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Crystallization of paracetamol from solution in the presence and absence of impurity

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Abstract

The bulk crystallization of paracetamol has been examined under controlled conditions in the presence and absence of the additive *p*-acetoxyacetanilide (PAA), as a function of both supersaturation and additive levels. The induction time to nucleation was found to increase with increase in PAA concentration in solution. The product micro-crystals were characterized for shape and strain/defect content using electron and optical microscopy and X-ray Laue diffraction techniques, respectively. A change in crystal habit of the pure crystals from columnar (dominant {110}) to plate-like (dominant {001}) was observed to occur with an increase in supersaturation level, whilst the addition of PAA invariably led to the development of columnar crystals with an aspect ratio that varied with impurity level and supersaturation. HPLC showed the PAA to be incorporated into the crystals with an average segregation coefficient of 14–18% depending on the supersaturation. The ready incorporation of PAA is attributed to the molecular similarity of this molecule to that of the host material. The incorporation is shown to cause a significant increase in the mosaic spread, implying the development of a significant strain/defect content in the crystals. The influence of the impurity on the time to nucleation is probably due to its effect in blocking the development of the critical nucleus. The potential implications of such variations in morphology and strain content in the design of the physical and chemical properties of the resulting particulates are discussed.

Keywords: Bulk crystallization; Crystal habit; Defect/strain content; Impurity incorporation; Induction period; Paracetamol; *p*-Acetoxy acetanilide

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Nomenclature

List of symbols

{hkl}	crystal faces
(hkl)	crystallographic planes
$\Delta\theta$	undercooling (°C)
S	relative supersaturation
c_e	equilibrium solubility (at $30-\Delta\theta$°C)
c_o	solubility at 30°C
Y	crystal yield
w_c	amount of material harvested
w_s	amount of material present in the original saturated solution
L	radial spot extension
D	distance between the flat film and the sample
η	mosaic spread of the crystals
θ	reflection angle
τ	induction time to nucleation
J	nucleation rate
β	shape factor
γ	surface free energy
Ω	molecular volume
K	kinetic factor
k	Boltzmann constant
r^*	radius of the critically sized nuclei
T	absolute temperature

1. Introduction

Crystallization is the critical process used by process industries to achieve the desired size, size distribution, shape and physical characteristics of a product material. Control of these properties presents a major challenge since they influence considerably downstream processing factors such as powder flow, comminution and solubilization. These latter properties also depend to a large extent on the bulk properties of the product such as defect content and purity. Whilst much effort has been directed successfully to the control of size and size distribution in crystallization, less success has been achieved in defining some other properties. There is a need to develop studies of crystallization to investigate how, on the bulk scale, variations in factors such as solvent, supersaturation, temperature, impurity content and hydrodynamics influence, and hence can be used to control, the bulk and surface properties of materials. The eventual aim is to engineer particles with a particular processing behaviour.

With this aim in mind, we have initiated, in collaboration with others and with the support of partners in the pharmaceutical industry, a comprehensive examination of the role of experimental factors in the definition of the crystal characteristics of typical product pharmaceuticals. In this first series of examinations the chosen drug substance is the common pharmaceutical paracetamol. In previous papers, we have reviewed the nature of the material and its mechanical properties (Finnie et al., 2001a; Prasad et al., 2000),

defined the mechanism and kinetics of crystal growth (Ristic et al., 2001), and studied the influence of generic impurities and degradation products on the growth process and defect content (Finnie et al., 2001b) of the crystals. The influence of the proximity of the growing crystals on the variation of the shape and size distribution of the product material has also been examined (Finnie et al., 1996). In the present paper, we address the nucleation and growth characteristics of paracetamol as a preliminary to defining conditions for the 'scale-up' of the crystallization process.

It has been long recognized that the presence of small amounts of impurities can have substantial effects on the kinetics of crystal nucleation, growth morphology and dissolution (Klug, 1993; Weissbuch et al., 1995). The presence of soluble impurities can suppress nucleation in aqueous solution. Mullin (1993) states that this may result from changes in the equilibrium solubility or the solution structure, or by physical or chemical adsorption of the impurity on homogeneous and heterogeneous nuclei. The presence of impurities may also influence profoundly the growth of a crystal. Some impurities can suppress growth entirely, some may enhance growth, whilst others may produce a selective effect, acting only on some crystallographic surfaces and modifying the crystal habit (Mullin, 1993).

Paracetamol (acetaminophen) is a widely used analgesic and antipyretic drug. Several researchers have reported the modification of the crystal habit and properties of paracetamol crystals by growth from aqueous solutions both in the pure state and in the presence of additives such as *p*-acetoxyacetanilide, agar, gelatin, polyvinylpyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) (Chow et al., 1985; Femi-Oyewo and Spring, 1994). More recently, Hendriksen et al. (Hendriksen and Grant, 1995; Hendriksen et al., 1998) have studied the general effect of a range of molecularly similar additives on the nucleation kinetics and crystallization of paracetamol.

From their studies, Femi-Oyewo and Spring found that the additives used modified significantly the crystal properties of paracetamol. The crystal shape changed from prismatic (pure) to rectangular shape with gelatin, triangular shape with agar and to a rod-like shape with PVP. The crystals obtained in the presence of agar and gelatine additives showed different compaction properties to those obtained with the pure material. The rate of drug release of compacts made from this material were also affected

Chow et al. (1985) in their paper report that the presence of the impurity PAA slows the crystallization of paracetamol and is incorporated into the crystal lattice by a small proportion ($>1\%$). They also report that the incorporation of PAA into paracetamol crystals progressively alters the crystal habit, increases the surface area and increases the dissolution rate. The later papers (Hendriksen and Grant 1995; Hendriksen et al., 1998) confirm the marked effect that the range of molecularly similar impurities have on nucleation behaviour, such as extending the induction time to nucleation compared with the pure system.

In the papers, little detail was presented, however, on the changing morphology of the crystals as a function of both supersaturation and additive concentration. In the present paper, we report systematic and controlled crystallization studies of paracetamol in the presence or absence of *p*-acetoxyacetanilide additive with the particular aim of controlling and defining the properties and behaviour of the material for downstream processes such as milling and powder flow. *p*-Acetoxyacetanilide was chosen since this molecule appears to have the most significant effect on morphology of the range of impurities studied previously (Chow et al., 1985; Hendriksen et al., 1998).

2. Materials and methods

2.1. Materials

Rhodapap paracetamol (Acetaminophen) was supplied by Rhone-Poulenc Chemicals Ltd. (Watford, UK). *p*-Acetoxyacetanilide (PAA) was prepared using the method of Chattaway (Chattaway, 1931) and was recrystallized from ethanol as white platey-prismatic crystals melting at ~ 155°C.

Great care had to be taken in handling the paracetamol prior to and during the experiments. It was found that oxidation of the material readily occurred when the aqueous solution was maintained in air creating a pink coloration that rapidly turned brown on standing. This change took place in periods of 1 month at room temperature, 1–2 weeks at 35°C and 1–2 days at 65°C. When this occurred, the coloured products became incorporated into the crystal during crystallization. More importantly however, the oxidation products had a major inhibiting influence on the nucleation and crystal growth process. The influence could be minimized by working at as low a temperature as reasonable and by excluding oxygen from the preparation and measurement system.

The chemical nature and detailed influence of these impurities are currently under investigation. In the present experiments, every effort was made to reduce their influence, which included the renewal of the solutions at regular intervals.

2.2. Methods

2.2.1. Nucleation studies

Nucleation was studied in a 25 ml capacity stirred cell provided with a thermostatted water jacket. Water was circulated through the jacket from a Haake (F3-CH) thermostat bath that could be controlled to ± 0.1°C. Crystallization in the cell was monitored by measuring the transparency of the solution with a colorimeter (Brinkman PC700) provided with a fibre optic probe that was inserted into the nucleation cell. Temperature, time to nucleation and solution transparency were monitored and recorded on a personal computer.

A saturated solution of paracetamol was made at 40°C by dissolving the appropriate amount of solid in doubly distilled water (Grant et al., 1984). After equilibration, the solution was filtered through a Buchner filter and transferred to a 500 cm^3 round-bottomed flask immersed in a thermostat bath at 30 ± 0.1°C. The solution was left to equilibrate with the precipitated solid at the bottom of the flask for a period of 48 h while stirring slowly. At this stage, there was no perceptible pink coloration in the solution. After equilibration, 20 ml of the solution were transferred by pipette to the crystallization cell, also at 30 ± 0.1°C, by filtering through a Whatman 50 filter paper. The solution temperature was reduced as rapidly as possible by a defined undercooling, $\Delta\theta$, to give a relative supersaturation, S [$S = \ln(co/ce)$, where ce is the equilibrium solubility at $30 - \Delta\theta$°C, and co is the solubility at 30°C] (Grant et al., 1984). The cooling rate of the solution was monitored using a copper–constantan thermocouple and found to be 1°C/min and linear ($\pm$ 5%).

Once the solution reached the specified temperature, it was stirred rapidly at ~ 200 rpm until precipitation occurred. When the transmittance had fallen to 70% of its initial value, the stirring was stopped and the product quickly filtered and dried. The time lapse between the solution reaching its particular undercooling temperature and the onset of opacity was taken as the induction time and was measured by the computer's internal clock. Nucleation was taken to have occurred when the transmittance through the solution was 10% lower than the average value of the clear solution. This value was chosen so that electronic noise (up to 4%) could not be mistaken for nucleation. Experiments were carried out over the supersaturation range from 7% ($\Delta\theta = 5$°C) to 55% ($\Delta\theta = 20$°C). Each experiment was repeated five to eight times at each supersaturation level to confirm reproducibility.

The nucleation studies were repeated with levels of PAA in the initial solution in the range 0.3–6.02% w/w in order to examine the influence of this impurity on the nature of the product crystals. This range was chosen to allow comparison with previous single crystal studies (Finnie et al., 2001b). The known amount of additive was added to the paracetamol solution saturated at 30°C and the solution left overnight to equilibrate. Precipitations were performed in the same manner as described for pure paracetamol.

At each additive level, the supersaturation was also varied to estimate the critical supersaturation level for nucleation in the presence of PAA.

Thirty minutes to 1 h after nucleation, the crystal yield, $Y = (w_c/w_s) \times 100$, where w_c is the amount of material harvested, and w_s is the

amount of material present in the original saturated solution, was measured in each experiment for both the pure and PAA doped samples.

2.2.2. Estimation of incorporated PAA

The amount of PAA incorporated in the paracetamol crystals was determined using high-performance liquid chromatography (HPLC). Samples crystallized in the presence of PAA, washed in methanol to remove traces of mother liquor, were dissolved in HPLC-grade methanol, filtered through a 0.45 μm Millipore filter and analysed using a Spectra-Physics SP 8810 Chromatograph with UV detector (Waters 486) and a Technopak C-18 reversed phase column (3.9 mm × 30 cm). The mobile phase consisted of 27% methanol and 73% water and the elution rate was 1 ml per minute. The retention times for paracetamol and PAA were 4 and 11 min, respectively. Calibration plots for both paracetamol and PAA showed the UV detector response at 248 nm to be a linear function of concentration over the range studied.

2.2.3. Scanning and optical microscopy

The morphologies of the bulk crystallized samples of pure and PAA-doped paracetamol were characterized using a GSM-840 JEOL scanning electron microscope and Reichert Polyvar 2- Leica optical microscope.

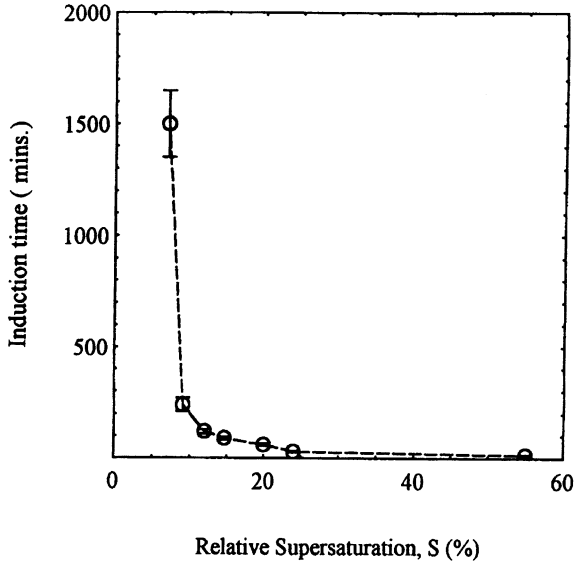

Fig. 1. Variation of induction time with relative supersaturation for pure paracetamol.

2.2.4. Characterization of mosaic spread (crystal strain) by Laue diffraction

Laue diffraction patterns were recorded for the crystals of pure and PAA-doped paracetamol using the high-intensity Wiggler beam line (station 9.7), at the EPSRC Synchrotron Radiation Facility, Rutherford/Appleton Daresbury Laboratory, Cheshire, UK, operating at an energy of ca. 2 GeV and a beam current of 50–200 mA. A modified Arndt–Wonacott oscillation camera (Arndt and Wonacott, 1977), commissioned for protein crystallography (Helliwell et al., 1986), was employed. The crystal-to-film distance was set at 50 mm, a collimator of 0.2 mm was used, and a fast shutter gave exposure times down to milliseconds with crystals as small as 50 μm.

The mosaic spread (η) of the crystals was calculated from the asterism observed in these diffraction patterns using the formula

$$l = 2\eta d/\cos^2 2\theta,$$

where l is the radial spot extension, d is the distance between the flat film and the sample, and θ is the reflection angle. The radial spread of the reflections was estimated visually using an eyepiece graticule. Several reflections, at different reflection angles were analysed and the results combined to give an average mosaic spread for a particular crystal (Ristic et al., 1988). Tests applied to determine whether paracetamol suffered radiation damage in the synchrotron beam were negative. The asterism was shown to remain constant and not to increase with continued irradiation.

3. Results

3.1. Pure paracetamol

3.1.1. Induction times and morphological changes

Pure paracetamol was precipitated under the conditions noted above. As shown in Fig. 1, the induction time to nucleation decreased with in-

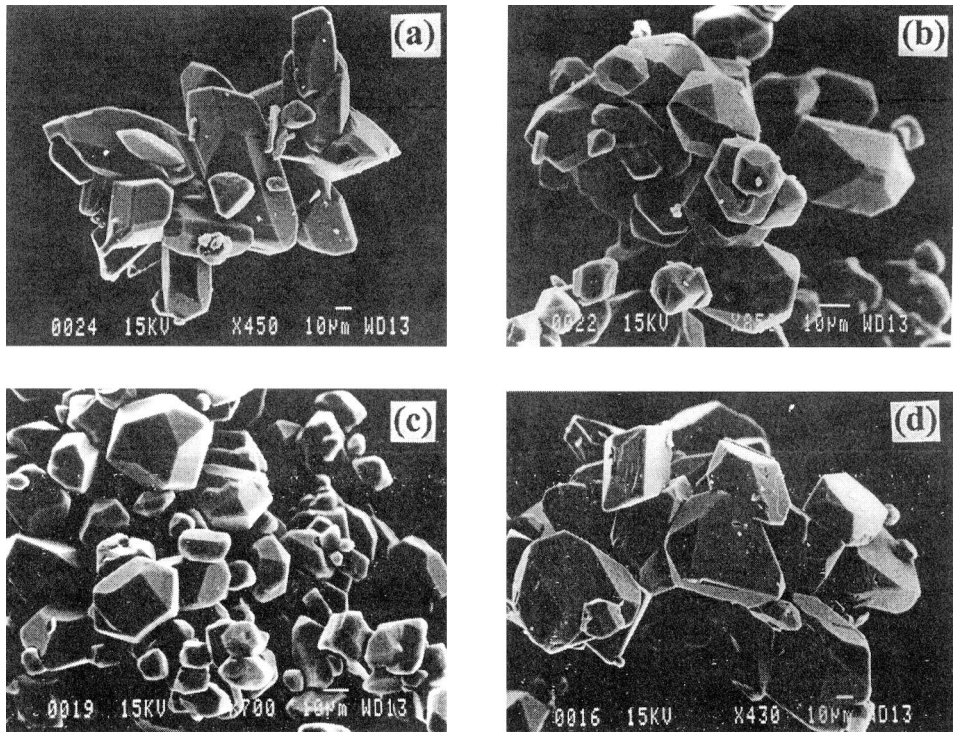

Fig. 2. Scanning electron micrographs showing the change of habit of paracetamol crystals from columnar to plate-like with increase in supersaturation (a) $S = 7\%$, (b) $S = 15\%$, (c) $S = 24\%$ and (d) $S = 55\%$.

creasing supersaturation level varying from 20 to 30 h at low levels of supersaturation to 15–30 min at higher supersaturation levels. Simultaneously, the crystal yield increased. Scanning electron micrographs of the product clearly show that the morphology of the microcrystals changes from columnar to plate-like with increasing supersaturation (Fig. 2). At low levels of supersaturation ($< 11\%$), columnar crystals with major {110} faces dominate, while at higher supersaturation levels ($> 11\%$), tablet or plate-like crystals with major {001} faces dominate. This variation in morphology with supersaturation is similar to that found previously in assemblies of small (2 mm) crystals (Finnie et al., 1996) and with large crystals (1 cm) (Finnie et al., 2001a,b). It reflects the variation of the growth rate and mechanism on the {110} faces noted in the last reference and which represents layer growth with small step heights at low supersaturation giving way to screw dislocation controlled growth at medium supersaturations and to macrostep layer growth at high supersaturations.

3.1.2. Mosaic spread analysis

Analysis of Laue diffraction patterns recorded for crystals prepared under controlled crystallization conditions showed a pronounced increase in radial asterism and hence mosaic spread with increase in supersaturation level (Fig. 3). The increase in mosaic spread was paralleled by a noticeable increase in solvent inclusion particularly in the {110} growth sectors of the crystals. This observation is in agreement with the results of X-ray topographic studies of larger pure paracetamol crystals, which show higher densities of dislocations and inclusions in the {110} sectors for crystals grown at high supersaturations when compared with those grown at low supersaturations (Finnie et al., 2001a,b; Ristic et al., 2001) These results also correlate well with the experiments of Chow and Grant (1988), which showed

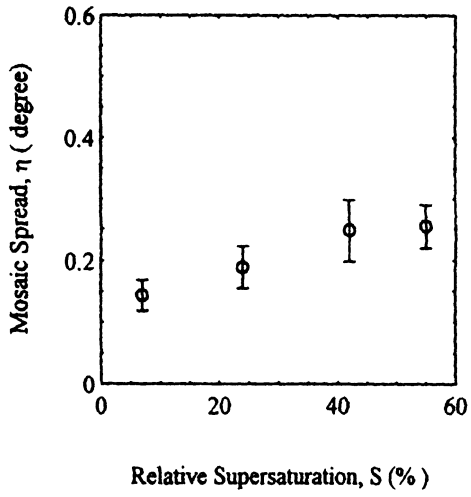

Fig. 3. Variation of mosaic spread (bulk lattice strain) with relative supersaturation for micro-crystals of paracetamol obtained under controlled conditions.

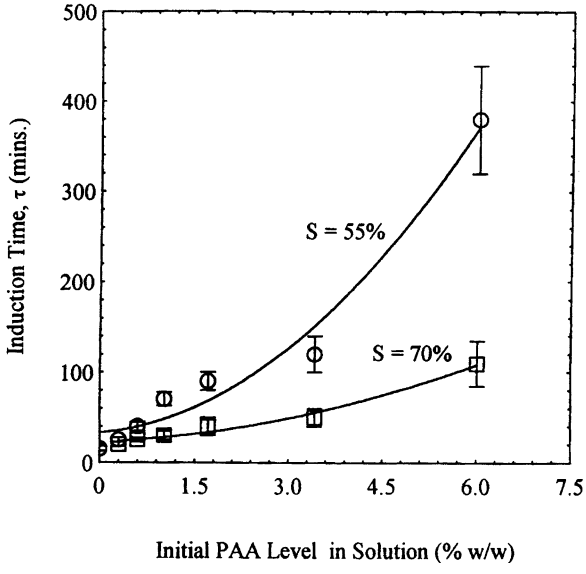

Fig. 4. Variation of induction time with PAA additive content (%w/w) in solution for two levels of supersaturation ($S = 55$ and 70%).

an increase in the water content of paracetamol micro-crystals grown under conditions of high supersaturation. In this last assessment, the location of the included solvent was not defined.

In considering these results, we wish to note that the bars on the points on Fig. 3 represent the range of the mosaic spreads measured for randomly selected particles within the size range 100–200 μm grown at one particular supersaturation and not the error on each measurement, which is much smaller. Thus, although there is an apparent overlap between successive points, the data define a gradual increase in the fraction of crystals, which have a higher mosaic spread. Regrettably, the time involved in making these measurements precludes the assessment of a larger number of samples. We feel, however, that a sufficient number of experiments were performed on randomly selected specimens to show that a significant change in strain/defect structure had occurred.

3.2. PAA-doped paracetamol

3.2.1. Induction times and morphological changes

To assess the influence of additive on the habit and other material properties, paracetamol was crystallized under controlled conditions in the presence of PAA (0.3–6.02% w/w) in solution over a range of supersaturations (24–86%). It was found that the induction time to nucleation increased with PAA level and the crystal yield decreased for any given supersaturation. In contrast, increases in supersaturation at constant impurity content yielded a decrease in induction time.

These variations are well exemplified in Figs. 4 and 5. The former shows the increase of induction time to nucleation with increasing PAA level for two levels of supersaturation (55 and 70%). It will be noted that the induction times are considerably greater than those for the pure solution, confirming the considerable inhibiting power of the impurity. As might be expected, Fig. 5 confirms that increases in supersaturation yield a decrease in the induction time at a constant impurity content. The variations in the latter case follow closely the same pattern as for the pure material. The critical supersaturations are, however, much higher, 80% supersaturation being required to yield an induction time of 30 min at 6.02% impurity content.

The crystal yields were similar to those achieved for the pure system at equivalent supersaturations and decreased almost linearly with increasing PAA level. This variation can be attributed to

resulting changes in effective supersaturation and the noted inhibition of growth.

The role of PAA in habit modification is well demonstrated in the optical transmission micrographs and scanning electron micrographs shown in Figs. 6 and 7. These show clearly that crystals with a columnar habit appear together with those of a plate-like habit from 0.602% w/w PAA upwards, while the columnar habit dominates completely above 1.02% w/w PAA. The critical PAA level at which the columnar crystals start to appear increases, with the PAA level being ~ 0.602% w/w at ~ 55% supersaturation and rising to 1.02% w/w at 70% supersaturation.

Variation of the supersaturation yields similar morphological changes. As the supersaturation was increased from 55 to 86% at a 6.02% w/w initial PAA level, the aspect ratio of columnar crystal decreased from 6.2 to 1.2, and the crystal morphology changed from long columnar to short columnar (Fig. 8). The same effect was observed when the supersaturation varied from 42 to 70% at a 3.42% w/w PAA level. As can be seen from Fig. 8, the change in habit is accompanied by the formation of macrosteps (growth steps of a height much greater than the interplanar distance, i.e. tens of hundreds of nanometres), particularly observable on the {110} surfaces. This behaviour potentially arises as a result of the competition between the increased impurity inhibition of growth and the high supersaturations necessary to overcome this inhibition. The latter influence results in sudden, rapid, increases in growth rate. In turn, this leads to the bunching of lower height steps to form the macro steps. As a consequence of hydrodynamic factors, these often can propagate more rapidly at the surface edge than at the base and hence overgrow to form overhangs and to trap inclusions. As we show elsewhere, such inclusions are more widespread in the doped crystals than in pure crystals where they are predominantly localized in the {110} sectors (Ristic et al., 2001).

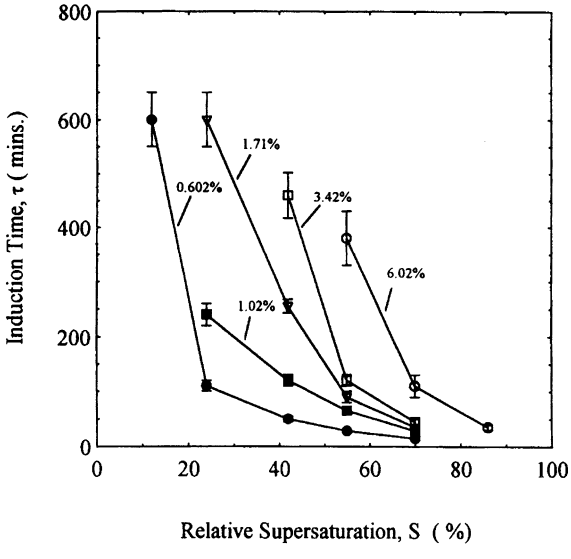

Fig. 5. Variation of induction time with relative supersaturation for paracetamol containing different PAA contents (0.602–6.02% w/w) in solution.

3.2.2. Incorporation of PAA in the crystals

The variation of the segregation coefficient, *K*eff (the ratio of the concentration of PAA in the product crystals to the concentration of PAA relative to paracetamol in solution after crystallization) with PAA (0–6.02% w/w) level in the solution at equilibrium is shown in Fig. 9. The values lie in the range 14–18% and show a minor dependence on supersaturation.

3.2.3. Strain in PAA-doped paracetamol crystals

The variation of the mosaic spread for paracetamol crystallized from solutions containing increasing amounts of PAA is shown in Fig. 10. The significant increase observed is no doubt due to the degree of crystal lattice distortion (strain) that results from the PAA incorporation. As we show elsewhere (Finnie et al., 2001a,b), this occurs principally into the {110} sectors. A significant amount also enters other sectors, however, contributing to an overall increase in strain in the crystal as a whole. The degree of increase in the mosaic spread with increase in PAA level was higher than that obtained with increase of supersaturation. This no doubt results from the more effective lattice distortion induced by the incorporated PAA molecules compared with the strain induced by rapid precipitation and/or solvent inclusion in the pure material. The above conclu-

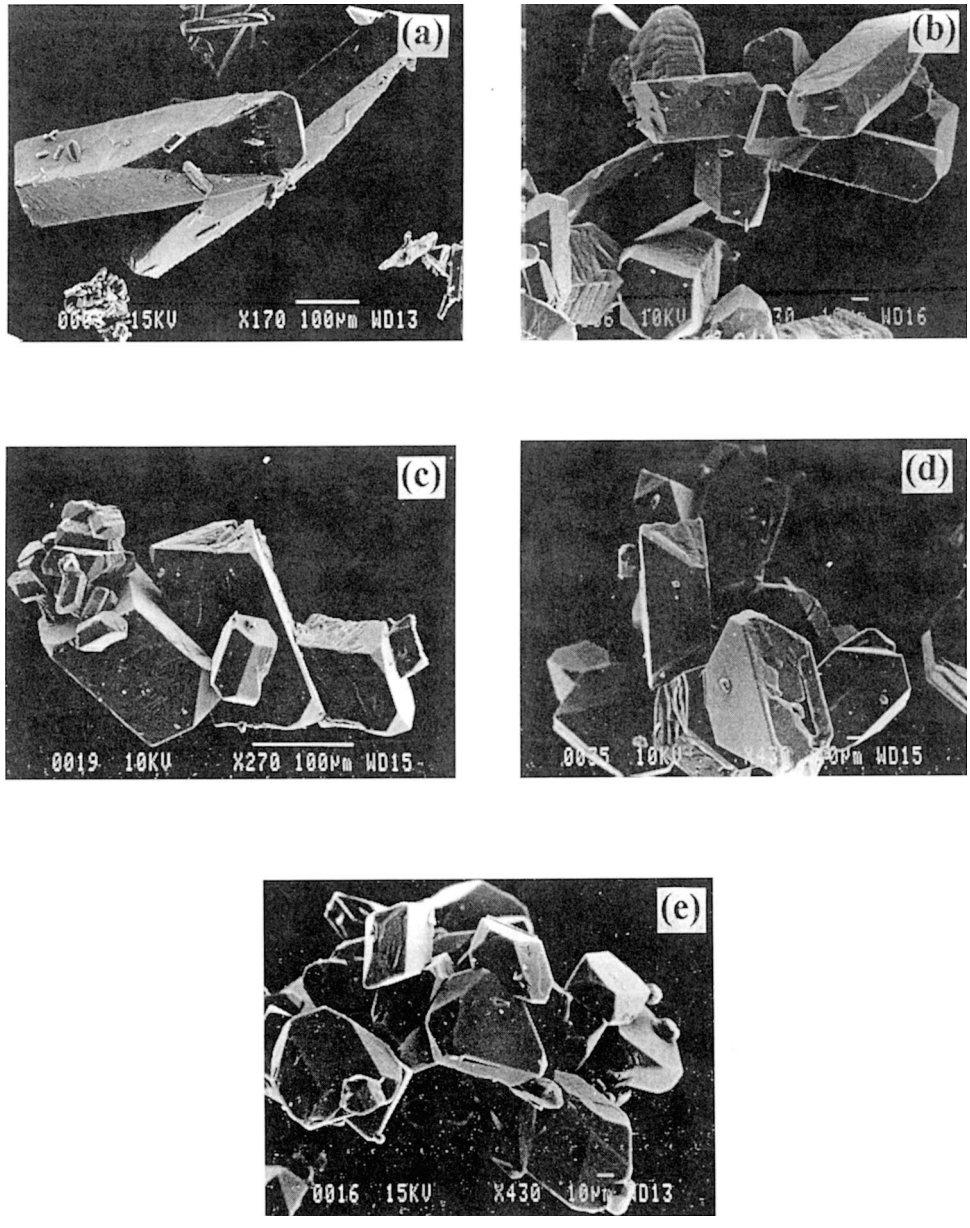

Fig. 6. Scanning electron micrographs showing the morphology of paracetamol crystallized in the presence of varied PAA content in solution ($S = 55\%$): (a) 6.02%, (b) 3.42%, (c) 1.71%, (d) 1.02% and (e) 0% w/w.

sion is supported by the X-ray topographic studies of this material (Finnie et al., 2001a,b), which show that crystals doped with 6.02% w/w PAA show high levels of included strain in the {110} sectors when compared with the same sectors in pure crystals.

4. Analysis and discussion

4.1. Theory

According to Becker and Döring (1935), Nielsen (1964) and Nielsen and Sohnel (1971), the rate of homogeneous nucleation can be expressed as

$$J = K \exp(-\beta\gamma^3\Omega^2/(kT)^3[\ln(S)]^2), \quad (1)$$

where K is the kinetic factor, k is the Boltzmann constant, β is the shape factor ($\beta = 16\pi/3$ for a spherical nucleus), γ is the surface free energy, Ω is the molecular volume and $S = c/c\mathrm{o}$ (c and $c\mathrm{o}$ are the concentration of supersaturated and saturated solutions at temperature, T), is the relative supersaturation ratio. The radius, r^*, of a critically sized stable nucleus is given by

$$r^* = (2\gamma\Omega/kT \ln S). \quad (2)$$

For a given volume of the solution, the rate of nucleation, J, is inversely proportional to the induction time, τ (van Hook and Bruno, 1949; Nielsen, 1964; Mullin, 1993) and from Eq. (1), one obtains

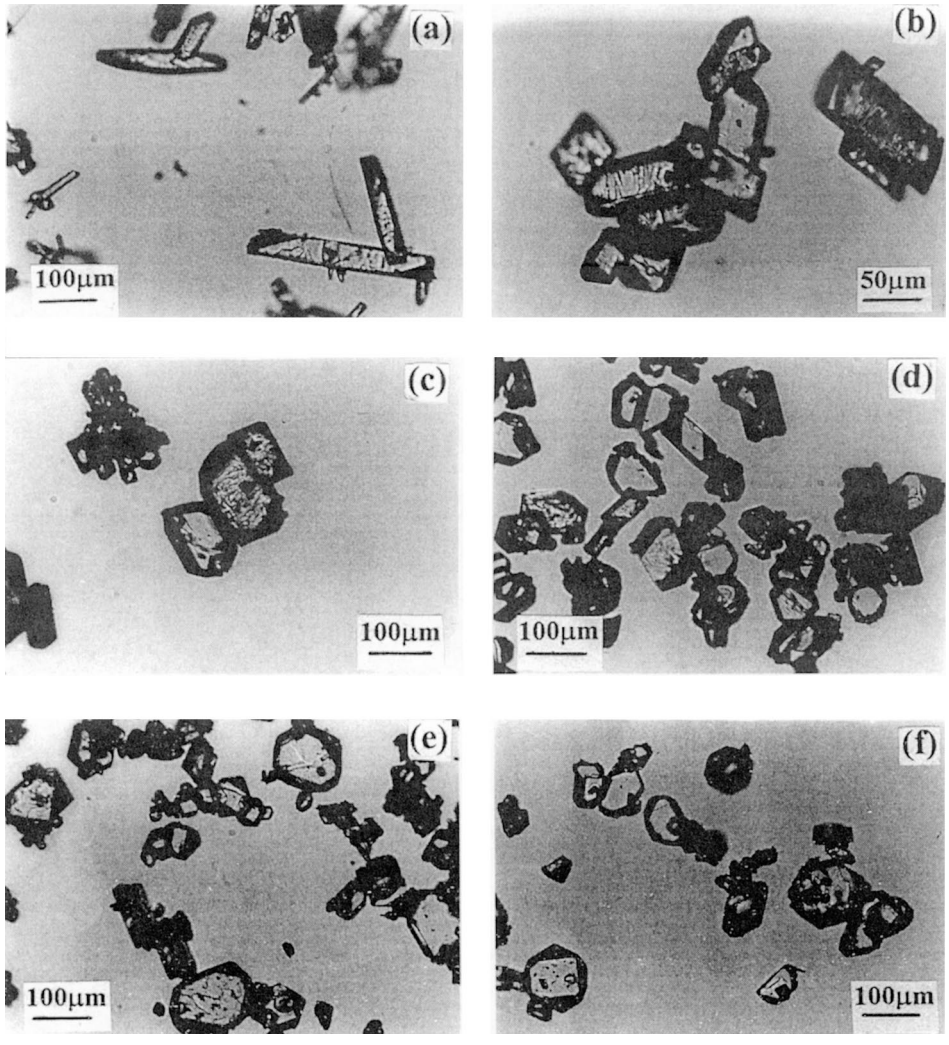

Fig. 7. Optical micrographs showing the morphology of bulk crystallized paracetamol at $S = 55\%$, in the presence of varied PAA content in solution: (a) 6.02%, (b) 3.42%, (c) 1.71%, (d) 1.02%, (e) 0.602% and (f) 0% w/w.

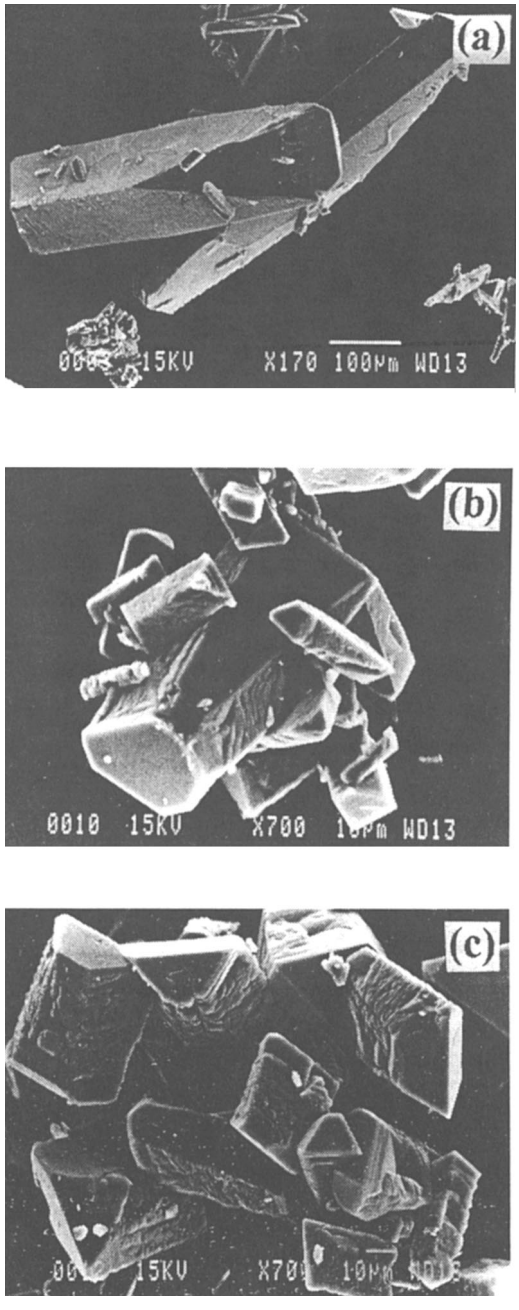

Fig. 8. Scanning electron micrographs showing the change in morphology of bulk crystallized paracetamol with supersaturation in the presence of constant PAA content, 6.02% w/w in solution: (a) $S = 55\%$, (b) $S = 70\%$ and (c) $S = 86\%$.

$$\ln \tau = A + \beta(\gamma^3 \Omega^2 / k^3 T^3)(1/(\ln S)^2), \quad (3)$$

where A is a constant. The linear dependence of $\ln \tau$ on $T^{-3}(\ln S)^{-2}$ gives the slope

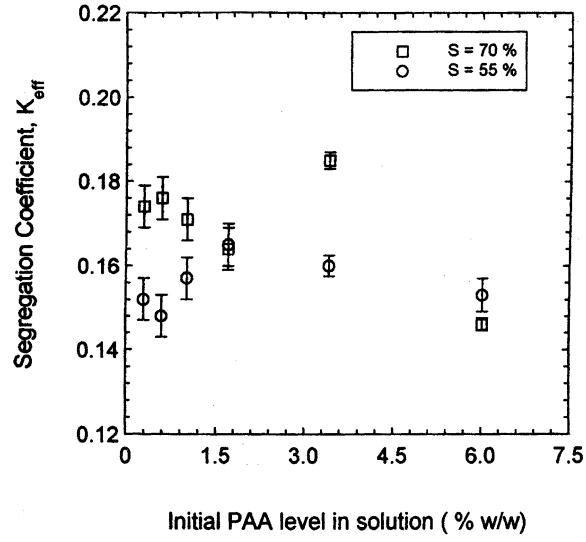

Fig. 9. Variation of segregation coefficient with the amount of PAA in solution for paracetamol bulk crystallized at two levels of supersaturation, $S = 55\%$ and $S = 70\%$.

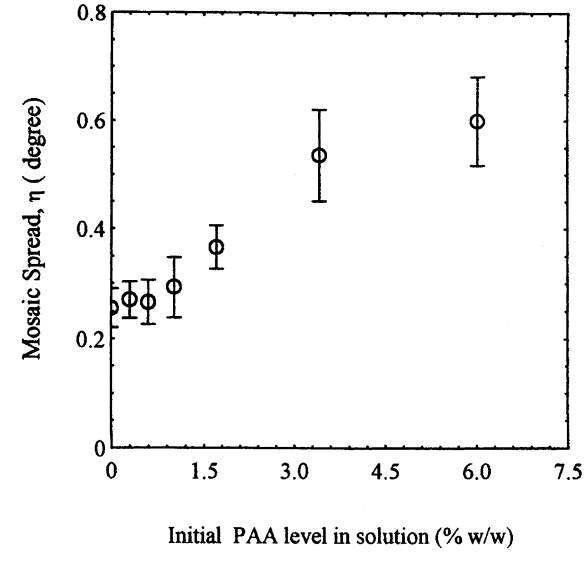

Fig. 10. Variation of mosaic spread (bulk lattice strain) with the amount of PAA present in the solution for micro-crystals of paracetamol obtained under controlled conditions ($S = 55\%$).

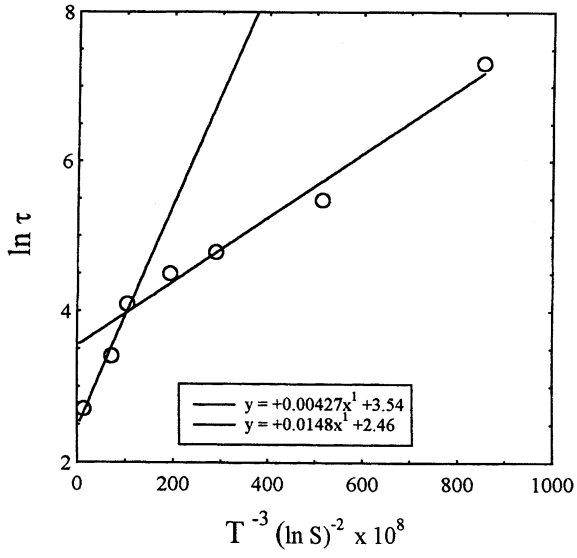

Fig. 11. Plot of the dependence of $\ln \tau$ on $T^{-3}(\ln S)^{-2}$ obtained for the nucleation of pure paracetamol.

$$m = \beta\gamma^3\Omega^2/k^3, \quad (4)$$

from which γ, surface free energy or interfacial tension can be estimated.

4.2. Pure paracetamol

On the basis of these theoretical considerations (Eq. (1)), the nucleation rate should increase with increasing supersaturation and temperature and decrease with increase in surface free energy. The degree of supersaturation is the critical parameter in controlling the rate of nucleation. The size of the critical nucleus reduces with increasing supersaturation. Thus the probability of nuclei surviving to form crystals is higher.

Fig. 11 shows the typical dependence of $\ln \tau$ on $T^{-3}(\ln S)^{-2}$ obtained from the experiments for pure paracetamol solution. The experimental variation can be divided into two linear dependences of high gradient at high supersaturations and low gradient at low supersaturations. These regions have been attributed by previous authors (Sohnel and Mullin, 1988; Mullin, 1993) to homogeneous nucleation and heterogeneous nucleation, respectively.

In this manner, the data follow the same pattern as that described by Hendriksen and Grant (Hendriksen and Grant, 1995) for pure paracetamol. Similarly, the surface free energy estimated from the slope of the linear portion of the high supersaturation region is 1.83 mJ m^{-2} in close agreement with their value of 1.840 mJ m^{-2}. This agreement extends to the observation of similar relationships between supersaturation and induction times to nucleation.

In contrast, our observations of the morphological changes differ from theirs in that, whereas they noted variations in aspect ratio with change in supersaturation, we observe a distinct change in morphology from columnar to plate-like with a dominance of different habit faces. We regard this distinction as important in the context of this paper since it imposes a major difference in the surface properties of the material, which in turn will influence its wider behaviour.

This change in morphology parallels the behaviour noted in previous studies of larger crystals and arises from the increase in the growth rate of the {110} faces from almost zero at low supersaturations to much higher values than those of the other faces at high supersaturations. This leads to a dominance of {110} at low supersaturations and {001} at high supersaturations. As for the larger (2 mm) crystals (Finnie et al., 1996), and due to the variation in supersaturation which inevitably exists in the slurry of growing crystals, both of the forms can exist at all concentrations but one dominates at the lower supersaturation and vice-versa. The cross-over point where both exist in approximately equal numbers is at 12% supersaturation. Attention is drawn to this variation in the comments on Fig. 2 (Section 3.1.1).

In parallel with the above variations, there is a small increase in the mosaic spread of the product crystals with supersaturation. This reflects an increase in the general defect content of the crystals and potentially results from the increased lattice strain in the rapidly precipitated particles or the inclusion of solvent under these conditions of growth. The latter could be a particular problem at high supersaturations. In the present case, however, any amounts of included solvent were too low to be detected accurately (York, private communication, University of Bradford, UK).

4.3. PAA-doped paracetamol

Previous examinations (Finnie et al., 2001a,b) have shown that PAA has a significant influence on the growth of paracetamol, inhibiting particularly the growth of the {110} faces. This influence has been ascribed to the close structural similarity of the PAA molecule to the host molecule, allowing it to adsorb strongly at the growing interface. It is obvious from the present and previous investigations that this material similarly influences the nucleation of the paracetamol, delaying this process and causing considerable increase in the induction time, τ, to nucleation.

The surface free energy values, which refer to homogeneous nucleation, evaluated from the linear plots of ln τ with $T^{-3}(\ln S)^{-2}$ (Eq. (3)), increase with increasing PAA content from 1.8 mJ m^{-2} for the pure material to 4.9 mJ m^{-2} at 6.02% w/w (Fig. 12). Such an increase in surface free energy can be correlated with an increase in the size of the critical nucleus and with a parallel decrease in the nucleation rate (Eqs. (1) and (2)). Additionally, the incorporation of the impurity into the developing nucleus could well render it less stable than those created in pure paracetamol solutions. This will particularly be the case if, as has been found in the case of the caproic acid impurity in adipic acid (Narang and Sherwood, 1978) and homologous impurities in the linear paraffin hydrocarbons (Stewart et al., 1990), the impurity concentrates preferentially in the developing nucleus. Preliminary experiments do indicate that this is likely to be the case in the paracetamol/PAA system. The combination of these factors means that larger activation energies will be required for nucleation by larger critical nuclei with the observed result that nucleation will be delayed. Thus, PAA is defined as a nucleation inhibitor. Similar influences of impurities have been noted by Wojciechowski (1989) for sodium chlorate and van der Leeden et al. (1992) for barium sulphate. In the latter case, the increase was ascribed to the power of the additive molecule to act as second-type heterogeneous nucleation centres (extra-active centres for 2D and 3D nucleation), which are less active than the active centres available in the absence of the additive.

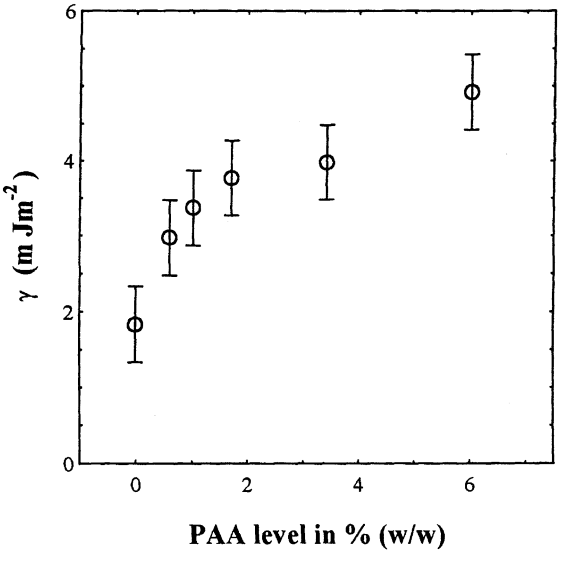

Fig. 12. Dependence of surface free energy, γ, on additive, PAA content in the nucleating solution.

As noted above, the second effect of the added impurity is to modify the morphology of the growing paracetamol crystals. The habit of crystals is determined by the relative growth rates of the individual faces, which can be influenced during crystallization by the presence of impurities and even the solvent itself (Klug, 1993; Weissbuch et al., 1995). In general, impurities are adsorbed on the growing crystal surfaces changing the relative surface free energies of the faces and blocking the active growth sites, which are essential to the incorporation of new solute into the crystal lattice. These effects may result in changes in growth kinetics and hence habit modification of the crystal face. They may also of course similarly influence the early growth of the nucleus and prevent it from maturing to the critical state

Impurity molecules such as PAA, which differ from those of paracetamol only by the substitution of the phenolic hydroxyl groups with acetyl groups, present a special case. The similarity of part of the molecule to the paracetamol molecule allows it to be absorbed strongly and preferentially into the growth terraces of particular faces; those that propagate by acceptance of the common structural unit phenyl-NH-CO-CH_3, pinning

growth steps and decreasing step velocity. An inevitable consequence of such strong absorption is the incorporation of the molecule preferentially into those faces that accept the equivalent portion of the paracetamol molecule. In the present case, this is the {110} face, although other faces are also influenced but to a lesser extent (Finnie et al., 2001a,b).

From previous studies (Finnie et al., 2001a,b), it would appear that incorporation of PAA influences the propagation of the steps to a greater extent than their generation. As a consequence, the observed growth hillocks become steeper. This results in a significant reduction in growth of the {110} faces whilst the less affected {001}, {20$\bar{1}$} and {011} faces suffer less inhibition resulting in the development of elongated, columnar crystals in the presence of PAA. This elongation increases with added impurity, resulting in the noted change in aspect ratio.

In contrast, increasing the supersaturation at constant impurity content leads to a decrease in the aspect ratio. This effect of supersaturation in the presence of the additive, which can be seen in Fig. 8, results from a greater increase in the growth rate of the {110} faces compared with the other faces under the increased driving force. This competition between impurity inhibition and supersaturation enhancement leads eventually to a massive formation of macro steps, particularly on {110} surfaces at high levels of impurity and supersaturation. (Fig. 8c). These macrosteps arise by bunching of mono steps (van der Eerden and Muller-Krumbhaar, 1986). Their formation is an inevitable precursor to solvent inclusion and hence to a decrease in the purity of the product.

The molecule of PAA is 1.24 times larger in volume than the paracetamol molecule (Finnie et al., 1999). An inevitable consequence of its incorporation into the growing crystal is the development of strain in the sector in which the incorporation occurs. A segregation coefficient of 16% implies that one molecular position in six is occupied by a PAA molecule and hence will yield a 3–4% distortion. In such a brittle material (Prasad et al., 2000), such strain will be retained and will not be released by plastic deformation. It is not surprising, then, that the mosaic spread of the doped crystals increases so significantly, as shown in Fig. 10, relative to that induced by variations in supersaturation in the pure material (Fig. 3). Such an increase in lattice strain could by itself influence the growth rate and may well be a contributory cause of the observed reduction in growth rate on impurity addition (Ristic et al., 1997; Zikic et al., 1998).

An addditional factor that will similarly influence the integral strain in the doped system is the disturbance that will occur to the hydrogen bonding network. Again, due to the high degree of incorporation, the effect will be significant but is less easy to quantify than the volume effect.

At this point, we should note that the results obtained in this study differ from those published in a previous assessment of the relationship between incorporated PAA content and strain in paracetamol crystals (Shekunov et al., 1997). We find none of the sudden increase and decrease in strain at low impurity content noted previously. In the case of our studies, a simple gradual increase was observed. The values for the mosaic spread of the crystals examined by the previous authors were considerably higher ($>10\times$) than for the present materials. This implies a greater variation in the general imperfection in the material, which would make it difficult to assess whether or not the noted variation was a real effect or simply reflected sample variability.

4.4. Nature of the particles

The changes produced by processing and discussed above will influence the nature of the product particles in two ways, producing variations in surface properties and in bulk defect structure or strain.

It is obvious from the present results that it is possible to generate from solutions of pure paracetamol, by increasing the supersaturation, a range of particles of varying, but well-defined, shape with dominant {110} or {001} surfaces. Consideration of the molecular diagrams of planes that intersect these faces shows that totally different aspects of the molecules that comprise the crystals will be presented at these faces (Fig. 13). At their simplest, the {110} surfaces will be dominantly

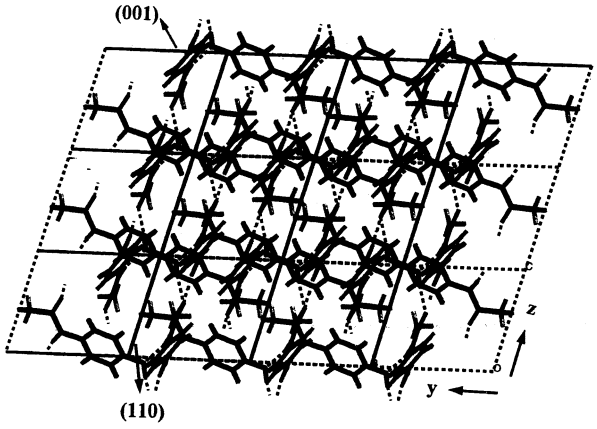

Fig. 13. Molecular packing of paracetamol crystal showing the intersection of (110) and (001) planes.

polar due to the emergence of the -NH.CO.CH_3 and -OH moieties, whereas the {001} will be considerably less so due to the emergence of the phenyl ring (Fig. 13). The range of crystal shapes produced from columnar {110} to plate-like {001} with varying fractions of each thus provides particles with a graded range of surface properties from dominantly polar to dominantly non-polar. In parallel, there is a small but significant increase in the defect content (mosaic spread) of the material.

In contrast, the impure crystals show a greater degree of similarity of habit exhibiting a columnar shape with dominant {110} surfaces but with a varying aspect ratio, that is to say, similar surface properties with some difference in shape.

For the doped crystals, however, the principal variation is in the strain content that develops from the inclusion of the additive. This is significantly greater than for the pure material. The overall result is the production of particles with a similar surface chemistry but with a differing strain content.

Thus, we are in a position to produce a series of particles of well-defined and variable shape, surface chemistry and strain/defect content, the properties of which can be generated reproducibly. Potentially, the variation of such properties will influence the efficiency and effectiveness of downstream processes such as powder flow, particle compaction, breakdown on milling and dissolution.

The materials, if they can be prepared in larger quantities and under conditions whereby the noted variations can be reproduced, offer an opportunity to assess the influence of fundamental factors on the noted downstream processes. On the basis of the present data, it is proposed that the scale-up of the production be developed to a level at which the material could be produced in the 100–500 g scale to confirm that the current variations hold under these conditions and then to examine the processes of milling, powder flow and dissolution of the resulting materials.

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