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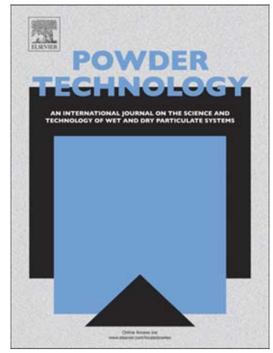

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Twin Screw Granulation – A Literature Review

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Abstract

This review article addresses the currently available literature on Twin Screw Granulation (TSG). TSG is an emerging technology rapidly gaining interest in the pharmaceutical industry as a method of continuous wet granulation. The control of the geometry of the granulator over the formation of granules and the mechanisms of granulation are discussed. Process parameters including liquid to solid ratio, binder viscosity, method of binder addition, screw speed and material feed rate and their control of granule quality are analysed. The need for further understanding of granulation mechanisms and the interaction between screw elements is highlighted. As well as the difficulties in equating process parameters between different granulators to ensure product consistency across sites. TSG is a process with great potential for implementation into continuous processing lines but process understanding must be developed to ensure predictable consistent granule quality.

Keywords

Twin Screw Granulation; Continuous Processes; Pharmaceutical Technology; Wet Granulation

1. Introduction

Granulation is a size enlargement process where particles are brought together to form larger permanent agglomerates. Granulation improves the physical properties of a material making it easier for handling and downstream processing. In pharmacy granules are typically used as an intermediary before compaction into tablets, the most common type of oral solid dosage. Mixing can be a desirable feature of granulation processes, particularly when homogenous distribution of precise low fractions of active ingredient are required.

Wet granulation is the most commonly used method of granulation. Wet granulation processes such as high shear granulation or fluidised bed granulation involve the addition of a solvent or binder solution to a powder bed to cause agglomeration. Traditionally the pharmaceutical industry has employed batch granulation techniques and has faced many obstacles to adopting continuous production. Perceived issues include cost, product quality, matching the low volume and flexibility in formulations required in some processes and the concerns of regulatory authorities regarding the inability to monitor “batch” quality.

Multiple factors have led to a shift in attitude in pharmaceutical manufacturing towards continuous processing. With the introduction of the concepts of Quality by Design (QbD) and Process Analytical Technology (PAT) in the Pharmaceutical industry by the FDA [1] in 2003 there has been a re-evaluation of current manufacturing techniques. Given the dwindling exploitable patent windows of modern Active Pharmaceutical Ingredients (APIs) the opportunity to improve process efficiency through continuous processing is now being seriously considered by the pharmaceutical manufacturing industry.

With the developing interest in continuous granulation the advantages over conventional batch granulation methods have become apparent:

- Continuous granulation is more suited to high volume production of material as the production of a similar volume using batch-wise production requires either multiple or very large granulators increasing space and energy demands;
- Similarly continuous granulation is more amenable to variation in production volume. Final product volumes are determined by the running time of the process and are not limited by batch sizes. This is particularly relevant in the production of small volumes, where under filled batch granulators can result in unpredictable poor quality granules;
- Continuous processes require less product development time as they are more adaptable to control strategies outlined by PAT;
- Continuous granulation processes can handle a higher throughput of material compared to traditional batch granulation processes while requiring a smaller equipment footprint [2].

Twin screw extrusion (TSE) is a continuous process widely used in the food, polymer and chemical processing industries for compounding and extruding. Over the last decade or so the use of twin screw extruders for granulation has attracted considerable and serious interest in the pharmaceutical industry. Manufacturers (Leistritz Extrusionstechnik GmbH - NANO 16 [3], Thermo Fisher Scientific – Pharma 16 TSG [4]) now offer extruders marketed as capable for granulation. The ConsiGma™ system from GEA Pharma Systems [5] incorporates the first proprietary use of twin screw granulation (TSG) as a continuous granulation module. ConsiGma™ is a complete continuous package comprising some or all of blending, TSG, drying (semi-continuous), milling and tableting.

Granulation in a twin screw extruder was first reported by Gamlen and Eardley in 1986 [6] in the production of paracetamol extrudates. Followed by Lindberg et al [7] who used a similar extruder in the production of an effervescent granulation [7] and produced a series of papers in 1987-1988 on the determination of residence time [8] and the effect of process variables on granule properties and equilibrium conditions [7,9].

A Patent for twin screw granulation was awarded to Ghebre-Sellasie et al [10] in 2002 for the use of a twin screw granulator in a single pass continuous pharmaceutical granulation process. Since then the level of interest and depth of research into TSG has greatly increased. Research work has been undertaken including;

- Work into understanding the geometry of the screws and equipment;
  - Screw configuration
  - Conveying elements – pitch and length
  - Kneading elements – thickness and angle
  - Cross sectional area
  - Length to Diameter (L/D) ratio
- Operation variables;
  - Liquid to Solid (L/S) ratio
  - Material properties – Excipient and binder formulation
  - Screw speed
  - Material feed rates
- Process outcomes and product quality;
  - Mixing and Residence Time Distribution (RTD)
  - Granule Particle Size Distribution
  - Torque
  - Granule porosity/density
  - Final tablet properties

Given both the need for viable continuous processing and the developing interest in twin screw granulation this article seeks to review and present currently available research work in an effort to further process understanding and development.

2. Components

A twin screw granulator consists of two intermeshed screws enclosed in a barrel. As such there is small variety between granulators and differences are typically limited to geometric constraints i.e. length, screw diameter and specific screw element geometry. Co-rotating twin screw extruders are more popular in industry and so far only co-rotating twin screw granulators have been investigated. The effectiveness of counter-rotating screws on granulation has not been explored. Twin screw granulators work by conveying material along their screw length while imparting the mechanical energy required for liquid distribution and granulation in mixing zones. As the screws are intermeshing they are self-cleaning with the flight of one screw scraping clear the surface of the other in rotation.

There exists a large number of twin screw granulators with varying size and geometry. Granulators in use have varied from initial experiments carried out on modified twin screw extruders [11,12], to purpose built continuous tableting systems in GEA Pharma Systems ConsiGma™ continuous granulation module [5]. As the dimensions and processing capacity of granulators can vary greatly granulators are most commonly defined by the ratio of screw Length to Diameter (L/D). However granulation does not scale up linearly based around similar L/D ratios and instead requires optimisation based on the geometry of the granulator [12].

Figure 1 – Components of a typical Twin Screw Granulation module

Figure 1 shows the typical components of a twin screw granulator. A variety of feeders exist to feed powder into the barrel inlet such as screw feeders, gravity feeders and vibratory feeders. One of the challenges associated with feeding is the delivery of consistent feed of material which can be particularly difficult when dealing with materials with poor handling properties. Cartwright et al [13] have examined feeding of a poorly flowing API using a variety of loss in weight feeders. To consistently feed the API to the granulator, the original rigid walled hopper twin screw feeder had to be replaced with one of flexible wall design to prevent powder bridging. Additionally the various designs of screws available to the twin screw feeder were evaluated; feeding at the desired range was only possible with one design of screw (core and spiral) at a severely reduced maximum feed capacity. The other screw designs would lead to compaction of the API material and eventually cause the feeder to jam. Three different flexible wall single screw gravimetric feeders were compared to the twin screw feeder, it was concluded that for the application the Brabender FW40 gave the best performance due to its mechanical design and broad weight capability of the load cell [13]. It should not be forgotten that tablets are multicomponent formulations. The decision must be made whether to premix ingredients and feed with a single feeder (and run the risk of segregation/demixing) or to have multiple feeders. The latter presents a physical challenge of installation as well as the need to provide feeders of a wide range of delivery accuracy. The benefit would be to eliminate a step within a processing line however it also increases the mixing burden of the TSG. Despite some work covering co-feeding relatively small proportions of API [13,14] this has not been covered in the literature and is worthy of investigation.

Material in the granulator typically experiences a rise in product temperature due to friction between the material and barrel and the extensive work caused by kneading elements. Temperature controlled jackets allow for precise control of product temperature through cooling or heating, in the case of hot melt granulation [15-18] temperature profiles along the length of the barrel are also possible with appropriate design of the jacket.

The screws used in twin screw granulators are typically modular and are built up of matching pairs of individual elements on the screw root. There are broadly three types of screw elements used in granulation **Conveying elements**, **Kneading blocks** and **Comb mixer elements**.

Figure 2 – Typical Screw Profile of a bilobal screw geometry

The profile of two screw elements is shown in **Figure 2**. All screw elements, with the exception of comb mixer elements, share the profile **ABCD** and hence all elements have the same cross sectional area. Conveying elements can be considered to be made of an infinite number of slices of profile **ABCD** offset at slight angle to each other to produce a continuous helical flight. Kneading elements clearly share the profile **ABCD** with defined thickness, typically at a minimum of 1/8 D or 1/4 D, where D refers to the screw diameter. Screws with a double-flighted profile are typically used in twin screw granulation. Granulation with screws with single, triple or higher flighted profiles has not yet been reported.

As all elements (with the exception of comb mixer elements) share the same profile, the cross sectional area of the screws does not change along their length. The screw cross sectional area determinines the free volume - the available volume within the barrel unoccupied by the screws. The cross-sectional area is dependent on the ratio of inner (Di) to outer (Do) diameter[19]. Consider the hypothetical case of two granulators of different free volume but otherwise identical geometry, operating at the same speed and throughput. The material passing through the extruder with the lower free volume might be expected to be squeezed and compacted more. Shear stress might also be higher as the average gap would be lower. Hence the ratio Di:Do is an important design and operation consideration. This has received scant attention in the literature.

2.1 Conveying Elements

Figure 3 Pair of intermeshed conveying elements (a) Isometric view to show self-wiping geometry (b) End view to show screw profile

Conveying elements (see Figure 3) are designed to impart low mechanical energy and act to transport material between mixing zones. As their main role is transportation of material they impart low shear force. Screws operate part filled, with fill level dependent on screw geometry, material feed rate and screw speed. The angle of pitch determines conveying capacity. For a given rotation speed, longer pitch elements will operate at lower fill level or accommodate higher throughput without over fill. It is not solely about transport between mixing zones however:

Djuric and Kleinebudde [20] found an increase in the proportion of fine and oversize granules with decreasing flight pitch. Short pitch conveying elements have more flight chambers with smaller volume in a given length. Material can potentially become unevenly distributed between these flight chambers and remain isolated from interaction with adjacent chambers. This promotes the formation of lumps and reduces agglomeration, giving high proportions of oversize agglomerates and fines. Granule porosity decreases slightly with increasing flight pitch and is attributed to increased densification in the barrel chamber. The cause of the increased densification was not explored and the result is unintuitive as the superior feeding properties of long pitch elements would imply a lower overall fill level and less compaction [20].

Thompson and sun [21] found the size distribution of granules produced using only conveying elements to be bimodal with a high proportion of fines. When the fill level was increased from 30% to 70% by reducing the screw speed, the size distribution of granules remained bimodal however a greater proportion of large granules were formed. The authors suggest that the greater channel fill insulates the granules from the high shear environment at the barrel wall, leading to less breakage. Additionally, higher fill leads to higher compressive forces leading to consolidation and granule growth. Although granules of sufficient quality for tableting could be produced using just conveying screws only at high barrel fill level, further optimisation would be required to reduce the high proportion of unwanted fines.

While granulation has been shown to be possible with conveying elements only [21,22] further research would be required to establish that adequate mixing is achieved.

2.2 Kneading Blocks

Figure 4 60° Forwarding kneading block (a) Isometric view and (b) End view to show shared profile with conveying elements

Figure 4 shows a typical kneading block used for granulation. Kneading blocks are made up of individual kneading discs and act as mixing zones in twin screw granulation. Kneading blocks impart high mechanical energy into the wetted mass of powder, producing high shear forces, compaction and distributive mixing. Pairs of kneading discs in kneading blocks provide a region of compaction in the intermeshing region of the screws. The compaction between discs causes densification and squeezes liquid to the outside of the granule allowing for growth through consolidation. The chopping and shearing motion of kneading block breaks apart large agglomerates and disperses liquid.

The kneading discs in a kneading block are typically offset at angles of 30°, 60° or 90°. Depending on the angle of offset kneading blocks can produce forwarding or reversing flow [19,23]. Kneading blocks offset at 30° forwarding and 60° forwarding have some conveying capacity and will tend to push material forward along the screw. Reversing kneading blocks force material back against the direction of flow leading to areas of high pressure and compaction. Although strong granules can be formed the risk of blockages is high [20]. 90° blocks have no inherent conveying capacity and are dependent on “pressure” driven flow [21].

Vercruysse et al [24] found the angle of kneading elements to have no significant effect on particle size distribution under the conditions investigated. However the number of kneading elements contributes significantly to the properties of granules [20,24]. An increase in the number of kneading elements leads to a reduction in the proportion of fines (defined as granules <150 µm) formed and an increase in the proportion of oversize agglomerates (>1400 µm). A correlation between the number of kneading elements and torque generated was found. Higher numbers of kneading elements lead to granules with higher density and longer dissolution times. The number of kneading elements significantly affects the heat generated in the barrel. Within the study, higher barrel temperatures were found to lead to less friable granules. This was thought to be due to the increased solubility of the lactose, theophylline mixture resulting in more solid bridges formed after recrystallization. An analysis of start-up time was undertaken and it was found that more kneading elements leads to a longer time to equilibrium (steady state torque and temperature). The time taken to equilibrium was suggested to be the period within which gradual layering of material on the barrel wall in mixing zones completes. It was suggested that material loss during start up could thus be minimised through a feedback control system within the temperature control jacket in order to compensate for heat generated through friction in mixing zones.

Thompson and Sun [21] found that the angle of kneading elements only affect granule properties when the fill level is high. At low fill only small changes in granule properties were observed for kneading discs offset at different angles. Thus the intermeshing region between kneading discs is the important factor in determining granule morphology. Long compressed granules with a ribbon like shape were formed in the intermeshing region, suggesting the thickness of the kneading discs in a kneading block controls the size of granules.

Van Melkebeke et al [14] found that the inclusion of a conveying element after a kneading block led to a reduction in oversize agglomerates, but otherwise no effect on granule properties. The porosity of granules produced with a single kneading block were similar for 30°, 60° forwarding and 90° offset angles however the median pore diameter from the 90° configuration was significantly lower . The neutral conveying characteristics at 90° led to higher material pressures and compaction. Tablets were formed by compression and while all granules had similar compressibility tablet strength decreased slightly at higher offset angle. However all tablets displayed similar disintegration times.

Periodic surging of material has been observed by Shah [25] and Thompson and Sun [21]. Surging could be eliminated through modification of the screw configuration and was a result of the specific equipment setup. Periodic surging is not typical of twin screw granulation and was attributed to the high flow resistance of the kneading block. However surging is likely a result of the liquid inlet port location relative to the kneading block rather than kneading block characteristics. Shah [25] explored atypical configurations where liquid was injected directly before the kneading block rather than in a relatively long conveying section. It is likely that the long residence time in the kneading block led to an overly wetted zone due to the constant liquid feed, resulting in sticky flow resistant material. A build-up of material in the conveying zone leading up to the kneading block would then be required to generate the throughput force required to dislodge the paste like pseudo-blockage, resulting in the periodic surging. Thompson and Sun [21] explored methods of liquid injection, the exact configuration is not described but was likely similar to that of Shah [25].

2.3 Comb mixer elements

Figure 5 Pair of Comb mixer elements (a) Isometric and (b) End view

Comb mixer elements shown in **Figure 5** are a type of distributive mixing element typically used in extrusion processes. Comb mixers are composed of rings arranged perpendicular to the direction of flow containing angular cuts in the ring wall to allow for the passage of material through the element. Comb mixers act to distribute and recombine flow streams in the extruder in a low shear environment providing good mixing of material. The angle of cut in the ring wall determines the direction of flow generated by the comb mixer element, comb mixers can generate forwarding or reversing flow either aiding or opposing downstream flow. As flow through comb mixer elements is dependent on material pressure flow they generally operate fully filled [21].

Thompson and Sun [21] investigated the effect of the Leistritz GLC-type comb mixer element. Their results showed that reversing mixer elements would lead to high pressure zones in the mixing section leading to extensive agglomeration of material and the formation of a large proportion of oversize agglomerates even at low fill level. At high fill level the high pressure zone caused by the mixing element would lead to blockage of the granulator. Forwarding mixer elements behave similarly to kneading elements, producing granules with a bimodal size distribution with increasing particle size with increasing fill level. Placing two comb mixers in series removed the effect of fill level on granule size distribution as the compaction and fracture of particles was mitigated between the two elements, leading to a uniform particle size distribution [21].

Comb mixer elements produce granules of greater density than conveying elements but lower density than kneading blocks. With high density granules being the least friable [20].

Figure 6 Optical micrographs demonstrating particle shape for specimens found on the 850 µm sieve for screws with the following element at location 180 mm from the screw tip: (a) 30 mm conveying, (b) 60° kneading block, (c) forwarding comb mixer, (d) series of two forwarding comb mixers, (e) 60° kneading block followed by forward comb mixing element, and (f) reverse comb mixer. Conditions: 7.5% (w/w) binder and 30% channel fill. Included scale bar represents 1 mm.

(Thompson, M. R. and J. Sun (2010) ***Wet granulation in a twin-screw extruder: Implications of screw design*** *Journal of Pharmaceutical Sciences 99(4): 2090-2103.*)

In **Figure 6** Thompson and Sun [21] demonstrate the wide range of granule shapes that could be produced in the same size range with various screw elements by twin screw granulation. From their findings they suggest that the particle shape could be tailored allowing a user another dimension of control unavailable in batch granulation techniques such as high shear mixing and fluidized bed granulation.

The shape of granule formed was dependent on the type of screw element used and was dominant over changes in formulation or binder concentration. It was suggested that the differences in granule shape observed in the study would persist for any comparable material system.

3. Mixing and Residence time

Characterization of the residence time distribution is an important step in design, improvement and scale-up of twin screw systems [26,27]. Typically higher mean residence times lead to better distributive mixing during extrusion, however the complex rheological mixtures used in granulation increase design complexity. Understanding of residence time distribution is a powerful tool in process design in producing high quality product while meeting design criteria. RTD represents the degree of axial mixing, where good mixing is important in smoothing out any variation in feed. RTD can either be measured by a stimulus response test [18,28-32] or direct measurement such as through particle tracking [33].

In a series of papers on the mechanics of twin screw granulation Dhenge et al [28-30] investigated the effect of process parameters on residence time. RTD was determined using an impulse response technique where a dye was added as a tracer. Given the short mean residence times measured (10-20 seconds) it should be noted the sampling interval was fairly broad at 10 seconds.

Mean residence time decreases with increasing screw speed due to the increased conveying capacity of the screws. Residence time was shown to decrease with increasing material feed rate. Dhenge et al [29] came up with the concept of “throughput force” to describe efficiency of transport. Low feed rates lead to small material throughput force and what was described as increased “back mixing” due to the smaller degree of forwarding flow, giving broader residence time distribution curves **Figure 7** [29]. Both an increase in liquid to solid ratio and binder viscosity leads to an increase in mean residence time and a broadening of residence time distribution curves. Both liquid to solid ratio and binder viscosity change the rheology of the mixture in the granulator, increasing either factor causes the wetted powder to become stickier and more resistant to flow **Figure 8** [30].

Figure 7 Residence time distribution curves at different powder feed rates.

(Ranjit M. Dhenge, James J. Cartwright, David G. Doughty, Michael J. Hounslow, Agba D. Salman, ***Twin screw wet granulation: Effect of powder feed rate,*** *Advanced Powder Technology, Volume 22, Issue 2, March 2011, Pages 162–166)*

Figure 8 Residence time distribution with increasing amounts of HPC at different liquid to solid ratios.

(Ranjit M. Dhenge, James J. Cartwright, Michael J. Hounslow, Agba D. Salman, ***Twin screw wet granulation: Effects of properties of granulation liquid****, Powder Technology, Volume 229, October 2012, Pages 126–136)*

Lee et al [33] used PEPT (Positron Emission Particle Tracking) to determine residence time in the granulator and RTD across individual screw elements. Due to the nature of PEPT residence time distribution was determined at low material flow rate and screw speed. Residence time was observed to decrease with increasing screw speed. Increasing the material feed rate also decreases the overall residence time as shown by Dhenge et al [29], due to the greater amount of material in the granulator producing more conveying capacity. Increasing the kneading disc offset angle increased the residence time due to the reduced conveying capacity at higher angles. At higher material feed rates and screw speeds the difference in residence time between 30° and 60° kneading blocks becomes less significant. It was suggested the higher material throughput allowed for more bypassing of the 60° blocks [33].

The extent of mixing of different screw configurations was compared by Lee et al [33] through normalisation of the residence time distribution. Near identical normalised RTD curves and Peclet numbers were found for screws with 30°, 60° and 90° kneading blocks. It was concluded that the extent of axial mixing is similar regardless of screw speed, powder feed rate and screw configuration [33]. This contradicts the results of Kumar et al [32] who found considerable variation in axial mixing and may be a feature specific to the low screw speeds and feed rates necessary for PEPT. Thus this is worthy of further investigation.

Using a method developed by Vercruysse et al [34], Kumar et al [32] carried out an extensive study on RTD and mixing within TSG. RTD was determined by near infra-red (NIR) chemical imaging of granules discharged onto a moving conveyor belt. RTD curves were determined and three factors quantified; the mean residence time (t_m), the Peclet number (Pe) and the normalised variance (σ_θ^2) a description of the breadth of the RTD curve which represents the extent of axial mixing. Screw speed, material feed rate, number of kneading elements and element offset angle were the parameters explored. Multivariate analysis was undertaken to determine the factors of greatest impact.Screw speed has the largest effect on t_m, higher speeds give shorter residence times. Screw speed has the greatest interaction with material feed rate which alone had relatively small effect on RTD. Screw speed and material feed rate were equated as the factors most important in generating "throughput force", a crucial factor in determining RTD and mixing behaviour. Both screw speed and material feed rate cause a reduction in t_m at higher values, however neither scales linearly, with a greater effect from transition from low to middle conveying capacities than middle to high. Higher screw speeds lead to improved axial mixing, indicated by a rise in σ_θ^2. This is most prevalent under low fill conditions with reduced material feed rate and few kneading elements. Under high fill conditions increasing screw speed will reduce mean residence time without improving axial dispersion as flow becomes plug like. At low screw speeds Pe rises sharply with feed rate, number of kneading elements and element angle indicating a transition to plug flow when there is low throughput force.

The offset angle of kneading discs only affects RTD when high numbers of kneading discs are used. The number of kneading discs has a considerable effect on RTD. As expected mean residence rises with increasing number of elements, however the relationship is not linear: the effect diminishes with increasing number [18,32]. Increase in the flow impediment through higher number of elements or more pronounced offset angle leads to longer mean residence times and by implication longer mixing times. However with high flow impediment variance is lower and Peclet numbers increase, indicating less axial mixing and more plug like flow. Thus to ensure good axial mixing it was concluded that throughput force must be correspondingly raised through screw speed [32]. While the RTD study of Kumar is in depth and extensive, further understanding of the relationship of flow impediment and throughput force is required, particularly in understanding the mechanisms of mixing elements. No data on granule properties was presented thus it is difficult to correlate changes in granule quality and mixing mechanisms with changes in axial dispersion.

An advantage of PEPT over other techniques is that it allows for analysis of residence time within individual screw elements as well as the entire screw length. Lee et al [33] determined that kneading blocks have a longer residence time than conveying zones and broader RTD curves, indicating the dispersive mixing of material passing through them. Analysis across individual elements also allows for calculation of the fill level in mixing and conveying zones, based on the steady state material throughput and the average residence time, as shown in **Figure 9**. Fill levels are shown to be proportional to the material input rate and inversely proportional to the screw speed. Fill levels across the kneading block are low for 30° and 60° offset angles indicating that the flow of material is mainly due to their inherent conveying capability. Fill levels across 90° blocks never reach 100%

occupancy and a fill gradient is established decreasing from the first kneading disc suggesting pressure driven flow of material.

Figure 9 Occupancy along granulator with (a) 30°; (b) 60° and (c) 90° mixing zones

(*c* = conveying; *k* = kneading)

(Kai T. Lee, Andy Ingram, Neil A. Rowson, ***Twin screw wet granulation: The study of a continuous twin screw granulator using Positron Emission Particle Tracking (PEPT) technique****, European Journal of Pharmaceutics and Biopharmaceutics, Volume 81, Issue 3, August 2012, Pages 666–673)*

Van Melkebeke et al [14] analysed the mixing efficiency in twin screw granulation through co-feeding of tracers. In separate experiments low volumes of tracer were fed as a separate dry stream (2.5% w/w) and within the granulation liquid (0.05% w/w). Analysis of granules showed tracer distribution was excellent for both feed methods with homogeneous tracer distribution across all granule sizes. Tracer distribution was also independent of time with small variance over one hour. As such it was determined that twin screw granulation displays good mixing efficiency independent of tracer addition method, screw configuration, granulation time and granule size. The conclusions for liquid tracer distribution contradict somewhat the results of El Hagrasy & Litster [35] who found the screw configuration to have considerable control over liquid distribution across the granule size range.

4. Liquid to Solid Ratio

Liquid to solid ratio is an important factor in twin screw granulation. TSG is advantageous in that the minimum liquid to solid ratio to consistently granulate a formulation is lower than in other conventional wet granulation techniques such as high shear mixing and fluidised bed granulation [11,12,36,37]. TSG is also more tolerant of high liquid to solid ratios and the point at which over-wetting occurs is higher than in high shear granulation [37]. Thus the operating range for TSG is broader providing a higher degree of process control. Minimum liquid levels are required for granulation to take place [11,12,38,39], similarly an upper limit exists beyond which powder becomes over wetted and forms a paste [11,12,21,38,39].

Twin screw granulation has some advantages over high shear mixing in its capability to granulate difficult to process active pharmaceutical ingredients. Keleb et al [36] were able to produce granules of pure paracetamol using water as a granulation liquid through twin screw extrusion granulation but were unable to do so by high shear mixing. Similarly through the use of a modified twin screw extruder Shah [25] was able to produce granules with high drug dosage at API to excipient ratios that would result in a tacky mess through high shear granulation.

The size distribution of granules produced by TSG is characteristically broad and bimodal at low liquid to solid ratios becoming narrow and monomodal at high liquid to solid ratio. However it is important to note that the monomodally distributed granules at high liquid to solid ratios are too large to be directly used for tabletting [28,31,37].

Multiple authors [2,18,31] found the average size of granules to increase with increasing liquid to solid ratio. Dhenge et al [2] suggest this is due to the higher liquid amount leading to greater liquid distribution and providing more surface wetting of granules. Contrary to this, in a separate paper Dhenge et al [28] found the average size of granules to decrease with increasing liquid to solid ratio however this was due to the shape of granules being produced. Low liquid to solid ratios would result in elongated granules which skew the size distribution. Granules produced at low liquid to solid ratios generally consist of a mixture of fines and large oversize agglomerates, increasing liquid to solid ratio gives both a reduction in both fines and oversize agglomerates [28]. However El Hagrasy et al [31] observed that some oversize lumps remained regardless of liquid to solid ratio, from which they inferred that kneading blocks partially break down lumps formed by liquid addition but do not cause complete liquid dispersion.

El Hagrasy et al [31] analysed the effect of changing liquid to solid ratio on formulations consisting of three different grades of lactose. Size distributions displayed the bimodal to monomodal shift at high liquid to solid ratio regardless of the grade of lactose. Despite one grade of lactose investigated, Supertab 30GR, having a narrow monomodal size distribution, the size distribution of granules at low L/S ratios were bimodal, similar to the other grades of lactose (Pharmatose 200 M and Lactose Impalpable).

El Hagrasy et al [31] believe the method of binder addition contributes to bimodality, analogous to spray versus drop-wise binder addition in high shear mixing. The current most commonly used method of liquid addition is by direct injection through liquid inlet ports, resulting in concentrated wetted areas, as with drop wise addition in high shear mixing. The granulator provides insufficient mechanical dispersion to give homogenous liquid distribution, resulting in large wetted agglomerates and small dry fines [31].

In a recent paper El Hagrasy and Litster [35] examined granule formation in the kneading elements of a twin screw granulator and developed concepts for the dominant rate processes. Liquid distribution was analysed and found to be unevenly distributed within the granule population, skewed toward the top end. Liquid distribution became more uniform in screw configurations that provided more densification and similarly with increasing kneading block length. As such for mixing zones with three kneading elements the liquid distribution could be ordered from best to worst as follows: 30°R > 60°R > 90° > 30°F > 60°F. Interestingly the 60°F setup, which is generally the most commonly used in current granulation work, displayed the worst liquid distribution, with characteristics closest to conveying elements [35]. Contrary to this Yu et al [40] found a notably higher improvement in liquid distribution homogeneity with increasing number of 60°F kneading elements than that observed by El Hagrasy and Litster [35]. This was attributed to the differences in liquid injection method. The granulator used by Yu et al [40] featured dual inlet ports set in parallel on top of either screw, the authors believe this setup results in a more uniform distribution during nucleation, making the granulator less reliant on mechanical dispersion. A similar result was obtained by Vercruysse et al [34] with the variance in moisture content reducing with when a larger number of elements was used.

El Hagrasy and Litster [35] suggested granulation rate processes in kneading sections according to the three dimensional shape characterisation of granules. Analysis of the morphology of the granules allowed for determination of the mechanisms behind formation. Two main rate processes by which the granule shape, size and liquid distribution are determined were suggested. The two main rate processes are: firstly: *Breakage and Layering* and secondly: *Shear-elongation and Breakage followed by Layering*. Breakage and layering occurs in neutral and forwarding kneading blocks (90° and 30°F), barring 60°F kneading blocks which display characteristics closer to conveying elements. Reversing geometries (30°R and 60°R) exhibit Shear-elongation combined with breakage and layering.

A point to note is that 60 granules for each configuration were chosen for shape analysis, all from the 2-2.8mm size range, corresponding to the second mode in the bimodal size distribution. As such the differences in shape between these and smaller granules was not considered. Presumably the shape of granules within this size range is considered comparable to granules of all sizes, which may not necessarily be a fair assumption.

Primary agglomerates are formed by drop nucleation at the point of liquid addition, resulting in large, low strength, intensely wetted agglomerates. In configurations where breakage and layering is the main rate controlling process these primary agglomerates are broken apart by the "chopping" motion from intersection of the kneading elements. This results in smaller rounded granules with exposed wetted edges. These newly formed wetted edges then allow for growth through layering as dry primary powder particles adhere to the surface.

In reversing configurations the kneading block operates fully filled and generates force against the direction of forwarding flow. Material passes through the kneading block as it becomes smeared out between the block and barrel wall, forced through by build up of material within the conveying section upstream of the kneading block. This is similar to flow through reversing geometries in extrusion processes. Shear-elongation occurs as the material becomes smeared against the barrel wall, causing densification and driving liquid to the outside of the granule structure. The thinning in structure during shear-elongation results in an easily broken "ribbon" that splits into thin, dense "flake-like" granules. The wetted surface of these flake-like granules formed in shear-elongation allows for secondary growth through a layering stage [35]. While it was shown that 30° reversing kneading blocks result in monomodal granules with the most uniform liquid distribution, it is important to note that other properties may mean these granules are impractical for downstream use. Their flake-like will result in difficulties with handling and particle flow. Furthermore the high densification that granules undergo during shear-elongation may result in granules with poor dissolution times, as well as low strength, friable tablets due to the low granule compressibility leading to poorly interlocked particles during tableting.

Figure 10 (a) Rough elongated granules produced at L/S of 0.25. (b) Rounder, smoother granules produced at L/S of 0.4.

*(Ranjit M. Dhenge, Richard S. Fyles, James J. Cartwright, David G. Doughty, Michael J. Hounslow, Agba D. Salman, **Twin screw wet granulation: Granule properties**, Chemical Engineering Journal, Volume 164, Issues 2–3, 1 November 2010, Pages 322–329)*

Many authors have examined the effect liquid to solid ratio has on the shape of granules produced by twin screw granulation. The aspect ratio of granules decreases with increasing liquid to solid ratio as particles become more rounded [28,30,41] . **Figure 10** shows granules produced at low and high liquid to solid ratios. At low liquid to solid ratios granules produced by twin screw granulation are long and elongated with rough surfaces. High L/S granules become more spherical with smooth surfaces due to surface wetting and increased granule deformability [28]. In the granulation of pure microcrystalline cellulose with water, Lee et al [37] produced granules with similar aspect ratios through both twin screw granulation and high shear mixing. However granules produced by twin screw granulation were found to have a much lower sphericity than high shear mixer granules. Scanning electron micrographs attribute this to the much rougher surfaces of granules produced by twin screw granulation. The porosity of granules decreases with increasing liquid to solid ratio [30,31], due to the greater wetting of the powder bed producing more deformable granules that are more easily compacted.

With the addition of liquid, wetted material becomes cohesive and resistant to flow. So granulator torque initially increases with rising liquid to solid ratio, until a critical liquid to solid ratio is reached beyond which the liquid acts as lubricant reducing friction and flow resistance [30].

5. Binder viscosity

In TSG an increase in viscosity of binder liquid (i.e. binder concentration) reduces the amount of liquid required to produce granules with a monomodal size distribution [30]. Dhenge et al [30] found the average size of granules to be proportional to the binder viscosity and a similar result was found by Keleb et al [12]. An increase in PVP concentration led to an increase in the mean granule size due to the superior binding properties of PVP over pure water. It is possible to produce granules within higher size classes at lower water concentrations with the addition of PVP [11,36].

When using screw configurations with conveying elements only the relationship between average granule size and binder viscosity is reversed. Dhenge et al [22] attributed this to the low shear environment caused by conveying screws leading to a dependence on drop penetration time for liquid dispersion. High viscosity binder solutions penetrate the bed slowly leading to poor liquid distribution and a high proportion of fines.

The relationship between binder viscosity and granule size is formulation dependent and will require process optimisation based around material. Yu et al [40] demonstrated that although d_{50} increases for hydrophilic formulations at higher binder concentration, when formulations contain substantial hydrophobic materials d_{50} is lower following the addition of binder than with pure water. This was explained by the preferential take up of liquid by hydrophilic components during nucleation resulting in more ungranulated hydrophobic fines. The presence of binder in the hydrophilic agglomerates increases their strength making them more resistant to breakage and redistribution of liquid. Further increases in binder viscosity result in higher d_{50} values as the increased strength of the hydrophilic agglomerates allow them to retain size and skew the size distribution [40].

Binder viscosity displays a small influence over the shape of granules, with more rounded granules formed at higher binder viscosity. Thompson and Sun [21] suggest that the effect of binder concentration on shape factor only occurs with conveying screw elements.

The porosity of granules decreases with increasing binder viscosity as stronger liquid bonds are formed under compaction and consolidation, leading to denser particles. Similarly the strength of granules increases with increasing binder viscosity due to the overall 'stickiness' of the material increasing, leading to a greater number of viscous bonds being formed during particle interaction [2,30,40].

Viscous binders change the rheology of the powder mixture. Dhenge et al [30] describe how viscous binders cause "thickening" leading to an increase in the cohesiveness and frictional resistance of the material to flow. This increases the energy required to rotate the screws which is observed as an increase in motor torque. The mean residence time increases due to the increased cohesiveness and resistance to flow. This increase in residence time in the granulator means intensified compaction and consolidation of granules. This explains the raise in granule strength and decrease in porosity observed in granules. Similarly aspect ratios are closer to unity as elongated granules are broken and compressed to more uniform shape [30].

Dhenge et al found [30] the surface tension of binders to have no notable effect on the residence time of the granulator or motor torque. However it should be noted that the concentrations of surfactants used in this study were low and surface tensions were similar. Surface tension produces no discernible changes in granule size, shape and morphology. This is due to viscous forces being far more dominant over surface forces, meaning that variation in surface tension has little effect on the mixture rheology [30].

5.1 Granulation Regime maps

Existing regime maps for batch wet granulation such as that for drum and high shear granulation developed by Iveson and Litster [42] are robust and play an important role in process development.

Understanding the granulation rate processes is essential for regime map development. Twin screw granulation differs from batch granulation in that it is a continuous, ideally steady state process. Granulation regimes occur simultaneously and are physically separated from each other, with nucleation, growth and breakage processes occurring one after the other along the length of the screws. As such granulation becomes unique for each screw configuration and the application of a general regime map may not be feasible [43]. Furthermore despite insightful studies [35,41] granulation rate processes of screw elements are still not well understood. This is frequently reflected in the lack of systematic arrangement in screw configurations, elements are approached as a series of “black boxes” or the screw unit as a single “black box”.

Nevertheless authors have made efforts to develop regime maps for twin screw granulation. Tu et al [43] developed regime maps based on variation in screw speed (and thus fill level) and L/S ratio; such regime maps are highly geometry, formulation and screw configuration dependent. This was demonstrated by re-feeding the granules in a series of passes through the granulator to imitate multiple mixing sections in a longer screw length. Multiple passes consolidated granules to a more homogenous state resulting in an increasingly uniform size distribution. However behaviour was different in a long single mixing section which was more prone to blockages, highlighting the interdependency of conveying and mixing elements. By non-dimensionalisation of the screw speed in terms of Froude number (Fr) an attempt was made to compare granules produced at similar values of Fr to that of previous work on high shear granulation. Froude number was identified as not a viable factor for comparison as screw speeds required for TSG were an order of magnitude higher than those investigated [43].

Similar to the regime map for drum and high shear granulation developed by Iveson and Litster [42], Dhenge et al [22,30] have developed two regime maps for twin screw granulation. A granulation regime map for screws including kneading elements [30] and for screws with conveying elements only [22]. Dhenge et al [30] suggest that as twin screw granulation is an open ended process growth mechanisms are not time dependent, therefore granulation is less dependent on rate processes and more dependent on the binding capability of the liquid. The binding capability of the liquid is determined by the liquid to solid ratio and the binder viscosity. The free volume in twin screw granulation is smaller than in high shear or fluidised bed granulation and the stresses acting on material are believed to be higher. As the stresses on the material are more important in determining rate mechanisms and granule properties the value of Stokes deformation used in Litster and Iveson's [42] regime map has been replaced by the deformation value (β) equal to the ratio of the stresses acting on powder or granules (σ) to the strength of granules (τ) [24]. The stresses (σ) acting on material are represented by the value of torque (T) divided by the volume of material in the barrel (V). The strength of granules was determined using Adams' model [44] following a uniaxial compression test of dried granules, which as stated should be ideally replaced by the wet granule strength [30]. This is a weakness of the regime maps and work is required to measure the wet granule strength.

Figure 11 Granule growth regime map for twin screw granulation with kneading elements.

(Ranjit M. Dhenge, James J. Cartwright, Michael J. Hounslow, Agba D. Salman, ***Twin screw wet granulation: Effects of properties of granulation liquid****, Powder Technology, Volume 229, October 2012, Pages 126–136)*

Figure 11 shows the granulation regime map for screws with kneading elements. There are four different regions in the regime map; "under-wetted (dry)", "crumb", "granules" and "over wetted or paste". The "under-wetted" region consists of un-granulated or poorly granulated powder, the boundary between the "under-wetted" and crumb region is determined by the liquid to solid ratio and binder viscosity. Small increases in liquid to solid ratio or binder viscosity will shift the material into the "crumb" region consisting of small or poorly granulated granules. Addition of higher amounts of liquid will lead to the "granule" region where consolidated, strong and stable granules are formed. Higher liquid to solid ratios or binder viscosities will result in "over-wetted material or paste". High deformation values at intermediate L/S & binder values can shift the system from the "granule" to the "crumb" regime; at high deformation values the system is weaker and granules are unable to support their structure under the stresses they are undergoing. The boundaries of the granule regime map are highly system dependent and will move according to the process parameters used such as screw configuration, material properties and operating conditions.

Figure 12 Granule regime map for TSG using conveying screws.

(Ranjit M. Dhenge, Kimiaki Washino, James J. Cartwright, Michael J. Hounslow, Agba D. Salman, ***Twin screw granulation using conveying screws: Effects of viscosity of granulation liquids and flow of powders****, Powder Technology, Available online 29 May 2012)*

The regime map for conveying screw in **Figure 12** is similar to that for screws with kneading elements, however it differs in the formation of nuclei in the crumb region. “Nuclei” refers to the wetted mass formed after liquid addition under the liquid injection port in the granulator. These are relatively well wetted but poorly formed, loose agglomerates. They remain fully formed when using conveying screws due to the low shear forces imparted on to the material and are easily broken down by kneading blocks.

6. Binder addition method

El Hagrasy et al [31] compared the results of adding dry binder (in the solid phase) to wet binder (in the liquid phase) on granulation. Formulations were a mixture of lactose and microcrystalline cellulose with HPMC as a binder. Granulation was carried out at a liquid to solid ratio of 0.3 and the effect of adding binder in the solid or liquid phase was compared. Three methods of binder addition were used: first with the HPMC binder mixed with the excipients fully in the solid phase, secondly in a 1:1 ratio in the solid phase and solubilised in the liquid phase, and finally with all the binder fully solubilised in the liquid phase. The size distributions for all conditions and grades of lactose were similar, however it was found that the greater the proportion of binder in the liquid phase, the lower the amount of fines and narrower the size distribution. This was attributed to the short residence in the granulator meaning the dry binder has insufficient time to solubilise and become fully distributed. The use of a wet binder allows for greater binder distribution, giving a smaller proportion of fines [31]. A similar result was observed by Vercruysse et al [24] who concluded binder was more effective when added in the liquid phase.

Typically granulation liquid is fed into the barrel through a single injection port. Shah [25] explored a range of locations for single and dual injection ports. How these were arranged relative to the screw configurations used is a little ambiguous. A single liquid injection port led to surging of material and "torque excursions" possibly due to over-wetting of material as described earlier. Optimisation of liquid injection was explored via dual ports. The set-up which resulted in minimum torque featured two ports both located in the feed conveying zone, the first port positioned at the point of powder feed inlet and the second immediately before the first pair of mixing elements. This also eliminated surging of material [25]. Vercruysse et al [34] determined the moisture content of granules as they were discharged through NIR chemical imaging. A periodic fluctuation in the granule moisture content corresponded to pulsation of the peristaltic pump delivering liquid. By running two pumps out of phase the fluctuation in moisture content was eliminated however the standard deviation in moisture content was only marginally improved. As the size distributions of granules were bimodal under these conditions according to the results of El Hagrasy and Litster [35], the variance in liquid distribution may be a result of the non-uniform liquid distribution of liquid across the size range exhibited in granules formed by 60°F kneading blocks. Contrary to the results of Shah [25] the use of dual injection ports led to no improvement in liquid homogeneity. The liquid injection port is the same as that of Yu et al [40] where each port consists of two nozzles mounted in parallel, one above each screw. Yu et al [40] believe this setup leads to superior liquid distribution during nucleation and may be the reason why Vercruysse et al [34] observed no differences with the addition of a secondary port.

The droplet size is important in high shear granulation. To explore the comparative effect in TSG Vercruysse et al [34] used nozzles of varying diameter to inject liquid assuming that the liquid would enter the granulator in discrete droplets proportional in size to the nozzle diameter. No effect on liquid homogeneity or particle size distribution was observed. However the assumption of droplet nucleation may not be valid, given the layering of material observed on barrel walls [24] liquid may be delivered into a region of saturated paste rather than forming separate droplets. Thus wetting during nucleation may be more reliant on liquid feed pulsation than theoretical droplet size.

Thompson et al [39,45] investigated the use of foam granulation in a twin screw extruder as a method of reducing surging and improving process stability. To achieve this a foamed binder was fed into the extruder through a side stuffer. The shear strength of the foam allows it to flow separately alongside the powder material and the slow drainage time into the powder bed gives a large wetted contact area, which allows for more homogenous growth of granules. The foam forms a boundary slip layer between the barrel wall and powder material during penetration, reducing the frictional forces and heat generated.

7. Fill level, Screw Speed and Feed rate interaction

The barrel fill level in granulation depends on three factors: the screw and barrel geometry, the screw speed and the material feed rate. High screw speed lowers fill level, high feed rate raises it, thus operating fill level is determined by these factors. The fill level is an essential factor in determining granule properties. High fill levels result in high compaction and densification, low fill levels can result in insulation of material from interaction. Fill level affects the residence time in dictating the throughput force for material to flow through mixing zones and affects mixing mechanisms [32]. Thus fill level is an essential consideration during scale up as behaviour may be totally different despite similar screw speeds and feed rates.

The free volume in the barrel is determined by the screw geometry and is therefore a fixed property, during operation the fill level can therefore be controlled by the screw speed and material feed rate. Granulator geometry has variation between different vendors including the clearance between the barrel wall and screws. These differences in clearance are believed to have impact on the granulation process and product quality. For example the residence time and thickness of the slip layer of material which forms against the barrel wall [32,33] which has repercussions for the "Shear elongation and breakage" rate process proposed by El Hagrasy et al [35]. Thus despite similar operating conditions operators may see variation in granule quality from different granulators.

Therefore knowledge of the fill level relative to operating conditions is important in interpreting the final properties of granules, however quantifiable determination of fill level is noticeably absent within papers, potentially due to the complexity in calculating free volume and determination of residence time. Additionally the axial variation of fill level as shown by Lee et al [33] increases complexity.

Fill level is an important factor which should be considered in comparison of different granulators. An additional property overlooked is Specific Mechanical Energy (SME), the energy input per unit mass, essentially power consumption divided by mass rate. SME would allow for direct comparison between different granulators and provide understanding into how granule properties relate to the energy input. Furthermore, SME has importance in an industrial context in determining running costs of equipment.

7.1 Screw speed

Screw speed has been reported to have a minor influence over the properties of granules formed by twin screw granulation [12,28,46]. This appears to contradict the fact that screw speed is a critical factor in determining the barrel fill level, which is crucial in determining granule properties. It may be that, as reported within typical operation limits screw speed has small effect over granule properties, however toward the upper and lower limits of barrel fill the properties of granules become more dependent on fill level. High screw speeds lead to short residence times in the granulator and the conveying capacity is greater [28].. At a constant feed rate, low screw speeds result in high torque values due to the greater mass load of material filling the granulator. High screw speeds give a reduction in torque as the increased conveying capacity of the screws results in a lower barrel fill level and a lower mass load [21]. Tan et al [47] suggest that at low screw speeds frictional resistance between material and the internal granulator surfaces plays a role in increasing the energy demand in addition to mass load. At high screw speed frictional resistance is considered less important.

Low screw speeds result in high fill levels in the granulator barrel, leading to material compaction where blockages can form at high mass loads. High screw speeds result in low barrel fill levels, where the screw channels may become starved of powder resulting in low compaction and particle interaction. As variation in fill level can result in considerable differences in binder distribution and granule properties screw speed is an important factor to be considered during scale up of twin screw granulation [48].

Dhenge [28] found a small reduction in the size of granules with increasing screw speed, the longer residence times at low screw speeds allow for greater growth of granules. The combination of higher shear and lower fill at high screw speed leads to poorly compacted, rough surface, elongated granules. Conversely granules produced at low screw speeds undergo greater compaction resulting in smooth surfaces and more spherical shape.

Similar results were found by Thompson et al [39] who suggest that the lower screw speed leads to an upstream pressure at the kneading block leading to greater compaction of material. Furthermore granules experience fewer "chopping" events as they flow through the kneading block, leading to less breakage. This is supported by the work of Kumar et al [32] who demonstrated that flow becomes more plug like at low screw speed. Thompson et al [39] found an increase in granule fracture strength with screw speed. Screw speed was inversely correlated with granule size, small granules produced at high screw speeds displayed higher fracture strengths than large granules produced at low screw speeds. However this may be the result of the size strength relationship of granules, a full evaluation should compare the strength of granules in comparable size classes in order to determine this.

Lee et al [37] observe that the influence of screw speed on average particle size only occurs at higher liquid to solid ratios. Variation in screw speed gave no change in average granule size at low liquid to solid ratio however at high ratios an increase in screw speed led to a decrease in average granule size. However screw speed produced no significant effect on granule porosity or strength.

7.2 Material Feed Rate

Many authors observe that the strength of granules is dependent on the fill level. The higher the feed rate, the more powder in the barrell and the denser and stronger the granules formed

[21,28,29,46,48]. Motor torque at steady state increases with increasing material feed rate [24,29]. Dhenge et al [29] took torque values to be an indication of the degree of compaction of the material in the granulator, as the porosity of granules decreased with increasing material feed rate, shown by X-ray tomography. The greater compaction of granules at higher feed rates leads to stronger granules with longer dissolution times [46,48].

Surface velocity of powder above conveying screws was determined by Dhenge et al [22] through Particle Image Velocimetry (PIV). The surface velocity of powder was higher at lower feed rates. Dhenge et al [22] suggest that the higher fill level at pronounced feed rates leaves less space for individual particle movement due to the close packing of particles. Powder moves in the form of compacts as opposed to individual particles. The higher fill level results in greater frictional forces between the powder and barrel wall, giving lower surface velocity. At low fill levels particles are able to move freely and experience less frictional resistance and therefore surface velocities are higher [22]. This is confirmed by Kumar et al [32] who observed poorer axial dispersion under higher feed rates.

Contrary to the results of Dhenge et al [22,28], Djuric et al [46,48] found the median size of granules to increase with increasing material input rate. The difference in results can be explained by the different screw configurations used in the studies. Djuric [46] compared two granulators with the same screw configuration but different size. Both had a single long kneading block. Dhenge et al [28] used the same number of kneading elements relative to screw length but arranged as two separate kneading blocks. The single long kneading block leads to enhanced compaction and consolidation meaning growth rates outweigh breakage rates. This provides evidence for the as yet unquantified fill dependency of granulation mechanisms and their variation with screw configuration.

The two granulators compared by Djuric et al [46] had similar screw configurations but different free volumes. A Leistritz extruder with a screw diameter of 27 mm and an APV Baker extruder with a screw diameter of 19 mm. Increasing the feed rate gave a considerable increase in median granule size in the granulator with smaller free chamber volume and only a small increase in median granule size in the granulator with a larger free chamber volume. Showing the importance for fill level consideration in scale up as well as material feed rate, screw speed and geometry.

Vercruysse et al [24] found no significant effect on the size distribution of granules with varying material feed rate. Although varying the feed rate gave different degrees of barrel filling and torque values there were no significant differences in size distribution. Fill levels were not quantified but may have been below levels that result in significant changes in degree of compaction similar to Thompson and Sun [21] who found the angle of kneading elements to only affect size distribution when the fill level is high, at 70% in their work.

Conclusions

Twin screw granulation is a technique rapidly growing in popularity for pharmaceutical processes. While research on TSG has advanced considerably within the past two decades there still exists considerable need and potential for developing process understanding and optimisation. The process is still frequently taken with a black box approach and granulation mechanisms must be better understood. Whilst insightful work has helped develop understanding into the mechanisms of mixing elements [32,35], the complex interaction between conveying and mixing zones and the dependency on process and formulation properties remains poorly comprehended.

Design of screw configuration remains very empirical, the traditional configuration is a long conveying section feeding into one or two mixing sections however it remains unknown if this is the optimum configuration. Adaption of screw configuration has been shown to have the potential for control of granule size and shape [21]. By developing understanding of the granulation mechanisms of screw elements and their interaction with each other a systematic approach can be taken by an operator to optimise the process in a true quality by design approach.

A challenge which exists in building understanding is knowing what factors to measure and how to measure them. Interpreting the granulation mechanisms is inherently difficult due to the complexity in visualising the active process. Techniques such as NIR chemical imaging employed by Kumar et al [32], PEPT employed by Lee et al [33] and 3D shape characterisation employed by El Hagrasy and Litster [35] are powerful tools in understanding flow and mixing properties. While traditional methods of granule quality measurement are essential due to the continuous nature of TSG there is a need to develop methods of in-line quality measurement. Fonteyne et al [49] have made progress in this area through the application of in-line sizing and NIR and Raman spectroscopy for continuous measurement of solid state distribution.

Currently work is being carried out on a variety of different granulators of varying geometry with often apparently contradictory observations. Because of this there exists a need to develop a quantifiable measurement to allow for comparison between different granulators. Fill level is a dimensionless quantity that can allow comparison but is incomplete in that residence time and energy input are not considered. Development of a quantifiable measurement will ease both scale up and process characterisation. Attempts to achieve this have been made through the development of regime maps [22,30,43] but these remain extremely equipment and formulation specific.

Despite the progress made in understanding TSG there is still difficulty in producing high quality granules. The characteristic bimodal granule size distribution adds complexity to downstream processing, similarly monomodal distribution granules formed at high L/S are consistently too large for tabletting without milling. Fines are often in abundance and factors leading to reduction in fines often result in higher proportions of oversize agglomerates [24,34]. There exists a large scope for process optimisation to increase the yield and the need to develop the understanding to achieve this.

Formulation varies widely within the different bodies of work on TSG and will have strong influence over granulation mechanisms and granule quality. While it has been demonstrated that TSG is effective in granulating high drug load formulations [16,17,25,38] and traditionally difficult to process materials [13] most papers are limited to easily processed common pharmaceutical excipients. Work has gone into understanding the process response to variation in formulation properties [40] but extensive optimisation will still be required for new process lines, particularly due to the unique flow properties associated with many APIs. Because of the variation found in model formulations there exists a need for a thorough exploration into process formulation dependence such that conclusions drawn from a wide variety of sources can be consolidated.

Finally modelling of twin screw granulation is an area conspicuously under-represented from research work, with only two instances of recently published work [50,51]. Development of robust models is an essential requirement for process understanding and scale up.

Nevertheless twin screw granulation remains an attractive method of continuous wet granulation. The wide scope and success of research work shows the potential of this emerging granulation process.

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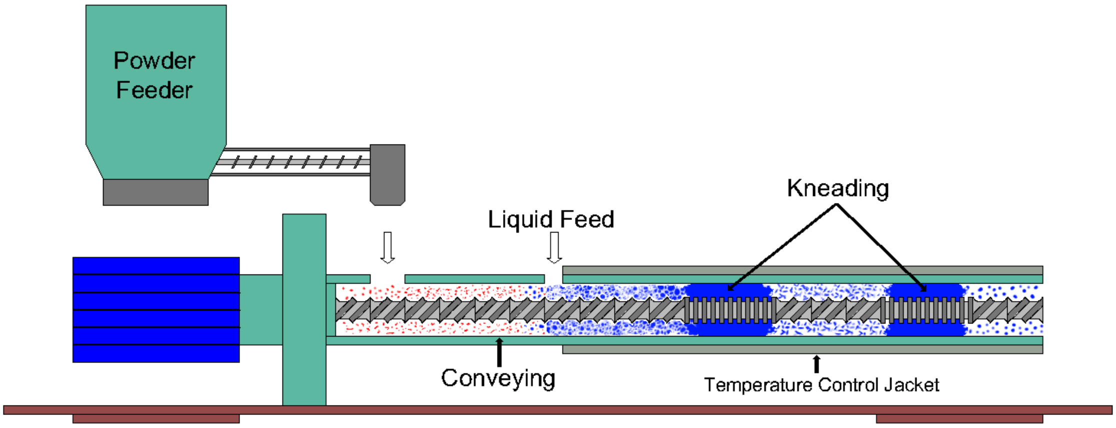

Powder
Feeder
Liquid Feed
Kneading
Conveying
Temperature Control Jacket

Fig. 1

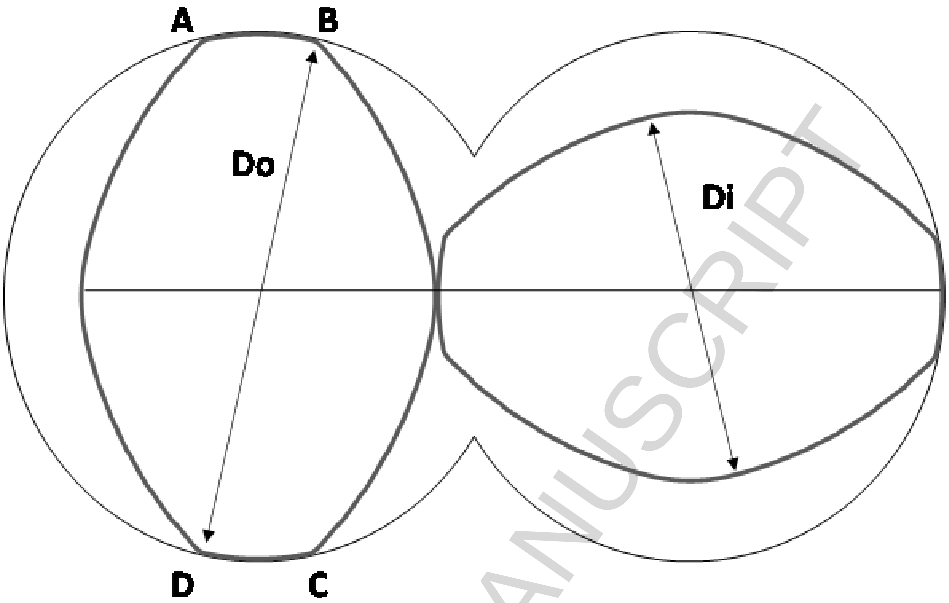


Fig. 2

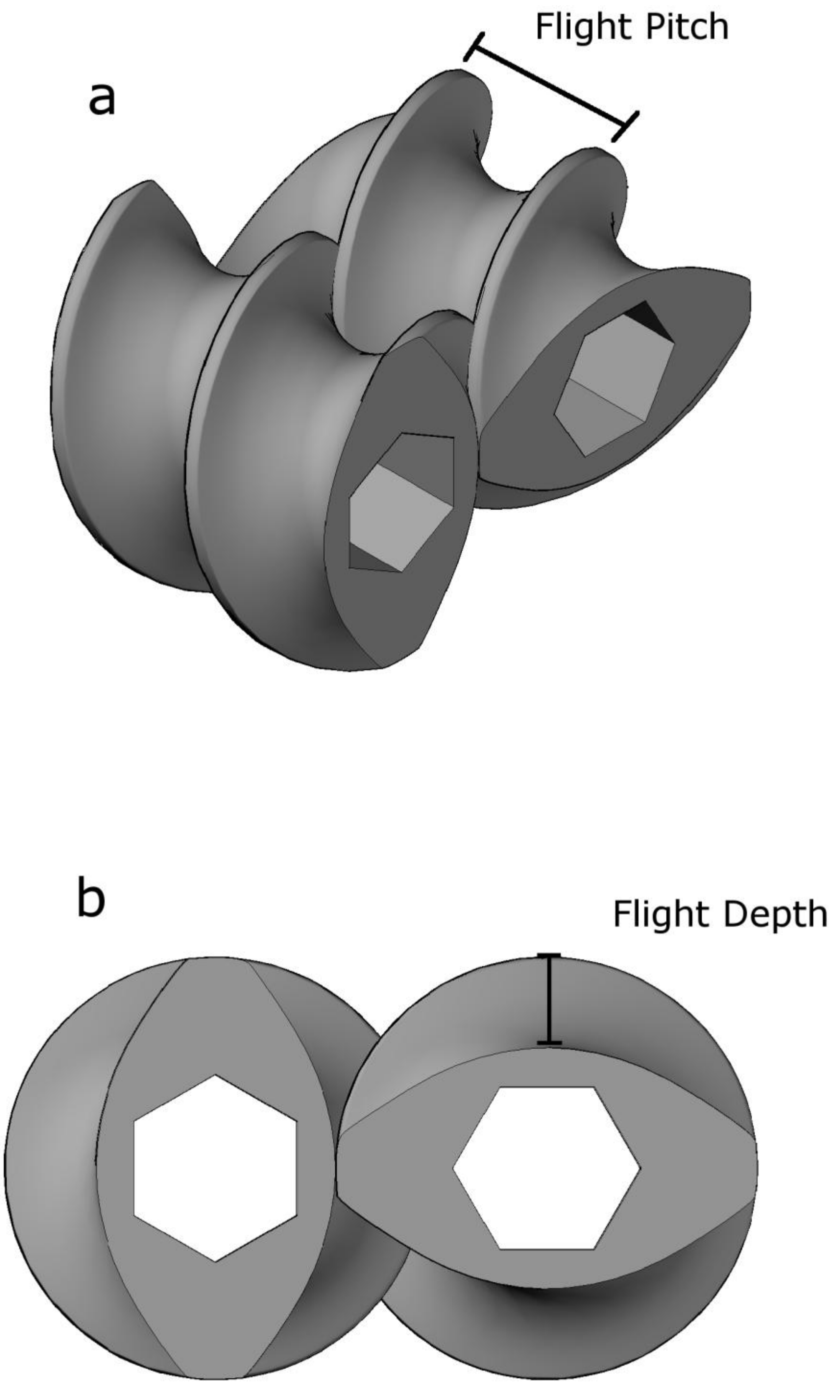
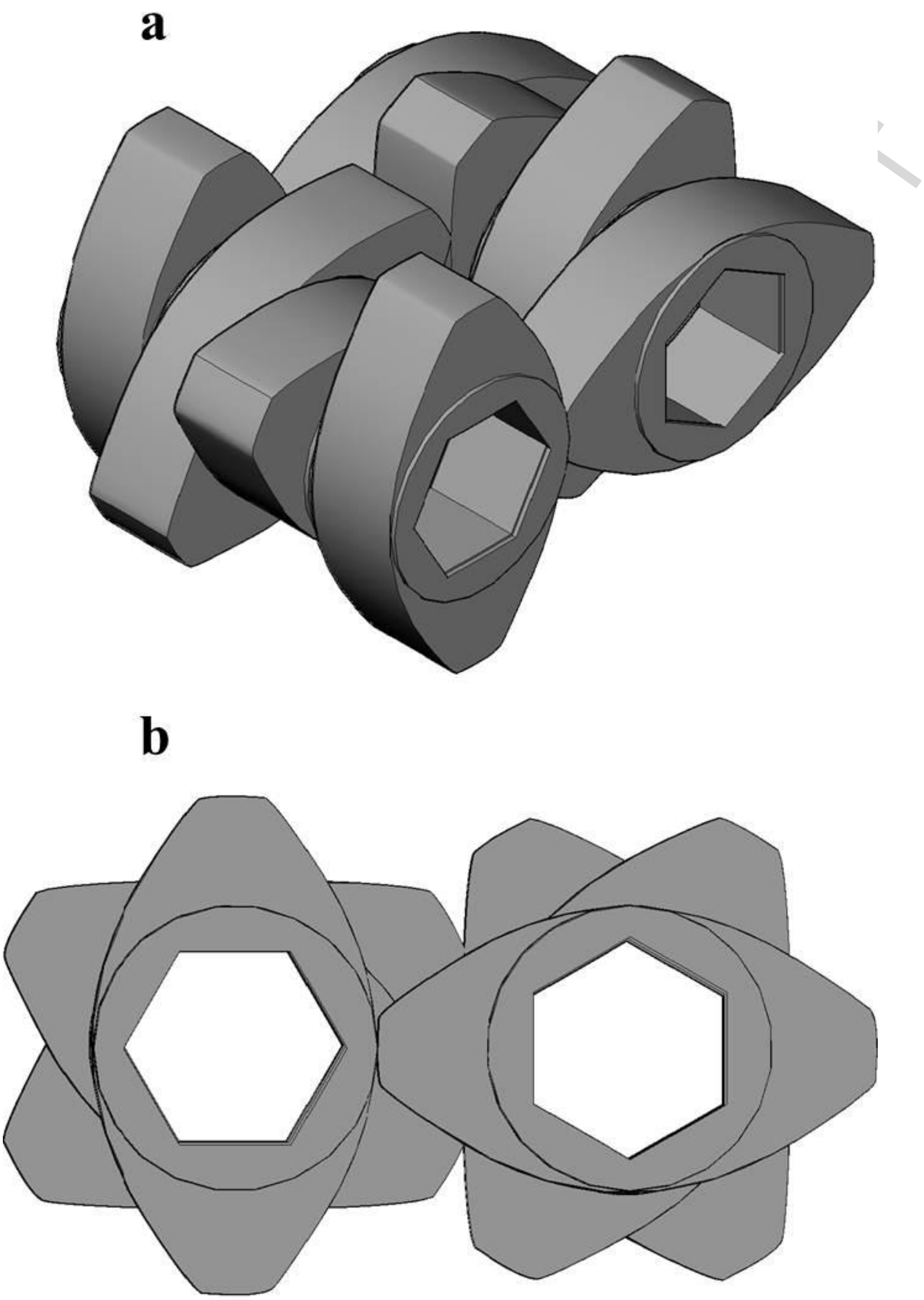


Fig. 3



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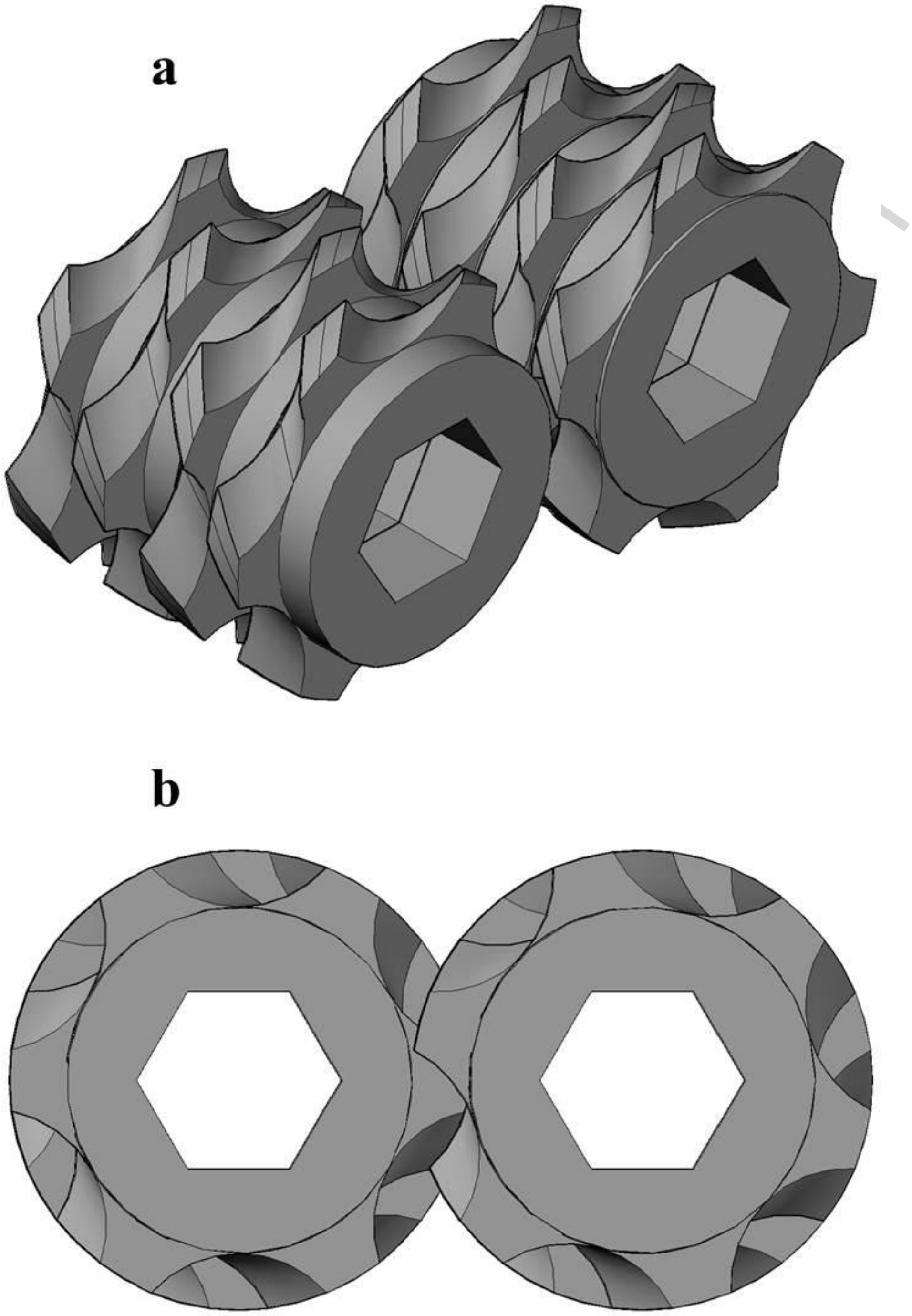

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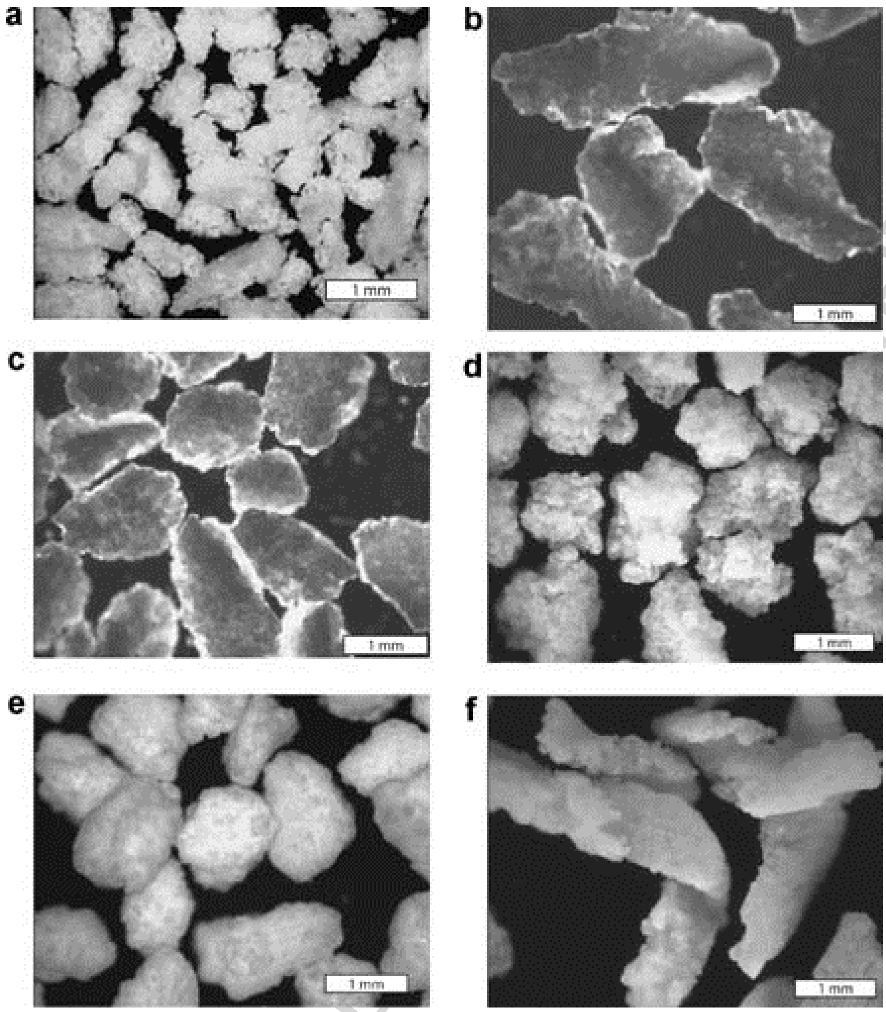

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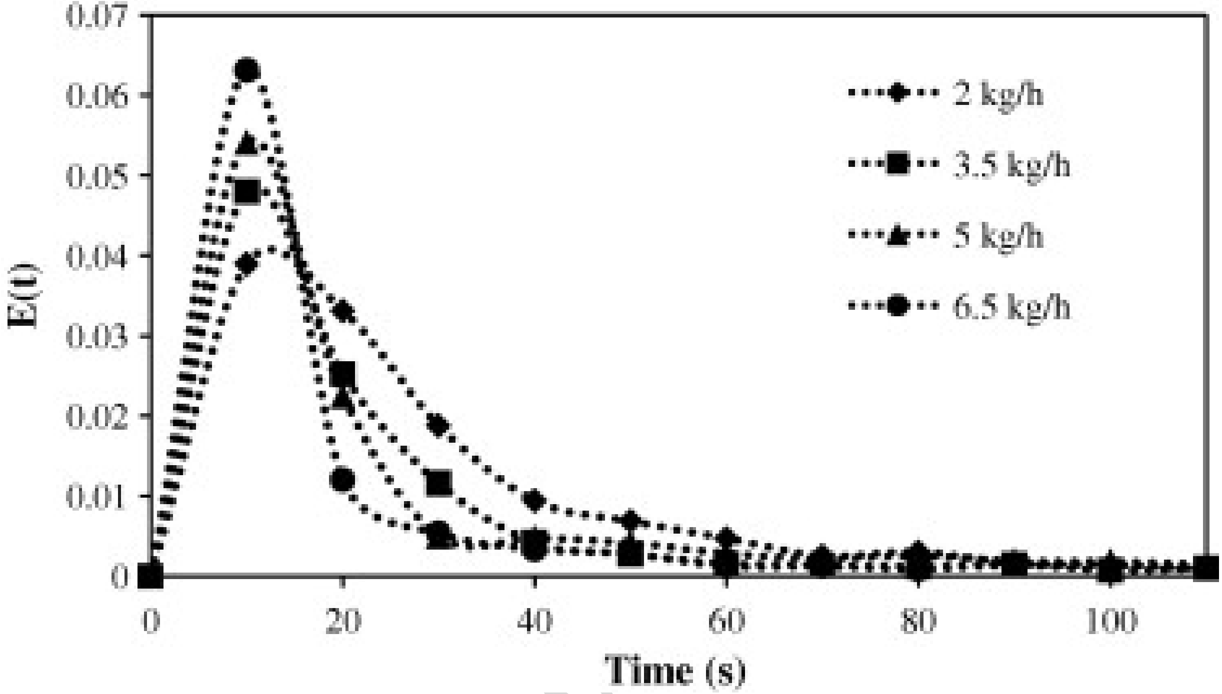
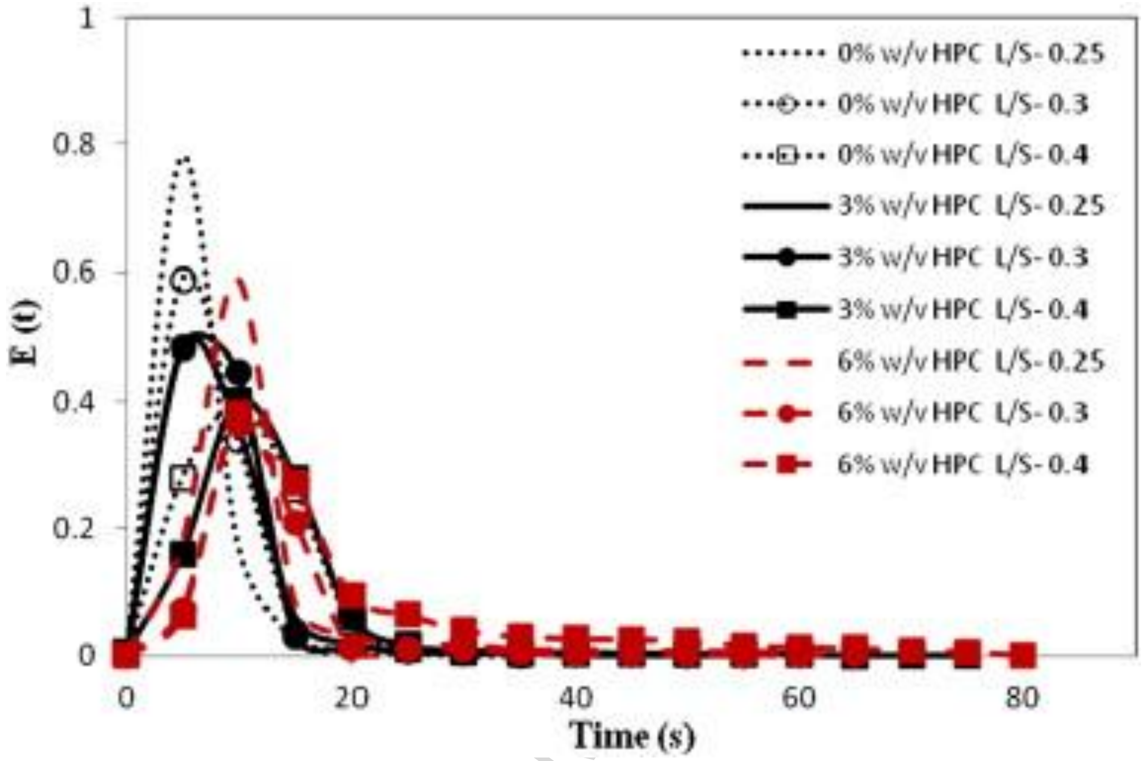

0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
E(t)
2 kg/h
3.5 kg/h
5 kg/h
6.5 kg/h
0
20
40
60
80
100
Time (s)

Fig. 7



1
0.8
0.6
0.4
0.2
0
E (t)
0
20
40
60
80
Time (s)
0% w/v HPC L/S- 0.25
0% w/v HPC L/S- 0.3
0% w/v HPC L/S- 0.4
3% w/v HPC L/S- 0.25
3% w/v HPC L/S- 0.3
3% w/v HPC L/S- 0.4
6% w/v HPC L/S- 0.25
6% w/v HPC L/S- 0.3
6% w/v HPC L/S- 0.4

Fig. 8

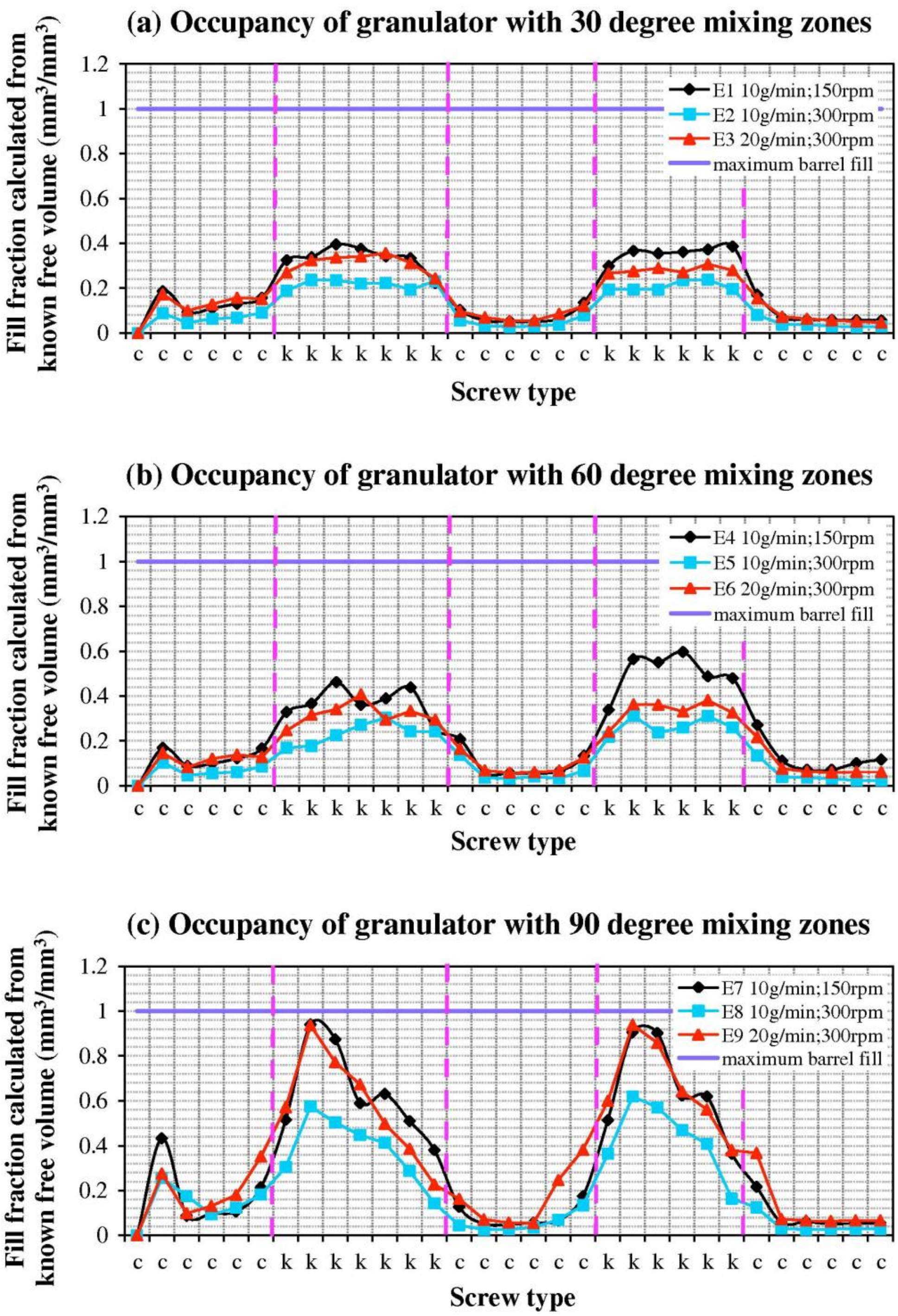

(a) Occupancy of granulator with 30 degree mixing zones
Fill fraction calculated from known free volume (mm³/mm³)
E1 10g/min;150rpm
E2 10g/min;300rpm
E3 20g/min;300rpm
maximum barrel fill
Screw type
(b) Occupancy of granulator with 60 degree mixing zones
E4 10g/min;150rpm
E5 10g/min;300rpm
E6 20g/min;300rpm
(c) Occupancy of granulator with 90 degree mixing zones
E7 10g/min;150rpm
E8 10g/min;300rpm
E9 20g/min;300rpm

Fig. 9

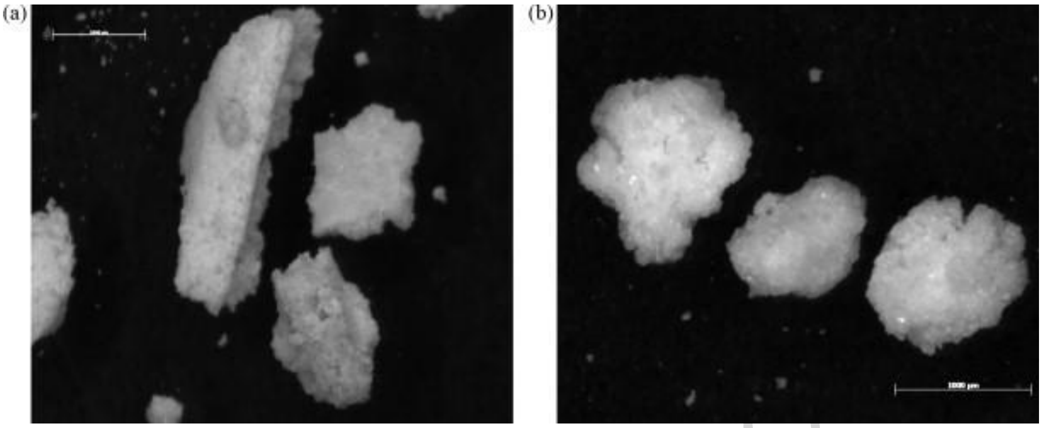


Fig. 10

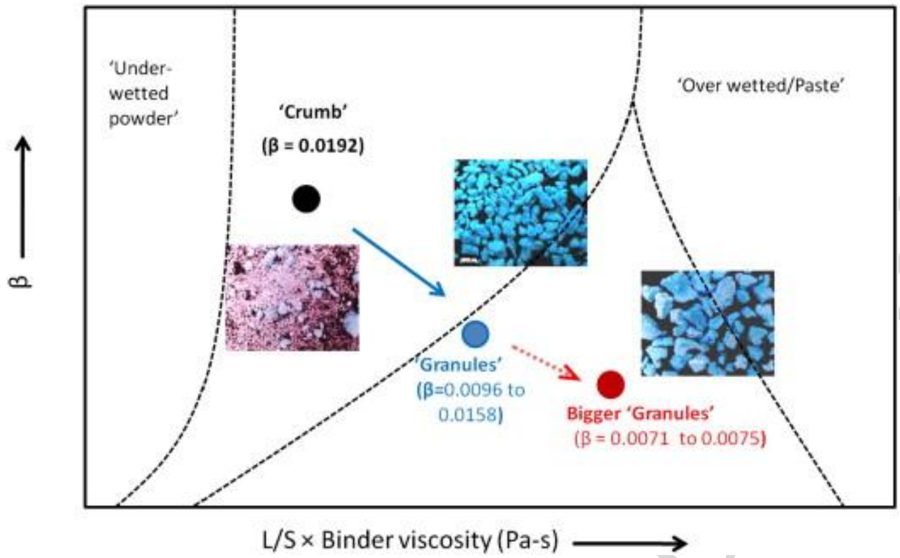
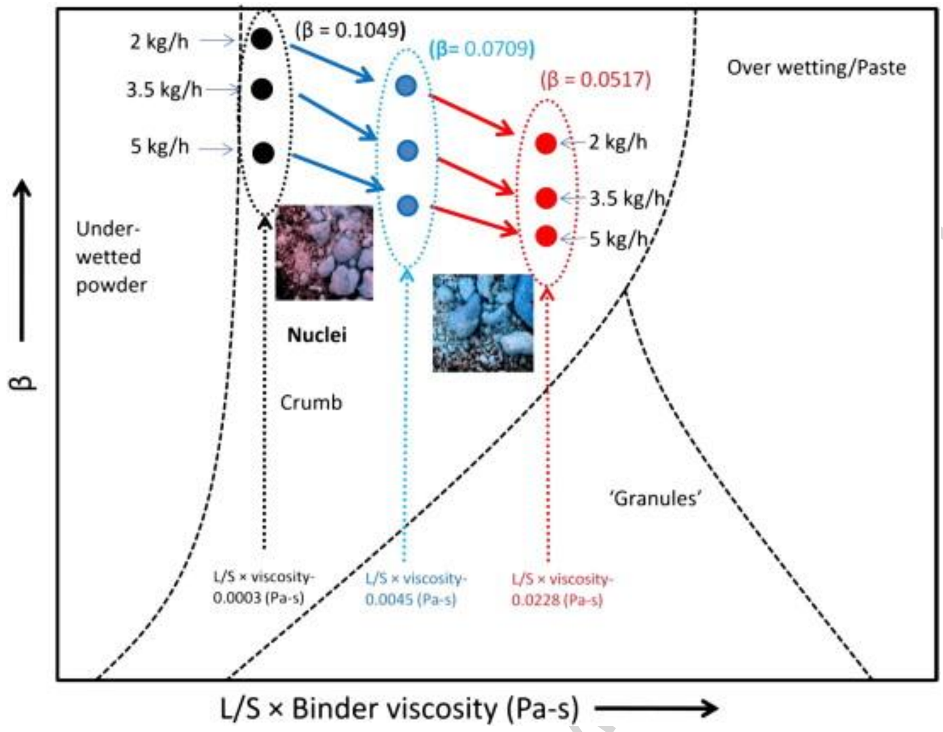
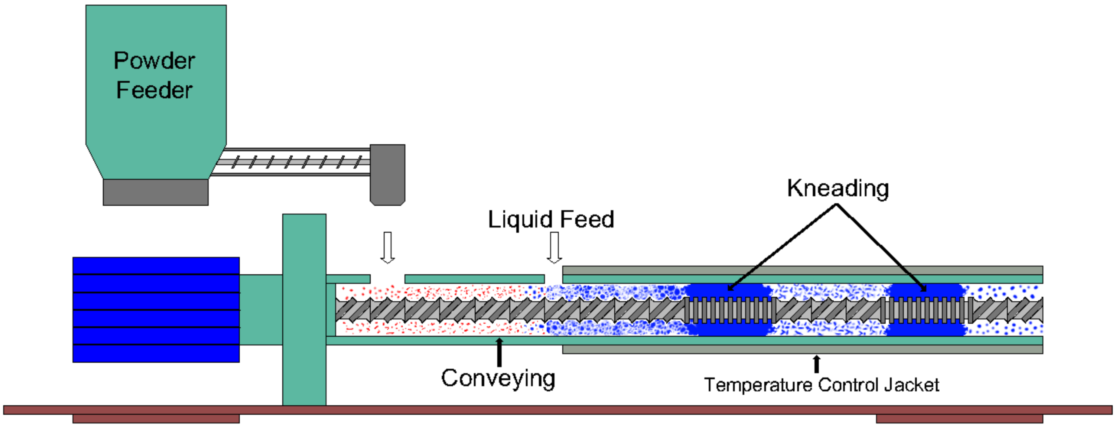

'Under-
wetted
powder'
'Crumb'
(β = 0.0192)
'Over wetted/Paste'
'Granules'
(β=0.0096 to
0.0158)
Bigger 'Granules'
(β = 0.0071 to 0.0075)
β
L/S × Binder viscosity (Pa-s)

Fig. 11



(β = 0.1049)
(β= 0.0709)
(β = 0.0517)
2 kg/h
3.5 kg/h
5 kg/h
Over wetting/Paste
2 kg/h
3.5 kg/h
5 kg/h
Under-wetted powder
Nuclei
Crumb
'Granules'
β
L/S × viscosity-0.0003 (Pa-s)
L/S × viscosity-0.0045 (Pa-s)
L/S × viscosity-0.0228 (Pa-s)
L/S × Binder viscosity (Pa-s)

Fig. 12



Graphical abstract