

MILLING OPERATIONS IN THE PHARMACEUTICAL INDUSTRY

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19.1 INTRODUCTION

Two aspects of a successful formulation are that it produces consistent results *in vivo* and it can be manufactured reproducibly. One of an engineer's main goals in pharmaceutical development is to design a process that results in a high level of consistency and control of final product performance from research through manufacturing. Particle size of ingredients in a formulation, especially the active pharmaceutical ingredient (API), greatly impacts bioperformance and process capability, and as such it is an important parameter to understand and control. Milling, or mechanical size reduction of solids, is frequently used to achieve API or formulated intermediate particle size control, and can also be used for reagent and excipient size control [1]. Size reduction can be performed with enough energy to break individual particles or with less energy, to break granules or agglomerates during formulation; it can be performed on dry solids, partially wet solids, or in slurry mode; it can be performed on reagents and excipients as well as final API. While there are other processing options that can be used to achieve these goals, milling is a powerful tool that is frequently chosen as a relatively straightforward way not only to evaluate whether particle size control will provide the desired performance and consistency, but also to effect the desired process or product performance control from early development through commercial-scale manufacturing.

Milling can increase the surface area of solids to increase their dissolution rate. This can be extremely important for

improving bioavailability of a formulated drug product. The Biopharmaceutics Classification system [2–4] is one way of characterizing whether increasing API dissolution rate may improve its bioperformance; in this system, compounds are classified as BCS II or IV when their solubility is low, based on a set of standard dissolution test conditions. While clearly particle size does not affect compound equilibrium solubility, dissolution rate is directly proportional to particle size (see Noyes–Whitney equation, Fick's first law).

Control of dissolution rate can also be important for facilitating or improving chemical reaction performance when a reagent is charged in solid form. Increasing surface area of the API can also increase its effectiveness as seed for crystallization. As discussed in previous chapters, providing enough available surface of the correct crystal form is important for controlling API crystal size and form uniformity.

Size reduction of API and/or excipients can also be important to ensure consistency of formulation processing. This processing frequently involves dry blending of API with one or more excipients, and the mean size and particle size distribution of the API relative to the excipients can influence the tendency of the API to segregate, or not mix uniformly with the other ingredients. Formulations where relatively small (mean size less than 10 μm) API is required include small unit dose formulations (submilligram) to ensure blend uniformity. Milled API results can aid in obtaining proportionately tight distributions and small API mean size, which

may be necessary to facilitate meeting these specifications [5]. Suspension or controlled release formulations may also have tight requirements on mean and top (largest) size in the API particle size distribution. For example, API that is used in dry powder or metered dose inhalers must have sizes less than 5–6 μm and more than 0.5–1 μm to reach deep lung and not be exhaled [6, 7].

In a milling operation, mechanical energy imparts stress to particles, and they are strained and deformed. When strained to the point of failure, cracks are formed and can propagate through the particle and result in breakage. Crystalline materials tend to break along crystal planes, while amorphous materials break randomly, and flawed particles will be easier to break than those with fewer internal weaknesses. When sufficient force is rapidly applied normal to a particle surface and directed toward its center, mass fracture, or breakage into a few large fragments, can occur. When force is applied more slowly, compression will be the main cause of particle breakage. If force is applied parallel to the surface of the solid, over time the particle can break into many fine particles, which is usually described as attrition [1]. Mill design and operation play a large role in determining which mode of breakage occurs.

There are several techniques available to characterize the distribution of particle and granule sizes produced by milling. Optical microscopy or image analysis is useful when little material is available, and observations of particle/granule morphology can be invaluable in troubleshooting milling problems or interpreting other particle size analysis results and powder flow behaviors. Laser light scattering particle size analysis requires more sample, but is commonly used to evaluate API particle size distributions. Solids to be analyzed can be dispersed in a carrier gas or liquid, and some force (air pressure or sonication) is applied to disrupt agglomeration and permit analysis of individual particles (Figure 19.1). This technique can also be used online as milling takes place and thereby permit additional process understanding and control [8–10]. Sieve analysis, or determining the amount of material that passes through or is retained on standard mesh screens is also used to assess size

distribution of granules in a formulation process. Perry's *Chemical Engineer's Handbook* [11] summarizes several size analysis techniques and provides additional references on this topic.

It is important to note that in certain situations milling can be challenging and alternative size reduction techniques should be considered. If the milling operation results in material that contains a high proportion of fines (particles much smaller than the average size), processing problems can occur in subsequent unit operations. Large proportions of fine particles can increase cohesive behavior of the bulk solid, resulting in poorly flowing powder as the API is handled during formulation [12]. When solids are milled in a slurry and then need to be isolated from the liquors, fines can pass through the filter media and reduce overall yield. Fines can also reduce cake and filter media permeability and reduce filtration productivity. At pilot and manufacturing scale, formulation usually involves mechanical solids feeding, which requires that the solids flow in a predictable manner. This "flowability" can be assessed in different ways [13–15] and there is no standard industry practice for this testing in pharmaceutical manufacturing. However, it is clear that solids that tend to demonstrate cohesive behaviors and clump or stick to equipment surfaces can be challenging to process reproducibly and efficiently in formulation without additional effort and safeguards.

Applying mechanical energy via milling does more than break crystals. As the applied energy increases to be sufficient to make individual crystals smaller, the force and stress that cause fracture can also induce changes in the crystal. These changes may manifest themselves in a variety of ways, from increasing numbers of surface cracks and flaws that may increase specific surface area and surface roughness to changes in crystal form, including conversion to an amorphous form. Both types of changes can affect performance in formulation/*in vivo* and can affect physical and chemical stability. This observation is more common for dry milling operations that break primary particles than it is for delumping/granule breaking operations or for wet milling. While milling-induced disorder likely occurs during a wet milling

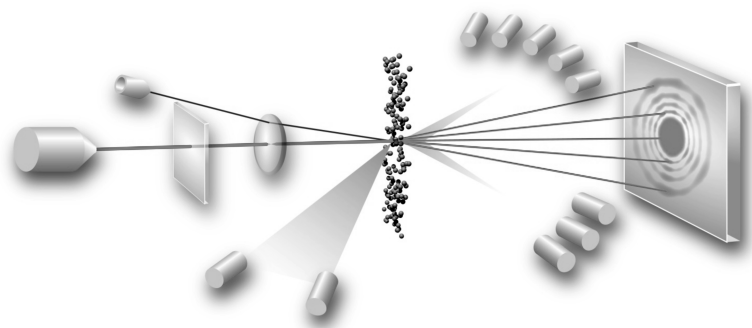


FIGURE 19.1 Laser light scattering device—Photo courtesy of Malvern.

process, contact of the crystal with a liquid medium facilitates surface annealing via dissolution and subsequent re-deposition, and the liquid present can transfer heat more readily than a gas stream. As understanding of solid surface chemistry and crystal structure has increased, and analytical detection and quantification capabilities have improved, these consequences of milling have become more frequently reported and studied. Ongoing work in this area continues to show that while milling can be a desirable way to control particle size, it is important to fully characterize the quality of the milled product. Some analytical techniques to assess amorphous content or crystal form include X-ray powder diffraction and differential scanning calorimetry, and techniques to assess surface energy include atomic force microscopy and inverse gas chromatography [16–18].

Each type of milling equipment is designed to impart different amounts of energy to the solids and therefore can produce different mean sizes and size distributions. Product requirements and process limitations will inform what target size and/or largest size is required. The following sections provide some guidance on how to use that information to select milling equipment and the key parameters that can influence its performance. The resulting mean particle size and particle size distribution depend not only on the mill but also on physical properties of the feed solids such as brittleness and hardness [19], as well as its initial size distribution. Generally speaking, the most efficient way to assess milling feasibility is to perform trial experiments. Even when combined with a size classification operation, it is not possible to use a mill to precisely “dial in” a mean size or particle size distribution with any reliability without the use of feedback control from in-line particle size analysis equipment. However, engineering understanding of mill operation and key process parameters permits effective scale-up of milling, so that the particle size to be achieved at large scale can be predicted accurately from carefully conducted gram scale bench experiments.

19.2 TYPES OF MILLING AND MILL EQUIPMENT

The two primary means of reducing particle size of a solid product are wet and dry milling as defined by the media in which the engineer chooses to carry out the milling activity. Selecting a milling strategy depends on a variety of factors including particle physical and chemical properties, chemical stability, and safety related issues.

API is most often isolated by crystallization, followed by filtration of the solids and a terminal drying step. Based on the thermodynamic and kinetic properties of the system, the physical properties of the solids of interest and the dynamics of the environment within the crystallizer, several outcomes are possible. Crystallizations that end in final isolated particles at the desired particle size distribution (PSD)

specification require no further processing to be carried into the downstream processing train, and are often the result of targeted particle engineering efforts [20–22]. Particles below the target PSD can either be tested for processability in the drug product manufacturing, or the size increased through modified crystallization strategies to yield larger particles of the desired PSD [15, 23]. Most often, and generally by design, the isolated crystals are larger than the target PSD as established through formulation development or bioavailability testing. In these situations, the resulting material must be milled to reduce the PSD to the target.

Deliberately growing particles larger than the target PSD may offer the advantage of cycle-time savings from reduced filtration time during isolation. While the filtration time can be reduced through increased pressure, equipment limitations and nonlinearity associated with compressible solids may result in diminishing returns. As a result, it is often advantageous to attempt to grow, isolate, and dry larger particles in the final processing steps of an API synthesis. In situations with solution instability, this may be the only suitable processing option as the time associated with milling a slurry could negatively impact API purity in these cases. Therefore, in considering the overall manufacturing efficiency associated with making API, the purposeful generation of large particles, which are later reduced in size, is a viable option to consider. In these scenarios, dry milling is the preferred technology for micronization.

Dry milling may also be preferred over wet milling due to incompatibility between the processing solvent and the available wet milling equipment, such as when the process stream is corrosive to stainless steel. Additionally, dry milling may be a desirable unit operation, if an isolation lends itself to some process advantage. Motivating factors driving an isolation prior to reducing particle size may include impurity removal or rejection resulting from a selective crystallization and rapid removal of the liquors.

Wet milling offers an advantage in that milling can be combined with terminal isolation such as selective crystallization of the desired product. When impurity removal is still of principle concern, techniques such as decantation, cross flow microfiltration with diafiltration, or filtration with re-slurry to remove crystallization, mother liquors may be employed as a way to remove rejected impurities or selectively switch to a desired solvent system.

An additional process design benefit is potentially realized with wet milling, as it allows for greater flexibility in terms of how a crystallization process is developed. As an example, as crystallization progresses the mean size of the crystals can be simultaneously reduced by milling during the crystallization process. This is time sparing and also presents crystallization benefits by continually exposing new surface area for use in the ongoing crystallization. Wet mills are also preferred if the material being milled exhibits undesirable physical properties or phase changes at higher temperatures.

The increased heat capacity of the liquid carrier media allows for smaller temperature fluctuations during milling. This can be especially important for materials that have either a low melting point, or are susceptible to crystal form conversion at lower temperature.

Wet milling may offer significant operating advantages over dry milling when the solvent system used for particle size reduction is directly compatible with the downstream drug product processing operation. Drug product unit operations including spray coating and wet granulation require the blend of the milled drug substance with liquid and may therefore be amenable to wet milling followed by direct use of the slurry stream in the formulation processing.

19.2.1 Dry Milling Setup

A general dry milling setup is shown in Figure 19.2. Unmilled solids are charged to the feed hopper via several methods, generally designed to contain any particle dusting during the charge operation. Solids are fed from the feed hopper through a feed device that will allow a constant mass flow to the milling unit. They are conveyed by either gravitational flow through the milling apparatus, screw conveyance, or by conveyance with a carrier gas such as nitrogen. Typically, rotary valves and screw feeders are used to ensure constant feed rates and prevent back flow of solids due to the slightly positive gas pressures on the mill itself. Feed hoppers are generally designed with sloped sides to enable proper solids flow into the rotary valve and screw feeder system. For poorly flowing solids, “bridge-breakers” or small agitators

designed to facilitate solids flow from the hopper into the screw feeder are also installed.

Gas is fed to the mill along with the solids. Depending on the type of mill being used, some of the gas may be introduced to the mill separately from the entering solids, such as in the design of a loop or spiral jet mill, or the gas may be used as a carrier fluid to convey the solids to the mill as is the case in a hammer or pin mill design. While air may be used to convey and mill the solids, nitrogen is most often used to ensure adequate inertion of the environment around the solid phase. For solids with a low melting point, or a propensity to undergo a pressure-induced phase transition to an amorphous solid, liquid nitrogen may be supplied via an orifice upstream of the milling operation to maintain cryogenic temperatures within the mill internals.

Depending on the mechanism of grinding within the mill, the residence time of the solids may vary from one to several seconds of residence time. Once milled, particles will exit the grinding chamber and be carried to product collection. When tighter particle size control is desired, a classifier may be installed in line, which allows for larger particles to be returned to the feed hopper while particles that have been adequately reduced will be routed to the collection area. Product collection from the gas stream will frequently use a cyclone to separate most of the larger solids from the gas stream, and then send the gas containing finer particles to a bag filter and HEPA filter for final dust removal.

In most size reduction milling equipment, residence time in the mill is a key parameter determining outlet particle size. As a result, the feed rate becomes a significant part of the

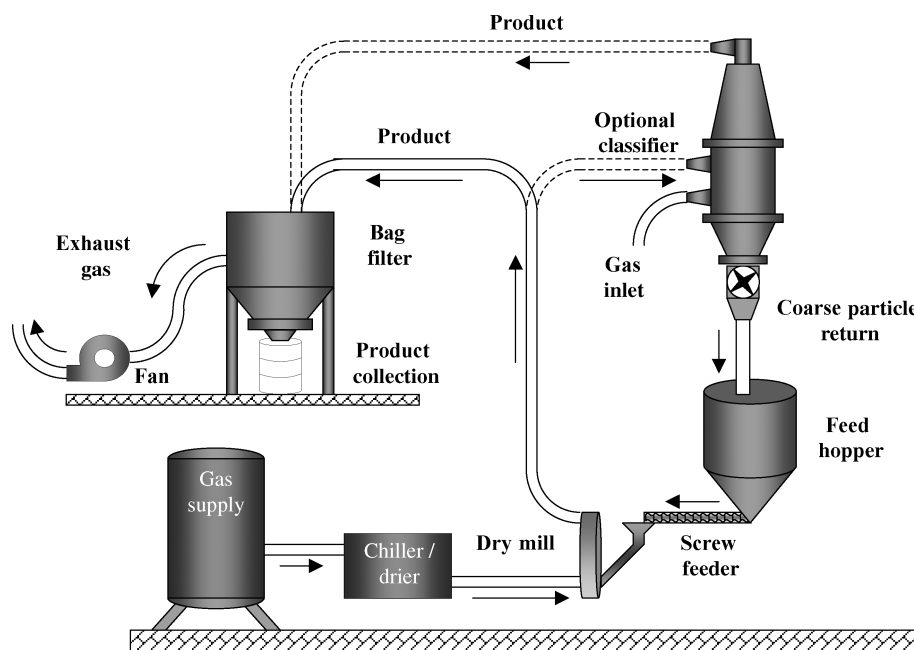


FIGURE 19.2 General setup for dry milling operations.

control strategy and must be carefully considered when determining scale-up parameters for milling equipment.

19.2.2 Dry Milling Equipment

Dry milling may be accomplished by grinding or high force collisions of particles with a moving pin or hammer. Alternatively, it may be accomplished by high energy particle–particle collisions as is the case with jet mills. The following sections briefly describe different types of dry mills. Note that for reduction of particle size to submicron, dry milling strategies are not usually adequate, and therefore wet milling strategies are typically employed. The table below summarizes some different types of dry mills, their key scale-up parameters, and typical minimum particle sizes they can produce. As noted above, solids residence time in the mill is always an important scale-up parameter for dry milling. This can be easily measured experimentally and can be controlled by limiting solid and gas feed rates to match mill efficiency.

Mill Type	Typical Minimum Milled Size (µm)	Key Parameters
Hammer mill	20–60	Mill speed, solids residence time, hammer type, screen size/type, feed size
Universal/pin mill	15–30	Mill speed, solids residence time, head type, feed size
Jet mill	2–10	Gas pressure, solids residence time

19.2.2.1 Hammer Mill Hammer mills involve feeding solids through a series of spinning hammers contained within a casing that may also contain breaker plates. Attrition of particles is accomplished through their impact with the hammers and the mill internals. A sieve screen at the mill outlet is used to limit the size of the particle that can exit the system. Hammer mills come in a wide range of motor speeds, and this is the most important parameter to investigate to ensure reliable scale-up. Screen design is another important parameter, in that size and shape of perforations in the screen will affect mill residence time or how easily milled particles escape the chamber. The hammer mill is not ideal for milling very abrasive materials because significant metal erosion/mill wear can result over time. It is also not preferred for milling highly elastic materials, which could blind the screen, reduce gas flow through the mill, and lead to overheating.

19.2.2.2 Universal/Pin Mill The term “universal” mill usually refers to a mill configuration where multiple milling heads can be used. These mills often can be fitted with pin, turbo-rotor, and hammer-type heads. Pin mills operate

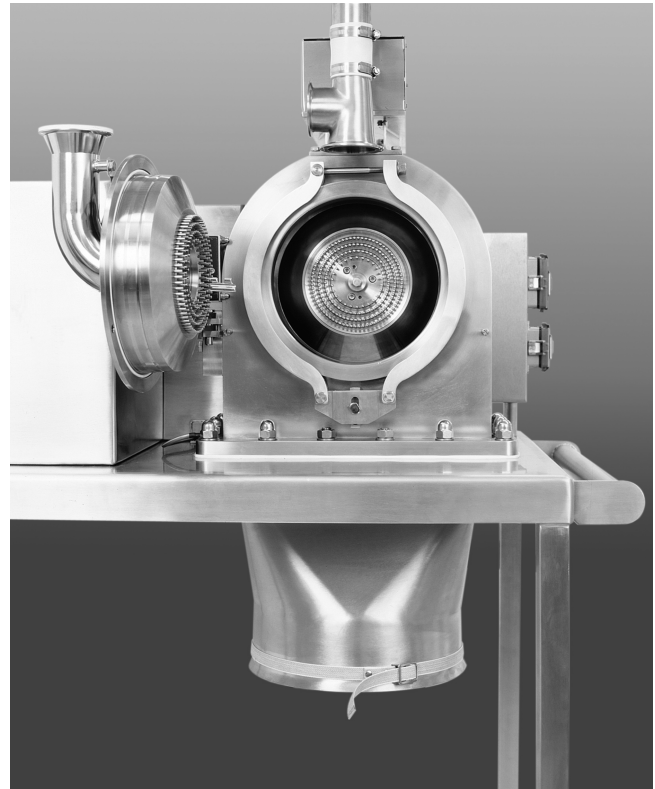


FIGURE 19.3 Pin mill internals—Photo courtesy of Hosokawa Micron Powder Systems.

similarly to hammer mills, but with typically faster rotor speeds and small clearances between rotating and stationary pins. Solids are fed to a milling chamber in a conveyance gas stream. The milling chamber contains a high-speed rotor–stator configuration of pins, which impact the particles as solids are directed from the center of the pin disc out through all the rows intermeshing pins (Figure 19.3). Control parameters to adjust and vary the output PSD include pin gap or pin spacing, the rotational speed of the rotor, solids feed rate, size of the mill, and velocity of the carrier gas used to convey the solids out of the mill.

19.2.2.3 Jet Mill Jet mills are an alternative to hammer or pin milling, where the primary mode of action is mechanical impact of the mill with the particle. With jet milling, micronization is accomplished mainly through particle–particle collisions caused by high velocity gas streams. Spiral jet mills, loop jet mills, and fluidized bed jet mills are examples of jet or fluid energy mills. These jet mills use the same general operating principle. Through the introduction of high-pressure air or other carrier gas (i.e., nitrogen) into specially designed nozzles, the potential energy of the compressed gas is converted into a grinding stream at sonic or supersonic velocities.

Differences in the various jet mills are predominantly in the geometry of the grinding chamber itself. Spiral mills

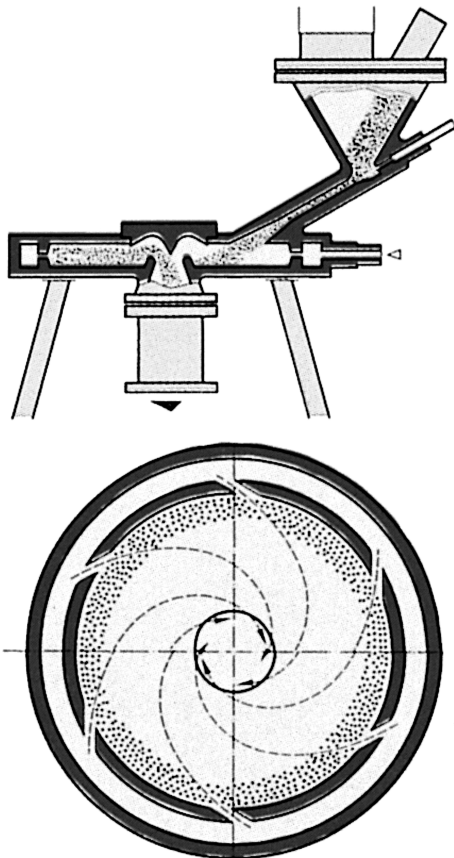


FIGURE 19.4 Spiral jet or “pancake” mill—Photo courtesy of Hosokawa Micron Powder Systems.

create a high velocity helix of gas that rotates around the center of the circular jet mill. Solids are introduced via a venturi feed eductor (Figure 19.4) and become entrained in the turbulent helical flow. The resulting high-energy collisions between particles as well as between the particles and the mill internals fracture particles to micron and submicron size. For loop jet mills, air or carrier gas is injected into an oval grinding loop or “race track” through specially designed nozzles (Figure 19.5). Solids are introduced in a manner similar to the spiral jet mill. In both designs, particles will stratify based on their relative inertia toward the outlet of the mill, resulting in larger particles remaining in the grinding chamber longer while smaller particles are carried out of the mill with the overall gas exhaust to the collection cyclone or chamber. This permits some internal classification and makes the spiral or loop mill performance somewhat less dependent on feed particle size, compared with hammer and pin mills. Key scale-up parameters are the grinder nozzle pressure and the mill residence time, typically determined as particle density in the mill (ratio of solid mass flow to volumetric gas flow through the mill).

In fluidized bed jet mills, the grinding chamber is oriented as a fluidized bed, with specially designed nozzles introducing the grinding gas at the bottom of the mill chamber, creating high intensity collisions between particles (Figure 19.6). Net vertical gas flow out of the mill fluidizes the milled material in the grinding chamber. Fluidized bed jet mills are usually fitted with a classification wheel. Based on the rotational speed of the classifier wheel, large particles gain radial momentum and are returned to the grinding zone of the

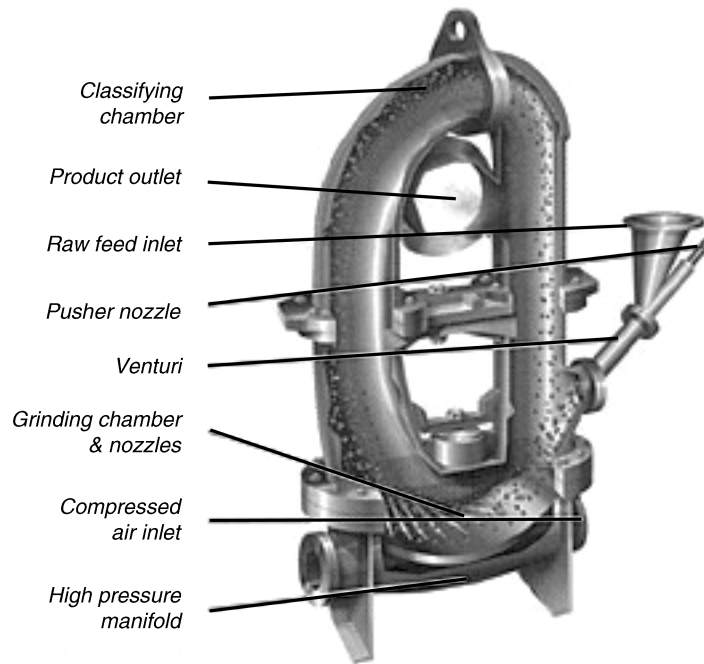


FIGURE 19.5 Loop jet mill—Photo courtesy of Fluid Energy & Co.

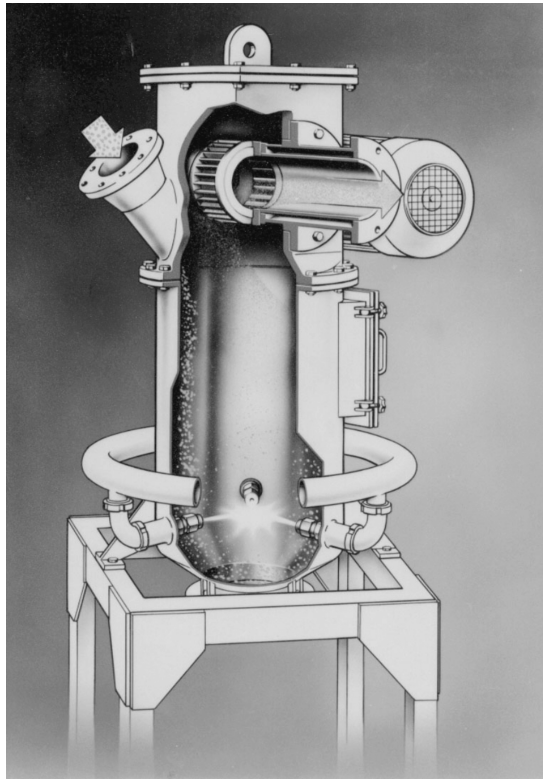


FIGURE 19.6 Fluidized bed jet mill with classification—Photo courtesy of Hosokawa Micron Powder Systems.

fluidized bed. Lighter particles can escape the mill through vanes in the classifier wheel, carried by the main gas exhaust. This type of arrangement can lead to much narrower particle size distributions than other types of jet milling equipment.

In addition to grinder pressure, classifier speed is clearly an important scale-up parameter. To control the solids residence time in the mill, nozzle diameter, total gas flow rate, and mill chamber pressure can be varied with solids feed rate, and these variables must be controlled on scale-up as well.

19.2.3 Wet Milling Setup

Milling a solid suspended in liquid is referred to as either wet or slurry milling. Figure 19.7 shows a generalized setup for a wet milling operation. Wet milling typically occurs in a recirculation loop from a well-mixed holding vessel. Solids are suspended in an appropriate solvent or solvent mixture, either through selective crystallization from that solvent mixture, or the reslurry of previously isolated solids. The system is agitated to maintain a well-mixed system and prevent plugging of the vessel outlet. The slurry is circulated through the wet mill, and cycled back to the holding vessel. The recirculation is continued until slurry samples from the vessel show adequate reduction in particle size. Because of the nature of the recirculation operation, there exists a residence time distribution for particles within the slurry vessel. Where some particles will have traveled through the recirculation loop in multiple passes, some will have not yet passed at all. As a result, the distribution of particle sizes can tend to broaden over time. Operating repeatedly in single pass or “once-through” mode may tighten the distribution, depending on solid properties.

Generally, a lower limit exists for the obtainable particle size. Figure 19.8 shows the d_{90} (90% of the particles have a diameter less than or equal to the d_{90}) of a slurry of drug substance as a function of the mill passes (defined as the ratio

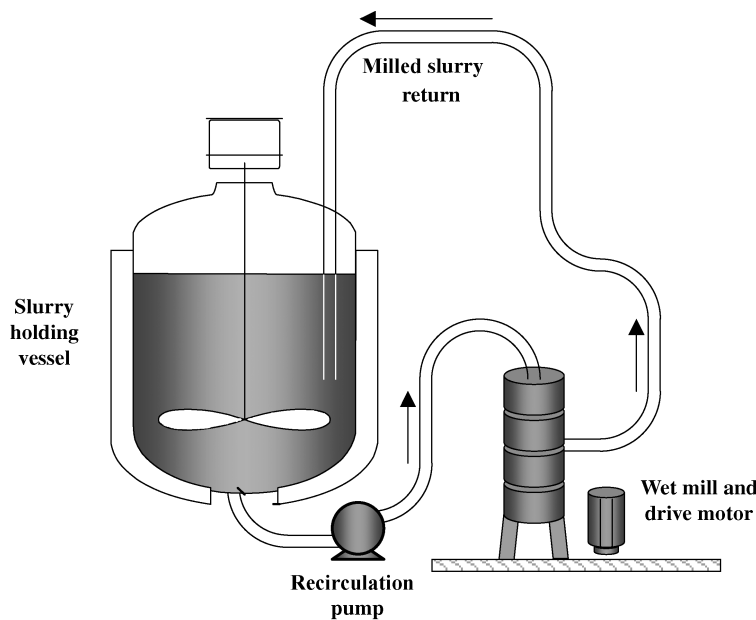


FIGURE 19.7 General setup for wet milling operations.

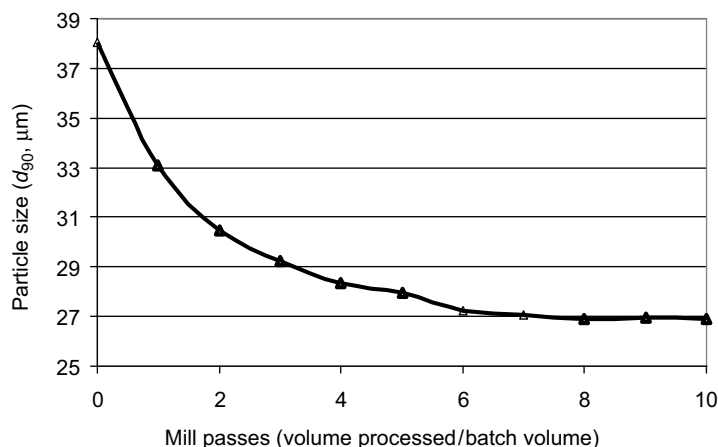


FIGURE 19.8 Particle size versus mill passes in a slurry milling operation.

of the volume of material processed to the volume of the slurry). As can be seen by the figure, a point of diminishing returns is often reached where further circulation through the mill does very little to further reduce the particle size, but will continue to increase the levels of fines produced by chipping rather than mass fracture.

19.2.4 Wet Milling Equipment

Wet milling offers many advantages to dry milling, although there are some limitations. One significant advantage is the ability to eliminate a separate unit operation of dry milling. Wet milling can be carried out as part of the final crystallization–isolation sequence. This approach eliminates the cycle time and cost associated with an extra unit operation, which can be particularly significant if special containment is necessary (see next section). Wet mills also provide the ability to protect the product from the heat input from some dry milling equipment.

As with dry mills, multiple types of wet mills are available. The three most commonly used in pharmaceutical manufacturing are toothed rotor–stator mills, colloid mills, and media mills. The table below summarizes typical minimum particle sizes and main scale-up parameters for these mills. If the mills are operated in recycle mode but not allowed to reach “steady state” milled particle size, feed particle size will also be an important scale-up parameter.

Mill Type	Typical Minimum Milled Size (μm)	Key Parameters
Toothed rotor–stator mill	20–30	Mill speed, tooth spacing
Colloid mill	1–10	Mill speed, rotor–stator design
Media mill	Submicrometer–1 μm	Mill speed, composition, amount, and size of media in mill

19.2.4.1 Toothed Rotor–Stator Mills Rotor–stator mills (Figure 19.9) consist of a rotating shaft (rotor), with an axially fixed concentric stator. Toothed rotor–stator mills have one or more rows of intermeshing teeth on both the rotor and the stator with a small gap between the rotor and stator.



FIGURE 19.9 Wet mill internals—Photo courtesy of IKA Works Inc.

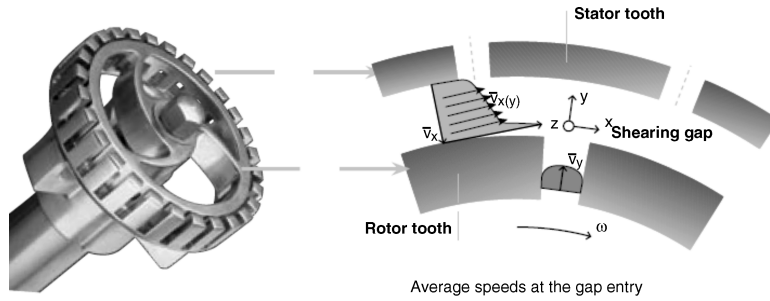


FIGURE 19.10 Rotor–stator working principle—Photo courtesy of IKA Works Inc.

Variations in the number of teeth, teeth spacing, angle of incidence, etc., all impact the milling efficiency of toothed rotor–stator mills [24–26].

The differential speed between the rotor and the stator imparts extremely high shear and turbulent energy in the gap between the rotor and the stator. In this configuration, particle size is reduced by both the high shear created in the annular region between the teeth and by the collisions of particles on the leading edge of the teeth (Figure 19.10). Size is affected by selecting rotor–stator pairs with different gap thickness, or by operating at different rotational rates (or tip speeds) of the rotor. Tip speed is a very important factor when considering the amount of shear input into the product. Tip speed (v_{ts}) is determined according to the following equation

$$v_{ts} = \pi D \omega \tag{19.1}$$

where D is the rotor diameter and ω is the rotation rate (rev/min).

The shear created between the rotor and the stator is a function of the tip speed and the gap thickness. The shear rate $\dot{\sigma}$ is given by

$$\dot{\sigma} = \frac{v_{ts}}{h} \tag{19.2}$$

where h is the gap distance.

Another important factor is the number of occurrences that rotor and stator openings mesh. This is known as the shear frequency (f_s) and is calculated as

$$f_s = N_r N_s \omega \tag{19.3}$$

where N_r and N_s are number of teeth on the rotor and the stator, respectively.

The shear number (N_{sh}) is given by

$$N_{sh} = f_s \dot{\sigma} \tag{19.4}$$

Depending upon the rotor–stator design, the number of rows should be accounted for when calculating the shear number. Scale-up of toothed rotor–stator mills is accomplished by determining for the material in question whether shear frequency or tip speed has greater control over milled size, and then working with rotor–stator design options and mill

speed to maintain the key parameter across scales. If milling will be stopped before steady state/minimum size is achieved, the process must also be scaled on batch turnovers or passes through the mill.

19.2.4.2 Colloid Mills Colloid mills are another form of rotor–stator mill. A colloid mill is composed of a conical rotor rotating in a conical stator (Figure 19.11). The surface of the rotor and the stator can be smooth, rough, or slotted. The spacing between the rotor and the stator is adjustable by varying the axial location of the rotor to the stator. The gap can be as little as a few hundred micrometers or as large as a few millimeters [17]. Varying the gap varies not only the shear imparted to the particles but also the mill residence time and the power density applied. Particle size is affected by adjusting the gap and the rotation rate, and these are the key parameters to maintain at increased scale.

19.2.4.3 Media Mills Media mills, also referred to as pearl or bead mills, are much different in operation than a

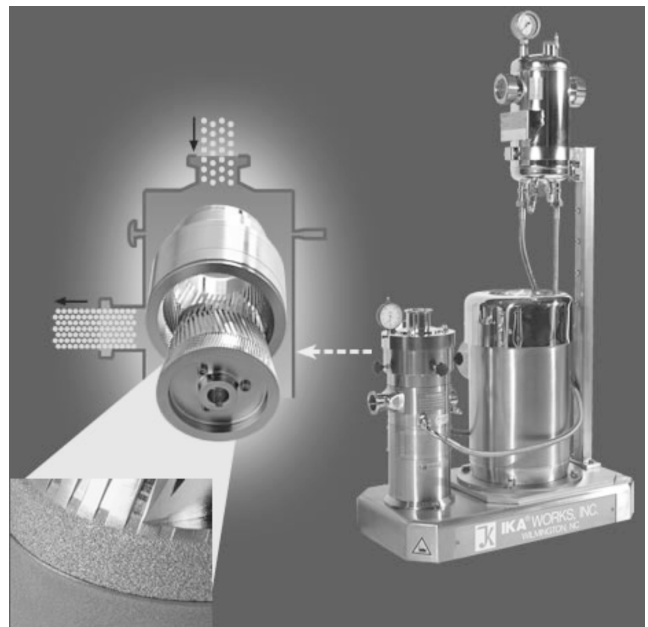


FIGURE 19.11 Colloid mill—Photo courtesy of IKA Works Inc.

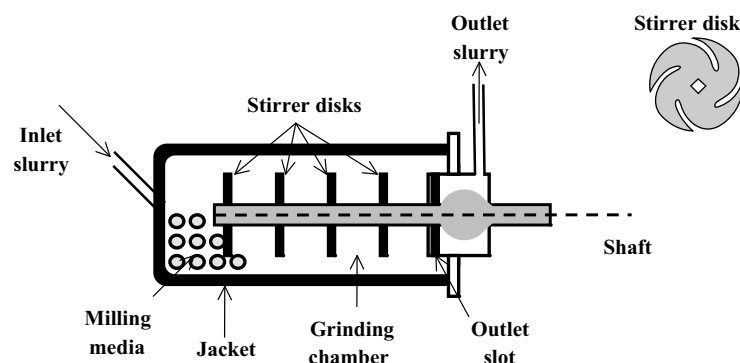


FIGURE 19.12 Schematic diagram of a media mill.

rotor–stator mill. The mill is composed of a milling chamber, milling shaft, and product recirculation chamber (Figure 19.12). The milling shaft extends the length of the chamber. A shaft can have either radial protrusions or fingers extending into the milling chamber, a series of discs located along the length of the chamber, or a relatively thin annular gap between the shaft and the mill chamber. The chamber is filled with spherical milling media usually less than 2 mm in diameter and typically 1 mm in diameter or less. Media are retained in the mill by a screen located at the exit of the mill. The rotation of the shaft causes the protrusions to move the milling media, creating high shear forces [27]. Scale up of media mills is accomplished by maintaining residence time in the mill, keeping the milling media size constant, and holding energy input constant.

The high energy and shear that result from the movement of the milling media is imparted to the particles as the material is held in the mill or recirculated through the milling chamber by an external recirculation loop. Particles are ground by a combination of particle–media, particle–particle, and particle–wall collisions. The result is the ability to create submicron particles. Thermally labile material is easily handled as the milling chamber is jacketed. By utilizing smaller media (less than 100 μm), nano-sized (20 nm) particles are achievable.

At the small size scales achievable by media milling, particle–particle interactions caused by van der Waals forces can begin to dominate [28]. By inclusion of certain additives to the dispersion fluid, the possible agglomeration and resulting reduced efficiency and reduced effectiveness of the mill can be mitigated. Surfactants can inhibit agglomeration by both electrostatic and steric stabilization [29]. Similarly, polymeric stabilizers can also be used to retard agglomeration. The smaller the particle produced, the greater the amount of surfactant needed, since the specific surface area of the particle increase with decreasing one over the radius of the particles.

Milling media are available as several materials glass, metals, ceramics such as zirconium oxide, and polymeric such as a highly cross-linked polystyrene resin. The proper

selection of the milling media is an important criterion in the milling process. Materials such as glass and metals are typically not used for APIs since some abrasion of the milling media can occur, potentially arising in extraneous material concerns. As a result, either polymeric or ceramic media are usually used.

19.3 SAFETY AND QUALITY CONCERNS

Chemical engineers must proactively address process safety concerns and quality risks associated with wet and dry milling processes. While these operations are not unique to the pharmaceutical industry, performing these operations on potent organic molecules can pose some unique challenges.

The main quality concern for both wet and dry milling is to minimize introduction of extraneous matter into the milled material. The most common material of construction of milling equipment is stainless steel, although ceramic, Hastelloy C, and various types of Teflon are also frequently used depending on the material to be milled. Abrasion of the mill surfaces by API or excipient particles can result in erosion of the mill material, and levels of residual metals such as Cr and Ni must be minimized relative to the human dose of API [30]. Assessing the hardness of the API during milling process development, either empirically through small-scale milling experiments or fundamentally through experiments such as indentation testing [19], will help prevent unexpected outcomes on scale-up.

The most obvious safety risk associated with dry milling is personnel exposure to highly potent airborne dust. This is especially important to consider during drug development, before full API safety testing has been completed, and a conservative equipment setup is recommended at early development stages. While most mill equipment is or can be enclosed during operation, minimizing this exposure risk, solids recovery/packaging operations and equipment cleaning should not be overlooked as opportunities for exposure. Typical methods to address this risk include clean-in-place systems and performing the entire milling operation in a

negative pressure isolator with HEPA filtered exhaust. Multiple levels of exposure control, beginning with these engineering controls and continuing through personal protective equipment (PPE), are often required to ensure adequate operator protection.

Perhaps less apparent but no less serious is the risk of dust explosion during dry milling or postmilling activities [31, 32]. There have been numerous reported incidents of explosions occurring in the chemical, food, and pharmaceutical industry, in situations where fine powders are dispersed in air and a spark may be present. The most straightforward way to address this risk in development is to mill in an inert atmosphere (no/limited oxygen), using nitrogen or argon, and maintaining a scrupulously clean processing area. When sufficient API is available (tens of grams), the explosive properties of the dust should be quantified to better understand dust explosion risks. Typical measurements include determining the minimum ignition energy (MIE) (smallest amount of energy required to ignite a dust cloud of optimal concentration) and minimum ignition temperature (minimum temperature at which a dust cloud will ignite) [33, 34]. If an explosive dust (MIE < 20 mJ) will be dry milled at pilot or manufacturing scale, engineering controls must be employed to minimize risk of explosion [35]. The force of a possible explosive event can be quantified by measuring K_{st} (expression of the burning dust's rate of pressure increase) and this parameter can be used in equipment/facility design. Engineering or design solutions include inertion of the process train and use of rupture disks or automatic shutoff valves that quickly close when pressure spikes are detected.

The most common risk associated with wet milling is that of accumulating a static charge in a recirculating loop, especially when a nonconductive solvent such as hexane, heptane, or toluene is used. Electrostatic charge accumulation results from frictional contact between flowing liquids and solids in recirculating loops and the surfaces of equipment (pipes, vessels, agitators). The resulting potential difference between batch and processing surfaces could lead to a static discharge, which could ignite a fire or explosion, especially while processing with flammable organic solvents. Conductivity of organic solvents can range from 10^7 to <1 pS/m. Another way to interpret these values is to estimate the time required for an accumulated charge to decay (a multiple of the relaxation time). For 99% charge decay this may range from milliseconds for water to several minutes for *n*-hexane [36]. Slurry conductivities of <100 pS/m are considered at high risk for electrostatic discharge if a mechanism for charge formation is present (such as a recycle loop or wet mill). Charges can be encouraged to dissipate by use of conductive equipment (stainless steel in place of Teflon-lined pipe) and grounding and bonding the equipment. Additional precautions include operating under nitrogen and keeping linear velocity through the recirculation loop as low as is

practical (while maintaining adequate flow rates to ensure that solids do not settle within the recirculation piping and low points in the loop).

19.3.1 Example Approach to Milling Scale-Up

Throughout the development cycle, different PSDs may be studied to determine the optimum size range for an API or excipient. Determining milling parameters to achieve these profiles has often been done in an empirical fashion through the use of test milling—portions of a material lot are subjected to different milling conditions, and the resultant output tested to determine particle size distribution. While useful in establishing milling ranges for one particular lot of material, test mill runs do not easily allow extrapolation to different milling input conditions. As Quality by Design expectations continue to increase within the pharmaceutical processing world, an understanding of milling parameters, as well as input PSD and their effect on final API attributes is desirable.

As an example, a simple model for particle breakage, like the one shown in equation 19.5, would likely predict an output parameter, such as the d_{50} of the PSD, as a function of one or more input parameters.

$$d_{50,\text{milled}} = \text{function}(\text{input size, mill energy, residence time}) \quad (19.5)$$

To utilize this type of model, the input properties must be chosen and parameters simulating residence time and energy input must be determined. As a first approach, a static parameter such as the unmilled d_{50} of the slurry could be chosen as the input size, the mass feed rate (m) to the mill chosen as a surrogate for residence time, and rotor tip speed (v) chosen for energy input.

$$d_{50,\text{milled}} = K(d_{50,\text{unmilled}})^{\alpha} m^{\alpha} v^{\beta} \quad (19.6)$$

Figure 19.13 shows the relationship between predicted and actual milled values using such a model following a calibration exercise to fit the exponents and the constant K .

While a rough trend may be observed between predicted and actual, the accuracy of this model is not sufficient for predicting actual output PSD. Examining further the choice of input parameters for the model, one can observe that while the d_{50} of an in-process sample from the crystallizer may describe the slurry PSD well prior to drying (Figure 19.14), this parameter may be insufficient to capture variations in actual mill input material following the final drying unit operation (Figure 19.15). The relatively unimodal peaks from the slurry samples clearly change to a wide variety of average sizes and modalities after drying in an agitated filter dryer. It is this variation in size entering the milling step that makes prediction difficult for a simple model such as that of equation 19.6.

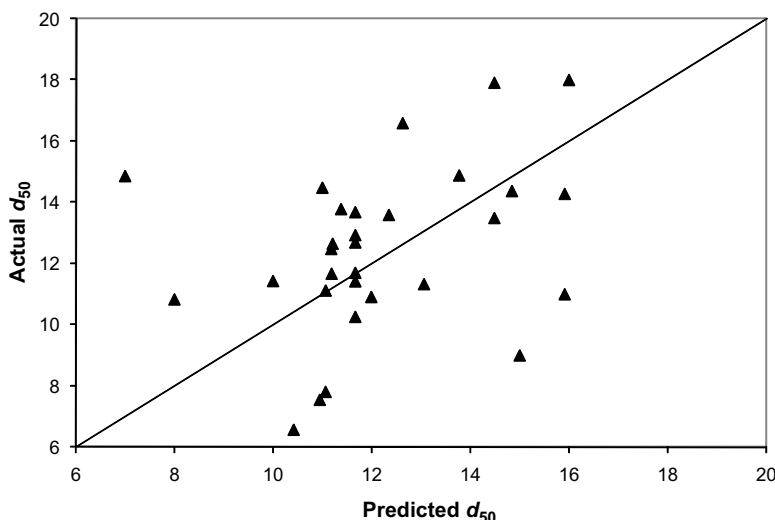


FIGURE 19.13 Predictive ability of a milling model utilizing unmilled slurry d_{50} as an input parameter.

To account for the variability seen in the dried material prior to milling, a simple summary statistic cannot be used. Rather, a measure of the entire PSD should be utilized to inform the model of the distribution of particle sizes moving into the breakage operation. Most particle size analyzers generate histograms with multiple channels of data describing the overall distribution of particle sizes in the sample. Chemometric methods such as principal component analysis (PCA) allow the full shape of the PSD to be reduced from a very large number of histogram components to 2–3 principal components describing the breadth, shape, and skewedness of the distribution. Using PCA in this manner maintains model inputs to a minimum number without significant loss in ability to characterize the full PSD spectrum.

After adding the principal components to the model to accurately represent the shape of the distribution, the equation becomes

$$d_{50, \text{milled}} = K(\text{PCA1})^\varphi(\text{PCA2})^\mu(\text{PCA3})^\delta m^\alpha v^\beta \quad (19.7)$$

where PCA1, PCA2, and PCA3 represent the three principal components of the PSD. This enhancement to the model, following a short number of calibration runs, allows much better prediction of output d_{50} , as shown in Figure 19.16.

The final predictive model is still limited to the API that was used to generate the data. However, the model allows for prediction as needed, and the process of constructing the model may provide valuable information regarding the API,

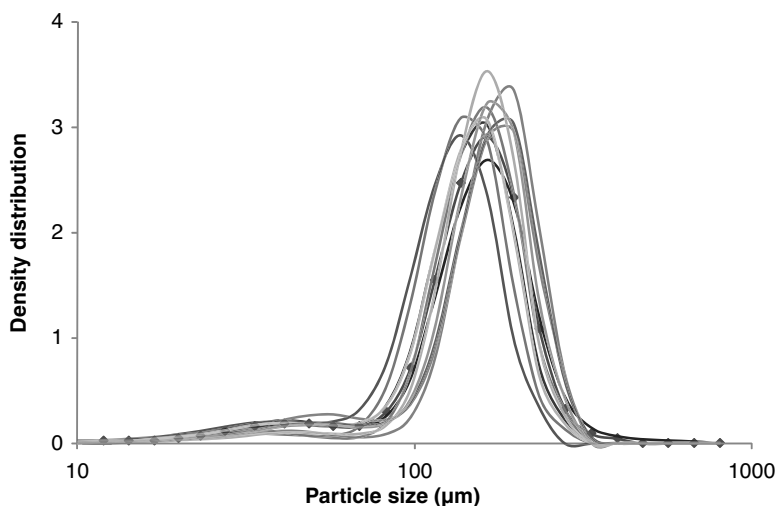


FIGURE 19.14 Particle size of the API coming out of the crystallizer.

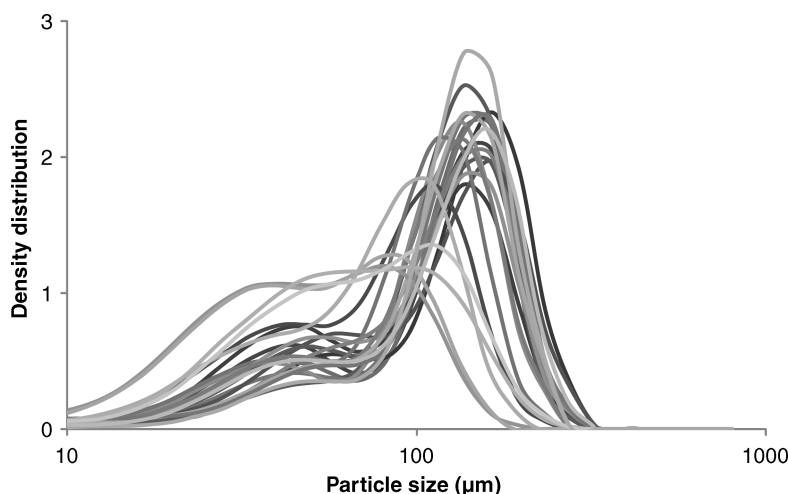


FIGURE 19.15 Particle size of API following agitated drying.

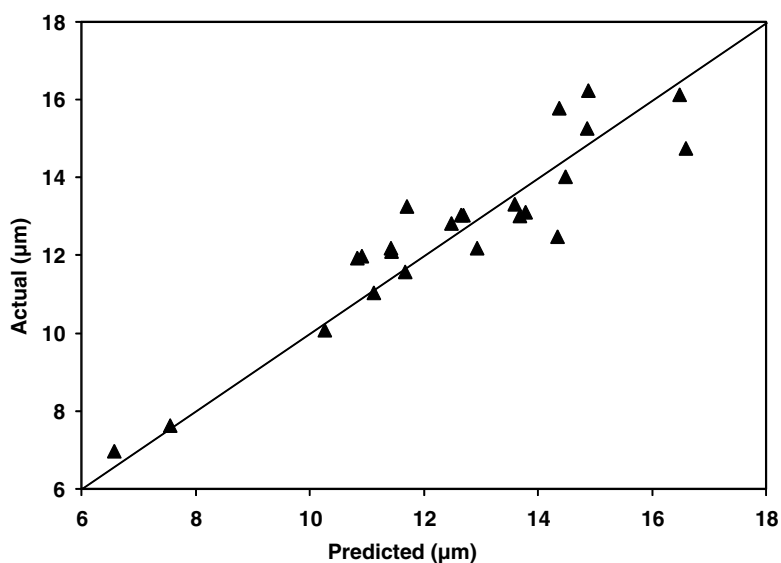


FIGURE 19.16 Predictive ability of a milling model incorporating full PSD spectrum as an input.

including the relative importance of inclusion of the entire PSD spectrum as well as the impact that filtration and drying technique may have upon milling performance.

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