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Modification of acetaminophen crystals. III. Influence of initial supersaturation during solution-phase growth on crystal properties in the presence and absence of *p*-acetoxyacetanilide

Albert H.L. Chow * and David J.W. Grant

Faculty of Pharmacy, University of Toronto, Toronto, Ont. (Canada)

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Summary

Acetaminophen (paracetamol, **P**) has been crystallized from aqueous solutions at various initial supersaturations (5.34–16.88 g dm^{-3}) with 0 or 500 mg dm^{-3} *p*-acetoxyacetanilide (**A**) and its physical properties examined. In the absence of **A**, an increase in the initial supersaturation, σ (i.e. the initial concentration of **P** minus the solubility of **P**), does not appear to change the crystal habit (polyhedral prisms), but substantially increases the water content (by a factor of 8), decreases the enthalpy of fusion, ΔH^f, melting point, T_m, and entropy of fusion, ΔS^f, (by 6–14, 0.3–1.4 and 6–13 % respectively) and reduces the intrinsic dissolution rate of the crystals to constant values for σ between 6.63 and 14.32 g dm^{-3}. On the other hand, when 500 mg dm^{-3} **A** are added to the solution, increasing the initial supersaturation broadens the crystal habit progressively, lowers and raises the water content, increases and decreases the ΔH^f, T_m and ΔS^f, reduces the uptake of **A** to approximately constant mole fractions around 0.0013, and enhances and then reduces the intrinsic dissolution rate of the crystals to values about 50% greater than that of the polyhedral prisms grown in the absence of **A**. The above observations demonstrate the pharmaceutical significance of supersaturation during crystallization as a modulator of the physical properties and aqueous dissolution rate of the **P** crystals.

Introduction

The possible use of various concentrations of the additive, *p*-acetoxyacetanilide (**A**), to control the physical properties and aqueous dissolution rate of acetaminophen (**P**) crystals has been studied and discussed by Chow et al. (1985). The influence of a second crystallization variable, the rate of stirring of the aqueous crystallization solution, on these properties has also been investigated and appraised (Chow and Grant, 1987). The present study is a systematic extension of our previous work and aims to elucidate how a third crystallization variable, the supersaturation level of the aqueous crystallization solutions, mediates the influence of **A** on the crystal growth and related pharmaceutical properties of **P**. The supersatura-

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* *Present address*: Faculty of Pharmaceutical Sciences, University of British Columbia, 2146 East Mall, Vancouver, B.C., V6T 1W5, Canada.
Correspondence: D.J.W. Grant, Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, Ont. M5S 1A1, Canada.

tion, which represents the driving force for crystallization, is expected to influence directly the kinetics of mass transfer of the major component, i.e. **P**, and of the minor components, i.e. **A** and water, to different extents (Mullin, 1972; Ny'vlt, 1971, 1978) and hence to bring about subtle differences in the physical properties of the crystals.

Materials and Methods

Reagents and materials

The sources and chemical purities of **P**, acetonitrile and methanol, as well as the preparation procedure for **A**, have been reported previously (Chow et al., 1985). Water was double-distilled in an all-glass apparatus.

Batch crystallization from water

The crystals were prepared according to the procedure reported by Chow et al. (1985) with the following modifications. **P** in various amounts (8.5–13 g) was crystallized from water (390 cm^3) containing 0 or 500 mg dm^{-3} **A** at a stirring speed of 240 rpm. The initial supersaturation, σ, in the present work is the initial concentration of **P** minus the solubility of **P** (16.45 g dm^{-3} at 30 °C).

Microscopy, X-ray powder diffraction, water determination, surface area measurements and dissolution studies

Optical microscopy, X-ray powder diffraction, water content determination, specific surface area measurements and dissolution studies of the crystals were carried out as described by Chow et al. (1985).

Quantitation of additive uptake, and differential scanning calorimetry

Quantitation of the uptake of **A**, and differential scanning calorimetry (DSC) employed the procedures described by Chow and Grant (1987). For DSC each sample of crystals was encapsulated in a hermetically sealed pan normally used for volatile samples. This procedure prevents possible loss of water and the organic substances during DSC (Chow et al., 1985).

Results and Discussion

Uptake of additive and water

Increasing the initial supersaturation, σ, of the defined crystallization solutions with 500 mg dm^{-3} **A** reduces the mole fraction of **A** in the crystals to a constant value (≈ 0.0013). This observation suggests that progressive rejection of **A** by increasing competition from **P** for adsorption sites of **A** in the lattice is being off-set by progressive capture of **A** by the acceleration of the growth of **P** crystals (Fig. 1).

Accompanying the reduction in the uptake of **A** are decreases (minimum at $\sigma = 6.63$ g dm^{-3}) and increases in water content of the crystals ($x_W = 0.014 - 0.009 - 0.027$; Fig. 1). The decreases in water content of the crystals grown at σ of 5.34 to 6.63 g dm^{-3} are consistent with the reduction of lattice disruption as a result of lower additive uptake, which therefore renders the lattice less accessible to the water. The increase in water content at σ above 6.63 g dm^{-3} ($x_W = 0.009 - 0.027$), corresponding to a lower uptake of additive ($x_A = 0.0016 - 0.0013$), accords with the competition between **A** and water for the adsorption sites in the lattice, as suggested by Chow et al. (1985).

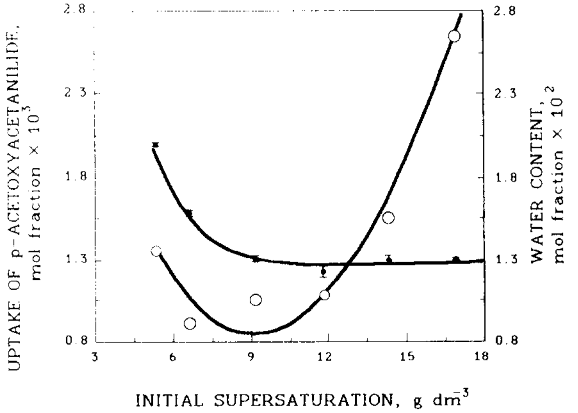

Fig. 1. Uptake of **A** (●) and water (○) by **P** crystals grown in the presence of 500 mg dm^{-3} **A** from aqueous solutions at various initial supersaturations and at 240 r.p.m. The vertical bars represent the S.D. of triplicate determinations. Each data point for the water content is the mean of duplicate measurements.

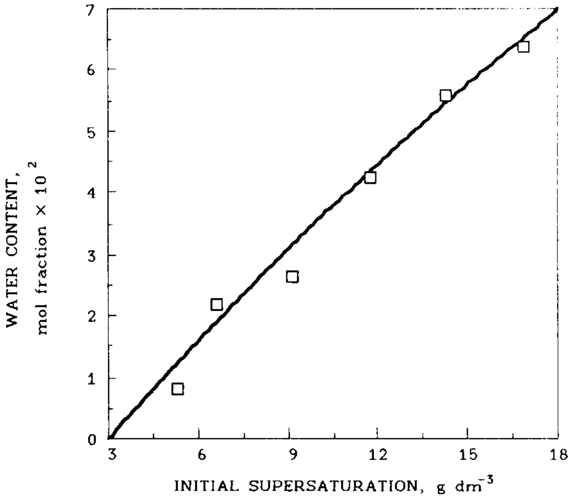

Fig. 2. Uptake of water by acetaminophen grown from pure aqueous solutions at various initial supersaturations and at 240 r.p.m. Each data point is the mean of duplicate determinations. The variation between measurements is less than 6%.

The exclusion of **A** from the crystallization solutions brings about substantial increases in the water content of **P** crystals (by a factor of 8) with increasing initial supersaturation (Fig. 2), suggesting increasing trapping of water by crystals of **P** which are growing increasingly rapidly. The above observations taken together with those reported previously (Chow and Grant, 1987) indicate that **A**, when incorporated into the lattice under the influence of high initial supersaturations, is less capable of deterring the ingression of water into the crystals than when built into the lattice under conditions of high stirring rates. Whilst this conclusion may be intuitively interpreted in terms of a greater drop in incorporated **A** for the former crystallization variable, the reason behind it is by no means as simple since the mole fraction of water in the crystals still rises, despite a constant doping level of **A** ($x_A \approx 0.0013$). Thus, the uptake of **A** and that of water under the two different conditions of crystallization probably do not share the same mechanism.

Crystal morphology and particle size

Raising the initial supersaturation beyond 6.63 g dm^{-3} in the solutions containing **A** (500 mg dm^{-3}) produces slightly shorter, broader and progressively more tabular crystals (Table 1), while the length/width ratio decreases progressively (Fig. 3). The omission of **A** from the solutions affords polygonal prisms whose sizes are virtually independent of the initial supersaturation (Table 1) and the length/width ratio also remains constant. That an increase in initial supersaturation above 6.63 g dm^{-3} reverses the habit elongation of **P** crystals indicates a progressive weakening of the selective inhibition of growth at different faces by **A**. This has been substantiated by the negligible effect of **A** in reducing the crystallization yield obtained at 2 h at supersaturations exceeding 11.76 g dm^{-3} (Fig. 4). It should be noted that the higher water content and lower uptake of **A** observed at higher initial supersaturations are in agreement with more rapid crystallization, which is reflected by an increase in growth yield harvested at 2 h. These observations further strengthen our earlier suggestion that the kinetics of crystal growth play a major role in determining the modes of incorporation of both **A** and water.

Fusion thermodynamic properties

Raising the initial supersaturation of the crystallization solutions containing 500 mg dm^{-3} **A**

TABLE 1

*Lengths and widths of **P** crystals grown with and without 500 mg dm^{-3} **A**, from aqueous solutions at various initial supersaturations and at 240 r.p.m.*

Initial supersaturation (g dm^{-3})	Length (μm ± S.D. *)	Width (μm ± S.D. *)
With A		
5.34	405.9 ± 191.9	52.5 ± 26.7
6.63	190.5 ± 114.8	16.8 ± 8.6
9.19	210.6 ± 44.9	31.4 ± 10.4
11.76	277.8 ± 61.0	79.4 ± 26.4
14.32	265.5 ± 51.4	122.7 ± 45.7
16.88	239.7 ± 63.3	128.7 ± 38.8
Without A		
5.34	165.7 ± 69.1	140.8 ± 54.6
6.63	220.8 ± 70.2	185.3 ± 61.9
9.19	207.4 ± 88.4	176.1 ± 74.8
11.76	247.7 ± 109.2	212.6 ± 94.4
14.32	268.6 ± 112.7	233.9 ± 98.5
16.88	290.3 ± 115.4	242.9 ± 94.0

* Indicates S.D. of 20 measurements.

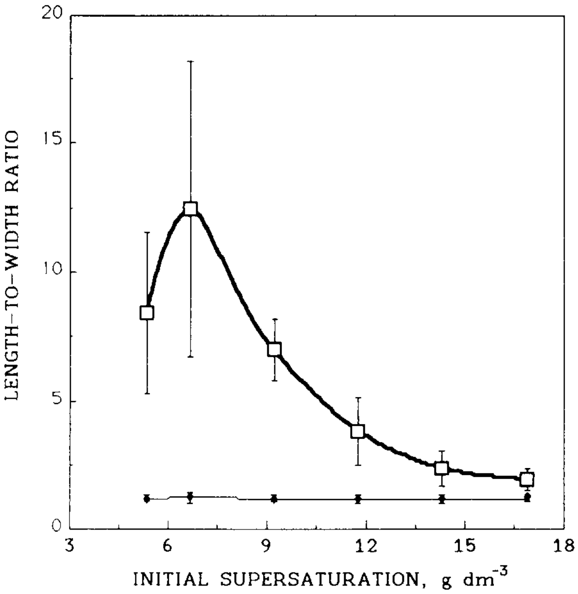

Fig. 3. Length-to-width ratios of **P** crystals grown in the presence (□) and absence (■) of 500 mg dm^{-3} of **A**, from aqueous solutions at various initial supersaturations and at 240 r.p.m. The vertical bars represent the S.D. of 20 measurements.

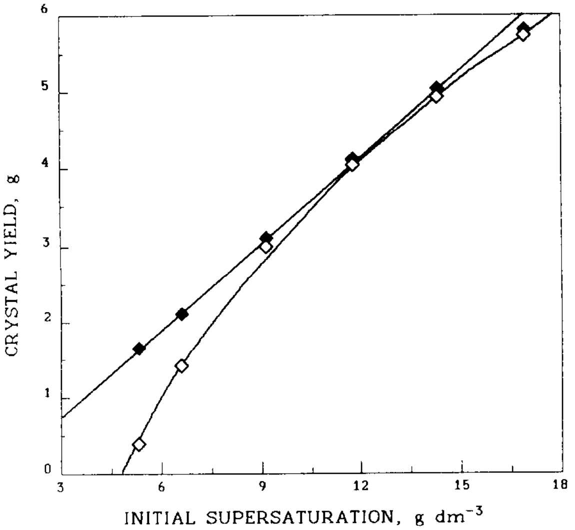

Fig. 4. Yields of **P** crystallized in the presence (◇) and absence (◆) of 500 mg dm^{-3} **A**, from aqueous solutions at various initial supersaturations and at 240 r.p.m. Each data point is the mean yield of 5 batches.

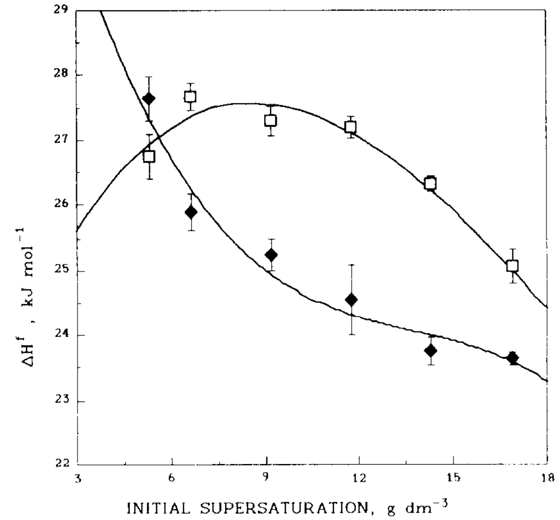

Fig. 5. Enthalpies of fusion, ΔH^f, of **P** crystallized in the presence (□) and absence (◆) of 500 mg dm^{-3} **A**, from aqueous solutions at various initial supersaturations and at 240 r.p.m. The vertical bars represent the S.D. of quadruplicate determinations.

increases and then decreases ΔH^f (Fig. 5) and T_m and ΔS^f (maxima at $\sigma = 6.63$ g dm^{-3}) of the crystals (Table 2), in parallel with decreases and increases in water content of the crystals (Fig. 1). On the other hand, when the initial supersaturation is increased in the absence of **A**, there occur appreciable decreases in ΔH^f (Fig. 5) and T_m and ΔS^f of the crystals by 6–14%, 0.3–1.4% and 6–13%, respectively (Table 2), corresponding to marked increases in incorporated water (Fig. 2).

To determine and compare the extent of lattice disruption brought about by the incorporated water and **A** under different crystallization conditions, the disruption index (d.i., the negative slope derived from the linear regression of the entropy of fusion, ΔS^f, on the ideal molar entropy of mixing, ΔS^{m}_{ideal}) for each preparation procedure defined above was calculated. The d.i. derived by varying the initial supersaturation of **P** in the presence of **A** was tested pairwise for significant differences ($P < 0.05$) against the d.i. derived by the same variation in the absence of **A** and in turn against the other 3 situations reported previously (i.e. varying the concentration of **A** for a constant stirring rate and constant supersaturation of **P**,

TABLE 2

Influence of various initial supersaturations during crystallization on the fusion properties of **P** *crystals grown from aqueous solutions stirred at 240 r.p.m.*

	T_m ± S.D.	ΔH^f ± S.D.	ΔS^f ± S.D.	$\bar{S}_A$	$\bar{S}_W$	$\bar{S}_P$	ΔS^m_{ideal}
Initial supersaturation with 500 mg dm^{-3} **A**							
5.34	441.9 ± 0.2	26.75 ± 0.36	60.1 ± 0.3	0.103	0.486	0.129	0.718
6.63	442.1 ± 0.1	27.66 ± 0.21	62.6 ± 0.5	0.085	0.358	0.089	0.532
9.19	442.1 ± 0.1	27.28 ± 0.23	61.7 ± 0.5	0.072	0.398	0.098	0.567
11.76	442.0 ± 0.0	27.19 ± 0.16	61.5 ± 0.4	0.068	0.411	0.101	0.580
14.32	441.8 ± 0.1	26.32 ± 0.11	59.6 ± 0.3	0.072	0.539	0.139	0.750
16.88	441.4 ± 0.3	25.06 ± 0.26	56.8 ± 0.6	0.072	0.800	0.228	1.099
Correlation coefficient, *r*	[−0.989]						−0.972
Standard error of estimate, $s_{y.x}$	[0.337]						0.486
Slope (− d.i.)	[−9.78]						−9.78
Standard error of slope	[0.71]						0.52
95% confidence interval of slope	[−11.75 to −7.81]						−10.86 to −8.70
Intercept (ΔS^f_0)	[67.3]						67.3
Standard error of intercept	[0.5]						0.4
95% confidence interval of intercept	[65.9 to 68.7]						66.5 to 68.1
Total number of data points, *n*	[6]						23
Initial supersaturation without **A**							
5.34	439.9 ± 0.2	27.64 ± 0.35	62.8 ± 0.8	0.335	0.070	0.405	
6.63	438.7 ± 0.4	25.90 ± 0.28	59.0 ± 0.6	0.697	0.181	0.878	
9.19	437.6 ± 0.2	25.23 ± 0.24	57.7 ± 0.6	0.797	0.217	1.014	
11.76	435.2 ± 1.2	24.55 ± 0.53	56.4 ± 1.1	1.112	0.344	1.456	
14.32	435.0 ± 0.5	23.77 ± 0.21	54.6 ± 0.5	1.334	0.449	1.783	
16.88	433.7 ± 0.6	23.64 ± 0.10	54.5 ± 0.3	1.461	0.514	1.975	
Correlation coefficient, *r*	[−0.971]						−0.951
Standard error of estimate, $s_{y.x}$	[0.830]						0.940
Slope (− d.i.)	[−5.13]						−5.13
Standard error of slope	[0.63]						0.35
95% confidence interval of slope	[−6.88 to −3.38]						−5.86 to −4.40
Intercept (ΔS^f_0)	[63.9]						63.9
Standard error of intercept	[0.9]						0.5
95% confidence interval of intercept	[61.4 to 66.4]						62.9 to 64.9
Total number of data points, *n*	[6]						24

Melting points, T_m, and molar entropies of fusion, $\Delta S^f = \Delta H^f / T_m$, of **P** crystals, and calculated ideal partial molar entropies, $\bar{S}_j = -Rx_j \ln x_j$, 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 ΔS^m_{ideal}; W-water. T is expressed in K, H in kJ mol^{-1}, S in J K^{-1} mol^{-1}, and initial supersaturation in g dm^{-3}.

Regression parameters and statistics in square brackets are based on the mean values of replicates.

Chow et al., 1985, and varying the stirring rate at a constant supersaturation of **P** either in the presence or in the absence of **A**, Chow and Grant, 1987). The statistics and parameters for the analysis and the linear plots are presented in Table 2 and Fig. 6 respectively. As before, the assumption of linearity for the relationship between ΔS^f and ΔS^m_{ideal} was first checked by scrutiny of the residual plots (both raw and standardized, Fig. 7) and by the lack-of-fit test.

Table 2 shows that the parameter estimates for both the negative slope (d.i.) and intercept (ΔS^f_0, the hypothetical entropy of fusion of pure, perfect crystals) in each case are statistically significant ($P < 0.05$) and have reasonably low standard errors, suggesting a strong relationship between ΔS^f

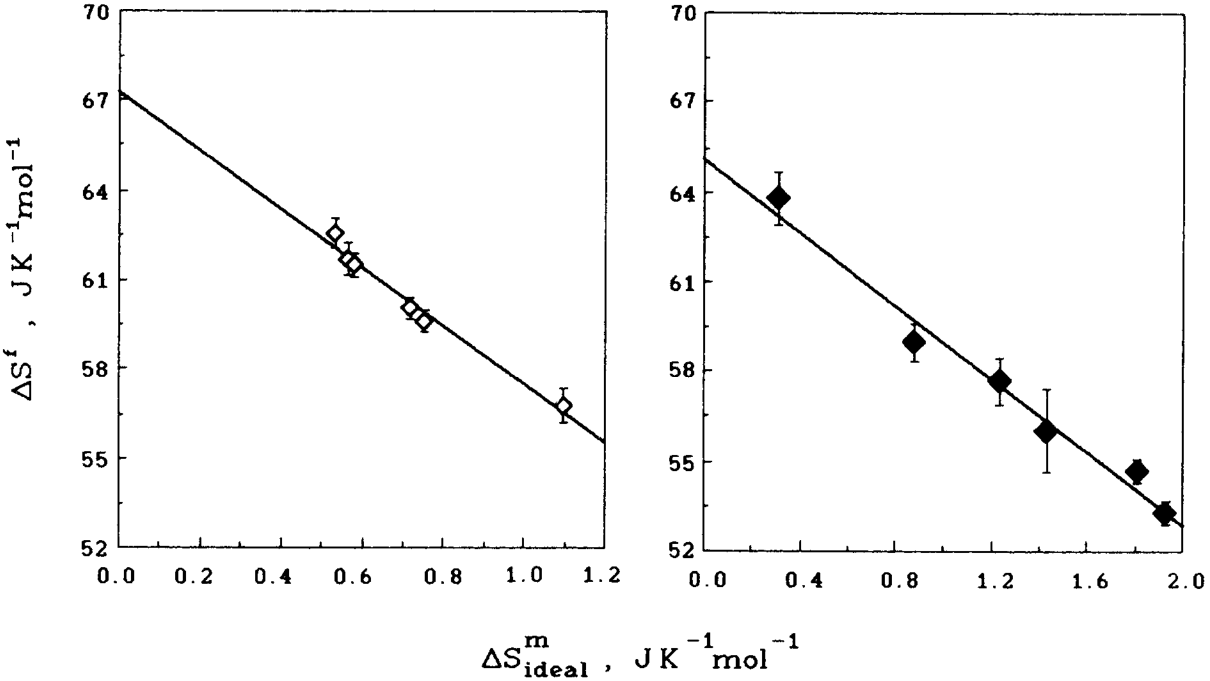

Fig. 6. Linear regression plot of the entropy of fusion, ΔS^{f}, against the ideal molar entropy of mixing, $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$, for **P** crystals grown in the presence (◇) and in the absence (◆) of 500 mg dm^{-3} **A** from aqueous solutions at various initial supersaturations and at 240 r.p.m. The vertical bars represent the S.D. of quadruplicate determinations.

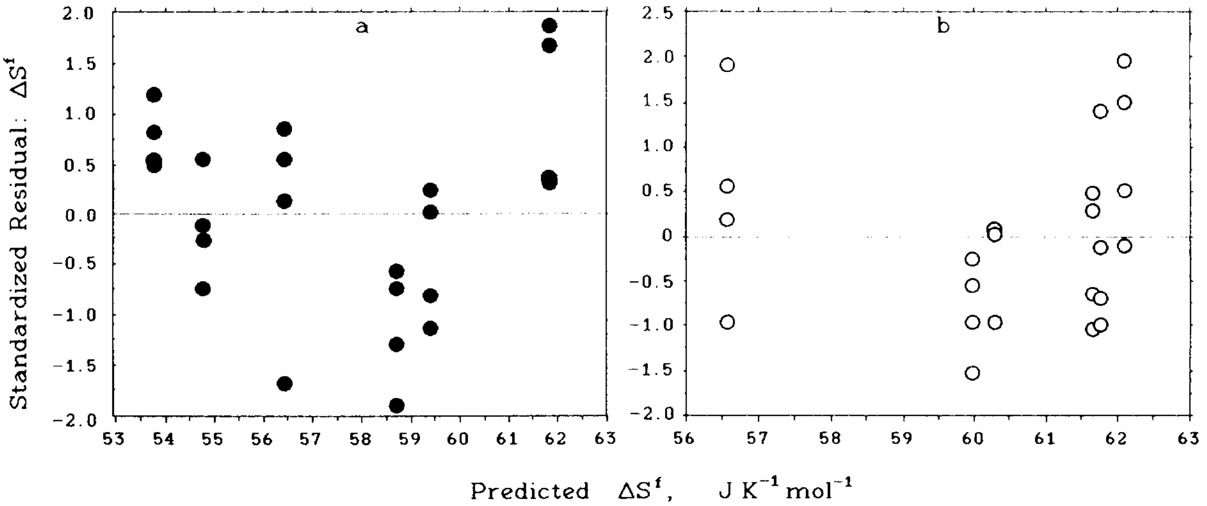

Fig. 7. Standardized residual plots (with respect to the S.D. of each residual) for the linear regression of the molar entropy of fusion, ΔS^{f}, on the ideal molar entropy of mixing, $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$, for **P** crystals grown in the presence (○) and absence (●) of 500 mg dm^{-3} of **A**, from aqueous solutions at various initial supersaturations and at 240 r.p.m.

and ΔS^{m}_{ideal}. However, the residual plots (Fig. 7) in both cases appear not to be very satisfactory since they seem to show downward followed by upward trends. In the case of crystallization in the presence of **A** at various initial supersaturations, the apparently systematic trend of the residuals is shown by the Durbin–Watson test (for serial correlation) to be statistically insignificant ($P < 0.05$). On the other hand, when the supersaturation of **P** is varied in the absence of **A**, there is a significant deviation from the assumed linear relationship between ΔS^{f} and ΔS^{m}_{ideal}, as demonstrated by curvature in the residual plots and by the statistically significant F value from the lack-of-fit test. The reasons why the latter case is the only exception among the present two and the previous three situations, mentioned in the preceding paragraph, are not known at this stage, but may be related to a breakdown of the assumption of linear dependence of ΔS^{f} on ΔS^{m}_{ideal} at high mole fractions of water in the crystals (i.e. $x_W > 0.05$), as stated in the theoretical derivation of the disruption index (Chow et al., 1985; York and Grant, 1985; Grant and York, 1986; Pikal and Grant, 1987).

Statistical comparison of the regression coefficients using the Student t-test indicates that the d.i. calculated for growth from solutions in the absence of **A** at various initial supersaturations (in the present study) is statistically comparable to those determined previously for the crystallization variables, the concentration of **A** and the stirring speed (Chow et al., 1985; Chow and Grant, 1987). This suggests that the intensity of lattice disruption engendered by **A** and/or water is quantitatively identical under these 3 different conditions. However, in the presence of **A**, changes in the supersaturation level of the solutions (in the present work) cause a much greater disruption of the crystal lattice, as implied by the significantly higher disruption index, 9.78 ($P < 0.05$). This value is statistically indistinguishable from that reported for the crystals grown in the presence of **A** at various stirring speeds, suggesting that the incorporated **A** and water are equally disruptive towards the crystal lattice under these circumstances. Similar to the effects of stirring discussed in a previous report (Chow and Grant, 1987), the greater lattice disruption resulting from the combined influence of **A** and initial supersaturation may also be explained by the differences in the mechanisms of the uptake of **A** and water and by an approximate additivity of the degree of lattice disruption from individual crystallization variables.

The intercept (i.e. $\Delta S^{f}_{0} = 67.3$ J K^{-1} mol^{-1}) obtained here for crystallization in the presence of 500 mg dm^{-3} **A** at different initial supersaturations (Table 2), is statistically equivalent to those of the two crystallization variables reported earlier, namely, the concentration of **A** at constant stirring speed with a constant initial supersaturation of **P** (Chow et al., 1985) and the stirring speed with 500 mg dm^{-3} **A** added (Chow and Grant, 1987). Variation of the initial supersaturation for crystallization from **A**-free solutions gives a similar intercept value (63.9 J K^{-1} mol^{-1}) which is statistically indistinguishable from that computed for variations of stirring speeds for growth from additive-free solutions. However, the intercept values for these two latter cases are significantly lower than those of the other 3 situations mentioned above, suggesting the coexistence of growth defects with

TABLE 3

Summary of the results of the Student t-tests for differences in the regression coefficients derived from linear regression of ΔS^{f} on ΔS^{m}_{ideal} among 5 different conditions of crystallization

Crystallization variables	SPEED with fixed [A]	SIGMA with fixed [A]	SPEED alone	SIGMA alone
[A]	$\beta1$: S $\beta0$: NS	$\beta1$: S $\beta0$: NS	$\beta1$: NS $\beta0$: S	$\beta1$: NS $\beta0$: S
SPEED with fixed [A]	–	$\beta1$: NS $\beta0$: NS	$\beta1$: S $\beta0$: S	$\beta1$: S $\beta0$: S
SIGMA with fixed [A]	–	–	$\beta1$: S $\beta0$: S	$\beta1$: S $\beta0$: S
SPEED alone	–	–	–	$\beta1$: NS $\beta0$: NS

[A] = concentration of **A** in mg dm^{-3}.
fixed [A] = concentration of **A** fixed at 500 mg dm^{-3}.
SPEED = stirring rate, in r.p.m.
SIGMA = initial supersaturation of **P**, in g dm^{-3}.
$\beta1$ = negative slope = disruption index (d.i.).
$\beta0$ = intercept = ΔS^{f}_{0} in JK^{-1}mol^{-1}.
S = significant at the 5% level.
NS = not significant at the 5% level.

the impurity defects in the crystals. A summary of the Student *t*-tests for significant differences in both the slope and intercept among the 5 different variations of crystallization conditions is shown in Table 3.

It must be pointed out here that the regression coefficients and related statistics calculated for the crystallization involving no additive at various initial supersaturations must be interpreted with caution since statistically significant non-linearity in the relationship between the measured ΔS^{f} and the calculated $\Delta S_{\text{ideal}}^{\text{m}}$ values has been demonstrated. The inclusion of this case in the present analysis is purely for the purpose of completeness and is not intended as a correct approach to comparing regression parameters for this or other similar cases. That ΔS^{f} is linearly related to $\Delta S_{\text{ideal}}^{\text{m}}$ for the stirring rate, but not for the initial supersaturation, despite comparable water contents of the crystals for both crystallization variables, substantiates the earlier suggestion that the incorporation of water into the crystals may not follow identical mechanisms under the control of either variable.

Specific surface area

Crystallization at various initial supersaturations in the presence of 500 mg dm^{-3} **A** affords an initial increase (maximum at $\sigma = 6.63$ g dm^{-3}) and a subsequent large decrease in specific surface area of the crystals (Fig. 8), in line with progressive broadening of the habit (Fig. 3). On the other hand, crystals prepared in the absence of **A** show slight decreases and then increases in specific surface area with increasing initial supersaturation (Fig. 8). The results agree with the ability of high initial supersaturations to reverse the habit elongation induced by **A**.

Dissolution rate

Crystallization with 500 mg dm^{-3} **A** under conditions of a stepwise increase in initial supersaturation slightly elevates (to a maximum at $\sigma = 6.63$ g dm^{-3}) and then drastically depresses the dissolution–time profile (Fig. 9) and the initial dissolution rate of the crystals (Fig. 10). The initial dissolution rate divided by the initial mass of crystals and by the initial specific surface area of

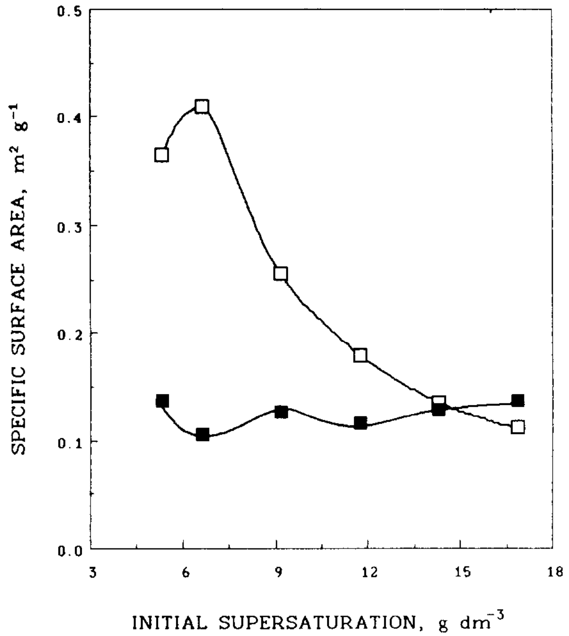

Fig. 8. Specific surface areas of acetaminophen crystals grown in the presence (□) and absence (■) of 500 mg dm^{-3} of **A**, from aqueous solutions at various initial supersaturations and at 240 r.p.m. Each data point is the mean of duplicate determinations. The variation between measurements is within 7%.

the crystals affords their intrinsic dissolution rate. The mean and standard deviation of the intrinsic dissolution rate, which are shown in Fig. 11, were calculated from those of the initial dissolution rate (Fig. 10) and from those of the surface area (±7%). Although the trends of initial dissolution rate are qualitatively similar to those of specific surface area (Fig. 8), the changes of intrinsic dissolution rate follow an entirely different pattern exhibiting a maximum at 9.19 g dm^{-3} and a minimum at 11.76 g dm^{-3} (Fig. 11). Crystals grown in the absence of **A** at increasingly high initial supersaturation, reveal slight decreases and then increases in the dissolution–time profile (Fig. 9) and initial dissolution rate (Fig. 10), in parallel with the slight downward and upward trends in their specific surface area values (Fig. 8). As a result, the intrinsic dissolution rate decreases to constant values for σ between 6.63 and 14.32 g dm^{-3} and then decreases further at higher initial supersaturations (Fig. 11).

As discussed in previous reports (Chow et al., 1985; Chow and Grant, 1987), 4 possible major

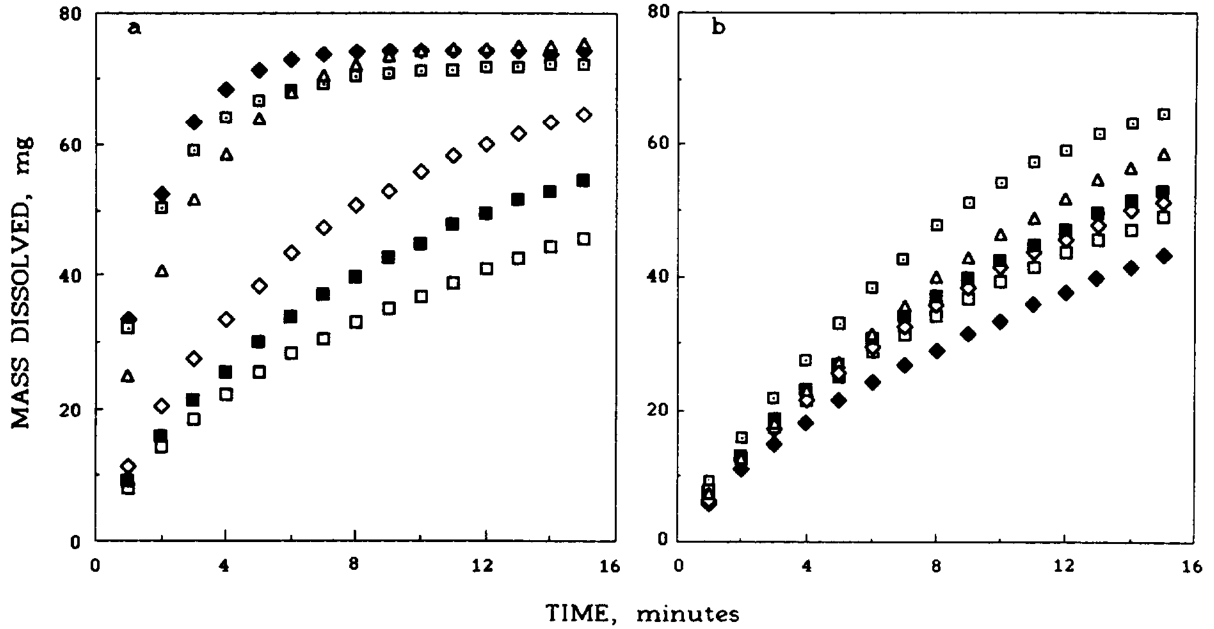

Fig. 9. Dissolution–time profiles of **P** crystals grown in the presence (a) and absence (b) of 500 mg dm^{-3} of **A**, from aqueous solutions at 240 r.p.m. and the following initial supersaturations: (⊡) at 5.34 g dm^{-3}, (◆) at 6.63 g dm^{-3}, (△) at 9.19 g dm^{-3}, (◇) at 11.76 g dm^{-3}, (■) at 14.32 g dm^{-3}, (□) at 16.88 g dm^{-3}.

factors influencing the dissolution rate of the **P** crystals can be identified, viz. (1) crystal anisotropy; (2) shape-related hydrodynamic conditions during dissolution; (3) crystal defects (impurity and growth defects) and (4) non-stoichiometric hydrates. As expected from their increases in water content, crystals grown from pure solutions at various initial supersaturations show a decreasing trend in their intrinsic dissolution rates, which appear, however, to be constant at supersaturation levels between 6.63 and 14.32 g dm^{-3}. The observed differences in the magnitude and trend of intrinsic dissolution rate values between the present case and that involving the change in stirring rate alone (Chow and Grant, 1987) appear quite intriguing, since the water contents of the crystals are comparable in both cases. This contrast could perhaps be reconciled in terms of the differences in the mechanisms of water incorporation, as suggested by the disparities in crystallization kinetics and in disruption indices between the two crystallization procedures. The changes in intrinsic dissolution rate become more difficult to interpret with respect to the water contents for

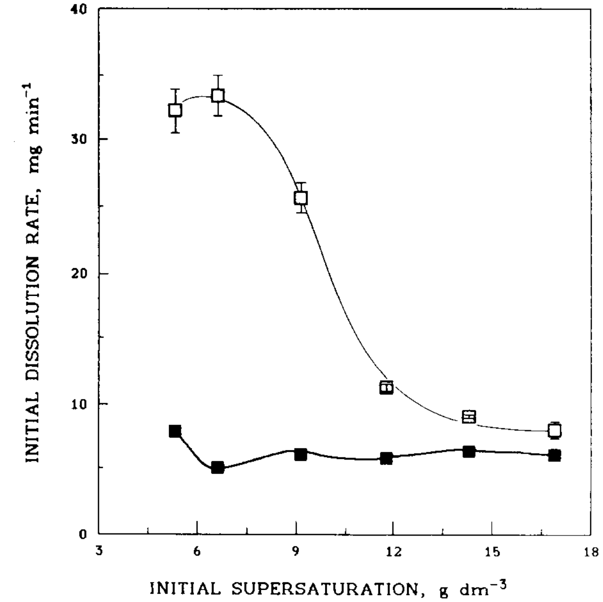

Fig. 10. Initial dissolution rates of **P** crystals grown in the presence (□) and absence (■) of 500 mg dm^{-3} of **A**, from aqueous solutions at various initial supersaturations and at 240 r.p.m. The vertical bars represent the S.D. of triplicate determinations.

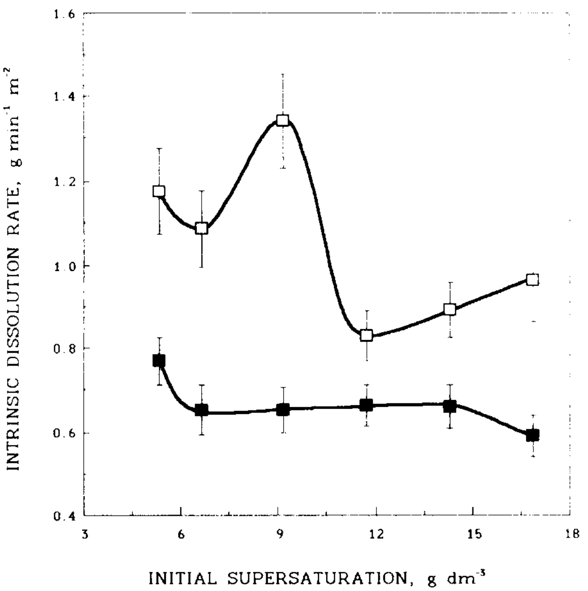

Fig. 11. Intrinsic dissolution rates of **P** crystals grown in the presence (□) and absence (■) of 500 mg dm^{-3} of **A**, from aqueous solutions at various initial supersaturations and at 240 r.p.m. The vertical bars represent the S.D. of triplicate determinations.

crystals grown in the presence of 500 mg dm^{-3} **A** under the influence of varying initial supersaturations (Fig. 1), since factors such as crystal anisotropy and habit-dependent hydrodynamic variations could exert preeminent influences on the dissolution rate of **P** crystals. In view of the multiplicity of factors involved, the intrinsic dissolution rate data in this paper and in previous reports (Chow et al., 1985; Chow and Grant, 1987) are best analyzed by multiple linear regression, which allows quantitative comparison and evaluation of the various factors affecting the dissolution rate of the crystals. While the present report is essentially phenomenological, the statistical analysis will be elaborated in a subsequent communication.

Conclusions

The principal findings of this study may be summarized as follows.

(1) Rapid crystallization under the influence of high supersaturation of **P** enhances the capture of water but diminishes the uptake of **A** by the **P** crystals.

(2) Water is the dominant disrupter of the crystal lattice, as suggested by the inverse relationship between ΔH^{f}, T_{m} or ΔS^{f} and the water content of the crystals. On the other hand, **A** appears to control the energy and entropy of the crystals indirectly via the regulation of the much larger amounts of water in the lattice. This view is substantiated by the large increases in water content and by the concomitant marked decreases in the various thermodynamic properties when **A** is omitted from the solution or when its influence is being diminished by increasing supersaturation of **P**.

(3) The extent of lattice disruption generated by the incorporated **A** and water under the influence of varying initial supersaturations, as measured by the d.i., is statistically commensurate with that brought about by varying the concentration of **A** or the stirring rate alone. However, when 500 mg dm^{-3} of **A** are present, a change in the initial supersaturation leads to considerably more intense lattice disruption which is comparable in magnitude to that resulting from a change of stirring rate. The extra defects created under the latter conditions may arise chiefly from growth, i.e. growth defects, as suggested previously (Chow and Grant, 1987).

(4) The crystal habit of **P** is a function of both the presence and concentration of **A**, but not of the initial supersaturation of **P**.

(5) The observed differences in dissolution rate cannot be solely explained by the differences in surface area, and may involve the following key factors: (a) crystal anisotropy; (b) habit-dependent hydrodynamic conditions during dissolution; (c) crystal defects and (d) non-stoichiometric hydrates.

(6) These observations demonstrate the important role in the crystallization process played by the initial supersaturation on the physical properties of drug crystals especially when grown in the presence of an additive or impurity.

(7) Thus, these findings complement and are consistent with those reported previously (Chow

et al., 1985; Chow and Grant, 1987) and further stress the mediating roles of crystallization conditions in governing the morphology, uptake of **A**, water content, lattice energy, lattice disorder and dissolution rate of the **P** crystals.

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