WET GRANULATION IN A TWIN SCREW EXTRUDER

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Abstract

This thesis covers a systematic examination of wet granulation in a twin screw extruder. Granulation of the excipient, α-lactose monohydrate, was done with the aid of PVP in an aqueous solution which acted as a binding agent. The influences on agglomeration by the following processing parameters were studied: screw elements design, screw rotational speed, binding solution concentration, and binder addition method. Qualitative efforts had also been made in modeling the process to gain valuable insight into how the elements affected agglomeration and granule rupture. A commercial software package – PFC^{2D}, based on the Discrete Element Method (DEM), was used to simulate the dynamic behavior of the screw elements in the barrel.

Within the optimal range of 7.5 - 10wt% binder concentration, all the screw profiles were studied for their capacity to produce desirable granules suited to solid oral dosage form production. By increasing the rotational speed from 30 RPM to 80 RPM, the granules size of the conveying, discharging and chopping elements decreased whereas this operating parameter had little effect on granule size within kneading blocks. The nominal particle size produced by a screw element increased from 300μm to 1mm when dispersive mixing was its dominant purpose (i.e. the kneading block), thereby meeting our criteria for a suitable granule in tabletting. Similar size development of the granules was not

found with the other conveying or distributive mixing elements. In regards to particle shape, the kneading blocks produced elongated shape granules while other elements tested in this study produced smaller, more spherical agglomerates. Either shape was found effective in tabletting.

Wet granulation was not feasible with more extreme concentrations of the aqueous binder (i.e. 5 wt% or 12 wt%) in this project, and the hand pre-blend method was the only approach found suitable for metering this additive into the system while maintaining steady feeding rates and output.

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The support from my family and my girlfriend give me power to step forward all the time.

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Nomenclature

Chopper	Chopping Elements
Comb	Discharging Element
Conveyor	Conveying Elements
ICTSE	Intermeshing Co-rotating Twin Screw Extruder
k_n	Normal Stiffness Coefficients
k_t	Tangential Stiffness Coefficients
Kneader	Kneading Elements
PSD	Particle Size Distribution
PVP	Polyvinyl-pyrrolidone
wt	Weight fraction [%]
θ	Angle of Repose
α	Lower Angle of Repose
β	Upper Angle of Repose

Chapter 1 Introduction

1.1 Background

Wet granulation is a preferred processing technique used for the preparation of pharmaceutical bulk solids for tabletting. Traditionally, such processes for the pharmaceutical industrial have been done in batch mode. In such cases, materials are charged into an enclosed mixing equipment; all of them being processed simultaneously for a predetermined time under a set of processing conditions to obtain a desired set of properties (Watano 2001). The uses of continuous processing methods, which have long been established in the food and plastics industries, have been hindered in the pharmaceutical sector due to heavy regulations (ex. USA Food & Drug Administration CFR Title 21 regulations for current Good Manufacturing Practices). Fortunately, recent changes in those regulations have made adoption of continuous processes much more attractive to this manufacturing sector.

Recent research has drawn attention to employing intermeshing co-rotating twin screw extruders (ICTSE), a main stay machine for the plastics industry, as a viable approach for expanding pharmaceutical's demand for wet granulation. This type of machinery can provide continuous processing which enables larger production capability and may entirely avoid scale-up problems seen with batch mixers. Several researchers have reported on the feasibility (Gamlen and Eardley 1986; Keleb et al.

2002) and operational parameters (Keleb et al. 2004; Kleinebudde and Lindner 1993; Shah 2005) of a twin screw granulation process. Their results showed a lower liquid content usage (advantageous for more rapid tablet drying) and higher tablet mechanical properties compare to the batch mixer products. Furthermore, the modular nature of the screw design for a TSE provided greater control over the processing conditions and product morphology. Few publications have considered the influence of screw design in this new approach to manufacture (Shah 2005; Van Melkebeke, Vervaet, and Remon 2008).

With twin screw extrusion as a new potential technology for particulate processing, it is likely that new screw element designs will have to be developed in order to satisfy the unique issues of dense granular flows. However, it is first necessary to establish the performance of available elements in granulation, and thereby, gain fundamental understanding.

1.2 Research Objectives

This research project is directed to gain a thorough understanding of the design parameters which affect wet granulation in an intermeshing co-rotating twin screw extruder. Granules in the order of 1mm in size are preferred for further processing. The effort was made in two aspects: experimental study and computational simulations. In order to examine the influence of liquid content fraction, screw configuration, screw speed and liquid addition methods, a series of experiments were conducted. Additionally, some simulation work was included in this thesis to provide a qualitative explanation for the observations made from the experiment-derived samples. At the time of writing this thesis, there are no known publications investigating these factors systematically. Hence, the results of this project will provide significant contribution to the science and engineering community and provide a reference for wet granulation screw design to the industry.

Chapter 2 Literature Review

2.1 Design Features of Twin Screw Extruders

2.1.1 Background

Intermeshing co-rotating twin screw extruders (ICTSE) are widely used in a diverse range of industries, especially in the plastics industry for compounding. Usually, ICTSE are made in a modular manner, both screw and barrel. The screw elements used perform a variety of functions during processing, i.e. solids-conveying, melting, mixing, species removal (venting) and pumping. An assembled screw from these different elements provides a tailored organization of flow stages to prepare a material meeting specific needs, often the uniform dispersion of inorganic fillers in a polymer matrix or the blending of two or more incompatible organic components.

Conveying elements and kneading disks are the most broadly used and studied among the main types of screw elements (Chen 1994; Potente, Ansahl, and Wittemeier 1990; White et al. 1988). Conveying elements have one (or more) continuous helical flight. Different types of conveying elements are available with varying pitch, flight tip width and channel free volume, and are based on their flow capabilities in regards to dragging material forwards or backwards. Kneading disks are usually used to accomplish the melting and mixing functions in polymer processing (Szydlowski and White 1988). The kneading disks often have the same bilobal cross section as conveying elements but lack a continuous flight. These disks are arranged in block assemblies with an angular offset. Figure 2.1 illustrates a conveying elements compared with a kneading elements with 60 ^{o} staggering angle.

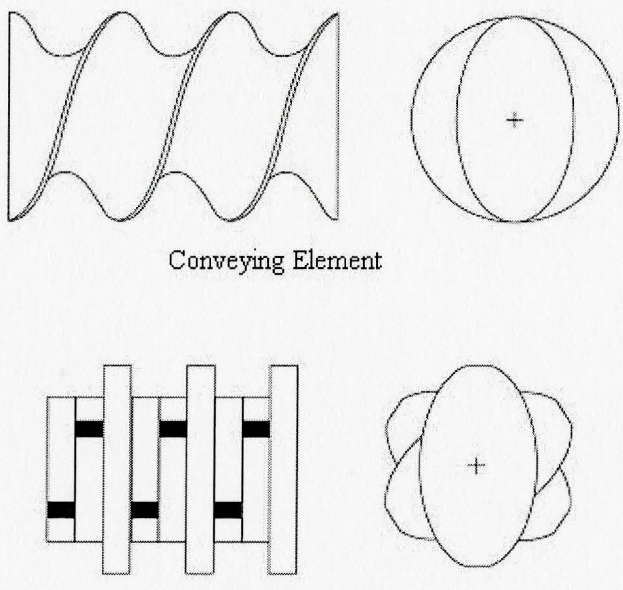


Figure 2.1 Conveying and kneading elements profiles, adapted from (Todd 1991)

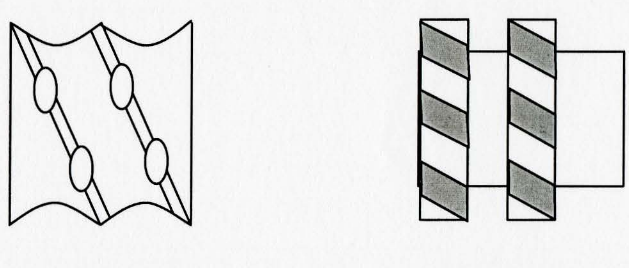


Figure 2.2 Chopping and discharging element profiles, adapted from (Brouwer and Todd 1999).

Manufacturers of ICTSE also offer various slotted mixing elements as alternatives to kneading blocks to achieve certain mixing functions. While a kneading block provides a strong smearing action through its dispersive forces, other slotted elements were designed for better distributive mixing by producing multiple divisions and recombination of a flowing material (Brouwer and Todd 1999). Two typical types of slotted elements which are commercially available include discharging elements (also referred to as comb mixers) and chopping elements. The chopping element has the same flights as a conveying element but with slots through the flights for backwards mixing, while the discharging element is composed of slotted annular rings perpendicular to the direction of flow (seen in Figure 2.2).

For all screw elements, several design parameters have a direct influence on their flow behavior, both pumping capacity and mixing efficiency, such as: number of flight threads, pitch, channel depth, flight tip width, helix angle, staggering angle, tip clearance, slot cut specification and so forth. While this thesis covers a broad range of screw elements, the following sections in the review looking at design parameters are limited to only a few types due to the limited range of examination in the literature

2.1.2 Elements of Flow in ICTSE

The flow pattern of polymer melt and pellets in the extruder has been widely studied by researchers. This section will review some of the established experimental and numerical theories. However, the cohesive particle flow in extrusion granulation is rarely reported in the literatures. Therefore this thesis will discuss particle flows based on the existing theories in plastic industry as references.

Due to the diverse geometries, the flow patterns within a twin screw extruder are very complex and still not fully understood. Briefly, there are three primary flow patterns in a TSE: drag flow, pressure flow and leakage flow (Lèon P.B.M. 1978). Drag flow involves restraining a fluid-like material between two parallel surfaces such as the barrel and screw surfaces of an extruder, where one moves at a higher relative velocity. Pressure flow is generated by restrictions in the flow path. The direction of pressure flow is opposite to that of the drag flow. Finally, there are many gaps between the barrel and screw elements which allow leakage. Leakage flows take place, either forwards or backwards, through these identifiable gaps which include over a flight, through gaps in the flight root, through the tetrahedron shaped spaces between the flight walls and through the nip between the sides of the intermeshing flights (Van der Goot, Poorter, and Janssen 1998).

According to their flow capacity, screw elements can be classified as forwarding and reversing elements. Forwarding elements serve to convey materials towards the die, while reversing elements tend to push material backward which usually involves forming dynamic seals with the material flow to generate pressure. By driving the material forwards, forwarding elements could be divided into two species: conveyers which primarily provide pumping force, and mixers which have less pumping effect.

The analysis of flow within conveying and kneading elements has been extensively conducted by various researchers. For conveying elements, it had been confirmed by researchers that the pumping capacity increases with the pitch (Huneault 1998; Kiani, Curry, and Andersen 1998; Robbe and Todd 2003; White 1987). Table 2-1 presents a comparison of the drag capacity of conveying elements with flights of different pitch. Results from those studies showed that increasing the screw pitch decreased the drag efficiency (i.e. ratio of drag flow to pitch), although the actual drag conveying capacity increased. On the other hand, the pressure flow was inversely proportional to the pitch. Besides the length of pitch, flight width also influenced the mass flow. A wider flight tip enlarges the contact area between the material and the flight which Figure 2.3 shows provided more restrictive forces when the material passed through the intermeshing region (Kiani, Curry, and Andersen 1998).

Carneiro and the coworkers (1999) presented a flow visualization study in an ICTSE operated under starve-fed conditions. Forwarding kneading elements with different stagger angles were used in their experiments. The flow patterns within these different kneading blocks are conceptually drawn in Figure 2.4. It can be observed that the neutral (90 °) kneader has no drag flow while the 60 ° kneader exhibits minor drag though much less than would be expected from a conveying element. Both drag flow and pressure flow were suitably present in the 30 ° kneader. The results by Carneiro contributed to a better knowledge of the flow pattern developed by various geometrical configurations. Similar observations for kneading elements with different staggering angle were reported by Bravo et al (2004). They also stated that an increase in the width of the disks would increase the amount of back flow generated.

The drag flow capacity of kneading blocks is lower than conveying elements (with the same apparent helix angle) because of their tendency for backflow through the gaps. These gaps significantly increase the pressure flow for kneading blocks.

In contrast, the leakage flow plays an important role in the slotted elements (i.e. distributive mixers). Ban, Kim, and White (2007) studied the flow in two distributive mixers via a numerical model. One of the mixers was a discharging element with 22 degree of teeth angle and 12 teeth in every circumference; the other mixer was a chopping element with 12 slits. According to the flow structure shown in Figure 2.5, there were obvious leakage flow through the slots cut of the flights going against the primary flow direction. This leakage flows reduced the pumping ability of mixers but enhanced distributive mixing.

Table 2-1 Drag capacity of conveying elements, adapted from (Kiani, Curry, and Andersen 1998) and (Todd 1997)

Pitch (mm)	Experimental Results	Simulation of Todd (Todd 1997)
25	18.1	18.16
40	28.8	29.06
80	N/A	43.58

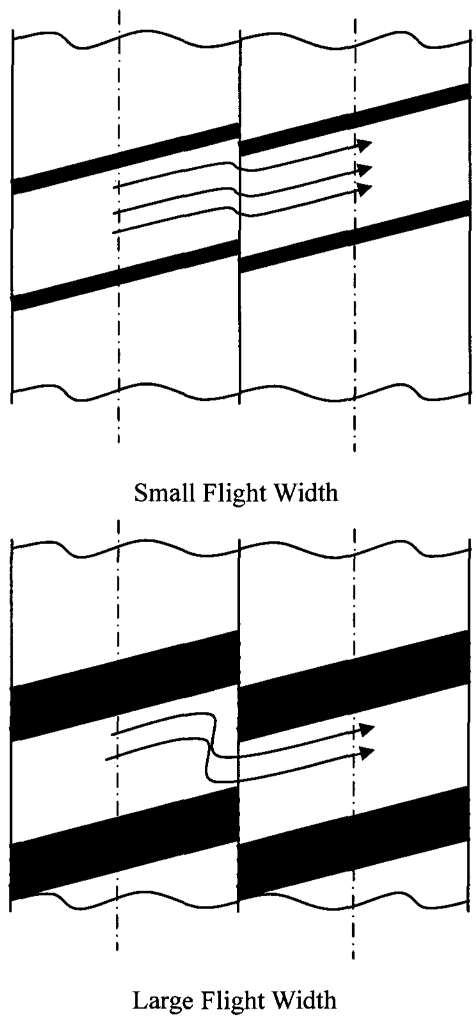


Figure 2.3 Restriction flow visualization in conveying elements. Black regions represent the flights while the arrows indicate the flow path. (Kiani, Curry, and Andersen 1998)

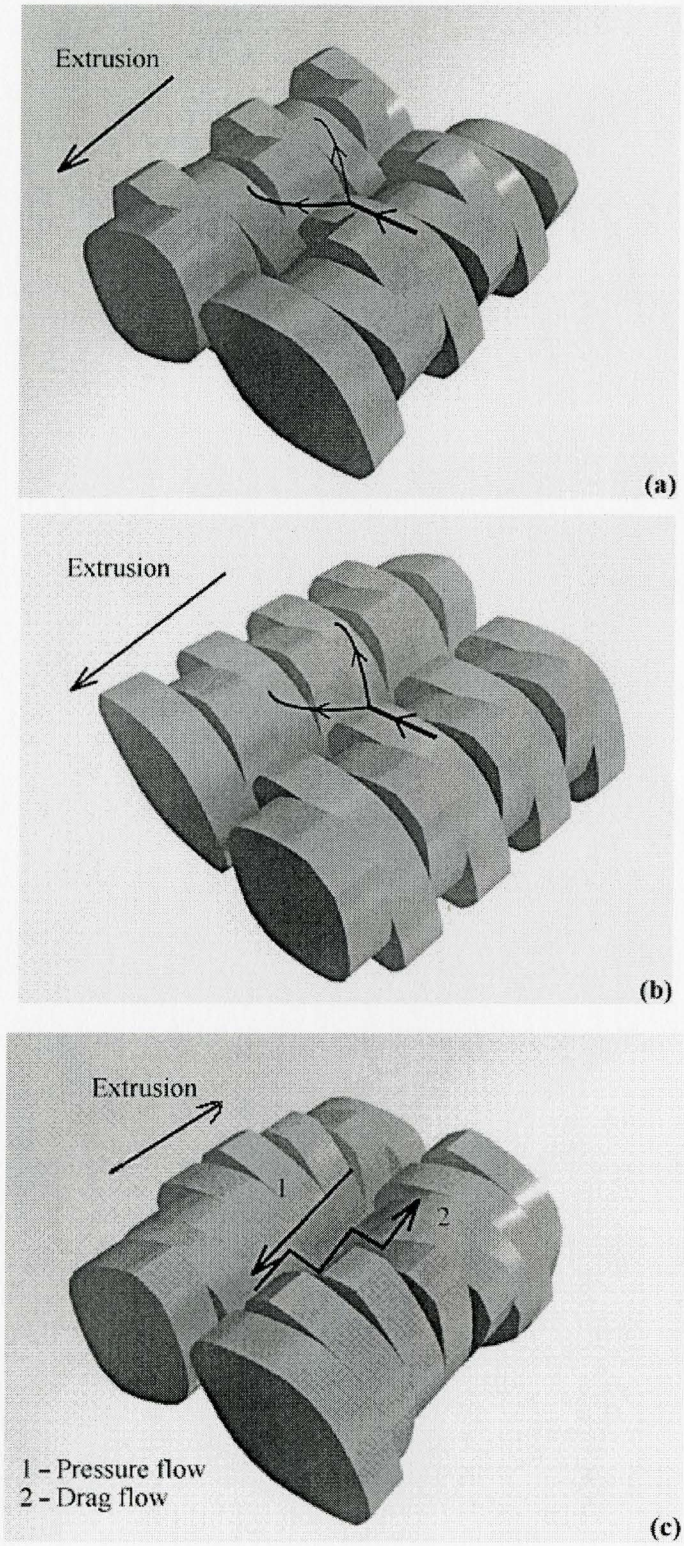
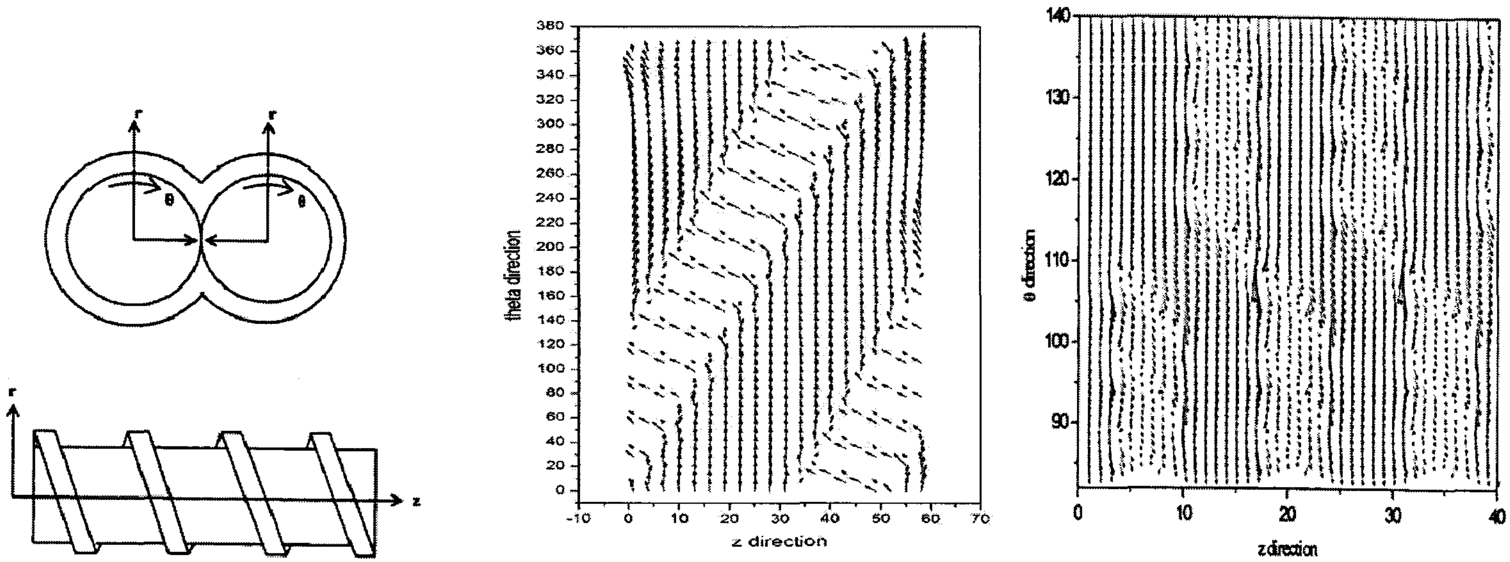


Figure 2.4 Schematics of flow pattern in forward kneading elements: (a) 60 °; (b) 90 °; (c) 30 °. Image taken from (Carneiro, Caldeira, and Covas 1999).



Coordinate system | Chopping Element | Discharging Element

Figure 2.5 The flow patterns of chopping and discharging elements together with corresponded coordinate system (Ban, Kim, and White 2007)

In conclusion, dispersive mixers tend to squeeze, shear, and elongate material, such as the aforementioned kneading elements. Distributive mixers tend to divide and recombine the material and ideally they do not possess high pressure gradients like dispersive mixers, but rather they should create easy paths for the dividing and recombining process (Vlachopoulos 2004). Discharging (comb) elements are typical examples of distributive mixers. In ICTSE, the mixing capacity is greatly influenced by the flight tip width. As we have seen in Figure 2.4 (a, b), each stream of material coming from a single channel is divided into two streams going into two channels. The ratio between the new flow passage and the width of the total passage indicates the mixing ability of the screws (Martelli 1983). The smallest possible tip width will give a mixing configuration while, on the other hand, a very large tip width will offer the greatest pumping contribution for conveying material towards the die. The following chart in

Figure 2.6 provides a comparison of the mixing capacity for typical forwarding elements which commercially available (adapted from Leistritz's extruder manual). From the mixing capability point of view, the neutral (90^{0}) kneader has the largest shear effect on the material, while the discharging element is the best distributive mixer. However, the conveying element has little mixing or shearing effect.

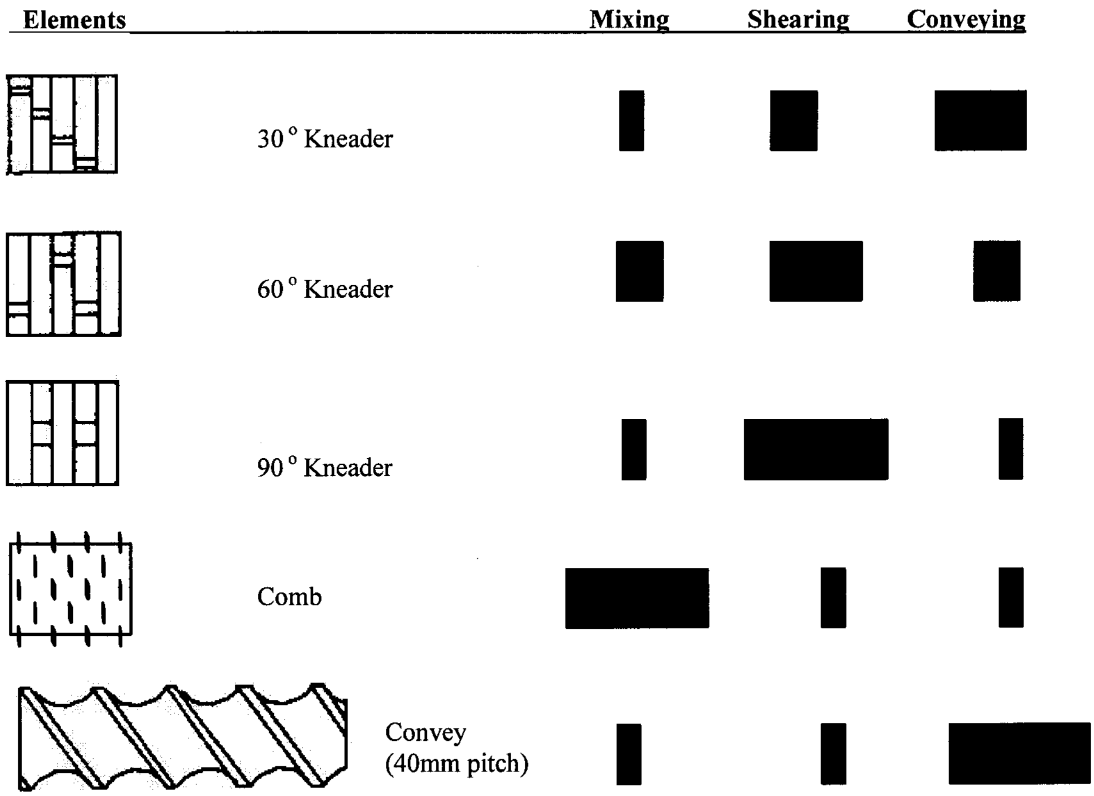


Figure 2.6 Mixing and conveying effect of forwarding screw elements, adapted from (Leistritz Inc. 1997)

2.2 Wet Granulation

2.2.1 Granulation Process

Wet granulation is a complex process with several competing physical phenomena occurring in a granulator which ultimately lead to the formation of granules. Granulation is defined as building up clusters from powders or powder/binder mixtures to produce a free-flowing cohesive material that can be further processed by compression or encapsulation (Mayur and Mollan 2003).

The mechanisms of granulation have been described previously by Sastry and Fürstenau (1977) which is now considered as classical theory. More details on these mechanisms have since been reported by several other researchers (Butensky and Hyman 1971; Mort and Tardos 1999; Tardos, Khan, and Mort 1997; Vonk et al. 1997). All of these theories could be summarized as cases of coalescence and/or breakage. Hence, granulation is commonly viewed as a combination of three sets of rate processes (sketched in Figure 2.7): i) wetting and nucleation; ii) consolidation and growth; iii) attrition and breakage (Iveson et al. 2001).

Wetting and nucleation introduce the liquid binder into contact with dry powder. Nucleation starts with one droplet. In this first step, the droplet reaches the powder bed and a nucleus is formed. This nucleus is a loose agglomerate and can be characterized by high porosity and low tensile strength (Vonk et al. 1997). In this process, the nuclei formation is a function of wetting thermodynamics and kinetics, while the binder dispersion is dependent on process variables (Liu et al. 2000). Granule growth is initiated when the solid mass is sufficiently wetted, and material

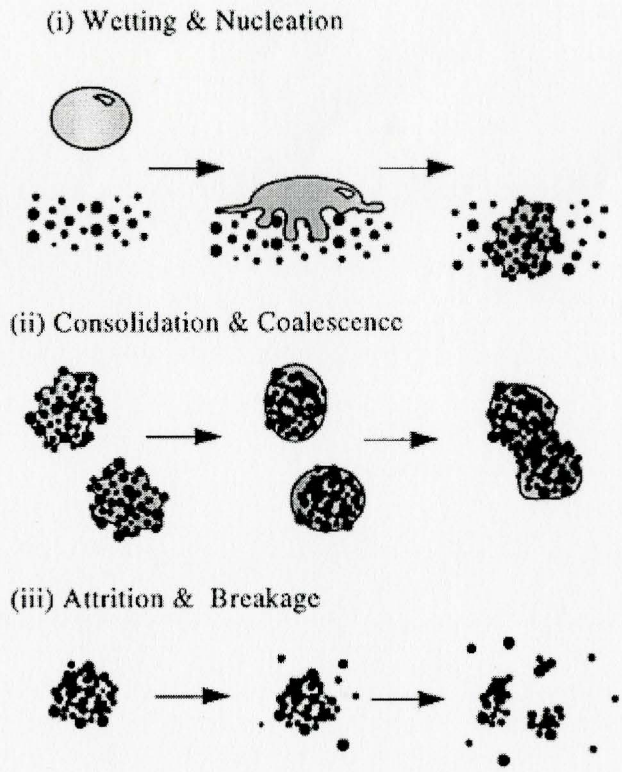


Figure 2.7 Schematic of granulation process (Iveson et al. 2001)

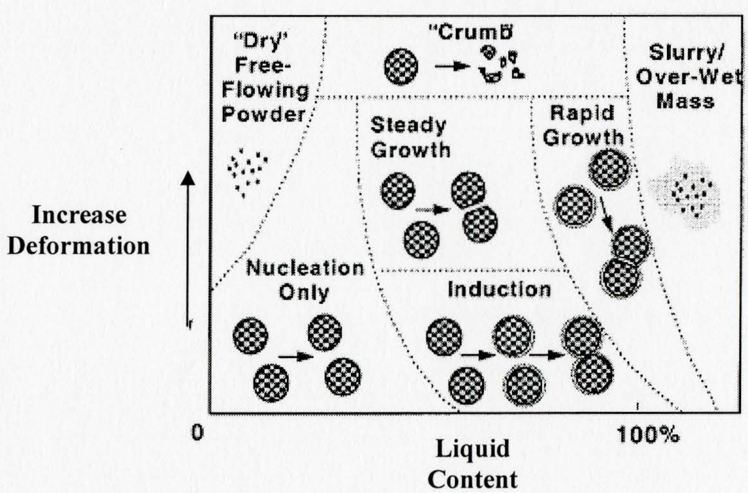


Figure 2.8 Granulation growth regime map, adapted from (Iveson and Litster 1998)

collides and sticks together in the granulator (Simons and Fairbrother 2000). As a result, the nuclei become more and more dense. Due to the densification, stronger pellets are formed which exhibit a higher chance of surviving from collisions in a mixer. Another consequence of the densification is that liquid is squeezed outwards to the granule surface, which increases the probability of coalescence (Vonk et al. 1997). In other words, the mechanical properties of the granules and the availability of liquid binder at or near the granule surface are two important factors for granule growth. Iveson and Litster (1998) proposed a granule growth regime map which conceptually described the resulting granule from the growth mechanism based on these two factors (shown in Figure 2.8). This regime map could be used to explain the commonly observed effects in granulation, e.g. how controlling the agitation speed and binder concentration would lead to a steady particle growth. In the last stage of granulation, the growth rate decreases as the tendency for particle break-up becomes imminent. Break-up includes breakage of wet granules and attrition or fracture of dried granules in the granulator (Tardos, Khan, and Mort 1997). Breakage of wet granules will influence and may control the final granule size distribution, while the attrition of dry granules generates dusty fines.

Particles prepared by the agglomeration of smaller particles represent the most common type of particles handled in pharmaceutical tablet production. In most of the tablet strength studies (Adams and McKeown 1996; Akande, Deshpande, and Bangudu 1991; Johansson et al. 1995), it has been suggested that the compressive strength is independent of pellet size. In Rehula's (1985) study, the strength of the tablet did increase when granules greater than 1.5mm were compacted. Johansson et al. (1998) found that larger pellets (in order of 1mm in their research) provided a higher deformability during the compression, which meant a lower porosity. This was due to increasing the size of particles will reduce the interparticle contact points during the compression and lead to increased pellet deformation. Therefore, 500μm-1mm is believed to be a desirable size range for this project.

2.2.2 Batch Processes, Fluidized Beds and High Shear Mixers

Tablets are the most widely used solid dosage form for pharmaceutical and nutraceutical ingredients because of their ease of manufacture and intake by patients. Wet granulation is the most popular technique to manufacture tablets, as it improves flow properties, reduces dust and segregation of particles and improves compressibility of powder mixtures (Keleb et al. 2004). The most common processes utilizing wet granulation techniques are high shear mixers and fluidized beds (Ennis 1996; Hegedus and Pintye-Hodi 2007; Knight 1993; Knight et al. 1998; Ritala et al. 1986) which both are based on batch operation.

Fluidized bed granulation of pharmaceuticals was first described by Wurster in 1959. In this type of granulation, the powder mix is maintained as a fluidized bed by air flow injected from the bottom. The binding liquid is sprayed above the powder bed, in a direction opposite to the air flow. A fluidized bed granulator is a very versatile piece of equipment because the mixing, wetting, and drying are all carried out in one unit (Faure, York, and Rowe 2001). However, by using a fluidized bed granulator, it is difficult to get high densification when processing low bulk density material. It is also characterized by a long residence time and high consumption of granulation liquid (Mayur and Mollan 2003). Scale-up and end point determination are still generally empirical and highly dependent on the experience of the operator.

In a high shear granulator, blending and wet massing are accomplished through high mechanical agitation by an impeller on the bottom of the unit and a chopper in the side wall. The shear and compaction forces exerted by the impeller provide the energy for mixing, densification and agglomeration. The chopper, on the other hand, cut the mixture clumps to aid the distribution of the binder and avoid excessive accumulation at the walls (Badawy et al. 2000). Because the process is considerably intensive, granulation must be controlled to prevent exceeding the end-point in terms of desired particle size. (Schaefer 1984). During granulation, sticky wet mass is thrown towards the wall, and the imbalance of impact pressure and the shear resistance of the nuclei will cause an inhomogeneity in the granule bulk density (Vromans, Poels-Janssen, and Egermann 1999). Nevertheless, during the last decade, high shear granulators have proven to be the first choice of the pharmaceutical industry.

2.2.3 Twin Screw Wet Granulation

The previously mentioned batch operations offer many advantages in respect of quality assurance as a batch can be rejected, both in plant and out in commercial markets, without substantial losses to the company. However, the scale-up of the batch processes from laboratory to industrial scale leads to many problems (Ameye et al. 2002; Leuenberger 2001). The variety in available batch mixers and many unit operations involved in batch preparation of tablets often does not facilitate the scale-up process. With the ever-increasing demand for solid dosage forms, the pharmaceutical industry is becoming more and more interested in continuous processes as they enable a larger production capability, reduced footprint and labour costs, and minimize scale-up concerns (Van Melkebeke, Vervaet, and Remon 2008). It is easy to take advantage of the existing experience of continuous production line in the food and plastic industry which have been well established already.

Extrusion is a well-understood processing technology that has been developed over the last century and commonly used in many industrial fields. The traditional use of extruders, and especially twin screw extruders, has been with the processing of foods and plastics. In the pharmaceutical industry the use of a twin screw extruder for wet granulation was first introduced by Gamlen and Eardley (1986). In the development of twin-screw extrusion for this field, current research has primarily focused on understanding the influence of process parameters and formulation variables on particle size and final tablet properties.

Kleinebudde and Lindner (1993) studied the influence of water content and screw speed on the performance of the extruder. Remon's research group at Ghent University (Keleb et al. 2002, 2004; Vermeire et al. 2005) studied the granulation of α-lactose monohydrate in a twin screw extruder using an aqueous polyvinylpyrrolidone (PVP) solution as a binding agent. Remon found that the granulation of lactose could be done with considerably less water in an extrusion process compared to a high shear mixer, which translates to lower drying times and lower operating costs. Optimizing the process parameters and the water concentration were required to obtain an acceptable yield, but had no important effect on the granule or tablet properties (Keleb et al. 2002). In regards to the extruder setup, the only variation to their machine design examined was whether their experiments included a die. Their screw design consisted of conveying elements with only a kneading block (one or two pair) included for mixing.

A research group at Pfizer (Shah 2005) studied wet granulation in a co-rotating twin-screw extruder and provided the first insight into the importance of screw design. They tested conveying elements and two mixing elements, kneading blocks (dispersive mixer) and discharging elements (distributive mixers). Kneading blocks tended to block the flow yet the discharging elements (otherwise known as comb elements) provided granulate discharge with evenly sized particles. In their study, liquid content was introduced by an injector mounted on the extruder, and mixed with excipient before entering the mixing zone.

In recent research by Melkebeke et al. (2008), the influence of kneading elements with different staggering angle on the mixing efficiency and tablet properties was investigated. It was observed that only a kneading block in the screw configuration was responsible for granule formation. Granule quality, such as friability, compressibility and porosity, obtained from kneaders with different staggering angle did not show significant variation. They also found that reducing the length of the granulation zone (8cm in their case compare to 38.5cm in Keleb's study (2004)) did not have a negative effect on granulation, and extra conveying elements after the mixing zone were essential to controlling granule size.

2.3 Discrete Element Method Modeling

Computer simulation allows the analysis of processes at a very small time and space scale and with no intrusion upon the system. Among all proposed simulation methods, discrete (or distinct) element method (DEM) appears to be a very promising technique for granular studies, being first introduced by Cundall and Strack (1979) to model particles of soil under shear. DEM simulates the individual particles making up a granular flow separately by numerically calculating their acceleration and displacement resulting from complex contact mechanics. Due to the relatively recent interest in granulation extrusion, no known models by DEM exist; however, related applications are known in the literature. Several researchers (Link et al. 2007; Tanaka, Kawaguchi, and Tsuji 1993) have studied the granulation process in a fluidized bed using DEM simulation while Gantt and Gatzke (2005) modeled the granulation process in a high shear granulator with the numerical technique and a new solids-conveying model for the single screw extruder was recently proposed based on DEM (Moysey and Thompson 2004; Moysey and Thompson 2005). However, at the point of writing this thesis, no published work on ICTSE exists in the open literature.

The main principles behind DEM are simple but very effective (Figure 2.9): consider all forces acting on a particle during a collision and integrate Newton's second law of motion in combination with constitutive expressions for its compliance to determine position and orientation (Stevens and Hrenya 2005). The following forces can be taken into account by this method: gravitation, contact forces due to collisions, solid–solid interactions such as electrostatic, Van der Waals, cohesive forces and bridging due to humidity or high-temperature operations and fluid–solid interactions in multiphase flows (Di Renzo and Di Maio 2004). The DEM approach is based on molecular dynamics, and it overcomes some of the disadvantages of continuum mechanics methods such as Finite Element Method (FEM) which ignore the individual characteristics of granular matter and rely on highly simplified bulk assumptions (Zhang and Li 2006). Therefore, it is considered to be an ideal method to analyze discontinuous granular systems.

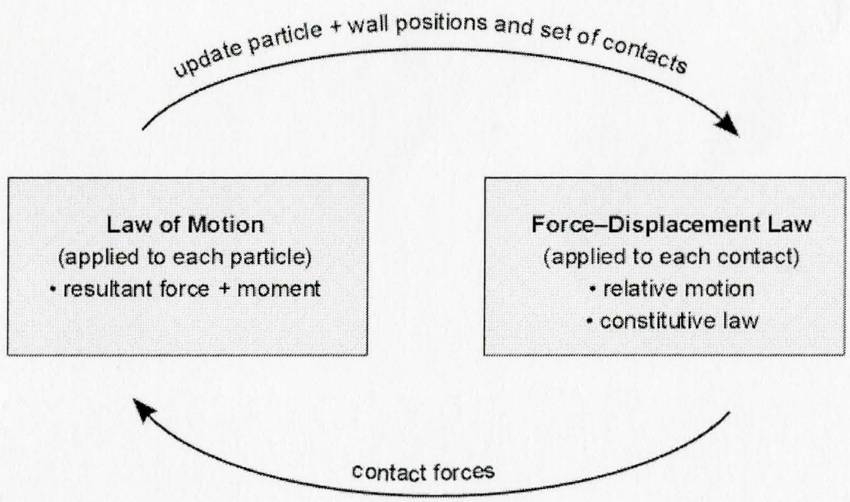


Figure 2.9 Calculation cycle of DEM simulation (Itasca Inc. 2004)

The main drawback to DEM is its high computing demand, because the method inherently uses an explicit time integration scheme and repeats sequential calculations over a limited time period with very small time steps (Asmar et al. 2002). However, due to ever-increasing computer power, the DEM approach is becoming more attractive though currently the number of particles that can be reasonably simulated remains significantly limited.

Chapter 3 Experimental Procedure

3.1 Materials

There were only two materials involved in the work. α-Lactose monohydrate was used as the model excipient (EMD Chemicals Inc., CA). Polyvinyl-pyrrolidone (PVP) 100 GM (Alfa Aesar, M.W. 40000) was selected as the binding agent. No model active ingredient was included. The particle size distribution of lactose is shown in Figure 3.1 where the average particle size was 97μm ± 10%.

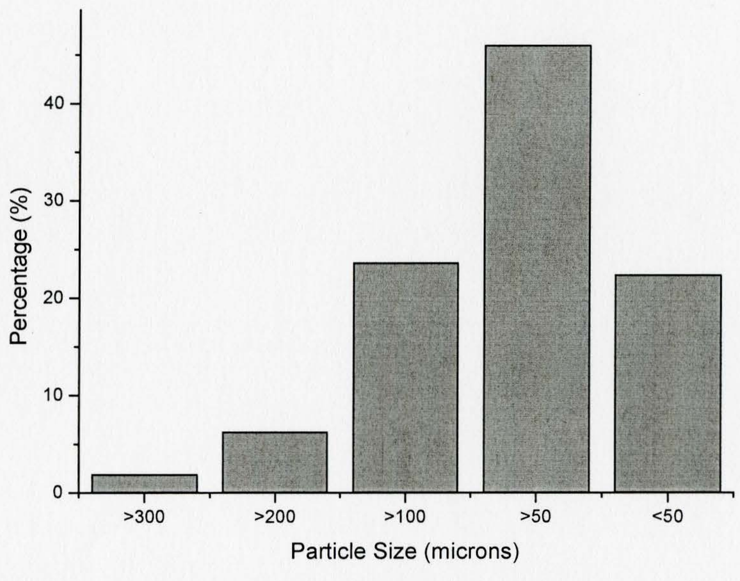


Figure 3.1 Particle size distribution of original lactose powder

3.2 Experimental Procedure

3.2.1 Material Preparation

The PVP was dispersed into an aqueous solution in order to blend it with the excipient. The prepared binder solution consisted of 33 wt% PVP in distilled water, and this ratio was held constant for all experiments discussed in this thesis. The PVP solution was blended at 5-12% (w/w) with lactose and fed into the twin screw extruder by one of three approaches: a) **Hand preblend** where the binder solution was first tumble blended with lactose by hand, and then added into the twin screw extruder from a Brabender T20 twin-screw gravimetric feeder; b) **Dropwise method** where the lactose was dry-fed by the aforementioned gravimetric feeder while the binder solution was delivered to the extruder by a low-flow peristaltic pump (Masterflex C/L) at a specified speed that was pre-determined; and c) **Spray method** where the lactose was dry-fed by the Brabender gravimetric feeder while the binder solution was delivered by a dual-manifold spray nozzle which was connected along with compressed air to the aforementioned peristaltic pump, and sprayed at a certain pumping speed and air pressure as the lactose fell into the feed zone of the extruder. The feeding system is sketched in Figure 3.2.

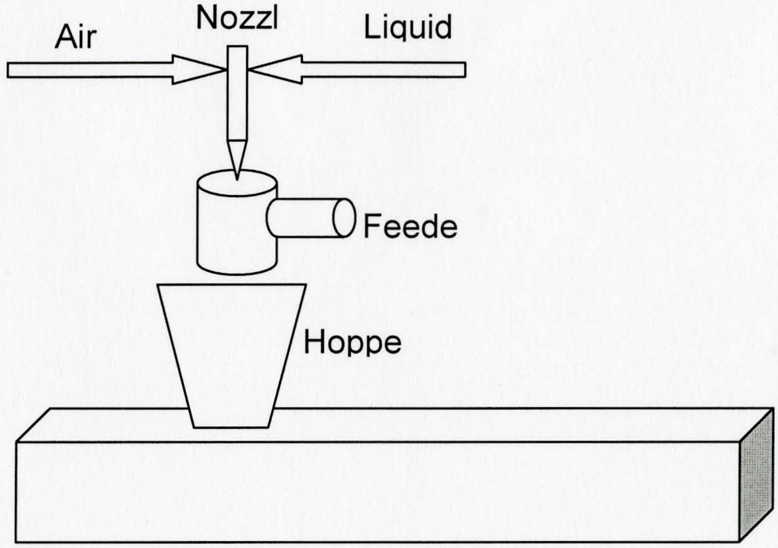


Figure 3.2 Apparatus position of feeding system

3.2.2 Wet Granulation

The experiments were performed in a 24 L/D Leistritz ZSE 27-HP co-rotating twin screw extruder using a simple screw profile, with an example shown in Figure 3.3. The early screw elements prior to the feed opening (not shown in figure) were intended to act as a powder seal, preventing lactose from being transported back towards the gear box. Different screw designs were examined which differed in the elements located at a position along the screw that was 180 mm from the tips. This location was chosen due to its correspondence with a vent opening in the barrel, allowing visual observations to be made as the tests proceeded. This zone of interest was the primary mixing area with only conveying elements located before and after to move the lactose forward. All the elements examined had a length of 30mm and were laid out as a single pair or double pair. The element types tested were: 1) conveying elements (conveyer) with a 30mm or 40mm pitch, 2) kneading blocks (kneader) with individual bimodal elements that were 30^{o}, 60^{o} or 90^{o} offset from one another, 3) discharging (comb) elements, either forwarding or reversing in their flow capacity, and 4) chopping element (chopper). Figure 3.4 shows examples of each element type. The temperature of all zones of the extruder was kept at $30^{o}C$ by water cooling. The throughput rate was held constant at 2 kg/h while the screw speed was set to either 30 RPM or 80 RPM; the degree of channel fill was set to either 30% or 70% by these screw speed and flow rate conditions. Sampling was started after 5min of running in order to first reach a steady processing state.

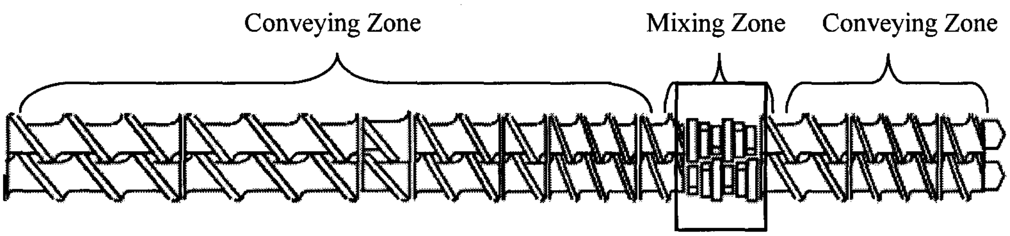


Figure 3.3 Example screw design with the highlighted section indicating the variable zone.

Generally, there were four varied factors in this granulation system: 1) screw profile, 2) binder concentration, 3) screw speed and 4) binder blend method. Particle size distribution (PSD) was the primary method of evaluation and in order to differentiate the results for the zone of interest from drag and compressive flow effects earlier in the process particle sizes were also evaluated at the gravimetric feeder outlet and the conveying elements before mixing zone. To get the PSD of the material at feeder outlet, samples were directly collected while the feeder running. To obtain the PSD of material before the mixing zone, the extruder was stopped after every 3min of running at which point the two screws were pulled out and samples were collected from the elements of concern. Sampling before the mixing zone was repeated numerous times until enough material was collected for testing purposes.

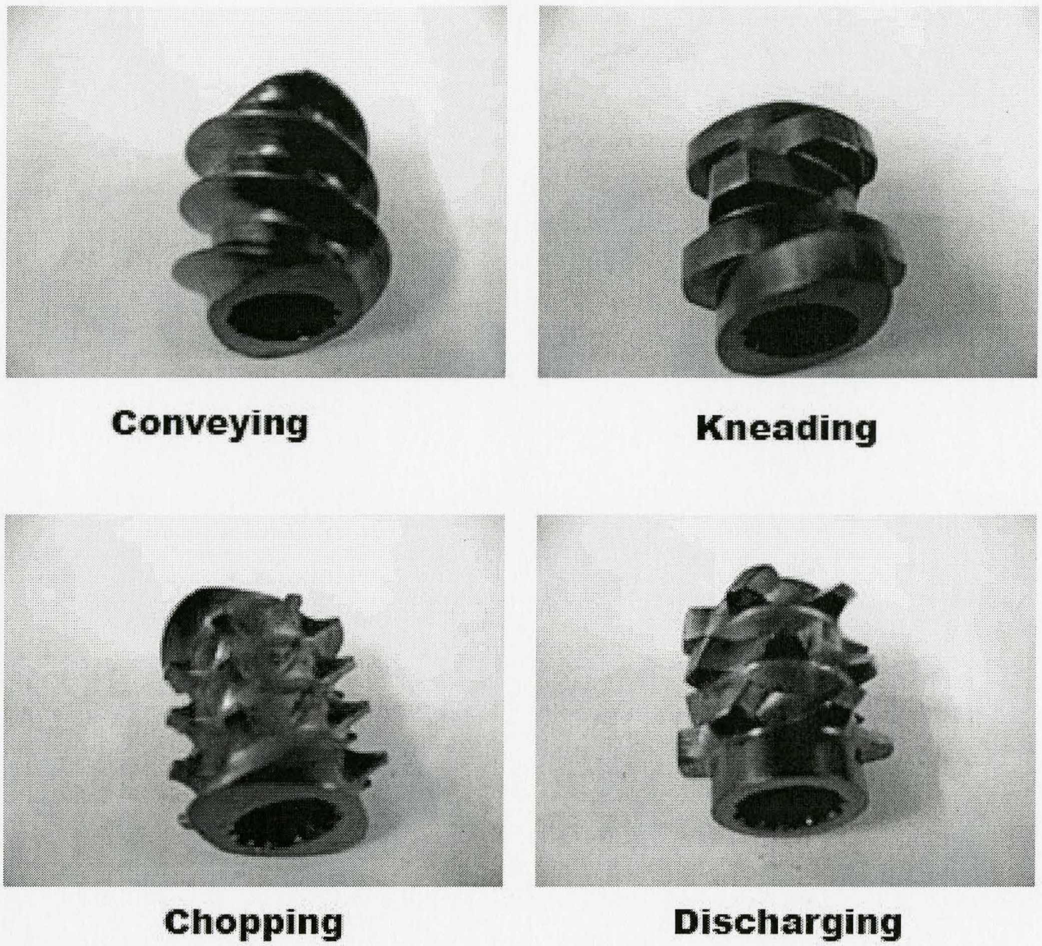


Figure 3.4 Examples of different screw elements

In order to study the influence of a screw element design on granulation, all elements were tested under 7.5 wt% binder condition (based on optimal operating conditions determined by Keleb et al. (2002, 2004)) prepared using the hand preblend method. To study the influence of binder concentration, a smaller subset of elements were selected, namely the conveying element with 30mm pitch, kneading element with 60 ° offset, forward discharging element and chopping element, to be studied using 5 wt%, 7.5 wt%, 10 wt% and 12 wt% binder added to the lactose, with all materials prepared by the hand preblend method. The influence of screw speed was studied concurrently within both of the two aforementioned studies. The different methods of adding the binder solution proved too difficult to use the same conditions for all runs and so will be discussed fully in Chapter 4.

3.3 Characterization

3.3.1 Particle Size Distribution

After collecting the granulated samples, they were air dried overnight at room temperature. The particle size distribution was determined by mechanical sieving using screens of differing mesh size (W.S. Tyler Inc. Model RX-29). The screens employed had the following opening sizes: 1180μm, 850μm, 500μm, 300μm, 250μm, 150μm, and 125μm. The sample amount was maintained approximately 100g and sieved by mechanical agitation for 20min. After this procedure, samples on every sieve were weighed and collected into separate bags.

3.3.2 Granule Shape

The shape of granules prepared under the different test conditions were inspected by a reflective light optical microscope (ZEISS Axioplan 2). Samples were mounted on slide and dispersed to prevent overlap. At least three regions were randomly picked from the sample on the slide for analysis. Digital micrographs were taken by light microscope from these regions with magnification of 25, and analyzed by commercial image analysis software: Eclipse, which provided major and minor axial dimensions and shape factor data.

Granule shape is compared in this thesis by means of particle micrographs and plots of shape factor. The shape factor of a particle in this thesis is defined as the ratio of minimum radius (the shortest radius pass the center of gravity) over maximum radius (the longest radius pass the center of gravity) of a particle, which means thread shape will have a 0 shape factor whereas shape factor of sphere is 1. Since particles sizes ≤ 300μm were largely spherical (as noted in Chapter 4), discussions of particle shape will be limited to sizes between 500μm - 1180μm. Larger particles were too few in quantity to make accurate measurements. In general, the presented shape factor of a single size range (i.e. 850μm, 500μm or 300μm) is the average shape factor of all the particles from three randomly selected micrographs of this size range.

3.3.3 Angle of Repose

The angle of repose provides a measure of the cohesive nature for granular material, though it includes sensitivity to sedimentation and particle shape. Both static and dynamic measures of the angle of repose have been conducted by researchers (Lavoie, Cartilier, and Thibert 2002; Liu, Specht, and Mellmann 2005;

Yang, Zou, and Yu 2003); however, only a dynamic value was sought in this work due to the nature of our granulation process. As there is no standardized methodology for this measurement, the determined values can only be considered for comparative purposes. Selected dried granules were tested in a rotation drum (aluminum surface with an inner diameter of 10cm) under room temperature for the angle of repose. The amount of material used was 40g (approximately 1/3 of the drum). The speed of the drum was set to 14 RPM. To measure the angle of repose, images were captured from recorded video. The angle relative to vertical plane was determined by image analysis software: SigmaScan.

3.3.4 Fluorescence

The fluorescent property of the extruded granules was examined by light microscope with a fluorescent filter in order to evaluate the uniformity of the binder coating. Samples were mounted on a slide and dispersed to prevent overlap. Experiments were conducted in a dark room. The PVP used in the current study exhibited fluorescent properties while the lactose did not, so measurement configurations, such as exposure time, were determined with pure PVP. For every granulated sample, at least five locations on the slide were randomly selected and digital micrographs with and with out filter present were taken.

3.3.5 Tablet Strength

In order to evaluate how particle shape and size influenced tablet compressive strength, samples were tabletted in a Carver Lab Press with 1000kg (2205lb_f) force. Six tablets were pressed for every sample, which each had a 300mg weight and dimensions of 12.00mm (dia.) x 1.90mm (thickness). The mechanical testing apparatus (Instron 3366) configured for compressive test is illustrated in Figure 3.5. The rate of compression was set to 0.50mm/min and the 4.5N load cell was used. Tablets were fixed to the same position before every test. Experiments procedure and data acquisition were controlled by computer, test was stopped when the tablet reach its break point.

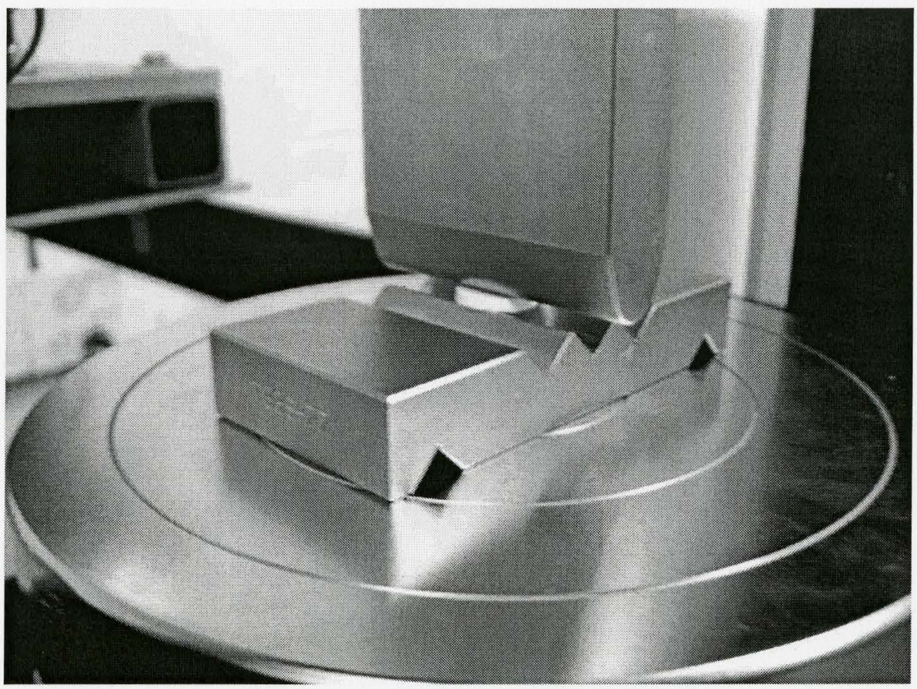


Figure 3.5 Apparatus for tablet compressive strength test

3.4 DEM Simulations

To gain a qualitative understanding of the dynamic behavior of particles in the conveying elements and kneading elements of the twin screw extruder and how the resulting particle shapes arose, these two element types were simulated in commercial two-dimensional DEM simulation software package: PFC^{2D} Ver. 3.1 by Itasca Consulting.

With too little data available on the particle properties for lactose, particularly with binder where the inter-particle features of viscous bridging forces dominate, the simulations were only intended to provide qualitative arguments focused on major factors leading to agglomeration and not accurately simulate all of the material behavior in the extruder. Further characterization of the micromechanics for the system needed to improve our model with cohesive particle behavior.

Readers are referred to the original paper by Cundall and Strack (1979) upon which the software package is based, for more details on the model. The linear spring-and-dashpot contact force-displacement model was selected for the work using normal stiffness coefficients (k_n) of 5 x 10^4 (particle) and 2 x 10^{11} (wall), and tangential stiffness coefficients (k_t) of 5 x 10^4 (particle) and 2 x 10^{11} (wall). The values were determined by the commonly used data and intended to build a 'hard' wall and 'soft' particle environment. The internal and external coefficients of friction were set to 0.9 and the circular particles were simulated with a diameter of 200μm (twice the measured lactose average diameter for easy to identify in the simulation). 3000 particles were included in the system. A sample code is appended (Appendix I).

Chapter 4 Results and Discussions

4.1 Introduction

As stated in Chapter 3, a series of experiments were designed based on statistical methods and carried out to examine the effects of four primary factors: 1) screw profile, 2) binder concentration, 3) screw speed and 4) binder blend method (i.e. method of binder addition to the lactose). The experiments that examined 5 wt% and 12 wt% binder concentration were two extreme conditions used to confirm the boundaries of the processing window for wet granulation of lactose. Unfortunately, at these extreme conditions no stable throughput conditions were obtained and so not all tests could be fully completed on these samples. Samples obtained from these experiments will be included in Section 4.6. Similarly, trials conducted to test dropwise and spray blend methods could not establish stable output conditions under our experimental environment. These experiments will also be discussed in Section 4.6. The majority of analysis was completed for the conditions using 7.5 wt% and10 wt% binder concentrations prepared by the hand preblend method, as these two levels of the binder resulted in stable extrusion operation without blockage or exceeding the torque limits of the machine. All experiments are listed in Table 4.1.

Table 4.1 All experiments conducted by hand preblend method

Elements	Conveyer (30mm pitch)	Kneader (30^o)	Kneader (60^o)	Kneader (90^o)	Comb Forward	Comb Reverse	Chopper
7.5% Binder, 30RPM	Y	Y	Y	Y	Y	Y	Y
7.5% Binder, 80RPM	Y	Y	Y	Y	Y	Y	Y
10% Binder, 30RPM	Y	N	Y	N	Y	N	Y
10% Binder, 80RPM	Y	N	Y	N	Y	N	Y

* Y means this condition is tested while N means not tested.

The following Sections 4.2-4.5 will provide a detailed discussion on the characteristics of the granules obtained, based on: particle size, granule shape, particle flowability and mixing quality. The granules were also pressed into tablets, and their compressive strength was examined. Section 4.7 provides qualitative discussion on the result based on DEM simulations. In the determination of particle size, numerous replicates of experiments were used. For the analysis of particle size distribution, the maximum standard error was 10%. The highest error coincided with the distributive mixers, comb and chopper elements. This is due to the non-uniformity of the agglomerate shape and the breakage effect of the distributive mixers which produced more fines than the dispersive mixer (kneading block). In the evaluation of granule shape, the maximum standard error was 0.2 which primarily appeared in larger granules. This is due to the fact that large granules possessed more irregular shapes and fewer particles could be included in the measuring area (i.e. field of view) compared to the fines. Other errors were presented on the corresponding charts.

4.2 Particle Size Distribution

4.2.1 Introduction

The effect of the different shear field of each element had on granulation, i.e. balancing particle growth versus rupture, was primarily assessed by particle size determination (PSD). Before comparing PSD in the mixing zone, particles were examined upstream to ensure a proper relationship between particle size and shape, and the intended mixing element could be established without artifacts related to conveying.

4.2.2 Particle PSD before Mixing Zone

This section is limited to analysis of samples collected from the feeder and from conveying elements located at 270mm and 360mm from the screw tip. Two different screw designs were used so that samples from 30mm or 40mm pitch conveying elements could be collected. The samples collected at the conveying elements were done by pulling out the screw from extruder (not collecting them from the die exit as other analysis sections). Conveying zones (both in the feeder and extruder screw) were not expected to have a major effect on granulation, but this section provides a baseline for all further discussions related to PSD in this thesis. Based on the optimal operating conditions determined by Keleb (2002, 2004), the experiments used a 7.5 wt% binder solution with the lactose, prepared by hand and drum tumbling. The screw speed for the tests discussed in this section was maintained at 80RPM.

The measured PSD for samples from the feeder exit and indicated screw elements are summarized in Figure 4.1. Considering the beginning particle size for the original lactose was 97μm (mean value), the PSD for material exiting the feeder indicated that by the hand pre-blending method less than half of the lactose particles were not already agglomerated into larger particles, the majority of the grown granules in the 500-800μm size range. Upon reaching the conveying region in the extruder screw used in this test, very little difference had occurred in particle size from the feeder exit, with a minor increase in the number of particles in the 500-800μm size range, preferentially for the conveyer with a 40mm pitch. The greater free volume of this larger pitched element resulted in lower shear acting on the particles and gave less opportunity for agglomerate rupture. In general, it would appear that any major increase in particle size found larger than those exiting the feeder in the subsequent sections of this study must be largely attributed to the introduced mixing elements and should not being considered affected by the conveying elements present in the screw leading up to the mixer or afterwards.

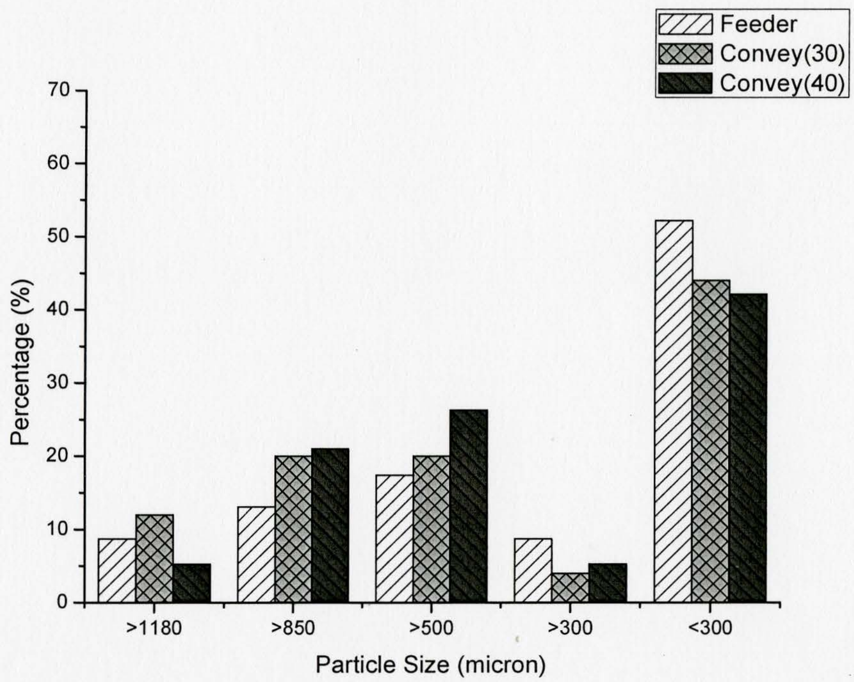


Figure 4.1 Particle PSD before entering mixing zone

4.2.3 Influence of Screw Profile

Elements in the mixing zone, either as a single pair or a combination of two pairs of elements, were studied to see how they affected particle growth and final particle shape. All experiments disclosed in this section were under 7.5 wt% binder concentration and 30% degree of channel fill (80RPM). All particle size distribution corresponded to samples collected at the die exit of extruder (180mm downstream of the mixing zone).

Figure 4.2 shows the PSD for different sets of kneading blocks with element staggers of 30°, 60°, and 90° offset. Use of any type of kneading block led to greater growth of particle size compare to conveying elements. Surprisingly, there was little difference between the three block types despite their different capacity for drag

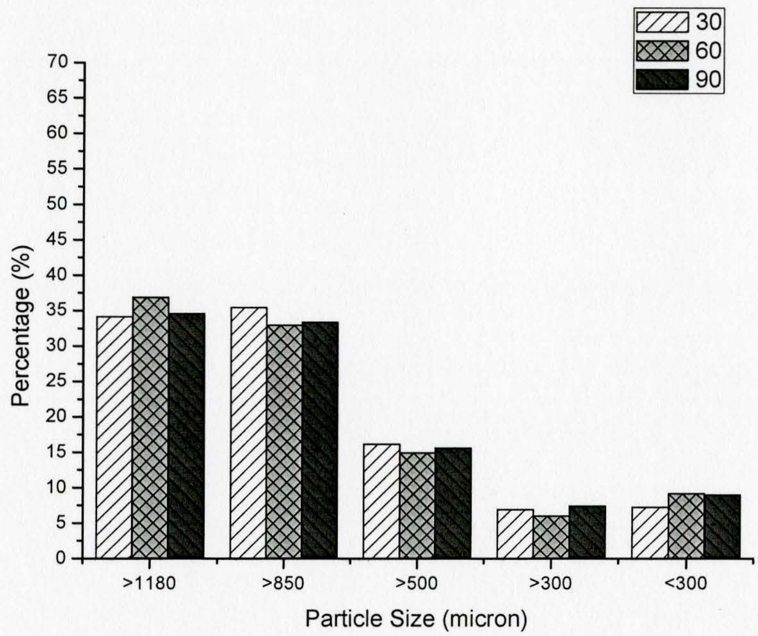


Figure 4.2 PSD for a set of kneading block

versus pressure-driven flow (refer to Figure 2.4). Similar findings were reported by other researchers (Van Melkebeke, Vervaet, and Remon 2008). This means that although the paddles were offset by different angle, the identical flight tips applied similar shear effect to the material. This is quite different from polymer melt which gains differing extent of mixing due to variance in the extensional flow through the kneader gaps. Therefore, in the subsequent results only the 60° kneading block will be discussed, and denoted simply as a kneading block (kneader) for brevity.

A set of discharging elements (combs) were examined. Unlike the kneaders which are intended for dispersive mixing, these combs provide the necessary spatial reorganization for distributive mixing. The open paths cut through the rings of the comb enabled the interaction of material between two streams, ultimately leading to a low degree of segregation. Forward combs were found to bring about particle size growth while the reverse combs could not provide useable throughput. With the reverse combs, although the slot cuts in the ring will let material flow forward, too much backwards pressure occurred due to the reverse geometry. The powder became densely compacted, thus preventing the rupture mechanism from controlling particle size. The exiting granules looked like roll-like reptating chains. Figure 4.3 compares the PSD for forward and reverse comb elements. Subsequently, in following sections only the forward discharging style of comb element will be discussed and denoted simply as a discharging element or comb for brevity.

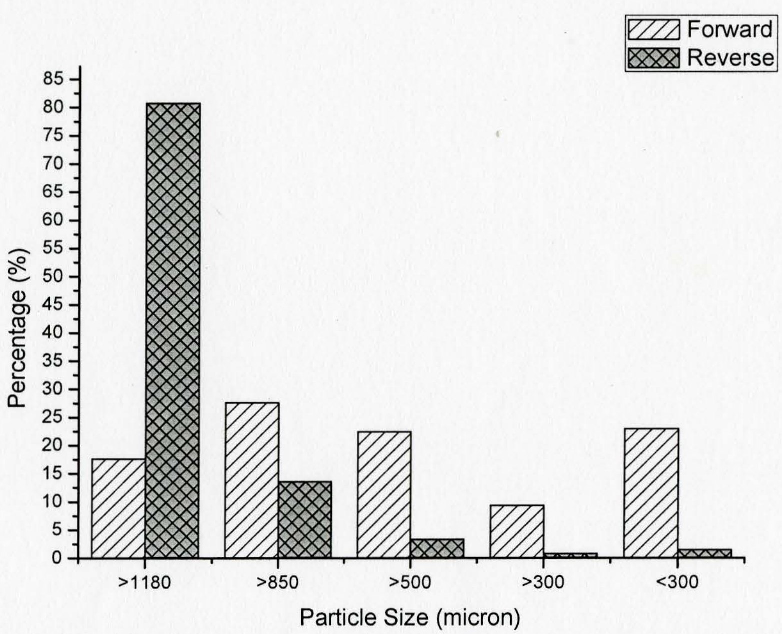


Figure 4.3 PSD for forward and reverse discharging elements

Figure 4.4 allows a comprehensive comparison to be made of the featured elements: kneading element, discharging element, 30mm conveying element and chopping element while Figure 4.5 directly compares the kneading element and discharging element and their respective combinations. With the highest shear force and fully filled mixing area, a kneader brings about the most significant particle size growth. Over 70% of the particles were larger than 850μm in size and the lowest amount of particle fines were found among all the elements. On the other hand, screw design with complete conveying elements bring about very little agglomeration, limited to the 500-800μm range, and thus appear primarily suited to pumping only. For the comb and chopper, both of these elements are classified as distributive mixers. The chopper resembles a conveying element but has interrupted helical flights and much narrower flights (refer to Figure 3.4). In comparison to a conveyor, comb exhibited a similar fraction of fines (particles under 300μm) but has a greater capacity to produce much larger granules (over 850μm). Conversely, comparing the comb with a kneader, it showed more controlled granulation with balanced granule growth and rapture mechanisms. The slot cuts not only enabled back flow and good mixing, but the flights also provided areas for certain consolidation and growth. Unexpectedly, the chopper has a negative influence on particle growth, leading to a high concentration of fines in the product than even exiting the feeder. The high degree of breakage was attributed to the small flight tip width and slot cuts of this unique element.

In Figure 4.5, for the kneader and comb combination, comb was placed immediately after kneader on the screw. The fraction of granules larger than 1180μm was reduced significantly by this combination compare to a single kneader profile. The consolidated granules after the kneader were broken up upon entering the comb.

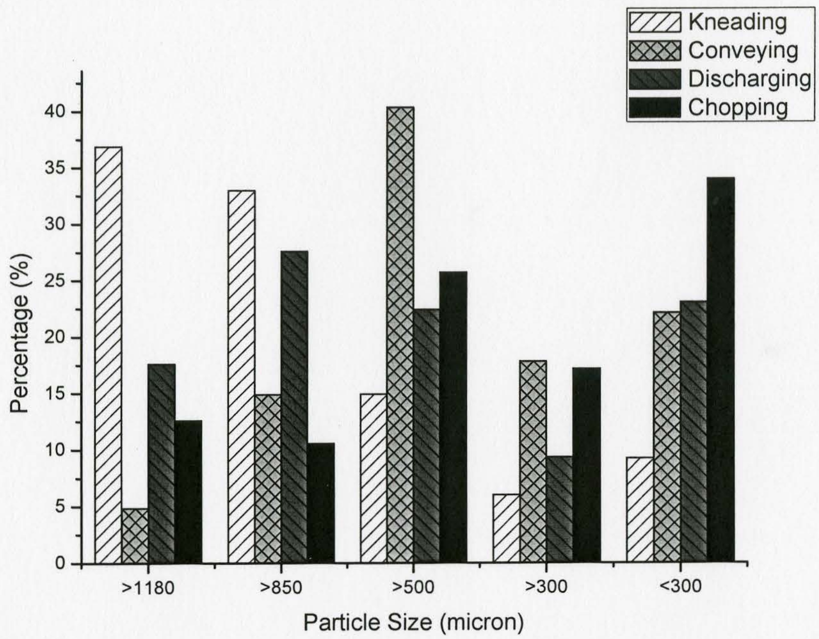


Figure 4.4 Comprehensive comparison of featured elements

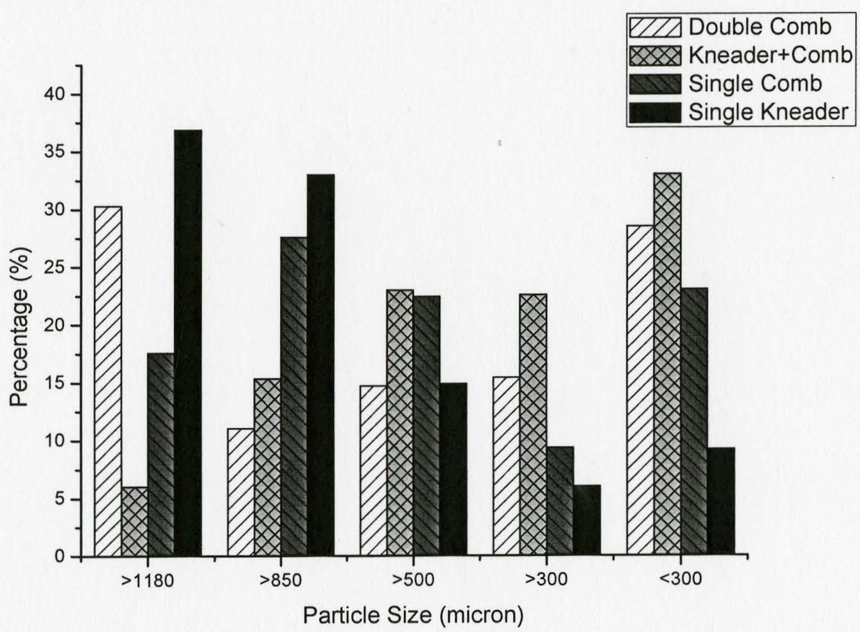


Figure 4.5 Comparison of elements combinations

It was thought that there was not sufficient binding agent present for continued agglomeration after breakage which led to over 50% of the granules being were under 500μm in size. In contrast, by extended mixing zone with two combs provided a notable increase of particles size over 1180μm in comparison to a single comb; both the coarse (over 1180μm) and fine (under 300μm) particles were increased by the double comb configuration.

Based on the discussion, all the examined elements were distinguishable from each other. Production by kneading elements (dispersive mixer) led to major particle sizes in the 850-1180μm range, while discharging elements led to smaller particle sizes between 500-850μm. Chopping elements and conveying elements could not provide enough granule growth, and the particle size was lower than 500μm for conveying elements whereas chopping elements produced primarily fines, with particle sizes lower than 300μm.

4.2.4 Influence of Screw Speed

By altering the screw speed between 80RPM or 30RPM, the mixture of lactose and binder was able to maintain a 30% or 70% degree of channel fill in the extruder. This degree of fill refers to the average fraction of the screw's free volume which is filled by material - it does not refer to the volume fill in the mixing zone which was always 100% filled. All experiments disclosed in this section were conducted using the 7.5 wt% binder concentration. All particle size distributions corresponded to samples collected at the die exit of the extruder.

Figure 4.6 to Figure 4.9 compare the PSD for featured elements under 30% or 70% degree of channel fill (80RPM or 30RPM). Generally speaking, screw speed had less effect on the dispersive mixing than distributive mixing. Higher rotational speed caused lower channel fill (in the conveying zones) and shorter residence time. According to the granulation growth regime map (refer to Figure 2.8), increasing deformation (i.e. increasing rotational speed) will decrease the growth and lead to more breakage. For the conveyor, comb and chopper, shortening the residence time reduced the chance for coalescence in the mixing zone and the increased shear led to more breakage. Hence, at 80RPM, all three screw element types showed a decrease in particles larger than 850μm and an increase in fines (particles smaller than 300μm). Conversely, for kneader the dominant granule growth is driven by the shear force exerted by the kneading paddles. Since the increased rotation speed did not change the shear effect too much, only a minor effect could be seen on the PSD.

In conclusion, increasing screw speed had a minor effect on kneading blocks however will enhance the distributive mixing in the other elements.

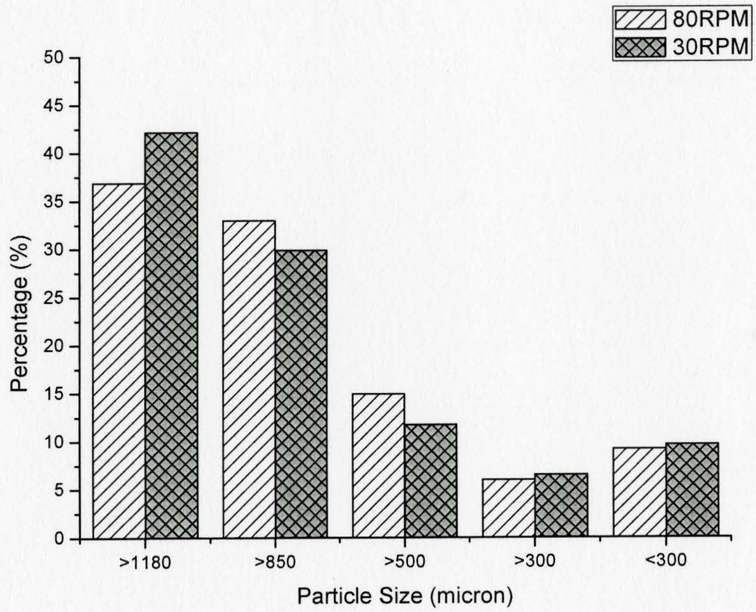


Figure 4.6 PSD for kneading elements under different screw speed

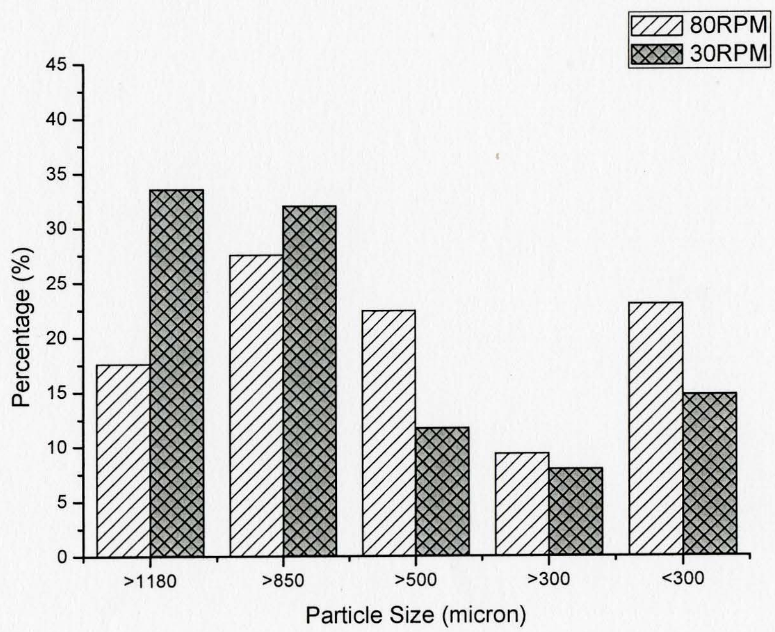


Figure 4.7 PSD for discharging elements under different screw speed

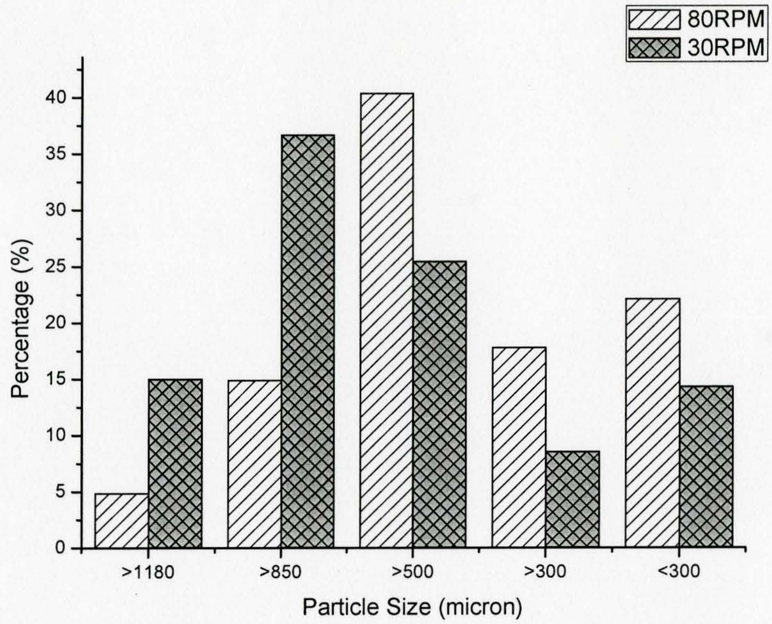


Figure 4.8 PSD for conveying elements under different screw speed

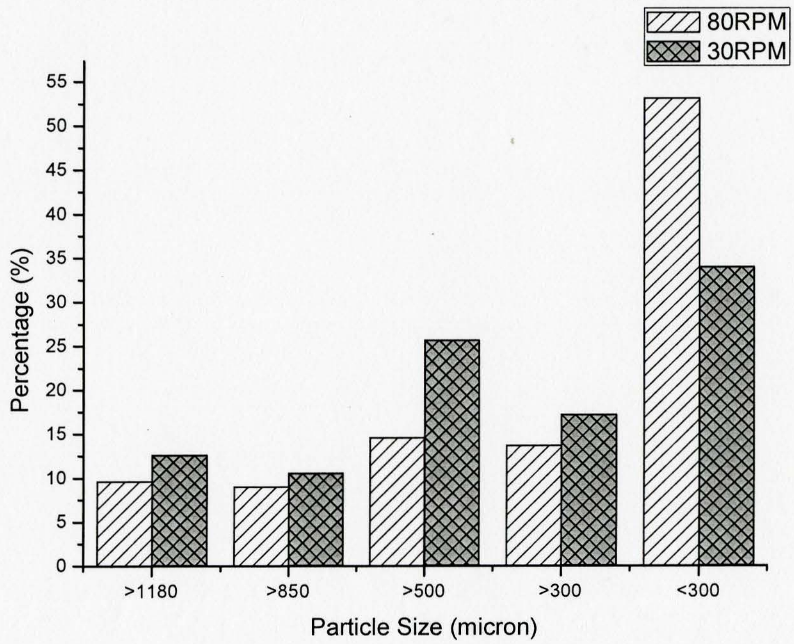


Figure 4.9 PSD for chopping elements under different screw speed

4.2.5 Influence of Binding Solution

This section will explain how the concentration of the binder solution in the lactose affected particle size distribution. Only single mixing elements were tested and all particle size distributions corresponded to samples collected at the die exit of the extruder.

Figure 4.10 to Figure 4.13 compare the PSD for featured mixing elements under 7.5 wt% or 10 wt% binder concentration. It was found that high binder concentration significantly contributed to the size enlargement process; there was a notable increase in the fraction of large granules in a sample from all of the elements tested. For the kneader and comb, over 50% of the measured particles were now larger than 1180μm. The chopper produced the majority of particles in the 300-850μm size range with a substantial decrease in the number of granules smaller than 300μm. Even by conveying element did the samples show a gain in particles larger than 1180μm. This can be easily explained by the higher liquid content enhancing the consolidation process. The oversaturated nuclei continually maintained binder at their surfaces, and the size enlargement process would not finish until the density of the granules exhausted the binder supply. More binding content also bring higher liquid bridge forces, which resulted in larger granules being capable of surviving collisions with other particles or the element flights. Hence, lower fines were found for all mixers.

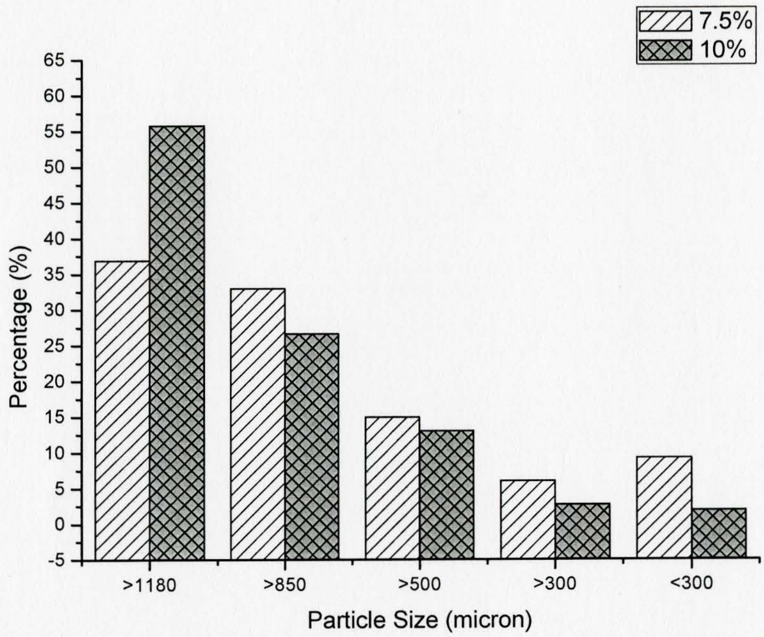


Figure 4.10 PSD for kneading elements under different binder concentration

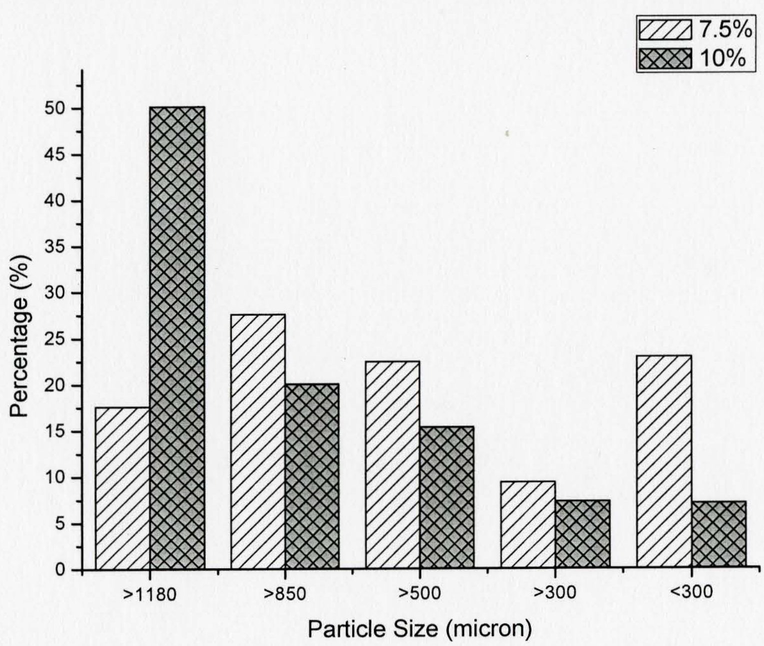


Figure 4.11 PSD for discharging elements under different binder concentration

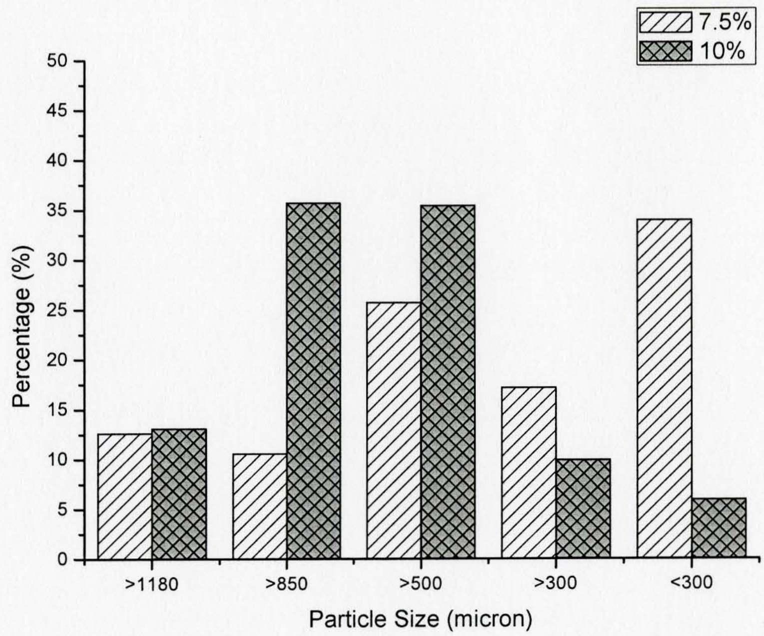


Figure 4.12 PSD for chopping elements under different binder concentration

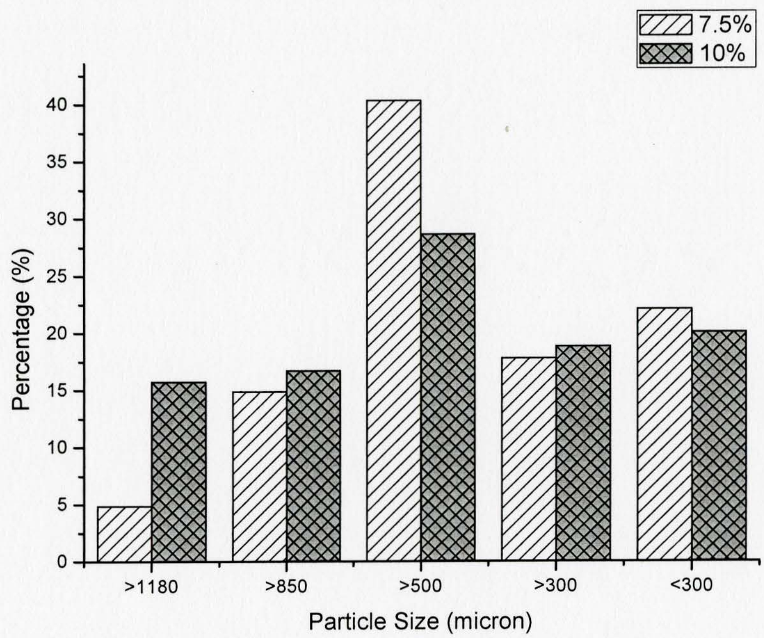
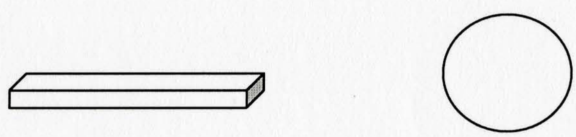


Figure 4.13 PSD for conveying elements under different binder concentration

4.3 Granule Shape

4.3.1 Introduction

It is generally well understood in the literature that granules (agglomerates) in the order of 1 mm in size are desired to reduce porosity in a final compressed tablet (Johansson, Nicklasson, and Alderborn 1998); however, there is very little information regarding particle shape. Particles were found to vary in shape from spheres to ribbon shape depending on the screw profile used in the extruder. Conceptual examples of each shape are shown in Figure 4.14. The following section discusses how the screw profile and binder concentration affected the particle shape. Granule shape is compared by means of particle micrographs and plots of shape factor. The shape factor of a particle here is defined as the ratio of minimum radius (the shortest radius pass the center of gravity) over maximum radius (the longest radius pass the center of gravity) of a particle, which means thread shape will have a 0 shape factor whereas shape factor of sphere is 1. A preliminary tablet compressive strength test was conducted to investigate the influence of particle shape on tablet strength.



(a) (b)

Figure 4.14 Demonstration of the particle shape, (a): ribbon shape (b): sphere

4.3.2 Influence of Screw Profile

Figure 4.16 to Figure 4.23 shows images of samples received from the different elements with 7.5% binder concentration and a 30% degree of channel fill (i.e. 80RPM). A series of images show representative particles in the range of 1180μm, 850μm and 500μm. Samples were randomly selected. According to the displayed particles, we could see kneading blocks produced elongated ribbon shape granules, though differences in the offset, i.e. 30°, 60° and 90° had no effect on particle shape. This shape is due to the squeeze forces applied to the material as it passes between the individual elements and the barrel wall. Granules from conveying elements were mostly spherical, but some resembled short rods. On the other hand, forward discharging elements, which primarily performed both packing and splitting functions, produced only spherical particles; however, as a result of high backwards force, reverse discharging elements formed large rolls of reptating chains (i.e. snaking coils). Chopping elements produced spherical granules similar to their conveying element counterparts. As a result of the distributive mixing in the comb element, granules from the kneader/comb and comb/comb combinations were also spherical. According to the mixing ability of elements (shown in Figure 2.6) and the particle shape results given, it was concluded that the presence of a distributive mixer (i.e. comb and chopper) will lead to spherical granule while the dispersive mixer (i.e. kneader) will produce elongated shape granules.

Figure 4.15 gives the determined particle shape factor for the featured elements (lines included only for clarity). They are consistent with the microscope observation above: the kneader produced the most irregular shape, and conveyor presented a constant shape factor in all particle size ranges examined. Comb and chopper both presented mostly spherical shape factors.

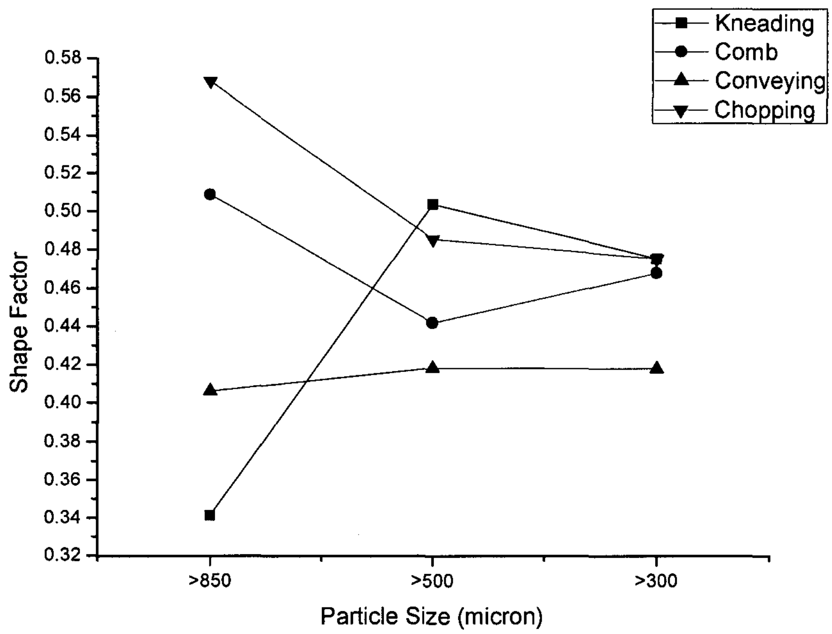


Figure 4.15 Particle shape factor for featured elements under 7.5 wt% binder concentration

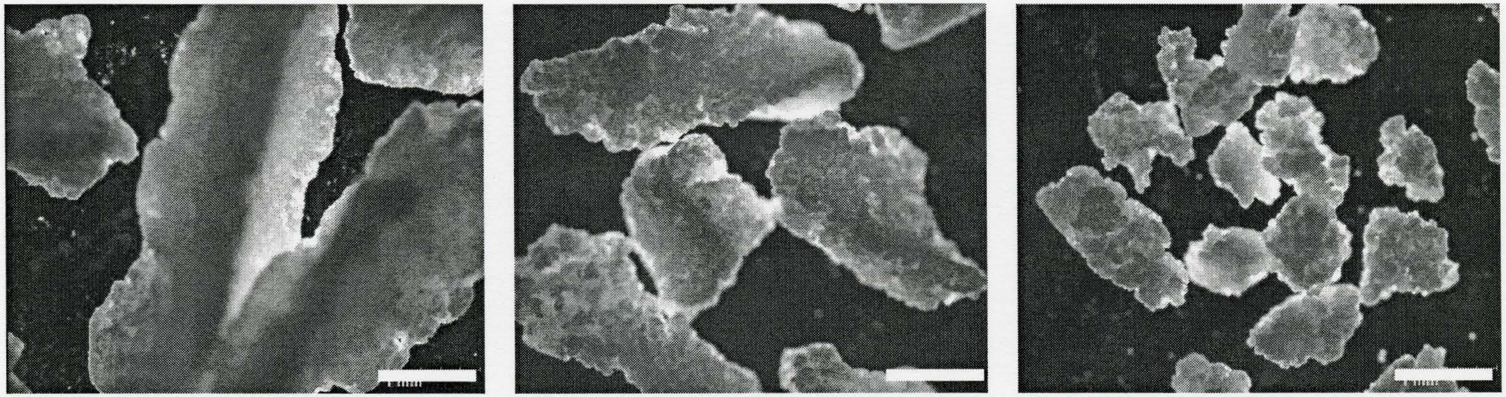


Figure 4.16 Particles images for 60 ° kneading elements (white scale bar indicates 1 mm)

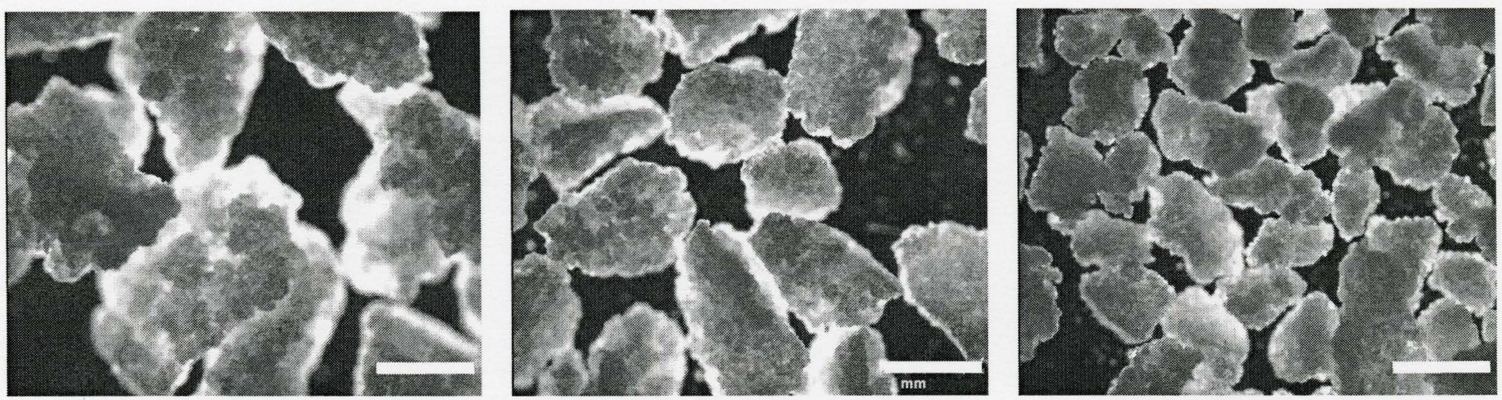


Figure 4.17 Particles images for forward discharging elements (white scale bar indicates 1 mm)

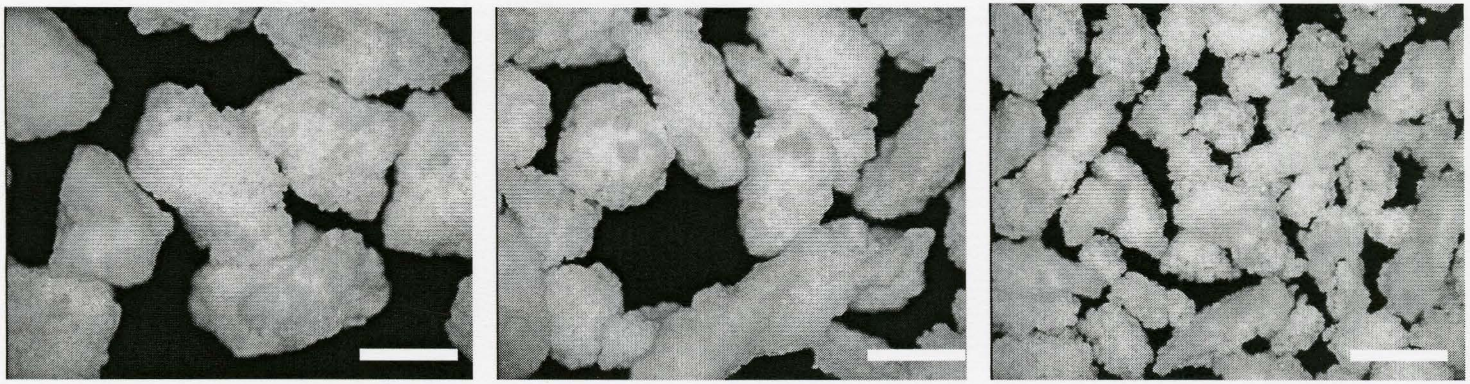


Figure 4.18 Particles images for conveying elements (white scale bar indicates 1 mm)

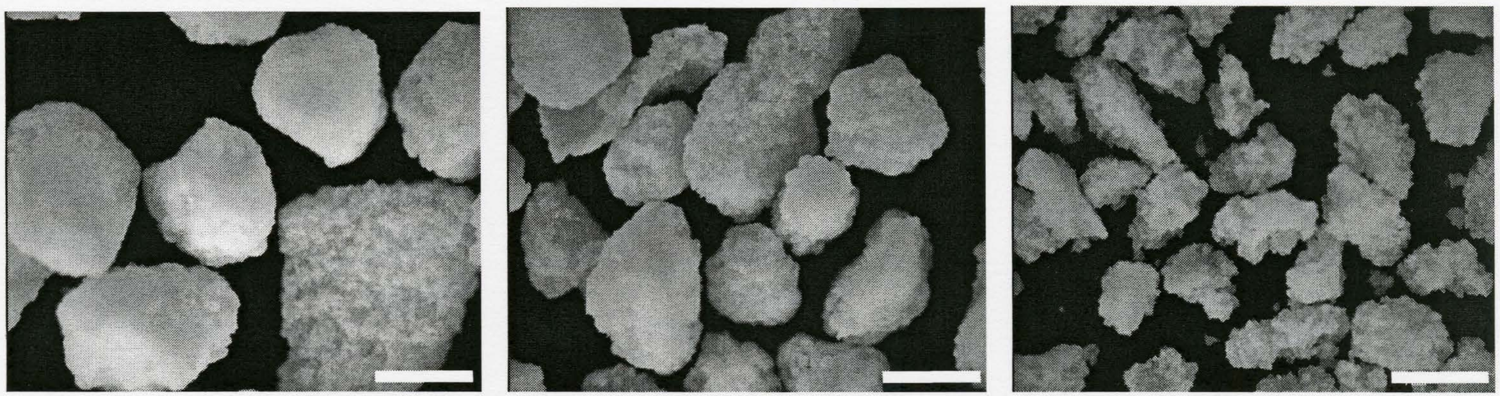


Figure 4.19 Particles images for chopping elements (white scale bar indicates 1 mm)

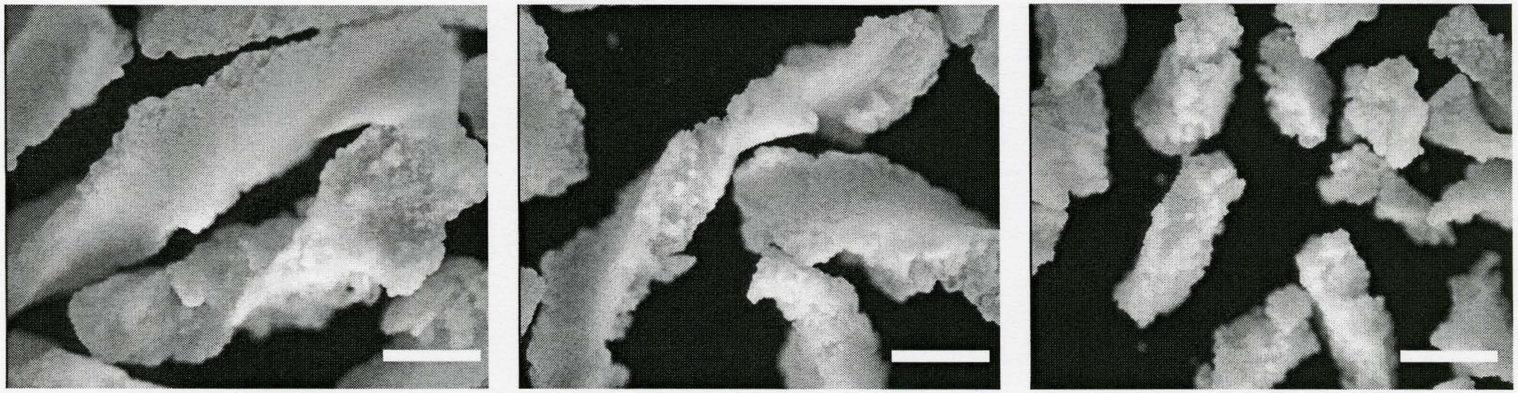


Figure 4.20 Particles images for 30 ° kneading elements (white scale bar indicates 1 mm)

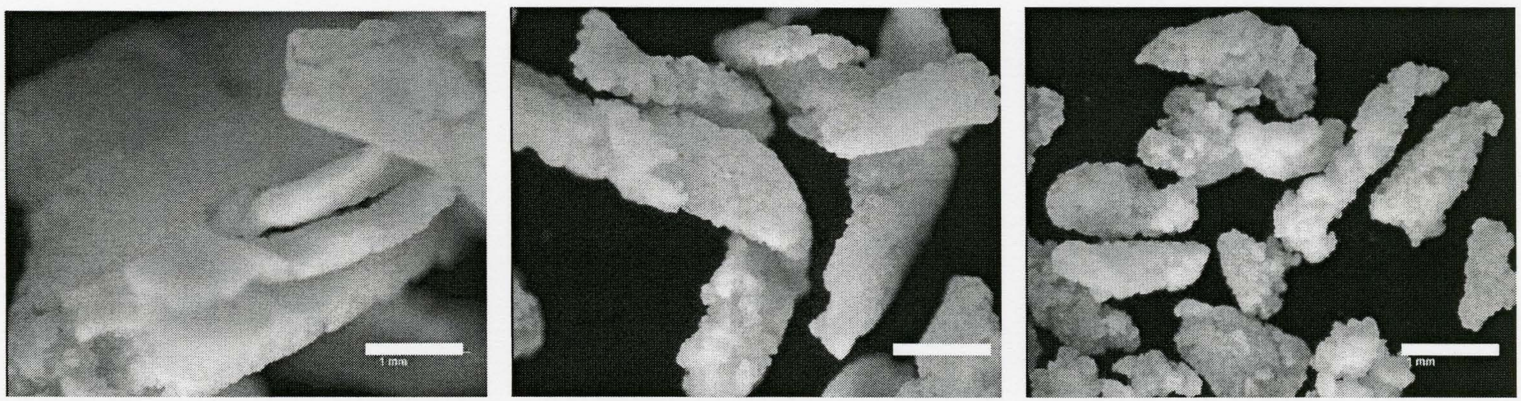


Figure 4.21 Particles images for reverse discharging elements (white scale bar indicates 1 mm)

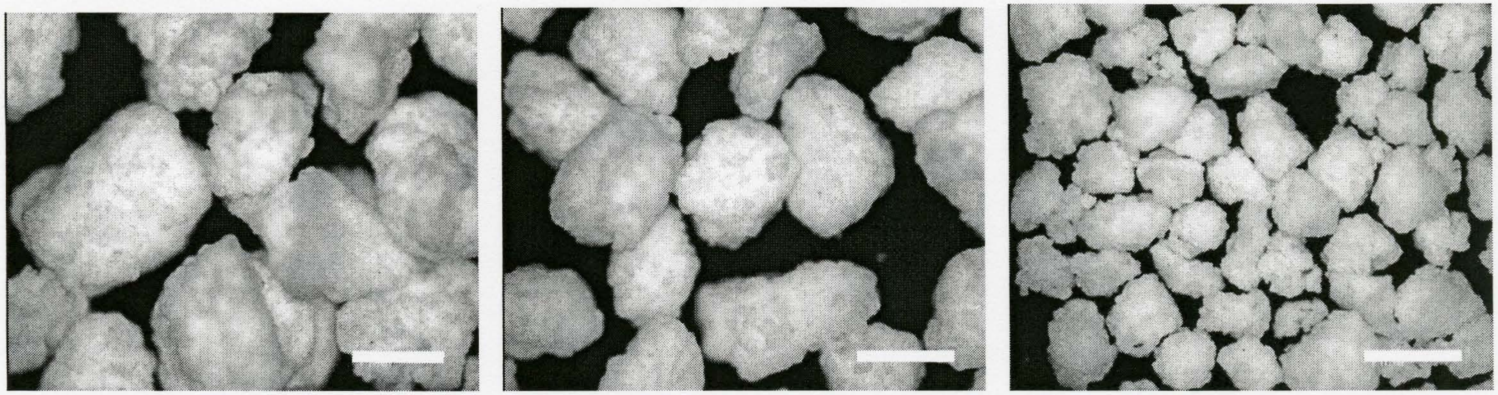


Figure 4.22 Particles images for kneading and discharging elements combination (white scale bar indicates 1 mm)

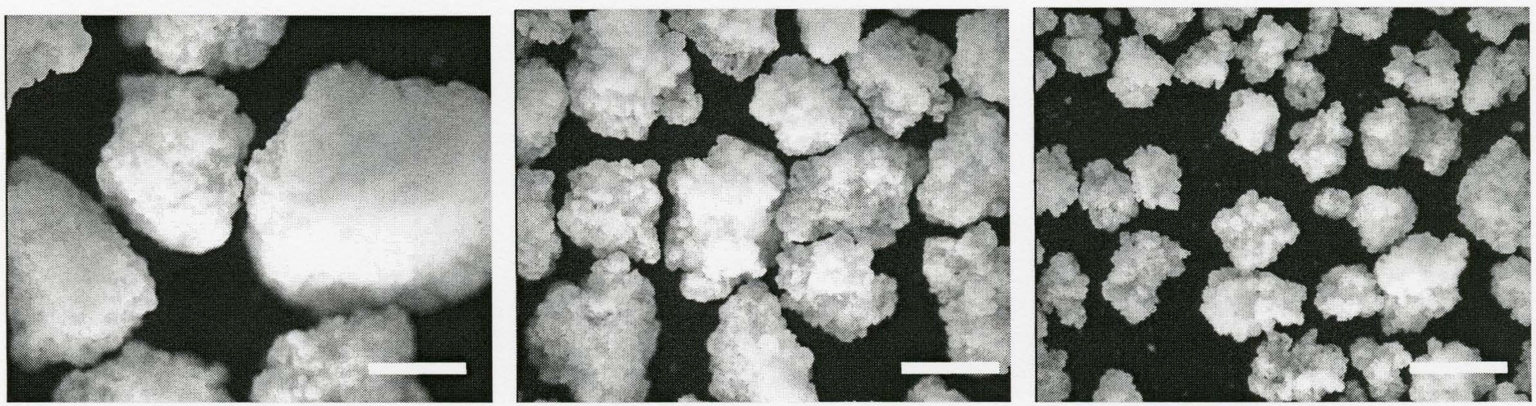


Figure 4.23 Particles images for double discharging elements combination (white scale bar indicates 1 mm)

4.3.3 Influence of Binding Solution

Particle shape was examined under 10 wt% binder concentration as well. Figure 4.24 shows the particle shape factor for featured elements under this condition (lines included only for clarity). Compared with Figure 4.15, similar trends were seen and the value for all the elements except the kneading element presented a most spherical shape factor. Another point worth mentioning is that both Figure 4.24 and Figure 4.15 find shape factor values close to 0.5 in the 300-500μm region. It indicates that the preliminary granules during granule growth had an oval shape. Based on Figure 4.24 and Figure 4.15, we conclude that binder concentration had a negligible influence on particle shape for mixing elements.

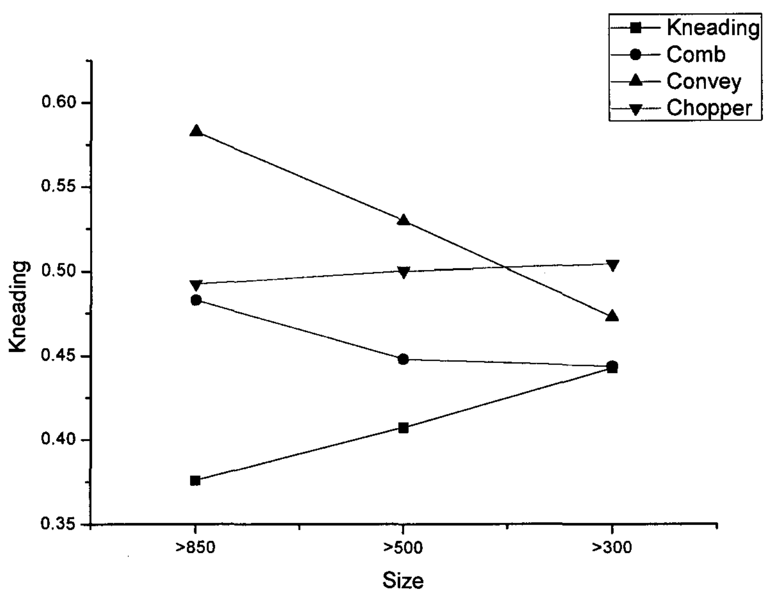


Figure 4.24 Particle shape factor for featured elements under 10 wt% binder concentration

4.3.4 Tablet Strength

Researchers have reported that the irregular shape of granules could affect the compressive strength of the tablets which compressed with those granules (Johansson and Alderborn 2001). The more irregular the granules, the higher the compressive strength obtained by the tablet. To evaluate the effect of the screw profile on tablet strength, granules were compressed into tablets for testing in a mechanical testing system. However, due to the non-uniformity of the granules, the results of the compressive strength test were not conclusive. Table 4.2 shows some of the test results. The force required to fracture a tablet varied considerably even when prepared from the same sample. This result was due to the irregularity of the granule shape. According to Figure 4.24 and Figure 4.15, the shape factor of samples were non-uniform, moreover, even particles in the same size interval have different shape. This caused the unstable fracture force of the compressed tablets. Therefore, the compressive strength of tablets could not be solely predicted based on the screw profile used to prepare the sample.

Table 4.2 Tablets compressive strength test results

Sample	Fracture Force (N) Test1	Fracture Force (N) Test2	Fracture Force (N) Test3
Conveyer	5.7	5.3	7.2
Comb	6.2	4.3	5.9
Kneader	6.7	4.6	6.8

4.4 Particle Flowability

The flowability of granules had been extensively (Crowder et al. 1999; Tan and Newton 1990; Taylor et al. 2000) studied by researchers since its influence on the performance of production and the final drug product. The flowability of granules produced in our TSE was evaluated by means of measuring the angle of repose. Samples studied in this section were agglomerated by featured mixing elements under 80RPM with 7.5% binder concentration.

To demonstrate the improvement in flowability after agglomeration, the angle of repose (θ) for the original lactose powder was first examined. As a result of its relatively poor flowability, lactose exhibited an avalanching motion in the rotating drum. This means that the material bed was "highly cohesive" allowing itself to be lifted as a rigid body by the rotating drum wall; the powders began to slide down in the form of an avalanche when the material reach the upper angle of repose (β), and as the avalanche stopped, the bed surface is inclined to the horizontal by the lower angle of repose (α). These two angles have been reported to be relevant to the dynamic angle of repose which was obtained in the tests for other extruded granules. According to (Liu, Specht, and Mellmann 2005), the dynamic angle of repose can be approximated as:

$$\theta \approx (\alpha + \beta) / 2 \qquad \text{(Eq. 4.1)}$$

On the other hand, granules after agglomeration showed a "free flow" motion during the rotating drum test – forming a rolling bed rather than avalanching bed.

Figure 4.25 shows the angle of repose of samples prepared by the different mixers in comparison to the original lactose. The angles of repose for granules were determined to be in the 41 - 43 ° range. For original lactose powder, the average of the upper and lower angle of repose of lactose was ~50 °. It is evident that wet granulation in TSE provided a significant improvement on the flowability of lactose. Higher error was obtained in lactose powder test; this is because the avalanching motion of the powder was not steady causing the angles differed from time to time.

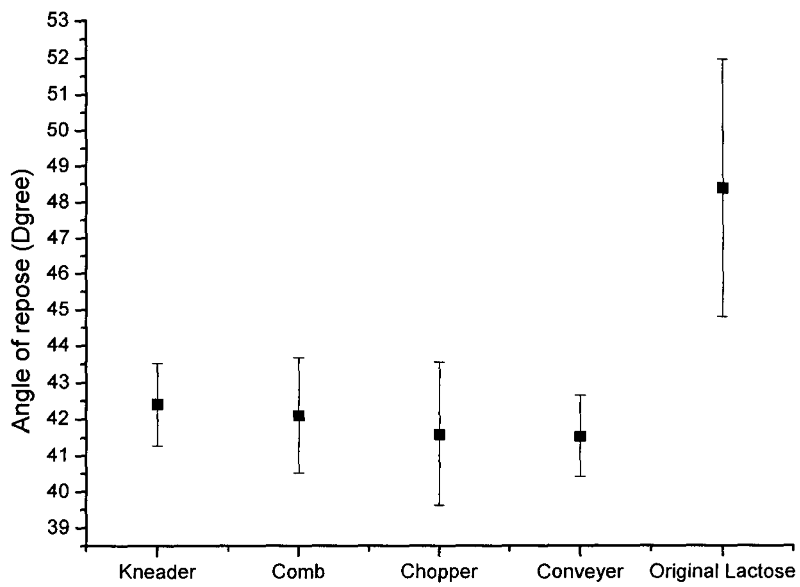
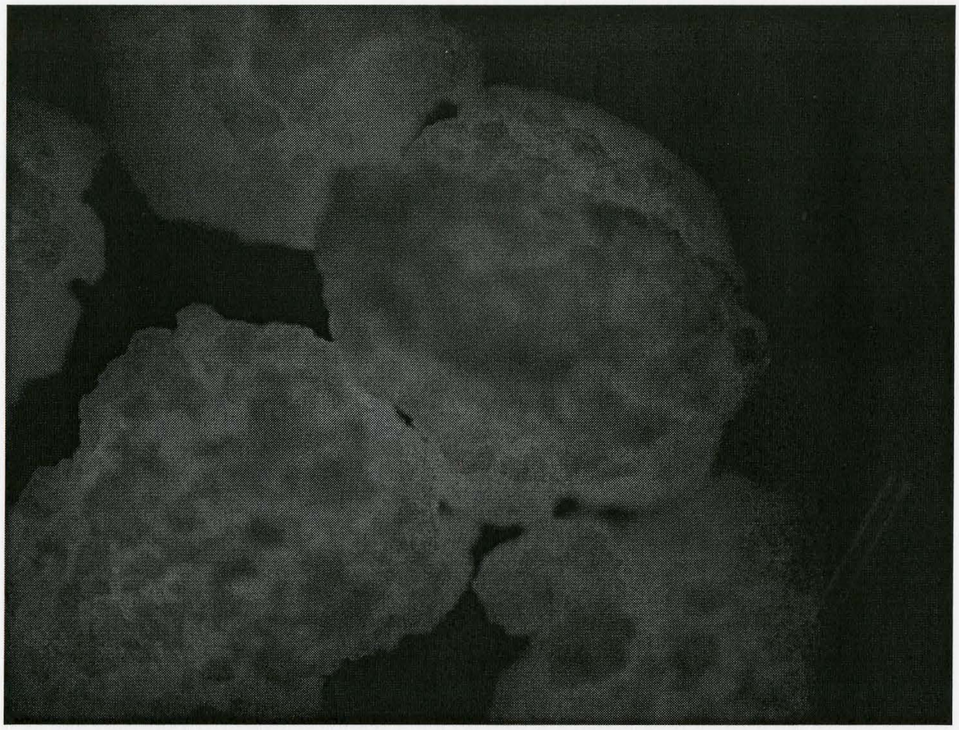


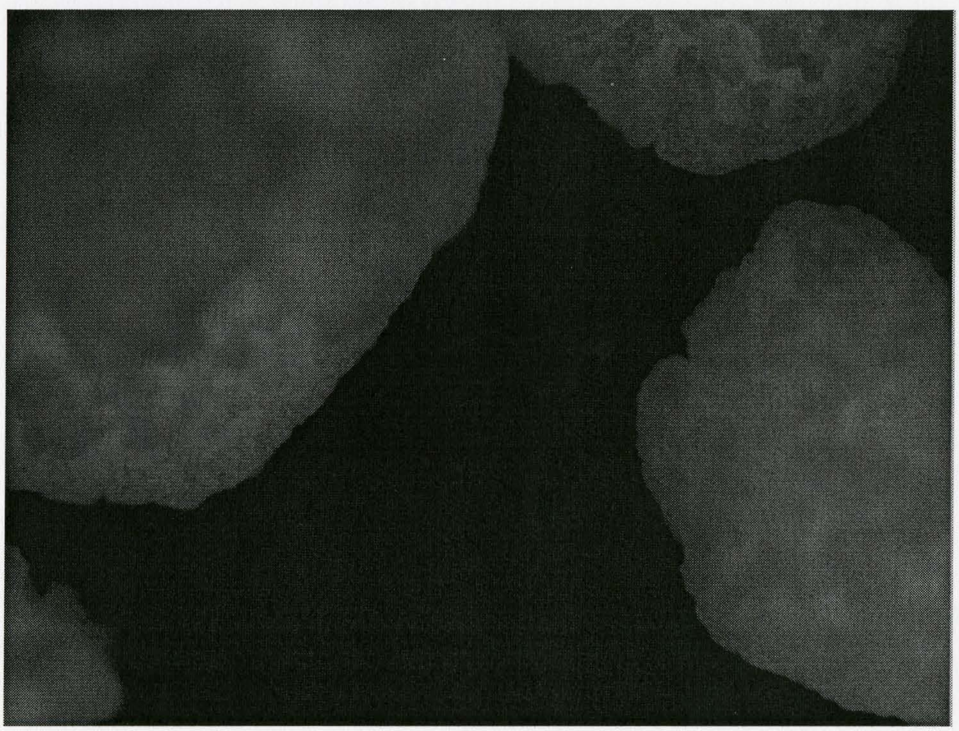
Figure 4.25 Angle of repose of granules and original lactose powder

4.5 Mixing Quality

In order to investigate the homogeneity of granulated lactose and PVP mixtures, particles were examined by light microscope with a fluorescent filter. The PVP used in this project was evaluated and confirmed to be fluorescent while lactose was not. The fluorescence distribution was hoped to indicate how well the PVP had dispersed into the lactose matrix. Figure 4.26 shows example micrographs taken of samples prepared by either chopping or conveying elements. All measurements by this technique showed the PVP was well dispersed regardless of the element and binder addition method used– all particles were fluorescent. However, we are still able to identify that there were a small number of dark spots on the particles; these were the lactose particles on the outer layer. Based on the results, it could be concluded that the binder had been homogenously mixed with lactose.



(a) Granules produced by chopping elements



(b) Granules produced by only conveying elements

Figure 4.26 Fluorescence images of conveying and chopping elements

4.6 Failed Experiments

4.6.1 5% and 12% Binder Conditions

There is as much to be learnt from failures as there is from successful trials. This is particular true for such a new type apparatus for particulate processing. In this regards, this section discusses formulations, and operating conditions which failed to produce a stable, continuous product. In these trials, 5 wt% and 12 wt% binder concentrations were considered opposite extreme conditions to outline the boundaries of the processing window. All of the lactose and PVP solution mixture were hand pre-blended. For 5 wt%, only the conveying element could be tested since the torque reached the system limit of the TSE. These experiments were not able to be completed; as material was fed into the extruder, a sharp noise became increasingly loud while the system load increased simultaneously. On the other hand, with 12 wt% binder condition, experiments were able to proceed and kneader and comb elements were tested. However, due to the high liquid proportion, lactose was not sufficiently consolidated by the process to produce any material for measurement. Only wet paste was obtained under this condition – the extruder is highly efficient at wetting the lactose excipient. Unfortunately, at these two extreme conditions no useable throughput was collected.

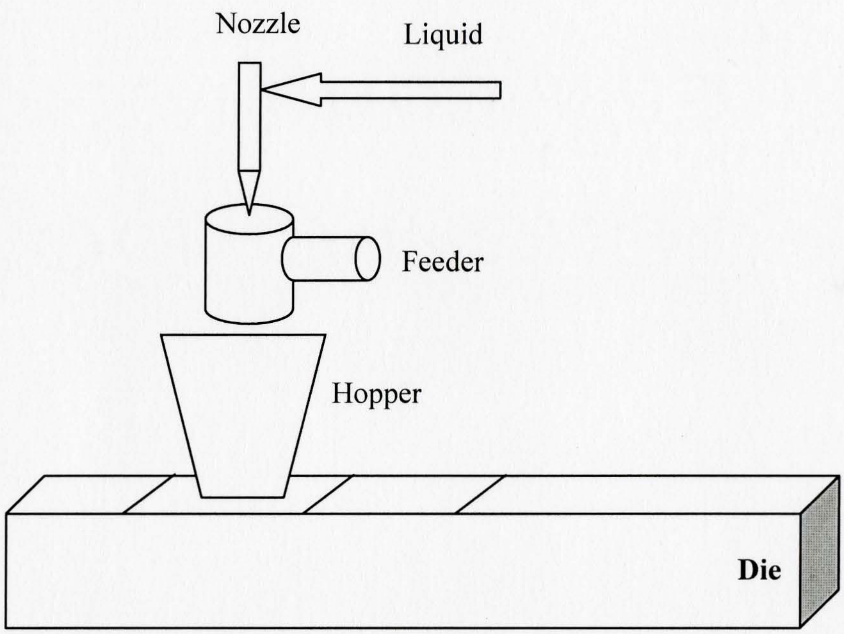
4.6.2 Dropwise and Spray Blend Methods

To improve the homogeneity of the binding agent in the matrix, dropwise and spray blend methods were tested. Both 7.5 wt% and 10 wt% binder concentrations were examined with these two methods. Unfortunately, both ways could not establish stable output conditions under our experimental environment. The common trouble was the appearance of a wet sticky chunk of lactose formed at the feeding zone after a short term of process.

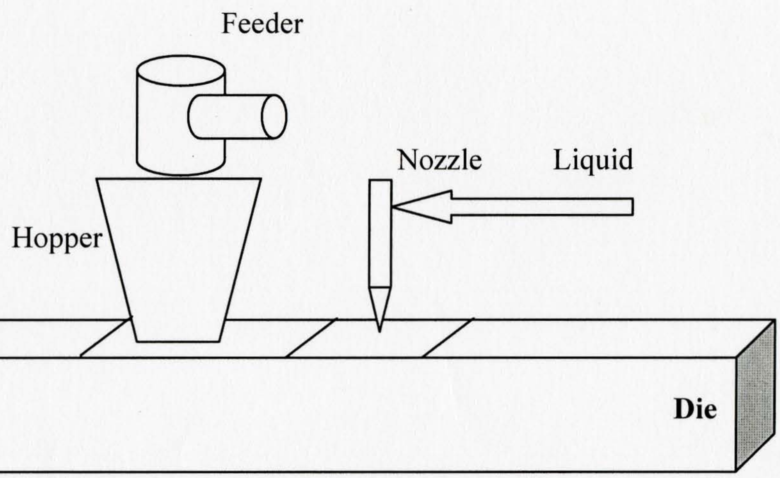
For dropwise method, two liquid feeding position were selected (seen Figure 4.27). Experiments run smoothly for first few minutes by using either of these two configurations. However, after the screws in feeding zone were wetted by the binding liquid, agglomeration became rapid at the screw surface. Instead of being pushed forward by the screws, the lactose powder became matted to the screw and the wet granules had difficulties proceeding forwards. This process would finally lead to a wet chunk stuck in the liquid feed opening (no matter where the liquid was fed). The chunks significantly affected the conveying and granulation downstream, which caused unstable output.

For the spray method, the apparatus setup was illustrated in Figure 3.2. The first problem met was due to the compressed air, causing the lactose powder to be blown out of the feed zone and producing an unstable feeding rate. After minimizing the lactose dust by controlling the air pressure and covering the hopper area, experiments were able to proceed. However, the same problems as the dropwise method appeared where the wet chuck formed, albeit slower in this case.

In conclusion, the binding agent could not be added into system by dropwise or the present spray methods, because the binder liquid could not efficiently wet the lactose. It is possible a more distributed addition method would work better, where the same liquid content is added over a great many locations. This is a future aspect to be explored.



a) Liquid feed on top of lactose



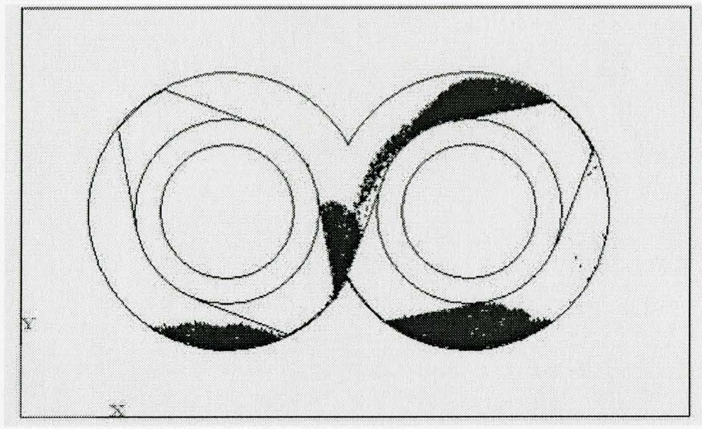
b) Liquid feed after lactose

Figure 4.27 Sketches of different dropwise liquid feeding method

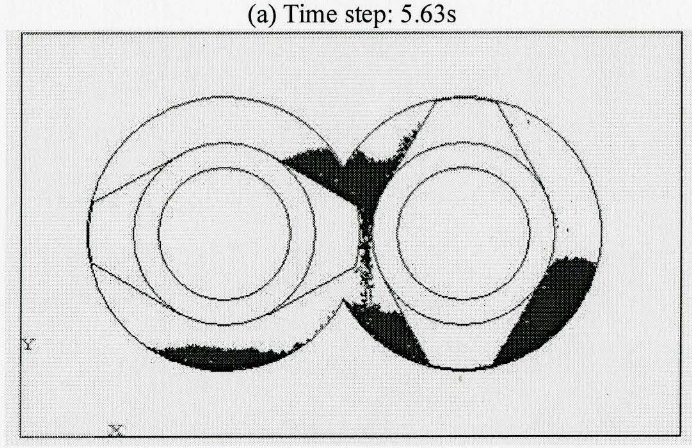
4.7 Simulation Results

DEM simulations were limited to a two-dimensional model. Due to the physical design of discharging and chopping elements, they could not be simulated properly. So the following discussion will only focus on the kneading block and conveying element. All simulations had the same parameter configurations and same amount particles in the system (which was 3000). In a two-dimensional circumstance, the porosity of an assembly was computed by the PFC^{2D} software using an area-based calculation (ratio of total void area to total area). Because this is different from the definition of porosity which is a volume-based calculation (ratio of total void volume to total volume), it was not feasible to perform a quantitative analysis. Therefore, only a qualitative discussion was presented in this section.

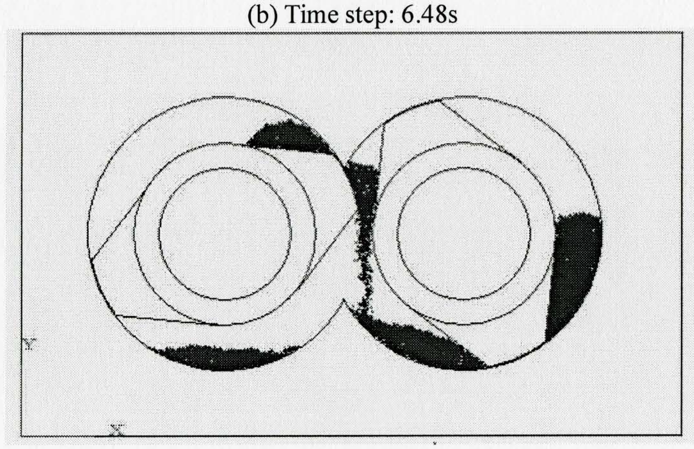
Figure 4.28 and Figure 4.29 show three different captured images from the simulation of the kneading and conveying elements. Based on the simulation, it was observed that granulation primarily took place at the intermeshing region. Seen in Figure 4.28, as the kneader paddle had a larger contact area with material than the conveyor (i.e. thicker flight land for the kneader than conveyor in these simulations), more materials were held in the intermeshing area, and, certainly, more shear was applied to the materials. In contrast, with the same amount of particles, a visible decrease of the pressure generated at the intermeshing region for conveying elements was noted, leaving the materials to mainly experience drag flow. However, due to the limitations of our two-dimensional simulations, particles in the nip between the intermeshing flights where high compressive forces are likely to be experienced by the powder could not be observed.



(a) Time step: 5.63s

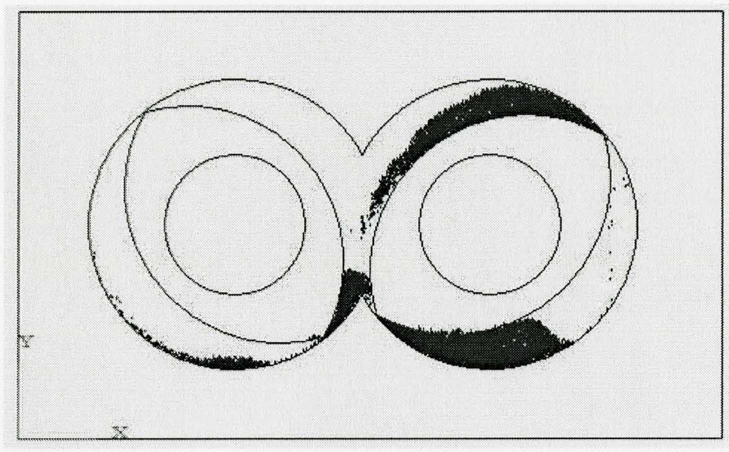


(b) Time step: 6.48s

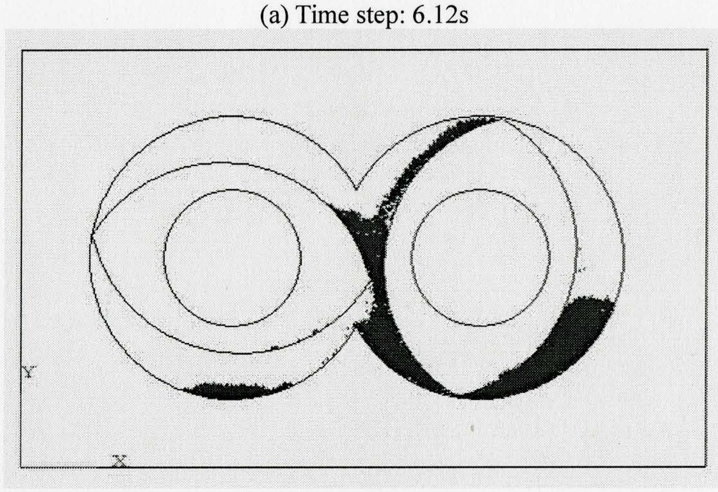


(c) Time step: 6.93s

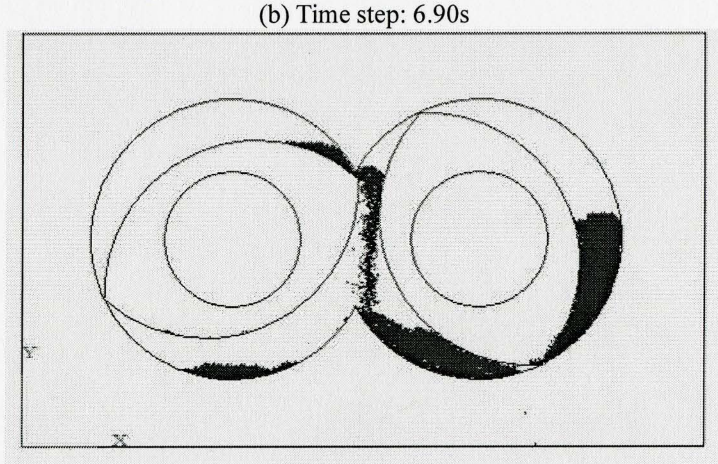
Figure 4.28 Captured images from the kneading block simulation



(a) Time step: 6.12s



(b) Time step: 6.90s



(c) Time step: 7.56s

Figure 4.29 Captured images from the conveying elements simulation

Chapter 5 Conclusion and Future Work

5.1 Conclusion

Wet granulation in a twin screw extruder has been systematically investigated in this thesis. Within the optimal range of 7.5 - 10wt% binder concentration, all the screw profiles were studied for their capacity to produce desirable granules suited to solid oral dosage form production. By increasing the rotational speed from 30 RPM to 80 RPM, the size of granules produced by conveying, discharging and chopping elements decreased whereas this operating parameter had little effect on granule size within kneading blocks.

The particle size produced by all tested elements was dependent on their mixing capability. Kneading blocks produced particles in the 850-1180μm size range, while discharging elements led to smaller particle sizes between 500-850μm. Chopping and conveying elements hindered granule growth, and the resulting particle size was lower than 500μm for conveying elements whereas chopping elements produced mainly fines, with particles smaller than 300μm. The shape of the granule was also distinctly affected by the choice of mixing element used in the screw design. Kneading elements tend to produce elongated shape granules while other elements produced more spherical agglomerates. The granule shape was not found to be effected by the binder concentration.

The angle of repose tests showed a significant improvement in flowability for our extruded granules compared with the original lactose powder; and optical observations using a fluorescent filter sensitive to the PVP component indicated good mixing has occurred under all conditions between lactose and PVP. The tablet strength test was not conclusive in our studies, possibly due to the good mixing and limited fines in the samples. Wet granulation was not feasible for very low or high binder concentrations (i.e. 5 wt% and 12 wt%) due to the uncontrolled densification of the particles. Aside from useful understanding of screw element design, this work also examined a variety of methods for introducing the binder solution, and among them only the hand pre-blend addition method was found to maintain a steady feeding rate and output.

In order to understand how particle size and shape was affected by the design of the screw element, simple modeling in 2-D was included in this thesis. The commercial software package – PFC^{2D} was used to simulate the dynamic behavior of particles within the screw elements during extrusion. Two-dimensional simulations of the kneading and conveying elements were completed, and it was observed that agglomeration was primarily happened in the intermeshing region of the extruder.

5.2 Future Work

From the experience of this project, further efforts could be made in the following aspects:

1. A more efficient way of adding binder solution into lactose solid bed should be employed. Although the present spay method was not able to get a steady output, it still provided the information that if the screws could be prevented from wetted by the liquid, a steady operation is possible.
2. A residence time distribution analysis should be conducted in order to

gain a thorough understanding of the mixing quality of the granules produced by mixing elements.

3. A three-dimensional DEM simulation is necessary to make a quantitative analysis for the granulation process in a twin screw extruder. Further characterization of the micromechanics for the system needed to improve our model with cohesive particle behavior.

Bibliography

Adams, M. J. and R. McKeown. 1996. Micromechanical analyses of the pressure-volume relationships for powders under confined uniaxial compression. Powder Technology 88, no. 2: 155-163.

Akande, O. F., A. V. Deshpande, and A. B. Bangudu. 1991. An evaluation of starch obtained from pearl-millet - pennisetum-typhoides - as a binder and disintegrant for compressed tablets. Drug Development and Industrial Pharmacy 17, no. 3: 451-455.

Ameye, D., E. Keleb, C. Vervaet, J. P. Remon, E. Adams, and D. L. Massart. 2002. Scaling-up of a lactose wet granulation process in mi-pro high shear mixers. *European Journal of Pharmaceutical Sciences* 17, no. 4-5: 247-251.

Asmar, B. N., P. A. Langston, A. J. Matchett, and J. K. Walters. 2002. Validation tests on a distinct element model of vibrating cohesive particle systems. *Computers & Chemical Engineering* 26, no. 6: 785-802.

Badawy, S. I. F., M. M. Menning, M. A. Gorko, and D. L. Gilbert. 2000. Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer. *International Journal of Pharmaceutics* 198, no. 1: 51-61.

Ban, Kyunha, Eungkyu Kim, and James L. White. 2007. A non-newtonian model of flow in a special mixing element region of a modular intermeshing corotationg twin screw extruder. In *ANTEC*.

Bravo, V. L., A. N. Hrymak, and J. D. Wright. 2004. Study of particle trajectories, residence times and flow behavior in kneading discs of intermeshing co-rotating twin-screw extruders. *Polymer Engineering and Science* 44, no. 4: 779-793.

Brouwer, Tera and david B. Todd. 1999. Flow patterns in special twin screw mixing elements. In *ANTEC*, I.

Butensky, M. and D. Hyman. 1971. Rotary drum granulation: An experimental study of the factors affecting granule size. *Ind. Eng. Chem. Fundam.* 10: 212-219.

Carneiro, O. S., G. Caldeira, and J. A. Covas. 1999. Flow patterns in twin-screw extruders. *Journal of Materials Processing Technology* 93: 309-315.

Chen, Z. Simulation of non-isothermal flow in twin screw extrusion. (accessed 4, 9).

Crowder, T. M., V. Sethuraman, T. B. Fields, and A. J. Hickey. 1999. Signal processing and analysis applied to powder behavior in a rotating drum. *Particle & Particle Systems Characterization* 16, no. 4: 191-196.

Cundall, P. A. and O. D. L. Strack. 1979. Discrete numerical-model for granular assemblies. *Geotechnique* 29, no. 1: 47-65.

Di Renzo, A. and F. P. Di Maio. 2004. Comparison of contact-force models for the simulation of collisions in dem-based granular flow codes. *Chemical Engineering Science* 59, no. 3: 525-541.

Ennis, B. J. 1996. Agglomeration and size enlargement - session summary paper. *Powder Technology* 88, no. 3: 203-225.

Faure, A., P. York, and R. C. Rowe. 2001. Process control and scale-up of pharmaceutical wet granulation processes: A review. *European Journal of Pharmaceutics and Biopharmaceutics* 52, no. 3: 269-277.

Gamlen, M. J. and C. Eardley. 1986. Continuous extrusion using a raker perkins mp50 (multipurpose) extruder. *Drug Development and Industrial Pharmacy* 12, no. 11-13: 1701-1713.

Gantt, J. A. and E. P. Gatzke. 2005. High-shear granulation modeling using a discrete element simulation approach. *Powder Technology* 156, no. 2-3: 195-212.

Hegedus, A. and K. Pintye-Hodi. 2007. Influence of the type of the high-shear granulator on the physico-chemical properties of granules. *Chemical Engineering and Processing* 46, no. 10: 1012-1019.

Huneault, M. A. 1998. Pressure generation and screw design in corotating twin screw extruders. *Journal of Reinforced Plastics and Composites* 17, no. 11: 1036-1046.

Inc., Itasca Consulting Group. 2004. *Pfc2d theory and backgroud.*

Inc., Leistritz. 1997. Extrusion manual. In.

Iveson, S. M. and J. D. Litster. 1998. Growth regime map for liquid-bound granules. *Aiche Journal* 44, no. 7: 1510-1518.

Iveson, S. M., J. D. Litster, K. Hapgood, and B. J. Ennis. 2001. Nucleation, growth and breakage phenomena in agitated wet granulation processes: A review. *Powder Technology* 117, no. 1-2: 3-39.

Johansson, B., M. Wikberg, R. Ek, and G. Alderborn. 1995. Compression behavior and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical-properties. International Journal of Pharmaceutics 117, no. 1: 57-73.

Johansson, B. and G. Alderborn. 2001. The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microcrystalline cellulose. *European Journal of Pharmaceutics and Biopharmaceutics* 52, no. 3: 347-357.

Johansson, B., F. Nicklasson, and G. Alderborn. 1998. Effect of pellet size on degree of deformation and densification during compression and on compactibility of microcrystalline cellulose pellets. *International Journal of Pharmaceutics* 163, no.

1-2: 35-48.

Keleb, E. I., A. Vermeire, C. Vervaet, and J. P. Remon. 2002. Continuous twin screw extrusion for the wet granulation of lactose. *International Journal of Pharmaceutics* 239, no. 1-2: 69-80.

Keleb, E. I., A. Vermeire, C. Vervaet, and J. P. Remon. 2004. Twin screw granulation as a simple and efficient tool for continuous wet granulation. *International Journal of Pharmaceutics* 273, no. 1-2: 183-194.

Kiani, Arash, John Curry, and Paul Andersen. 1998. Flow analysis of twin screw extruders - pressure and drag capability of various twin screw elements. In *ANTEC,* 1:48.

Kleinebudde, P. and H. Lindner. 1993. Experiments with an instrumented twin-screw extruder using a single-step granulation extrusion process. *International Journal of Pharmaceutics* 94, no. 1-3: 49-58.

Knight, P. C. 1993. An investigation of the kinetics of granulation using a high-shear mixer. *Powder Technology* 77, no. 2: 159-169.

Knight, P. C., T. Instone, J. M. K. Pearson, and M. J. Hounslow. 1998. An investigation into the kinetics of liquid distribution and growth in high shear mixer agglomeration. *Powder Technology* 97, no. 3: 246-257.

Kristensen, H. G. and T. Schaefer. 1987. Granulation - a review of pharmaceutical wet-granulation. *Drug Development and Industrial Pharmacy* 13, no. 4-5: 803-872.

Lavoie, F., L. Cartilier, and R. Thibert. 2002. New methods characterizing avalanche behavior to determine powder flow. *Pharmaceutical Research* 19, no. 6: 887-893.

Leuenberger, H. 2001. New trends in the production of pharmaceutical granules: Batch versus continuous processing. *European Journal of Pharmaceutics and*

Biopharmaceutics 52, no. 3: 289-296.

Link, J. M., W. Godlieb, N. G Deen, and J. A. M. Kuipers. 2007. Discrete element study of granulation in a spout-fluidized bed. *Chemical Engineering Science* 62, no. 1-2: 195-207.

Liu, L. X., J. D. Litster, S. M. Iveson, and B. J. Ennis. 2000. Coalescence of deformable granules in wet granulation processes. *Aiche Journal* 46, no. 3: 529-539.

Liu, X. Y., E. Specht, and J. Mellmann. 2005. Experimental study of the lower and upper angles of repose of granular materials in rotating drums. *Powder Technology* 154, no. 2-3: 125-131.

Lèon P.B.M., Janssen. 1978. *Twin screw extrusion.* New York: Elsevier.

Martelli, Fabrizio G. 1983. *Twin-screw extruders: A basic understanding.*

Mayur, Lodaya and Matthew Mollan. 2003. Twin screw wet granulation. In *Pharmaceutical extrusion technology*, ed. Ghebre-Sellassie Isaac, 133:323-344. Great Britain: Taylor & Francis Group.

Mort, P.R. and G Tardos. 1999. Scale-up of agglomeration process using transformations. *Kona* 17: 64-75.

Moysey, P. A. and A. R. Thompson. 2004. Investigation of solids transport in a single-screw extruder using a 3-d discrete particle simulation. *Polymer Engineering and Science* 44, no. 12: 2203-2215.

Moysey, P. A. and M. R. Thompson. 2005. Modelling the solids inflow and solids conveying of single-screw extruders using the discrete element method. *Powder Technology* 153, no. 2: 95-107.

Potente, H., J. Ansahl, and R. Wittemeier. 1990. Throughput characteristics of tightly intermeshing co-rotating twin screw extruders. *International Polymer Processing* 5, no. 3: 208-216.

Rehula, M., 1985. The effect of granule size on dissolution of drugs from tablets. Folia Pharmacol. 8, 101-107.

Ritala, M., O. Jungersen, P. Holm, T. Schaefer, and H. G. Kristensen. 1986. A comparison between binders in the wet phase of granulation in a high shear mixer. *Drug Development and Industrial Pharmacy* 12, no. 11-13: 1685-1700.

Robbe, Anne M. V. and D.B. Todd. 2003. Flow behavior of newtonian fluid through conveying elements and kneading blocks. In *ANTEC.*

Sastry, K.V.S and D.W. Fürstenau. 1977. Kinetic and process analysis of the agglomeration of particulate materials of green pelletization. In *Agglomeration,* ed. K.V.S. Sastry, 77:381-402. New York: AIME.

Schaefer, T. 1984. Granulation in different types of high-shear mixers. Part 4. Effect of liquid saturation on the agglomoration. *Pharmaceutical Industry* 46, no. 7: 763.

Shah, Umang. 2005. Use of a modified twin screw extruder to develop a high-strength tablet dosage form. In. Pharmaceutical Technology.

Simons, S. J. R. and R. J. Fairbrother. 2000. Direct observations of liquid binder-particle interactions: The role of wetting behaviour in agglomerate growth. *Powder Technology* 110, no. 1-2: 44-58.

Stevens, A. B. and C. M. Hrenya. 2005. Comparison of soft-sphere models to measurements of collision properties during normal impacts. *Powder Technology* 154, no. 2-3: 99-109.

Szydlowski, W. and J. L. White. 1988. A non-newtonian model of flow in a kneading disk region of a modular intermeshing corotating twin screw extruder. *Journal of*

Non-Newtonian Fluid Mechanics 28, no. 1: 29-46.

Tan, S. B. and J. M. Newton. 1990. Powder flowability as an indication of capsule filling performance. *International Journal of Pharmaceutics* 61, no. 1-2: 145-155.

Tanaka, T., T. Kawaguchi, and Y. Tsuji. 1993. Discrete particle simulation of flow patterns in 2-dimensional gas-fluidized beds. *International Journal of Modern Physics B* 7, no. 9-10: 1889-1898.

Tardos, G. I., M. I. Khan, and P. R. Mort. 1997. Critical parameters and limiting conditions in binder granulation of fine powders. *Powder Technology* 94, no. 3: 245-258.

Taylor, Michael K., Jeri Ginsburg, Anthony J. Hickey, and Ferdous Gheyas. 2000. Composite method to quantify powder flow as a screening method in early tablet or capsule formulation development. *AAPS Pharm. Sci. Tech.* 1, no. 3: 18.

Todd, D. 1997. Practical aspects of processing in intermeshing twin screw extruders. In *ANTEC*, 43:116.

Todd, D. B. 1991. Drag and pressure-flow in twin-screw extruders. *Kunststoffe-German Plastics* 81, no. 11: 1055-1056.

Tsuji, Y., T. Kawaguchi, and T. Tanaka. 1993. Discrete particle simulation of 2-dimensional fluidized-bed. *Powder Technology* 77, no. 1: 79-87.

Van der Goot, A. J., O. Poorter, and Lpbm Janssen. 1998. Determination of the degree of fill in a counter-rotating twin screw extruder. *Polymer Engineering and Science* 38, no. 7: 1193-1198.

Van Melkebeke, B., C. Vervaet, and J. P. Remon. 2008. Validation of a continuous granulation process using a twin-screw extruder. *International Journal of Pharmaceutics* 356, no. 1-2: 224-230.

Vermeire, A., E. I. Keleb, F. Kiekens, I. Van Driessche, S. Hoste, J. P. Remon, and C. Vervaet. 2005. Tablets prepared by single-step granulation/tabletting: Interparticulate binding mechanism and stability. *Pharmaceutical Development and Technology* 10, no. 3: 397-403.

Vlachopoulos, John. 2004. *Introduction to plastics processing*: McMaster University.

Vonk, P., C. P. F. Guillaume, J. S. Ramaker, H. Vromans, and N. W. F. Kossen. 1997. Growth mechanisms of high-shear pelletisation. *International Journal of Pharmaceutics* 157, no. 1: 93-102.

Vromans, H., H. G. M. Poels-Janssen, and H. Egermann. 1999. Effects of high-shear granulation on granulate homogeneity. *Pharmaceutical Development and Technology* 4, no. 3: 297-303.

Watano, S. 2001. Direct control of wet granulation processes by image processing system. *Powder Technology* 117, no. 1-2: 163-172.

White, J. L., J. K. Kim, W. Szydlowski, and K. Min. 1988. Simulation of flow in compounding machinery - internal mixers and modular corotating intermeshing twin-screw extruders. *Polymer Composites* 9, no. 5: 368-377.

White, James L. Composite models of modular intermeshing corotating and tangential counter-rotating twin screw extruders. (accessed 4, 7).

Yang, R. Y., R. P. Zou, and A. B. Yu. 2003. Microdynamic analysis of particle flow in a horizontal rotating drum. *Powder Technology* 130, no. 1-3: 138-146.

Zhang, R. and J. Q. Li. 2006. Simulation on mechanical behavior of cohesive soil by distinct element method. *Journal of Terramechanics* 43, no. 3: 303-316.

Appendix I

Source Code for PFC^{2D} 3.10

Simulation of Conveying Elements

```
;===== ========================================;
;
;              create the twin screw extruder
;
;===== ===========================================;
new
set random
set disk on
title 'twin screw model'
macro WALL_K 'kn=2e11 ks=2e11 f 0.9'
macro LEFT_CENTER '0.02 0.02'
macro RIGHT_CENTER '0.0437 0.02'
macro SPIN_SPEED '8.37'
;== ========= Draw the device ===================
;========= outline the boder
wall id=21 nodes ( 0, 0) (0.065, 0)
wall id=22 nodes (0.065, 0) (0.065, 0.04)
wall id=23 nodes (0.065,   0.04) ( 0,   0.04)
```

```
wall id=24 nodes ( 0,   0.04) ( 0, 0)

;========= 2 barrels

wall id=1 type circle cent LEFT_CENTER angle 28.5,331.5 rad 0.0135 WALL_K

wall id=2 type circle cent RIGHT_CENTER angle 208.5,151.5 rad 0.0135 WALL_K

;======== outline the flights

;=left

wall id=121 type circle cent LEFT_CENTER rad 0.0065 WALL_K

wall id=13 type circle cent 0.02548,0.02 angle 112.4,247.8 rad 0.01448 spin SPIN_SPEED x 0.02 y 0.02 WALL_K ;left arc

wall id=14 type circle cent 0.01452,0.02 angle 292.2,67.6 rad 0.01448 spin SPIN_SPEED x 0.02 y 0.02 WALL_K ;right arc

wall id=151 type circle cent RIGHT_CENTER rad 0.0065 WALL_K

wall id=16 type circle cent 0.0437,0.02548 angle 202.3,337.7 rad 0.01448 spin SPIN_SPEED x 0.0437 y 0.02 WALL_K    ;bottum arc

wall id=17 type circle cent 0.0437,0.01452 angle 22.3,157.7 rad 0.01448 spin SPIN_SPEED x 0.0437 y 0.02 WALL_K    ;top arc

;========================================= ================

plot create twin

plot set back white

plot add wall black

plot add axes brown

plot show

save twin_convey.sav
```

```
;============= ========================================;

;

;                Generate particles

;

;======= ==================================================;

new

restore twin_convey.sav

set random

set disk on

set gravity 0 -10


plot show

plot add ball black


damp default local 0.0

damp default viscous normal 2



gen id=1,1000 rad=(0.00001, 0.00001) x=(0.0081,0.01) y=(0.014,0.026)
;no_shadow t=200000

property color 3


gen id=2000,3000 rad=(0.00001, 0.00001) x=(0.038,0.049) y=(0.030,0.032)
t=200000 ;no_shadow
```

```
gen id=4000,5000 rad=(0.00001, 0.00001) x=(0.038,0.049) y=(0.0088,0.0108)
t=200000 ;no_shadow
;==== from literature

property density 1525 kn 5e4 ks 1e4 f 0.9

initial radius mul 10

def run_pb

    loop n (1,15000)
        command
        ;plot show
        prop pb_kn=1e7 pb_ks=1e7 pb_rad=0.00001
        prop pb_nstren=1e4 pb_sstren=1e4


        cyc 500
        end_command
    endloop
end

plot add pbond blue
```

```
set plot avi size 800 600
movie avi_open file convey_disON_v2_kn5e4_pb1e7_pbs1e4_pbr00001-3000.avi
movie step 20000 1 file convey_disON_v2_kn5e4_pb1e7_pbs1e4_pbr00001-3000.avi

;cyc 1000000
run_pb
save convey_disON_v2_kn5e4_pb1e7_pbs1e4_pbr00001-3000.sav

movie avi_close file convey_disON_v2_kn5e4_pb1e7_pbs1e4_pbr00001-3000.avi
```