Semister - III Pharmaceutics

Subject: Advanced pharmaceutics

UNIT - I

Size Reduction:

It is the process of Reducing the particle size of a substance (or) a compound into finer state

- It is also called as Comminution / Grinding / pulverisation

If particle size is reduced manually - Manual Size Reduction

" " " mechanically - milling

↓

Different types of mills are used based on the substance to be reduced

- Different types of processes are used for size reduction Eg: cutting, chopping, Crushing, Grinding, Milling, Trituration (depending upon Type of equipment)

- The selection of equipment depends on.

- ✓ physical properties of material to be reduced
- ✓ Initial particle size
- ✓ Degree of size Reduction

Objectives of Size Reduction

1) Size reduction increases the surface area
2) To increase the absorption of substances/pharmaceuticals " "
3) To enhance the solubility " " "
4) To increase the bioavailability " " "
5) To enhance the therapeutic effectiveness of compound
6) To increase the stability of the substance
7) To increase/enhance the physical appearance i.e, Colour texture and taste etc.
8) To enhance the rate of drying

Factors Affecting Size Reduction:

Following factors should be taken into consideration while reducing the particle size:

(1) Physical properties of drugs:
It includes Hardness, Toughness & Moisture Content

a) Hardness: It affects the process of size Reduction It is easier to break soft material to small size than hard material.

b) Toughness: Crude drugs of fibrous nature / ↑ Moisture Content drugs are tough in nature. It is difficult to break soft but tough material, than a hard but brittle substance.

c) Moisture Content: The presence of moisture affects many physical properties which in turn affects size reduction The material should be either wet (or) dry. It should not be damp.

(2) Melting point & softening point

↓

Due to the heat generated during mechanical size reduction, most of the thermolabile substances tend to stick with each other, which affects with size reduction

↓

Waxy substances/drugs containing oil/fat becomes soft during size reduction, if heat is generated

(3) The size of starting material:
The ratio of feed size to product size is very important If the size of original drugs is too large it may be difficult to reduce the size of the powder. Hence, they can be reduced in several stages. Eg: preliminary crushing, followed by coarse powders and then fine Grinding.

④ Purity:
Due to the wear and tear of the various equipments used for size reduction, there will be impurities in powder. So, the mills before size reduction to avoid contamination, should be thoroughly cleansed.

⑤ physiological Effect: Some drugs are very potent and may be harmful. During particle size of those substances, there may be some effect to the person operating the mill. In those cases enclosed mill/closed mill can be used.

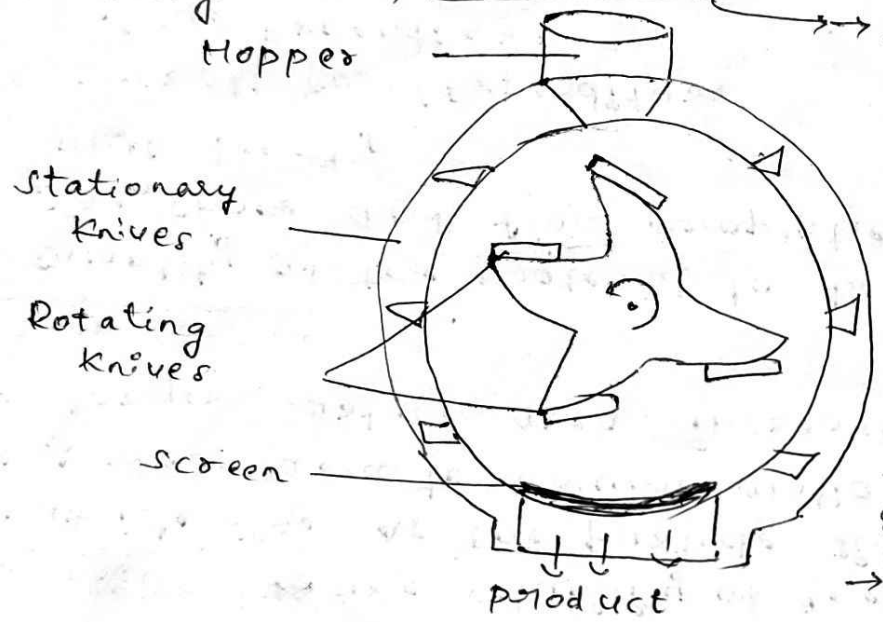
⑥ Bacterial Contamination: most of the chemical compounds may be prone to bacterial contamination. To avoid that size reduction should be done in aseptic conditions.

⑦ Solubility: The solubility of the drug is related to particle size. As the particle size becomes smaller, the surface area to volume ratio increases. The larger surface area, increases solubility.

⑧ Other Factors:
- ✓ Quantity of the material to be reduced
- ✓ Size, shape and flow properties
- ✓ Bulk density
- ✓ overall cost/Expenditure
- ✓ Labour Expenditure
- ✓ power consumption
- ✓ Space occupied
- ✓ Time

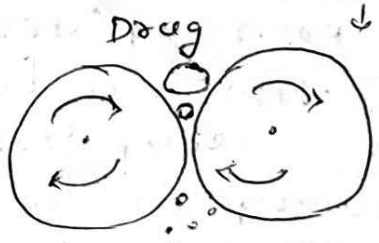
Methods Of Size Reduction: These methods can be used fo... vegetable drugs - stems, roots, bark

1) Slicing And Cutting
- It may be done with sharp knife/scissors/sharp object
- It may be done in transverse/longitudinal direction
- used to fasten the drying of crude vegetable drugs like leaves & roots
- For large scale, **Cutter Mill** is used.



→ It has 2 knives stationary & rotating
↓ Mounted on machine | ↓ attached to rotor & rotates at high speed
→ upper part → has hopper
lower part - screen of desired size
→ The material to be reduced is placed in hoppe & collected from screen
→ used for soft materials like roots, peels.

2) Bruising (or) Contusion:
- The particle size is reduced by striking Heavy block.
- For ordinary use Motor & pestle can be used
- large scale - **Roller Mill** is used.



↓ - It has 2 Equal sized rolls made of stone/Metal with adjustable gap.
- one is rotated mechanically other rotates freely.
- The material to be reduced is dropped b/w the rolls. The speed of rolls & gap can be adjusted
- It is mainly used for cracking seeds

3) Rasping (or) Grating:
- Soft drugs are cut in tranverse direction & can be broken easily.
- It can be done by saw in small scale and saw mill in large scale.

4) Grinding:
- The substances are reduced to coarse to fine powders
- Pestle & Motor can be used.
- Also called as Trituration.

Size Reduction 2 types < Manual size Reduction
< Mechanical " "

I) Manual Size Reduction: Done by
(a) Trituration: It is done by rubbing the substance in motor & pestle to make it into fine powder.
- Glass/porcelain motor & pestle can be used
- For Hard material steel motor & pestle are used

(b) Levigation: /wet Griding (Eg: water, alcohol etc)
- The substance is triturated with few drops of liquid in which it is insoluble in motor & pestle
- That liquid is called levigating agent (LA)
- commonly used in dertamological & opthalamic ointments.

LA + Solids —mix→ smooth paste

(c) pulverization: Solid substances are mixed with suitable solvent & triturated
- The solvent can be removed at the end.

Eg: Camphor (Drug) + alcohol/ether (↓ solvent) ⟶ powdered, easily evaporated after powder formation.

II) Mechanical Size Reduction
- Mostly used in Large scale work
- Different Mills are used:
1) Ball Mill
2) Hammer Mill
3) Edge runner Mill
4) End " "
5) Disintegrator
6) Hand Mill
7) Colloidal Mill
8) Fluid Energy Mill

Mechanism of Size Reduction

1) Cutting: The Material is cut into small pieces with sharp instrument
2) Compression: The material is crushed with application of pressure
3) Impact: The material which is stationary is hit by moving object at high speed / material strikes the stationary surface and broken into smaller particles
4) Attrition: pressure is applied the material, where there is an agitation of the material, which results in shear forces, thereby reducing the particle size.

BALL MILL:

Principle: Impact & Attrition.

Instrumentation:

- It consists of a cylindrical container made of steel/porcelain which is filled with balls made of steel / porcelain
- Length of cylinder is slightly greater than diameter (2-5cm)
- Balls are used as Grinding Medium.
- If pebbles/rods/bars are used instead of balls, they are called as pebble mill / rod Mill / bar Mill.
- Inner surface of cylinder is lined with steel/ porcelain
- The cylinder is placed on a metallic frame & rotated horizontally manually/mechanically and is closed tightly with a lid.
- If steel balls are used they may be contamination, hence porcelain/rubber can be used

Working:

- The material to be reduced is placed in the cylindrical vessel along with the balls
- Initially, the mill is rotated slowly; Speed, in Very imp.
- High speed rotation should be avoided, because the balls may reach the top position and will not fall on the drug

- After some time, the reduced material is taken out from vessel
- The reduced material is passed through of sieve to obtain desired particle size
- Smaller balls are more efficient & produce fine particles

Advantages

1) Economical
2) Simple to use
3) Can Reduce the size of wide variety of materials
4) Easy to clean.
5) can be Easily sterilized, hence can be used for optholamic products
6) Have large Grinding surface.
7) can be used for wet and dry grinding.

HAMMER MILL

principle: Impact

Instrumentation

- It consists of a steel casing to which central shaft is enclosed
- The central shaft is attached to a disc containing many swinging hammers.
- On the upper part, it consists of Hopper through which sample is introduced.
- On the lower part, screen of desired size is placed
- This is similar to disintegrator, the only difference is hammer mill contains hammer which are swinging in nature, but in disintegrator they are fixed

Working:

- The material to be reduced is added through hopper
- It reaches the mill centrifugally.
- As, the shaft rotates, the hammers swing in radial direction

- Due to the swinging motion, particle size is reduced
- The powder is passed through screen and collected
- The unreduced particles will be in the mill and the process will be continued.

Advantages:
1) Simple to operate
2) Rapid in Action
3) Can be used for different types of materials
4) Less chances of contamination
5) particle size can be reduced easily, by changing the speed of Hammers.

DISINTEGRATOR

Principle: Impact & Grinding

Instrumentation:
- Consists of steel drum shaped chamber.
- In that chamber - 4 beaters are fixed to a disc which is attached to a shaft rotating at 5000-7000rpm
- upper surface - Hopper for introduction of sample
- lower part - sieve to seperate the reduced particles

Working:
- The drug to be reduced is placed in the Hopper
- It reaches the steel chamber
- The material is broken by the direct attack of beaters
- By the impact, the material is thrown against the chamber with great force
- The reduced particles are then passed through sieve of desired size.

Advantages
1) used for very hard drugs
2) used to powder crude vegetable drugs

3) used for milling ointments

FLUID ENERGY MILL → 2000kg/hr

Principle: Attrition.
When 2 objects strike with each other & one of them will be broken into smaller pieces

- Also called as Jet Mills / Micronizers
- It Donot Have any moving part.

Instrumentation:
- It Consists of Hollow chamber fitted with no of nozzles through which air / steam is passed.
- Feed inlet is attached to the cylinder
- A cyclone is attached through which fine powder is collected.

Working:
- pre-grinded material is added through Feed inlet.
- Through nozzles, steam / air / gas is passed, which causes the material to circulate at High speed
- Due to High speed, the materials strike with one another
- Due to centrifugal force, large size particles move to grinding zone & further undergo grinding.
- Small particles are collected in cyclone collector

Advantages:
1) Donot Have any moving part.
2) No Heat is Generated during the process, hence Can be used for thermolabile substances like vitamins, Enzymes
3) Can be used for sensitive materials.
4) Reduces the size upto 5 microns.

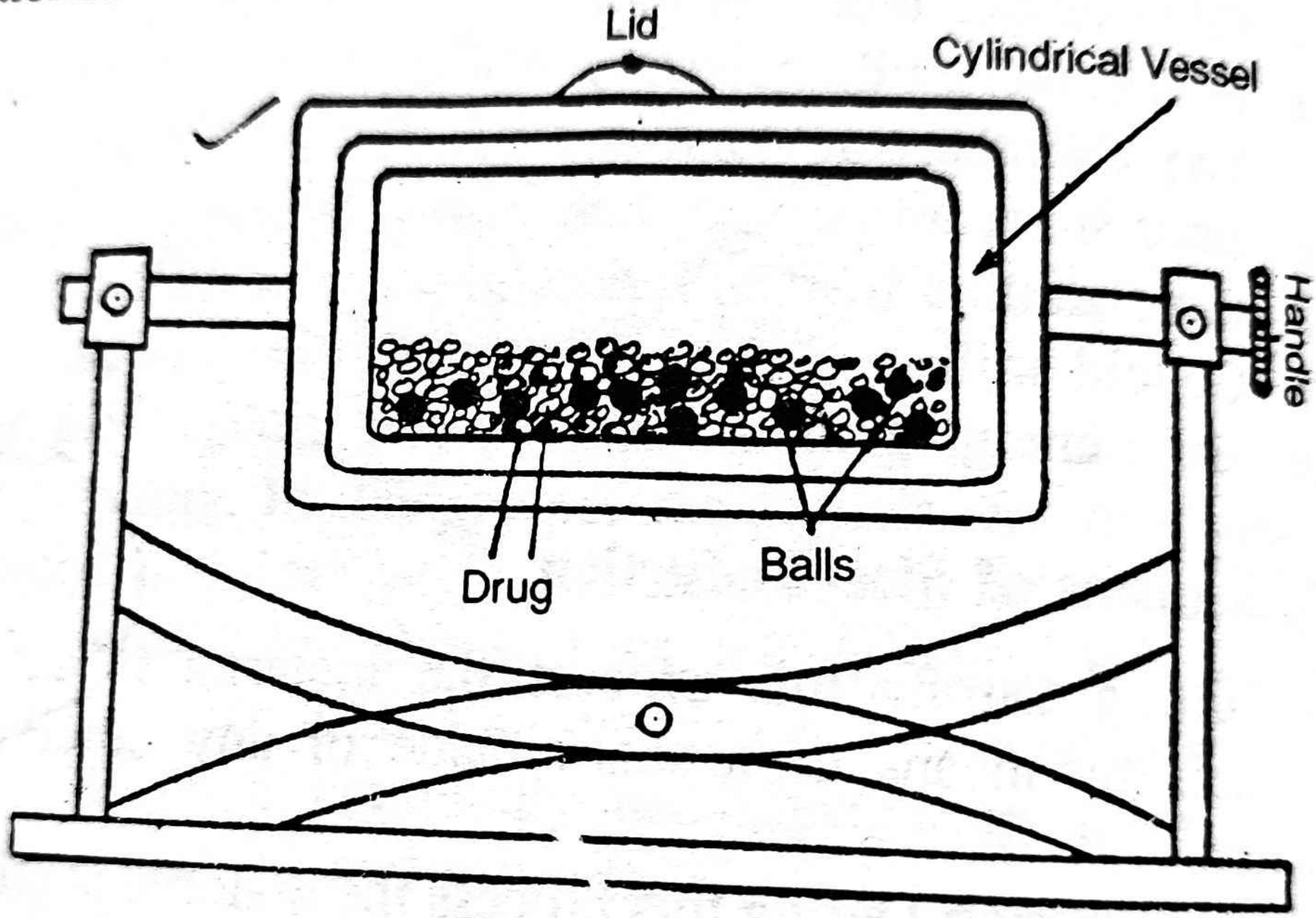


Fig. 5.3 Ball mill

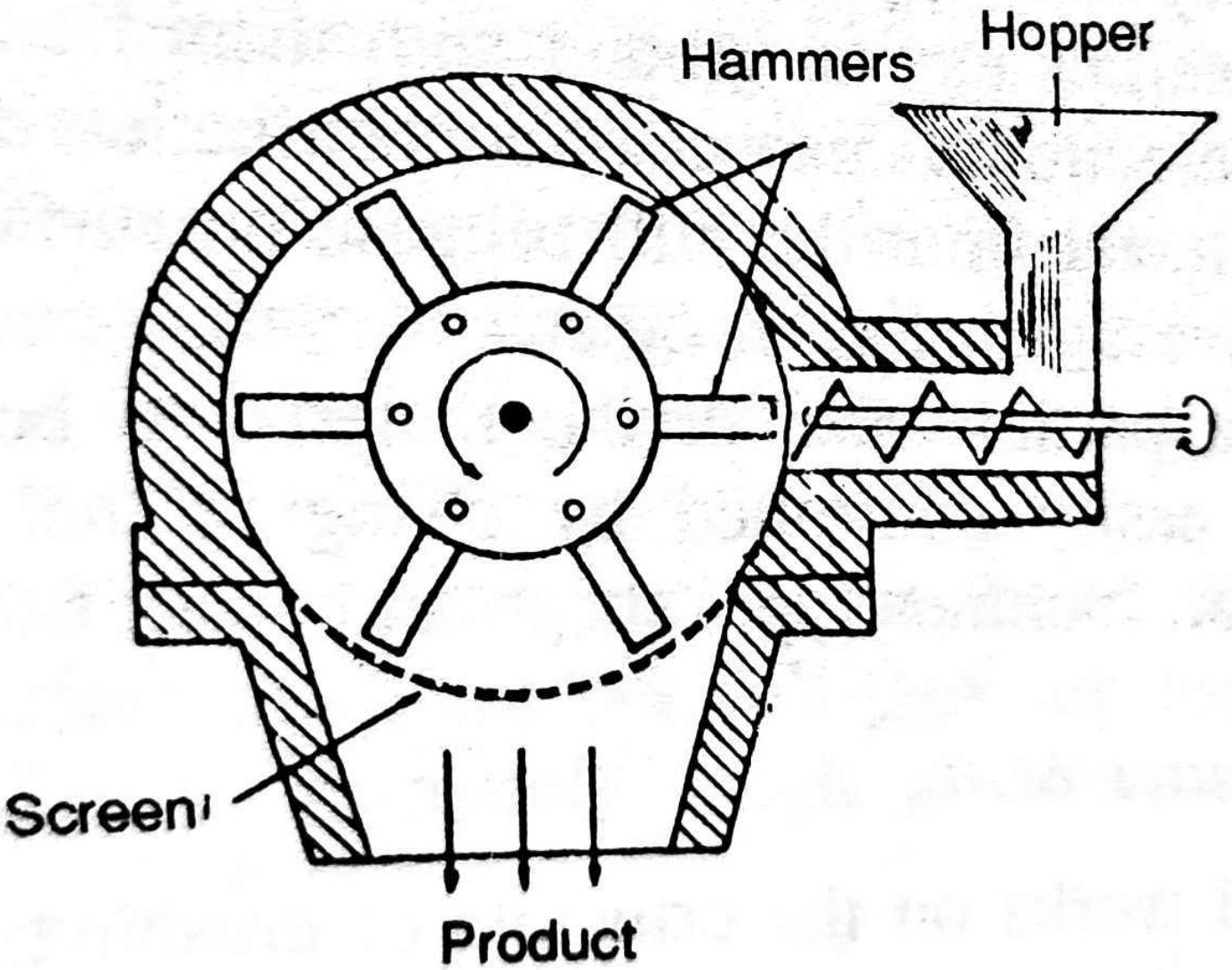


Fig. 5.4 Hammer mill

1) used to
2) used to powder crude

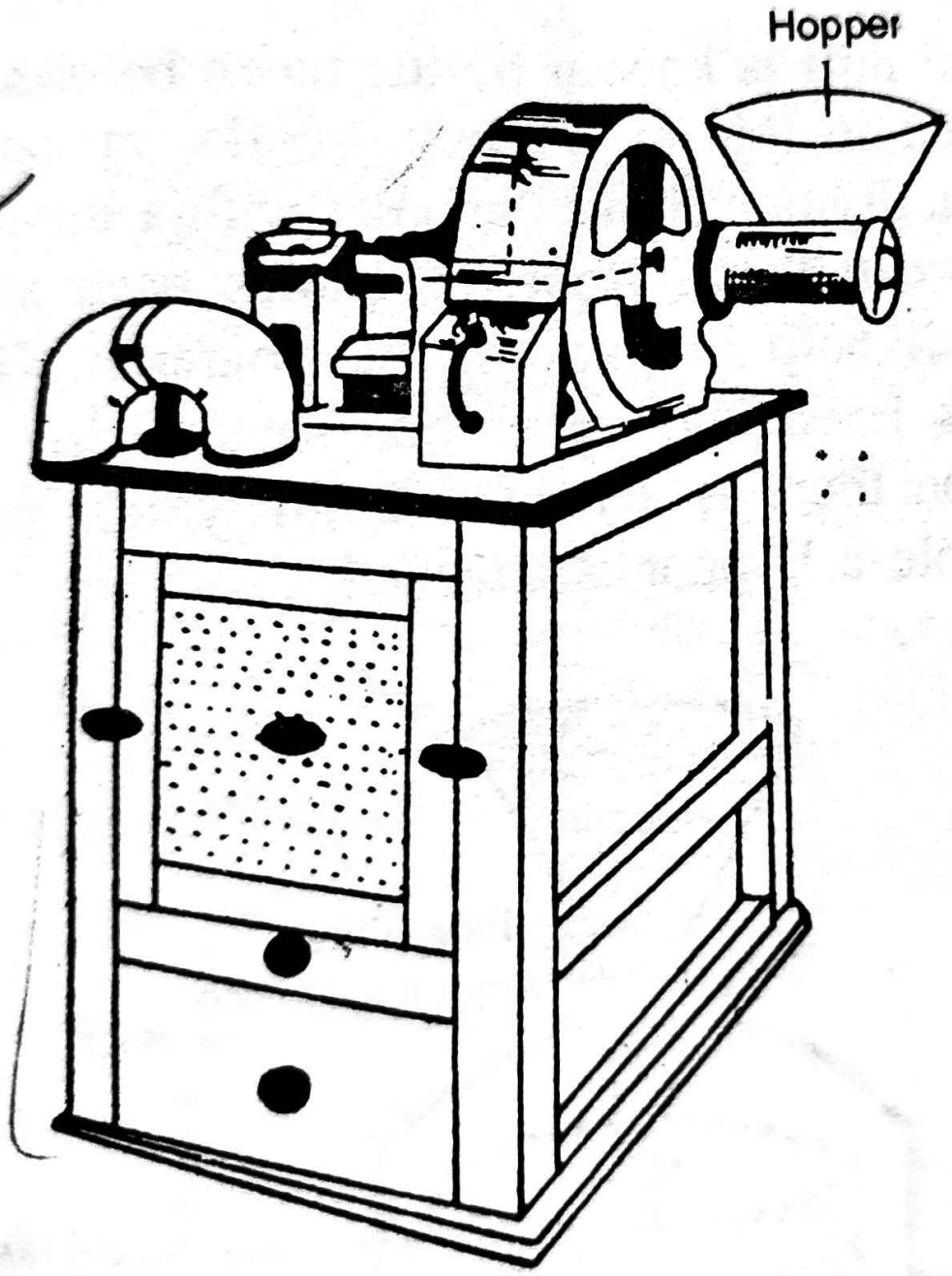


Fig. 5.7 Disintegrator

into the chamber through

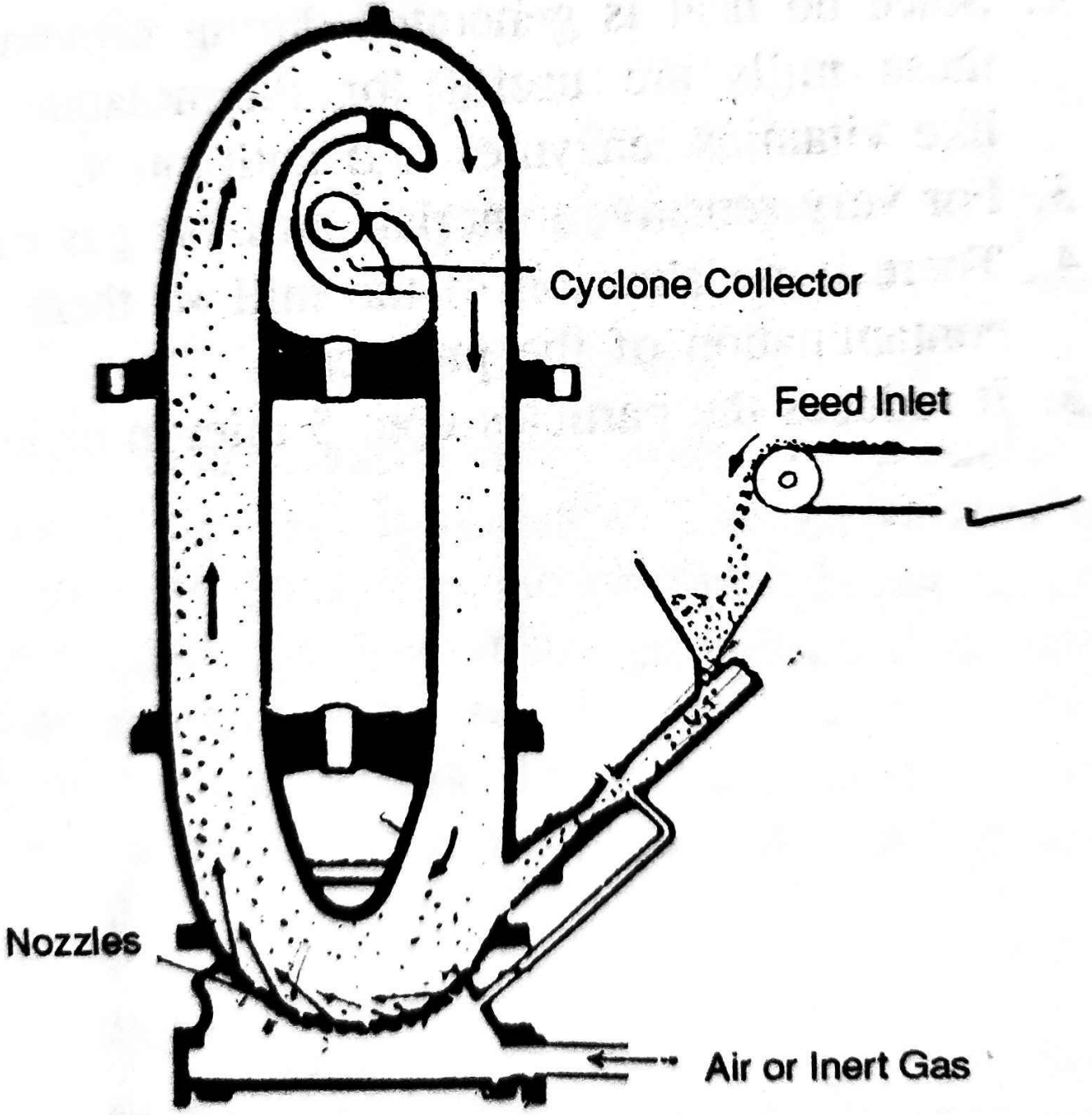


Fig. 5.11 Fluid energy mill

Size Separation

It is the process that involves the seperation of particles of desired size from the mixture of various sized particles

- It is also called as sieving/screening/sifting

Objectives of size separation:

→ To maintain uniform particle size
→ To Improve Absorption
→ To obtain stable separation
→ To improve mixing
→ To avoid several variations → Quality control of Raw materials.

Official standards of powders:

Indian pharmacopeia has prescribed standards for powders for pharmaceutical purposes.

- They are mainly divided to 5 types depending on the degree of coarseness (or) fineness.

IP 1996 specifies 5 grades of powders.

Sl no:	Grade of powder	Sieves through which all particles pass	Nominal mesh Aperture size
1	Coarse powder	10	1750 µm
2	Moderately Coarse powder	22	710 µm
3.	Moderately Fine powder	44	355 µm
4	Fine powder	85	80 µm
5	very Fine powder	120.	125 µm.

(1) Coarse powder: (10/44): A powder all the particles pass through sieve NO 10 with Nominal mesh aperture of 1750 µm and not more than 40% pass through Sieve 44 with Nominal mesh aperture of 355 µm

(2) Moderately coarse powder: (22/60):
particles pass through Sieve 22 → Nominal Aperture 710 µm
NMT 40% " " " 60 → " " 250 µm

(3) Moderately fine powder: (44/85)
particles pass through Sieve 44 → Nominal Aperture 355 µm
NMT 40% " " " 85 → " " 180 µm

(4) Fine powder: (85)
Particles pass through Sieve 85 → " " 180 µm

(5) Very Fine powder: (120)
particles pass through Sieve 120 → " " 125 µm.

Size Separation by Sifting

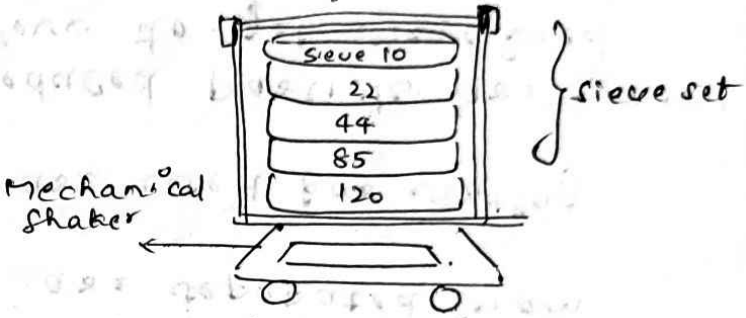
Sifting/ Separation/Sieving is the process by which different grades of powders are separated from each other.
- Different grades of sieves are used for sifting of powders.
- After size reduction, the reduced particles are passed through specific grades of sieve to get required size particles
- The Bigger particles are returned to machine for Grinding
- After final grinding & Sieving, if the material donot pass through sieve, then it is called as Tailing
- It should not be discarded, added to next batch
- The sieves used in pharmacy consist of circular frame made up of metal fitted with wire made of steel/ copper/nylon.etc.

Sifting/Sieving Method:

- In this method, the fine powder is separated from coarse powder by using different sieves

Working & Construction:

- Sieves are arranged in form of set in descending order i.e, sieve of larger size at top and smallest at bottom.
- The bottom sieve is attached to receiving pan
- The material to be separated is kept in upper most sieve
- The sieves are shaken with the help of mechanical shaker
- After the process, the material collected/retained in each sieve is weighed



Advantages:

1) Inexpensive
2) Easy to use

SEDIMENTATION METHODS:

→ Sedimentation Methods are used for suspensions containing particle size of 0.5μm.

→ This method depends on the rate of sedimentation of particles.

particle size can be expressed by stoke's law/Equation

$$de = \sqrt{\frac{18\eta}{(\rho-\rho_o)g} \cdot \frac{x}{t}}$$

de = Stoke's diameter
η = viscousity
x/t = rate of sedimentation
g = gravitational constant
ρ = density of particle
ρ_o = " " medium

- The equipment used for this method is called as Andreason Apparatus.

Construction: It contains a tall vessel called sedimentation vessel.
- vessel is fitted with 10ml pipette with stopcock
- The liquid is added to the vessel.

- The samples are withdrawn from the pipette at suitable time intervals.
- The samples are dried and weighed
- The larger particles settle down faster., than smaller ones
- Thus, we can say the samples withdrawn faster has larger particles & samples withdrawn later has small particles.
- The particle size can be calculated using stokes Equation

CYCLONE SEPARATOR | used for seperation of suspensions (mostly solid in gas type)

Construction:
- It contains a cylindrical vessel with conical base
- upper part is fitted with Tangential inlet & fluid outlet
- Lower base is fitted with solid outlet.

Working:
- The suspension is introduced through tangential inlet. at high speed.
- A rotary movement takes placed in the vessel (cyclone) so the fluid will be removed from fluid outlet at top
- The solid particles due to the centrifugal force are thrown down towards the solid outlet.
- cyclone separator is similar to sedimentation, but the only difference is in cyclone separator, separation takes place with the help of centrifugal force, in sedimentation through Gravitational force.

Limitations/ Drawbacks:
- Only coarse particles are separated, fine particles are carried by the fluid.

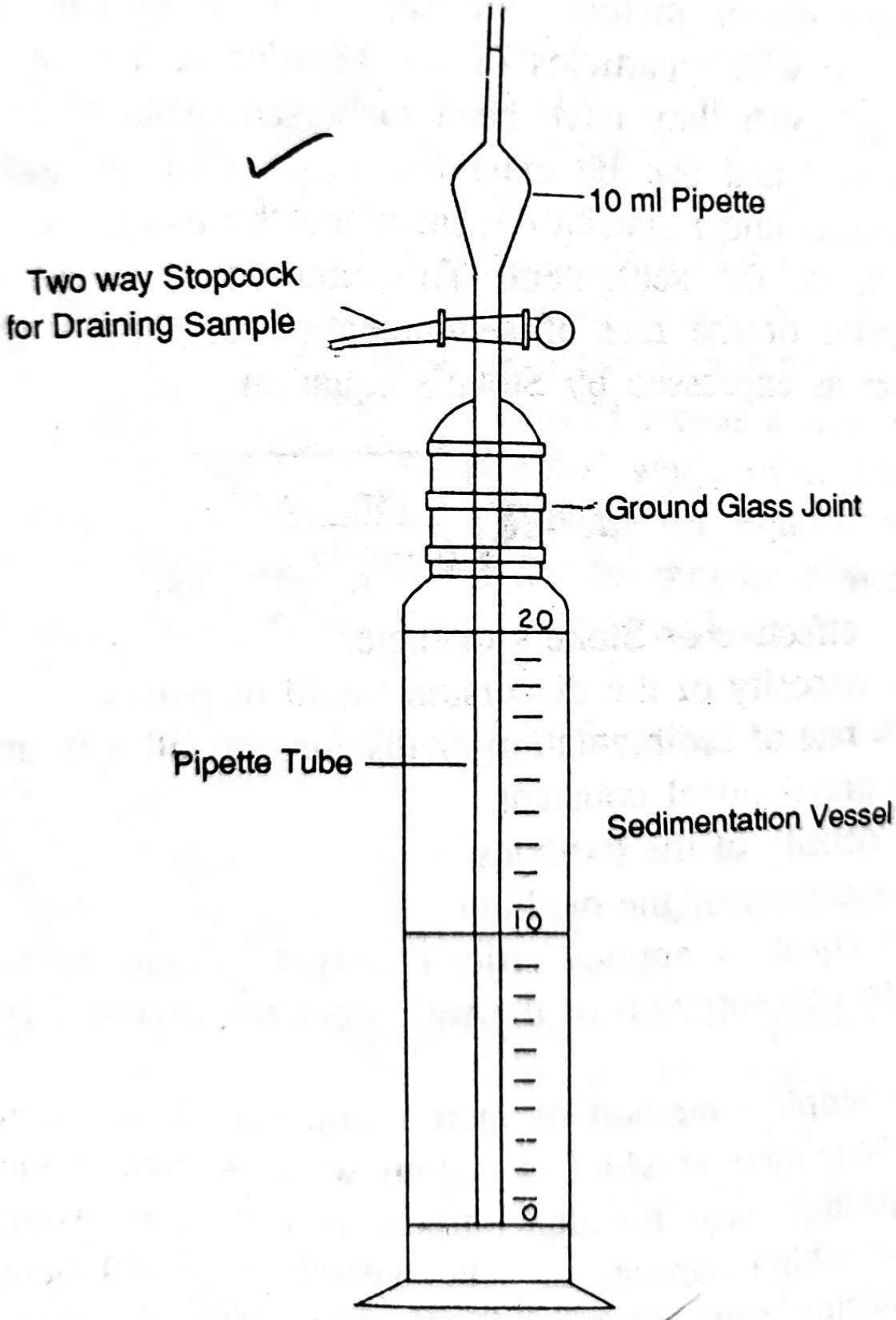


Fig. 6.1 Andreasen apparatus

and ultimately removed from there through the solids outlet.

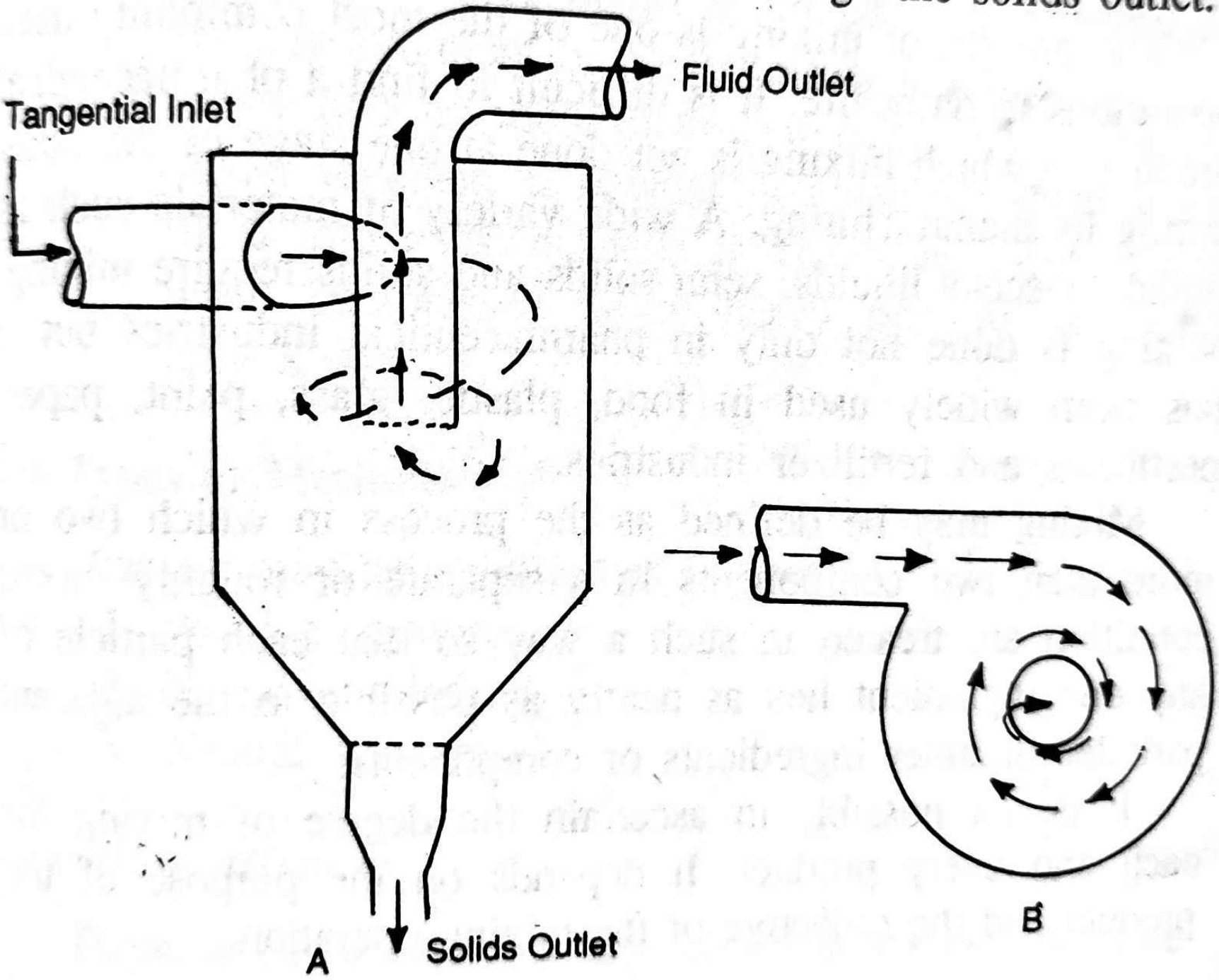


Fig. 6.2 Cyclone separator **(A)** Elevation **(B)** Plan

Cyclone separators can be used for separating suspensions