Advances in Powder Micronization Technology for the Pharmaceutical Industry

by

Alpine Product Manager
Hosokawa Micron Powder Systems

Introduction

The demand for pharmaceutical materials including finely ground active substances and excipients is growing. Injectable drugs and dry powder inhalants require particle-size distributions in the range of D_{97} of 2–20 microns, with a steep distribution curve and a minimum of fine and oversized particles. This can be accomplished by either wet or dry processes.

Conventional dry size reduction of pharmaceutical powders is accomplished by impact size reduction. Equipment commonly used falls into the category of either mechanical impact mills or fluid-energy impact mills. Examples of mechanical impact mills are hammer and screen mills, pin mills, and air-classifying mills. Spiral jet mills and fluidized-bed jet mills are examples of fluid-energy impact mills.

Among the considerations for selection of a size-reduction system are product purity, reproducible particle-size control, cleanibility, and process validation. Fluid-energy impact mills are normally used for micronization of pharmaceutical powders and will be discussed here today.

What is Powder Micronization?

Micronization is a term used to describe size reduction where the resulting particle-size distribution is less than 10 microns. Micronization size reduction involves acceleration of particles so that grinding occurs by particle-to-particle impact or impact against a solid surface. Fluid-energy mills are used for micronization because of the high impact velocities possible as a result of particle acceleration in a fast gas stream. Particle velocities in a jet mill are in the range of 300 to 500 meters per second, compared to 50 to 150 meters per second in a mechanical impact mill. In fact, the generic term has been used to describe various types of spiral jet mills or "pancake mills." This mill type has been used effectively for many years for size reduction in the micronization range.

There are many and varied reasons that manufacturers choose to grind pharmaceutical powders. Among these are increased surface area, improved bio-availability, and increased activity. Dry powder inhalants and injectable compounds benefit from finer and more defined particle-size distributions.

Reproducible steep particle-size distributions, those with a minimum of fine particles and strict control of oversized particles, combined with improved methods to measure particle-size distributions has led to a change in micronizing techniques. The spiral jet mill is gradually yielding to the next generation of higher-technology fluidized-bed jet mills. The fluidized-bed jet mill combines high-energy micronization with an integral forced vortex air classifier. This combination allows greater control of the maximum product particle size and usually a reduction in generated fines.

Spiral Jet Mill Micronization

The spiral jet mill is suitable for the fine and ultrafine size reduction of materials up to a Mohs' hardness of 3 that display brittle crystalline grinding characteristics. They are typically used in applications where a high ultrafine portion is required.

The spiral jet mill is simple in design, consisting of a flat cylindrical grinding chamber with several nozzles arranged tangentially in the peripheral wall, a pneumatic feed injector, and a feed funnel. Operation is just as simple. The feed is accelerated into the grinding chamber through the feed injector. The material inside the grinding chamber is subjected to two opposing forces: the free vortex created by centrifugal force (mass force) imparted on the particles by the nozzles, and the drag force created by the airflow as it spirals toward the center of the mill. The larger particles are affected to a greater degree by the mass force, circulating around the periphery of the mill and colliding with other particles. As the particles become finer, the drag force exerts a greater effect, drawing the particles with the airstream to the central outlet of the mill.

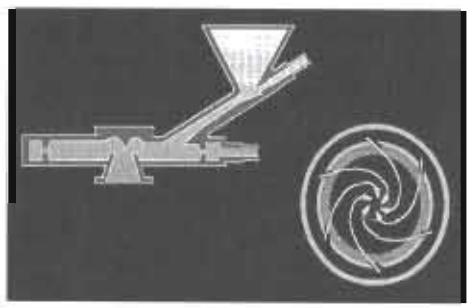


Figure 1. Spiral Jet Micronizer

Feed particle size is critical, restricted by the size of the feed injector. For mills of 200–300 mm, the feed size can be a maximum of 1.5 mm. For smaller-size mills, the feed size is correspondingly finer.

There are several factors, both operational and physical, which affect the fineness of the end product, such as feed rate, nozzle size, nozzle pressure, nozzle angle, airflow rate, feed particle size, chamber diameter and width, and product outlet diameter.

All of these variables can be adjusted during operation, but it is more likely that once operation has begun, only

Grinding chamber diameter (mm)	50	100	200	315
Powder fineness (d_{97} in microns)	3–80	4–90	5–100	6–110
Throughput at d_{97} = 10 microns (kg/hr)	0.6–1	2.5–4	10–15	20–35
Throughput at d_{97} = 20 microns (kg/hr)	1–2	4–8	20–30	45–70
Air volume (m^3/hour)	15	50	190	460

Table 1

feed rate will be varied to meet the required particle-size distribution.

The size range of spiral jet mills employed in size reduction of pharmaceutical powders includes units from 50 mm to 500 mm, but most are in the 100 mm and 200 mm size range. Table 1 shows some typical mill sizes with their relative fineness and throughput ranges.

There are several manufacturers of spiral jet mills which meet the general design and performance criteria outlined above. There may be slight differences in design, manufacturing methods, and product-collection requirements. There are two types of spiral jet mill designs, with single or dual product-collection points. A jet mill system with a single product-collection point is easier to clean and sterilize, is more compact, and does not split the product into two fractions. It is also easier to design in 10 BAR PSR construction.

Spiral jet mills are effective tools for micronization, especially in the pharmaceutical industry, but they have several limitations. First, as mentioned above, is the limitation in feed size due to the method of product injection. Oversized feed particles can cause blockage in the feed hopper and result in variations in particle-size distribution caused by fluctuating feed rates. This can be controlled by presizing the feed, using a properly designed feed system, and applying vibration to dislodge buildup in the feed chute. There is also the possibility of buildup and scaling in the mill due to the impact which occurs on the mill walls. This is especially a problem with sticky substances such as steroids. But perhaps the most serious drawback is the lack of control of particle-size distribution, especially top size limitation. These process limitations led to the development of the fluidized-bed jet mill.

Fluidized-Bed Jet Mill Micronization

The fluidized-bed jet mill is suitable for the fine and ultrafine size reduction of any material up to a Mohs' hardness of 10 that can be fluidized by the expanded compressed gas in the grinding chamber. They are typically used in applications where a fine to ultrafine micronization is required, and they are not limited by feed size, heat sensitivity of the material, or abrasive characteristics. They are characterized by decreased energy consumption, reduced wear and buildup in the grinding chamber, steeper particle-size distribution, and low noise emission.

The fluidized-bed jet mill actually consists of two distinct segments and thus processes. The lower grinding section comprises the actual grinding chamber with several nozzles arranged radially in the chamber wall and a gravity feed inlet.

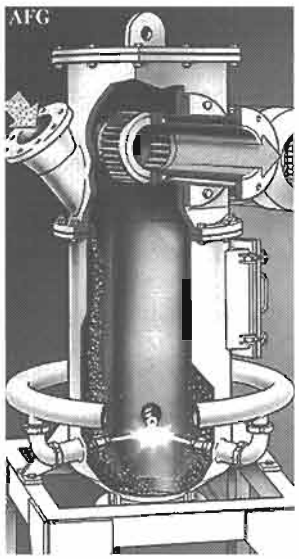


Figure 2. Fluidized-Bed Jet Mill

The upper classifier section is a centrifugal forced vortex air classifier which is responsible for particle-size control. The two processes work together to give the fluidized-bed jet mill its characteristic steep particle-size distribution and sharp top size control.

Operation of the fluidized-bed jet mill is quite simple. Feed material is introduced to the grinding chamber through a large gravity feed inlet. During normal operation, there is a fluidized bed of material inside the grinding chamber. Material is entrained by the high-velocity gas streams created by the nozzles, and size reduction occurs as a result of particle-to-particle collision in the gas stream and at the focal point of the nozzles. The expanded gas conveys ground particles upward toward the centrifugal air classifier. The classifier allows material of a given fineness to exit the mill while rejecting oversized particles back into the grinding chamber for additional size reduction. An equilibrium is established with an internal recirculation: the introduction of fresh feed material and a constant discharge of ground material from the mill.

The key to maintaining a consistent particle-size distribution is the integral air classifier. Air classification is defined as the separation of bulk material according to the settling velocity in a gas. As in the spiral jet mill, the same two opposing forces—mass force and drag force—are acting on the particles. Mass force is the force exerted on the particle by acceleration due to gravity, inertia, or centrifugal force. Drag force is the force exerted on a particle by the surrounding medium as affected by its aerodynamic properties. In a centrifugal air classifier the mass force is exerted on the particle by the peripheral velocity of the classifier wheel.

The drag force is exerted on the particle by the carrying fluid, which in the case of a jet mill is the expanded grinding gas. The particle size at which the mass force and drag force act equally on the particle is defined as the cut point. As in the spiral jet mill, the mass force exerts a greater influence on the particles which are coarser than the cut size, and they are returned to the grinding zone of the jet

mill. The drag force acts upon the particles which are finer than the cut size, and they are carried through the classifier wheel and recovered as product.

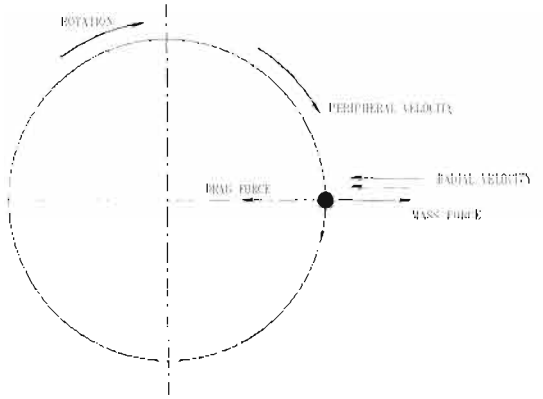
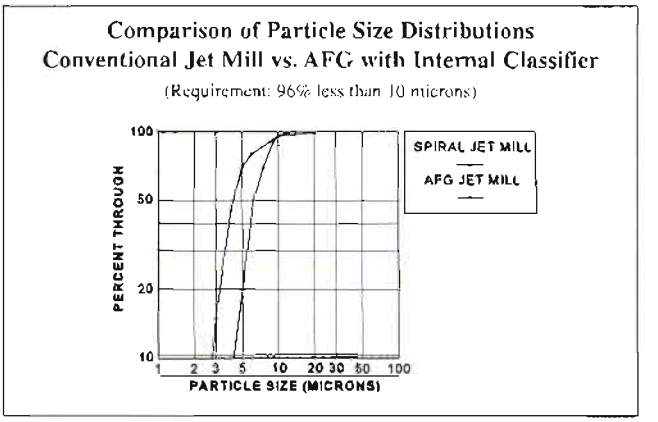


Figure 3. Classification Forces

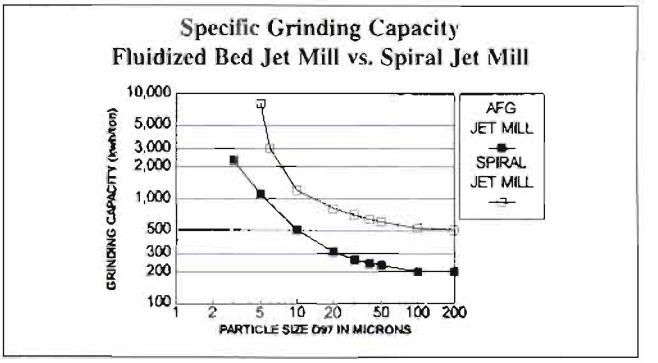
Most of the limitations inherent in the spiral jet mill do not exist in the fluidized-bed jet mill. There is no real limitation on feed size as the gravity feed inlet varies in size from two to six inches. The problem of material buildup and scaling in the mill is also virtually nonexistent. Material does not circulate or impact against the mill walls; in fact, the vertical velocity of air and product in the chamber is only about 1.5 meters per second. The most important improvement in the fluidized-bed jet mill process is the ability to control the particle-size distribution of the product. The upper particle size of the product is strictly controlled by adjustment of the integral air classifier. By increasing the rotational velocity of the classifier wheel, a greater mass force is exerted on the particles, and smaller particles will be rejected and returned to the grinding zone. The end result is a finer particle-size distribution. Conversely, decreasing the classifier speed will allow larger particles to pass through the classifier wheel, the end result being a coarser particle-size distribution. Airflow also has an effect. A higher airflow through the classifier wheel results in an increased drag force and a coarser particle-size distribution. With this degree of control, a fluidized-bed jet mill is able to produce an infinitely adjustable particle-size distribution.

Table 2 illustrates the effect of adjustment of various operating parameters on the particle-size distribution (PSD).

Because of the integrated classifier, spatter grain particles are virtually eliminated from the finished product. Control of the upper particle size also reduces the possibility of overgrinding the product in order to ensure a top size. The first graph, comparing the resulting particle-size distribution from a fluidized-bed jet mill to that from a spiral jet mill clearly shows a more precise cut point and a reduction in the ultrafine fraction.



The following graph indicates the improvement in specific energy which can be expected when processing in a fluidized-bed jet mill.



Fluidized-bed jet mills are available in sizes ranging from 100 mm to 1250 mm grinding-chamber diameter. For most pharmaceutical applications, though, the most common sizes are 100 mm to 400 mm. Table 3 shows some typical mill sizes with their relative fineness and throughput ranges.

Table 2. Adjustment of Particle Size in an Alpine® AFG Fluidized-Bed Jet Mill

Nozzle Diameter	Grinding Pressure	Total Air Volume	Classifier RPM	Particle Size
Constant	Constant	Constant	Higher	Finer
Constant	Constant	Constant	Lower	Coarser
Constant	Higher	Higher	Constant	Coarser
Constant	Lower	Lower	Constant	Finer
Smaller	Constant	Lower	Constant	Finer
Larger	Constant	Higher	Constant	Larger

Grinding chamber diameter (mm)	100	140	200	400
Powder fineness (d_{97} in microns)	2–40	3–60	4–100	5–120
Grind Air volume (m^3/hr) Minimum Maximum	 50 70	 110 150	 200 300	 800 1200
Throughput at d_{97} = 10 microns (kg/hr)	5–8	10–15	20–30	80–120
Throughput at d_{97} = 20 microns (kg/hr)	10–15	20–30	40–60	160–240

Table 3

If there is a limitation at all to a fluidized-bed jet mill, it is the ability to process very small samples. During normal operation, there is a certain quantity of product in internal recirculation and a small amount of residual material left in the mill at the conclusion of the process. This can be an inconvenience if only small sample quantities are available, and these applications would be better served in a spiral jet mill.

Processing Pharmaceutical Powders

In the past several years, the requirements of the pharmaceutical industry have changed. There are many new demands on the processor to manufacture powders with finer and tighter particle-size distributions, fewer spatter grains, and reduced contamination. In addition, processes are required with increased efficiency, better process control, and provision of documentation validating the complete system. Further, regulatory agencies such as FDA and OSHA demand greater operator safety and product protection. These are options that reflect these requirements :

- clean in place
- sterilize in place
- explosion protection or containment
- product protection
- operator protection
- higher surface finish

These requirements have led to the development of both a spiral jet mill and a fluidized-bed jet mill that will meet the requirements of the pharmaceutical industry into the next century.

The Pharma Design spiral jet mill features:

- a monobloc grinding chamber, a one-piece construction free of welding seams and dead spaces. The main parts of the machine, including nozzles and all connections, are CNC machined from one-piece solid stainless steel. With this type of highly sophisticated manufacturing technique, a mill is produced without welding and without cracks and crevices.
- a surface finish that is standard Ra = 0.8 microns, with optional Ra = 0.4 microns or electropolishing. This level of finish is necessary to ensure low levels of surface contamination and to maintain batch integrity.
- a grinding chamber cover that is secured with triclamps or a triclover fitting.
- a mill that is mounted vertically to allow cleaning fluids or steam to drain from a bottom fitting without residue.
- connections to the mill that are all aseptic triclamps.
- a design for CIP/SIP.
- feed that is controlled by loss in weight feeders combined with an optical monitoring device or capacitance level indicator.

These features have resulted in the state-of-the-art spiral jet mill pictured below.

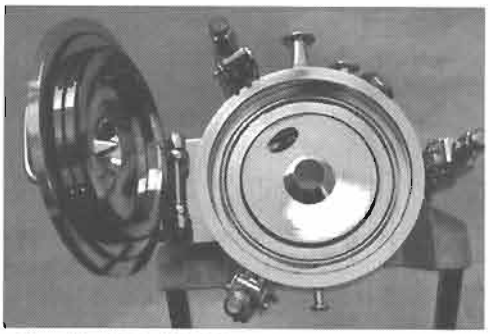


Figure 4. Monobloc Spiral Jet Micronizer

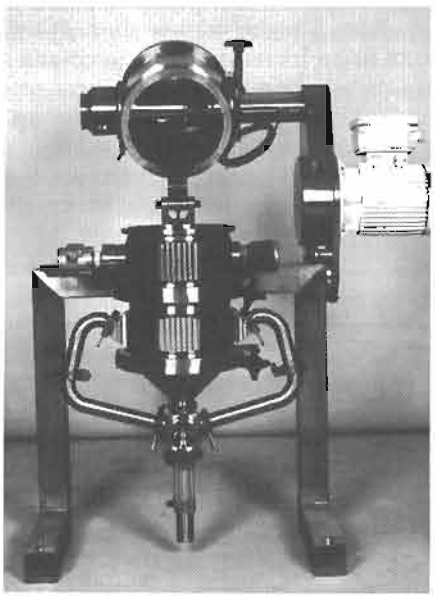


Figure 5. Monobloc Fluidized-Bed Jet Micronizer

A Pharma Design fluidized-bed jet mill was developed concurrently with the Pharma Design spiral jet mill. The same design parameters were taken into consideration, including monobloc one-piece construction, but with two very notable exceptions. While a spiral jet mill has no moving parts, a fluidized-bed jet mill has an integral air classifier. The classifier wheel is also manufactured in monobloc construction, and the new Pharmaplex bearing design was incorporated into the AFG fluidized-bed jet mill. This new and innovative bearing design allows for CIP/SIP cleaning. The Pharmaplex bearing, monobloc mill construction, and internal finish make the AFG the state-of-the-art fluidized-bed jet mill for pharmaceutical processing.

As pharmaceutical powders are potentially explosive, the issue of explosion safety also has to be addressed. There are several methods to protect against explosion of powder: inerting with nitrogen or other gas, containment of the explosion gases within the confines of the grinding system, explosion suppression, and venting. Most pharmaceutical process systems use either inert-gas processing or pressure containment up to 10 BAR.

An inerted system uses nitrogen or another inert gas as the grinding medium. The system can be rather complex with closed-loop gas piping and an elaborate control system to monitor and control the oxygen level in the system. A closed-loop system designed to recycle the grinding gas is more economical to operate than a single-pass system.

A containment-designed system requires a mill that is more robustly built to withstand an internal pressure of up to 10 BAR G. There are also other considerations to protect the operator and contain the product: the location and type of all seals, the mill clamping arrangement, and total containment of the mill inlet and outlet. Because there is only a slight additional cost to manufacture a pressure-resistant mill, most of the pharmaceutical jet mills manufactured by Hosokawa Alpine are standard 10 BAR PSR construction. The same mill can then be used for either an inerted or a containment system.

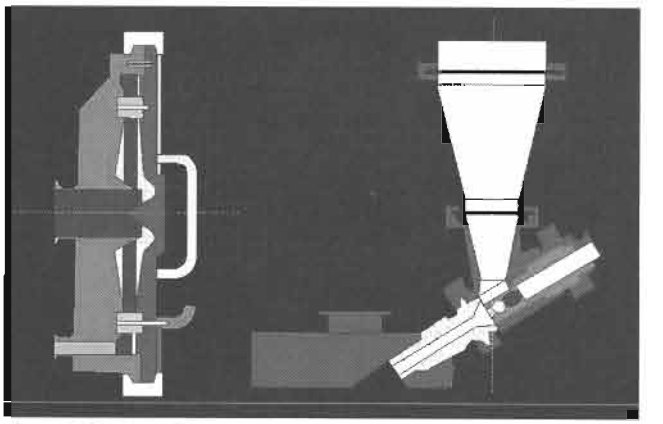


Figure 7. Sectional Drawing of a Spiral Jet Micronizer

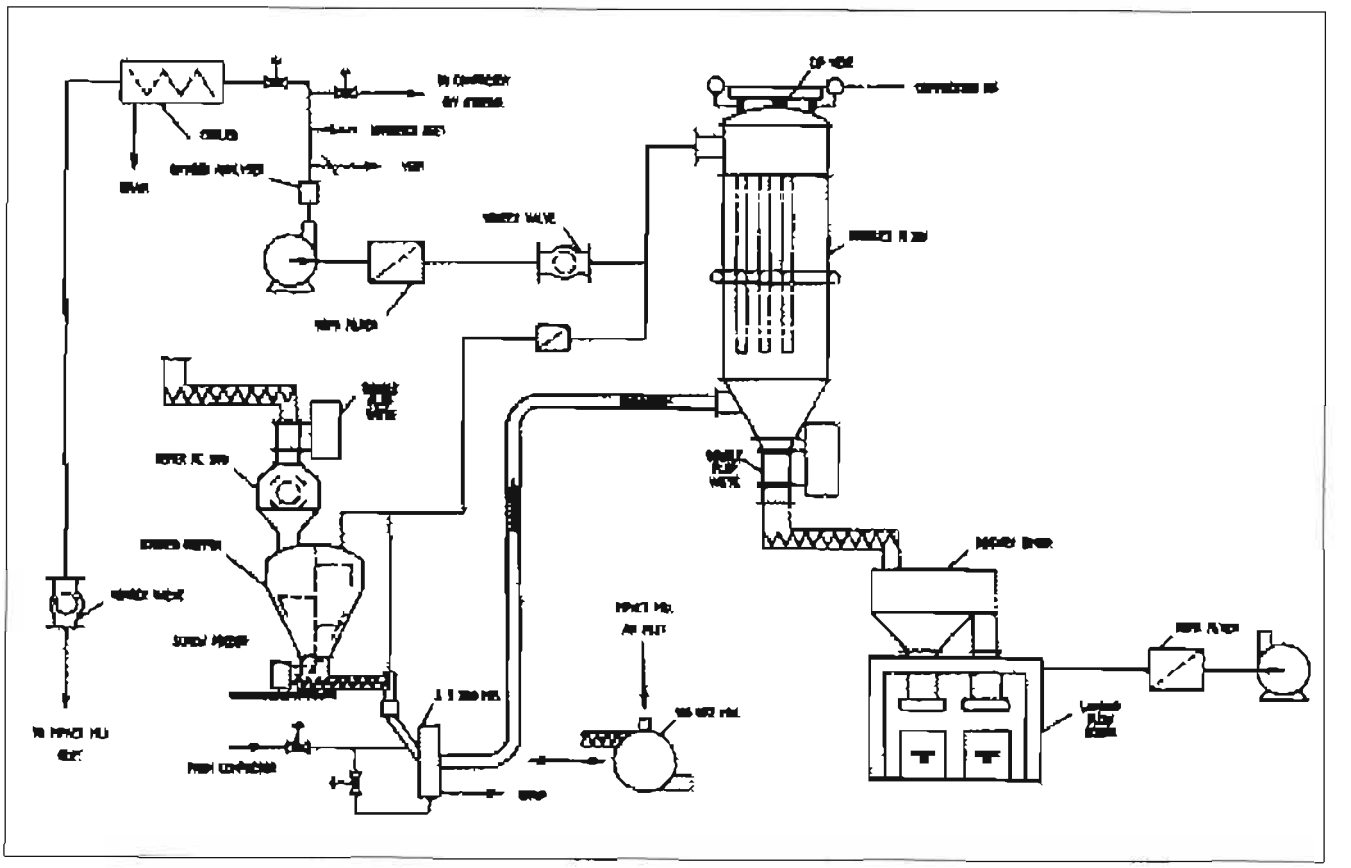


Figure 6. Closed-Loop Inert Spiral Jet Mill System Process Flow Diagram

In addition to the mill, all other system components must be protected against the pressure wave and flame front resulting from an explosion. In most cases the feeder and dust collector are designed for containment, and an explosion barrier valve protects the downstream HEPA filter and exhaust fan.

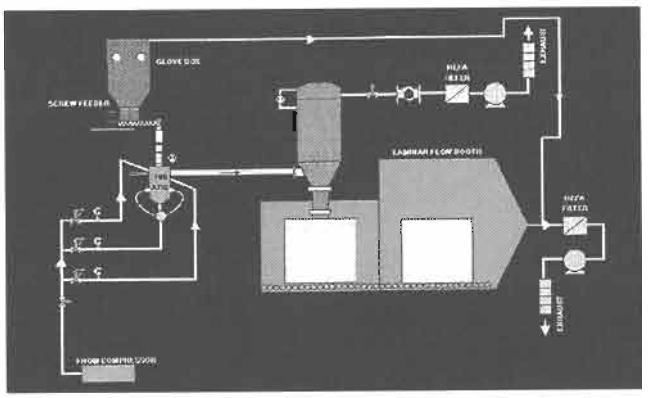


Figure 8. 10 BAR PSR System Process Flow Diagram

Designing for sterilization in place (SIP) requires a number of design considerations, including:

- surface finishes to Ra = 0.4 microns
- seals must withstand sterilization pressures of up to 3 BAR G and temperatures of 130–140°C.
- high points must be vented and low points drained.
- equipment must be capable of being dried by either hot sterile air or vacuum.
- pressure and temperature measurements

The same considerations must be taken for the complete system as the jet mill itself. Most times, the sterilization process is applied only to selected system components. The barrier valves already in the system isolate the sterile components from the nonsterile components during the sterilization process. The barrier valves remain closed during sterilization and then are open for the grinding process.

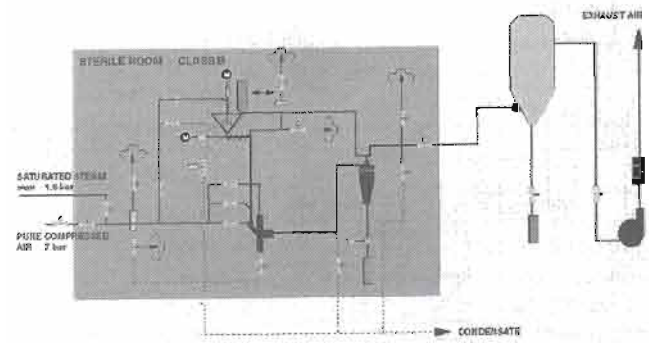


Figure 9. Spiral Jet Mill Sterilize-in-Place Process Flow Diagram

The term "clean in place" is very loosely defined and can result in confusion between the processor and equipment manufacturer. There are several methods for cleaning equipment in place.

- Manually disassemble and clean at a remote washing station.
- Rinse the equipment of loose dust, then disassemble and clean at a remote station.
- Manually remove the difficult-to-clean items from the machine, then clean the housing in place.
- Automatically wash the entire system in place, without opening, using a validated cleaning process.

Only the last method is a true "clean-in-place" operation. Most plants, however, will use a combination of the above methods to accomplish the task.

As with sterilize-in-place systems, clean-in-place systems have some design considerations that have to be addressed, including:

- surface finish
- location and selection of seals
- mandatory draining of all low points
- accessibility to cleaning fluid of all surfaces
- easy drying of the system

An example of a state-of-the-art fluidized-bed jet mill system is the Hosokawa Alpine 100 AFG Multiprocessing System, pictured below.

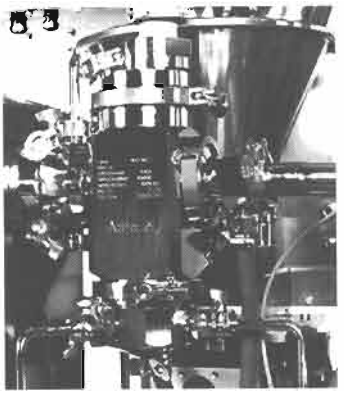


Figure 10. Hosokawa Alpine Clean-In-Place 100 AFG Multiprocessing System

Before the decision is made to design a clean-in-place system or to offer an existing CIP machine for an application, the product itself must be tested for solubility in a particular cleaning agent. If the material is not soluble or only moderately soluble, a manual cleaning program will have to be instituted.

Finally, the collection system has to be designed for both high collection efficiency and incorporation into a clean-in-place design. A recent development by Hosokawa responded to this demand. A new type of reverse-pulse jet filter with full clean-in-place capability was awarded first prize from the Interphex Pharmaceutical Exhibition in London for the most innovative design (see Figure 11).

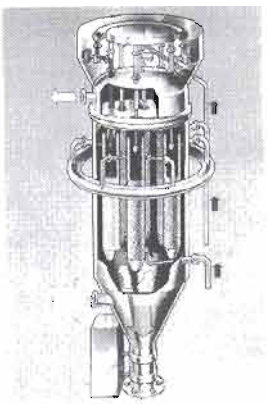


Figure 11. Hosokawa MikroPulsaire CIP/SIP Product Collector

Case Study — Spiral Jet Micronizing System

The client: An international pharmaceutical company
Location: England
Process requirements:

The process involved passing a dried pharmaceutical powder through a prebreaker and into a buffer feed hopper. From there it was accurately metered by volumetric feeder in a spiral jet micronizer. The product was micronized and the material collected in a reverse jet filter, eventually passing out through a double-flap air seal into a mixer.

The key process issues which affected the design of the plant were:

- The product was potentially explosive, and a suitable protection method had to be chosen.
- The equipment was to be installed in a class 10,000 clean room.
- The equipment had to be as far as possible fully clean-in-place.
- Potential product contamination from filter fibers or seals shedding small particles had to be minimized.

Test work:

A comprehensive schedule of tests were completed on all the critical processing steps. These tests were:

- prebreaker trial
- screw feeder trial
- micronizer trial comprising
  1. powder-conveying and pressure-drop trial
  2. clean-in-place wet-cleaning trial

From the test work it was established that the spiral jet micronizer was able to meet the requirements of the particle-size specification providing the screw feeder could consistently feed a steady metered feed rate to the unit without fluctuation.

The wet-cleaning trials showed us that the screw feeder and reverse jet filter could be cleaned in place, and a validatable cleaning method was established. However, the micronizer was not going to be suitable for clean-in-place as the tests showed some hard product buildup within the grinding chamber. This would require some manual cleaning to remove.

A detailed set of tests were also carried out to establish the potential explosive properties of the product. Analysis of the test results showed that although the micronized product was explosive, the degree of risk was not high. Therefore, it was decided to pursue a philosophy of explosion containment and a 10 BAR pressure shock-resistant plant was supplied.

Surface finish:

The internal surfaces within the process equipment were all polished to an Ra = 0.5 micron with subsequent electropolishing. It was found that the electropolishing helped to reduce the surface tension on the cleaning fluid and therefore improved the performance of the clean-in-place procedures.

Validation

The driving force behind the development of the advances in powder micronization technology discussed in this paper have come from statements made by regulatory agencies such as the Food and Drug Administration (FDA).

"Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics."

A high-quality system that will produce a consistent high-quality product batch to batch is only one of the requirements. Documentation to back up the process design as well as the process capabilities of the machine must be in place.

There are four main validation stages relating to the mechanical process design:

- design qualification (DQ)
- installation qualification (IQ)
- operation qualification (OQ)
- performance qualification (PQ)

As an equipment manufacturer, we are involved in the first three of these stages, even at times producing all of the required DQ, IQ, and OQ documentation and implementing the protocols.

Conclusions

The new spiral jet micronizer and fluidized-bed jet micronizer designs described herein will meet the following requirements:

- fully clean-in-place and sterilize-in-place
- allow very low levels of occupational exposure limits
- meet 10 BAR pressure shock-resistant criteria
- surface finish specification of Ra = 0.4 microns with further electropolishing
- new bearing housing designs for CIP/SIP

Further, the fluidized-bed jet micronizer has certain advantages over a spiral jet mill design:

- control of particle-size distribution and upper particle-size limitation due to the integral air classifier
- reduction of specific energy
- operation with lower noise emissions
- process of sticky materials without scaling and buildup in the mill

The writer gratefully acknowledges the assistance of Mr. Andrew McLeish, Hosokawa Micron Limited, for his invaluable contribution.

Reprinted with permission from The Journal of Pharmaceutical Processing