

Extrusion Granulation

The application of continuous extrusion via twin screw extruders (TSE) for pharmaceutical solid dosage form production is growing in popularity as a preferred option to more traditional granulation techniques. The TSE offers several advantages as a method of granulation formation including continuous processing with reproducibility and combination of a variety of process steps within one piece of equipment, i.e. distributive and dispersive mixing, granulating and devolatilization. The production method provides gentle product handling at short residence time and low temperature. Two methods in which the extruder is used for solid dosage form production are wet granulation and hot melt extrusion. With its special versions of the ZSK twin screw extruders suitable for the production of pharmaceutical compounds, Coperion is one of the pioneers in the development of pharmaceutical extrusion. Coperion has references for pharmaceutical extruders in the sizes ZSK 18 to ZSK 70. The good mixing behavior and the devolatilization possibilities of the co-rotating twin screws make this system particularly suitable for pharmaceutical extrusion. During wet granulation and hot melt extrusion 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



Coperion's twin screw extruder ZSK 18 MEGAlab and Coperion K-Tron LIW feeders - both in pharmaceutical design

of mixing ingredients and regulated mass transfer. Coperion K-Tron Pharmaceutical Loss-in-weight (LIW) feeders are used in conjunction with extruders in the pharmaceutical industry for both liquid and powder feeds. Typically, feed streams are introduced to the extruder in a "starve-fed" manner, where the rate is set by the feeders and is independent of the extruder screw speed.

Twin Screw Hot Melt Extrusion

Melt extrusion or "hot 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 hot melt extrusion, a powder blend of the active pharmaceutical ingredient (API), a polymer, and various excipients are transferred by closely intermeshing twin screws through the process section of the ZSK extruder. Due to the mechanical energy input the crystalline lattice energy of the API is overcome and the polymer is melted. By choosing the right combination of API and polymer a molecularly dispersed solution of the API in the polymer is achieved. With a properly designed HME process the API does not recrystallize in the hardened polymer and provides greatly improved bio-availability and a controlled release profile. The extrudate can then be formed into a variety of shapes, including granules and

pellets or prepared for milling and tablet pressing. The result of HME is a water soluble state of the API with high and reliable drug absorption.

The technique of hot melt extrusion 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 process section of the extruder. Other process advantages include low residence time, easy scale-up to production scale and excellent process reproducibility.

In addition to its use for solid dosage forms, melt extrusion is also used for bioadhesives and transdermal patches with delivery direct to the skin or mucosa. Additionally, it is currently being

Solid Dosage Form Manufacture via Twin Screw Extrusion

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.

Twin Screw Extrusion Wet Granulation

Wet granulation via TSE refers to the process of mixing finely powdered excipients and API ingredients together with a liquid binder 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 level of mixing within the extruder, a great deal of flexibility in the characteristics of the resulting granulate can be obtained. This versatility, in combination with the ability to wet granulate in a continuous manner rather than more costly traditional batch techniques, has caused this mode of granulation to grow in popularity. Key operational benefits of the TSE can also include a reduction in the level

of excipients required, another method in controlling costs.

The Role of LIW Feeders in TSE

The constant delivery of both the active ingredient(s) and the carriers is critical to the overall uniform output of the TSE. 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 preblend of material directly to the extruder, but in some cases the components of the granulation are fed individually, each based upon 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.

LIW Principle

Coperion K-Tron pharmaceutical screw feeders can be

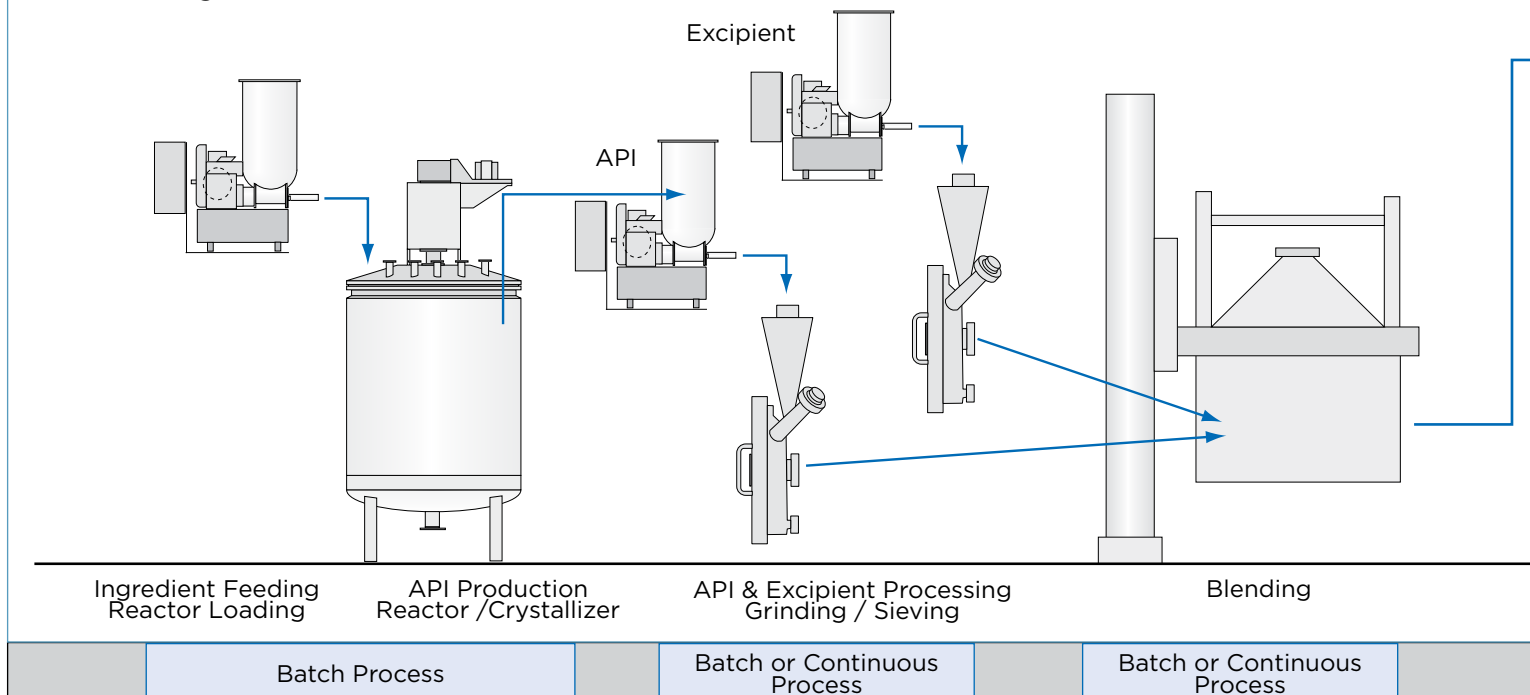
supplied in either volumetric or gravimetric configurations. Volumetric screw feeders are generally not used for metering dry ingredients into extruders for pharmaceutical applications because of the high fluctuations in the mass flow rate. When feeding materials with high variations in bulk density, volumetric feeders can have relatively high fluctuations in feed rate due to fluctuations in the filling of the screws. This variation in feed rate results in inconsistencies in material delivery to the extruder below, thus causing variations in end product quality. In the case of cohesive materials, which is often the case with API's and micronized excipients, it is possible in volumetric mode to have little or no material discharging while the screws are running due to bridge building or packing in the hopper. Since the feed rate in a volumetric feeder is purely a function of screw speed, the feeder and the extrusion process below have no way of detecting this error.

Often even the use of level sensors in the feed hopper may not alert the process of this problem in a timely fashion, and off-spec product may result for a period of time.

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 feeding device used in the pharmaceutical industry is the loss-in-weight screw feeder. A loss-in-weight feeder estimates the mass flow rate (quantity per time) by dividing the weight reduction by the time interval.

Coperion K-Tron's gravimetric feeders utilize load cells with patented SFT technology to constantly measure the weight of the pharmaceutical product delivered to the process below. At short time intervals, the weight of the system is measured and transmitted to the controller. The real time mass flow rate is calculated from the weight reduction per unit time.

Process Diagram



In order to compensate for the difference between the setpoint and the measured value of mass flow, the screw motor speed is continuously modified. Loss-in-weight feeding affords broad material handling capability and

thus excels in feeding a wide range of materials from low to high rates. With this technology, a constant mass flow is ensured thus also ensuring for consistent product output from the extruder.

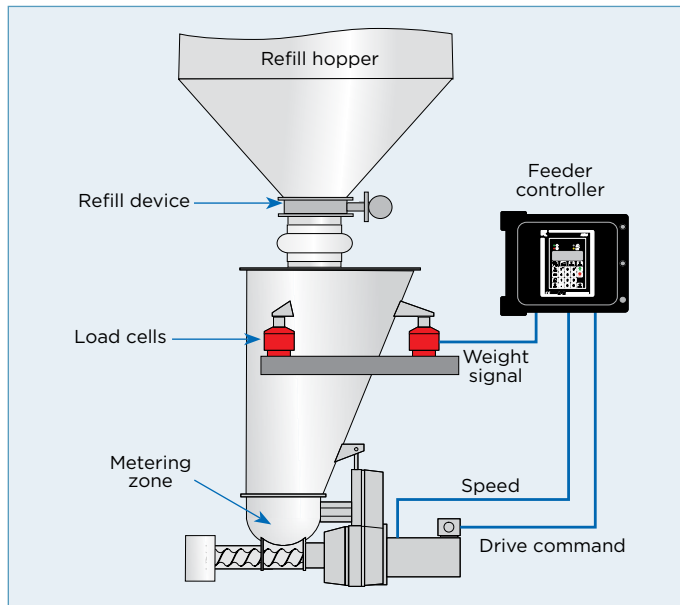
Liquid Additives

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 placing the liquid tank on SFT load cells with the same loss-in-weight control described above. Instead of changing the screw speed, the same signals are used to control the pump speed. Coperion K-Tron liquid feeders which include the Coperion K-Tron patented scale technology are provided to integrate the loss-in-weight algorithm with the stroke of the liquid pump, in order to deliver a more accurate and consistent liquid mass flow to the process. The benefits of this load cell arrangement as opposed to a mass flow meter include easier calibration, lack of a pressure drop experienced by the measuring device, suitability for liquids in excess of 150°C, and

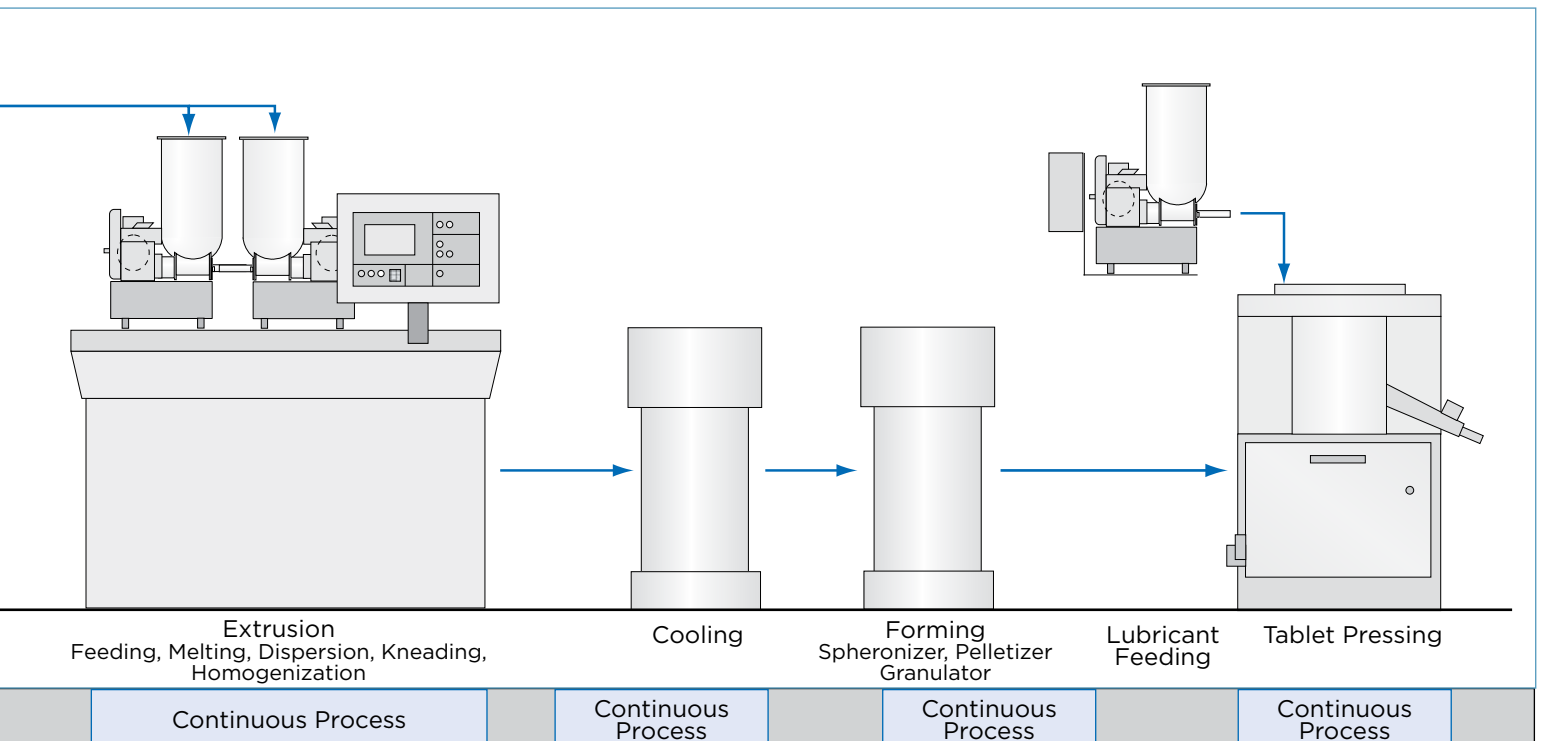
most importantly, higher accuracy in feed and control.

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 vacuum transfer principle are often used as refill devices, particularly for continuous operations. When refilling 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, which is sufficient to avoid exceeding a specific refill time limit. This time limit must be relatively short, in order 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



Loss-in-weight Feeder Principle



Solid Dosage Form Manufacture via Twin Screw Extrusion



must be quick and sure. A slow tapering off of the refill flow needlessly lengthens refill time. Any leakage of the refill device may cause an unavoidable measurable weight disturbance, but will always result in a flow error in the positive direction. There are several choices for the type of valves utilized. 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, Coperion K-Tron vacuum receivers are often utilized as refill hoppers, offering a method of transfer of the product direct to the LIW feeder hopper. (NOTE: for further details on refill operations, see Coperion K-Tron application sheet A-800407 "Refilling Loss-in-Weight Feeders via Pneumatic Conveying in Continuous Pharmaceutical Processes")

Coperion Advantage

> Coperion's ZSK extruders and Coperion K-Tron's pharma feeders are designed specifically for the pharmaceutical industry; all product contact parts are constructed to conform with strict cGMP standards and are standard in 316L stainless steel, designed with ease of cleaning in mind. Only tested, certified materials and FDA approved oils/lubricants are used.

- > Coperion's ZSK extruder has a compact design and therefore low space requirement.
- > The self-cleaning feature of the twin screws of the ZSK extruder allows for fast recipe and product changes. ZSK extruders are designed for easy operation and easy access for cleaning and maintenance.
- > Special control systems available for ZSK extruders can be tailored to the requirements of laboratory operation and clean-room production.
- > Coperion and Coperion K-Tron can provide integrated controls for the raw material handling, feeding and extrusion process including CFR21 Part 11 based control platforms to ensure optimal performance and reliability.
- > Coperion K-Tron's P-Series line of pneumatic receivers is designed for cleanability and ease of access, with all materials of construction FDA approved.
- > Coperion K-Tron's patented SFT digital weighing technology delivers the high accuracy requirements needed for maintaining control of the addition of costly ingredients.
- > Coperion K-Tron SFT weighing technology features a resolution of 1:4,000,000 in 80 ms, as well as built in immunity to plant vibration and fluctuations in temperatures.



Coperion K-Tron gravimetric pharma feeder with tri-clamp connection

- > The refill array provided with the Coperion K-Tron controller allows for consistent fill and quality.
- > Coperion K-Tron is able to provide a wide variety of screw and agitator designs, in order to give best results for the high variety of ingredients.
- > All components include a quick clean, easy disassembly design complete with fully welded and polished housings and triclover clamps/ferrules.
- > Global systems engineers with extensive application experience for pharmaceutical ingredient material handling, feeding and extrusion ensure optimal design emphasis on cleanability, product and process safety, and increased efficiency.
- > Coperion K-Tron can provide systems suitable for various containment and OEL levels, as well as specific cleaning and sanitation requirements.
- > Superior global service network to ensure 24-7 support and coverage of your processing line.

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