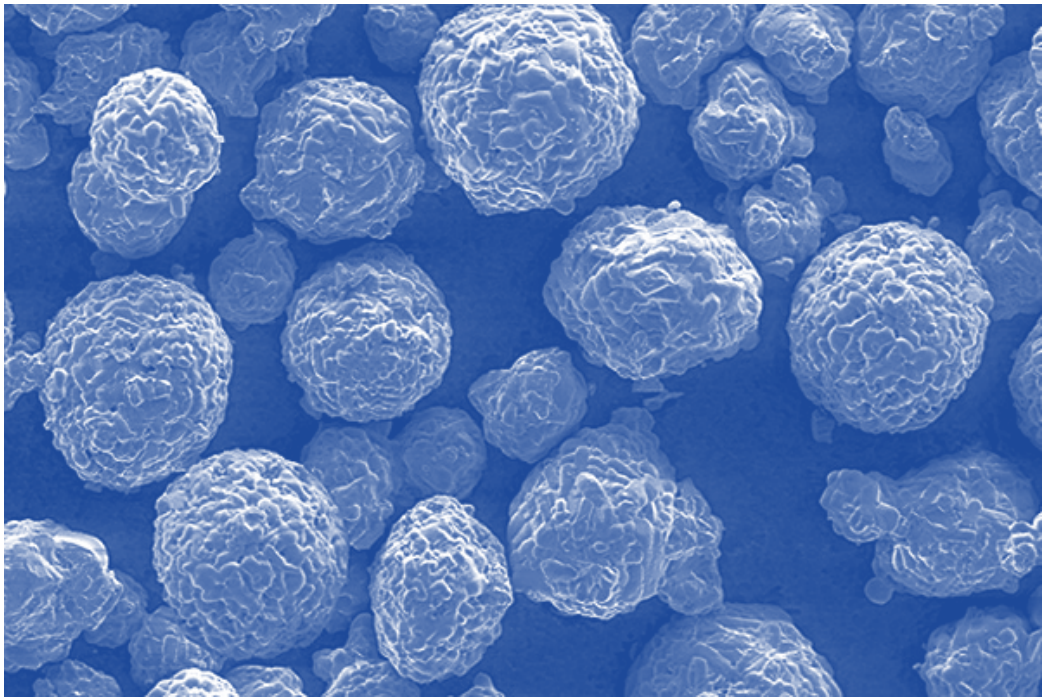
University of Kerbala

Physical Pharmacy

Lecture 6

# Particle Size Analysis



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# Overview

## Particle Size and Size Distribution

- Equivalent Spherical Diameter
- Particle Size Distribution
- Average Particle Size

## Methods for Particle Size Measurement

- Optical Microscopy
- Sieving
- Sedimentation
- Particle Volume Measurement

## Other Particle Properties

# Learning Objectives

1. Understand the concept of particle size and their impact on pharmaceutical processing/preparation.
2. Be familiar with the units for particle size, area, and volume and typical calculations.
3. Describe how particles can be characterized and why these methods are important.
4. Discuss the methods for determining particle size.
5. Discuss the role and importance of particle shape and surface area.
6. Understand the methods for determining particle surface area.
7. State other fundamental properties for any collection of particles.

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# Particle size and Size Distribution

Importance of Particle Size
Equivalent Spherical Diameter
Particle Size Distribution
Average Particle Size

# Importance of Particle Size

Particle size of drugs in pharmaceutical products can affect:

1. The release of drugs from dosage forms that are administered orally, parenterally, rectally, and topically.
2. The physical stability and pharmacologic response of suspensions, emulsions, and tablets.
3. Flow properties and mixing of granules and powders in tablet and capsule manufacture.

# Equivalent Spherical Diameter

For asymmetrical particles, *equivalent spherical diameter* is used to express the particle size:

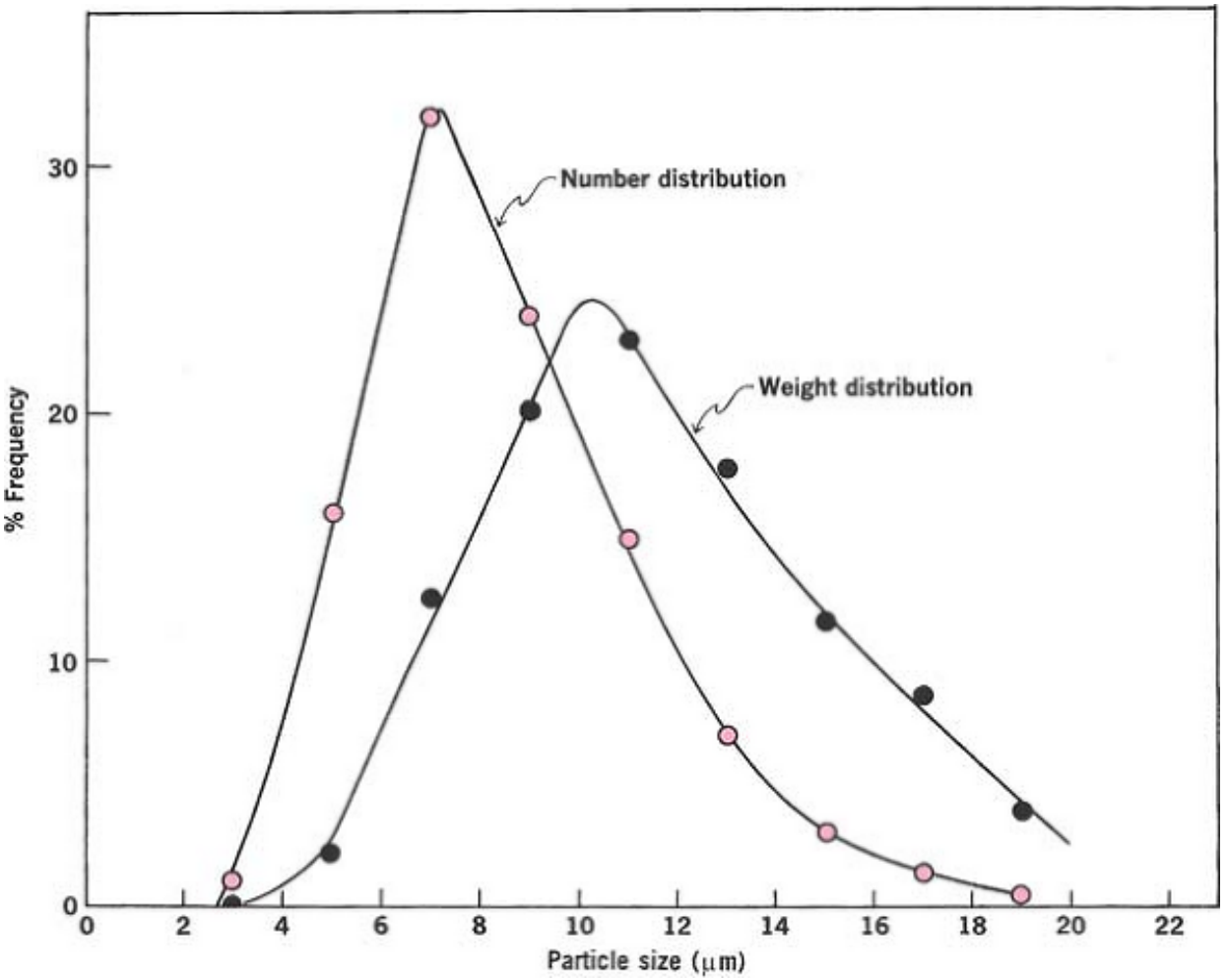
1. ***Surface diameter (ds)*:** the diameter of a sphere having the same surface area as the particle.
2. ***Volume diameter (dv)*:** the diameter of a sphere having the same volume as the particle.
3. ***Projected area diameter (dp)*:** the diameter of a sphere having the same projected area as the particle when viewed normal to its most stable plane.
4. ***Stokes diameter (dst)*:** the diameter of a sphere undergoing sedimentation at the same rate as the particle.

# Particle Size Distribution

Particles are usually polydisperse; therefore, the size range of the particles and the number or weight fraction of each particle size need to be determined (this is called *particle-size distribution*).

When the number or weight fraction of each particle size is plotted against the size range, a *frequency distribution curve* is obtained.

# Particle Size Distribution




Frequency distribution curve

# Average Particle Size

The average particle size ($\boldsymbol{d_{mean}}$) can be determined by *Edmundson equation*:

$$\boldsymbol{d_{mean}} = \left( \frac{\Sigma \boldsymbol{n d^{p+f}}}{\Sigma \boldsymbol{n d^{f}}} \right)^{1/p}$$

$\boldsymbol{n}$ = number of particles in a certain size range

$\boldsymbol{d}$ = midpoint of certain particle size range

$\boldsymbol{p}$ = index related to the size of the individual particles

$\boldsymbol{f}$ = frequency index

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# Methods for Particle Size Measurement

Optical Microscopy
Sieving
Sedimentation
Particle Volume Measurement

# Methods for Particle Size Measurement

The most widely used methods in pharmaceutical practice for particle size measurement include:

1. **Optical Microscopy**
2. **Sieving**
3. **Sedimentation**
4. **Particle volume measurement**

The choice of methods depends on:

1. Size range required to be measured
2. Precision required
3. Quantity of sample to be analysed
4. Whether particle shape/image is required

# Optical Microscopy

For particle-size measurement in the range of 0.2 to about 100 μm.

A suspension of particles is mounted on a ruled slide and placed on a mechanical stage. The microscope eyepiece is fitted with a micrometer by which the size of the particles can be estimated.

Electronic scanners have been developed to remove the necessity of measuring the particles by visual observation.

# Optical Microscopy

## Advantages

1. Can detect the presence of agglomerates and particles of more than one component.
2. Can determine particle shape.

## Disadvantages

1. The diameter is obtained from only two dimensions of the particle: length and breadth, No depth (thickness).
2. Need high number of particles to be counted (300–500) to obtain a good estimation of particle size distribution which makes the method slow and tedious.

# Sieving

For coarse particles (44 to 125,000 μm)

The sample is placed on the top of series of standard sieves in a mechanical shaker. The powder is shaken for a definite period of time, and the material that passes through one sieve and is retained on the next finer sieve is collected and weighed.

# Sieving
## Disadvantages

1. Sieving errors can arise from a number of variables including:
   a) Sieve loading
   b) Duration of agitation
   c) Intensity of agitation.
2. Sieving can cause attrition of granular pharmaceutical materials.
3. Need large volumes of samples
4. Very small particle size (< 5 μm) can not be measured.

# Sedimentation

Different particle sizes settle at different rates through a suspending medium; therefore, the particle size in the subsieve range (0.5-44 μm) can be obtained by gravity sedimentation as expressed in **Stokes's law**:

$$v = \frac{h}{t} = \frac{d_{st}^2 (p_s - p_0) g}{18\, \eta_0}$$

$$d_{st} = \sqrt{\frac{18\, \eta_0 h}{(p_s - p_0) g t}}$$

$v$ = rate of settling; $h$ = distance; $t$ = time; $d_{st}$ = mean particles diameter

$\rho_s$ = density of the particles; $\rho_0$ = density of the dispersion medium

$g$ = acceleration due to gravity; $\eta_0$ = viscosity of the medium

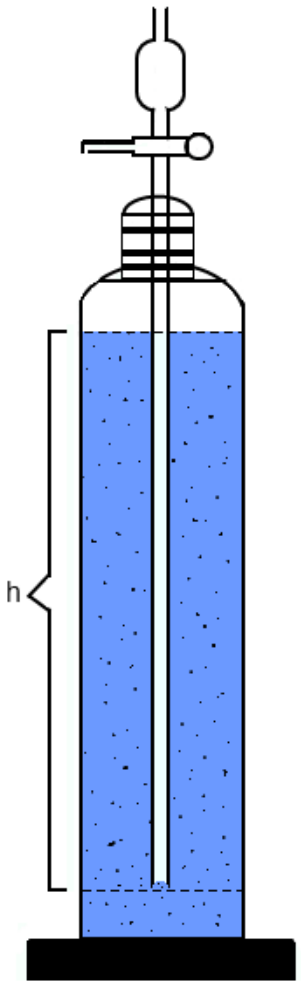
# Sedimentation

The Andreasen apparatus is based on the principle of sedimentation

It consists of a vessel containing a 10 mL pipette. The apparatus is clamped securely in a constant-temperature bath.

A 1% or 2% suspension of particles in a medium containing a deflocculating agent **(why?)** is placed into the vessel and shaken to distribute the particles.

At various time intervals, 10 mL samples are withdrawn, then evaporated and weighed.




## Advantages of Andreasen Pipette

Ease of analysis, accuracy, and low cost

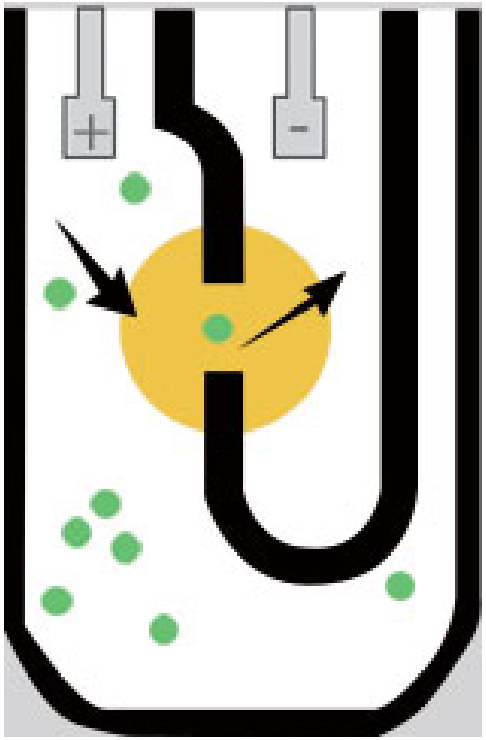
# Particle Volume Measurement

A popular instrument for measuring the volume of particles is the Coulter counter

The particle diameter measurement range is (0.1 - 1000) μm.

When a particle suspended in a solution containing electrolytes passes through a small orifice between two electrodes, it generates an increased resistance between the two electrodes.

Such a change is proportional to the volume of the particle as the particle displace its own volume of electrolytes.



# Other Particle Properties

Particle Shape and Surface Area
Porosity
Density

# Particle Shape and Surface Area

The shape and the surface area of a particle can affect:

1. Flow and packing properties of a powder (affected by particle shape).
2. Surface adsorption and dissolution rate studies (affected by particle surface area).

***Specific surface*:** is the surface area per unit volume, $S_v$, or per unit weight, $S_w$.

$$S_v = \frac{surface\ area\ of\ particles}{volume\ of\ particles}$$

$$S_w = \frac{surface\ area\ of\ particles}{weight\ of\ particles}$$

$$S_v = Sw \times d$$

$d$: true density of the particles

# Particle Shape and Surface Area

## Surface Area Measurement

### *Adsorption method*

The amount of gas or liquid adsorbed onto the sample of powder to form a monolayer is a direct function of the surface area of the sample. The larger the specific surface, the greater is the amount of adsorption.

### *Air permeability method*

The rate at which a gas or liquid permeates a bed of powder is related to the surface area exposed to the permeant. The greater the specific surface, the greater is the resistance to air flow.

# Porosity

Suppose a powder, such as zinc oxide, is placed in a graduated cylinder and the total volume is noted. The volume occupied is known as the *bulk volume* ($V_b$).

The bulk volume of the powder consists of the *true volume* ($V_p$) of the solid particles plus the volume of the spaces between the particles. The volume of the spaces, known as the *void volume* ($v$), is given by the equation:

$$v = V_b - V_p$$

***Porosity*** or ***voids*** (**ε**) of the powder is defined as the ratio of the void volume to the bulk volume of the packing:

$$\varepsilon = \frac{v}{V_b} = \frac{V_b - V_p}{V_b}$$

**(**Porosity is frequently expressed in percent, $\varepsilon \times 100$)

# Porosity
## Example

**A sample of calcium oxide powder with a true density of 3.203 and weighing 131.3 g was found to have a bulk volume of 82.0 cm³ when placed in a 100 mL graduated cylinder. Calculate the porosity.**

The volume of the particles is

$V = 131.3/3.203 = 41\ cm^3$

The porosity is

$$\varepsilon = \frac{V_b - V_p}{V_b} = \frac{82 - 41}{82} = 0.5 \text{ or } 50\ \%$$

# Density

*Density* is defined as weight per unit volume.

It is difficult to determine the volume of particles containing microscopic cracks, internal pores, and capillary spaces.

Three types of densities can be defined:

## True Density

***True density*** is the density of the material itself, exclusive of the voids and internal pores in the crystal lattices.

It can be calculated by dividing the mass of the powder by its true volume

It can be measured by helium pycnometer, where the volume occupied by a known mass of powder is determined by measuring the volume of the gas displaced by the powder.

# Density

## Bulk Density

***Bulk density*** is the mass of the powder divided by its bulk volume (which is measured by graduated cylinder)

## Granule Density

***Granule density*** is the mass of the powder divided by the volume of the particles together with their internal pores

It is determined by a method similar to true density. Mercury is used because it fills the void spaces but fails to penetrate into the internal pores of the particles.

# References

Sinko, P. J. M. A. N. 2006. *Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences,* Philadelphia, Lippincott Williams & Wilkins.