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The crystallization behaviour of sulphathiazole

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Previous investigations into the dissolution kinetics of sulphathiazole Form 1 have shown the process to be first order with respect to driving force. However, below 37° first order kinetics did not apply, due to the surface reaction becoming the rate controlling factor. The present study examines the kinetics of crystallization over the temperature range 25 to 50°. Crystallization is a process greatly dependent upon the high-entropy surface integration step which, unlike the dissolution process, is much more sensitive to crystal growth inhibitors. In the absence of inhibitors crystallization above 34° follows first order kinetics but below 34° the process changes to third order. Similar temperature effects on the dissolution of sulphathiazole have been previously reported.

The dissolution rate constants of sulphathiazole under varying conditions of temperature were shown by Carless & Jordan (1974) to be limited by the interfacial reaction occurring at the solid-liquid boundary at temperatures below 37°. Above this temperature, the interfacial reaction became infinitely rapid so that dissolution could be assumed to be limited only by the diffusion of the dissolved solid away from the solid surface.

Crystal growth under conditions of controlled temperature fluctuation is believed to occur by a dissolution–crystallization–dissolution–recrystallization process.

The calculation of the kinetics of dissolution is relatively easy because the theoretical treatment proposed by Levich (1962) can be used to calculate dissolution rate constants for a diffusion-controlled process. These can be compared with observed rate constants obtained from experimental data, using a Noyes-Whitney type equation. Similar treatment cannot be applied to crystallization. However, Mullin & Gaska (1969) have investigated growth rates in a fluidized bed crystallizer using potassium sulphate at different levels of supersaturation and temperatures. They found that growth rate is related to the difference between saturation and supersaturation concentration (i.e. ΔC) by

$$Rg = Kg\,(C - C^t)^n \qquad (1)$$

$$\text{or} \quad Rg = Kg\,(\Delta C)^n$$

where Rg = growth rate; Kg = rate constant; C = supersaturation concentration; C^t = saturation concentration at time, t; n = concentration exponent; ΔC = supersaturation concentration.

The overall growth kinetics of potash alum at 32° have been shown by Mullin & Garside (1967 a,b) to follow a non-first order law. Garside & Mullin (1968) suggest that a significant rise in the value of the concentration exponent, n, is indicative of a change from a diffusion-controlled to a surface integration controlled process which is analogous to interfacial reaction controlled dissolution.

Our aim was to establish the nature of the recrystallization controlling process(es) for sulphathiazole at temperatures varying from 25 to 50° by determining the concentration exponent, n, from experimental data (log growth rate against log ΔC plots).

Trace amounts of F, D and C Blue No. 1, which is a certified, water-soluble foodstuff dye (sometimes used as a colourant in formulated preparations), has been shown to greatly influence the rate of dissolution (Piccolo & Tawashi, 1971). Although we have confirmed this, the effect of the cationic water-soluble dye, malachite green, was found to be greater and work on the influence of this dye on the crystallization of sulphathiazole is also included.

MATERIALS AND METHODS

Sulphathiazole Form 1 was prepared by recrystallization of micronized sulphathiazole B.P.C. (Evans Medical Limited, Speke, Liverpool, U.K.) from distilled water at 60°, the hot liquor being allowed to cool slowly for 5 h before the crystals were filtered off. These were then allowed to dry in air for three days before being sieved to yield a narrow cut fraction. The geometric mean diameter of the fraction (Coulter Counter) was 32 μm. By introducing a dyestuff into the recrystallization medium (distilled water) crystals were produced containing dye molecules distributed throughout the sulphathiazole structure. Dye concentrations of 0·0002, 0·002 and 0·010% in aqueous solution were used. All recrystallized materials were characterized by infrared and differential scanning calorimetry.

Malachite green (basic colour type 4), colour index 42000) was supplied by British Drug Houses (Poole, Dorset, U.K.); by paper chromatography with 25%

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n-butanol in water as the mobile phase, it gave only one spot R_F value 0·366 (other dyes e.g. F, D and C Violet No. 1, produced up to three separated spots using the same technique.) Further purification was not thought necessary.

Distilled water saturated with sulphathiazole powder was equilibrated at temperatures which allowed the amount of drug to be in excess of the saturation concentration at the temperatures chosen (25, 30, 34, 37, 40, 45 and 50°).

The difference between saturation and supersaturation concentration, defined as ΔC, was the driving force for the crystallization experiments. Another series of experiments was carried out at a constant temperature of 45°, for different values of ΔC. All supersaturated solutions were passed through a membrane filter (0·65 μm) into a heated Buchner flask and were then equilibrated at 20° in excess of the chosen temperature before being added to the crystallizer which contained 300 mg of seed crystals. The final volume was 200 ml. A three-bladed paddle attached to a motor (Citenco Limited, Boreham Wood, Herts., U.K.) provided constant agitation conditions of 300 rev min^{-1} which was just sufficient to prevent sedimentation of the seed crystals.

Samples (approximately 2 ml) were taken by a syringe at appropriate times and passed quickly through a Swinnex unit containing a membrane filter (0·45 μm) into a vessel at a temperature well in excess of the operational temperature to avoid further crystallization. Aqueous dilutions were then prepared from this solution and assayed by spectrophotometry at 283 nm.

The weight of sulphathiazole still present in the solution could be calculated and from a knowledge of the concentration of the starting solution, the amount of drug deposited on the seed crystals could be calculated. The weights were then plotted against time, to yield crystallization curves.

When crystallization of samples prepared from dye solutions was investigated, the same dye concentration was included in the crystallization medium as was used for the preparation of the seed crystals to ensure that the crystal structure would be comparable with that of the original seed crystals.

RESULTS

Growth 'rates' were measured by assessing the total weight of sulphathiazole gained by the crystals, i.e. lost from solution, in a standard time and then expressed as mg s^{-1} drug taken up by the crystals. The standard time was chosen so that ΔC changed approximately 10%, as suggested by the work of Mullin & Gaska (1969) for the determination of growth rates. Growth rates at different temperatures are shown in Table 1. A plot of growth rate against ΔC showed a deviation from a straight line at temperatures below 34° (Fig. 1A). Growth rates at constant temperature are given in Table 2; Fig. 1B shows a direct relation between growth rate and ΔC.

Table 1. *Values for growth rate at different temperatures.*

T°C	ΔC mg %	Rg mg s^{-1}	Crystal growth rate* mg g^{-1} cm^{-2} ΔC^{-1}
25	47	0·43	0·044
28	57	1·04	0·088
30	61	1·23	0·097
34	71	1·8	0·122
37	84	2·15	0·123
40	94	2·8	0·144
45	121	3·69	0·147
50	158	4·6	0·141

Rg = growth rate.
*Based on specific surface of 0·126 m^2 g^{-1}.

The logarithmic plot of Fig. 1A produced two linear relations (Fig. 2) the slopes of which were direct measures of concentration exponent (n) and were calculated to be 3·04 at temperatures in excess of 34° and 0·942 at temperatures below 34°.

In an attempt to express the effect of temperature on growth rate independent of concentration driving force, growth rates (calculated in terms of unit

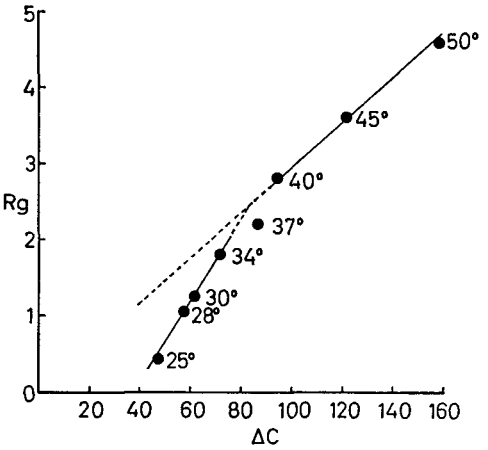

FIG. 1A. Effect of concentration difference (ΔC) (mg %) on growth rate (Rg) (mg s^{-1}) at various temperatures.

Table 2. *Values for growth rate at constant temperature.*

T°C	ΔC mg %	Rg mg s^{-1}	Crystal growth rate* mg h^{-1} cm^{-2} ΔC^{-1}
45	41	1·2	0·141
45	63	1·84	0·141
45	80	2·25	0·136
45	94	2·8	0·144

Rg = growth rate.
*Based on specific surface of 0·126 m^2 g^{-1}.

surface area and at a constant concentration difference of 5 mg % i.e. mg h^{-1} cm^{-2} ΔC^{-1}) were plotted against temperature (Fig. 3). Surface areas were calculated by application of the Hatch-Choate equation, using a Heywood shape factor of 7·35, to Coulter Counter size analyses.

Growth inhibition with malachite green dye. Growth rates were calculated in a similar manner and, when plotted against ΔC, were found to yield a straight line relation, the slope of which decreased with increasing dye concentration (Table 3). Plotted on logarithmic axes (Fig. 4), again the straight line relations were retained and the exponents of ΔC derived from these plots, therefore, were constant over the whole temperature range studied.

Concentration exponents were obtained by standard statistical analysis of the data, which also showed the correlation coefficient for the straight lines to be always greater than 0·986 for growth rate against ΔC plots and 0·95 for log growth rate against log ΔC plots.

The introduction of a dye into the crystallized sulphathiazole produced rectilinear growth rate *vs* temperature plots (Fig. 5) whilst over the same temperature range (in the absence of dye), a different relation was obtained (Fig. 3).

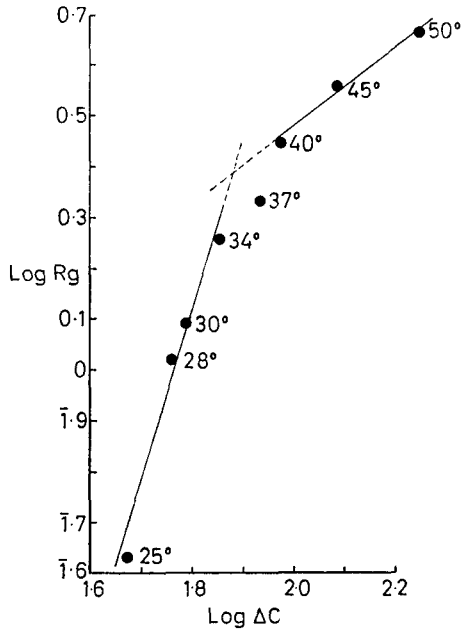

FIG. 2. Effect of log ΔC (mg %) on log growth rate (Rg) (mg s^{-1}) at various temperatures.

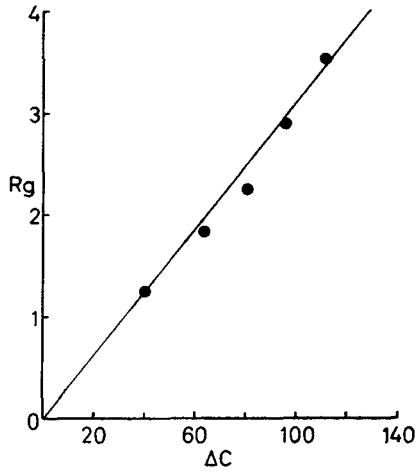

FIG. 1B. Effect of concentration difference (ΔC) (mg %) on growth rate (Rg) (mg s^{-1}) at constant temperature 45°.

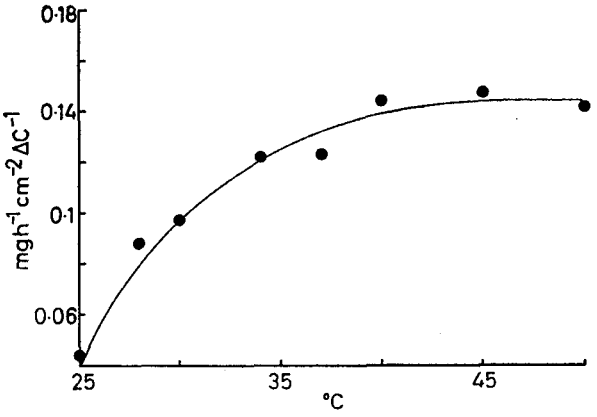

FIG. 3. Effect of temperature (°C) on crystal growth rate (mg h^{-1} cm^{-2} ΔC^{-1}) in the absence of dye.

Table 3. *Values for concentration exponent (n) in crystals containing dye.*

Dye concn % w/v	Slope of Rg against ΔC plots × 10^3	Concentration exponents 25–34°	34–50°
0		3·04	0·94
0·0002	8·19	2·0	2·0
0·002	7·94	2·25	2·25
0·010	4·38	4·0	4·0

Rg = Growth rate mg s^{-1}.
ΔC = Concentration difference mg %.

DISCUSSION

In the past crystal growth data have been explained in terms of the diffusional theory. The rate of diffusion has already been shown by Mullin & Gaska (1969) to influence the growth rate. However, the theory has usually assumed that the growth kinetics are first-order with respect to the concentration difference or that the surface integration of drug molecules is also a first-order consideration. The growth kinetics of potash alum crystals at 32° has been found not to be a first-order process (Mullin & Garside, 1967) and this also seems to be the case with sulphathiazole.

Fig. 2 shows a significant change in slope, and therefore, the exponent of ΔC, between 25 and 50°. Table 3 shows that, between 25 and 34°, this exponent (n) is 3·04 which is significantly larger than the value obtained between 34 and 50° (0·942). We postulate that this indicates a change from a situation in which the integration of molecules into the surface is the process-limiting factor to one in which the surface integration step is assumed to be infinitely rapid and the process is limited by the rate of diffusion of the drug molecules to the surface.

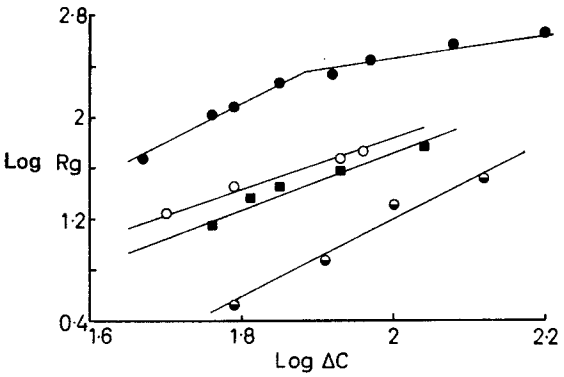

FIG. 4. Effect of log ΔC (mg %) on log growth rate (Rg) (mg s^{-1} × 10^3) for systems containing dye. Key: ● no dye; ○ 0·0002%; ■ 0·002%; ◒ 0·01% dye.

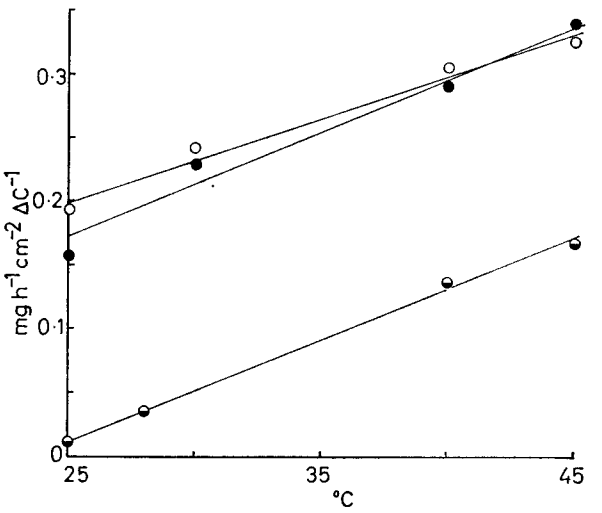

FIG. 5. Effect of temperature (°C) on crystal growth rate (mg h^{-1} cm^{-2} ΔC^{-1}) in the presence of dye. Key: ○ 0·0002%; ● 0·002%; ◒ 0·01% dye.

These findings seem to add weight to the validity of the work of Mullin & Gaska (1969) (equation 1). The presence of a finite surface integration step in the growth of sulphathiazole crystals below 34° correlates well with our dissolution kinetic studies in which the interfacial reaction at the solid–liquid boundary was found to be the dissolution rate limiting factor at temperatures below 37°.

The duplicate crystallization experiments carried out at the constant temperature of 45° shows a linear relation between growth rate and ΔC as illustrated in Fig. 1B. Our dissolution results (Carless & Jordan, 1974) and present crystallization studies at temperatures varying from 25 to 50° suggest that a purely diffusion-controlled process is operating at 45° which accounts for the linearity of this plot.

It would appear that the process by which the drug crystal dissolves or grows is limited at the same crucial temperature by the surface reactivity or integration capability of the substance i.e. the processes are equivalent with respect to temperature. Further confirmation of this limitation at about 34° is illustrated by Fig. 3 in which growth rate (independent of ΔC) increases with temperature to a constant value above 34°. The separate investigation of growth rates at the constant temperature of 45° (Table 2) also shows the values of growth rate to remain constant as ΔC varies. This is consistent with the diffusion controlled process being independent of the thermodynamic activity of the surface since

the rate of the interfacial reaction is not the process limiting step. Below 34°, the rate of the interfacial reaction is the process controlling factor, and Fig. 3 shows the process to be temperature dependent.

Dissolution kinetic studies showed that the introduction of a dye into the crystallized sulphathiazole reduced the activity of the surface significantly, so that the dissolution process was limited by the interfacial reaction throughout the temperature range studied (25–45°) (Carless & Jordan, 1974). We believe that the same is true for crystallization of sulphathiazole although much lower concentrations of dye are required due to the sensitivity of the surface reaction involved in crystallization. Between 25 and 45° the presence of dye produced rectilinear relations between log growth rate and log ΔC (Fig. 4), which suggests that growth is completely controlled by the surface integration step over the whole temperature range. Agreement between the averge concentration exponent derived from these plots ($n = 2{\cdot}75$) and the value obtained in the absence of dye between 25 and 34° ($n = 3{\cdot}04$), confirms this suggestion. Also, Fig. 5 shows that the presence of dye in the crystals causes the growth rate (independent of ΔC) to vary uniformly with temperature throughout the whole temperature range whereas, in its absence, growth rate became independent of temperature above 34° (Fig. 3) due to the presence of diffusion control.

The calculation of growth rates in a short, standard time was thought to ensure that they were comparable with dissolution rates measured under sink conditions. Furthermore, growth rates calculated at a constant value of ΔC of 5 mg % ensures that $C^t \leqslant 0{\cdot}1$ C (from equation 1), even at the lowest temperature studied, which is equivalent to dissolution sink conditions as well as providing values of growth rate independent of ΔC. If these are now expressed at constant initial surface area, i.e. mg h^{-1} cm^{-2} 5 mg$\%^{-1}$ or mg h^{-1} $cm^{-2}\Delta C^{-1}$, then these would then be analogous to intrinsic dissolution rates under sink conditions. Subsequently, we have observed the kinetics of dissolution and crystallization and, generally, dissolution proceeds two to five times faster than crystallization, which correlates well with the findings of Garside & Mullin (1968) for potash alum.

An understanding of the rate controlling step in crystallization is important when investigating crystal growth produced by temperature fluctuations (Carless & Foster, 1966). With sulphathiazole, for instance, different processes operate when a suspension of the drug experiences temperature fluctuations in the range 25–50°, so making a theoretical prediction of crystal growth impossible. The presence of a crystal inhibitor renders crystal growth more likely to surface integration limitation over the whole of this temperature range.

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