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Modification of acetaminophen crystals: influence of growth in aqueous solutions containing *p*-acetoxyacetanilide on crystal properties

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Summary

Acetaminophen (paracetamol, P) was crystallized under defined conditions from water containing various concentrations of *p*-acetoxyacetanilide (A). The uptake of A by growing crystals, determined by HPLC, is approximately proportional to the initial concentration of A in the crystallization medium, 0–1000 $mg \cdot dm^{-3}$ causing 0–3×10^{-3} mole fraction to be incorporated into the crystals at 30°C. A at $\geqslant 1250$ $mg \cdot dm^{-3}$ causes incorporation to level off at ca. 4.5×10^{-3} mole fraction, corresponding to the solid solubility limit of A in P at 30°C. Washing the crystals with iso-octane indicates that negligible quantities of A are adsorbed onto the crystal surfaces. Increasing uptake of A (0–0.0015 mole fraction) displaces water from the crystals (from 0.041 to 0.013 mole fraction) and increases the enthalpy of fusion, ΔH^f, by 1–9%, the melting point, T_m, by 0.1–0.6%, and the entropy of fusion, ΔS^f, by 1–8%, suggesting increases in lattice strength and order. Above 0.0015 mole fraction of A, water uptake rises (0.013–0.024 mole fraction), while ΔH^f, T_m and ΔS^f decrease, suggesting weakening and disruption of the crystal lattice. ΔS^f is a linear function of the calculated ideal entropy of mixing of P + A + W with a slope of −6.5. This suggests that a much greater disordering of the crystal lattice is created by the impurity defects as compared with simple random mixing of the molecules.

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Various sieve fractions covering the range 30–800 μm show negligible differences in ΔH^f and T_m. X-Ray powder diffraction failed to detect any significant change in lattice dimensions ($< 0.5\%$). Increasing concentrations of A produce progressive elongation of P crystals, the length/width ratio reaching a maximum at 1000 mg · dm^{-3} A, and decreasing at higher concentrations. The specific surface area of a defined sieve fraction of P crystals is reduced by growth in 100 mg · dm^{-3} A, corresponding to tabular habit, but is augmented by growth in 300–1100 mg · dm^{-3} A, corresponding to progressive habit elongation. The initial dissolution rate of the same defined sieve fraction of P crystals also decreases slightly in the presence of 100 mg · dm^{-3} A, but increases to a maximum at 700 mg · dm^{-3} and then decreases slightly at higher concentrations of A. The initial dissolution rate per unit surface area (intrinsic dissolution rate) displays an approximately parabolic shape with a maximum at 600 mg · dm^{-3} corresponding to a maximum increase by a factor of 2.1.

The results point to the origins of certain batch-to-batch variations in pharmaceutical raw materials and demonstrate that growth of drug crystals in the presence of low concentrations of additives can be used to control water content, crystal energy, crystal order and dissolution rate, perhaps by altering the density of crystal imperfections.

Introduction

Recent work in our laboratories with adipic acid, a pharmaceutical excipient and safe food additive, has shown that the physical properties of its crystals, such as habit, energy, density, specific surface area and dissolution rate, are modified by the deliberate addition of trace amounts of fatty acids to the aqueous crystallization medium (Fairbrother and Grant, 1978, 1979; Chow et al., 1984). The additives are incorporated into the crystals. The above compounds consist of monofunctional straight-chain aliphatic molecules whose packing in the crystal lattice is relatively simple.

These studies have here been extended to polyfunctional aromatic molecules. For this purpose, the widely-used analgesic and antipyretic drug, acetaminophen (paracetamol, P), has been selected to ascertain the extent to which the principles already established for adipic acid are applicable to a common drug. The specific reasons for the choice of P are as follows: (a) the solubility in water (16.45 g · dm^{-3} at 30°C; Grant et al., 1984) is such that water can be used as a very pure, cheap solvent enabling crystals to be harvested from it in good yield; (b) the crystals obtained from aqueous solution are well-formed and their various crystal habits give no evidence of polymorphic forms or hydrates, as shown by differential scanning calorimetry, hot-stage microscopy and X-ray diffraction; and (c) P was deemed to be a suitable drug for future studies of the influence of crystal properties on mechanical processing after the present foundations have been laid.

The additive used to modify the crystal properties of P is *p*-acetoxyacetanilide (A), a synthetic impurity (Fairbrother, 1973) and a suggested prodrug of P (Dittert

et al., 1968; Bauguess et al., 1975). The choice of this additive therefore serves: (a) to probe the influence of a synthetic impurity on possible batch-to-batch variations of a solid drug; and (b) to evaluate the possible use of a prodrug to modulate the crystal properties of the parent drug. It turns out that the water content of the crystals, which is controlled by A, is probably a crucial intermediary in explaining the observed effects of A.

Materials and Methods

Reagents and materials

P (USPXX, m.p. 170–171°C) was the purest available commercially and was supplied by Frank W. Horner Ltd., Mississanga, Ont. and by McNeil Consumer Products, Guelph, Ont. Both samples gave only one sharp peak in DSC and HPLC (with methanol–water systems) and were analytically indistinguishable. The adsorbed water was removed, if necessary, by drying over phosphorus pentoxide under vacuum at 22°C. A was prepared from P by the method of Chattaway (1931) and was recrystallized from ethanol as white crystals melting at 153–155°C. Acetanilide (m.p. 113–115°C) was supplied by J.T. Baker Chemicals, and was recrystallized from ethanol–water. Acetonitrile and methanol used for high-performance liquid chromatography were HPLC grade reagents supplied by Fisher.

Batch crystallization from water

P (9 g) was dissolved in 390 cm^3 of distilled water at 55°C and A (0–2000 $mg \cdot dm^{-3}$) was added to form a clear solution. After equilibration, the solution was transferred to a 500 cm^3 three-necked, round bottomed flask immersed in a thermostatic water bath at 30.0 ± 0.1°C. When the temperature of the flask contents had fallen to 42°C, the supersaturated solution was seeded with 1 mg of a defined sieve fraction (30–75 μm, 400–200 mesh) of P seed crystals and stirred at 240 ± 1 rpm for 2 h. These conditions correspond to an initial supersaturation of 6.63 $g \cdot dm^{-3}$ at 30°C. The crystals obtained were then rapidly filtered off, spread on a glass Petri dish, air dried overnight and further dried over phosphorus pentoxide in a vacuum desiccator for 2 days before use. This procedure removes all the adsorbed water and only the adsorbed water, because: (a) no further water loss occurs between 2 days and 1 month; and (b) grinding the crystals, even for less than 1 min, removes virtually all the water.

Equilibrium solubility studies

The equilibrium solubilities of P in water at 30, 40 and 50°C in the absence and presence of 500, 1000 and 1500 $mg \cdot dm^{-3}$ A were measured as described by Grant et al. (1984).

Water content determination

The water content of 0.5 g samples of a defined sieve fraction (250–355 μm, 60–45 mesh) of P crystals was determined by Karl Fischer titration using Metrohm

equipment (655 Disomat, 614 Impulsomat, and 605 pH-meter). The Karl Fischer reagents (Eugen Scholz modification) and the hydration standard, sodium tartrate dihydrate, were Hydranal grade, manufactured by Riedel-de Haën, Seelze, F.R.G., and supplied by Crescent Chemicals, Hauppauge, NY, U.S.A. Since the process of drying the crystals after harvesting effectively removes all the adsorbed water and only the adsorbed water, the water content being determined after drying is that within the crystal lattice of P.

Incorporation of additive into growing crystals

The uptake of A by P crystals was determined by high-performance liquid chromatography using a Perkin-Elmer Series 4 Chromatograph with a UV detector (LC-85), an automated sampling system (ISS-100), a data processing station (Sigma 15), and a Beckman Ultrasphere C-18 reversed-phase column (4.6 mm × 15 cm). The mobile phase consisted of 27% methanol and 73% water which was eluted at 2 cm^3 per min. The doped crystals (ca. 50 mg) and acetanilide as the internal standard were dissolved in acetonitrile (5 cm^3) and 5 mm^3 samples were injected (0.05–0.25 μg A + 0.2 μg acetanilide). The retention times of P, A and acetanilide were 1.52, 5.78 and 4.69 min, respectively. Calibration plots using different amounts of A and a fixed amount of acetanilide as the internal standard showed that the UV detector response at 248 nm was a linear function of the amount of A over the concentration range employed. The original P crystals were found not to contain detectable amounts of UV-absorbing impurities, such as other aromatic compounds which are the only significant organic impurities.

Microscopic methods, calorimetric techniques, X-ray powder diffraction and specific surface area measurements

Optical microscopy, scanning electron microscopy (SEM), hot-stage microscopy (HSM), differential scanning calorimetry (DSC), X-ray powder diffraction and specific surface area measurements (SSA) were carried out as described by Chow et al. (1984).

Crystal size measurements were carried out on 20 crystals using optical microscopy. For each crystal the longest dimension was taken as the length and the shortest dimension as the width on a normal 2-dimensional representation. The mean values of each dimension over 20 crystals are depicted in Figs. 4 and 7.

DSC measurements were carried out in sealed pans to prevent sublimation of P and loss of water. Indium was used as the calibration standard. From the single observed endotherm the melting point, T_m, of the crystals was taken to be the temperature at the point of intersection of the leading line of steepest slope and the base line. The enthalpy of fusion, ΔH^f, of the crystals was calculated from the peak area which was determined by cutting and weighing. The precision of this procedure was 0.5–1.0% using chart paper either from Perkin-Elmer or from Graphic Controls Canada, Gananoque, Ont. Thus, the extent of each standard deviation bar in Fig. 2 is mainly a result of sample-to-sample variation. Neither P nor A underwent significant decomposition up to and beyond the melting point because: (a) the baseline of pure samples of A and P continued to be flat at temperatures above that

of the peak; and (b) the shape and area of the melting endotherm were respectively the same for the resolidified melt as for the original, pure crystals of A or P.

X-Ray diffraction failed to detect any differences in lattice dimensions ($< 0.5\%$) for representative samples of P crystals with and without A. DSC and HSM showed that A causes only small changes in melting parameters and does not elicit any polymorphic transitions. Thus, A does not bring about gross changes in crystalline structure of P and polymorphism can be ruled out.

For SSA 0.25–0.5 g samples were outgassed by repeated adsorption of nitrogen at 77K and desorption under vacuum at 25°C; six cycles were normally sufficient to obtain constant values of SSA. Nitrogen gas was also used as the adsorbate and for calibration. To reduce small instrumental variations, the volume of nitrogen gas injected for calibration was adjusted to within 30%, and preferably to within 10%, of the volume of the gas desorbed. The amount of nitrogen gas desorbed was found to be strictly proportional to the mass of solid sample used as the adsorbent.

Dissolution rate

The surface-dried P crystals were sieved for 15 min and 75 mg of the fraction 355–500 μm (45–35 mesh) were added at zero time to 750 cm^3 of outgassed distilled water containing Brij 30 (1 in 20,000 v/v), which afforded instantaneous wetting of the crystals. The USPXX/NFXV (1982) dissolution test using Apparatus 2 with paddle stirring at 50 rpm was employed in an automated dissolution apparatus (Dissoette, Hansen Corporation, Northbridge, CA). Triplicate samples of 3.0 cm^3 were withdrawn every minute and the mass of P dissolved was calculated from the concentration after correcting for the change in volume of the dissolution medium. The concentrations of dissolved P were determined by UV spectrophotometry of diluted 1 cm^3 aliquots at 242 nm (λ_{max}) using a Carl Zeiss spectrophotometer PMQ II. Mean concentrations and standard error bars are presented. In order to reduce the dissolution rate of P crystals sufficiently to enable the initial dissolution rate to be determined from the initial slope of the dissolution–time curve, the temperature of the thermostatic water bath was reduced to 4.0 ± 0.1°C by means of a "cold-finger" cooler (Lauda IC-6, Brinkman Instruments).

Results and Discussion

Uptake of additive and water

The mole fraction of A, x_2, in the crystals of P increases with increasing concentration of A in the defined crystallization solution (Fig. 1a), but at concentrations of A > 1250 $mg \cdot dm^{-3}$ in solution, x_2 levels off at about 0.0045. This plateau value evidently corresponds to the solid solubility limit of A in the P crystals at 30°C under the conditions of crystallization defined above.

Increasing initial supersaturation of P in solution, for a given concentration of A and stirrer speed, progressively reduces uptake of A (Fig. 1c) which expresses increasing competition of P for the adsorption sites on the surface of the growing crystals. The adsorbed molecules of A, however, do not permanently reside on the

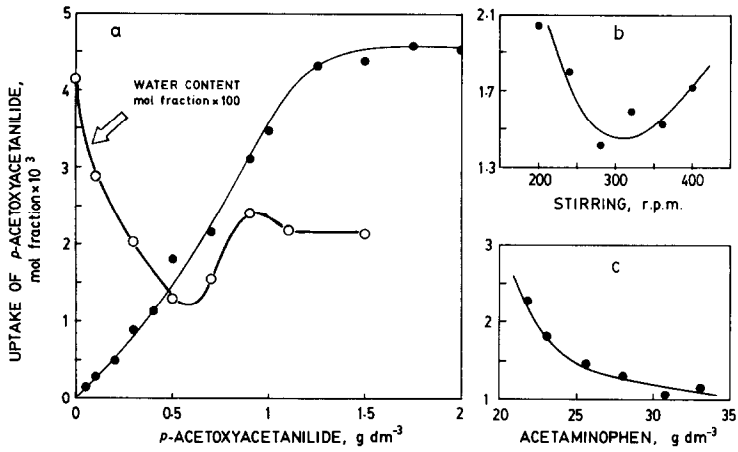

Fig. 1. Incorporation of *p*-acetoxyacetanilide, A, (●) by acetaminophen crystals grown from aqueous solutions at 30°C. a: influence of concentration of A at a stirring speed of 240 rpm and at an initial acetaminophen concentration of 23.1 $g \cdot dm^{-3}$. The water content (○) of the crystals is also presented, though on a smaller scale. b: influence of stirring speed at defined initial concentrations (500 $mg \cdot dm^{-3}$ of A and 23.1 $g \cdot dm^{-3}$ of acetaminophen). c: influence of initial concentration of acetaminophen at a stirring speed of 240 rpm and with 500 $mg \cdot dm^{-3}$ A. Each data point is the mean of triplicate determinations.

crystal surface but become covered by P molecules in the growing crystals, since washing of the crystals with iso-octane, in which A is appreciably soluble, removes negligible amounts of A.

The water content of the crystal lattice of P, after crystallization at 30°C under the defined conditions in the presence of various concentrations of A, is shown in Fig. 1a. Increasing concentration of A (0–500 $mg \cdot dm^{-3}$), corresponding to increasing uptake of A (0–0.0015 mole fraction, Fig. 1a) leads to a marked decrease in water content (by a factor > 3), suggesting displacement of water from the crystal lattice by incorporation of A. A further increase in the concentration of A (700–1500 $mg \cdot dm^{-3}$), corresponding to a further increase and a levelling in the uptake of A (0.0022–0.0045 mole fraction), leads to a marked increase in water content (by a factor of ca. 2), suggesting that this high mole fraction of A in the crystals is so disruptive that water is permitted to re-enter the crystal lattice. The influences of relatively small amounts of A (0–0.002–0.0045 mole fraction) on the displacement and uptake of much larger amounts of water (0.041–0.013–0.024 mole fraction) is quite striking. These observations may be clarified by the application of thermodynamic principles.

Thermodynamic properties

The enthalpy of fusion (ΔH^f, from DSC) and the melting point (T_m, from DSC and HSM) were used as measures of crystal energy. For the reasons given by Chow et al. (1984), particle size may influence these properties. However, various sieve fractions of P which had been crystallized from water gave values of ΔH^f and T_m which were essentially constant within experimental error. Nevertheless, P crystals (3

mg) of a defined sieve fraction (250–355 μm, 45–60 mesh) were used for measurements of ΔH^f and T_m.

Increasing concentration of A in the defined crystallization solution (Fig. 2) increases ΔH^f to a maximum at ca. 600 mg · dm^{-3} A and then decreases ΔH^f to a value close to that in the absence of A. With increasing concentration of A, T_m changes in parallel with ΔH^f, but the standard deviations are such that the differences between the measured T_m values are statistically insignificant (Table 1). The changes in ΔH^f (Fig. 2) and T_m (Table 1) are notably in the opposite sense to the changes in water content (Fig. 1a) and to the changes elicited by fatty acids on adipic acid crystals (Chow et al., 1984).

The changes in ΔH^f (+1.0 to +8.8% in Fig. 2) are about 10 times larger than the changes in T_m (+0.14 to +0.64%), so the changes in the entropy of fusion, ΔS^f, (Table 1) closely parallel the changes in ΔH^f. According to the arguments presented by Chow et al. (1984), *increases* in ΔH^f and ΔS^f correspond to *decreases* in enthalpy, internal energy and entropy of the crystal lattice, H_{solid}, U_{solid} and S_{solid}, respectively, according to the equations:

$$\Delta H^f = H_{liquid} - H_{solid}; \qquad \Delta U^f = U_{liquid} - U_{solid}; \qquad \Delta S^f = S_{liquid} - S_{solid} \tag{1}$$

(The primary assumption here is that the enthalpy, internal energy and entropy of the relatively disordered liquid state, H_{liquid}, U_{liquid} and S_{liquid}, respectively, are less sensitive to the presence of impurities than the highly ordered crystalline state.) Thus, the incorporation of small amounts of A (0–0.002 mole fraction) into the

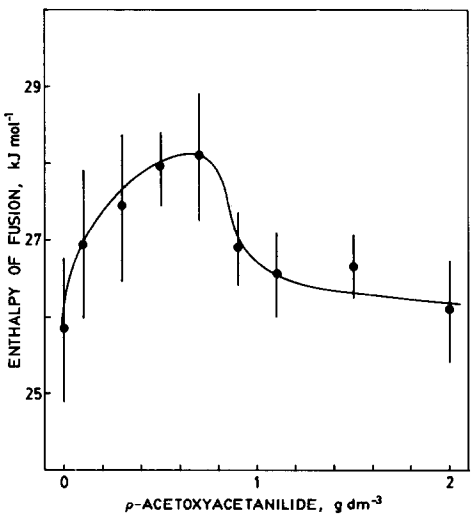

Fig. 2. Effect of added concentrations of *p*-acetoxyacetanilide, A, on the enthalpy of fusion, ΔH^f, of acetaminophen crystals (250–355 μm) grown at 30°C and at 240 rpm from aqueous solutions containing an initial concentration of 23.1 g · dm^{-3} acetaminophen. The vertical bars indicate the standard deviations.

TABLE 1

MELTING POINTS, T_m, AND MOLAR ENTROPIES OF FUSION, $\Delta S^f = \Delta H^f/T_m$, OF ACETAMINOPHEN CRYSTALS, AND CALCULATED IDEAL PARTIAL MOLAR ENTROPIES, $\bar{S}_j = -\cdot Rx_j \ln x_j$, IDEAL MOLAR ENTROPIES OF MIXING, $\Delta S^m_{ideal} = \Sigma \bar{S}_j$, OF THE COMPONENTS IN THE CRYSTALS AND THE STATISTICS OF THE LINEAR CORRELATIONS OF ΔS^f AGAINST THE CALCULATED IDEAL ENTROPIES, WHERE P = ACETAMINOPHEN, A = *p*-ACETOXYACETANILIDE AND W = WATER

Initial concentration of A ($mg \cdot dm^{-3}$)	T_m(K) ($\pm$S.D.)	ΔH^f($kJ \cdot mol^{-1}$) ($\pm$S.D.)	ΔS^f	$\bar{S}_A$	$\bar{S}_W$	$\bar{S}_P$	$\bar{S}_A + \bar{S}_W$	$\bar{S}_A + \bar{S}_P$	$\bar{S}_W + \bar{S}_P$	ΔS^m_{ideal}
			($J \cdot K^{-1} \cdot mol^{-1}$)				($J \cdot K^{-1} \cdot mol^{-1}$)			($J \cdot K^{-1} \cdot mol^{-1}$)
0	439.1 (3.0)	25.82 (0.94)	58.8	0	1.096	0.337	1.096	0.337	1.433	1.433
100	441.6 (0.6)	26.94 (0.95)	61.0	0.018	0.851	0.239	0.870	0.257	1.090	1.108
300	441.2 (0.9)	27.43 (0.95)	62.2	0.051	0.656	0.173	0.707	0.225	0.829	0.880
500	441.9 (0.3)	27.93 (0.48)	63.2	0.095	0.467	0.121	0.562	0.216	0.589	0.683
700	441.9 (0.7)	28.09 (0.82)	63.6	0.110	0.536	0.145	0.646	0.255	0.682	0.791
900	441.2 (0.4)	26.90 (0.48)	61.0	0.149	0.746	0.223	0.895	0.372	0.969	1.118
1100	441.1 (0.5)	26.54 (0.55)	60.2	0.173	0.691	0.209	0.864	0.382	0.900	1.073
1500	440.3 (0.5)	26.66 (0.41)	60.5	0.198	0.678	0.210	0.876	0.408	0.888	1.086
2000	439.7 (1.7)	26.07 (0.67)	59.3	Yields too low for reliable Karl Fischer titration of water content						
Correlation coefficient, r				0.089	−0.868	−0.919	−0.960	−0.706	−0.883	−0.955
Residual standard deviation, σ				1.715	0.855	0.678	0.479	1.219	0.808	0.513
Slope				1.98	−7.14	−22.24	−9.09	−14.70	−5.43	−6.53
Standard error of slope				8.98	1.67	3.89	1.07	6.01	1.18	0.83
ΔS^f Intercept				61.1	66.4	65.9	68.7	65.8	66.3	68.0

The acetaminophen, P, crystals were grown in aqueous solution containing an initial concentration of 23.1 $g \cdot dm^{-3}$ acetaminophen and various concentrations of *p*-acetoxyacetanilide, A, at 30°C.

crystals of P leads to the displacement of much larger amounts of incorporated water and reduces the energy and entropy of the crystal lattice, or, in other words, increases its strength and degree of order. On the other hand, the incorporation of larger amounts of A (0.002–0.0045 mole fraction) reverses these effects, decreasing the strength and order of the crystal lattice and allowing water to re-enter. Thus, both A and water disrupt the crystal lattice of P, but their effects are balanced, though unequally, since small amounts of A can displace much larger amounts of water.

Thermodynamic interpretation

Our fundamental assumption is that each additive or impurity within the crystals modifies the disorder of the crystal lattice and thereby exerts the observed effects. We therefore consider the entropy to be one of the most useful thermodynamic functions of the system.

The partial molar entropy, $\bar{S}_j$, of a component substance, j, in an ideal solution depends only on its mole fraction, x_j, thus:

$$\bar{S}_j = -Rx_j \ln x_j \tag{2}$$

The ideal molar entropy of mixing, ΔS^m_{ideal}, of two or more component substances is the sum of the respective partial molar entropies, thus:

$$\Delta S^m_{ideal} = \Sigma \bar{S}_j = -R \Sigma x_j \ln x_j \tag{3}$$

Eqns. 2 and 3 are applied to each component of the crystals in the present work, i.e. acetaminophen, subscript P, *p*-acetoxyacetanilide, subscript A, and water, subscript W, thus:

$$\Delta S^m_{ideal} = -R(x_p \ln x_p + x_A \ln x_A + x_W \ln x_W) \tag{4}$$

For our purposes ΔS^m_{ideal} represents the disorder which would be created in the perfect crystal lattice of P by the mere presence of A and water randomly distributed throughout the crystals as in a substitutional solid solution. Under these somewhat artificial circumstances, it is assumed that preferential lattice sites are absent and that molecules of A and water do not create additional disorder, such as impurity defects and their attendant dislocations. If the actual entropy of mixing is greater than ΔS^m_{ideal}, as might intuitively be expected, the incorporation of A and/or water into the lattice of P to produce point defects may be causing regions of lattice strain which produce additional crystal imperfections, such as line defects (dislocations).

Table 1 shows the ideal values of $\bar{S}_j$ and ΔS^m_{ideal}, calculated from the analytical data (Fig. 1a) for the crystals under study, and the statistical parameters for the linear correlation of ΔS^f against each of these quantities. The greater the influence of a given component on the actual entropy of the crystals, S_{solid}, the closer will the correlation coefficient, r, approach -1 and the smaller will be the residual standard deviation for the regression of ΔS^f against this ideal entropy. (The correlation is

negative on account of the negative sign in Eqn. 1 (right) in which S_{liquid} is less sensitive to the impurities. The number of adjustable parameters is two in every correlation.) Table 1 shows that the relative importance of the components in controlling S_{solid} increases in the order: A < A + P < W < W + P < P < A + W + P < A + W. The two additives taken together, i.e. A + W, give a slightly better correlation than do all three components taken together, i.e. A + W + P, perhaps because x_p was calculated as $(1 - x_A - x_W)$, which may increase the errors in ΔS^m_{ideal}. Fig. 3 shows the most important linear correlation, which is that between ΔS^f and ΔS^m_{ideal}, calculated from Eqn. 4 and including all three components.

The liquid state will approximate more closely to an ideal solution than the solid state. Thus, the concept of regular solutions, originally developed by Hildebrand, Scatchard and coworkers (Hildebrand et al., 1970) for liquid solutions, assumes that the entropy of mixing of the liquids is equal to the ideal value. The regular solution concept presupposes that the intermolecular interactions are simply London dispersion forces and excludes specific interactions and specific orientational effects, such as hydrogen bonding. Thus, the changes in S_{liquid} brought about by the presence of A and water in P, though smaller than the changes in S_{solid}, are probably not equal to ΔS^m_{ideal}.

If both the solid and the liquid state were to behave as ideal solutions, S_{solid} and S_{liquid} would be linear functions of ΔS^m_{ideal} with a regression coefficient of -1, and therefore ΔS^f (Eqn. 1) would be independent of ΔS^m_{ideal}. The actual linear relationship (Fig. 3) between ΔS^f and ΔS^m_{ideal} has a slope of -6.5 (Table 1) which confirms that the crystal lattice is much more sensitive to the disordering effects of the

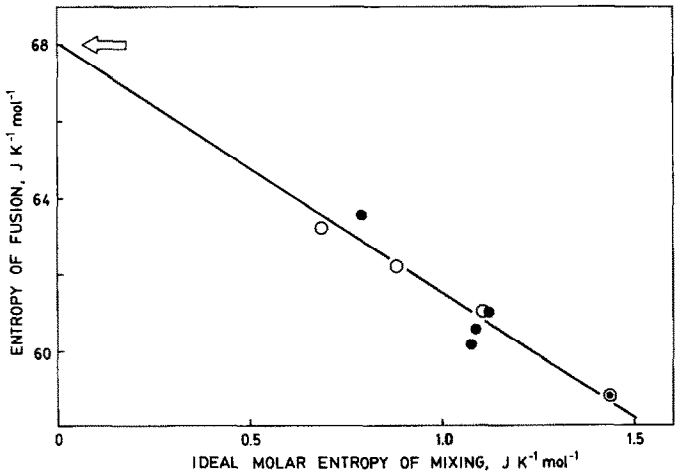

Fig. 3. Correlation between the molar entropy of fusion, ΔS^f, of acetaminophen, P, crystals (crystallized from water, W, containing various concentrations of *p*-acetoxyacetanilide, A) and the ideal molar entropy of mixing of the components of the crystals (P+A+W). ⊙, crystals grown in the absence of A; ○, crystals in which water is being displaced by A; ●, crystals grown in the presence of higher concentrations of A, which leads to re-entry of water. Intercept, ⇐, indicates the hypothetical entropy of fusion of a pure crystalline sample of acetaminophen.

additives than the liquid state, the difference being 6.5 times the ideal entropy of mixing. This implies that each foreign molecule introduces an impurity defect which produces further crystal imperfections (i.e. point defects and dislocations) and thereby disorders the crystal lattice to a much greater extent than by simple molecular substitution. This accords qualitatively with the known influence of additives or impurities on the structure and properties of metals (Reed-Hill, 1973). The effects on organic crystals, such as P (in the present work), adipic acid (Chow et al., 1984) and other drugs and excipients, are likely to be particularly pronounced on account of low molecular and crystal symmetries, complicated intermolecular interactions involving hydrogen bonding and significant lattice interstices. (The intercept of the regression line on the ΔS^f axis in Fig. 3 signifies the entropy of fusion of a pure crystalline sample of P, i.e. $\Delta S^f = 68.0\ J \cdot K^{-1} \cdot mol^{-1}$. From this, the enthalpy of fusion of pure P at the melting point is $30.1\ kJ \cdot mol^{-1}$.) Further experimental data and theoretical developments in this area are required and will be developed in a later publication (York and Grant, 1985).

Crystal morphology and particle size distribution

Growth of P in the presence of increasing concentrations of A (corresponding to progressive uptake of A by the crystals) reduces the crystal width from ca. 200 μm to a broad minimum of 20 μm between 400 and 1000 $mg \cdot dm^{-3}$ of A and then increases the crystal width to 80 μm at 2000 $mg \cdot dm^{-3}$ (Fig. 4a). Increasing concentrations of A, however, have variable effects on the length of the crystals (Fig. 4a). As a result, the ratio length/width increases with increasing concentration of A reaching a maximum at about 1000 $mg \cdot dm^{-3}$ and then decreases at higher concentrations (Fig. 4b). In addition, a slight tendency towards the formation of

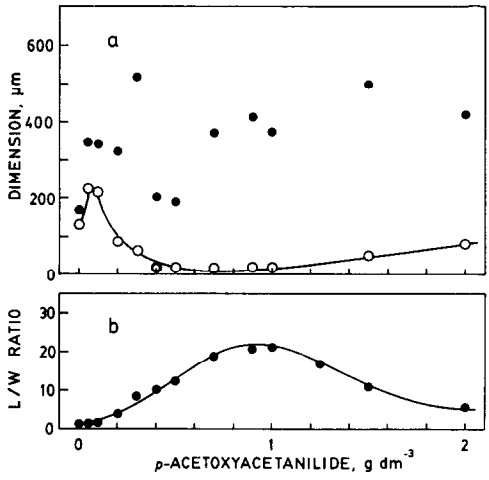

Fig. 4. Effect of added concentrations of *p*-acetoxyacetanilide, A, on (a) the length, L (●), and width, W (○), and on (b) the length/width ratio, L/W, of acetaminophen crystals grown at 30°C and at 240 rpm from aqueous solutions containing an initial concentration of 23.1 $g \cdot dm^{-3}$ acetaminophen.

multiple "twins" increases from 300 to 1100 mg · dm^{-3} of A. These habit changes were studied by optical microscopy (Fig. 5) and confirmed by SEM which also showed flat, featureless faces (Fig. 6).

The stirring rate (200–400 rpm) during crystallization in the presence of 500 mg · dm^{-3} of A does not significantly affect the length (326 ± 197 μm), width (30 ± 38 μm) and morphology of the crystals, whereas increasing initial concentration of P (21.8–33.3 g · dm^{-3}) at a defined stirring rate (240 rpm) produces slightly shorter, broader and more tabular crystals (Figs. 7a and b).

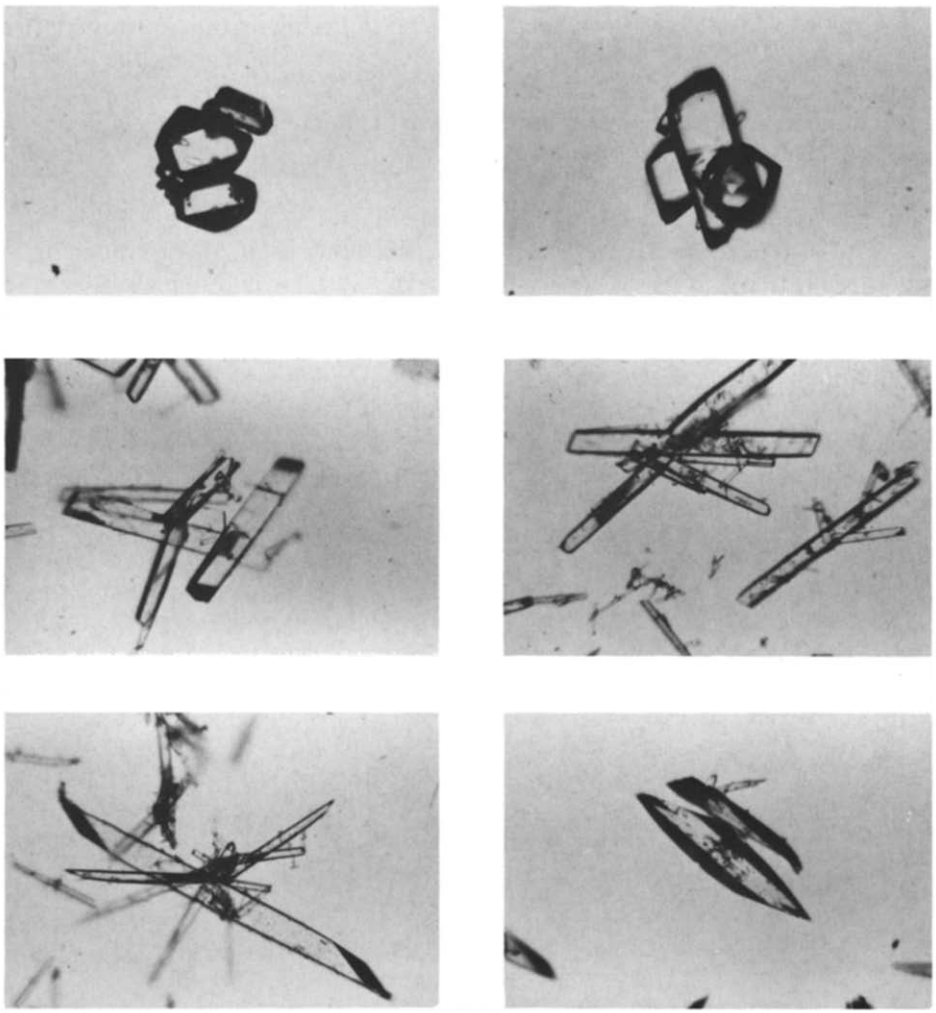

Fig. 5. Transmitted light optical photo-micrographs of acetaminophen crystallized from water containing the following concentrations of *p*-acetoxyacetanilide.under defined conditions: upper left, 0 mg·dm^{-3}; upper right, 100 mg·dm^{-3}; centre left, 300 mg·dm^{-3}; centre right, 400 mg·dm^{-3}; lower left, 900 mg·dm^{-3}; lower right, 2000 mg·dm^{-3}. Magnification ×50.

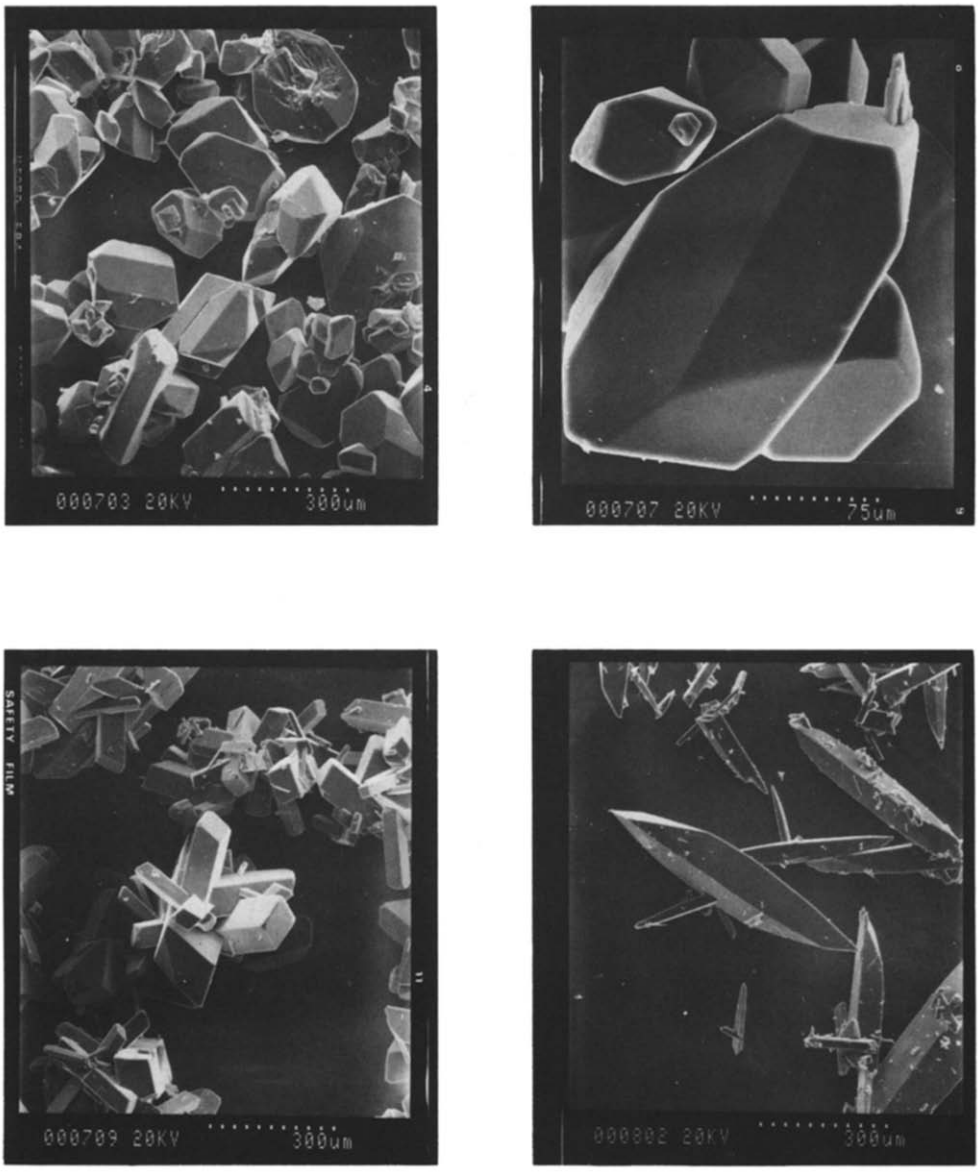

Fig. 6. Scanning electron micrographs of the surfaces of acetaminophen crystallized from water containing the following concentrations of *p*-acetoxyacetanilide under defined conditions: upper left, 0 $mg \cdot dm^{-3}$; upper right, 0 $mg \cdot dm^{-3}$ (higher magnification); lower left, 200 $mg \cdot dm^{-3}$; lower right, 1500 $mg \cdot dm^{-3}$.

The influence of A on the morphology of P crystals indicates differential inhibition of crystal growth at different crystal faces. Increasing concentration of A also reduces drastically the yield of crystals harvested at a defined time (2 h) after seeding (Fig. 8), indicating general, concentration-dependent inhibition of crystal

Fig. 7.

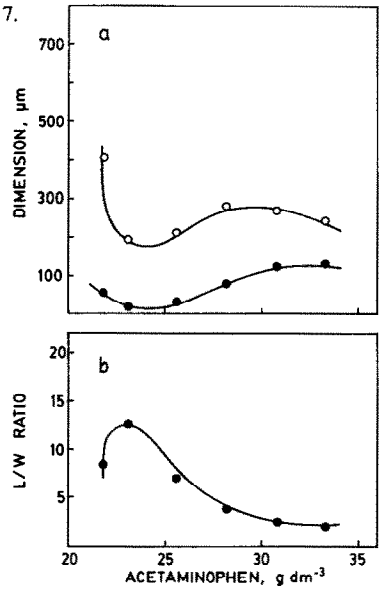

Fig. 8.

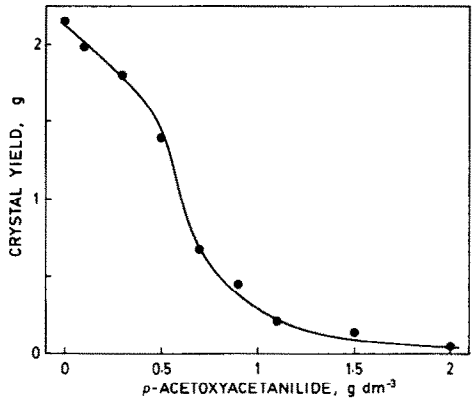

Fig. 7. Effect of different initial concentrations of acetaminophen on (a) the length, L (○), and width, W (●), and on (b) the length/width ratio, L/W, of acetaminophen crystals grown at 30°C and at 240 rpm from aqueous solutions containing initially 500 mg·dm^{-3} of *p*-acetoxyacetanilide.

Fig. 8. Effect of added concentrations of *p*-acetoxyacetanilide, A, on the yield of acetaminophen crystallized at 30°C and at 240 rpm from aqueous solutions containing initially 9 g of acetaminophen in 390 cm^3 of water. Each data point represents the mean yield of eight batches harvested 2 h after initial seeding.

growth. The reduction of the growth yield of the crystals might be attributable to a reduction in the supersaturation, brought about by an enhancement of the solubility of P by A. However, although the equilibrium solubility of P in water at 30°C and 40°C is increased by the presence of A (Table 2), the cosolvent effect of A (about 4% at 1512 mg·dm^{-3} at 30°C and 40°C) is too small to play a major role in the

TABLE 2

EQUILIBRIUM SOLUBILITIES, g·dm^{-3} (±S.D.), OF ACETAMINOPHEN IN WATER AT VARIOUS TEMPERATURES IN THE PRESENCE OF VARIOUS CONCENTRATIONS OF *p*-ACETOXYACETANILIDE, A

Temperature (°C)	Concentration of A (mg·dm^{-3})			
	0	576	933	1512
30	16.62 (0.05)	16.94 (0.06) [a]	17.25 (0.01) [a]	17.33 (0.11) [a]
40	22.82 (0.36)	23.59 (0.13) [a]	23.47 (0.13) [a]	23.68 (0.09) [a]
50	32.57 (0.29)	32.23 (0.26)	32.62 (0.50)	31.89 (0.37)

[a] These solubilities are significantly different from those in the absence of A (2-tailed paired *t*-test: $P < 0.05$; n = 3).

retardation of crystallization. The slowing of crystal growth by A may increase the ability of the growing P crystals to reject water from their lattices, thereby accounting for the reduction of water content at low concentrations of A (Fig. 1a).

A few crystallization studies with the omission of seeding have also been performed to examine the effect of A on nucleation. When the concentration of A in the crystallization medium is at or above 500 mg · dm^{-3}, without seeding, crystallization does not occur within the first 2 h. There appears to be a direct relationship between the concentration of A and the induction period prior to crystallization, suggesting concentration-related inhibition of nucleation.

Specific surface area

Depending on its concentration, A exerts a considerable influence on the specific surface area (SSA) of a defined sieve fraction (355–500 μm, 45–35 mesh) of P crystals. Crystallization in 100 mg · dm^{-3} A reduces the SSA of the crystals, corresponding to tabular habit, whereas growth in 300–1100 mg · dm^{-3} A yields crystals with higher SSA than that of the pure prismatic crystals (Fig. 9), corresponding to progressive habit elongation (Figs. 5 and 6). The increases in SSA might also arise from the increases in surface irregularities (i.e. dislocation cracks and pits) brought about by A and/or by the liquid nitrogen treatment during SSA measurement. However, SEM shows no significant differences between the appearance of the surfaces of the pure and the doped crystals (Fig. 6) and between the nitrogen-treated and the untreated samples. Thus, the introduction of surface irregularities would seem to be remote.

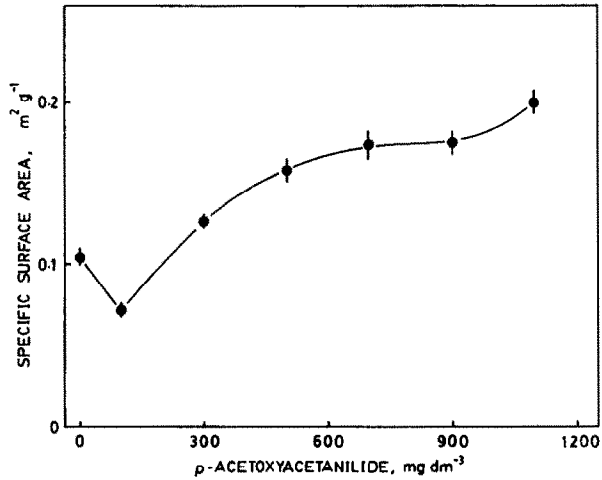

Fig. 9. Effect of added concentrations of *p*-acetoxyacetanilide, A, on the specific surface area of acetaminophen crystals (355–500 μm) grown at 30°C and at 240 rpm from aqueous solutions containing an initial concentration of 23.1 g · dm^{-3} acetaminophen. The vertical bars indicate the standard deviations.

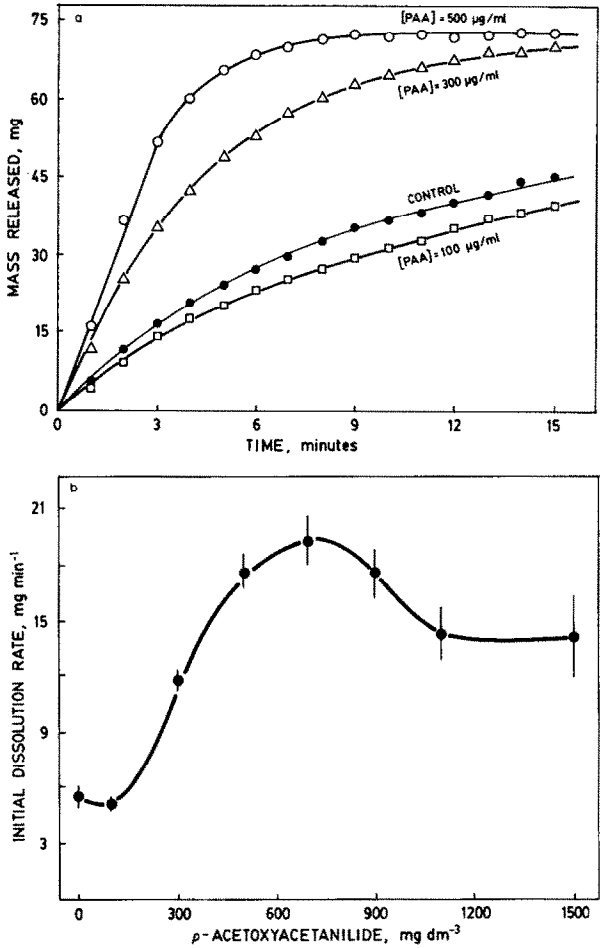

Fig. 10. a: dissolution–time profiles of acetaminophen crystals (75 mg, 355–500 μm) in water at 4°C. The crystals were grown at 30°C and at 240 rpm from aqueous solutions containing initially 23.1 g·dm^{-3} acetaminophen and the following concentrations of *p*-acetoxyacetanilide, A. ●, zero; □, 100 mg·dm^{-3}; △, 300 mg·dm^{-3}; ○, 500 mg·dm^{-3}. b: effect of added concentrations of *p*-acetoxyacetanilide, A, on the initial dissolution rate of acetaminophen crystals (355–500 μm) grown at 30°C and at 240 rpm from aqueous solutions containing an initial concentration of 23.1 g·dm^{-3} acetaminophen. The vertical bars depict the standard deviations.

Dissolution rate

The initial dissolution rate and, indeed the entire dissolution profile, of a defined sieve fraction (355–500 μm, 45–35 mesh) and mass (75 mg) of P crystals depend strongly on the concentration of A in the crystallization solution (Fig. 10a and b), decrease to a minimum at 100 mg · dm^{-3} and then increase at higher concentrations. Owing to the differences in shape, sieving may not afford satisfactory sizing of the crystals, and the observed changes in dissolution rate may be simply related to changes in surface area. Thus, to account for the effect of surface area, the initial

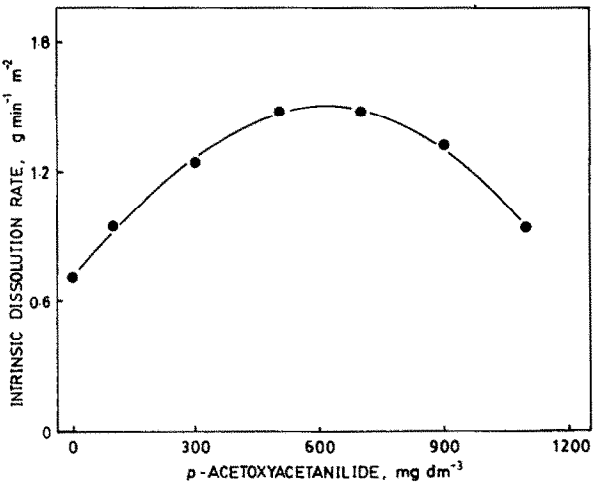

Fig. 11. Effect of added concentrations of *p*-acetoxyacetanilide on the dissolution rate per unit surface area ("intrinsic dissolution rate") of acetaminophen crystals (355–500 μm) grown at 30°C and at 240 rpm from aqueous solutions containing an initial concentration of 23.1 $g \cdot dm^{-3}$ of acetaminophen.

dissolution rate per unit surface area (i.e. the intrinsic dissolution rate) of the crystals was studied as a function of the additive concentration. As can be seen in Fig. 11, the intrinsic dissolution rate increases up to a maximum at ca. 600 $mg \cdot dm^{-3}$ A (by a factor of 2.11) and decreases thereafter. The approximately parabolic trend observed probably involves a complex interplay of a number of factors which are elaborated below.

For an essentially surface reaction-controlled dissolution process, different faces or surfaces of the crystals generally display different rates of dissolution, depending on their interactions with the solvent involved. With water as the solvent, the polar crystal faces will tend to dissolve faster than the less polar ones. Accordingly, the overall dissolution rate is more appropriately expressed as a function of the relative contribution of individual faces possessing different polarities. It is known that crystals in different habits have different dissolution rates, e.g. nickel sulphate α-hexahydrate (Burt and Mitchell, 1979, 1980) and acetylsalicylic acid (Watanabe et al., 1982). In each example, the observed effects are attributed to the different intrinsic dissolution rates of the different faces whose relative areas differ from habit to habit. In the present case, the observed increases in dissolution rate of P crystals grown in the presence of increasing concentrations of A may be ascribed to a relative preponderance of the more polar surfaces brought about by the differential inhibition of growth at different faces by A, as alluded to previously.

The presence of the A molecules within the crystals may also play a contributory role in dissolution. It is generally known that impurity atoms, ions or molecules built into the crystal lattices frequently generate crystal defects and dislocations, which, being in high energy states, are the preferred sites of dissolution. Thus, the rapidity of the dissolution or chemical reaction of a solid is governed by the availability of

these sites (Burt and Mitchell, 1981; Boldyrev et al., 1979; Byrn, 1982). In the present work, it can be envisaged that A and water may exert similar effects on the dissolution kinetics of P crystals, the extent of which depends on its incorporation. At low concentrations of A (100–500 $mg \cdot dm^{-3}$), enhancement of the intrinsic dissolution rate predominates (Fig. 11), perhaps because the water content is reduced (Fig.1a), even though the crystal energy and entropy are also falling. Shefter and Higuchi (1963) have shown that the dissolution rate and intrinsic solubility increase with decreasing stoichiometric water content (i.e. anhydrate > hydrate). Similar considerations may apply to the non-stoichiometric water in the P crystals in the present work. At concentrations exceeding 700 $mg \cdot dm^{-3}$ A, additional factors having an opposing effect may exert overwhelming influences on the intrinsic dissolution rate (Fig. 11), namely the increase in water content (Fig. 1a), the much lower water solubility of A than P and the ability of A to block the higher energy sites of the surfaces of the crystals, making them less available for active dissolution. In support of the latter suggestion, certain dyes retard the dissolution of drugs such as sulphonamides and phenobarbital, by adsorption at the active sites of dissolution (Tawashi and Piccolo, 1970; Piccolo and Tawashi, 1970, 1971a and b).

Conclusions

The picture which emerges from the present work is as follows. (a) P, when crystallized from water, incorporates about 0.5% w/w, or about 4 mole%, water. While the percentage by weight may seem small, or perhaps even negligible, the fact that the molecular weight of water (18.02) is much less than the molecular weight of most drugs (often by a factor of about 10) indicates that water may be present in the crystals at levels of several mole percent. (b) This incorporated water exerts a disruptive influence on the crystal lattice, thereby increasing the crystal energy and entropy, and therefore lowering ΔH^f and ΔS^f, as compared with perfect, pure crystals. (c) Growth of crystals in the presence of A slows crystallization and causes A to be incorporated by a fraction of one mole percent. (d) Low levels of incorporated A lead to the exclusion of about 10 times the amount of water on the mole fraction scale. (e) The displacement of water, the major disruptive impurity, partially relieves the lattice strain, lowering the crystal energy and entropy and therefore increasing ΔH^f and ΔS^f. The increase in entropy of the crystal lattice greatly exceeds that expected from ideal mixing. (f) Growth of the crystals in the presence of higher concentrations of A causes increased incorporation of A which itself causes increased disruption of the crystal lattice, allowing water to be re-admitted. (g) The increased levels of additive, A, and/or the impurity, water, cause a further increase in lattice strain, thereby increasing the crystal energy and entropy and therefore lowering ΔH^f and ΔS^f. (h) Growth in the presence of still higher concentrations of A causes the crystal lattice to become saturated with A ($x_A = 0.0045$), produces a constant water content of the crystals ($x_W = 0.022$) and constant values of $\Delta H^f \approx 26.5$ $kJ \cdot mol^{-1}$, $T_m = 440$ K and $\Delta S^f \approx 60$ $J \cdot K^{-1} \cdot mol^{-1}$. This behaviour indicates a steady state of partial disorder in the crystal lattice.

As well as decreasing the crystal energy and entropy, the incorporation of traces of the additive, A, into P crystals progressively alters the crystal habit, increases the specific surface area and increases the dissolution rate. The increases in dissolution rate cannot be explained by the increases in specific surface area alone, since the intrinsic dissolution rate also increases. The concomitant involvements of anisotropy, water content, point defects and dislocations of the crystal lattice probably play crucial roles in the control of dissolution rate. Higher concentrations of A cause increases in crystal energy (decrease in ΔH^f, Fig. 2) but a decrease in the intrinsic dissolution rate (Fig. 11) suggesting inhibition of the higher energy sites on the crystal surface.

These observations could have significant implications for the behaviour, design and quality control of solid dosage forms, since: (a) traces of additives, if non-toxic, may provide means of controlling water content, crystal energy, crystal order, dissolution rate and possibly bioavailability; (b) the presence of impurities, particularly water, may account for certain batch-to-batch variations in the properties of solid drugs and excipients; and (c) crystallization in the presence of traces of additives may be used to reduce the water content of drug crystals.

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