Loss-In-Weight Feeding And Continuous Extrusion: New Options In Pharmaceutical Processing

The combination of twin-screw extruders and loss-in-weight feeding and pneumatic refill systems is quickly becoming the manufacturing process of choice when developing pharmaceutical solid dosage forms.

BY SHARON NOWAK AND CHARLIE MARTIN

The application of continuous extrusion via twin-screw extruders (TSEs) for pharmaceutical solid dosage-form production is growing in popularity as a preferred option to more traditional and costly granulation and dosage-form fabrication techniques. Two methods in which the extruder is used for solid dosage-form production are wet granulation and hot-melt extrusion (HME). During extrusion in both of these methods, pellets, granules, liquids, and powders must be fed accurately and continuously throughout the run and refill operations in order to ensure consistency of formulation, constant throughput, proper order of mixing ingredients, and regulated mass transfer.

Use of TSEs coupled with accurate LIW feeding and pneumatic refill systems is quickly becoming the manufacturing process of choice when developing pharmaceutical solid dosage forms.

Extrusion Defined

Extrusion is a continuous process where active pharmaceutical ingredients (APIs) are mixed with excipients. Inside the screw extruder, a number of basic process functions are performed including conveying of material, melting, mixing, venting, and developing die and localized pressure. The motor facilitates the extrusion process via the rotation of the screw or screws, which in turn impart shear and energy into the extrudate.

With a single-screw extruder, one screw rotates inside the barrel and is used for conveying, melting, devolatizing, and pumping. In addition, some degree of mixing is also done for specific applications. Single-screw extruders are primarily used as pumps, with less emphasis on mass transfer operations such as mixing and devolatilization.

TSEs, as the name implies, utilize two screws side by side within a barrel. These can be co-rotating and/or counter-rotating. For a co-rotating TSE, the screws are termed "self-wiping," as the opposing surface velocities in the intermesh regions cause the material to follow a figure-eight pattern. In counter-rotation, the surface velocities of the screws in the intermesh region are in the same direction, which results in materials being forced between the screws where extensional shear (and mixing) occurs. The application will dictate whether co-rotation or counter-rotation is best for the job — both modes are used in the pharmaceutical industry.

The use of two screws in TSEs results in a much more versatile design, as the number of configurations for the screws increases substantially. The screws are the heart of any TSE, and the design of the screw can directly impact the quality of the solid dosage form. Screw elements are flighted for material transport and nonflighted to create shear regions for melting or mixing. The flight depth of the screw, for example, is an important design parameter; a deeper flight depth increases the flow volume of the machine but limits the torque potential.

Screw designs can be shear intensive and/or shear passive with efficiencies defined in terms of dispersive and distributive mixing. In dispersive mixing, the particles are broken down. Conversely, in distributive mixing, the materials are uniformly blended and not broken down. This distributive mixing effect is often implemented for mixing heat and shear-sensitive materials like APIs with minimal degradation.

Twin-Screw Hot-Melt Extrusion

Melt extrusion (HME) is a process which has been popular for many years in the plastics industry. It has emerged within the pharmaceutical industry as a method to develop solid dosage forms without the use of water or solvents as liquid-granulating binders. Instead, materials which melt at the extruder processing temperatures act as these binders. During the process of HME, the API is embedded in a carrier formulation often composed of one or more "meltable" substances and other functional excipients. The drug compound remains in a state of molecular dispersion as the polymer hardens. The extrudate can then be formed into a variety of shapes, including granules and pellets. It is important to note that for a pharmaceutical material to be processed via HME, it must be able

to deform easily inside the extruder and solidify upon its exit.

The technique of HME for pharmaceutical products offers a new delivery platform for a variety of active ingredients. Analysis of hot-melted granules has shown better API dispersion and content uniformity due to the additional mixing which occurs within the barrel of the extruder. The additional mixing is caused by the rotating screws, which causes deaggregation of suspended particles within the molten polymer, resulting in a more uniform dispersion. In addition, solvents and water are not necessary as in other granulation techniques, therefore reducing the number of processing steps and eliminating time-consuming drying steps. Other process advantages include low residence time, easy scale-up to production scale, and excellent process repeatability.

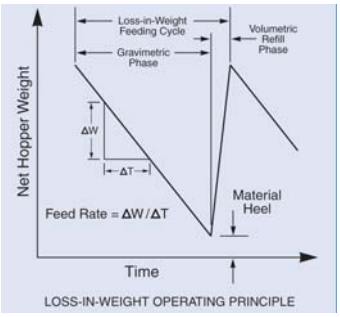
HME is also used for bioadhesives and transdermal patches with delivery direct to the skin or mucosa. It is being widely used as a method for the production of edible films thus allowing delivery of the drug compound in an easier form than tablets or capsules.

TSE Wet Granulation

Wet granulation via TSE refers to the process of fine-powdered excipients and APIs, together with a liquid binder, being mixed within the extruder to produce an enlarged granulate with characteristics necessary for the formation of tablets and other solid dosage forms. Due to the ability to change the levels of mixing within the extruder, a great deal of flexibility in the resultant characteristics of the granulate can be obtained. Because the overall residence time is very short, it is possible to achieve a quick steady state operation. This versatility, in combination with the ability to wet granulate in a continuous manner, has caused this mode of granulation to also grow in popularity. Key operational benefits of the TSE can also include a reduction in the level of excipients required, another method in controlling cost.

The Role Of LIW Feeders In TSE

In both HME and TSE wet granulation, the constant delivery of both the active ingredient(s) and the carriers is critical to the overall uniform output of the TSE. The high accuracy of the feeding system is imperative to maintain uniform quality of the product. For this reason, loss-in-weight (LIW) feeders are used to ensure that the ingredients are delivered at a constant mass flow throughout the extrusion process. In many cases, the LIW feeders supply a pre-blend of material directly to the extruder, but in some cases where a true continuous process is required, the components of the granulation are fed individually, each based on the proportional amount in the drug formulation. In all cases, the resultant product quality is a direct result of the level of accuracy in mass flow achieved by the LIW feeder.



LOSS-IN-WEIGHT OPERATING PRINCIPLE

LIW Principle

Pharmaceutical screw feeders can be supplied in both volumetric and gravimetric configurations. Volumetric screw feeders are generally not used for metering dry ingredients into extruders for pharmaceutical applications because of the high fluctuations in the mass flow rate. Since the feed rate in a volumetric feeder is purely a function of screw speed and uniform screw fill, the feeder and the extrusion process below have no way of detecting this error.


LIW pharmaceutical feeder with integrated vacuum receiver for refill.

A gravimetric feeding device consists of the feeding module, the feeder hopper, a refill device, a weighing device, and a control system. The most common type of gravimetric feeder device used in the pharmaceutical industry is the LIW screw feeder. An LIW feeder calculates the mass flow rate (quantity per time) by dividing the weight reduction by the time interval. Gravimetric feeders are mounted on load cells. At short time intervals, the weight is measured and transmitted to the controller. The real-time mass flow rate is calculated from the weight reduction per unit time. In order to compensate for the difference between the set point and the measured value of mass flow, the screw motor speed is continuously modified.

LIW feeding affords broad material-handling capability and thus excels in feeding a wide range of materials from low to high rates. In operation, the feeder, hopper, and material are continuously weighed, and the feeder's discharge rate (which is the rate at which the feeding system is losing weight) is precisely controlled to match the desired feed rate. With this technology, a constant mass flow is ensured thus also ensuring for consistent product output from the extruder.

Liquid Additives

The LIW Principle is also used for the accurate delivery of the liquid medium to the extrusion process. Liquids are typically fed through a variety of pumps with variable speed drives. The mass flow rate can be measured and controlled by a liquid tank placed on load cells with the same LIW control described above. Instead of changing the screw speed, the same signals are used to control the pump speed. Liquid feeders are provided to deliver a more accurate and consistent liquid mass flow to the process. The benefits of this LIW arrangement, as opposed to using a mass flow meter, include easier calibration, lack of a pressure drop experienced by the measuring device, suitability for liquids in excess of 150ºC, and most importantly, higher accuracy in feed and control.

LIW Refill

Refilling a LIW feeder that is feeding to a continuous extrusion process can be almost as critical as choosing the right feeder technology. Since the objective of feeder refill is to refill as quickly as possible, pneumatic receivers that operate under a dilute-phase vac-

uum transfer principle are often used as refill devices, particularly for continuous operations. When refilling a LIW feeder in a continuous pharmaceutical process, it is imperative that the refill devices be reliable to maintain constant flow of either the API or excipient to the process within a specific refill time limit. This time limit must be relatively short to allow the feeder to return to a true gravimetric operation and ensure constant mass flow of the product to the process. Additionally, the flow cutoff action of the selected device must be quick and sure. A slow tapering off of the refill flow lengthens refill time, and any leakage of the refill device may result in a flow error in the positive direction. There are several choices for the type of valves used. Options include slide gates, flap valves, modulating butterfly valves, and rotary valves. Butterfly valves are usually the valve of choice in the pharmaceutical industry due to their easy-to-clean design, and also due to their availability in high-containment options. In addition, vacuum receivers are often used as refill hoppers, offering a method of transfer of the product direct to the LIW feeder hopper.

Conclusion

As outlined above, the use of TSEs coupled with highly accurate LIW feeding and refill systems is quickly becoming the manufacturing process of choice when developing pharmaceutical solid dosage forms. The extrusion and feeding process offers several advantages as a method of granulation formation including the continuous processing and combination of a variety of process steps within one piece of equipment, i.e., distributive and dispersive mixing, granulating, and drying. Benefits of both HME and wet granulation extrusion include absence of solvents and higher repeatability than typical batch processes, as well as improved drug performance due to the high-content uniformity of the active material in the finished dosage form.

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Sharon Nowak *serves as K-Tron Process Group's global business development manager. She works closely with sales, marketing, R&D, and systems engineering departments to identify new applications and focus on the very specific needs of these industries. She has a 20-year background in the process equipment industry for food and pharmaceuticals, and a degree in chemical engineering from Rutgers University.*

Charlie Martin *has worked in the extrusion industry since 1984 in a variety of technical and marketing capacities. As general manager, he is responsible for marketing and development efforts for the Leistritz product line of co-rotating and counter-rotating twin-screw extruders and systems in North America. Martin earned his undergraduate degree from Gettysburg College and his master's from Rutgers University*