Particle Size Reduction

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Particle Size Reduction

- Other terms used to describe the operation: milling, grinding, crushing, chopping, comminution, micronizing.

- Most materials used in pharmaceuticals must be milled at some stage during the production of raw material or dosage form

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Particle Size Reduction

- ***Objectives of particle size reduction:***
  1. Facilitating drug release (dissolution rate)
  2. Exposing cells prior to extraction
  3. Reducing the bulk volume of material
  4. Facilitating drying
  5. Helping good mixing
  6. Increasing adsorption capacity
  7. Some excipients need to be in very fine powder to do well their function (lubricants, colors)

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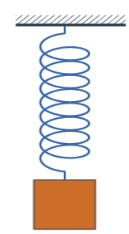
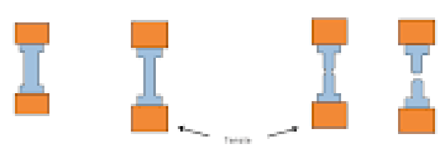
Theory of Size Reduction



Fracture mechanics

- Reduction of the particle size requires application of mechanical stress to the material.
- Materials respond to stress by <u>**yielding**</u>, with consequent generation of <u>strain</u>.
- **Hooke's law.**

- **Stress**: force
- **Strain**: deformation or elongation of a solid body due to applying a strs/force
- **Elastic**: reversible
- **Plastic**: permanent , irreversible



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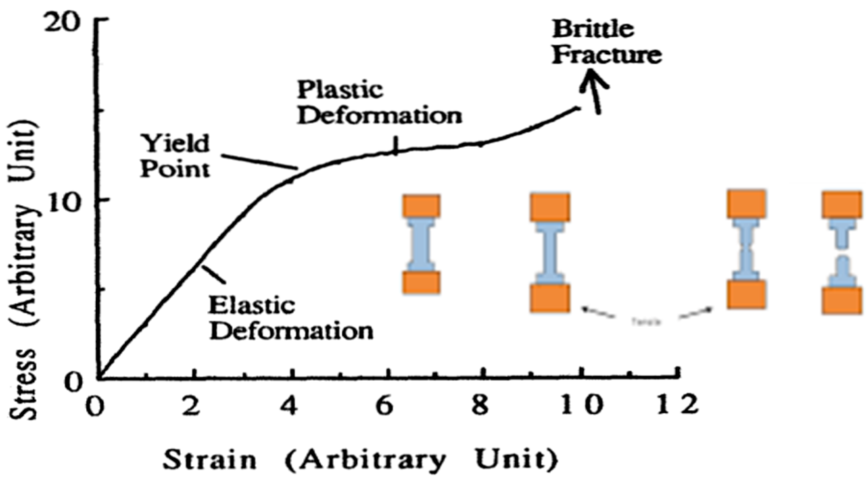

Fig. 19.1 Stress–strain diagram for a solid.

the yield point is the point on a stress-strain curve that indicates the limit of elastic behavior and the beginning of plastic behavior

Theory of Size Reduction

Fracture mechanics

- The initial portion of the stress-strain diagram is linear and is defined by Hooke's law.
- In this portion the deformation is reversible (elastic deformation), i.e. the particle retains its shape if the stress is removed.
- After a certain point (yield point) the relation becomes nonlinear and the deformation becomes irreversible (plastic deformation).

Theory of Size Reduction

Fracture mechanics

<u>Crack propagation</u>

- Size reduction begins with the opening of any small cracks that were initially present.
- Flaws (defect)
- Larger particles fracture more readily than small particles as they contain more cracks.

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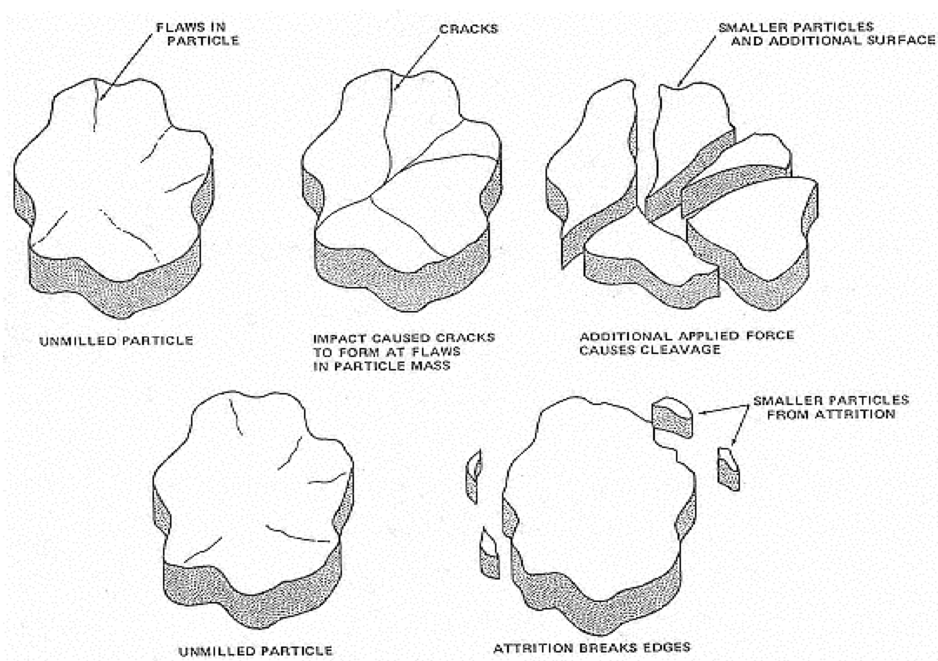

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Influence of material properties on size reduction

Surface hardness **(*Mohs' scale*)**

- The hardness of material can be described qualitatively by its position in Mohs' scale.
  - Materials from 1-3 are described as soft
  - Materials from 8-10 are described as hard
- Hardness is related to abrasiveness.
- Hard materials may cause abrasion to the mill.

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Influence of material properties on size reduction

Material structure

- **Crystalline materials** fracture along crystal cleavage planes; noncrystalline materials fracture at random.

- ***Fibrous materials*** (e.g. crude drugs) need cutting or chopping action and can not be milled effectively by compression or impact.

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Influence of material properties on size reduction

Moisture content

- The presence of more than 5% water hinders comminution and often produces a sticky mass upon milling.

Stickiness

- Sticky materials may adhere to the surface of milling machine or the screen
- This is a problem of gummy and resinous materials.

Toxicity and harm
Potential of explosion (fine)

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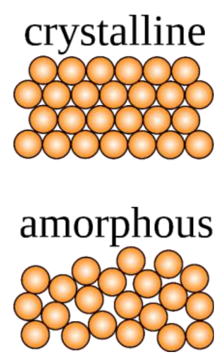
Effect of size reduction on material properties

Milling of material may lead to:

1. Change of the polymorphic form
2. Dehydration of hydrates
3. Development of amorphous structure
4. Damage of thermolabile drugs due to heat involved.
5. Development of free static charge



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Energy requirements

The most efficient mills utilize as little as 2% of the energy input to fracture particles.

- The rest of energy is lost in:
  1. elastic deformation of unfractured particles
  2. transport of materials within the milling chamber
  3. friction between particles
  4. friction between particles and mill
  5. heat
  6. vibration and noise

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Energy requirements

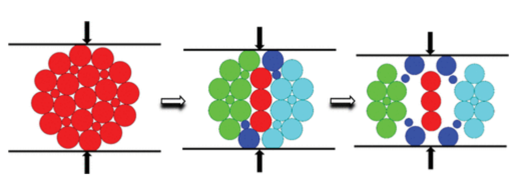
Rittinger's theory

$$E = K_R(S_n - S_i)$$

S_i : the initial surface area,

S_n : new surface area

K_R = Rittinger's constant of energy per unit area



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Energy requirements

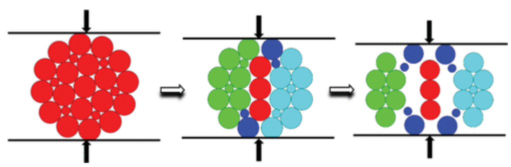
Kick's theory

$$E = K_K \log \frac{d_i}{d_n}$$

d_i : the initial particle diameter,

d_n : new particle diameter

K_K = Kick's constant of energy per unit mass



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Energy requirements

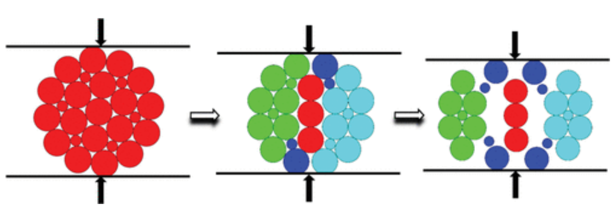
Bond's theory

$$E = 2k_B \left[\frac{1}{d_n} - \frac{1}{d_i} \right]$$

K_B : Bond's work index,

d_i : the initial particle diameter,

d_n : new particle diameter



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Influence of milling on size distribution

- As milling progresses, the mean particle size decreases, and a material with initially a monomodal size distribution develops a bimodal size distribution.
- The primary component gradually decreases in weight and the secondary component increases in weight.
- Continued milling tends to eliminate the primary component to give a positively skewed (log normal) distribution with narrow size range.
- Milling rate follows first order kinetics

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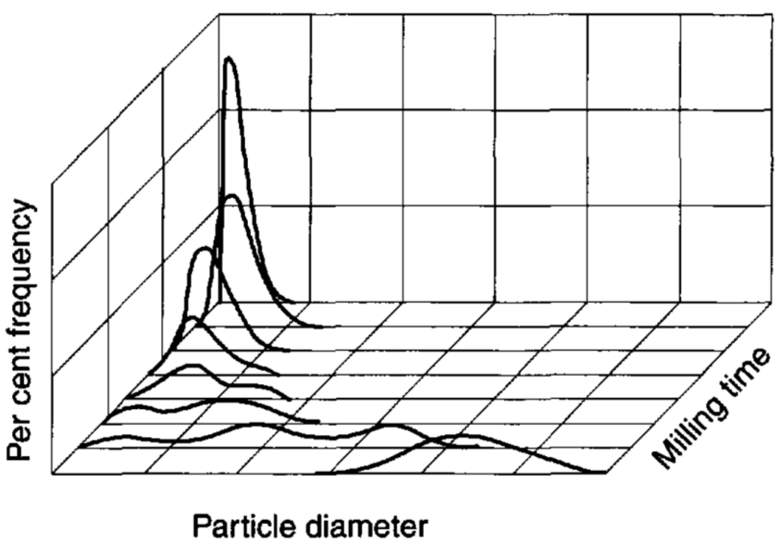

Fig. 11.2 Changes in particle size distributions with increased milling time.

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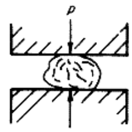
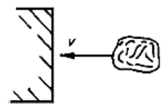
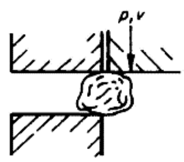
Mechanisms of size reduction

Force	Schematic diagram	Principle	Example of equipment
Compressive		Nutcracker	Crushing rolls
Impact		Hammer	Hammer mill
Attrition		File	Disc attrition mill
Cut		Scissors	Rotary knife cutter

Mechanisms of size reduction

- There are four different mechanisms of size reduction:

a) <u>Cutting</u>

The material (particle) is cut by means of sharp blades or knives.

b) <u>Compression</u>

The particle is crushed by application of pressure.

Mechanisms of size reduction

c) Impact

The particle is hit by an object moving at high speed, or a moving object strikes a stationary surface.

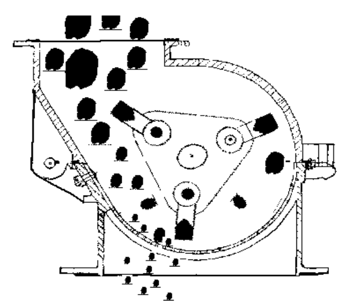
D) Attrition

This involves breaking down of the material by rubbing between two surfaces that are moving relative (**parallel**) to each other.

Size reduction methods

A mill consists of three basic parts:

1) Feed chute
2) Grinding part
3) Discharge chute



- The manner (way and rate) in which an operator feeds a mill affects the product.
- In most cases the grinding effect is a combination of different mechanisms.

Size reduction methods

- There are two ways of feeding: choke feeding and free feeding.
- In open-circuit milling, the operation is carried out so that the material is reduced to a certain size by passing it once through the mill.
- In closed-circuit milling, the discharge from the milling is passed through a classifier and the over-size particles are returned to the grinding chamber.
- closed-circuit milling is most valuable in reduction to fine and ultrafine size.

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Cutting methods

- Cutter mill
  - Principle of operation: It consists of a feed, a series of knives attached to a rotor which act against a series of knives attached to the mill casing, and a screen fitted in the base which control the particle size.
  - **Uses**:
    - Coarse degree of size reduction of dried granulations
    - Grinding of crude drugs such as roots and barks before extraction

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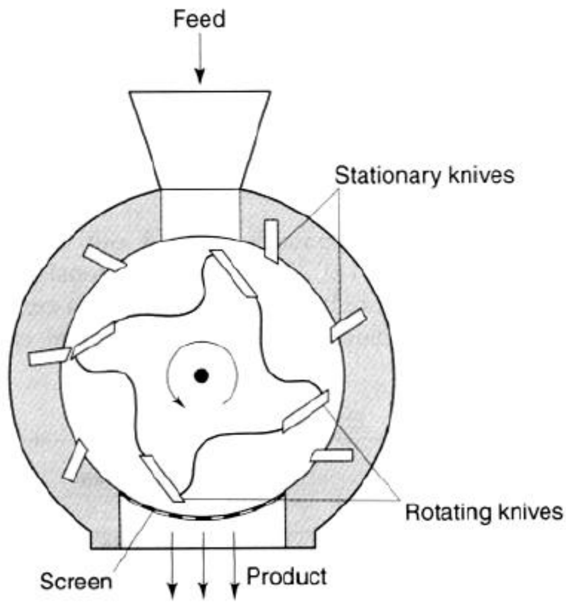

Fig. 11.6 Cutter mill.

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Compression methods

- Size reduction by compression can be carried out on a small scale by pestle and mortar.
- End runner and edge runner mills are mechanized forms of mortar and pestle-type compression.

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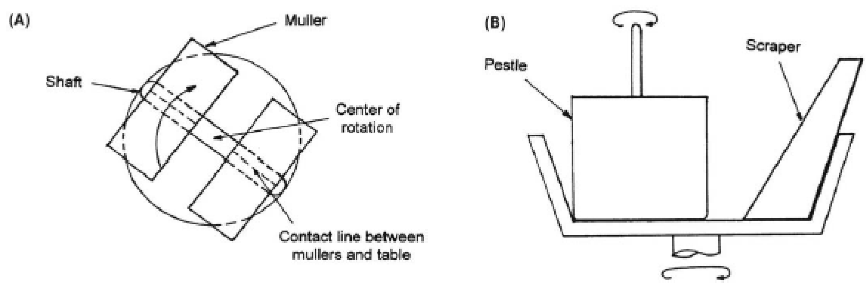


FIGURE 12.3 (A) Edge runner mill and (B) end runner mill.

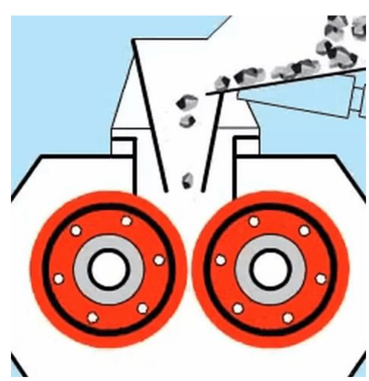
Compression methods

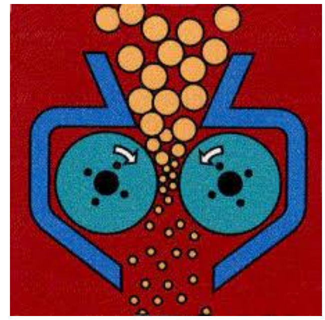
Roller mills

– Roller mills use two cylindrical rolls, mounted horizontally, and rotating about their longitudinal axis

– One of the rolls is driven directly while the second is rotated by friction as material is drawn through the gap between the rolls.

– Compression and attrition





Roller mill (compression method)

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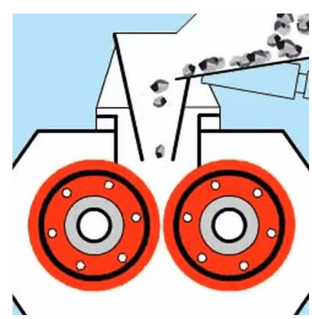
Compression methods

<u>Roller mills</u>

– The *<u>gap</u>* between the rolls can be adjusted to control the degree of size reduction.

– Roller mills are used for <u>crushing</u> such as cracking seeds prior to extraction.

– This form should not be confused with the type used for milling ointments and pastes where both rolls are driven but at different speeds, so that size reduction occurs by <u>attrition</u>.



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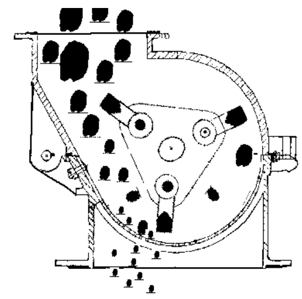
Impact methods

- <u>Hammer mills</u>
  - –Principle of operation:
    - •It consists of a strong metal case enclosing a central shaft , to which a series of four or more hammers are attached.
    - •The material is ground by impact of the hammer or against the plates around the periphery casing.
    - •The material is <u>retained until</u> it is small enough to pass through the screen that forms the lower portion of the casing.



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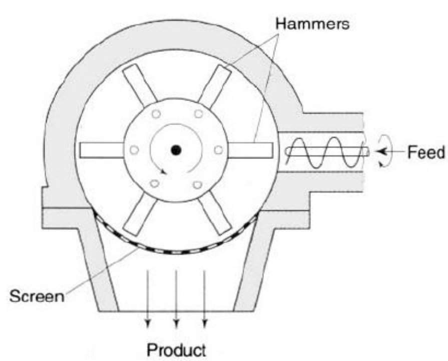

Fig. 11.9 Hammer mill.

Hammer mill

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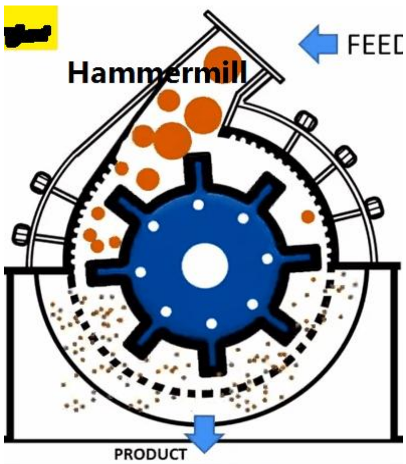
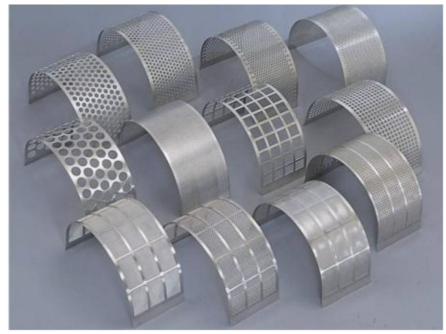
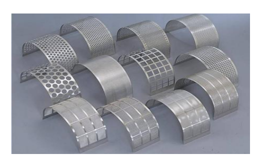




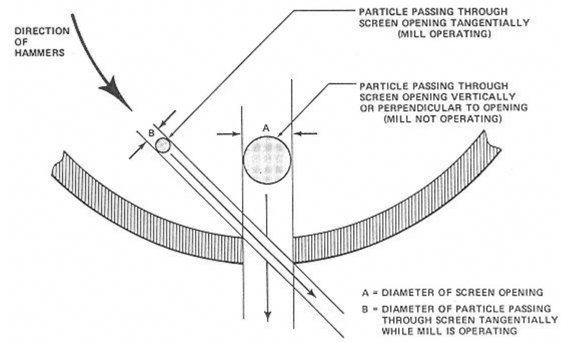
Screens for hammer mill

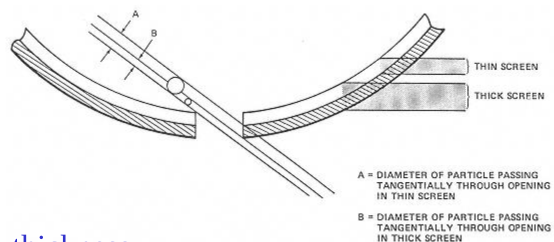
Impact methods

- Hammer mills
  - Various shapes of hammers may be used.
  - The rate of feed must be controlled.
  - The speed of hammer is crucial. Low speed gives mixing rather than grinding while with higher speed, no enough time for the material to fall in the screen.
  - Thickness of screen affects the size of product



Effect of exiting particle angle through mill screen on exiting particle size.





Effect of mill screen thickness on exiting particle size.

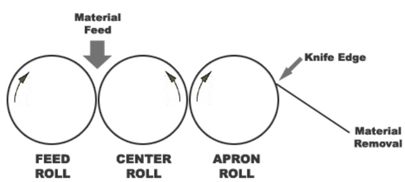
Impact methods

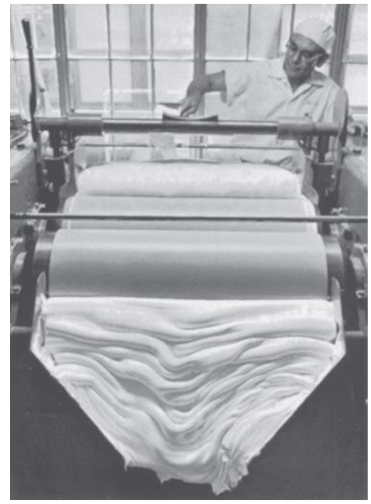
- Hammer mills
  – ***Advantages***:
    1. Rapid in action.
    2. Can be used almost for any type of milling (dry material, ointments and slurries).
    3. The size of product can be controlled by controlling the rotor speed, type and number of hammers, and screen size and thickness.

Attrition methods

Roller mills

- Principle of operation :
  - Roller mills use the principle of attrition for milling solids in suspensions, pastes or ointments.
  - Two or three porcelain or metal rolls are mounted horizontally with an adjustable gap, and rotate at different speed so that the material is sheared as it passes through the gap.





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Attrition methods

Colloid Mills

- Colloid mills are a group of machines used for wet grinding dispersion, and preparation of emulsions.
- They operate by shearing relatively thin layers of material between two surfaces, one of which (rotor) is moving at a high angular velocity relative to the other (stator).
- The clearance is adjustable from virtually zero upward.
- The rotor is rotated at several thousand revolutions per minute, and the slurry of already fine material passes through the clearance under the action of centrifugal forces.
- Although very fine dispersions can be produced, they are not, as the name implies, of colloidal dimensions.

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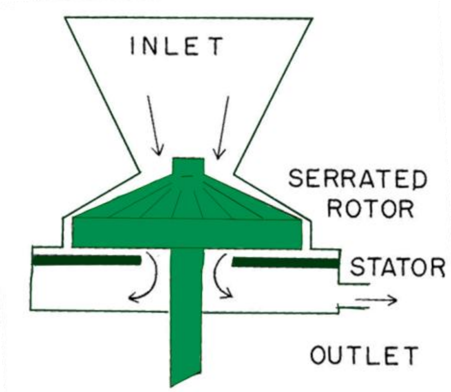


FIG. 2-15. *Colloid mill with a rotor and stator with a narrow clearance that may be adjusted.*

The clearance is adjustable from virtually zero upward.

Combined impact and attrition methods

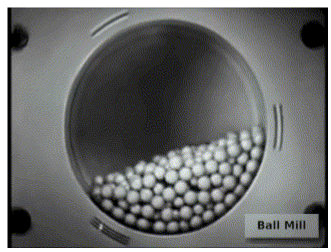
<u>Ball mills</u>

- ***Principle of operation***
  - Ball mills consist of a hollow cylinder mounted such that it can be rotated on its horizontal longitudinal axis.
  - Their size range from laboratory to industrial (Cylinder can be greater that 3 m).
  - The cylinder contain balls that occupy 30 – 50 % of the total volume.

Combined impact and attrition methods

Ball mills

- ***Principle of operation***
  - Ball size depends on feed and mill size.
  - Balls with different diameter help to improve the product as the large balls tend to breakdown the coarse feed materials and the smaller balls help to form the fine product by reducing void spaces between balls.



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Combined impact and attrition methods

Ball mills

- The amount of material in the mill and the speed of rotation are very important factors.
- Too much feeding produces a cushioning effect and too little causes loss of efficiency and abrasion of the mill.
- At high speed, the balls are thrown out onto the mill wall by centrifugal forces, where at low speed the balls slide over each other with negligible amount of size reduction.

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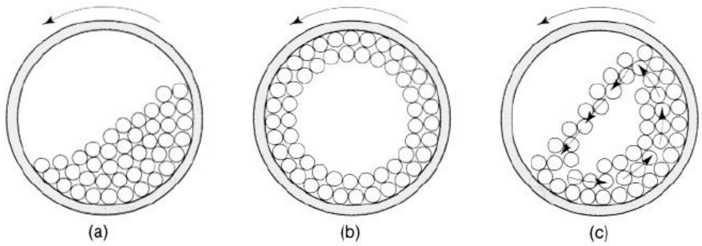

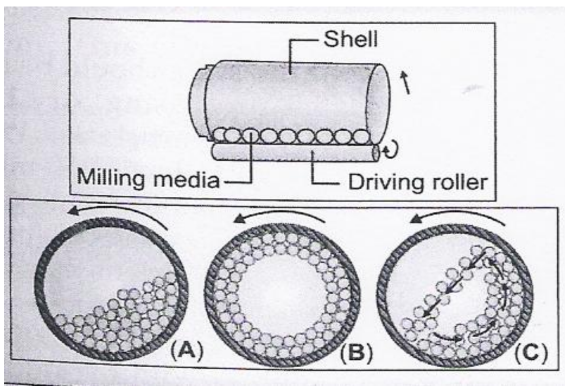

(A)Sliding at low speed,
(B) Centrifuging at high speed,
(C) Cascading at optimum speed.

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Combined impact and attrition methods

- <u>Vibration mills</u>
  - Principle of operation
    - The vibration mills are filled to about 80% total volume with porcelain or steel balls.
    - During milling the whole body of the mill is vibrated and size reduction occurs by repeated impactions.
    - Comminuted particles fall through a screen at the base of mill.

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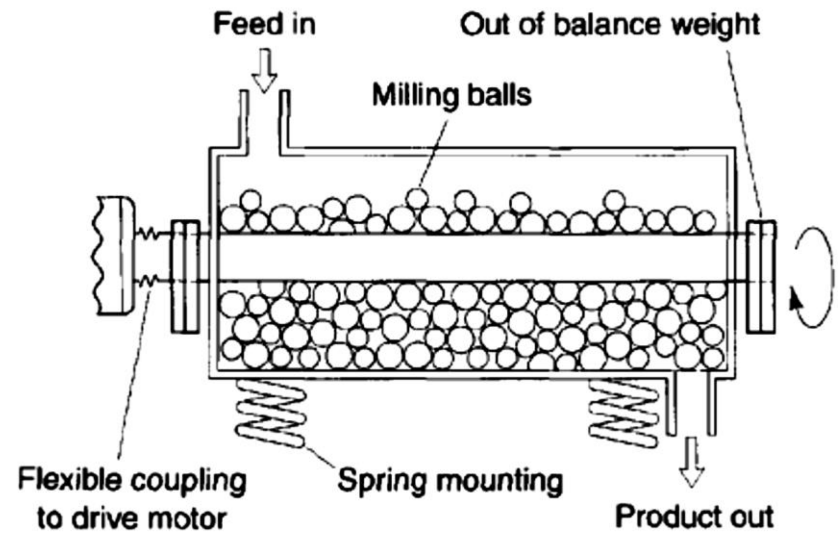

Fig. 11.10 Vibration mill.

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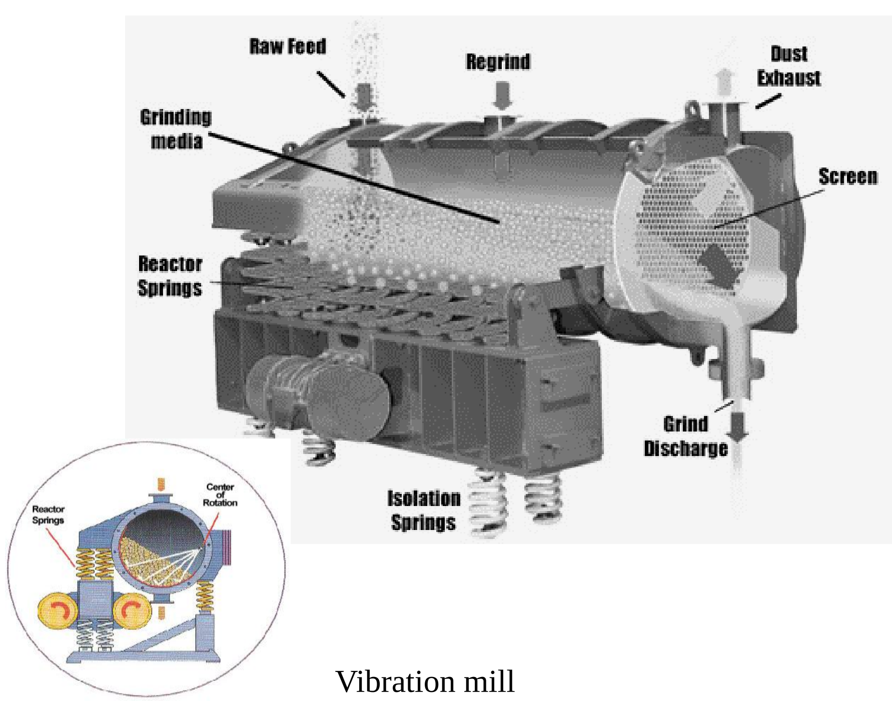

Vibration mill

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Combined impact and attrition methods

- Fluid energy mill
  - A typical form of this mill consists of a hollow toroid (loop) which has a diameter of 20 – 200 mm depending on the height of the loop which may be up to 2 m.
  - A fluid, usually air, is injected at high pressure through nozzle at the bottom of the loop, resulting in a high velocity circulation in a very turbulent manner.

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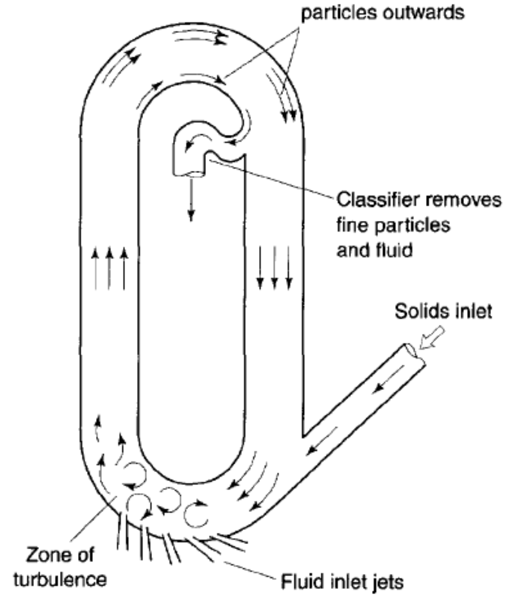

Fig. 11.14 Fluid energy mill.

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Combined impact and attrition methods

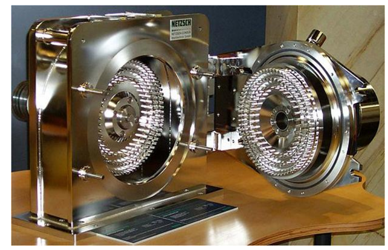
- Fluid energy mill
  - The high kinetic energy of the air causes impact and some attrition forces to occur between the introduced particles which result in size reduction.
  - If fine powder is intended, the feed should be pre-milled to about 150 – 840 μm.
  - A classifier is incorporated so that particles are retained until sufficiently fine.

Combined impact and attrition methods

- Fluid energy mill
  - Advantages:
    1. Suitable for fine powder.
    2. Expansion of gases at the nozzle leads to cooling effect. This counteract the frictional heat, which may affect heat sensitive materials.

Combined impact and attrition methods

- Pin mill
  - Principle of operation
    - It consists of two disks with closely spaced pins rotate against one another at high speed.
    - Particle size reduction occurs by impaction with pins and by attrition between pins as the particles travel outwards under influence of centrifugal force.



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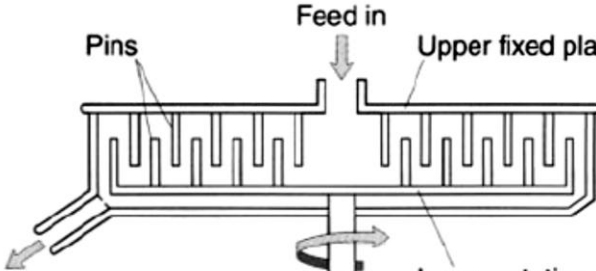
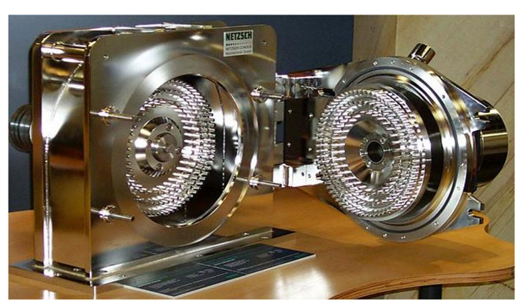


Fig. 11.15 Pin mill.



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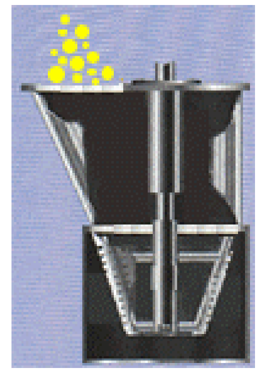
Conical screen mill

- The conical mill operates by having the product being fed into the mill by gravity or vacuum.
- A rotating impeller forces the material outward to a conical screen surface, where it is sized and passed through the openings in the screen.
- The particles are subjected to impaction, attrition and compression.



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Conical screen mill

- Conical mills come in a variety of sizes from tabletop lab models to full-size high-capacity machines for use in processing large quantities of material, and the impeller and screen can be customized for each individual use.

- The machines can be used not only to reduce the size of particles, but also for deagglomeration, sieving, dispersion, and mixing.

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Conical screen mill

- The <u>applications</u> for a conical mill in pharmaceutical industry include:
  - Reclaiming broken pharmaceutical tablets by grinding them back into powder for re-forming.
  - Sizing wet granulated particles before drying, and sizing dry granulated particles after they've dried before tabletting.

- The conical mill has some marked advantages over the hammer mill:
  1. low noise, heat and dust
  2. a more uniform particle size
  3. flexibility to mill wet and dry material
  4. higher capacity

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Conical screen mill

<u>Critical milling factors</u>

A. Impeller type
B. Screen type
C. Impeller/screen gap
D. Velocity
E. Feed and discharge condition

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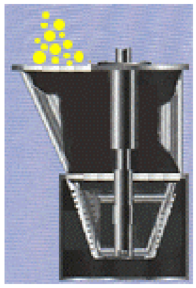
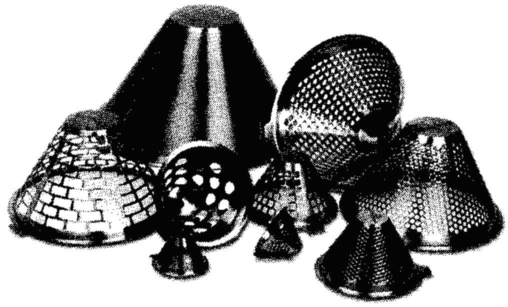


Conical mill



Examples of conical screens

Examples of conical mill impellers

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Wet and dry milling

- The choice of dry or wet milling depends on the use of the product and its subsequent processing.

- If the product undergoes physical or chemical interaction with water, dry milling is recommended.

- Wet milling eliminates dust hazards and is beneficial to grind to lower size limits than dry milling.

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Inert milling

- Under inert gas (nitrogen)
- For explosive, combustible and oxidizable products

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Cryogenic milling

- Milling under low temperature
- Uses liquid nitrogen or carbon dioxide.
- Applications:
  - to enhance milling for soft, elastic and low-melting point materials by freezing them and making them brittle.
  - for milling of heat sensitive products

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Selection of particle size reduction method

The selection of a size reduction method depends on:

1) Material properties

- Hardness
- Structure (Cutter mill for fibrous materials)
- Toxicity (Closed mills like ball mill)
- Explosion (wet grinding or use inert gas)

2) Properties of final product

- Degree of size reduction
- Shape (Attrition methods give spheroidal particles with better flow properties)

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Selection of particle size reduction method

Size required	**example of mill**
Very coarse powder product (>1000 µm)	Cutter mill, Conical mill, Roller mills Hammer mills
coarse powder product (50-1000 µm)	Ball mills, Conical mill, Cutter mill, Hammer mills, Pin mill, Roller mills, Vibration mills
Fine powder product (< 50 µm)	Ball mills, Colloid mill, Fluid energy mill, Pin mill, Vibration mills

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Selection of particle size reduction method

The selection of a size reduction method depends on:

3) Need for dust control

- Use closed mills (e.g. costly or toxic material)

4) **Sanitation**

- Ease of cleaning, sterilization
- For milling of sterile material the mill should be totally isolated (e.g. Ball mill).

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Selection of particle size reduction method

The selection of a size reduction method depends on:

5) Capacity of the mill and production rate requirements

6) Economical factors

- Cost
- Power consumption
- Space occupied

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