Micromeretics

Ms. Saroj. R.Valvi

Asst. Prof.

(Dept. of Pharmaceutics)

JES's College of Pharmacy, Nandurbar

Unit IV

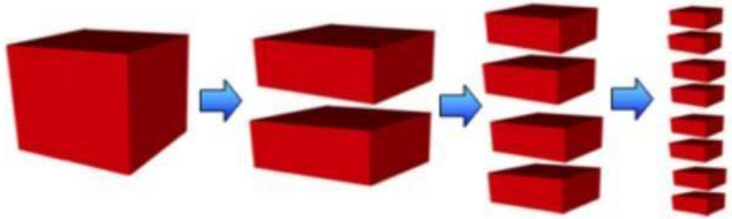
Micromeretics: Particle size and distribution, mean particle size, number and weight distribution, particle number, methods for determining particle size by different methods, counting and separation method, particle shape, specific surface, methods for determining surface area, permeability, adsorption,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

- Micromeritics involve the study of small particles and of a few microns size.
- It involves the characterization of individual particles, particle size distribution and powders.
- Particles are characterized by the following properties.
  - Size
  - Shape
  - Volume
  - Surface area
  - Density
  - Porosity
  - Flow
- Particle size is normally denoted in micrometers μm.

  1 μm = 10^{-3}mm or 10^{-6}m.

Micromeritics

- Units of particle size is **Micrometers (μm)**
- **μm = μ = 10^{-6}m**
- As particle size **decreases**, surface area **increases**



- Can be related to physical, chemical and pharmacological properties of drugs.

Applications

- Release and dissolution:

  Particle size and surface area influence the release of the drug from a dosage form that is administered orally, rectally, parentrally, and topically. Higher surface area brings about intimate contact of the drug with the dissolution fluids and increases the drug solubility and dissolution. In general, higher the surface area, better the release. Hence faster is the dissolution.

- Absorption and drug action:

  Particle size and surface area influence the drug absorption and the therapeutic action. Higher the dissolution, faster the absorption. Hence, quicker and greater is the drug action.

- Physical stability:

  Particle size influences the physical stability of suspensions and emulsions. Smaller the size of particles, better the physical stability of the dosage form owing to Brownian movement of the particles in the dispersion.

- Dose uniformity:

  Good flow properties of granules and powders are important in the manufacture of tablets and capsules. The distribution of particles should be uniform in terms of its number and weight. At the same time, the flow of granules should be uniform in order to ensure precise weight of the tablet and drug content.

Particles - Characteristics

- Particles characteristics influence the dissolution rate, absorption rate, content uniformity, taste, texture, color & stability.
- Each particle can be characterized & expressed by the following properties:
  - Size
  - Shape
  - Volume
  - Surface area

Particle size

- The shape of particles present in a powder is normally not spherical, but asymmetrical(uneven).
- Therefore, it is difficult to express the size as a meaningful diameter.
- However, particle size is expressed as the diameter which is related to an equivalent spherical diameter.
- Size of the particles may be expressed as follows:
  - Surface diameter, ds: is the diameter of a sphere having the same surface area as that of the asymmetric particle.
  - Volume diameter, dv: is the diameter of a sphere having same volume as that of the asymmetric particle.
  - Projected diameter, dp : is the diameter of a sphere having the same area of the asymmetric particle as observed under a microscope.

- Stokes' diameter, dst : is the diameter of an equivalent sphere undergoing sedimentation at the same rate as the asymmtric particle.
- Sieve diameter, dsieve : is the diameter of a sphere that passes through the same sieve aperture as the asymmetric particle.
- Volume-surface diameter, dvs : is the diameter of a sphere that has same volume to surface area ratio as the asymmetric particle.

Particle Shape

- Particle shape is related to geometric shape will influence the surface regularity.
- Particle shape will influence the surface area, flow of particles, packing & compaction properties of the particles.
- The surface area per unit weight & unit volume are important in the studies of absorption & dissolution.
- It is possible to determine whether the shape of a particle is spherical or asymmetric.
- A sphere has minimum surface area per unit volume.
- Therefore, these properties can be compared for spheres & asymmetric particles, in order to decide the shape.

Powder size

- Powder is considered as a collection of particles.
- If the powder contains particles of one size, the powder is termed monosize or monodisperse.
- Uniform size particles are normally obtained by passing the powder through the sieves of the desired aperture.
- Mono-size particles are important in pharmacy in the following areas:
  - Standardization of instruments, particle size analyser.
  - Accurate determination of pore size in case of filters.
  - For effective immunization, normally, antigens are made to adsorb on uniform sized particles.
  - For diagnostic purposes.

Particle size determination methods

- The particle size of a pharmaceutical substance is strictly maintained in order to get optimal biological activity.

Examples of drugs with particle size – pharmacopoeial control

Drug	Dosage Form	Size Requirement
Aspirin	Soluble Tablets	Sieve no. 180
Hydrocortisone	O/W Cream	90% = < 5µm, < 50 µm
Insulin Zinc (amorphous)	Injections	< 2µm
Insulin Zinc (crystalline)	Injections	10 > 40 µm

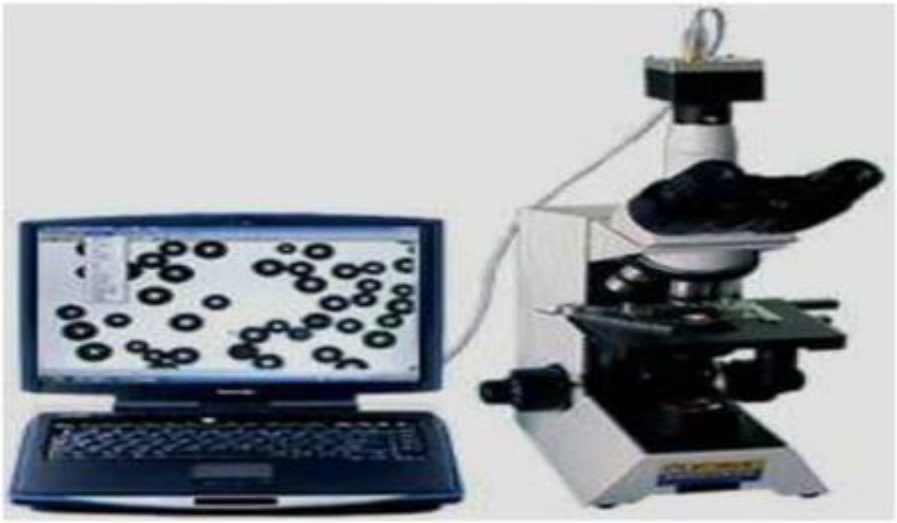
- Methods to estimate particle size are:

1. Optical microscopy
2. Sieving method
3. Sedimentation method
4. Conductivity method

- None of these methods are truly direct, because visual observation & measurement of all three dimensions of the particle is not possible.
- Data obtained by one method may not match data provided by other methods.
- Selection of a method largely depend on its intended applications, desired type of diameter & type of distribution required.
- Most methods have limitations in the range of sizes they cover.

Optical Microscopy

- Particle size in the range of the 0.2-100μm can be measured by optical microscopy.
- In this method, the size is expressed as dp(Pojected diameter), which describes the diameter of a sphere having the same area as the asymmetric particle when observed under a microscope.
- This method directly gives number distribution, which can be further converted to weight distribution.
- The optical microscope has a limited resolving power.
- The lower limit can be brought down using ultra microscope & electron microscope.



The microscope eyepiece is fitted with a micrometer by which the size of the particles may be estimated.

- Optical microscopy method is used to determine:

a) Particle size analysis in suspensions

b) Globule size distribution in emulsions

c) Particle size analysis in aerosols

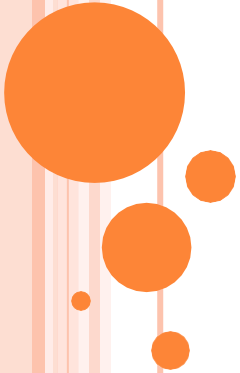
- Depending on the amount of solids or globules, if necessary a dilution of sample can be made using an appropriate vehicle.

Practical consideration:

- The microscope method of measurement should be carefully standardized, otherwise considerable errors may be introduced.
- The sources of error include the choice of diameter, technique of slide preparation & sampling.
- The value of projected diameter depends on the orientation of the particle on the slide.

Other Diameters:

1. Projected area diameter
2. Martin diameter
3. Feret diameter



Advantages:

1. Microscopy allows the observer to view the particles.
2. Agglomeration of particles & any contamination in the powder can be detected.
3. Particles in the dispersion must be free from motion. This can be avoided by mounting the sample with a cover-slip.
4. Easy & simple.

Disadvantages:

1. Diameter is obtained from only two dimensions. i.e., length & breadth.
2. Depth of the particles is not measurable.
3. This method is slow & tedious, because a large number of particles must be measured to get a good estimate.
4. Large sample is required.

Sieving method

- Particles having size range between 50 & 1500μm are estimated by sieving method.
- In this method, the size is expressed as dsieve, which describes the diameter of a sphere that passes through the sieve aperture as the asymmetric particle.
- This method directly gives weight distribution.
- The sieving method finds application in dosage form development of tablets & capsules.
- Normally 15% of fine powder (passed through mesh 100) should be present in granulated material to get a proper flow of material & achieve good compaction in tabletting.
- Therefore, % of coarse or fine powder can be quickly estimated.

- Standard size sieves are available to cover a wide range of size.
- These sieves are designed to sit in a stack so that material falls through smaller and smaller meshes until it reaches a mesh which is too fine for it to pass through.

- Sieves for pharmaceutical testing are constructed from wire cloth with square meshes, woven from wire of brass, bronze, stainless steel or any other suitable material.
- Sieves should not be coated or plated.
- There must be no reaction between the material of the sieve & the substance to be sieved.

Standard sieves & their dimensions as per IP are given in Table:

Sieve number	Aperture Size µm	Sieve number	Aperture Size µm
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

Method:

- Standard sieves of different mesh numbers are available commercially as per the specifications of I.P. & U.S.P.
- Sieves are arranged in a nest with the coarsest at the top sieve.
- This sieves set is fixed to the mechanical shaker apparatus & shaken for a certain period of time(20 min).
- The powder retained on each sieve is weighed.
- Frequently , the powder is assigned the mesh number of the screen through which it passes or on which it is retained.
- It is expressed in terms of arithmetic or geometric mean of the two sieves.
- This is reported as undersize.

Advantage:

- It is inexpensive, simple, & rapid with reproducible result.

Disadvantage:

- lower limit of the particle size is 50μm.
- If powder is not dry, apertures become clogged with particles, leading to improper sieving.
- During shaking, attrition (particles colliding with each other) occurs causing size reduction of particles.
- This leads to errors in estimation.

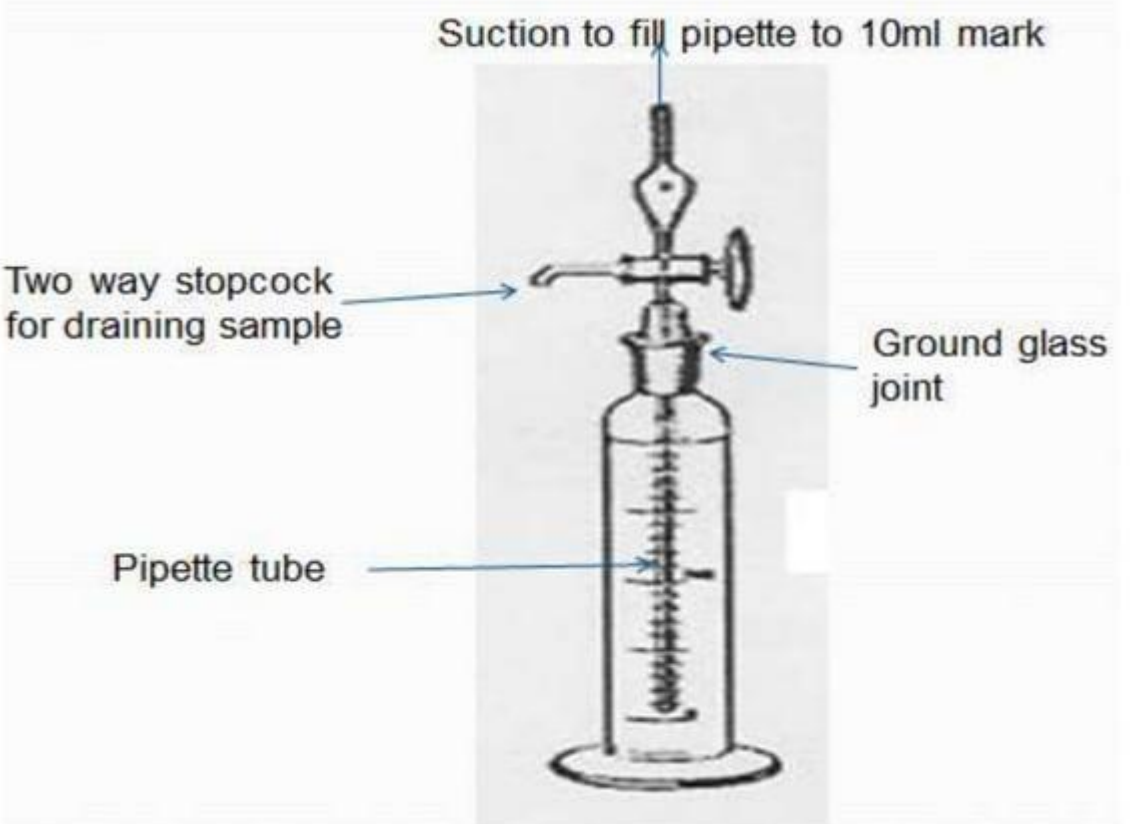
Sedimentation method

- Sedimentation method may be used over a size range of 1 to 200μm.
- In this method, size is expressed as Stokes diameter, dst, which describes the diameter of as equivalent sphere having the same rate of sedimentation as that of the asymmetric particle.
- Sedimentation of particles may be evaluated by different methods.
- Some of these are Andresen pipette method, balance method & hydrometer method.
- Andresen pipette method is discussed here.

- Sedimentation method finds applications in:
  1) Formulation & evaluation of suspension
  2) Formulation & evaluation of emulsions
  3) Determination of molecular weight of polymers
- Physical stability of a suspension depends on the rate of settling of particles in the dosage forms. Similar arguments have been proposed for the evaluation of physical stability of emulsions.

Principle:

- The rate of settling of particles in a suspension or emulsion may be obtained by stokes' law. The equation is rearrange to get the stokes' diameter, dst, of particles.
- Equation holds good for spheres falling freely at a constant rate without hindrance. However, equation can be extended to irregularly shaped particles of various sizes.
- Here it is assumed that the rate of settling of the particles is same as the sphere & therefore, size is expressed as of an equivalent sphere.
- When the powder is suspended in a vehicle, initially the particles of larger diameter settle due to heavy weight.
- After sometime, particles of intermediate diameter will settle. Finally, the particles of smaller size settle.
- Hence, the study involves the sampling during sedimentation at different time intervals.


Suction to fill pipette to 10ml mark
Two way stopcock for draining sample
Ground glass joint
Pipette tube

Method:

- The Andresen apparatus is usually consists of a 550ml cylindrical vessel containing a 10ml pipette sealed to a ground glass stopper.
- When the pipette is placed in the cylinder, its lower tip is 20 cm below the surface of the suspension.

Procedure:

- Prepare 1 or 2% suspension of the powder in a suitable medium.
- A deflocculating agent will help in uniform dispersion of the suspension.
- Transfer the suspension in to the Andresen vessel.
- Place the stopper & shake the vessel to distribute the suspension uniformly.

- Remove the stopper & place the two-way pipette & securely suspend the vessel in a constant temperature water bath.
- At different time intervals, 10ml samples are withdrawn using two way stopcock & collected in a watch-glass.
- Samples are evaporated & weighed.
- The weight or amount of particles obtained in each time interval is referred to as weight undersize.
- The weights are converted in to cumulative weight undersize.
- Particles diameter is calculated from stokes' law, with 'h' in equation being the height of the liquid above the lower end of the pipette at the time of withdrawing the samples.
- Four curves are plotted & statistical diameters are calculated.

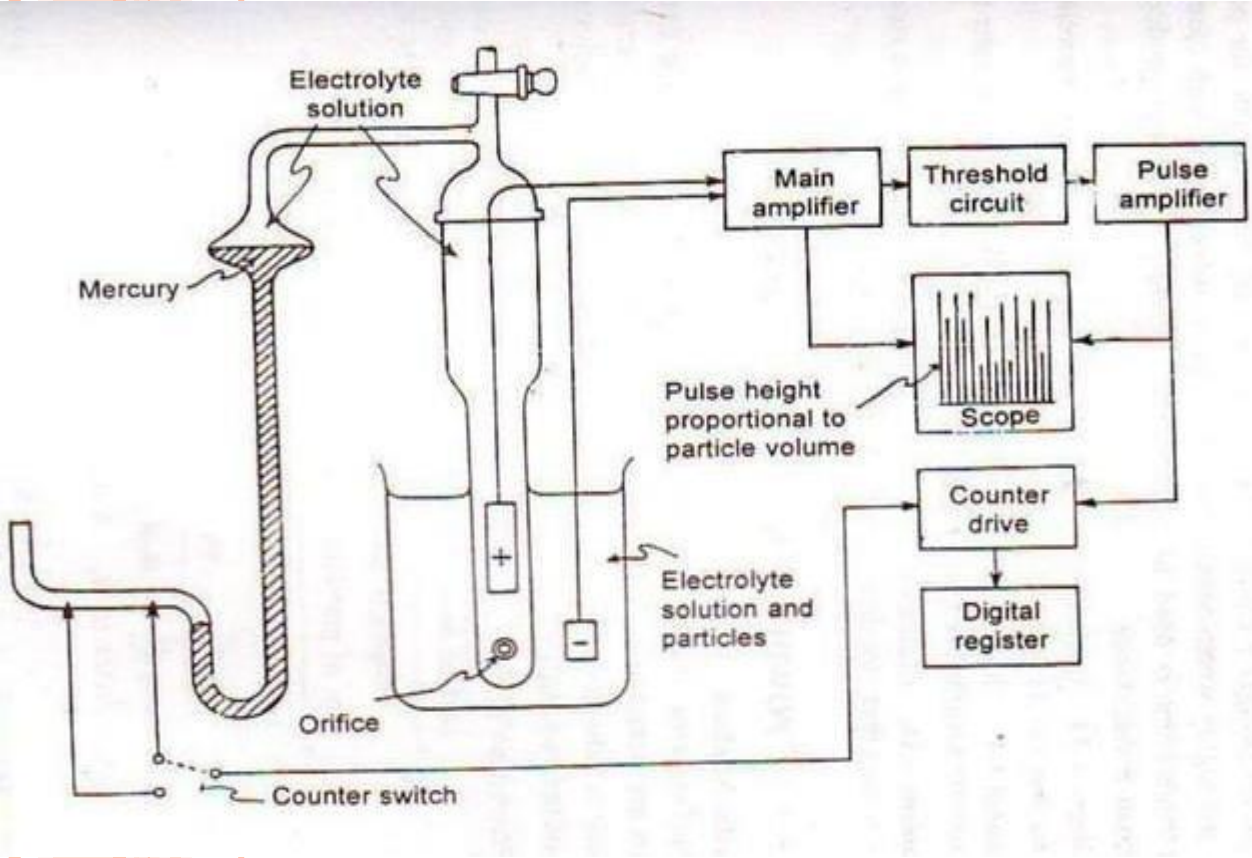
Conductivity Method

- Particle size ranging from 0.5 to 500μm is measured by conductivity method. This method gives number distribution.
- In fact, particle volume is measured & converted in to particle diameter.
- Coulter counter is used to measure the particle volume.
- Thus, in this method, size is expressed as volume diameter, dv, which describes the diameter of the sphere having the same volume as that of the asymmetric particle.
- This is a quick & accurate method, but the instrument is expensive.

- This method finds the application in the study of----
  - Particle growth in suspensions & emulsions.
  - Dissolution of drugs in a desired medium, &
  - Effect of antibacterial agent on the growth of microorganism.

Principle:

- Working principle of the coulter counter may be explained with the help of figure.
- Particles are suspended in a conducting electrolyte(say sodium chloride).
- This dispersion is filled in the sample cell, that has an orifice & maintains contact with the external medium.
- Electrodes are placed in the solution (inside the cell) & suspension (outside as shown in figure).
- A constant voltage is applied across the two electrodes.


Electrolyte solution
Mercury
Main amplifier
Threshold circuit
Pulse amplifier
Pulse height proportional to particle volume
Scope
Counter drive
Digital register
Electrolyte solution and particles
Orifice
Counter switch

- In this position current passes.
- When a suspended particles travel through the orifice, it displace its own volume of electrolyte in to the beaker.
- The net result is a change in electrical resistance.
- This change in electric resistance is termed as voltage pulse, which is related to the particle volume.
- This voltage pulse is amplified & fed to a pulse height analyzer.
- This analyzer is previously calibrated in terms of particle size for different threshold settings.
- For a given threshold value, the pulses are electronically counted.
- By changing threshold settings gradually, number of particles of each size range is obtained.

- Thus the particle size distribution can be obtained.
- Conductivity method is also known as stream scanning, i.e., a fluid suspension of particles passes through a sensing zone, in which individual particles are electronically sized, counted & tabulated.

Advantages:

- Using coulter counter apparatus, approximately 4000 particles per second can be counted.
- Therefore size distribution analysis can be completed in a relatively short period of time.
- It gives reasonably accurate results.

Disadvantage:

- This method may be unsuitable for polar and highly water soluble material due to salvation.
- In such cases, if a nonsolvent is used to suspend the particles, it may produce adequate conductance.

Powder surface area determination Methods:

- Specific surface: surface area of a powder can be calculated using particle size data which are obtained by one of the methods mention already. Specific surface is defined as the surface area per unit weight (Sw) or unit volume(Sv) of the material.
- Estimation of Sv:

  Sv = Surface area of particles / Volume of particles

  = No. of particles × surface area of each particle /

  No. of particles × Volume of each particle
- Estimation of Sw:

  Sw = Surface area / Weight

  = Surface area/density × Vol.

- The commonly used methods are:
  a. Adsorption
  b. Air Permeability

Adsorption Method:

- Particles having large specific surfaces are good adsorbents of gases & solutes from solution.
- Amount of gas that is adsorbed to form a monomolecular layer on the adsorbent is a function of surface area of the powder.
- This principle is used to estimate the specific surface.
- This method is also used to estimate surface diameter, ds.

Air Permeability Method:

- The instrumentation is simple & determination is quick.
- This method also used to estimate surface diameter, ds.
- This method is useful in controlling batch to batch variations in production of powders.
- It is official in I.P. Bephenium hydroxynaphthoate (an anthelminic) is administered as a suspension.
- The I.P. prescribes the specific surface area limit of not less than 7000 cm^2 /g.
- As the specific surface is reduced, the activity of the drug also falls.
- According to I.P., griseofulvin, an antifungal antibiotic, should have the surface area of not less than 13000 to 17000 cm^2 /g.
- If it is less, the absorption of the drug will fall.

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.
- The air, when allowed to pass, travel through these capillaries & thus this method is related to surface area of powder.
- When air is allowed to pass through the powder bed 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, Sw, the greater the resistance to flow.
- The permeability of air for a given pressure drop is inversely proportional to specific surface.

Method:

- This method is official in I.P. Fisher subsieve sizer instrument is commercially available.
- Assembling of the apparatus is shown in figure.
- It consist 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 & negligible vapor pressure.
- The air pump builds up air pressure & is connected to a constant pressure regulator.
- Air is passed through the dryer to remove any moisture.
- Air then allowed to flow through the packed powder in the sample tube.

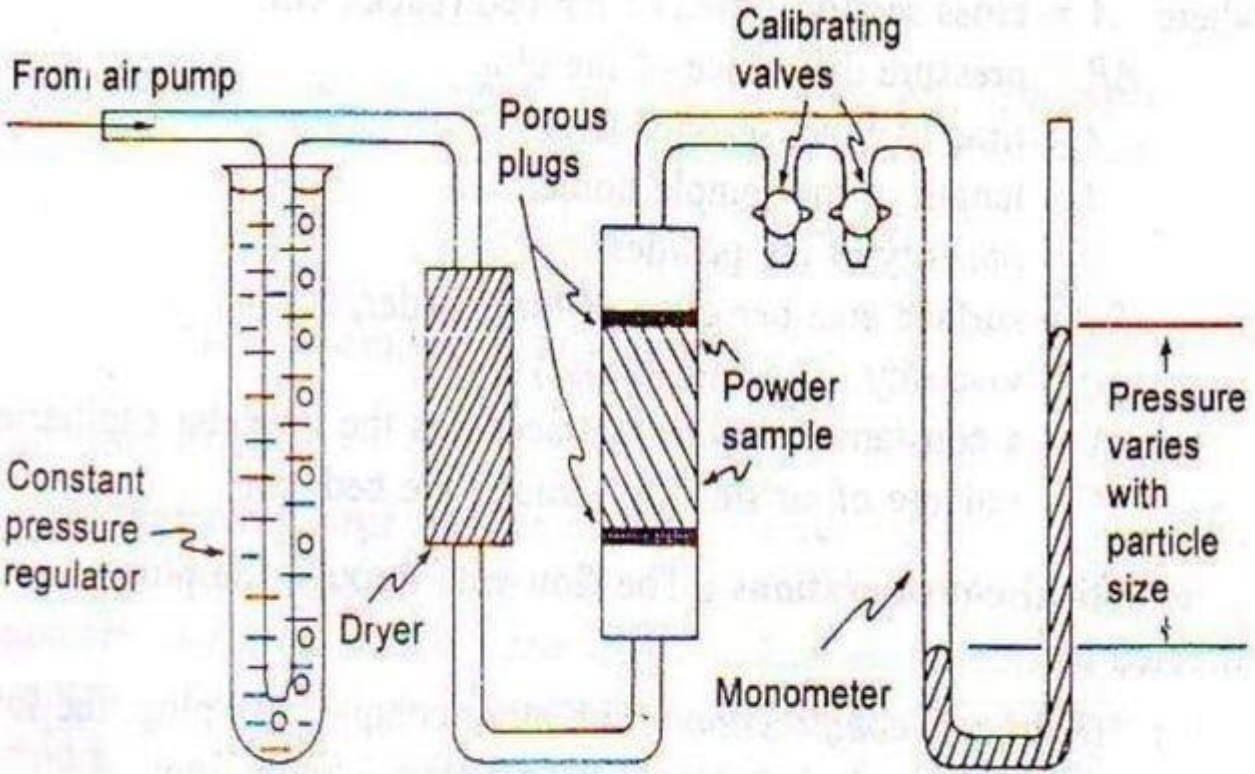


Figure 6-11. The Fisher subsieve sizer.

- The flow of air is measured by the manometer.
- The level of the fluid in the manometer indicates the average diameter of the particles.
- Commercial equipment is standardized to eliminate the mathematical computation.
- Average particle diameter can be read from the calculator charts supplied with the equipment.
- The porosity of the powder (ε) & viscosity (η) are estimated separately.

Derived Properties of Powder

- The fundamental properties of particles are discussed in earlier.
- Size or diameter is a fundamental property of a particle.
- Volume, density, porosity etc., are the properties derived from fundamental properties.
- For example, volume of the particle is calculated from the diameter of the particle.
- However, derived properties can also be directly determined without the use of fundamental properties.
- These derived properties are important in pharmacy.

- A few application are given below:

✓ Porosity: influence the dissolution of the drug.

✓ Bulk density: help in selecting container for packaging a dosage form

✓ Flow Properties: help in maintaining a uniform weight of tablets or capsules during production.

- **True Density:**

It is the density of the material itself. It is defined as :

True Density = Weight of powder / True volume of powder

The density is dependent on the type of atoms in a molecule, arrangement of the molecule & the arrangement of molecules in the sample.

Apart from true density, powder is also characterized by granule density & bulk density.

- The most common methods used in the determination of the true density are Gas displacement, liquid displacement & flotation in a liquid.
- Helium & nitrogen gases obey the ideal gas law at ambient temperatures & pressures. However, helium is preferred because of its smaller size.

Porous solids – Helium displacement method:-

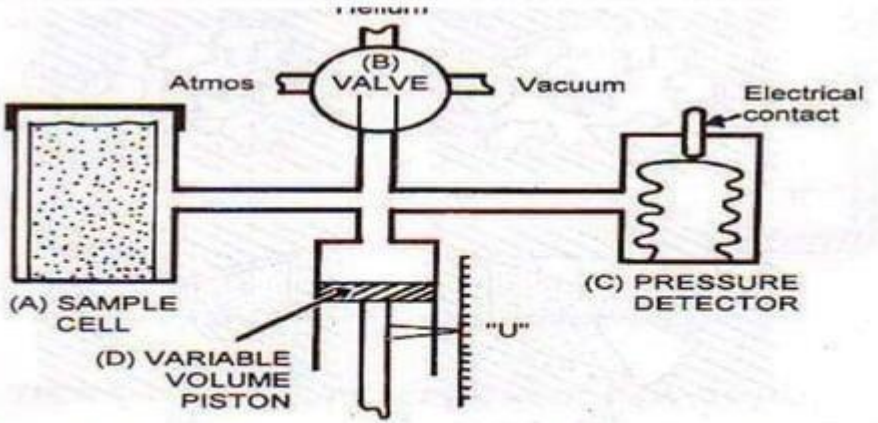


Figure 6-13. Parts and arrangement of helium pycnometer for determining the true volume of a powder

- Helium penetrates the smallest pores & cervices. Therefore, this method gives a value closer to its true density.
- This is the valuable tool to estimate the true density, particularly for porous solids.
- Helium pycnometer 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 & 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 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 pycnometer is determined.
- The air present in the sample holder is removed by applying vacuum.
- Then, helium gas is passed in to the apparatus through the valve(B).
- The pressure is adjusted & set a particular valve with the help of a movable piston(D).
- At this piston, the reading on the scale denotes *U1,* this represents the volume of empty cell.
- In the next step, pycnometer is calibrated by placing a standard sample of known true volume (Vc) (Stainless steel spheres) in the sample holder.
- The sample holder is sealed & air is removed.
- The same amount of the helium gas is introduced.

- Pressure is adjusted to present valve by moving the piston suitably.
- At this stage, the scale reading is denoted by U2.
- The difference between U1 & U2 gives the volume occupied by the sphere.
- The last step involves the determination of volume of the sample.
- The stainless steel sphere is replace by the test sample powder.
- The air in the pycnometer is replace by the helium gas.
- The pressure is adjusted with the help of piston.
- At this state, the piston reading is denoted by Us.
- The difference between U1 & Us gives the volume occupied by the sample.

Liquid displacement method:-

- Liquids such as water & ethyl alcohol can not occupy the pores & cervices.
- If the powder is nonporous, this method is used.
- Select a solvent in which the powder is insoluble & heavy.
- Normally, the values obtained are somewhat lower than the helium displacement method.
- Pycnometer or specific gravity bottle may be used.

Weight of pycnometer = w1

Weight of pycnometer + Sample(or glass beads) = w2

Weight of Sample = w3 = w2 – w1

Weight of pycnometer with powder & filled with solvent = w4

Weight of the liquid displaced by solids = w4 – w2

True Density = w2 – w1 / w4 – w2 .

Granule density:

- Granule density is determined for the granules that are employed in the manufacture of tablets.
- Granule density defined as:

Granule Density = granule weight / granule volume

- The volume of granules can be measured by mercury displacement method.
- Mercury is suitable because it fills the voids, but fails to penetrate the internal pores of the particles.
- The use of mercury is also based on its high contact angle of about 140° & its nonwetting characteristics.
- Granule volume is related to weight of the mercury that is displaced by the granules in pycnometer.
- This method is as same as that reported in the liquid displacement method.

Bulk density:

- It is defined mathematically as:

  Bulk density(ρ) = mass of a powder (w) / bulk volume (Vb)
- When particles are packed loosely, lots of gaps between particles are observed.
- Hence bulk volume increases making the powder light.
- Based on bulk volume, powders are classified as 'light' & 'heavy'.
- Light powders have high bulk volume.
- On the other hand, smaller particles may sift between the larger particles, the powder assume low bulk volume or high bulk volume.
- Such powders are called heavy powders.
- The bulk density depends on particle size distribution, shape & cohesiveness of particles.

Method:

- A powder (about 60gm) is passed through a standard sieve No. 20.
- A weight amount (about 50gm) is introduced into a 100ml graduated cylinder.
- The cylinder is fixed on the bulk density apparatus & the timer knob is set (regulator) for100 another 50 taps may be continued & the final volume is noted.
- Further, another 50 taps may be continued & the final volume is noted.
- For reproducible results, the process of tapings may be continued until concurrent volume is achieved.
- This final volume is the bulk volume.
- Then bulk density is calculated using equation.

- Bulk volume is also measured by dropping the cylinder (containing powder) onto a hard wooden surface 3 times from a height of 1 inch at 2 seconds intervals.
- Sometimes, to get an appropriate volume, the container has to be dropped or tapped 500 times.
- The bulk densities of some pharmaceutical powders are given below:

Substance	Bulk Density	True Density
Microcrystalline Cellulose	0.39	1.55
Talc	0.94	2.7
Lactose	0.74	1.54
Magnesium Oxide	1.00	3.65
Titanium Dioxide	0.63, 0.83	4.26

Applications:

- Bulk density is used to check the uniformity of bulk chemicals. (quality control tool)
- 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 & bigger the size of the capsule.
- It helps in selecting the proper size of a container, packing material, mixing apparatus in the production of tablet & capsules.

Porosity:

- It is important to summarize the following relationship in terms of volume.

True volume = Volume of the powder itself.

Granule volume = Volume of the powder itself + Volume of intra particle spaces (represented by pores & cervices.)

Bulk volume = Volume of the powder itself + Volume of intra particle 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

Porosity = Void volume / Bulk Volume

Applications:

- Certain powders contribute immensely to the porosity of the tablet.
- Porosity influences the rate of disintegration & dissolution.
- Higher the porosity, the faster the rate of dissolution.
- Based on porosity values, solids Can be classified as porous & nonporous.
- Porosity is applied in the studies on adsorption & diffusion of drug materials.

Flow Properties:

- Irregular flow of powder from the hopper produces tablets with non uniform weights.
- As a result, content uniformity & dose precision can not be achieved in the production of tablets & capsules.
- Flow properties depends on the particle size, shape, porosity & density of the bulk powder.
- These factors are enumerated here.

1. Particle size
2. Nature of particles
3. Moisture content
4. Angle of repose
5. Dispersibility

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 pile of the powder & the horizontal plane.**

$$\tan \Theta = h / r$$

Angle of Repose	Flow
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Hausner ratio

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured or bulk density}}$$

Hausner ratio was related to interparticle friction:

- Value less than 1.25 indicates good flow (=20% Carr).

Hausner ratio

- The powder with low interparticle friction, such as coarse spheres.
- Value greater than 1.5 indicates poor flow (= 33% Carr's Compressibility Index)).
- More cohesive, less free-flowing powders such as flakes.
- Between 1.25 and 1.5 added glidant normally improves flow.
- > 1.5 added glidant doesn't improve flow.

Carr's consolidation index:

$$= \text{Tapped density} - \text{fluff density} / \text{tapped density} \times 100$$

- This property is also known as compressibility.
- It is indirectly related to the relative flow rate, cohesiveness & particle size.
- It is simple, fast & popular method of predicting powder flow characteristic.

Carr's compressibility index

Relationship between powder flowability and % compressibility

Flow description	% Compressibility
Excellent flow	5 – 15
Good	16 – 18
Fair	19 – 21
Poor	22 – 35
Very Poor	36 -40
Extremely poor	> 40

Thank You!!!!