PHYSICAL PHARMACEUTICS-II

UNIT 4 NOTES

MICROMERETICS

- PARTICLE SIZE DISTRIBUTION
- MEAN PARTICLE SIZE
- PARTICLE SIZE DETERMINATION
- COUNTING AND SEPARATION METHODS
- PARTICLE SHAPE
- PARTICLE SURFACE
- SURFACE AREA DETERMINATION
- DERIVED PROPERTIES OF POWDERS

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MICROMERITICS

- Micromeritics is the field of science that deals with the study of small particles especially powders.
- It deals with the characterization of particles and their sizes, shapes, surface area, porosity and flow properties.

APPLICATION OF MICROMERITICS

① Improves Drug Dissolution Rate

- Smaller particles have larger surface area, increasing dissolution.

② Enhance Bioavailability

- Faster dissolution leads to better absorption of drugs.

③ Ensures Uniform Mixing

- Uniform particle size helps in even distributing of drug in formulations.

④ Affects flow properties

- Good flow is essential for tablet and capsule manufacturing.

⑤ Controls Drug Stability

- Proper particle size avoids sedimentation in suspensions.

⑥ Improves Compressibility

- Affects tablet hardness and uniform weight during compression.

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⑦ Important for Inhalation Products

Particle size determination of lung deposition in aerosol therapy.

PARTICLE SIZE

- Particle size refers to the dimension or diameter of indivisual particles in a powdered material, typically expressed in micrometers (μm) or nanometers (nm).
- It is important for understanding physical and chemical properties, of material.
- If particle shape is sphere, then its size can be readily measured in terms of its diameter.
- But pharmaceutical powder particles are generally non spherical in Nature, hence their particle size is expressed in equivalent diameters as follows:

ⓐ Surface diameter, d_s

ⓑ Volume diameter, d_v

ⓒ Projected diameter, d_p

ⓓ Stokes diameter, d_{st}

ⓔ Sieve diameter, d_{sieve}

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① **Surface Diameter (ds):**

Diameter of sphere having the same sulface area as particle.

② **Volume diameter (Vd):**

Diameter of sphere having the same volume as particle.

③ **Projected diameter (dp):**

Diameter of circle that has the same area as the 2D Projection (shadow) of the particle.

④ **Stokes Diameter (dst):**

Diameter of sphere that settles as the same rate as the particle in a fluid (used in sedimentation method).

⑤ **Sieve Diameter (dsieve):**

Diameter of sphere that just passes through the same sieve opening as the particle.

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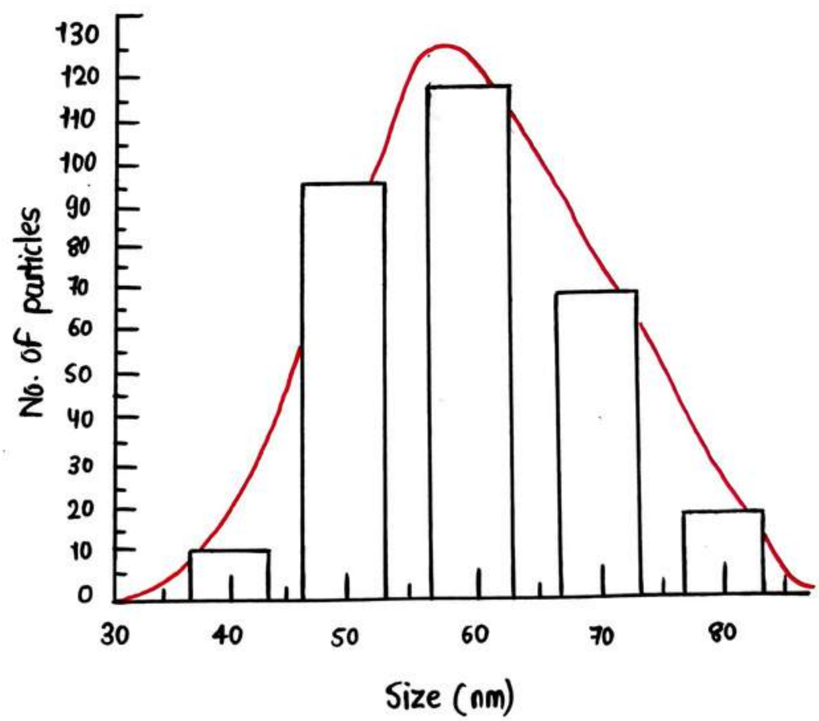
PARTICLE SIZE DISTRIBUTION

- Particle size distribution refers to the range and proportion of different particle sizes present in a powder or granular material.
- It gives information about how particles of various sizes are distributed in a sample.
- To visualize PSD, a Frequency Distribution Curve is used. It is a graph where:
  - The X-axis repressants particle size (in μm or nm).
  - The Y-axis repressants the frequency or percentage of particles of that size.



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MEAN PARTICLE SIZE

- Mean particle size is the average size of all particles in a sample.
- It gives a single value that repressants the central tendency of the particle size distribution.

$$\boxed{\text{Mean particle size} = \frac{\Sigma n \cdot d}{\Sigma n}}$$

Here, n = numbers of particles
d = particles diameter

EXAMPLES

S.N.	n	d	n.d.
1	5	2	10
2	10	3	30
3	12	5	60
4	15	6	90
5	13	10	130
	Σn = 55		Σnd = 320

$$\boxed{\text{Mean particle size}} = \frac{\Sigma nd}{\Sigma n} = \frac{320}{55} = 5.81$$

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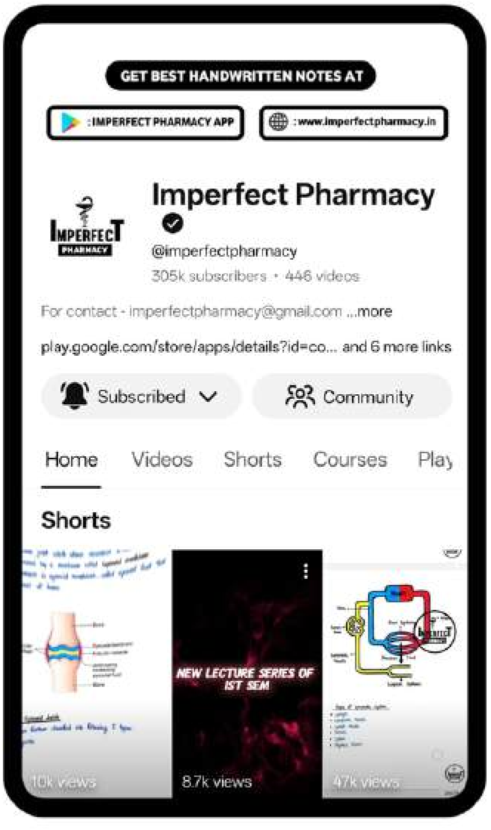

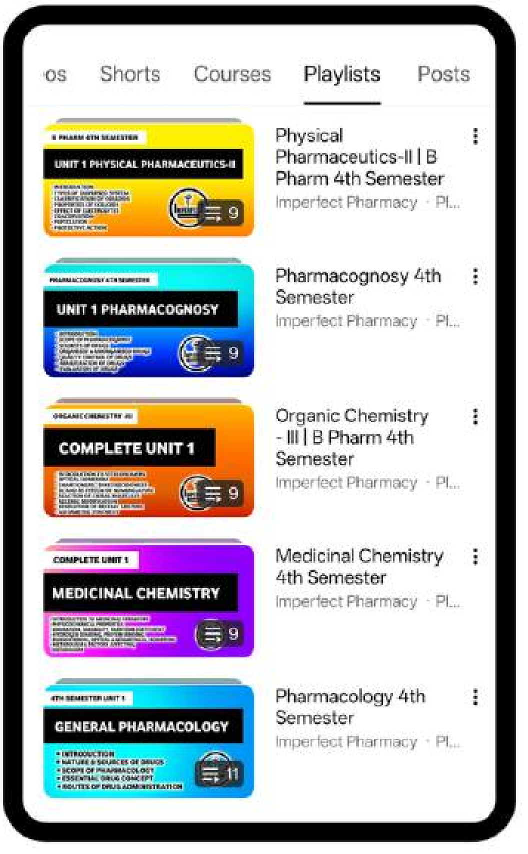

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METHOD FOR PARTICLE SIZE DETERMINATION

Particle size of a powder can be determine by various methods as follows:

① Separation methods
- Sieving method
- Sedimentation method

② Counting methods
- Microscopy (Optical, Electron)
- Conductivity (Coulter counter method)

③ Surface area determination
- Air permeability
- Adsorption Method

SEPARATION METHOD

- These are methods used to separate particles based on their size & then measure how much of each size is present.
- It invoes two methods:
  - Sieving method
  - Sedimentation method

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(a) SIEVE METHOD

Sieve method is a technique used to separate particles based on their size using a set of metal sieves with different-sized holes.

Working Mechanism

- A stack of sieves is arranged from top to bottom with decreasing hole size (biggest holes at the top, smallest at the bottom).
- A known amount of powder is placed on the top sieve.
- The stack is shaken or vibrated for a fixed time.
- Particle pass through the sieves based on their size:
  - Large particles stay on the top sieves.
  - Smaller particles go through and collect on lower sieves.
- The amount of powder on each sieve is weighed to find particle size distribution.

APPLICATION

- Powders with particle size > 38 microns
- Granules, tablet powders and industrial materials.

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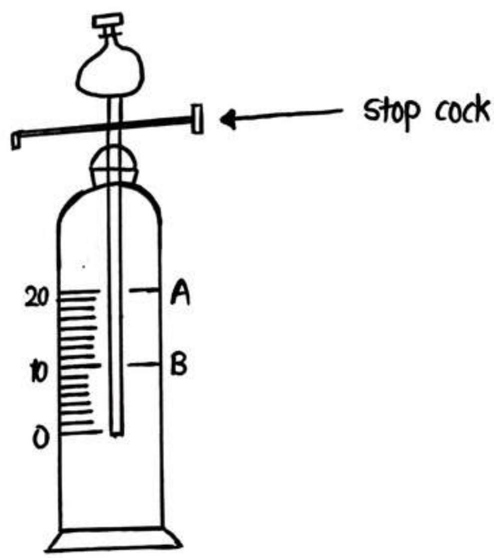
ⓑ SEDIMENTATION METHOD

It is a method to determine particle size based on how fast particles settle in a liquid, measured using a device called the Andreasen pipette.

PRINCIPLE

- Particles settle in a liquid under gravity.
- According to Stokes' Law, Larger particles settle faster, and smaller particles remain suspended longer.



Andreasen pipette

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PROCEDURE

- A known amount of powder is dispersed in liquid in a long cylinder.
- The suspension is throughouly shaken and then allowed to stand.
- At fixed time intervals (e.g., 5 min, 10 min), a sample is taken from a fixed depth using the Andreasen pipette.
- The sample is dried and weighed.
- The amount of settled particles is calculated and used to determine particle size by using given formula.

$$\boxed{d_{st} = \sqrt{\frac{18\eta}{(\rho_1 - \rho_2)g}\,\frac{h}{t}}}$$

Here, d_{st} - Stoke's diameter

h - distance of fall in time t

ρ_1 - density of particles

ρ_2 - density of dispersion medium

η - viscosity of medium

APPLICATIONS

- Used for fine powders (1 to 100 microns).
- Pharmaceutical suspensions, paints, inks etc.

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② COUNTING METHOD

- Counting methods involve counting the number of particles & measuring their sizes directly, usually using a microscope or an electronic counter.
- It involves two methods:
  - Microscopic method
  - Coulter counter method.

ⓐ MICROSCOPIC METHOD

In this method, a microscope is used to observe and measure indiuisual particles on a side.

PROCEDURE

- A small amount of powder is spread on a side.
- The particles are observed under a microscope (optical or electron).
- The diameter of each particle is measured using a calibrated eyepiece.

APPLICATIONS

- Used for small samples and irregular particles.
- Useful in research labs.

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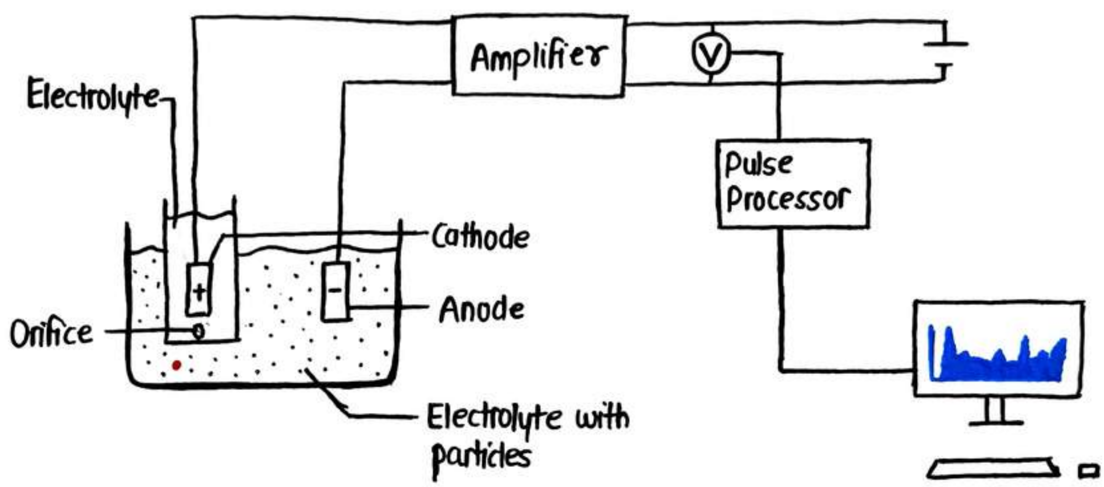
(b) Coulter Counter Method

This is an electronic method where particles suspended in an electrolyte are counted and sized as they pass through a tiny hole (orifice).

Principle

- When a particle passes through the hole, it displace electrolyte, causing a change in electrical resistance.
- This change is measured and used to count and size the particle.

Construction



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PROCEDURE

- Powder is dispersed in a conducting liquid.
- The liquid is passed through a small hole (orifice).
- Each particle passing through causes a pulse (change in resistance).
- The number and size of particles are recorded electronically.

APPLICATIONS

- Used for very fine powders/particles.
- Widely used in pharmaceuticals, blood cell counting.

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③ SURFACE AREA DETERMINATION

- In this we find out the total surface area of particles in a powder.
- Surface area is inversely related to particle size - smaller particles have a larger surface area.
- It can be determined by following two methods:
  - Adsorption Method
  - Air permeability Method

@ ADSORPTION METHOD

Adsorption method is used to determine the specific surface area of a powder by measuring how much gas or solute (from liquid) gets adsorbed onto the surface of its particles.

PRINCIPLE

- The amount of gas or solute adsorbed is directly proportional to the surface area of powder.
- The more the surface area, the more gas/solute will get absorbed.

TYPES

i) Gas Adsorption Method (e.g. BET Method)

- A dry gas like nitrogen is passed over the powder.
- The volume of gas adsorbed is measured.
- Based on this, surface area is calculated using BET Equation.

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$$\boxed{\frac{P}{V(P_o - P)} = \frac{1}{V_m b} + \frac{(b-1)P}{V_m b P_o}}$$

BET Equation

ii) Solute Adsorption Method

- Powder is added to a known concentration of solute in liquid (e.g. dye in water).
- After adsorption, the decrease in solute concentration is measured using a colorimeter or spectrophotometer.
- The amount adsorbed is used to calculate surface area.

(b) Air Permeability Method

Air permeability method is used to determine the specific surface area of a powder by measuring how easily air passes through a packed bed of a powder.

Principle

- When air is passed through a compressed powder bed, the flow rate and pressure drop depend on the surface area of the particles.
- Smaller particles (with larger surface area) offer more resistance to airflow.
- Using these values, surface area is calculated using the Kozeny-Carmen equation.

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KOZNEY-CARMAN EQUATION

$$\boxed{V = \frac{A}{\eta S_w^2} \cdot \frac{\Delta P t}{K l} \cdot \frac{\varepsilon}{(1-\varepsilon)^2}}$$

Where,

V = Volume of air flowing through the bed in t seconds (cm^3).

l = length of the capillary tube (cm).

A = Cross-section area of the bed (cm^2)

k = constant

ΔP = Pressure drop across the powder bed.

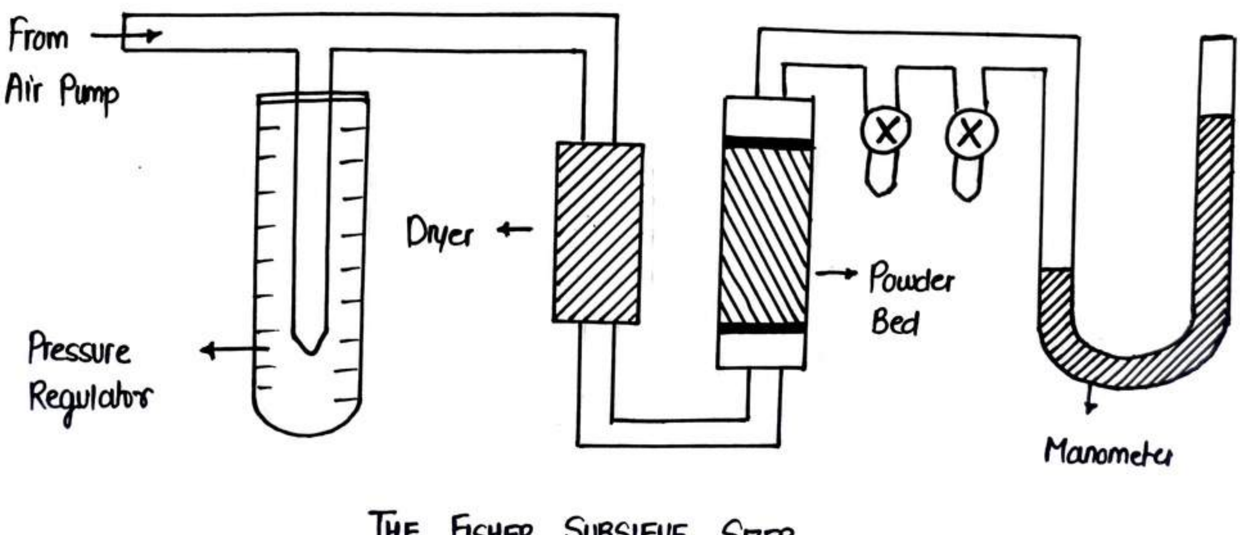
ε = Porosity of the powder = $\dfrac{V_b - V_p}{V_b}$

Here, V_b = Total volume of the bed

V_p = True volume of the powder bed.

η = Viscosity of the fluid (air) (Poise).

S_w = Specific surface area of the powder (cm^2/gm).



THE FISHER SUBSIEVE SIZER

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PROCEDURE

- A known amount of powder is packed tightly into a sample holder.
- Air is passed through it at a controlled rate.
- The pressure difference and air flow are measured.
- Surface area is calculated from these readings.

ADVANTAGES

- Simple and quick method.
- No need for special gases or complex setup.

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DERIVED PROPERTIES OF POWDERS

- Derived properties of powders are not directly measured but are calculated from basic (fundamental) properties like particle size, shape and density.
- These derived properties are important in pharmaceutical formulation, tablet manufacturing and powder flow studies.
- These properties includes :
  - Porosity
  - Packing arrangements
  - Densities
  - Bulkiness
  - Flow properties

DENSITIES

- In, micromeritics, densities are important derived properties used to understand the behaviour of powders in formulation, compaction, and flow.
- It is of following 3 types:
  - Bulk density
  - True density
  - Tapped density

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① BULK DENSITY

Bulk density is the mass of powder per unit volume, including the space between particles (voids).

Formula

$$\text{Bulk density} = \frac{\text{Mass of Powder}}{\text{Bulk Volume}}$$

Importance

- Indicates how powders fill a container.
- Affects flow, mixing and compaction.

② TRUE DENSITY

True density is the density of the actual solid material, excluding any voids or air spaces b/w particles.

Formula

$$\text{True density} = \frac{\text{Mass of Particles}}{\text{True Volume(only solid part)}}$$

Importance

- Used to calculate porosity.
- Remains constant for a material regardless of particle packing.

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③ Tapped Density

Tapped density is the density of the powder after mechanical tapping, which reduces the volume by settling the particles closer.

Formula

$$\boxed{\text{Tapped density} = \frac{\text{Mass of Powder}}{\text{Tapped Volume}}}$$

Importance

- Reflects packing ability of a powder.
- Used to calculate flow indices like Carr's Index and Hausner Ratio.

Property	Include Voids ?
Bulk density	Yes
True density	No
Tapped density	Yes (reduced)

POROSITY

- Porosity is the measure of void spaces (empty spaces) between particles in the powder.
- It indicates how much of the powder volume is not occupied by solid material.

Formula

$$\boxed{\text{Porosity } (\%) = \left(1 - \frac{\text{Bulk density}}{\text{True density}}\right) \times 100}$$

Explanation

- Bulk density: includes both the solid and void volume.
- True density: is the density of the only solid part.
- The difference tells us how much space is taken up by air or voids.

PACKING ARRANGEMENTS

- Packing arrangements refers to the way particles are arranged or packed together in a given space.
- It influents how tightly or loosely particles are packed, which affects porosity, density and flow of the powder.

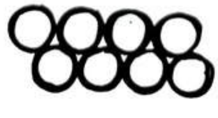
TYPES OF PACKAGING ARRANGEMENTS

① Cubic Packing (Loose Packing)

- Particles are arranged in a cube-like pattern.
- Porosity : High (~47.6 %)
- Packing fraction : ~52.4 % of the volume is occupied by particles.

② Rhombohedral / Hexagonal Packing (Tight Packing)

- Particles are arranged in a compact Hexagonal manner.
- Porosity : Low (~25.9 %)
- Packing fraction : ~ 74.1 %. of the volume is occupied by particles.



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Significance In Pharmaceutics

- Affects bulk density and porosity.
- Influences tablet compression and flowability.
- Loose packing → Poor flow but better compressability.
- Tight Packing → Better flow but harder to compress.

Bulkiness

- Bulkiness is the reciprocal of bulk density.
- It indicates the volume occupied by a unit mass of powder, including the void spaces b/w particles.

$$\boxed{\text{Bulkiness} = \frac{1}{\text{Bulk density}}}$$

Units

Usually expressed as ml/g or cm^3/g.

Significance In Pharmaceuticals

- Higher Bulkiness – lighter powder, occupies more volume
- Important for packaging, transport, and storage of powders.
- Affects tablet size, capsule filling, and dosage accuracy.

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Flow Properties Of Powders

- Flow properties of a powder refer to its ability to move or flow under specified conditions.
- These properties are essential in pharmaceutical & industrial process where powders must flow uniformly for operations like mixing, filling, tableting & encapsulation.

Factors Affecting Flow Properties

- Larger particles tend to have better flow due to reduced cohesive forces.
- Spherical particles generally flow more easily due to less friction. Particles with high moisture content tend to clump or adhere to each other.
- Higher difference b/w Bulk & Tapped density suggest poor flow & higher comperessibility.

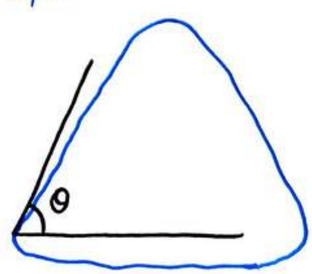
Measurement Of Flow Properties

Several methods are used to evaluate the flow properties of powders in preformulation studies.

(1) Angle Of Repose

The angle formed between horizontal surface & slope of a pile of a powder is known as angle of repose.

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



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Here, θ = Angle of repose
h = hieght
r = radius

Angle of repose < 30° = Excellent flow
Angle of Repose ~ 30°-40° = Good to fair flow
Angle of Repose > 40° = Poor flow

② CARR'S INDEX

Carr's index measures the compressibility of a powder by comparing the difference b/w tapped density & Bulk density.

$$\boxed{\text{CARR'S INDEX} = \frac{\rho_{Tapped} - \rho_{Bulk}}{\rho_{Tapped}} \times 100}$$

CARR'S INDEX (%)	FLOWABILITY
5-15	Excellent
16-20	Good
21-25	Fair
26-31	Poor
>32	Very poor

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③ Hausner Ratio

Hausner ratio is the ratio of tapped density to bulk density, indicating flow characteristics of powder.

$$\text{Hausner Ratio} = \frac{\rho_{Tapped}}{\rho_{Bulk}}$$

Hausner Ratio	Flowability
1.00 - 1.11	Excellent
1.12 - 1.18	Good
1.19 - 1.25	Fair
1.26 - 1.34	Poor
> 1.35	Very Poor

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