WELCOME

Size Reduction (MILLING)

BY

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CONTENTS :

- Introduction to size reduction.
- Objectives of size reduction.
- Modes in size reduction.
- Classification of pharmaceutical miller.
- Factors effecting selection of a mill.

MILLING

Introduction:

- 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.
- Size reduction process also termed as comminution, crushing, or disintegration, dispersion, or pulverization or grinding.

MILLING

Introduction:

- Size of particles is conventionally expressed in terms of mesh
- Mesh: number of opening per inch square.

❑ Milling equipment is classified according to the size of the final milled product into:

1. Coarse: for particles size large than 20 mesh
2. Intermediate: 20 to 200 mesh (840 to 74 micron)
3. Fine: for particles size < 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, 1190 micron) and for milling crystalline API to a 120-mesh, 125 micron) powder.

WHY ?????

- Materials are rarely found in the size range required, SO there is a need either to decrease or to increase the particle size.
- Milling increase specific surface of the substance, which affect the therapeutic efficiency of medical substance especially if the material have low solubility.
  - In general, a 10-fold decrease in particle size, → a 10-fold increase in surface area.
  - specific surface is defined as the surface area per unit weight
- It significantly increase the speed of substance and diffusion processes

Pharmaceutical Application of Size Reduction :

- Dissolution and therapeutic efficacy
- Extraction:
- Drying:
- Flowability:
- Mixing or blending
- Formulation:

Pharmaceutical Application Of Size Reduction :

1. **Dissolution and therapeutic efficacy:**
   - ↓ PS of medicinal compounds (e.g Griseofulvin) that possess low solubility in body fluids, →↑ Surface Area of contact between the solid and the dissolving fluid →↑ dissolution rate →↑ therapeutic efficiency → ↓ frequency of administration

2. **Extraction: -**
   - Extraction or leaching from animal glands (liver and pancreas) and crude vegetable drugs is facilitated by comminution.
   - ↓ PS →↑ Surface Area of between the solvent and the solid→↓ distance the solvent has to penetrate into the material → The time required for extraction is shortened.

2. **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.

Pharmaceutical Application Of Size Reduction :

4. Drying:

- The drying of wet masses may be facilitated by milling
- ↓ PS →↑ the surface area and ↓ 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

5. Mixing or blending: -

- if the ingredients are of approximately the same size → mixing is easier and more uniform.
- This provides a greater uniformity of dose.
- artificially colored solid pharmaceuticals are milled→ distribute the colouring agent → prevent mottling → uniform batch-to-batch,

Pharmaceutical Application Of Size Reduction :

6. Formulation:

- *Improve Appearance:* *e.g.,* ointments, pastes and creams.
  - Milling provides a smooth texture and elegant appearance
  - Improve their physical stability.

- *Improve Stability:* especially for biphasic systems .
  - Emulsion – ↓size of oil droplets → ↓ rate of creaming
  - Suspension – ↓ PS → ↓ rate of sedimentation.

- *Aerosol and Inhalation preparations: -*
  - PS affects (determines) the position and retention of particles in bronchioles & less irritation.

- *compressed tablets and capsules*
  - ↓ PS → ↑ the ability of lubricant to coat the surface of the granules or powder.
  - A fine PS is essential if the lubricant is to function properly.

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 material (Glycyrrhiza, Rauwolfia) can not be crushed by pressure or impact → they must be cut.
- Friable material (dried filter cake, sucrose) tend to fracture so → it may be milled by an attrition, impact or pressure

2. Particle Shape

- An impact mill produces sharp, irregular particles, which may not flow readily.
- When specifications demand free-flowing spheroidal particles, an attrition mill is best.

Factors influencing milling

3. Moisture Content

- It is found that materials contain > 5 % of water → hinder grinding.
- Under these conditions the material tends to produces a sticky mass upon milling.
- This effect is greater with fine particles than larger ones.
- At water conc. > 50 %, → the mass become a slurry, or fluid suspension → the process then is a wet milling which often aids in size reduction.
- An ↑ in moisture content → can ↓ the rate of milling to a specified product size.
- In general, grinding can be carried out satisfactorily outside these limits.

Factors influencing milling

4. Temperature

- The heat generated during milling softens and melts materials with a low mp.
- **Examples:**
  - Synthetic gums, waxes (SA), 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.
- **Examples**, when cortisone acetate crystals are allowed to equilibrate with an aqueous vehicle, subsequent wet milling → provides a satisfactory suspension.

Technique of milling

1. Special Atmosphere:

- Hygroscopic material can be milled in a closed system supplied with dehumidified air
- Thermolabile easily oxidizable, and combustible material should be milled in a closed system with an inert gas (N2 or CO2)
- Almost any fine dust (dextrin, starch, sulfur) is an explosive mixture under certain conditions, especially if the processing generates static electrical charges.

2. Temperature control

- As only a small % of milling energy is used to form new surfaces, → the bulk of milling energy is converted to heat, which may ↑ the temperature of the material by many degrees → lead to solid melting, decompose or explode.
- The milling chamber should be cooled by a cooling jacket or a heat exchanger to prevent changes of milled material and stalling توقف of the mill.
- Waxy and low m.p materials as Stearic acid or beeswax fed to mill simultaneously with dry ice.

Technique of milling

3. Pretreatment :

- For mill to operate satisfactory, the feed should be in the proper size and enter at a uniform rate.
- Pretreatment of fibrous materials with high pressure rolls or cutter facilitates commination
- Pre-sizing is essential for granules or intermediate-sized particles with low fines.

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 oversize particles for a second milling.
- Air separation, conveyor and collection element usually integrated with mill for material to be reduced to micron size.

Technique 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.

dry milling is recommended for:

- The product undergoes physical or chemical change in water.

Wet milling :

- It is beneficial in further reducing the size, but flocculation restricts the lower limit to approximately 10 µm.
- It eliminates dust hazards, and is usually done in low-speed mills, which consume less power

Mechanisms of Comminution

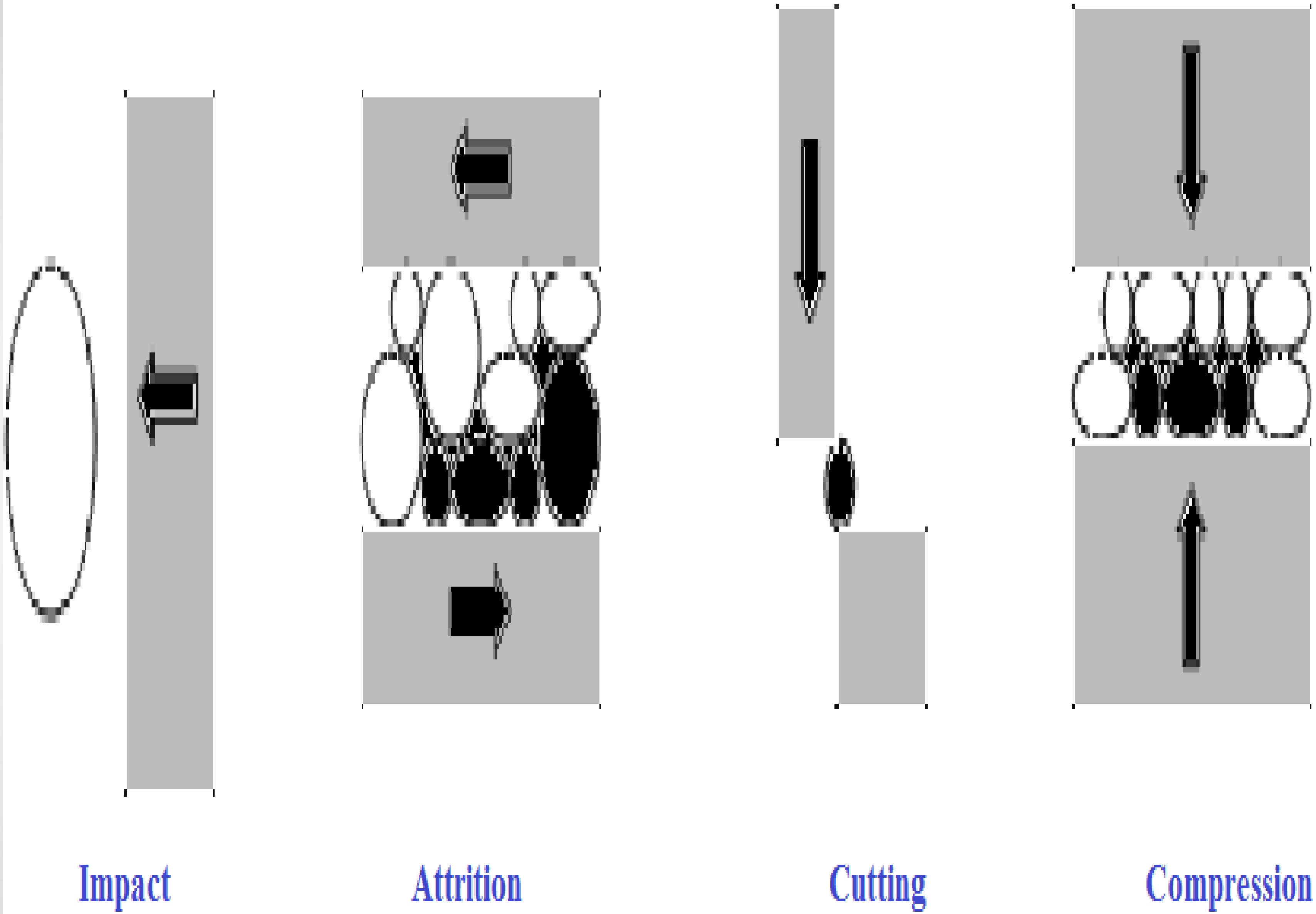
- Mills employ energy to decrease material size.
- Four strategies reduce size:

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

2. Compression: The material is placed between the two surfaces and is crushed by the application of pressure.

3. Impact: It involves contact of material with an object moving at high speed 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:** 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.

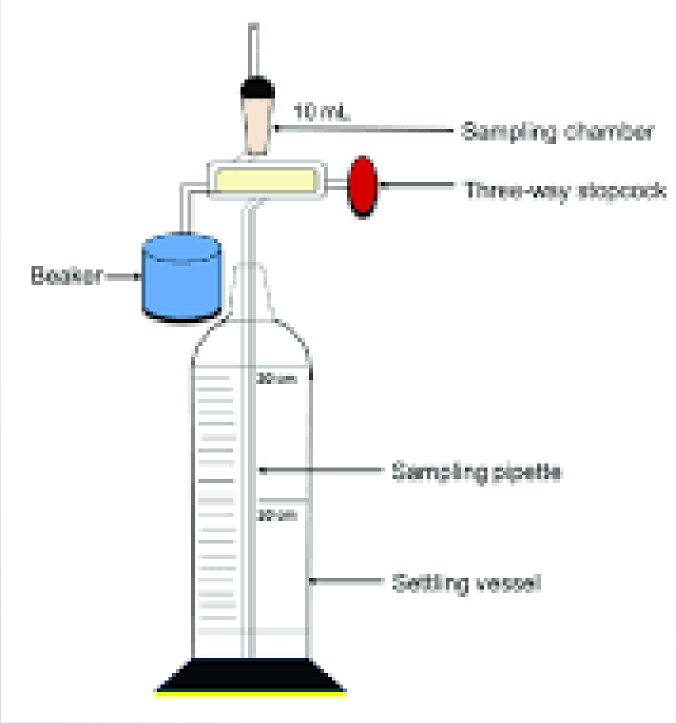

Impact
Attrition
Cutting
Compression

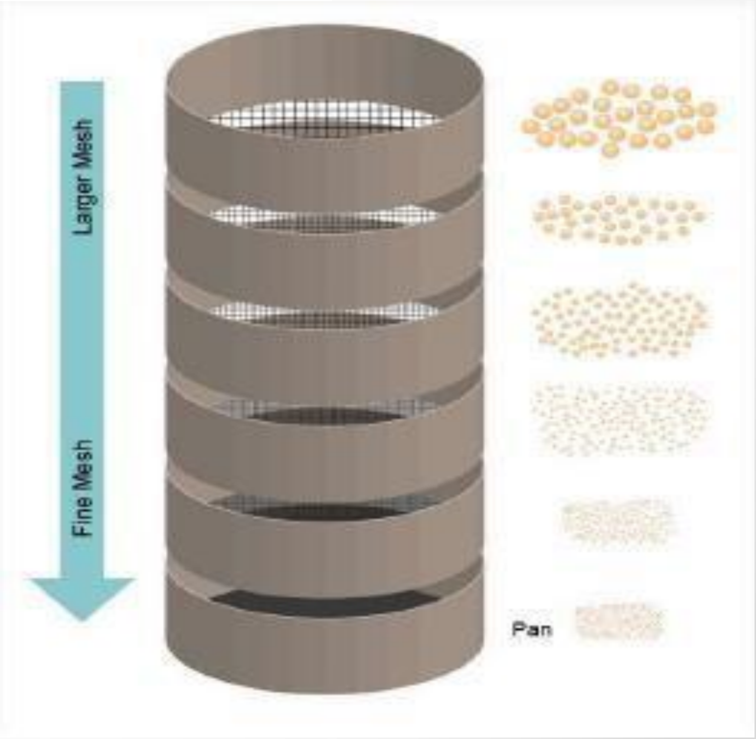
Size distribution and measurements

1.Microscopy

2.Sieving

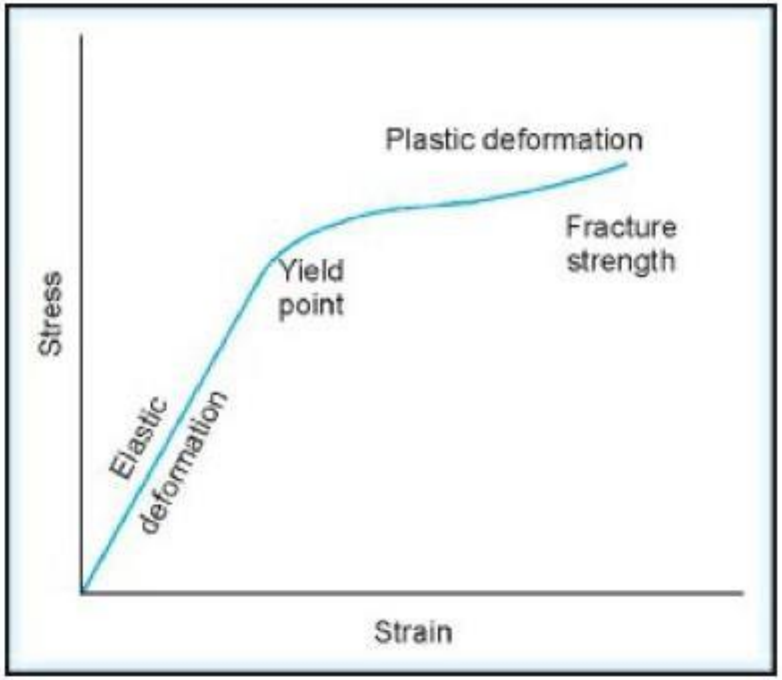
3.Sedimentation





Theory of comminution

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



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 (dyne/cm^2).
- The stress-strain curve becomes nonlinear at the yield point, which is a measure of the resistance to permanent deformation.

Theory of comminution

- 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. لقوة تأثير
- 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 is fractured تعرض لتأثير مفاجئ وتم كسره, it yields a few relatively large particles and several fine particles, with relatively few particles of intermediate size
- If the impact energy is ↑,→
  - larger particles are of a smaller in size and greater number,
  - while fine particles ↑ in number but not size greatly changed.
- It seems that the finer particles' size is related to the material's internal structure, whereas the larger particles' size is more related to comminution process.
- Size reduction begins with the opening of any minor cracks that were initially present. شقوق طفيفة كانت موجودة في البداية

Theory of comminution

- If the force of impact does not exceed the elastic limit (region of Hooke's law), → 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.
- When a force exceeds the elastic limit, → the particle fractures.
- As a material fractures, the points of force application 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 deforms under shear or compression until the energy exceeds the weakest flaw and cause fractures or cracks of the particles.
- The strain energy required for fracture is proportional to the length of the crack formed since the additional energy needed to extend the crack to fracture is supplied by flows of the surrounding residual strain energy to the crack.

Equipments

All milling equipment have three basic components:

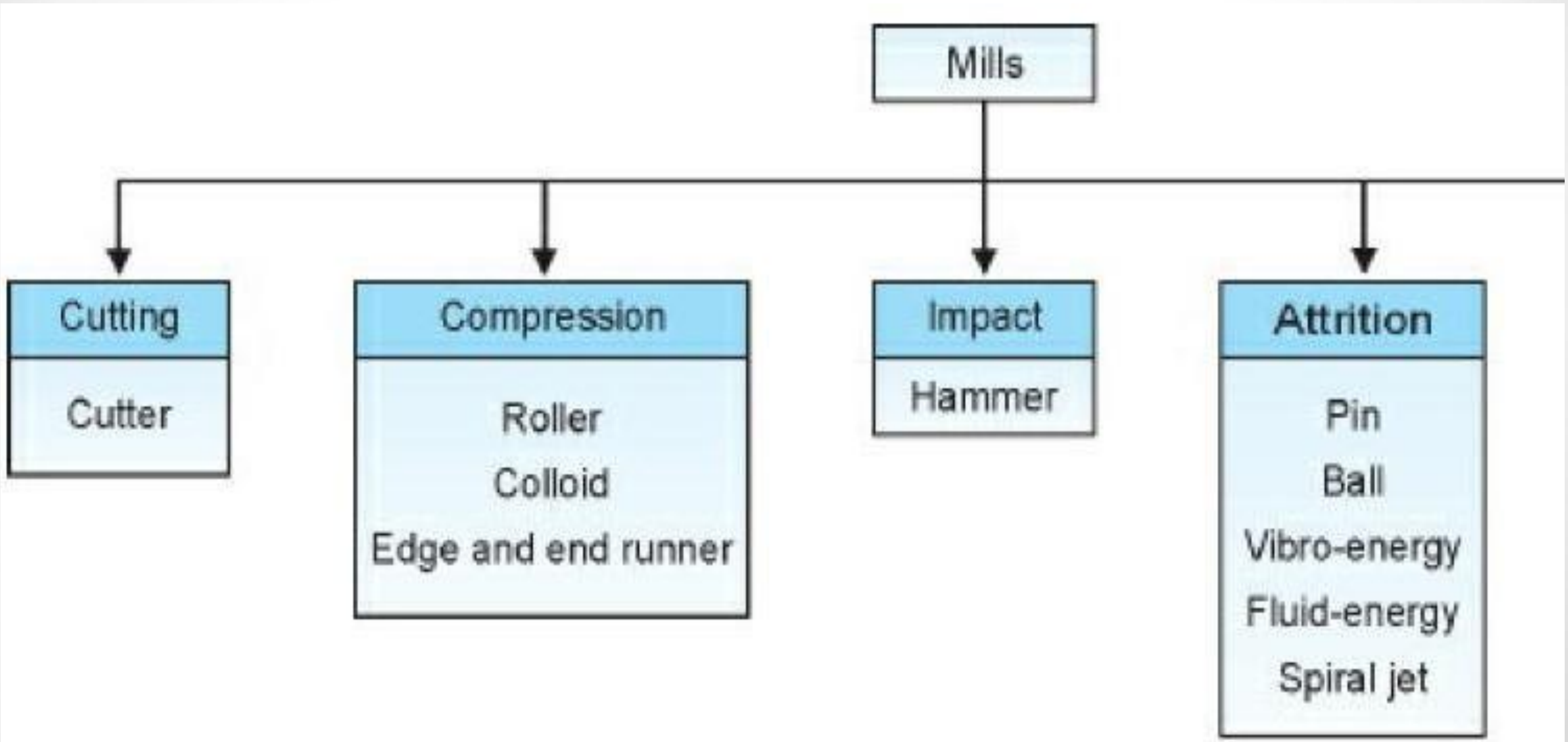
1. Feed chute → which delivers the material
2. Grinding mechanism (milling chamber) → usually consisting of a rotor and stator. الدوار والجزء الثابت.
3. A discharge chute → A receiver or collector in which the milled product is deposited.

- Cutting, compression, impact, and attrition are the operating principles.
- In most mills, the grinding effect is a combination of these actions.

- Open-circuit milling: If the milling operation reduces the material to the desired size by running it once through the mill.
- A closed-circuit mill: is one in which the discharge from the milling chamber passes through a size-separation device or classifier and returns oversize particles to the grinding chamber for further reduction.
  - It is most valuable in reduction to fine and ultrafine size.

Equipments

The Figure below shows the classification of the most commonly used mills in the pharmaceutical industry.



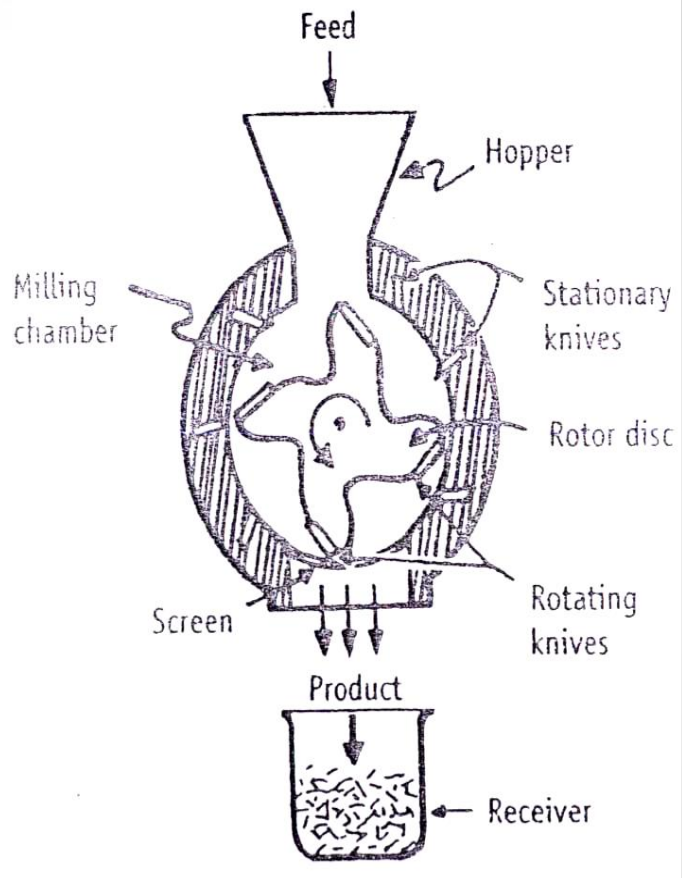
1. Cutting

- **Rotary cutter mill :**

Mechanism: it provide a successive cutting or shearing action rather than attrition or impact.

❑ **Construction:**

- Cutter mill has two type of knives
  – Stationary & Rotatory.
- Rotating knives: has a horizontal rotor disc with 2 to 12 knives spaced uniformly on its periphery, turning at high speed from 200 to 900 rpm.
- Several stationary knives are mounted horizontally in the cylindrical casing of the machine.



- The upper part has a hopper for the feed, and the bottom of the casing holds a detachable screen that controls the size of the material discharged from the milling zone.
- Reduced material is collected beneath the screen.

1. Cutting

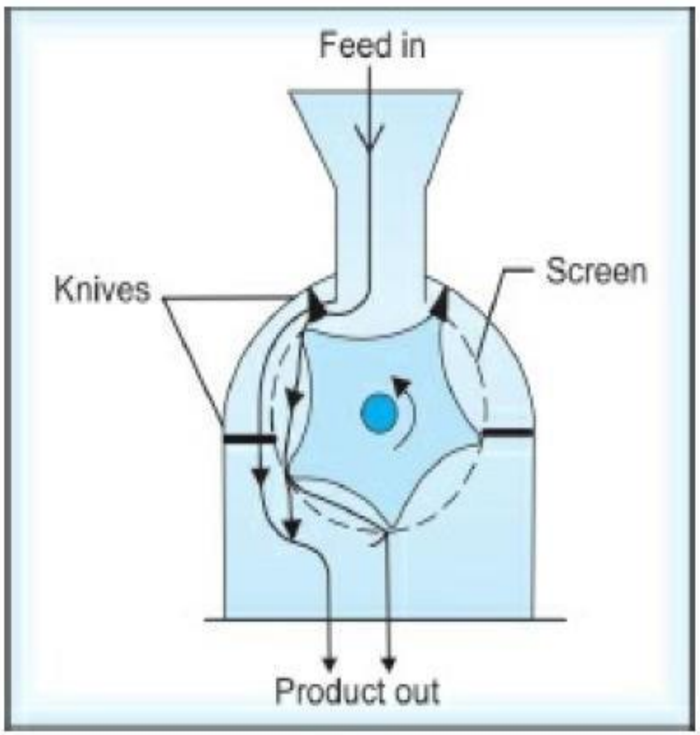
Rotary cutter mill:

❑ **Uses** :

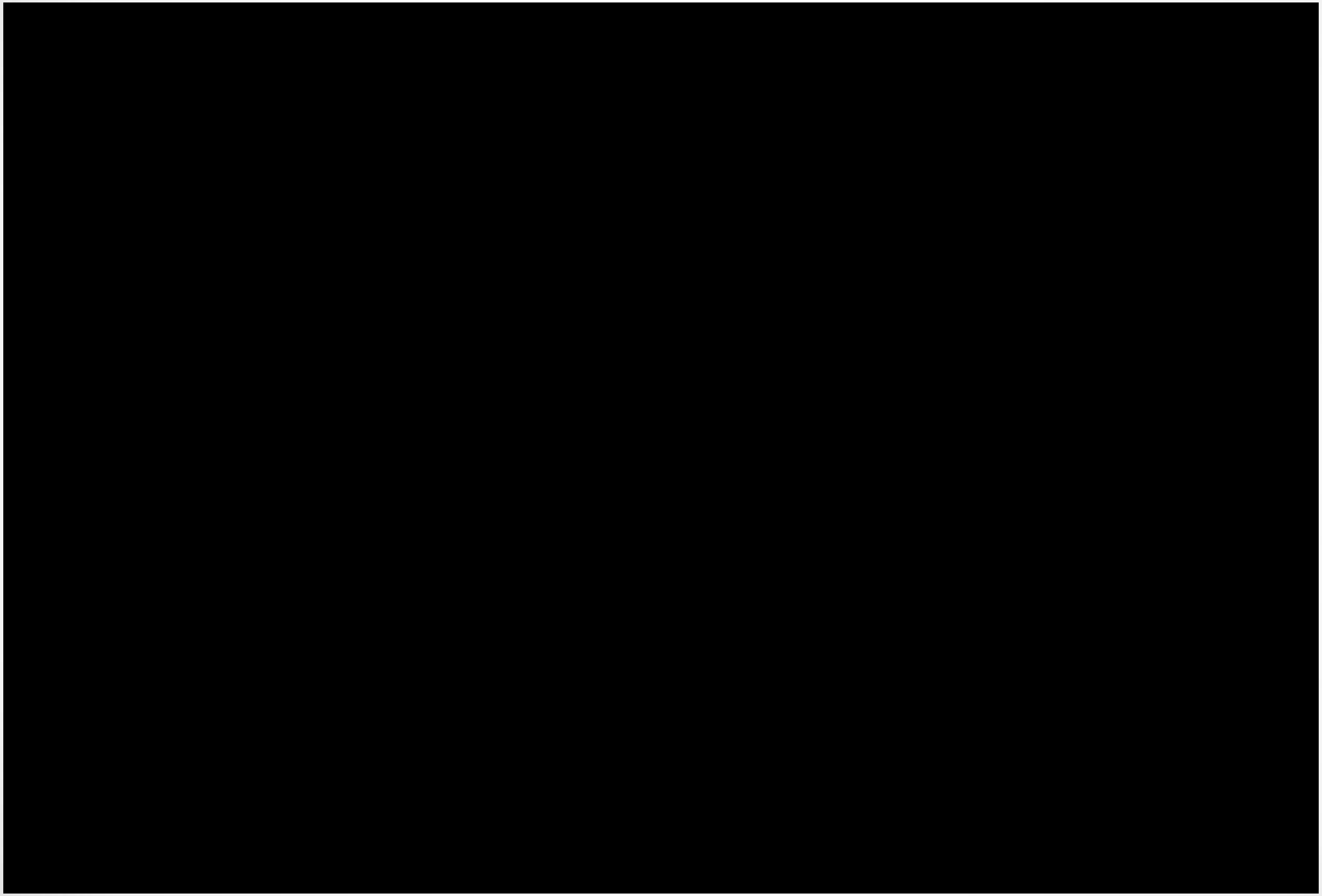
1. For coarse degree (20 – 80 #) of size reduction.
2. For tough صلبة, or fibrous ليفية, materials. Ex. Roots, Peels, Woods, other plant parts, animal tissue prior drug extraction.

N.B. The particle size and shapes are determined by:

- the rotor size,
- gap between the rotating & stationary knives
- opening of the sieve



1. Cutting



2. Compression

Roller mill :

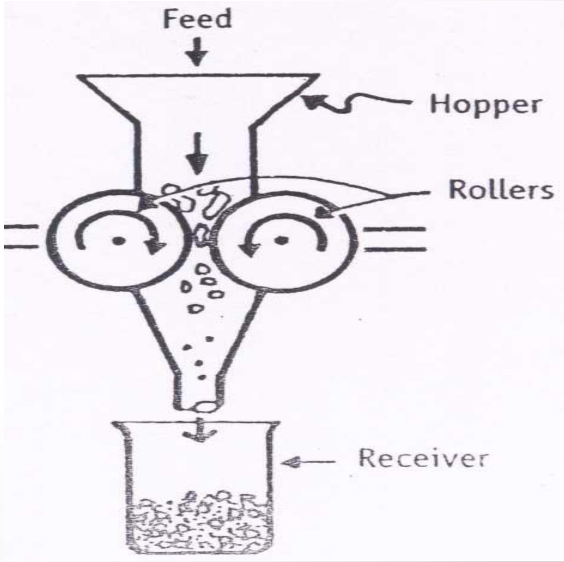
❑**Mechanism:** combination of compression and shearing action

- It consists of two to five smooth roller operating at different speed.

❑**Construction**:

❑it consists of two cylindrical rollers made of stone or metal mounted horizontally & rotate along their axis.

- One of the rolls is driven directly using a motor, while the second is rotated by friction (runs freely) as the material is drawn through the gap between the rolls.
- The gap between the rollers can be controlled to obtain the desired particle size.



2. Compression

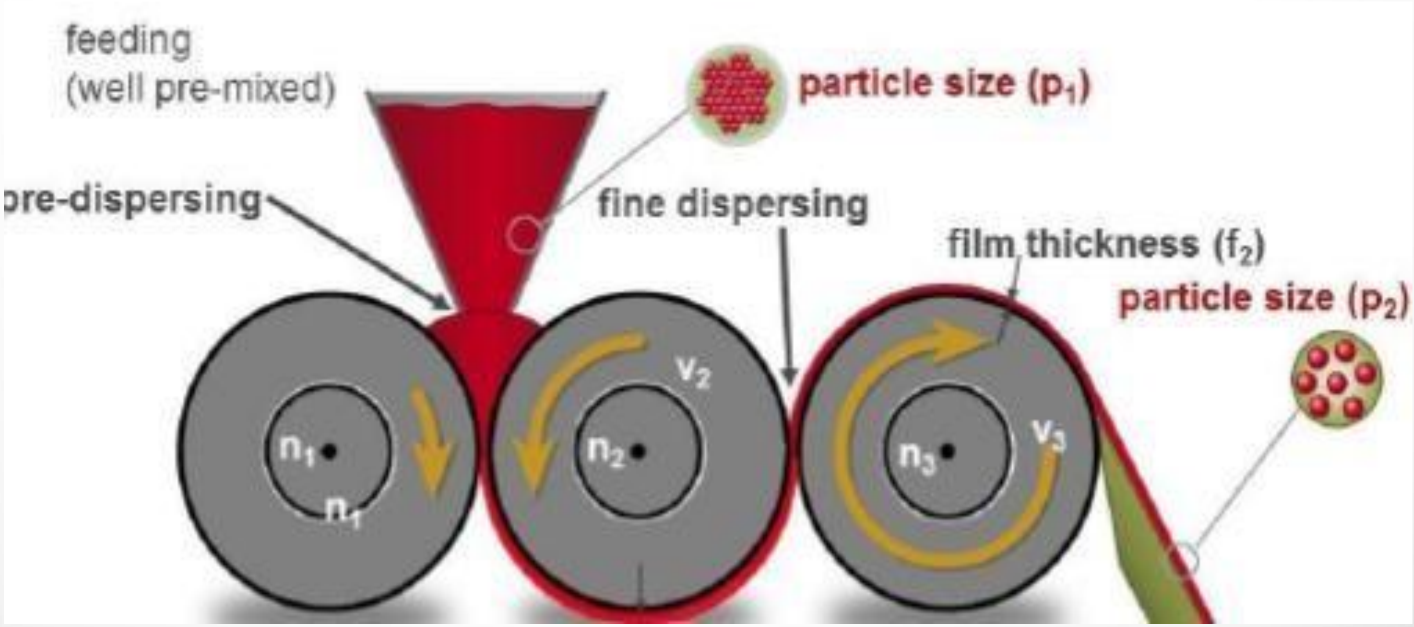
Roller mill :

APPLICATIONS: -

1. A form of roller mill used for milling ointments, pastes and suspension

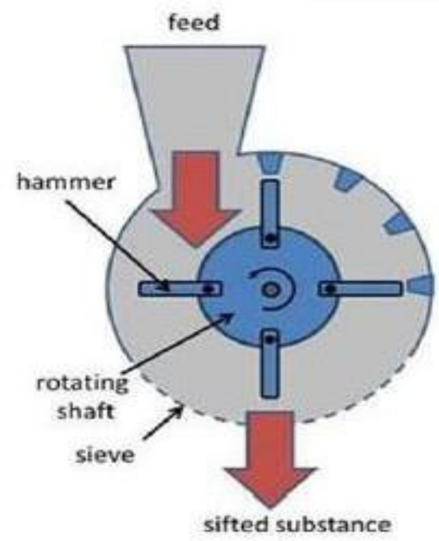
N.B.: where both rolls are driven but at different speeds, so that size reduction occurs by attrition.

- Particle size 20 – 200 mesh



3. IMPACT

Hammer mill :



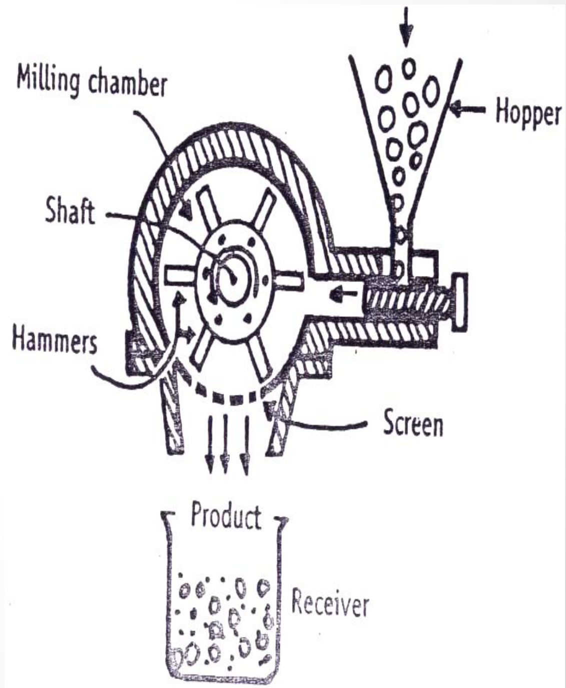
- ❑**Principle**: Impact
- ❑Intermediate crusher

  Feed P.S.:0.5-50 mm,

→ Product P.S.: 0.1-5 mm

❑**Construction**:

- Stout metal casing, with screen in the lower part, enclosing a central shaft to which several swinging hammers مطارق متأرجحة (four or more) are fixed with swivel joints بوصلات دوارة and fitted horizontally or vertically, is made of hardened steel.
- Hammers swing out to a radial position when shaft is rotated.
- Hammers blades can be flat edges or sharp edges or both on each side.



3. IMPACT

Hammer mill :

WORKING: -

- Material is fed at the top or center in the grinding zone, in which the hammers revolve at very high speed (up to 10,000 rpm).
- Material is thrown out centrifugally and is grinded by impact of hammers or against the plates around the periphery of mill 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 (< mesh size) to pass through the screen → are discharged almost as fast as they are formed
  - Oversize particles will be retained and recycled until they are small enough to pass through the screen that makes up the lower portion of the casing..

3. IMPACT

Hammer mill :

- The particle size that can be achieved will depend on (controlled by):
  - the type of milling tool selected (hammer type, size of mesh),
  - rotor speed (calculated as tip speed at the outermost rotating part),
  - solid density in the mill
  - or solid feed rate
- What are the important processing variables for hammer mills?
  - hammer tip speed طرف المطرقة
  - hammer mill screen size.

- From Figure (a),→ an increase in hammer tip speed → 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

- Figure (b) → 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

3. IMPACT

Hammer mill :

❑Applications.

- The hammer mill can be used for almost any type of size reduction.
- Its versatility تعدد استخداماته makes it popular in the pharmaceutical industry, where it is used to
  1. mill dry materials, and wet filter-press cakes,
  2. Mill ointments, and Slurries,
  3. Useful for preparation of wet granules for tablets and close control of the particle size of powders (more uniform than sieve granulation)

Advantages

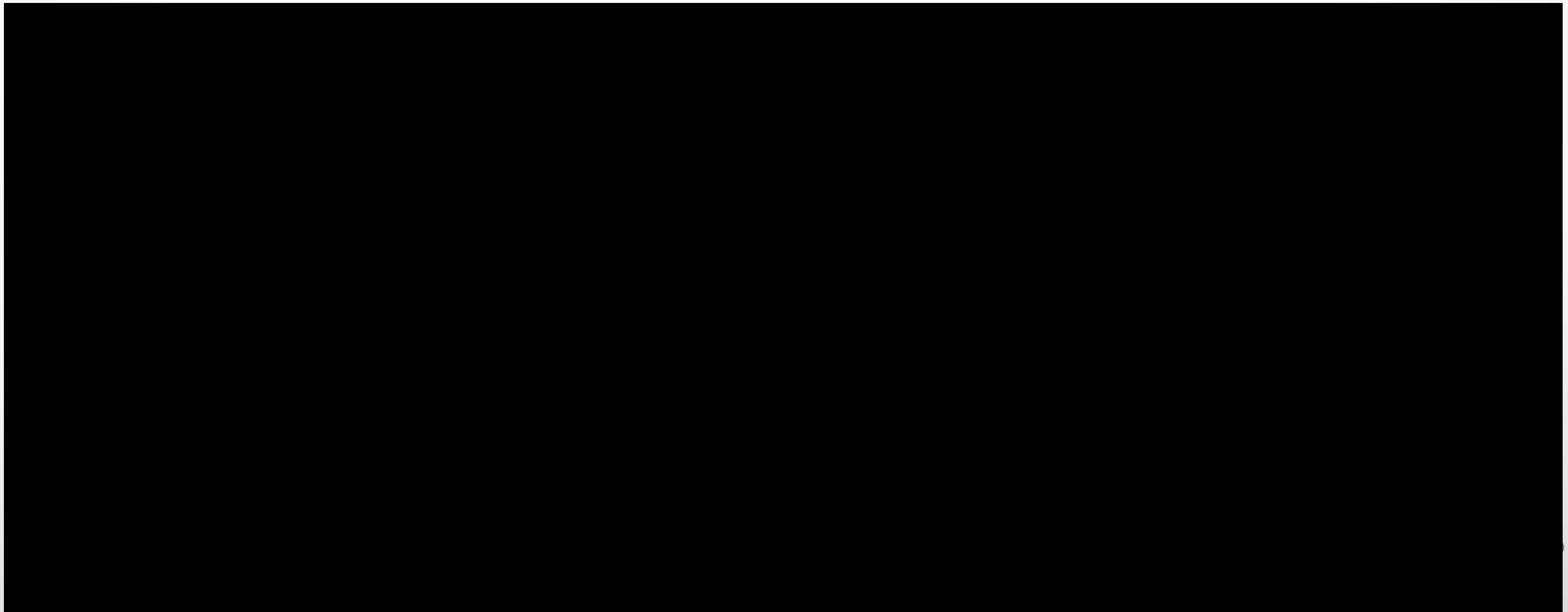
- Hammer mills are compact with a high capacity (i.e., occupies small space).
- Size reduction of 20 to 40 μm may be achieved
- It is simple to install (setup) and operate.
- The product can be easy controlled by variation of rotor speed and screen size
- They are easy to clean
- Operation is continuous and may be operated in a closed system, → to reduce dust and explosion hazards
- It produce narrow size distributions.

Disadvantages

- Sticky material cannot be grinded as it may, clogged the screens.
- Not useful for abrasive material
- More heat is generated, because of high speed of operation so it is not suitable for thermolabile material or drug containing gum, fat or resin.

3. IMPACT

- A hammer mill must be operated with internal or external classification to produce ultrafine particles
- Because inertial forces قوى القصور الذاتي 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 particular size fracture decrease 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

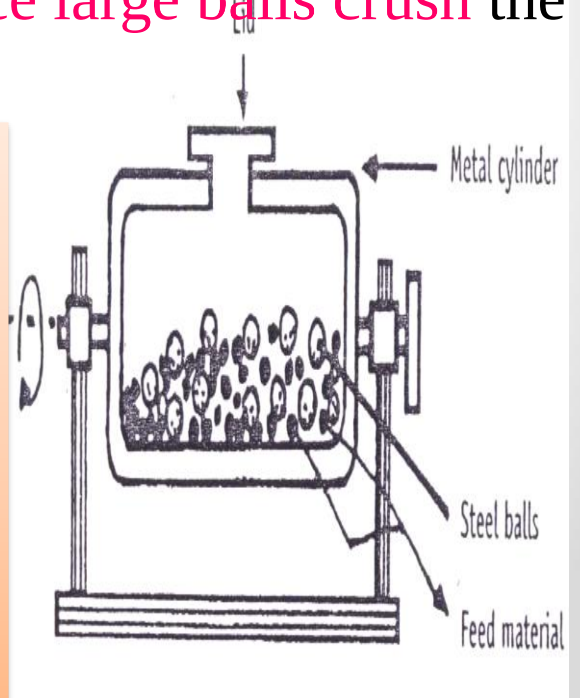


4. Combined Impact and Attrition

1. Ball mill (Fine crusher)

Construction:

- It 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" or "pebbles" of porcelain, steel, or stainless steel that act as grinding mediums, occupying 30 to 50% of the mill's volume.
- The ball size depend on the feed size and mill diameter
- Varying sizes of balls gives a better product, since large balls crush the feed & smaller ones give fine product.



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

1. Ball mill (Fine crusher)

❑Principle:

- Particles receive impact from balls and then subjected to attrition as the balls slide over each other.→→
  - i.e., at a slow speed, the balls roll and cascade over one another, → providing an attrition action
  - As the mill speed increases, the balls are carried up the sides of the mill and fall freely onto the material, → causing impact action, → most size reduction.

Advantages

1. It used for either wet or dry milling
2. It used for batch or continuous operation.
3. It is useful for grinding unstable or explosive materials by sealing them in an inert atmosphere.
4. Ball mills can be sterilized and sealed **for sterile milling** of ophthalmic and parenteral products.
5. Ball milling's installation, operating, and labor cost are low.
6. Ball mills are best (unsurpassed) for fine grinding of hard and **abrasive materials**.

Disadvantages

1. Noisy especial if casing is metal.
2. Slow process.
3. Tedious cleaning
4. high power consumption
5. Not suitable for soft & sticky materials

1. Ball mill (Fine crusher)

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

- **At low angular velocities,** → (Gravitational force exceeds frictional force)
  - The mass of balls will slide or roll over each other. Figure (1). → negligible amount of size reduction will occur
- **At high angular velocities,** (No Impact + Attrition), → Figure (2).
  - The centrifugal force becomes greater than the gravitational force and the balls will be thrown out to the mill wall (held at the mill walls without milling). → → no grinding occur.
- **At correct speed** → At about two-thirds of the critical angular velocity
  - where centrifuging occurs, → the ball are carried to the top of the mill then fall in cascade across the diameter of the mill → The maximum size reduction will take place, Figure (3).

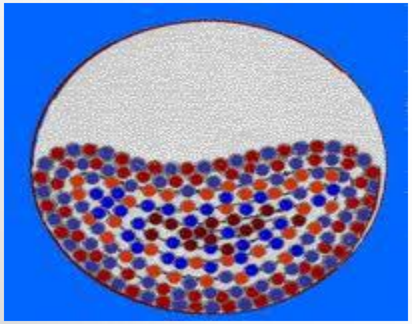


Fig. 1:. Low speed

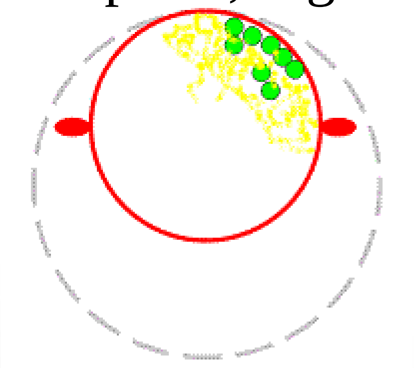


Fig. 2:. High speed

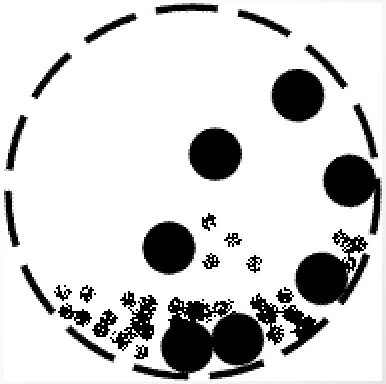
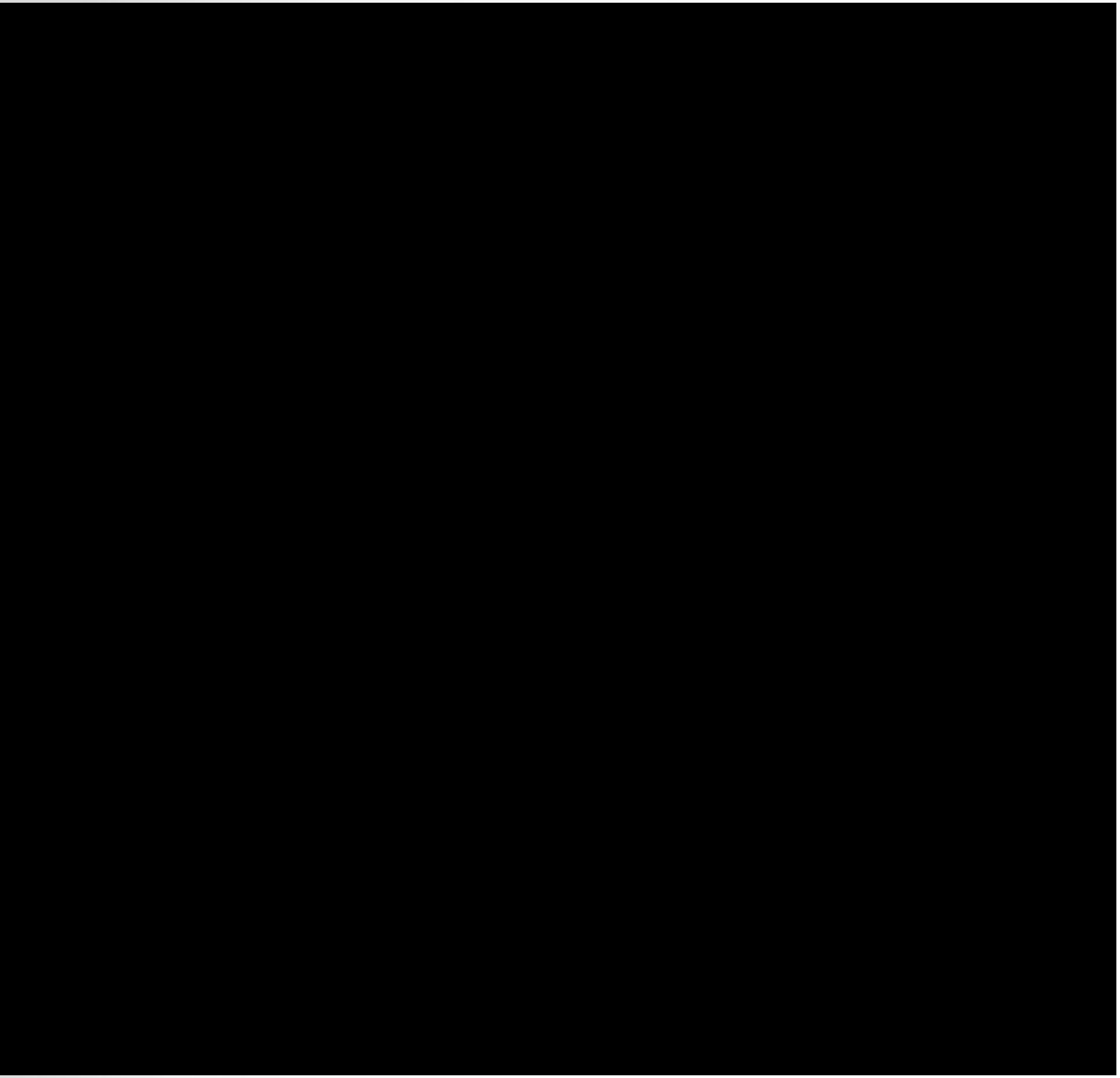
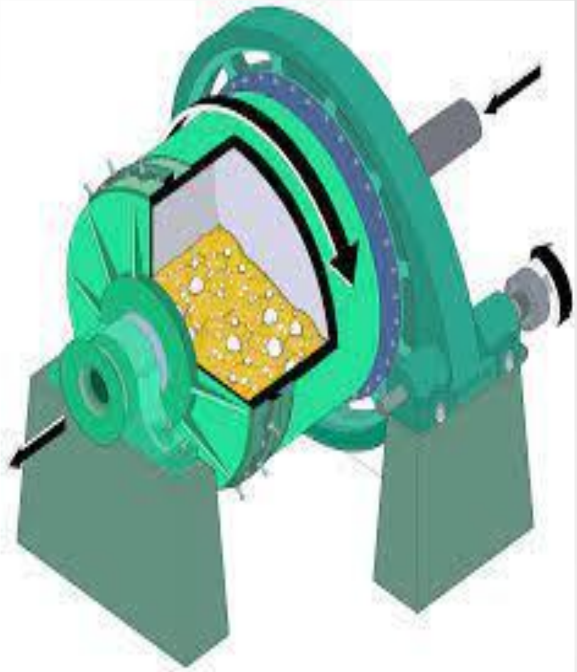


Fig. 3 :. Correct speed



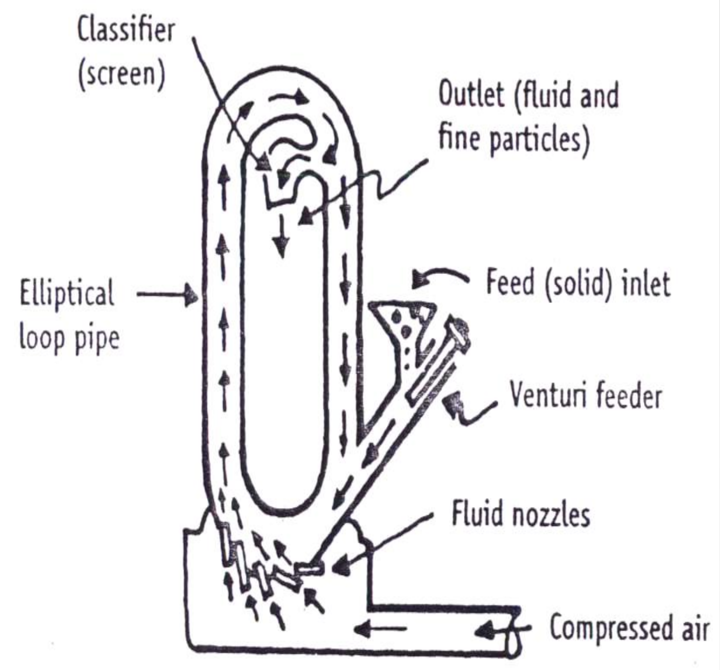


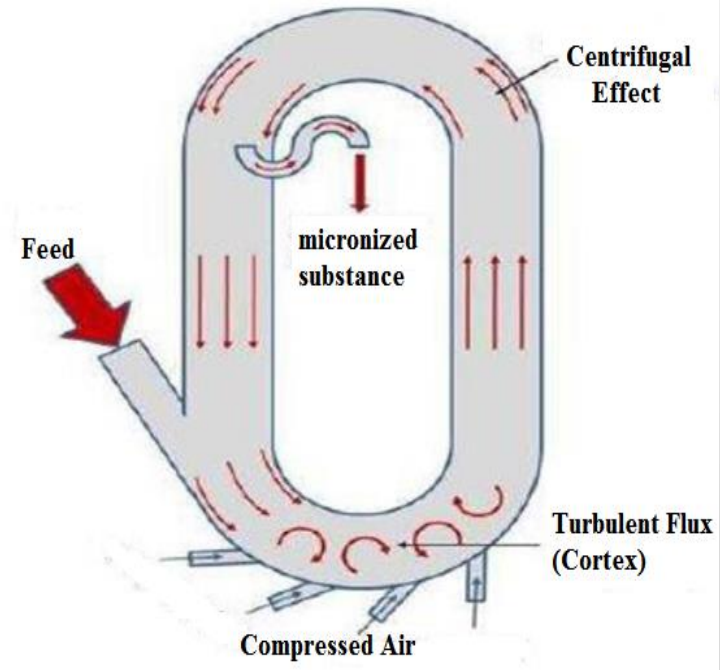
II. Fluid energy mill

❑ **Principle**: Impact & inter-particulate attrition between rapidly moving particles

❑ **Construction**:

- It consist of a loop of pipe (elliptical بيضاوي tube) of 2 m height and 20 to 200 mm diameter.
- 2 to 6 grinding nozzles are present at the bottom of the loop.
- A fluid is usually compressed air, because most pharmaceuticals have a low melting point or are thermolabile.
- There is an internal classifier too, by which finer & lighter particles are discharged and heavier particles are retained until reduction to small size.





II. Fluid energy mill (micronizer)

❑Working

- Material is fed near the bottom of the mill.
- The material is suspended and conveyed at high velocity by air or steam, which is passed through nozzles at pressures of 100 to 150 pound per square inch (psi).
- The violent turbulence of the air and steam → reduces the particle size mostly by inter-particulate attrition.

What are the most important machine-related factors?

- The grinding chamber geometry
- The number and angle of the nozzles.
- in selecting it, → The cost of a fluid-energy source and dust collection equipment must be considered.
- The cost of the mill

II. Fluid energy mill

Advantages

1. This technique allows the rapid production of the smallest particle < a few µm (1-20 micron)..
2. The expansion of gases at the orifice leads to a cooling effect that counteracts the heat generated by milling, making it useful for thermolabile pharmaceuticals such as vitamins, antibiotics, enzymes, and hormones.
3. The classifier, permits close control of the particle size there by narrow size distribution.
4. Because of the high value of the materials processed in the pharmaceutical industry, high capital and running costs may not be a so serious

Disadvantages

1. High cost.
2. Premilling is required (~ to 20-100 mesh) to facilitate milling
3. This type of mill could build-up of compressed products in the mill. This can change milled particle size by changing the mill's open volume or classifier's open area, especially if the classifier vanes or gas nozzles are blocked.

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
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).

General characteristics of various types of mills

Type of mill	Action	Product size	Used for	Not used for
Cutter	Cutting	20-80 mesh	Fibrous, crude animal and vegetable drugs	Friable material
Hammer	Impact	24-325 mesh	Almost all drugs	Abrasive material
Roller	Pressure	20-200 mesh	Soft material	Abrasive material
Fluid energy	Attrition and impact	1-3 0micro	Moderately hard and friable material	Soft and sticky material
Ball mill	Attrition and impact		Fine grinding of abrasive material	Soft material


THANK YOU!