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The crystallization of aspirin from ethanol

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The rate of growth of aspirin crystals has been examined in a circulatory crystallizer in which the crystals are held in suspension as a fluidized bed. The deposition rate was measured, as a function of both the degree of supersaturation and the solution temperature, by observing the rate of weight increase and the change in particle size distribution of the crystals. The dependence of the mass transfer coefficient for the process upon the temperature was of the Arrhenius type, the activation energy being 21·8 kcal/mole. This indicates that the surface reaction step is rate-controlling, diffusional transport to the crystal surface being rapid. The density of aspirin solutions in alcohol has also been measured as a function of temperature and concentration.

ALTHOUGH the crystal form of many substances has been determined, and the molecular arrangement within the unit cell characterized, there is a dearth of experimental work on the rate at which crystals are formed by deposition from solution onto seed crystals. This is true for pharmaceutical materials in general and for aspirin in particular. Although much must be known within industry about its crystallization, little has been published.

In crystallization systems in general, Ting & McCabe (1934) showed that the Ostwald concept of a metastable region bounded by the solubility line and a "supersolubility line" was an oversimplification, the position of the supersolubility line being a function of the rates of cooling and of agitation as well as of the presence and amount of seed material. However, the Ostwald picture is of great practical importance and is widely used in crystallizer design. Rumford & Bain (1959) pointed out that the rate of formation of nuclei was an exponential function of supersaturation: the supersolubility line is therefore not a boundary, but merely a region where the ease and rapidity of formation of nuclei suddenly increases.

Two theories have been advanced to explain the mechanism and rate of crystal growth, that is the deposition of material onto crystals previously produced by nucleation or added as seed crystals.

The Noyes & Whitney (1897) diffusional theory assumed that the amount of material deposited was proportional to the concentration difference between the crystal surface and the bulk of the solution, the limit on the rate of deposition being the rate of diffusion through a laminar boundary layer. It was also suggested that the rate-controlling step was some form of surface reaction.

Valeton (1923) suggested that the overall process involved two stages, namely diffusion from the solution to the crystal surface, followed by a surface reaction in which the molecules arranged themselves into the crystal lattice. The two stages can be represented by the equations (1) and (2) which refer to diffusion and surface reaction respectively.

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$$\frac{dM}{dt} = K_D (C_1 - C_2) \quad (1)$$

$$\frac{dM}{dt} = K_R (C_2 - C_3) \quad (2)$$

where dM/dt is the mass rate of deposition per unit area of the crystal surface, C_1 and C_2 are the concentrations in the bulk of the solution, and at the crystal surface-solution interface; C_3 is the equilibrium saturation concentration, and K_D and K_R are the mass transfer coefficients for the diffusion and surface reaction steps.

As is usually the case in mass transfer, only an overall coefficient is determinable, and the interface concentration C_2 is inaccessible to measurement. The overall mass transfer obeys the equation, formed by adding equations (1) and (2).

$$\frac{dM}{dt} = K (C_1 - C_3) \quad (3)$$

where $1/K = 1/K_D + 1/K_R$. Either K_D or K_R may be the limiting factor on the deposition rate, but a single rate measurement will not disclose which it is. Knowledge of the diffusivity of the solute, or experiments covering a range of temperature, will enable a decision to be made. In this paper, the temperature variation of K leads to the view that the activation energy of the process is such that the surface reaction is the rate-controlling step.

Experimental

MATERIALS

The aspirin used was acetylsalicylic acid B.P. (Laporte Industries Ltd).

The ethanol was absolute ethanol, R. R. grade, (James Burrough Ltd.). This had a strength of 99·7% v/v and a maximum water content of 0·3% v/v.

APPARATUS

The apparatus used was a continuously circulating crystallizer of the type designed and reported by Mullin & Garside (1968). It is shown diagrammatically in Fig. 1. Solution is circulated by the stainless steel pump A. It passes through a variable-area flowmeter B, which is a more convenient method of flow measurement than is the orifice plate of the original design, then through a heating section C where any small crystal nuclei are dissolved. This heating section is in two parts, a main section rated at 2·5 kW and a small section for fine control of temperature rated at 100 W. The hot solution is then cooled by the water condenser D to the temperature required for the experimental section E in which the crystals are grown. Control of the temperature governs the extent of supersaturation, and a contact thermometer F allows the temperature to be held to within 0·05°.

Crystals for growth are contained in the vertical tube E, either freely or in a small cage G to prevent loss and to enable them to be removed easily.

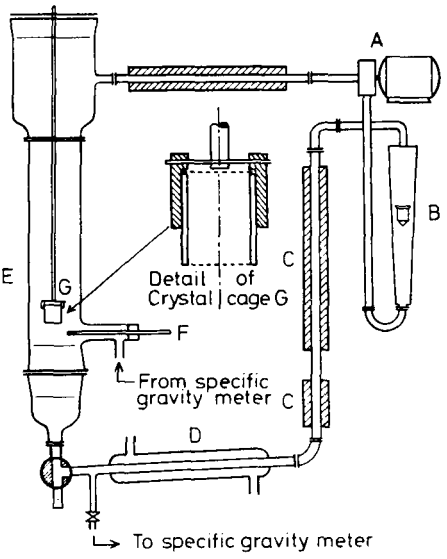

FIG. 1. The continuous circulation crystallizer. The pump A sends solution through flowmeter B, heater C and cooler D to the experimental section E, where crystals are grown as a fluidized bed, at a temperature controlled by contact thermometer F, in sample cage G. Sample cage G is shown in detail in the centre of the figure.

In either case the solution circulation velocity is maintained at a rate sufficient to ensure that the crystals are supported by the liquid to form a small fluidized bed, each crystal then being separate from its neighbours. The solution is taken from the top of the experimental section E through a heated tube back to the pump and round the circuit again.

The solution was continuously sampled, being bled off just before the experimental section and passed to a specific gravity meter (Sangamo Ltd.) connected to a chart recorder. The density measurement allowed the concentration of acetylsalicylic acid to be calculated to within better than 0·01%.

In the earlier crystallization runs, the initial seed crystals were added to the wider bore calming region at the top of the experimental section; fluid velocity was then reduced to allow them to fall to the crystallization region and then increased sufficiently once more to support them. As the seed crystals increased in size, the specific gravity meter showed a decrease in solution concentration. Sufficient warm concentrated aspirin solution was then added to bring the concentration back to the starting value. Small quantities of the seed crystals were removed at 5 min intervals over about 1½ hr, dried, and sieve analyses made.

For temperatures at the higher values within the range examined, difficulty was experienced in maintaining a constant concentration without affecting the stability of the apparatus; consequently a different method was used for some of the later experiments. A small weight of 30/40 seed

crystals (0·2 g) was contained in a crystal cage detailed in the centre of Fig. 1. This was a Perspex tube with a stainless steel mesh at each end. The cage was placed in the crystallizing region for intervals of time between 1 and 30 min, using a stainless steel rod to which the cage could be attached by a stainless steel pin. On removal from the crystallizer, the crystals were quickly drained, dried and placed in a desiccator until required for sieve analyses. After each product removal the solution in the crystallizer was heated to dissolve any solid material, the concentration adjusted, the solution cooled to the required crystallization temperature and a fresh batch of identical seed crystals immersed for a different time. During any run the product crystal weight did not increase to beyond 0·8 g, which caused a depletion of 0·6 g of aspirin from the 10 litres of solution contained in the crystallizer.

Crystallization runs were made at various degrees of supersaturation in the temperature range 27–50°.

Sieve analyses were made using a nest of 2 in diameter Endecott test sieves, with precautions as outlined by Mullin (1961). Each sieve fraction was examined to ensure that clumping had not taken place, then weighed and, in selected cases, photographed. Results were plotted in various ways to show any particle size distribution changes occurring. Cumulative weights of crystals retained by each sieve were plotted against mean equivalent particle diameter retained by each sieve on log probability paper, so that the mean equivalent particle diameter for each product batch could be found.

The density of solid aspirin was found by the usual specific gravity bottle technique and the shape of the crystals found from photomicrographs. These two factors enabled the weight and surface area of a crystal to be estimated from the mean equivalent particle diameter. Aspirin crystallizes in the monoclinic system, with unit cell dimensions $a = 11{\cdot}446$, $b = 6{\cdot}596$ and $C = 11{\cdot}388$ Å. The axis angle is 95° 33′ (Wheatley, 1964). After inspection of actual crystals, it was decided to take the crystal shape, for calibration purposes, to be a hexagonal prism with a length to width ratio of 1·3. The volume is $0{\cdot}843\ d^3$, where d is the diameter of the crystal measured between opposing apices of the hexagonal cross-section. The density of crystalline aspirin was $1{\cdot}2$ g/cm^3, so that the weight of a crystal of nominal width d is $1{\cdot}098\ d^3$ g. The surface area of the crystal is $5{\cdot}198\ d^2$. Since the crystal diameter d is also the mean equivalent particle diameter for sieve analysis, the rate of deposition of aspirin per unit area of exposed surface can be calculated from measurements of the initial and final particle size distribution and from the change in weight of the sample. Since the solution concentration is known, the mass transfer coefficient for the crystallization process at a particular temperature can be calculated, provided the equilibrium solubility for aspirin in ethanol is known as a function of temperature.

The solubility of aspirin in ethanol was therefore measured. Saturated aspirin solutions at 20 and 50° were shaken (48 hr) with solid aspirin at various temperatures between 20 and 50° in an apparatus developed for the purpose. This consisted of two round-bottomed flasks connected

neck to neck by a tube containing a quantity of glass wool to act as a filter. The saturated solution and solid particles were contained in one flask. After the required time the apparatus was inverted, still in the water bath at the required temperature, so that solid particles were held back by the glass wool. Approximately 20 ml samples of the filtered solution were removed and weighed. The ethanol was evaporated off by heating in an oven for 4 hr, and the solid material weighed. In other experiments the samples were weighed and assayed for aspirin by the official B.P. method.

During crystallization experiments, conditions were sometimes attained where neither growth nor dissolution of seed crystals occurred over a 20-min period. These conditions were taken as the equilibrium conditions and, using them, a much better solubility line was obtained. Further confirmation was obtained by extrapolating plots of growth rate against concentration back to zero growth rate.

The metastable limit for aspirin in ethanol was investigated by cooling different strength solutions at a constant rate, with a constant circulation rate in the crystallizer and noting the temperature at which the solution became opaque. Although this is not strictly the point at which spontaneous nucleation takes place, it is the point at which the nuclei have formed and grown to a size sufficient to produce opacity. It was taken as the nucleation temperature.

The density of a range of solutions of different concentrations was measured by the specific gravity meter at a number of controlled temperatures. The results of these experiments were used to set the meter temperature-compensating device; they enabled the density of aspirin solutions in ethanol to be plotted as a function of both concentration and temperature.

Results and discussion

The relation between the density of solutions of aspirin in ethanol and concentration and temperature was obtained. The measured data were plotted in the form of graphs of density against temperature, with concentration as a parameter. A series of parallel straight lines was obtained. They are represented by the equation;

Density (g/cm^3) $= 0{\cdot}8066 - 0{\cdot}00082T + 0{\cdot}0033C$ where T is the temperature (°C) and C is the concentration (% w/w).

From the nucleation observations and the determinations of concentration and temperature at which no crystal growth or dissolution took place, a solubility-supersolubility diagram can be obtained (Fig. 2). The metastable region lies between the solubility line, which is well-defined, and the spontaneous nucleation line, which cannot be fixed to the same degree of precision. The results from the equilibrium solubility determinations by evaporation and by the B.P. assay for aspirin are also shown. These lie in the metastable region, indicating that in this system the attainment of equilibrium is difficult unless there is pronounced relative motion of crystals and mother liquor: such motion occurs in the

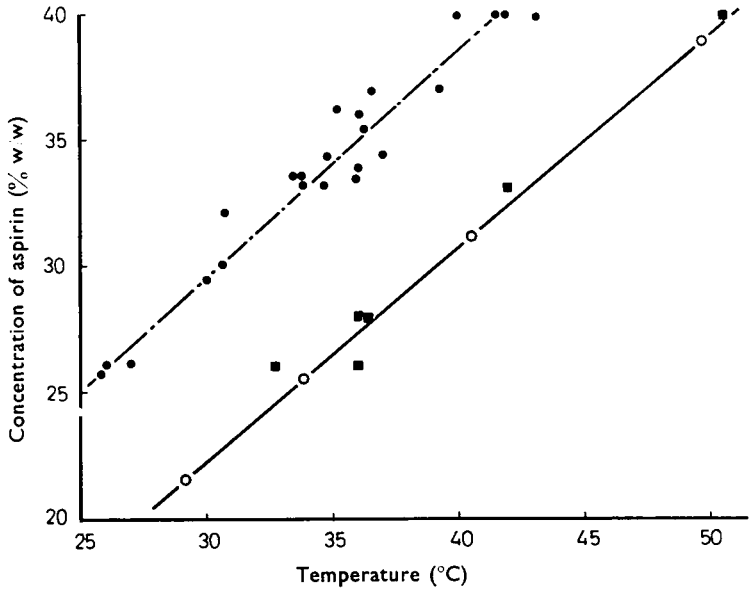

FIG. 2. Solubility-supersolubility diagram for the aspirin-ethanol system. ○ Determined in the crystallizer. ■ Determined in the solubility apparatus. ● Nucleation.

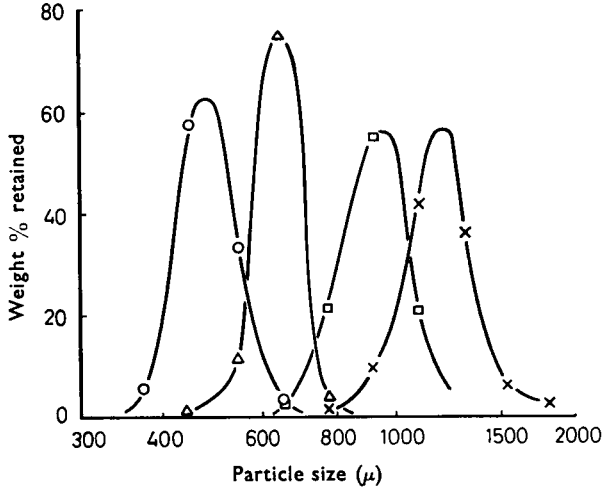

FIG. 3. Seed and product crystal size distribution. ○ Seed. △ 23 min. □ 58 min. × 102 min.

circulatory crystallizer used, but not in the normal solubility-measuring apparatus.

Repeated temperature cycling of the same solution did not change the nucleation point. This behaviour is in contrast to that found for potassium sulphate by Gaska (1966), where temperature cycling appeared to destroy some form of heterogeneous catalytic agent for nucleation.

Storage of the solution for periods of more than 12 hr in the crystallizer caused a slight fall in the nucleation temperature, suggesting that some decomposition had occurred, although it has been stated (Wing, 1956) that aspirin is stable for at least 2 years in ethanol. The two cases are not strictly comparable since our solutions are both heated and agitated in contact with glass, plastic and stainless steel, whereas those of Wing were presumably stored in closed all-glass containers. Another possibility is that the ethanol had picked up some water from the atmosphere.

These preliminary experiments defined the limits between which aspirin can be deposited onto seed crystals. A number of runs were made to measure the rate of deposition onto seed crystals at various temperatures and degrees of supersaturation. The supersaturation unit chosen is the

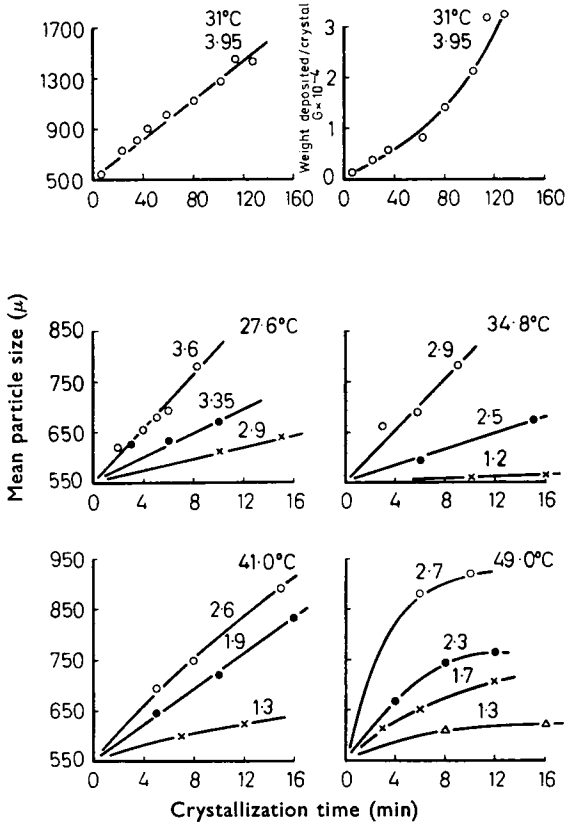

FIG. 4. Change of mean crystal size with time at various conditions of temperature and supersaturation. The figures on the lines represent $\triangle c$. The upper curves are for a 20 g batch of crystals grown at 31°, keeping the concentration in the system constant by adding strong aspirin solution. The curves for 27·6°, 34·8°, 41·0° and 49·0° were obtained by growing small samples of seed crystals, about 0·2 g in weight, for different times.

excess percentage, w/w, of aspirin over and above the equilibrium solubility, i.e.

(% of aspirin in solution contacting the crystals)
— (% of aspirin in equilibrium solution at the same temperature).

This quantity is given the symbol $\triangle c$.

Fig. 3 shows the particle size distribution for the seed crystals, which were identical for all the crystallization runs made. Also shown are some typical product crystal size distributions. The size range tended to broaden with increasing crystallization time, probably because of stratification in the bed of crystals. Larger crystals tend to spend more time at the bottom of the bed, where they meet fresh mother liquor and therefore tend to grow faster. If the seed size distribution and the product size distributions are plotted on log-normal probability paper, straight lines are obtained, parallel to the seed line, showing that the size distributions are all log-normal and similar. This means that valid conclusions may be drawn from the change in mean particle size of a batch of crystals as they grow. This simplifies the analysis of the results. Fig. 4 shows a plot of mean particle size as a function of crystallization time for various temperatures and degrees of supersaturation. Most experiments up to 40° produced a series of straight lines with slopes depending on the concentration difference present. These graphs could be compared with linear growth rate results, if in our experiments the relative growth rate of each face remained the same. Since no great crystal shape change occurs in the range of concentration difference studied, this is probably valid.

TABLE 1. MEASURED MASS TRANSFER COEFFICIENTS FOR THE CRYSTALLIZATION OF ASPIRIN FROM ETHANOL AT VARIOUS TEMPERATURES AND DEGREES OF SUPERSATURATION

Experiment No.	Temperature, °C	Solution concentration, % w/w	$\triangle c$ % w/w	Mean K, 10^{-3}g/cm² min %
1	31·0	27·0	3·95	0·122
2	37·5	35·5	6·9	0·281
3	50·0	40·5	1·3	0·923
	40·5		2·2	
4	41·2	33·3	1·6	0·386
	39·2		3·3	
	33·4		2·9	
5	33·8	28·0	2·5	0·177
	35·4		1·2	
	27·2		3·6	
6	27·5	23·5	3·4	0·120
	28·1		2·9	
	28·8		1·9	
7	29·7	40·0	1·1	0·434
	50·5		0·4	
	29·1		3·1	
8	29·7	24·6	2·6	0·093
	48·5		2·3	
9	49·2	40·2	1·7	0·823
	49·7		1·3	
	40·0		2·6	
10	41·0	33·4	1·9	0·368
	41·7		1·3	

Table 1 shows the parameters for each of the nine major experiments carried out. From each experiment, a linear relation was obtained between the weight deposited per unit area of crystal surface per unit time,

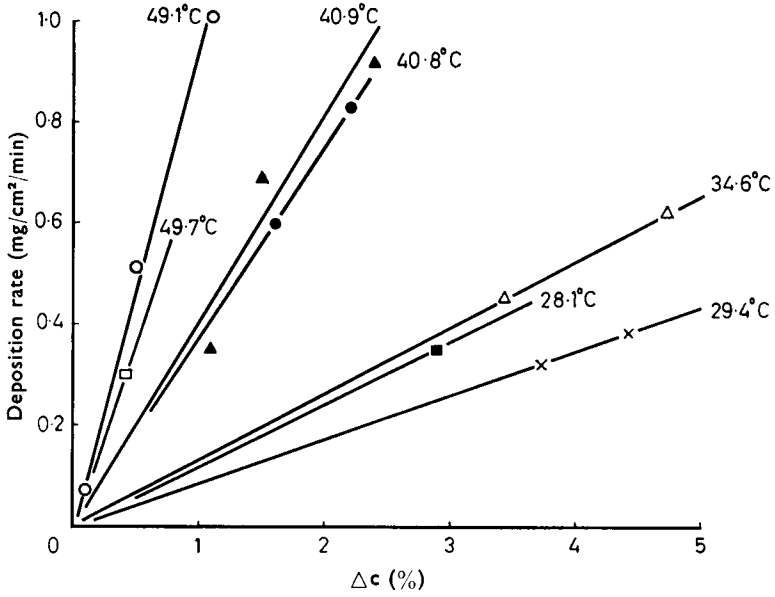

FIG. 5. Weight of aspirin deposited per cm² of mean area of crystal per min as a function of concentration driving force, Δc. The slope of each line is the mass transfer coefficient, K, measured in grams deposited/cm²/min/unit percentage concentration difference. The figures on the lines represent the temperatures of crystallization.

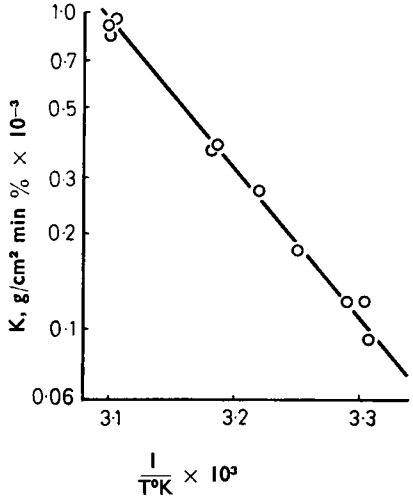

FIG. 6. Arrhenius plot of log K against 1/T, leading to a value of 21·8 kcal/mole for the activation energy.

and the concentration driving force, $\triangle c$, for the deposition process. This is shown in Fig. 5. The slope of the line is the mass transfer coefficient, K, usually expressed as grams deposited per cm^2 per sec per unit concentration difference. The linear relation between rate of deposition per unit area and the concentration difference $\triangle c$ is an indication that K is constant for any given experiment, and is therefore a function only of temperature.

The variation of K with temperature was found to follow an Arrhenius type law. Fig. 6 shows a plot of log K against 1/T where T is the temperature in °K. The equation of the straight line is

$$\log K = \frac{-4760}{T} + \text{constant.}$$

The Arrhenius equation is $K = A \exp(-E/RT)$, or $\log K = \frac{-E}{2{\cdot}303\ RT}$ + constant. Thus we have $\frac{E}{2{\cdot}303\ R} = 4760$ or $E = 21{\cdot}8$ kcal/mole.

This value may be compared with van Hook's (1944) values for sucrose, which are 22 kcal/mole at 0° C falling to 6·5 kcal/mole at 70° C. This was for crystallization from water. A value of 21·8 kcal/mole is indicative of the rate-determining step being the incorporation of a molecule onto the crystal lattice, rather than the rate at which the molecules are able to diffuse to the crystal surface. Diffusion-controlled mechanisms usually give activation energy values nearer to 5 kcal/mole, (cf. the crystallization of sodium chloride from water, Rumford & Bain, 1959).

Since it is the step of incorporation into the lattice which is rate-limiting in the growth of aspirin under the conditions of these experiments, it might be expected that where incorporation is rapid, a larger number of imperfections would be built into the crystal. The hardness of a crystal which had been grown more rapidly would then be expected to be less, and its ultimate compressive strength would be reduced compared to a more slowly-grown specimen. Preliminary measurements of microhardness and tensile strength support this conclusion.

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