

Subject Name: Physical Pharmaceutics –II Module -IV

Subject Code: BP 403T

Objectives of the course

- Understand various physicochemical properties of drug molecules in the designing the dosage forms

Learning outcomes

- Students learnt about the properties, nature and general characteristics of particles and powder.

Structure of Module –IV BP 403T

Learning Material

Micromeritics-

Particle size and distribution, mean particle size, number and weight distribution, particle number, methods for determining particle size by different methods, counting and separation method, particle shape, specific surface, methods for determining surface area, permeability, adsorption, derived properties of powders, porosity, packing arrangement, densities, bulkiness and flow properties.

MICROMERITICS



Micromeritics & Powder Technology: Preformulation & formulation aspects

Syllabus

- ▶ Basics of micromeritics- Fundamental and derived properties of powders and their measurement- particle shape & size, surface area, densities, flow properties, packing properties, fluidization of powders.
- ▶ Large scale manufacturing aspects- Unit operations and equipment used: Size reduction, size separation, powder mixing, segregation of mixed powders; **packaging** & Q.C. of powders.
- ▶ Brief coverage of following powders- Dusting powders, Oral rehydration powders, Dry syrup formulations

What is Micromeritics?

The Science and Technology of small particles is known as Micromeritics.

It is the study of various characteristics like

- Particle size and size distribution
- Particle shape and surface area
- Porosity, Density, Flow property etc...



Need/ Importance/ Application of Micromeritics

- ▶ Knowledge and control of the size and the size range of particle is of profound importance in pharmacy
- ▶ **Size and surface area** can be related to the physical, chemical and pharmacological properties of a drug.

1. Drug release and dissolution: Particle size affects drug release from dosage forms that are administered orally, parenterally, rectally and topically. Higher surface area brings about intimate contact of the drug with the dissolution fluids in

Need/ Importance/ Application of Micromeritics

2. Absorption and drug action: Particle size and surface area influence the drug absorption and subsequently the therapeutic action. Higher the dissolution faster the absorption. Hence quicker the drug action

3. Physical stability : Particle size influences the physical stability of suspensions and emulsions. Smaller the size better is the physical stability (*as it would take more time for particles to agglomerate*)

4. Dose uniformity: Particle size and shape also governs **flow properties** of powders and granules in tableting.

- ▶ Any interference in the flowability of powders or granules may alter the weight of the powder blend and thus amount of drug incorporated into the tablet or capsules and **thereby reduce the uniformity of the dose.**

Examples...

- Reduction of particles size improves surface area and can help in improving solubility of certain drugs. e.g. The solubility of **Griseofulvin** can be greatly increased by particle size reduction.
- Reduction of particles size can increase the rate of absorption of and consequently bioavailability of many drugs e.g. **tetracycline, aspirin and sulphonamides, nitrofurantoin** etc..

Properties of Powders

1. **Fundamental properties** :-These properties relate to the individual particle.
2. **Derived properties** :- They are dependent on fundamental properties & define the factors relating to their measurement.

Fundamental properties:-

1. Particle size and size distribution
2. Particle shape
3. Particle surface area
4. Particle weight
5. Particle number

Derived properties:

1. Density of powders (a) bulk density (b)tapped density (c) granular density (d>true density
2. Flow properties of powders
3. Porosity
4. Bulkiness

Fundamental properties of powders

I. Particle size

- ▶ Denoted in **micrometers**
(formerly called as microns)
- ▶ One micrometer is equal to **10^{-3} mm** or **10^{-6} m**
- ▶ One millimicrometer is called one **nanometer (nm)**
- ▶ One nanometer = **10^{-9} m** or **10^{-6} mm** or **10^{-3} μm**

$$1 \text{ m} = 1000 \text{ mm}$$

$$1 \text{ mm} = 1000 \mu\text{m}$$

$$1 \mu\text{m} = 1000 \text{ nm}$$

Particle size determination (PSD) -Methods

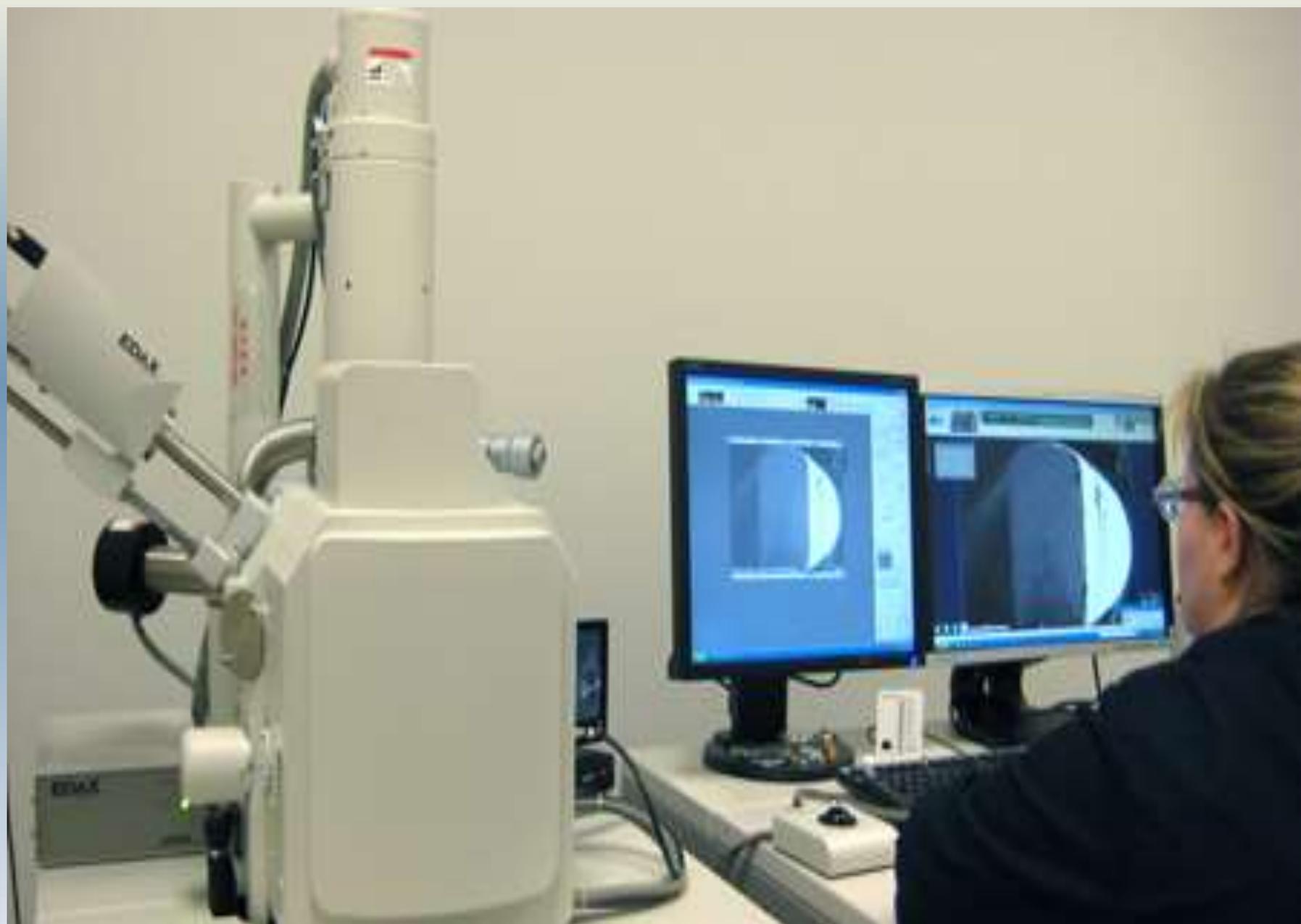
1. Optical Microscopy
2. Sieving Method
3. Sedimentation Method
4. Conductivity Method

1. Optical Microscopy

- ▶ Particle size in the range of 0.2 – 100 μm can be measured.
- ▶ This method gives number distribution which can be converted to weight distribution
- ▶ Optical microscope lens has limited resolving power
- ▶ Advanced microscopes have better resolving power and can measure size in nano range: Ultramicroscope, Electron microscope- Scanning Electron microscope (SEM), Transmission Electron microscope (TEM).
- ▶ **Application: Particle size analysis in suspensions, aerosols, globule size analysis in emulsion**

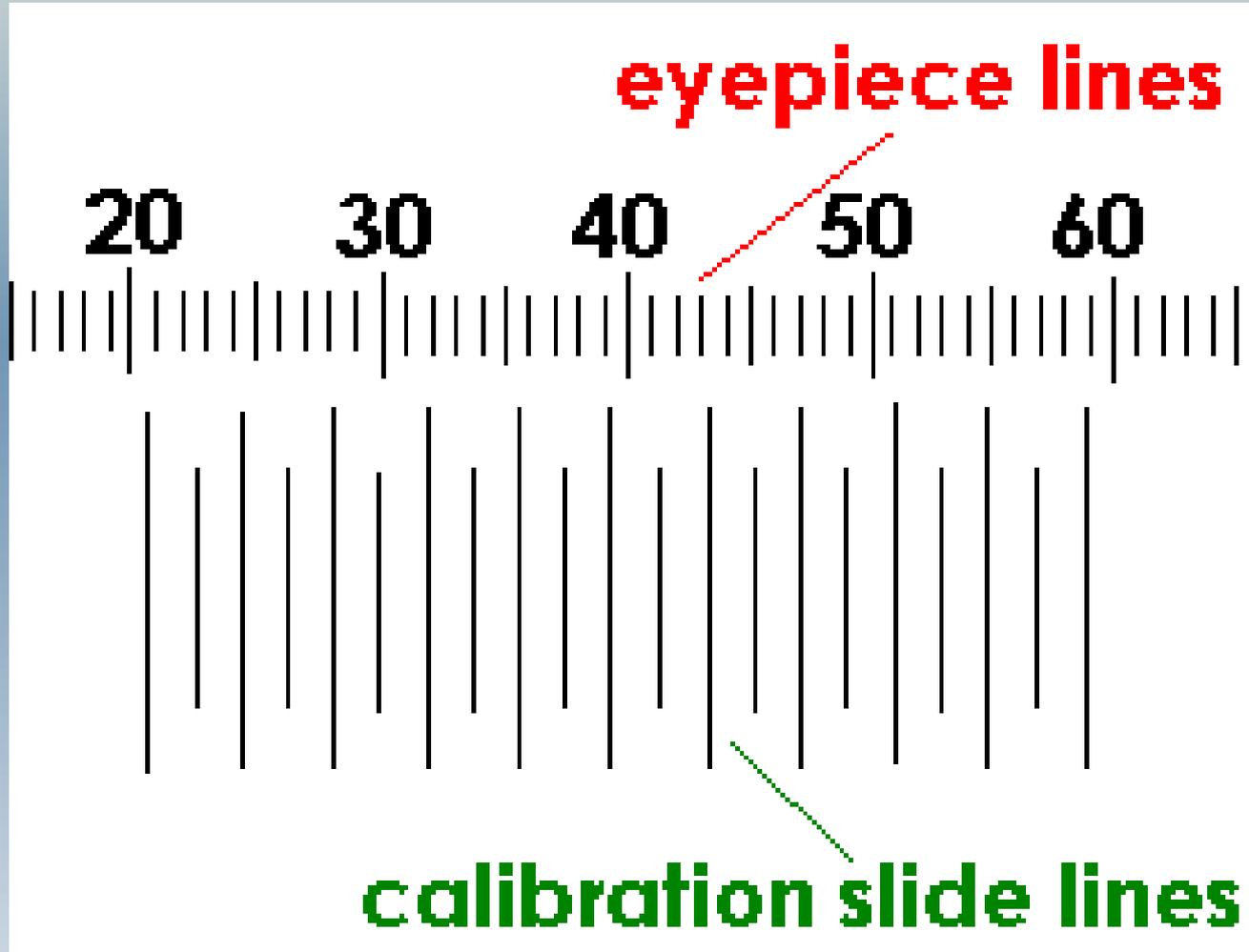
Procedure:

1. Eye piece of the microscope is fitted with a micrometer.
2. This eye-piece micrometer is calibrated using a standard stage micrometer.
3. The powder sample is dispersed in a suitable vehicle in which it does not dissolve and its properties are not altered. (eg. water, paraffin oil.)
4. This sample is mounted on a slide and placed on the stage under the objective of microscope.
5. Around 625 particles are visualized. their diameter is noted and mean is computed.









Advantages

- ▶ One can view particles
- ▶ Any aggregates detected
- ▶ Contamination of particles detected
- ▶ Use of cover slip for arresting motion of particles
- ▶ Easy and simple

Disadvantages

- ▶ Length and breadth can be detected but depth or thickness of particles cannot be measured
- ▶ Slow- time consuming , tedious, inaccurate
- ▶ Number of particles to be measured is more
- ▶ Large sample required

2. Sieving Method

- ▶ Sieving method is an ordinary and simple method.
- ▶ It is widely used as a method for the particle size analysis
- ▶ Sieve analysis is usually carried out using dry powders. Although, for powders in liquid suspension or which agglomerate during dry sieving, a process of wet sieving can be used.

- ▶ Sieving method directly gives weight distribution.
- ▶ It find application in dosage form development of tablets and capsules.
- ▶ Normally, 15% of fine powder should be present in granulated material to get proper flow of material and achieve good compaction.
- ▶ Thus percent of coarse, moderate, fine powder is estimated by this method.

Method:

- ▶ Sieve analysis utilizes a wire mesh made of brass, bronze or stainless steel with known aperture (hole) diameters which form a physical barrier to particles.
- ▶ The standard sieve sizes are as per the pharmacopoeia
- ▶ Most sieve analyses utilize a series, stack (layer) of sieves **which have the coarser mesh at the top of the series and smallest mesh at the bottom** above a collector tray
(The mesh size goes on decreasing from top to bottom)

Method:

- ▶ A sieve stack usually comprises 6-8 sieves.
- ▶ Powder is loaded on to the coarsest sieve of the stack and then it is subjected to mechanical vibration for specified time, eg 20 minutes.
- ▶ After this time, the powder retained on each sieve is weighed
- ▶ The particles are considered to be retained on the sieve mesh with an aperture corresponding to the sieve diameter.
- ▶ The size is estimated as per the standards given in pharmacopoeia

TABLE 6-5

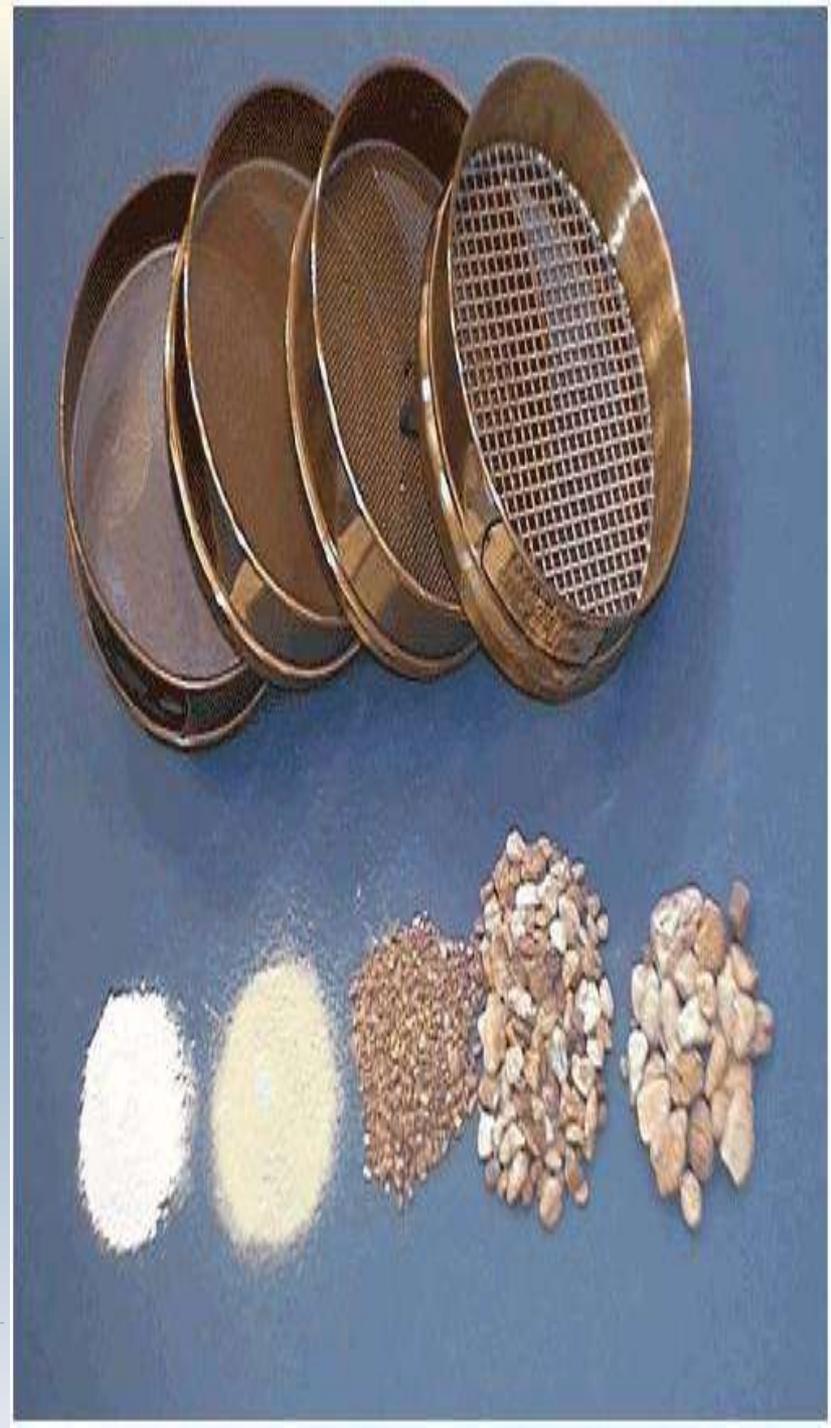
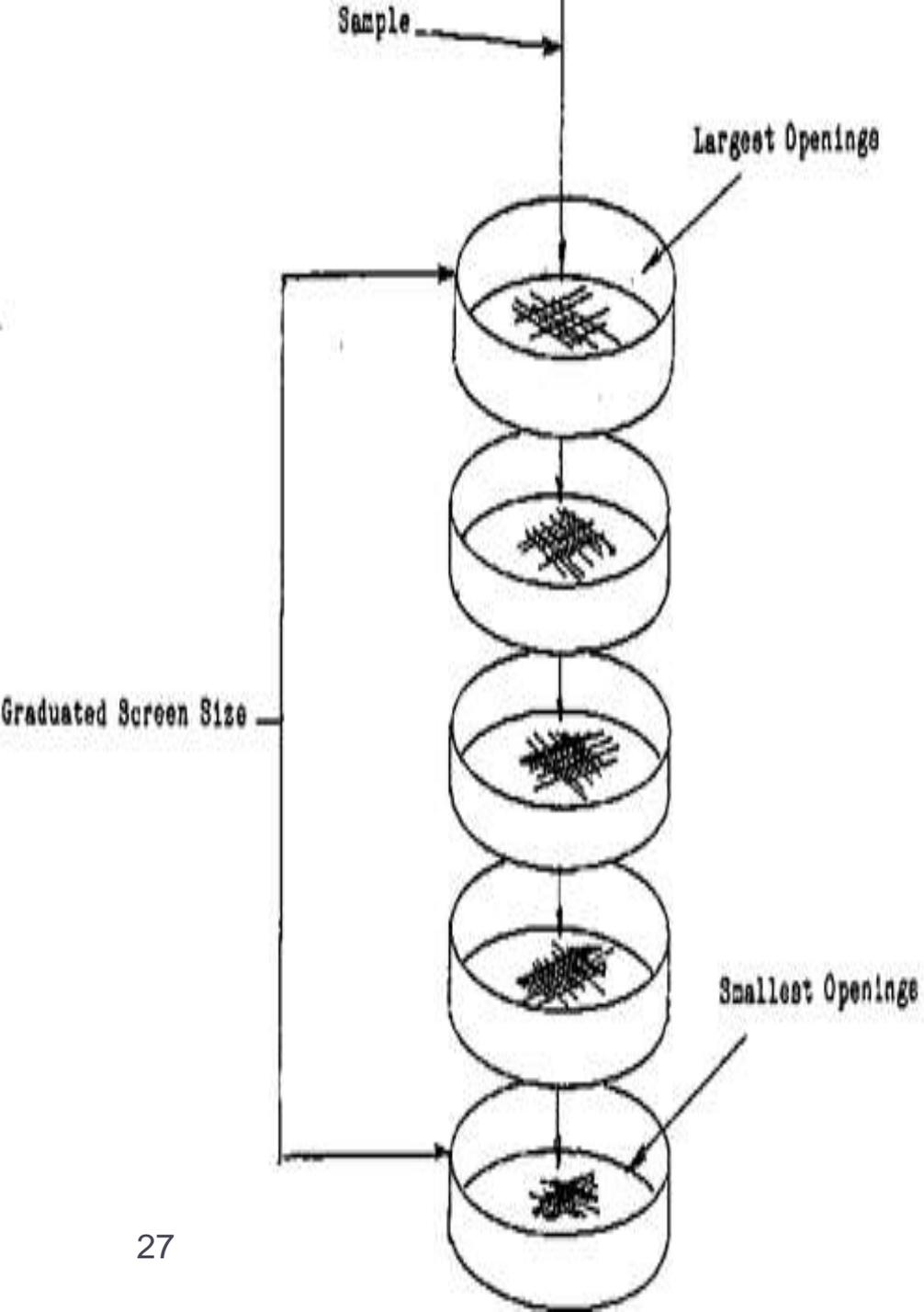
Designations and Dimensions of I.P. Specification Sieves

<i>Sieve number</i>	<i>Aperture size micrometer</i>	<i>Sieve number</i>	<i>Aperture size micrometer</i>
10	1700	44	325
12	1400	60	250
16	1000	85	35
22	710	100	36
25	600	120	34
30	500	150	36
36	425	170	35

TABLE 6-6
Weight-size Distribution of a Granular Materials
as Measured by the Standard Sieves

<i>Sieve number (passed/ retained)</i>	<i>Arithmetic mean size of opening μm</i>	<i>Weight retained on a sieve g</i>	<i>Per cent weight retained (undersize)</i>	<i>Cumulative per cent retained</i>
30/45	470	57.3	13.0	13.0
45/60	300	181.0	41.2	54.2
60/80	213	110.0	25.0	79.2
80/100	163	49.7	11.3	90.5
100/140	127	20.0	4.5	95.0
140/200	90	22.0	5.0	100.0





- ▶ Care should be taken to get reproducible results.
- ▶ The type of motion, time of operation, speed, weight of powder should be fixed and standardized.

Advantages- Inexpensive, Simple, Rapid, Reproducible results (if parameters are standardized)

Disadvantages- lower limit is 50 microns

- ▶ Powder if moist, can cause clogging of apertures
- ▶ Attrition between particles during the process may cause size reduction giving inaccurate results.

3. Sedimentation Method

- ▶ In this method particle size can be determined by examining the powder as it sediments out.
- ▶ **Sample preparation:** Powder is dispersed in a suitable solvent
- ▶ If the powder is hydrophobic, it may be necessary to add dispersing agent to aid wetting of the powder.
- ▶ In case where the powder is soluble in water it will be necessary to use non- aqueous liquids or carry out the analysis in a gas.

Principle of Measurement

- ▶ Particle size analysis by sedimentation method can be divided into two main categories according to the method of measurement used.
- ▶ *One of the type is based on measurement of particle in a **retention zone**.*
- ▶ *Another type uses a **non-retention measurement zone**.*
- ▶ An example of a non-retention zone measurement is known as the pipette method.

Andreasen pipette method:

- ▶ One of the most popular of the pipette methods was that developed by Andreasen and Lundberg and commonly called the Andreasen pipette.
- ▶ *In this method , known volumes of suspension are drawn off and the concentration differences are measured with respect to time.*
- ▶ It involves measuring the % of solids that settle with time in a graduated vessel.

Construction:

- ▶ The Andreasen fixed-position pipette consists of a 200 mm graduated cylinder which can hold about 500 ml of suspension fluid.
- ▶ A pipette is located centrally in the cylinder and is held in position by a ground glass stopper so that its tip coincides with the zero level.
- ▶ A three way tap allows fluid to be drawn into a 10 ml reservoir which can then be emptied into a beaker or centrifuge tube.

Method:

- ▶ A 1% suspension of the powder in a suitable liquid medium is placed in the pipette.
- ▶ At a given intervals of time, samples are withdrawn from a specified depth without disturbing the suspension.
- ▶ The amount of powder can be determined by **weight** following drying or centrifuging; alternatively, chemical analysis of the particles can be carried out.

- ▶ The particle size is determined in terms of **stokes' diameter** (*the diameter of a particle measured during sedimentation at constant rate*) using modified Stokes' equation

$$d_{st} = \frac{18\eta h}{(\rho_s - \rho_f)F_g t}$$

- ▶ d_{st} : stokes' diameter
- ▶ η : viscosity of medium
- ▶ h : sedimentation height
- ▶ $\rho_s - \rho_f$: difference in density of particle and fluid
- ▶ F_g : force of gravity
- ▶ t : sedimentation time

- ▶ A pipette is located centrally in the cylinder and is held in position by a ground glass stopper so that its tip coincides with the zero level.
- ▶ A three way tap allows fluid to be drawn into a 10 ml reservoir which can then be emptied into a beaker or centrifuge tube.
- ▶ The amount of powder can be determined by weight following drying or centrifuging.
- ▶ The data of cumulative weight is used for the determination of particle weight distribution, number distribution etc..

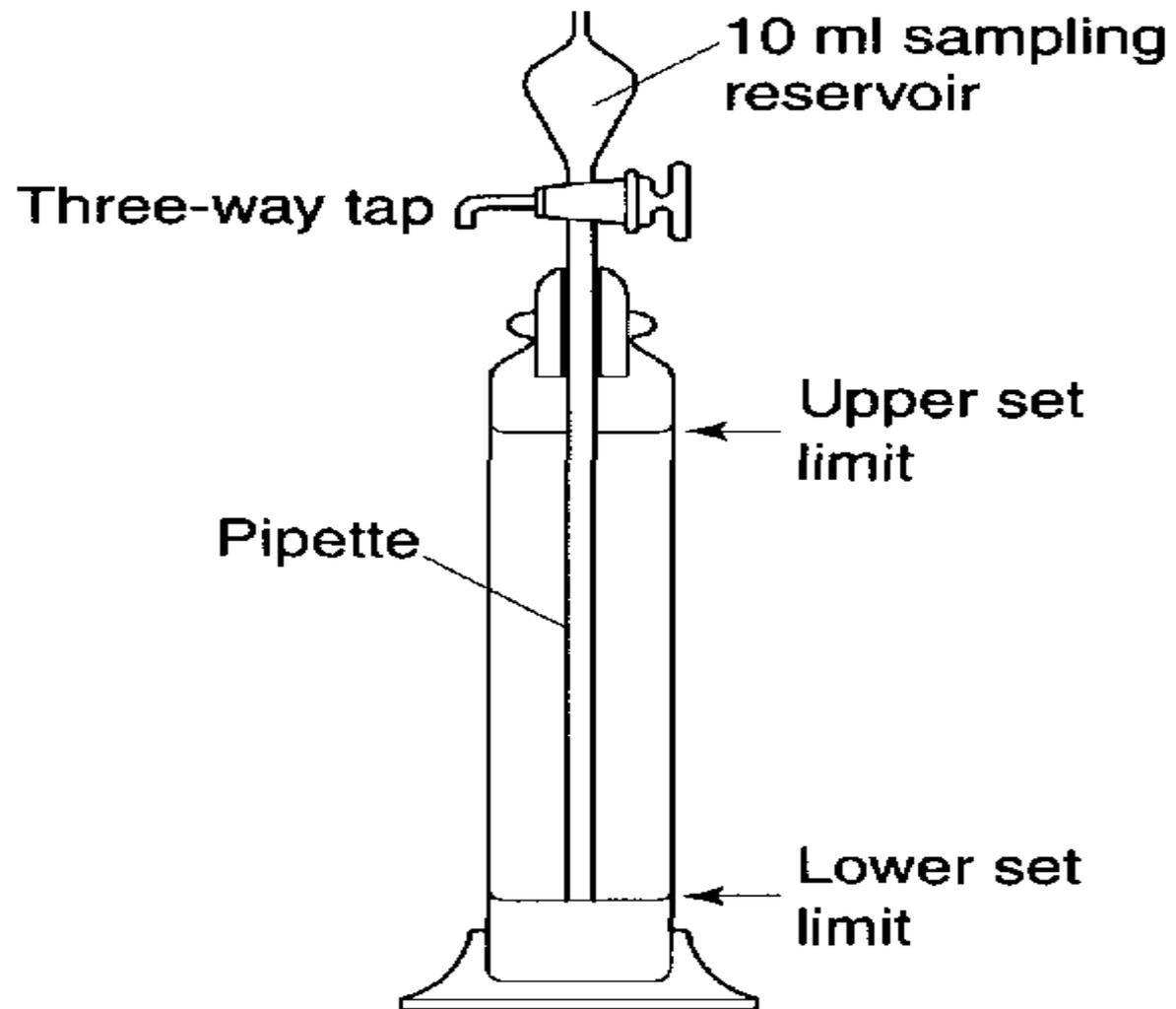


Fig. 10.19 Diagram of Andreason pipette.

- ▶ The second type of sedimentation size analysis, using **retention zone methods**, also uses Stokes' law to quantify particle size.
- ▶ One of the most common retention zone methods uses a **sedimentation balance**.
- ▶ In this method the amount of sedimented particles falling on to a balance pan suspended in the fluid is recorded.

▶ The continual increase in weight of

4. Conductivity methods

There are various subtypes. Two popular methods are-

- ▶ **Electrical stream sensing zone method (Coulter counter)**
- ▶ **Laser light scattering methods**

*It is based on the principle of **change in light intensity**. The measurement of this change in light intensity gives estimate of particle size.*

Electrical stream sensing zone method(Coulter counter)

Sample Preparation:

- ▶ Powder samples are dispersed in an electrolyte to form a very dilute suspension.
- ▶ The suspension is usually subjected to ultrasonic agitation to break up any particle agglomerates.
- ▶ A dispersant may also be added to aid particle deagglomeration.

Electrical stream sensing zone method(Coulter counter)

Method

- ▶ The particle suspension is drawn through an aperture accurately drilled through a sapphire crystal set into the wall of a hollow glass tube.
- ▶ Electrodes, situated on either side of the aperture are surrounded by an electrolyte solution.
- ▶ These electrodes monitor the change in electrical signal which occurs when a particle momentarily occupies the orifice and displaces its own volume of electrolyte.

Electrical stream sensing zone method(Coulter counter)

Method

- ▶ The volume of electrolyte fluid which is displaced in the orifice by the presence of a particle causes a change in electrical resistance between the electrodes which is proportional to the volume of the particle.

Advantage:

- ▶ Particle size ranging from 0.5 – 500 microns
- ▶ Gives number distribution, Particle volume measured and can be converted to diameter.
- ▶ Accurate, sensitive, fast technique.
- ▶ 4000 particles per second can be counted.

Disadvantage

Expensive

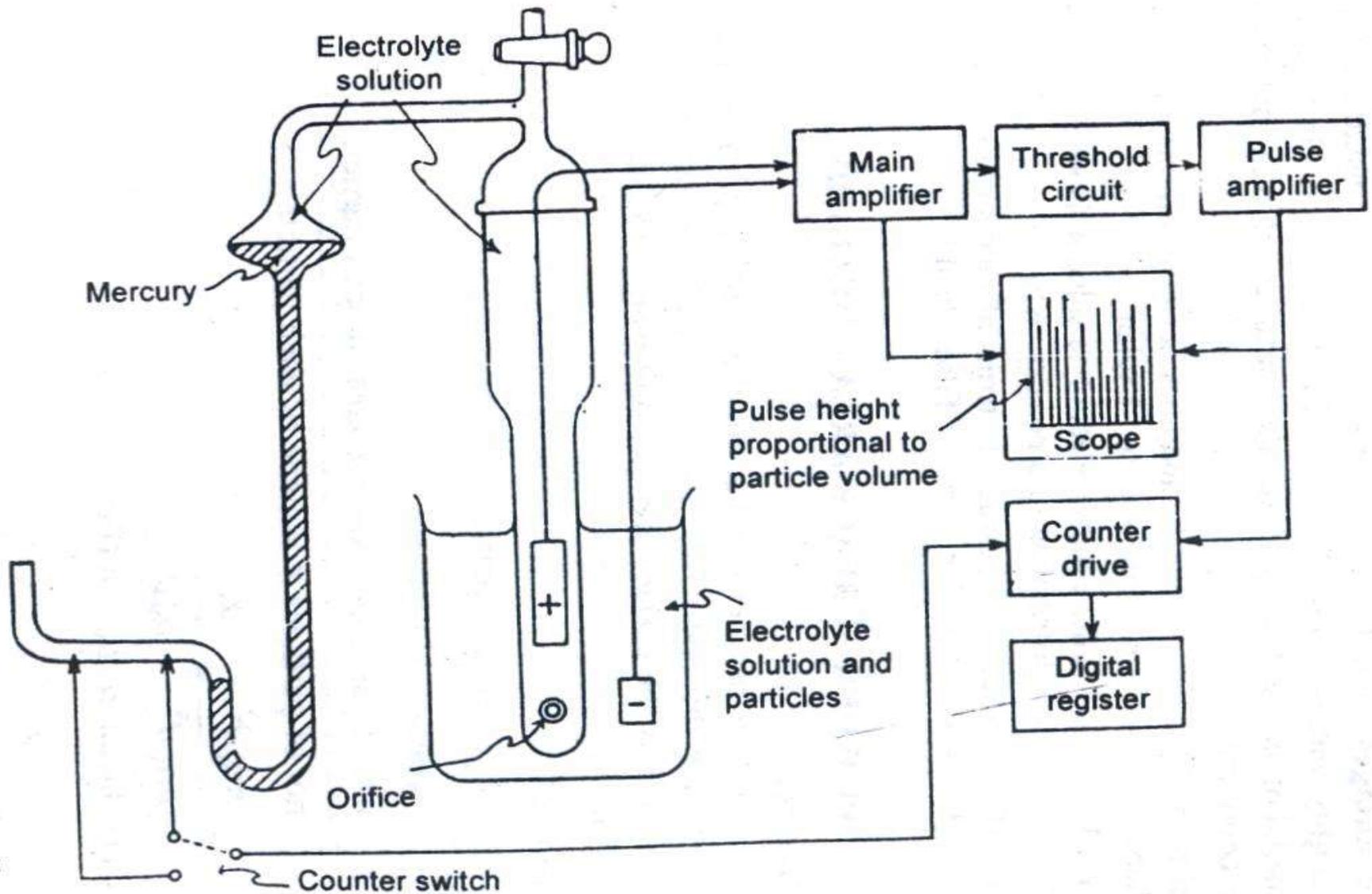
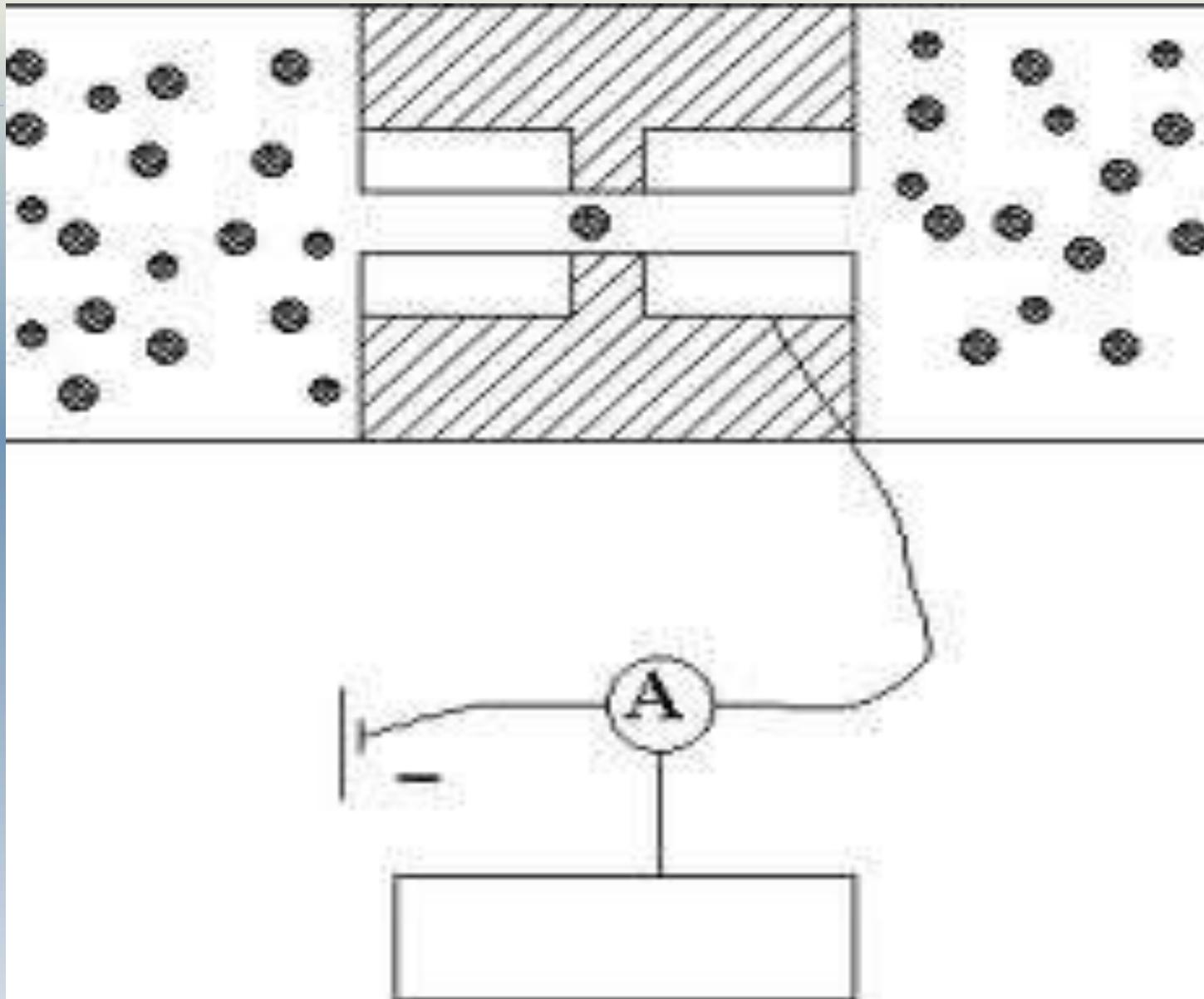


Figure 6-9. Schematic diagram of Coulter counter used to determine particle volume.

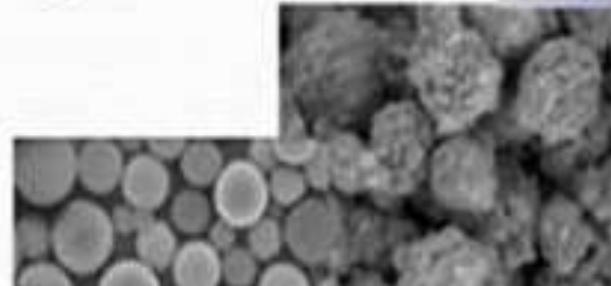
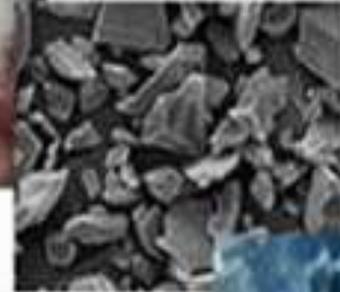


II. Particle Shape Determination

- Particle shape also has influence on surface area, flow properties, packing and compaction of the particles.
- Spherical particles have minimum surface area and better flow properties.
- Shape can also have influence on rate of dissolution of drugs.
- Techniques of determination are:
 - ✓ Microscopy (*refer in particle size determination*)
 - ✓ Light scattering

Particle Shape

- Acicular – needle-shaped
- Angular – sharp-edged
- Crystalline – geometric shape
- Dendritic – branched crystalline shape
- Granular equidimensional irregular shape
- Spherical – global shape



III. Surface Area Determination

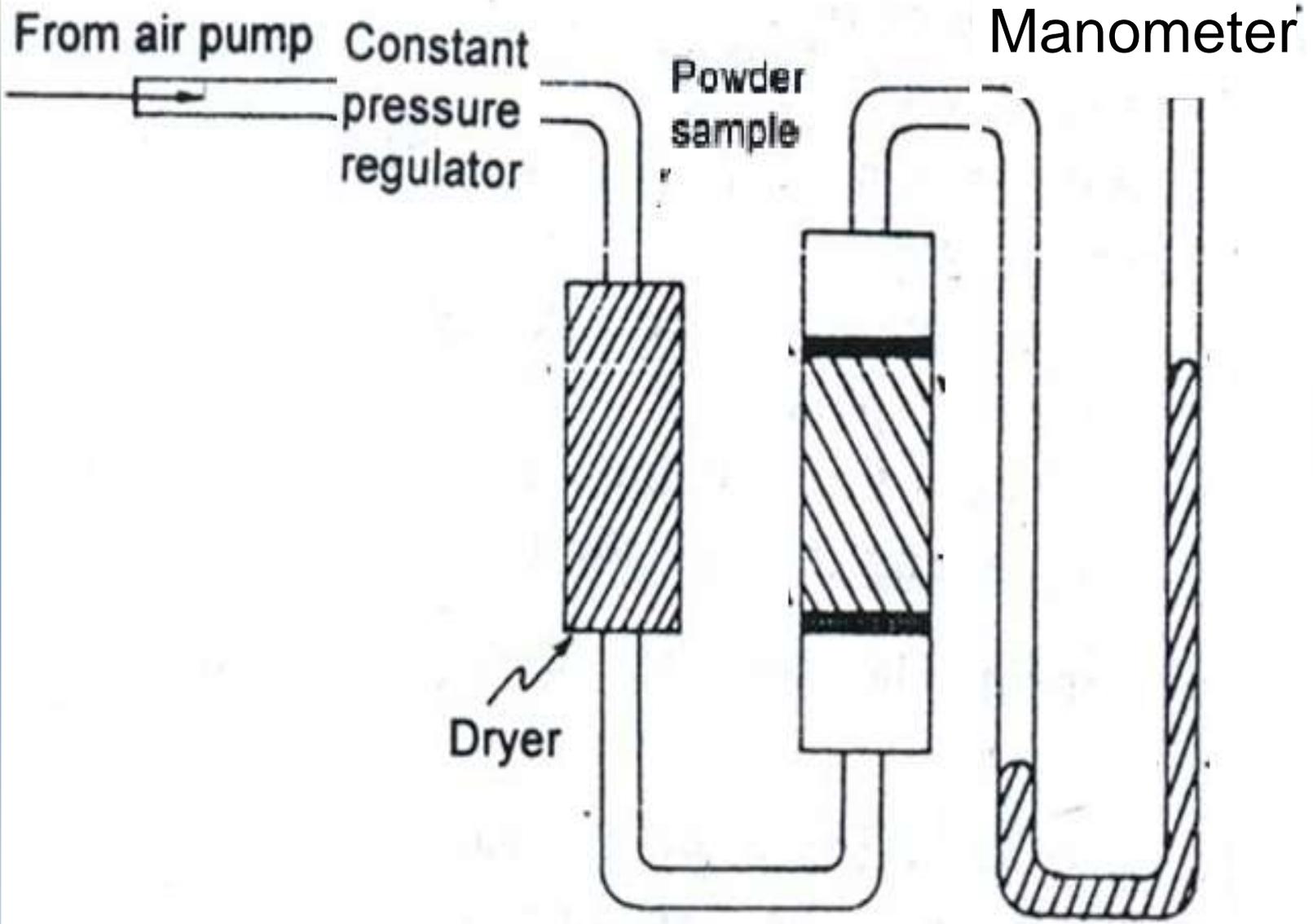
1. Adsorption method:

- **Surface area** is most commonly determined based on **Brunauer-Emmett-Teller (BET)** theory of adsorption.
- Most substances adsorb a monomolecular layer of gas under certain conditions of partial pressure of gas and temperature.
- The adsorption process is carried out **at liquid nitrogen temperatures -196°C** .
- Once surface adsorption has reached equilibrium, the sample is heated at RT and Nitrogen gas is desorbed. Its volume is measured.
- As each N_2 mol. occupies fixed area, one can compute surface area of pre-weighed sample.

Surface Area Determination

2. Air Permeability method:

- ▶ Powder is packed in sample holder
- ▶ Packing appears as series of capillaries
- ▶ Air is allowed to pass through the capillaries at constant pressure
- ▶ Resistance is created as air passes through capillaries thus causing pressure drop.
- ▶ Greater the surface area greater the resistance
- ▶ Air permeability is inversely proportional to the surface area



- **Surface area** of a powder can be calculated using particle size data obtained from any suitable method.
- Specific surface area i.e. surface area per unit weight (S_w) or unit volume (S_v) can be estimated as follows:
- $S_v = \frac{\text{surface area of particles}}{\text{volume of particles}}$
- $S_v = \frac{\text{no. of particles} \times \text{surface area of each particle}}{\text{no. of particles} \times \text{volume of each particle}}$

Surface area is an important parameter as the bioavailability of certain drugs is dependant on surface area. eg. Bephenium (anthelminitic), Griseofulvin (anti-fungal)- if the surface area is less than specified, the absorption decreases.

Derived properties of powders

Derived properties of powders

- ▶ Size or diameter is a fundamental property of a particle.
- ▶ Volume, density, porosity etc. are the properties derived from fundamental properties.
- ▶ e.g. Volume can be calculated from the diameter of the particle ($\frac{4}{3} \pi r^3$).
- ▶ However, derived properties can also be calculated without the use of fundamental properties.

DENSITY

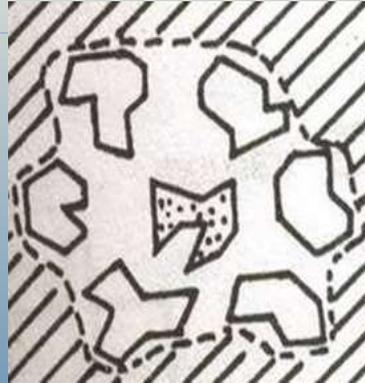
- **Apparent bulk density-** is determined by pouring presieved (40#) bulk drug into a graduated cylinder via a funnel and note the volume as is (g/ml) *without subjecting to any external force.*
- **Tapped density:** The cylinder is subjected to fixed no. of taps on a mechanical tapper apparatus (approx. 100) until the powder bed has reached minimum.
(useful for determining the appropriate size for capsule formulation)

Bulk Density Apparatus

Bulk density

= Mass of the powder

Bulk volume



Tapped bulk density

= Mass of the powder

Tapped Bulk volume



Applications

- ▶ Decides **the size of the capsule** based on bulk and tapped volume of a given sample
 - ▶ Higher the bulk volume, lower the bulk density and bigger the size of the capsule
- ▶ Helps to decide **proper size of a container or packing material**

- ▶ **Light powders**

- ▶ **When particles packed loosely**

- ▶ **Lots of gaps between particles**

- ▶ **Bulk volume increases**

- ▶ **Light powders have high bulk volume**

- ▶ **hence low density**

DENSITY

- **True density:** Volume occupied by voids (inter-particle spaces) and intraparticle pores are not included in this measurement.
- Calculated by suspending drug in solvents of various densities & in which the compound is insoluble.
- After vigorous agitation, samples are centrifuged briefly, and then left to stand undisturbed till settling/ flotation has reached equilibrium. The sample that remains suspended corresponds to the true density of the material. Calculated with a pycnometer.



TRUE DENSITY DETERMINATION

- Helium displacement method (for porous powders)
- Liquid displacement method (for non porous powders)

TRUE DENSITY DETERMINATION

■ Liquid displacement method

(for non porous powders)

- Select the solvent in which powder is insoluble
- Pycnometer or sp. gravity bottle is used.
- Wt. of pycnometer: w_1
- Wt. of pycnometer + sample: w_2
- Sample wt.: $w_3 = w_2 - w_1$
- Wt. of pycnometer + sample + solvent: w_4
- Wt. of liquid displaced by sample: $w_5 = w_4 - w_2$
- Thus, true density = w_3 / w_5

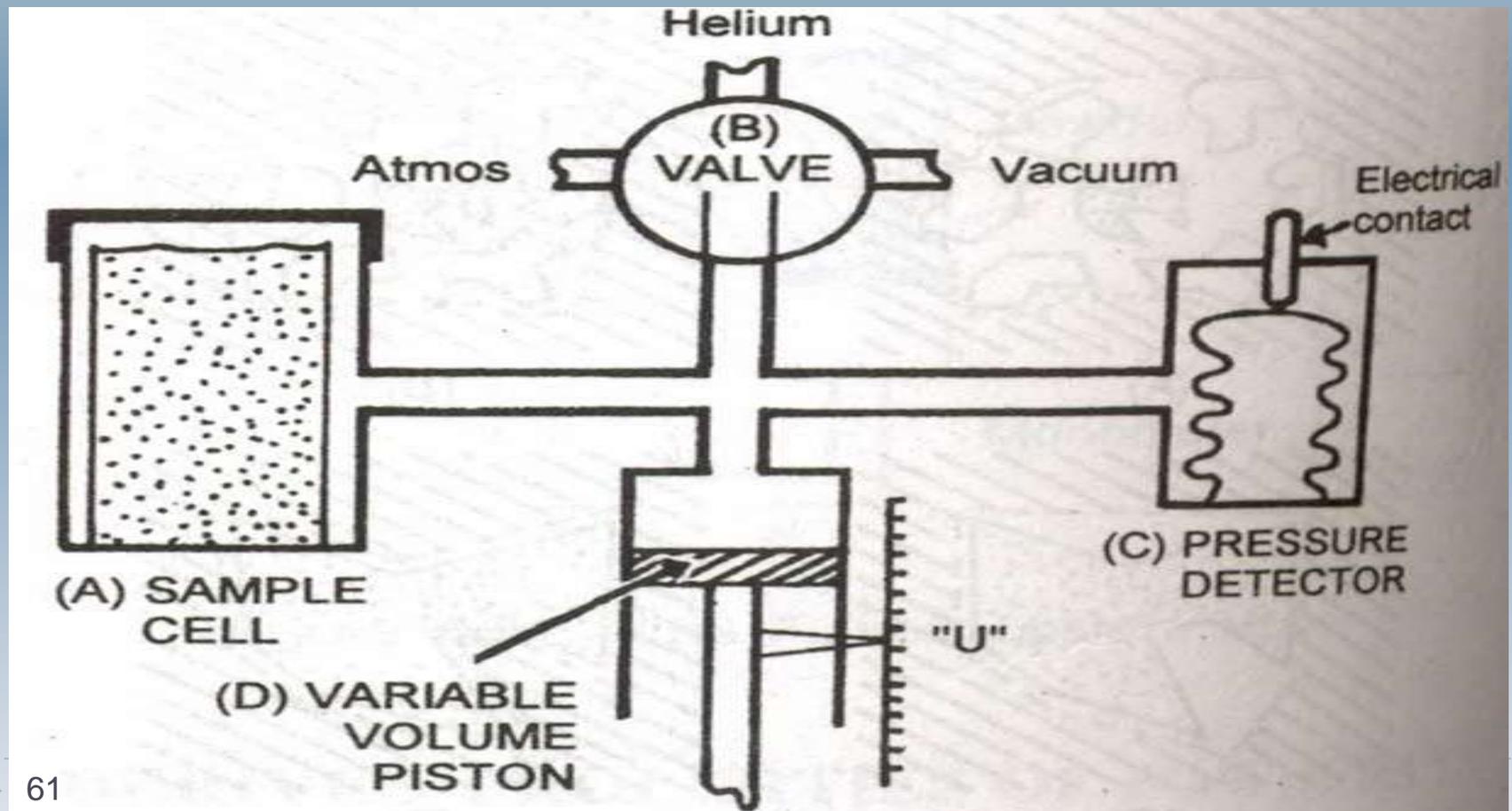


Helium displacement Method

- ▶ Helium gas is selected as it does not adsorb on solid sample.
- ▶ It enters the pores.
- ▶ very useful for estimating the true density of porous solids

▶ Helium Pycnometer

- ▶ Sample holder (A)
- ▶ Valve (B)
- ▶ Pressure detector (C)
- ▶ Piston (D)



- ▶ **Sample holder**

- ▶ Sealed after placing the sample

- ▶ **Valve**

- ▶ Connected to sample holder
- ▶ Has provisions for removing air from the sample holder and introducing helium gas

- ▶ **Pressure detector**

- ▶ Maintains preset constant pressure

- ▶ **Piston**

- ▶ Reads the corresponding pressure
- ▶ It is also related to the volume of the powder

Working:

- ▶ Air in the sample holder removed by vacuum
- ▶ Helium gas introduced through valve
- ▶ Pressure adjusted and set at particular value with the help of piston
- ▶ At this position, the reading on the scale denotes U_1

U_1 = volume of empty sample holder

- ▶ Place standard known true volume V_{std} of stainless steel spheres
- ▶ Air removed and helium gas introduced through valve
- ▶ Pressure adjusted to preset value with the help of piston
- ▶ At this position, the reading on the scale denotes U_2
- ▶ The difference between U_1 and U_2 gives the volume occupied by the standard.
- ▶ The last step involves determination of volume of sample. The standard is replaced with sample and the reading is noted, U_s .

- ▶ The difference between U_1 and U_s gives the

- ▶ $V_{\text{std}} = \text{True volume of std. sample}$
- ▶ $V_{\text{test}} = \text{true volume of the test sample}$
- ▶ $U_1 - U_2 = \text{Volume occupied by the std. sample}$
- ▶ $U_1 - U_s = \text{Volume occupied by the test sample}$

$$V_{\text{test}} = \frac{V_{\text{std}}}{U_1 - U_2} \cdot (U_1 - U_s)$$

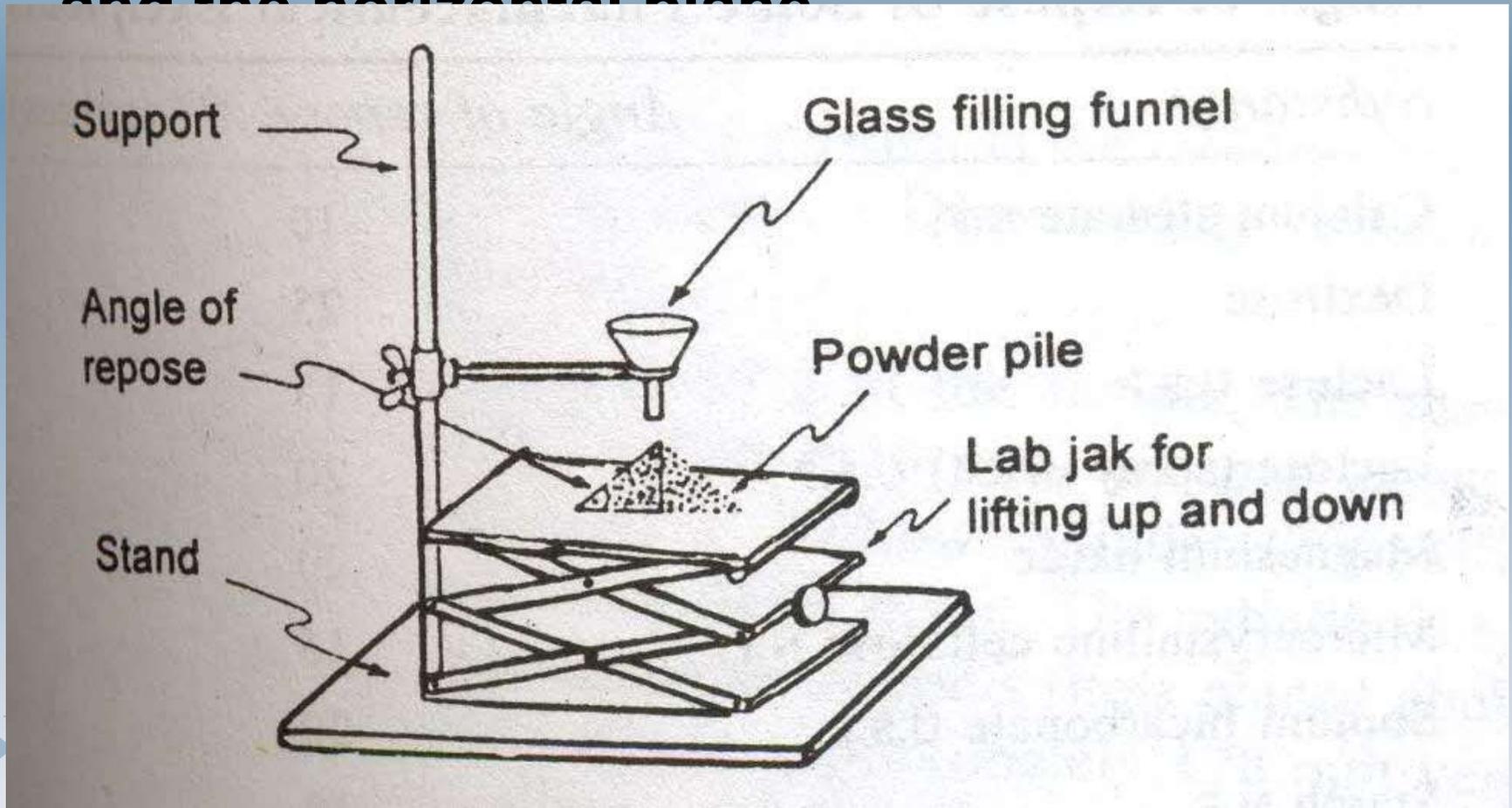
Powder flow properties

- Pharmaceutical powders may be broadly classified as free-flowing or cohesive.
- Most flow properties are significantly affected by changes in **particle size, density, electrostatic charges, adsorbed moisture.**
- Good flow property is required for easy and uniform flow from hopper to die cavity ensuring accurate weight and dose.

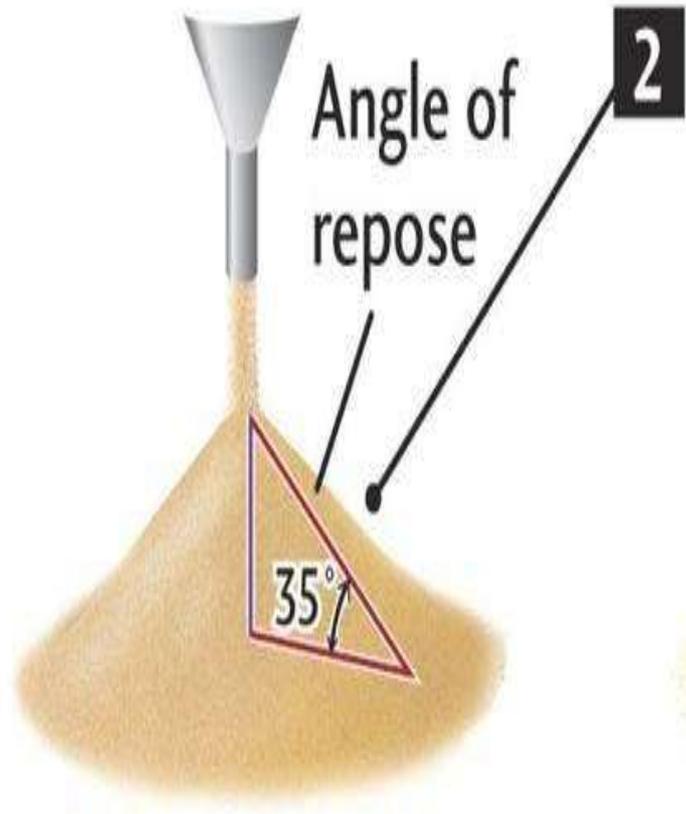


Angle of repose is calculated for estimating flow properties.

It is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane



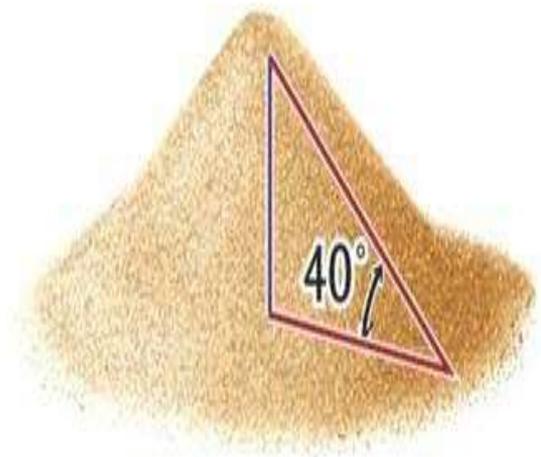
1



Angle of repose

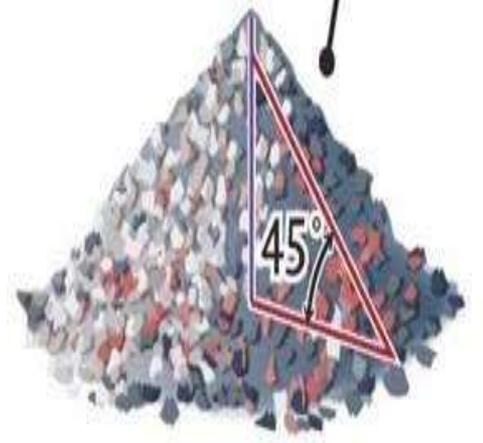
35°

Fine sand



40°

Coarse sand



45°

Angular pebbles

Powder flow properties estimation

- Simple flow rate apparatus consisting of a metal tube from which drug flows through an orifice onto an electronic balance, which is connected to a recorder.
- **Angle of repose** determination using **reposograph**
- Another method is % compressibility (**Carr's index**)
=
$$\frac{(\text{bulk volume} - \text{tapped volume}) \times 100}{\text{bulk volume}}$$
- ▶ **Hausner's ratio** = tapped density/ Bulk density
Or
Bulk volume/ tapped volume

Compressibility Index (%)	Flow Character	Hausner Ratio
10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

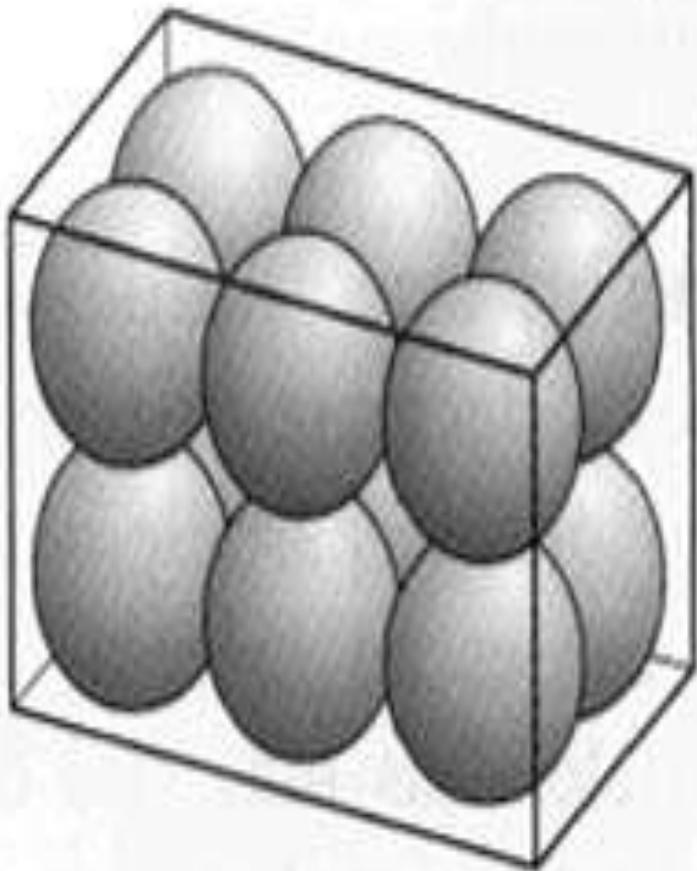
Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Packing properties (Porosity)

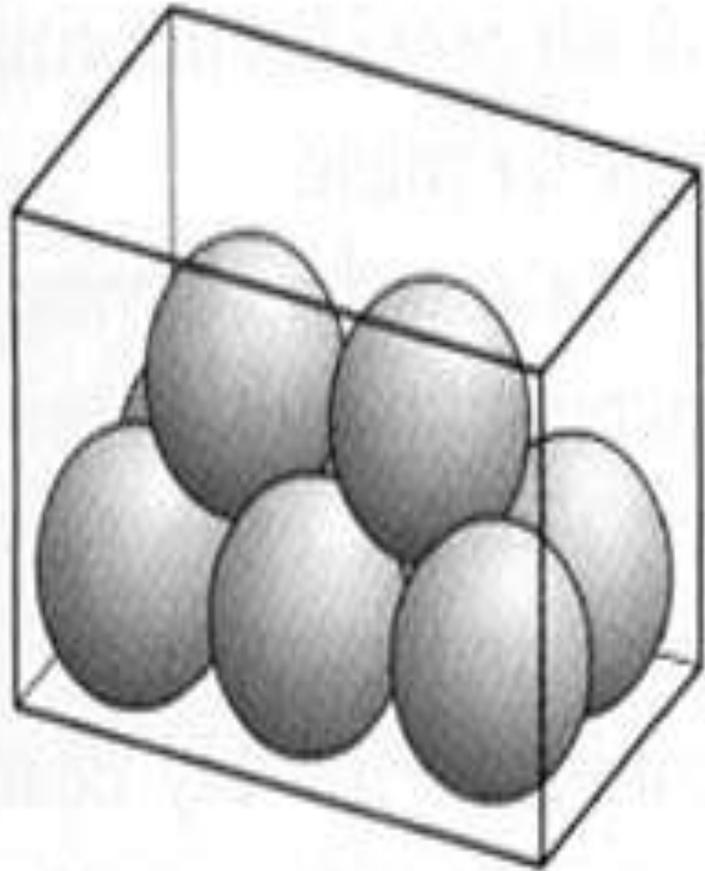
- ▶ **Porosity definition:** *It is the ratio of the volume of voids between particles, plus the volume of pores, to the total volume occupied by the powder, including voids and pores.*
- ▶ A set of particles can be filled into a volume of space in different ways.
- ▶ This is because by slight vibration, particles can be mobilized and can occupy a different spatial volume than before.
- ▶ This changes the bulk volume because of rearrangement of the packing geometry of the particles.
- ▶ In general, such geometric rearrangements result in a transition from loosely packed particles to more tightly

Packing properties (Porosity)

- ▶ Example: : A set of monosized spherical particles can be arranged in many different geometric configurations.
- ▶ In Fig.a, when the spheres form a cubic arrangement, the particles are most loosely packed and have a porosity of 48%
- ▶ In Fig.b, when the spheres form a rhombohedral arrangement, they are most densely packed and have a porosity of only 26%
- ▶ The porosity used to characterize packing geometry is linked to the bulk density of the powder.



(a)



(b)

Packing properties (Porosity)

- ▶ Thus bulk density, is a characteristic of a powder rather than individual particles and can be variable.
- ▶ The bulk density of a powder is always less than the true density of its component particles because the powder contains interparticle voids.
- ▶ **Thus, powder can possess a single true density but can have many different bulk densities, depending on the way in which the particles are packed and the bed porosity.**

Powder fluidization

- ▶ Fluidization can be a highly effective method for **handling a fine bulk material** in an aerated or liquid-like condition. Air or another gas can be used for powder fluidization either in a fully fluidized state or only in a localized manner with small amounts of gas flow.
- ▶ Typical bulk solids suitable for fluidization have a fine particle size, a low permeability, and low cohesive strength.

Advantages:

- ▶ Elimination or reduction of poor flow problems of powder, Increased discharge rate from hopper
- ▶ Reduction in mixture segregation

Large Scale Equipment

I. Particle-size reduction

- ▶ The need of size reduction can be to improve solubility thus improve its bioavailability. In case of disperse systems, it helps in improving stability (*discussed earlier*).
- ▶ The function of size reduction may also be to aid efficient processing of solid particles by facilitating better powder mixing.
- ▶ There are also some special functions of size reduction, such as reducing the bulk volume of a material to improve transportation efficiency.

Size Reduction methods

1. **Cutting method: Cutter mill**
2. **Compression method: Endrunner and edge runner mill**
3. **Impact method: Hammer mill, vibration mill**
4. **Attrition method: Roller mill**
5. **Combined impact and attrition: ball mill, Fluid energy mill**



Size Reduction methods

1. Cutting method- Cutter mill

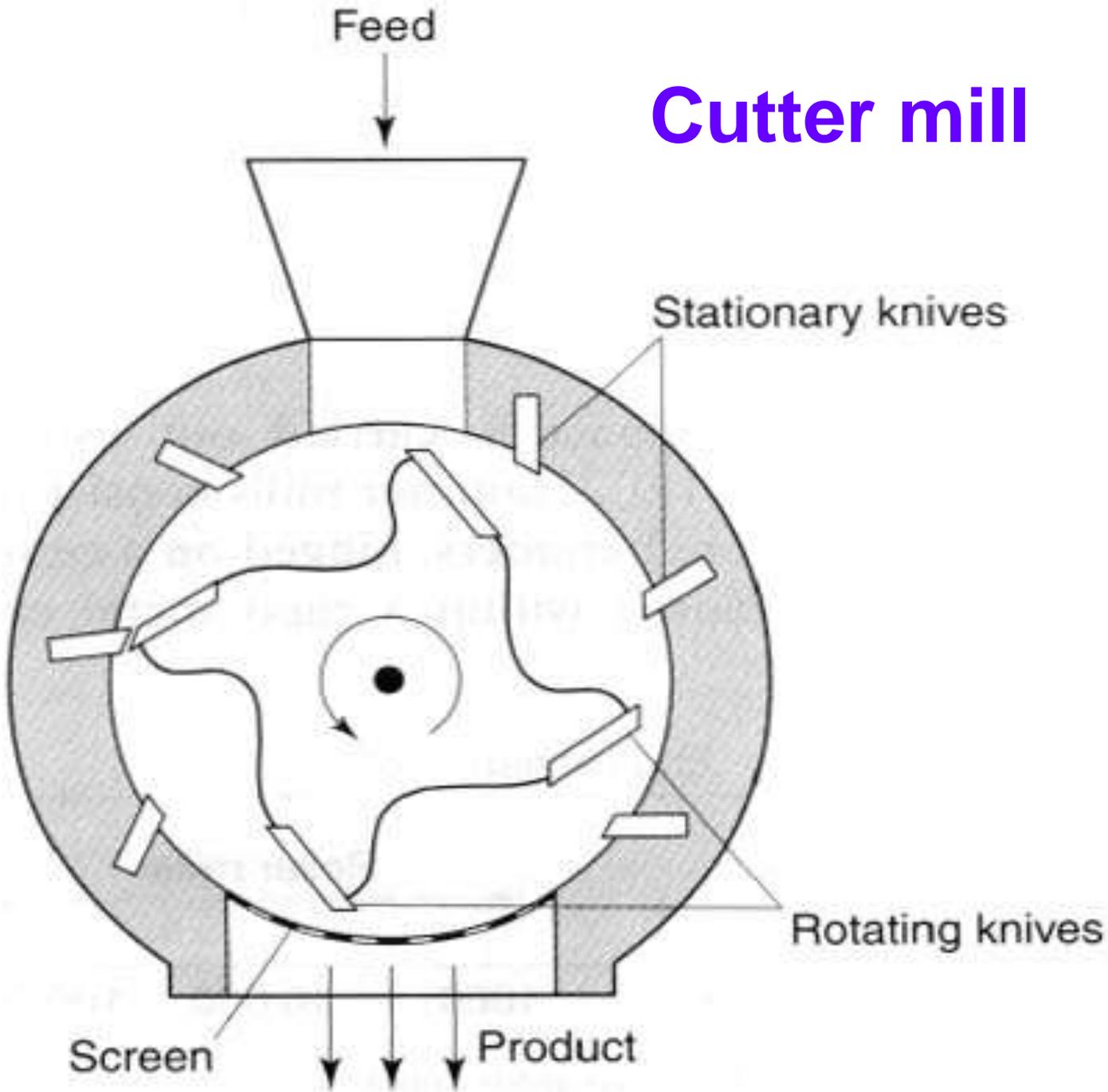
- ▶ A cutter mill consists of a **series of rotating knives** attached to a horizontal rotor which act against a series of **stationary knives** attached to the mill casing.
- ▶ During milling, size reduction occurs by fracture of particles between the two sets of knives, which have a clearance of a few millimetres.
- ▶ A screen is fitted in the base of the mill casing and acts to retain material in the mill until a sufficient degree of size reduction has been

- ▶ The high shear rates present in cutter mills are useful in producing a **coarse degree of size reduction** of dried granulations prior to tableting.
- ▶ Used for fibrous crude drugs such as roots, peels or barks prior to extraction.

Cutting Mill



Cutter mill



II. Compression method-

- ▶ Size reduction by compression can be carried out on a small scale using a **mortar and pestle**.
- ▶ **End-runner and edge-runner mills** are mechanized forms of mortar and pestle.
- ▶ In the **end-runner mill** a heavy pestle is turned by the friction of material passing beneath it as the mortar rotates under power.
- ▶ **The edge-runner mill** has the pestles mounted horizontally. It rotates against a bed of powder, so that size reduction occurs by attrition as well as compression.
- ▶ Scrapers are employed in scraping the material constantly from the bottom of the vessel. Such techniques are now rarely used in pharmaceutical

EDGE-RUNNER MILL



END-RUNNER MILL



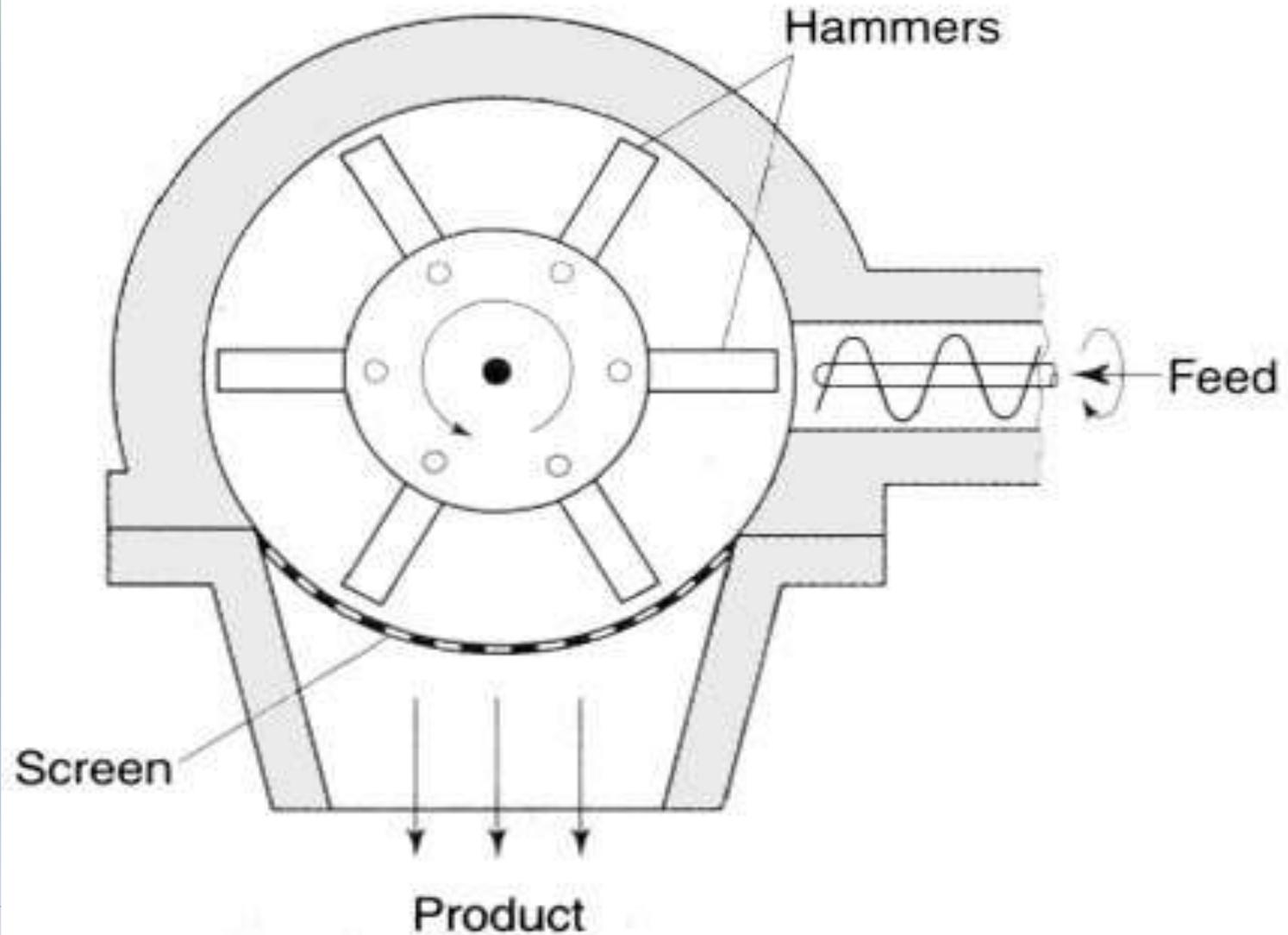
III. Impact method

- ▶ Size reduction by impact is carried out using a **hammer mill**.
- ▶ Hammer mills consist of a series of four or more hammers, hinged on a central shaft which is enclosed within a rigid metal case.
- ▶ During milling the hammers swing out radially from the rotating central shaft.
- ▶ **The velocity of the hammer is so high that most particles undergo brittle fracture.**

Impact method

- ▶ Hammer mills tend to produce powders with narrow size distributions.
- ▶ Particles are retained within the mill by a screen, which allows only adequately comminuted particles to pass through.
- ▶ According to the purpose of the operation, the hammers may be square-faced, tapered to a cutting edge or have a stepped form.

Hammer mill



Vibration mill

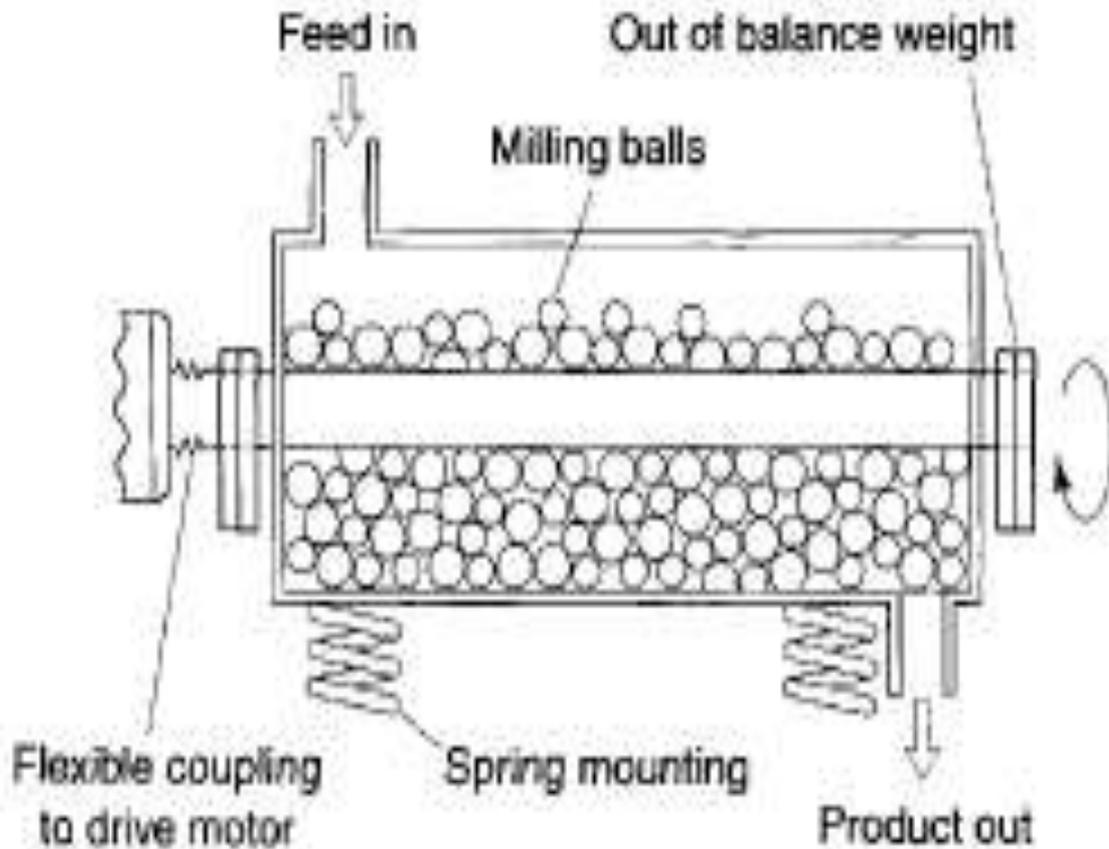


Fig. 11.10 Vibration mill.

- Vibration mills are filled with porcelain or steel balls.
- During milling the whole body of the mill is vibrated
- Size reduction occurs by repeated impaction.

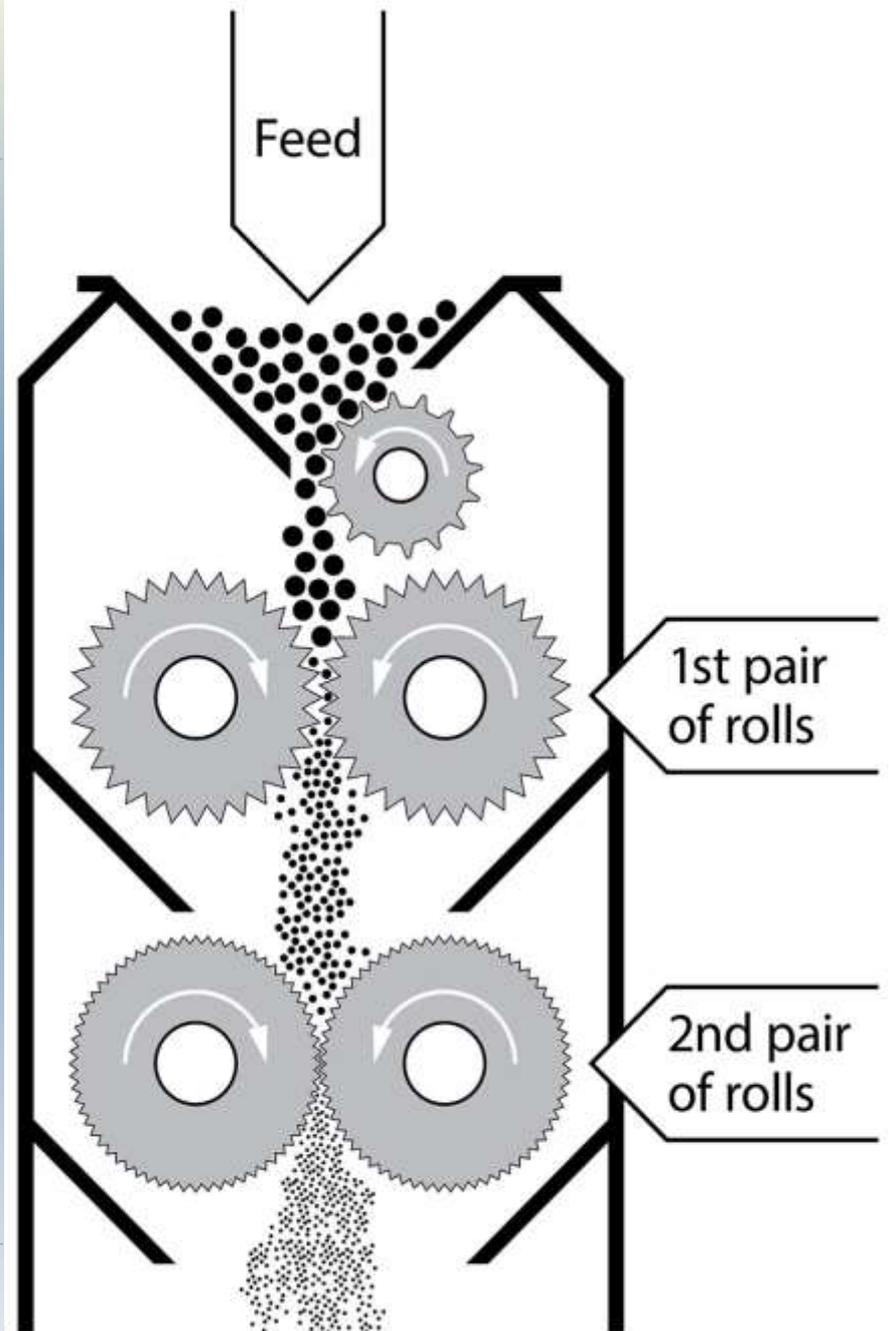
IV. Attrition method

- ▶ **Roller mills** use the principle of attrition to produce size reduction of solids in suspensions, pastes or ointments.
- ▶ Two or three **porcelain or metal rolls** are mounted horizontally with an adjustable gap, which can be as small as 20 μm .
- ▶ The rollers rotate at different speeds in counter-clockwise manner so that the material is sheared as it passes through the gap and is transferred from the slower to the faster roll, from which it is removed by means of a scraper.

FULLY HYDRAULIC THREE ROLLER MILL



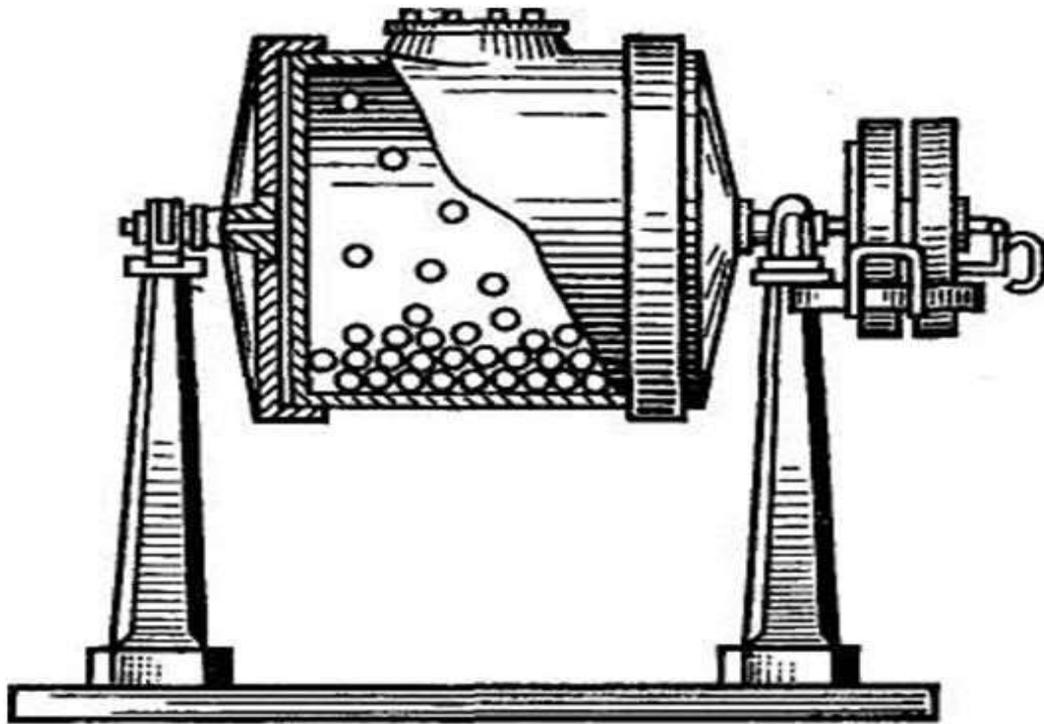
PHOTO CREDIT : HW ANALY MACHINE INDUSTRIAL CO., LTD.



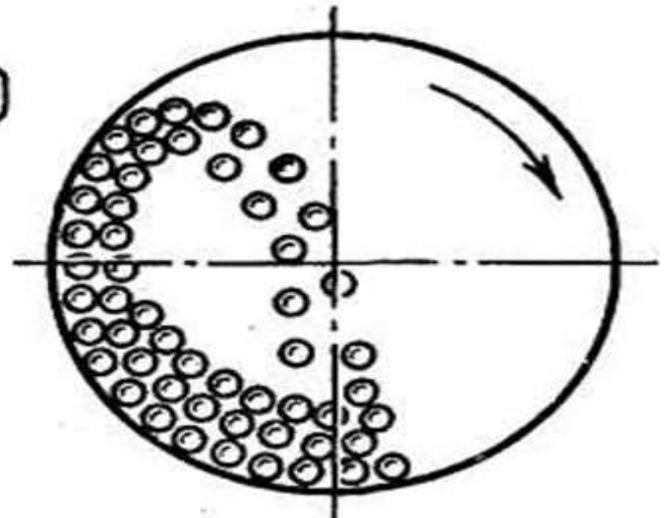
V. Combined impact and attrition methods

- ▶ A **ball mill** is an example of a comminution method which produces size reduction by both **impact and attrition of particles**.
- ▶ Ball mills consist of a hollow cylinder mounted such that it can be rotated on its horizontal longitudinal axis.
- ▶ Mills usually contain balls with many different diameters owing to self-attrition, and this helps to improve the product as the large balls tend to break down the coarse feed materials and the smaller balls help to form the fine product by reducing void spaces between balls.

Ball mill



a



b

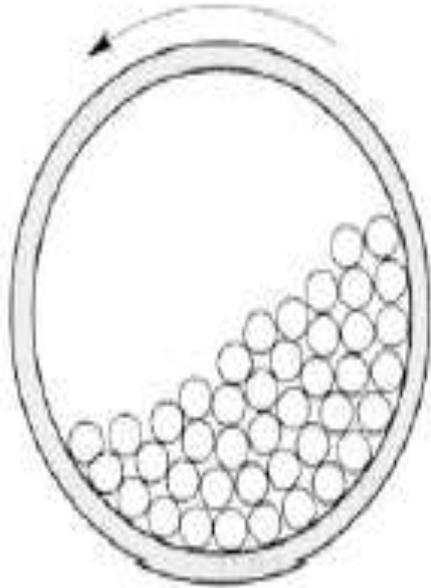
V. Combined impact and attrition methods

- ▶ The **amount of material in a mill** is of considerable importance: too much feed produces a cushioning effect and too little causes loss of efficiency and abrasive wear of the mill parts.
- ▶ The factor of greatest importance in the operation of the ball mill is the **speed of rotation**.
- ▶ At low velocities- balls move with drum and very little relative movement of balls is achieved so the size reduction is minimal.

V. Combined impact and attrition methods

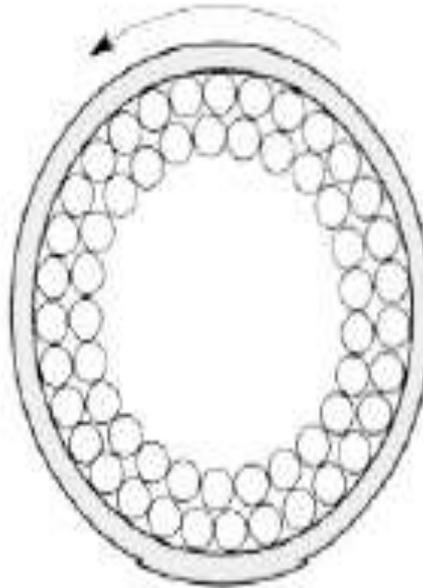
- ▶ At high angular velocities the balls are thrown out on to the mill wall by centrifugal force and no size reduction occurs.
- ▶ At about two-thirds of the critical angular velocity where centrifuging occurs, a **cascading action** is produced.
- ▶ By this means, the maximum size reduction occurs by impact of the particles with the balls and by attrition.

low velocity



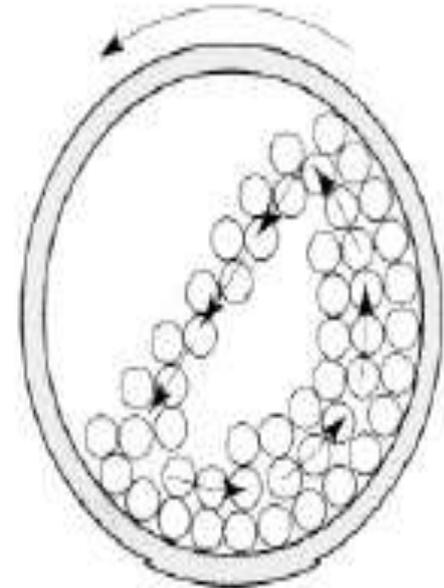
(a)

high velocity



(b)

moderate velocity



(c)

11.13 Ball mill in operation, showing correct cascade action.

V. Combined impact and attrition methods

- ▶ **Fluid energy milling** is another form of size-reduction method which acts by particle impaction and attrition.
- ▶ This type of mill or 'micronizer' consists of a hollow toroid (*structure with a hole; like a doughnut*) 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 as a high-pressure jet through nozzles at the bottom.
- ▶ The high velocity of the air gives rise to zones of turbulence into which solid particles are fed

V. Combined impact and attrition methods

- ▶ The high kinetic energy of the air **causes the particles to impact -with other particles** with sufficient momentum for fracture to occur.
- ▶ Turbulence ensures that the level of particle-particle collisions is high enough to produce substantial **size reduction by impact and some attrition.**
- ▶ A **particle size classifier** is incorporated in the system so that particles are retained in the toroid until sufficiently fine and remain entrained in the air stream that is exhausted from the mill

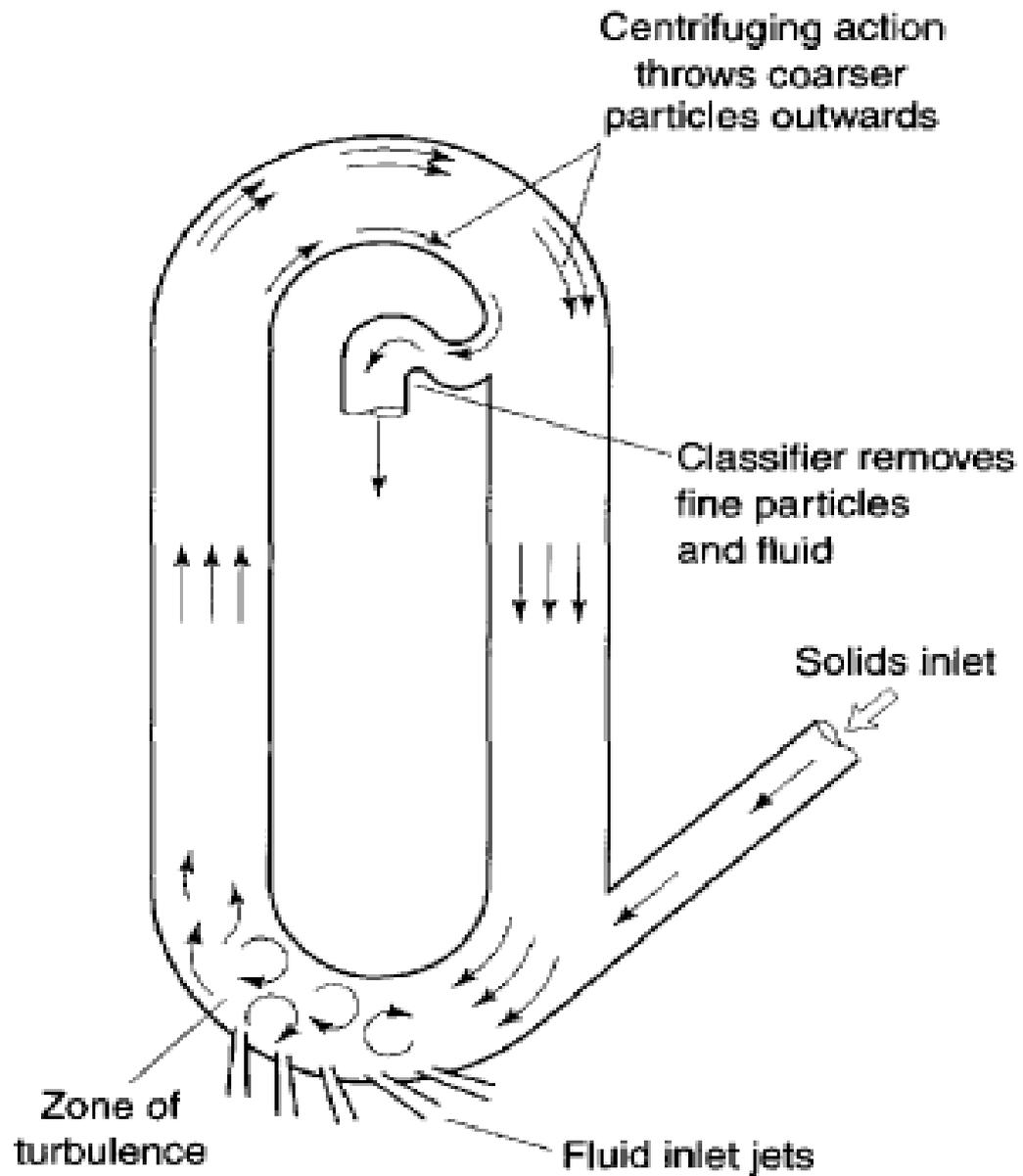


Fig. 11.14 Fluid energy mill.



Jet Mill MC 300 KX-TD

PHOTO CREDIT: SERVOLIFT

Particle-size separation

II. Particle-size separation

- ▶ Size separation is a process by which powder particles are classified into separate particle size ranges.

SIZE-SEPARATION METHODS

1. **Size separation by sieving**
2. **Size separation by fluid classification-**
 - Sedimentation method**
 - ▶ **Elutriation method**
 - ▶ **Cyclone methods**

1. Size separation by sieving

Principle and construction:

Same as described in size reduction

- ▶ The use of sieving in size separation usually **requires processing of larger volumes of powder** than are commonly found in size analysis operations.
- ▶ For this reason, the **sieves used for size separation are often larger in area** than those used for size analysis.

1. Size separation by sieving

▶ There are several techniques for separating particles into their appropriate size fractions efficiently.

1. **Agitation methods-** *Size separation is achieved by electrically induced oscillation or mechanically induced vibration of the sieve meshes, or alternatively by gyration, in which sieves are fitted to a flexible mounting which is connected to an flywheel.*

The rotation of the flywheel imparts a rotary movement of high intensity to the sieve and causes the particles to spin, thereby continuously changing their orientation and increasing their

▶ 102



1. Size separation by sieving

- ▶ ***Brushing methods-*** *A brush is used to re-orientate particles on the surface of a sieve and prevent apertures becoming blocked.*
- ▶ ***A single brush can be rotated about the midpoint of a circular sieve or, for large-scale processing, a horizontal cylindrical sieve, is employed, with a spiral brush rotating about its longitudinal axis.***



1. Size separation by sieving

- ▶ **Centrifugal methods** - *Particles are thrown outwards on to a vertical cylindrical sieve under the action of a high-speed rotor inside the cylinder.*
- ▶ *The current of air created by the rotor movement also assists in sieving, especially where very fine powders are being processed.*

II. Size separation by fluid classification

1. *Sedimentation method*

- ▶ Size separation by sedimentation utilizes the differences in settling velocities of particles with different diameters, and these can be related according to Stokes' equations
- ▶ *eg. use of Andreasen pipette:*
- ▶ Disadvantages of this method is that they it is a batch processes and discrete particle fractions cannot be collected, as samples do not contain specific size ranges.

1. *Sedimentation method*

- ▶ An alternative technique is to use a **continuous settling chamber** so that particles in suspension enter a shallow container, in a streamline flow.
- ▶ Particles entering at the top of the chamber are acted upon by a driving force which can be divided into two components:
- ▶ A **horizontal component** equal to the suspension fluid velocity, and a
- ▶ A **vertical component** which corresponds to Stokes' settling velocity and is different for
- ▶ ¹⁰⁸each particle size

1. *Sedimentation method*

- ▶ The coarsest particles will have the steepest settling paths and will **sediment closest to the inlet**, whereas the finest particles with low Stokes velocity component will have the shallowest settling paths and **will sediment furthest from the fluid suspension feed stream**
- ▶ Particles separated into the different hopper-type discharge points can be removed continuously.

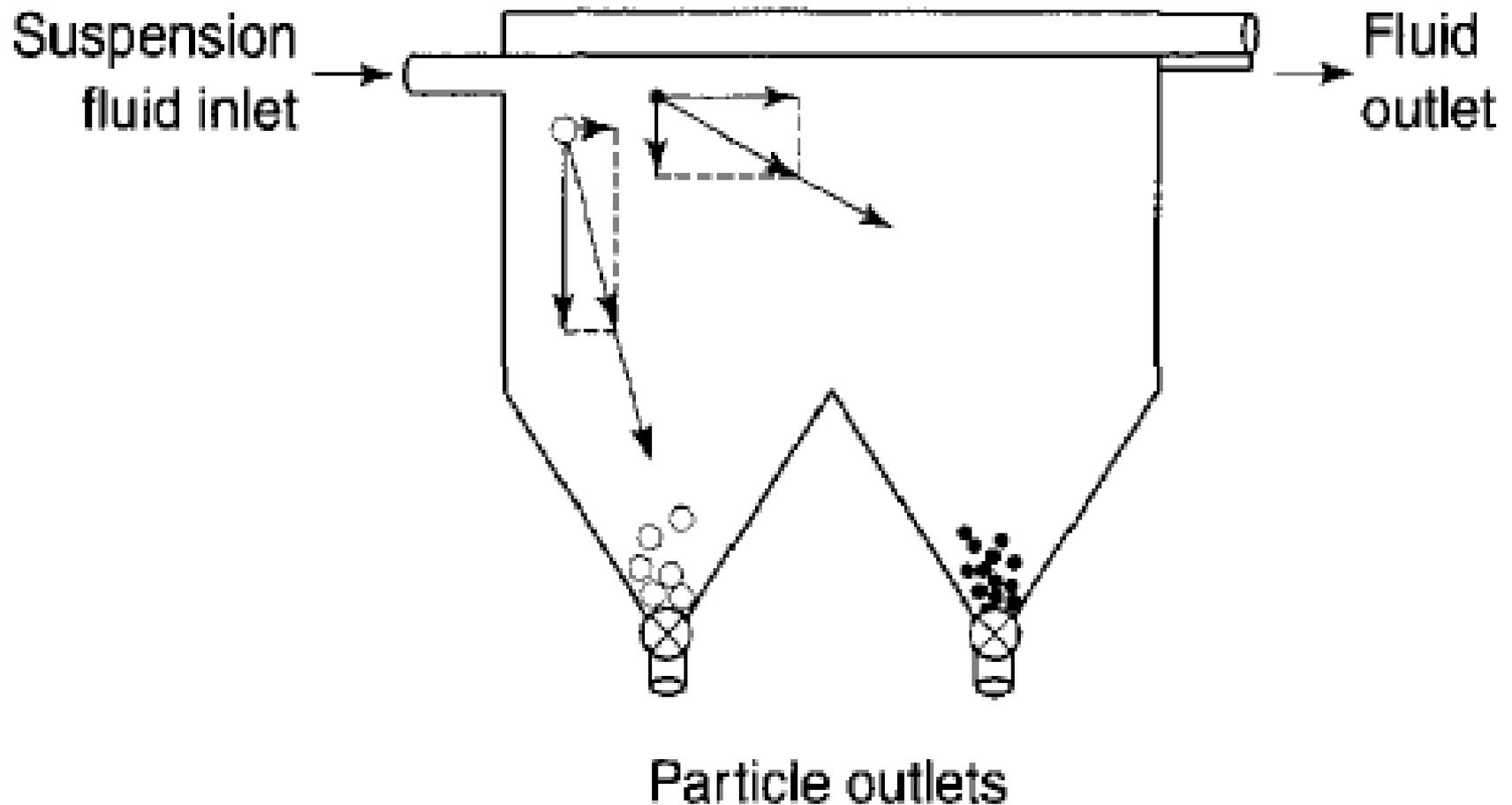


Fig. 12.4 Continuous settling chamber showing vectors of particle movement for different sizes.

II. Elutriation method

Principle:

- ▶ In sedimentation methods the fluid is stationary and the separation of particles of various sizes depends solely on particle velocity.
- ▶ Therefore, the division of particles into size fractions depends on the ***time of sedimentation***.
- ▶ ***Elutriation is a technique in which the fluid flows in an opposite direction to the sedimentation movement, so that in gravitational elutriators particles move vertically downwards while the fluid travels***

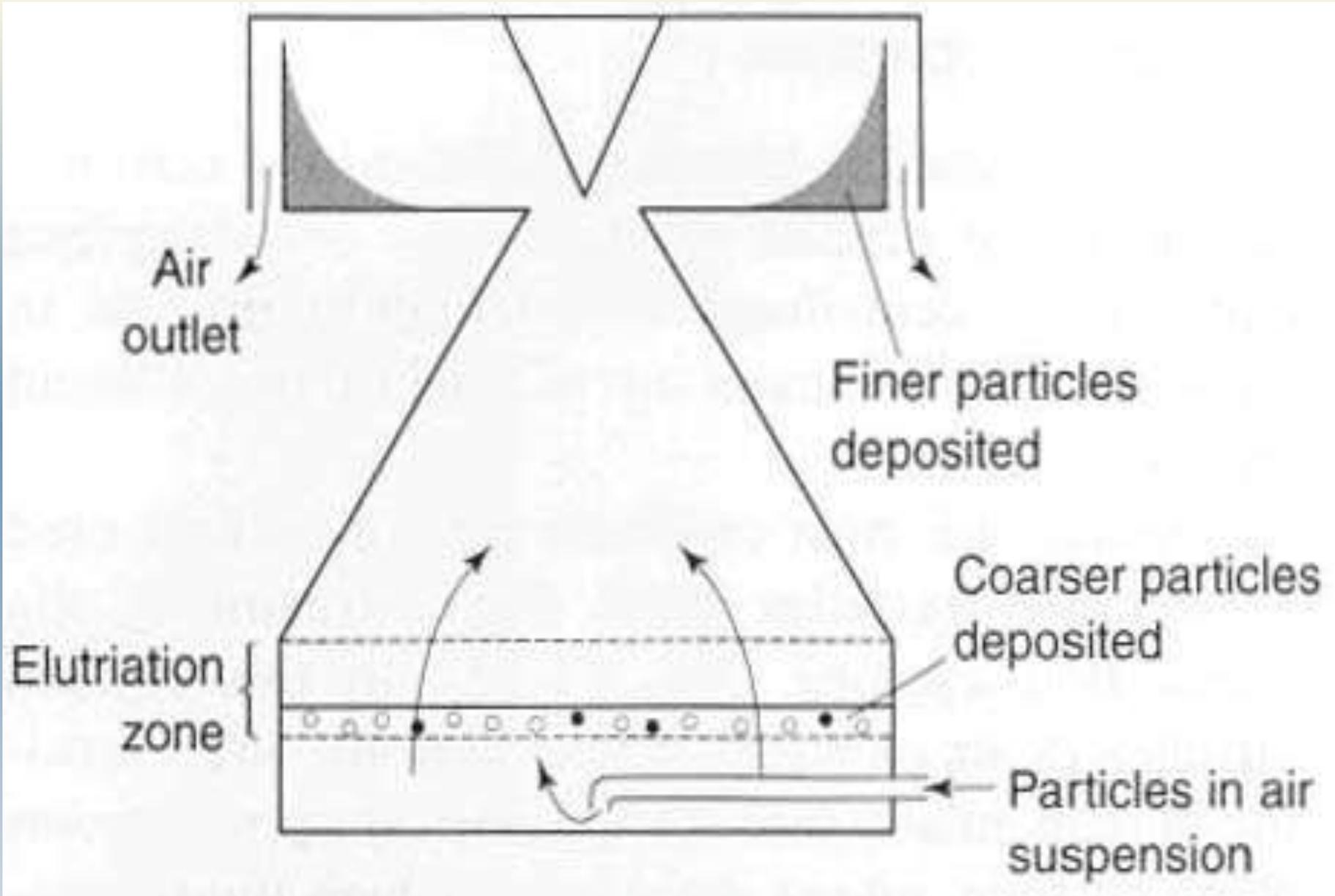
II. Elutriation method

Principle:

- ▶ If the upward **velocity of the fluid is less than the settling velocity of the particle, sedimentation occurs** and the particle moves downwards against the flow of fluid.
- ▶ Conversely, if the settling velocity of the particle is less than the upward fluid velocity, the particle moves upwards with the fluid flow.
- ▶ ***Therefore, in the case of elutriation, particles are divided into different size fractions depending on the velocity of the fluid***

II. Elutriation method

- ▶ Air may be used as the counter-flow fluid in place of water for elutriation of soluble particles into different size ranges.
- ▶ There are several types of air elutriator, which differ according to the airflow patterns used.
- ▶ Particles are held on a supporting mesh through which air is drawn.
- ▶ The desired particle size fraction can be separated **by selecting the appropriate airflow rate and rotor speed.**



AIR ELUTRIATOR

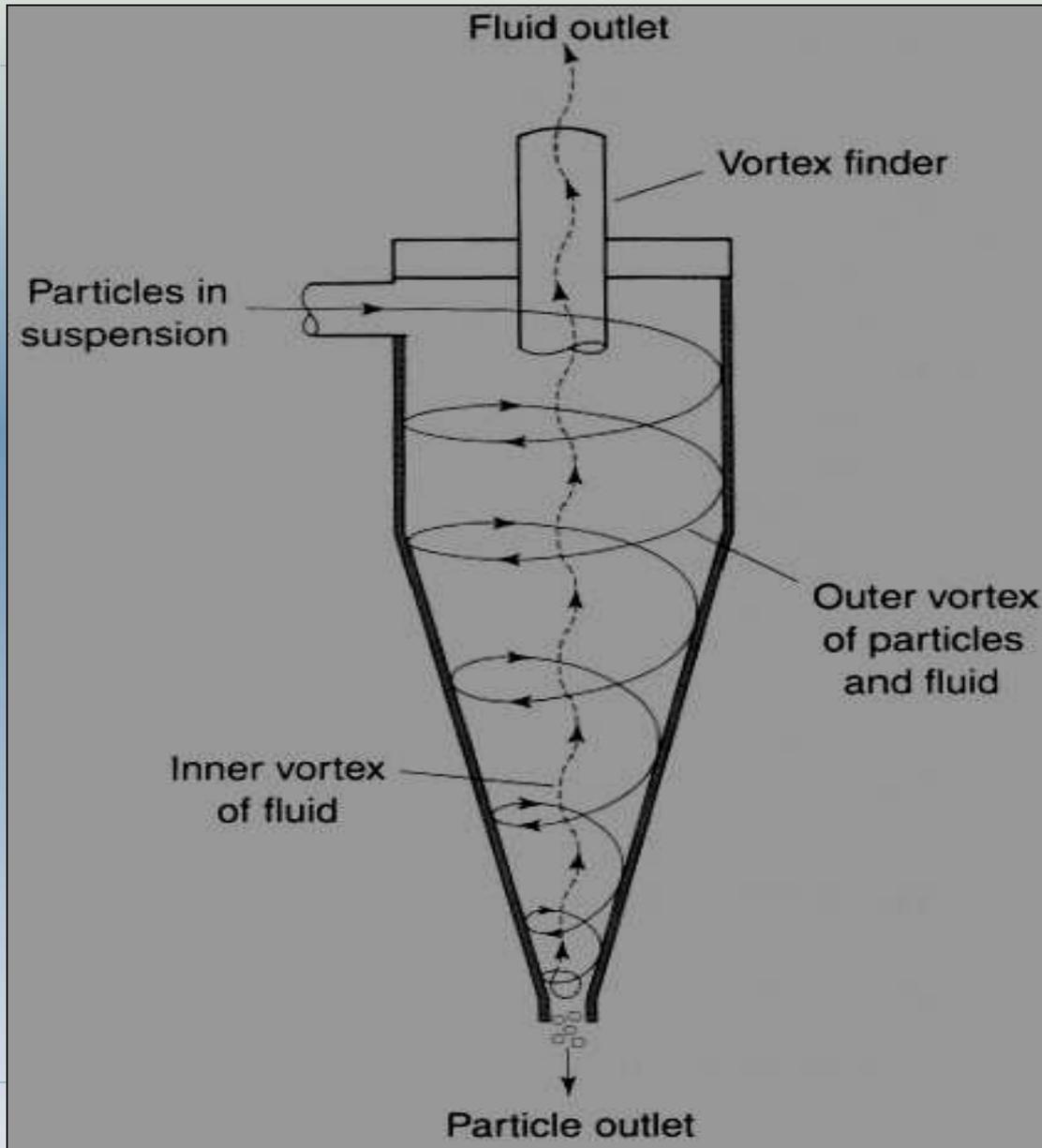
III. Cyclone methods

- ▶ Cyclone separation can take the form of a centrifugal elutriation process or a centrifugal sedimentation process in which **particles sediment out of a helical gas or liquid stream.**
- ▶ The most common type of cyclone used to separate particles from fluid streams is the **reverse-flow cyclone.**
- ▶ In this system, particles in air or liquid suspension are often introduced tangentially into the cylindrical upper section of the cyclone, where the relatively high fluid velocity produces

II. Cyclone methods

- ▶ *Coarser particles separate from the fluid stream and fall out of the cyclone through the **particle outlet**, whereas finer particles remain entrained in the fluid stream and leave the cyclone through the **vortex finder**.*
- ▶ A series of cyclones having different flow rates or different dimensions could be used to separate a powder into different particle-size ranges.

Reverse-flow cyclone separator



III. Powder Mixing and Demixing



Powder Mixing

The importance of mixing

- ▶ Pharmaceutical products contain several ingredients to formulate required dosage form eg. Tablets contain variety of excipients like- diluents, binders, disintegrants and lubricants
- ▶ Whenever a product contains more than one component a mixing or blending stage is required to ensure an **even distribution of the active component** for uniform drug distribution and release at a desired rate, for even appearance, etc

Mixing

- ▶ Pharmaceutical mixing may be defined as a unit operation that aims to bring each component as near as possible to each unit of the other components.
- ▶ If this is achieved it produces a theoretical 'ideal' situation, i.e. a ***perfect mix***.

Powder segregation (demixing)

- ▶ Segregation is the opposite effect to mixing, i.e. components tend to separate out.
- ▶ Care must be taken to avoid segregation during handling after powders have been mixed, e.g. during transfer to filling machines, or in the hopper of a tablet/capsule/sachet-filling machine.
- ▶ Segregation will cause an increase in **content variation** , **weight variation** in samples causing a batch to fail a uniformity of content test.

Reasons for Powder segregation (demixing)

- ▶ Segregation arises because powder mixtures are not composed of mono-sized spherical particles, **but contain particles that differ in size, shape and density.**
- ▶ These variations mean that particles will tend to behave differently when forced to move and hence, tend to separate.
- ▶ Segregation is more likely to occur, if the powder bed is subjected to vibration.
- ▶ ***Reasons are – particle size effects, density effects, shape effects..***

Particle-size effects

- ▶ A difference in the particle sizes of components of a formulation is the main cause of segregation in powder mixes in practice.
- ▶ Smaller particles tend to fall through the voids between larger ones and so move to the bottom of the mass.
- ▶ This is known as ***percolation segregation***. eg in cereal packets or jars of coffee, where the smaller 'particles' settle towards the bottom of the container

Particle-size effects

- ▶ During mixing, larger particles will tend to have greater kinetic energy imparted to them (owing to their larger mass) and therefore move greater distances than smaller particles before they come to rest.
- ▶ This may result in the separation of particles of different size, an effect referred to as ***trajectory segregation***.

Particle-size effects

- ▶ During mixing, or when a material is discharged from a container, very small particles ('dust') tends to be 'blown' upwards by turbulent air currents, and remains suspended in the air.
- ▶ When the mixer is stopped or material discharge is complete, these particles will sediment and subsequently form a layer on top of the coarser particles.
- ▶ This is called ***elutriation segregation and is also referred to as 'dusting out'***.

Particle-density effects

- ▶ If components are of different density, the more dense material will have a tendency to move downwards even if the particle sizes are similar.

Particle-shape effects

- ▶ Spherical particles exhibit the greatest flowability and are therefore more easily mixed, but they also segregate more easily than non-spherical particles.
- ▶ Irregularly or needle-shaped particles may become interlocked, reducing the tendency to segregate once mixing has occurred.

Approaches to reduce/ prevent segregation

- ▶ **Selection of particular size** fractions (e.g. by sieving to remove fines or lumps) to achieve drug and excipients of the same narrow particle size range;
- ▶ **Size reduction** (Milling of components) to reduce the particle size (excessive size reduction should be avoided)
- ▶ **Controlled crystallization** during production of the drug/excipients to give components of a particular crystal shape or size range.

- ▶ **Selection of excipients** which have a **density similar** to the active component (s)
- ▶ Granulation of the powder mixture (size enlargement) so that large numbers of different particles are evenly distributed in each granule.
- ▶ Reduce the extent to which the powder mass is subjected to vibration or movement after mixing;
- ▶ Use equipment where several operations can be carried out without transferring the mix, e.g. a fluidized-bed drier or a high-speed mixer

Powder mixing equipment

1. *Tumbling mixers/blenders*
2. *High-speed mixer-granulators*
3. *Fluidized-bed mixers*
4. *Agitator mixers*



1. ***Tumbling mixers/blenders***

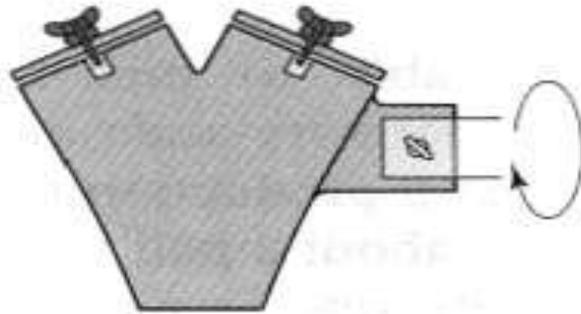
- ▶ Tumbling mixers are commonly used for the **mixing/blending of granules or free-flowing powders.**
- ▶ There are many different designs of tumbling mixer, e.g. **double-cone mixers, twin-shell mixers, cube mixers, Y-cone mixers and drum mixers** etc (see diagram)
- ▶ Mixing containers are generally mounted so that they can be rotated about an axis.
- ▶ When operated at the correct speed, the desired tumbling action is achieved.

1. *Tumbling mixers/blenders*

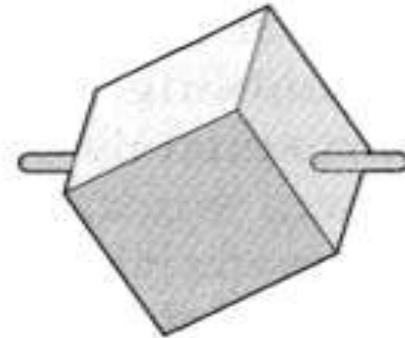
- ▶ Too high a rotation speed will cause the material to be held on the mixer walls by centrifugal force, and too low a speed will generate little shear mixing.
- ▶ The addition of '**prongs**', **baffles** or **rotating bars** also helps in good mixing.
- ▶ Tumbling mixers are available from approx 50 g, e.g. for laboratory-scale development work, to over 100 kg at a production scale.
- ▶ The rate of mixing depends on mixer design.
- ▶ The material typically occupies about a half to $\frac{2}{3}^{\text{rd}}$ of the mixer volume.

1. *Tumbling mixers/blenders*

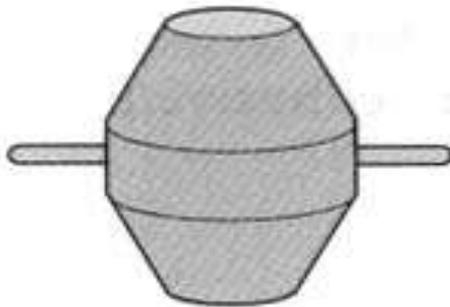
- ▶ Tumbling mixers are **good for free-flowing powders/granules** but poor for cohesive/poorly flowing powders.
- ▶ A common use of tumbling mixers is in the blending of lubricants, glidants or external disintegrants with granules prior to tableting.



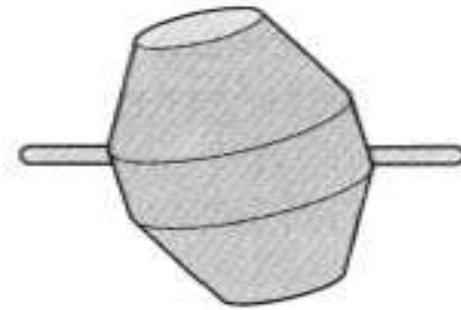
Y-cone mixer



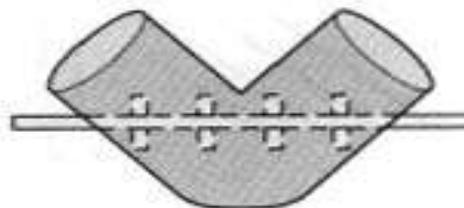
Rotating cube



Double cone



Oblique cone



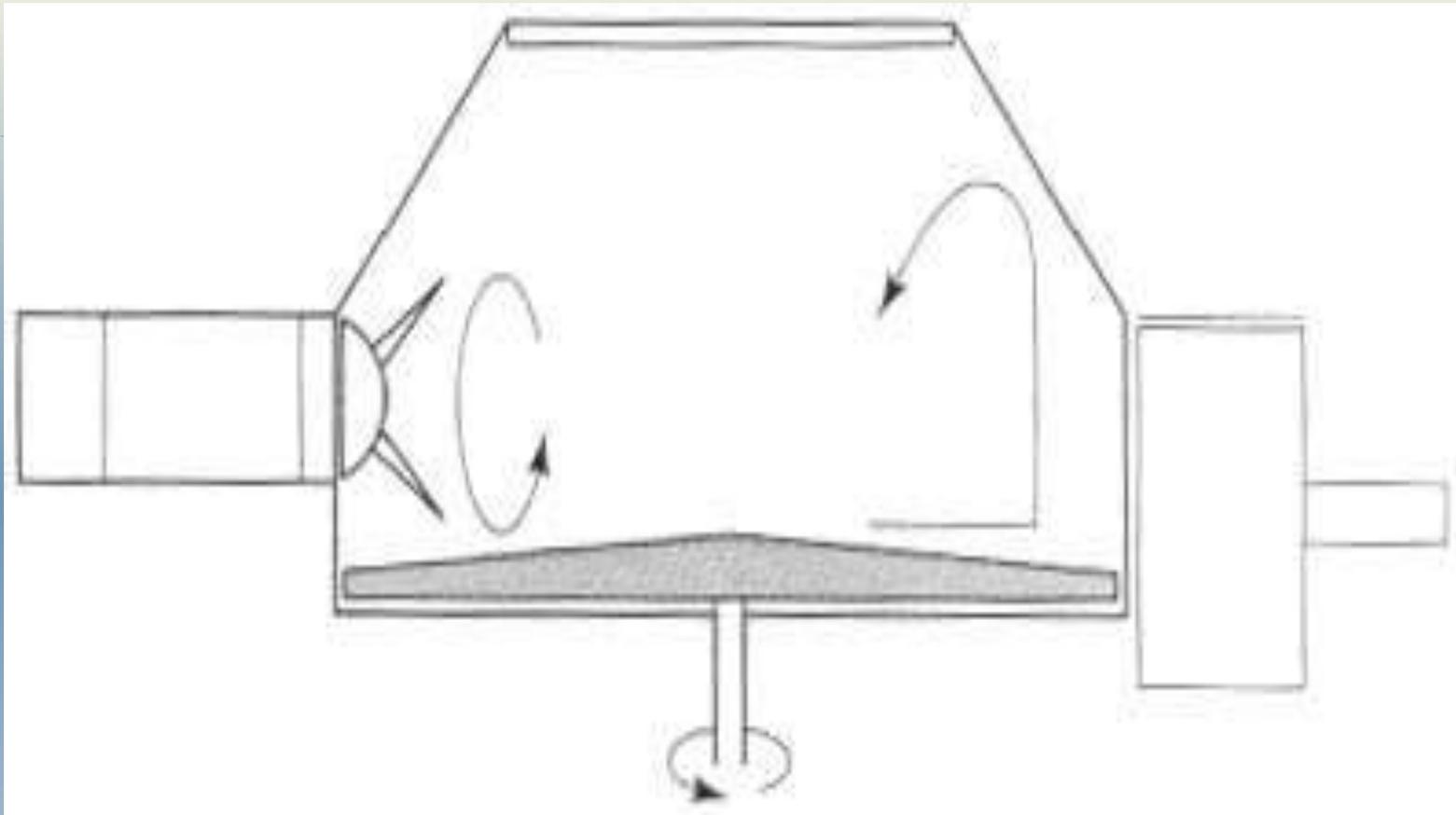
Twin shell (V) mixer
with agitator bar

2. *High-speed mixer-granulators*

- ▶ In pharmaceutical product manufacture it is often preferable to use one piece of equipment to carry out more than one function.
- ▶ An example of this is the use of a **rapid mixer-granulator (RMG)**
- ▶ As the name suggests, it can both mix and granulate a product, thereby removing the need to transfer the product between pieces of equipment and so reducing the opportunity for segregation to occur.
- ▶ The **centrally mounted impeller** blade at the bottom of the mixer rotates at high speed, throwing the material towards the wall by centrifugal force.

2. ***High-speed mixer-granulators***

- ▶ The particulate movement within the bowl tends to mix the components quickly owing to high shear forces (arising from the high velocity)
- ▶ **Once mixed, granulating agent can be added and granules formed *in situ* using a slower impeller speed and the action of the side-mounted chopper blade.**
- ▶ Because of the high-speed movement care must be taken to prevent material fracture.
- ▶ ***e.g. Diosna[®] mixer-granulator***



Diagrammatic representation of a high-speed mixer-granulator.

3. Fluidized-bed mixers

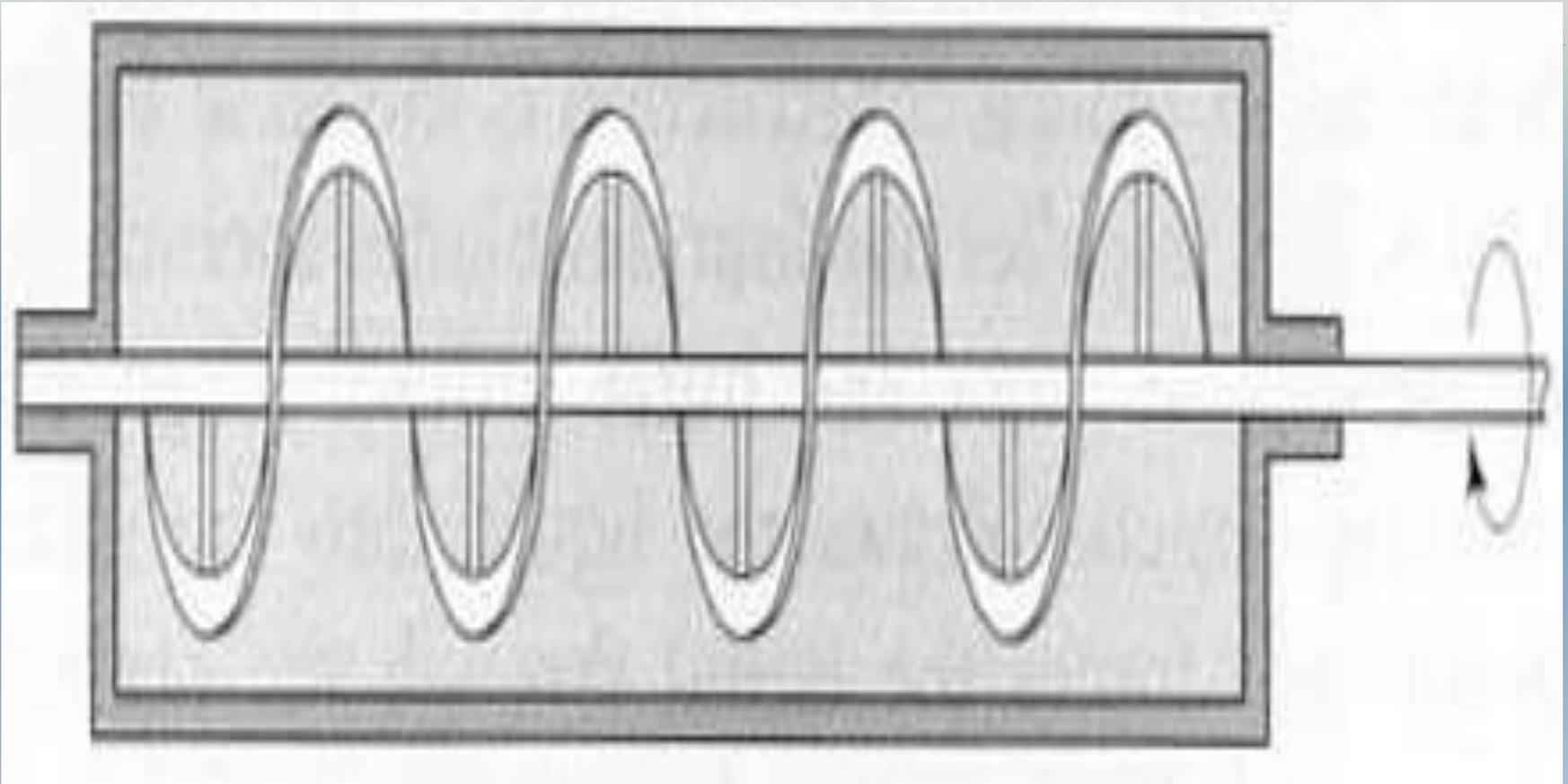
(construction and diagram: fluid energy mill)

- ▶ The main use of fluidized-bed equipment is in the drying of granules or the coating of multi-particulates
- ▶ Fluidized-bed equipment can, however, be used to mix powders prior to granulation in the same bowl.
- ▶ Fluidization is achieved by the introduction of pressurized fluid (can be air, gas or suitable solvent) through the particulate medium.
- ▶ This results in suspension of particles in fluid,
▶ ¹³⁷ which can be mixed, separated, or pumped

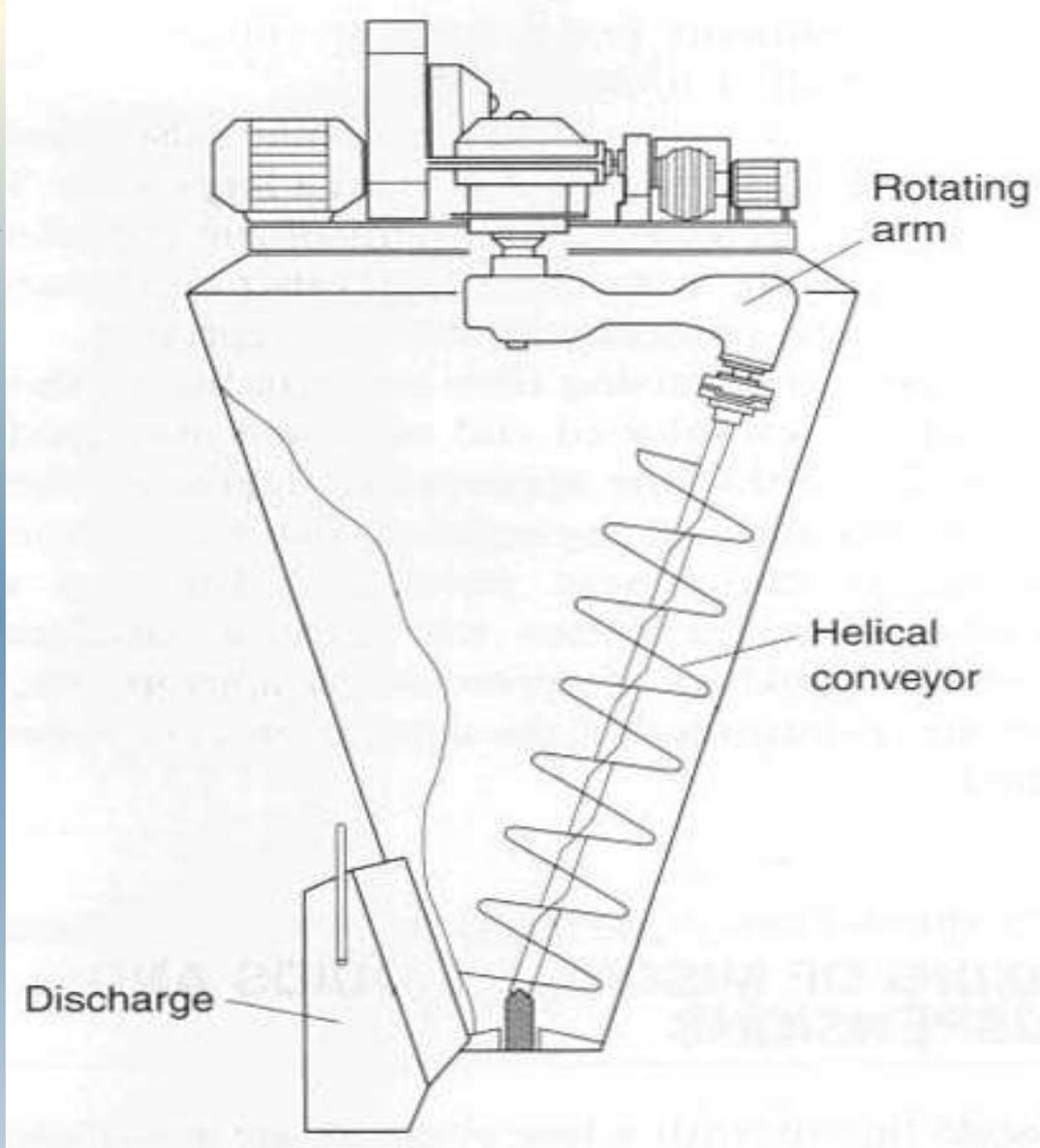
4. *Agitator mixers*

- ▶ This type of mixer depends on the motion of a blade or paddle through the product, and hence the main mixing mechanism is convection.
- ▶ Examples include the **ribbon mixer, Nautamixer., Planetary mixer.**
- ▶ In the **ribbon** mixer, mixing is achieved by the rotation of helical blades in a hemispherical trough. (*similar to screw conveyor*)
- ▶ The 'Dead spots' are difficult to eliminate in this type of mixer and the shearing action caused by the movement of the blades may be insufficient to break up drug aggregates.

- ▶ The ribbon mixer, however, **mix poorly flowing material** and is less likely to cause segregation than a tumbling mixer.
- ▶ The **Nautamixer** consists of a conical vessel fitted at the base with a rotating screw, which is fastened to the end of a rotating arm at the upper end.
- ▶ The screw conveys the material to near the top, where it cascades back into the mass.
- ▶ The mixer thus combines convective mixing (as the material is raised by the helical conveyor) and shear and diffusive mixing (as the material cascades downwards).



Ribbon agitator powder mixer



Nautamixer

QC of Powders

QC of Powders *(elaborate as per marks)*

1. Particle size and shape determination
(Methods: Sieving, Sedimentation, Microscopy, light Scattering etc...)
 2. Surface area *(BET, air permeability)*
 3. Density - Bulk density , tapped density, true density
 4. Granule density, strength and friability
 5. Flow properties- Angle of Repose, Compressibility Index, Hausner's ratio
 6. Moisture content
 7. Percentage fines
-

QC of Powders

Granule density, strength and friability-

Granule density = Granule weight/ Granule volume

- ▶ *Granule volume is determined by mercury displacement method. Mercury is used as it enters voids but does not enter the pores of the particles.*
- ▶ *Mercury also has non wetting characteristics. Method similar to true density determination*

Strength – using hardness tester

Friability: using friabilator (Roche[®] friabilator)



Roche[®] friabilator

QC of Powders

MOISTURE CONTENT

- ▶ The amount of moisture present in the granule is called moisture content.
- ▶ Generally granules contain 2% moisture.
- ▶ It is required for the binding of the powder or granules during compression in die cavity.
- ▶ Percentage of moisture is calculated by using **moisture balance or IR balance.**
- ▶ IR balance consist of simple balance containing IR bulb which produces heat inside the chamber.

QC of Powders

MOISTURE CONTENT

- ▶ A small amount of sample is placed in IR balance and weight is recorded (Initial reading)
- ▶ IR balance is operated at specified time and temperature.
- ▶ Sample is reweighed (Final reading)
- ▶ Moisture content = $[(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] * 100$



QC of Powders

PERCENTAGE FINES

- ▶ Fines indicate particles of very minute size.
- ▶ Fine powder is necessary for the tablet compression because if 100% granules are used then it is difficult to maintain hardness of tablet as they have (voids) free space in the die cavity and after compression tablet will crack due to these void spaces.
- ▶ % fines can be calculated by using sieve method.
- ▶ % fine should not be more than 15%

Dusting powders,
Oral rehydration powders,
Dry syrup formulations

1. Powders

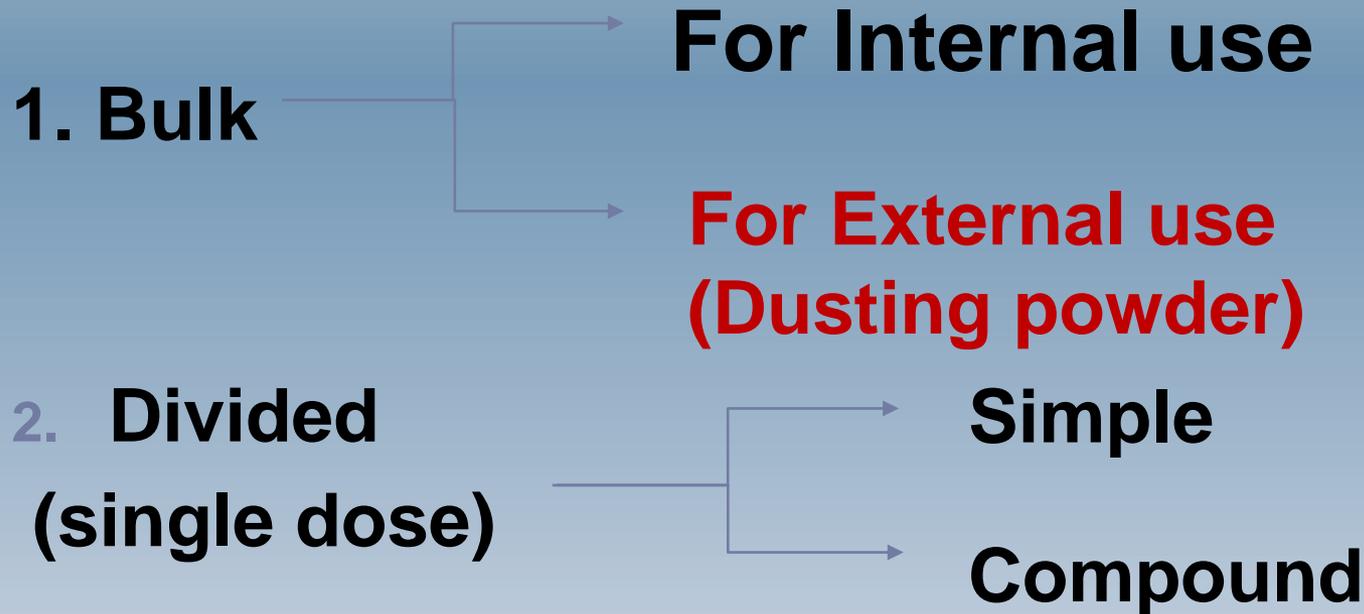
Advantages

- ▶ *Useful for Bulky drug, large dose (e.g. Antacids)*
- ▶ *Swallowing easy. Tablets are difficult to swallow for children, elderly.*
- ▶ *Faster dispersal and absorption of medicaments*
- ▶ *Insoluble drugs which cannot be formulated as solutions can be given in powder form*
- ▶ *Drugs which are unstable in liquid form can be given as powders*

Disadvantages of Powders

- ▶ *Dose accuracy is not there in bulk powders (1 tsp, 1 tbsp need to be taken).*
- ▶ *Difficult to carry/administer, chances of spillage while opening paper packets*
- ▶ *Not suitable for deliquescent (tendency to absorb moisture), volatile, oxygen sensitive drugs*
- ▶ *Time consuming to manufacture*
- ▶ *Cannot completely mask bitter taste*

Powders classification



1. Dusting powders

- ▶ Dusting powders contain ingredients used for therapeutic, prophylactic or lubricant purposes and are intended for external use..
- ▶ Two types:
 1. Medical dusting powders
 2. Surgical dusting powders
- Medical dusting powders
 - Used for superficial skin conditions, not on wounds, abraded/ broken skin
 - Thus sterility not required but it should be free from pathogens.

Some mineral ingredients like kaolin, talc may be contaminated with spores of tetanus, gangrene, anthrax and should be sterilized before use.

- e.g. *Zinc undecenoate dusting powder BPC (contains light kaolin, starch, zinc undecenoate... It is antifungal preparation)*

▶ Surgical dusting powders

- Used in body cavities, wounds, burns, umbilical cord of infants. Thus it should be sterile.
- Contains antibacterial agent
- Diluent used may be sterilisable maize starch
- e.g. *Chlorhexidine and hexachlorophene dusting powder*

- ▶ Dusting powders are normally dispensed in glass or metal containers with a perforated lid.
- ▶ The powder must flow well from such a container, so that they can be dusted over the affected area. The active ingredients must therefore be diluted with materials having reasonably good flow properties, e.g. purified talc or maize starch.
- ▶ Proprietary dusting powders are available, mostly as antifungal, antibacterial and skin disinfectants.
- ▶ e.g. **Candid Dusting powder**

Insufflations:

- It is also a type of dusting powder (for external use)
- Insufflation (Latin: insufflare for "to blow into") is the act of blowing something (such as a gas, powder, or vapor) into a body cavity
- It is used to produce local effect e.g. In treatment of ear, nose, throat infections or systemic effect (eg. pituitary insufflation BPC)
- Diluents used are Lactose, sterilizable maize starch used
- Sterility is required if preparation is for open wounds or raw surfaces

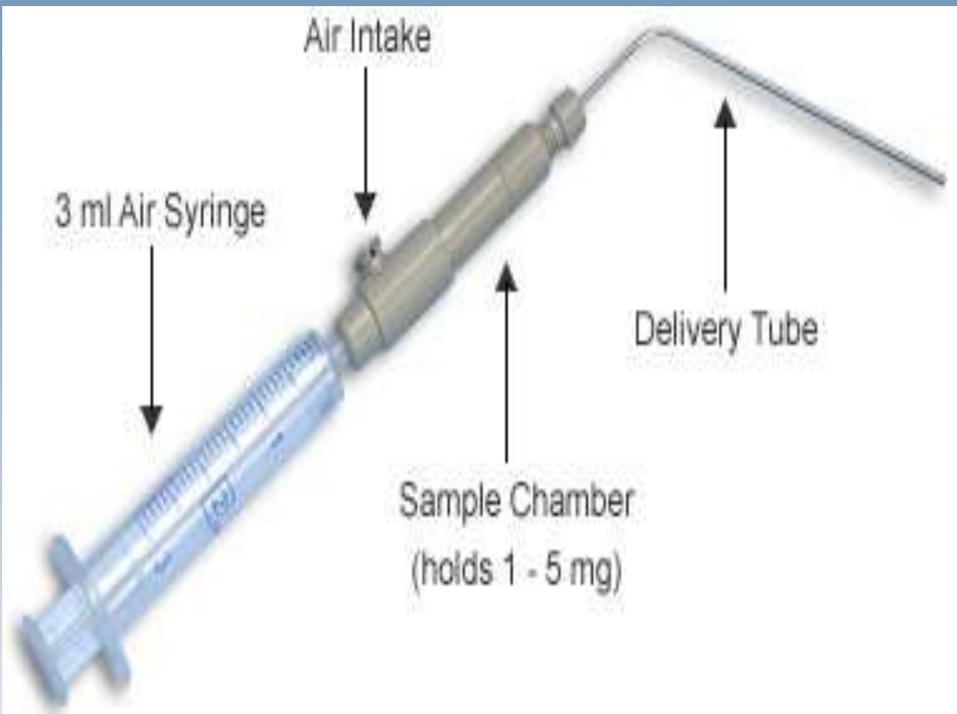


- **Used with an insufflator.**

- Insufflator blockage can be a problem because of

- clumping of particles thus should be stored in dry place

- lack of uniform dosage is also a drawback.



ORAL REHYDRATION SALTS

- ▶ **Also known as Oral rehydration powders/therapy (ORS/ORT)** is a type of fluid replacement used to prevent and treat dehydration, especially that due to diarrhea
- ▶ It involves drinking water with modest amounts of sugar and salts specifically sodium and potassium.
- ▶ Oral rehydration therapy can also be given by a nasogastric tube in severe, bedridden patients.

ORAL REHYDRATION SALTS

- ▶ In diarrhea, sodium-rich intestinal secretions are lost before they can be reabsorbed.
- ▶ This can lead to life threatening dehydration or electrolyte imbalances within hours when fluid loss is severe.
- ▶ The objective of therapy is the replenishment of sodium and water losses by ORT or intravenous infusion.

ORAL REHYDRATION SALTS

- ▶ Oral Rehydration Salts are dry, homogeneously mixed powders containing **Dextrose, Sodium Chloride, Potassium Chloride and either Sodium Bicarbonate or Sodium Citrate** for use in oral rehydration therapy after being dissolved in the requisite amount of water.
- ▶ They may contain suitable **flavouring agents** and, where necessary, suitable **flow promoting agents** in the minimum quantity required to achieve a satisfactory product.

ORAL REHYDRATION SALTS

- ▶ They should not contain artificial sweetening agents like mono/ polysaccharides.
- ▶ If saccharin/saccharin sodium or aspartame is used in preparations meant for paediatric use, the concentration of saccharin should be such that its daily intake is not more than 5 mg/kg of body weight and that of aspartame should be such that its daily intake is not more than 40 mg/kg of body weight.
- ▶ *Refer Journal for formula and role of ingredients*

Mfg.
date

Batch
No.

ORAL REHYDRATION SALTS

Each sachet contains the equivalent of:

Sodium Chloride	3.5 g.
Potassium Chloride	1.5 g.
Trisodium Citrate, dihydrate	2.9 g.
Glucose Anhydrous	20.0 g.

DIRECTIONS

Dissolve in ONE LITRE of drinking water.

To be taken orally-
Infants - over a 24 hour period
Children - over an 8 to 24 hour period,
according to age or as otherwise
directed under medical supervision.

CAUTION: DO NOT BOIL SOLUTION

MANUFACTURER: Jinas Bros., Packaging Co.
Kansas City, Missouri, U.S.A.

ORAL REHYDRATION SALTS I.P.

ELECTRAL®

BASED ON W.H.O. FORMULA

Contents : 21.80 g
NOT FOR INJECTION



21.80 g of Electral in 1 Litre of water supplies electrolytes in the following concentrations

ELECTROLYTES mOsmol / Litre	
Sodium	75
Potassium	20
Chloride	65
Citrate	10
Dextrose	75
Total Osmolality	245

COMPOSITION

Each sachet (21.80 g) contains

Sodium Chloride I.P.	2.80 g
Potassium Chloride I.P.	1.50 g
Sodium Citrate I.P.	2.90 g
Dextrose Anhydrous I.P.	13.50 g
Excipients	0.1



MANUFACTURED BY
FDC Limited
Regd. Office: B-9, MID-C, New, P.O., Kumbhari, 401 128

Dry syrup formulations

- ▶ For patients who have difficulty taking capsules and tablets, e.g. young children or elderly, a liquid preparation of a drug offers a suitable alternative.
- ▶ However, many drugs, e.g. antibiotics, are physically or chemically unstable when formulated as a solution or suspension.
- ▶ The method used to overcome this instability problem is to manufacture the dry ingredients of the liquid preparation in a suitable container in the form of a powder or granules.

Dry syrup formulations

- ▶ While consuming the product, stated quantity of water (given on product label) is added to reconstitute the solution or suspension.
- ▶ This enables product to remain stable without degradation.
- ▶ Once it is reconstituted, the preparation should be used within a few days.
- ▶ Shelf-life of the reconstituted syrup depends on the stability of API (*in general, it can be 1-2 weeks*)
- ▶ Examples are Erythroped Suspension and Amoxicillin Oral Suspension.



LOT:
EXP:



Manufactured by:
ANI Pharmaceuticals, Inc.
Baudette, MN 56623

Store granules, prior to mixing, below 86°F (30°C).

DIRECTIONS FOR PREPARATION: Slowly add 70 mL of water and shake vigorously to make 100 mL of suspension.

After mixing, refrigerate and use within ten days.

When prepared as directed, each 5 mL teaspoonful contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin in a cherry-flavored suspension.

Bottle contains erythromycin ethylsuccinate equivalent to 4 g erythromycin. Child-resistant closure not required; exemption approved by U.S. Consumer Product Safety Commission.

May be taken without regard to meals. Shake well before using. Oversize bottle provides shake space. Keep tightly closed.

Usual Dose: Children: 30 to 50 mg/kg/day in divided doses. See package insert for adult dose and full prescribing information.

NDC 62559-440-01

Erythromycin Ethylsuccinate

for Oral Suspension USP

Erythromycin activity
200 mg per 5 mL

when reconstituted

Rx only

100 mL
(when mixed)

9855 Rev 09/16

ani
Pharmaceuticals, Inc.