Physical Pharmacy II
2nd stage
College of Pharmacy

lec: 9
MICROMERITICS

By : Dr. Nizar Awish Jassem
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MICROMERITICS

- Knowledge and control of the size and the size range of particles are of profound importance in pharmacy.
- Clinically, **the particle size of a drug** can affect its release from dosage forms that are administered orally, parenterally, rectally, and topically.
- The successful formulation of suspensions, emulsions, and tablets, from the viewpoints of both physical stability and pharmacologic response, also depends on the particle size achieved in the product.

Particle size and size distribution

- In a collection of **particles of more than one size** (polydisperse sample), two properties are important, namely
  a. the **shape and surface area** of the **individual** particles and
  b. the **size range and number** or weight of **particles** present and, hence, **the total surface area**.
- The **size of a sphere** is readily expressed in terms of its **diameter**.
- As the degree of **asymmetry of particles** **increases**, however, so does the **difficulty of expressing size** in terms of a **meaningful diameter**.
  - Under these conditions, there is **no one unique diameter for a particle.**
  - So we use the idea of an **equivalent spherical diameter**, which *relates the size of the particle to the diameter of a sphere having the same surface area, volume, or diameter*.
- **The surface diameter**, **ds**, is *the diameter of a sphere having the same surface area as the particle in question.*
- *The diameter of a sphere having the same volume as the particle is the* **volume diameter**, **dv** .
- **The size** can also be expressed as the **Stokes diameter**, **dst**, which describes an equivalent sphere undergoing sedimentation at the same rate as the asymmetric particle.

Particle size and size distribution

- Key concept:
  - The science and technology of small particles was given the name **micromeritics** by *Dalla Valle*.
  - Colloidal dispersions are characterized by particles that are too small to be seen in the **ordinary microscope**, whereas the particles of pharmaceutical emulsions and suspensions and the —fines of powders fall in the range of the **optical microscope**.
  - Particles having the size of coarser powders, tablet granulations, and granular salts fall within the **sieve range**.
  - The unit of particle size used most frequently in micromeritics is the micrometer, μm, also called the micron, μ, and equal to 10^{-6} m, 10^{-4} cm, and 10^{-3}mm.
  - Any collection of particles is usually **polydisperse**.
  - It is therefore necessary to know not only the size of a certain particle but also how many particles of the same size exist in the sample.
  - Thus we need an estimate of the **size range** present and the **number or weight fraction** of each particle size.
  - This is the **particle-size distribution**, and from it we can calculate an average particle size for the sample.

- **Edmundson** derived a general equation for the average particle size

$$d_{mean} = \left(\frac{\sum nd^{p+f}}{\sum nd^{f}} \right)^{1/p} \qquad (18\text{–}1)$$

- In equation (18–1), **n** is the **number of particles** in a size range whose **midpoint**, **d**, is one of the equivalent diameters mentioned previously.
- The term **p** is an **index** related to the size of an individual particle, because d raised to the power p = 1, p =2, or p = 3 is an expression of the particle length, surface, or volume, respectively.
- **The value of the index p** also decides whether the mean is arithmetic (p is positive) , geometric (p is zero), or harmonic (p is negative).
- When the frequency index, f, has values of 0, 1, 2, or 3, then the size frequency distribution is expressed in terms of the total number, length, surface, or volume of the particles, respectively.

- **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, a so-called is obtained. frequency distribution curve
- Typical examples are shown in Figures 18–1.
- Such plots give a visual representation of the distribution that an average diameter **cannot** achieve.
- This is important because it is possible to have **two samples** with the same average diameter but **different distributions**

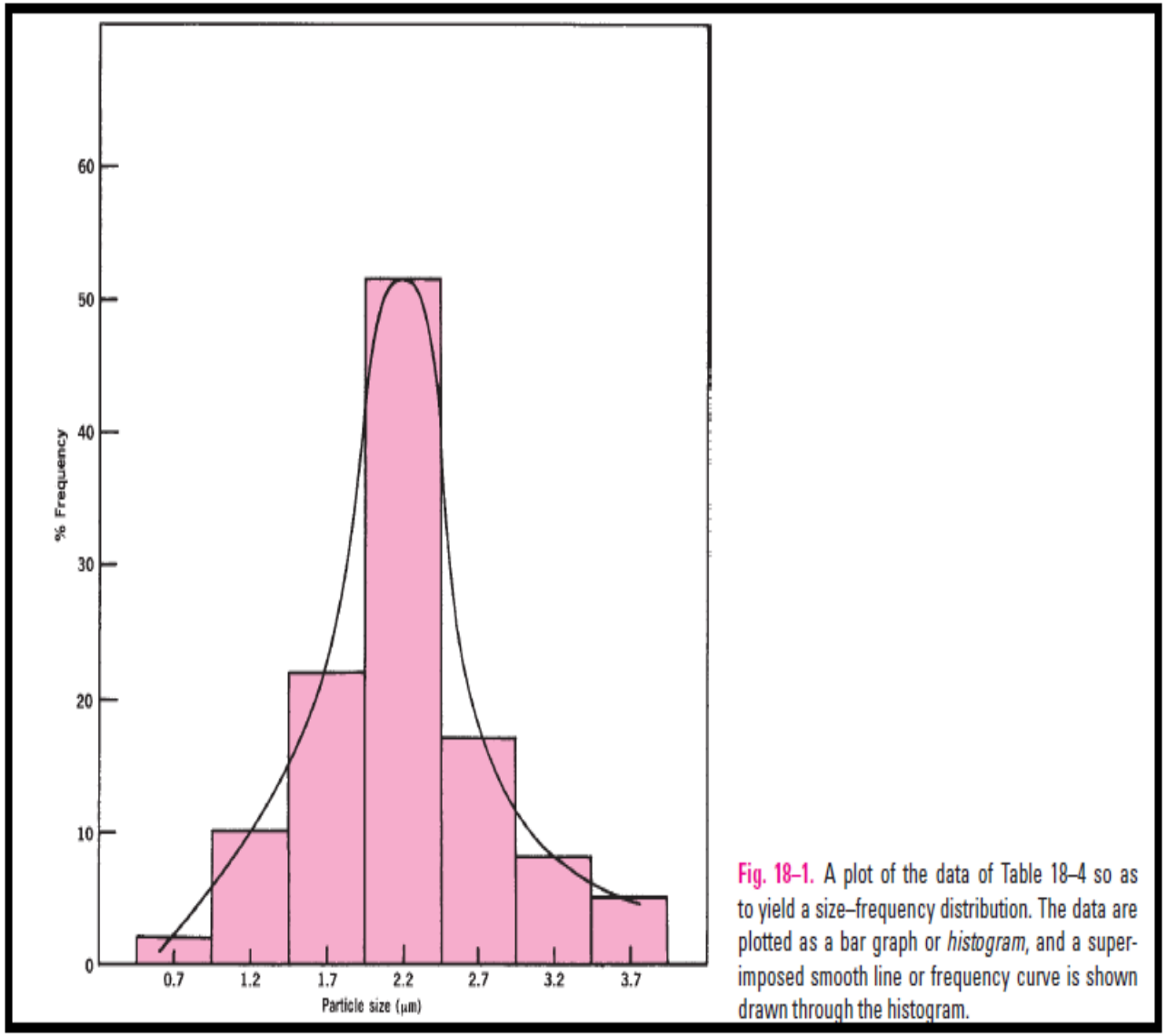

Fig. 18–1. A plot of the data of Table 18–4 so as to yield a size–frequency distribution. The data are plotted as a bar graph or *histogram*, and a superimposed smooth line or frequency curve is shown drawn through the histogram.

Methods of determining particle size

- Many methods are available for **determining particle size**; **Microscopy, sieving, sedimentation.**
- **None** of the measurements are **truly direct methods**.
- Although the **microscope** allows the observer to view the actual particles, the results obtained are probably **no more —direct** than those resulting from other methods because *only two of the three particle dimensions are ordinarily seen*.
- The **sedimentation methods** yield a *particle size relative to the rate at which particles settle through a suspending medium*.
- However, the technique gives **no information** as to the shape of the particles.
- Thus, in all these cases, the size may or may not compare with that obtained by the microscope or by other methods.

Methods of determining particle size

Optical Microscopy:

- It should be possible to use the **ordinary microscope** for particle-size measurement in the range of 0.2 to about 100 μm.
- According to the microscopic method, The microscope eyepiece is fitted with a micrometer by which the size of the particles can be estimated.
- **The particles** are *measured along an arbitrarily chosen fixed line*, generally made **horizontally** across the center of the particle.
- **A disadvantage of the microscopic method** is that the diameter is obtained from only two dimensions of the particle: length and breadth.
- **No** estimation of the **depth** (thickness) of the particle is ordinarily available.
- In addition, **the number of particles that must be counted** (300–500) to obtain a good estimation of the distribution makes the method somewhat slow and tedious.
- Nonetheless, microscopic examination (photomicrographs) of a sample should be **undertaken** even when other methods of particle-size analysis are being used, because the presence of agglomerates and particles of more than one component may often be detected

Methods of determining particle size

Sieving:

- This method uses a series of standard sieves.
- Sieves are generally used for grading coarser particles; if extreme care is used, however, *they can be employed for screening material as fine as 44 µm*.
- According to the method of the U. S. Pharmacopeia for testing powder fineness, a mass of sample is placed on the proper sieve 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 errors** can arise from a number of variables including sieve loading and duration and intensity of agitation.
- Sieving can cause attrition of granular pharmaceutical materials.
- Care must be taken, therefore, to ensure that reproducible techniques are employed so that different particle-size distributions between batches of material are not due simply to different sieving conditions.

Methods of determining particle size

Sedimentation:

- The particle size in the subsieve range can be obtained by gravity sedimentation as expressed in Stokes's law,

$$v = \frac{h}{t} = \frac{d_{st}^2(\rho_s - \rho_0)g}{18\eta_0} \qquad (18\text{–}5)$$

or

$$d_{st} = \sqrt{\frac{18\eta_0 h}{(\rho_s - \rho_0)gt}} \qquad (18\text{–}6)$$

where **v** is the rate of settling, h is the distance of fall in time **t**, **dst** is the mean diameter of the particles based on the velocity of sedimentation, ρ_s is the density of the particles and ρ_0 that of the dispersion medium, **g** is the acceleration due to gravity, and η_0 is the viscosity of the medium

- The equation holds exactly **only** for spheres falling freely with out hindrance and at a constant rate. Is applicable to irregularly shaped particles as long as one realizes that the diameter obtained is a relative particle size equivalent to that of sphere falling at the same velocity as that of the particles under consideration.
- The **particles** must not be aggregated or clumped together in the suspension because such clumps would fall more rapidly than the individual particles and erroneous results would be obtained.

- **Example**; 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 7.30×10^{-3} ; 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.

We have

$$d_{st} = \sqrt{\frac{18\eta_0 h}{(\rho_s - \rho_0)gt}}$$

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

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

Particle shape and surface area

- Knowledge of the shape and the surface area of a particle is desirable. **The shape affects** the flow and packing properties of a powder as well as having some influence on the surface area.
- **The surface area** per unit weight or volume is an important characteristic of a powder, as the surface area increases the **solubility** increases.
- **Particle Shape**; A **sphere** has minimum surface area per unit volume.
- **The more asymmetric** a particle, the greater is the surface area per unit volume.
- A spherical particle is characterized completely by its diameter.
- As the particle becomes **more asymmetric**, it becomes **increasingly difficult to assign a meaningful diameter** to the particle—hence, as we have seen, the need for equivalent spherical diameters.

Particle shape and surface area

- It is a simple matter to obtain the surface area or volume of a sphere because for such a particle

$$\text{Surface area} = \pi d^2 \qquad (18\text{–}10)$$

where d is the diameter of the particle.

Specific Surface; is the surface area per unit volume, Sv, or per unit weight, Sw,

$$S_v = \frac{\text{Surface area of particles}}{\text{Volume of particles}} \qquad (18\text{–}14)$$

Methods for determining surface area

- The surface area of a powder sample can be computed from knowledge of the particle-size distribution obtained using one of the methods outlined previously.
- Two methods are commonly available that permit direct calculation of surface area.
  - **In the first**, the amount of a gas or liquid solute that is adsorbed onto the sample of powder to form a monolayer is a direct function of the surface area of the sample.
  - **The second method** depends on the fact that the rate at which a gas or liquid permeates a bed of powder is related to the surface area exposed to the permeant.
- **Adsorption Method**; Particles with a large specific surface are good adsorbents for the adsorption of gases and of solutes from solution.
  - In determining the surface of the adsorbent, the volume in cubic centimeters of gas adsorbed per gram of adsorbent can be **plotted** against the pressure of the gas at constant temperature.
- **Air Permeability Method**; The principal resistance to the flow of a fluid such as air through a plug of compacted powder is the surface area of the powder.
  - The greater is the surface area per gram of powder, Sw, the greater is the resistance to flow.
  - Hence, for a given pressure drop across the plug, permeability is inversely proportional to specific surface; measurement of the former provides a means of estimating this parameter

Derived properties of powders

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.
- If the powder is nonporous, **the bulk volume** of the powder consists of the true volume 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;

$$v = V_b - V_p \qquad (18\text{–}25)$$

where Vp is the true volume of the particles.

- **The porosity or voids ε** of the powder is defined as *the ratio of the void volume to the bulk volume of the packing:*

$$\varepsilon = \frac{V_b - V_p}{V_b} = 1 - \frac{V_p}{V_b} \qquad (18\text{–}26)$$

- Porosity is frequently expressed in percent, ε × 100.

Example, Calculate Porosity:

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 cm^3 when placed in a 100 mL graduated cylinder. Calculate the porosity.

The volume of the particles is

$$131.3\ g/(3.203\ g/cm^3) = 41.0\ cm^3$$

From equation (18–25), the volume of void space is

$$v = 82.0\ cm^3 - 41.0\ cm^3 = 41.0\ cm^3$$

and from equation (18–26) the porosity is

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

packing arrangements

- Powder beds of uniform-sized spheres can assume either of two ideal packing arrangements:
  a. closest or rhombohedral
  b. most open, loosest, or cubic packing
- **The theoretical porosity** of a powder consisting of uniform spheres in closest packing is 26% and for loosest packing is 48%.
- The arrangements of spherical particles in closest and loosest packing are shown in Figure 18–16

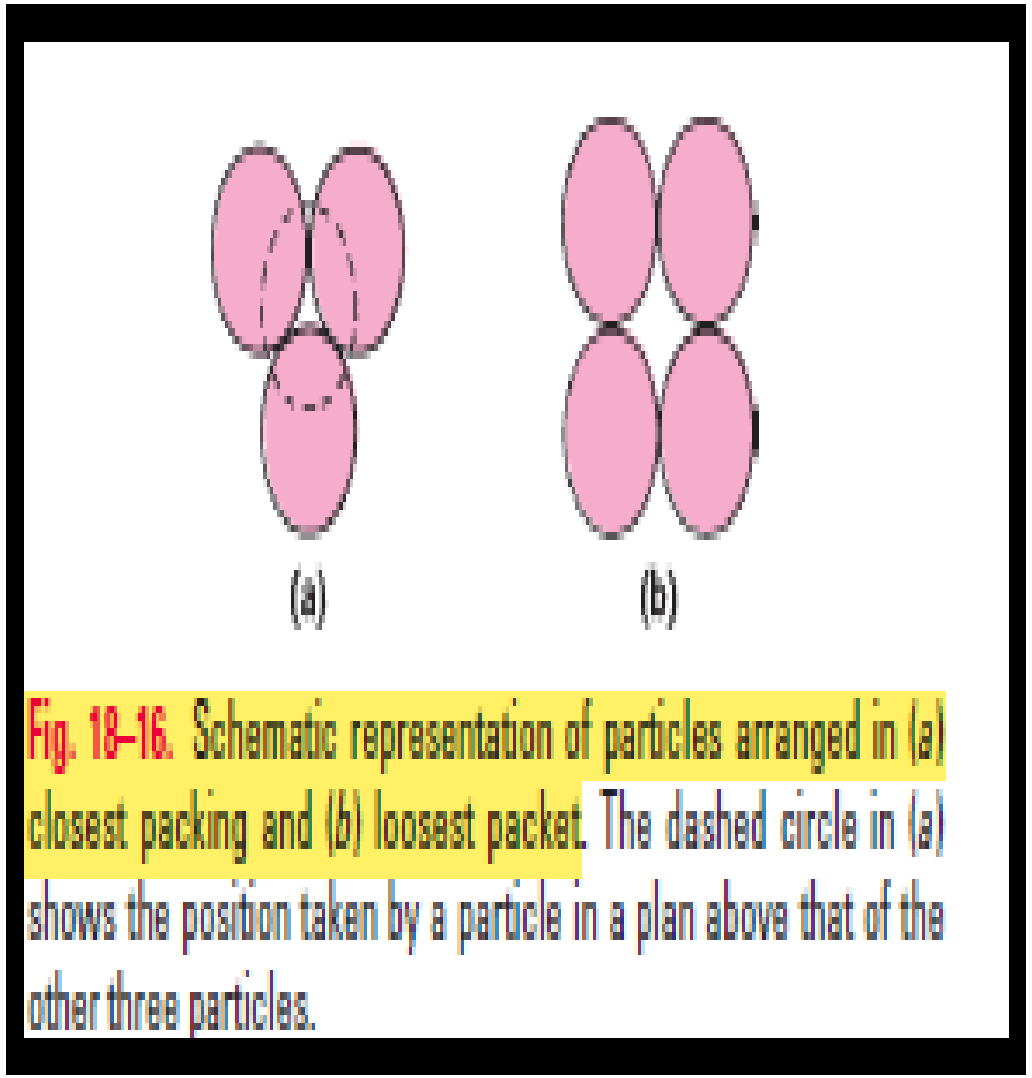

Fig. 18–16. Schematic representation of particles arranged in (a) closest packing and (b) loosest packet. The dashed circle in (a) shows the position taken by a particle in a plan above that of the other three particles.

packing arrangements

- **The particles** in real powders are **neither** spherical in shape **nor** uniform in size.
- It is to be expected that the particles of ordinary powders may have any arrangement **intermediate** between the two ideal packings of Figure 18–16, and most powders in practice have porosities between 30% and 50%.
  - **If the particles are of greatly different sizes**, however, the smaller ones may shift between the larger ones to give porosities **below the theoretical minimum of 26%.**
  - **In powders containing flocculates or aggregates**, which lead to the formation of bridges and arches in the packing, the porosity may be **above the theoretical maximum of 48%.**
  - In real powder systems, then, almost any **degree of porosity is possible.**
  - **Crystalline materials compressed** under a force of 100,000 lb/in^2 can **have porosities of less than 1%.**

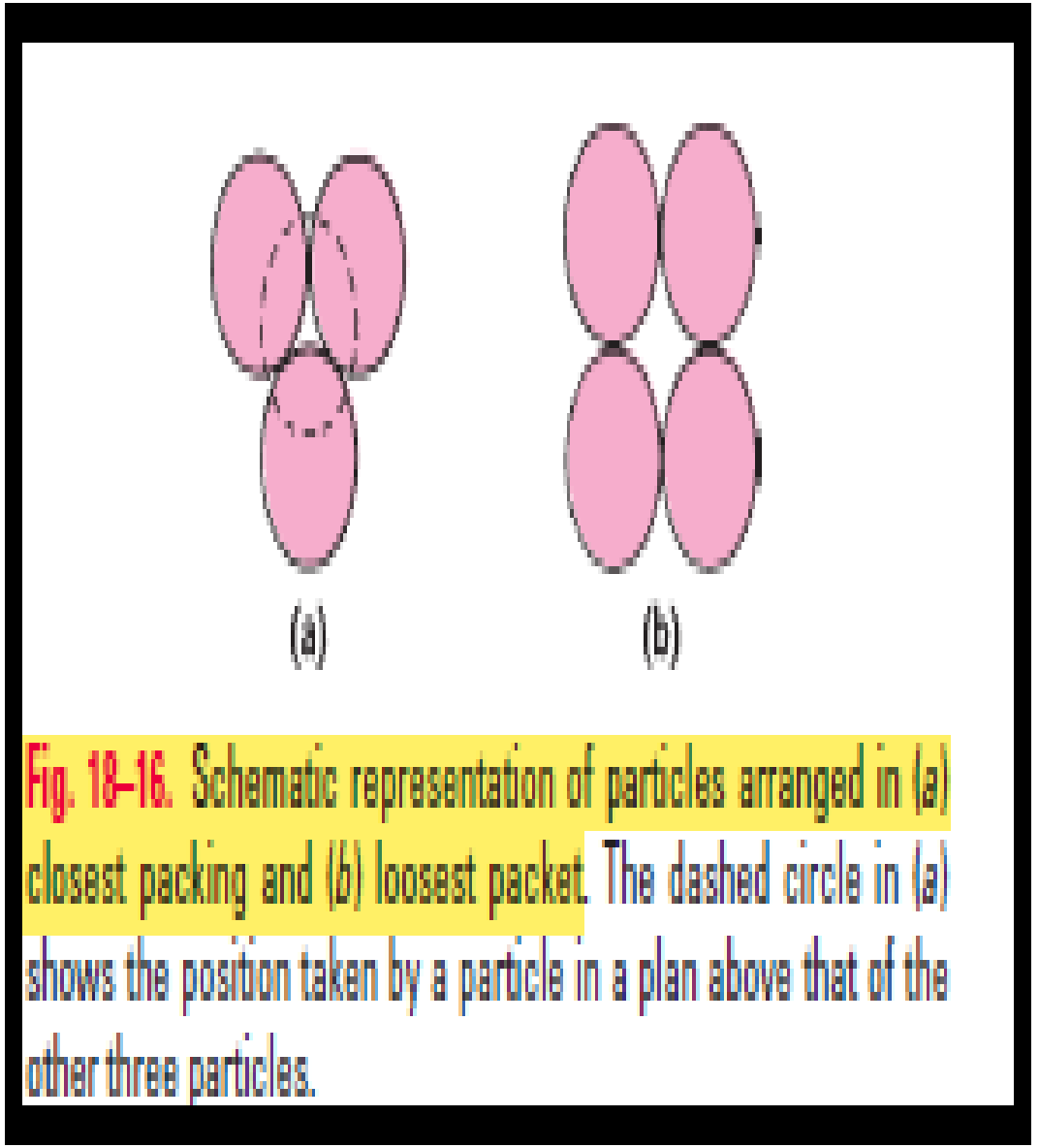

Fig. 18–16. Schematic representation of particles arranged in (a) closest packing and (b) loosest packet. The dashed circle in (a) shows the position taken by a particle in a plan above that of the other three particles.

densities of particles,

- **Density** is universally defined as weight per unit volume.
- Three types of densities can be defined
  a. **the true density** of the material itself, exclusive of the voids and intraparticle pores larger than molecular or atomic dimensions in the crystal lattices
  b. **the granule density** as determined by the displacement of mercury, which does not penetrate at ordinary pressures into pores smaller than about 10 μm, and
  c. **the bulk density** as determined from the bulk volume and the weight of a dry powder in a graduated cylinder.
- True density, ρ, is the density of the actual solid material.
- **Methods** for determining the density of **nonporous** solids by displacement in liquids in which they are insoluble are found in general pharmacy books.
- If the material is **porous**, as is the case with most powders, the true density can be determined by use of a helium densitometer.
- **The bulk density** of a powder depends primarily on particle-size distribution, particle shape, and the tendency of the particles to adhere to one another.
- The particles may pack in such a way as to leave large gaps between their surfaces, resulting in a light powder or powder of low bulk density.
- On the other hand, the smaller particles may shift between the larger ones to form a heavy powder or one of high bulk density.

bulkiness and flow properties

- **Bulkiness;** (Specific bulk volume), is the **reciprocal** of bulk density
  - Bulkiness = 1 / bulk density
  - It is an important consideration in the packaging of powders.
- The bulk density of calcium carbonate can vary from 0.1 to 1.3, and the lightest or bulkiest type would require a container about 13 times larger than that needed for the heaviest variety.
- Bulkiness **increases** with a **decrease** in particle size.
- In a mixture of materials of different sizes, however, the smaller particles shift between the larger ones and tend to reduce the bulkiness.
- **Flow Properties**; powders may be free-flowing or cohesive (—sticky).
- The factors that affect the flow properties of powders Of special significance are particle size, shape, porosity and density, and surface texture.
- Those properties of solids that determine the magnitude of particle–particle interactions .

bulkiness and flow properties

- With relatively small particles (less than 10 µm), particle flow through an orifice is restricted because the cohesive forces between particles are of the same magnitude as gravitational forces.
  - For large particles: Gravity dominates → good flow
  - For small particles (<10 µm):Cohesive forces (van der Waals, electrostatic) dominate Particles stick together → poor flow
  - ➢ Because these latter forces are a function of the diameter raised to the third power, they become more significant as the particle size increases and flow is facilitated.
    - **Gravitational force ∝ particle volume ∝ d^3**
    - **Cohesive forces ∝ surface area ∝ d^2**
    - Therefore: When particle size increases , Gravity increases faster than cohesion → **better flow**

bulkiness and flow properties

- Flow through an orifice depends on:
  - Particle size
  - Orifice siz
- When particle size is:
  - **Too small → cohesion dominates → poor flow**
  - **Optimal → A maximum flow rate is reached, after which the flow decreases as the size of the particles approaches that of the orifice [Too large (near orifice size) → blockage → reduced flow]**

- If a powder contains a reasonable number of small particles, **the powder's flow properties** may be **improved** by removing the —fines or adsorbing them onto the larger particles.
- Occasionally, poor flow may result from the presence of moisture, in which case drying the particles will reduce the cohesiveness.
  - Moisture forms **liquid bridges**
  - Increases cohesion → **poor flow**
    - Drying improves flow