Micromeritics

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Outline

- Micromeritics and Solid dosage forms
  - Micromeritics
    - Particle size and size distribution
    - Methods for determining particle size
    - Particle shape and surface area
    - Properties of powders

Micromeritics.....

- The term micromertics was introduced by Dallavale in 1948 to describe the science of small particles.

- Brought together information on particle size measurement, size distribution, and packing arrangements.

➢ Definition:

It is the science and technology of small particles

deals with fundamental and derived properties of individual

and collection of particles

- In the field of pharmacy, micromertics has become an important area of study because it influences a large number of parameters

  - Research and development

  - manufacturing of dosage forms such as
    - ✓ suspension to be reconstituted
    - ✓ tablet
    - ✓ capsule

- Study of particle size and size distribution has many application in pharmacy

- Physical properties of powder are dependent on particle size and size distribution
  - bulk density, compressibility, porosity

- Flow properties of the powder
  - spherical particles good flow property
  - asymmetrical particles poor flow property

- Release & dissolution
  - Higher surface area allows intimate contact of the drug with the dissolution fluids *in vivo* & increases the drug solubility & dissolution

- Absorption & drug action
  - Higher the dissolution, faster the absorption & hence quicker & greater the drug action

- Physical stability
  - suspensions & emulsions. Smaller the size of the particle, better the physical stability of the dosage form.

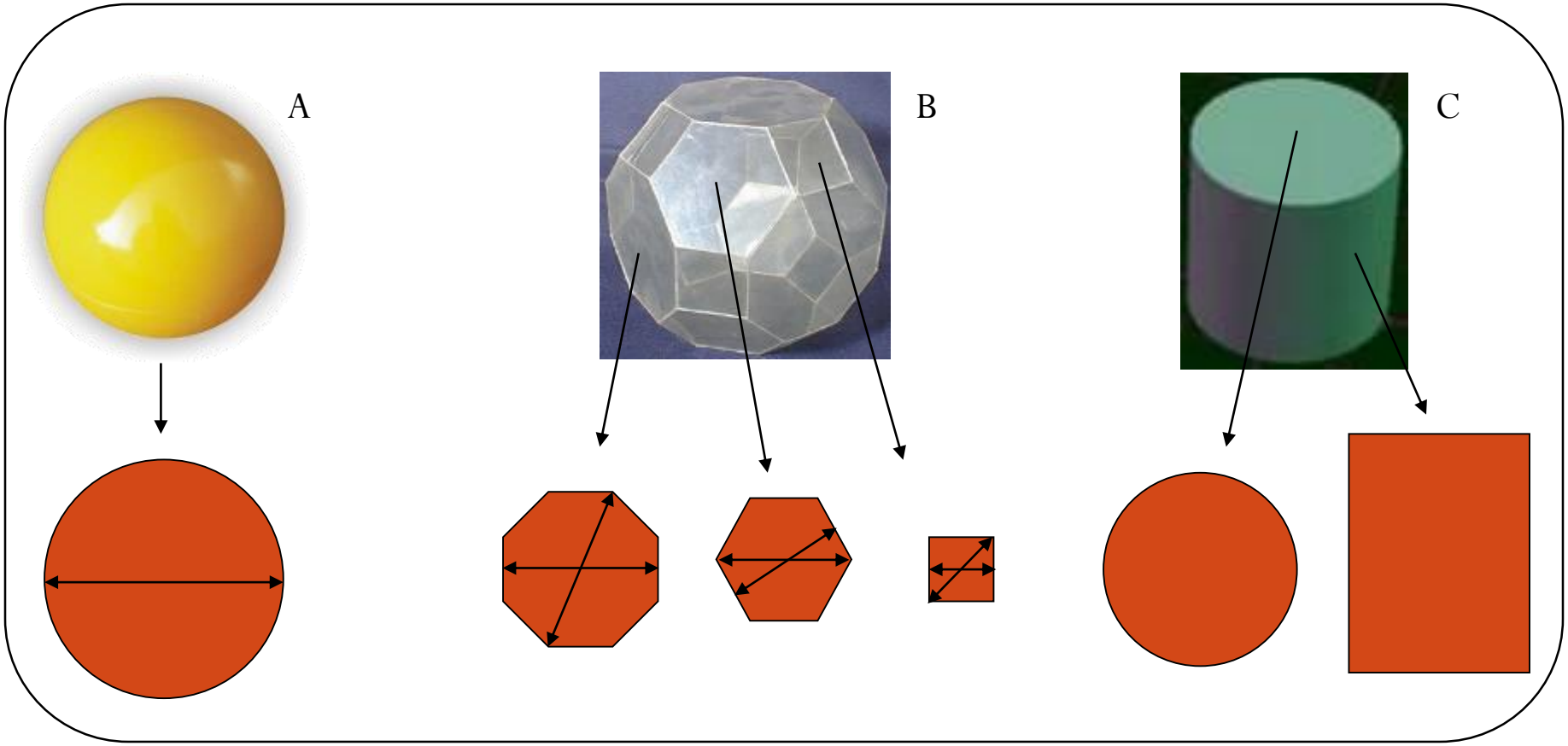
- Dose uniformity
  - Good flow properties of granules & powders are important in the manufacturing of tablets & capsules

Fundamental properties of collection of particles

- These are properties from which other properties can be derived
  - Particle size and size distribution
  - Particle shape and surface area
  - Particle number and weight
  - Particle volume

Particle size and size distribution

- Particle shape plays an important role in particle size determination
- Particles possess different shapes, for example, rod, cubical, granular, etc
- The size of a spherical particle can be easily expressed in terms of its diameter


A
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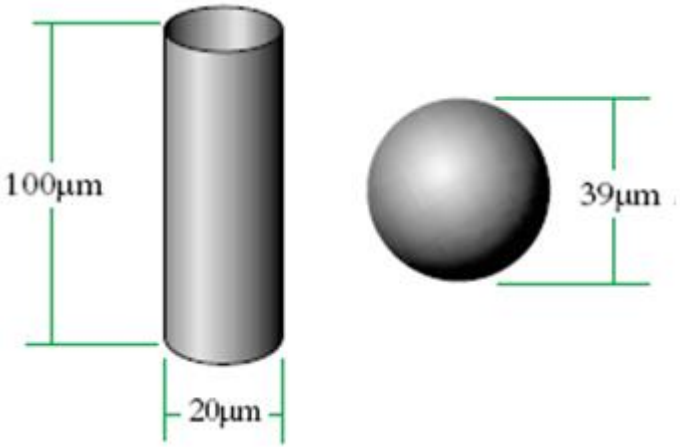
Particle size and size distribution……

- Particles can be asymmetric and symmetric
- The size of a spherical particle can be easily expressed in terms of its diameter

- So, for a perfect sphere;
  - surface area, $S = \prod d^2$
  - Volume, $V = \frac{\prod d^3}{6}$



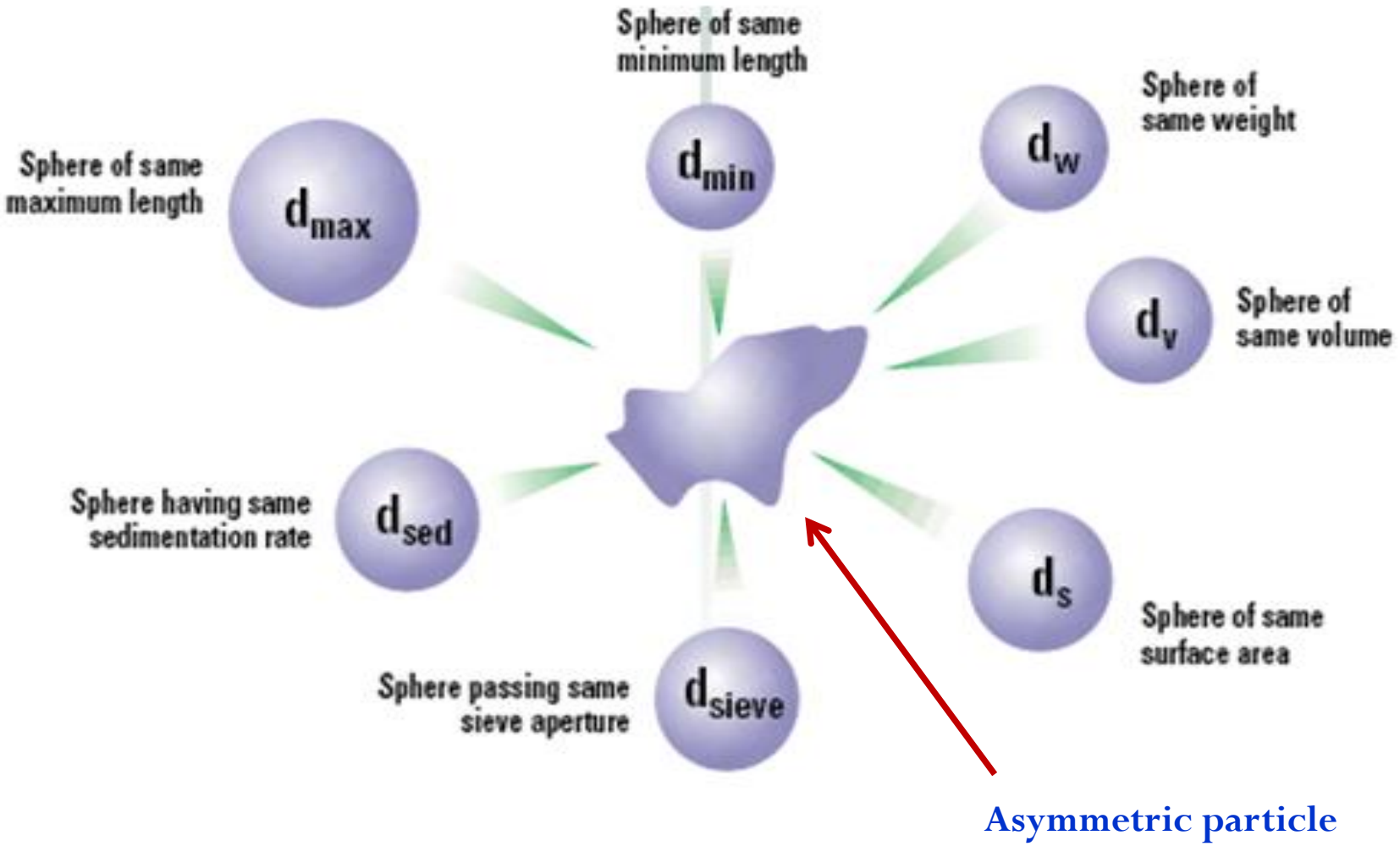
- Non-spherical particles also has a definite surface area and volume but being asymmetric its apparent length varies with its orientation

- Hence, it is not possible to express its size in terms of its diameter

- various *equivalent diameters* have been developed to relate the size of such particles to that of a sphere with identical diameter, surface area, or volume.

- Surface diameter , d_s the diameter of a sphere having the same surface area as that of the asymmetric particles in question.

- Volume diameter, d_v the diameter of a sphere having the same volume as that of the asymmetric particles in question.



Different Equivalent Spheres

- Projected diameter, d_p the diameter of a sphere having the same observed area as that of the asymmetric particles in question
  - when viewed normal to its most stable plane.
    - Usually determined using microscopic techniques

- Stock diameter, d_{st} the diameter of a sphere with the same density as the asymmetric particles in question and which undergoes sedimentation at the same rate as the asymmetric particles in a given fluid
  - d_{st} is usually determined using sedimentation methods

- Any collection of particles is polydisperse
  - ✓ mixture of particles with varying size and shape

- Thus, we need an estimate of the size range present and the number or weight fraction of each particle size.

- This is called the particle size distribution and from this the average particle size of the collection of particles can be derived.

Average particle size

- The particle size of a powder is analyzed microscopically and the number of particles in each size range is determined

Size range (μm)	Mean size range (in μm) (d)	No particle in each size range (n)	nd
0.5-1.0	0.75	4	3
1.0-1.5	1.25	18	22.5
1.5-2.0	1.75	39	68.25
2.0-2.5	2.25	73	164.25
2.5-3.0	2.75	24	66
3.0-3.5	3.25	14	45.5
3.5-4.0	3.75	2	7.5
		$\Sigma n=174$	$\Sigma nd=377$

- From the data the average particle size of the powder may be calculated as

- Particle size = $$\frac{\sum nd}{\sum n}$$

$$= 377/174$$

$$= 2.16\ \mu m$$

Particle size distribution

The particle size distribution in a powder may be quantified by

1. determining the number of particles present in each size range

2. determining the weight of particles present in each size range

- When this number /weight of particles lying within a certain size range is plotted against size range or mean particle size
  - ✓ frequency distribution curve is obtained
    - ➢ number frequency distribution curve
      - ◗ number of particles vs mean particle size
    - ➢ weight frequency distribution curve
      - ◗ weight of particles vs mean particle size

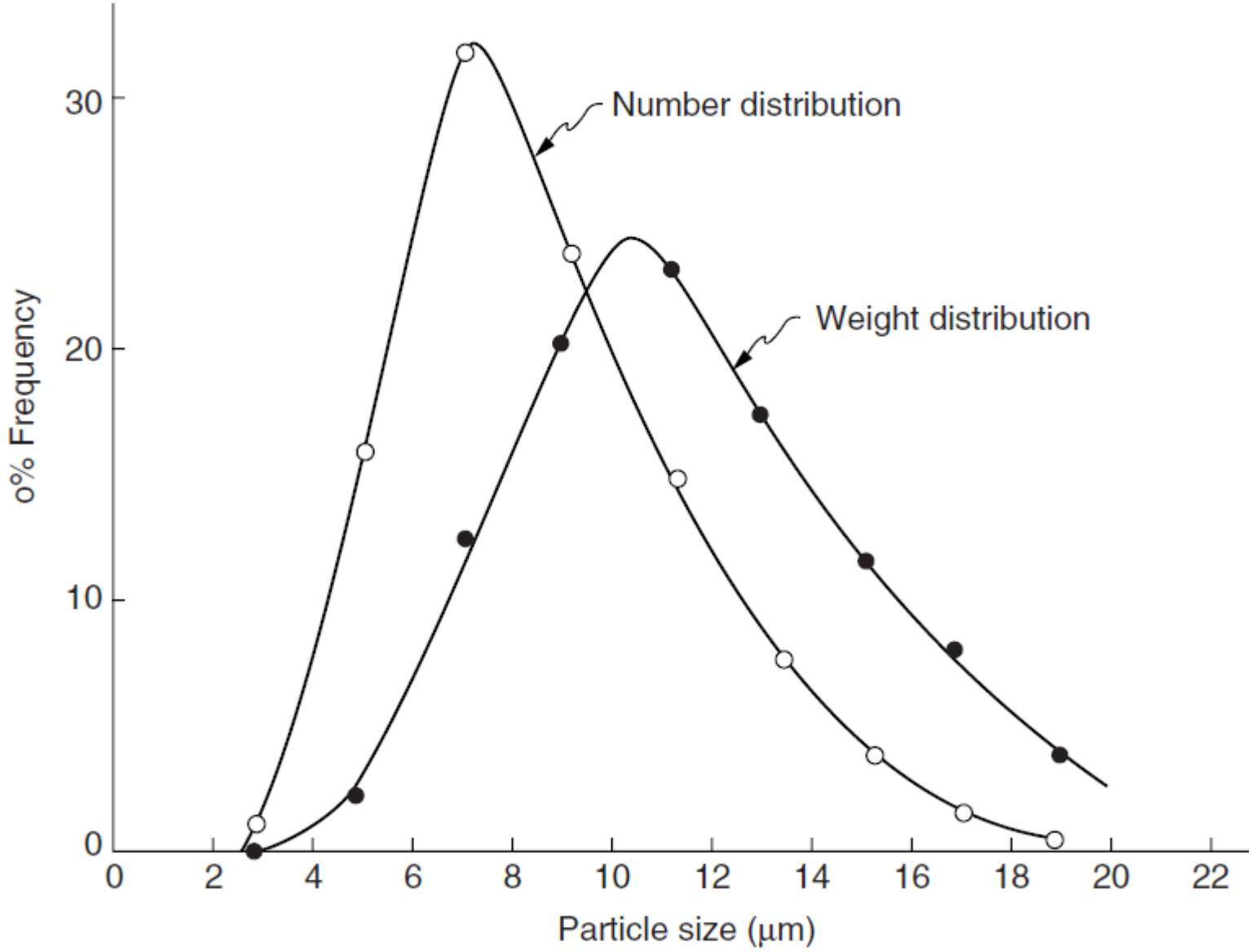


FIGURE . A frequency distribution plot.

- Two sample of powder may have the same average diameter but may not have the same frequency distribution.

- So, expression of the size in terms of average diameter may not give a clear expression of the particle size distribution

- From frequency distribution curve
  - particle size distribution
  - the particle size which occur most frequently

- Particle size can be expressed in two ways

1. Monodisperse particle size

- its characteristics can be described by a single diameter or equivalent diameter

2. Polydisperse particle size- common encounter in pharmaceutical powder

- A poly dispersed powder system is said to have **a normal distribution** if **a typical bell shaped** frequency distribution curve is obtained

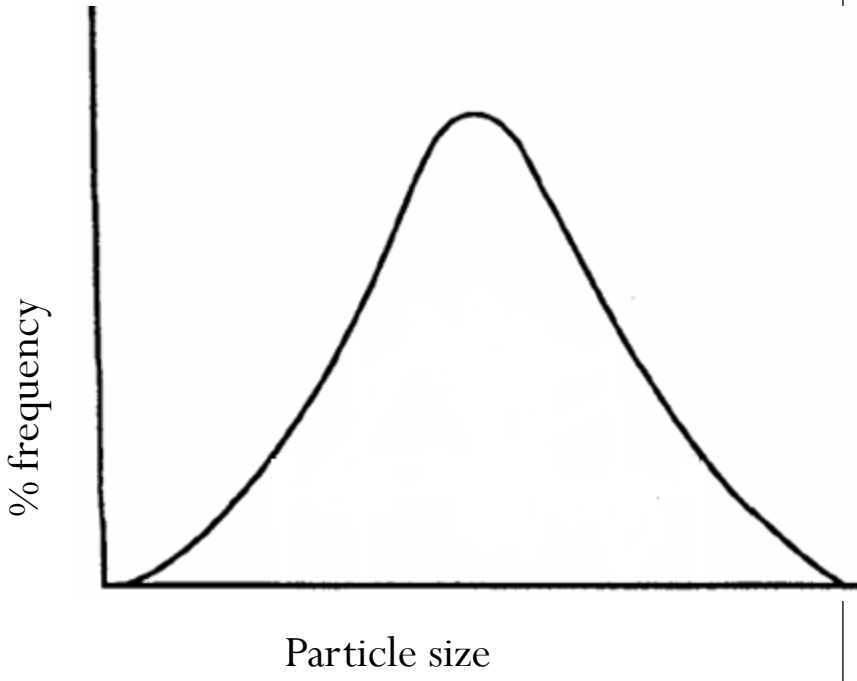


Fig. normal or Gaussian size frequency distribution curve

- However, normal distribution is not common in pharmaceutical powder which are commonly processed by milling or precipitation

- More commonly asymmetric or skewed distribution is obtained

- A frequency curve with an elongated tail towards higher size ranges is **positively skeiwed;** the reverse case exhibits **negative skewness.**

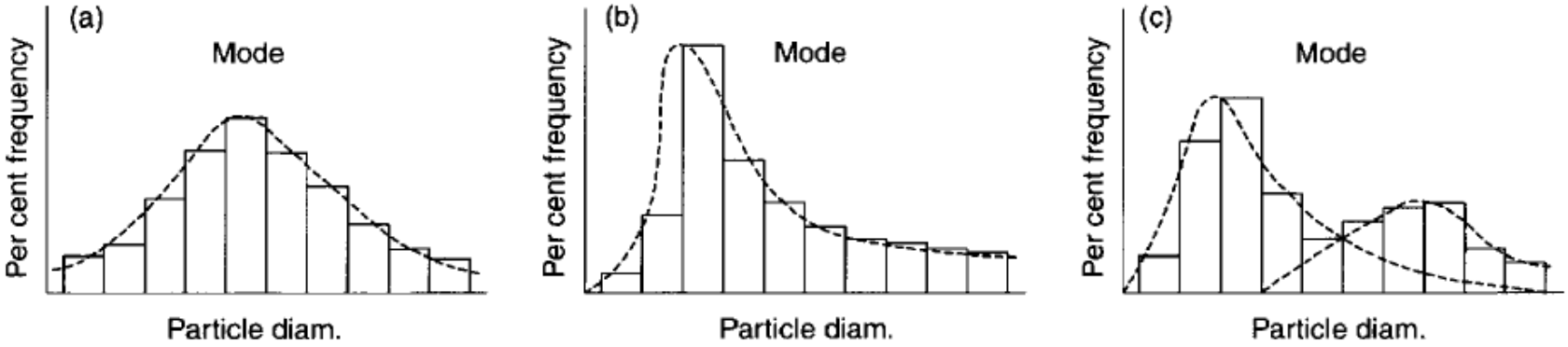


Fig. Frequency distribution curves corresponding to (a) a normal distribution, (b) a positively skewed distribution and (c) a bimodal distribution.

- Such a curve can be converted to a normal bell shaped curve by plotting frequency vs. the logarithm of the particle size diameter
  - log-normal distribution curve

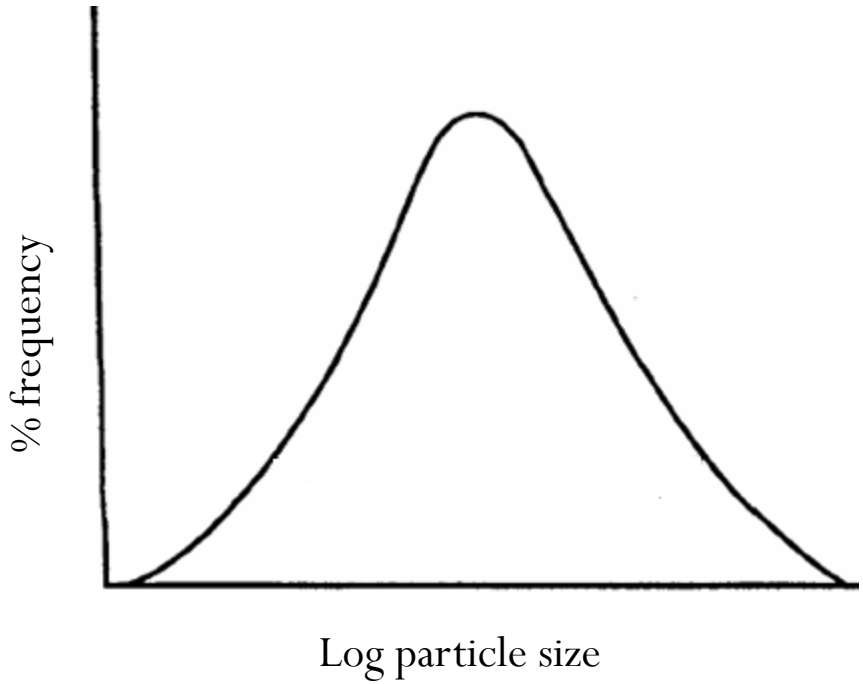


Fig. log normal distribution curve obtained for a polydisperse powder

- Alternatively, a particle size distribution can be obtained by sequentially adding the percent frequency values (Table 2) to produce a cumulative percent frequency distribution

- If the addition sequence begins with the coarsest particles, the values obtained will be cumulative percent frequency undersize;

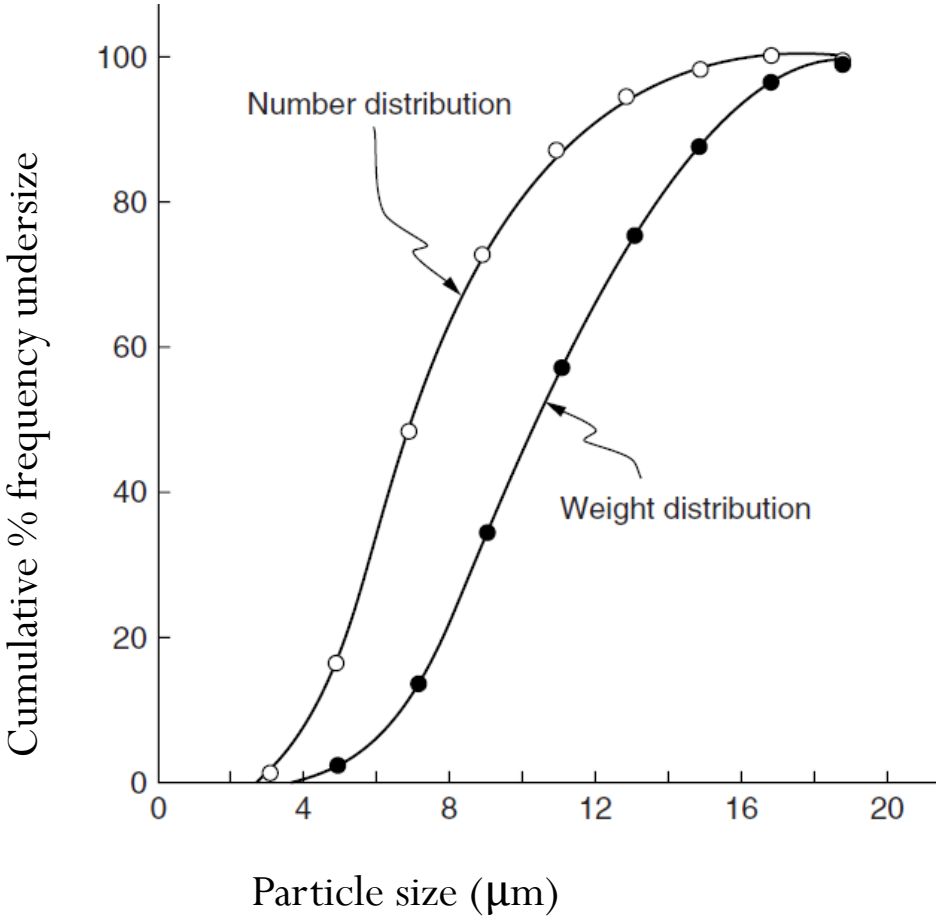
- The reverse case produces a cumulative percent frequency oversize

Table 2 Cumulative frequency distribution data

Equivalent particle diameter (μm)	Per cent frequency (from Table 10.1)	Cumulative per cent frequency Undersize	Oversize
20	4.5	4.5	100
40	9.1	13.6	95.5
60	18.2	31.8	86.4
80	36.4	68.2	68.2
100	18.2	86.4	31.8
120	9.1	95.5	13.6
140	4.5	100	4.5

• cumulative percent frequency distribution

gives sigmoid curve with the mode being the particle size of the greatest slope.



- When the log of the particle size is plotted against the cumulative percent frequency on probability scale a linear relationship is obtained.

- This is known as the log probability plot.
  - Geometric mean diameter.

    It is the log of the p.s equivalent to 50% on the probability scale, i.e., the 50% size.

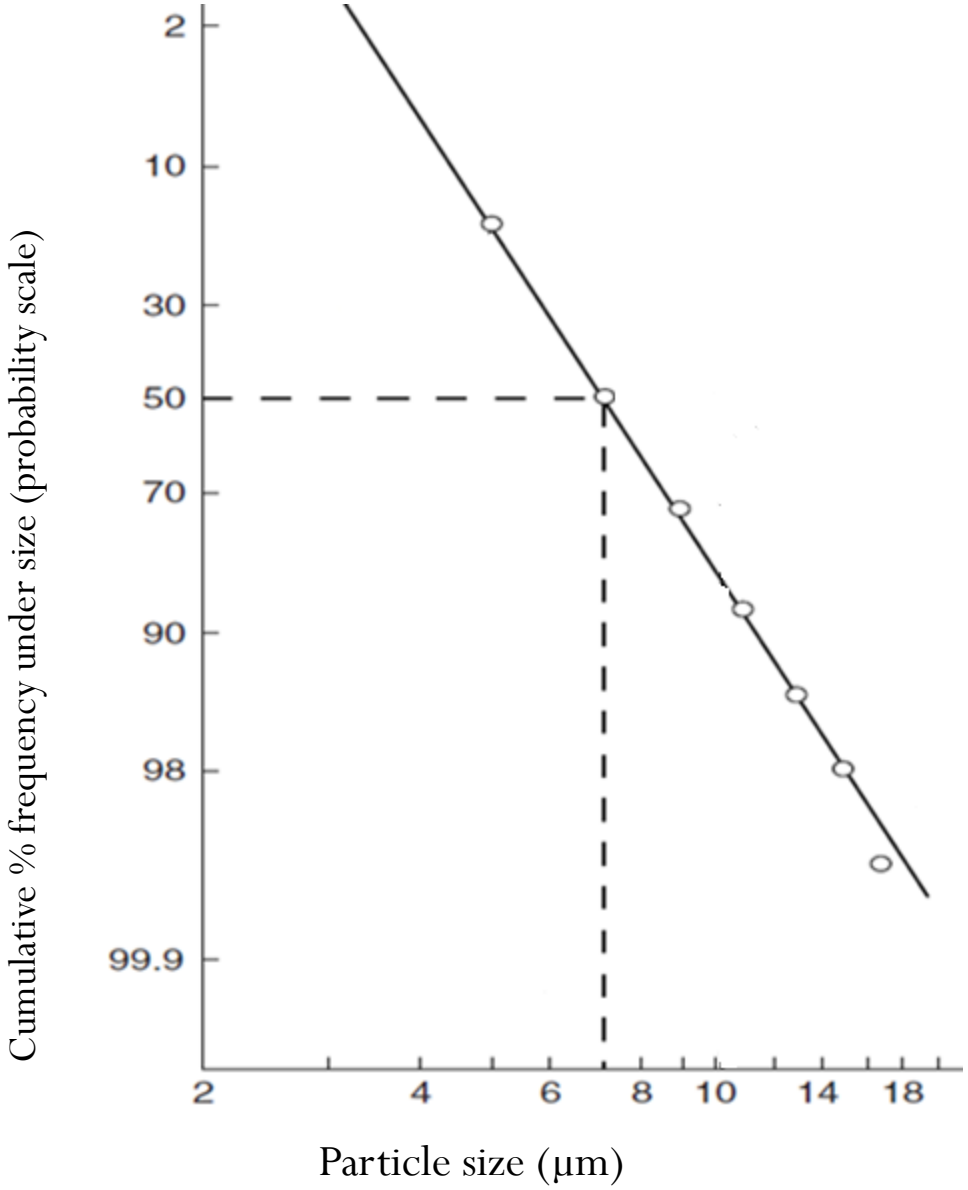


Fig. Log probability plot

- Types of Diameter
  - particle size (diameter) can be described by different expression

➢ A mean particle diameter

- the sum of all individual diameter divided by the total number of particles .
  - ✓ sensitive to extreme value
  - ✓ represent the size present in the greatest number

- Median diameter

  a diameter for which 50% of the particles are less the stated size.

- Mode diameter

  represent the particle size occurring most frequently in the sample

- Mean volume surface diameter

  used to express powder particle size in terms of surface area per unit volume.

$$d_{ave} = \frac{\sum nd^3}{\sum n^2}$$

assignment

- How to describe particle size distributions quantitatively
  - ***skewness***
  - ***kurtosis***

Methods of particles determination

- Particle-size analysis methods can be divided into different categories based on several different criteria:
  - size range of analysis
  - wet or dry methods
  - manual or automatic methods
  - speed of analysis

  Hence,

  - ✓ Microscopic
  - ✓ Sieving technique
  - ✓ Sedimentation
  - ✓ Coulter counter

➢ Microscopy

- The microscope eyepiece is fitted with a micrometer by which the size of the particles may be estimated.
  - The effective size range for analyzing particles is about 0.25 to 100 µm.
- Dilute suspension of the particles whose size are to be determined is prepared in a liquid in which it is insoluble.
- A drop of suspension is placed on the slide
- The eyepiece of the microscope is fitted with micrometer
- The particles observed are counted
- for ease the field can be projected or photographed

- average diameter of a particulate system is obtained by measuring the particles at random along a given fixed line

- At least 300- 500 particles must be counted in order to obtain a good size distribution analysis of data.

- Advantages

  - ✓ Providing a direct visual representation of the particles
  - ✓ Requires an extremely small amount of sample
  - ✓ Needs no calibration by other methods
  - ✓ The equipment is relatively inexpensive to acquire and maintain
  - ✓ It can provide details about shape, crystal habit, and homogeneity within the sample in addition to size

- Disadvantage

✓ The measured diameter of the particles represents two dimensions only

✓ Slow and tedious process

➢ Sieving

- Uses nests of standard sieves stacked one over the other.
- Involves mechanical shaker.
- The particles on each sieve sizes are collected and weighed.
- Useful for coarse particles (>50μm)

Table Openings of Standard Sieves, U.S. Series

Assigned number	Sieve opening
2	9.5 mm
3.5	5.6 mm
4	4.75 mm
8	2.36 mm
10	2.00 mm
14	1.40 mm
16	1.18 mm
18	1.00 mm
20	850 μm
25	710 μm
30	600 μm
35	500 μm
40	425 μm
45	355 μm
50	300 μm
60	250 μm
70	212 μm
80	180 μm
100	150 μm
120	125 μm
200	75 μm
230	63 μm
270	53 μm
325	45 μm
400	38 μm

In determining particle size by this method,

- a nest of sieves with the coarsest on top is placed on the shaker, and the powder sample of known weight is placed on the top of the sieve & shaken for a definite period of time.

- The powder is classified as having passed through one sieve and being retained on the adjacent finer sieve.
  - Mass, collected on each sieve
  - Percentage of sample, collected on each sieve
  - Cumulative percentage of sample retained on each sieve

- Particle diameter is considered as the size of the arithmetic or geometric mean of the opening of the two sieves.

- Whichever size is chosen, it should be stated and used throughout the study.

- For example, the diameter of particles that pass a 40-mesh sieve and are retained on a 60-mesh sieve (i.e., 40/60) may be expressed as the arithmetic mean of the opening of two sieves

$$\frac{0.42 + 0.25}{2} = 0.335\square\text{m}$$

- The size of the particles can also be expressed as the geometric average of the two sieve openings:

$$\left(0.42 \times 0.25\right)^{1/2} = 0.324\square\text{m}$$

- The weight of the powder retained on each sieve is weighed and, assuming log-normal distribution, the cumulative percent by weight of powder retained is plotted on a probability scale against the logarithm of the arithmetic mean size of the opening of two successive screens.

- Disadvantage

✓ aggregation- due to electrostatic charge or moisture

actual size is not determined

✓ Attrition- size reduction

✓ Sieve loading and duration of mechanical shaking can influence the results

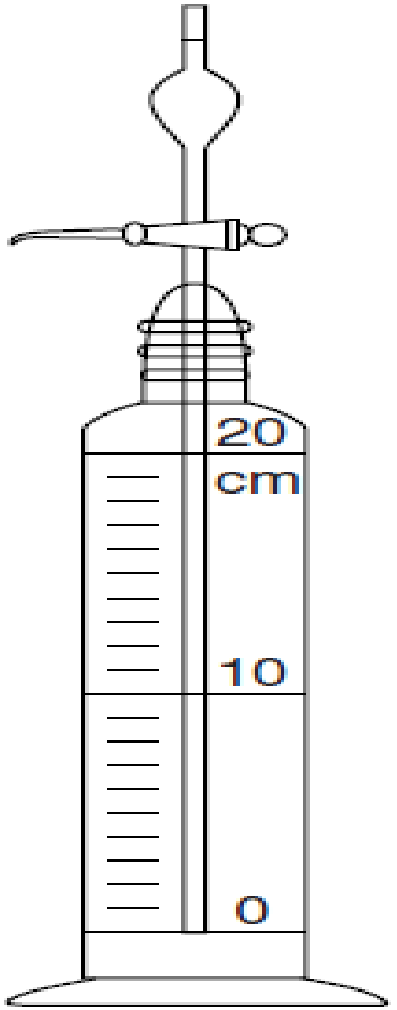
Sedimentation

- Andreason pipette is used for particle size distribution determination

- The particle size in sub-sieve range can be obtained by gravity sedimentation as expressed in Stokes's law (0.8 to 300μm)

Andreason pipette

- 550 ml stoppered cylindrical vessel with 5.5 cm internal diameter
- The stopper has an integral 10 ml bulb pipette
- Its lower tip should be 20 cm below the surface of the suspension



- 1 or 2% suspension of the powder is placed in the vessel up to 550 ml mark.
- Shaked for uniform distribution of the particles within the medium
- Left undisturbed in constant temperature bath
- 10 ml sample is drawn at various time interval
- The samples are evaporated and weighed

- The particle diameter corresponding to the various time period is calculated using the Stocks equation

$$V = \frac{h}{t} = \frac{d^2_{st}(\rho_s - \rho_o)g}{18\eta_o}$$

- ✓ *V is the rate of settling*
- ✓ *H is the distance of fall in time*
- ✓ d_{st} *is the mean diameter of the particles based on the velocity of sedimentation*
- ✓ ρ_s *is the density of the particles*
- ✓ ρ_o *is the density of dispersion medium*
- ✓ η_o *is the viscosity of the medium*
- ✓ g acceleration due to gravity

- Advantage

i. the apparatus is inexpensive and the technique is simple

ii. The results obtained are precise provided the technique is adequately standardized

- Disadvantages

1. Method is laborious since separate analysis are required for each experimental point on the distribution curve
2. Very small particles cannot be determined accurately since their settling is unduly prolonged

Stokes Diameter

- A sample of powdered zinc *oxide*, density 5.60 g/cm^3 is allowed to settle under the acceleration of gravity, 981 *cm/sec*^{2} at 25 °C. The rate of settling *v* is 7.30 x 10^{-3} cm/sec; the density of the medium is 1.01 g/cm^3, and its viscosity is 1 centipoise = 0.01 poise or 0.01 g/cm sec. Calculate the Stokes diameter of the zinc oxide Powder.

$$d_{st} = \sqrt{\frac{(18 \times 0.01 \text{ g/cm sec}) \times (7.30 \times 10^{-3} \text{ cm/sec})}{(5.60 - 1.01 \text{ g/cm}^3) \times (981 \text{ cm/sec}^2)}}$$

$$= 5.40 \times 10^{-4} \text{ cm or } 5.40\ \mu\text{m}$$

- For Stokes's law to apply, a further requirement is that the flow of dispersion medium around the particle as it sediments is *laminar* or *stream line*.

- Whether the flow is turbulent or laminar is indicated by the dimensionless *Reynolds number, R*, which is defined

$$R_e = \frac{v\, d\rho_0}{\eta_0} \qquad (18\text{–}7)$$

- According to Heywood.' Stokes's law cannot be used if ***R*** is greater than 0.2 because turbulence appears at this value.

- the limiting particle size under a given set of conditions can be calculated as follows

$$v = \frac{R_e \eta}{d\rho_0} = \frac{d^2(\rho_s - \rho_0)g}{18\eta} \qquad (18\text{–}8)$$

and thus

$$d^3 = \frac{18R_e\eta^2}{(\rho_s - \rho_0)\rho_0 g} \qquad (18\text{–}9)$$

EXAMPLE 18-41

A powdered material, density 2.7 g/cm^3, is suspended in water at 20 °C. What is the size of the largest particle that will settle without causing turbulence? The viscosity of water at 20 °C is **0.01** poise or g/cm sec, and the density is 1.0 g/cm^3.

$$d^3 = \frac{(18)(0.2)(0.01)^2}{(2.7 - 1.0)1.0 \times 981}$$

$$d = 6 \times 10^{-3}\ \text{cm} = 60\ \mu\text{m}$$

E.g 2

- If the material used in the above e*xample* is flow suspended in a syrup containing 60% by weight of sucrose, what will be the critical diameter**,** that is the maximum diameter for which *R* does not exceed 0.2? The viscosity of the syrup is 0.567 poise, and the density is 1.3 g/cm^3.

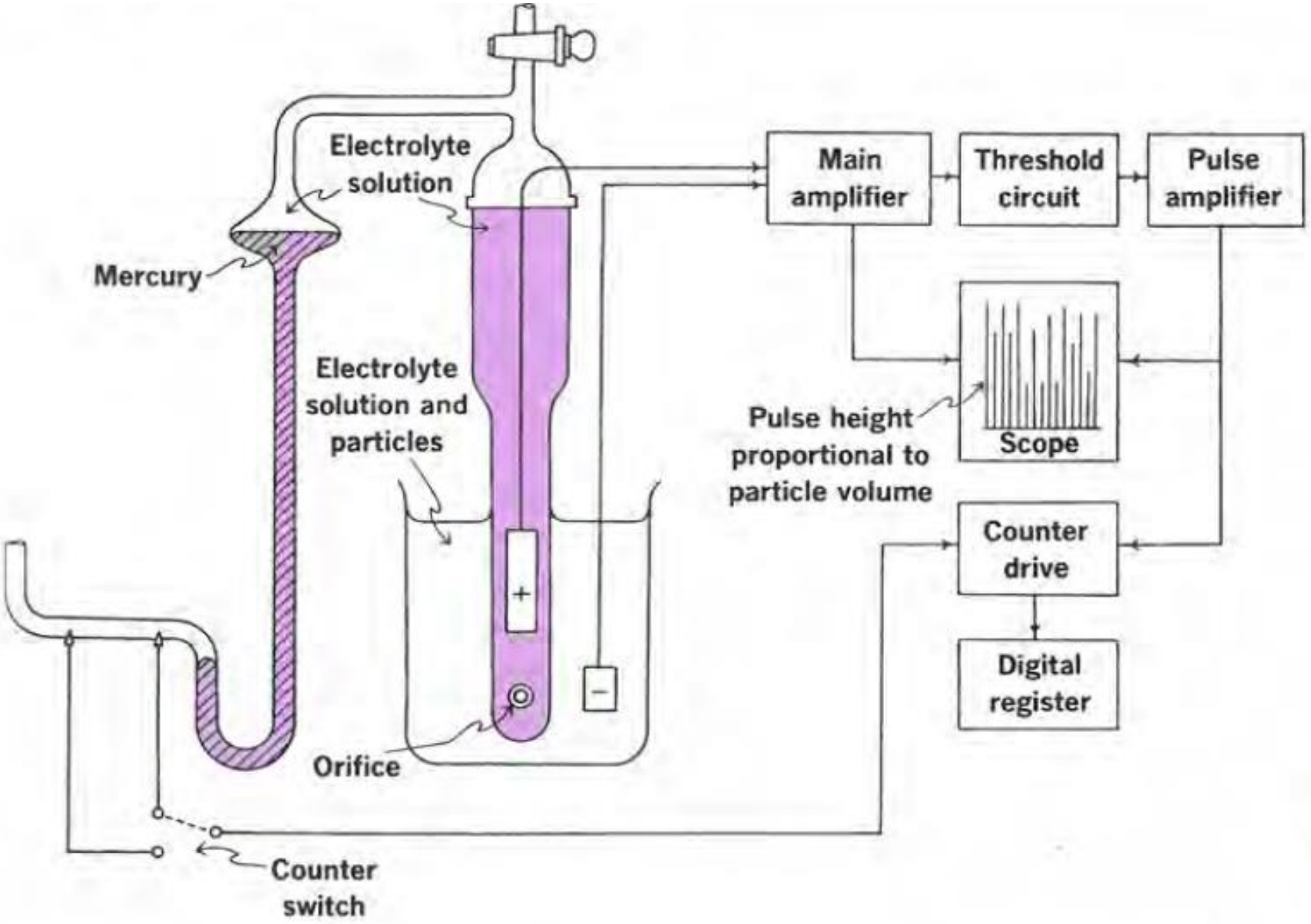
$$d^3 = \frac{(18)(0.2)(0.567)^2}{(2.7 - 1.3)1.3 \times 981}$$

d =8.65 x 10^{-2}cm = 865µm

Method for Particle Volume Measurement

Coulter Counter Method

- Principle: when a particle suspended in a conducting liquid passes through a small orifice (opening), on either side of which are electrodes, a change in electric resistance occurs.
- Powder samples are dispersed in the electrolyte to form a very dilute suspension.
- A known volume of the suspension is pumped through the orifice so that only one particle passes at a time through the orifice
- A constant voltage is applied across the electrodes so as to produce a current.
- As the particle travels through the orifice, it displaces its own volume of electrolyte and this results in an increased resistance b/n the two electrodes.

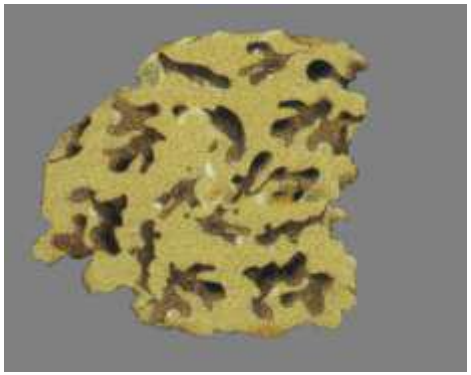

Electrolyte solution
Mercury
Electrolyte solution and particles
Orifice
Counter switch
Main amplifier
Threshold circuit
Pulse amplifier
Pulse height proportional to particle volume
Scope
Counter drive
Digital register
+
−

Derived properties of powders

1. Porosity of powder

- The quality or state of being porous

- Powders can be
  - i. Porous (most pharmaceutical solids are porous, i.e., they have internal pores or capillary)
    - Bulk volume > true volume
  - ii. Non-porous



When a powder, is placed in a graduated cylinder: the total volume occupied is known as the bulk volume Vb .

• bulk volume (Vb) = true volume (Vp) + volume of spaces b/n particles.

The volume of the spaces, the void volume, $V = Vb - Vp$

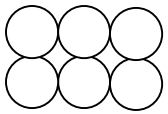
The porosity (ε) of powder is determined as the ratio of void volume to bulk volume.

• Porosity $= \varepsilon = \frac{Vb - Vp}{Vb} = 1 - \frac{Vp}{Vb}$

  • frequently expressed in percent, $\varepsilon \times 100$

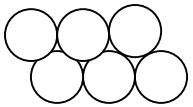
- Packing Arrangement in Powder Beds
  - Two types of packing are possible

- Cubic packing
  - Most open/ Loosest packing (ε=48%)



Rhombohedral packing

closest packing (ε=26%)



- pharmaceutical powders have porosity range from 30 and 50%.
- When the particles of varying sizes are present, porosity lower than the theoretical minimum of 26% is also possible. Why ?
- If the powder contains floccules or aggregates, the porosity may go beyond the theoretical maximum of 48%. Why ?
- Highly compressed crystalline materials, $\varepsilon < 1\%$

Example

- A sample of calcium oxide powder with a true density of 3.203 and weighing 131.3g was found to have a bulk volume of 82 cm3 when placed in a 100-ml graduated cylinder. Calculate the porosity ?
    - Ans.=50%

- Calculate the percent porosity of TiO_2 having a true density of 4.26g/cm3 and 100g sample of which was found to occupy a bulk volume of 80 mL.
    - Ans=70%

2. Densities of particles:

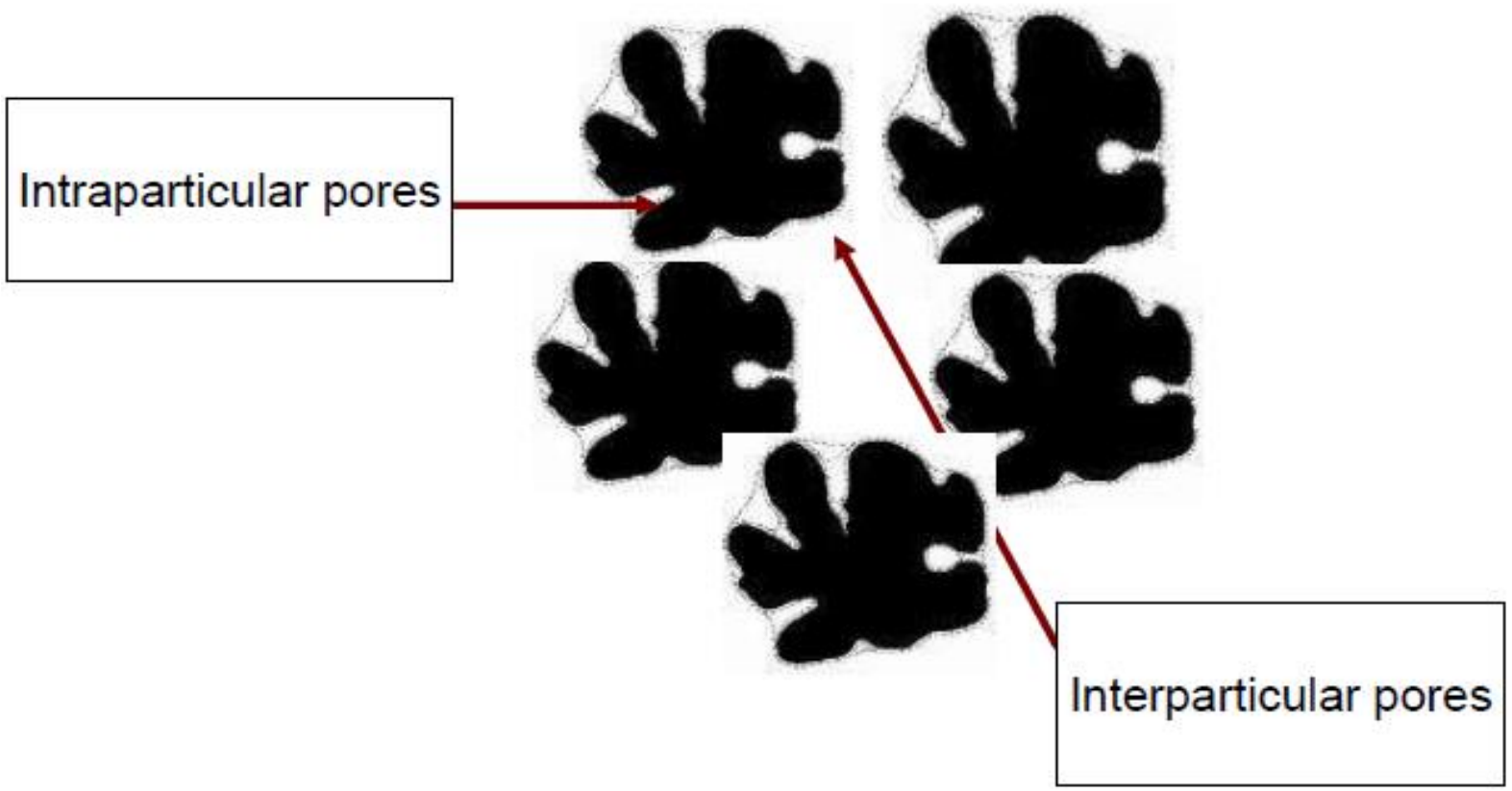
Density is defined as weight per unit volume (W/V).

Types of densities:

A- true density

The true density, or absolute density, of a sample excludes the volume of the pores and voids within the sample.

- Methods
  - ✓ Liquid displacement method
  - ✓ Gas displacement method (He, H_2)-better penetration ability


Intraparticular pores
Interparticular pores

B. Granule density (ρ_g)

- Mass of the granular powder and the volume occupied by the granular material together with its intra particle space

- Method-using Liquid displacement Method (Mercury)

$$\varepsilon_{intra} = \frac{V_g - V_p}{V_g} = 1 - \frac{V_p}{V_g} = 1 - \frac{\rho_g}{\rho_p}$$

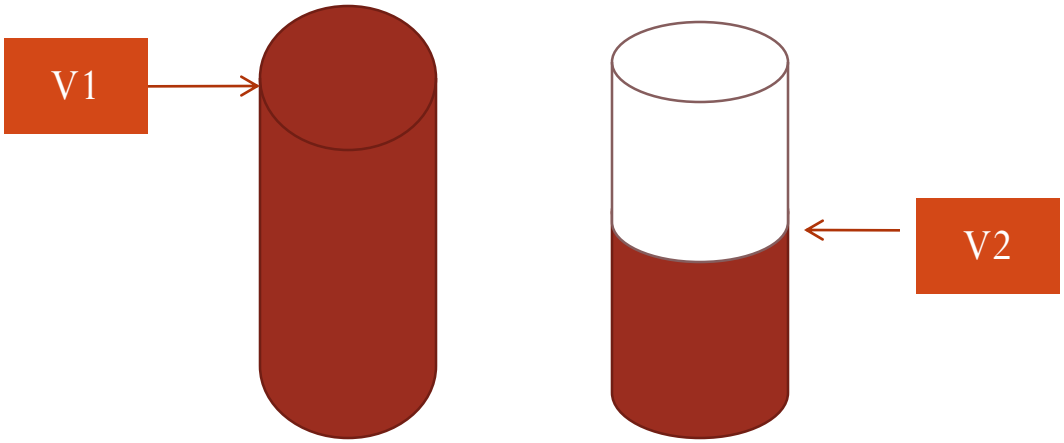
C- bulk density (ρ_b)

- It is the ratio of the mass of the powder and its bulk volume
- includes the volume of all of the pores within the sample.
- Weighed quantity of the powder material is introduced into a graduated measuring cylinder and is tapped mechanically or manually till a constant volume is obtained.

- This volume, known tapped volume of the powder is noted and includes the true volume of the powder as well as the volume occupied by the interparticle and intraparticle spaces.

D. Tapped density (ρ_T)

- It is the ratio of mass of powder to tapped volume



$$\rho_b = \frac{M}{V_1}$$

$$\rho_T = \frac{M}{V_2}$$

Tap densitometer

Example:

- Estimate the Intraparticle porosity of sulfadiazine granules having a granule density of 1.12 g/cm^3 and true density of 1.5g/cm^3.

$$\varepsilon_{inter} = \frac{V_b - V_g}{V_b} = 1 - \frac{V_g}{V_b} = 1 - \frac{\rho_b}{\rho_g}$$

- Ans=25.3%

3. Bulkiness = Specific bulk volume

- The reciprocal of bulk density
- Bulkiness usually increases with a decrease in particle size. However, in a mixture of particles with different sizes, the bulkiness may get reduced. Why??

Application of Bulkiness

- It is a useful property to be considered while choosing a suitable container for packaging or during filling of drug powders in to capsules.

- The bulk density of calcium carbonate vary from 0.1 to 1.3, and the lightest (bulkiest) type require a container about 13 times larger than that needed for the heaviest variety.

4. Flow properties of powders

- Powders may be free-flowing or cohesive (“sticky”).
- Important parameter to be considered in the production of pharmaceutical dosage forms.

- Example:
  - ✓ dies filling during tableting
  - ✓ capsules filling

    directly depend on the flow properties of the powder

Flow properties of powders depends on;

i. Cohesiveness or stickiness between particles due to presence of Van der Waals, surface tension and electrostatic forces.

- Cohesiveness of particles has been found to depend upon a number of factors

a. Particle size and shape
   - ✓ Very fine particles tend to be more cohesive due to their large surface area

b. Density or porosity of the powders
   - ✓ dense materials tend to be less cohesive than lighter ones

c. The presence of adsorbed materials on the powder surface
   - ✓ Moisture increase cohesiveness of particles

ii. Adhesion between the particles and the container wall due to the above forces.

iii. Friction between particles due to surface roughness.

iv. Physical interlocking of particles specially if these are of irregular shape

Many common manufacturing problems are attributed to powder flow:

- Uneven powder flow
    - excess entrapped air within powders → capping or lamination.
    - increase particle's friction with die wall causing lubrication problems, and
    - increase dust contamination risks during powder transfer.
    - non-uniformity of dose
- non-uniformity (segregation) in blending

Assessment of flow properties of powders

1- Carr's compressibility index

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Poured or bulk density}}{\text{Tapped density}} \times 100$$

- Bulk density = weight / bulk volume
- Tapped density = weight / true volume

- 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

2- Hausner ratio:

- Hausner ratio was related to interparticle friction:

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

- Value less than 1.25 indicates good flow
  - The powder with low interparticle friction, such as coarse spheres.
- Value greater than 1.5 indicates poor flow
  - 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.

3.Angle of Repose (θ)

- The sample is poured onto a horizontal surface and the angle of the resulting pyramid is measured.
- The user normally selects the funnel orifice through which the powder flows slowly and reasonably constantly.

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

where,

θ, angle of repose, h & r are height and radius of the powder, respectively

- Angle of repose is a function of the surface roughness.
  - The rougher and more irregular the surface of particles, the more the angle of repose
- As the particles become less and less spherical, the angle of repose increases while the bulk density and flowability decreases.

Angle of repose (θ)	Flow properties
$<25^o$	excellent
$25 - 30^o$	good
$30 - 40^o$	satisfactory
$40 - 50^o$	poor
$>50^o$	very poor

Factors affecting the flow properties of powders

Alteration of Particle's size & Distribution

- There is certain particle size at which powder's flow ability is optimum.
- Coarse particles are more preferred than fine ones as they are less cohesive.
- The size distribution can also be altered to improve flowability by removing a proportion of the fine particle fraction or by increasing the proportion of coarser particles, such as occurs in granulation.

Alteration of Particle Shape & texture

- Particle's shape: generally, more spherical particles have better flow properties than more irregular particles.
- Spherical particles are obtained by spray drying, or by temperature cycling crystallization.

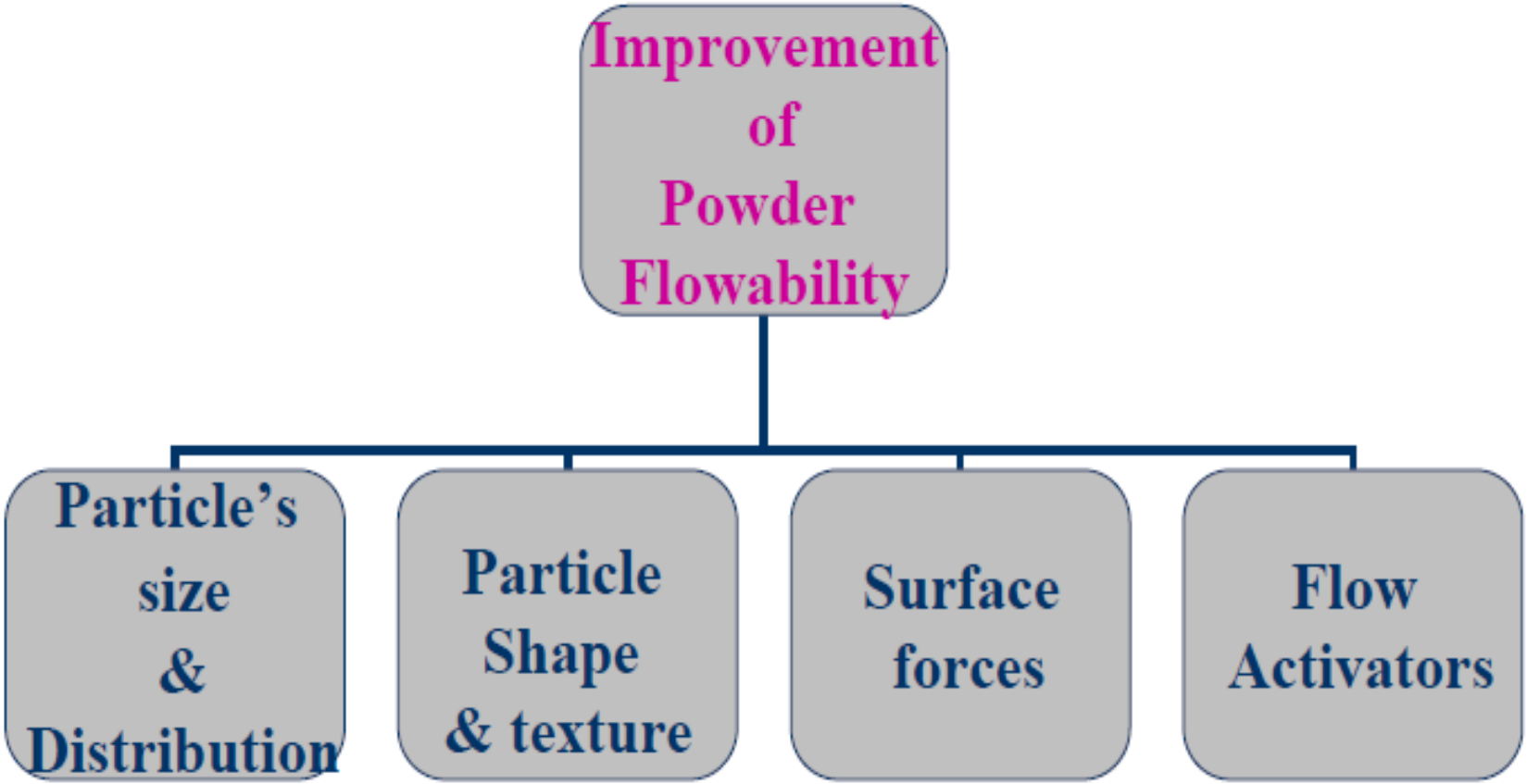
- Particle's texture:
  - ✓ particles with very rough surfaces will be more cohesive and have a greater tendency to interlock than smooth surfaced particles

Alteration of Surface Forces

- Reduction of electrostatic charges can improve powder flowability. Electrostatic charges can be reduced by altering process conditions to reduce frictional contacts.
- Moisture content of particle greatly affects powder's flowability.
- Adsorbed surface moisture films tend to increase bulk density and reduce porosity.
- Drying the particles will reduce the cohesiveness and improve the flow.
- Hygroscopic powders, stored and processed under low humidity conditions.

Formulation additives (Flow activators)

- Flow activators are commonly referred as glidants.
- Flow activators improve the flowability of powders by reducing adhesion and cohesion.
- e.g. talc, maize starch and magnesium stearate


Improvement of Powder Flowability
Particle's size & Distribution
Particle Shape & texture
Surface forces
Flow Activators

Solid oral dosage forms

- Oral dosage forms are taken orally
  - a local effect in the mouth, throat, or GIT
  - a systemic effect in the body after absorption from the mouth or GIT.

- Oral dosage forms can be divided into two main groups
  - solid DF
  - liquid DF

- Solid oral dosage forms

1. Powder and granules
2. Tablets
3. Capsules

- *conventional oral solid dosage forms will be defined as those solid dosage forms* taken by or given orally to patients and intended to deliver the drug to the site of action without any time delay

Powders and granules

- Powders are dry mixtures of finely divided medicinal and non-medicinal agents intended for internal or external use.

- Powders may be dispensed to a patient
  - Multiples dose (bulk form such as powders measured by the spoonful to make a douche solution)
  - Single dosage units

- Powders represent one of the oldest dosage forms.

- However, with the increased use of highly potent compounds, they have been largely replaced by
  - capsules and tablets.

- In certain situation, powders still possess advantages
  - powders disperse & dissolve more readily than compacted dosage forms.
  - Children and adults who have trouble swallowing tablets or capsules may find powders more acceptable.

1. Oral Powders

- Oral powders generally can be supplied as finely divided powders or effervescent granules.

- The finely divided powders are suspended or dissolved in water or mixed with soft foods such as applesauce before administration.
    - Antacids and laxative powders
    - Powdered antibiotic syrups to be reconstituted before administration are also classified as oral powders.

2. Douche Powders

- Douche powders are completely soluble and are dissolved in water prior to use as antiseptics or cleansing agents for a body cavity.

- They most commonly are intended for vaginal use, although they may be formulated for nasal, otic, or ophthalmic use.

3. Insufflations

- Insufflations are finely divided powders introduced into body cavities such as the throat.
- **An insufflator** (powder blower) usually is employed to administer these products. The Norisodrine Sulfate Aerohaler Cartridge (Abbott) is an example.
- In the use of this aerohaler, inhalation by the patient causes a small ball to strike a cartridge containing the drug. The force of the ball shakes the proper amount of the powder free, permitting its inhalation.

- Another device, the **Spinhaler turboinhaler** (Fisons), is a propeller-driven device designed to deposit a mixture of lactose and micronized cromolyn sodium into the lung as an aid in the management of bronchial asthma. However, the difficulty in obtaining a uniform dose has restricted their general use.

4. Oral Antibiotic Syrups

- For patients who have difficulty taking capsules and tablets,
- but many antibiotics are physically or chemically unstable when formulated as a suspension or solution.
    - Prepared in the form of a powder or granules.
- When the pharmacist dispenses the product, a given quantity of water is added to constitute the solution or suspension.

- Sometimes the amount of water added is varied to obtain nonstandard doses of the antibiotic as shown in the following example.

- If a prescription for an amoxycillin product calls for the addition of 80 ml of water to make 100 ml of constituted solution containing 125 mg amoxycillin per 5 ml, how should the instruction be changed to obtain 100 mg amoxycillin per 5 ml?

5. Effervescent Granules

- Effervescent granules contain sodium bicarbonate and either citric acid, tartaric acid, or sodiumbiphosphate in addition to the active ingredients.

- On solution in water, carbon dioxide is released because of the acid-base reaction.

- Citric acid: 3 NaHCO3 + $C_6H_8O_7.\mathbf{H_2O}$ = $C_6H_5Na_3O_7$ + 3 CO_2 + 3 H_2O
- Tartaric acid: 2 $NaHCO_3$ + $C_4H_6O_6$ = $C_4H_4Na_2O_6$ + 2 CO_2 + 2 H_2O

- The release of the water of crystallization makes the powder coherent and helps form the granules.

- The effervescence from the release of the carbon dioxide masks the taste of salty or bitter medications.

Preparation of effervescent granules

- **Wet method:** By the addition of a binding liquid (Alcohol is frequently used).
- **Dry method:** Heating effloresced powder to liberate the water of crystallization which then acts as the binding agent

Wet Granulation

- **Procedure:**

1- The powders are mixed without pressure in a suitable container.

2- Alcohol is added in portions with stirring until a dough like mass is formed.

3- The materials are then passed through sieve # 6.

4- The resulted granules are dried at a temperature not exceeding 50°C.

5- The granules are packed in air tight containers

Dry granulation

- **Procedure:**

1- All ingredients, except citric acid monohydrate, are dried and passed through sieve # 60.

2- The powders are thoroughly mixed and citric acid crystals are added at last (un-effloresced citric acid contains one molecule of water of crystallization).

3- The mixture is spread in a shallow dish and placed in an oven previously heated (99- 105°C). Upon heating citric acid crystals, the water of crystallization effloresces and citric acid transforms to the powder form.

ADVANTAGES & DISADVANTAGES OF POWDERS AND GRANULES

Advantages of powders and granules :

1. Solid preparations are more stable than liquid preparations. e.g. the shelf life
    - powders for antibiotic syrups, is 2 to 3 years,
    - reconstituted with water it is 1 to 2 weeks.
2. Powders and granules are convenient forms in which to dispense drugs with a large dose.

- E.g. if the dose of a drug is 1 to 5 g it is not feasible to manufacture tablets.

3. Orally administered powders & granules of soluble medicaments have a faster dissolution rate than tablets or capsules

4. Powders offer a lot of flexibility in compounding solids.

Disadvantages of powders and granules :

1. Bulk powders or granules are far less convenient for patients to carry than a small container of tablets or capsules.

2. The masking of unpleasant tastes may be a problem with this type of preparation.

3. Bulk powders or granules are not a good method of administering potent drugs with a low dose.

4. Powders and granules are not a suitable method for the administration of drugs that are inactivated in the stomach

5. Powders and granules are not well suited for dispensing hygroscopic or deliquescent drugs.

PREPARATION OF POWDERS AND GRANULES

- During the manufacture and extemporaneous preparation of powders, the general techniques of weighing, measuring, sifting, and mixing are applied.

- The manually operated procedures usually employed by pharmacists for preparing powders are

  co-milling,

  trituration,

  pulverization by intervention, and

  levigation

- Trituration, reduce the particle size of powders by grinding with a mortar and pestle.
- pulverization is also used for reducing the particle size of solids.
- e.g., camphor, which can't be pulverized easily by trituration (sticky properties);
- however, on the addition of a small amount of alcohol or other volatile solvent, this compound can be reduced readily to a fine powder because when the solvent is permitted to evaporate a fine powdered material is formed.

- Levigation is the process in which a non solvent is added to solid material to form a paste, and particle-size reduction then is accomplished by rubbing the paste in a mortar with a pestle or on an ointment slab using a spatula.

- When blending two or more powders the method of geometric dilution is preferred, especially for unequal quantities of powders.

- ensures uniformly distribution of small quantities of ingredients, usually potent drugs

Steps

1. Weigh ingredients
2. Place the ingredient with the smallest quantity in a mortar.
3. Combine this powder with an amount of the material present in the second largest quantity approximately equal to the amount already in the mortar.

4. Triturate the powders until a uniform mixture is formed.

5. Add another amount of the second ingredient equal in size to the powder volume already in the mortar and triturate well.

6. Continue adding powder to the mortar in this fashion until all the powder ingredients have been added.

COMPOUNDING PHARMACEUTICAL POWDERS

- When working with powders pharmacists should look out for efflorescent powders
- efflorescent powders include caffeine, citric acid, codeine phosphate, ferrous sulfate, and atropine sulfate.

- Hygroscopic and deliquescent powders should also be handled with care since these substances become moist because of their affinity for moisture in the air. Double wrapping is desirable for further protection.

- Extremely deliquescent compounds cannot be prepared satisfactorily as powders.

- Eutectic Mixtures: mixture of substances that liquefy when mixed, rubbed or triturated together. The melting points of many eutectic mixtures are below room temperature.
  - **Examples:** menthol- thymol- phenol- salol- camphor…

- using inert adsorbent such as starch, talc, lactose to prevent dampness of the powder

- dispensing the components of the eutectic mixture separately.

PACKAGING OF POWDERS AND GRANULES

- Oral powders may be dispensed in
  - in divided powders wrapped in materials such as bond paper and parchment, polyethylene envelopes
  - in bulk

    are dispensed in papers, metal foil, small heat-sealed plastic bags, or other containers

- Hygroscopic and volatile drugs can be protected using a waxed paper, double-wrapped with a bond paper

SIZE CLASSIFICATION OF POWDERS

After preparation powders are classified according to their particle size.

In order to qualify the particle size of a given powder, the USP uses the following descriptive terms:

- Very coarse powder: All particles pass through a No. 8 sieve (2.38 mm) and not more than 20% pass through a No. 60 sieve.
- Coarse powder: All particles pass through a No. 20 sieve (0.84 mm) and not more than 40% pass through a No. 60 sieve.

- Moderately coarse powder: All particles pass through a No. 40 sieve (0.42 mm) and not more than 40 % pass through a No. 80 sieve.
- Fine powder: All particles pass through a No. 60 sieve (0.25 mm) and not more than 40% pass through a No. 100 sieve.
- Very fine powder: All particles pass through a No. 80 sieve (0.18 mm). There is no limit to greater fineness.