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PHYSICAL PHARMACEUTICS - II
UNIT 4

TOPIC :

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

Micromeritics

Micromeritics is the science that deals with the study of small particles, especially powders. It focuses on the characterization of particle size, shape, surface area, porosity, and flow properties.

Applications of Micromeritics in Pharmacy

1. **Improves Drug Dissolution Rate**
   - Smaller particles provide a larger surface area, leading to faster dissolution.
2. **Enhances Bioavailability**
   - Rapid dissolution improves drug absorption, increasing bioavailability.
3. **Ensures Uniform Mixing**
   - Uniform particle size allows even distribution of drug in formulations.
4. **Affects Flow Properties**
   - Good flow is essential for tablet and capsule manufacturing.
5. **Controls Drug Stability**
   - Proper particle size prevents sedimentation in suspensions and ensures stability.
6. **Improves Compressibility**
   - Influences tablet hardness and uniform weight during compression.

Particle Size

Particle size refers to the dimension or diameter of individual particles in a powdered material. It is usually expressed in micrometers (μm) or nanometers (nm).

Importance in Pharmacy:

- Determines physical and chemical properties of powders.
- Crucial for inhalation products to predict lung deposition in aerosol therapy.
- Influences dissolution, bioavailability, flow properties, and stability.

Particle Size of Non-Spherical Particles

Most pharmaceutical powders are non-spherical, so particle size is expressed using equivalent diameters:

1. **Surface Diameter (ds):**
   - Diameter of a sphere having the same surface area as the particle.
2. **Volume Diameter (dv):**
   - Diameter of a sphere having the same volume as the particle.
3. **Projected Diameter (dp):**
   - Diameter of a circle that has the same area as the 2D projection (shadow) of the particle.
4. **Stokes Diameter (dst):**
   - Diameter of a sphere that settles at the same rate as the particle in a fluid (used in sedimentation method).
5. **Sieve Diameter (dsieve):**
   - Diameter of a sphere that just passes through the same sieve opening as the particle.

Particle Size Distribution (PSD)

Particle size distribution refers to the range and proportion of different particle sizes present in a powder or granular material.

Purpose:

- Provides information on how particles of various sizes are distributed in a sample.
- Important for dissolution, flow properties, compressibility, and stability of formulations.

Visualization:

- PSD is typically visualized using a Frequency Distribution Curve:
  - **X-axis:** Particle size (μm or nm)
  - **Y-axis:** Frequency or percentage of particles of that size

Mean Particle Size

Mean particle size is the average size of all particles in a sample. It represents the central tendency of the particle size distribution.

$$\text{Mean particle size} = \frac{\sum (n \cdot d)}{\sum n}$$

Where:

- n = number of particles
- d = particle diameter

Methods for Particle Size Determination

Particle size of powders can be determined by three main categories of methods:

1. **Separation Methods**
2. **Counting Methods**

1. Separation Methods

These methods separate particles based on size and measure the amount of each fraction.

a) Sieve Method

- Technique to separate particles using a stack of metal sieves with decreasing hole sizes.
- **Procedure:**
    1. Arrange a stack of sieves (largest holes at the top).
    2. Place known amount of powder on the top sieve.
    3. Shake or vibrate for a fixed time.
    4. Particles pass through sieves according to size.
    5. Weigh powder retained on each sieve to determine particle size distribution.
- **Applications:**
    - Powders > 38 µm
    - Granules, tablet powders, and industrial materials

b) Sedimentation Method

- Determines particle size based on the rate of settling in a liquid.
- **Principle:**
    - According to Stokes' Law, larger particles settle faster, smaller particles remain suspended longer.
- **Apparatus:** Andreasen pipette

- **Procedure:**
    1. Disperse powder in a liquid in a long cylinder.
    2. Shake thoroughly and allow to settle.
    3. At fixed intervals, withdraw samples from a fixed depth.
    4. Dry, weigh, and calculate particle size using:

2. Counting Methods

Counting methods measure the number and size of particles directly.

a) Microscopic Method

- Uses a microscope to observe and measure individual particles.
- **Procedure:**
    1. Spread small amount of powder on a slide.
    2. Observe under optical/electron microscope.
    3. Measure diameter of each particle using a calibrated eyepiece.
- **Applications:** Small samples, irregular particles, research labs

b) Coulter Counter Method

- Electronic method where particles suspended in a conducting liquid are counted and sized as they pass through a tiny orifice.
- **Principle:**
    - Particles displace electrolyte, causing a measurable change in electrical resistance.
- **Procedure:**
    1. Disperse powder in a conducting liquid.
    2. Pass suspension through small orifice.
    3. Each particle generates a pulse (change in resistance).
    4. Number and size of particles are recorded electronically.
- **Applications:** Very fine powders, blood cell counting, pharmaceutical research

Surface Area Determination

Surface area determination is the measurement of the total surface area of particles in a powder. Smaller particles have larger surface area, which affects dissolution, bioavailability, and flow properties.

Methods:

1. **Adsorption Method**
2. **Air Permeability Method**

1. Adsorption Method

- Measures the specific surface area by determining how much gas or solute from a liquid adsorbs onto the surface of particles.
- **Principle:** The amount of adsorbed gas/solute is **directly proportional** to the surface area. Higher surface area → more adsorption.

Types:

1. **Gas Adsorption Method (e.g., BET Method)**
   - Dry gas (like nitrogen) is passed over the powder.
   - Volume of gas adsorbed is measured.
   - Surface area is calculated using BET Equation:

$$\frac{P}{V(P_0 - P)} = \frac{1}{V_m C} + \frac{(C-1)P}{V_m C P_0}$$

V_m = monolayer gas volume, P = equilibrium pressure, P_0 = saturation pressure, C = constant

2. **Solute Adsorption Method**
    - Powder is added to a known concentration of solute (e.g., dye in water).
    - After adsorption, decrease in solute concentration is measured (colorimeter/spectrophotometer).
    - Surface area is calculated from the amount adsorbed.

2. Air Permeability Method

- Determines specific surface area by measuring how easily air passes through a packed bed of powder.
- **Principle:**
    - Air flow rate and pressure drop depend on particle surface area.
    - Smaller particles (larger surface area) → higher resistance to airflow.
- **Equation (Kozeny-Carman Equation):**

$$v = \frac{A}{n_m^2} \cdot \frac{\Delta Pt}{k} \cdot \frac{\varepsilon}{(t - \varepsilon)^2}$$

Where:

- v = volume of air through the bed in time t
- A = cross-sectional area of bed
- k = constant
- ΔP = pressure drop
- ε = porosity of powder bed ($\frac{V_b - V_p}{V_b}$)
- V_b = total volume of bed, V_p = true volume of powder
- η = viscosity of air
- S_w = specific surface area

Procedure:

1. Pack known amount of powder into a holder.
2. Pass air at controlled rate.
3. Measure pressure difference and airflow.
4. Calculate surface area using Kozeny-Carman equation.

Advantages:

- Simple and quick
- No special gases or complex setup required

Derived Properties of Powders

Derived properties are calculated from fundamental properties like particle size, shape, and density rather than being measured directly.
These properties are essential in pharmaceutical formulation, tablet manufacturing, and flow studies.

Common Derived Properties Include:

- Porosity
- Packing arrangements
- Densities
- Bulkiness
- Flow properties

DENSITIES

Densities are key derived properties in micromeritics, used to understand powder behavior in formulation, compaction, and flow.

Three Types of Densities:

1. Bulk Density

- Mass of powder per unit volume including void spaces between particles.

Formula:

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

- **Importance:**
  - Indicates how powders fill a container
  - Affects flow, mixing, and compaction
- **Voids included:** Yes

2. True Density

- Density of the actual solid material, excluding air spaces between particles.

Formula:

$$\text{True Density} = \frac{\text{Mass of Particles}}{\text{True Volume of Particles}}$$

- **Importance:**
  - Used to calculate porosity
  - Remains constant regardless of particle packing
- **Voids included:** No

3. Tapped Density

- Density of the powder after mechanical tapping, which reduces volume by settling the particles closer.

Formula:

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

- **Importance:**
    - Reflects packing ability of a powder
    - Used to calculate flow indices like Carr's Index and Hausner Ratio
- **Voids included:** Yes (reduced)

Porosity

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

Formula:

$$\text{Porosity (\%)} = \left(\frac{\text{Tapped or Bulk Volume - True Volume}}{\text{Tapped or Bulk Volume}}\right) \times 100$$

Or equivalently:

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

Explanation:

- Bulk density includes both solid and void volume.
- True density accounts for solid material only, excluding voids.
- The difference between true density and bulk density reflects the volume occupied by air or void spaces.

Importance in Pharmaceuticals:

- Helps in flow and packing behavior of powders.
- Affects tablet compression and uniformity of dosage forms.
- Influences dissolution rate and bioavailability.

Packing Arrangements

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

Types of Packing Arrangements

1. **Cubic Packing (Loose Packing)**
   - Particles arranged in a cube-like pattern**.**
   - **Porosity:** High (~47.6%)
   - **Packing fraction:** 52.4% of the volume is occupied by particles.
   - **Flow & Compressibility:** Poor flow, better compressibility.
2. **Rhombohedral/Hexagonal Packing (Tight Packing)**
   - Particles arranged in a compact hexagonal pattern**.**
   - **Porosity:** Low (~25.9%)
   - **Packing fraction:** 74.1% of the volume is occupied by particles.
   - **Flow & Compressibility:** Better flow, harder to compress.

Significance in Pharmaceuticals

- Affects bulk density and porosity.
- Influences tablet compression and powder flowability.
- Loose packing: Poor flow, better compressibility.
- Tight packing: Better flow, more difficult 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 between particles.

$$\text{Bulkiness} = \frac{1}{\text{Bulk Density}}$$

Units: Usually expressed as mL/g or cm^3/g

Significance in Pharmaceuticals

- Higher bulkiness: Powder is lighter and occupies more volume.
- Important for packaging, transport, and storage of powders.
- Influences tablet size, capsule filling, and dosage accuracy.

Flow Properties of Powders

Flow properties of a powder refer to its ability to move or flow under specified conditions.

Importance in Pharmaceuticals:

- Essential in processes like tablet compression, capsule filling, and powder mixing.
- Ensures uniformity in dosage forms and smooth manufacturing operations.

Factors Affecting Flow Properties

1. **Particle Size:** Larger particles flow better due to reduced cohesive forces.
2. **Particle Shape:** Spherical particles flow more easily due to less friction.
3. **Moisture Content:** High moisture causes clumping and poor flow.
4. **Density Difference:** Higher difference between bulk density and **tapped density** indicates poor flow but higher compressibility.

Measurement of Flow Properties

1. Angle of Repose (θ)

- The angle formed between a horizontal surface and the slope of a powder pile.

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

- **h:** height of powder pile
- **r:** radius of base

Angle of Repose (θ)	Flowability
< 30°	Excellent
30–40°	Good to Fair
> 40°	Poor

2. Carr's Index (Compressibility Index)

- Measures compressibility by comparing bulk and tapped densities.

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Carr's Index (%)	Flowability
5–15	Excellent
16–20	Good
21–25	Fair
26–31	Poor
> 32	Very Poor

3. Hausner Ratio

- Indicates flow characteristics by comparing tapped density to bulk density.

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

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