PHARMACEUTICAL ENGINEERING

Size Reduction and Size Separation

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Size Reduction

Size reduction is the process of reducing the particle size of a substance to a finer state of subdivision to smaller pieces to coarse particles or to powder. Size reduction process is also referred to as comminution and grinding. When the particle size of solids is reduced by mechanical means it is known as milling.

Raw materials often occur in sizes that are too large to be used and, therefore, they must be reduced in size. The size reduction operation can be divided into two major categories depending on whether the material is a solid or a liquid. If the material is solid, the process is called grinding and cutting, if it is liquid, emulsification or atomization. All depend on the reaction to shearing forces within solids and liquids. Different raw materials vary in their size, shape, brittleness and toughness and the product required may vary from a coarse powder to a powder of the micron size. Different types of machinery are available to suit the specific process requirements.

Objectives of Size Reduction

- Size reduction increases the surface area of drugs that help in rapid solution formation in the case of chemical substance.
- The extraction from animal glands such as liver and pancreas and from crude vegetable drugs is facilitated with an increase in surface area because solvent can easily penetrate into the tissues resulting in quick extraction of their active constituents.
- To increase the therapeutic effectiveness of certain drugs by reducing the particle size e.g., the dose of griseofulvin is reduced to half than that of originally required.
- The mixing of several solid ingredients is easier and more uniform if the ingredients are reduced to same particle size.
- In the case of powdered pharmaceutical dosage forms the crystalline drugs are powdered before mixing them with other drugs in order to mix all the drugs uniformly and to avoid recognition of crystalline drugs by the patients.
- In the manufacture of Tablets relatively few drugs can be compressed directly, generally they are mixed with excipients and made in the form of suitable size granules which are then compressed.
- The stability of emulsions is increased by decreasing the size of the oil globules.
- Particle size plays an important role in the case of suspensions. If the size of the particles is too small, they may form a cake which may not re-disperse easily but on the other hand large size particles settle quickly but form a loose cake which may re-disperse easily on shaking.
- The physical appearance of ointments, pastes and creams can be improved by reducing its particle size.
- All the ophthalmic preparations and preparations meant for external application to the skin must be free from gritty particles to avoid irritation of the area to which they are applied.

- The rate of absorption of a drug depends on the dosage form, route of administration and particle size. The smaller the particle size, quicker and greater will be rate of absorption.

Factors Affecting Size Reduction

Hardness: Hardness is a surface property of the material, although it is frequently confused with a property that could be better described as strength. Thus, it is possible for a material to be very hard, but if it is brittle also then size reduction may present no special problems. An arbitrary scale of hardness has been devised known as Moh's Scale; a series of mineral substances has been given hardness numbers between 1 and 10, ranging from graphite to diamond. Up to 3 are known as soft and can be marked with the fingernail. Above 7 are hard and cannot be marked with a good pen knife blade, while those between are described as intermediate. In general, the harder the material the more difficult it is to reduce in size.

Toughness: Toughness of a material is sometimes more important than hardness, a soft but tough material may present more problems in size reduction than a hard but brittle substance for example it is difficult to break rubber than a stick of blacboard chalk.

Toughness is encountered in many pharmaceutical materials, particularly in fibrous drugs, and is often related to moisture content.

For some materials, toughness can be reduced by treating the material with a liquefied gas such as liquid nitrogen, substances can be cooled to temperatures lower than -100 to -150° C. The method has additional advantages, in that there is a reduction in the decomposition of thermolabile materials, in the loss of volatile materials, in the oxidation of constituents, and in the risk of explosion. This procedure is little used, as it is expensive but also due to engineering problems: for example, the metals of the machinery also become brittle at such low temperatures, and normal lubricants solidify.

Abrasiveness: Abrasiveness is a property of hard materials (particularly those of mineral origin) and may limit the type of machinery that can be used. During the grinding of some very abrasive substances the final powder may be contaminated with more than 0.1 percent of metal worn from the grinding mill.

Stickiness: Stickiness is a property that causes considerable difficulty in size reduction, for material may adhere to the grinding surfaces, or the meshes of the screen may become choked. If the method used for size reduction produces heat then substances that are gummy or resinous may be troublesome to the size reduction process. Sometimes the addition of inert substances may be of assistance such as kaolin to sulphur. The reverse of this property, which can be described as slipperiness, for want of a better term, can also give rise to size reduction difficulties, since the material acts as a lubricant and lowers the efficiency of the grinding surfaces.

Softening temperature: During size reduction process sometimes heat is generated which may cause some substances to soften, and the temperature at which this occurs can be important. Waxy substances, such as stearic acid, or drugs containing oils or fats are examples that may be affected. Some methods can be used to overcome this like cooling the mill, either by a water jacket or by passing a stream of air through the equipment. Another alternative is to use liquid nitrogen, as discussed earlier.

Material structure: Some substances are homogeneous in character, but the majority show some special structure, for example, mineral substances may have lines of weakness along which the materials splits to form flake-like particles, while vegetable drugs have a cellular structure often leading to long fibrous particles.

Moisture content: Moisture content influences a number of properties that can affect size reduction, for example, hardness, toughness or stickiness. In general materials should be dry or wet and not merely damp. Usually, less than 5 percent of moisture is suitable if the substance is to be ground dry or more than 50 if it is being subjected to wet grinding

Physiological effect: Some substances are very potent and small amounts of dust have an effect on the operators. To avoid this dust, enclose mills must be used, systems that can extract air are also desirable, and wet grinding also, if possible, as it eliminates the problem entirely.

Purity required: Certain types of size reduction apparatus cause the grinding surfaces to wear, and such methods must be avoided if a high degree of purity of product is needed. Similarly, some machines will be unsuitable if cleaning between batches of different materials is difficult.

Ratio of feed size to product ratio: Machines that produce a fine may be necessary to carry out the size reduction process in several stages with different equipment, for example, preliminary crushing, followed by coarse grinding and then fine grinding.

Bulk density: The capacity of most batch mills depend on volume, whereas processes usually demand solid materials by weight. Hence, all other factors being equal, the output of the machine is related to the bulk density of the substance.

Mechanism and Principles of Size Reduction

The mechanism of size reduction may vary with the nature of the material and each drug may require separate treatment. Fracture occurs preferentially along lines of weakness. Fresh surfaces may be created or existing cracks and fissures may be opened up, the former requiring much more energy. Most of the time there is a tendency towards agglomeration of particles after formation. From the point of view utilization of energy size reduction is a very inefficient process as only a small percentage of the energy supplied is utilized in subdividing the particles. Much of the energy is spent in overcoming friction and inertia of machine parts, friction between particles and deforming the particles without breaking them. This energy is released as heat.

Laws governing energy and power requirement of Size Reduction process: Grinding is a very inefficient process and it is important to use energy as efficiently as possible. Unfortunately, it is not easy to calculate the minimum energy required for a given reduction process, but some theories have been advanced which are useful. A number of theories have been advanced to predict the energy requirements of a size reduction process, but none give accurate results.

These theories depend upon the basic assumption that the energy required to produce a change dL in a particle of a typical size dimension L is a simple power function of L:

$$dE/dL = KL^{n} \qquad (1)$$

Where dE is the differential energy required, dL is the change in a typical dimension; L is the magnitude of a typical length dimension and K, n, are constants.

Kick assumed that the energy required to reduce a material in size was directly proportional to the size reduction ratio dL/L. This implies that n in equation. (1) is equal to -1. If

$$K = K_K f_c$$

Where K_K is called **Kick's constant** and f_c is called the crushing strength of the material, we have:

$$dE/dL = K_K f_c L^{-1}$$

Which, on integration gives:

$$E = K_K f_c \log_e(L_1/L_2) \qquad (2)$$

Equation (2) is a statement of **Kick's Law**. It implies that the specific energy required to crush a material, for example from 10 cm down to 5 cm, is the same as the energy required to crush the same material from 5 mm to 2.5 mm.

Rittinger, on the other hand, assumed that the energy required for size reduction is directly proportional, not to the change in length dimensions, but to the change in surface area. This leads to a value of -2 for n in equation. (1) as area is proportional to length squared. If we put:

$$K = K_{Rfc}$$

and so

$$dE/dL = K_R f_c L_{-2}$$

Where K_R is called **Rittinger's constant**, and integrate the resulting form of eqn. (1), we obtain:

$$E = K_R f_c (1/L_2 - 1/L_1) \qquad (3)$$

Equation (3) is known as **Rittinger's Law**. As the specific surface of a particle, the surface area per unit mass, is proportional to $1/L$, eqn. (3) postulates that the energy required to reduce L for a mass of particles from 10 cm to 5 cm would be the same as that required to reduce, for example, the same mass of 5 mm particles down to 4.7 mm. This is a very much smaller reduction, in terms of energy per unit mass for the smaller particles, than that predicted by Kick's Law.

It has been found, experimentally, that for the grinding of coarse particles in which the increase in surface area per unit mass is relatively small, Kick's Law is a reasonable approximation. For the size reduction of fine powders, on the other hand, in which large areas of new surface are being created, Rittinger's Law fits the experimental data better.

Classification of Size Reduction equipments

A wide variety of size reduction equipment is available. Equipment may be classified into three classes according to the nature of the forces applied. In the first class, size reduction is accomplished by application of continuous pressure and this class includes equipment for coarse crushing. In the second class, reduction is effected by blow or impact. An example of impact is breaking of a brittle lumpy material by throwing against a wall when the material breaks into pieces due to sudden release of force. In the third type shearing forces are applied by grinding or abrasion and this class gives fine grinding. There is no sharp dividing line between these classes since some mills use a combination of these forces for size reduction. Thus a broad classification could be a crushing, impact and grinding mills.

Before size reduction, materials must be thoroughly dried to avoid accumulation in the mill and possible jamming with wet material and to prevent agglomeration of the particles after size reduction. Crystalline inorganic and organic medicinal compounds which are isolated by normal precipitation and crystallization methods do not require any form of preliminary treatment but they must be thoroughly dried. On the other hand vegetable drugs, due to their wide variation in physical state, may require an initial reduction to small pieces. Materials like camphor and spermaceti, the particles of which tend to cohere as quickly as they are produced, need wetting with alcohol before size reduction to avoid this difficulty.

On the small-scale initial size reduction of vegetable drugs may be done by slicing, rasping or contusion. Slicing or cutting may be done both transversely and longitudinally so that the tissues may be laid open as completely as possible for quicker drying of the material. Rasping or grating can be done with a nutmeg grater and is mainly used for soaps and waxes that are normally required in coarse state. Contusion or bruising is accomplished by beating the drug in a heavy motor. The shape and material of construction of mortars and pestles vary. They may be made of iron, marble, porcelain, glass, steel etc. The bottom surfaces of the mortar and pestle may be shallow or round. Shallow mortars give more grinding effect and are more efficient for size reduction of dry materials and for preparation of fine emulsions.

Grinding and Cutting

Grinding and cutting reduce the size of solid materials by mechanical action, dividing them into smaller particles. The most extensive application of grinding in the food industry is in the milling of grains to make flour, but it is used in many other processes, such as in the grinding of corn for manufacture of corn starch, the grinding of sugar and the milling of dried foods, such as vegetables.

Cutting is used to break down large pieces of food into smaller pieces suitable for further processing, such as in the preparation of meat for retail sales and in the preparation of processed meats and processed vegetables.

In the grinding process, materials are reduced in size by fracturing them, the material is stressed by the action of mechanical moving parts in the grinding machine and initially the stress is absorbed internally by the material as strain energy. When the local strain energy exceeds a critical level, which is a function of the material, fracture occurs along lines of weakness and the stored energy is released. Some of the energy is taken up in the creation of new surface, but the greater part of it is dissipated as heat. Time also plays a part in the fracturing process and it appears that material will fracture at lower stress concentrations if these can be maintained for longer periods. Grinding is, therefore, achieved by mechanical stress followed by rupture and the energy required depends upon the hardness of the material and also upon the tendency of the material to crack.

The force applied may be compression, impact, or shear, and both the magnitude of the force and the time of application affect the extent of grinding achieved. For efficient grinding, the energy applied to the material should exceed, by as small a margin as possible, the minimum energy needed to rupture the material. Excess energy is lost as heat and this loss should be kept as low as practicable.

The important factors to be studied in the grinding process are the amount of energy used and the amount of new surface formed by grinding.

Mechanism of Size Reduction:

Cutting – here the material is cut by means of a sharp blade or blades.

Compression – in this method, the material is crushed by application of pressure.

Impact – impact occurs when the material is more or less stationary and is hit by an object moving at high speed or when the moving particle strikes a stationary surface. In either case, the material shatters to smaller pieces. Usually both will take place, since the substance is hit by a moving hammer and the particles formed are then thrown against the casing of the machine.

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.

Methods of size reduction: Cutting and compression have limited uses in Pharmaceutical practice, impact and attrition are used much more widely, both separately and in combination, and there is a great variety in each type. The machines used for size reduction are often termed as mills.

Grinding Equipment

Grinding equipment can be divided into two classes - crushers and grinders. In the first class the major action is compressive, whereas grinders combine shear and impact with compressive forces.

Equipments based on the mechanism of Cutting : Cutting machinery is simple, consisting of rotating knives in various arrangements. The knives are kept sharp so that they cut rather than tear. An example is the bowl chopper in which a flat bowl containing the material revolves beneath a vertical rotating cutting knife.

1. Crushers: Jaw and gyratory crushers are heavy equipment and are not used extensively in the food industry. In a jaw crusher, the material is fed in between two heavy jaws, one fixed and the other reciprocating, so as to work the material down into a narrower and narrower space, crushing it as it goes. The gyrator crusher consists of a truncated conical casing, inside which a crushing head rotates eccentrically. The crushing head is shaped as an inverted cone and the material being crushed is trapped between the outer fixed, and the inner gyrating, cones, and it is again forced into a narrower and narrower space during which time it is crushed. Jaw and gyratory crusher actions are illustrated in **Figure 1(a)** and **(b)**.

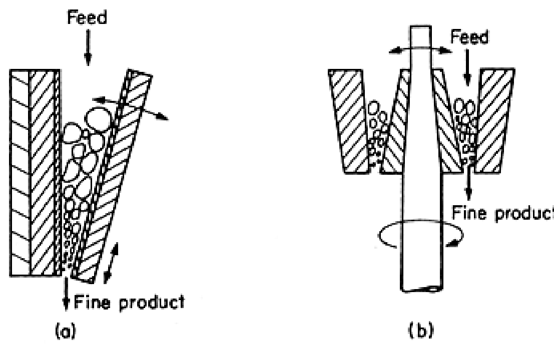


Figure 1- Crushers: (a) jaw, (b) gyratory

Crushing rolls consist of two horizontal heavy cylinders, mounted parallel to each other and close together. They rotate in opposite directions and the material to be crushed is trapped and nipped between them being crushed as it passes through. In some case, the rolls are both driven at the same speed. In other cases, they may be driven at differential speeds, or only one roll is driven. A major application is in the cane sugar industry, where several stages of rolls are used to crush the cane.

Equipments based on the mechanism of Impact :

1. Hammer mills: In a hammer mill, swinging hammerheads are attached to a rotor that rotates at high speed inside a hardened casing. The principle is illustrated in **Figure 2(a)**.

The hammer mill consists of a steel casing in which a central shaft is enclosed to which a number of swinging hammers are attached. When the shaft is rotated the hammers swing out to a radial position. On the lower part of the casing a screen of desired size is fitted which can be easily replaced according to the particle size required. The material is crushed and pulverized between the hammers and the casing and remains in the mill until it is fine enough to pass through a screen which forms the bottom of the casing. Both brittle and fibrous materials can be handled in hammer mills, though with fibrous material, projecting sections on the casing may be used to give a cutting action. The hammer mills are available in various designs and shapes. In pharmaceutical industry they are used for grinding dry materials, wet filter cakes, ointments and slurries.

Advantages:

1. It is rapid in action, and is capable of grinding many different types of materials.
2. They are easy to install and operate, the operation is continuous.

3. There is little contamination of the product with metal abraded from the mill as no surface move against each other.
4. The particle size of the material to be reduced can be easily controlled by changing the speed of the rotor, hammer type, shape and size of the screen

Disadvantages:
1. The high speed of operation causes generation of heat that may affect thermolabile materials or drugs containing gum, fat or resin. The mill may be water-cooled to reduce this heat damage.
2. The rate of feed must be controlled carefully as the mill may be choked, resulting in decreased efficiency or even damage.
3. Because of the high speed of operation, the hammer mill is susceptible to damage by foreign objects such as stones or metal in the feed. Magnets may be used to remove iron, but the feed must be checked visually for any other contamination.

The hammer mill is capable of producing intermediate grades of powder from almost any substance, apart from sticky materials that choke the screen. Applications include the powdering of barks, leaves, roots, crystals and filter cakes. With cutting edges to the hammers, the method has proved to be especially useful for granulation, the damp masses being cut to granules by the hammers when they are found to produce greater uniformity than is obtained by sieve granulation.

2. Plate mills: In plate mills the material is fed between two circular plates, one of them fixed and the other rotating. The feed comes in near the axis of rotation and is sheared and crushed as it makes its way to the edge of the plates; see Figure 2(b). The plates can be mounted horizontally as in the traditional Buhr stone used for grinding corn, which has a fluted surface on the plates. The plates can be mounted vertically also. Developments of the plate mill have led to the colloid mill, which uses very fine clearances and very high speeds to produce particles of colloidal dimensions.

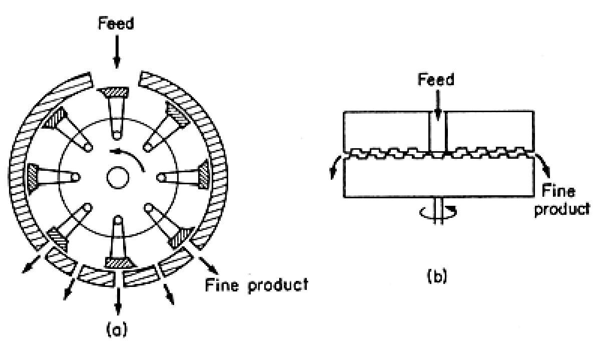


Figure 2 -Grinders: (a) hammer mill, (b) plate mill

Equipments based on the mechanism of Attrition: Size reduction by attrition can be effected in the laboratory by using pestle and mortar or, if a small-scale mechanical method is required, the roller mill can be used.

1. Roller mills: Roller mills are similar to roller crushers, but they have smooth or finely fluted rolls, and rotate at differential speeds. They are used very widely to grind flour. Because of their simple geometry, the maximum size of the particle that can pass between the rolls can be regulated. If the friction coefficient between the rolls and the feed material is known, the largest particle that will be nipped between the rolls can be calculated, knowing the geometry of the particles.

The roller mills use the principles of attrition for the size reduction of solids in suspensions, pastes, or ointments. Two or three rolls, usually in metal or in porcelain, are mounted horizontally with a very small, but adjusTable, gap between. The rolls rotate at different speeds, so that the material is sheared as it passes through the gap and is transferred from the slower to the faster roll, from which it is removed by means of a scraper. The method is very effective for size reducing and dispersing solids in semi-solid media.

Triple Roller mill: Various types of roller mills consisting of one or more rollers are commonly used but triple roller mill is preferred. It is fitted with three rollers that are composed of a hard abrasion-resistant material. They are fitted in such a way that they come in close contact with each other and rotate at different speeds. The material that come, in-between the rollers is crushed and reduced in particle size. The reduction in particle size depends on the gap between the rollers and difference in their speeds. In figure 3, the material is allowed to pass through hopper A, in-between the rollers B and C where it is reduced in size. Then the material is passed between the rollers C and D where it is further reduced in size and a smooth mixture is obtained.

The gap between rollers C and D is usually less than the gap between B and C, after passing the material between rollers C and D the smoothened material is continuously removed from roller D by means of scraper E, from where it is collected in a receiver.

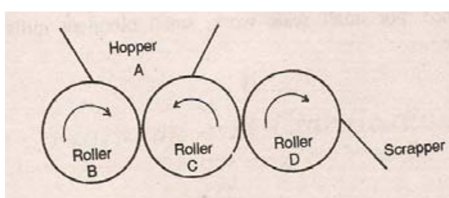


Figure 3 -Triple-Roller mill

On large scale, mechanical ointment roller mills are used to obtain an ointment of smooth and uniform texture. The performed coarse ointments are forced to pass through moving stainless steel rollers where it is reduced in particle size and a smooth product which is uniform in composition and texture is obtained. For small scale work, small ointment mills are available.

Equipments based on the Combined Impact and Attrition: The mechanisms of impact and attrition can be combined in two forms of mill. In the ball mill the particles receive impacts from balls or pebbles and are subjected to attrition as the balls slide over each other. In fluid energy mills the impacts and attrition occur between rapidly moving particles.

1. Colloid mill: Colloid mill works on the principle of shearing. The colloid mill is useful for milling, dispersing, homogenizing and breaking down of agglomerates in the manufacture of food pastes, emulsions, coatings, ointments, creams, pulps, grease etc. The main function of the colloid mill is to ensure a breakdown of agglomerates or in the case of emulsions to produce droplets of fine size around 1 micron. The material to be processed is fed by gravity to the hopper or pumped so as to pass between the rotor and stator elements where it is subjected to high shearing and hydraulic forces as illustrated in figure 4(a) and (b). Material is discharged through a hopper whereby it can be recirculated for a second pass. For materials having higher solid and fibre contents conical grooved discs are preferred. Cooling and heating jacket arrangements are provided as a standard feature on both these mills.

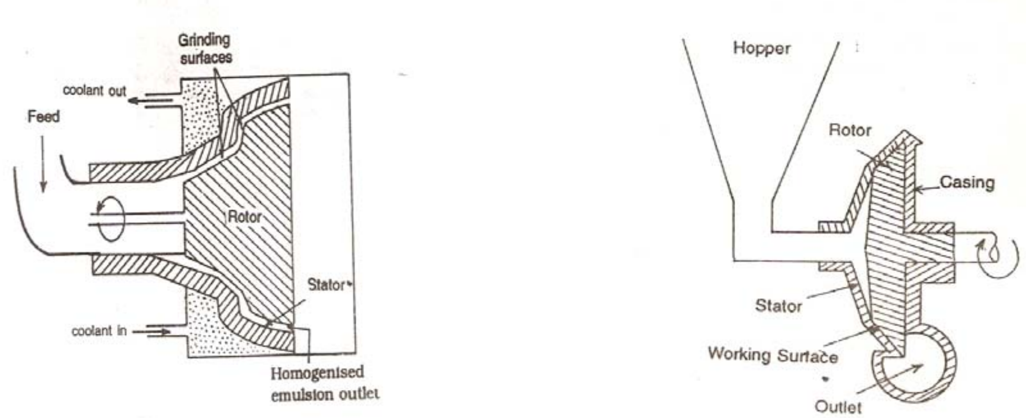
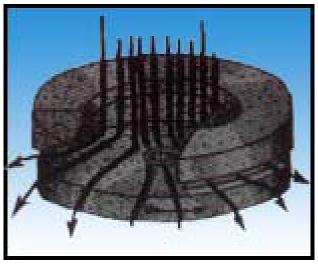


Figure 4(a): Premier Colloid mill (conical grinding surface) (b): Colloid mill (stepped grinding surface)

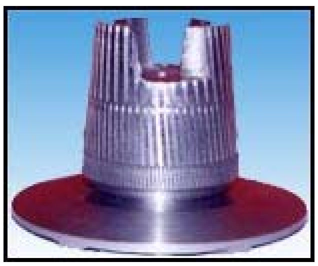
Rotational speed of the rotor varies from 3,000-20,000 r.p.m. with the spacing between the rotor and stator capable of very fine adjustment varying from 0.001 inch to 0.005 inch depending on the size of the equipment. Colloid mills require a flooded feed, the liquid being forced through the narrow clearance by centrifugal action and taking a spiral path. In these mills almost all the energy supplied is converted to heat and the shear forces can unduly increase the temperature of the product. Hence most colloid mills are fitted with water jackets and it is also necessary to cool the material before and after passing through the mill.

In the Premier colloid mill, intense shearing action is produced between the rotor running at several thousand rpm with its working surface in close proximity to the stator. A 5-inch diameter rotor runs at 9000 r.p.m. and has an output of 40-60 gallons depending on the viscosity of the liquid. The gap between the two surfaces is adjustable from 0.3-0.002 inch and the distance is measured by means of a feeler gauge. Crude mix is fed via the hopper to the centre of the rotor. The material is flung outward and after homogenization across the shearing surfaces, it is discharged. If the feed is very slow, many hundreds of revolutions will take place while the contents of the gap traverse the working faces and consequently the globules will be subjected to a greater shearing action than effected at the maximum rate of feed. The materials must be supplied at such a rate that the space between the rotor and stator is kept entirely filled with liquid. Figure 4 (c) shows different parts of a colloid mill



Grinding disc

Toothed colloid mill



Rotor of Toothed colloid mill

Stator of Toothed colloid mill

Figure 4 (c) - Different parts of a colloid mill
(Courtesy – Frigmaires Engineers, Mumabai)

In toothed colloid mill the grinding gap between the rotor and the stator is adjustable. Different grinding sets can be used, depending on the product. The coarse toothed set is for size reduction of solids in suspensions and coarse toothed set is for smaller particle sizes and finer dispersions.

Colloid Mills are used in the production of ointment, cream, gels and high viscous fluids for grinding, dispersing and homogenizing in one operation.

Advantages

- Extremely fine particle distribution through optimal shear force.
- High capacity with minimal space requirements.
- Rapid handling and easy cleaning.
- Virtually unlimited application due to highly flexible homogenisation system.

2. Ball mill: Ball mill is a type of crusher, is a cylindrical device (figure 5-a) used to grind (or mix) materials like ores, chemicals, ceramics and paints. Ball mills rotate around a horizontal axis, partially filled with the material to be ground plus the grinding medium. Different materials are used for media (figure 5-b), including ceramic balls, flint pebbles and stainless steel balls. An internal cascading effect reduces the material to a fine powder. Industrial ball mills can operate continuously fed at one end and discharged at the other. Large to medium ball mills are mechanically rotated on their axis, but small ones normally consist of a cylindrical capped container that sits on two drive shafts (pulleys and belts are used to transmit rotary motion). A rock tumbler functions on the same principle. High quality ball mills are potentially expensive and can grind mixture particles to as small as 0.0001 mm, enormously increasing surface area and reaction rates.

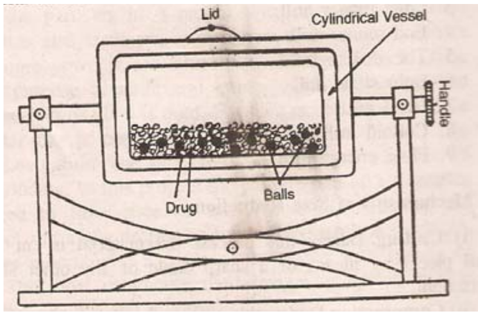


Figure 5-a Ball mill

Figure 5-b An example of Grinding media for ball mill
(Lead antimony-grinding media with aluminum powder)

The material to be ground is added so that it is slightly more than fills the voids between the pellets. The shell is rotated at a speed which will cause the pellets to cascade, thus reducing particle sizes by impact. It has been proposed that in the plastics industry the term ball mill be reserved for metallic grinding media, and the term pebble mill for non-metallic grinding media.

There are many types of grinding media suitable for use in a ball mill, each material having its own specific properties and advantages. Common in some aplications are stainless steel balls. While usually very effective due to their high density and low contamination of the material being processed, stainless steel balls are unsuitable for some applications, including:

- Black powder and other flammable materials require non-sparking lead antimony, brass, or bronze grinding media
- Contamination by iron of sensitive substances such as ceramic raw materials. In this application ceramic or flint grinding media is used. Ceramic media are also very resistant to corrosive materials.

Ball mills are very effective for grinding smooth, aqueous or oily dispersions by wet grinding since it will give particles of 10 microns or less.

Advantages:
1. Ball mill is capable of grinding a wide variety of materials of differing character and of different degrees of hardness.
2. It can be used in a completely enclosed form, which makes it especially suitable for use with toxic materials.
3. It can produce very fine powders.
4. It can be used for continuous operation, and a classifier can be used in conjunction with the mill, so that particles of suitable size are removed while oversize particles are returned.
5. It is equally suitable for wet or dry grinding processes.

Disadvantages
1. Wear occurs, principally from the balls, but partially from the casing and this may result in the product being contaminated, with abrasive materials this may exceed 0.1 percent,

but even ordinary substances may be contaminated with 0.03 percent metal after grinding.

2. In some cases, this may not be significant, but in others it may be of great importance.
3. Soft or sticky materials may cause problems by caking on the sides of the mill or by holding the balls in aggregates.
4. The ball mill is very noisy machine, particularly if the casing is of metal, but much less so if rubber is used.
5. Relatively long time of operation.

Ball mills are applicable to a wide variety of materials, large ones being used for grinding ores prior to manufacture of pharmaceutical chemicals and small versions for the final grinding of drugs or for grinding suspensions.

3. Fluid energy mill: It consists of a loop of a pipe, which has a diameter of 20 to 200 mm, depending on the overall height of the loop which may be up to about 2 meters, a fluid, usually air, is injected at high pressure through nozzles at the bottom of the loop, giving rise to a high velocity circulation in a very turbulent condition, as shown in Figure 6. Solids are introduced into the stream and, as a result of the high degree of turbulence, impact and attritional forces occur between the particles. A classifier is incorporated in the system, so that particles are retained until sufficiently fine.

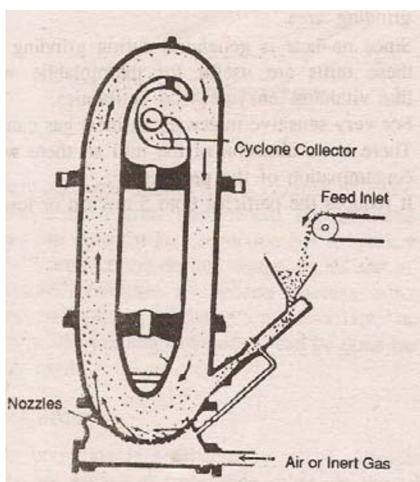


Figure 6 - Fluid energy mill

The feed to the mill needs to be pre-treated to reduce the particles size to the order of 100 mesh, enabling the process to yield a product as small as 5 micrometers or less. Despite this, mills are available which are capable of outputs up to 4 mg per hour.

Advantages:

1. The particle size of the product is smaller than that produced by any other method of size reduction.

2. Expansion of gases at the nozzles leads to cooling, counteracting the usual frictional heat which can affect heat-sensitive materials.
3. Since the size reduction is by inter-particulate attrition there is little or no abrasion of the mill and so virtually no contamination of the product.
4. For special cases with very sensitive materials it is possible to use inert gases.
5. Having a classifier as an integral part of the system permits close control of particle size and of particle size distribution.

The method is used where especially fine powders are required, and antibiotics, sulphonamides and vitamins are typical examples.

Table 1 shows general characteristics of various types of mills.

Table 1-General characteristics of various types of mills

S.No.	Name of the mill	Mechanism of action	Uses
1	Hammer mills	Impact	Used for almost all the drugs
2	Roller mills	Attrition &compression	Soft materials
3	Colloid mills	Imapct & attrition	Used for almost all the drugs Brittle
4	Ball mill	Imapct & attrition	drugs
5	Fluid energy mil	Imapct & attrition	Moderately hard and friable materials

Factors influencing choice of Size Reduction machinery

1. **Nature of the raw material:** Drugs must be thoroughly dried before they are subjected to size reduction. Drugs like belladonna, gentian, liquorice and squill are returned to the drying rooms to the drying rooms after they have been partially comminuted, as they rapidly absorb absorb moisture from the atmosphere and as the moisture may not be removed from all parts of the drug during the initial drying stage. In the case of water insoluble substances, wet grinding of the material can be done. For the preparation of aqueous dispersions of drugs this method is very effective since deflocculating agents may be included to prevent agglomeration of the particles.

Substances that are hygroscopic or volatile or very poisonous or that need-prolonged trituration are more easily prepared in closed porcelain ball mills. Fibrous material seed tearing apart of the fibres and this can be achieved in high-speed impact mills. Substances of a resinous or oily nature shall not be subjected to heavy pressures or much heat as a pasty mass may result. Hence, a ball mill will not be suitable and they are better grounded in a micronizer or a hammer mill. The replacement of air by an inert gas is necessary when grinding readily oxidizable materials and ball mills and high-speed impact mills are generally used in this way.

2. **Nature of the product:** A powdered drug produced in a ball mill differs from the product in a micronizer or a disintegrator even though both powders may be screened to the same fineness. Differences exist in the shape of the particles, their toughness and their internal pore structure. Powder obtained from grinding mills like ball mill is more compact and less porous than that obtained in high speed impact mills like a disintegrator. For the grinding of a sterile material under aseptic conditions, a mill is required that can be easily sterilized and sealed to prevent contamination during the grinding operation. A batch operation porcelain ball mill is most suitable for this purpose. When iron and copper contamination of pharmaceutical products is to be avoided stainless steel or ceramic material may be used for the surfaces of a mill coming into contact with the drug.

3. **Degree of comminution required:** The degree of comminution of materials varies according to the purpose for which they are required. For the preparation of galenicals, the size of the vegetable drug powder employed for extraction varies from coarse to fine powder. Tincture preparation requires bruised to moderately coarse powders. For percolation, drug powders should not contain a large proportions of fines to avoid uneven extraction. Coarse to moderately coarse powder, with a minimum of fine powder, are all most easily obtained by using high speed mills of the impact type. Materials such as cascara, liquorice, belladonna leaf and root and ginger are all easily broken down in such mills. The grindability of different grades of a vegetable drug usually varies and during comminution the softer portions get size reduced first. Therefore it is sometimes useful to screen out the powdered drug and return the coarser material to the mill for further size reduction. This prevents continued milling of the softer portions resulting in formation of too much fines. The same principle is also applicable to crystalline drugs although they are of uniform composition. The rate of absorption of sparingly soluble drugs, either through the Gastro-intestinal tract or when administered parenterally, depends on particle size. Penicillin in a medium of aluminium monostearte and arachis oil appears to be most effective when 90 % of the particles are smaller than 5 micrometers. The relatively insoluble sulphonamides attain their maximum antibacterial activity at crystal sizes of about 1 micrometer or below. For insufflations the drug should be smaller than about 5 micrometers.

Pharmaceutical Applications of Size Reduction

- Size reduction increases the surface area per unit weight also known as the specific surface area. This increased specific surface affects the therapeutic efficiency of medicinal compounds that possess a low solubility in body fluids by increasing the area of contact between the solids and the dissolving fluid. Thus, a given weight of finely powdered medicinal compound dissolves in a shorter time than does the same weight of a coarse powder. For example, the control of fineness of griseofulvin led to an oral dosage regimen half that of the originally marketed product.
- Particle size control influences the duration of adequate serum concentration, rheology, and product syringeability of a suspension of penicillin G procaine for intramuscular injection.
- The rectal absorption of aspirin from a theobroma oil suppository is related to particle size.
- There is an increase in antiseptic action for calomel ointment when the particle size of calomel is reduced.

- The size of particles used in inhalation aerosols determines the position and retention of the particles in the bronchopulmonary system.
- Size may affect texture, taste and rheology of oral suspensions in addition to absorption.
- The time required for dissolution of solid chemicals in the preparation of solutions is shortened by the use of smaller particles.

Size Separation

The control of particles size and size range is of great importance in Pharmaceutical industry. Though various types of machines are used for size reduction, it is not necessary that they will produce the desired size particles and of uniform size. Any solid material, after size reduction, never gives particles of the same size but contains particles of somewhat varying sizes. To control the particle size distribution, the size-reduced material must be sifted to sifting to get fractions of narrow size ranges. The desired fractions are finally mixed, if necessary, in such a way to get a powder having the needed average particle size. Thus one can say that size separation is usually an integral part of size reduction in industrial pharmacy.

Particle size analysis

There are a large number of methods by which particle size of powders can be analyzed but sieving and sedimentation methods are commonly used.

I. Sieving

Sieving is the most widely used method for particle size analysis because it is inexpensive, simple and rapid with little variation between operators. Sieving or sifting is a process by which different grades of powders are separated from each other. In the laboratory different grades of sieves are used for sifting the powders and preparing the granules of required particle size. After comminuting any material it is passed through a specific grade sieve to get the required size particles. The bigger particles are returned to the machine for regrinding. After final grinding and sieving, the material which does not pass through the sieve is known as *tailing* which should never be rejected because they may contain the medicinally active constituents. The tailing may be added to the next batch of the drug to be ground.

Most of the sieves used are of the wire mesh type, the number of the sieve indicates the number of meshes included in a length of 25.4 mm (1 inch) in each direction parallel to the wires, it is the number of meshes that is specified and not the number of wires. Thus a No. 10 sieve has 10 meshes per inch in each direction.

Standards for Powders

British Pharmacopoeia has laid down standards for powders for pharmaceutical purposes, the B.P. states that the degree of coarseness or fineness of a powder is differentiated and expressed by the size of the mesh of the sieve through which the powder is able to pass. The B.P. specifies five grades of powder and these are shown in Table 2, which gives the name by which the grade of powders is known and the number of the sieve through which all the particles must pass.

Table 2-British Pharmacopoeia Powders

Grade of Powders	Sieve through which all particles must pass
Coarse	10
Moderately coarse	22
Moderately fine	44
Fine	85
Very fine	120

However, this is an inadequate definition of powders, since particles that will pass through a 120 sieve will also pass through a 10 sieve. Hence, the very fine powder meets the same definition as a coarse powder. Therefore a limit must be placed on "fines" in the coarser grades of powders and it is obvious that this can be done by specifying two sieves for each powder-a large size through which all particles must pass and a smaller size through which the particles will not pass. This is not practicable, however, since a size reduction process inevitably produces particles finer than is indicated. Due to this, the B.P. specifies a second, smaller size of sieve for the coarser powders but states that not more than 40 percent shall pass through. Thus the objective is to obtain a powder with all the particles between specified maximum and minimum sizes but because of practical size reduction difficulties, at lest 60 percent of the powder between those sizes is acceptable.

The relevant grades of powders and sieve numbers are shown in Table 3.

Table 3-British Pharmacopoeia Powders

Grade of Powders	Sieve through which all particles must pass	Sieve through which not more than 40 percent of particles pass
Coarse	10	44
Moderately coarse	22	60
Moderately fine	44	85
Fine	85	Not Specified
Very fine	120	Not Specified

Sieving methods: Sieves should be used and stored with care, since if the sieve becomes damaged or distorted then it is of little value. Particles, if small enough, will pass through a sieve easily if it is shaken, tapped, or brushed.

Mechanical Sieving methods: Mechanical sieving devices are usually based on methods that agitate or brush the sieve or use centrifugal force.

1. Agitation methods: Sieves may be agitated in a number of different ways, for example-
a. Oscillation- The sieve is mounted in a frame that oscillates back and forth. The method is simple, but the material may roll on the surface of the sieve, and fibrous materials in particular tend to “ball”.

b. Vibration – Here, the mesh is vibrated at high speed, often by means of an electric device using the 50-Hertz alternations of alternating electric current. The rapid vibration is imparted to the particles on the sieve and the particles are less likely to “blind” the mesh.

c. Gyration – The gyratory method uses a system in which the sieve is on a rubber mounting and connected to an eccentric flywheel. Thus, the sieve is given a rotary movement of small amplitude, but of considerable intensity, giving a spinning motion to the particles. This increases the chances of a particle becoming suitably oriented to pass through the mesh, so that the output is usually considerably greater than that obtained with oscillating or vibratory sieves.

Agitation methods may be made continuous, by inclination of the sieve and the provision of separate outlets for undersize and oversize particles. This applies irrespective of the method of agitation.

2. Brushing methods: A brush can be used to move the particles on the surface of the sieve and to keep the meshes clear. A single brush across the diameter of an ordinary circular sieve, rotating about the mid-point is effective, but in large-scale production a horizontal cylindrical sieve is employed, with a spiral brush rotating on the longitudinal axis of the sieve.

3. Centrifugal methods: Mechanical sieve of this type normally uses a vertical cylindrical sieve with a high-speed rotor inside the cylinder, so that particles are thrown outwards by centrifugal force. The current of air created by the movement assists sieving also, and is especially useful with very fine powders.

Wet sieving: The methods described above use the powder in dry state, which may lead to difficulties with some materials. As in size reduction, wet sieving is more efficient than the equivalent dry process, particles being suspended readily and passing easily through the sieve with less blinding of the meshes.

Materials used for Sieves

The only official specification for materials for the construction of sieves is that the wire should be of uniform, circular cross-section. In addition, however, the material should have suitable strength to avoid distortion and be resistant to corrosion by any substances that may be shifted.

1. Metals

a. Iron: Iron wire has the advantage because its cheap, but it has a disadvantage that rusting occurs very readily and iron contamination of products is usually undesirable.

Coated iron: Iron wire may be coated as a protection from corrosion by galvanizing or tinning, but there is a tendency for the diameter to become variable. Some sieves are coated after manufacture, which increases the protection against corrosion and increases the strength also, but is likely to lead to some variation in the mesh size. Like all coatings, it remains effective if it is not damaged.

b. Copper: Copper wire is readily available and is used commonly. Copper has the advantage that it avoids the risk of iron contamination, but it is a soft metal and the meshes can be distorted easily.

Copper alloys

A number of alloys of copper, for example brass and phosphorous-bronze, resemble copper in possessing good resistance to corrosion by most materials but strength is very much greater so that there is less risk of the meshes being distorted in use.

c. Stainless steel: Stainless steel is the most expensive of the metals from which sieves are made, stainless steel is the most satisfactory, having good resistance to corrosion by all materials that are likely to be sieved, as well as adequate strength. Sieves with stainless steel meshes are recommended for pharmaceutical purposes for the above reasons.

2. Non-Metals: Sieves with meshes from non-metals are used when it is important that all risk of metallic contamination be avoided. Non-metals are used also in sieves with fine meshes, since many non-metal fibres are stronger than a metal wire of comparable thickness.

Materials of natural origin, for example hair and silk, were used originally, but synthetic fibres have proved to be more satisfactory. Man-made fibres, such as nylon and terylene, are excellent, having considerable strength and resistance to corrosion. In addition, these materials can be extruded in all diameters, enabling a wide variety of sieves to be made.

II. Size separation by settling

When particles are too small to be screened effectively or when large quantities of material are to be handled, methods involving differences in the rates of settling of particles of different sizes and of different materials are used. If two particles of different settling rates in water are placed in an upward flowing stream and if the velocity of water is adjusted so that it lies between the settling rates of the two particles, the slowing settling particles will move downward against the water stream and a separation is thereby obtained as illustrated in figure 7.

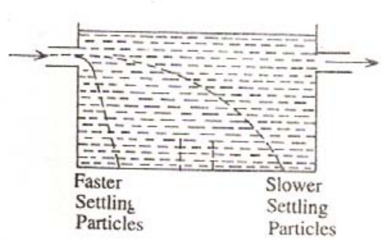


Figure 7: Simple Hydraulic Separation

Consider there are two particles having different settling rates admitted horizontally into a small tank containing water, both particles start to settle. The faster settling particle reaches the bottom of the tank before the slower moving particle. The settling rates of a particle depends both on their size and their shapes. Since the water velocities in any one cross section of the above classifying devices are not uniform, with particles of uniform density but varying in size and shape, the methods do not give fractions having all the particles in a relatively small size range but rather fractions having a mixture of sizes with the average size smaller in one fraction and larger in the other. Hence these procedures are called *classification methods* rather than size separation methods. The settling rate of a particle also depends on its density. If the material to be classified is a mixture of materials of different densities and sizes, the coarser fraction will be richer in the heavier component and the finer fractions will be richer in the lighter component.

Classification equipment may involve simple settling as above or the settling may be aided by mechanical devices. The system may operate only on the water entering with the material or a stream of additional water may be supplied. This additional water is called hydraulic water, if the apparatus is to settle out all the solids introduced and give a clear overflow, the process is called sedimentation.

Sedimentation methods: Sedimentation methods are based on the measurement of the rate at which particles of the powder settle out from a liquid in which they have been dispersed.

Settling is the process by which particulates settle to the bottom of a liquid and form sediment. Also called sediment.

Settling velocity or fall velocity or terminal velocity of a (sediment) particle is the rate at which the sediment settles in still fluid. It is sensitive to the shape (roundness and sphericity) and to the viscosity and density of the fluid. It integrates all of these into a key transport parameter. For dilute suspensions, **Stokes' Law** predicts the settling velocity of small spheres in fluid, either air or water. Stokes' law finds many applications in the natural sciences, and is given by:

$$w = \frac{2(\rho_p - \rho_f)gr^2}{9\mu}$$

where w is the settling velocity, ρ is density (the subscripts p and f indicate particle and fluid respectively), g is the acceleration due to gravity, r is the radius of the particle and μ is the dynamic viscosity of the fluid.

The pipet method (Andreason) as shown in figure 8, is the simplest means of incremental particle size analysis. The Andreason apparatus consists of a tall vessel called sedimentation vessel having capacity of 500 ml. the vessel is fitted with ground glass joint through which a 10 ml pipette fitted with two-way stopcock for draining sample is passed.

A 1 % suspension of the powder is prepared in a suitable liquid medium which is then placed in the sedimentation vessel. As measured by the pipette 10 ml samples are withdrawn at specified intervals of time from a specified depth below the surface without disturbing the suspension. The samples are dried and the residue is weighed. As the sizes of the particles are not uniform, the particles settle at different rates. The larger particles settle at a faster rate and fall below the pipette tip sooner than the smaller particles, thus each sample withdrawn has a lower concentration and contains particles of smaller diameter than the previous sample. From the weights of the dried samples the percentage of the initial suspension is calculated for particles having sizes smaller than the size calculated by Stoke's equation for that time.

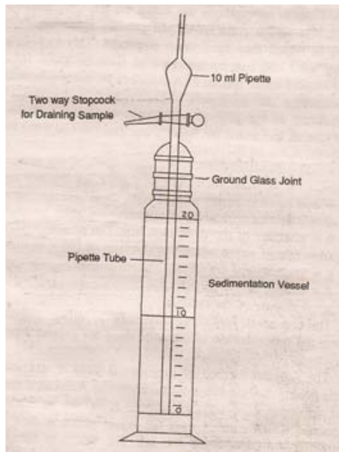


Figure 8 - Andreason Pipette

The process of sedimentation is employed in the operation of thickeners to settle out the solids in slurry and attain a clear overflow of the liquid. One assumption made in the operation of thickeners is that the material to be settled is in the form of flocs which are aggregate of finer materials sufficiently uniform in size and shape so that they settle at uniform velocities under conditions of hindered settling in the initial stages. Figure 9 shows a glass cylinder in which a batch settling operation is being conducted. The cylinder contains an initial uniform suspension, from this initial uniform suspension, any coarse material first falls to the bottom (layer E). Next a layer of settled solid (layer D) forms with a transition zone of partly thickened material above it C. The boundary between C and D is usually obscure and is marked by vertical channels through which water is escaping from the lower layers which are under compression. Next is a zone B of the material at the original concentration and finally a layer of clear water. The boundary between A and B is usually sharp. As thickening progresses, layer B and C ultimately disappear, but layer D may shrink further because of compression. In such batch settling tests carried out at laboratory scale conditions and zone boundaries may vary with time.

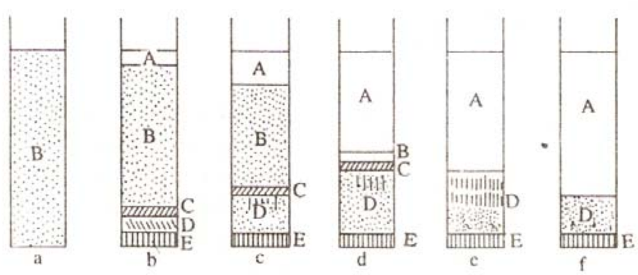
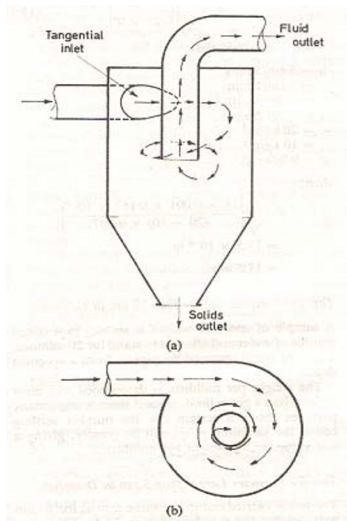


Figure 9 -Typical slurry-settling tests; A. clear liquid; B. slurry at original concentration C. Transition zone; D. Thickened slurry in compression zone; E. Coarse solid

Cyclone Separator

The cyclone separator consists of a cylindrical vessel with a conical base, as shown in figure 10. The suspension is introduced tangentially at fairly high velocity, so that a rotary movement takes place within the vessel. And the fluid is removed from a central outlet at the top. The rotary flow within the cyclone causes the particles to be acted on by centrifugal force, solids being thrown out to the walls, hence falling to the conical base and out through the solids discharge. Cyclones can be used with liquid suspensions of solids, but the most common application is with suspensions of a solid in a gas, usually air.



a) Elevation, b) Plan
Figure 10 - Cyclone Separator

The separator is still a form of sedimentation, but with centrifugal force used instead of the gravitational force. Hence, depending on the fluid velocity, the cyclone can be used to separate all particles or to remove only coarser particles and allow fine particles to be carried through with the fluid.

Air classifiers

The Air Classifier is a centrifugal type classifier used to separate dry powdered materials into fine and coarse fractions. It may be operated in closed circuit with a grinding mill or used in open circuit operation, receiving the feed from hoppers, bins screens. Air classification is a process of approximate sizing of dry mixtures of different particle sizes into groups or grades at cut point ranging from 10 mesh to sub-mash sizes.

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Suggested Reading

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