MICROMERITICS

Definition:

- Micromeritics is the science and technology of small particles. Knowledge and control of the size and the size range of particles are of significant importance in pharmacy because the size and surface area of a particle related to the physical, chemical and pharmacologic properties of a drug.
- The particle size of a drug can affect its release from dosage forms that are administered orally, parenterally, rectally and topically.
- In the area of tablet and capsule manufacture, control of the particle size is essential in achieving the necessary flow properties and proper mixing of granules and powders.

Applications:

1. Release and dissolution.
2. Absorption and drug action.
3. Physical stability.
4. Dose uniformity.

1. 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.

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 and hence quicker and greater the drug action.

3. 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.

4. Dose uniformity.

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

Particle size and size Distribution: When a powder sample contains of uniform size, it is said to be monodisperse. In collection of particles of more than one size, it is said to be polydisperse. The pharmaceutical powders are almost always be polydisperse and hence it is necessary to charcterise particle size and their distribution. For characterisation two properties are important i.e., (a) the shape and surface area of the individual particles, and (b) the size range and number or weight of particles present and hence, the total surface area. The size of a sphere can completely be expressed in terms of its diameter. When particle is asymmetrical the diameter which is related to an equivalent spherical diameter, which relates the size of the particles to the diameter of a sphere having the same surface area, volume or diameter

The size of particles may be expressed as:

(i) Surface diameter, ds : Is the diameter of a sphere having the same surface area as that of the asymmetric particle.

(ii) Volume diameter, dv : Is the diameter of of a sphere having same volume as that of the asymmetric particle.

(iii) Projected diameter, dp : Is the diameter of sphere having the same observed area as the particle when viewed normal to its most stable plane.

(iv) Stokes'diameter, dst : Is the diameter of an equivalent sphere undergoing sedimentation at the same rate as the asymmetric particle.

(v) Sieve diameter, d sieve: Is the diameter of a sphere that will just pass through the same square or sieve aperture as the particle.

(vi) Volume-surface diameter; dvs : Is the diameter of a sphere that has the same volume to surface area ratio as the asymmetric particle.

Frequency distribution curve:

In this type, number or weight of particles lying within particular size range is plotted against the mean particle size. In general the normal distribution curve is expected to be symmetrical (bell shaped) around the mean, which is also the mode. In this type of distribution, the positive and negative deviations from the mean are uniform and it is represented by standard deviation. Larger particles obtained by granulation can be described by normal distribution. In this case, arithmetic mean and standard deviation are considered.

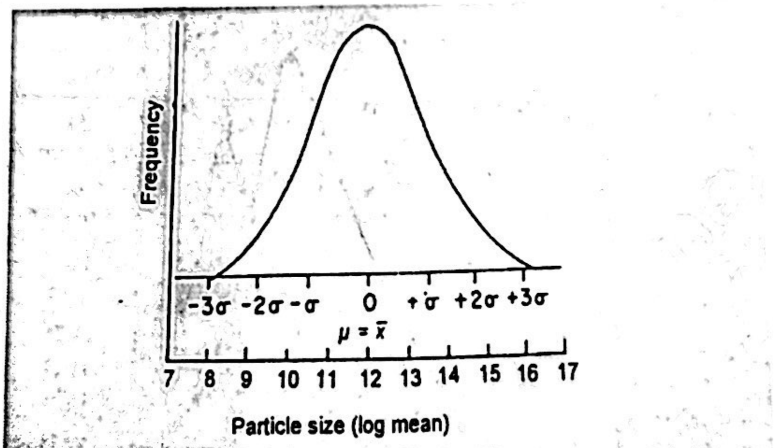


Figure 6-2. Normal distribution curve (bell shaped curve). The peak is the mean or the mode. Distribution of deviations is uniform around the mean.

Normal distribution is usually not found in pharmaceutical powders because of uneven size reduction process. The distribution of particles in a powder is termed as unsymmetric or skewed, i.e. uneven around the mean. If frequency curve is elongated towards higher size range, the pattern is known as positive skewness. If frequency curve is elongated towards lower size, the pattern is known as negative skewness. It is normally shows a long tail of larger particle size.

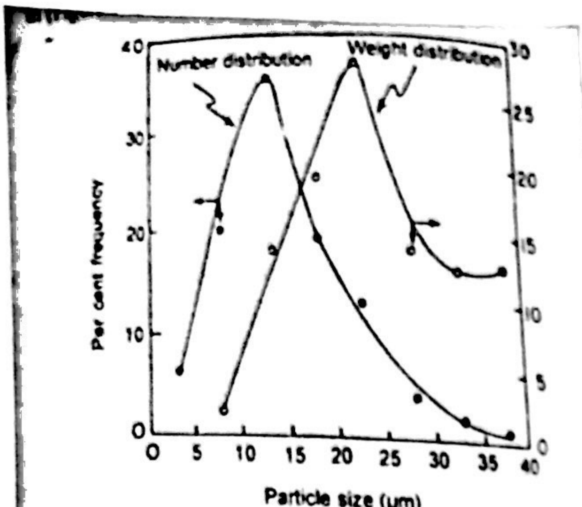
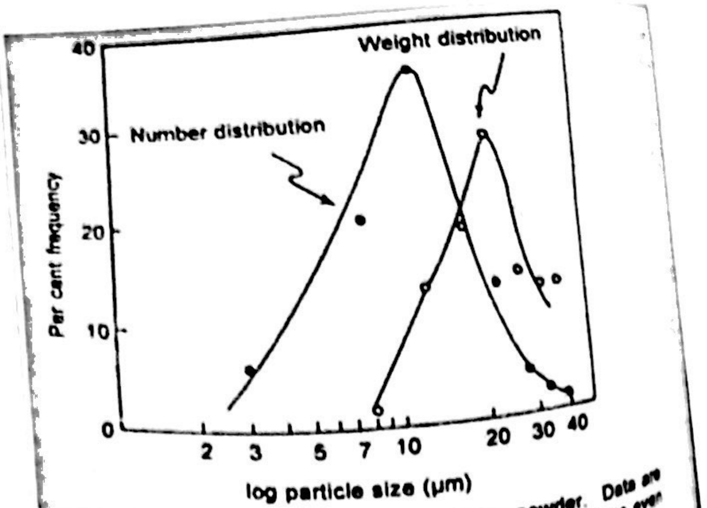


Figure 6-3. Normal distribution curve for a powder. Data are taken from Table 6-1. Uneven distribution around the mean. Long tail of larger particles (x axis column 2, y axis: columns 4 and 5)



re 6-4. Log-normal distribution curve for a powder. Data are n from Table 6-2. Distribution of particles is more or less even nd the mean (x axis: column 2; y axis: columns 3 and 5).

Log-normal distribution curve:

In this type, frequency on y axis is plotted against log mean particle size on x axis. Advantage of this curve is that the distribution pattern is made symmetrical. When compared to normal distribution curve. Powders obtained by crystallization and milling methods exhibit log-normal distribution. Powder blend obtained from granulation may have different type of distribution.

Cumulative frequency distribution curve:

In this plot, cumulative percentage over size (or under size) is drawn against particle size. If summation of frequencies is carried out from the bottom upward, the result expressed as the percentage particle over size. Summation downwards gives percentage undersize. Data yield a sigmoid curve with the mode, i.e. particle size at the greatest slope. The advantage of this plot is that one can directly read the percentage within any given size range without any difficulty. The disadvantage is that scattering of points cannot be identified.

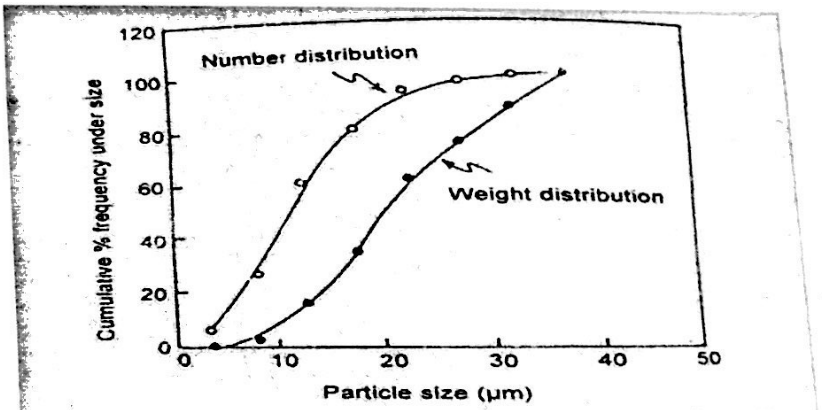


Figure 6-5. Cumulative frequency distribution curve. Data are taken from Table 6-2 (x axis: column 1; y axis: columns 4 and 6)

Log –Probability plot:

A plot is drawn by taking log particle size on x axis and cumulative percent frequency of the probability scale on y axis. In this plot, the cumulative curve is converted into a straight line. A straight line is completely defined by one point and the slope. For the number distribution, slope gives geometric standard deviation σg. The reference point gives geometric mean diameter, dg, which is equal to the median or the diameter at 50% on probability scale.

Probability plot is necessary when certain data points are not well defined. For example, in the sieve analysis, how much material has passed through the top sieve is known. For this data point, we have to identify the midpoint interval of the top, which is not known.

The advantages of probability graph are:

1. Error of data points are averages by taking a best fit line.
2. Linearity or lack of linearity can be identified.

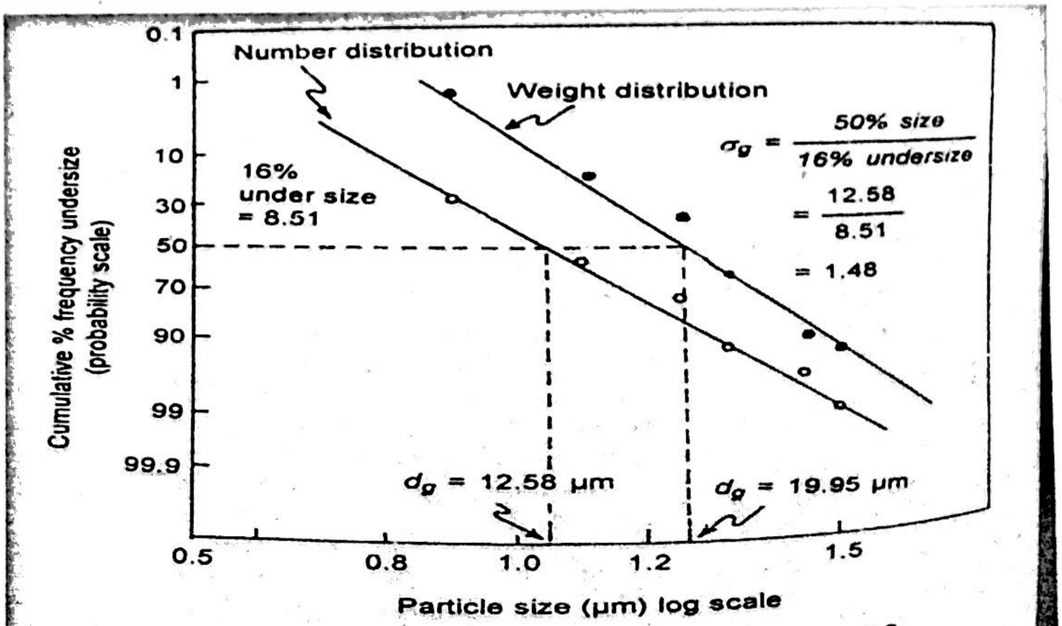


Figure 6-6. Log probability plot. Data in Table 6-2. x axis: column 2; y axis: columns 4 and 6.

Particle size determination-Methods:

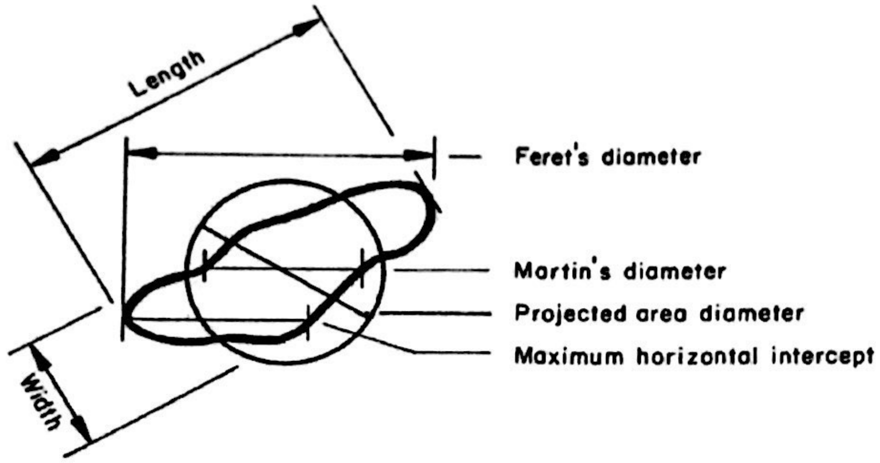
Many methods available for determining particle size such as optical microscopy, sieving, sedimentation and particle volume measurement.

1. Optical microscopy (range: 0.2-100 µm).
2. Sieving (range: 40-9500 µm).
3. Sedimentation (range: 0.08-300 µm).
4. Particle volume measurement or conductivity method (range: 0.5-300 µm).

1. Optical microscopy:

The optical microscopy can be used to measure the particles size in the range of 0.2 µm to about 100 µm. In this method the size is expressed as d_p projected diameter. By this method the number distribution data can be obtained and it can be converted to weight distribution. The resolving power of optical microscope is less as compared to ultramicroscope or electron microscope. In this method, an emulsion or suspension, diluted or undiluted, is mounted on a slide or ruled cell. Eye-piece of the microscope is fitted with a micrometer, called ocular micrometer. The eyepiece or ocular micrometer is calibrated using a stage micrometer. The slide or ruled cell is placed on a mechanical stage. The size of particle is determined with the help of ocular micrometer. The field can be projected onto a screen where particles are measured more accuratly and photograph can be taken. The optical microscopy method can be used to determine the particle size analysis in suspensions, in aerosols or in emulsion (droplet size). In order to get statistically valid results the counting of particles should be in the range of 500 to 1000 particles for every sample.

From the obtained data the size frequency distribution curves, cumulative frequency curves are plotted. Other popular measurements includes - Feret diameter, the Marti diameter and projected area diameter.



Popular measurements:

Feret's Diameter— The distance between imaginary parallel lines tangent to a randomly oriented particle and perpendicular to the ocular scale.

Martin's Diameter— The diameter of the particle at the point that divides a randomly oriented particle into two equal projected areas.

Projected Area Diameter— The diameter of a circle that has the same projected area as the particle.

Length— The longest dimension from edge to edge of a particle oriented parallel to the ocular scale.

Width— The longest dimension of the particle measured at right angles to the length

Advantages

1. Microscopy method allows the direct observation (shape and size) of particles
2. The field can be projected and a photograph can be taken.
3. Aggregation of particles can be easily detected.
4. Provides accurate results and reproduciability.

5. Simple and economic.
6. Easy to handle.

Disadvantages

1. Diameter is obtained from only two dimensions of the particle i.e., length and breadth. No estimation of depth (thickness) of particle.
2. The method is slow and tedious, because the number of particles that must be counted (300-500) to obtain a good estimation of the distribution.
3. Time consuming method.
4. Large sample is required.

2. Sieving method:

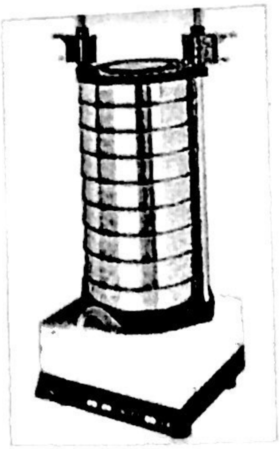
Particles having size range between 40 to 9500μm are estimated by sieving method. In this method, the size is expressed as d_{sieve}, which describes the diameter of a sphere that passes through the sieve aperture as the asymmetric particle. This method directly gives **weight distribution**. This method is also known as **analytical sieving**.

The sieving method finds application in dosage form development of tablet and capsules. Normally 15% of fine powder should be present in granulated mass to get as proper flow and achieve good compaction in tabletting. Therefore, percent of coarse or fine powder can be quickly estimated. In addition, sieving also separated the powder can be quickly estimated. In addition, sieving also separates the powder into fractions of desired size.

Sieves for pharmaceutical testing are considered 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 construction of the sieve and the substance to be sieved.

Method:

Standard sieves of different mesh numbers are available commercially as per the specification of IP and USP. Sieves are arranges in a nest with the coarsest at the top. A sample of the powder is places on the top sieve. This sieves set is placed in the mechanical shaker apparatus and shaken for a certain period of time. The powder retained on each sieve is weighed. Frequently, the powder is assigned the mesh number of the screen through which it is passed or on which it is retained. It is expressed in terms of **arithmetic or geometric mean** of the two sieves. Data are analyzed for normal, log-normal, cumulative percent frequency distribution and probability curves. The relevant diameter such as geometric mean weight diameter and standard deviation can be obtained.



Advantages

1. It is simple for handling.
2. It is inexpensive and rapid.
3. Provides reproducible results.
4. Specially useful for weight distribution.
5. It can be used for very small particles having particle diameter upto 5J.lm.

Disadvantages

1. It cannot used for very small particles is below 5J/m.
2. The powder sample should be dried every time, otherwise it may clog with particles, resulting improper sieving.
3. During shaking, attrition of particles may cause reduction of particle size. This may leads to errors in estimation.
4. Time consuming method.
5. Approximate results can be obtained.

3. Sedimentation method:

The sedimentation method can be used for formulation and evaluation of suspensions. emulsions and determination of molecular weight of polymers. The particle size in the subsieve range may be obtained by gravity sedimentation and is expressed as stokes' diameter, dst' in Stokes' law.

$$d_{st} = \sqrt{\frac{18\mu h}{(\rho_s - \rho_l)gt}}$$

Where,

d_{st} = Stokes diameter of the particle

μ= viscosity of the medium

h = height of fall in time

Ps = density of the particles

Pl= density of the medium

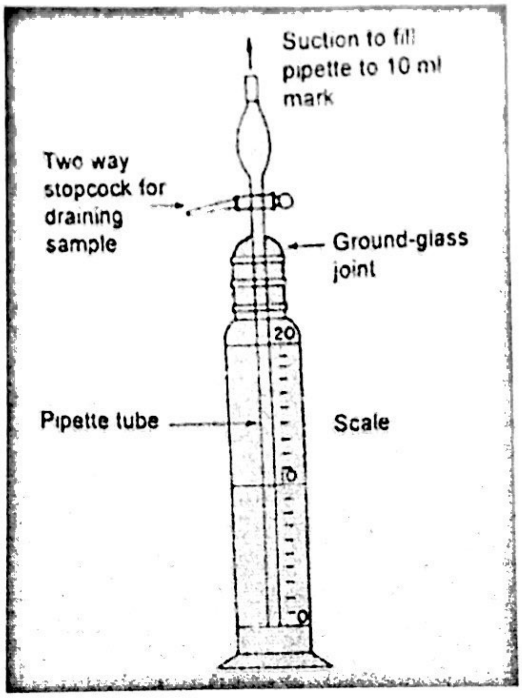
g = acceleration due to gravity

t = time interval

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

The procedure is as follows:

1 or 2% suspension of powder in a suitable medium firstly prepared and to that add suitable deflocculating agent. Transfer this mixture (suspension) into the Andreasen vessel. Place the stopper and shake the vessel to distribute the particles uniformly throughout the suspension and the apparatus is place in a constant temperature bath. Remove the stopper and attach two-way stopcock. At various time intervals, 10ml samples are withdrawn and discharged by means of the two way stopcock. The samples are evaporated and weighed or analyzed by any method, correcting for the deflocculating agent that has been added. The weight or the amount of particles obtained in each time interval is referred to as weight undersize. The weights are converted into cumulative weight undersize.



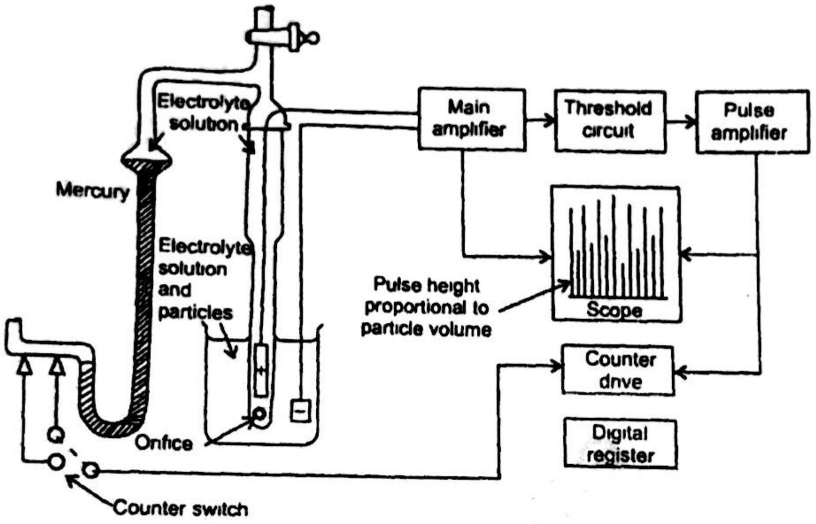
4. **Particle volume measurement or conductivity method:**

The popular instrument to measure the volume of particles is the coulter counter. This method gives number distribution. Here the particle volume is measured and is converted into particle diameter, and size is expressed as volume diameter d_v. The method is useful in the study of particle growth in suspension and solutions, useful in dissolution studies and to study the effect of antibacterial agents on the growth of microorganisms. This method gives quick and accurate results.

The working principle of coulter counter is that when a particle suspended in a liquid containing electrolyte (sodium chloride) passed through a small orifice, and maintains contact with the external medium. Generally, a known volume of a dilute suspension is pumped through the orifice. The suspension is sufficiently diluted so that only one particle can pass at a time through an orifice. A constant voltage is applied across the two electrodes. Here the current produces. When a suspended particle travels through the orifice, it displaces its own volume of electrolyte. The resistance, between two electrodes increases. The net result is a change in the electrical resistance, which is related to the particle volume, causes a voltage pulse. The voltage pulse are amplified and fed to a pulse height analyzer calibrated in terms of particle size.

The pulses are electronically counted for a given threshold value. By adjusting the threshold setting the number of particles of each size range is obtained. Thus the particle size distribution can be obtained.

The instrument is capable of counting particles at the rate of approximately 4000 per second. The data may be converted from a volume distribution to a weight distribution.



Coulter counter apparatus

Advantages

1. It gives very fast results [approximately 4000 particles per second].
2. Short period of time is required for size distribution analysis.
3. It provides accurate results.
4. It can be used to measure particulate contamination in parenteral solutions.
5. Submicron particle sizing instrument, the coulter Model N4 has been developed for analyzing particles in the range of 0.003 to 0.3 μm.
6. It is used in the study of the clustering process and the packing of the mineral components of renal stones.
7. It is also useful in quality control of large volume parenteral [LVP] solutions.

Disadvantages

1. It is not suitable for polar and highly water soluble materials due to solvation.
2. It is expensive method.

Specific surface:

Specific surface is defined as the surface are per unit weight (Sw) or unit volume (Sv) of the material.

Determination of surface area:

The commonly used methods are:

1. Adsorption method
2. Air permeability method

Specific Surface

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

$$= \frac{\text{number of particles} \times \text{Surface area of each particle}}{\text{number of particles} \times \text{Volume of each particle}}$$

$$= \frac{\eta \alpha_s d^2}{\eta \alpha_v d^3} = \frac{\alpha_3}{\alpha_v d}$$

$$S_w = \frac{\text{Surface area}}{\text{Weight}} = \frac{\text{Surface area}}{\text{Density} \times \text{Volume}}$$

$$S_w = \frac{S_v}{\rho} = \frac{\eta \alpha_s d_{vs}^2}{\eta \alpha_v d_{vs}^3 \times \rho}$$

$$= \frac{\alpha_s}{\alpha_v \, d_{vs} \, \rho}$$

When the particles are spherical, above equation simplifies to

$$S_w = \frac{6}{\rho d_{vs}}$$

Since $\frac{\alpha_s}{\alpha_v}$ = 6.0 for a sphere.

Adsorption method:

Principle: 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.

$$\frac{p}{y(p_0 - p)} = \frac{1}{y_m b} + \frac{(b-1)}{y_m b}\,\frac{p}{p_0} \qquad (18)$$

where p = pressure of the adsorbate, mmHg

y = 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

When, $p/p_0 = 1$, the vapor pressure p is equal to saturation vapor pressure. Quinsorb QS-16 is used for obtaining the data needed to calculate the surface area.

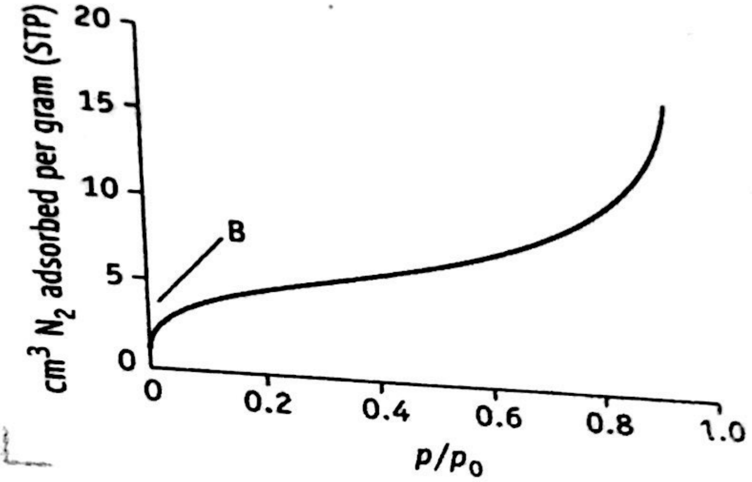


Fig. 6-12 Adsorption isotherm showing the volume of nitrogen gas absorbed on the powder. The first inflection point, B, represents the completion of monomolecular layer (y_m).

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 o desorption of nitrogen gas. The area under the curve is proportional t the gas adsorbed on the particles. The adsorption is measured, at severa pressures, so that BET equation plot can be obtained. Gaussian or bell shaped curve is plotted on a strip chart recorder.

Advantages : Quintasorb is versatile in the sense that it permits the use of a number of gases (or gas mixtures) over a range of temperatures. It allows the evaluation of characteristics of porous material. In addition, it can be used to measure true density of the powder, pore size and pre volume distribution. These can be used for studying physisorption and chemisorption. It is applicable to a wide range of surface areas.

Air Permeability Method – Fisher-Subsieve Sizer

Air permeability method is offical 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.

$$V = \frac{A}{\eta S_w^2} \bullet \frac{\Delta Pt}{Kl} \bullet \frac{\varepsilon}{(I - \varepsilon)^2} \qquad \ldots(19)$$

where 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

ε = porosity of the powder

S_w = surface area per gram of the powder, m^2/g

h = viscosity of the air Pa.s

K = a constant (5.0±0.5) that accounts the irregular capillaries

V = volume of air flowing through the bed, m^3

Poiseulle's equation is same as that used in Ostwald's viscometer, the principle of flow of liquids through the capillary tube. Fisher subsieve sizer instrument is commercially available.

Method : Assembling of the apparatus is shown in Figure 6-13. 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.

The porosity of the powder (ε) and viscosity of air (η) are estimated separately. A and l are constants represent sample holder. ΔP and V can be obtained from the experiment and substituted in equation (19) in order to estimate the surface area.

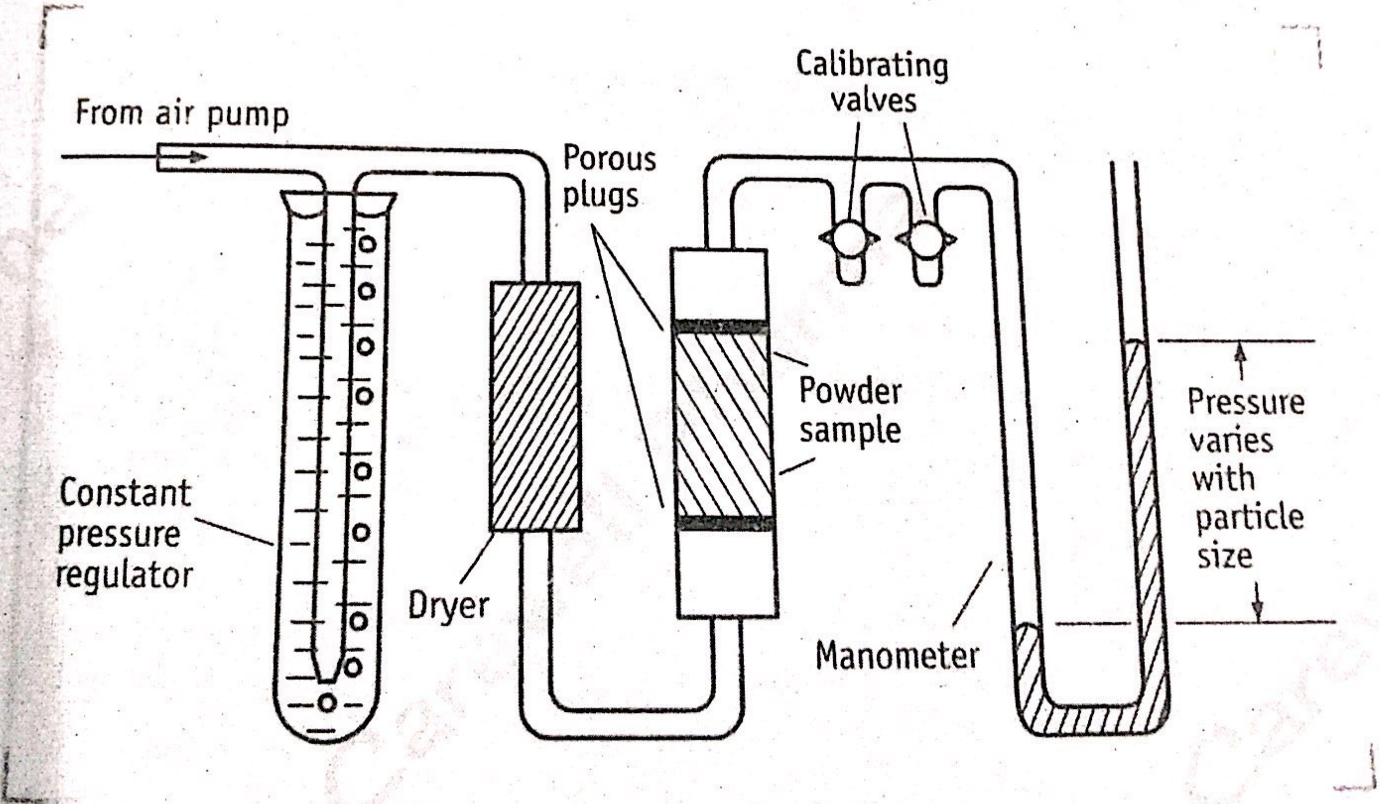


Fig. 6-13 The Fisher subsieve sizer.

If the powder has decreased porosity, the d_{vs} also decreases. Therefore, over a range of porosities, the minimum value of diameter is achieved.

Advantages

1. Simple instrumentation and high speed, it is widely used pharmaceutically for specific surface determinations.
2. Bephenium hydroxynaphthoate, official in the B.P.C., 1973 is standardized by air permeability method.
3. 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 cm^2/g. As the specific surface of the material is reduced, the activity of the drug also falls.
4. Air permeability method, officially in U.S. pharmacopoeia used for determining the specific surface area of griseofulvin.
5. 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:

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

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.

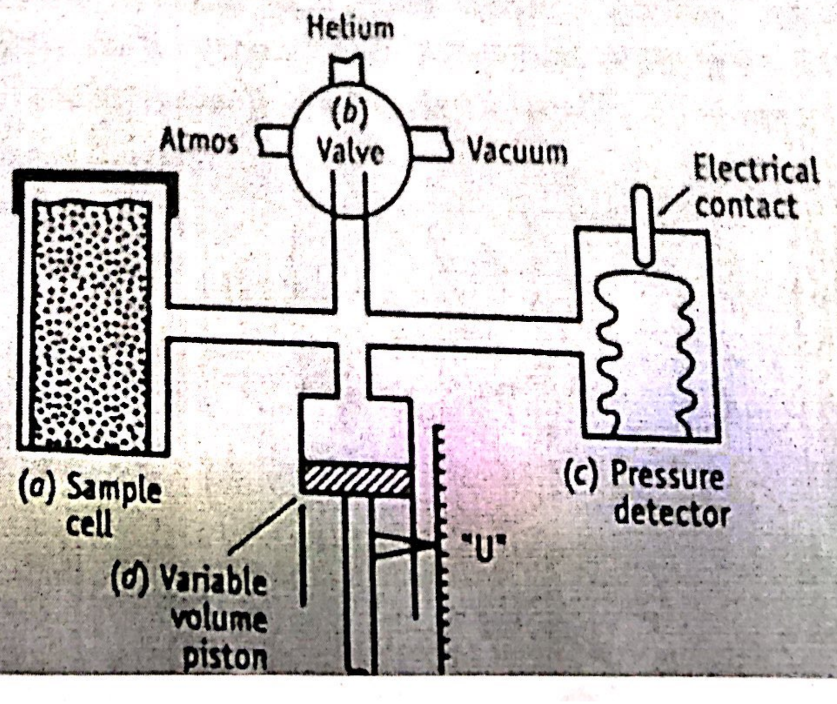
Volume occupied by voids and intraparticle pores are not included in true density. The most common methods used in the determination of the true density are gas (helium or nitrogen) displacement, liquid displacement and flotation in a liquid. Helium and nitrogen gases obey the ideal gas law at ambient temperatures and pressures. However, helium is preferred because of its smaller size. Both gases do not adsorb on the material.

Volume occupied by voids (inter-particle spaces) and intraparticle pores are not included in true density (Figure 6-15). The true densities of some pharmaceutically important powders are listed in Table 6-7.

The most common methods used in the determination of the true density are gas (helium or nitrogen) displacement, liquid displacement and flotation in a liquid. Helium and nitrogen gases obey the ideal gas law at ambient temperatures and pressures. However, helium is preferred because of its smaller size. Both gases do not adsorb on the material.

Porous solids—Helium displacement method : Helium penetrates the smallest pores and crevices. Therefore, this method gives a value closer to its true density. This is a valuable tool to estimate the true density, particularly for porous solids.

Method : The schematic representation of helium pycnometer is shown in Figure 6-16. 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_1. This represents the volume of empty cell.

In the next step, pycnometer is calibrated by placing a standard sample of known true volume (V_s) (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 difference between U_1 and U_2 gives the volume occupied by the sphere.

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_s gives the volume occupied by the sample.

The operating equation for the instrument is:

$$V_t = \frac{V_s}{U_1 - U_2}[U_1 - U_s] \qquad \text{...(21)}$$

where V_t = true volume of the sample, cm^3.

True volume and weight of the sample are substituted in equation (20) gives the true density.

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) = $w_4 - w_2$

$$\text{True density} = \frac{w2-w1}{w4-w2}$$

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

$$\text{True density} = \frac{w1}{V}$$

Granule density: Granule density is determined for the granules that are employed in the manufacture of tablet.

Granule density is defined as:

$$\text{Granule density, } \rho g\ \frac{\textit{Granule density}}{\textit{Granule volume}}$$

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 140^0 and its nonwetting characteristics.

Bulk density: It is defined as:

$$\text{Bulk density } (\rho_b) = \frac{\textit{mass of a powder } (w)}{\textit{bulk volume } (Vb)}$$

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" and "heavy". Light powders have high volume.

Tapped volume: The powder is passed through a standard sieve no. 20. The weighed powder (100gm) is transferred into a 250ml measuring cylinder. The level of powder is made without compacting. The unsettled apparent volume is measured (V_0) to the nearest graduated unit. The cylinder is fixed on the bulk density apparatus and the timer knob is set for 100 tapping. The cylinder is tapped and volume readings are taken until little further volume change is observed.

$$\text{Tapped density} = \frac{\textit{mass of a powder } (m)}{\textit{volume of the powder bed at zero tapping } (V0)}$$

Applications:

1. Bulk density is used to check the uniformity of bulk chemicals.
2. The size of the 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.

$$\text{Capsule volume} = \frac{\textit{capsule fill weight of formulation}}{\textit{tapped bulk density}}$$

3. It helps in selecting the proper size of a container, packing material, mixing apparatus in the production of tablets and capsules. The capacity of a mixing bowl is usually expressed in cubic feet or liter. Normally, the volume of formulation and an excess of 10% of the volume is considered for the selection of container for the mixing process.

Capacity of mixing bowl = $\frac{weight\ of\ batch}{bulk\ volume}$

Porosity:

True volume = Volume of the powder itself.

Granule volume = Volume of the powder itself + volume of interparticle spaces.

Bulk volume = Volume of the powder itself + volume of interparticle 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 $\varepsilon = \frac{void\ volume}{bulk\ volume}$

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

Porosity is frequently expressed in per cent.

Percent, $\varepsilon = 1 - \frac{Vp}{Vb}$ X 100

The above equation can also be expressed in terms of density values.

Percent, $\varepsilon = \frac{\rho p - \rho b}{\rho b}$ X 100

Applications:

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

FLOW PROPERTIES:

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 pile of the powder and the horizontal plane.

By definition

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

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

Where h = height of pile, cm

r = radius of the base of the pile, cm

θ = angle of repose.

The lower the angle of repose, the better the flow property. Rough and irregular surface of particles gives higher angle of repose.

Procedure: A glass funnel is held in place with a clamp on a ring support over a glass plate. The glass plate is placed on a micro-lab jack. Approximately 100 gm of powder is transferred into the funnel keeping the orifice of the funnel blocked by the thumb. As the thumb is removed, the lab-jack is adjusted to lower the plate and maintain about 6.4 mm gap between the bottom of the funnel stem and the top of the powder pile. When the powder is emptied from the funnel, the angle of the heap to the horizontal plane is measured with a protractor.

The height of the pile (h) and the radius of the base (r) is measured with the ruler. The angle of repose is this estimated. Cohesive powders yield better results if measurements are carried out using a funnel with a 30 mm stem opening.

Scale of flowability

Angle of repose	Flow property
25-30	Excellent
31-35	Good
36-40	Fair, aid is not needed
41-45	Passable, may hang up
46-55	Poor, must agitate or vibrate
56-65	Very poor
> 66	Very very poor

ANGULAR TESTS: Angular tests are applicable to relatively free flowing powders containing particles larger than 100 µm. such powders cannot be investigated satisfactory using shear cells and tensile strength apparatus.

- If granulation is tested for flow, then flow meter is the method of choice.
- If known forces are utilized during the flow, shear cell is a method of choice.

These are strictly empirical between the degree of compaction and powder flow. Based on experimental variables, one of the following can be used.

- Height of funnel is fixed, but the height of powder varies, as the pile is formed.
- Base diameter is fixed or diameter is fixed or diameter of powder cone may be allowed to change, as the pile is formed.

Angular properties of powders also depend on the details of the measurement. Angle of repose is not an intrinsic property of a powder and is primarily a function of surface roughness. Angle of repose provides qualitative information.

- Rough and irregular surface of particles give higher angle of repose.
- Cohesive particles tend to form higher heaps, which cannot spread out. Angle of repose of such powders will be higher or poor flow.

Drained angle: It is the angle observed, when powder flows from a conical surface onto a flat bottomed container, if the powder is discharged through the orifice in the base. The drained angle is affected by the degree of consolidation of the material in the hopper. Method – wise it is like angle of repose.

Poured angle: The poured angle of repose can be measured, when the powder is allowed to pour onto the flat surface. The angle is measured from the height of the heap. A protector is commonly used for measurement. In this case, the word conical surface was not mentioned. For the some powder, drained angle is larger than the poured angle. In case of poured angle, the particles slide and roll down from the powder surface. In case of drained angle, convergence occurs, i.e. particles get mixed up with the remaining pile and nesting in the container.

Dispersibility: Dispersibility of a powder is the ability of a material to flow or pour easily over a plane. Dispersibility, dustiness and flow ability are inter-related terms.

Method: Weigh approximately 10 gm of the sample. The material is dropped enmasse from a total weight on to a tarred watch glass through a hollow cylinder placed vertically 102 mm above the watch glass. The cylinder is secured to a support stand by 102 mm diameter support rings placed above and below the cylinder. The drop point is approximately 178 mm vertically above the top of the cylinder. The material landing within the watch glass is weighed. Any loss of powder during the fall is the result of dispersion. The percent Dispersibility is calculated using the relationship.

$$\text{Dispersibility (\%)} = \frac{weight\ of\ powder\ in\ watch\ glass}{initial\ weight\ of\ the\ sample} X\ 100$$

Carr's index: It is defined as:

$$\text{Consolidated index} = \frac{tapped\ density - fluff\ density}{tapped\ density} X\ 100$$

This property is known as compressibility. It is indirectly related to the relative flow rate, cohesiveness, particle size, shape and moisture content. It is simple, fast and popular method of predicting powder flow characteristics.

Fluff density is the ratio of mass of powder to the fluff volume. Fluff volume is the volume occupied by a certain mass, when gently poured into a measuring cylinder. This is known as aerated density.

Tapped density is the ratio of mass of powder to the tapped volume. Tapped volume is the volume occupied by the same mass of powder after a standard tapping of a measure.

Compressibility index can be a measure of the potential strength that a powder could build up in its arch in a hopper and the ease with which such an arch could be broken. It is a simple and fast method.

Method: using a suitable adhesive, the base of a 10 ml. tarred measuring cylinder is fixed to the standard rubber bung at the top of the 250 ml cylinder. A powder sample is transferred into the tarred 10 ml cylinder with the help of a funnel. The 250 ml measuring cylinder is placed on the tapping apparatus. The initial volume occupied by the powder is denoted as V_0.

The contents are tapped in the following order., 2,4,6,8,10,20,30 and 50 taps. After completing the tapping, the volume is denoted as V_2, V_4 .....V_{50}.

The powder is carefully collected from the cylinder and weighed (W).

$$\text{Fluff density } (\rho b, minimum) = \frac{W}{V0} g/cm3$$

$$\text{Tapped density } (\rho b, maximum) = \frac{W}{V50} g/cm3$$

Hausner ratio: It is defined as:

$$\text{Hausner ratio} = \frac{V_0}{V_f}$$

Where V_0 = volume of the powder bed at initial stage, ml
V_f = volume of the powder bed after tapping, ml

Hausner ratio is related to the morphological behavior. For example, flow properties increasing sphericity. The V_f means repeated taps or as needed, until the difference between the successive measurements is less than 2%.

Particle Number: The particle number is important in dose of drugs specially for potent drugs or drugs having low dose. Knowledge of particle number is important in preparation of tablets and capsules. The number of particles per unit weight, N, is expressed in terms of volume-number mean diameter, dvn. Assuming that the particles are spheres, the volume of a single particle is $\frac{\pi dvn^3}{6}$ and the mass (volume x density) is $\frac{\pi d^3 vn\rho}{6}$ gram per particle. The number of particles per gram may be obtained from following relationship.

$$\frac{(\pi d_{vn}^3)/6g}{\text{Particle}} = \frac{1g}{N}$$

So,

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