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Selection of Size Reduction Technique in API (Pharmaceutical) Industry

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Abstract

The size reduction generally induced amorphization and/or structural disordering of the drug crystal (mechanochemical activation). The size reduction enhances drug dissolution and solubility include alterations in the size, specific surface area and shape of the drug particles. Size reduction technology such as milling now enable the production of drug micro- and nano-particles on a commercial scale with relative ease. This review will provide a background on milling followed by the introduction of common milling techniques employed for the size reduction of drugs. Salient information contained in the cited examples are further extracted and summarized for ease of reference by researchers keen on employing these techniques for drug solubility and ease in formulation preparation.

Keywords:* *Micronisation; Milling; Size reduction; Bulk drug; Particle size; Active pharmaceutical ingredient

Introduction

The size reduction of APIs is increasingly becoming a key capability of industries like pharmaceutical, food, pigments, minerals, chemical etc. Micronization is a term used to describe size reduction of solid material where the resulting particle-size distribution is less than 10 microns. In many cases, the micronization process is often considered as a black box that produces fine powder and coarse particles enter. The basic mechanism of size reduction is based on impact, compression, shear and attrition. Although it may vary with the nature of material. The particle properties of material like shape, size, static charge, agglomeration, roughness, adhesiveness, morphology, wettability, density, surface chemistry, plasticity, hardness, brittleness and hygroscopicity play an important role during micronization.

Within this paper several size reduction techniques together with principle, working and applicability of equipment is presented for the first time. While from this study we conclude that the effective technique for essential particle size range. the conclusion is corroborated by experimental evidence and previously reported data in the academic literature and provides an insight into the interaction between fine grinding techniques and its usage.

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Size reduction laws

1. *Kicks law* states that the energy required to reduce the size of particles is directly proportional to the ratio of the initial size to the final size of the material [1].
2. *Rittinger's law* states that the energy required for size reduction is proportional to the change in surface area of the pieces [2].
3. *Bond's law* states that the work required to form particles of size Dp from very large feed is proportional to the square root of the surface to volume ratio of the product [3].
4. *Griffith theory* the amount of force to be applied depends on the crack length and focus of stress at the atomic bond of the crack apex [4].

Need of particle size reduction

The demand for milling or jet milling of API is growing steadily to achieve crystal level particle size. Micronisation ensures the safe and effective delivery of APIs in new formats with increase in surface area. It helps particles to enable the solubility of Active Pharmaceutical Ingredients (APIs) which directed to effectiveness of a drug. The solubility is a key factor in bioavailability, micronization reduces particles down to the micrometer or in some cases nanometer size, that can be used to improve the bioavailability of poorly soluble APIs by increasing particle surface area and accelerating dissolution rates. The mixing of several solid ingredients easier and more uniform if reduces the particle size and it also resulted to reduce rate of sedimentation. The rate of adsorption of any drug depends on three things i.e. the dosage form, rout of administration and particle size. The smaller the particle size, quicker and greater will be the rate of adsorption. 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 2-20 microns with a steep distribution curve and a minimum of fine and over-sized particles. Milling is a highly effective technology for reducing particle size of inhalation.

Types of size reduction technique's used in API industries

Size reduction is a unit operation process and the operations include grinding, compression and impact forces. The traditional techniques for micronization have been based on friction to reduce the particle size and this is accomplished by milling or grinding particles. Modern techniques also known as supercritical fluids, which make the API soluble. Micronization is most often used to describe processes that reduce particle size by using fluid energy, such as a jet mill, rather than by mechanical means. During particle size reduction operation knowing the properties of the material to be processed is essential. Probably the most important characteristic governing size reduction is hardness because almost all size-reduction techniques involve somehow creating new surface area and this requires adding energy proportional to the bonds holding the feed particles together. Size reduction process is also termed as comminution or diminution or pulverization. Normally, size reduction may be achieved by two methods, namely crystallization or mechanical process. In the crystallization method, the substance is dissolved in an appropriate solvent. In the mechanical process, the substance is subjected to mechanical forces using grinding equipment (ball mill, roller mill, colloid mill etc.) (FIG. 1.).

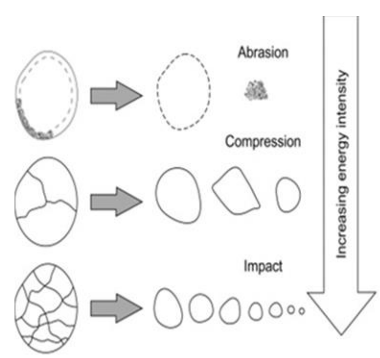

FIG. 1. **Energy intensity VS size reduction mechanism**

The mechanisms used for particle size reduction are,

i. Impact: Particle is stationary and hit by an object moving at high speed(hammer).
ii. Compression: Particle is crushed by two rigid forces.
iii. Shear or cutting: the material is crushed by means of a sharp blade.
iv. Attrition: Breaking the edges of the solid either by impact or particle collision or arising from particles scraping against one another or against the rigid surface [5].

(FIG.1) shows the Energy intensity or consumption as a function of size reduction. As energy intensity increases finer product particle size accomplish [6]. There is wide variety of miller amiable for wet and dry material size reduction in Pharmaceuticals, Chemicals, Cosmetics, Ceramics, Colors etc. industries. Making the best choice of equipment has significant impacts on product quality and costs. The majorly used equipment are explained with their principle, operation and significance.

Multi Mill

The Multi mill working principle involves a variable force rotate blades having both knife and sharp edges with validated screen size to reduce particle in a controlled manner. The mechanism of multi mill is based on pulverization process, knife is used to cut the large particles into small size particle, these big particles are made from granules during the crystallization or drying operation. Multi mill is used for high speed Granulating, Pulverizing, Mixing, Shredding and Chopping etc. of a wide range of wet and dry materials without special attachments.

Material fed in the hopper, goes down to the processing chamber where it moves to the periphery and passes through the screen radially and tangentially. Finally, the processed material gets collected in the container kept below the processing chamber. The direction of beaters can be changed by reversible switch from knife to impact forward and vice versa. Output and quality of the final product depends on three main factors shape of beaters (knife/impact edges), speed and screen size.

Jet Mill

The Air jet mill works on fluid energy precisely aligned jets create a vortex inside the milling chamber. Material is entered in vortex and high-speed rotation subjects the material to particle-on-particle impact, creating increasingly smaller fines. While centrifugal force drives large particles toward the perimeter, fine particles move toward the center where they exit through the vortex finder. Jet mill is one-step grinding in a continuous or batch process with no dead zones to trap material, no moving parts to wear, no grinding media or lubrication to contaminate milled products. Jet milling uses pressurized gas to create high particle velocity and high-energy impact between particles. Compared with mechanical milling, jet milling reduces metal contamination and because process temperature is relatively constant, it can be used for heat-sensitive products. Jet milling has relatively low productivity, large equipment size and high process-gas flow requirements. Using Jet mill particles size can be reduces to below 5 microns.

During operation of jet mill, the material is fed into this vortex along an engineered tangent circle and accelerates. Strong velocity gradients near the jet cause the suspended particles of the material to collide with each other and reduce themselves by attrition and collision. Size reduction is the result of the high-velocity collisions between particles of the process material itself. No grinding media is involved. The jet fluid exits through an outlet at the center of the chamber either from top and draws the micronized the particles with it to the cyclone collection system. Heavier oversized particles are held in the grinding chamber by centrifugal force, until micronized to a desired size.

Cad Mill

Cad mill works on the principle of variable force that mill material in between beaters and screen to the required mesh/micron size which can be collected at the bottom of the container. Quality and output depend upon the three main variables beaters shape (knife/impact forward), speed and screen size. While the knife edge for coarse or large particles and impact or flat edge for finer particles. The speed of beater varies from 1000-2250-4500. Highspeed for fine grinding, low speed for coarser particles. Cad mill consist of quality hopper, feed throat and processing chamber with beaters assembly, heavy duty motor, star delta starter with overload relay, three speed step pulley, suitable screen, cladded base having tubular legs with castors, optional jacket for the feed throat and processing chamber for cooling.

Co Mill

Co-Mill is designed for low heat, low sound, low energy consumption operation and speed variation. Particles fall from the hopper into the blades of the mill which are moving at a very high RPM. The impact of the blades on the particles is the cause of the sizing. The blade has sharp edge on one side and blunt on the other.

During Co mill operation product is poured into the feed hopper of the Co Mill. In the conical screen chamber, a rotating impeller imparts a vortex flow pattern to the in-feed product. The product is forced outward to the screen surface by centrifugal acceleration, ensuring continuous delivery into the "action zone" between the screen and impeller. No heating of product during granulation, due to better air circulation and lesser impact action. In the "action zone" the material is uniformly sized and instantaneously passed tangentially through the screen openings. The finished product is discharged at the bottom of the milling chamber. Cone mills used for achieving de-lumping, dispersion, Deagglomeration, fine grinding, dry and wet milling uniform size reduction, sieving and mixing in the pharmaceutical, food, fine chemical, personal care and cosmetics industries. The output of co mill is near to the size of sieve used approx. 80%-90%. Adjustable clearance between rotor and cone sieve.

Criteria of selection

Food, pharmaceutical, pigment manufacturers and ingredient suppliers have access to a wide range of high-tech milling methods. Each one offers advantages for achieving product characteristics such as particle size and moisture content, along with other considerations such as cost, footprint and the need for ancillary equipment. Each method has also given rise to a diverse range of size reduction equipment. In fact, there may be more than one solution when selecting milling equipment. According to Suha Ozsoylu, director of operations at Hosokawa Micron Powder Systems, the most important step in selecting size reduction equipment is establishing the target size reduction of the product. This target is typically based on the particle size and particle size distribution desired, typically expressed in terms of milling the material down to a given particle size distribution in microns. End products that demand the vast majority of particles consistently measure the same size. For example, cake flour, often requires a different approach to milling than end products that include a range of different sizes. The particle size directly affects the amount of surface area and the interactions among other ingredients.

Discussion

Size reduction offers several advantages such as content uniformity, uniform flow, facilities mixing, and drying, etc. Moreover, due to advance technologies the concept of size reduction become wider and has application in different field like pharmaceutical manufacturing of novel and conventional dosage forms, drug delivery, supercritical fluid technology, nanotechnology, etc. At the most basic level, we can define a particle as being a discrete sub-portion of a substance. For the purposes of this guide, we shall narrow the definition to include solid particles, liquid droplets or gas bubbles with physical dimensions ranging from sub-nanometer to several millimeters in size. The most common types of materials consisting of particles are:

All particle size reduction technologies have addressed the certain drawbacks of the standard techniques. The processes lead, in general, to faster top-down process steps, improved physical stability, and smaller particle sizes than the standard comminution processes such as high-pressure homogenization or wet bead milling. The small particle sizes have a direct impact on the dissolution rate and bioavailability of poorly soluble drugs after oral, topic, and I.V. administration. The research performed to solve the technical challenges of the different technologies in order to achieve improved particle size reduction effectiveness and better formulations for new, problematic compounds. In the future, it is expected that more screenings will be performed employing the principle of design of experiments to systematically analyze the critical factors for the production of nanosuspensions. In this way, it will be possible to establish optimal process parameters to achieve final mean particle sizes below 100 nm for a wide variety of compounds. A plethora of size reduction equipment of varying sizes and capacity are available currently and have ability to handle a wide variety of feeds. The nature of feed to be processed is also as critical as the choice of size reduction equipment. Overall, size reduction helps in achieving uniform mixing, homogeneity and ideal flow of the materials.

Conclusion

The selection of the most appropriate milling technology for an application requires experience and trials. Achieving particle size below d90 200 µ multi mill with above 2800 rpm, for particle size below d90 100 µ cad mill above 4800 rpm and particle size below d90 20 µ jet mill is crucial. Before application of these machines powder safety data should be evaluated.

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