Milling

Milling Concept

Few materials used in pharmaceuticals exist in the optimum size, and most must be comminuted at some stage or the other during the production of a dosage form.

Milling is the mechanical process of reducing the particle size of solids.

Various terms (comminution, crushing, disintegration, dispersion, grinding, and pulverization) have been used synonymously with milling depending on the product, equipment, and the process

Milling equipment is classified as coarse, intermediate and fine according to the size of the final product. Size is conventionally expressed in terms of mesh (number of opening per inch square)

1. Coarse for particles size larger than 20-mesh
2. Intermediate (20-200) mesh (74 -840 micron)
3. Fine for particles size smaller than 200-mesh

A given mill can be used successfully to prepare particles in more than one class. (ex. Hammer mill used for granulation (16-mesh) and for milling crystalline API to a 120-mesh powder)

PHARMACEUTICAL APPLICATIONS

Numerous examples have been quoted to stress the importance of fine particles in pharmacy and milling or grinding offers a method by which these particles can be produced. The surface area per unit weight, which is known as the *specific surface*, is increased by size reduction. In general, a 10-fold increase in surface area has been given by a 10-fold decrease in particle size. This increased surface area affects:

1)Dissolution and therapeutic efficacy: Dissolution and therapeutic efficiency of medicinal compounds that possess low solubility in body fluids are increased due to increase in the area of contact between the solid and the dissolving fluid

2) **Extraction:** Extraction or leaching from animal glands (liver and pancreas) and crude vegetable drugs is facilitated by comminution. The time required for extraction is shortened by the increased area of contact between the solvent and the solid and the reduced distance the solvent has to penetrate into the material.

3)Drying: The drying of wet masses may be facilitated by milling, which increases the surface area and reduces the distance that the moisture must travel within the particle to reach the outer surface. In the manufacture of compressed tablets by wet granulation process, the sieving of the wet mass is done to ensure more rapid and uniform drying

PHARMACEUTICAL APPLICATIONS

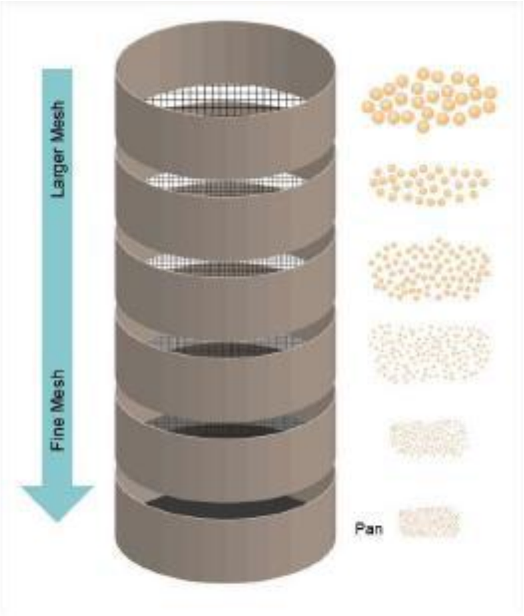
4)Flowability: The flow property of powders and granules is affected by particle size and size distribution. The freely flowing powders and granules in high-speed filling equipment and tablet presses produce a uniform product.

5)Mixing or blending: The mixing or blending of several solid ingredients of a pharmaceutical is easier and more uniform if the ingredients are of approximately the same size. This provides a greater uniformity of dose. Solid pharmaceuticals that are artificially coloured are often milled to distribute the colouring agent to ensure that the mixture is not mottled and uniform from batch-to-batch.

6)Formulation: Lubricants used in compressed tablets and capsules function by virtue of their ability to coat the surface of the granulation or powder. A fine particle size is essential if the lubricant is to function properly. The milling of ointments, creams, and pastes provides a smooth texture and better appearance in addition to improved physical stability. Also, the sedimentation rate of suspensions and emulsions is a function of particle size and is reduced by milling

SIZE DISTRIBUTION AND MEASUREMENTS

1. Microscopy
2. Sieving
3. Sedimentation



THEORY OF COMMINUTION

The mechanical behavior of solids, under stress are strained and deformed, is shown in the stress-strain curve which

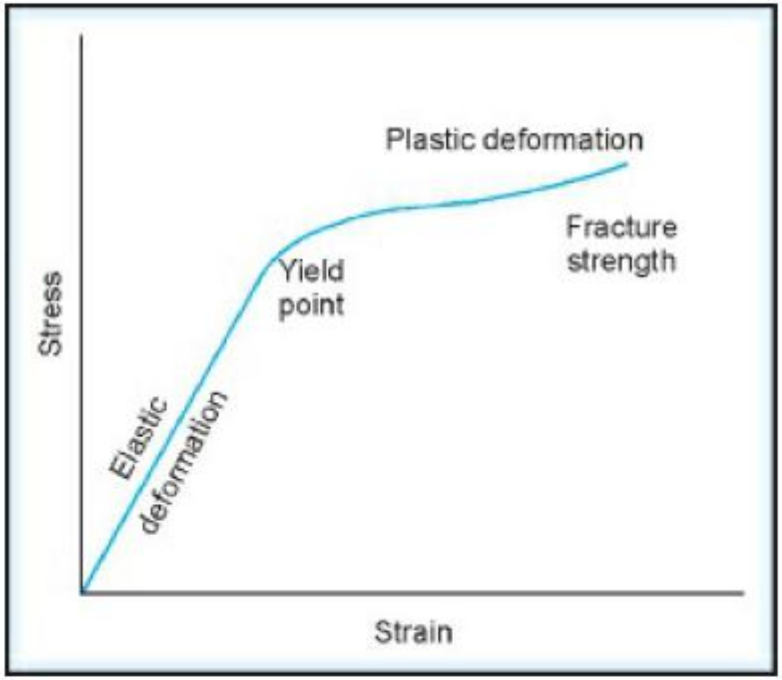


Fig. 2.1: Stress-strain diagram for a solid

The initial linear portion of the curve is defined by Hooke's law(stress is directly proportional to strain), and Young's modulus (slope of the linear portion) expresses the stiffness or softness of a solid in dynes per square centimeter. The stress-strain curve becomes nonlinear at the yield point, which is a measure of the resistance to permanent deformation. With still greater stress, the region of irreversible plastic deformation is reached. The area under the curve represents the energy of fracture and is an approximate measure of the impact strength of the material.

In all milling processes, it is a random matter if and when a given particle will be fractured. If a single particle is subjected to a sudden impact and fractured, it yields a few relatively large particles and a number of fine particles, with relatively few particles of intermediate size. If the energy of the impact is increased, the larger particles are of a smaller size and greater number, and although the number of fine particles is increased appreciably, their size is not greatly changed. It seems that the size of the finer particles is related to the internal structure of the material, and the size of the larger particles is more closely related to the process by which comminution is accomplished.

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If the force of impact does not exceed the elastic limit, the material is reversibly deformed or stressed. When the force is removed, the particle returns to its original form, and the mechanical energy of stress in the deformed particle appears as heat

A force that exceeds the elastic limit fractures the particle, As fracture occurs, the points of application of the force are shifted. The energy for the new surfaces is partially supplied by the release of stress energy

The useful work in milling is proportional to the length of new cracks produced. A particle absorbs strain energy and is deformed under shear or compression until the energy exceeds the weakest flaw and causes fracture or cracking of the particle. The strain energy required for fracture is proportional to the length of the crack formed, since the additional energy required to extend the crack to fracture is supplied by the flow of the surrounding residual strain energy to the crack.

Mechanisms of Comminution

Mills are Equipments designed to impart energy to the material and cause its size reduction. There are four main methods of effecting size reduction, involving different mechanisms:

1)Cutting: It involves application of force over a very narrow area of material using a sharp edge of a cutting device.

2)Compression: In compression, the material is gripped between the two surfaces and crushed by application of pressure.

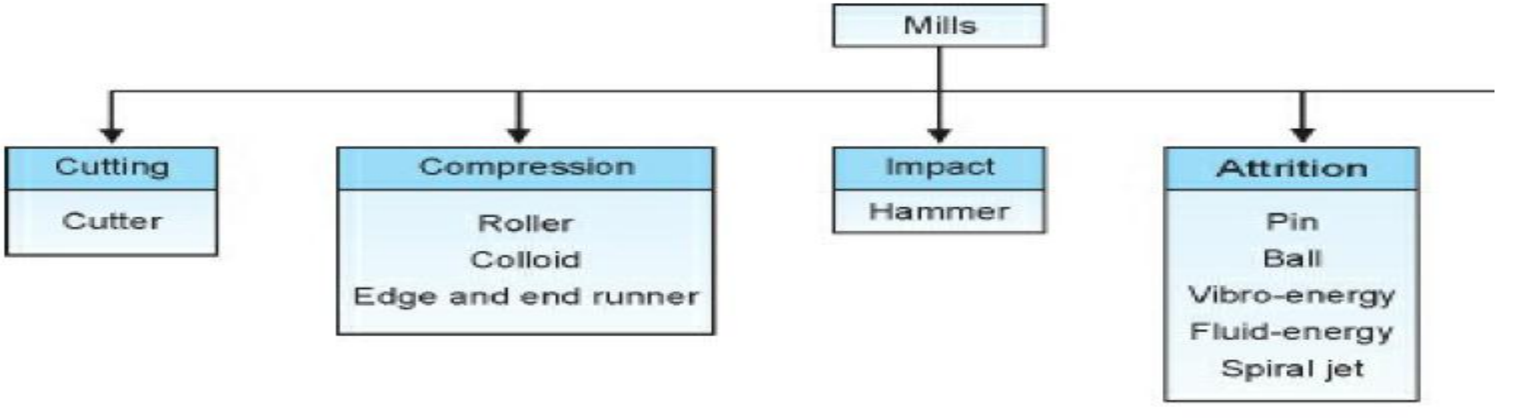
3)Impact: It involves the contact of material with a fast moving part which imparts some of its kinetic energy to the material. This causes creation of internal stresses in the particle, there by breaking it.

4)Attrition: In attrition, the material is subjected to pressure as in compression, but the surfaces are moving relative to each other, resulting in shear forces which break the particles.

EQUIPMENTS

A mill consists of three basic parts: (1) feed chute, which delivers the material, (2) grinding mechanism, usually consisting of a rotor and stator, and (3) a discharge chute.

The principle of operation depends on cutting, compression, impact from a sharp blow, and attrition. In most mills, the grinding effect is a combination of these actions. If the milling operation is carried out so that the material is reduced to the desired size by passing it once through the mill, the process is known as open-circuit milling. A closed circuit mill is the one in which the discharge from the milling chamber is passed through a size-separation device or classifier, and the oversize particles are returned to the grinding chamber for further reduction of size. Closed-circuit operation is most valuable in reduction to fine and ultrafine size. The classification of most commonly used mills in pharmaceutical manufacturing is given in Fig

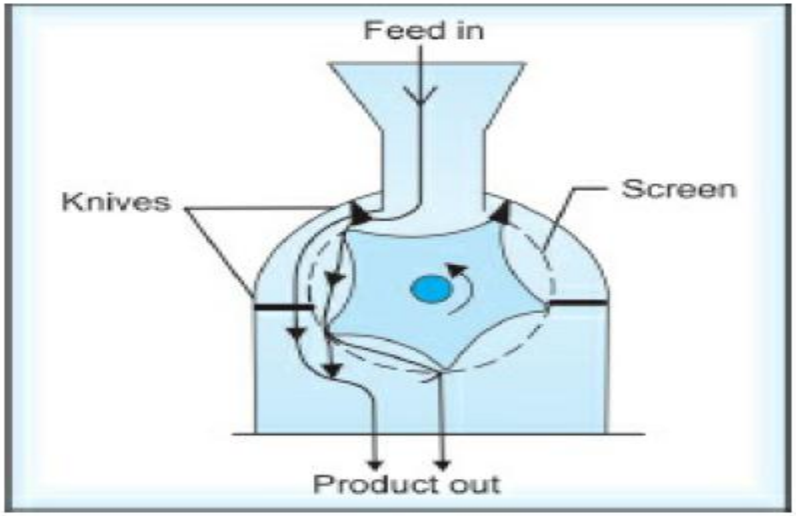


Cutter Mill

The rotary knife cutter has a horizontal rotor with 2 to 12 knives spaced uniformly on its periphery turning from 200 to 900 rpm and a cylindrical casing having several stationary knives

The bottom of the casing holds a screen that controls the size of the material discharged from the milling zone.

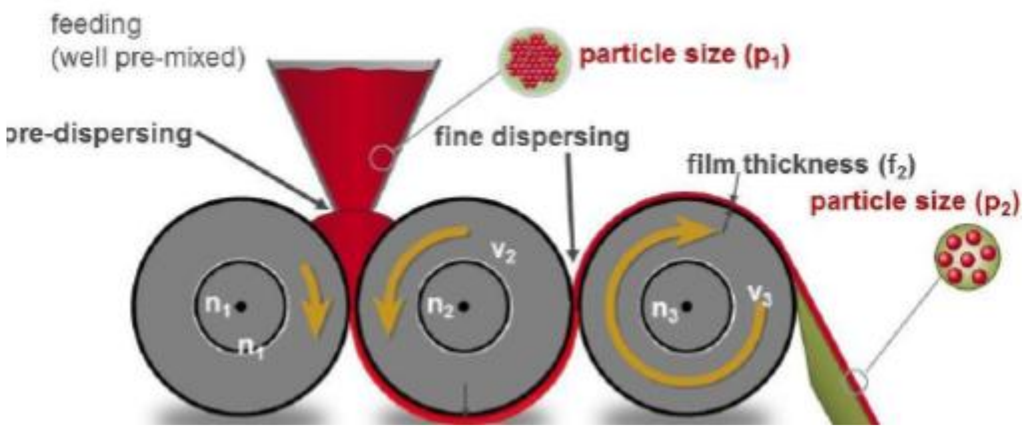
Cutting mills are used for tough, fibrous materials and provide a successive cutting or shearing action rather than attrition or impact.



ROLLER MILL

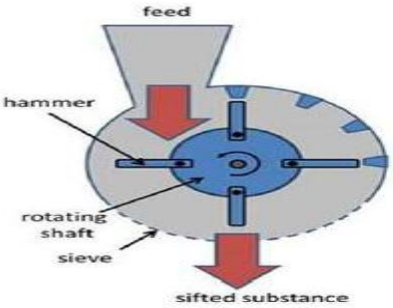
•It consists of two to five smooth roller operating at different speed.
•Mechanism by combination of compression and shearing action.
Two cylindrical rolls mounted horizontally and rotated about their long axes.
one of the rolls is driven directly while the second is rotated by friction as material is drawn through the gap between the rolls.

A form of roller mill used for milling ointments, pastes and suspension where both rolls are driven but at different speeds, so that size reduction occurs by attrition.



Hammer Mill

Construction and working. The hammer mill is an impact mill using a high speed rotor (up to 10,000 rpm) to which a number of swinging hammers are fixed



The material is fed at the top or center, thrown out centrifugally, and ground by impact of the hammers or against the plates around the periphery of the casing. The clearance between the housing and the hammers contributes to size reduction.

The material is retained until it is small enough to fall through the screen that forms the lower portion of the casing. Particles fine enough to pass through the screen are discharged almost as fast as they are formed

The particle size that can be achieved will depend on the type of milling tool selected, rotor speed (calculated as tip speed at the outermost rotating part), and solid density in the mill or solid feed rate

Important processing variables for hammer mills are hammer tip speed and hammer mill screen size.

As can be seen in Figure (a), an increase in hammer tip speed contributes to a higher particle size reduction and thus a relatively fine mash. With an increase in hammer tip speed, the particles will follow a pathway closer to the screen due to the centrifugal force

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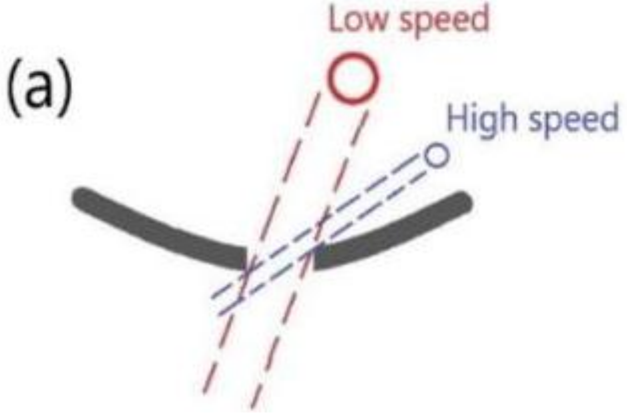
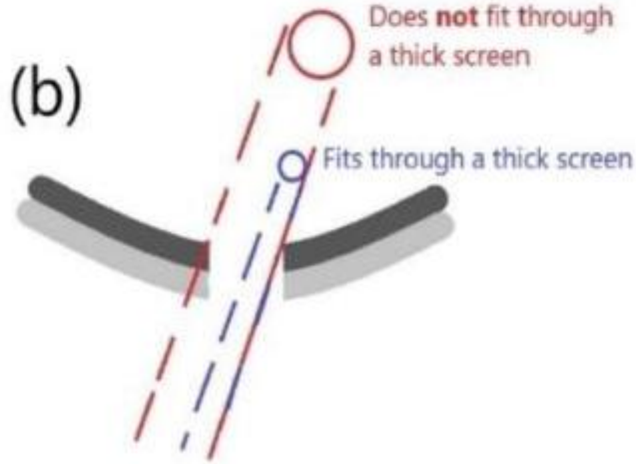


Figure (b) shows that an increase in hammer mill screen thickness will also result in a relatively finer mash, as the coarser particles can only pass through the screen under a relatively narrow range of angles



Applications. The hammer mill can be used for almost any type of size reduction. Its versatility makes it popular in the pharmaceutical industry, where it is used to mill dry materials, wet filter-press cakes, ointments, and Slurries, also a hammer mill can be used for granulation and close control of the particle size of powders

Advantages and disadvantages.

Hammer mills are compact with a high capacity. Size reduction of 20 to 40 μm may be achieved, however, a hammer mill must be operated with internal or external classification to produce ultrafine particles. Because the inertial forces vary with mass as the inverse cube of the diameter, small particles with a constant velocity impact with much less kinetic energy than larger ones, and the probability that particles less than a certain size will fracture decreases rapidly

In addition, small particles pass through the screen almost as fast as they are formed. Thus, a hammer mill tends to yield a relatively narrow size distribution. Hammer mills are simple to install and operate. The speed and screen can be rapidly changed. They are easy to clean and may be operated as a closed system to reduce dust and explosion hazards

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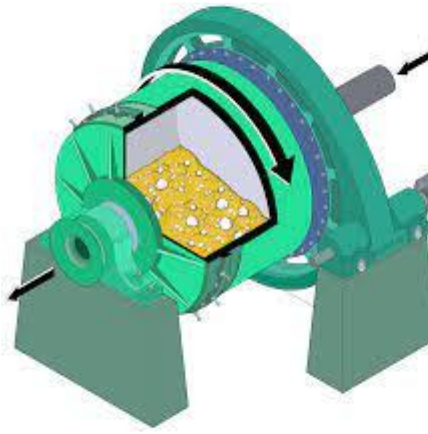
Ball Mill

Construction and working., the ball mill consists of a horizontally rotating hollow vessel of cylindrical shape with the length slightly greater than its diameter. The mill is partially filled with balls of steel or pebbles, which act as the grinding medium

Most ball mills utilized in pharmacy are batch-operated, however, continuous ball mills are available, which are fed through a hollow trunnion at one end, with the product discharged through a similar trunnion at the opposite end. The outlet is covered with a coarse screen to prevent the loss of the balls.

In a ball mill rotating at a slow speed, the balls roll and cascade over one another, providing an attrition action. As the speed is increased, the balls are carried up the sides of the mill and fall freely onto the material with an impact action, which is responsible for most size reduction



The factor of greatest importance in the operation of the ball mill is the speed of rotation.

1-At low angular velocities (Fig. a) the balls move with the drum until the force due to gravity exceeds the frictional force of the bed on the drum, and the balls then slide back to the base of the drum. This sequence is repeated, producing very little relative movement of balls so that size reduction is minimal.

2- At high angular velocities (Fig. b) the balls are thrown out on to the mill wall by centrifugal force and no size reduction occurs.

3-At about two-thirds of the critical angular velocity where centrifuging occurs (Fig. c), a cascading action is produced

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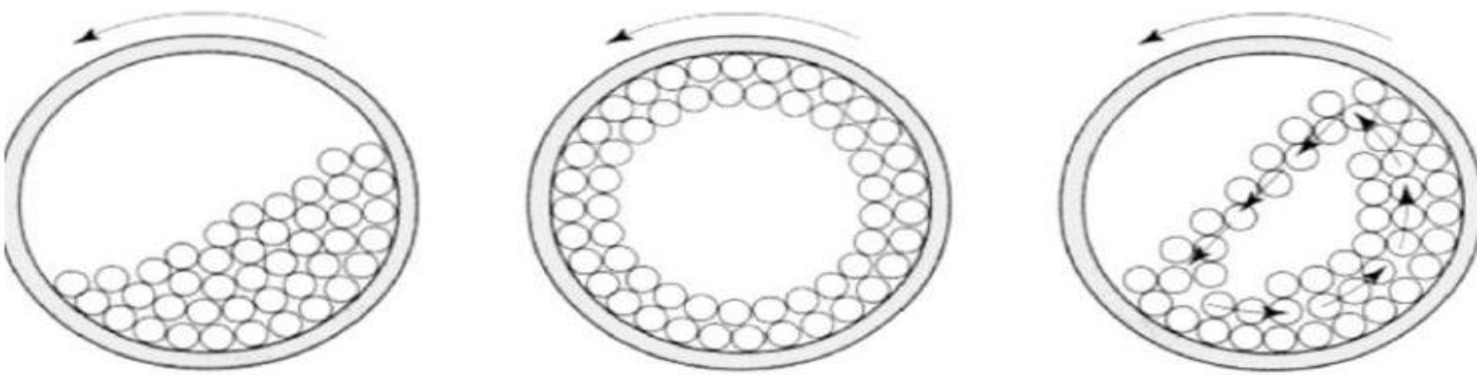


(a) (b) (c)

Advantages and disadvantages.

In addition to being used for either wet or dry milling, the ball mill has the advantage of being used for batch or continuous operation

In a batch operation, unstable or explosive materials may be sealed within an inert atmosphere and satisfactorily ground. Ball mills may be sterilized and sealed for sterile milling in the production of ophthalmic and parenteral products.

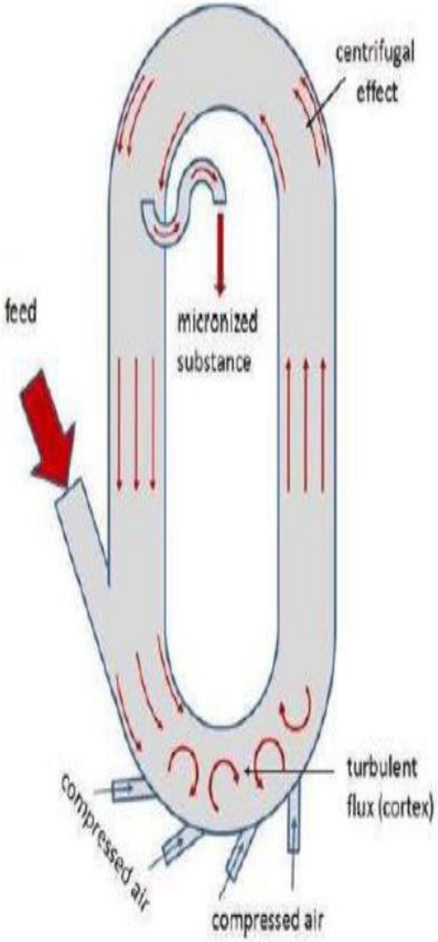
The installation, operation, and labor costs involved in ball milling are low. Finally, the ball mill is unsurpassed for fine grinding of hard and abrasive materials.

Fluid-energy Mill

Construction and working.

In the fluid-energy mill or micronizer, the material is suspended and conveyed at high velocity by air or steam, which is passed through nozzles at pressures of 100 to 150 pounds per square inch (psi).

The violent turbulence of the air and steam reduces the particle size
chiefly by inter particular attrition.
Air is usually used because most pharmaceuticals have a low melting point or are thermo labile. As the compressed air expands at the orifice, the cooling effect counteracts the heat generated by milling



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The most important machine-related factors are the grinding chamber geometry and the number and angle of the nozzles. In selecting fluid-energy mills for production, the cost of a fluid-energy source and dust collection equipment must be considered in addition to the cost of the mill

Advantages and disadvantages.

Powders with all particles below a few micrometers may be quickly produced by this method. The disadvantage of high capital and running costs may not be so serious in the pharmaceutical industry because of the high value of the materials which are often processed.

One drawback of this type of mill is the potential for build-up of compressed product in the mill. This can affect milled particle size by changing the open volume in the mill or open area in the classifier, especially if classifier vanes or gas nozzles become plugged or blocked

FACTORS INFLUENCING MILLING

The properties of a solid determine its ability to resist size reduction and influence the choice of equipment used for milling. The specifications of the product also influence the choice of a mill.

1) Nature of Material

The physical nature of the material determines the process of comminution. Fibrous materials (*Glycyrrhiza, Rauwolfia*) cannot be crushed by pressure or impact and must be cut. Friable materials (dried filter cake, sucrose) tend to fracture along well-defined planes and may be milled by attrition, impact, or compression

2)Moisture Content

The presence of more than 5% water hinders comminution and often produces a sticky mass upon milling. This effect is more pronounced with fine materials than with larger particles. At concentrations of water greater than 50%, the mass becomes a slurry, or fluid suspension. The process is then a wet milling process, which often aids in size reduction. An increase in moisture can decrease the rate of milling to a specified product size

3)Temperature

The heat during milling softens and melts materials with a low melting point. Synthetic gums, waxes, and resins become soft and plastic. Heat-sensitive drugs may be degraded or even charred. Pigments (ocher and sienna) may change their shade of color if the milling temperature is excessive. Unstable compounds and almost any finely-powdered material may ignite and explode if the temperature is high.

4)Particle Shape

An impact mill produces sharp, irregular particles, which may not flow readily. When specifications demand a milled product that will flow freely, it would be better to use an attrition mill, which produces free-flowing spheroidal particles.

5)Polymorphism

Milling may alter the crystalline structure and cause chemical changes in some materials. Wet milling may be useful in producing a suspension that contains a metastable form of material causing crystal growth and caking. For example, when cortisone acetate crystals are allowed to equilibrate with an aqueous vehicle, subsequent wet milling provides a satisfactory suspension.

TECHNIQUES OF MILLING

In addition to the standard adjustments of the milling process (i.e., speed, screen size, design of rotor and load), special techniques of milling may be Useful.

1) Special Atmosphere

Hygroscopic materials 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. Almost any fine dust (dextrin, starch, sulfur) is a potential explosive mixture under certain conditions and especially if static electrical charges result from the processing.

2)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. This heat may raise the temperature of the material by many degrees, and unless the heat is removed, the solid will melt, decompose, or explode. To prevent these changes in the material and avoid stalling of the mill, the milling chamber should be cooled by means of a cooling jacket or a heat exchanger

3)Pretreatment

For a mill to operate satisfactorily, the feed should be of the proper size and enter at a fairly uniform rate. If granules or intermediate sized particles are desired with a . minimum of fines, pre-sizing is vital. Pretreatment of fibrous materials with high-pressure rolls or cutters facilitates comminution

4)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 oversized particles for a second milling

5) Wet and Dry Milling

The choice of wet or dry 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, Wet grinding is beneficial in further reducing the size, but flocculation restricts the lower limit to approximately 10 µm. Wet grinding eliminates dust hazards, and is usually done in low-speed mills, which consume less power

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SELECTION OF A MILL

In general, the materials used in pharmaceuticals may be reduced to a particle size less than 40-mesh by means of ball, roller, hammer, and fluid-energy mills.

The choice of a mill is based on :

(1) Product specifications (size range, particle size distribution, shape, moisture content and physical and chemical properties of the material),

(2) capacity of the mill and production rate requirements

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(3) versatility of operation (wet and dry milling, rapid change of speed and screen, safety features),

(4) dust control (loss of costly drugs, health hazards and contamination of plant),

(5) sanitation (ease of cleaning and sterilization),

(6) auxiliary equipment (cooling system, dust collectors, forced feeding and stage reduction)

,

(7) batch or continuous operation

(8) economical factors (cost, power consumption, space occupied and labor cost).