Sensitivities in Wet Granulation Processes

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Summary

Wet granulation is the process used to convert fine powders into larger granules. It is an extremely widespread process used in many industries because it has many advantages such as improved flowability and easier post processing. Despite this until recently it was poorly understood and regarded as an ‘art not a science’. In recent years there has been a great deal of research into the understanding of the process and development of models to attempt to predict the outcome of the process based on the process variables.

This study investigates, multidimensionally, the sensitivity of a laboratory scale granulation procedure to variation in binder composition, impeller speed, binder addition rate and solid:liquid ratio, by analysing the change in particle size and composition. The granulation was carried out using solid sodium carbonate particles granulated by addition of a liquid binder composed of Polyethylene Glycol (PEG) and water. The obtained results were used to test a pre-existing multivariate population balance model.

The particles initially displayed little or no growth initially as binder was added, but at a critical value the rate of growth increased rapidly. The process demonstrated the existence of an optimum impeller speed, for particle size increase, of approximately 1040 rpm. When variation in binder composition was investigated, particles with the lowest amount of PEG within the binder showed a growth rate of approximately double the higher PEG:water ratios, which displayed similar response. Binder addition rate was also tested and showed that the rate of growth of particles was independent of the rate of binder addition, over the small ranges considered.

A novel procedure for analysing the composition of particles was developed, using the difference in mass of granules over a number of heat treatment steps. This showed that the larger granules contained greater proportions of binder within them.

The experimental results were compared to simulations from an existing granulation model to test its performance. It was found that the model predicted differing behaviour to the experimental data.
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1 Introduction

1.1 Background

Granulation is the conversion of fine powders into larger grains, otherwise called granules. The use of powders or dusts introduces difficulties such as flow problems, inhalation and product losses and as well as explosion risks (Iveson et al., 2001). By removing the use of powders in a process granulation can introduce a number of other advantages including improved flow properties, reduced caking, increased bulk density, control of solubility, control of surface-to-volume ratio (Ennis and Litster, 1997); hence granulation, or agglomeration, adds value to a product (Mort et al., 2001), so is a much desired process. Wet granulation is achieved by addition of a liquid binder to the powder; liquid bridges act to bring the powder particles together leading to the formation of granules (Ax et al., 2008). On an industrial scale this can be achieved by contacting a liquid with the solid powder, for example by spraying, in any suitable unit operation, such as a fluidised bed or mixer (Braumann et al., 2007).

Due to the great number of advantages detailed above, granules and granulation have widespread use in many industries including foodstuffs, detergents, pharmaceuticals, agricultural products (e.g. fertiliser), consumer goods (e.g. soap powder) and speciality chemicals (Iveson et al., 2001). The ability of granules to have a large surface to volume ratio also leads to uses involving catalysts. Estimations by Iveson et al. (2001) indicate that in the chemical industry alone 60 % of products are manufactured as particulates, with a further 20 % using powders as ingredients; the combined value of these products is estimated at US$1 Trillion per annum, in the United States alone.

Research into granulation has been ongoing for 50 years, with large volumes of work published over many disciplines (Iveson et al., 2001). However over the past 25 years particle technology has moved from under funded, scattered research to, the current, thriving engineering discipline (Michaels, 2003) Granulation has been recognised as an example of particle design; where granules are designed to perform particular functions, and therefore have to have specific product attributes such as granule size and distribution, shape, porosity, binder distribution and fracture toughness (Mort, 2005; Sanders et al., 2003). These product attributes are
determined by a combination of the process for production and the formulation (feed properties) involved (Litster, 2003; Iveson et al., 2001). However, granulation is a very complex process with many different process variables (Sanders et al., 2003; Mort, 2005), these include:

- Process time
- Impeller speed
- Initial particle size distribution
- Binder properties
- Temperature
- Liquid/Solid ratio
- Binder addition methods

1.2 Granulation Mechanism

The mechanism for growth of particles is a three part process consisting of the processes below, depicted in figure 2.1 (Rajniak et al., 2007; Iveson et al., 2001).

![Figure 2.1: Process by which granulation occurs. Adapted from Iveson et al. (2001)](image)
Nucleation describes the contacting of the initial, dry powder, with the liquid binder and the subsequent formation of nuclei occurring as a result of the capturing of powder particles by the binder droplets. Investigations, by Hapgood et al. (2002), into the process of nucleation have led to an increased understanding of the underlying science and produced regime maps to predict the behaviour; whether the nucleation is droplet-controlled, with each droplet forming a single nuclei, or due to mechanical dispersion, where clusters of nuclei, formed by multiple droplets coalescing, are broken up into multiple nucleates under shear (Poon et al., 2008). Despite this understanding the knowledge in this area is still considerably less than that of aggregation and growth of particles (Iveson et al., 2001).

Granule growth occurs in two ways: Coalescence or agglomeration describes the collision of two larger particles colliding, resulting in them sticking together. In order for this to happen they must collide with a great enough energy, as well as being coated by sufficient liquid binder. Layering, a special case of coalescence, is used to indicate a situation where fine material sticks to the surface of a larger granule (Iveson et al., 2001). The growth is affected by particle size and mechanical properties, binder and bulk powder properties (Cameron et al., 2005). Consolidation affects the granulation by reducing granule porosity; this affects the binding of particles within a granule, and hence having an affect on the mechanical properties. As a result of this not only agglomeration, but also consolidation, is an important mechanism in determining the growth of particles.

Breakage and attrition are the processes which act to decrease the size of a granule, by fracturing it into smaller particles. Breakage of wet particles during granulation has a number of outcomes and effects; it acts to influence, and even control, the final size distribution (Iveson et al., 2001) or to limit maximum granule size (Reynolds et al., 2005) as well as ensuring (compositional) homogeneity of the mixture (van den Dries et al., 2003). However, Iveson et al. (2001) report that the attrition of dry particles should be avoided as it leads to the generation of dusty fine particles, whose removal is invariably the primary aim of granulation.

1.3 Current Understanding

Granulation is one of the least understood, therefore inefficient, processes in process industries. Until the last decade it was regularly described as ‘an art not a science’ (Litster,
2003) and engineers are unable to fully predict the behaviour of the process based on the fundamental properties, nor are they able to successfully predict, fully, the properties of the product based upon the formulation procedure (Cameron et al., 2005; Iveson et al., 2001). In order to establish a granulation process, without being able to predict the behaviour, a combination of pilot plants and scale-up must be used; these are both time consuming and expensive (Pietsch, 2001) as well as contributing to a large failure rate before the industrial scale is reached (Iveson and Litster, 1999). For example, at Merck, to scale up from a laboratory formulation to a full-scale operation, there are approximately six steps where process conditions, such as spray rates, impeller speed and mixing times are established experimentally on a ‘trial and error’ basis (Michaels, 2003). It would be simpler, more efficient and a great deal cheaper to have an approach that allows the conversion of small-scale experiments directly to full-scale processes (Mort, 2005). This requires prediction of the process behaviour and product properties from the experimental set-up and raw materials.

Methods such as these are becoming a reality and there is now qualitative, as well as some quantitative, understanding of the underlying science behind granulation and the effects of individual variables on the process and product (Iveson et al., 2001; Litster 2003). For example research has been carried out into the effect of initial particle size (Walker et al., 2000), effect of binder content (Bergman et al., 1998). An increased understanding of the science allowed the creation of regime maps, such as those produced by Mort and Tardos (1999) and Litster (2003), to describe various mechanisms of the granulation process, additionally Iveson and Litster (1998) produced a map that is able to predict behaviour of the entire process for drum granulators.

Information about the mechanisms and regimes of the various mechanisms of granulation can be used to create detailed models of the entire process (Lee et al., 2008). These models use population balance equations (PBEs) to track individual particles, considering all the mechanisms (transformations) of granulation, to produce simulations for the behaviour. Significant work has been carried out into production of such models. Traditional models use one dimensional PBEs, (e.g. Adetayo et al., 1995; Kapur and Fuerstenau, 1969) that assume granule size is the only independent property that affects the growth behaviour (Iveson, 2002). Despite this assumption they have been successful in modelling small scale granulation experiments, of a single component, with an even binder dispersion (Iveson, 2002). However it is known, as stated in section 1.1, that
granulation is a complex process dependent on many other independent parameters, not just size. Therefore it is important for modelling of larger, more complex, systems to use a multidimensional PBE that is able to consider these additional variables. Braumann et al., (2007) and Lee et al., (2008) are examples of such models.

For simulations to be as accurate, and useful, as possible, comparison of the results with experimental results and refinement of the model parameters must take place to create well suited models (Fig 1.2).

![Figure 1.2: Theoretical approach to the production and use of models in granulation (adapted from Sanders et al., 2003)](image)

### 1.4 Motivation and Aim

Granulation is a process that has many independent variables that affect the behaviour of the process, and therefore the attributes of the final granular product. The process, and product attributes, have varying sensitivities to changes in the process conditions. This study aims to advance understanding of the influence of process conditions upon the granulation procedure and its sensitivities to them. A better knowledge will enhance the understanding of both the process behaviour and mechanisms, which aids in producing well suited models. Accurate predictions of the process behaviour bring great benefits in the scale-up of processes from the laboratory to industrial scale.

This study developed an experimental technique for carrying out wet granulation using a desktop mixer granulator with subsequent analysis of the granules being carried out in a
multidimensional manner, investigating composition as well as size (section 2). These techniques were used to investigate the sensitivities of the granulation procedure to changes in the impeller speed and composition of the liquid binder and the results examined (section 4). These results were then compared to simulations obtained from a pre-existing multivariate PBE model in order to test the model and compare the sensitivities obtained (section 5).

2 Experimentation

In order to investigate the influence of the process parameters on a granulation process, granules were manufactured and analysed on a lab scale with the equipment, materials and methods described below.

2.1 Apparatus and Materials

A bench scale granulator (Kenwood food mixer (FP108)) was used as the reactor vessel, with the knife blade attachment used as the impeller. An optical tachometer (Model TM 2011, RS Instruments, Corby. UK) was used to measure the speed of the impeller.

A balance (Sartorius) (accurate to the nearest $\pm 0.1$ g) was used for all weighing for granulation. For all weighing during the composition analysis a Precisa 205A balance was used (accurate to the nearest $\pm 0.0001$ g).

An Endecotts EVS1 Auto-shaker was used for all the sieving carried out. An optical device (JM Canty Solids Sizer ) and a laser diffraction (Coulter-Beckmann LS 230 ) device were used for particle sizing.

Anhydrous Sodium Carbonate Powder (Fluka Chemicals co.) was used for the bulk solid particulates and a solution of de-ionised water and polyethylene glycol (PEG) 4000 (Fluka Chemicals co.) was used for the liquid binder. A citric acid based organic liquid food dye (Super cook) was also added to the binder.
2.2 Granulation Method

Making Binder - The liquid binder is made by dissolving polyethylene glycol 4000 (PEG) powder with de-ionised water. A qualitative, visual assessment of the mixing of the binder, when added to the reactor, was made; hence a small amount of blue liquid food dye (<1 % by volume) was added to the binder.

Binder Addition – 300 g of Sodium Carbonate powder was added to the mixer before the experiment was started. Binder was added drop-wise, from a 10 ml syringe to the reactor in a stepwise manner, over a set period of time. During the addition steps the impeller was agitating the reactor at a set speed. Binder was added until the composition in the reactor was such that it consisted of an allotted weight percentage of binder.

Taking samples - Samples were taken from the mixer after each binder addition step, as well at some other stages, from various points in the reactor to make the samples as representative as possible. The samples taken were then used for analysis of the process.

2.3 Analysis Techniques

Samples of the mixture were analysed to determine properties such as size and particle composition.

2.3.1 Particle Size

Size is the parameter that it is desirable to control in many granulation procedures (Watano, 2001; Tardos et al., 1997; Mort, 2005) and the most widely used for particle description (Realpe and Velazquez, 2008; Iveson et al., 2001; Knight et al., 1998). It is therefore logical that particle analysis in this investigation should examine the changes in granule size during the granulation. Three Techniques were used to analyse particle size.

JM Canty Solids Sizer

The JM Canty Solids Sizer is an optical sizing device. The sample is loaded onto a chute, which vibrates, causing the particles to move down it. At the end the particles fall freely in front of a camera (Figure 3.1).
The camera produces images of the particles (Fig 2.2) which are analysed, by the attached data analysis unit, to produce data for the major and minor axis length, area and perimeter of the individual particles. In total, 10,000 particles were used for each sample.

Each particle within the ensemble obtained was characterised, in terms of size, by an equivalent diameter corresponding to the geometric mean of the major and minor axes. This assumes that the particles are spherical, an assessment made based on visual assessment of the particles by microscopy.

The sample ensemble can be represented by a number of different measures but most commonly used are volume based particle size distribution (PSD), geometric volume mean value ($\bar{L}_v$) and standard deviation of the volume mean ($\sigma$).

The geometric volume mean size of a sample, $\bar{L}_v$, was calculated according to the following equation.
\[ L_3 = \sum_{i=1}^{n} V_i \ln d_i \times \exp \left( \frac{1}{\sum_{i=1}^{n} V_i} \right) \]  

(2.1)

where \( n \) represents the total number of particles in the sample and \( V_i \) and \( d_i \) are the volume and diameter, respectively, of an individual granule as described by

\[ d_i = \sqrt{L_{i,maj} \times L_{i,min}} \]  

(2.2)

\[ V_i = \frac{\pi d_i^3}{6} \]  

(2.3)

where \( L_{i,maj} \) and \( L_{i,min} \) are the major and minor lengths of the particle. In addition to the volume mean size of the sample a standard deviation, \( \sigma \), is calculated as,

\[ \sigma = \exp \left[ \sqrt{\sum_{i=1}^{n} V_i \ln \left( \frac{d_i}{L_3} \right)} \right] \]  

(2.4)

Sieving

An Endecotts EVS1 auto-sieve was used for sorting of particle samples by size. The fractions that were used are shown in table 2.1.

<table>
<thead>
<tr>
<th>Sieve Fraction (( \mu )m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &gt; 850 )</td>
</tr>
<tr>
<td>300 - 850</td>
</tr>
<tr>
<td>212 - 300</td>
</tr>
<tr>
<td>150 - 212</td>
</tr>
<tr>
<td>106 - 150</td>
</tr>
<tr>
<td>&lt;106</td>
</tr>
</tbody>
</table>

Beckman Laser Diffraction

The Beckman-Coulter LS230 is a laser diffraction device. Samples are loaded into the device, where they are analysed in a single scan, and analysed using both the Fraunhofer
and Mie theories of light scattering. It provides sizing in the range 0.04-2000 µm. This results in some of the larger granules produced being too large for detection by this device; as a result it was used for calibrating other sizing techniques.

2.3.2 Composition Analysis

Another product characteristic that was investigated was that of particle composition. This means, the proportion of the particles that were made up of sodium carbonate, water, and PEG. Whereas traditionally size has been the major measure by which granulation procedures, and samples, have been analysed, taking into account composition allows a more complete, multidimensional, assessment to be achieved. This analysis is achieved by recording the mass changes caused by the removal of components due to thermal treatment of the sample (figure 2.3).

![Figure 2.3: Procedure for analysing composition](image)

The analysis was performed on the final sample from the granulation procedure. Firstly the sample was sieved, allowing the investigation of composition variation with size, and samples from each of the sieve fractions were weighed. The samples were then left placed in an oven at 110 °C for at least 24 hours, until mass consistency had been achieved, in order to remove water, before being reweighed to determine the mass of water removed. They were then placed in a furnace at 550 °C for a further 12h, again until mass consistency had been achieved, which removes the PEG from the sample and then a final mass taken, after cooling in a desiccator. Using the mass lost after each heating stage the
weight percentage, in the original sample, of each component can then easily be calculated.

2.4 Characterising Apparatus

Before experimentation was performed it was important to characterise and calibrate the set-ups of the apparatus used. This was particularly important for the speed of the impeller and the set up of the Canty Solids Sizer.

2.4.1 Mixer Speed

The mixer speed was varied by controlling the voltage supplied to it using a variac. In order to characterise this, an optical tachometer was used to measure the rotation speed of the impeller at various input settings of the variac dial. A linear relationship between voltage and impeller speed has been found (figure 2.4).

![Figure 2.4: Voltage – impeller speed characteristic of granulator](image-url)
2.4.2 Canty Solids Sizer

The Canty Solids Sizer works by the inbuilt camera producing a 2D image which is then analysed by the software to obtain data for area, perimeter, major and minor axes. The software is able to take the greyscale image, analyse each pixel's intensity and assign it a numerical value based on this (between 0, for black, and 255, for pure white). These values provide the data by which the software obtains the measurements.

The image is set up so that the particles are of a high intensity (white) and the background is of low intensity (black), see figure 2.2; the software is then able to use this contrast to detect and measure particles. The ‘threshold’ of the device, i.e. what intensity is determined to be part of a particle, can be adjusted, having an effect on the results obtained.

In order to determine a suitable value for this variable the device was calibrated using salt and sugar particles. These were first tested in the Beckman Laser Diffraction machine before being tested in the Canty Solids Sizer. The threshold of the device was varied to produce a particle size distribution that was similar produced by laser diffraction. The threshold used was 160.

2.5 Experimental Procedures

This section deals with the outlining of the specific variable values and procedures used in the experiments performed as well as the experimental design matrix used.

The main procedure for the granulation was performed by continuously adding binder, with the mixer on, in a series of three minute steps, with each step increasing the weight percentage of binder in the mixing vessel by 5% up to a maximum concentration of 25 wt%; this concentration is a measure of the solid to liquid ratio in the reactor. The 25 wt% was chosen after preliminary experiments showed the mixture often became too wet, forming a slurry, at higher ratios. After each step, mixing was stopped for 1 minute as a sample was taken from the reactor, a sample of sodium carbonate was also taken prior to the first addition of binder. The binder addition profile can be seen in figure 2.5. In order to achieve the smoothest continuous addition profile possible each measure of binder was divided equally into three separate syringes, which were used, in turn, to add binder for a minute each.
This granulation procedure was performed with variations in binder composition (10, 20 & 50 wt% PEG to water) and mixer speed (660, 1040, 1390 rpm). This results in the examination of the granulation process' parameter sensitivity in terms of the following variables

- Binder Composition
- Mixer speed
- Solid:Liquid ratio

Composition analysis took place on samples taken at 19 min, i.e. 75:25 solid:liquid ratio in the reactor. Figure 2.6 displays a matrix of the experimental design used in this investigation.
In addition to the experiments described above further experiments were performed to test the sensitivity to changes in the rate of binder addition to the reactor. The procedure and set-up were identical to that listed above and a binder consisting of 25 wt% PEG was used, along with an impeller speed of 1040 rpm. Variation of the rate of addition was achieved by shortening the time taken for each binder addition to 2 min and 1 min and the results recorded. The binder profiles that were used for these experiments are displayed in figure 2.7.

![Figure 2.7: Alternative binder addition rates used](image)

### 3 Results

#### 3.1 Particle Sizing

Results are presented in terms of both mean diameter and standard deviation as described in section 2.3.1. The variation in mean size clearly provides an indication of the growth behaviour of the granules whereas the standard deviation provides insight into the degree of spread of the diameters of the particles within the sample. Presenting results in terms of a PSD provides the most information, however in order to compare samples, and sensitivities, it is simpler to present data in terms of mean and standard deviation. Two results were taken for each experimental set-up and an average value used. NB Lines have been included through the experimental data for clarity in this section.

#### 3.1.1 General Trends

The results for the mid point of the experimental design matrix (figure 2.6) demonstrate the typical granule growth behaviour determined in this investigation and its dependence upon
the liquid:solid ratio in the reactor. The results (Figure 3.1) demonstrate a period of initially no growth in granule diameter, and in fact a slight decrease, up to a time of 11 mins, which corresponds to 15 wt% of the total material in the reactor being binder. For higher percentages of binder within the reactor there is a rapid increase in particle size and mean particle size doubles.

Figure 3.1: Change in Particle mean size for a binder composition of 25 wt% PEG solution and mixer speed of 1040 rpm

The corresponding standard deviation, shown in Figure 3.2 shows a similar pattern to that of the mean (fig 3.1), although with an anomalous result at 3 minutes. This is an unsurprising result as this is as a direct result of the granule growth behaviour of the mixture; the agglomeration that leads to the growth of particles, and hence an increase in mean size, is not undergone by all of the particles and as a result there is a spreading of the PSD, rather than a shifting of the peak, that causes the increase in standard deviation.

Figure 3.2: Standard Deviation for 25 wt% binder and 1040 rpm
In addition to the effect of liquid:solid ratio, the sensitivities of the granule growth to both mixer speed and binder composition were investigated.

3.1.2 Effect of Impeller Speed

The pattern for granule growth is similar in all cases to that seen in figure 3.1: Initially the samples for all of the speeds display a period of slow size increase, before a rapid size increase at higher liquid:solid ratios.

The results for the binder, composed of 10:90 PEG to water ratio (figure 3.3), and the highest ratio, 50:50, binder (figure 3.5) (50:50 PEG:water) appear to demonstrate an optimum impeller speed for the induction of growth in mean particle size. The volume mean granule size is highest for the intermediate impeller speed, of 1040 rpm, for the final two samples (15 and 19 minutes) in each case.

A possible explanation for this would be due to the fact that the impeller speed not only aids mixing and provides the shear stress necessary for aggregation, but also affects the rate of breakage within the process. An increase in the impeller speed causes the increased particle size, evident between 660 and 1040 rpm, however at a speed of 1390 rpm significant breakage occurs, limiting the growth in mean particle size. However, the results for the intermediate binder composition (figure 3.4) display an alternative pattern, with an increase in overall granule size with a decrease in impeller speed.

If the final sample at 19min (25 wt% of liquid binder in the mixture) is observed, the lowest mixer speed, of 660 rpm, shows a larger mean granule size, than the samples for the highest mixer speeds of 1390 rpm at all binder compositions. However, at the lowest PEG:Water ratio (figure 3.3) the period of slow growth extends to 15 min, before a rapid increase in mean size occurs.

The standard deviations (figures 3.6 – 3.7) again show an increase in size as time increases, although there is no consistent sensitivity; the three different impeller speeds each have the highest standard deviation at one binder composition.
Figure 3.3: Mean granule size for variation in mixer speed for 10 wt% PEG binder

Figure 3.4: Mean granule size for variation in mixer speed for 25 wt% PEG binder

Figure 3.5: Mean granule size for variation in mixer speed for 50 wt% PEG binder
Figure 3.6: Standard deviations for variation in impeller speed for 10 wt% PEG binder

Figure 3.7: Standard deviations for variation in impeller speed for 25 wt% PEG binder

Figure 3.8: Standard deviations for variation in impeller speed for 50 wt% PEG binder
3.1.3 Effect of Binder Composition

Variations in the binder composition lead to variation in the granulation behaviour. Therefore alterations to the PEG:water ratio were made to create changes in the properties of the binder e.g. viscosity. Comparing the effects of varying this composition at constant mixer speed (see figures 3.9 - 3.11) it is clear that the PEG:water ratio binder, i.e. consisting of 10 wt% PEG in the binder, produces the greatest size of granules for all three of the mixer speeds used. For the last measurement taken, at 25 wt% of the total reactor concentration being binder (or 19 minutes), the mean granule size is approximately double the size of the granules produced using the 25 wt% and 50 wt% PEG binders. Initially the size is similar for all three binder compositions, and the growth rate is very low, before the mean size increases more rapidly between 11 and 19 minutes for the 10:90 binder.

If the results for the 25:75 and 50:50 PEG:water binders are considered (figures 3.9 and 3.11), it is seen that for both the lowest and highest speeds, the granule growth behaviour is almost identical for each composition. However the intermediate speed of 1040 rpm (figure 3.10) the binder composed of 50 wt% PEG, yields a mean particle size that is greater than that for the 25 wt% PEG binder.

As with variation in mixer speed (section 3.1.2) the pattern for an increase in standard deviation along with growth in mean size is observed (Figures 3.12-3.14). However, for 1040 rpm (figure 3.13), in contrast to the other two speeds, the 50:50 binder displays the largest standard deviation, even larger than the standard deviation of the composition with largest mean granule size (10 wt% PEG).

In general it appears that the standard deviations do not display as much of a pattern, or defined sensitivity, as the mean size in these experiments. This could be an indication of non-conformities with the spreading of the binder within the vessel.
Figure 3.9: Mean granule size for variation in binder composition for mixer speed of 660 rpm.

Figure 3.10: Mean granule size for variation in binder composition for mixer speed of 1040 rpm.

Figure 3.11: Mean granule size for variation in binder composition for mixer speed of 1390 rpm.
Figure 3.12: Standard deviation for variation in binder composition for mixer speed of 660 rpm

Figure 3.13: Standard deviation for variation in binder composition for mixer speed of 1040 rpm

Figure 3.14: Standard deviation for variation in binder composition for mixer speed of 1390 rpm
3.1.4 Variation in Binder Addition Rate

There appears to be no significant change in granule growth behaviour due to changing the rate of binder addition to the profile that can be observed by the results achieved in this experimentation under the degree of accuracy achieved by the procedure (fig 3.15); this would suggest that there is no advantage to choosing to operate under a reduced addition rate. A faster binder addition rate would lead to a reduced overall processing time; which would represent a promising and intriguing result. However, this does not mean that rate of binder addition does not have any affect on the process, merely that there is no sensitivity that can be detected in this set-up. Variation of rate by larger, order of magnitude, degrees may lead to detectable parameter sensitivities.

![Graph showing effect of binder addition rate](image)

Figure 3.15: Effect of binder addition rate, measured at 25 wt% PEG binder and 1040 rpm

3.1.5 Errors in Sizing Procedure

During the course of the investigation difficulties in performing, and analysing, experimentation with a high level of accuracy and reproducibility were highlighted. As was described in section 1.1 the process has many different variables that affect the outcome of the granulation, although efforts were made to control all inputs to the system, deviations in the granulation procedure do arise.

Errors occur as a result of the mixing within the reactor vessel itself. ‘Dead spots’ are present, inside the reactor, where the mixing of binder is not as successful. Since the analysis of the samples assumes homogeneity in the mixture this will introduce a degree
of error. However the ‘dead’ zones in the mixture were small and mainly situated at the bottom of the reactor, underneath the mixing blades. This region was not used for sampling, and the areas that were used appeared to be homogenous in terms of binder mixing, from a visual inspection. Additionally these zones were small when compared to the total reactor volume. Hence it appears the result of ‘dead’ zones in the mixture would be to increase the local liquid:solid ratio to a small degree when compared with that used in analysis. Another process that has the same effect is ‘wall build up’; i.e. particles that become stuck to the wall and therefore do not mix fully with the bulk material. The experiment was designed to reduce the amount of wall build up, by stopping the experiment at 25 wt% binder to solid ratio because at higher liquid:solid ratios the effects of wall build up were far greater due to the ‘wetness’ of the mixture. Additionally, despite the calibration, errors in the mixing speed were present. The rotation of the blades was not at a constant speed and the values in fig 2.4 had to be estimated from a fluctuating reading.

Further to the problems in the granule production method there are also difficulties in attaining accurate sizing results via this method due to the inherent ‘wetness’ of the particles. This causes a multiple problems in performing the experiments and analysis. Firstly there can be problems with the granules sticking to the feed chute of the Canty Solids Sizer. The device relies on being able to achieve a steady flow of free falling particles from the end of this chute, producing an image such as figure 2.2. The poor flow of particles along the chute, due to sticking, can lead to the particles falling as ‘clusters’ rather than individual particles; the edges of particles within these ‘clusters’ overlap, resulting in the Canty Solids Sizer detecting these groups of particles as a single, large, particle due to it’s inability to detect the location of the individual edges. This problem can be partially mitigated by using careful adjustment of the frequency of the chute vibrations, combined with some brushing, to stop the particles sticking to the chute; however it still represents a major source of error within the system. Another problem that impacts the reliability of the data is the granules sticking together in between sampling and analysis; in essence a degree of granulation is continuing to occur despite the removal from the mixer. The result of this is that some of the particles analysed can be larger than those in the mixer. The effect of this phenomenon is minimalized by analysing the particles as soon after sampling as possible, within 15 minutes, however it cannot be entirely removed.
3.2 Composition Results

The results below are those obtained from the compositional analysis of the granules as described in section 2.3.2. The ‘total binder wt%’ is a combination of the wt% of PEG and water and should be 25 % to correspond with the bulk composition of the mixture.

The results for 25 wt% PEG binder at the lowest, and intermediate, impeller speeds show increased weight percentage of total binder, as well as both PEG and water, within the particles for an increase in particle size (figures 3.16 and 3.17). This is the result that would be expected intuitively, as a larger percentage of binder is more likely to result in an agglomeration of particles in the case of a collision.

![Figure 3.16: Composition variation with size for a 25 wt% PEG binder operated at 660 rpm](image1)

![Figure 3.17: Composition variation with size for a 25 wt% PEG binder operated at 1040rpm](image2)

For the same binder composition at the highest speed (figure 3.18) it appears that there is a similar pattern of increased binder composition for larger particles. However the total binder wt% for the size range of 300-850 µm is considerably lower, due to the fact that the composition of water has decreased considerably.
The results do not take into account the presence of binder trapped within concealed pores in the granules. This could explain the fact that the total binder percentage in the particle appearing to be lower than the 25 wt% that is present in the bulk mixture. This percentage, although it does introduce some error into the results, appears to be small. However, if the procedure could be modified to calculate composition with a high enough degree of accuracy this result might be used as a measure of trapped binder rather than being a source of error. This is a further parameter that may be gathered and used for model development in the future.

For the lowest PEG wt% binder, operated at 1390 rpm (figure 3.19), it can be seen that again there is a general pattern of increasing binder content with size. However, as in
Figure 3.18, there is an anomalous result, this time at a size fraction between 212 and 300 µm and producing a value much higher than the other results.

Figure 3.20: Composition variation with size for a 10 wt% PEG binder operated at 1040 rpm (300-850 µm not recorded)

Figure 3.21: Composition variation with size for a 10 wt% PEG binder operated at 660 rpm

Figure 3.22: Composition variation with size for a 50 wt% PEG binder operated at 1040 rpm

The remainder of the results do not display a consistent pattern or trend (figures 3.20 – 3.22); this results in it being difficult to consider sensitivities of the granule compositions, to the process conditions. Possible sources for errors are explained below.

The major source of error in the results probably arises from difficulties in the sieving procedure. As in the case with the size analysis, size changes in the particles continue to occur after the mixing has stopped; in this case due to the vibration of the auto sieve. This combined with the sticking of powder to the sieve, due to the particle ‘wetness’, leads to it
being difficult to accurately separate the particles into size fractions based upon those present in the mixer.

Additionally adsorption of moisture from the atmosphere, between heat treatment and the subsequent weighing, introduces an under-estimate in the quantity of PEG and water removed by the system. The adsorption of additional water causes a mass increase of the samples, between the heating and subsequent weighing steps. Hence due to the use of mass variation as a measure of composition the amount of PEG and water contained in the system is underestimated.

In order to quantify this error, control samples were tested along with the granules from the reactor. These controls were samples of the initial sodium carbonate powder without any liquid binder having been added. So any mass variation in these control samples gave an indication of the effect of moisture adsorption, as well as systematic measuring errors. These were found to be 0.85 wt% and 0.54 wt% in the quantities of water and PEG respectively.

As this is a process based on weighing there is obviously systematic error within the process based upon the accuracy of the balance. However, these are small (± 0.00005 g) compared to mass losses of a minimum of 0.3 g per heat treatment, i.e. a maximum percentage error (N.B. different to wt%) of ± 0.16 % this represents a negligible value when compared to other sources.

The method has succeeded in producing results with a consistent, expected trend for many of the settings. However, inconsistencies in some of the results indicate the presence of significant errors and the need for process refinement for the determination of sensitivities of the granule composition to process conditions. Despite this, the technique provides a basis for obtaining valuable, multidimensional, data for use in future model testing and further refinement should lead to the production of accurate results.

4 Model Testing

The ultimate aim of the ongoing research in granulation is to enhance the understanding of the process behaviour and mechanisms. This means it is desirable to possess well suited process models whose capability can be improved by comparison with experimental results. Therefore the final stage of the study was to test the pre-existing multidimensional population-balance model. (Braumann et al., 2007). The model was used to compare the
results, and sensitivities, produced to those obtained, experimentally, in the above sections. Further from this, preliminary alterations were made in order to improve the simulation results, although full scale model refinement was beyond the scope of this investigation.

4.1 Model Details

The model used is a modified version of that described in Braumann et al., (2007). It works by tracking the structural and compositional features of individual particles resulting in the multidimensional analysis of the granulation behaviour. Although full details of the model are beyond the scope of this report, some important characteristics are described below.

4.1.1 Transformations

Predictions of the behaviour are based on the following series of discrete transformations, based upon micro-scale models, that are involved in the granulation behaviour.

1. Binder addition
2. Particle coalescence
3. Compaction (porosity reduction);
4. Chemical reaction;
5. Penetration - mass transfer of liquid into the pores
6. Breakage

The stochastic modelling framework used produces a multivariate population balance, which is capable of tracking multiple product attributes via the performing of concurrent transformation. As such it is able to bridge the scales from micro-scale predictions, based upon first principles, to results on the macro, process scale.

4.1.2 State Space

A key feature of this model is its ability to perform in a multivariate manner; each particle is described by multiple attributes, not simply size as has traditionally been the case (Adetoyo et al., 1995). Each particle, within the model, is described by five independent variables:
1. Original Solid volume, \( s_o \) – the amount of the granule comprised of the original particles
2. Reacted Solid Volume, \( s_r \) – the solid products of reactions involving the binder
3. External Liquid volume, \( l_e \) – the volume of liquid binder on the surface of the granule
4. Internal Liquid Volume, \( l_i \) – the volume of the liquid binder contained within the pores of the granule
5. Pore volume, \( p \) – the total pore volume of the granule

These core variables can be used to determine further, more traditional, measures. Total particle volume, \( V \), is given by

\[
V = s_o + s_r + l_e + p
\]

(4.1)

From this diameter is easily obtainable as the model assumes the particles are all spherical.

**4.1.3 Model Modifications**

The model used contains a number of modifications from the one used in previous work. Coalescence is affected due to the fact the collision rate of particles is now also a function of the impeller speed. The penetration of binder into the solid particles has been altered to depend on binder viscosity. Additionally modifications determine that solidification of binder reduces the likelihood of a particle breaking, at a given particle composition and size.

**4.2 Simulation Results**

The modelling strategy was to fit the model, as well as possible, to the experimental data for the centre point of the experimental matrix (fig 2.6), in terms of volume mean size and corresponding standard deviation. Once this was achieved the process parameters were varied to test the sensitivities to binder composition, impeller speed and binder addition rate. Due to the large number of parameters within the model, parameter assessment, and full scale model refinement, was beyond the scope of this study. Hence the best fit
achieved (figure 4.1) does not display the exact trend seen in the simulation, but does display an increasing growth rate, with time, and agreement in magnitude of the final value. It was not possible to recreate the initial period of limited growth, seen in the experimental data, in the simulations.

These settings were then used to test the parameter sensitivities of the model. The results for a 25 wt% PEG in the binder (Figure 4.2) demonstrate that as mixer speed is increased the mean granule size decreases, which is the same trend as seen in the experimental results (fig 3.4). If the sensitivity of the standard deviation is considered, it can be seen that the same decrease in value, with an increase in impeller speed, is observed in the simulation (Fig 4.2), with the lowest speed having a much larger magnitude than the two higher speeds. The experimental results display the same trend between the lowest two speeds, however the highest speed displays a greatly varying trend (Fig 3.7).
The simulation results for the lowest PEG:water ratio (Figure 4.3) also demonstrate this sensitivity which is contrary to the optimum impeller speed predicted by experimentation (Fig 3.3). However the standard deviations do predict the same sensitivity, although, as in Fig 4.2, the lowest impeller speed displays a much larger standard deviation; this magnitude is not replicated in the experimental data (Fig 3.6).

The 50:50 PEG:water simulations (fig. 4.4) also produce different sensitivities as experimental results (fig. 3.5) demonstrating very little change in growth behaviour.
irrespective of mixer speed and the same trend for standard deviation as witnessed in fig. 4.2 and 4.3.

In analysing the sensitivities to binder composition it can be seen that an increasing wt% of PEG in the binder the degree of granulation decreases (fig 4.5). This is in direct contrast to the experimental data, in which the lowest PEG wt% displayed the greatest degree of granulation. The standard deviation also increases as the wt% of PEG in the binder increases; this is a different sensitivity to that produced experimentally.
Hence it can be seen that, although the model is capable of producing macro-scale predictions based upon microscale models for multiple variables over a number of transformations, it produces different results to those produced experimentally. Although the matching of the sensitivity to varying mixer speed for an intermediate speed, as well as an increasing rate of growth, are promising developments, it is clear that further development of the model, and its parameters must be made, to allow this consistency to occur, particularly with respect to the delayed granule growth, and the experimental sensitivities.

5 Conclusions and Further Work

A technique has been developed to study the parameter sensitivity of laboratory-scale wet granulation in a multidimensional manner. The sensitivities of the process to variation in binder composition, impeller speed, binder addition and liquid:solid ratio were studied by alteration in the process conditions. The procedure was performed by adding liquid binder to the solid, in the reactor, in a step-wise manner, with samples taken after every addition to analyse the process.

Particle analysis was carried out in terms of size, using an optical sizing device, and composition. The novel technique used for composition analysis utilises mass differences as a measure of composition change during heat treatment, and is particularly promising due to it obtaining data, that was previously unavailable. The results showed that as particle size is increased the binder content within the particles increases. However, difficulties in the procedure mean that further improvements must be made before the reliability is such that it can be used to accurately compare sensitivities to process conditions.

The growth behaviour of the particles displayed a two region response. Initially there was a period of limited, or no growth, up to 15:85 liquid:solid ratio in the vessel, before particle size increased rapidly at higher values. Results for variation in impeller speed show an optimum value, in terms of particle growth, of approximately 1040 rpm, due to the influence of the impeller on both agglomeration and breakage. The binder with the lowest PEG wt% demonstrate a degree of granule growth of approximately double that of the other compositions, irrespective of the speed used. The rate of binder addition did not appear to have any significant impact on granulation over the range of values used, suggesting that it is often possible to slightly reduce the operating time, hence increasing the efficiency, without greatly affecting the product formed.
The major error source in these readings was due to ‘clustering’ of particles in the sizing procedure as they fall in front of the camera. Additionally there were problems with particles sticking to equipment and continuing to react once they had been removed from the granulator, due to their inherent wetness. For this reason one possible improvement would be to introduce a drying stage once the granulation had been completed.

The data and sensitivities gathered were used to test an existing multidimensional model. The sensitivities obtained were also contrasting to the experimental results. Thus it is clear that this model requires further refinement before it is able to fully predict the experimentally found results. Although its ability to match the sensitivities to variations in binder speed for a binder composition of 25 wt% PEG is a promising development.

Further research should centre on trying to improve the accuracy of the experimental procedures, particularly with respect to sizing, where an alternative method could be considered. Another improvement would be using a more reliable impeller because the impeller used displayed some variation in speed at a constant voltage. Also improving the binder addition method, for instance to a spray method, would improve the binder dispersion within the mixer, and would act to improve the homogeneity within the reactor. The finding of an optimum impeller speed could be tested further by performing experiments at more impeller speeds to attempt to confirm this result and to determine the exact optimum speed. The composition analysis technique should also be developed further as it presents extremely valuable data which would be extremely useful for model development if it could be used to analyse sensitivities.
6 Nomenclature

- \( d \) Individual particle diameter, m
- \( l_e \) External Liquid Volume, m³
- \( l_i \) Internal Liquid Volume, m³
- \( \bar{L}_3 \) Geometric volume mean particle diameter, m
- \( L_{maj} \) Major axis length, m
- \( L_{min} \) Minor axis length, m
- \( s_o \) Original Solid Volume, m³
- \( s_r \) Reacted Solid Volume, m³
- \( V \) Individual particle volume, m³
- \( p \) Porosity
- \( \sigma \) Standard deviation of the geometric volume mean size

7 References


Braumann, A., 2008. *Private Communications*


