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Choosing a micronizer for inhalation powders

Selecting the right mill can impact product performance, energy consumption, and the ease of scale-up, cleaning, and operation

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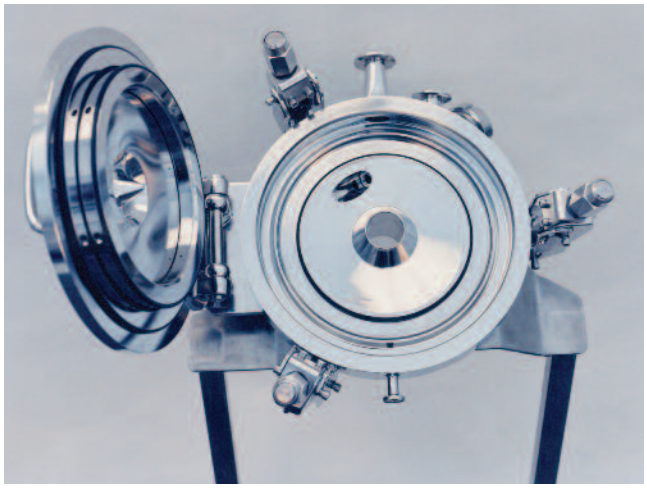


Micronization plays an important role in the manufacturing of inhalation powders, and the selection of micronizing equipment during development can affect the long term performance of the product. The increasing demand on particle fineness and improvement in actual attainable final sizes has led to a redefinition of the term "micronization." In the milling industry, micronizing had been associated most commonly with particles less than 20 µm (<0.02 mm); however, in recent years, the word has come to refer specifically to particle size reduction to less than 10 µm.

The narrow distribution of particle sizes having the ability to reach the lung makes the milling of APIs and excipients used in inhalers critical. Most researchers have found through extensive research and experimentation that the most effective aerodynamic particle size for reaching the airways is between 1 to 5 µm. Particles over 5-6 µm usually deposit in the oral cavity, from which they will get cleared, providing minimal clinical benefit. Particles less than 0.5 µm will be too light and get blown back out from the respiratory track during exhalation, rendering this fraction of the drug ineffective as well.

Types of mills available

A good understanding of the basic micronization techniques can help product developers select the most appropriate mill for development and eventual scale-up. The most commonly available options include different methods of jet milling, as well as various media (ball) mills, which may run either wet or dry (see photos above).

While these different milling processes can all generate particles in the desired range for inhalation, they can produce significant differences in morphology and particle size distribution, potentially affecting product performance, which makes proper mill selection important from the start. In addition, ease of cleaning and economics of operation may enter into the selection of a micronizing mill.

Since morphology of the milled product depends strongly on the properties of each specific material, media mills may achieve better physicochemical properties for certain inhalation APIs; however, most manufacturers seem to prefer jet mills, except where the particle size distribution requirements fall into the submicron range. In general, jet milled particles tend have a rounder shape than do ball milled particles, which may be a desirable property for a given active.

Beginning the development process with a jet mill can provide a certain comfort level for inhalation product developers because jet milling scales up predictably from the lab to production scale. Calculating the energy consumption per kg of feed material using the nozzle gas velocity and the mass of gas passing through the nozzles provides a reliable basis for scale up.

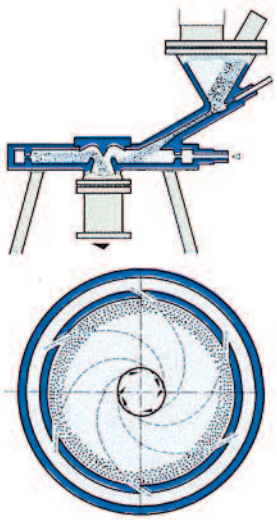
Spiral jet mills

In the jet milling arena, the options include spiral jet mills, target jet mills (which are not widely used), and fluidized bed jet mills. Due to the simplicity of its design, which makes it extremely easy to clean, as well as easy and comparatively economic operation in comparison to the alternatives, the pancake-style spiral jet mill usually ranks as by far the best choice of micronizer for the pharmaceutical industry (see Figure 1).

In an industry where cleanability rates second only to achieving the desired particle size as the most important factor in mill selection, the fact that spiral jet mills contain no moving parts, coupled with a very basic design that eliminates cracks and crevices, makes them preferable to both ball mills and jet mills with internal classifiers, especially where cross contamination might be an issue. These types of mills clean very easily via flooding or sterilization, and accessibility to the internals makes cleaning verification an easy task, providing significant time savings in cases where several cleaning cycles could be a part of each campaign.

Figure 1

Flow pattern of Spiral Jet mill vairables



A spiral jet mill consists of a flat cylindrical chamber with grinding gas injected through peripheral nozzles, which generates a high velocity internal vortex. The feed material, injected into the vortex via an eductor system, undergoes size reduction as a result of both interparticle collisions and particle collisions with the chamber walls of the micronizer. Larger particles stay on the outer spiral and continue their high speed interactions due to centrifugal forces, while particles that have reached the appropriate size move to the center discharge opening with the internal vortex (drag force).

Controlling the feed rate or the grinding gas pressure provides primary control of the particle size distribution achieved, although numerous designs incorporating some means of static classification on the outlet of spiral jet mills are also available. At its simplest, set-up for this type of mill requires nothing more than a filter bag at the outlet and manual controls. As with most size reduction equipment, manipulating several secondary parameters can add a level of control to the output of the micronizer. For spiral jet mills, adjusting the nozzle diameter and the nozzle angle allows operators to adjust the particle size of the output (Table 1). The table below does not include air volume as a variable since this is a byproduct of the nozzle diameter and the grinding pressure.

Spiral jet mills do have certain limitations. The feed material flows through an eductor that has very narrow passages, limiting the feed particle size. Because spiral jet mills require long retention times for top size control, they may cause up to 15% higher energy consumption than micronizers with dynamic inter-

Table 1

Cause and effect for Spiral Jet mill variables

Feed rate	Grinding pressure	Nozzle diameter	Nozzle angle	Particle size
Lower	Constant	Constant	Constant	Finer
Higher	Constant	Constant	Constant	Coarser
Constant	Higher	Constant	Constant	Constant
Constant	Lower	Constant	Constant	Finer
Constant	Constant	Smaller	Constant	Finer
Constant	Constant	Larger	Constant	Coarser
Constant	Constant	Constant	Higher	Coarser
Constant	Constant	Constant	Lower	Finer

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nal classifiers for comparable grinds. Also, any variations in feed rate or characteristics, especially with cohesive powders, can cause blockages in the feed eductor, leading to blowback. Especially for potent compounds, blowback could lead to significant additional cleaning and downtime.

Fluidized bed jet mills

In fluidized bed jet mills, a bed of material forms around a fulcrum of high velocity nozzles (typically 3) that cause particle to particle collisions resulting in size reduction without impacting any of the mill's interior surfaces. Avoiding collisions with the mill wall helps to prevent contamination by metal particles abraded from the chamber interior.

This type of mill includes a dynamic classifier, which works by balancing the centrifugal force generated by the rotation speed versus the drag force resulting from the grinding gas flowing through the classifier. The presence of a dynamic classifier in the fluidized bed jet mill ensures repeatability of the final product particle size distribution, which is particularly important for inhalation powders. However, while the dynamic classifier produces much tighter particle size distributions while using less energy than a spiral jet mill, the classifier also makes these mills much more difficult to clean.

Operating these systems also requires much more attention than for spiral jet mills, even for small scale operations (R&D to pilot scale) due to the need for ancillaries such as a suction fan, bag house, and control panel needed to maintain the proper bed level for efficient grinding. The relationships between grinding pressure, nozzle diameter, and the flow generated as shown in the formula below require multiple adjustments to produce the desired particle size distribution for the product (see Table 2).

$$\dot{V} = 9.5 \times D^2 \times p_o \times \sqrt{\frac{1}{T_o}} \times n \; [m^3/h]$$

Note: Formula applies only to the range $p_o \geq 1$ bar overpressure, whereby:

$\dot{V}[m^3/h]$ = flow rate of working air

D[mm] = nozzle diameter

p_o[bar] = absolute pressure in front of grinding nozzles

T_o[°kelvin] = temperature of working air

n = number of nozzles

In addition, because enough material must be present to form a fluid bed for the proper grinding to take place, this type of mill requires comparatively larger quantities of material feed. As the bed level begins to shrink when the feed is turned off, particle size variations can start to occur at the end of a grinding session, meaning that some of the bed material might have to be left in the grinding zone unprocessed. As a result, fluid bed jet mills may be unsuitable for small batches or for very high value materials. The smallest unit currently available has a 100 mm chamber diameter; however, smaller units with a 40 mm chamber diameter are coming into the market to address these concerns.

Table 2

Cause and effect for Fluid Bed Jet Mill variables

Feed rate	Grinding pressure	Classifier RPM	Particle size
Constant	Constant	Higher	Finer
Constant	Constant	Lower	Coarser
Constant	Higher	Constant	Coarser
Constant	Lower	Constant	Finer
Smaller	Constant	Constant	Finer
Larger	Constant	Constant	Coarser

On the other hand, fluidized bed jet mills have other advantages that make them attractive, especially for certain types of drugs. Since the interior mill surfaces are not involved in the grinding process, this type of a mill can be used to micronize extremely abrasive materials, up to a Mohs hardness of 10, although this is usually not a consideration for inhalation powders. More importantly, unlike the spiral jet mills, fluid bed jet mills introduce feed through fairly large opening, eliminating limitations on feed particle size. Also, the relatively large chamber and high gas flow in a fluid bed jet mill result in a cooler grind, which is especially significant for heat sensitive materials. In cases where the material properties make a fluidized bed mill a better choice, CIP or SIP systems utilizing retractable bearing assemblies can be used to make cleaning easier.

Future technologies

As the technology moves forward, researchers are experimenting with new processes to create nanoparticles. To date, manufacturing API in these small sizes requires applying either wet media mill or particle formation methods, both of which use liquid processes. Using the nano-size API particles in dry powder form without forming agglomerates has proven virtually impossible. However, to increase their dissolution rate and bioavailability, the nanoparticles can be dispersed and coated onto the surface of conventional micronized excipient for DPI applications.

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