

THE EVALUATION OF POWDERS

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MATERIALS in powder form exhibit so many unique properties that they could be regarded as constituting a fourth state of matter. Compacted by vibration and pressure, they exhibit the rigidity of a solid body, if rounded in shape and suitably graded they will flow like a liquid, whilst if of very small size the particles link into chains forming an open system of the same order of density as a gas. Powder particles are normally solid, though the more general term of particulate matter is not so restricted and may apply to systems in which the particulate matter exists in any phase, i.e., as liquid particles in an emulsion or in a mist, or even as a system of gas bubbles in a liquid.

Pharmacy, however, is mainly concerned with particles in the solid state and this paper is restricted to a consideration of such materials. The field of powder technology study owes its fascination to the fact that there are many fundamental particle properties which apply to powders used in all industries, and yet each industry has specific problems of its own.

It is not easy to define an upper limit to the size of an individual particle, for a particle is a discrete portion of matter which is small in relation to the space in which it is considered, and the absolute size of the particle is irrelevant. Particulate materials, or powders in the present context, consist of a number of particles which may be dispersed or may be in loose contact though still retaining their individuality, i.e., do not adhere to each other. Such systems may be static or in motion. For practical purposes, however, an arbitrary definition of the size of powder particles is necessary, and B.S. 2955 states that a powder shall consist of discrete particles of dry material with a maximum dimension less than $1,000 \mu$ (1 mm.). This definition merely puts an upper limit to the size of powders and methods of determining the size distribution of the constituent particles must be developed for the purpose of devising industrial specifications or for research on their properties. Before such methods of analysis are described, however, the basic fundamental properties of particles will be defined and discussed, since it is upon these principles that size analysis methods are founded.

FUNDAMENTAL AND DERIVED PROPERTIES

The manifold properties of powders can be elucidated only by making a distinction between those fundamental properties which can be defined individually, and derived properties which depend on some combination of the fundamental properties together with other factors such as the chemical constitution and the circumstances of usage. These fundamental properties are:

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- (i) The size of an individual particle.
- (ii) The size distribution and the mean size of a system of particles.
- (iii) The particle shape.
- (iv) The particle density, including the influence of porosity.

Relatively simple examples of derived properties are:

- (i) The specific surface.
- (ii) The bulk density.
- (iii) The terminal velocity of fall in a fluid, as used for the purpose of sizing analyses.

There are, however, much more complex properties concerning the applications of powders, such as the rate of solubility in liquids, the rheological properties, and the clinical efficacy in pharmaceutical preparations, each of which is in itself a subject for research.

In the following sections of the paper, a brief description is given of the above fundamental properties.

The Size of an Individual Particle

An irregularly shaped particle has no unique dimension and its size can only be expressed in terms of the diameter of a sphere that is equivalent to the particle with a regard to some stated property. Such equivalent spheres are those which:

- (i) have the same projected area as the particle when viewed in a direction perpendicular to the plane of greatest stability, symbol d_a ;
- (ii) have the same volume as the particle, symbol d_v ;
- (iii) have the same surface area as the particle, symbol d_s ;
- (iv) have the same free-falling velocity in a fluid as the particle, symbol d_f . (If the diameter/velocity relationship follows Stokes's Law, the symbol d_{st} is used.)
- (v) correspond to a square aperture of side A through which the particles will just pass.

These equivalent diameters are based on different properties of the particle, hence their numerical values can only be identical for spherical particles and the divergencies will increase with greater irregularity in shape.

The various methods of particle size determination measure different equivalent diameters, for example the microscope method of measurement gives the equivalent diameter (i) above, sedimentation and elutriation analyses are expressed in terms of the diameter (iv) above whilst sieve analyses are in terms of (v) above. Consequently it is essential when reporting on a sizing analysis to specify the method used, since this can affect appreciably the numerical values obtained. The general relationship

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between these various equivalent sizes can be determined experimentally, or calculated if the shape characteristics of the particles are known and are expressed in a numerical manner. Such relationships are discussed in greater detail later in this paper, though Fig. 1 shows graphically some of these equivalent diameters.

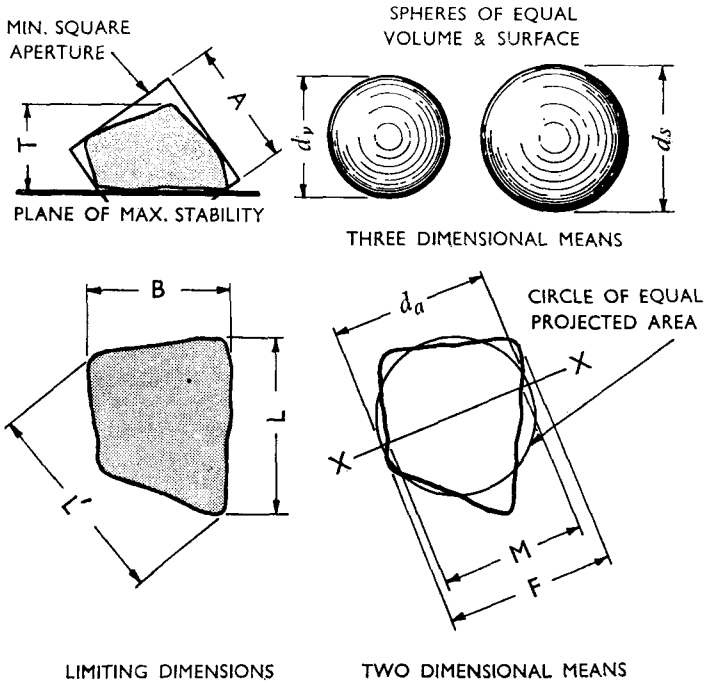


FIG. 1. Equivalent particle diameters.

The Mean Size of a System of Particles

A system of particles is characterised by the properties of total number, length, surface area, and volume (weight, if density is uniform) of particles. If a system of non-uniformly sized particles is to be represented by a system of uniformly sized particles having the same shape (and density), the two systems can be equivalent as regards two, but only two, of the above properties. The size of the particles in the uniform system is then the mean size or mean diameter of the non-uniform system with respect to these two properties.

Mathematical expressions for these mean diameters can be derived if the complete size range of the particles is subdivided mathematically into a number of small groupings each of size range δx and with assumed uniform diameters of x_1, x_2, \dots . The symbol x is used for diameter because the method of measurement for individual particles is not specified, and all particles are assumed to have the same shape. Let the numbers of particles in these groupings be $\delta N_1, \delta N_2, \dots$ respectively. Then the aggregate length, surface area, and volume of the particles in

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each grouping are represented by the expressions $x_1\delta N$, $x_1^2\delta N$, and $x_1^3\delta N$, respectively, and the totals for the whole of the powder by the summations $(x_1\delta N_1 + x_2\delta N_2 + \dots) = \Sigma x\delta N$, and similarly for terms with higher powers of x . The expression $\Sigma x^3\delta N$ may be replaced by $\Sigma\delta V$, and the expression $\Sigma x^2\delta N$ by $\Sigma\delta V/x$, where δV represents the volume of particles in a grouping, or the weight if the density is assumed to be uniform for all particles. Table I shows in summarised form the mathematical expressions and the nomenclature for the various mean diameters.

TABLE I
DERIVATION OF MEAN DIAMETERS

Nomenclature and properties concerned	Expressions for means	Symbols
Number length mean diameter	$\frac{\Sigma x\delta N}{\Sigma\delta N}$	x_{nl}
Number surface mean diameter	$\frac{\sqrt{\Sigma x^2\delta N}}{\Sigma\delta N}$	x_{ns}
Number volume mean diameter	$\frac{\sqrt[3]{\Sigma x^3\delta N}}{\Sigma\delta N}$	x_{nv}
Length surface mean diameter	$\frac{\Sigma x^2\delta N}{\Sigma x\delta N}$	x_{ls}
Surface volume mean diameter	$\frac{\Sigma x^3\delta N}{\Sigma x^2\delta N}$ $= \Sigma\delta V/\Sigma\delta V/x$	x_{sv}
Volume moment mean diameter	$\frac{\Sigma x^4\delta N}{\Sigma x^3\delta N}$ $= \Sigma x\delta V/\Sigma\delta V$	x_{vm}
Weight moment mean diameter	or $\frac{\Sigma x^4W}{\Sigma\delta W}$	x_{wm}

If this notation is combined with that described above for the different methods of measuring individual particles, then the resultant symbol defines completely the method of measurement and the properties represented by the mean diameter. For example, the result of measuring particles by means of the optical microscope and counting the number of particles corresponding to various size ranges would be expressed as $d_{a, nl}$. The surface volume diameter calculated from the results of a sedimentation analysis by means of Stokes's equation would be $d_{st, sv}$. The average value of the cumulative undersize weight percentage curve obtained by sieving, plotted against sieve aperture, would be A_{vm} or A_{wm} .

Although the system of nomenclature described above may seem somewhat complex the Author is convinced from many years of experience that it is the only system that will provide a unique definition of particle properties.

Particle Shape

This property has especial importance in connection with pharmaceutical products since it affects the surface area, bulk density, and other characteristics of the powder. Various types of particle shape have been defined in B.S. 2955 as Acicular, Angular, Crystalline, Dendritic, Fibrous, Flaky, Granular, Irregular, Nodular, Spherical. Such descriptions, however, are inadequate for the purposes of calculating particle properties which incorporate the effect of shape.

The surface area of a particle is proportional to the square of some characteristic dimension and the volume of the particle to the cube of this dimension; the constants of proportionality depend upon the dimension chosen to characterise the particle and the projected area diameter is

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used for this purpose throughout the following discussion. Hence it can be stated that :

$$\text{Surface of particle} = fd_a^2 = \pi d_s^2 \quad \dots \quad (1)$$

$$\text{Volume of particle} = kd_a^3 = \pi d_v^3/6 \quad \dots \quad (2)$$

where f is the surface coefficient and k is the volume coefficient. These equations also enable the relationship between d_a , d_s , and d_v to be calculated.

The volume coefficient k may be determined from a knowledge of the number, mean size, weight, and density of the particles composing a fraction graded between close size limits. It is, however, more difficult to determine by measurement the external surface area of small particles, but the surface coefficient f may be determined by geometrical analogy from measurements made on larger particles. The general term "shape" comprises a combination of the geometrical form of the particle and the proportions of the particle. Thus one can visualise that in the special case of particles that are equi-dimensional, i.e., for which the limiting dimensions, length, breadth and thickness, are equal, the volume coefficient k has a unique value, termed k_e , which is solely a function of the geometrical form. The following equation then relates the coefficients k and k_e according to the proportions of the particle :

$$k = k_e/m\sqrt{n} \quad \dots \quad (3)$$

where m is the ratio of breadth to thickness and n is the ratio of length to breadth.

An experimental investigation (Heywood, 1954) on the geometrical properties of large particles led to the derivation of the following relationship between f and k_e :

$$f = 1.57 + C \left(\frac{k_e}{m} \right)^{4/3} \left(\frac{n+1}{n} \right) \quad \dots \quad (4)$$

in which C is a coefficient depending upon geometrical form and other symbols are as defined above.

TABLE II
SHAPE COEFFICIENTS FOR EQUIDIMENSIONAL PARTICLES

Shape group	k_e	C	$Ck_e^{4/3}$
Geometrical forms :			
Tetrahedral	0.328	4.36	0.986
Cubical	0.696	2.55	1.571
Spherical	0.524	1.86	0.785
Approximate forms :			
Angular: Tetrahedral	0.38	3.3	0.91
Prismoidal	0.47	3.0	1.10
Sub-angular	0.51	2.6	1.06
Rounded	0.54	2.1	0.92

Table II shows the values of the coefficients k_e and C for certain geometrical forms and also for irregular particles which have been divided into four shape groups, for each of which these coefficients have been determined experimentally.

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Using these coefficients, it is possible by making a visual assessment of the particle shape and proportions through the microscope, to calculate with reasonable accuracy the appropriate values of the coefficients f and k .

Density

This property is needed to relate the volumes and weights of particles. There are, however, complexities in the determination due to the fact that many materials contain pores which may be sealed or closed and so do not communicate with the external surface, or alternatively are open, and connected to the surface. Hence there are three values for the density of a particle which have been defined in B.S. 2955 in the following manner:

True density: Mass of a particle divided by the volume of the particle excluding open and closed pores.

Apparent particle density: Mass of a particle divided by the volume of the particle excluding open pores but including closed pores.

Effective particle density: Mass of a particle divided by the volume of the particle including open and closed pores.

These densities will be designated here by the symbols σ , σ_a and σ_e respectively. True density, σ , refers to the density of the material composing the particle, irrespective of the structure. Apparent density, σ_a would be used if the particle was immersed in a fluid that penetrated the open pores, e.g., in sedimentation calculations. The effective density σ_e would apply when the external surface was regarded as the boundary of the particle or when the ambient fluid was unable to penetrate the open pores.

Methods for determining particle density are described in B.S. 3483.

Surface Structure and Specific Surface

The permeable characteristics of particles are well known and the surface structure of many materials may contain sub-microscopical fissures or pores. The versatile scientist Hooke was aware in 1665 of the porous structure of charcoal, and indeed made an estimate of 5,725,350 pores in a circular area 1 inch in diameter! An interesting analogy suggested by Sir Eric Rideal (1934) was the area of a ploughed field. The projected surface of such a field as shown on a map would be less than the external surface allowing for the furrows, whilst the whole surface accessible to the air through the pores of the surface could be one hundred times as great as the external surface.

The three methods for determining the specific surface of a powder are:

(i) By calculation from the sizing analysis, and including the effect of the shape coefficients defined above. The following equation can be derived to express this factor:

$$\begin{aligned} S_{\text{cal}} &= \frac{f}{\sigma_e k} \cdot \frac{\sum x^2 \delta N}{\sum x^3 \delta N} \\ &= \frac{f}{\sigma_e k} \cdot \frac{1}{x_{sv}} = \frac{f}{\sigma_e k} \cdot \frac{10^4}{d_{a,sv}} \text{ cm.}^2/\text{g.} \dots \dots \quad (5) \end{aligned}$$

where $d_{a, sv}$ is the surface volume mean diameter in microns, based on projected area measurements and σ_s is the effective density.

Such a calculation gives the minimum value of specific surface; the result is dependent on a precise knowledge of the surface volume mean diameter for the particles, which is not easy to determine accurately for very fine powders. Consequently this method should only be applied to relatively coarse powders and it is preferable to determine the surface experimentally by one of the following procedures.

(ii) Surface determination by permeability measurements. There is a mathematical relationship between the resistance to flow of a fluid through a packed bed of particles, the porosity of the bed and the surface area of the particles in contact with the fluid in flow. Liquids or gases may be used for the measurement, though air is the most frequently used medium in practice. Several designs of suitable equipment have been described in publications (Lea and Nurse, 1947; Rigden, 1943, 1947), one of which has been standardised for the testing of Portland Cement. Specific surface measurements made by the permeability method will include the effect of minute surface irregularities, but not the surface of the sub-microscopical pores which are inaccessible to the fluid flow; hence such values are usually slightly greater than those calculated from the sizing analysis.

(iii) Monomolecular layer adsorption can be used to determine directly the specific surfaces of very fine powders (Joy, 1953). The magnitude of the surface determination will depend on the extent to which the adsorbed molecules can penetrate the submicroscopical fissures; thus if relatively large dye molecules dispersed in a liquid are used for the determination, the surface area will be less than if gas molecules are used. The equipment for determination of specific surface by gas adsorption is fairly elaborate, and the procedure has not yet been standardised. It is possible that eventually some simplified methods may be developed for routine testing. The ratio of surface determined by adsorption to that determined by permeability is often found to be of the order of 3:1, and may be as high as 10:1.

Bulk Density of Dry Powders

A study of the classical systems of packing for spheres of uniform size has shown that the porosity, or void space, varies from 48 per cent for cubical packing to 26 per cent for rhombohedral packing, which is the irreducible minimum for such systems (Graton and Fraser, 1935). Furthermore, the voidage or porosity of such systems is independent of the size of the spheres. Practical conditions differ greatly from these simple classical systems, in that the particle size is not uniform, the particle shape may diverge from the spherical, and fine particles can adhere together forming loose chains or bridges with a high voidage. Although smaller particles can fit within the interstices between large particles, thus decreasing the voidage, in fact, the looser packing of the finer particles may nullify this effect, and the resulting voidage for mixed sizes may be greater than the theoretical for closely packed uniform spheres. Indeed, there is

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approximate proportionality between specific surface and voidage in a dry powder, and the latter has been proposed as a rough measure of specific surface (Heywood, 1946).

Increased packing densities may be obtained by mixing powders in the wet state, whereby aggregates are dispersed, but this may not be feasible for some types of powder. The greatest density with dry packing is probably attained when a fine powder is mixed with a relatively coarse powder which is closely sized, but there should be a gap between the two powder sizes which should have a ratio of approximately 6:1. A paper on this subject led to the following two generalised conclusions:

(i) With relatively large particles, where cohesion effects are negligible and the accidental formation of arches or vaults is avoided, the porosity is decreased when the particles extend over a wide range of sizes.

(ii) With powders consisting of fine particles relatively large void spaces are formed by arching of the particles and by cohesion into chain formations. These effects increase the porosity and usually more than nullify the effect of particle variation, so that fine powders may have very high porosities.

The above features are illustrated by the following Figures. The arching of the particles, in this case steel ball bearings poured between two glass plates, is well shown by Fig. 2 (from Brown and Hawksley,

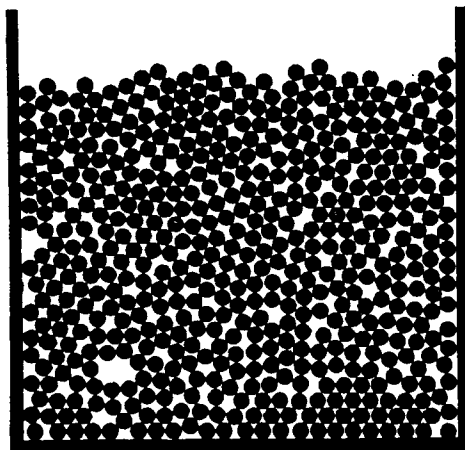


FIG. 2. Packing of $\frac{1}{4}$ inch ball bearings between glass plates, showing stable arches and high porosity at the walls of the container. (From Brown and Hawksley, 1945, *Coal Res.*, 143, with permission).

1945). The effect of the wall of the vessel in promoting large void areas is noticeable. The structure of very fine powders, such as carbon black and zinc oxide smoke is shown by the electron microscope photographs in Fig. 3. The voidage or porosity of such systems may be 96 to 98 per cent (Heywood, 1946). As examples of the porosity of ground minerals,

a limestone of which 46.5 per cent passed a 200 mesh B.S. sieve had a porosity when loosely poured of 51.7 per cent, but when ground to 93.7 per cent passing 200 mesh B.S. sieve the porosity was 71.0 per cent. A further study of the subject may be made from the references quoted at the end of the paper (Graton and Fraser, 1935; Melmore 1942; Heywood, 1946).

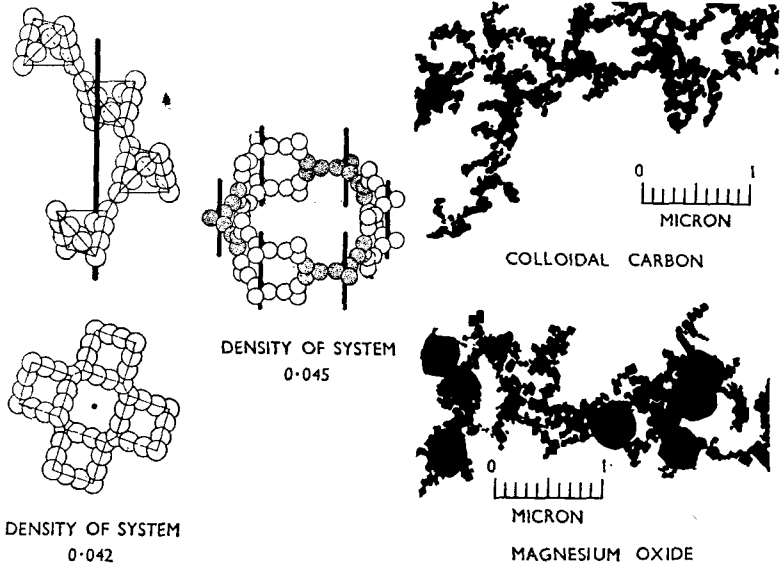


FIG. 3. Open packings of low density and electron microscope photographs of small particles. (From Heywood, 1946).

PROCEDURES FOR PARTICLE SIZE ANALYSIS

There is no single method of size analysis which can be used to cover the whole range of particle size concerned in industrial practice. Sieving procedures may be used for particles that are larger than 60μ and below this size there is a variety of sub-sieve size analysis procedures using different principles of operation. In nearly all of these, however, the particle size concentration relationship is determined indirectly, such as by measuring free-falling velocity in a fluid, by the absorption of electromagnetic radiation (light, X-ray, β or γ radiation), or by means of some electrical property. The microscope is the nearest approach to a direct method of measurement but even in this case the particle is only seen as a projected image in one plane. The effect of these different methods of analysis on the numerical results has been referred to in the section on "Size of an Individual Particle" above.

During the last thirty years, many individual investigators have published the results of their researches on methods of sizing analysis and described the designs of equipment used. There is still, however, considerable confusion as to the best methods to employ and the procedures to be adopted. Co-operative research between laboratories and scientific

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organisations is essential for further progress leading to standardisation of accepted methods.

The British Standards Institution first published in 1931 a specification B.S. 410 for the dimensions and tolerances of Test Sieves and B.S. 1796 on methods for the use of such sieves was issued in 1952. Specifications for methods of determination of the particle size of powders are now ready for publication as B.S. 3406 in the following sections: Part 1. Sub-division of gross sample down to 0.2 ml. Part 2. Liquid sedimentation methods. Part 3. Air Elutriation Methods. Part 4. Optical Microscope Method.

TABLE III
SCOPE OF METHODS OF PARTICLE SIZE ANALYSIS

Method of analysis	Lower size limit; microns	Equivalent diameter measured
Sieving: B.S. Sieves. Normal. Finest in series. Electroformed holes.	75 45 20	<i>A</i>
Microscope: Optical: theoretical limit of resolution. practical limit of measurement. Electron; normal.	0.2 1.0 0.01	<i>d_a</i> or <i>d_s</i> *
Elutriation: Gravitational: air or water. Centrifugal: air. water, hydraulic cyclone.	5-10 5 8	<i>d_t</i> or <i>d_f</i> †
Sedimentation: Gravitational; liquid. Particle concentration measured by differential manometer; pipette extraction; collection on balance or in tube; hydrometer or "divers"; absorption of light, X-Ray, β or γ radiation; radioactive emanation. Gravitational: air. Centrifugal: liquid. Particle concentration may be measured by most of methods used for gravitational settlement.	2 1 0.05	<i>d_t</i> or <i>d_f</i> †
Automatic counting: Scanning of microscope slide or photomicrograph, or flying spot microscope. Coulter Counter; change in electrical resistance as particle passes through orifice.	1 0.2	<i>d_a</i> or <i>d_s</i> † <i>d_v</i>

* The diameter *d_a* implies that the particle is observed perpendicularly to the plane of maximum stability. In the case of very fine particles observed through the optical microscope, and certainly in the case of the electron microscope, the deposit of particles may have a random distribution of orientation and the mean projected diameter measurement tends to the diameter of the sphere of equivalent surface, *d_s* (Pidgeon and Dodd, 1954). This follows from a theorem of Cauchy that the surface area of a particle is 4 times the mean random area of projection (Cauchy, 1841).

† If Stoke's Law is valid the symbol *d_t* is used; at particle sizes greater than this limit the appropriate free-falling velocity should be calculated as explained in the section "Motion of Particles in a Fluid," p. 8.

These specifications are necessarily restricted to well established methods of size analysis but the detailed instructions given should guide those unaccustomed to such work and greatly improve the comparative accuracy of the analytical results obtained at different laboratories.

The Society for Analytical Chemistry formed a Particle Size Analysis Sub-committee in March, 1961. A review issued in March, 1963 (*Analyst*, 1963) has classified the known existing methods for particle size analysis, with a brief description of the scope and procedure for each method.

The data has been extracted from published papers and is not intended to be critical, but has the object of assembling in one document an account of methods which have been devised for sizing analysis. The work will be carried to a further stage involving a detailed examination of a number of particle size analysis methods and will involve comparative experiments with the aid of all types of laboratories concerned in this subject. Table III shows briefly the scope of the various methods of size analysis and in the following sections of the Paper a short description is given of the salient features of these methods.

Sieving Procedures

Sieving is an important method of sizing, particularly for vegetable products and for the coarser organic preparations that cannot be sedimented in water. If conducted properly the analyses are accurate and reproducible, but if performed incorrectly the results can be very misleading. The sieving process consists of two stages, firstly the elimination of the fine dust particles which are much smaller than the mesh apertures, though this may be difficult if the powder is sticky, and secondly the elimination of the near mesh particles which will only just pass through the apertures. This latter process can never be complete and the end-point of the analysis should correspond to a defined rate of passage, say 0.1 per cent of the sample weight per min., though a defined time of sieving may be adopted for routine testing if this is known to be adequate (Heywood, 1938, 1945).

The weaving tolerances of wire sieves have been standardised in Great Britain by B.S. 410 and standard procedures for sieving are described in B.S. 1796. This specification should be consulted for full details, but the essential features for dry sieving are a rapid tapping and shaking motion combined with periodical cleaning of the sieves with a soft brush to clear the apertures of dust. Only when the fine dust has been eliminated does separation of the near mesh particles commence. The fine dust particles are more rapidly eliminated by wet sieving, i.e., washing the dust through the sieve with a fine jet of liquid. This can only be done if a suitable liquid is available that does not dissolve the powder. The residue on the first sieve should be dried after washing, and re-sieved in the dry state; this is essential since surface tension will hinder the wet near-mesh particles from passing the apertures.

Skilled operators can repeat analyses by hand-sieving with accuracy and speed, but sieve-shaking machines are now often used in laboratories for routine testing. These can be quite satisfactory provided the sieve cleaning process is performed at intervals, otherwise the apertures may become completely choked by a difficult powder. Visual observations will show a change to a granular appearance of the residue on the sieve after the fine dust has been eliminated. Particles having the form of thin flakes or long needles (acicular) are difficult to sieve to finality, since they will only pass the apertures when presented in a favourable position.

The method of reporting sieving results is a matter of importance if ambiguity is to be avoided. The term "on" a certain sieve should not be

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used since this could mean the percentage weight retained between two sieves or the cumulative percentage weight of the sample which is larger than the sieve concerned. The report should state definitely that w per cent passes through sieve X and is retained on sieve Y , or that the cumulative percentage undersize through sieve Y is W per cent.

Simple methods of graphical expression of the characteristics of a powder are more easily interpreted and a plot of cumulative percentage undersize by weight against sieve aperture to a logarithmic scale fulfils most purposes. This system of plotting can also be used to show the combined results of a sieving analysis and a sub-sieve analysis, e.g., by sedimentation.

Microscopical Measurement

Direct measurement of particles by means of the optical microscope or by the electron microscope may be necessary under certain circumstances, such as when the sample available is very minute, but in general, the procedure is time consuming and needs great care and experience to obtain accurate results. Since for most powders the frequency of occurrence of particles increases rapidly as the size diminishes, it is necessary to measure very large numbers of particles to ensure a representative count. Even using the method devised by Fairs (1951) and described in detail in B.S. 3406 Part 4, by which group counting is used at three degrees of magnification, the work required is still formidable. Furthermore the results are obtained on a number frequency basis, and though these can be converted to a weight basis by calculation, the error may be considerable when one realizes that one particle 100μ in diameter has the same weight as a million particles 1μ diameter. The situation is different when the particle size range is small, or for blood counts which are fairly uniform, and may be improved in the future by the development of automatic electronic counting and sizing methods. Although the theoretical lower limit of resolution of the optical microscope is 0.2μ , it is generally considered that measurements cannot be made with accuracy below 1μ diameter, even with monochromatic light illumination.

The size of the particles is estimated by comparison with a series of circles on an eyepiece graticule which are superimposed on the microscope field of view. Statistical methods by which an intercept of the particle image is measured, such as the dimensions M and F in Fig. 1, are now obsolete.

Apart from size measurement, however, it is always advisable to examine a sample of powder through the optical microscope to determine the approximate size range, to assess the particle shape and to investigate the suitability of dispersing agents if a sedimentation analysis is intended.

The limit of resolution of the electron microscope is of the order 0.01μ . Size measurements by this means suffer the same disadvantages as with the optical microscope but to an even more pronounced degree. However, much can be learned about the characteristics of the powder by such examination, particularly of the shape of the fine particles and whether these are single or composed of aggregates of even smaller particles.

Motion of Particles in a Fluid

Since the methods of size analysis described in the following two sections are based on the terminal velocity of a particle settling in a fluid, a brief account is given here of the factors on which this is dependent.

A particle settling under gravitational acceleration attains a terminal velocity at which the drag or resistance to motion balances the effective weight of the particle immersed in the fluid. If the fluid motion round the particle is laminar or streamline in character, then the relationship between the terminal velocity and the size is given by Stokes's Law, namely:

$$u_{st} = \frac{d_{st}^2(\sigma_a - \rho)}{18 \eta} g \quad \dots \quad \dots \quad (6)$$

Where u_{st} is the terminal velocity, σ_a the apparent particle density, ρ the density of the fluid, g the gravitational acceleration, η the absolute viscosity of the fluid and d_{st} the Stokes diameter of the particle, all factors in C.G.S. units.

However, above certain limiting particle sizes and velocities, turbulent flow round the particle involves a drag force additional to that due to viscous forces. The criterion of flow conditions is the dimensionless group termed the Reynolds Number, namely:

$$Re = \frac{u_{st}d_{st}\rho}{\eta} \quad \text{or} \quad \frac{u_f d_f \rho}{\eta} \quad \dots \quad \dots \quad (7)$$

in which u_f and d_f refer to free falling velocities and diameters in the flow regime beyond the validity of Stokes's Law.

Stokes's Law cannot be used if the Reynolds Number exceeds 0.2 (Heywood, 1953) and the corresponding critical value of d_{st} is given by the following equation:

$$d_{st}^3 = \frac{3.6\eta^2}{(\sigma_a - \rho)\rho g} \quad \dots \quad \dots \quad (8)$$

If settlement is by centrifugal force, then the appropriate acceleration must be substituted for g in the above equation. The critical value of d_{st} is 65μ for particles of density 2.7 g./cm.^3 settling gravitationally in water at 15° , and 35μ for the same particles settling in air. Hence it is improbable that many powdered materials used in pharmacy will be beyond the range of Stokes's Law. However, the correct free falling velocities for larger particles may be calculated by a method described in a publication by the writer (Heywood, 1962), or determined from tables given in Appendix A, B.S. 3406 Part 2 for water and Part 3 for air.

Elutriation

This is a process of grading particles by means of an upwardly moving current of fluid, normally water or air. It has the especial advantage of subdividing a powder into a number of closely sized fractions which may subsequently be examined for chemical or clinical properties. As a sizing procedure, the method is lengthy and would only be adopted when essential, such as in cases where the powder may not be wetted. The

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Haultain, Roller, and Gonell type air elutriators are widely used in industry, the two latter being described with details for operation in B.S. 3406 Part 3. This specification also describes a miniature elutriator which can easily be constructed in a laboratory workshop.

Air elutriation under the action of centrifugal forces accelerates the procedure and can be accomplished by a proprietary machine termed the BAHCO Classifier (*Analyst*, 1963). Centrifugal force can also be used for water elutriation, and a specific design of hydraulic cyclone for this purpose is described by the reference given (Kelsall and McAdam, 1963).

Sedimentation Analyses

The normal procedure is to allow a homogeneous suspension of the particles in a liquid to settle under gravity, and to determine at suitable intervals of time from the commencement of setting either the relative concentration of particles at a known depth below the surface or the mean concentration from the surface level to a known depth (Heywood, 1953). The former is termed an incremental method, and the latter a cumulative method; in both cases the size of the particle is calculated by means of Stokes's Law from the known velocity of fall corresponding to the time of determining the concentration. The definition of particle size is thus the diameter of a sphere of equivalent terminal or free-falling velocity.

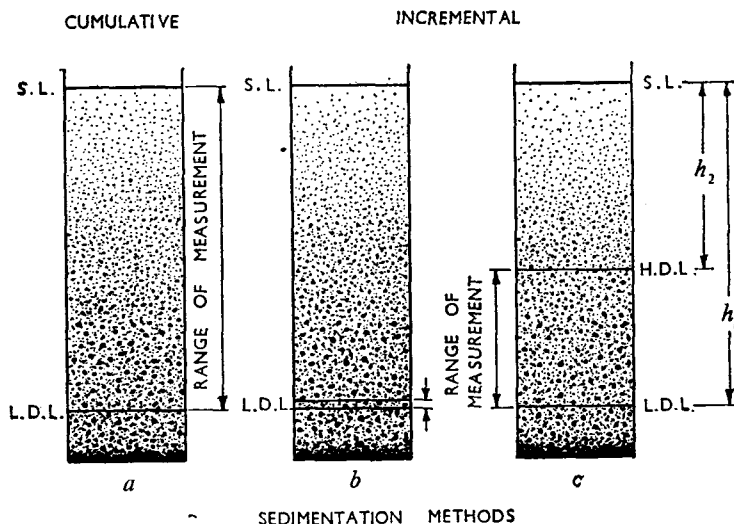


FIG. 4. Ranges of density measurement for sedimentation size-analysis methods. (From Heywood, 1945, *Trans. Inst. Min. Met.*, 15, 373-390, with permission).

These procedures are illustrated in Fig. 4. If h_1 is the sedimentation height from the lower datum level to the surface level and h_2 the height from the upper datum level to the surface; then for cumulative methods $h_2 = 0$, whilst for incremental methods $h_2 = h_1$ and $h_1 - h_2 = 0$. This

condition, however, would involve sampling across a plane perpendicular to the sedimentation column, which is physically impossible. In some methods of test, i.e., by pipette extraction, the ratio $(h_1 - h_2)/h_1$ is about 4 per cent and the theoretical conditions are approximately attained, in others, i.e., the hydrometer method, $(h_1 - h_2)/h_1$ may approach 50 per cent and the method cannot be regarded as truly incremental. Cumulative methods may use the sedimentation balance, with or without automatic recording of the weight of sediment, or a tube at the base of the sedimentation column as a means of collecting the settled material.

Incremental methods give a direct measure of the particle concentration against equivalent size; in cumulative methods the experimentally determined concentration measurements at various times must be subjected to a differentiation process, which can be performed in a tabular manner or graphically, in order to obtain the relationship between particle concentration and equivalent size.

Concentration may be measured in a variety of ways. The simplest method is direct extraction of a small sample by means of a pipette, followed by evaporation of the liquid and weighing of the residual particles (Andreasen, 1928). Alternatives are density measurement by hydrometer or preferably by "divers," relatively small glass vessels adjusted to a known density which are in equilibrium with the suspension at a level where the density is the same (Berg, 1958; Jarrett and Heywood, 1954). If a piece of magnetic alloy is inserted in the diver its position may be indicated by a sensitive electronic indicator surrounding the sedimentation tube. Concentration may also be assessed by the absorption of electromagnetic radiation which may be visual light (Rose, 1950), X-rays, β - or γ -emanation (Connor and Hardwick, 1960). Such methods are particularly suited to the automatic recording of variation in concentration with time of settlement.

Effective dispersion of the particles is essential. A defloculating agent should be added if water is used as the sedimenting liquid. Calgon is very effective for many powders, and sometimes a wetting agent is also required; pH value may need adjusting to an optimum value. In all cases, the sample should be dispersed by a high speed mechanical stirrer before pouring into the sedimentation vessel.

A proprietary apparatus, the Micromerograph, enables particles to be sedimented in an air column, the powder being dispersed at the top of the column and the rate of collection measured on a balance pan at the bottom of the column (Kubitschek, 1960).

As with elutriation, the application of centrifugal force greatly speeds the rate of settlement of particles of about 1μ diameter, and is essential for particles below this size since the effect of Brownian motion begins to invalidate the sedimentation process. Descriptions of a number of designs for centrifugal sedimentation have been published, though not all of these have yet reached the stage of final development (*Analyst*, 1963). In all cases the size of the particle is calculated from the time of centrifuging and the rate and radius of rotation, but Stokes's Law ceases to be applicable at smaller sizes than for gravitational settlement. The

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particle concentration may be measured by the same procedures as used for gravitational settlement.

Special mention should be made of the Coulter Counter which has recently been developed (*Analyst*, 1963). This is not a sedimentation procedure though the particles are dispersed in an electrolytic liquid. The very dilute suspension flows through an orifice which is part of an electrical circuit. As each particle passes through the orifice a change in electrical resistance occurs, which is a function of the volume of the particle. The electrical impulses are counted and monitored so that the relationship between number of particles and relative volume may be obtained directly. The significant particle size is the diameter of the sphere of equivalent volume, d_v , and the instrument is unique in this respect.

Equivalent Diameters and Comparative Surface Measurements

The relationship between equivalent diameters of particles as defined in the Section on size of an Individual Particle, p. 2, cannot be expressed in a simple numerical manner for all types of particle. Relative values for angular particles which are neither unduly flaky nor acicular have been quoted in B.S. 3406 as follows:

Projected area	Sieve	Stokes diam.
1.4	1	0.94

Individual experiments must however be made if accurate ratios for specific materials are required. This can be done by using two respective methods on the same powder over a range of overlap, e.g., by sieving or sedimentation, so that the correlation factor can be determined.

Specific surface determinations show an even greater variance according to method. Haynes (1961) quotes specific surfaces of clays determined by BET adsorption of 3 to 5 times the values calculated from sedimentation analyses. Adsorption of air or methylene blue gave values of the same order as the BET method, though greater in some cases. The BET values were 5 to 10 times greater than determinations by the air permeability method, though this latter method is not very suitable for clays.

Lea and Nurse (1947) also give some relative specific surface values. In general, nitrogen adsorption gave values 2 to 10 times the calculated external surface and about 2 to 6 times the values by air permeability. Air permeability values exceeded those obtained by light extinction by about 50 per cent. Thus surface values obtained by different methods cannot be compared directly and the factors can vary greatly for different materials. There is much scope for research in the future to extend knowledge on the many variables concerned.

SPECIFIC PROBLEMS IN PHARMACY

The foregoing sections have dealt with fundamental problems of particle technology in general. The writer does not claim any detailed knowledge of pharmacy, but there are a few features concerning this field

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on which comment could be made and attention drawn to certain instances where special treatment may be needed because of unusual characteristics of the products concerned.

Sieves should be used for the analysis of the coarser fractions of milled vegetable products, followed by air elutriation or air sedimentation if sub-sieve analysis is required, since with such materials wet methods would be inappropriate. Many pharmaceutical products are soluble in water and hence any sub-sieve analysis must be performed in a liquid to which they are inert, though this should not present any fundamental difficulty. Again, many of the crystalline materials may have a lamina or acicular shape which will complicate the sizing procedure.

Of the many properties mentioned by K. A. Lees in his conjoint paper, that of specific surface appears to be paramount. Since in general the specific surface varies inversely as particle size, this latter is a dominant factor in the properties of pharmaceutical materials.

Control of particle size may be accomplished by:

- (i) reduction from a larger size down to the size required by mechanical milling
- or (ii) growth from molecular size by controlled crystallisation or precipitation up to the desired size.

Breakdown by mechanical milling will unavoidably produce a hetero-sized distribution ranging from a minimum to the maximum particle size. When a brittle particle is fractured it breaks down to a spectrum of sizes and in general the frequency of particle occurrence is inversely proportional to the particle size. Some control in the final size range may be accomplished by a supplementary process, e.g., air elutriation, or classification in a hydraulic cyclone, but it is virtually impossible to obtain a monosized system of particles on an industrial scale by grinding methods. Controlled crystallisation or precipitation may however be used to produce a powder which does approximate to a mono-sized distribution. Many such powders consist of extremely fine particles for the sizing of which some centrifugal method of sedimentation would be essential.

FUTURE DEVELOPMENTS IN SIZING ANALYSES

The equipment for sizing analysis, particularly that described by the British Standards Institution specifications, is necessarily such as can be constructed in a well equipped laboratory workshop and generally requires manual control and operation. It is inevitable that the development of particle size analysis equipment will follow the general trend of scientific progress in extending the use of electronic systems of measurement, together with automatic recording and control (Connor, 1963; Lambert, 1963). Some indication has been given in earlier sections of the paper of the way in which such developments are taking place but a word of warning should be interpolated. Too often is electronics regarded as a substitute for experience, but in fact the experienced operator is still invaluable and with simple equipment can obtain analyses that are

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reliable even if more time consuming. This statement is not intended to deprecate the labour saving value of electronic equipment, but merely to emphasise that some alternative system of checking results is essential.

Particle size analysis as a process, is merely a means to an end, the end being the application of the powder to some industrial or scientific purpose; in so far as this Conference is concerned, the field of pharmaceutical applications. These purposes have been outlined in the paper by K. A. Lees, and it is apparent that the closest co-operation is needed between laboratory research and clinical experience to solve the many problems involved. Such clinical tests are difficult to make and lengthy in time, but without them we may be in danger of amassing much fundamental knowledge which cannot be applied in practice.

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DISCUSSION

DISCUSSION

Caking and aggregation should be avoided in fine particle systems. How aggregation affected solution rate largely depended upon the nature of the drug itself. As the particle dissolved, molecules left the solid phase and concentrated in a saturated layer on the surface of the particle; solution was the dissipation of that layer throughout the bulk of the liquid, and the speed at which this occurred governed further solution of the particle. It was agreed that a study of fine particles might be useful in relation to prolonging as well as increasing the rate of absorption of drug. Separation of powder from granules could not be avoided where there was freedom of motion but it might be reduced by increasing the adhesion of the particles by coating them. The problem of separation of powders during storage was most serious when there was a small proportion of active ingredient, but this could be overcome by ensuring the absorption of the active ingredient on a diluent with a suitable surface area. The shape of the insoluble particles was the predominating factor governing the viscosity of suspensions. In producing particles to a certain size range it was often better to start with a large particle and mill it down, destroying the crystal shape, rather than to attempt to crystallise directly to a mean particle size. The stability of a drug could be affected by its particle size and a reduction in size often increased the breakdown of dry particles. Contrary to the general rule, a decrease in the particle size of aspirin anhydride resulted, in the absence of oxidative mechanisms, in an increase in stability. This was due to a release of mother liquor. The presence of grit particles in a preparation might conveniently be detected by a conical gauge apparatus utilised in the paint industry. It was suggested that surface energy might be the factor involved in the relationship between particle size and solubility. Protective colloids such as methylcellulose could minimise the tendency for crystal habit to change, but in some circumstances a colloid might cause aggregation. The danger of attempting to represent the characteristics of a complex powder by means of a one-point measurement was stressed.