rapid hydration of powders and this resulted in stronger and smoother granules (Fig. 11b).

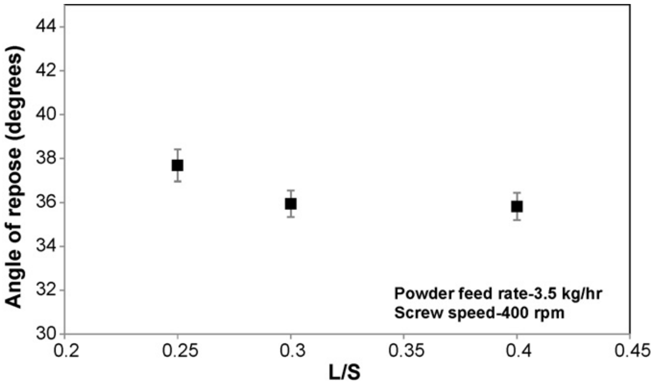

Fig. 12. Angles of repose for three L/S indicating flowability.

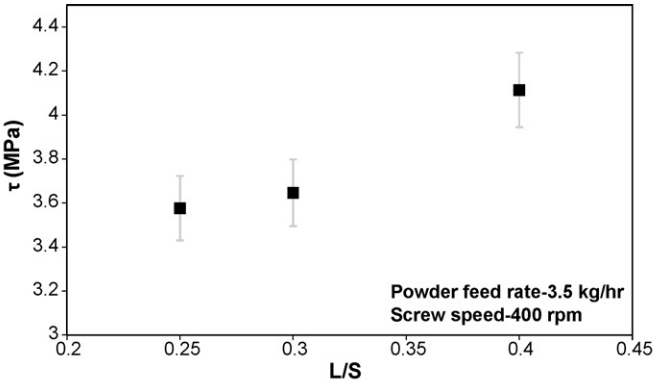

Fig. 13. Granules strength for three L/S.

3.3. *Influence of screw speed*

Fig. 14 shows influence of screw speed on residence time of the powder material inside the barrel and torque produced during granulation. As expected the residence time decreased with increase in screw speed. The decrease in residence time was due to high conveying capacity of rapidly moving screws. Fig. 14 also shows the influence of screw speed on torque produced during the granulation of powder material. At low speed the screws found hard to convey high load of powder mass and resulted in high torque. The increase in screw speed significantly decreased the torque as the

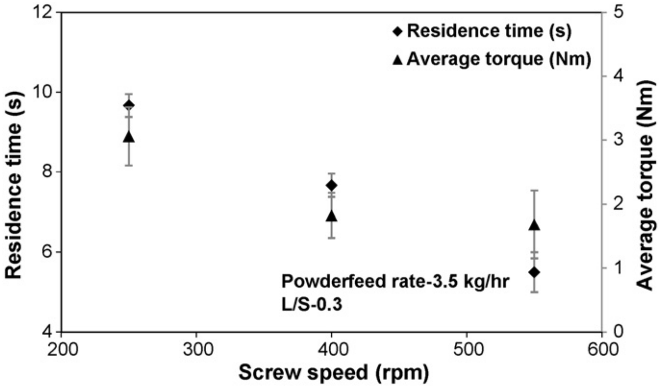

Fig. 14. Residence time and average torque produced at screw speeds of 250, 400 and 550 rpm.

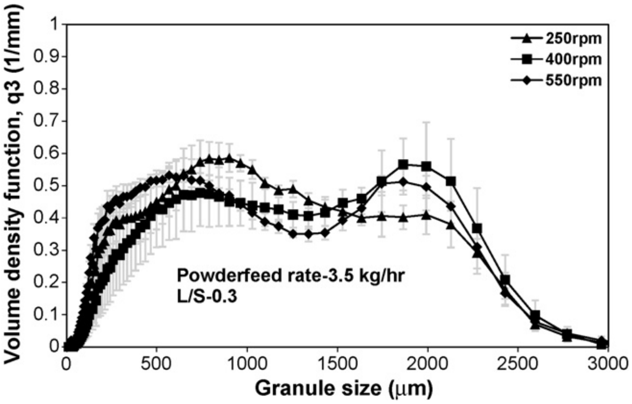

Fig. 15. Size distributions for three screw speeds.

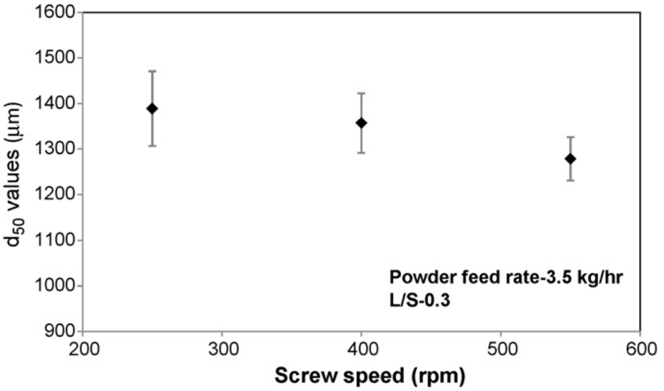

Fig. 16. d_{50} values for changing screw speeds.

rapidly moving screws were starved of powder and this decreased the powder mass load.

The residence time and torque followed similar trends when granulation was carried out at powder feed rate of 2 kg/h, L/S of 0.25 and powder feed rate of 5 kg/h, L/S of 0.4 at screw speed of 250, 400 and 550 rpm, respectively (data not shown here).

The effect of varying the screw speed was found to have a minimal effect on the size of the granules. The size distribution (Fig. 15) showed an increase in granule size at 250 rpm but a drop in size from 400 to 550 rpm. The reason for this may be that at low screw speed, the channel fill increased, as did the residence time of the material in the granulator. The additional time in the granulator allowed more granules to grow at lower screw speeds. Fig. 15 shows that at lower screw speeds, fewer small size granules were left and less oversized agglomerates were produced than at the higher screw speeds where the screw channels were starved of powder. This starved state led to limited compaction of powder.

Fig. 16 shows the d_{50} values at the different screw speeds. The average granule size decreased with increase in screw speed however there was not a significant difference between d_{50} values at all three cases due to mixed proportions of small and large aggregates. The slight decrease in granule size at 550 rpm may be attributed to the presence of relatively higher proportion of small granules.

The shape of the granules was irregular and the surface was rough at varying screw speeds (Fig. 17a and b). With an increase in screw speed, elongated and irregular shaped granules increased due to increase in shearing forces. The result of the increased shear was the erosion of granules into fragments and the rough surface was the result of limited compaction of material. The low residence time prevented the powders compacting at higher screw speeds and thus prevented the powders from interlocking on the granules surface consequently making the granules less spherical at higher screw speeds.

The flowability and strength of granules were marginally hindered by varying screw speeds.

4. Conclusion

The alteration in process parameters had vital influence on the residence time and average torque produced during the granulation which ultimately influenced the granule properties. The most pronounced effect on granule properties was observed when the liquid to solid ratio was changed. This had the largest effect on the granular properties. The fraction of both very small and very large granules was lowered and this led the size distribution to become monomodal. As well as this, the granules that were produced at a higher fraction of liquid had a improved flow that resulted from an improved shape (i.e. more spherical and better surface characteristics); an improved strength was also achieved due to the stronger liquid bridges that formed between the particles.

When the formulation was granulated at different powder feed rates, the increase in feed rate lead to granules of a relatively similar size. However, the fraction of smaller granules in the extruded material was high at higher powder feed rates. This indicates the increase in compaction of the powder mass at higher stresses indicated by the increased torque values. The surface characteristics of the granules improved showing stable and relatively uniform granule structures. The flowability was marginally influenced by varying feed rates. The strength of the granules was found to be a function level of channel fill. In turn, this determined the extent of stress experienced by the powder mass. In higher powder feed rates this was greater and hence produced stronger granules. The screw speed surprisingly had a minor influence on the all the granule properties.

From the results it may be concluded that the properties of granules produced using a twin screw granulator depends on individual process variables. Therefore an optimisation of the process condition is necessary for this formulation, in order to obtain viable granules. Despite the variation in size and other granular attributes that resulted from changes to the process parameters, the twin-crew granulator produced granules consistently at a high throughput showing its unique ability in the emerging field of continuous granulation.

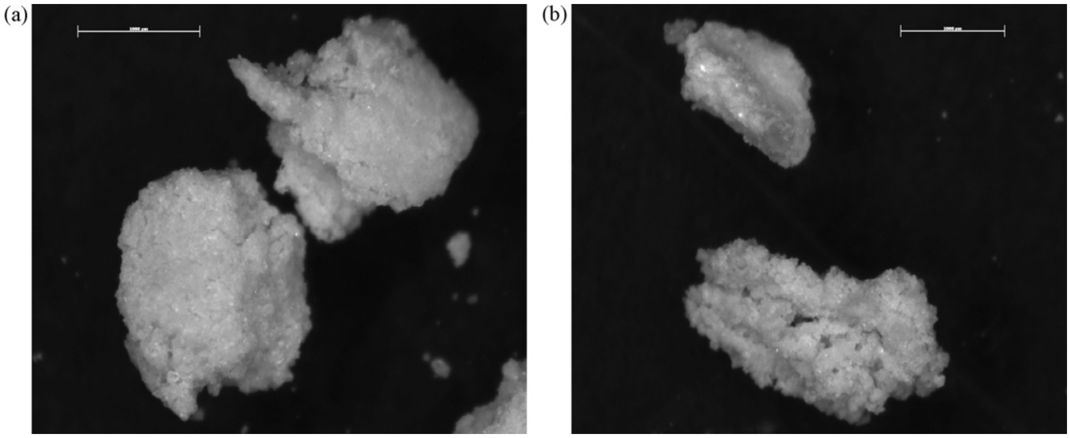

Fig. 17. (a) Granules produced at 250 rpm screw speed, scale is for 1000 µm. (b) Granules produced at 550 rpm screw speed, scale is for 1000 µm.

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