Influence of type of granulators on formation of seeded granules

INFLUENCE OF TYPE OF GRANULATORS ON FORMATION OF SEEDED GRANULES

V. R. Kitching, N. H. Jamaluddin, A. Kelly, N. Rahmanian

Chemical Engineering Department, Faculty of Engineering and Informatics, University of Bradford, Bradford BD7 1DP, UK
Email: N.Rahmanian@bradford.ac.uk

ABSTRACT

Seeded granulation is the process of making core-shell granules and it occurs when larger core particle is surrounded by fine particles. The large particle acts as a nucleus and becomes wetted, then the nucleus gets covered in fine particles, forming a seeded granule. The process of seeded granulation increases the uniformity of the granule structure and mechanical properties such as strength, size and shape . This has potential applications in the pharmaceutical industry as it allows for even drug distribution through the granules resulting in a more attractive product and efficient drug manufacture.

In the current study, calcium carbonate powder (Durcal 65) is used with a polyethylene glycol (PEG 4000) binder. Continuous hot melt granulation was carried out in a twin-screw extruder was investigated. In hot melt granulation, the PEG binder was fed into the extruder as a solid and was melted during the process. The granules produced underwent characterisation testing to find the size distribution and strength. Internal and external structures of the produced granules were investigated through SEM imaging. These results were compared with granules obtained by a Cyclomix batch granulator. The mean size and strength of hot melt granulation were lower than batch produced granules. The twin-screw extruder produced between 5-15% seeded granules depending on screw configuration. The use of an extruder to produce seeded granules is a promising continuous method, but further investigation is needed.

KEYWORDS

Seeded granulation, Twin-screw extruder, melt granulation, strength analysis, SEM imaging

1. INTRODUCTION

Granulation occurs when fine particles bind together in the presence of agglomerate to form a larger particle known as a granule [1]. There are four wetting configurations involved in granulation; pendular, funicular, capillary, and droplet. In the pendular stage, the binding agent is added to fine particles. When bonds begin to form between the particles and the binder, the system is in the funicular stage. In the capillary stage, the binding agent is trapped between the fine particles and ideal granules are formed. The droplet stage is to be avoided as this forms overwetted particles [2].

There are various methods used industrially to produce granules. Granules can be produced in both wet and dry configurations. In wet granulation, a liquid binder is added to the particles and are mixed either by fluidisation or application of shear forces [3]. There are three stages involved in the agglomeration process required for wet granulation; wetting and nucleation, coalescence and growth, and breakage [4]. Dry granulation uses either roller compaction or slugging methods to produce granules from fine powders. These methods can be used to form granules of particles that would undergo a reaction with commonly used liquid binders; here granules form due to the pressure applied to the particles [5].

Seeded granules are typically formed in a high shear wet granulation (HSWG) batch process. They were first observed for HSWG of calcium carbonate with an aqueous solution of PEG being used as a binder [4]. The formation of seeded granules involves a large particle becoming wetted; this then forms a nucleus that fine particles bind to it. The even distribution of fine particles surrounding the nucleus produces strong granules [6]. This was first reported by Rahmanian et al. [6-13] as part of the concluded EPSRC project sponsored by four industrial collaborators, P&G, Pfizer, Hosokawa Micron B.V. (the Netherlands) and Borax Europe Ltd in a granulation consortium led by the University of Leeds [11]. Efforts have also been made to model and simulate the process of seeded granulation using DEM analysis to get better understanding of the mechanism of formation of seeded granules [1, 14]

The formation of seeded granules in HSWG requires a binary distribution of fine and large particles as this allows for the formation of a nucleus for the fine particles to bind to. The impeller rotation speed in the batch granulator also needs to be over 100 rpm to increase the contact between the fine particles and the nucleus as this allows for the formation of a greater number of seeded granules [1].

Continuous granulation process can occur in a twin-screw extruder (TSE), the use of a TSE in granulation has grown largely due to the economic advantage of continuous process. Using an extruder also reduces the need to process the feed materials and produces stable granules with desirable characteristics compared to those made in batch processes [15]. Extruded granules have a high bulk density and a narrow particle size distribution. It is also relatively easy to change the ratio of feed materials to change the properties of the products as there is no set ratio required in TSE granulation [2].

There have been various investigations into the influence of screw configuration on the properties of the granules produced. There are two main types of elements that are used in extruder screws; they are conveying elements and kneading elements. Typically, in extrusion granulation at least 90% of the screw length is made up of conveying elements. Conveying elements impart much lower shear forces than kneading elements [16].

Extruder kneading or mixing elements can occur at a 30°, 60° and 90° pitch; the pitch of the mixing elements has a large impact on the properties of the produced granules. As the pitch increases so do the shear forces on the system. A 90° pitch mixing element does not convey the material forwards, but the 30° and 60° elements do [17]. Granules produced by 90° mixing elements are not as strong as those produced by 60° mixing elements [16].

The speed of the extruder screw also impacts on the production of granules. At low screw speeds, the level of fill in the extruder barrel is higher. Having a high barrel fill causes an increased rate of mixing between the particles and the binding agent. It is desirable to have a high level of barrel fill as it will lead to the production of more granules and fewer fine particles [18].

The aim of this work was to investigate the formation of seeded granules in a TSE. Initially, melt and wet granulation were trialled using a standard extruder screw configuration of six mixing elements at 90° pitch towards the end of the screw. This screw configuration ran at various screw speeds to produce granules. Particle size analysis and strength testing were undertaken in order to refine the process and produce higher quality granules. The parameters that can be changed are the screw configuration, the screw speed and the ratio of the feed materials.

2. EXPERIMENTAL METHOD

2.1 Initial Experimental Work

Two stages of experiments were involved in this investigation; an initial experimental run to try to form seeded granules by hot melt TSE and then the method was refined. The extruder barrel can be split into 10 zones which were used to decide the position of the mixing elements. Splitting the barrel into multiple zones also allowed for effective temperature control. For the initial run of the experiment the screws used in the extruder barrel had six 90° mixing elements at position 9 on the screw; this can be seen in Figure 1.

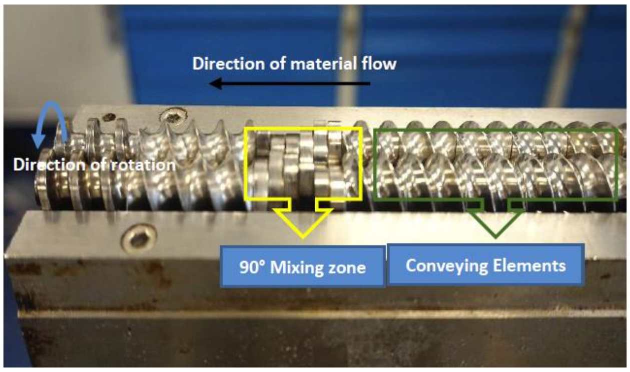


Figure 1. TSE mixing zone set up for the initial melt granulation trials.

For melt granulation, the screw configuration shown in Figure 1 was used. The temperature profile along the screw was zone 2 at 25°C, zone 3 at 30°C, zone 4 at 50°C and zones 5-10 being heated to 70°C to ensure that the PEG had melted. In this experiment, a 10% binder concentration was desired. To obtain this 900g of calcium carbonate and 100g of PEG 4000 were mixed together and then fed from the hopper at a rate of 0.66 kg/hr. Each experiment was run at extruder screw speeds of 50, 100, 150 and 400 RPM.

Granules obtained from the extruder for all settings underwent particle size analysis and strength testing; the values obtained were compared against published values for batch granulation processes. To find the particle size distribution of the granules produced by the TSE a sieving analysis was carried out on the granules. The size of the sieves ranged from 2.8 mm to 53 μm. The desired granule size chosen is between 500-600 μm to allow for a logical comparison with the previous work on HSWG. The granules in this size range underwent strength analysis and structure characterisation using SEM imaging to discover whether the seeded structure was present. The sieving was carried out manually and was done consistently and carefully to ensure there was no attrition of the granules occurred [19]. The strength of the produced granules in the size range of 500-600 μm was investigated using a Z5 AML Tensometer.

The external SEM images of produced granules in the size range of 500-600 μm were produced. The granules were on slides that had been coated with carbon paint and then sprayed with a thin layer of gold to increase the conductivity of the slide; producing a clearer image. To view the internal structure of granules and discover the potential of seeds, the granules were set in epoxy resin which was polished to allow the internal structure to become visible.

2.2 Initial Results

The preliminary hot melt extruder granulation trials were successful in producing granules. The formed granules had a wide range of particle sizes with TSE extrusion producing a large proportion of coarse particles. Table 2 shows the percentage of coarse, fine, and desired particle sizes obtained for TSE melt granulation.

Table 2. The mass percentage of granules in the desired, coarse and fine size range from the hot melt TSE granulation.

Screw Speed (RPM)	Desired Particle Size (90-1000 μm)	Coarse Particles (>1000 μm)	Fine Particles (<90 μm)
50	56	28	16
100	52	43	5
150	52	42	6
400	61	32	7
Average	55	36	8

There was a high level of variation in strength values from 0.01-1.1N for the screw speeds of 50 and 100 RPM. For screw speeds of 150 RPM and over the maximum granule strength decreases to 0.8N. The average strength of granules produced for each screw speed was plotted and is shown in Figure 2.

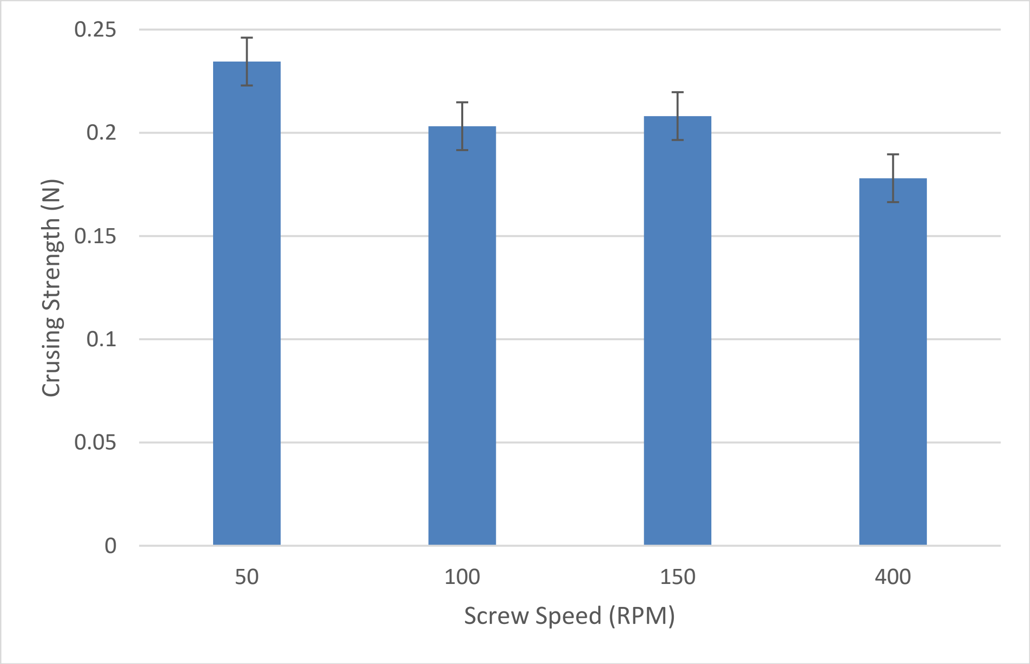


Figure 2. The mean crushing strength for granules produced by melt granulation in a TSE, the error bars represent the standard deviation.

2.3Refined Experimental Procedure

The screw configuration used in the experimental work had six mixing elements at a 90° pitch, this would result in extremely high levels of shear on the particles that may reduce the likelihood of seeds forming as 90° mixing elements have been shown to produce more porous and irregular shaped granules than mixing elements at 30° or 60°[20]. This may have been the cause for the high number of coarse granules and low strength of the granules. Therefore, the impact of the screw configuration on the granule properties was investigated. Figure 3 shows the various screw configurations used in the experiment. As the mixing elements generate lower shear the screw speed was lower than in the initial experimental procedure to allow for a higher level of barrel fill. This should limit the mass of fine particles produced.

Table 3. The various screw configurations used for the extruder runs where (1) is all conveying elements, (2) is mixing elements in zone 8 of the screw, (3) has mixing elements in zone 4 of the screw

Extruder Zone	Configuration		
	1	2	3
1	Conveying	Conveying	Conveying
2	Conveying	Conveying	Conveying
3	Conveying	Conveying	Conveying
4	Conveying	Conveying	60° Mixing
5	Conveying	Conveying	Conveying

6	Conveying	Conveying	Conveying
7	Conveying	Conveying	Conveying
8	Conveying	60° Mixing	Conveying
9	Conveying	Conveying	Conveying
10	Conveying	Conveying	Conveying

Table 3 shows the three screw configurations that were tested in the refined process. In the first configuration all conveying elements were used; the purpose of this was to investigate whether the shear field in an extruder could successfully produce seeded granules or if higher levels of shear stress were needed. It has also been discovered that using only conveying elements in an extruder screw leads to the formation of spherical granules [21]. For the second configuration the majority of the screw is made of conveying elements with a small section of 60° mixing elements being present in zone 8 of the screw. Having one section of mixing elements towards the end of the screw is a standard screw configuration for extruded granulation [16]. Using 60° mixing elements will lead to strong granules being formed [22]. In the third configuration the small section of 60° mixing elements is in zone 4 of the screw; this is due to research suggesting that a long conveying section after mixing elements can reduce the number of oversized granules that are formed [16]. Mixing elements at 60° angles were used in order to produce strong granules [22].

From Table 2 it is evident that there are too many coarse particles produced, this could be due to the binder content being too high to produce granules of the desired size in an extruder. Therefore, the binder content was reduced to 5%. Decreasing the binder content may also be able to produce granules of higher strength for the size range 500-600 μm as a higher binder content causes uneven distribution of the binder throughout the granules, resulting in larger granules being much stronger than the granules in the desired size range [23].

The feedstock for each extrusion run was 550g to allow for a minimum of 300g of product for further testing. To ensure a 5% binder content 27.5g of PEG 4000 was added to 522.5g of calcium carbonate. These were thoroughly mixed in a plastic bag to ensure a uniform distribution of binder in the $CaCO_3$ particles. This mixture was then fed into the hopper to supply the extruder at a constant rate. The hopper was set to a speed of 50 RPM for all experiments. The temperature along the extruder was carefully controlled to allow for the PEG 4000 to melt. The extruder barrel was split into 10 zones and the temperature of each zone was specified. For the refined experiment, there was no heating in zone 1, the temperature for zone 2 was specified at 35°C. At zone 3 the temperature was increased to 45°C and zones 4-10 were set at 70°C. To ensure the extruder system was calibrated to the desired properties the first 10 minutes of the product were discarded. After 10 minutes the product was collected to undergo further testing.

3. RESULTS AND DISCUSSIONS

3.1 Particle Size Analysis

Figure 3 shows the accumulative weight percentage of particles produced for all extruder configurations at the three specified screw speeds.

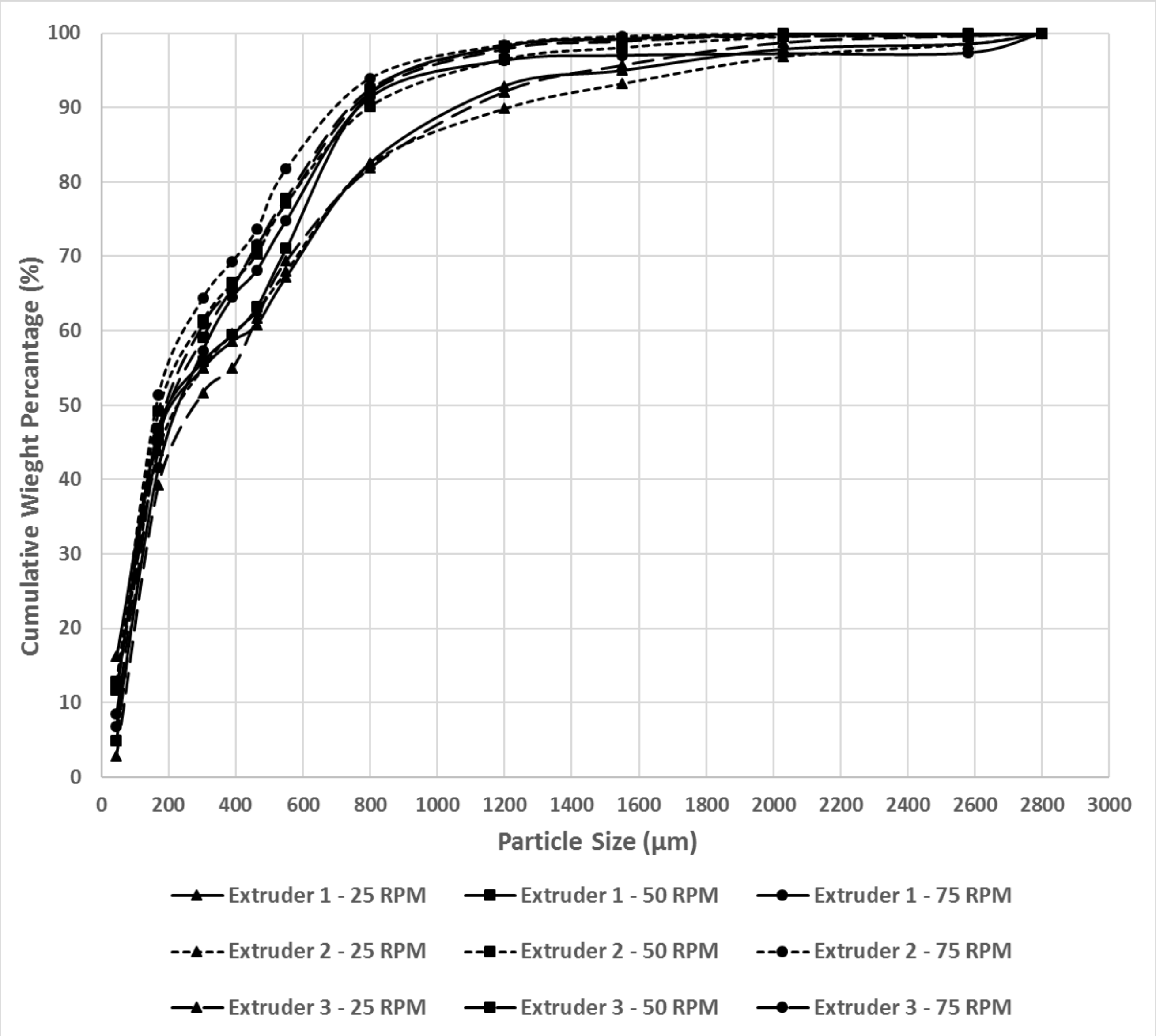


Figure 3. The Cumulative weight percentage for particle size for granules produced using screw configuration 1, 2, and 3 at three different speeds of 25, 50 and 75 RPM

From Figure 3 it is clear that at lower screw speeds there is a higher proportion of large granules formed. This result is matched with what it it has previously been reported in the literature that a slow screw speed increases the barrel fill causing larger particles to form [18]. Extruder configuration '1' has a large proportion of fine particles at all screw speeds. This may be due to the screw being all conveying elements; as there is less shear on the particles and binder there may be less granulation occurring resulting in smaller granules and more unbonded particles.

Figure 3 also shows that using extruder configuration '3' at a low speed of 25 RPM produced the lowest percentage of fine particles. Fines are referring to the particles that are under 90µm. The desired range of granule size is from 90µm to 1000µm.

From Figure 3 it is clear that at higher speeds there are more particles of the desired size formed. This can be due to fewer coarse particles forming as there is a lower retention time in the extruder at a higher speed. This trend is apparent for every screw configuration. The faster speed reduces the fill level of the extruder barrel causing less mixing between the particles and the binder, resulting in particles of smaller size [18]. This can be observed as the percentage mass of fines for each extruder setting increases as the screw speed increases.

Screw configuration '3' produced the largest percentage of granules in the desired size range. This can be seen by all three mass percentages being greater than the average mass percentage of the desired particle range. This configuration also produces the lowest percentage of fine granules with the values for the different screw speeds all being lower than the average mass percentage.

Having mixing elements in the screw configuration produced granules of a more consistent and desirable size. A Further investigation into the impact of screw configuration could be carried out by increasing the number of mixing elements present in the screw and changing the pitch of those elements to try to find the optimum configuration.

3.2 Strength analysis

After the granule sizes were separated, granules in the range of 500-600 μm underwent compression tests to determine the average breaking strength of these granules. From each batch, 40 granules were tested using a Z5 AML Instruments Tensometer. The crushing strength of the granules produced in TSE granulation can then be compared to the known crushing strength values of seeded granules produced in batch granulators. Figure 4 shows the average strength of the produced granules for all extruder configurations and screw speeds and compares them to the strength of batch produced granules.

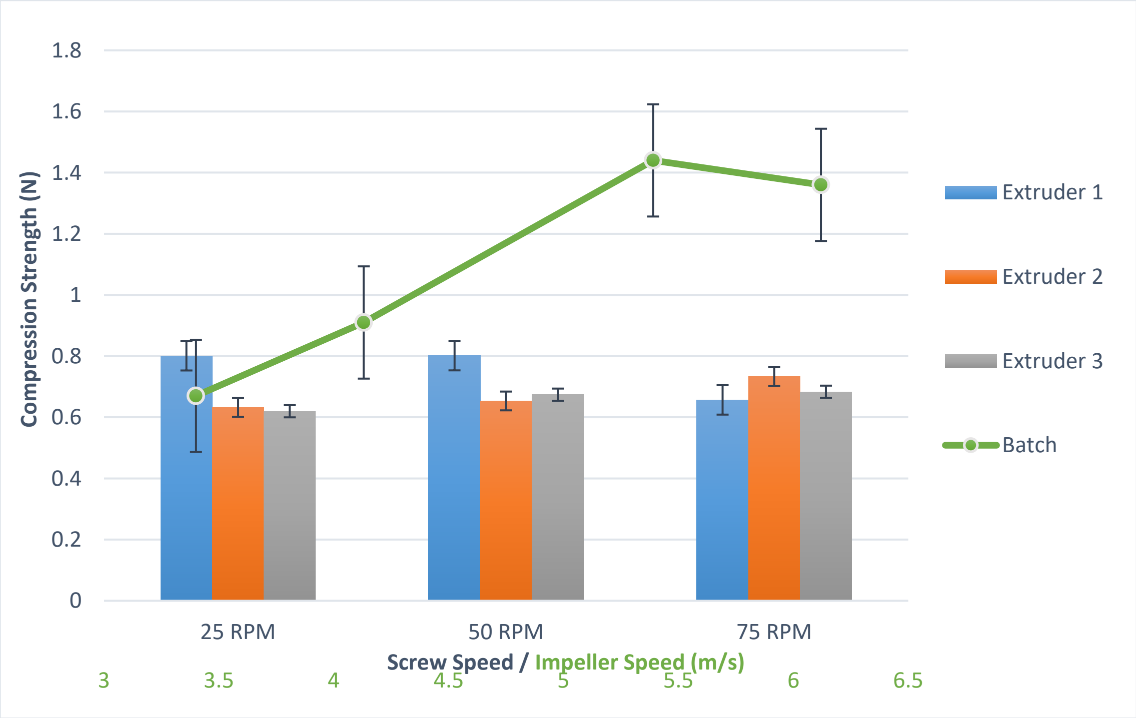


Figure 4. Average compression strength for the different extruder configurations and screw speeds in comparison to the strength of batch produced granules with varying impeller speeds, information from [9]

From Figure 4 it is clear that the strengths of granules produced in the extruder are 25% lower than those produced in batch processes that used impeller tip speeds of 4.13 m/s for all of the screw speeds that were tested. The extruded granules had very similar compression strengths to batch granules produced using an impeller tip speed of 3.4 m/s. This can be due to the low speeds used in the extruder not allowing for the high levels of mixing required to allow for full seeding of the granules. The extruder speeds of 25, 50 and 75 RPM relates to an equivalent impeller tip speed of 0.02, 0.04 and

0.06 m/s which is much lower than that of the batch granulator due to the mode of operation. In a batch process, the shear is caused by the impeller and higher speeds will cause higher shear, but the screw configuration is responsible for the shear in extruders [6]. Although a higher extruder screw speed will increase the shear it will not need to be as high as the speeds needed in batch granulators [16]. In Figure 7 the lowest value of impeller speed is 3.5 m/s [9], which gives an approximate mean crushing strength of 0.75 N. In Figure 4 the extruder average strengths range between 0.6 and 0.8 N showing that although the extruder has much lower speeds it is possible to obtain granules with similar strength values; suggesting that seeded granules may have been formed in the extruder granulation process.

The compressions strengths of the granules are very close for extruder configuration 1 where there are only conveying elements for all screw speeds. The granules produced at 25 and 50 RPM have the same average strength of 0.8 N, this decreases to 0.6 N for the granules produced at 75 RPM; this is a 25% decrease. Increasing the screw speed may have increased the shear in the extruder causing the particles to break and therefore they would not be as strong. The decrease in strength could also be due to the granules tested having a greater variation in shape as the granules produced at lower speeds are generally more spherical than at higher speeds [18]. This can be observed in these results even though the same binder concentration and extruder temperature were used for every screw configuration and speed.

Figure 4 shows the strength of the granules produced using extruder configurations 2 and 3 increase as the screw speed increases. This increase is due to the higher speed causing greater agitation of the binder and the particles as they pass through the mixing elements. As there is more mixing the PEG will be more evenly dispersed throughout the granule creating a stronger structure [16]. This increase in strength is also due to the increased level of shear on the calcium carbonate and PEG 4000 as they pass through the mixing elements. Seeded granules form in high shear batch granulators and increasing the level of shear in the extruder barrel will lead to a higher probability of seeded granule formation up to a certain level; if the shearing is too high then granulation is poor. Testing at different screw speeds and barrel fill levels will allow for the optimum level of shear to be found.

3.3 Discussion

The refinements made to the experimental procedure allowed for granules with more desirable characteristics to form. A comparison of the values from Table 2 and Figure 3 demonstrates the increased level of particles in the desired size range. In both the initial set-up and the refined set up, a screw speed of 50 RPM was used to generate granules, this allows for a direct link between the initial set-up and the refined results. For this screw speed, the percentage of granules in the desired size range increased by a minimum of 10% for each of the new screw settings. The optimal screw setting seems to be mixing elements towards the start of the screw as this allows for the granules to undergo the intense mixing but still have enough conveying elements left for the seeding process to occur.

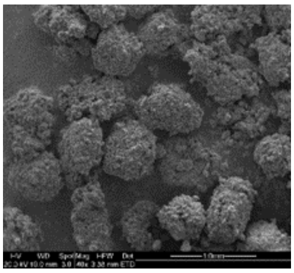
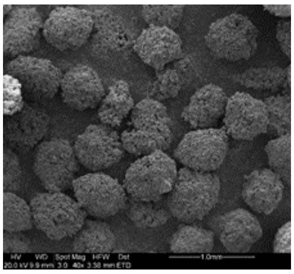
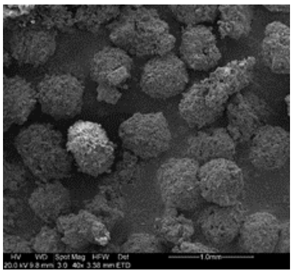
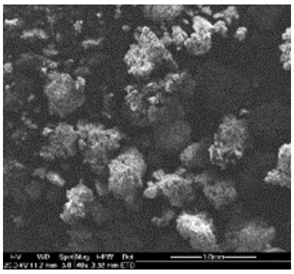
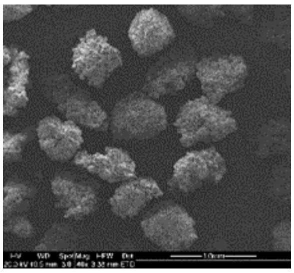
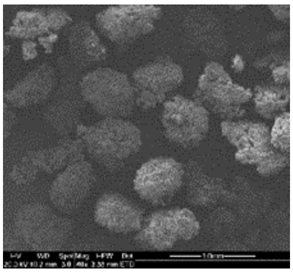
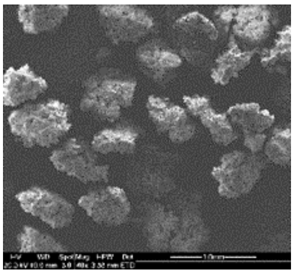
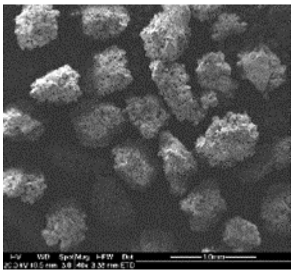
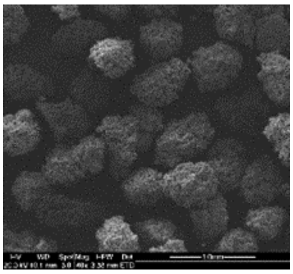
With the lower binder content, there does seem to be a greater volume of fine particles produced; this can be seen by comparing Table 2 and Figure 3. This suggests that although lowering the binder content reduces the percentage of coarse granule formation it also increases the percentage of particles that do not undergo the granulation process. From Figure 3 it is clear that having mixing elements closer to the start of the extruder screw and using a speed of 25-50 RPM allows for less than 5% of the mixture consisting of fine particles; this is lower than the percentage of fine particles shown in

Table 2. To try to further reduce the production of fines a longer mixing section could be used or the binder content could be increased slightly.

The strengths of the granules produced by the refined method are approximately 300% greater than those produced in the initial method. The highest value for compression strength for the initial granules is approximately 0.21 N; this is a very low value of strength for calcium carbonate and PEG granules. This low strength can be due to large granules forming along the conveying elements then being broken by the high shear of the six mixing elements that are at a 90° pitch. The broken granules would have an unequal dispersion of PEG causing them to be weak [24].

The shape of a produced granule has a large impact on its strength. Rounder granules are generally stronger as they have a more even dispersion of binder in the granule. Elongated shapes tend to be weaker and have much lower crushing strengths [16]. The difference in crushing strengths for different shaped granules is due to the configuration of the fractures caused by crushing. When a spherical granule undergoes a crushing test, there are fractures along planes of the granule, but it largely remains intact. This differs greatly in an irregular shaped granule as they shatter when low compression displacement occurs [25]. At lower screw speeds the shapes of the produced granules are much more consistent than those produces at high speeds. This can be seen by viewing the SEM images in Table 4.

Table 4. External SEM imaging of granules produced by all screw configurations at different screw speeds of 25, 50 and 75 RPM under 40X magnification

Configuration	Screw Speed		
	25 RPM	50 RPM	75 RPM
1			
2			
3			

As Table 4 shows the granules produced by extruder setting 1 at both 25 and 50 RPM are consistently spherical and therefore, should have a higher compression strength as spherical granules retain their shape when compressive forces are applied; giving them a high compression strength [25]. The compression strength for these granules are shown in Figure 4 and are both at approximately 0.8 N; higher than the granules produced at 75 RPM. As shown in Figure 4 the granules produced at 75 RPM have a compression strength of approximately 0.65 N. As Table 4 shows there are some spherical granules and some elongated ones. This suggests an uneven distribution of PEG resulting in the granules having lower strength.

In Table 4 it is apparent that as mixing elements are present in the screw the increase in screw speed increases the sphericity of the granules. The increased sphericity can be due to the increased speed and the mixing elements imparting more shear on the mixture of calcium carbonate and PEG resulting in a more even binder distribution. This will also increase the strength of the granules as can be seen in Figure 4.

When mixing elements are present in the extruder there is an overall trend of the granule strength increasing as the screw speed increases. The average strength ranges from 0.6 N to 0.75 N; this suggests that there may be some seeding in the particles. In batch conditions seeded granules produced at 3.5 m/s had a mean granule strength of approximately 0.7 N for granules in the size range 500-600 μm. The average crushing strength of the granules followed the trend of increasing as the impeller speed increases [16]. In the extruder the speeds were much lower, ranging from 0.02 to 0.06 m/s. The low strength does suggest that some seeding, if present may not be in the centre of the granule as this would probably lead to the lower strength [4].

The granules produced by all three configurations at a speed of 75 RPM were chosen as the higher speed produced more uniform sets of data as the variation coefficient and particle size span were smallest for each screw configuration when a speed of 75 RPM was used. These granules also all had a strength of 0.6-0.7 N which allows for a more even comparison between the impact of the screw configuration on the formation of seeded granules.

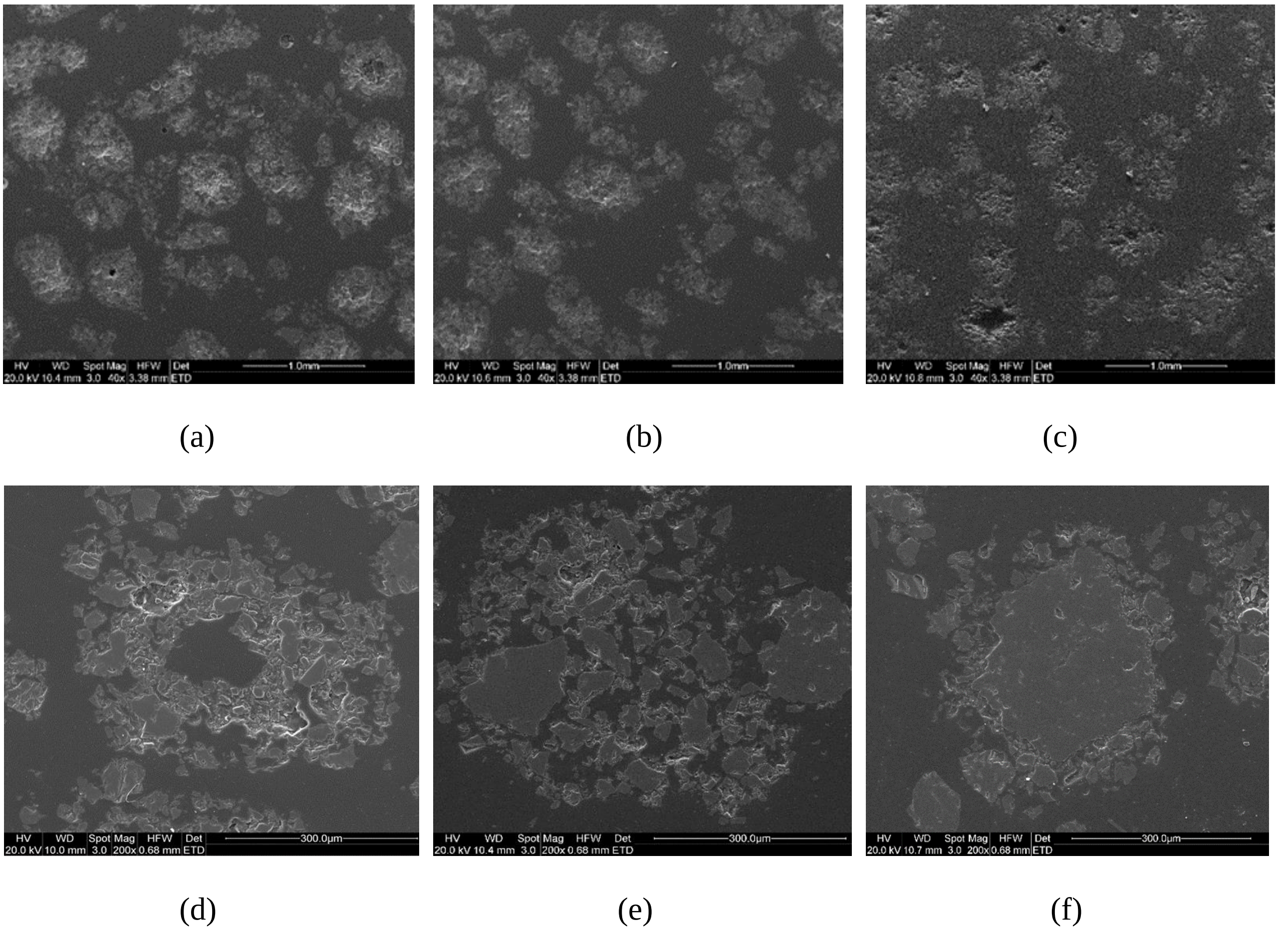


Figure 5. Internal SEM Imaging of granules, (a) is granules produced using configuration 1 at 75 RPM at 40X magnification, (b) is granules produced by configuration 2 at 75RPM at 40X magnification, (c) is granules produced by configuration 3 at 75RPM at 40X magnification,, (d) is a granule with a central cavity at 200X magnification, (e) is a granule with an off-centre seed at 200X magnification, (f) is a granule with a large central seed at 200X magnification.

In Figure 5 the internal structure of the granules can be seen and the presence of some seeding in the granules can be observed. A seed is defined as a particle larger than 125 μm being present in the granule structure. Cavities formed during the polishing process made identifying the percentage of seeded granules formed difficult. For configuration '1', as shown in Fig.5a between 5-8% of the granules formed were seeded, this value is increased for configuration '2', shown in Fig.5b as there were 8-12% seeded granules formed. Configuration '3' had the largest proportion of seeded granules formed with 10-15% of the granules being seeded; the internal structure of granules is seen in SEM image of this configuration as shown in Fig.5c. The percentage of seeded granules produced by extruded granulation is much lower than those produced through high shear batch granulators as they range from 65-100% [25].

An SEM image of a granule with a cavity can be seen in Fig.5d; this cavity is larger than 125 μm which indicates that a seed may have been present in the granule. Some granules had clearly observable seeds such as those shown in Fig,5e and Fig.5f. In Fig,5e the seed is off to the side of the granule. The presence of a seeded granule increases the strength in comparison to non-seeded granules however the seed being off centre will not be as strong as a large central seed. The granule shown in Fig.5f has a large central seed which indicates that it will be a strong granule. Configuration 3 produced the largest number of seeded granules and, as seen in Figure 4, it has the highest strength of the granule batches produced at 75 RPM.

4. CONCLUSION

Using the particle size analysis and the strength of the granules it appears that having the mixing zone towards the beginning of the screw is beneficial in reducing the number of oversized and fine granules. The produced granules are also very similar in strength to the batch granules produced. The strength of the granules increases as screw speed increases when mixing elements are present however, increasing the screw speed can also decrease the mass percentage of desired sized particles or increase the number of fines generated. To compromise on this the best model currently is using two mixing elements of a 30° pitch at position 4 of the screw with a speed of 50 RPM.

As the produced granules have similar strength and size distributions to batch produced seeded granules, there is some evidence of successful seeding using TSE granulation after the experimental procedure was refined. The refinement allowed for more granules in the desired size range to be produced; they also had a much greater strength suggesting that a 90° pitch mixing element is too harsh for the granules and causes attrition.

From the internal SEM imaging, it is clear that high shear is beneficial to producing extruded granules as the screw configurations that contained mixing elements had higher percentages of seeded granules present that the configuration of only conveying elements.

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