REVIEW ARTICLE

An overview of size reduction technologies in the field of pharmaceutical manufacturing

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Size reduction is a process of reducing large solid unit masses into small unit masses, coarse particles or fine particles. Size reduction process is also termed as *comminution* or *diminution* or *pulverizations*. In addition to the standard adjustments of the milling process (i.e., speed, screen size, design of rotor, load), special techniques of milling may be useful including special atmosphere, temperature control, sonocrystallization, supercritical fluid process. etc. Moreover, some advance technologies of size reduction including Micron Technologies, Gran-U-Lizer™ Technology, Jet-O-Mizer™ and Microfluidics® have been popular. Various application of size reduction concept covers oral delivery of poorly soluble drugs, micronization, nanotechnology (micro- and nano suspensions), etc. This systemic review highlights advantages and disadvantages, mechanisms, theories, techniques, advances, and pharmaceutical applications of size reduction technology.

Key words: *Micronization, milling, particle size, size reduction*

INTRODUCTION

Size reduction is a process of reducing large solid unit masses (vegetable or chemical substances) into small unit masses, coarse particles or fine particles.[1]

Normally, pharmaceutical powders are polydisperse, i.e., consisting particles of different sizes. Polydisperse powders create considerable difficulties in the production of dosage forms. Particles of monosize (equal size) may be ideal for pharmaceutical purposes. In practice, powders with narrow range of size distribution can obviate the problems in processing them further. Size reduction alone is not sufficient to obtain mono-size or narrow size range powder. Therefore, size reduction and size separation should be combined to obtain powders of desired size. There are numerous industries that depend on size reduction to improve performance or to meet specifications. The chemical, pharmaceutical, food, and mining industries all rely on size reduction. Its uses include grinding polymers for recycling, improving extraction of a valuable constituent from ores, facilitating separation of grain components, boosting the biological availability of medications and producing particles of an appropriate size for a given use. There are many types of size-reduction equipment, which are often developed empirically to handle specific materials and then are applied in other situations. 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. Flow properties can be major factors, too, because many size-reduction processes are continuous, but often have choke points at which bridging and flow interruption can occur.[1-3]

Size reduction process is also termed as comminution or diminution or pulverization. Normally, size reduction may be achieved by two methods, namely precipitation or mechanical process. In the precipitation method, the substance is dissolved in an appropriate solvent. This method is suitable for the production of raw materials and bulk drugs. Inorganic chemicals, such as calcium carbonate, magnesium carbonate, and yellow mercuric oxide, are prepared by precipitation method. In the mechanical process, the substance is subjected to mechanical forces using grinding equipment (ball mill, roller mill, colloid mill, etc.).

Various factors like hardness, toughness, stickiness, slipperiness, moisture content, melting or softening point, abrasiveness, and others (material structure, size, shape, flow, and bulk density of product) ratio of feed size to product size, affect the size reduction [Table 1].[2-4]

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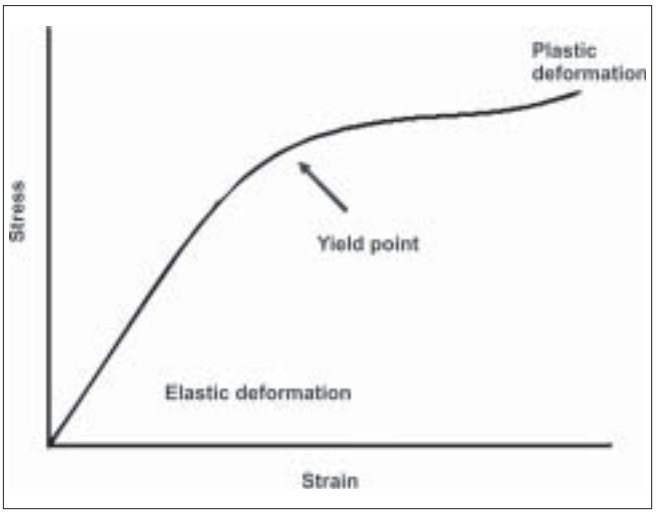

Figure 1: Stress strain curve for a solid

MECHANISMS OF SIZE REDUCTION

The mechanisms have demonstrated that stresses of varied nature are required to achieve size reduction. The common modes of size reduction are explained as follows [Table 2]:

THEORIES OF COMMINUTION

When various modes of stress are applied on a powder, the particles get strained. This stress-strain relationship is shown in Figure 1.[5,6,8,9,11-14]

In Figure 1, the initial linear portion is defined by Hookers law. It states that stress is proportional to strain. The slope of linear portion represents Young's modulus. It expresses the stiffness or softness in megapascals. If the force of impact (stress) does not exceed the elastic limit (region of Hooke's law), the material is reversibly deformed. When the force is removed, the particle returns to original condition. The elastic limit is known as yield value. The stress energy in the deformed particle appears as heat. Example is plastic material such as polymer. The stress-strain curve becomes nonlinear at the yield point. This is a measure of the resistance to permanent deformation. Beyond the yield point, the region represents irreversible plastic deformation. The area under the curve represents the fracture toughness (or modulus of toughness). This is an approximate measure of the impact strength of the material. Fracture of a particle can be obtained when the force exceeds the elastic limit [Table 3].

TECHNIQUES OF MILLING

In addition to the standard adjustments of the milling process (i.e., speed, screen size, design of rotor, load), special techniques of milling may be useful [Table 4].[6,15-22]

Table 1: Advantages and disadvantages of size reduction[4]

Advantages	Disadvantages
Content uniformity and uniform flow	Drug degradation
Effective extraction of drugs and effective drying	Poor mixing
Improved rate of absorption, physical stability, and dissolution rate	Contamination
It increases surface area and viscosity	Others like some instrument related problems e.g., noisy environment
It facilitates bioavailability, mixing and drying	
In aerosol and inhalation preparation, ophthalmic, and parenteral suspension	

Table 2: Mechanisms of size reduction[5-8,10]

Method	Examples	Approximate particle size (μm)
Approximate increases in fineness of product		
Cutting	Scissors Shears Cutter mill	100-80,000
Compression	Roller mill Pestle-Mortar	50-10,000
Impact	Hammer mill Disintegrator	50-8000
Attrition	Colloidal mill Roller mill	1-50
Impact and attrition fluid energy mill	Ball mill	1-2000

Table 3: Theories of size reduction

Theory	Principle
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.
Kick's law	Work required to reduce the size of a given quantity of material is constant for the same reduction ratio regardless of the original size.
Rittinger's law	Worked use for particulate size reduction is directly proportional to the new surface produced.
Bond's law	Worked used to reduce particle size is proportional to the square root of the diameter of the particle produced.

ADVANCES IN SIZE REDUCTION TECHNOLOGY

Micron technologies

Micronizing (defined as particles smaller than 20 μm) often enhances solubility and improves bioavailability, allowing you

Table 4: Some important techniques of size reduction

Techniques	Description
Special atmosphere	Hygroscopic material can be milled in a closed system supplied with dehumidified air. Thermolabile, easily oxidizable, and combustible materials should be milled in a closed system with an inert atmosphere of carbon dioxide or nitrogen and temperature control.
Temperature control	As only a small percentage of the energy of milling is used to form new surface, the bulk of the energy is converted to heat. To prevent these changes in the material and to avoid stalling of the mill, the milling chamber should be cooled by means of a cooling jacket or a heal exchanger.
Subsequent treatment	If extreme control of size is required, it may be necessary to recycle the larger particles, either by simply screening the discharge and returning the oversize particles for a second milling, or by using air-separation equipment.
Wet and dry milling	The choice of dry or wet milling depends on the use of the product and its subsequent processing. If the product undergoes physical or chemical change in water, dry milling is recommended. In dry milling, the limit of fineness is reached in the region of 100 microns when the material cakes on the milling chamber. The addition of a small amount of grinding aid may facilitate size reduction.
Sonocrystallization	Sonocrystallisation utilizes ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients (API).
Spray drying	Spray drying is a commonly used method of drying a liquid feed through a hot gas. Typically, this hot gas is air but sensitive materials such as pharmaceuticals and solvents like ethanol require oxygen-free drying and nitrogen gas is used.
Supercritical fluid process	It can be defined as a dense noncondensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of fluid that largely determine its solvents power. Drug particles are solubilized within SCFs, they may be recrystalized at greatly reduced particle sizes.

SCF: Supercritical fluid process

to optimize the formulation of your product and reduce the therapeutic dose. With a reproducible and controlled particle size of active pharmaceutical ingredients and excipients, manufacturing of finished dosage form could be improved. The most commonly used pieces of equipment are tangential fluid energy mills or pancake mills. High-pressure air/gas is introduced causing particle-to-particle collision and micronization.[23]

Gran-U-Lizer™ technology

Manufacturing Process Equipment's (MPE) high-power Gran-U-Lizer™ size reduction technology is specifically designed to maximize yield and minimize fines in the grinding process. Since each particle passes through each nip once, there is little regrinding of already ground material. This results in a very tight particle size distribution and minimum number of very small particles ("fines").[24]

A superior particle size distribution with fewer unwanted fines can be obtained for numerous drug products, nutriceuticals, excipients, and cosmetics. It is widely used in numerous dry food grinding mill applications like coffee, flax seed, pepper, rice, salt, sugar, and sweeteners. MPE Gran-U-Lizers are ideal for a multitude of mineral grinding applications where final product yield and a minimization of fines are essential. Typical applications of this technology include activated carbon, coke (metallurgical, petroleum), phenolic resins, super absorbents (SAP).

Jet-O-Mizer™ particle size reduction systems

The Jet-O-Mizer jet mill has been developed with many distinct design features to consume less power, provide a greater range of throughput (1 to 12,000 lb/h) and ensure exceptional finished product quality. Specific raw material characteristics and production requirements are integrated into a Jet-O-Mizer system. It offers outstanding efficiency and versatility in fine grinding (0.5-45 microns) and classification.[25]

Some of the important features of this system are high-efficiency chamber design, adjustable classification zone, no attritional heat, and combined operations (physical or chemical).

It is used for different types of materials like hard, abrasive, sanitary, sterile, heat-sensitive, agricultural, volatile, and synthetic materials.

Microfluidics particle size reduction

Creating a suspension of a solid material generally requires significant reduction of the particle size and the addition of surfactants and other materials to prevent particle agglomeration. The ultrahigh shear developed by the Microfluidizer® processor reduces the particle size of active pharmaceutical ingredients to useful sizes and the high turbulence ensures that the resulting particles are efficiently coated. A major advantage of the Microfluidizer technology is that the processor produces the desired small particles with a narrower size distribution than other methods resulting in a very stable product with a long shelf-life.[26]

When formulating emulsions, especially oil-in-water emulsions for oil-soluble pharmaceuticals; a common objective is that the resulting emulsion be sterilized by filtration. In practical terms, this means that virtually all of the particles in the emulsion are sufficiently small as to not clog the filtration device. Due to the high shear forces available and the flexible design of the Microfluidizer processor, numerous pharmaceutical products have been prepared that permit efficient formation of the emulsion as well as producing a product that can be filter sterilized [Tables 5 and 6].

CONCLUSION

The chemical, pharmaceutical, food, and mining industries all rely on size reduction. Size reduction technology has considerable importance in the pharmaceutical field. It 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.

Table 5: Some pharmaceutical applications of size reduction technology

Applications	Descriptions	Ref.
Milling of agglomerates in an impact mill	The breakage behavior of agglomerates after milling with multiple impacts investigates the effects of the formulation and the influences of the mill settings. With respect to the formulation it has been found that both the size of the particles before granulation and the amount of binder used determine the breakage behavior. Both parameters have an influence on the strength of the granule to be milled.	[27-31]
Oral delivery of poorly soluble drugs	The bioavailability of low solubility drugs is often intrinsically related to drug particle size. By reducing particle size.	[32]
Micronization	Due to the nature of the respiratory tract, depending on the indication for which the product is being developed, particle size of pharmaceutical powders for use in inhalation is critical. It will dictate which areas of the respiratory tract are targeted in order for the product to have the greatest efficacy. Micronisation technique is, and has been for a number of years, the preferred option to obtain a size reduction of a drug substance suitable for an inhalation formulation; it can provide consistent results and is a very cost effective way of achieving small particle sizes.	[33]
Handling the powder flow problem	The first, and most common, instrument for powder flow testing is the Jenike Shear Cell. Recent technological developments are now poised to deliver those advantages. Powder handling and processing tends to be problematic because powders exhibit properties similar to both solids and liquids. Normally, they are surrounded by air and the degree of aeration can affect the way the powder behaves. Many common manufacturing problems are attributed to powder flow, including non-uniformity (segregation) in blending, under- or over-dosage, inaccurate filling, obstructions and stoppages.	[34]

Application of size reduction concept

Table 6: Other applications of size reduction concept

Applications	Description	Ref.
Supercritical fluid technology	Supercritical fluid technology offers the possibility to produce dry powder formulations suitable for inhalation or needle-free injection. It facilitates controlled particle formation at near-ambient temperatures and integrates particle formation and solvent removal into a single step. In this, applied fluid is carbon dioxide which does not leave toxic residues associated with the product.	[35,36]
Precipitation: using CO_2 and CO_2-philic antisolvents	Generation of Micro particles. Precipitation with compressed antisolvents (PCA) is a technology for generation of monodisperse ultra fine particles.	[37]
Precipitation: Solid drug nanoparticles	The drug is first dissolved in a solvent, and this solution is mixed with a miscible antisolvent. Mixing processes vary considerably. Precipitation of amorphous material may be favored at high super saturation when the solubility of the amorphous state exceeded.	[38,39]
Supercritical antisolvent with enhanced mass transfer	It utilizes supercritical carbon dioxide as the antisolvent, but the solution jet is deflected by a surface vibrating at an ultrasonic frequency atomizing the jet into much smaller droplets. Production of organic-solvent free particles, mild operating temperatures for processing biological materials, and easier micro-encapsulation of drugs for controlled release of the therapeutic agents.	[40]
Nanotechnology (Micro- and Nano suspensions)	In parenteral drug delivery. Wet milling: Active drug in the presence of surfactant is defragmented by milling. Nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient fact	[41-43]

Application of size reduction concept

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Source of Support: Nil, **Conflict of Interest:** None declared.