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Topic: Particle size and distribution

Micromeritics

- In the area of tablet and capsule manufacture, control of the particle size is essential in achieving the necessary flow properties and proper mixing of granules and powders.

Particle Size and Size Distribution

- In a collection of particles of more than one size, two properties are important, namely.

1. The shape and surface are of the individual particles.

2. The particle size and size distributions (The size range and number or weight of particles).

Particle Size

- The size of a sphere is readily expressed in terms of its diameter.
- The **Surface diameter, d_s,** is the diameter of a sphere having the same surface area as the particle.
- The **Volume diameter, d_v,** is the diameter of a sphere having the same volume as the particle.
- The **Projected diameter, d_p,** is the projected diameter of a sphere having the same observed area as the particle.
- The **Stokes diameter, d_{st},** is the diameter which describes an equivalent sphere undergoing sedimentation at the same rate as the asymmetric particle.

ders.

PARTICLE SIZE DETERMINATION—METHODS

The particle size of a pharmaceutical substance is strictly maintained in order to get optimal biological activity. A few examples of substances and their size ranges are given in Table 6-4.

TABLE 6-4

Examples of Drugs With Particle Size—Pharmacopœial Control

Drug	*Dosage Form*	*Size Requirement*
Aspirin	soluble tablets	sieve no. 180
Hydrocortisone	o/w cream	90 % = <5 μm, <50 μm
Insulin zinc (amorphous)	Injections	<2 μm
Insulin zinc (crystalline)	injection	10 >40 μm
Betamethasone	tablets	90% <5 μm, not 50 μm

Methods to estimate particle sizes are:

a. Optical Microscopy
b. Sieving Method
c. Sedimentation Method
d. Conductivity Method

None of these methods are truly direct, because visual observation and measurement of all three dimensions of the particle is not possible. Data obtained by one method may not match data provided by other methods. Selection of a method largely depend on its intended applications, desired type of diameter and type of distribution required. Most methods have limitations in the range of sizes they cover.

Optical Microscopy

Particle size in the range of 0.2-100 μm can be measured by optical microscopy. In this method, the size is expressed as d_p (*projected diameter*), which describes the diameter of a sphere having the same area as the asymmetric particle when observed under a microscope. This method directly gives number distribution, which can be further converted to weight distribution. The optical microscope has a limited resolving power (of the lens). The lower limit can be brought down using ultramicroscope and electron microscope.

Optical microscopy method is used to determine:

(a) particle size analysis in suspensions
(b) globule size distribution in emulsions
(c) particle size analysis in aerosols

Depending on the amount of solids or globules, if necessary a dilution of sample can be made using an appropriate vehicle.

Method : Eye-piece of the microscope is fitted with a micrometer. This eye-piece micrometer is calibrated using a standard stage micrometer. Take the powder sample and prepare a suspension with a suitable vehicle such as paraffin oil. When water is used as a vehicle, verify the aspects of hydration (swelling) of the particles. The sample of suspension is mounted on a slide or a ruled cell and placed it on the mechanical stage. The size of the particle is estimated with the help of the eye-piece micrometer. Around 625 particles must be counted in order to estimate the true mean. This is necessary because particles are not spherical and assessment will be subjective and inaccurate, unless a large sample is measured.

The size frequency distribution curves such as normal (Figure 6-3), log-normal (Figure 6-4), cumulative frequency (Figure 6-5) and probability (Figure 6-6) curves are plotted. Finally, the statistical diameters for the powder are estimated.

Estimation of diameter can be improved by projecting the field of the specimen on a screen, or by taking a photograph. Electronic scanners have been developed to remove the necessity of measuring particles by visual observation.

Practical considerations : The microscope method of measurement should be carefully standardised, otherwise considerable errors may be introduced. The sources of error include the choice of diameter, technique of slide preparation and sampling. The value of projected diameter depends on the orientation of the particle on the slide.

1. The diameter obtained in this method is actually the diameter of circle, whose area is equivalent to the projected area of the particle. The diameter is estimated using a graticule which is placed in the microscope eye-piece.

2. A less tedious method is the double image microscope. In this procedure, two identical images are observed in the field of view. A beam splitting divice (that is present between the objective and eye piece) moves the image apart. The amount of displacement is indicated on a scale, when the images are edge to edge contact. The diameter can be read from the electrical meter in the Timbrell instrument.

While measuring the diameter, eye piece is adjusted horizontally across the center of the particle.

Other Diameters

Popular measurements are:

(i) projected area diameter
(ii) Martin diameter
(iii) Feret diameter

For the purpose of measurement, the following Figure 6-7 can be considered.

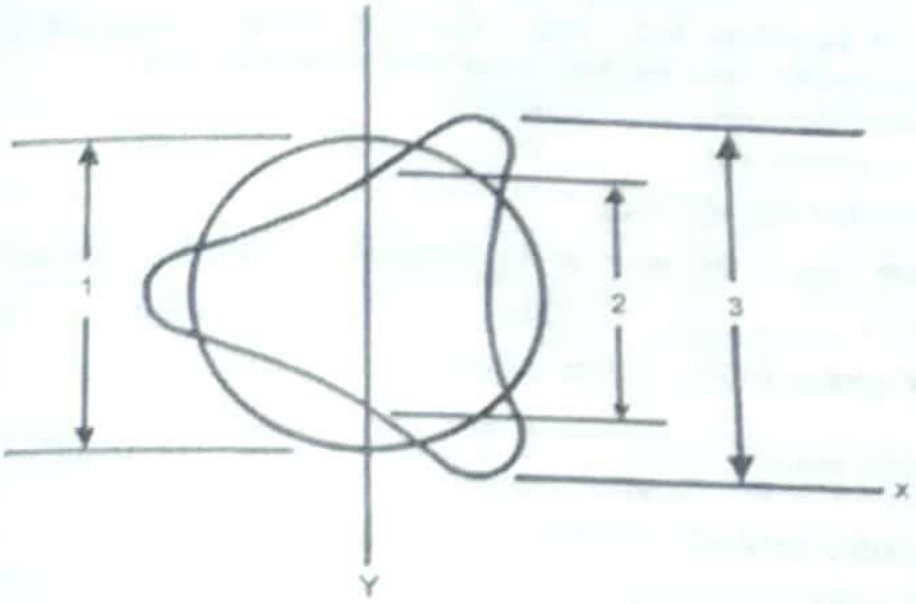

Figure 6-7. Some popular methods to express the particle diameter by microscopy method. Key 1—projected area diameter; 2—Martin diameter; 3—Feret diameter.

Projected area diameter : It is the diameter of a circle with the same area as that of the particle observed to the surface on which the particles rest. It corresponds to the number 1 in Figure 6-7.

Martin diameter : It is the length of the line that bisects the particle image. A line may be drawn in any direction, but must be drawn in the same direction for other particle measured. The martin diameter is represented by the number 2 in Figure 6-7.

Feret diameter : It is the distance between two tangents on opposite sides of the particle parallel to some fixed direction. It corresponds to number 3 in Figure 6-7.

Advantages:

1. Microscopy allows the observer to view the particles.
2. Agglomeration of particles and any contamination in the powder can be detected.

3. Particles in the dispersion must be free from motion. This can be avoided by mounting the sample with a cover-slip.
4. Easy and simple.

Disadvantages:

1. Diameter is obtained from only two dimensions. i.e., length and breadth. Depth of the particles is not measureable.
2. This method is slow and tedious, because a large number of particles (500) must be measured to get a good estimate.
3. Large sample is required.

Practice problem 6-4. The sample of silica is analyzed by means of