Micromeritics

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Introduction

The science and technology of small particle is termed as micromeritics by JM Dalla Valle. It is the study of the fundamental and derived properties of the individual as well as collection of particles. The knowledge and control of the size of the particles is of important in pharmacy.

Importance of micromeritics

Importance:

1. Size, size range, and hence surface area of particle of a drug inference its physical, chemical and pharmacological properties.

2. Particle size affects the release of the drug from its dosage forms.

3. The formulation, physical stability and therapeutic response of suspension, emulsion and tablet dosage form depend on the particle size achieved in the product.

4. In the area of tablet and capsule manufacturing, control of the particle size is essential in achieving the necessary flow properties and proper mixing of granules and powders.

Importance of micromeritics

Before eliciting any therapeutic response, drug should enter into the systemic circulation across the lipid bilayer of the GIT, and mostly unionised drug in the form of solution can cross the lipid bilayer by simple diffusion and ionized forms are absorbed by carrier mediated mechanism. So it implies that, before absorption, drug should undergo solubilisation because most of the drugs are solid in nature (exception- Trinitroglycerine which is a liquid).

Importance of micromeritics

- Particle size is related to the solubility and dissolution of the drug. When particle size is reduced by any means, new surface is produced by disruption of the intermolecular bonds that generates surface energy (J/m2) which is the excess energy at the surface as compared to the bulk.
- It is clear that reduction in particle size resulted in increase in surface area.
- When surface area is increased, surface free energy is also increased according to Gibbs theory $\Delta G = \gamma_{SA}.\Delta A$ the equations it is observed that reduction of particle size results in increase in surface free energy.

Importance of micromeritics

- Thermodynamically, the free energy changes involved in the different stages of wetting are $\Delta G_A = \gamma_{S/L} - \gamma_{S/A} - \gamma_{L/A}$ for adhesional wetting, Thermodynamically, the tri-phasic equilibrium can be expressed by Young's equation: $\gamma_{S/A} = \gamma_{S/L} - \gamma_{L/A}\cos\theta$ and the free energies can be expressed in terms of contact angle i.e., $\Delta G_A = -\gamma_{L/A}(1 + \cos\theta)$ for adhesional wetting,
- Therefore, when free energy is increased due to size reduction of the particle, contact angle is reduced and the liquid adhere to the solid surface following immersion and spreading throughout the liquid thereby increase in dissolution.

Importance of micromeritics

- Particles of colloidal dispersions are to small and visualized by ordinary microscope whereas very fines are visualized by optical microscopy. Large particles or granules are fall under the sieve range. The unit of the particle size in micrometrics is micron (μ).
- μ = 10^{-6}m = 10^{-4}cm = 10^{-3}mm
- nm = mμ = 10^{-9}m

Particle size and size distribution

In a collection of particles of more than one size, two properties are important:

i) shape and surface area of the individual particles

ii) size range and number of particles or weight.

The size of a spherical particle is expressed in its diameter. As a degree of asymmetry of the particle increases, expression of size in a meaningful diameter is difficult. In such situation no one unique diameter is there and an equivalent spherical diameter must be made which can relate the size of the particle to the diameter of a sphere having same surface area, volume or diameter.

Diameters

a. **Surface diameter** (d_s) =it is the diameter of a sphere having the same surface area as the particle in question.

b. **Volume diameter** (d_v) = It is the diameter a sphere having the same volume as the particle.

c. **Projected diameter** (d_p) =It is the diameter of a sphere having the same observed area as the particle when viewed normal to its most stable plane.

d. **Stokes diameter** (d_{st}) = It is the diameter of an equivalent sphere undergoing sedimentation at the same rate as the asymmetric particle.

Particle size and size distribution

In a collection of particles, it is important to know not only the size of particles, but also the number of particles having same size is important too. The particle size distribution is essential where estimation of size range and the corresponding numbers or weight fractions are needed for calculation of average particle size for a sample.

Average particle size

Edmundson's derived equation $d_{mean} = (\frac{\sum nd^{p+f}}{\sum nd^{f}})^{1/p}$

n is the number of particle in a size range having mean size range or diameter d. p is the index related to the size of particles. p= 1, 2 or 3 represents the length, surface or volume respectively. The frequency with which a particle occurs in a certain size range is expressed as nd^f where f is the frequency index and f= 0, 1, 2 and 3 correspond to number, length, surface and volume respectively.

Calculation of statistical diameter from data obtained from microscopic (Normal distribution)

Table: 1

Size range (µm)	Mean size range d (µm)	Number of particles in each size range (n)	nd	nd^2	nd^3	nd^4
0.50-1.00	0.75	2	1.50	1.13	0.85	0.64
1.00-1.50	1.25	10	12.50	15.63	19.54	24.43
1.50-2.00	1.75	22	38.50	67.38	117.92	206.36
2.00-2.50	2.25	54	121.50	273.38	615.11	1384.00
2.50-3.00	2.75	17	46.75	128.56	353.54	972.24
3.00-3.50	3.25	8	26.00	84.50	274.63	892.55
3.50-4.00	3.75	5	18.75	70.31	263.66	988.73
		$\sum n = 118$	$\sum nd = 265.50$	$\sum nd^2 = 640.89$	$\sum nd^3 = 1645.25$	$\sum nd^4 = 4468.95$

Calculation of statistical diameter from data obtained from microscopic (Normal distribution)

Table: 2

$\left(\frac{\sum nd^{p+f}}{\sum nd^{f}}\right)^{1/p}$	p	f	Type of mean	Size parameter	Frequency	Mean diameter	Value for data in the above table (μm)
$\frac{\sum nd}{\sum n}$	1	0	Arithmetic	Length	Number	d_{ln}	2.25
$\sqrt{\frac{\sum nd^2}{\sum n}}$	2	0	Arithmetic	Surface	Number	d_{sn}	2.33
$\sqrt[3]{\frac{\sum nd^3}{\sum n}}$	3	0	Arithmetic	Volume	Number	d_{vn}	2.41
$\frac{\sum nd^2}{\sum nd}$	1	1	Arithmetic	Length	Length	d_{sl}	2.41
$\frac{\sum nd^3}{\sum nd^2}$	1	2	Arithmetic	Length	Surface	d_{vs}	2.57
$\frac{\sum nd^4}{\sum nd^3}$	1	3	Arithmetic	Length	Weight	d_{wm}	2.72

Particle 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, frequency distribution curve is obtained. This plot gives a visual distribution but average diameter can't be achieved. It is possible to have same average diameter of two samples with different distribution.

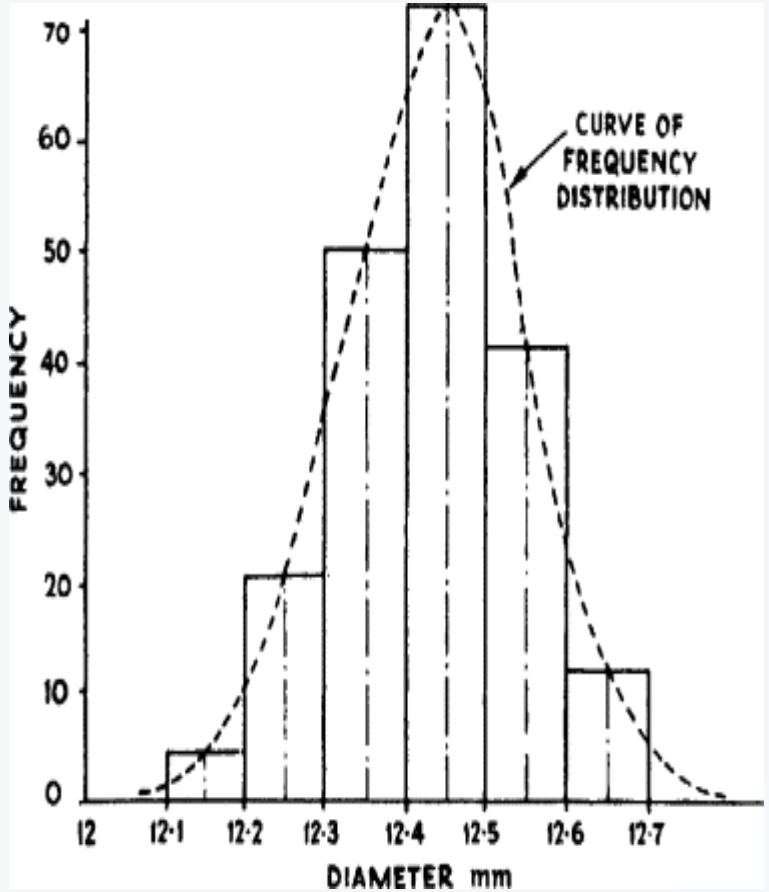


Fig.: 1

Particle size distribution: Number & weight

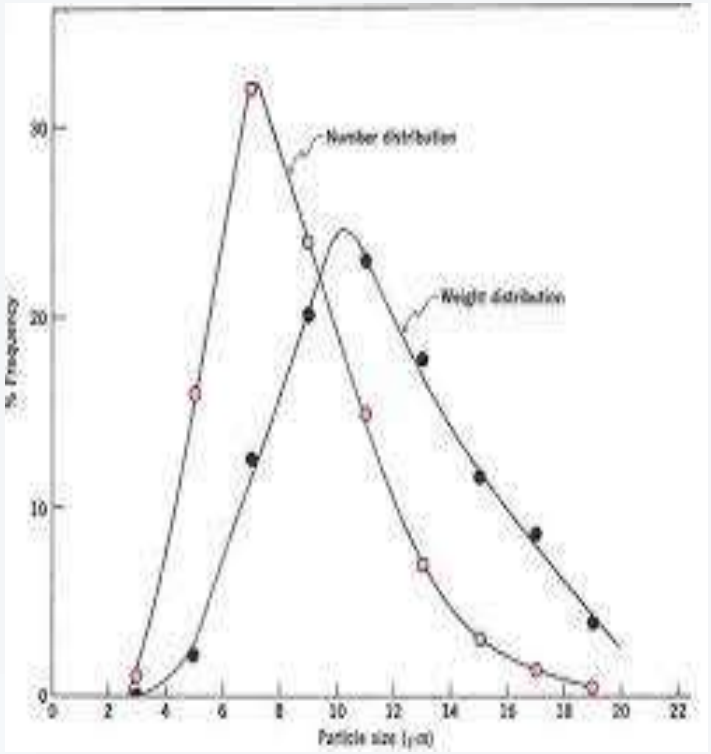


Fig.3: **Frequency distribution plot (log-normal relation)**

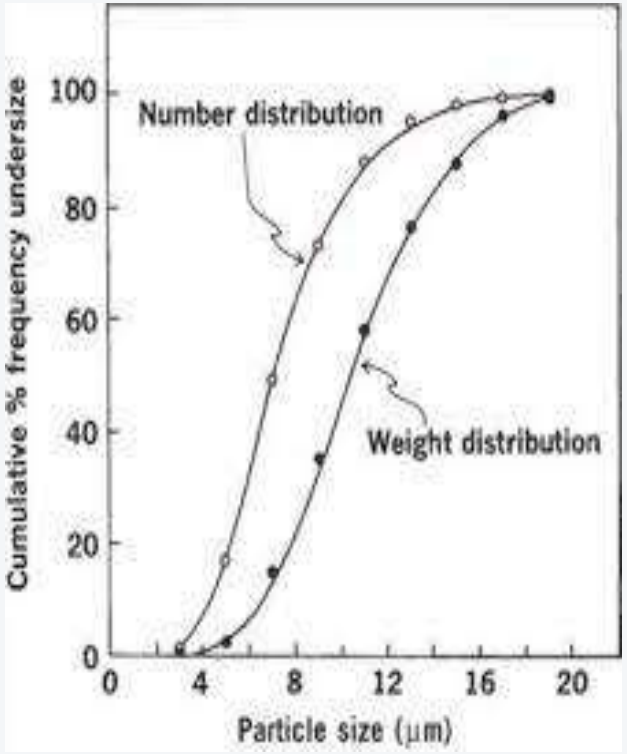


Fig.4: **Cumulative frequency plot**

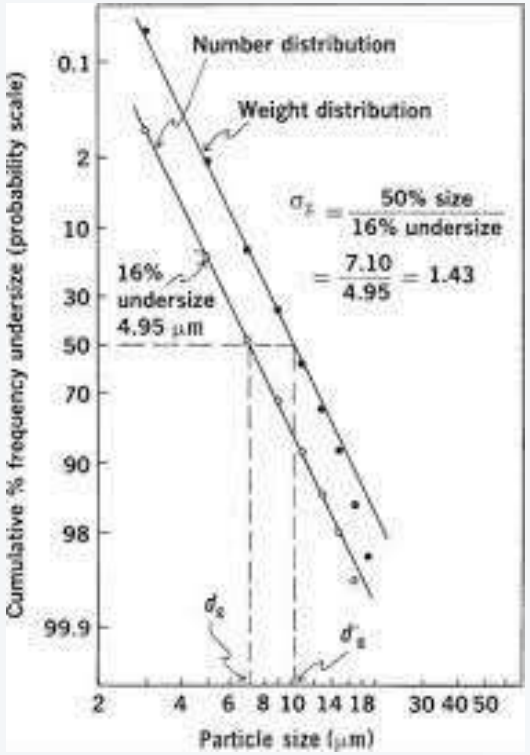


Fig.5: **Log-probability plots**

Conversion of number distribution to weight distribution (Log-Normal distribution)

Size range (μm)	Mean of size range d (μm)	No. of particles in each size range (n)	% n	Cumulative % frequency undersize (No.)	nd	nd^2	nd^3	% nd^3 (Wt.)	Cumulative % frequency undersize (Wt.)
2-4	3	2	1	1	6	18	54	0.03	0.03
4-6	5	32	16	17	160	800	4000	2.31	2.34
6-8	7	64	32	49	448	3136	21952	12.65	14.99
8-10	9	48	24	73	432	3888	34992	20.16	35.15
10-12	11	30	15	88	330	3630	39930	23.01	58.16
12-14	13	14	7	95	182	2366	30758	17.72	75.88
14-16	15	6	3	98	90	1350	20250	11.67	87.55
16-18	17	3	1.5	99.5	51	867	14739	8.49	96.04
18-20	19	1	0.5	100	19	361	6859	3.95	99.99

$$\sum n = 200$$

Hatch-Choate equation

The distribution may be represented by number or weight distribution or conversion of number to weight or vice versa. The distribution is expressed by log-normal curve or using Hatch-Choate equation.

Table 3: Hatch-Choate Equations for computing statistical diameter from Number & Weight Distributions

Diameter (Mean)	Number Distribution	Weight Distribution
d_{ln}	$log\, d_{ln} = log\, d_g + 1.151\ log^2 \sigma_g$	$log\, d_{ln} = log\, d'_g - 5.757\ log^2 \sigma_g$
d_{sn}	$log\, d_{sn} = log\, d_g + 2.303\ log^2 \sigma_g$	$log\, d_{sn} = log\, d'_g - 4.606\ log^2 \sigma_g$
d_{vn}	$log\, d_{vn} = log\, d_g + 3.454\ log^2 \sigma_g$	$log\, d_{vn} = log\, d'_g - 3.454\ log^2 \sigma_g$
d_{vs}	$log\, d_{vs} = log\, d_g + 5.757\ log^2 \sigma_g$	$log\, d_{vs} = log\, d'_g - 1.151\ log^2 \sigma_g$
d_{wm}	$log\, d_{wm} = log\, d_g + 8.059\ log^2 \sigma_g$	$log\, d_{wm} = log\, d'_g + 1.151\ log^2 \sigma_g$

Particle number

Particle number, a significant expression is the number of particles per unit weight ‘N’. Assuming that the particles are spheres, the volume of the single particle is $\pi d_{vn}^3 \rho / 6$ and mass is $\pi d_{vn}^3 \rho / 6$ g

So, $$\frac{\pi d_{vn}^3 \rho / 6}{1\ particle} = \frac{1g}{N}$$

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

Methods for determining particle size

None of the methods are truly direct methods. Although the microscopic method allows to view the actual particles but the result obtained is probably no more direct than other methods since only few particles are ordinarily seen.

Microscopy

Normal size range detectable

Optical ≥ 0.2-100 µm

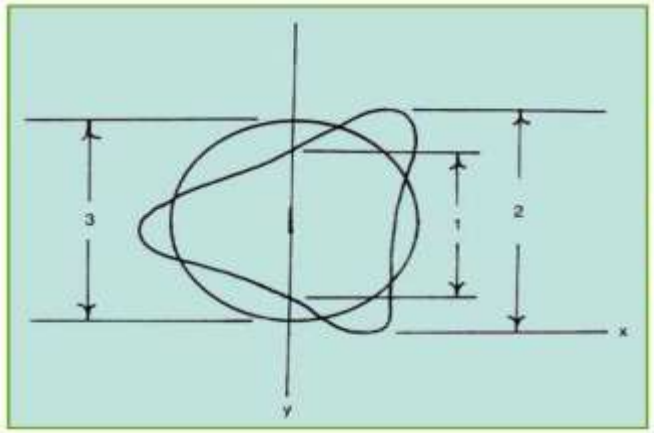
Electron ≥ 0.01-100 µm

A sample suspension of particle is spread over a slide and examine under the microscope fitted with micrometer. The field can be projected onto a screen or detector or photo can be taken for measurement. The particles are measured along an arbitrarily chosen fixed line, generally horizontal line across the center of the particle.

A size-frequency curve may be drawn for determination of the statistical diameters of the distributions.

Disadvantage of the microscopic method is that the diameter obtained is two dimensional. Depth of the particle measurement is not possible.

Microscopy



- 1 : Martin diameter
- 2 : Feret's diameter
- 3 : Projected diameter

Martin's diameter: Length of a line that bisects the particle image. The line may be drawn in any direction but it should be in the same direction for all particles.

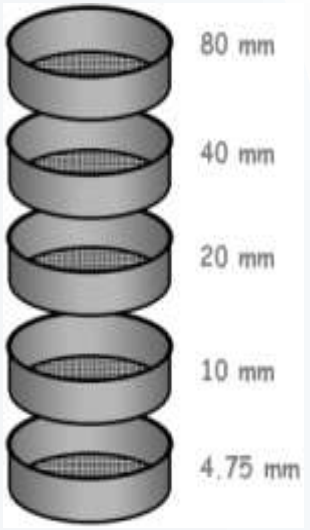
Feret's diameter: The distance between two tangents on opposite side of the particle parallel to same fixed direction.

Projected diameter: Diameter of a circle with the same area as that of the particle observed perpendicular to the surface on which the particle rests.

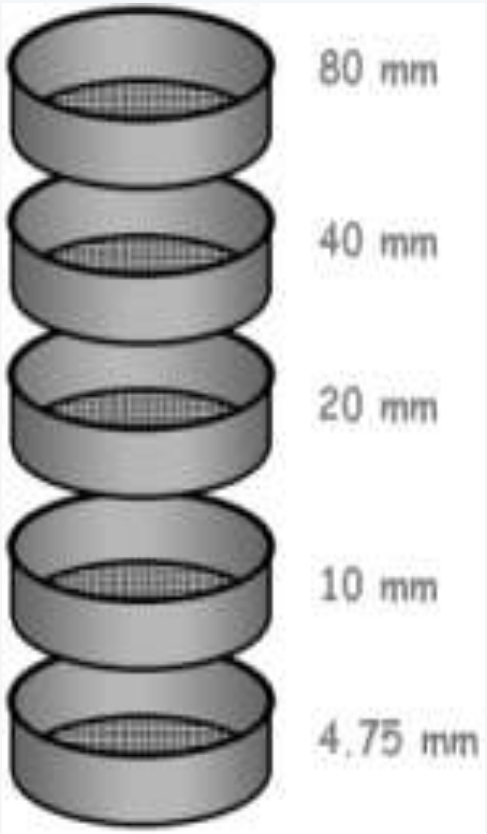
Sieving

Normal size range detectable ≥ 50 µm

Standard sieves calibrated by the National Bureau of Standards are placed in descending order i.e., large size sieve is at the top and smallest is at the bottom. Known weight sample is placed at the top and sieves are shaken either by agitation, brushing or centrifugation. Weight of the powder retain by each sieve is determine and percentage retention is calculated. The mean size of the sieve through which powder passes and retains is calculated. A log normal distribution curve is plotted using cumulative percent by weight powder retain on a probability scale against logarithm of mean size. From the table 3 diameter may be obtained.



Sieving



Sieving

Grade (BP)	No. of sieve through which all particles must pass
Coarse Powder	10
Moderately Coarse Powder	22
Moderately Fine Powder	44
Fine Powder	85
Very Fine Powder	120
Ultra Fine Powder	90% of particles ⩾5µm & none ⩾50µm

Sedimentation

Stoke's law:

$d_{st} = \sqrt{\frac{18\eta v}{g(\rho_s - \rho_l)}}$, where d_{st} is Stoke diameter, v is settling velocity, η is medium viscosity, ρ_s is density of solid, ρ_l is density of liquid, g is gravitational force (9.81 m s^{-2}).

Liquid medium	200 – 2µm
Air medium	100 – 1µm

Sedimentation

The **Stoke's** equation holds exactly only for spheres falling freely without hindrance and at a constant rate. The law is applicable for irregular particles relative to the particle size equivalent to that of sphere falling at the same velocity. The particles must not be aggregated. The flow of dispersion medium should be laminar or streamline. The falling of particles should not produce any turbulence and it is indicated by Reynolds number $R_e = \frac{vd\rho_0}{\eta_0}$, v is the velocity of the fluid, d is the diameter of the pipe, ρ_0 is the density of the fluid and $\eta_0$is the viscosity of the fluid. The Stoke's law can't be applicable if $R_e > 0.2$ since turbulence appears at this point.

Sedimentation

Andreasen pipette apparatus

Andreasen apparatus is consists of 550 ml vessel containing a 10 ml pipette sealed into a ground glass stopper. When the pipette is in place, its lower tip is 20 cm below the surface of the suspension. 1-2% suspension of the particle in a medium with suitable deflocculating agent is introduced into the vessel and fills up the mark 550 ml. The stoppered vessel is then shaking to uniform distribution of the particles throughout the medium and the vessel, stand it at a constant temperature bath.

Sedimentation

Andreasen pipette apparatus

At various time intervals, 10 ml samples are withdrawn evaporated and weight of particles is determined. The particle diameter corresponding to the various time periods is calculated. The dried sample obtained at a particular time period is the weight fraction having particle size less than the size obtained at before the time. The weight of each sample is called weight under size. The sum of the successive weights is called cumulative weight under size. The data may be represented as frequency distribution plot, Cumulative frequency plot or log probability plot.

Sedimentation

SediGraph 5100

SediGraph 5100 instrument has been developed for particle size determination based on sedimentation. Here low energy X-ray beam is passes through the suspension and the X-ray pulse is collected by the detector. From the X-ray pulse count the particle size distribution and the mass of the particles for each particle diameter are derived. The system is completely automated. It can measure particles of size 0.1-300 µm at 10-40 °C.

Sedimentation

MATEC Applied Sciences has developed a particle size measurement system for submicron size 0.015-1.1µm. It consists of a capillary tube through which 1 ml 2-4% suspension containing suitable surfactant is passes. The suspension must be filtered before feeding through 5µm filter. The larger particles attain greater velocity than smaller one is the basis of this instrument. The average particle size of size distribution is determined by number or volume of the particles. It requires maximum 8 minutes time.

Elutriation

Separation of lighter particles from heavier one using vertical air or liquid stream, particles are collected at different region of the tube of elutriator)

Liquid medium 100 – 10µm

Air medium 100 – 2µm

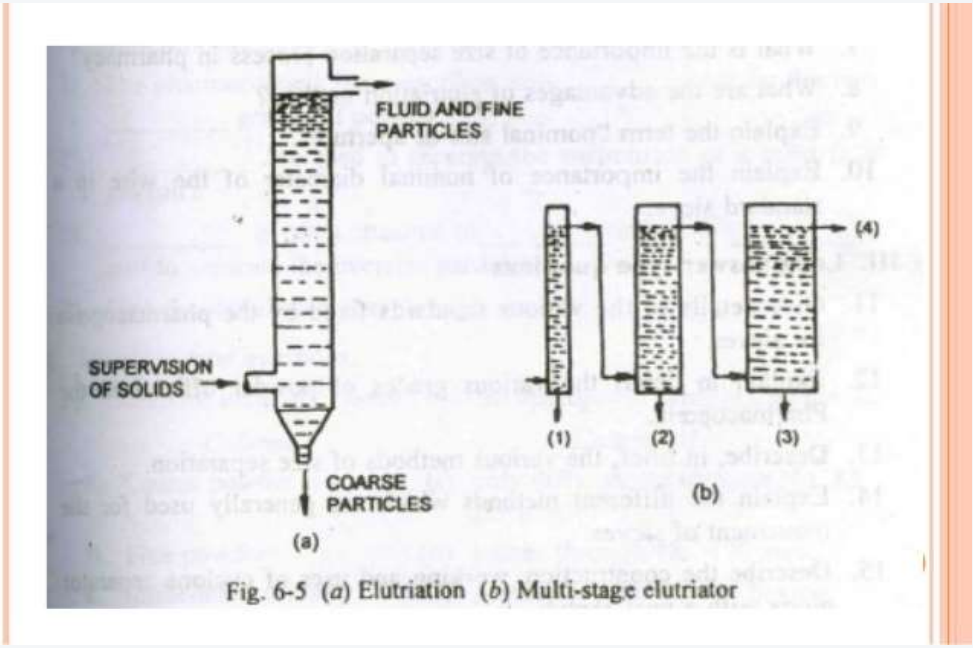


Fig. 6-5 (*a*) Elutriation (*b*) Multi-stage elutriator

Elutriation

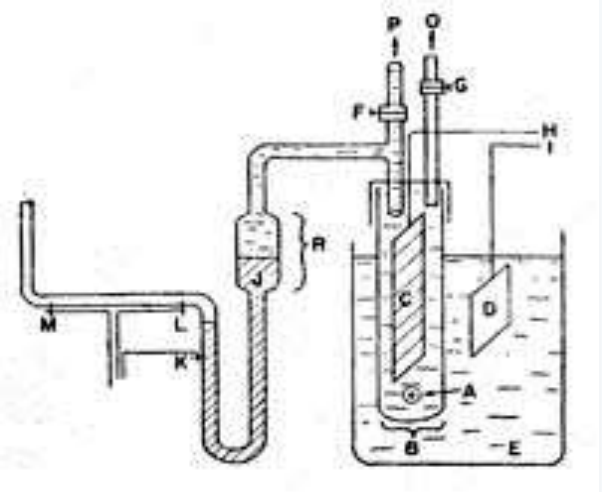
Fluid flows in the opposite direction of the settling movement of the particles. Sedimentation is possible for the particles having velocity greater than the liquid. Particles settling slower will be trapped and moved with liquid overflow. The feed is introduced from the bottom. Liquid is allowed to move vertically upward direction, particles are settled down due to the gravitational force. Particles are separated into two fractions in a single column. Different cross sectional column may be attached and more fractions of particles may be separated from the overflow fluid containing particles. The fluid flow rate is kept constant but velocity become decreases due to the increase in cross sectional area. More coarse particle retain in the first column and fine particles will be retain by the next columns depending on the liquid velocity and cross sectional area.

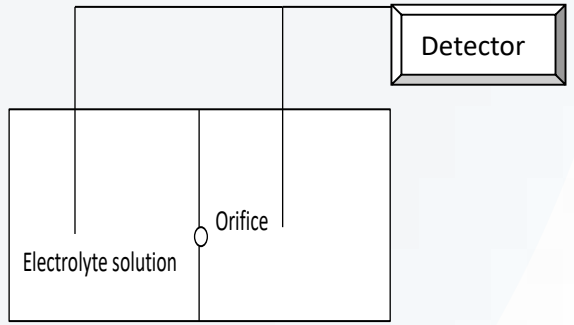
Elutriation

Sedimentation	Elutriation
Process of settling particles	Separation of lighter particles from heavier one
Liquid is kept stationary	Liquid moving opposite direction to the sedimentation
Particles moving in the direction of gravitational force	Some particles moving against the direction of gravitational force
Heavier particles settle fast	Particles having more settling velocity settle fast
The time required for separation decides size separation	Liquid velocity and cross sectional area decides size separation

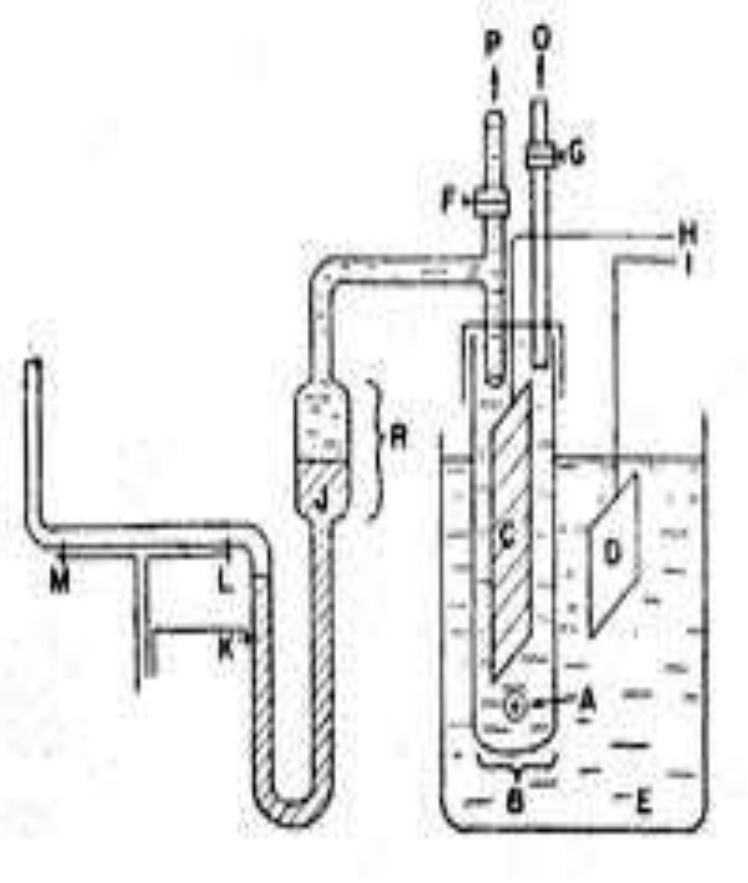
Coulter counter

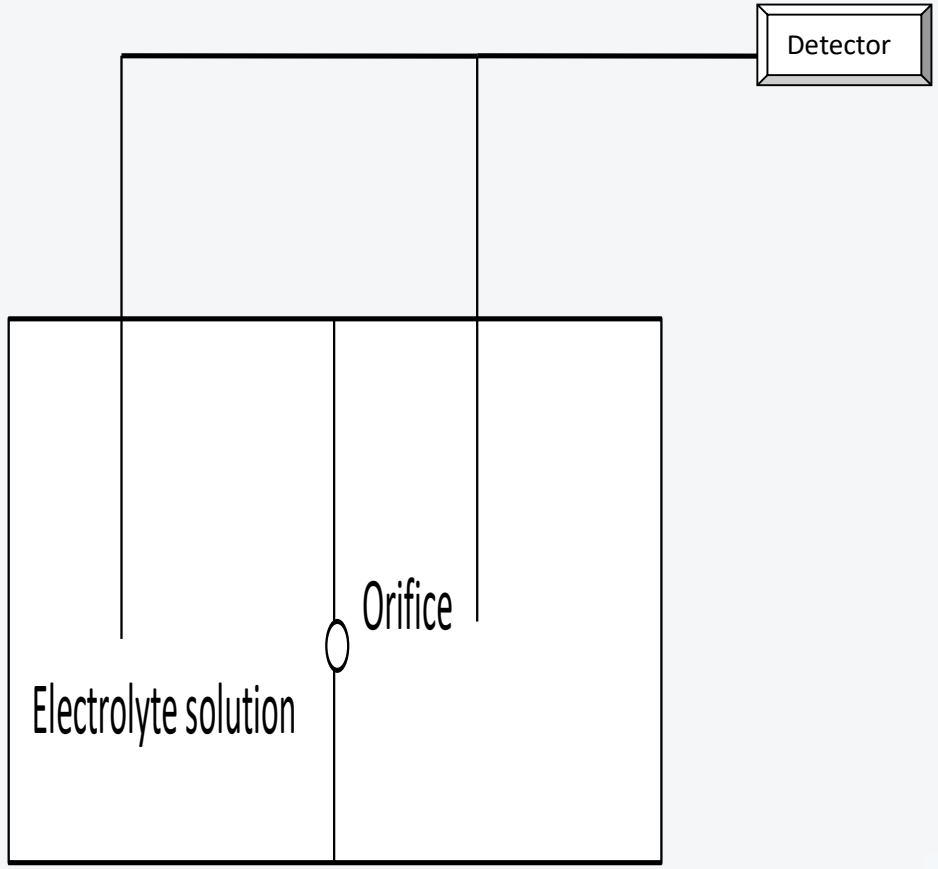
Principle: The transient current drop is proportional to particle volume. Two chambers are filled by electrolyte solution and chambers are connected by small orifice. Electrical circuit with detector is connected to the chambers. Particles are pulled through the orifice concurrent with electrical current, cause electrolyte displacement due to particles. That produces a small change in voltage or current drop, which is proportional to the particle volume that travels the orifice. Then particle diameter is calculated considering the particle as sphere.





Coulter counter





Newer development

HAIC/Royco light blockage instrument works on the principle of light blockage. The particles interrupt a light beam and decrease the amount of light that reaches to a photo detector. This decrease in light transmission produces a voltage pulse proportional to the projected area of each particle. The results are highly correlated with the National Bureau of Standards reference particles.

Coulter Model N4 can measure 0.003-0.3µm particles based on the photo correlation spectroscopy that senses the Brownian motion of the suspended particles. A laser beam is passes through the sample and sensor detects the light scattered by the particles undergoing Brownian motion.

Scanning electron microscopy, X-ray analysis and micro computerized mercury porosimetry are also investigated for particle size determination.

Porosity

Open intra-particulate voids: Voids within a particle but open to the external environment.

Closed intra-particulate voids: Voids within a particle but closed to the external environment.

Inter-particulate voids: The void space between individual particles.

True volume (V_t): The total volume of the solid particles excluding all spaces greater than molecular dimension.

Bulk volume (V_b): The total volume of the solid particles under a particular packing condition during measurement.

Granular volume or particle volume (V_g): The total volume of the solid particles including open and closed intra-particulate voids but excluding inter-particulate voids.

Porosity

Porosity (E): The ratio of the total volume of void space to the bulk volume of the material.

$$V_v = V_b - V_t$$

$$E = \frac{V_b - V_t}{V_b} = 1 - \frac{V_t}{V_b}$$

$$\% \text{ Porosity } = (1 - \frac{V_t}{V_b}) \times 100$$

Density

The ratio of mass to volume is density

True density $\rho_t = \frac{M}{V_t}$

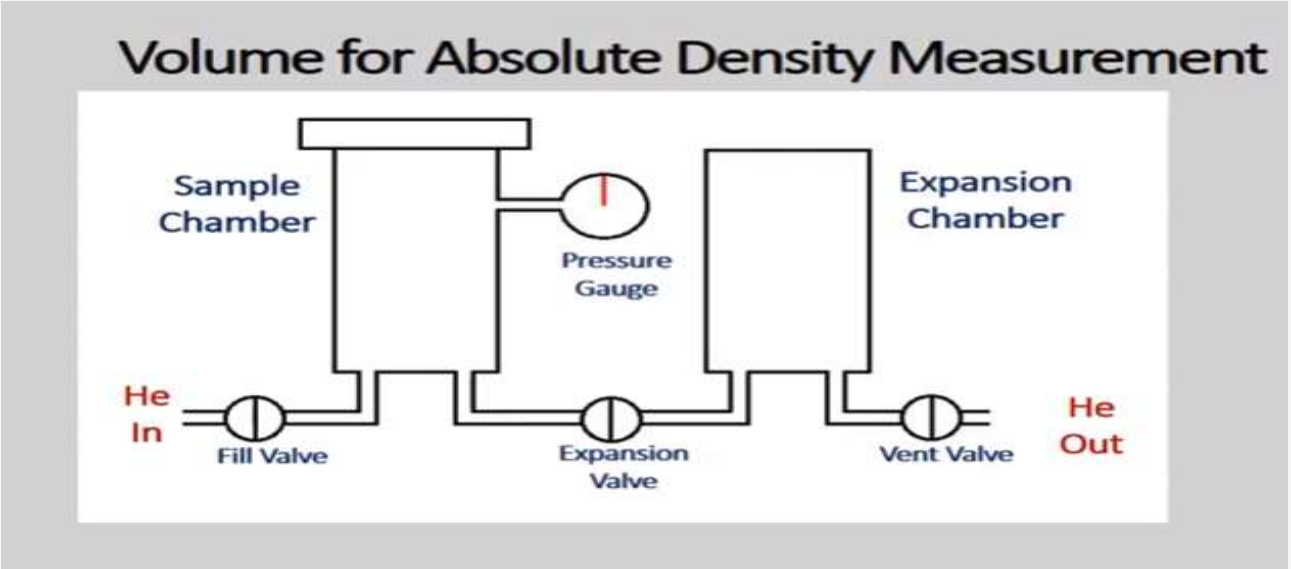
The granular density $\rho_g = \frac{M}{V_g}$

Bulk density $\rho_b = \frac{M}{V_b}$

Relative density $\rho_r = \frac{\rho}{\rho_t}$

ρ_r is the relative density and it is maximum to 1 when all the air spaces have been eliminated. ρ is the density of sample powder under specific condition.

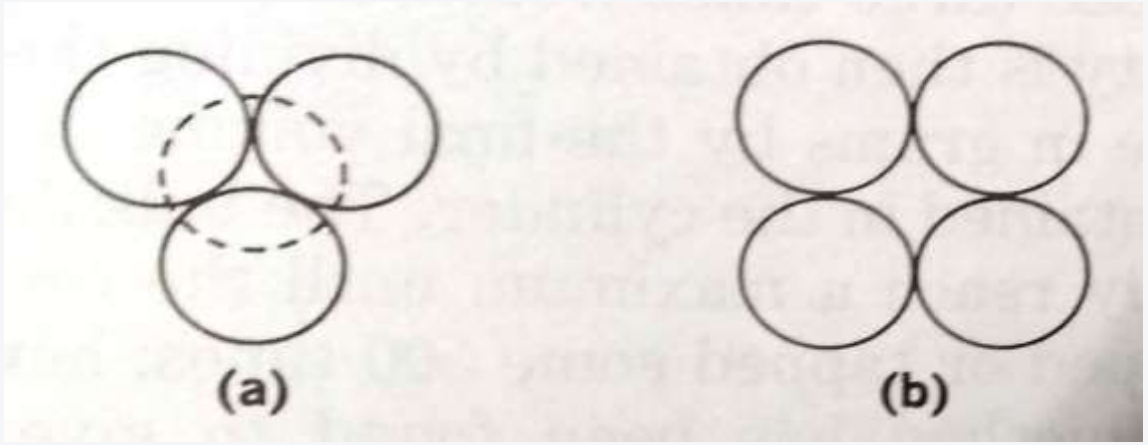
Density



True or absolute density is calculated based on the Boyle's law $P_1V_1 = P_2V_2$

The working equation of a gas pycnometer wherein the sample chamber is pressurized first is as follows: $V_S = V_c + \frac{V_E}{1-\frac{P_1}{P_2}}$, V_s is the sample volume, V_c is the volume of the empty sample chamber, V_E is the expanded volume

Packaging arrangement



Ideal packing arrangements

(i) Closest or rhombohedral

(ii) loosest or cubic packing

Packaging arrangement

The theoretic porosity of powder consisting of uniform spheres in closest packing is 26% and for loosest packing is 48%. The real powder particles are neither spherical nor uniform in size. It is to be expected that the particles of ordinary powders may have an arrangement of either one identical packaging and the porosity of the powder is in between 30-50%. If particle size is greatly differ, smaller particle may fill the gaps then the porosity may reduce to below 26%. In powders containing flocculates or aggregates may form bridge and the porosity may increase to above 48%. In powder any degree of porosity is possible. Compression of crystalline materials under 100000 lb/in^2 pressure can have porosity less than 1%.

Flow properties

The maximum angle possible between pile of powder and the horizontal plane.

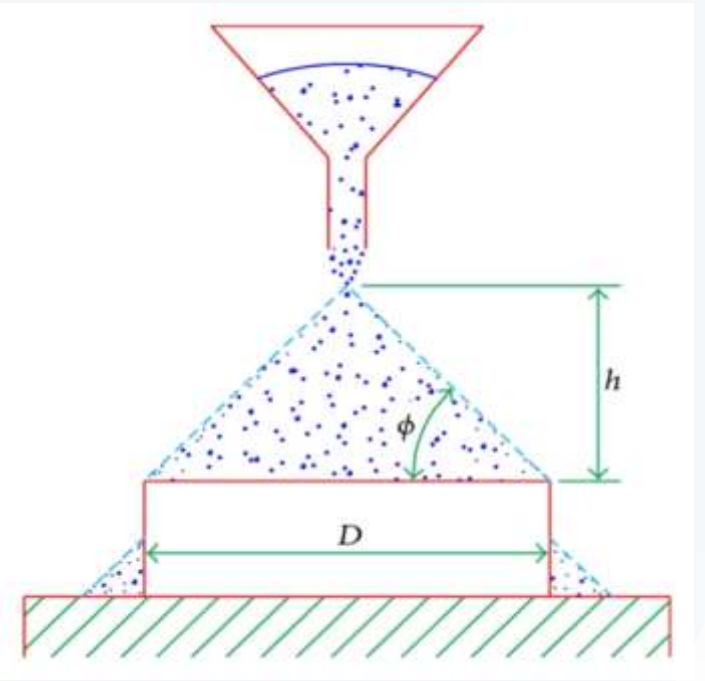
Angle of repose $\theta = \tan^{-1}\frac{2h}{D}$, $\theta \leq 30°$: free flowing; $\theta \geq 40°$: poor flow

Hausner's ratio $H = \frac{\rho_T}{\rho_B}$, $H > 1.25$: poor flowing

Carr'sindex $C = \frac{V_B - V_T}{V_B} = \frac{\rho_T - \rho_B}{\rho_T} = 1 - \frac{\rho_B}{\rho_T} = \left(1 - \frac{1}{H}\right)$,

$C > 25$: poor flowing and poor tableting,

$C < 15$: goor flow and good tebleting.



Bulk density measurement (USP)

Method I—Measurement in a Graduated Cylinder

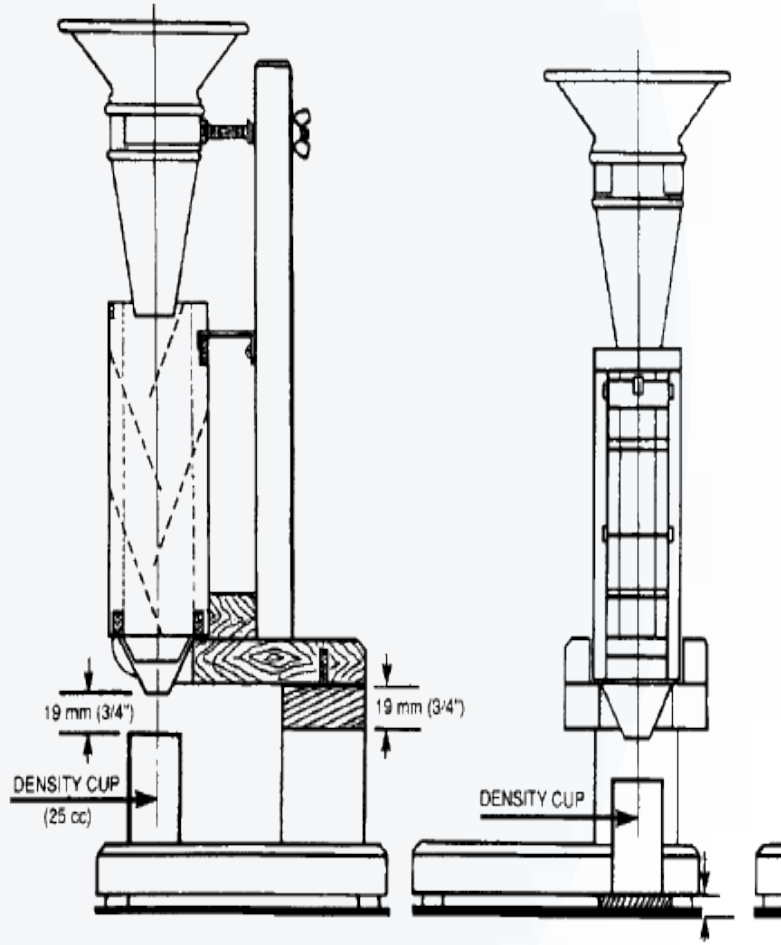
Procedure— Powder sample is passes through a 1.00-mm (No. 18) screen to break agglomerates. Sample quantity (M) is 100 g $\pm 0.1\%$ (untapped apparent volume of 150 to 250 mL) using a dry 250-mL graduated cylinder or if it is not possible to use 100 g, the amount of the test sample and the volume of the cylinder may be modified and the test conditions specified with the results. A 100-mL cylinder is used for apparent volumes between 50 mL and 100 mL. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in g per mL, by the formula: (M) / (Vo).

Generally replicate determinations are desirable for the determination of this property.

Bulk density measurement (USP)

Method II—Measurement in a Volumeter

ASTM B 329-90 (Scott Volumeter), consists of a top funnel fitted with a 1.00-mm (No. 18) screen or the screen opening specified in the individual monograph. The funnel is mounted over a baffle box containing four glass baffle plates over which the powder slides and bounces as it passes. At the bottom of the baffle box, a funnel is fixed that collects the powder and allows it to pour into a cup of specified capacity mounted directly below it. The cup may be cylindrical (25.00 ± 0.05) mL volume with an inside diameter of (30.00 ± 2.00) mm or a square (16.39 ± 0.05) mL volume with inside dimensions of (25.4 ± 0.076) mm.



Bulk density measurement (USP)

Procedure— Allow an excess of powder to flow through the apparatus into the sample receiving cup until it overflows, using a minimum of 25 cm^3 of powder with the square cup and 35 cm^3 of powder with the cylindrical cup. Carefully scrape excess powder from the top of the cup by smoothly moving the edge of the blade of a spatula perpendicular to and in contact with the top surface of the cup, taking care to keep the spatula perpendicular to prevent packing or removal of powder from the cup. Remove any material from the sides of the cup, and determine the weight, M, of the powder to the nearest 0.1%. Calculate the bulk density, in g per mL, by the formula: (M) / (Vo), in which Vo is the volume, in mL, of the cup. Generally replicate determinations are desirable for the determination of this property.

Tapped density measurement (USP)

Method I

Procedure— Powder sample is passes through a 1.00-mm (No. 18) screen to break agglomerates. A dry 250-mL glass graduated cylinder (readable to 2 mL) weighing 220 ± 44 g is mounted on a holder weighing 450 ± 10 g. Sample quantity (M) is 100 g $\pm 0.1\%$ using a dry 250-mL graduated cylinder or if it is not possible to use 100 g, the amount of the test sample and the volume of the cylinder may be modified by using a suitable 100-mL graduated cylinder (readable to 1 mL) weighing 130 ± 16 g and mounted on a holder weighing 240 ± 12 g. The modified test conditions are specified with the results. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume, Vo, to the nearest graduated unit.

Tapped density measurement (USP)

Mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume, Va, to the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, Vb, to the nearest graduated unit. If the difference between the two volumes is less than 2%, Vb is the final tapped volume, Vf . Repeat in increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%. Calculate the tapped, in g per mL, by the formula: (M) / (Vf). Generally replicate determinations are desirable for the determination of this property.

Tapped density measurement (USP)

Method II

Proceed as directed under Method I except that a suitable mechanical tapped density tester that provides a fixed drop of 3 mm (±10%) at a nominal rate of 250 drops per minute is used.

Thank you