PROCESSES, CHALLENGES, AND THE FUTURE OF TWIN-SCREW GRANULATION FOR MANUFACTURING ORAL TABLETS AND CAPSULES

Adopting twin screw granulation can aid in the transition from batch to continuous processes for pharmaceuticals.

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The Formulation Design and Development section submitted this article.
The majority of marketed tablets and capsules products are manufactured using granulation processes including wet, melt, and dry granulation. These granulation techniques are also used across many other industries, such as the food and polymer industries. Powders are granulated to prevent material segregation and to improve powder properties (e.g., flowability and compressibility). While other industries transitioned wet and melt granulation from batch to continuous processes using twin-screw extruders in the 1970s, the adoption of twin-screw granulation (TSG) has been slow in the pharmaceutical industry. As pharmaceutical scientists become more familiar with TSG, and with the recent interest in continuous manufacturing, an increasing number of process patents and products utilizing the TSG platform is anticipated. This article highlights four aspects of TSG: (a) granule formation mechanisms, (b) benefit over conventional batch processes, (c) process control and monitoring, and (d) history, recent progresses, and the future.
GRANULE FORMATION MECHANISMS: TWIN-SCREW CONTINUOUS GRANULATION

The twin-screw extruder (TSE) is available in a variety of configurations with the corotating, intermeshing, twin-screw extruder being the most commonly used for granulation applications. This TSE design is also considered “self-wiping,” because the opposing surface velocities inherent with the intermeshing motion lead to material removal from the surface. The screws consist of conveying and mixing elements (Figure 1). Conveying elements transfer material along the barrel, while mixing elements contribute to both distributive mixing and dispersive mixing during TSG. Distributive mixing involves division and recombination, while dispersive mixing involves planar mixing and extensional mixing.¹ Depending on their geometry, mixing elements can be predominantly distributive, predominantly dispersive, or a balance of both. Images of representative conveying and mixing elements are shown in Figure 1.

The TSE is regarded as a small volume, continuous mixer. A 27 mm Leistritz extruder at 24 length/diameter configuration could operate at a production rate of 15 to 30 kg/hr. The total free volume inside the extruder at this configuration is only about 250 mL. This small mixing volume and corresponding mass transfer distance improves the product consistency by ensuring that all granules have similar shearing history. This is why the term “small volume” mixer is used to describe TSE. As shown in Figure 2, materials are bounded and divided into different regions by the screw flights and barrel wall. Depending on the location relative to the barrel and screw elements, materials experience different intensity of mixing in different regions. High-intensity mixing regions are highlighted in red, while regions of low-intensity mixing are in blue.

Twin-screw granulation has traditionally been divided into two categories: twin-screw wet granulation (TSWG) and twin-screw melt granulation (TSMG).

TWIN-SCREW WET GRANULATION

In TSWG, granulation fluid (e.g., water or solvent, optionally containing a polymeric binder or foam) is introduced into the extruder via a liquid injection port either as liquid or foam.² TSWG is mechanistically similar to batch high-shear wet granulation.
As the granulation progresses along the barrel in TSWG, the powder blend undergoes wetting and nucleation, consolidation and coalescence, and attrition processes to transform it into granules. Wetting and nucleation take place in conveying regions to form large, nonuniform agglomerates. These agglomerates are sheared, fractured, and compressed. As a result, consolidation and coalescence take place. Granules grow denser, stronger, and more uniform in the mixing regions.3, 4

Water or solvent can be removed from wet granules via different processes post-granulation. Large-scale fluid-bed drying is still commonly used as a batch process to dry the wet granules prepared using TSWG. The ConsiGma continuous tableting system designed by GEA contains a segmented dryer consisting of multiple individual drying modules. When drying endpoint (product temperature or residual moisture) is reached for one drying module, granules are discharged and a new pack of wet granules is loaded. Continuous dielectric (microwave) drying has also been utilized and was first disclosed in the continuous pharmaceutical granulation patent by Warner Lambert.5

Leistritz Extrusion Corp. has developed a continuous flash drying process (Figure 3). The drying process begins in the extruder via a vent. After discharge, hot air is then used to drive off the remaining residual water and to transfer the granules into a mill for size reduction.

**TWIN-SCREW MELT GRANULATION**

As a solvent-free alternative to TSWG, twin-screw continuous melt granulation (TSMG) uses a thermal binder instead of a liquid binder. Melt granulation is especially suitable for drugs that undergo undesired physical or chemical changes in the presence of water or solvent.6, 7 Limited studies have investigated the mechanisms of the melt granulation process. Due to the thermal and mechanical energy input, thermal binders turn into low viscosity liquid (e.g., polyethylene glycol and glycerol behenate) or viscoelastic polymer melt (e.g., hydroxypropyl cellulose) inside the extruder barrel. Molten thermal binders bridge the powder particles together to form larger agglomerates. Coating of thermal binders on the surface of granules has been observed using Time-of-Flight secondary ion mass spectrometry for the surface composition analysis of granules.8

**BENEFITS OF TWIN-SCREW CONTINUOUS GRANULATION OVER BATCH GRANULATION**

Batch high-shear granulators generally consist of mixing blades positioned inside large...
mixing chambers. The mixing and agglomeration occur at the high shear zones, such as those located between the tips of the rotating blades and the wall of the mixing chamber for a high shear granulator. On the other hand, for TSG, different stages of the granulation process take place at different screw segments.

Batch granulation operates under the globally starved (the extruder barrel is 30 to 70 percent filled during processing) and unpressurized conditions. Even though the TSE operates under globally starved conditions, the processing section of a TSE consists of both starved (partially filled in conveying elements) and pressurized (fully filled in mixing elements) segments dictated by the screw elements. Powder is randomly subjected to the high shear zone in a batch granulator, potentially resulting in nonuniform mixing dynamics. In TSG, the material is forced through a sequence of starved and pressurized zones. As a result, granules prepared using TSG have a more uniform mixing history, where incoming blend is processed in a principle of first-in, first-out with a given residence time distribution. This allows the system to operate in a state of control and to ensure the consistent quality of granules.

Three distinct advantages of TSG are (1) more homogeneous distribution of drug, excipient, and binder solution; (2) reduced level of binder solution to achieve the desired granules; and (3) shorter processing time. Granulation time is on the order of about 10 seconds for TSG. In comparison, granulation time for a batch process is on the order of minutes. This shorter processing time makes it feasible to explore high processing temperatures that are not practical for batch process.

Besides the improved quality of granules, TSG provides the following benefits when utilized as a continuous process:

- Less binder solution is needed.
- Smaller production facilities and less capital investment are required.
- Modular construction allows flexibility in the configuration of the processing section.
- On-line and real-time monitoring of product quality is possible rather than postproduction testing.
- More efficient manufacturing with shorter production cycle and lower product cost.
- Simpler process optimization and scale up are possible.
- Use of the same equipment train for a much broader production volume and quicker response to changes in market demand is possible.

### PROCESS CONTROL AND MONITORING

ATSE line consists of a drive section (motor and gearbox), a process section (barrel and screw), and an electrical and control panel. The TSE is starve-fed with the output rate controlled by the feeder. The energy required to transform the powder blend to granules predominantly comes from the mechanical energy input by the motor via rotating screws into the material. Heat conducted from the barrel can also play a significant role, especially for small-diameter extruders. The modular design of the barrel and screw makes TSE an extremely versatile granulator. Screw elements and barrel design at any given segment can vary to accommodate various unit operations such as direct powder feeding, powder side stuffing, liquid injection, conveying, mixing, venting, and devolatilization (removal of water and solvents).

Key processing variables include screw speed, barrel temperature, and feed rate. Screw speed is controlled by a variable speed AC drive, motor, and gearbox. Generally, screw speed is set between 50 to 1000 rpm. Heating and cooling of the barrel are controlled by cartridge heaters and a cooling liquid such as a water/propylene glycol mixture. Temperatures can also be set by liquid temperature control units, as required in explosion-proof rated environments. For wet granulation, the barrel temperature is set at or slightly above the ambient temperature. For melt granulation, barrel temperature is set above the melting and glass transition temperature of thermal binders and is typically in the range of 80 to 130 Celsius. Feeding of powder and binder
solution is controlled using a loss-in-weight powder feeder (the entire feeder and material are continuously weighed, and the feeder speed is adjusted automatically to achieve the target feed rate) and pump (gear or peristaltic pump for liquid, and side-stuffer for foam), respectively. Twin-screw continuous granulation operates in an open-end discharge mode. A restraining plate or outboard bearing prevents the screw from moving axially without obstructing the granule flow.

Precise process control to ensure consistent product quality requires monitoring the process parameters at different locations along the barrel. The parameters include temperature, pressure, and torque. A thermocouple or infrared probe can monitor the temperature of the material. Specific mechanical energy (SME), the amount of motor power input into each kilogram of material processed, could be derived from the motor torque readout. However, SME is not as critical as that for a melt extrusion process, due to the lower energy-space at which granulation operations are conducted. Because of the multifactor nature of the TSG process, multivariate analysis can be performed to understand the effect of processing variables and to identify key risk factors.

Process analytical technology (PAT) should be implemented to monitor the properties of granules on-line and in real time. Raman and near infrared spectroscopy have been applied to monitor drug and water content. Acoustic emission is a noninvasive tool to monitor the granule size distribution.13 Granelle monitoring technologies, such as the Eyecon imaging system, can also be used to assess granulation characteristics.13

HISTORY, RECENT PROGRESSES, AND THE FUTURE IN PHARMACEUTICAL APPLICATION

The food and polymer industries were dominated by products manufactured by high-shear batch granulation into the 1960s. The transition to TSG to enable continuous manufacturing in the 1970s was based on the improved “product uniformity” and “mixing quality.” Application of TSWG to prepare pharmaceutical dosage forms was first reported by Gamlen and Eardly in 1986 to improve compaction properties of acetaminophen. Granules containing 80 percent acetaminophen were prepared. The granulation process was significantly facilitated by the presence of hypromellose in the binder solution.15 In 2000, Ghebre-Sellassie and his colleagues at Warner Lambert filed the first patent application on continuous pharmaceutical wet granulation using TSE. The inventor disclosed a continuous granulation line consisting of twin-screw granulation, milling (optional), microwave drying, and dry milling. The

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process was successfully demonstrated at a 15 kg per hour output rate.5

A significant amount of research in TSWG was pioneered by Dhenge’s research team at the University of Sheffield, United Kingdom, and Thompson’s research team at McMaster University, Canada. They have conducted extensive study in the granule formation mechanisms, effect of screw design, and effect of processing parameters (e.g., liquid-to-solid ratio, location of liquid injection, binder concentration, and degree of fill).3, 4, 16, 17

Eucreas tablets, an immediate-release tablet of metformin and vidaglaptin, are the first commercial product prepared using TSMG. The product was developed at Novartis. Metformin hydrochloride granules are prepared using TSMG. The product was developed at Novartis University, Canada. They have conducted an extensive study in the granule formation mechanisms, effect of screw design, and effect of processing parameters (e.g., liquid-to-solid ratio, location of liquid injection, binder concentration, and degree of fill).3, 4, 16, 17

CONCLUSION

The adoption, implementation, and expanded applications of twin-screw granulation and the potential to integrate it into continuous manufacturing systems in the pharmaceutical industry resemble what occurred in the food and polymer industry five decades ago. Valuable knowledge, technical expertise, and manufacturing experience gained in these industries would allow for expeditious adoption and implementation of this established processing technology to replace existing batch granulation processing. With concerted effort and commitment from the pharmaceutical industry, equipment suppliers, excipients companies, and regulatory agencies around the advancement of continuous manufacturing, the evolution of twin-screw continuous granulation is expected to continue.

REFERENCES