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Effect of Mixing Elements on Granule Formation in Hot Melt Twin Screw Granulation

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Twin screw granulation (TSG) has been applied to wet granulation, although its application in melt granulation has been more limited. This work explores potential advantages of hot melt granulation using twin screw extrusion. Four main operating and formulation parameters were investigated: screw speed, number of mixing elements, temperature, and binder percentage. Combinations of these factors were then studied to determine their impact on the quantity and characteristics of granules within the desired size range of 125 – 1000 μm. A screening design of experiments (DOE) study was used with each factor set at three levels, to investigate individual factor effects and interactions. Two types of mixing elements were studied: kneading block (KB) and chaotic elements. The type and number of mixing elements were found to be paramount in contributing to the quantity and characteristics of granules formed. Results obtained agreed with previous findings in literature on the influence of different screw elements on the characteristics of granules formed by twin screw granulation. Additionally, the study revealed the unique impact which different mixer elements have on both granule production and characteristics. Depending on the specific need or use of granules in required applications, the granulation process can be effectively designed to meet the end product quality and outcome.

1. Introduction

Originally used in the polymer and plastics industries (Seem et al., 2015), twin screw granulation is gaining rapid growth and finding applications in many other industries in particular the pharmaceutical industry (Markarian, 2018). This is due to the focus on continuous processing and manufacturing, to meet the needs of shorter processing times, increased efficiency, minimal to no waste and increased production profits (Malhotra, 2015). Whilst wet granulation is the most popular technique applied in granulators such as high shear mixers and fluid bed granulators (Litster et al., 2002), TSG offers more operational flexibility. Here, the size enlargement mechanism typically requiring a liquid binder (Snow et al., 1997) is achieved without any liquid, but with the introduction of the binder in solid form. Temperatures above the binder's melting point are introduced into the process to facilitate its melting and subsequent coating of powders in producing granules. Many authors have worked on TSG using the more known industrial co-rotating screw model (Seem et al., 2015) but with different materials (i.e., powders and binders) and for varying purposes.

Korsheed et al. (2019) studied the effect of wet granulation on granule product tabletting using microcrystalline cellulose (MCC) and mannitol in the presence of water. Dhenge et al. (2012) focussed on the contributions of liquid to solid ratio, powder feed rate and viscosity of liquid binder (i.e., hydroxypropycellulose - HPC) on granule properties. Many others also studied the impact of various operational conditions on granule properties but did not focus on the contribution of the number of mixing elements used although some sort to understand the influence of particular mixer element types in the granulation process. According to Dhenge et al. (2012) a total of 16 kneading discs/elements were used, 8 elements each forming a mixing zone. They concluded that the first mixing zone of 8 kneading elements, resulted in material consolidation and breakage, while the second zone produced larger sized granules from its consolidation and coalescence action. However, these findings may have been influenced by operating conditions, confounding any clear contribution of the number of elements used nor the type of actual mixer elements chosen. Additionally, the observation of the absence of significant changes in the particle size distribution of products studied by

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Vercruysse et al. (2012) when using kneading elements (KB) of varying offset angles, suggests the need to identify the contribution of the type and number of mixer elements. Hence, there is a need for a detailed study in understanding the choice of screw elements, with their associated contributions to the granulation process. This research thus, aims to determine the influence of two types of mixer elements namely, chaotic and KB elements.

2. Materials, methods, and measurement

2.1 Materials

Calcium carbonate ($CaCO_3$) powder of mean particle size (Dv50) 96.6 μm and polyethylene glycol (PEG) of molecular weight 4000 were used, as the excipient and solid binder, respectively. These materials are used as a model as they are not expensive as compared to pharmaceutical. This enables us to fundamental understand the process before the subsequent application to other materials in the future. $CaCO_3$ of hardness 3.0 – 4.0 on Mohs scale of hardness and density range 2.7 – 2.95 (g/cm^3) was used with the corresponding melting points 825°C (alpha) and 1339°C (beta), and a pH 8 – 9.

2.2 Methods

Four key factors, with the potential to impact the production of 125 – 1000 μm sized granules were chosen and a screening design of experiments (DOE) methodology was employed (see Figure 1). These factors are Screw Design (i.e., number and type of mixing elements), Screw Speed (rpm), Set extruder temperature (°C) and Binder Percentage (%). Each of these factors were set at three levels within the DOE experiments conducted. Number of mixing elements was set at zero, two and four, with zero representing no mixing element thus an all-conveying screw configuration. To meaningfully set the levels of temperature, the melting point of PEG 4000 was first determined via differential scanning calorimetry (DSC) and found to be 60.7 °C. Thus, the lower limit for temperature in the DOE was chosen as 60 °C.

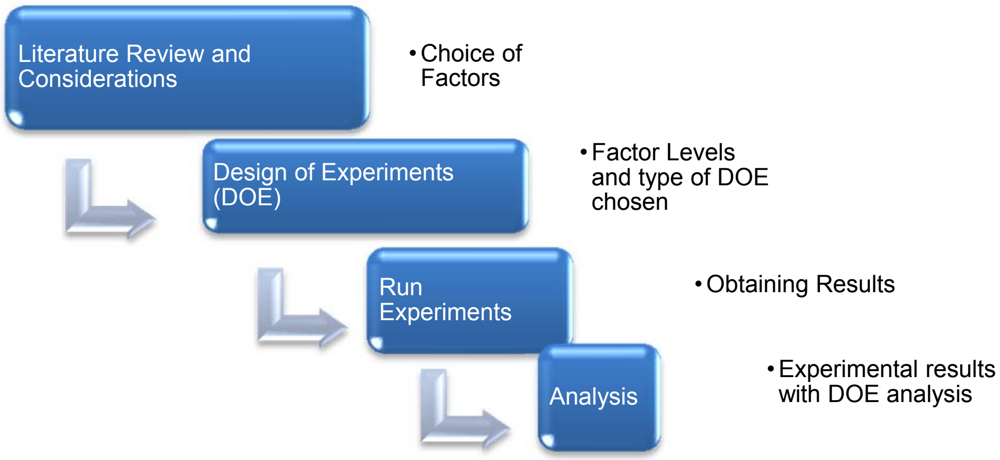


Figure 1: Research methodology process chart.

In conducting experiments and obtaining results for further analysis with set conditions in the screening DOE chosen, feed rate of material moving into the twin screw for granulation was kept constant at 0.82 kg/h, throughout all experiments. Feed rate was calibrated by collecting the amount of material exiting the feeder after 120 s under varying discharge rates (see Table 1).

Table 1: Experimental feed rate determination.

Test	Discharge (%)	Throughput (g)	Feed rate (g/min)	Feed rate (kg/h)
1	2.00	3.76	1.88	0.11
2	4.00	20.93	10.47	0.63
3	6.00	38.98	19.49	1.17
4	8.00	58.00	29.00	1.74
5	10.00	58.51	29.26	1.76

2.2.1 Experimental setup and screw configuration

A Pharma16 co-rotating twin screw extruder by Thermo Fisher Scientific (see Figure 2) was used with the die section removed such that granulated material exiting the barrel could be collected directly. Extruder screw speed and barrel temperature were set using the instruments control panel. The barrel comprised ten separately controlled zones (see Figure 3). Zones 2 and 3 (z 2 and z 3) were kept at constant temperatures of 25 °C and 45 °C respectively throughout all experiments.

Figure 2: External view of Pharma 16 twin screw co-rotating extruder; inverted triangle with the temperature probe; oval shape is the extruding barrel section containing the twin screws; the rectangular shape is the control and display unit (ThermoFischer Scientific)

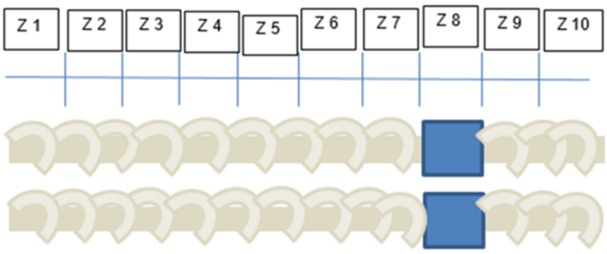
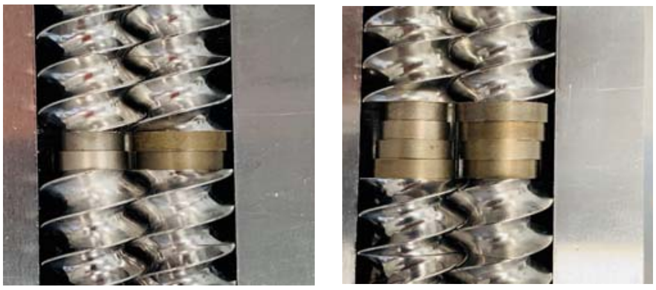


Figure 3: Schematic of co-rotating screw configuration showing mixing zone at zone 8 (z 8)

(a) (b)

Figure 4: Kneading element configuration; (a) 2 KB and (b) 4 KB.



(a) (b)

Figure 5: Chaotic element configuration; (a) 2 Chaotic and (b) 4 Chaotic

Mixer elements used in all experiments conducted are as shown in Figures 4 and 5, with KB elements at an offset angle of 30 °.

2.3 Measurements

Particle size distribution (PSD) of the feed powder ($CaCO_3$) and granules were performed using British Standard (BS) sieves in combination with an automated sieve shaker (Retsch AS 200). The structure and shape of granules formed were also observed using an FEI Quanta400 environmental SEM (E-SEM) with Oxford IncaSight EDX and corresponding observations recorded and interpreted.

3. Results and discussion

The quantity, shape and structure of the granules produced are related to the type and number of mixing elements. Results of the DOE experiments and the material yield obtained are displayed in Tables 2 and 3 for KB and chaotic elements, respectively. Separate DOE runs were performed for each geometry of mixing element.

Table 2: DOE table of results on quantity of 125 – 1000 μm sized granules for kneading elements

	Factors				Response
Run order	Number of elements	Screw speed (RPM)	Temperature (°C)	Binder percentage (%)	Granule size 125–1000 μm (%)
1	4	150	65	15	60.7
2	4	50	60	15	38.2
3	4	100	70	5	62.4
4	2	100	65	10	70.3
5	2	150	70	15	25.5
8	4	150	60	5	23.7
11	2	50	60	5	24.4
13	4	50	70	10	57.5

Table 3: DOE table of results on quantity of 125 – 1000 μm sized granules for chaotic elements

	Factors				Response
Run order	Number of elements	Screw speed (RPM)	Temperature (°C)	Binder percentage (%)	Granule size 125–1000 μm (%)
1	4	150	65	15	23.3
2	4	50	60	15	40.8
3	4	100	70	5	69.2
4	2	100	65	10	68.8
5	2	150	70	15	19.4
8	4	150	60	5	25.2
11	2	50	60	5	25.9
13	4	50	70	10	67.4

3.1 Granule size distribution (GSD)

With reference to Tables 2 and 3 on the quantity of desired size granules formed, together with percentage product plots (Figures 6a and b), the effect of the type of mixing element under same operating conditions is seemingly consistent regardless of the type of element (i.e., KB or Chaotic). However, a slightly higher percentage of granules was recorded for KB than chaotic (see Run 4 in Tables 2 and 3), especially for only 2 mixing elements at higher temperatures and binder percentages. The discrepancies observed in the percentage of desired granules produced between KB and chaotic elements (see Tables 2 and 3), under same factor conditions, is a strong indication of the unique influence the type and number of mixing elements has on granule formation.

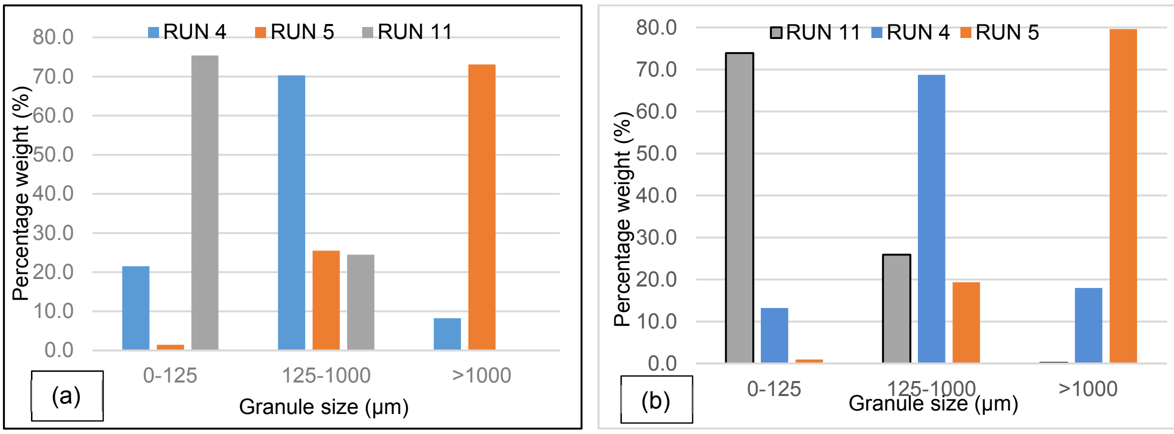


Figure 6: (a) GSD for 2 KB elements (b) GSD for 2 chaotic elements

3.2 SEM granule image analysis

The morphological properties and texture of granules produced with KB and chaotic elements are reported below using 2 and 4 mixing elements.

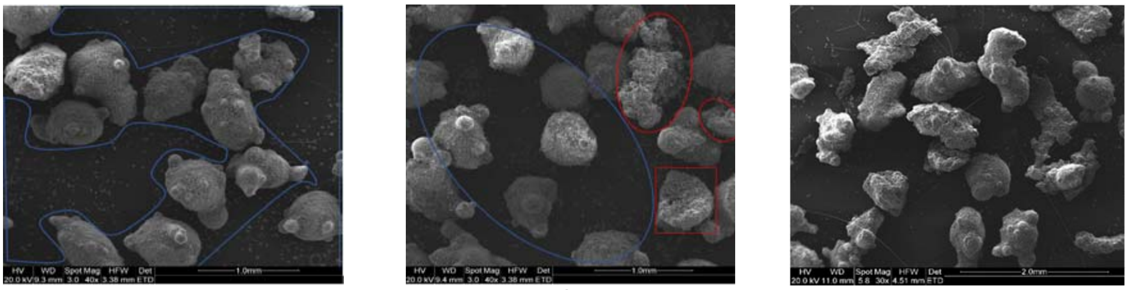


Figure 7: 40X SEM images of (a) 2 KB and (b) 2 chaotic under 50rpm / 60 °C / 5% with (c) 4 KB. Blue regions showing more fines, red ovals showing crushed granules and the red rectangle showing evidence of granule breakage

KB elements tended to exhibit more crushing mechanistic action while also shearing granules as seen in Figure 7 (a) and (c). However, the effect of shearing is seen with increased KB elements from 2 to 4 and particularly at the lowest temperature of 60 °C. This effect is also dominant at higher temperatures but only with corresponding higher binder percentages as for run 1 in Table 2. The crushing and shearing action resulted in more fines, which is in agreement with Thompson and Sun (2010) and Mu and Thompson (2012) on the consolidation action of kneading elements.

4. Conclusions

The type of mixing element and its number of individual mixers strongly impact the quantity of 125 – 1000 μm granules formed and this cannot be downplayed in the decision-making process of manufacturing and production. It was found that at the temperature of 60°C and with 4 KB elements, the kneading action of shearing is strongly observed with a change in granule shapes with more elongated forms than spherical shapes seen for only 2 mixing elements (either kneading or chaotic). These elongated shapes were, however, not prevalent at very high speeds thus, the effect of KB elements is only obvious at very low screw speeds and lowest temperature. Chaotic elements facilitate more granule growth (agglomeration) whilst KB elements achieve less agglomerate growth with better production of desired granule sizes under suitable operational conditions. KB granules are more compact and denser than those of chaotic elements and have higher strength as is suggestive from SEM. Depending on the end use of products and their quality requirements, this study offers the opportunity for manufacturers to choose the most suited mixer element and its number of individual discs which will be cost effective, efficient, profitable, and sustainable in the production of desired physical properties of granules including strength, density, porosity etc.

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