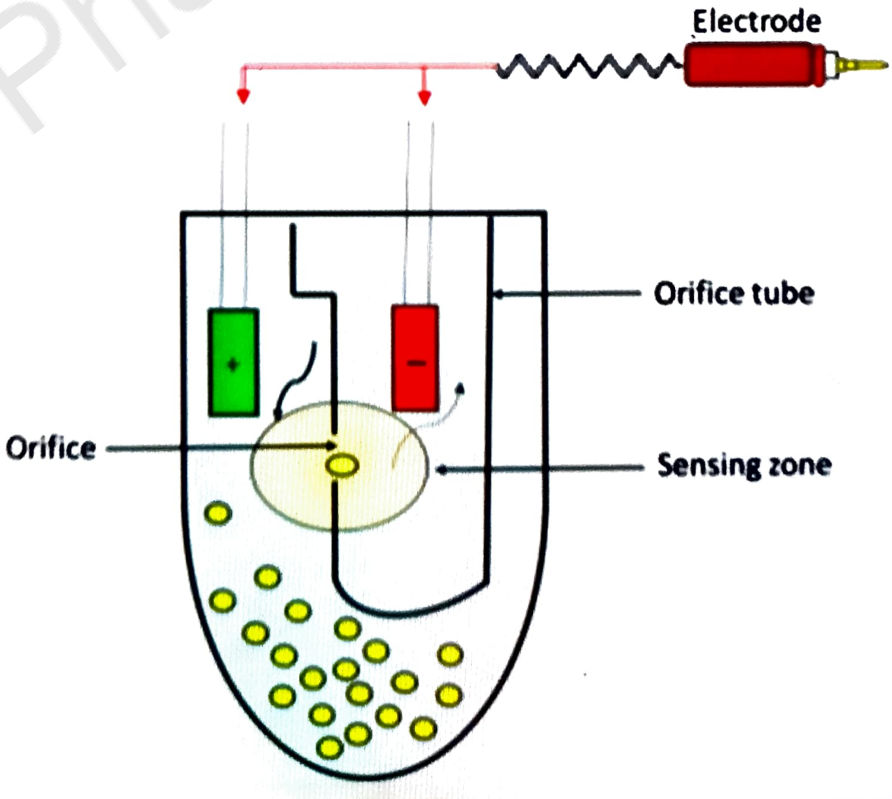
UNIT-IV MICROMERETICS

Points to be covered in this topic

- INTRODUCTION
- PARTICLE SIZE AND DISTRIBUTION
- METHODS FOR DETERMINING PARTICLE SIZE
- METHODS FOR DETERMINING SURFACE AREA
- DERIVED PROPERTIES OF POWDERS

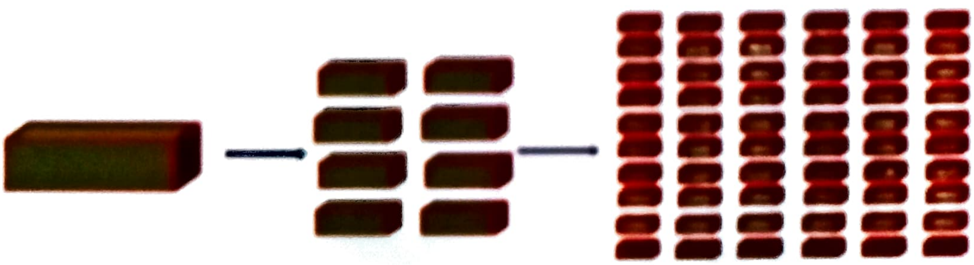


INTRODUCTION

- **Micromeritics** is the **science and technology** of small particles.
- It also involves the study of the **fundamental** and derived properties of the individual, as well as a **collection of particles.**
- The term was given by **J.M. Dalla Valle.**
- The unit of particle size used is the **micrometer,** µm, micron, µ, and equal to 10^{-6}m.

IMPORTANCE OF MICROMERITICS IN PHARMACY

- The **size** and **surface area** of the particles affects the **physical, chemical and physiological** properties of a drug.
- The **particle size** of a **drug affects** the rate of release of drug from a dosage which is **administered orally**, **parenterally**, **rectally** and topically.
- The **dissolution rate** is faster from a smaller **particle size** because of its high specific **surface area.**
- The **sedimentation rate** in suspension is faster with **larger particles.**
- Therefore, to make a **stable suspension** or emulsion the particle size **must be controlled.**
- For the precise determination of the **pore size** of the filters the **particle size is required.**
- The **flow properties** of powders in the manufacture of a **solid dosage form** (such as tablets or capsules) depend on **particle size, size distribution, and size distribution.**



PARTICLE SIZE AND DISTRIBUTION

- A **powder sample** is characterized by **particles shape, particles size** and particle size distribution.
- If all the particles have the **same diameter** then the powder sample is called a **monodisperse system**, but if all the particles are **not a equal size** , then that sample is called **Polydisperesed system.**
- The size of a sphere is **readily expressed** in terms of its **diameter.**

✓ Surface diameter (d_s)

- The **diameter** of a sphere having the **same surface area** as the particle

$$ds = \sqrt{\frac{S}{\pi}}$$

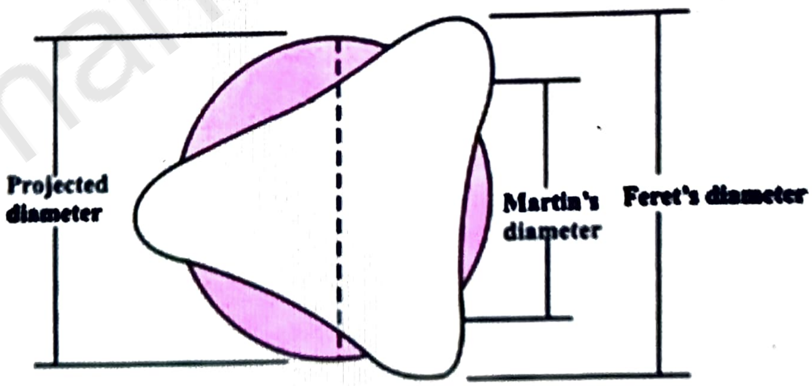
✓ Volume diameter

- The **diameter** of a sphere having the **same observed area** as the particle.

$$dv = \left(\frac{6V}{\pi}\right)^{\frac{1}{3}}$$

✓ Projected diameter

- The **projected diameter** of a sphere having the **same observed area** as the particle.



✓ Stokes diameter

- The diameter which describes an **equivalent sphere** undergoing **sedimentation** at the same rate as the **asymmetric particle.**

✓ Feret's diameter

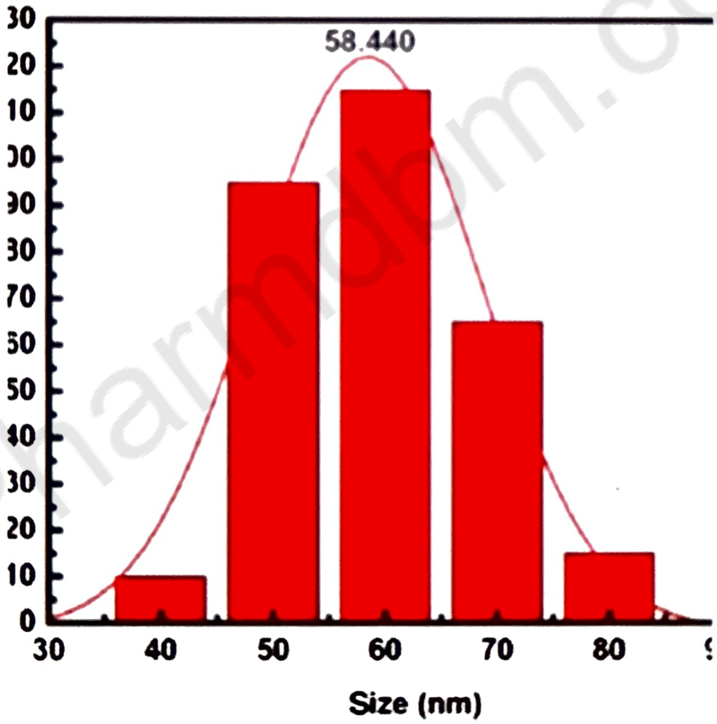
- It is the distance between **two tangents** on **opposite sides** of the particle parallel to **some fixed direction.**

✓ Martin's diameter

- **Martin's diameter** is the length of a line that **bisects the particle image.**
- The line can be drawn in **any direction** but must be in the **same direction** for all particles measured.

➤ SIZE DISTRIBUTION

- When the number or **weight of particles** lying within a **certain size range** is plotted against the **size range or mean particle size**, a so-called **frequency distribution curve** is obtained.
- This is important because it is possible to have **two samples** with the same average diameter but **different distributions.**



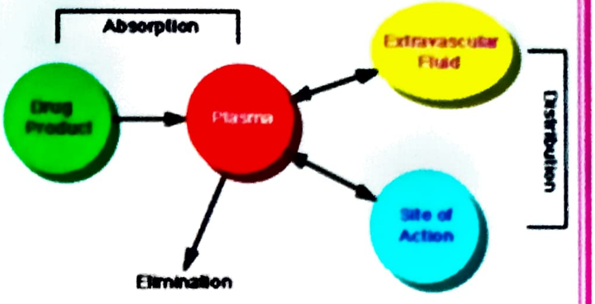
➤ MICROMERITICS APPLICATIONS

❖ RELEASE AND DISSOLUTION

- **Particle size** and **surface area** influence the release of a drug from a **dosage form.**
- **Higher surface area** allows intimate contact of the drug with the **dissolution fluids** in vivo and increases the **drug solubility** and dissolution.

❖ ABSORPTION AND DRUG ACTION

- **Particle size** and **surface area** influence the drug absorption and subsequently the **therapeutic action.**
- Higher the **dissolution, faster** the **absorption** and hence **quicker and greater** the drug action.



❖ PHYSICAL STABILITY

- The **particle size** in a formulation influences the **physical stability** of the **suspensions and emulsions.**
- Smaller the **size of the particle**, better the **physical stability** of the dosage form.

❖ DOSE UNIFORMITY

- **Good flow properties** of granules and powders are important in the manufacturing of **tablets and capsules.**

➢ PARTICLE NUMBER

- It is defined as **Number of particles** per unit **weight.**
- Suppose that the **particles in powder** are spherical then the volume of a **single particle** is $\pi d_{vn}^3/6$, and mass will be $(\pi d_{vn}^3 \rho)/6$g per particle.
- The number of particles per gram can be obtained as

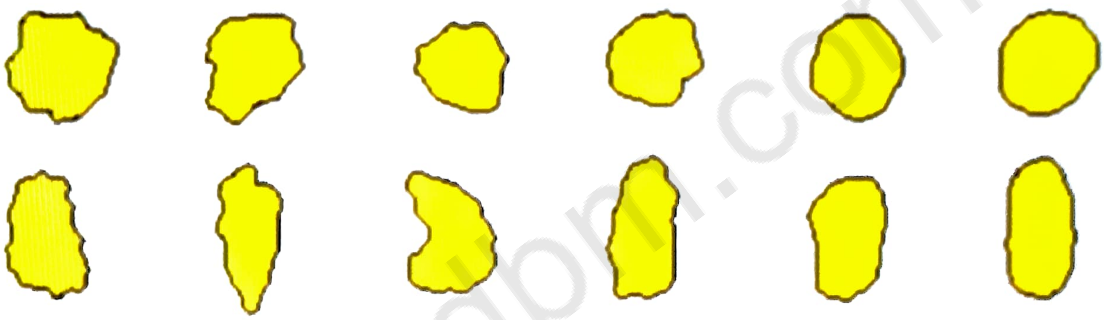
$$N = \frac{6}{\pi d_{vn}^3 \rho}$$

✓ **Where**

- d_{vn} = mean **diameter** based on volume and number
- ρ = **density of particle**

➤ PARTICLE SHAPE

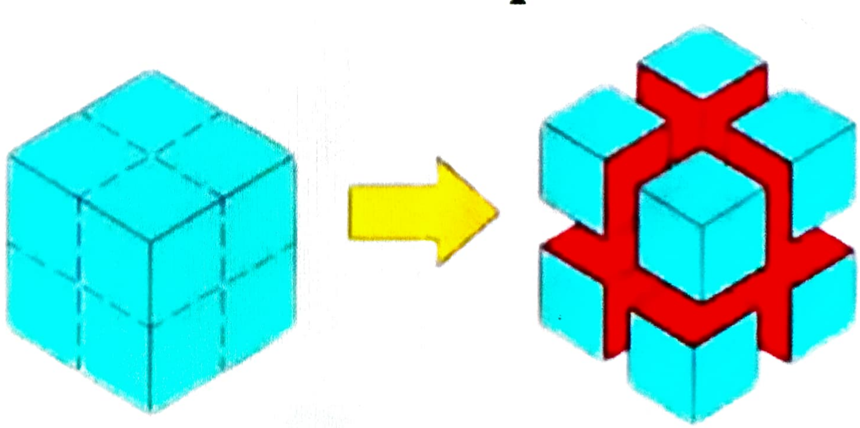
- The **shape affects** the flow and **packing properties** of a powder.
- A **spherical particle** is **fully characterized** by its diameter.
- As the particle becomes **more asymmetrical**, it becomes increasingly difficult to **assign a diameter.**
- In this case equivalent **spherical diameter** is measured in case of **asymmetric particles**, surface area or volume is expressed as
- Surface area = $\alpha_s d_p^2 = \pi d_s^2$
- Where α_3 is the surface area factor and d_3 is the **equivalent surface diameter.**



➤ SPECIFIC SURFACE

- The **specific surface** of powder is defined as the **surface area per unit volume (S_v)** or per unit **weight (S_w).**
- For **asymmetric particles** where the characteristic dimension is not define, specific surface area **per unit volume** is expressed as

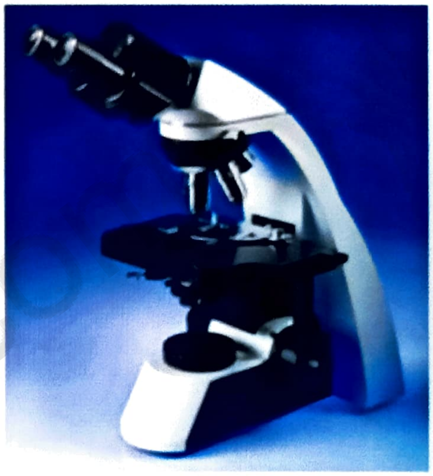
$$S_v = \frac{\text{Surface area of particles}}{\text{Volume of particles}}$$



METHODS FOR DETERMINING PARTICLE SIZE

- There are **various methods** to estimate **particle sizes** are
  1. **Optical microscopy**
  2. **Electron microscopy**
  3. **Sieving method**
  4. **Sedimentation method**
  5. **Coulter counter method**

❖ OPTICAL MICROSCOPY (range of analysis 0.2 - 100μm)



- This method is used to **determine projected area diameter**, **ferrets diameter** and **martin's diameter.**
- This methods directly provide **number distribution method.**

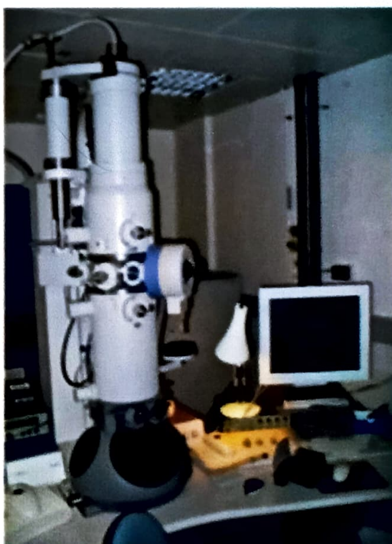
✓ **Advantage**

- **Agglomerates or contamination** can be detected.

✓ **Disadvantages**

- **Slow and tedious** method.
- This method measure **only length** and **breadth of particle.**
- Not used to **measure depth** of particles.

❖ ELECTRON MICROSCOPY



- Both the scanning **electron microscope (SEM)** and **transmission electron microscopy (TEM)** analysis are used to measure the **lower limit of particle size.**
- Scanning **electron microscopy** is particularly appropriate when a three – **dimensional particle image** is required.

❖ SIEVING METHOD (Range of analysis 50-1500μM)

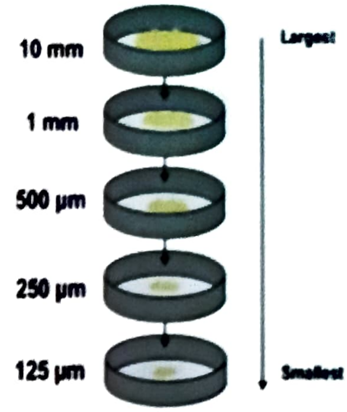
- This method is used to **determine sieve diameter (ds).**
- Sieving method is an **ordinary and simple method.**

✓ **Advantage**

- Simple and **inexpensive method.**

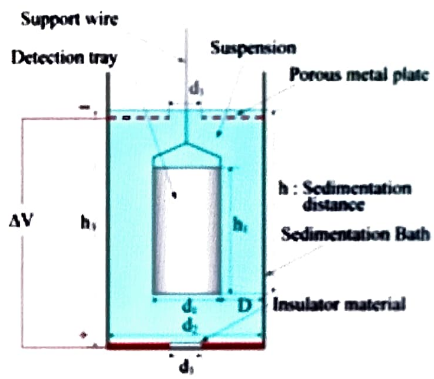
✓ **Disadvantage**

- Particles **below size of 50 μm** difficult to measure.
- Chances of **clogging of sieve.**
- Chances of **attrition during shaking.**
- Need **large amount** of powder.



❖ SEDIMENTATION METHOD (RANGE OF ANALYSIS 1 - 200μM)

- This method is used to **measure the stokes diameter(d_{st}),** the diameter of a particle measured **during sedimentation** at constant speed under **laminar flow conditions** and the **frictional drag diameter**, a sphere having an **equivalent drag force** to a particle of the same diameter in the **same fluid** at **same velocity.**



- **Rate of sedimentation** of particle on their size is determined by **stokes law.**

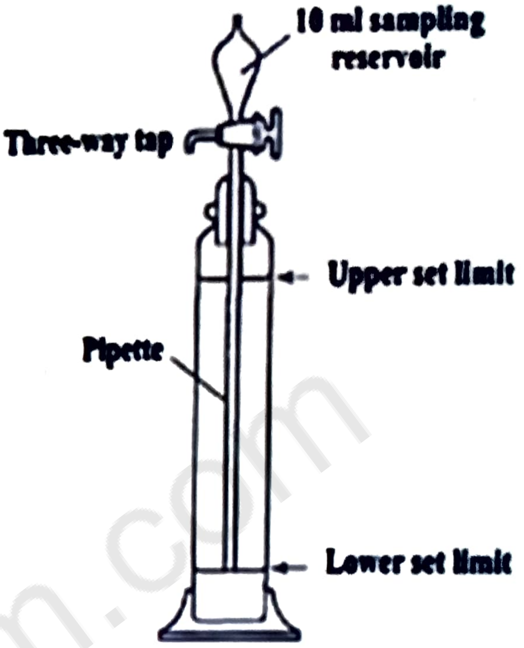
$$d_n = \sqrt{\frac{18\eta_0 h}{(\rho_s - \rho_0)gt}}$$

✓ **Where,**

- **h** = distance of fall in time t
- **p_s** = density of particle
- **p_0** = density of dispersion medium
- **g** = acceleration due to gravity
- **η_0** = viscosity of medium

✓ Andreason pipette method

- Andreason pipette is widely used method to determine particle size distribution by sedimentation method.

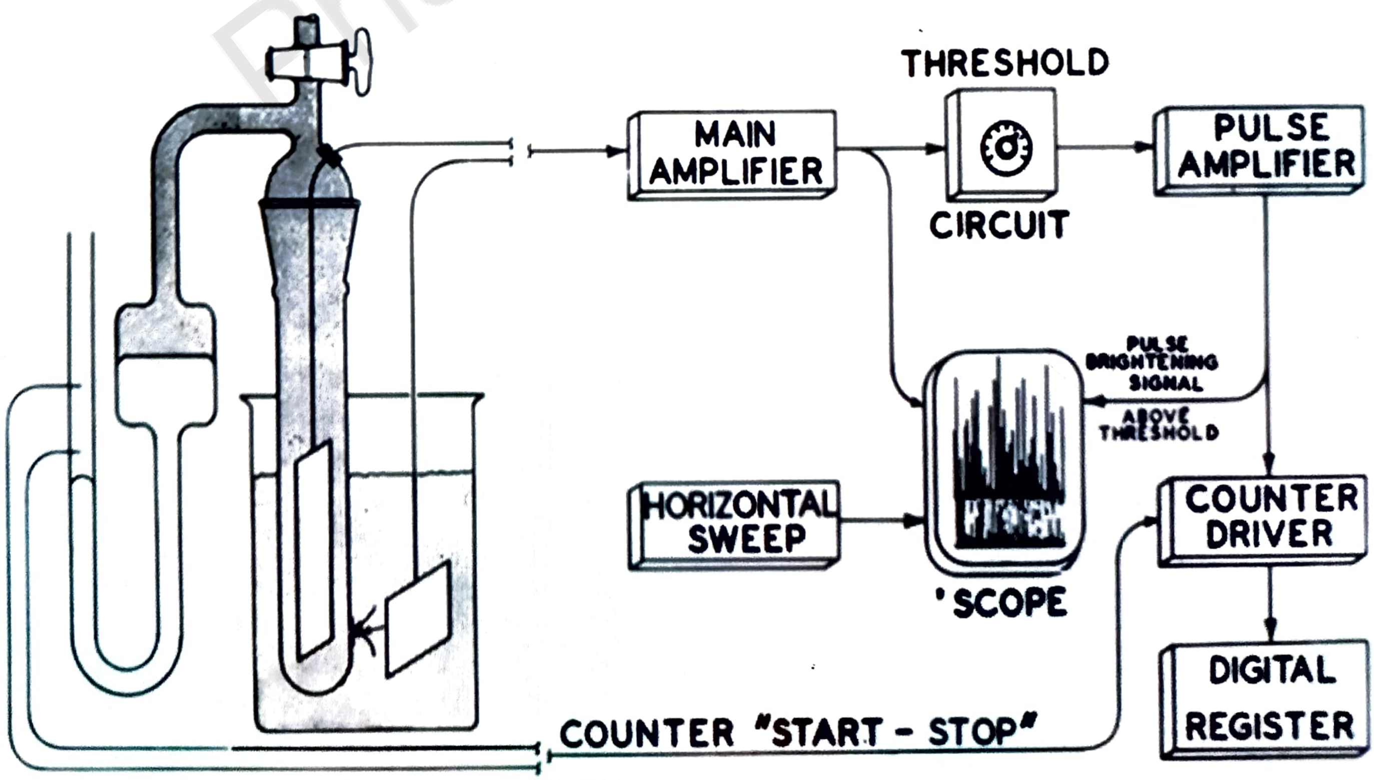


- It usually consists of a 550 ml beaker containing 10 ml pipette sealed in a ground glass stopper.
- When the pipette is placed in the cylinder, its lower tip is 20 cm below the surface of the suspension.
- A 1% or 2% suspension of the powder in a medium containing a suitable deflocculating agent is introduced into the vessel.
- The vessel is stoppered and agitated to distribute the particles evenly along the suspension.
- The vessel is firmly held in a constant temperature bath.
- At different time intervals, 10 ml samples are drawn.
- The samples are evaporated and weighed.

- **Advantage**
  - Precise result obtained
- **Disadvantage**
  - Labarious method
  - Very small particles cannot be measured accurately due to prolong settling rate.

❖ COULTER COUNTER METHOD (range of analysis – 0.1-1000μm)

- This method is used to **determine particle volume.**
- The size is expressed as **volume diameter**, dv **Coulter Counter Method** (Electrical stream sensing zone method) is a sophisticated method.
- A known volume of a **diluted suspension** is pumped through the orifice to either **side of the electrodes.**
- **Electrodes** located on either side of the **aperture and surrounded** by an electrolytic solution.
- A **constant voltage** is applied through the **electrodes** to produce a current.
- The change in the **electrical signal** that occurs when a particle occupies the **orifice momentarily** and displaces its own volume of electrolyte.
- The change in resistance between **electrodes** cause voltage pulse which is **amplified and processed** electronically.
- The **magnitude of pulse** is generated which is proportional to the volume of the particle.



✓ **Advantages**

- It is one of the **precise and accurate method**.
- **Analysis range** is wide.

✓ **Disadvantages**

- **Aggregation** of particle produce wrong result.
- **Coarse particles** blocking a small diameter orifice.

METHODS FOR DETERMINING SURFACE AREA

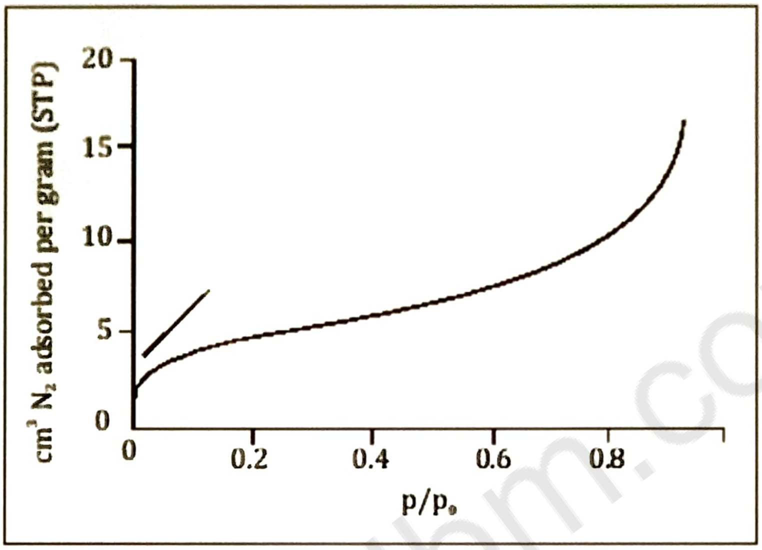
- The **commonly used methods** are :
  - ✓ **Adsorption method**
  - ✓ **Air permeability method**

➤ ADSORPTION METHOD

- A **large specific surface** allows **good adsorption** of gas and/or solutes from a solution.
- The **volume of gas** (in m^3) adsorbed per gram of **adsorbent** (solid) can be plotted against the **pressure of gas** introduced at constant temperature.
- **At low pressure**, the gas adsorbs on the **surface of adsorbent** and form a monolayer.
- At saturation, the **amount of adsorbed** is a function of surface area of powder.
- At **high pressure**, the adsorbed layer becomes multi-molecular.
- The completion of **mono-molecular film** can be identified using BET equation. At that stage, the volume (y_m) adsorbed per **one gram** can be obtained.

$$\frac{p}{y(p_0 - p)} = \frac{1}{y_m b} + \frac{(b - p)}{y_m b} \cdot \frac{p}{p_0}$$

- P = pressure of the adsorbate, mmHg
- V = volume of vapor gas per gram, g
- P_0 = vapor pressure at saturation (monolayer), mmHg
- Y_m = amount of vapor adsorbed per unit mass of adsorbent when the surface is covered with monomolecular layer, g
- b = constant, proportional to heat of adsorption and latent heat of condensation of subsequent layers.



❖ PROCEDURE

- A known weight of powder is introduced into the sample tube.
- The sample is mounted to the out-gassing station to remove gas.
- Then the sample tube is mounted to the analysis station.
- A mixture of helium and nitrogen are used as adsorbate gas.
- Nitrogen gas adsorbs on the powder and helium does not adsorb (inert). Vapour dosing options are available with the instrument.
- A mixture of gases is passed through sample tube (containing powder) at a specific pressure and temperature (thermostat facility).
- The amount of nitrogen gas adsorbed and desorbed is measured using a thermal conductivity detector.
- The signal height is proportional to the rate of adsorption or desorption of nitrogen gas.
- The area under the curve is proportional to the gas adsorbed on the particles.

➤ AIR - PERMEABILITY METHOD – FISHER - SUBSIEVE SIZER

- **Air permeability method** is official in IP.
- This method also used to **estimate surface diameter , d_s**

❖ PRINCIPLE

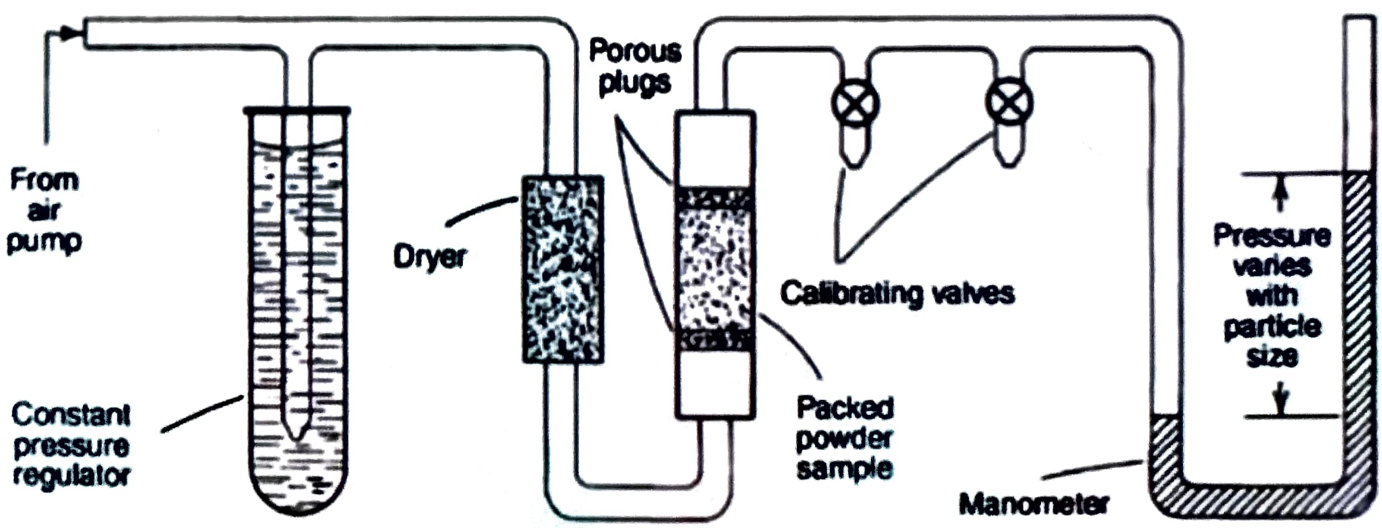
- **Powder is packed** in the **sample holder** as a compact plug.
- In this **packing, surface-surface contacts** between particles appear as a series of capillaries.
- The surface of these **capillaries** is a function of the **surface area** of the powder.
- When air is **allowed to pass**, air travel through these capillaries and thus this method is related to **surface area** of powder.
- When air is allowed to pass at a **constant pressure**, the bed resists the flow of air.
- This results in a **pressure drop.**
- The greater the **surface area** per gram of the powder, S_w the greater the **resistance to flow.**
- The **permeability of air** for a given pressure drop is **inversely proportional** to specific surface.
- The **Kozeny-Carman equation** is used to estimate the **surface area** by this method.
- This is based on the principle of **Poiseulle's equation.**

$$v = \frac{A}{\eta S_w^2} \cdot \frac{\Delta Pt}{Kl} \cdot \frac{\varepsilon}{(1-\varepsilon)^2}$$

- A = **cross sectional area** of the bed (pack), m^2
- ΔP = **pressure difference** of the plug, Pa (or mmHg)
- t = **time of flow** , s
- L = **length** of the sample holder, m
- η= **porosity** of the powder
- S_w = **surface area** per gram of the powder , m^2/g
- h= **viscosity** of the air pa.s
- K = **constant**
- V = **volume** of air flowing through the bed , m^3

❖ METHOD

- It consists of a **sample tube** containing the **packed powder** sample with one **end connected** to an **air pump** through a **constant pressure** regulator.
- The other end is attached to a **calibrated manometer** containing a suitable liquid of **low viscosity** and negligible **vapor pressure.**
- The **air pump builds** up air pressure and is connected to a **constant pressure** regulator.
- **Air is passed** through the dryer to **remove** any moisture. Air is then allowed to flow through the **packed powder** in the sample tube.
- The **flow of air** is measured by the **manometer.**
- The level of the fluid in the **manometer** is related to the average diameter of the particles.
- The higher the **surface area**, the **greater is the resistance**, the **pressure drop** is higher and manometer level decreases.
- **Commercial equipment** is standardized to eliminate the **mathematical computation.**
- Average **particle diameter** can be read from the calculator charts supplied with the equipment.



- **Simple instrumentation** and high speed, it is widely used pharmaceutically for **specific surface determinations.**
- **Bephenium hydroxynaphthoate**, official in the 1973 is standardized by air permeability method.
- Activity of some drugs is related to the **specific surface**. Ex: Anthelmintic drugs in **suspension dosage form** must possess a surface area of not less than **7000 cm²/g.**
- As the **specific surface** of the material is reduced, the activity of the drug also falls.
- Air permeability method, officially in **U.S. pharmacopoeia** used for determining the **specific surface area** of griseofulvin.
- This method is also used for **measuring the fineness** of Portland cement

DERIVED PROPERTIES OF POWDERS

➢ TRUE DENSITY

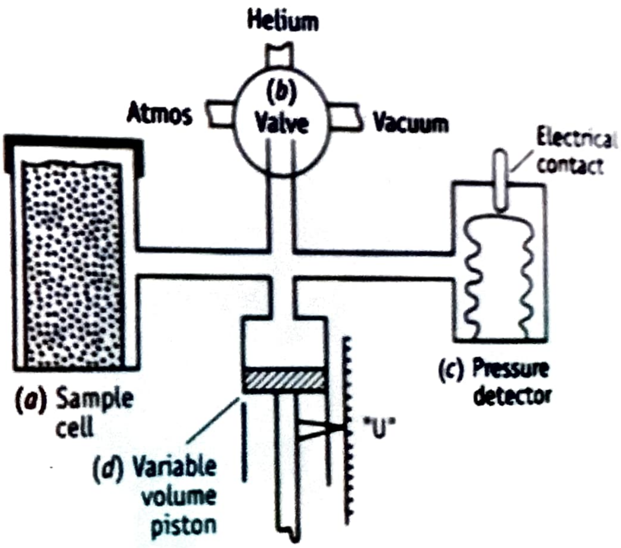
- It is the **density** of the material itself. It is defined as :
- **True density, ρ_p =**

$$\text{True density, } \rho p = \frac{\text{weight of powder}}{\text{true volume of powder}}$$

- The **density is dependent** on the type of atoms in a molecule, arrangement of the atoms in a molecule and the **arrangement of molecules** in the sample.
- Apart from **true density**, powder is also characterized by **granule density** and bulk density.

❖ Porous solids – helium displacement method

- **Helium penetrates** the smallest pores and crevices.
- This is **valuable tool** to estimate the **true density**, particularly for porous solids.



✓ **Method**

- It consists of a sample holder (A), which can be sealed after placing the sample.
- The valve (B) is connected to the sample holder.
- It has provisions for removing the air from the sample holder and introducing the helium gas.
- Helium gas is selected as it does not adsorb on the solid sample.
- A pressure detector (C) is included in order to maintain preset constant pressure.
- It has sealed bellows which maintains the electric contact at a particular pressure.
- A piston (D) is attached in order to read the corresponding pressure, which is also related to the volume of the powder.
- Initially, the volume of empty pycnometer is determined.
- The air present in the sample holder is removed by applying vacuum.
- Then helium gas is passed into the apparatus through the valve (B).
- The pressure is adjusted and set a particular value with the help of a movable piston (D).
- At this position, the reading on the scale denotes U.
- This represents the volume of empty cell.
- In the next step, pycnometer is calibrated by placing a standard sample of known true volume (V_c) (stainless steel spheres) in the sample holder.
- The sample holder is sealed and air is removed.
- The same amount (as used in the first step) of the helium gas is introduced.
- Pressure is adjusted to preset value by moving the piston suitably.
- At this stage, the scale reading is denoted by U_2.
- The last step involves the determination of volume of the sample.
- The stainless steel sphere is replaced by the test sample powder.
- The air in the pycnometer is replaced by helium gas (same quantity as used in earlier steps).

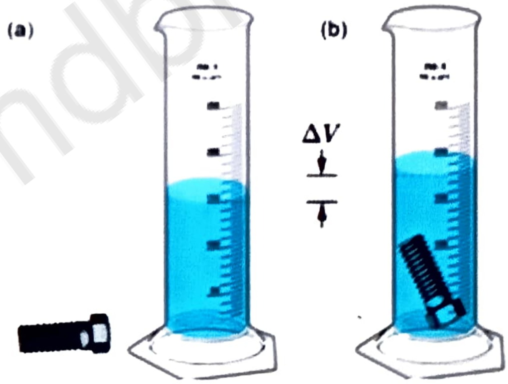
- The **pressure is adjusted** with the help of piston.
- At this state, the **piston reading** is denoted by U_s.
- The difference **between U_1 and U_2**, gives the volume occupied by the sample.
- The **operating equation** for the instrument is

$$V_1 = \frac{V_T}{U_1 - U_2}\left[U_1 - U_s\right]$$

- Where V_t = true volume of the sample, cm^3

❖ Liquid displacement method

- Liquids such as **water and ethyl alcohol** cannot occupy the pores and crevices.
- If the **powder is nonporous**, this method is used.
- Select a solvent in which the powder is **insoluble and heavy.**
- Normally, the values obtained are somewhat lower than the **helium displacement method.**



✓ Method

- **Pycnometer** or **specific gravity** bottle may be used.
- Weight of pycnometer = w_1
- Weight of pycnometer + sample (or glass beads) = w_2
- Weight of sample = $w_3 = w_2 - w_1$
- Weight of pycnometer with powder and filled with solvent = w_4
- Weight of the liquid displaced by solids (related to volume of liquid displaced) = $w_4 - w_2$
- **True density** = $\frac{w2 - w1}{w4 - w2}$

➢ COMPRESSED POWDERS

- The powder sample is **compressed** into a **tablet** using a punching machine with **1,00,000 lb/sqin.**
- Now estimate the **true density.**
- Weight of the tablet = w_1
- Volume of the tablet = **V** (measure the dimensions with capillaries)
- True density = w_1/V

➢ GRANULE DENSITY

- Granule density is determined for the **granules** that are employed in the **manufacture of tablets.**
- Granule density is defined as : **Granule density, ρ_g** = **granule weight / granule volume**

➢ BULK DENSITY

- It is defined mathematically as :
- **Bulk density (ρ_b)** = **mass of a powder (w) / bulk volume (V_b)**

➢ TAPPED DENSITY

- Tapped density = **m(mass) / V_0** = (volume of the powder bed at zero tapping)

✓ **Application :-**

- Bulk density is used to **check the uniformity** of bulk chemicals
- The size of capsule is mainly determined by **bulk volume** for a given dose of material. The higher the **bulk volume**, lower will be **bulk density** and **bigger the size** of the capsule.

➢ POROSITY

- **True volume** = Volume of the powder itself.
- **Granule volume** = Volume of the powder itself + volume of intraparticle spaces.
- **Bulk volume** = Volume of the powder itself + volume of intraparticle spaces + volume of inter- particles spaces (voids).

- If the powder is nonporous i.e. **no internal pores** or capillary spaces, the bulk volume consists of **true volume plus** the volume of spaces between the particles, i.e. void volume,
- **Void volume** = V= bulk volume - true volume or Vb - Vp
- The **porosity or solids**, ε, of the powder is defined as:
- **Porosity or voids** , ε = void volume /bulk volume

$$\varepsilon = \frac{\text{bulk volume - true volume}}{\text{bulk volume}} = \frac{Vb - Vp}{Vb}$$

- Porosity is **frequently expressed** in percent.
- Percent, ε = **1-vp/vb ×100**
- The above equation can also be expressed in terms of density values.
- Percent, ε = $\rho_p - \rho_b / \rho_b \times 100$

➤ FLOW PROPERTIES OF POWDERS

- **Flowability** is the ability of a **powder to flow through** reliably.
- Flow properties **influence mixing** and **de-mixing of powders.**
- These also influence the **design of formulation** and selection of process equipment.

❖ ANGLE OF REPOSE

- The **flow characteristics** are measured by angle of repose. Improper **flow of powder** is due to **frictional forces** between the particles. These frictional forces are quantified by **angle of repose.**
- Angle of repose is defined as the **maximum angle** possible between the surface of a of the **Carl powder** and the **horizontal Plane**

$$\tan\theta = \frac{h}{r}$$

$$\theta = \tan^{-1}\frac{h}{r}$$

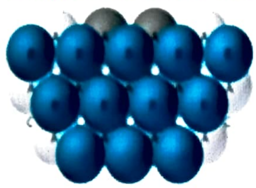
- Where h = **height of pile**, cm
- r = **radius of the base** of the pile, cm
- θ = **angle of repose**

PACKING ARRANGEMENTS

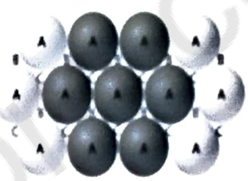
- The **arrangement of particles** in a powder influences the volume occupied by it.
- As a result, **bulk density** and **subsequently porosity** are affected.
- In view of its applications in **disintegration** and **dissolution process**, it may be necessary to understand the **packing of particles** in a powder both in theory and practice.
- When **particles are considered** to be of **uniform size** of spheres, then any one of the following **packing arrangements** are possible theoretically.

(1) Closet or rhombohedral packing

(2) Most open, loosest or cubic packing



closest or rhombohedral packing (26% porosity)



most open, loosest, or cubic packing (48% porosity)

- In **practice, particles** in a powder are neither **spherical nor uniform** in size.
- Therefore, any type of packing between these **ideal situations** is possible.

(a) **Porosities of powder** (spherical particles) are about **26%**. It means **closed packing.**

(b) Porosities of powder (spherical particles) are about **48%**. It means **loose packing.**

(c) Porosities of powders, in general, are **between 30% and 50%.**

(d) Porosities **below 30%** are possible, if the particles differ greatly in the size distribution. The **small particles** accommodate the voids between **large particles.**

(e) Porosities above **50% are possible**, when the particles are **aggregated and flocculated.**