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Review

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.

Contents

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 is 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

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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 the current manufacturing techniques. 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. The 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 whilst 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. [9] who used a similar extruder in the production of an effervescent granulation [9] 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 whilst 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 exist a large number of twin screw granulators with varying sizes 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].

Fig. 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