

Introduction

Size reduction mills are used widely throughout the pharmaceutical industry for the reduction of active ingredients (API's), as well as bulk pharmaceuticals (BPI's) and excipients such as lactose, HPMC (hydroxypropylmethyl cellulose) and others. Size reduction is used to increase surface area and improve formulation dissolution properties. It is also used to maintain a consistent average particle size distribution (PSD) for the formulation, thus allowing for a better quality mixture when creating solid dosage forms such as tablets and capsules.

Conventional dry size reduction in the pharmaceutical industry is accomplished by impact. This impact size reduction generally falls into two categories: mechanical impact and impact via fluid energy. Examples of mechanical impact mills are hammer mills and pin mills; while spiral jet mills, loop jet mills, and fluidized bed jet mills are examples of micronizers or fluid energy mills.

Feeders for Milling

In most size reduction mills, the feed rate into the mill is an important factor in determining particle size distribution.

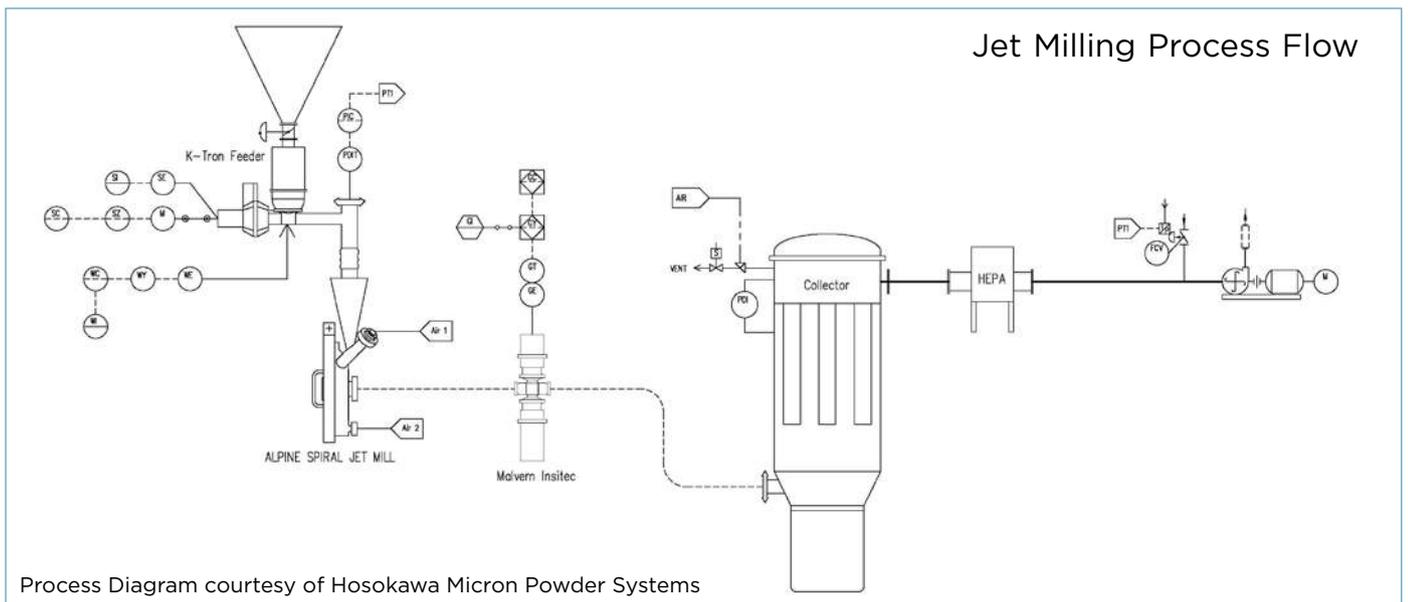
Since the resultant distribution is largely dependent upon residence time in the milling device, the feeder is an important tool in controlling this residence time, and subsequently the resulting PSD.

The types of feed devices used in the industry vary from rotary valves to vibratory tray devices and screw feeders (single and twin screw types). However, as with any process, the product flow characteristics will often determine the best feed method. Since most pharmaceutical powders and formulations can have difficult flow characteristics, the twin screw feeder is often the method of choice. The "self-wiping" action of the intermeshed screw flights lends itself perfectly for the feeding of difficult and cohesive powders.

Sticky powders that are particularly cohesive, or non-granular materials with high aspect ratios, can tend to pack and will often cause clumping in a vibratory tray, or packing in the vanes of a rotary valve. This agglomeration in the feeder disrupts the even metered flow required for the milling operation below, thus causing a shift in the resultant particle size distribution.



JetPharma spiral jet mill with Coperion K-Tron feeder



Process Diagram courtesy of Hosokawa Micron Powder Systems

Milling and Micronization of Pharmaceutical Powders

Typical Feed Rates

Feed rates for pharmaceutical size reduction or micronization can range anywhere from 20 g/hour (for small jet mill operation) to production mill rates of up to 840 kg/hr, as shown in the twin screw feeder rate chart below. As with all feeders, this rate range is dependent upon the type of screw configuration chosen as well as the drive type and available turn down ratio, i.e. speed controller with a DC motor with an available turn-down or 100:1 vs. speed control with a frequency inverter and an available turndown of 17:1.

Volumetric vs. Gravimetric

Depending upon the accuracy of feed required, the screw feeder can be supplied in either a volumetric or a gravimetric configuration. If the material or formulation is free flowing and of constant density, then the traditional range of accuracy experienced with the K-Tron volumetric twin screw feeder is often acceptable. However, it should be noted that when feeding materials with high variations in bulk density, volumetric feeders can have

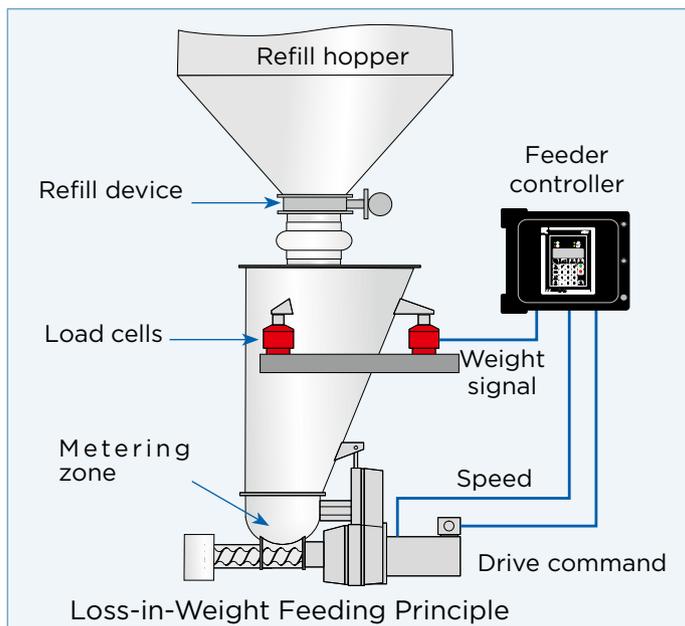
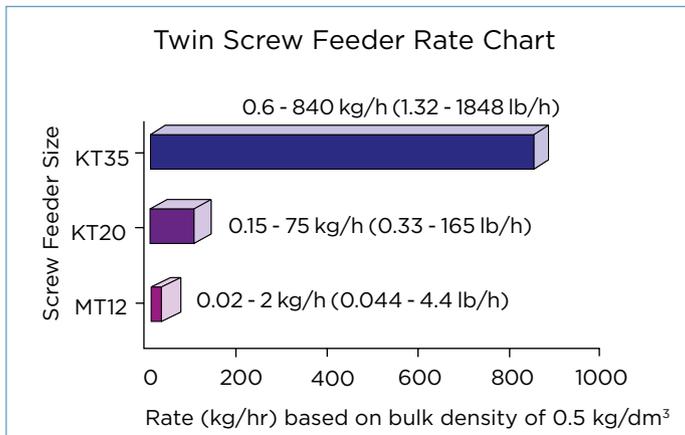
relatively high fluctuations in feed rate due to the resulting fluctuations in the filling of the screws. In the case of cohesive materials, it is possible in volumetric mode to have almost no material discharging while the screws are running, such as in cases of bridge building or packing in the hopper. Since the feed rate in a volumetric feeder is purely a function of screw speed, the feeder, and milling process below, has no way of detecting this upset condition. Oftentimes, even the use of level sensors in the feed hopper may not alert the process of this upset in a timely fashion, and off-spec particle size distributions may occur for a significant time. This is especially relevant in high energy mills with relatively short residences times, such as jet mills or micronizers.

Coperion K-Tron's gravimetric feeders utilize load cells with patented Smart Force Transducer (SFT) technology to constantly measure the weight of pharmaceutical product delivered to the process below. Loss-

in-weight feeding affords broad material handling capability and thus excels in feeding a wide range of materials from low to high rates. In operation, the entire 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. Due to their ability to provide a more accurate feed rate, despite the difficult flow properties of the pharmaceutical material, gravimetric feeders are becoming increasingly popular for a wide variety of milling and micronizing operations.

Coperion K-Tron gravimetric loss-in-weight twin screw feeders offer the following features:

- Constant feed rate with high short term accuracy and low set point deviation
- Gravimetric control consistently checks the material weight thus alerting of any problems in flow to/from the feeder hopper



Coperion K-Tron LIW pharma feeder on platform scale



Coperion K-Tron feeder with Hosokawa Alpine UPZ pin mill in isolator

- The patented SFT digital weighing technology delivers the high accuracy requirements needed for maintaining control of pharmaceutical systems
- The SFT weighing technology features a resolution of 1:4,000,000 in 80 ms, as well as built in immunity to fluctuations in plant vibration and temperatures
- Simple measurement and display of feed rate, via mass flow
- Continuous level control by analyzing net weight

Handling Highly Potent Active Ingredients

Many milling and micronization operations involve the size reduction of highly potent active pharmaceutical ingredients (API's). As the potency of these dry compounds increases, project engineers are often faced with the requirement to place the entire feeding and milling operation in an isolator or glove box. The purpose of these isolators can be twofold: protection of the operator from the hazards of the drug and protection of the dry compound from the



Coperion K-Tron Pharma feeder with isolator plate mount

hazards of the surrounding environment. In designing such milling systems, it is imperative that the feeding device used be completely accessible and dismantled through the use of gloves in glove ports.

Integration of the Coperion K-Tron Pharma Feeder to the wall of the isolator can be done by means of varied plate mount designs, with the motor and gearbox completely isolated from the glove box. To connect the wall of the glovebox with the wall integration plate of the feeder, a static seal (gasket or O ring) or an inflatable seal can be used. It should be noted that this design is only possible with volumetric feeders, because there is no friction free flexible connector available that does not affect the weight measurement. In the case of gravimetric feeders, the complete feeder is placed in the glove box, with a fully vented enclosure around the feeder motor and the gearbox.

When delivering highly potent material to the feeder hopper, split butterfly valves are often used for isolation of the container after product delivery. The feeder hopper is equipped with a docking device to mate with the corresponding active or passive device on the transfer container. This can be the case when docking from IBC's, or simple small canisters.

Cleaning Requirements

Careful consideration must be given to the cleaning requirements, not only for the feeder but also for the entire milling process. All gaskets and O-rings must be compatible with the solvents or detergents used for cleaning. Flexible feeder hopper walls or liners have a tendency to wear and abrade depending upon the cleaning method, thus degrading into the product and destroying the batch. In addition, these materials have a tendency to stain when used with tinted or colored formulations, thus being even harder to clean. For these reasons, stainless steel is recommended for hoppers and contact surfaces, with a minimum surface finish of 0.8 micron Ra.

In the case of wet-in-place (WIP) designs, static or retractable spray balls can be installed in the feeder hopper to allow for a complete rinsing of the feeder device before it is dismantled for further cleaning and inspection.

Nitrogen Purging

Since the organic nature of many pharmaceutical materials results in a high potential for explosion, particularly in a milling device, the complete system is often purged with nitrogen. This nitrogen gas inerts the system

Milling and Micronization of Pharmaceutical Powders



to minimize the risk for explosion. Nitrogen purge fittings can be equipped in the feeder hopper as well as on all shaft seals. The use of positive pressure purges on the shaft seals thus serves a dual purpose: they aid in the inerting of the feeder as well as preventing the material from bypassing the seals and passing on to the bearing area. In the cases where high pressure gas is used for jet milling, and a closed connection is used between the feeder and the mill inlet, it is also recommended that a pressure compensation or balancing line be incorporated between the feeder outlet and the feeder hopper. The use of such a line ensures pressure balancing to avoid high vacuum, which can cause material to be sucked past the screws, as well as possible overpressure, which can prevent flow to the mill below.

Pressure Shock Resistant Milling Systems (PSR)

In some cases requiring explosion protection, the complete mill system is designed for explosion containment. All system components in the containment zone are designed to withstand an internal pressure rise up to

10 bar(g). Since designing a screw feeder for such a pressure can be extremely expensive and cost prohibitive, an oversized rotary valve, for pressure containment, is installed below the feeder outlet, prior to the mill inlet. This valve does not meter or control flow. It is oversized to simply allow flow through it and then seal or isolate the milling system in the event of a pressure rise. By installing this device after the feeder, the standard pharma design feeder can be utilized, without the requirement of a pressure containment design.

Coperion K-Tron Advantage

The Coperion K-Tron pharmaceutical design twin screw feeder offers a completely sanitary and easy to clean design for the high demands of the pharmaceutical industry. Features include:

- All stainless steel construction, without the use of flexible liners which may abrade and wear due to cleaning cycles and detergents/solvents used
- Fully enclosed motor and gearbox, to ensure a clear separation between the "process" and technical area, thus



Coperion K-Tron LIW pharma feeder on compact platform scale

- preventing added cleaning concerns
- Unique and fully purged shaft sealing arrangements to ensure no leakage of product into the bearing/seal area
- All machined and polished construction, eliminating the use of cast constructions, thus removing any possible pits and crevices
- All welds continuous and polished
- Easy dismantling without the use of tools through the use of triclover clamps and connections
- Options available for inerting, pressure compensations, glove box integrations, product isolations, rinse in place cleaning
- The Coperion K-Tron Control Module (KCM) provides integrated control of motor drive functions. In addition, specialized SCADA based control systems, with CFR 21 Part 11 control platforms, can be added for displaying individual line capacity and overall recipe of the blend.

Alpine is a registered trademark of Hosokawa Micron International Inc.



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