J. Pharm. Pharmacol., 1965, **17**, 193–201 Received October 22, 1964

Research Papers

A method for determining the solution rate of fine particles

I. C. EDMUNDSON AND K. A. LEES

A method is presented for determining the solution rate of fine particles, crystalline hydrocortisone acetate being used as the model substance. The method's innovation is that it takes account of the changing particle size distribution during the solution process, using a Coulter counter to observe this. The solution rate may be expressed as diameter loss per unit time ($d_t = d_o - k_2t$). The solution rate of hydrocortisone acetate under the conditions of the experiment was found to be linear and to correspond to a diameter loss of 1·68 μ/hr, equivalent to 108 $\mu g/cm^2$ of surface/hr. Corrections for the Noyes–Whitney effect were made.

In recent years interest has been growing in the solution rate of drugs of low solubility and in the relationship between solution rate, particle size and absorption of drugs. Wagner (1961) and Lees (1963) have reviewed examples of drugs for which the clinical response to an oral dose depends on particle size and have suggested that the solution rate may be a limiting factor in the absorption of drugs of low solubility. Nelson (1959) found that the absorption of tetracycline and of some of its less soluble salts was limited by solution rate.

Edwards (1951) measured the solution rates of disintegrated aspirin tablets, but in his calculations he replaced the heterogeneous particle sizes of his samples by hypothetical spheres of uniform size; his rate constants are related to initial specific surface area rather than to individual particle sizes.

Other workers (Parrott, Wurster & Higuchi, 1955; Nelson, 1957; 1958; 1959; Higuchi, Parrott, Wurster & Higuchi, 1958) have determined the solution rates of several drugs of low solubility. Recognising the difficulties associated with ill-defined or changing surface areas, they have worked with geometric shapes, such as relatively large spheres or discs, whose surface areas either remained virtually constant or could be measured readily. On the other hand, the treatment of fine particles, as described in publications, has been theoretical rather than experimental.

We have therefore developed a direct method of determining the solution rates of fine particles that does not require the particles to be of specified size, shape or uniformity, yet discriminates between particles of different sizes.

An electronic apparatus for particle size analysis, described by Coulter (1956) and Berg (1959), has several advantages for this purpose. Because an aqueous (saline) suspension of the particles is used, the analysis can be performed while the particles are dissolving and without removing them from the suspension. Wide ranges of pH, electrolyte content and viscosity of the solvent are permissible, so that the method may be applied to a variety of liquids, including natural body fluids and their synthetic

From: Glaxo Laboratories Ltd., Greenford, Middlesex.

imitations. The method is rapid enough to keep pace with a constantly changing size distribution as the particles diminish in size by solution. Individual particles are counted, and significant results can be obtained at low concentrations (by either weight or number of particles).

Because the Coulter counter responds to particle volume rather than to particle diameter or other particle attribute (Kubitschek, 1960), the results of examining material of known density can be expressed accurately in terms of weight.

Solution is normally assumed to be a surface phenomenon, the weight of material dissolved being proportional to the total surface area of the solid and to the time during which it is exposed to the solvent.

When particles dissolve, their surface area will diminish as solution proceeds. If allowance is to be made for this, and also for possible non-uniformity in size of the particles, calculations of volume and surface become complicated (see Hixson & Crowell, 1931; Wilhelm, Conklin & Sauer, 1941; Higuchi & Hiestand, 1963). An alternative assumption is that solution is an etching process in which a given surface recedes in depth to an extent proportional to time.

Dimensional analysis shows that these two assumptions are equivalent. Let k_1 be the solution rate, d the diameter of particles (dimension L) and t the time for solution (dimension T); then—

$$\begin{aligned} k_1 &= \text{solution rate,} \\ &= \text{volume/unit time/unit area,} \\ &= L^3T^{-1}L^{-2} \\ &= LT^{-1} \qquad .. \quad .. \quad .. \quad .. \quad .. \quad (1) \end{aligned}$$

If complicating factors, such as the increasing concentration of the solution, particle shape, anisotropy of the material and the higher solubility of smaller particles, are neglected for the moment, and if variables such as temperature and degree of agitation are standardised, it can be assumed that diameters will decrease linearly with time and that the diameter of any particle at any instant in time will be given by—

$$d_t = d_o - k_2t \qquad .. \quad .. \quad .. \quad (2)$$

The dimensional analysis is valid for equidimensional isotropic particles such as spheres or cubes that dissolve equally along all axes. Equation (2) is valid for anisotropic particles such as crystals, provided that the solution rate along different axes is proportional to axis length; d then becomes the cube root of particle volume or the equivalent volume diameter (d_v).

Experimental

The method was tested on hydrocortisone acetate as an example of a sparingly soluble compound whose clinical efficacy might depend on particle size and solution rate. The sample used in this work was a fraction of narrow size-range, prepared by repeatedly settling and decanting a suspension of crystalline hydrocortisone acetate in water previously

saturated with hydrocortisone acetate. The fraction collected required 55 to 65 min to settle 20 cm. The original material had been crystallised from acetone in the presence of water. The absence of acetone from within the particles was confirmed by gas chromatography.

The photograph (Fig. 1) shows the uniformity of size and shape of the particles in the sample.

FIG. 1. Hydrocortisone acetate crystals, ×222.

The characteristic dimensions of a number of typical crystals were measured microscopically (cf. Michaels & Colville, 1960) and found to agree substantially with the crystallographic description given by Shell (1955), despite a more than ten-fold difference in the size of the crystals. Fig. 2 is an isometric projection constructed from the means of the microscopical measurements; the enclosing rectangular prism has the proportions of length, breadth and depth of the particle as usually defined in particle size microscopy (Heywood, 1947).

APPARATUS

A Coulter electronic counter, Model A, fitted with a 100 μ orifice tube and a 2 ml manometer was used in this work. The electrolyte was a 1% solution of sodium chloride, with 0·002% polyethylene glycol 600 monooleate and 0·008% propylene glycol as wetting agent; this concentration of sodium chloride was chosen as suitable for the required range of particle size and as a rough approximation to the ionic concentration of gastric juice. The threshold scale of the counter was calibrated by counting a suspension of 200 mg of the hydrocortisone acetate sample in 1 litre of electrolyte previously saturated with hydrocortisone acetate. The calibration constant, K, was calculated from the equation

$$K = \sqrt[3]{\frac{6VC}{\pi\rho\Sigma(\Delta n)\bar{t}}} \quad .. \quad .. \quad .. \quad (3)$$

where V is the manometer volume (μl), C is the concentration of particles in the suspension (μg/litre), ρ is the density of the hydrocortisone acetate (1·289), Δn is the count increment between successive threshold values and

$\bar{t}$ is the average threshold value for a given count increment. Particle diameter was calculated from the equation

$$d_v = K \sqrt[3]{\bar{t}} \quad .. \quad .. \quad .. \quad .. \quad (4)$$

where d_v is the 'volume diameter' in μ (the diameter of a sphere that has the same volume as the particle).

The aperture current settings were calibrated directly by determining the threshold settings required to give equivalent counts at different settings.

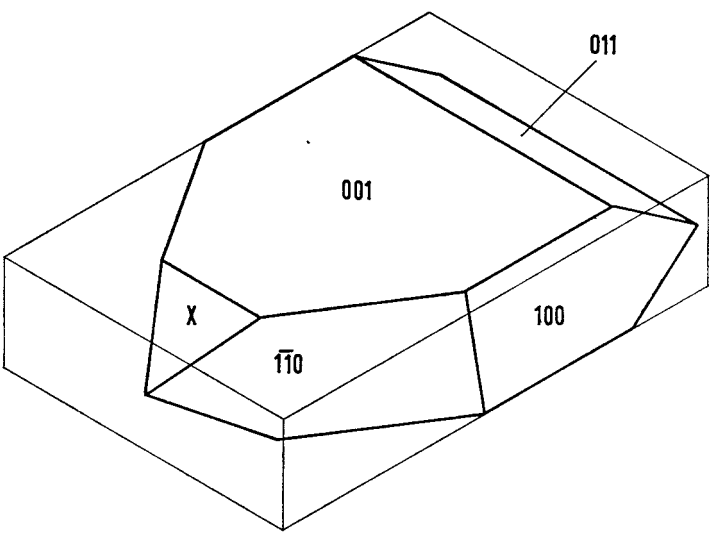

FIG. 2. Typical hydrocortisone acetate crystal in isometric projection, constructed from the means of microscopical measurements. The face numbers are as designated by Shell (1955). Face 031 was not discernible on our small crystals and face 110 was absent on most. Face X was not described by Shell. Dimensions of the enclosing rectangular prism are length, 33 μ; breadth, 22 μ; depth, 7·5 μ.

Background and coincidence corrections were made in the normal way; the former were negligible at all times, and the latter were no more than 5% of the observed count in the calibration experiment and negligible in the solution-rate experiment.

SOLUTION RATE

A suspension of particles was prepared by vigorously stirring 1·0 mg of the sample into 1 litre of electrolyte. The concentration of a saturated solution of hydrocortisone acetate in electrolyte having been found previously, by means of ultra-violet spectrophotometry, to be 10 ppm at 25° (see also Macek, Baade, Bornn & Bacher, 1952), the electrolyte would have been 10% saturated if the whole sample weight were dissolved.

Throughout the experiment the bulk suspension was maintained at 24–26° in a conical flask and transferred as required to keep the Coulter

beaker full. The suspension in the beaker was stirred by propeller at a sufficient speed to keep the particles in suspension without incorporating air bubbles. The bulk suspension was maintained in similar motion by hand swirling.

Counting was begun at an instrument setting corresponding to about the sample's initial mean particle diameter. The total count for 4 successive 2 ml portions was recorded, together with the elapsed time. After each 8 ml total had been completed, the diameter setting was reduced by 1 μ. When the count reached a maximum, counts of a second series, in descending order of diameter, were begun. Nine such series were completed in a period of 5 hr.

This method of determining solution rate depends on observing a diminishing number of particles at a given diameter setting. Therefore, to ensure that particles were not disappearing from the system because of some effect other than slow solution, the first, fourth and seventh series of counts were taken up to the maximum, to demonstrate that the same population was being counted.

Results

The initial size distribution of the sample as determined in the Coulter calibration experiment is shown in Fig. 3. The peaks of the distributions by number and by weight are at 18 μ and 20 μ respectively, the closeness

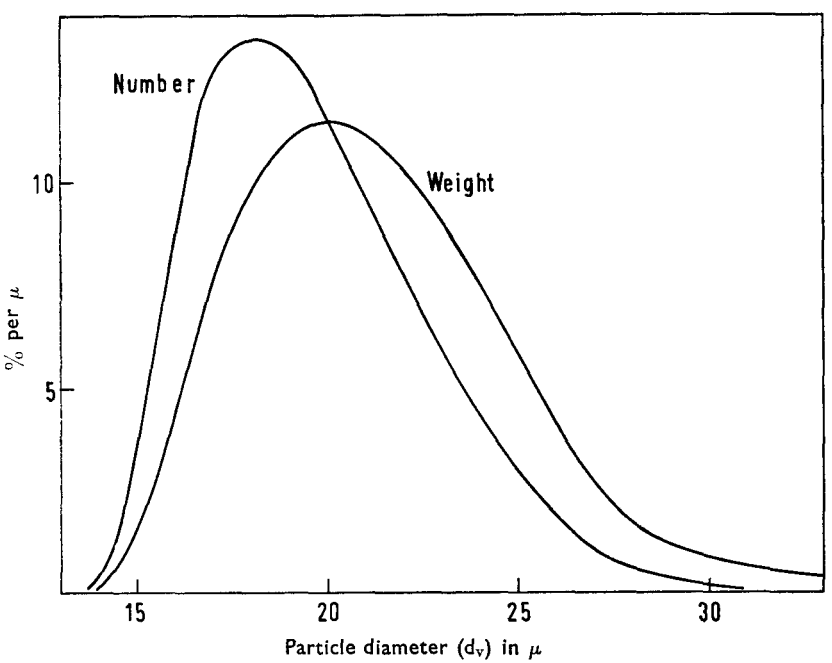

FIG. 3. Hydrocortisone acetate particle size distribution, by number and weight, determined during calibration of the Coulter counter.

of these figures indicating the narrow distribution of particle sizes. Confirmation of these results was obtained from the microscopical measurements. Calculated from the shape shown in Fig. 2, the length of a typical crystal is 1·8 times the diameter of a sphere of the same volume. The mean crystal length was found to be about 33 μ; division of this figure by 1·8 gives an equivalent volume diameter of 18·3 μ.

The experimental readings from the solution-rate experiment are shown in Fig. 4, the numbers of particles oversize in each 8 ml of suspension being plotted against time. Lines join the points representing equal diameters. Horizontal lines, corresponding to initial particle diameters of about 16 μ, 18 μ and 20 μ, cut the iso-diametric curves in their substantially straight portions. These intersections indicate the time taken for particles of about average size to be dissolved away to particles of smaller diameters.

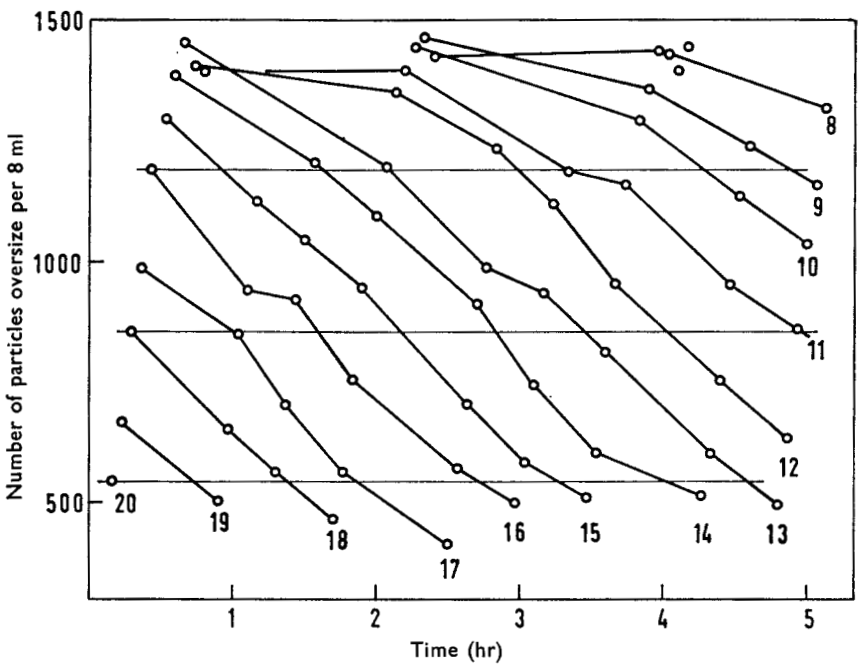

FIG. 4. Hydrocortisone acetate solution rate. The heavy lines join readings at equal diameter settings (μ). The intersections between horizontal lines and iso-diametric lines indicate the successive reductions in particle diameter.

The rate of solution is shown more clearly in Fig. 5, in which the intersections from Fig. 4 are plotted as diameter against time. The points appear to fit three parallel straight lines, as would be expected from eqn 2. However, the concentration of dissolved hydrocortisone acetate was rising during the experiment. Noyes & Whitney (1897) have shown that the rate of solution at any instant is proportional to the difference between

the concentration of a saturated solution and the concentration in solution at that instant,

$$\text{Rate of solution} = k_3(C_s - C_t) \quad .. \quad .. \quad (5)$$

This effect has been taken into account in calculating the theoretical curves that have been fitted to the experimental points in Fig. 5. The curves appear almost straight because, although 80% by weight of the sample had dissolved in 5 hr, the solution was then only 8% saturated and the solution rate at 5 hr was still 92% of the initial rate.

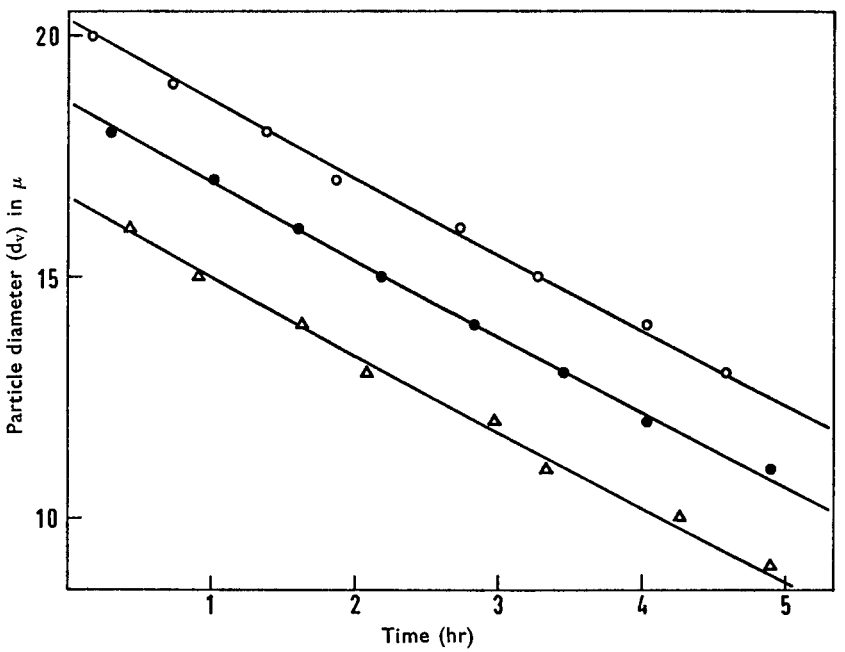

FIG. 5. Hydrocortisone acetate solution rate. Intersections from Fig. 4, at a count level of 1190, ○; at a level of 850, ●; at a level of 540, △. The theoretical curves correspond to the initial solution rate calculated as one average for all the intersections and make allowance for the increasing concentration of hydrocortisone acetate in solution.

The initial rate of solution and the theoretical curves for the Noyes–Whitney effect were calculated in stages by numerical methods. On the assumption that each size fraction lost diameter at the same rate, and with the knowledge that the sample weight was 10% of that required to saturate the electrolyte, the relative rates of solution were calculated from eqn 5 for nine successive 1 μ reductions in diameter over the whole distribution (Fig. 3).

These relative rates were calculated to relative times for each 1 μ reduction of diameter of a 20 μ particle. When the values of $d_v^{2/3}$ were plotted against relative times, the resulting curve was a straight line for the whole of its length.

In the next stage, straight lines were fitted to the experimental points of Fig. 5 by the method of least squares, with time and $d_v^{2/3}$ as co-ordinates. The slopes of these lines gave the initial rates of solution, $k_3(C_s - C_0)$, as 1·68 μ/hr at the 1,190 count level, 1·70 μ/hr at the 850 level, and 1·65 μ/hr at the 540 level, a mean initial rate of 1·68 μ/hr.

By use of this mean rate, the relative times of the previous Noyes–Whitney curve were converted to real times, thus giving the real slope of the curve. This theoretical curve, with its slope maintained, was fitted in turn to the three sets of experimental points by the method of least squares; the goodness of fit is apparent in Fig. 5.

Discussion

VALIDITY

To assess the validity of the method and its significance, one must consider critically the assumptions that have been made.

The method gives a true result in terms of weight of substance (volume × density) dissolved, provided that the Coulter instrument gives a true measure of particle volume. Kubitschek (1960) has demonstrated that the threshold scale response of the instrument is linear with volume over a wide range and has argued from earlier work by Fricke (1924) that the response is substantially independent of particle shape; the error due to the shape of the hydrocortisone acetate particles can be calculated to be less than 1% for an instrument calibrated with standard spherical particles. However, the method of calibration employed by us, together with the narrow size-range of the sample, ensures accurate volume measurement and automatic allowance for the shape factor.

Further reference to the shape factor is made in the section below on Shape and Surface Area.

The Noyes–Whitney concentration effect has been allowed for in Fig. 5 by assuming that particles of different sizes dissolve at the same rate. For the size-range involved, this assumption can be justified in three ways from the experimental evidence.

(1) Particles of average size dissolved at a linear rate until their diameter had been reduced to almost half the original diameter.

(2) The original sample contained an insignificant weight of particles having diameters less than half that of the largest (Fig. 3).

(3) A line drawn across Fig. 4 at the maximum count level, though cutting the iso-diametric curves where their shape is less well defined, does give substantially, although less reliably, the same rate constant as that given by the lines drawn at the lower count levels.

SHAPE AND SURFACE AREA

The Coulter experiment, taken alone, gives no direct information about particle shape. The expression of solution rate as diameter loss per unit time (eqn 1) therefore refers to the diameter of a hypothetical sphere having the same volume as the particle. Similarly, if the measured rate

is expressed as weight per unit surface area per unit time ($LT^{-1} = L^3T^{-1}L^{-2}$), the reference is to the surface area of the same hypothetical sphere, not to the true surface area of the particle.

The microscopical evidence of tabular shape and the demonstrated linearity of solution rate (eqn 2) together imply that the particles maintained the same shape during the course of the experiment; in other words, if the particles were originally twice as long as they were broad, the rate of reduction in length must have been double the rate of loss of breadth.

The observed solution rate at zero concentration, 1·68 μ diameter loss/hr, is equivalent, when expressed in terms of weight and surface, to a rate at a given instant of 108 μg of hydrocortisone acetate/hr/cm^2 of total surface area at that instant.

This solution rate is probably faster than that expected for pure diffusional rate control (Higuchi & Hiestand, 1963), because convection currents around the falling particles would keep the concentration low near each particle (Nielsen, 1961); from the initial gravitational settling rate of the crystals it can be calculated that each crystal of mean length 33 μ requires only 0·6 sec to settle into a zone of fresh solvent.

It is probable that the major part of the forces moving the particles relative to the solvent was due to gravity rather than to the gentle agitation that was required to keep the particles in suspension. Thus, variation in the degree of stirring, limited by the need to avoid production of air bubbles, was insufficient significantly to affect the apparent solution rate.

Acknowledgements. We thank Mr. J. L. Martin for the gas chromatography and Mr. J. P. R. Tootill for helpful discussion.

References

Berg, R. H. (1959). *Symposium on Particle Size Measurement, Special Technical Publication No.* 234, pp. 245–255, Philadelphia: American Society for Testing Materials.
Coulter, W. H. (1956). *Proc. nat. Electron. Conf.*, **12**, 1034.
Edwards, L. J. (1951). *Trans. Faraday Soc.*, **47**, 1191–1210.
Fricke, H. (1924). *Phys. Rev.*, **24**, 575–587.
Heywood, H. (1947). *Symposium on Particle Size Analysis*, pp. 14–24, London: Institution of Chemical Engineers.
Higuchi, W. I. & Hiestand, E. N. (1963). *J. pharm. Sci.*, **52**, 67–71.
Higuchi, W. I., Parrott, E. L., Wurster, D. E. & Higuchi, T. (1958). *J. Amer. pharm. Ass., Sci. Ed.*, **47**, 376–383.
Hixson, A. W. & Crowell, J. H. (1931). *Industr. Engng Chem.* (*Industr.*), **23**, 923–31.
Kubitschek, H. E. (1960). *Research*, **13**, 128–135.
Lees, K. A. (1963). *J. Pharm. Pharmacol.*, **15**, *Suppl.*, 43*T*–55*T*.
Macek, T. J., Baade, W. H., Bornn, A. & Bacher, F. A. (1952). *Science*, **116**, 399.
Michaels, A. S. & Colville, A. R., Jr. (1960). *J. phys. Chem.*, **64**, 13–19.
Nelson, E. (1957). *J. Amer. pharm. Ass., Sci. Ed.*, **46**, 607–614.
Nelson, E. (1958). *Ibid.*, **47**, 297–299.
Nelson, E. (1959). *Ibid.*, **48**, 96–103.
Nielsen, A. E. (1961). *J. phys. Chem.*, **65**, 46–49.
Noyes, A. A. & Whitney, W. R. (1897). *J. Amer. chem. Soc.*, **19**, 930–934.
Parrott, E. L., Wurster, D. E. & Higuchi, T. (1955). *J. Amer. pharm. Ass., Sci. Ed.*, **44**, 269–273.
Shell, J. W. (1955). *Analyt. Chem.*, **27**, 1665–1666.
Wagner, J. G. (1961). *J. pharm. Sci.*, **50**, 359–387.
Wilhelm, R. H., Conklin, L. H. & Sauer, T. C. (1941). *Industr. Engng Chem.* (*Industr.*), **33**, 453–457.