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Physical Pharmacy

PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES

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Micromeritics

The science and technology of small particles have been given the name *micromeritics* by Dalla Valle.[1] 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 approximate size ranges of particles in pharmaceutical dispersions are listed in Table 16–1*a*. The sizes of other materials, including microorganisms, are found in Tables 16–1*b* and *c*. 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, or 10^{-3} mm. One must not confuse μm with mμ, the latter being the symbol for a millimicron or 10^{-9} m. The millimicron now is most commonly referred to as the nanometer (nm).

Knowledge and control of the size, and the size range, of particles is of profound importance in pharmacy. Thus, size, and hence surface area, of a particle can be related in a significant way to the physical, chemical, and pharmacologic properties of a drug. 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. 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. These and other factors reviewed by Lees[2] make it apparent that a pharmacist today must possess a sound knowledge of micromeritics.

PARTICLE SIZE AND SIZE DISTRIBUTION

In a collection of particles of more than one size (i.e., in a polydisperse sample), two properties are important, namely (1) the shape and surface area of the individual particles, and (2) the size range and number or weight of particles present and, hence, the total surface area. Particle size and size distributions will be considered in this section; shape and surface area will be discussed subsequently.

The size of a sphere is readily expressed in terms of its diameter. As the degree of assymmetry of particles

TABLE 16–1*a*. *Particle Dimensions in Pharmaceutical Disperse Systems*

Particle Size			
Micrometers (μm)	Millimeters	Approximate Sieve Size	Examples
0.5–10	0.0005–0.010	—	Suspensions, fine emulsions
10–50	0.010–0.050	—	Upper limit of subsieve range, coarse emulsion particles; flocculated suspension particles
50–100	0.050–0.100	325–140	Lower limit of sieve range, fine powder range
150–1000	0.150–1.000	100–18	Coarse powder range
1000–3360	1.000–3.360	18–6	Average granule size

also equals 1.43. Customarily, the prime is dropped since the value is independent of the type of distribution. The geometric mean diameter (the particle size at the 50% probability level) on a weight basis, d'_g, is 10.4 μm, whereas $d_g = 7.1$ μm.

Provided the distribution is log-normal, the second approach is to use one of the equations developed by Hatch and Choate.[8] By this means, it is possible to convert number distributions to weight distributions with a minimum of calculation. In addition, a particular average can be readily computed by use of the relevant equation. The Hatch–Choate equations are listed in Table 16–5.

Example 16–1. From the number distribution data in Table 16–4 and Figure 16–5, it is found that $d_g = 7.1$ μm and $\sigma_g = 1.43$, or log $\sigma_g = 0.1553$. Using the relevant Hatch–Choate equation, calculate d_{ln} and d'_g.

The equation for the length–number mean, d_{ln}, is

$$\begin{aligned} \log d_{ln} &= \log d_g + 1.151 \log^2 \sigma_g \\ &= 0.8513 + 1.151(0.1553)^2 \\ &= 0.8513 + 0.0278 \\ &= 0.8791 \\ d_{ln} &= 7.57\ \mu\text{m} \end{aligned}$$

To calculate d'_g, we must substitute into the following Hatch–Choate equation:

$$\begin{aligned} \log d_{ln} &= \log d'_g - 5.757 \log^2 \sigma_g \\ 0.8791 &= \log d'_g - 5.757(0.1553)^2 \end{aligned}$$

or

$$\begin{aligned} \log d'_g &= 0.8791 + 0.1388 \\ &= 1.0179 \\ d'_g &= 10.4\ \mu\text{m} \end{aligned}$$

One can also use an equation suggested by Rao,[9]

$$d'_g = d_g\, \sigma_g^{(3 \ln \sigma_g)} \qquad (16\text{–}2)$$

to readily obtain d'_g, knowing d_g and σ_g. In the present example,

$$\begin{aligned} d'_g &= 7.1(1.43)^{(3 \ln 1.43)} \\ &= 10.42 \end{aligned}$$

The student should confirm that substitution of the relevant data into the remaining Hatch–Choate equations in Table 16–5 yields the following statistical diameters:

$$d_{sn} = 8.07\ \mu\text{m}; \qquad d_{vn} = 8.60\ \mu\text{m};$$
$$d_{vs} = 9.78\ \mu\text{m}; \qquad d_{wm} = 11.11\ \mu\text{m}$$

Particle Number. A significant expression in particle technology is the *number of particles per unit weight N*, which is expressed in terms of d_{vn}.

The number of particles per unit weight is obtained as follows. Assuming that the particles are spheres, the volume of a single particle is $\pi d_{vn}^3/6$, and the mass (volume × density) is $\pi d_{vn}^3 \rho/6$ g per particle. The number of particles per gram is then obtained from the proportion

$$\frac{(\pi d_{vn}^3 \rho)/6\ \text{g}}{1\ \text{particle}} = \frac{1\ \text{g}}{N} \qquad (16\text{–}3)$$

and

$$N = \frac{6}{\pi d_{vn}^3 \rho} \qquad (16\text{–}4)$$

Example 16–2. The mean volume number diameter of the powder, the data for which are given in Table 16–2, is 2.41 μm or 2.41×10^{-4} cm. If the density of the powder is 3.0 g/cm³, what is the number of particles per gram?

$$N = \frac{6}{3.14 \times (2.41 \times 10^{-4})^3 \times 3.0} = 4.55 \times 10^{10}$$

METHODS FOR DETERMINING PARTICLE SIZE

Many methods are available for determining particle size. Only those that are widely used in pharmaceutical practice and are typical of a particular principle are presented. For a detailed discussion of the numerous methods of particle size analysis, the reader should consult the texts by Edmundson[5] and by Allen,[10] and the references given there to other sources. The methods available to determine the size characteristics of submicrometer particles have been reviewed by Groves.[11] Such methods apply to colloidal dispersions (see Chapter 15).

Microscopy, sieving, sedimentation, and the determination of particle volume are discussed in the following section. None of the measurements are truly direct methods. Although the microscope allows the observer (1) to view the actual particles, the results obtained are probably no more "direct" than those resulting from other methods since only two of the three particle dimensions are ordinarily seen. The sedimentation methods yield a particle size relative to the rate at (2) which particles settle through a suspending medium, a measurement important in the development of emulsions and suspensions. The measurement of particle volume, using an apparatus called the Coulter counter, allows one to calculate an equivalent volume diameter. 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; the size is most

TABLE 16–5. ***Hatch–Choate Equations for Computing Statistical Diameters from Number and Weight Distributions***

Diameter	Number Distribution	Weight Distribution
Length–number mean	$\log d_{ln} = \log d_g + 1.151 \log^2 \sigma_g$	$\log d_{ln} = \log d'_g - 5.757 \log^2 \sigma_g$
Surface–number mean	$\log d_{sn} = \log d_g + 2.303 \log^2 \sigma_g$	$\log d_{sn} = \log d'_g - 4.606 \log^2 \sigma_g$
Volume–number mean	$\log d_{vn} = \log d_g + 3.454 \log^2 \sigma_g$	$\log d_{vn} = \log d'_g - 3.454 \log^2 \sigma_g$
Volume–surface mean	$\log d_{vs} = \log d_g + 5.757 \log^2 \sigma_g$	$\log d_{vs} = \log d'_g - 1.151 \log^2 \sigma_g$
Weight–moment mean	$\log d_{wm} = \log d_g + 8.059 \log^2 \sigma_g$	$\log d_{wm} = \log d'_g + 1.151 \log^2 \sigma_g$

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