Module 2: Milling (Particle Size Reduction)

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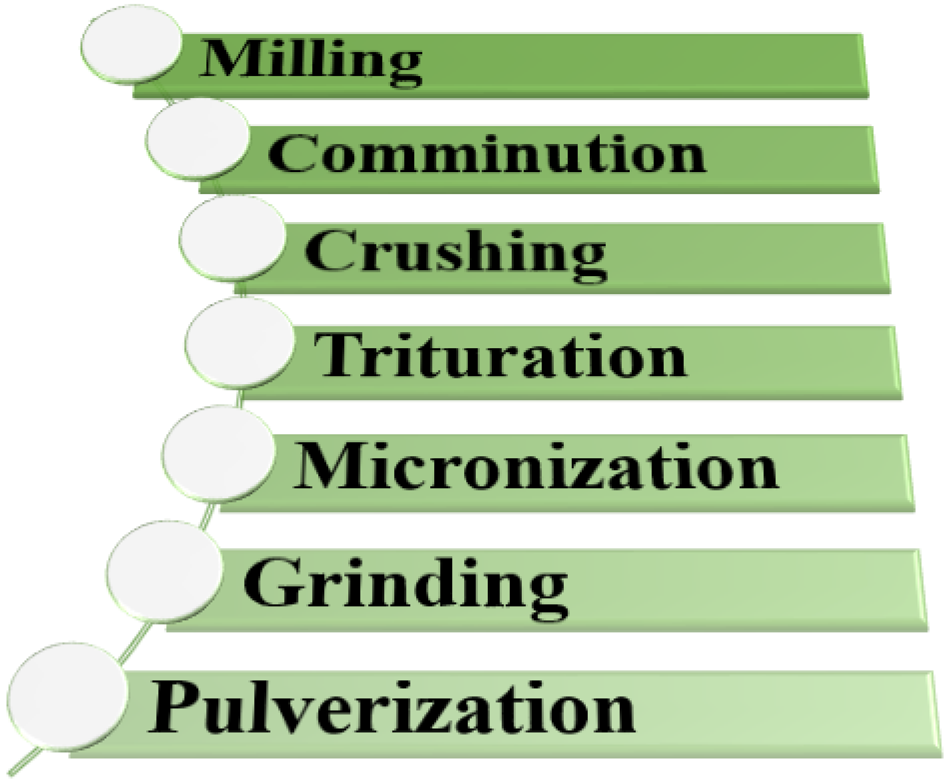
Milling: Introduction

- Milling can be defined as the **mechanical process** of **reducing** the particle size of **solids**.
- Various terms have been used but mainly milling and **comminution** depending on the product, equipment, and process:
- Crushing
- Disintegration
- Dispersion
- Grinding
- Pulverization

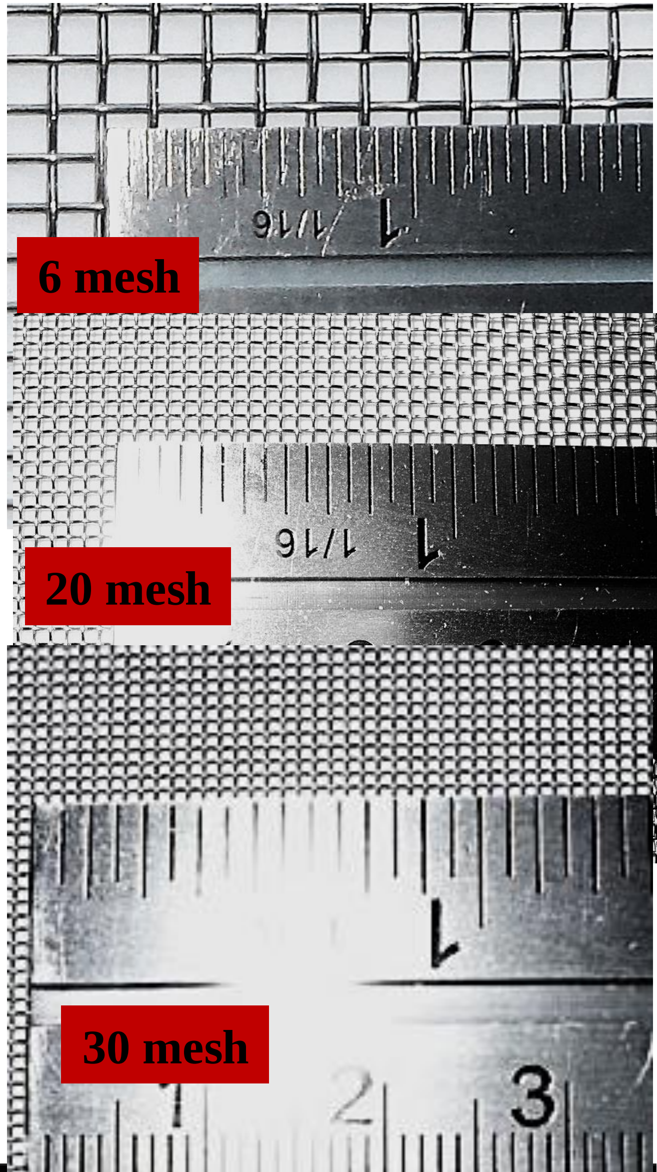


Milling: Introduction

- **Milling equipment is classified** according to the size of the milled **product:**
- Size is conventionally expressed in terms of mesh (number of openings per inch square)

1. **Coarse** for particle size larger than 20 mesh,
2. **Intermediate:** size 20- 200 mesh (74-840 microns)
3. **Fine** (smaller than 200 mesh.

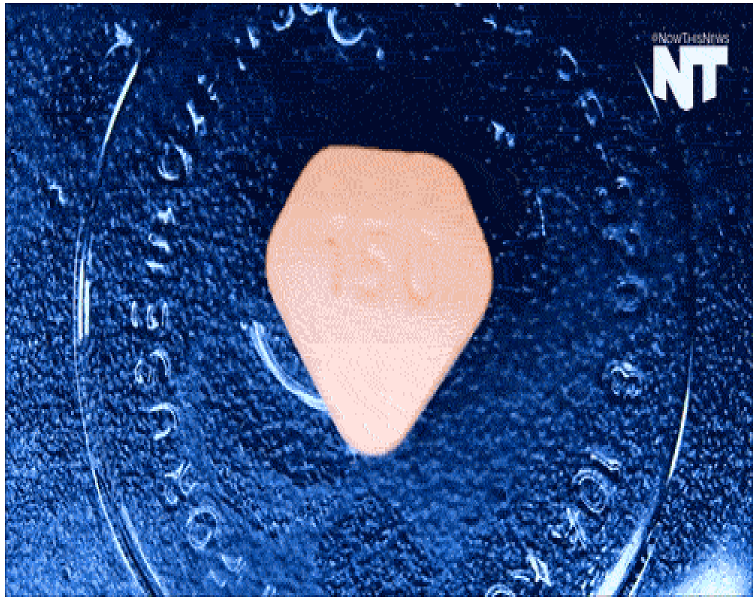
- A given mill can be used successfully to prepare particles in more than one class. (ex. Hammer mill used for granulation (16-mesh) and for milling crystalline API to a 120-mesh powder)

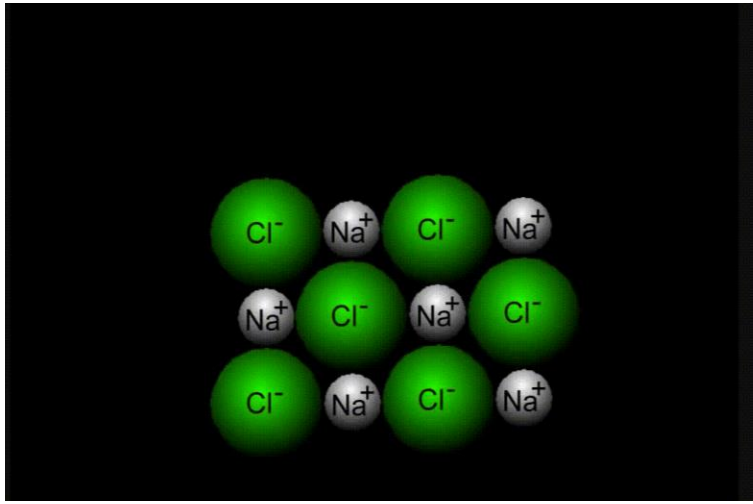


- Numerous examples have been quoted to stress the importance of fine particles in pharmacy and milling or grinding offers a method by which these particles can be produced.
- The surface area per unit weight, which is known as the specific surface area, is **increased** by size reduction.
  - In general,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

1. Dissolution and therapeutic efficacy:

- Dissolution and therapeutic efficiency of medicinal compounds that possess low solubility in body fluids are increased due to an increase in the area of contact between the solid and the dissolving fluid.





Advantages of Milling

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**: smaller particles with large specific surface areas will require less time for optimum drying.
   - This is because of the reduction of 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.

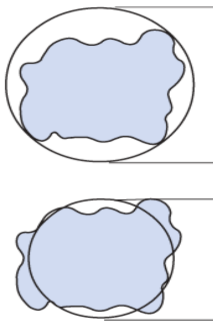
4. **Flowability:** The flow property of powders and granules is affected by particle size and size distribution.
   - The freely flowing powders and granules in high-speed filling equipment and tablet presses produce a uniform product.

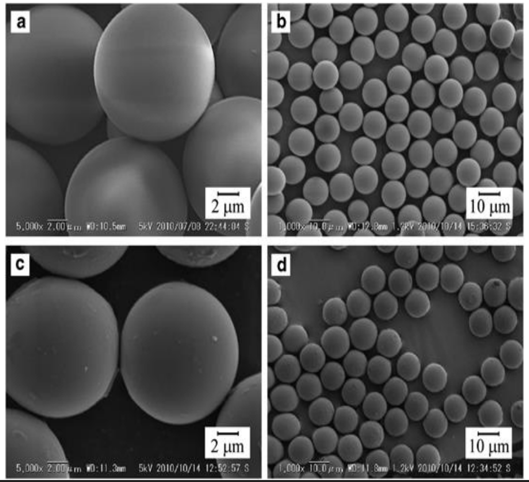
Advantages of Milling

5. **Mixing or blending:** The mixing or blending of several solid ingredients of a pharmaceutical is easier and more uniform if the ingredients are approximately the **same size**.
    - This provides greater uniformity of dose. Solid pharmaceuticals that are artificially colored are often milled to distribute the coloring agent to ensure that the mixture is not mottled and uniform from batch to batch.
6. **Formulation**: such as when using a **lubricant** during tablet formulation that needs to cover formulation granules. So, the finer the lubricant the better the coverage.
    - Another example is when formulating an ointment or cream where the fine particles will provide 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 Measurement

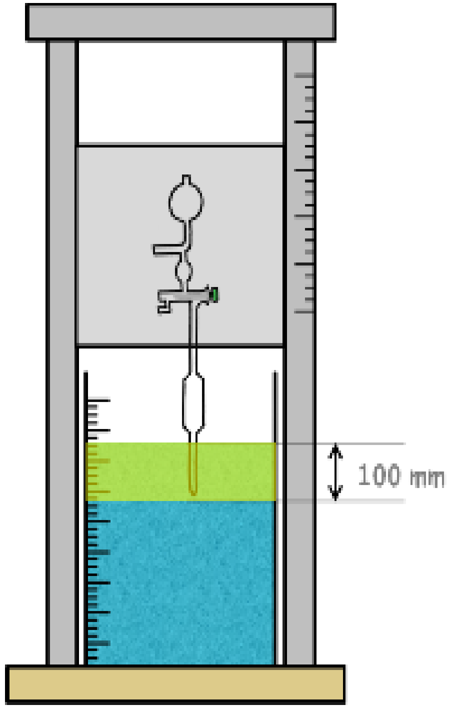
- Naturally occurring particulate solids & milled solids, the shape of particles is **irregular** & the size of the particles varies within the range of the largest & smallest particles.
- There is **no known** method of defining an irregular particle in geometric terms; however statistical methods have been developed to **express the size** of an irregular particle in terms of **diameter**.
- For an irregular particle, an equivalent particle with the same surface or volume may be substituted.
- For the convenience of mathematical treatment, an **irregular** particle is considered in terms of an **equivalent sphere**. So the irregular particle is expressed as diameter.

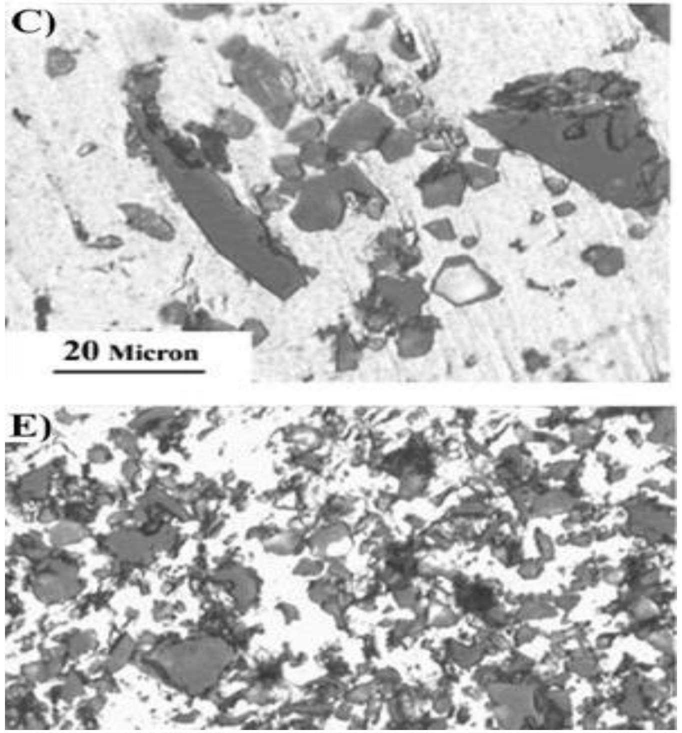


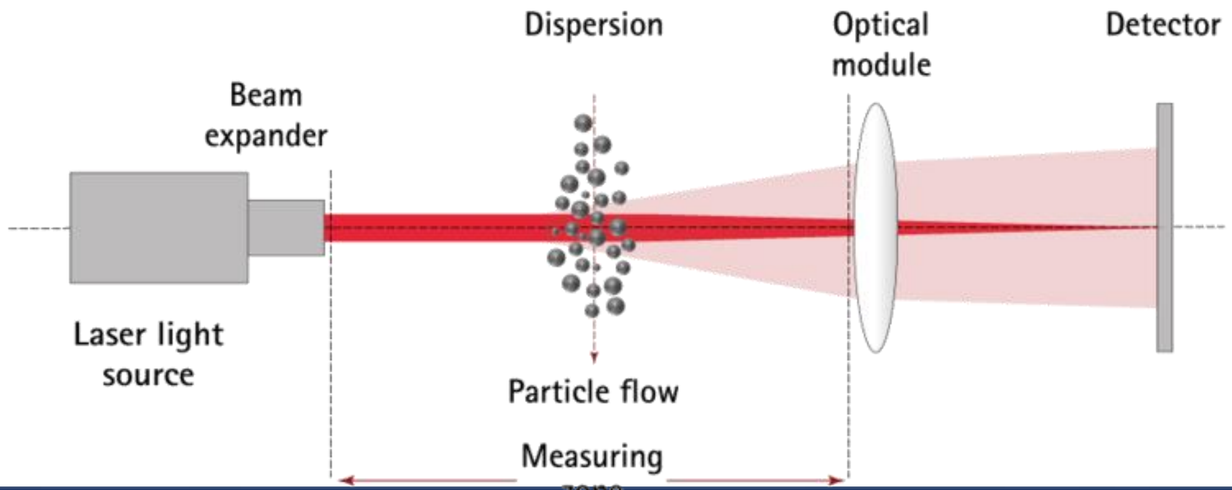


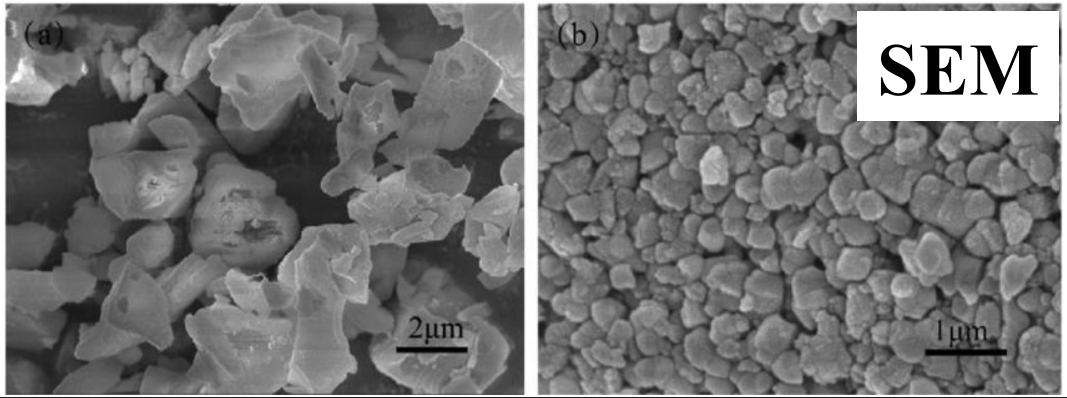
Method of Size Measurement

1. **Microscopy:**
2. **Sieving**
3. **Sedimentation**

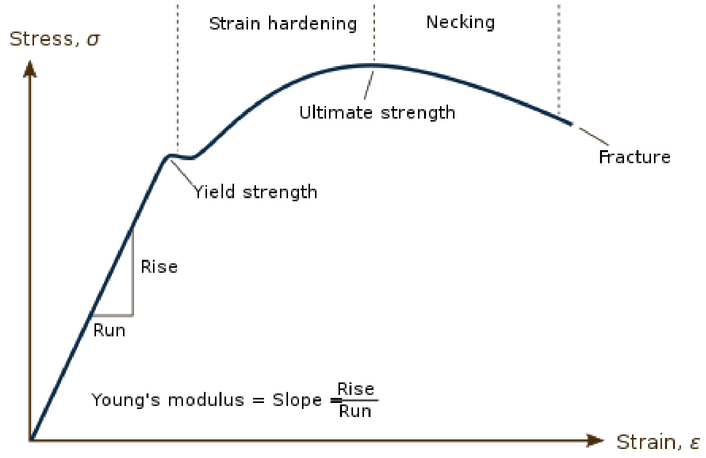


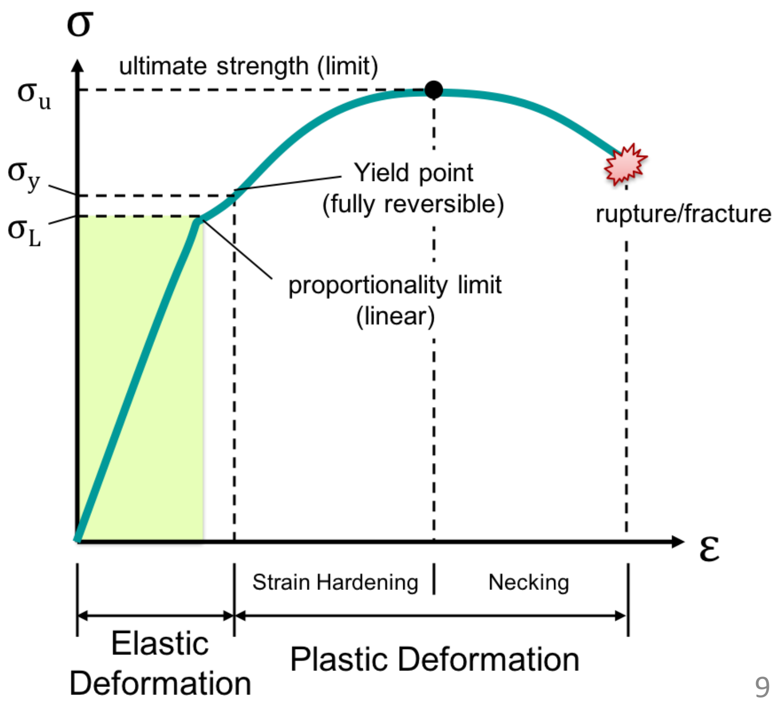






- The mechanical behavior of solids, under stress, is **strained and deformed**, which is shown in the stress-strain curve.
- The initial linear portion of the curve is defined by:
  I. **Hooke's law**(stress is directly proportional to strain),
  II. and Young's modulus (slope of the linear portion) expresses the stiffness or softness (dyne/cm^2) 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 material's impact strength.





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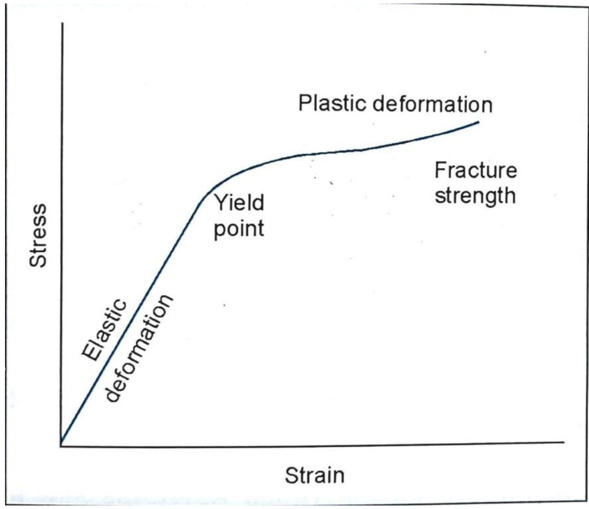
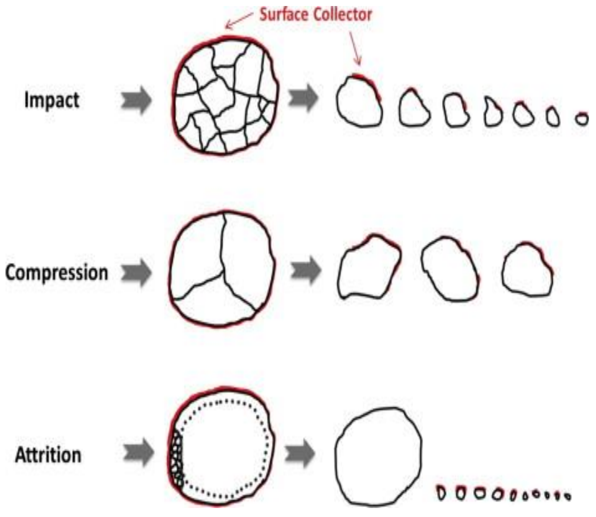
Theory of Comminution

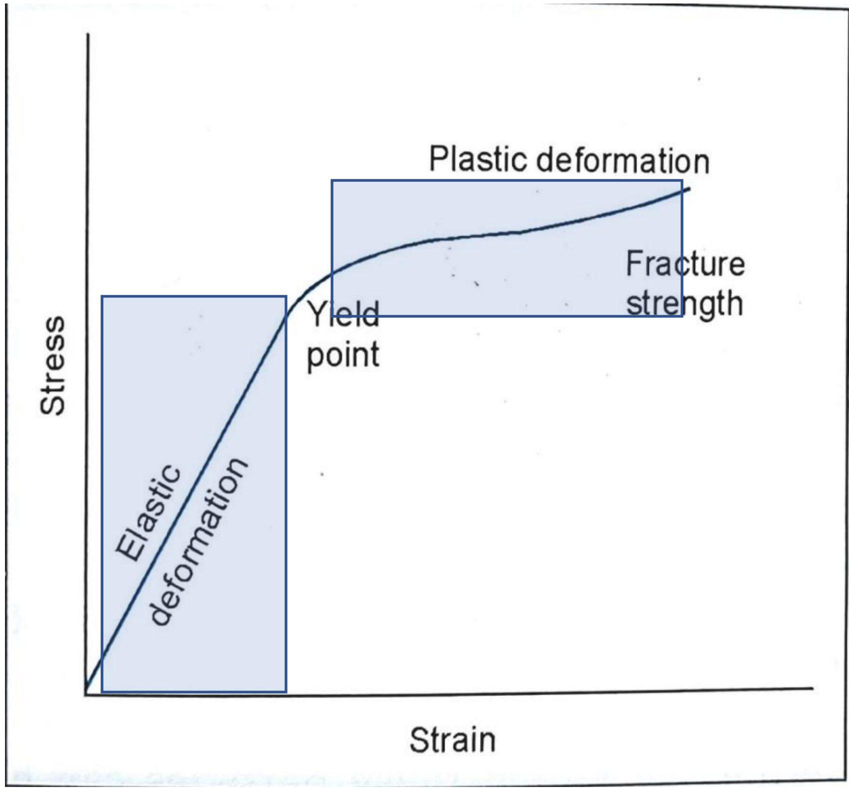
- In all milling processes, it is a **random matter** if and when a given particle will be fractured.
- If a single particle is subjected to a sudden impact and fractured, it yields a few relatively large particles and a number of fine particles, with relatively few particles of intermediate size.
- **If** the energy of the impact is increased, the larger particles become of a smaller size and greater number,
- and although the number of fine particles 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.





Theory of Comminution

- **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 particles appears as heat.
- If The force of impact 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.



Theory of Comminution

- It has been proposed that **any force** of milling produces a **small flaw** in the particle.
- A particle absorbs strain energy and is deformed under shear or compression until the **energy exceeds** the weakest flaw and causes a 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 Milling (comminution)

- Mills are Equipment 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 the application of force over a very narrow area of material using the **sharp edge** of a cutting device.
2. **Compression:** The material is **gripped between the two surfaces** and crushed by the application of pressure.
3. **Impact:** Involves the contact of material with a **fast-moving part** that imparts some of its kinetic energy to the material.
    - This causes the creation of internal stresses in the particle, thereby breaking it.
4. **Attrition:** The material is subjected to **pressure** as in compression, **but** the surfaces are **moving** relative to each other, resulting in shear forces that break the particles.

Milling Equipment

- Any mill consists of three parts:

1. **Feed chute (unit):** to deliver the material.
2. **Grinding mechanism (Milling tools):** act to reduce sample particle size. Usually consists of a rotor and stator.
3. **Discharge chute (unit):** to deliver the material out of the mill.

- The principle of operation depends on cutting, compression, impact from a sharp blow, and attrition.
  - **Note**: 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 one in which the discharge from the milling chamber is passed through a **size-separation device** or classifier, and the oversized 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.

Equipment

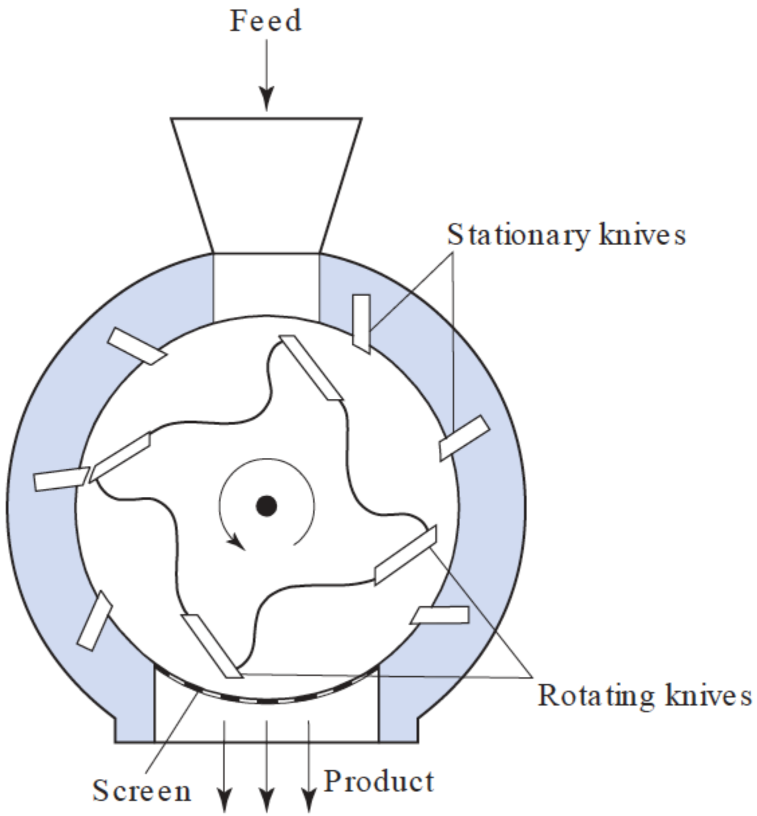
- The classification of most commonly used mills in pharmaceutical manufacturing is given in Fig

Mills

Cutting	Compression	Impact	Attrition
Cutter mill	Roller	Hammer	Pin
	Colloid		Ball
	Edge and End		Vibro-energy
			Fluid-energy
			Spiral Jet

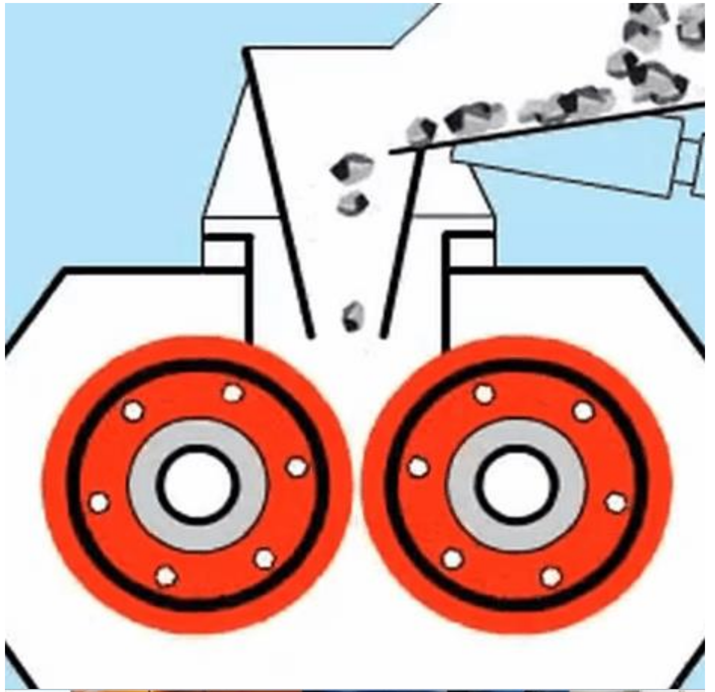
1- Cutter Mill

- The rotary knife cutter has a horizontal rotor with 2 to 12 knives spaced uniformly on its periphery turning from **200 to 900 rpm** in a cylindrical casing.
  - And a **stationary 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.



2- Roller Mills

- It consists of **two (can be five)** smooth rollers operating at different speeds.
- Thus the size reduction is affected by a combination of **compression and shearing action**.
- Two cylindrical rolls are 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.
- **If** the two rolls are rotated at different speeds → size reduction occurs by **attrition.**
    - This type is used for milling **ointments, pastes, and suspension**.



3- Hammer Mill (Impact Mills):

- **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 the **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

https://youtu.be/fSTvbE77ucE

Hammer Mill

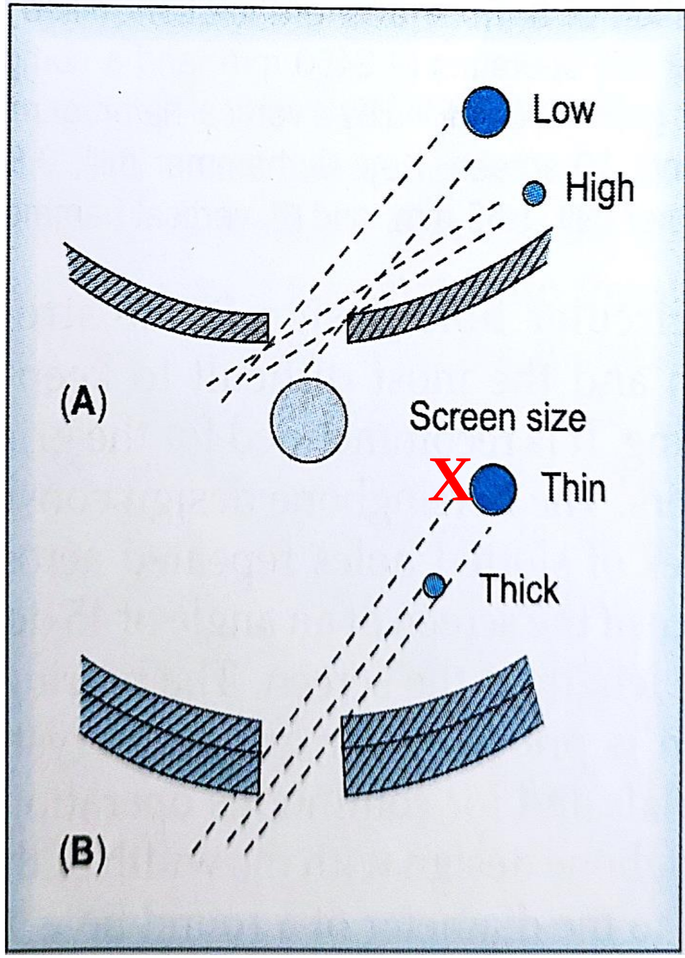
- The particle size that can be achieved will **depend on:**

1. The type of milling tool selected,
2. Rotor speed (calculated as tip speed at the outermost rotating part), and
3. Solid density in the mill or solid feed rate.

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

Hammer Mill

- As shown in Figure (a), an increase in **hammer tip speed**, contributes to a higher particle size reduction and thus relatively fine mash.
  - The particles will follow a pathway closer to the screen due to the centrifugal force → not easy to exit → returned to the milling area → become finer.
  - For a given screen: **a smaller particle** size is obtained at a **higher speed**,
- 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. →
  - For a **given rotor speed** and screen opening, a **thicker screen** produces a **smaller particle**,



- **Applications**:
  - It is the **most widely** used milling equipment in the pharmaceutical industry and can be used for almost any type of size reduction.
  - Due to this versatility, it has become 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.

1. Rapid, convenient, compact, and inexpensive method of producing fine drug powders of about **20-40 µm**.
2. Hammer mills are simple to install and operate.
3. The speed and screen can be rapidly changed.
4. They are **easy to clean** and may be operated as a closed system to reduce dust and explosion hazards.
5. A hammer mill tends to yield a relatively **narrow size distribution**. This is because:
   a) Small particles pass through the screen almost as fast as they are formed.
   b) Because the inertial forces vary with mass as the inverse cube of the diameter, Small particles with a constant velocity are impacted with much less kinetic energy than larger ones, and the probability that particles less than a certain size will fracture decreases rapidly.

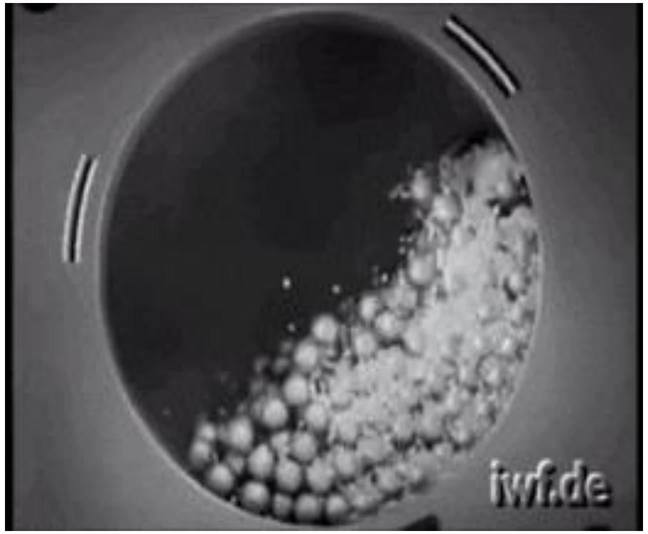
- **Disadvantage**: a hammer mill must be operated with internal or external classification to produce ultrafine particles (not very easy to produce ultrafine particles).

4- Ball Mill

- This combines **impaction and attrition mechanisms.**

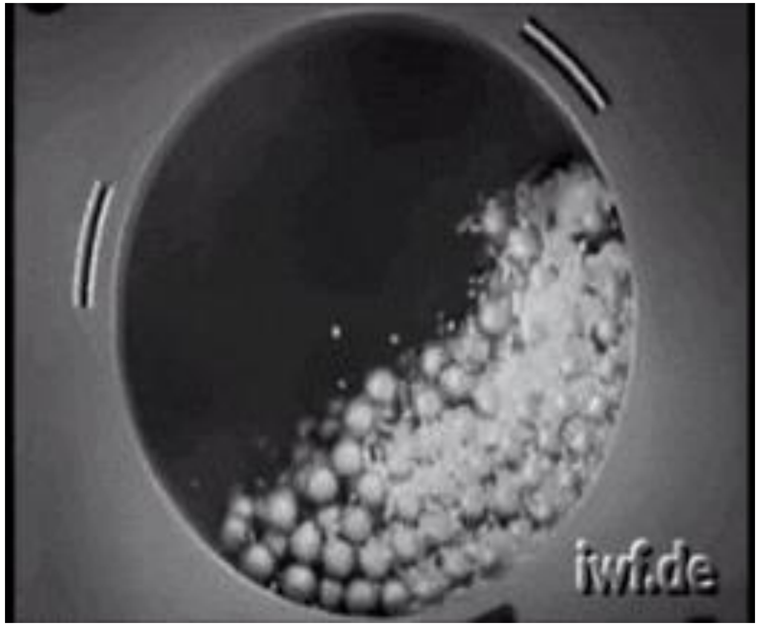
Construction and working:

- The ball mill consists of a horizontally rotating hollow vessel of cylindrical shape with a 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 trough a similar trunnion at the opposite end.
    - The outlet is covered with a **coarse screen** to prevent the loss of the balls.



Ball Mill

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



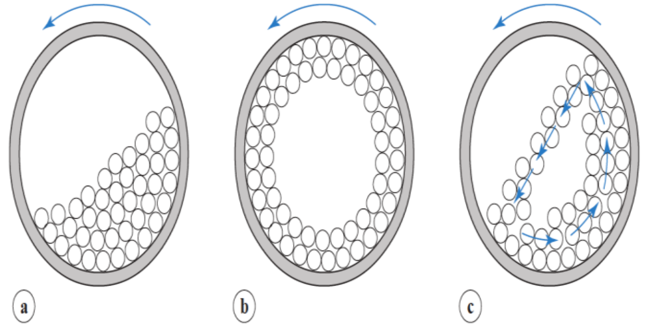


Fig. 10.13 • Ball mill in operation, showing correct cascade action (c).

Rotation Speed

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

1. At low rotating speed(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 onto 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

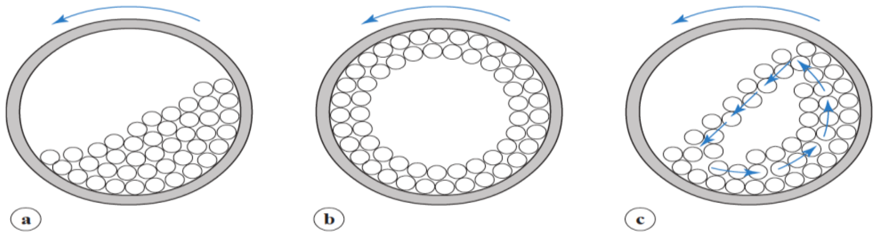


Fig. 10.13 • Ball mill in operation, showing correct cascade action **(c)**.

Advantages and disadvantages

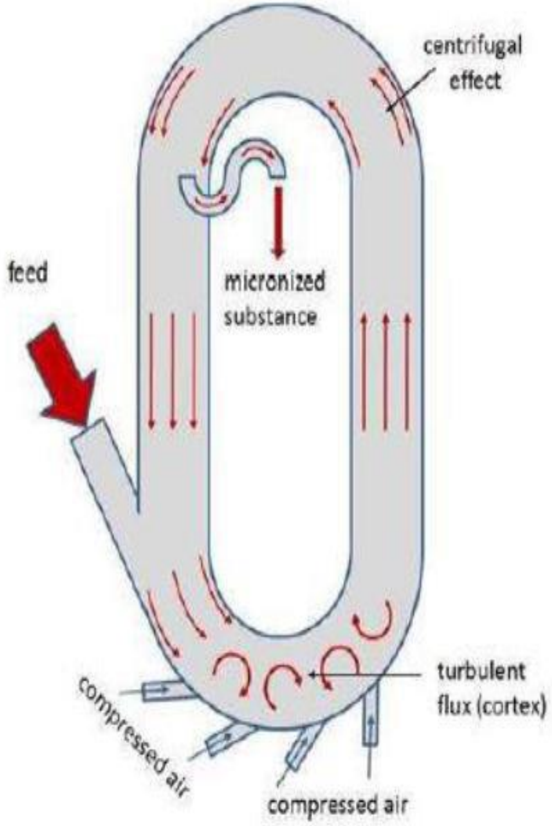
- **Advantages:**

1. Used for either wet or dry milling.
2. Used for batch or continuous operation
   - In a batch operation, **unstable or explosive** materials may be sealed within an inert atmosphere and satisfactorily ground.
3. Ball mills may be **sterilized** and sealed for sterile milling in the production of ophthalmic and parenteral products.
4. The installation, operation, and labor **costs** involved in ball milling are **low**.
5. Finally, the ball mill is unsurpassed for **fine grinding** of hard and abrasive materials.

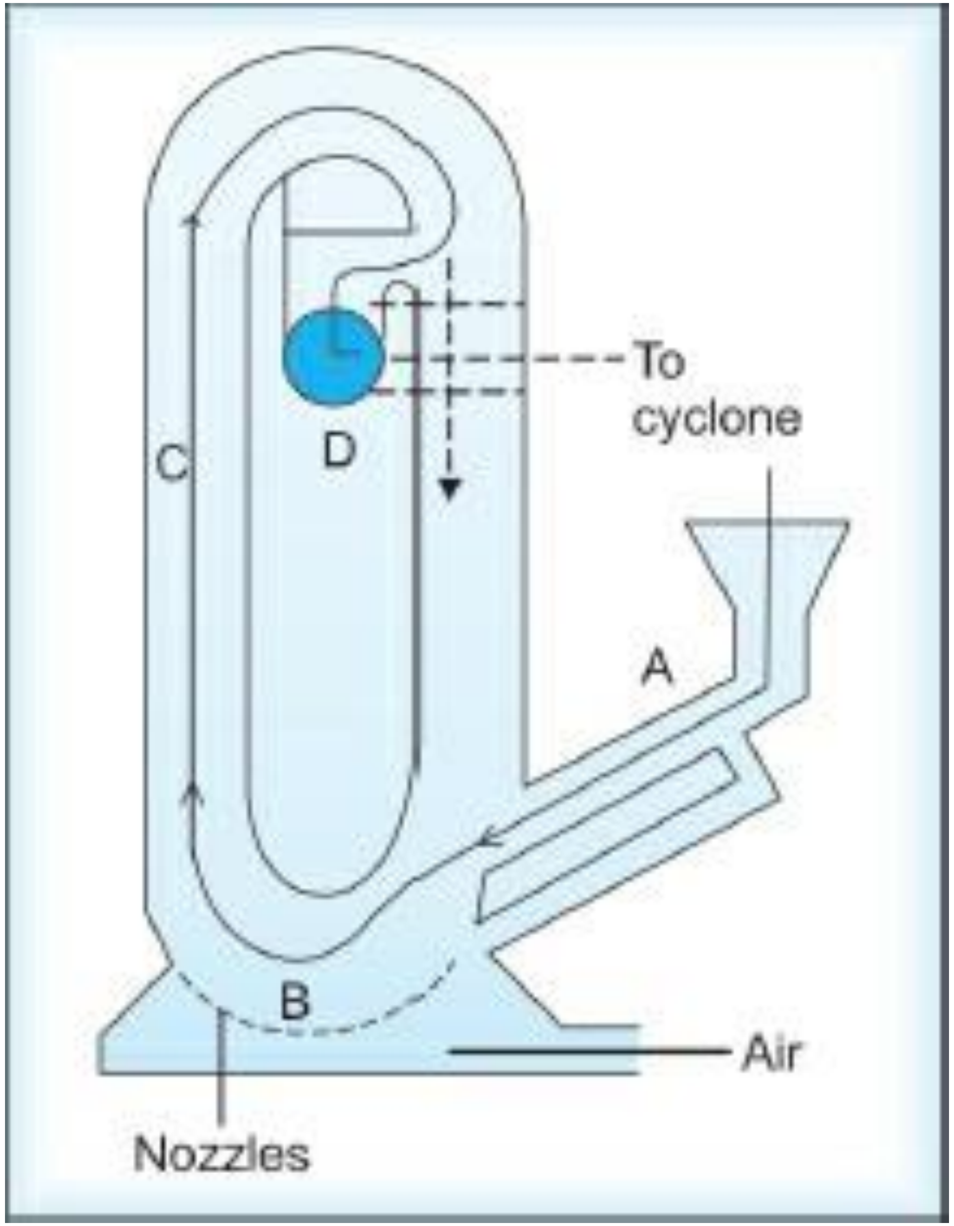
- **Disadvantage**: This type of mill is **difficult to clean** and takes a **long time** for satisfactory milling.

Fluid-energy Mill (micronizer)

- **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.



- The most important machine-related factors are:
  1. The grinding chamber **geometry**.
  2. and the **number and angle** of the nozzles.



Fluid-energy Mill (micronizer)

- 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** that are often processed.
- **Disadvantage:**
- One drawback of this type of mill is the potential for the 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 the classifier vanes or gas nozzles become plugged or blocked.

Factors Influencing Milling

- The **properties of a solid (feed)** 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**.

Factors Influencing Milling

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. **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.

Factors Influencing Milling

4. **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.

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 the 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 potentially explosive mixture under certain conditions especially if static electrical charges result from the processing.

Techniques of Milling

2. Temperature Control

- As only a small percentage of the energy of milling is used to form new surfaces, 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.

Techniques of Milling

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 or **returning** the oversized particles for a second milling.

Techniques of 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 a 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.

Mill Selection

- In general, the materials used in pharmaceuticals may be reduced to a particle size of less than **40 mesh** using 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.
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 plants).
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).