Particle size analysis

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SELECTION OF A PARTICLE SIZE ANALYSIS METHOD

PARTICLE SIZE AND THE LIFETIME OF A DRUG

The dimensions of particulate solids are of importance in achieving optimum production of efficacious medicines. Figure 33.1 shows an outline of the lifetime of a drug; during stages 1 and 2 when a drug is synthesized and formulated, the particle size of drug and other powders is determined and influences the subsequent physical performance of the medicine and the pharmacological performance of the drug.

Particle size influences the production of formulated medicines (stage 3, Fig. 33.1) as solid dosage forms. Both tablets and capsules are produced using equipment which controls the mass of drug and other particles by volumetric filling. Therefore, any interference with the uniformity of fill volumes may alter the mass of drug incorporated into the tablet or capsule and thus reduce the content uniformity of the medicine. Powders with different particle sizes have different flow and packing properties which alter the volumes of powder during each encapsulation or tablet compression event. In order to avoid such problems the particle sizes of drug and other

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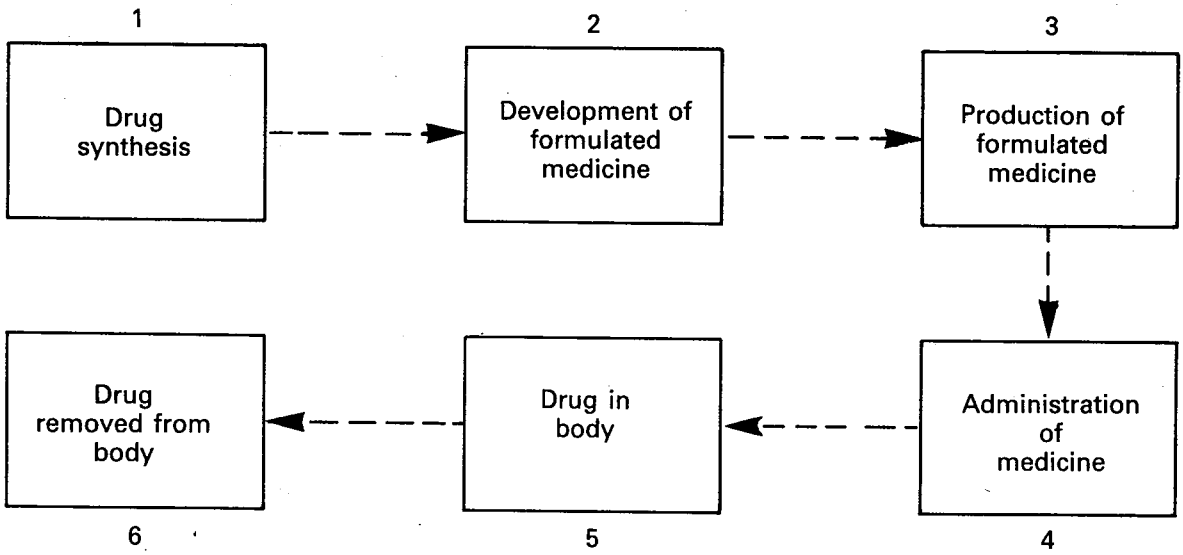

Fig. 33.1 Schematic representation of the lifetime of a drug

powder may be defined during formulation so that problems during production are avoided.

Following administration of the medicine (stage 4, Fig. 33.1), the dosage form should release the drug into solution at the optimum rate. The rate of solution depends on several factors, one of which will be the particle size of drug as predicted from the following theoretical considerations. Noyes and Whitney first showed that the rate of solution of a solid was related to the law of diffusion and proposed that the following equations could be used to predict the rate of solution of a wide variety of solutes.

$$\frac{dx}{dt} = c(C_s - C) \tag{33.1}$$

$$c = \frac{1}{t} \log_e \frac{C_s}{C_s - C} \tag{33.2}$$

where C is the concentration of solute in solution at time, t; C_s is the solubility of solute and c is a constant which can be determined from a knowledge of solute solubility. The constant c was more precisely defined by Danckwerts, who showed that the mean rate of solution per unit area under turbulent conditions was given by

$$\frac{dx}{dt} = D\sigma (C_s - C) \tag{33.3}$$

where D is a diffusion coefficient and σ is the rate of production of fresh surface. $D\sigma$ can be interpreted as a liquid film mass transfer coefficient which will tend to vary inversely with particle size, since a reduction in size generally increases the specific surface area of particles. Thus, particles having small dimensions will tend to increase the rate of solution. For example, the drug griseofulvin has a low solubility by oral administration but is rapidly distributed following absorption; the solubility of griseofulvin can be greatly enhanced by particle size reduction, so that blood levels equivalent to, or better than, those obtained with crystalline griseofulvin can be produced using a microcrystalline form of the drug. Similar examples of a reduction in particle size improving the rate of solution include tetracycline, aspirin and some sulphonamides. A reduction of particle size to improve rate of solution and hence bioavailability is not always beneficial. For example, small particle size nitrofurantoin has an increased rate of solution which produces toxic side effects because of its more rapid absorption.

It is clear from the lifetime of a drug outlined above that a knowledge and control of particle size is of importance both for the production of medicines containing particulate solids and in the efficacy of the medicine following administration.

PARTICLE SIZE

Dimensions

When determining the size of a relatively large solid it would be unusual to measure fewer than three dimensions, but if the same solid was broken

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up and the fragments milled, the resulting fine particles would be irregular with different numbers of faces and it would be difficult or impractical to determine more than a single dimension. For this reason a solid particle is often considered to approximate to a sphere which can then be characterized by determination of its diameter. Because measurement is then based on a hypothetical sphere which represents only an approximation to the true shape of the particle, the dimension is referred to as the equivalent diameter of the particle.

Equivalent diameters

It is possible to generate more than one sphere which is equivalent to a given irregular particle shape. Figure 33.2 shows the two-dimensional projection of a particle with two different diameters constructed about it. The projected area diameter is based on a circle of equivalent area to that of the projected image of a solid particle; the projected perimeter diameter is based on a circle having the same perimeter as the particle. Unless the particles are unsymmetrical in three dimensions then these two diameters will be independent of particle orientation. This is not true for Feret's and Martin's diameters (Fig. 33.3) the values of which are dependent on both the orientation and the shape of the particles. These are statistical diameters which are averaged over many different orientations to produce a mean value for each particle diameter. Feret's diameter is determined from the mean distance between two

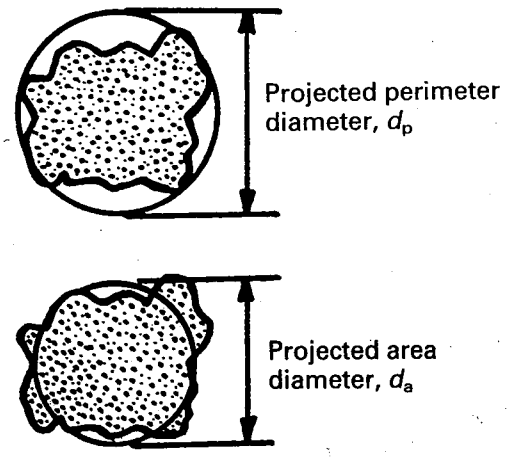

Fig. 33.2 Different equivalent diameters constructed around the same particle

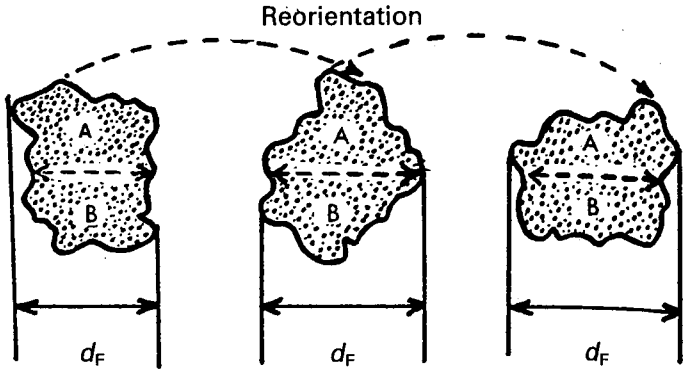

Fig. 33.3 Influence of particle orientation on statistical diameters. The change in Feret's diameter is shown by the distances, d_F; Martins diameter d_M corresponds to the dotted lines in the mid-part of each image

parallel tangents to the projected particle perimeter. Martin's diameter is the mean chord length of the projected particle perimeter, which can be considered as the boundary separating equal particle areas (A and B in Fig. 33.3).

It is also possible to determine particle size based on spheres of, for example, equivalent volume, sedimentation volume, mass or sieve mass of a given particle. In general, the method used to determine particle size dictates the type of equivalent diameter which is measured although interconversion may be carried out and this is sometimes done automatically as part of the size analysis.

Particle size distribution

A particle population which consists of spheres or equivalent spheres with uniform dimensions is monosized and its characteristics can be described by a single diameter or equivalent diameter.

However, it is unusual for particles to be completely monosized; most powders contain particles with a large number of different equivalent diameters. In order to be able to define a size distribution or compare the characteristics of two or more powders consisting of particles with many different diameters, the size distribution can be broken down into different size ranges which can be presented in the form of a histogram plotted from data such as that in Table 33.1. Such a histogram presents an interpretation of the particle size distribution and enables the percentage of particles having a given equivalent diameter to be determined. A histogram representation allows

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Table 33.1 Frequency distribution data

Equivalent particle diameter (μm)	*Number of particles in each diameter range (frequency)*	*Per cent particles in each diameter range (per cent frequency)*
2	1	4.5
4	2	9.1
6	4	18.2
8	8	36.4
10	4	18.2
12	2	9.1
14	1	4.5

Table 33.2 Cumulative frequency distribution data

Equivalent particle diameter (μm)	*Per cent frequency (from Table 33.1)*	*Cumulative per cent frequency*	
		Undersize	*Oversize*
2	4.5	4.5	100
4	9.1	13.6	95.5
6	18.2	31.8	86.4
8	36.4	68.2	68.2
10	18.2	86.4	31.8
12	9.1	95.5	13.6
14	4.5	100	4.5

different particle size distributions to be compared; for example, the size distribution shown in Fig. 33.4(b) contains a larger proportion of fine particles than the powder in Fig. 33.4(a) in which the particles are normally distributed. The peak frequency value, known as the *mode*, separates the normal curve into two identical halves, because the size distribution is fully symmetrical. Not all particle populations are characterized by symmetrical normal size distributions and the frequency distributions of such populations exhibit skewness (Fig. 33.4(b)). A frequency curve with an elongated tail towards higher size ranges is positively skewed (Fig. 33.4(b)), the reverse case exhibits negative skewness. These skewed distributions can sometimes be normalized by replotting the equivalent particle diameters using a logarithmic scale and are thus usually referred to as log normal distributions. In some size distributions, more than one mode occurs; Fig. 33.4(c) shows bimodal frequency distribution for a powder which has been subjected to milling. Some of the coarser particles from the unmilled population remain unbroken and produce a mode towards the highest particle size, whereas the fractured particles have a new mode which appears lower down the size range.

An alternative to the histogram representation of a particle size distribution is obtained by sequentially adding the per cent frequency values as shown in Table 33.2, to produce a cumulative per cent frequency distribution. If the addition sequence begins with the coarsest particles, the values obtained will be cumulative per cent frequency undersize; the reverse case produces a cumulative per cent oversize. Figure 33.5 shows two cumulative per cent frequency distributions. Once again it is possible to compare two or more particle populations using the cumulation distribution representation. For example, the size distribution in Fig. 33.5(a) shows that this powder has a larger range or spread of equivalent diameters in comparison with the powder represented in Fig. 33.5(b). The particle diameter corresponding to the point which separates the cumulative frequency curve into two equal halves, above and below which 50% of the particles lie (point *a* in Fig. 33.5(a)). Just as the median divides a symmetrical cumulative size distribution curve into two equal halves, so the lower and upper

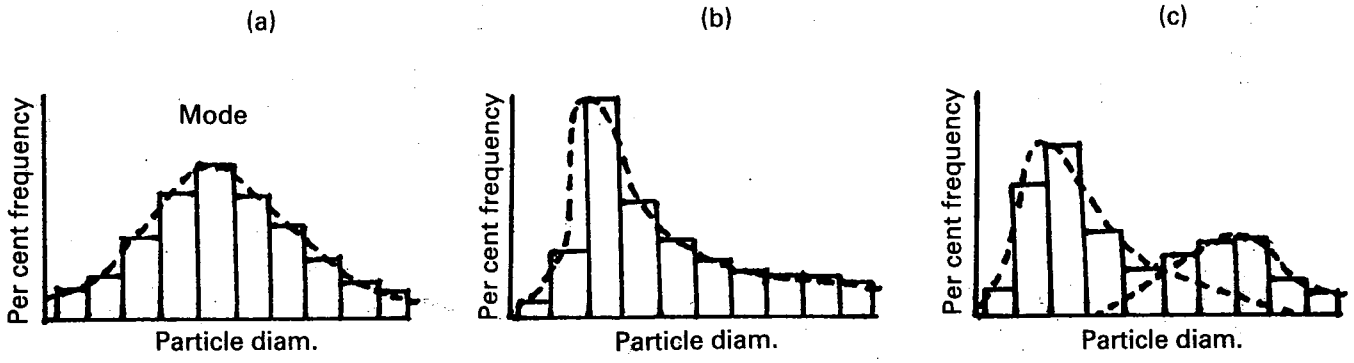

Fig. 33.4 Frequency distribution curves corresponding to (a) a normal distribution, (b) a positively skewed distribution and (c) a bimodal distribution

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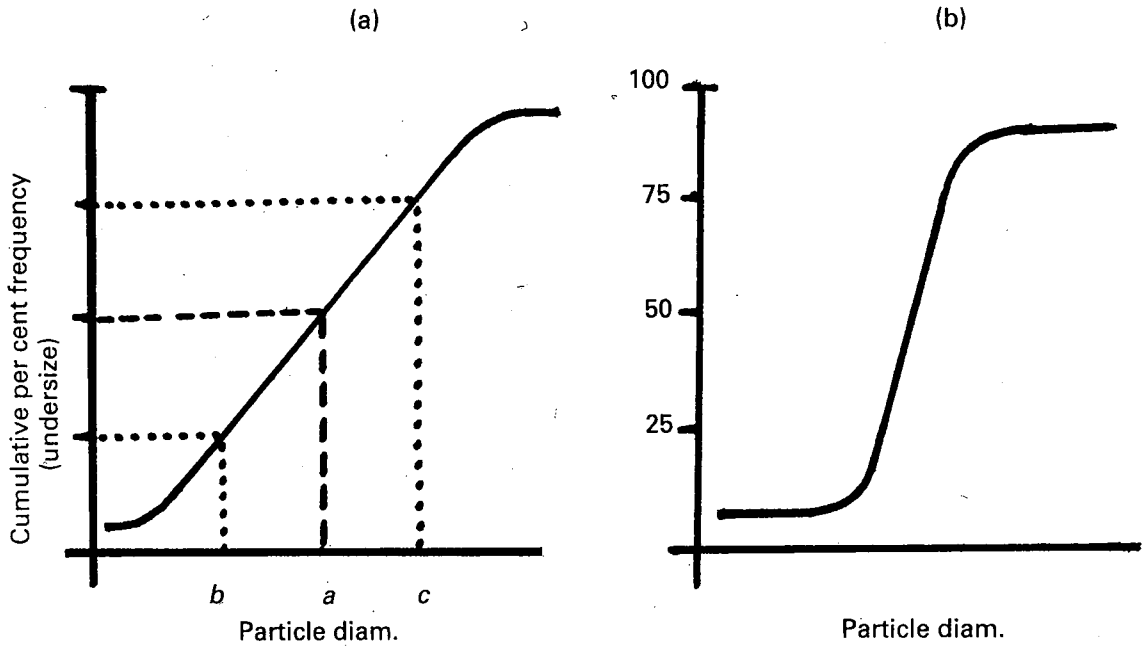

Fig. 33.5 Cumulative frequency distribution curves. Point *a* corresponds to the median diameter; *b* is the lower quartile point and *c* is the upper quartile point

quartile points at 25% and 75% divide the upper and lower ranges of a symmetrical curve into equal parts (points *b* and *c* in Fig. 33.5(a)).

Statistics to summarize data

Although it is possible to describe particle size distributions qualitatively it is always more satisfactory to compare particle size data quantitatively. This is made possible by summarizing the distributions using statistical methods.

In order to quantify the degree of skewness of a particle population, the interquartile coefficient of skewness (IQCS) can be determined

$$\text{IQCS} = \frac{(c - a) - (a - b)}{(c - a) + (a - b)} \qquad (33.4)$$

where a is the median diameter and b and c are the lower and upper quartile points (Fig. 33.5).

The IQCS can take any value between -1 and $+1$. If the IQCS is zero then the size distribution is practically symmetrical between the quartile points. To ensure unambiguity in interpreting values for IQCS a large number of size intervals is required.

To quantify the degree of symmetry of a particle size distribution a property known as kurtosis can be determined. The symmetry of a distribution is based on a comparison of the height or thickness of the tails and the 'sharpness' of the peaks with those of a normal distribution. 'Thick' tailed, 'sharp' peaked curves are described as leptokurtic whereas 'thin' tailed, 'blunt' peaked curves are platykurtic and the normal distribution is mesokurtic.

The coefficient of kurtosis, k (shown below), has a value of 0 for a normal curve, a negative value for curves showing platykurtosis and positive values for leptokurtic size distributions

$$k = \frac{n\,\Sigma(x - \bar{x})^4}{(\Sigma(x - \bar{x})^2)^2} - 3 \qquad (33.5)$$

where x is any particle diameter, $\bar{x}$ is mean particle diameter and n is number of particles.

Again, a large number of data points is required to provide an accurate analysis.

The mean of the particle population referred to above in Eqn 33.5, together with the median (Fig. 33.5) and the mode (Fig. 33.4) are all measures of central tendency and provide a single value near the middle of the size distribution which represents a central particle diameter. Whereas the mode and median diameters can be obtained for an incomplete particle size distribution, the mean diameter can only be determined when the size distribution is complete and the upper and lower size limits are known. It is also possible to define and determine the mean in

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