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The effects of additives on the growth and morphology of paracetamol (acetaminophen) crystals

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Abstract

It is well known that the presence of impurities can dramatically affect the nucleation, morphology, and chemical properties of crystals. Although literature is replete with examples of impurity or additive-induced modifications of crystals, few have examined the interaction of these compounds with distinct growing faces. In this study, we utilize atomic force microscopy (AFM) and scanning electron microscopy (SEM) to investigate the influence of two structurally related additives of paracetamol (acetaminophen) on its crystal morphology. We also probe, in situ, the effects of these additives on the morphology and growth rate of steps on the (0 0 1) face of the crystal. This study, in conjunction with further investigations, aims to establish the specific mechanisms of inhibition of these additives on each face of paracetamol, and provide a means of overcoming the poor compaction behaviour of paracetamol.

Keywords: Additive; Atomic force microscopy; Crystal growth; Crystal morphology; Paracetamol; Acetaminophen

1. Introduction

1.1. The effects of impurities on crystal nucleation and growth

It has long been recognized that the presence of trace amounts of impurities can have substantial effects on the kinetics of crystal nucleation, growth morphology, and dissolution (Klug, 1993; Weissbuch et al., 1995). During growth, impurities can adsorb onto the crystal surfaces, changing the relative surface free energies of the faces and blocking the active growth sites. Some impurities can suppress growth entirely, some may enhance growth, whilst others may produce a selective effect, acting to varying degrees on each crystallographic surface, and consequently modifying the crystal habit (Mullin, 1993).

The classic model of Cabrera and Vermilyea (1958) proposes that impurities can adsorb onto terraces or steps of growing crystals, and become almost immobile. Impurities which have adsorbed onto a terrace cannot be passed by a straight growing step, because impurities act as local pinning points. Therefore, these impurities serve as a "fence" to growing steps. Conse-

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quently, growing steps must bend in order to squeeze through the impurity "fence" and, as a result, the velocity of the steps is reduced compared to that of straight steps growing in the absence of impurities.

1.2. Impurities in pharmaceutical compounds

Impurities may be additives that are introduced for specific purposes, such as to modify the crystal habit or control the crystal size, or may be impurities that result from the synthesis or degradation of the desired end product. If the solubility of an impurity or additive is close to that of the product, its removal during the purification process may be difficult. Impurities or additives have the potential to modify the solubility of the primary solute and thus affect the crystallization process.

Structurally related compounds are common impurities in pharmaceutical components. These compounds become incorporated with varying efficiencies, and can, hence, influence the nucleation and subsequent crystal growth rate of the solute. As the distinct faces of crystals are influenced to different degrees, due to their contrasting molecular organization, morphological changes are often observed, sometimes at concentrations as low as several parts per million (Shekunov et al., 1997). The presence of structurally related compounds has been shown to distinctly alter the habit of pharmaceutical excipients, such as adipic acid (Fairbrother and Grant, 1978; Chow et al., 1984; Davey et al., 1992; Myerson and Jang, 1995) and α-lactose monohydrate (Garnier et al., 2002). It has been suggested that growth of drug crystals in the presence of low concentrations of structurally related additives can provide a means of controlling water content, crystal energy and order, dissolution rate, and possibly bioavailability (Chow et al., 1985).

Literature is replete with references to the additive-induced effects on crystalline drug compounds (Fairbrother and Grant, 1978; Chow et al., 1984; Davey et al., 1992; Duddu et al., 1993, 1996; Myerson and Jang, 1995; Garnier et al., 2002; Gu and Grant, 2002). Of these studies, only a limited number are sufficiently quantitative to provide adequate insight into the specific mechanisms involved. For pharmaceutical technology, understanding of these mechanisms may help to control the quality and purity of raw crystalline substances and, consequently, to improve the manufacture and performance of the final dosage forms (Shekunov et al., 1997).

1.3. Paracetamol and its structurally related additives

Paracetamol, also known as *p*-hydroxyacetanilide or acetaminophen, was first launched as a drug in 1956 and has now grown to be the most widely accepted antipyretic and analgesic in the world.

Two crystalline polymorphs of paracetamol have been reported, although evidence has been published which suggests that a third polymorph could exist (Di Martino et al., 1997). The crystal structures of the two known forms of paracetamol are monoclinic (Haisa et al., 1976; Nichols, 1998) and orthorhombic (Haisa et al., 1974; Di Martino et al., 1996, 1997; Nichols, 1998; Nichols and Frampton, 1998). The monoclinic form is the thermodynamically stable polymorph at room temperature and, hence, is the commercially used form of paracetamol. A particular problem with the monoclinic form of paracetamol is that it displays poor compaction behaviour, that is, it resists compression into tablets (Femi-Oyewo and Spring, 1994; Garekani et al., 2000a,b). Currently, there is considerable interest in modifying the properties of paracetamol using different crystallization techniques or additives in order to improve the compaction behaviour of the crystals (Fachaux et al., 1993, 1995a,b; Femi-Oyewo and Spring, 1994; Garekani et al., 2000a,b).

A primary feature of the paracetamol crystal structure is hydrogen bonding. This bonding leads to the formation of hydrogen bonded chains of molecules, packed in a herring bone conformation within the crystal structure. The molecular structure of a paracetamol crystal on the (0 0 1) face is shown in Fig. 1. The molecules form corrugated hydrogen bonded sheets which stack in the [0 1 0] direction. The consecutive stacks are bound by van der Waals interactions (Finnie et al., 2001). The degree of hydrogen bonding which occurs within the paracetamol crystal has been quantified as 8.31 kcal mol^{-1} (Hendriksen et al., 1998), which corresponds to approximately 30% of the total lattice energy. Thus, any additive which disrupts the hydrogen bonding network within the crystal has the potential to significantly alter its growth rate and, ultimately, its morphology.

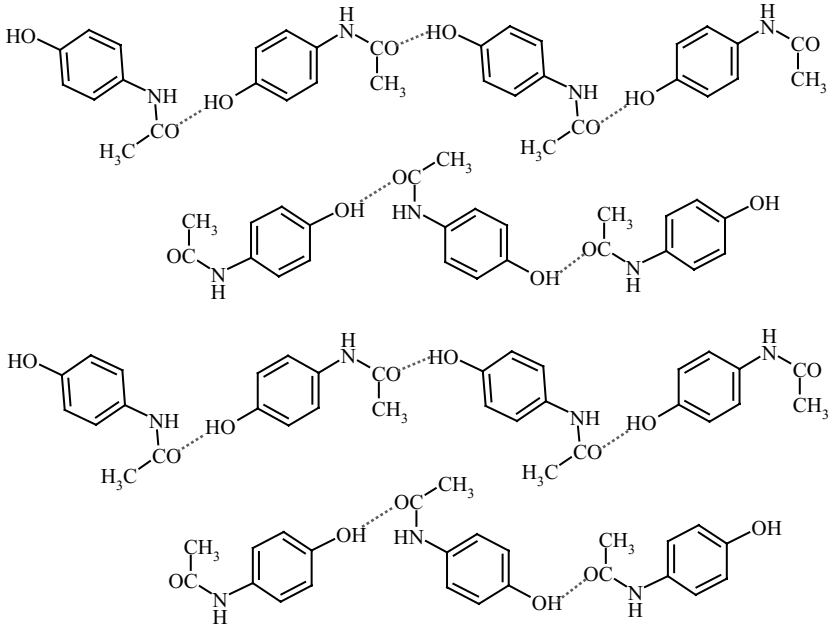

Fig. 1. Diagrammatic representation of the molecular packing of paracetamol on the (0 0 1) face of the crystal. Both [0 1 0] and [1 0 0] directions are shown. The molecules adopt a "herring bone" arrangement, where the molecules within each layer are held together by hydrogen bonds, indicated by dashed red lines. Adapted from (Finnie et al., 2001).

There are six structurally related additives of paracetamol which have been observed to inhibit the nucleation and growth rates of paracetamol crystals to varying degrees. These are acetanilide, *p*-acetoxyacetanilide (PAA), orthocetamol, methylparaben, *p*-acetoxybenzoic acid (PABA), and metacetamol. Of these additives, the effects of PAA on paracetamol crystallization have been the most extensively studied (Chow et al., 1985; Chow and Grant, 1988a,b; Hendriksen and Grant, 1995; Shekunov et al., 1997; Hendriksen et al., 1998; Prasad et al., 2001). The effects of PAA on the morphology, nucleation (Hendriksen and Grant, 1995; Hendriksen et al., 1998; Prasad et al., 2001), growth, dissolution (Shekunov et al., 1997), and the physical and chemical properties (Chow et al., 1985; Prasad et al., 2001) of paracetamol have all been investigated. On the contrary, the influence of the remaining additives on only the nucleation and morphology of paracetamol crystals has been reported (Hendriksen and Grant, 1995; Hendriksen et al., 1998).

Hendriksen et al. (1998) have proposed that structurally related additives may influence the nucleation and growth of paracetamol crystals in three principal ways. Additives may:

(i) block adsorption of solute molecules and therefore induce morphological changes;
(ii) dock onto the surface and become incorporated into the crystal lattice;
(iii) disrupt the emerging nucleus and thus inhibit the nucleation process.

Each of these interactions depends upon the molecular similarity of the additive to paracetamol, both energetically and sterically. The blocking, docking, and disrupting behaviours of the six structurally related additives which inhibit paracetamol growth have been extensively studied by Hendriksen et al. (1998). However, these studies have been conducted on entire crystals. We, therefore, wish to supplement this information by performing AFM studies on the in situ growth on the (0 0 1) face of paracetamol crystals, in the presence and absence of additive molecules. As the growth experiments performed in this study will be carried out on the faces of complete monoclinic crystals, the disruptive effects of the additives cannot be quantified.

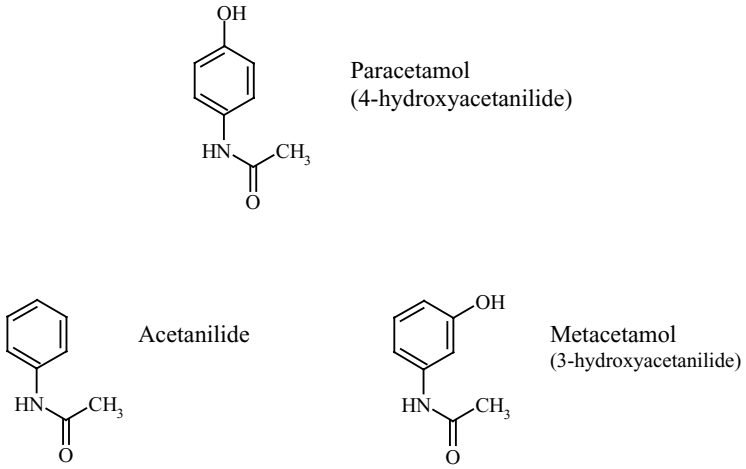

Fig. 2. The molecular structures of paracetamol, acetanilide and metacetamol, two of the structurally related additives which are known to inhibit paracetamol crystal growth.

In addition, the AFM is unable to monitor the incorporation of additive molecules into the growing crystals and, hence, the docking activities of the additives cannot be further investigated through these experiments. However, this method does enable the blocking activities of the additives to be both visualized and quantified. For these studies, two of the lesser studied additives have been selected, namely acetanilide and metacetamol. The molecular structures of paracetamol, acetanilide, and metacetamol are shown in Fig. 2. The blocking activities of these two additives, as described by Hendriksen et al. (1998), are summarized in the following section.

1.4. Blocking activity of acetanilide and metacetamol

"Blocking" is the ability of an adsorbed additive molecule to hinder the subsequent adsorption of further layers of host molecules. As the additive molecules block different faces of the crystal to varying degrees, the growth rates of some faces will be dramatically altered, whilst others will remain unchanged. Consequently, the morphology of the resulting paracetamol crystals may be altered.

Hendriksen et al. (1998) have shown that the presence of acetanilide during crystallization of paracetamol caused appreciable morphological changes, despite its relatively low level of uptake into paracetamol crystals. It was therefore considered a potent blocking molecule.

Metacetamol also caused a high degree of morphological change, inducing a large shift in the aspect ratio. The aspect ratio is defined as the ratio of distances between the centre of the crystal and the furthest and nearest faces. However, its uptake level was much higher than that of acetanilide and was thus considered to be a less effective blocker (Hendriksen et al., 1998). The reasons proposed by Hendriksen et al. for the observed morphological effects of these additives are discussed further.

In order to successfully block the adsorption of a host molecule in a subsequent crystalline layer, a blocking molecule must present a conformation sterically and energetically different from that of paracetamol. If we consider a face or faces in which paracetamol molecules are oriented with their acetamido groups positioned inwards (away from the crystal-solution interface), we can discuss the potential blocking effects of these additives. Acetanilide has no group in the *p*-position (Fig. 2), so no steric hindrance is present. However, it does not possess a proton donor to contribute to the existing hydrogen bonding network, and hence it strongly blocks further addition of paracetamol molecules (Hendriksen et al., 1998). Similarly, metacetamol presents no great steric hindrance. It possesses an OH group in the *m*-position, allowing the hydrogen bonding net-

work to be largely preserved, although distorted. As a result, metacetamol appears to be a less effective blocker than acetanilide (Hendriksen et al., 1998).

We envisage that growth in the presence of molecules which efficiently block adsorption of paracetamol onto the (0 0 1) face of the crystal should result in a change in morphology of growing steps, and should reduce the growth rate of steps, with respect to those grown in the absence of any additive. These properties would be apparent through AFM imaging. If these predictions prove to be accurate, similar experiments can be conducted to establish the blocking activity of each of the six additives on this and the other faces of paracetamol crystals. These data could be applied to the modification of paracetamol crystals, in order to optimize their compaction behaviour.

2. Materials and methods

2.1. Preparation of monoclinic paracetamol crystals grown in the presence and absence of an inhibitor

All crystals were prepared using a modified version of the cooling method described by Hendriksen et al., (1998). Pure paracetamol crystals were prepared by dissolving 2.674 g of paracetamol (99%, Sigma Aldrich, Dorset, UK) in 200 ml of HPLC grade water, which had been filtered once. This solution was heated to 40 °C, with a stirring rate of 238 rpm, until all of the solute had dissolved. It was then transferred to a refrigerator and maintained at 5 °C. The solubility (mol%) of paracetamol at 5 °C was calculated using Eq. (1) (Shekunov and Grant, 1997; Finnie et al., 1999):

$$\ln c_0 = \frac{12200}{T + 49.69 \ln T - 330.4} \quad (1)$$

where c_0 is the concentration of paracetamol in a saturated solution, i.e. the solubility of paracetamol at a given temperature, and T the absolute temperature in Kelvin. The solubility of paracetamol at this temperature was calculated as 0.103 mol%, which correlates to a solubility of 8.65 g/l. The supersaturation (σ) of the crystallization media was calculated using Eq. (2).

$$\sigma = \ln\left(\frac{c}{c_0}\right) \quad (2)$$

where c is the concentration of paracetamol in the growth medium. The σ value of the crystallization media was calculated as 0.44. The crystals formed in solution over a period of 4–5 days, after which they were filtered, air-dried, and stored in a desiccator. Crystals containing additives were prepared in the same manner as described above, with an additive concentration equivalent to 4 mol%, with respect to paracetamol. This additive level was chosen as it has been previously used to investigate the effect of these compounds on the crystallization of paracetamol (Hendriksen et al., 1998). Thus, 0.096 g of acetanilide (97%, Sigma–Aldrich, Dorset, UK) or 0.107 g of metacetamol (97%, Sigma–Aldrich, Dorset, UK) were added to the solution prior to heating. Again, crystals formed over a period of 4–5 days, and were subsequently filtered, air-dried, and stored in a desiccator. The morphology and surface features of these crystals were examined using SEM and AFM. Crystals were immobilized on AFM sample stubs using Tempfix (Agar, Stansted, UK) prior to examination.

2.2. Preparation of paracetamol/additive solutions for growth studies

Growth solutions, without any additive present, were prepared by dissolving 0.192 g of paracetamol (99%, Sigma–Aldrich, Dorset, UK) in 10 ml HPLC grade water, which had been filtered once. These solutions were heated to 40 °C, with a stirring rate of 238 rpm, until all of the solute had dissolved. They were then allowed to cool to room temperature (25 °C), before being placed in the AFM liquid cell with a paracetamol crystal sample. Growth solutions containing an additive were prepared in the same manner as described for pure paracetamol solutions, and contained an additive concentration equivalent to 4 mol%, with respect to paracetamol. In the case of the acetanilide-containing solution, 0.007 g of acetanilide were added to the solution prior to heating, whereas 0.008 g of metacetamol were added to its respective solution. All growth solutions were prepared immediately prior to each experiment. The solubility of paracetamol (mol%) was calculated using Eq. (1). The solubility of paracetamol at this temperature (25 °C) was calculated as 0.171 mol%, which correlates to 14.36 g/l. Hence, using Eq. (2), the supersaturation of paracetamol, σ, in the solutions used for the growth

experiments was calculated as 0.29. It should be noted that structurally related compounds are known to increase the solubility of paracetamol (Chow et al., 1985; Hendriksen and Grant, 1995). However, the degree to which acetanilide and metacetamol affect the solubility of paracetamol is yet to be determined, and hence the solubility of paracetamol in the growth solutions is taken to be that of a pure solution.

Prior to each experiment, paracetamol crystals were immobilized on AFM sample stubs, and then onto a suitable liquid cell using Tempfix (Agar, Stansted, UK). In each growth experiment, approximately 2.5 ml of the respective solution was placed in the liquid cell. Each sample was imaged continuously using AFM, after addition of the growth medium, to assess the growth rate in each solution, and to establish the extent of inhibition induced by acetanilide and metacetamol.

2.3. AFM analysis

Contact mode imaging was employed throughout, using a ThermoMicroscopes Explorer AFM (Veeco, Bicester, Oxon, UK). V-shaped silicon nitride cantilevers (200 μm length) with integrated pyramidal tips (Nanoprobes, Veeco, Santa Barbara, CA) and spring constant ranging from $k = 0.01$–$0.064\,\mathrm{Nm}^{-1}$ were used. During scanning, care was taken to continually adjust the set point voltage to the lowest value for which tip-crystal contact could be maintained, in order to minimize the force applied to the crystal surface. The utilization of minimal force has allowed the crystal surfaces of various compounds to be imaged during growth without degradation of their growing steps (Land and De Yoreo, 2000).

The speed of acquisition of the images was determined by the rate of change of the features on the crystal surface. The employed scan rate was typically 10–15 Hz. Both topography and deflection images were acquired in all experiments. Deflection images emphasize areas of rapid topography changes, such as steps, but do not give any information about relative heights of features on the surface.

2.4. SEM analysis

All samples were initially gold coated for 2 min using a Balzers SCD 030 Sputter Coater (Balzers Union Limited, Liechtenstein), operated at 0.1 mbar with a sputtering current of 30 mA. A Philips 505 SEM (Philips Electron Optics, Eindhoven, The Netherlands) was used to image all samples under a range of magnification settings at a voltage of 23 KeV, with a spot size of 50 nm.

3. Results and discussion

3.1. Morphology of crystals grown in the presence and absence of the additives acetanilide and metacetamol

The SEM image in Fig. 3 illustrates the habit of the pure monoclinic paracetamol crystals. The tabular morphology attained by this crystal is consistent with that of paracetamol crystals grown at σ values greater then 0.15 (Finnie et al., 1999; Prasad et al., 2001), here $\sigma = 0.44$. An illustration of the morphology of paracetamol crystals grown at $\sigma > 0.15$ is given in Fig. 4.

Fig. 5 shows AFM images of the surface of a paracetamol crystal. These images show steps ranging in height from 1 to 21 nm. The small, single molecular steps (black arrow), which were previously found to

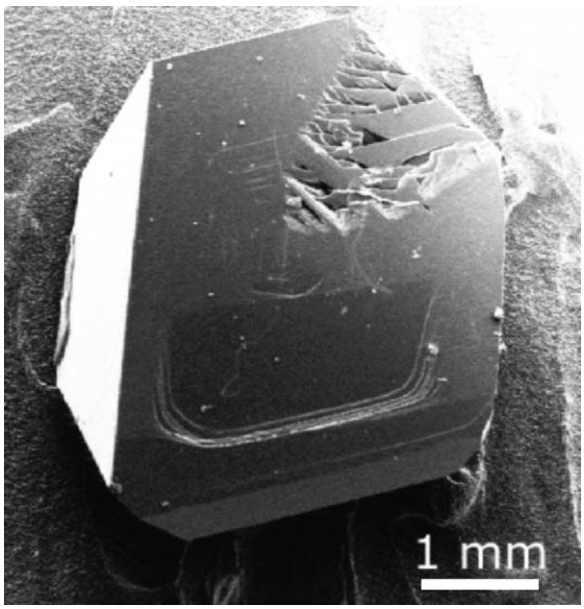

Fig. 3. An SEM image of a paracetamol crystal showing its tabular habit. The magnification of the image is 16.4×.

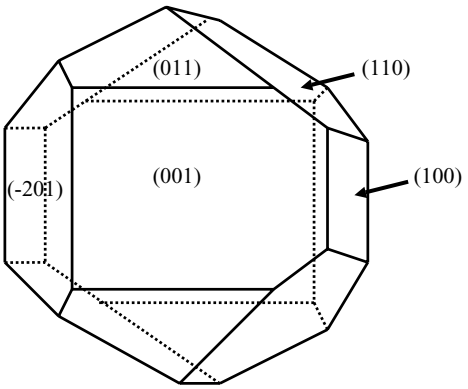

Fig. 4. Diagrammatic representation of the morphology of paracetamol crystals grown at supersaturation values greater than 0.15. Adapted from (Finnie et al., 1999).

be 1 nm in height (Ristic et al., 2001), are curved in appearance, whereas the larger, multi-molecular steps (white arrow) have straight edges.

Fig. 6 shows a typical SEM image of a paracetamol crystal grown in the presence of 4 mol% acetanilide. Hereafter, these crystals shall be referred to as PA crystals. It is evident from this image that the habit of PA crystals is comparable with that of paracetamol crystals, however, PA crystals are smaller than paracetamol crystals. The AFM image shown in Fig. 7 reveals the surface features of the PA crystals. The image portrays steps which have thin, branched terraces, rather than having curved or straight edges, as seen for pure paracetamol crystals (Fig. 5). The steps, which are approximately 20 nm in height, may adopt this branched appearance due to the "pinning" of steps by the acetanilide molecules, as discussed previously. A large number of holes, indicative of defects, are also present in the surface.

A typical SEM image of a paracetamol crystal grown in the presence of 4 mol% metacetamol is shown in Fig. 8. Hereafter, these crystals shall be referred to as PM crystals. Clearly, PM crystals attain a columnar habit, distinctly different from the tabular morphology observed with both paracetamol and PA crystals. From these data it is evident that the aspect ratio of the paracetamol crystal is more significantly affected by the addition of metacetamol to the crystallization medium than by acetanilide. These data are consistent with previous findings which calculated aspect ratios of paracetamol crystals grown in the absence of any additive as 1.2, whereas those grown in the presence of 4 mol% of metacetamol or acetanilide had aspect ratios of 7.33 and 2.84 respectively (Hendriksen et al., 1998).

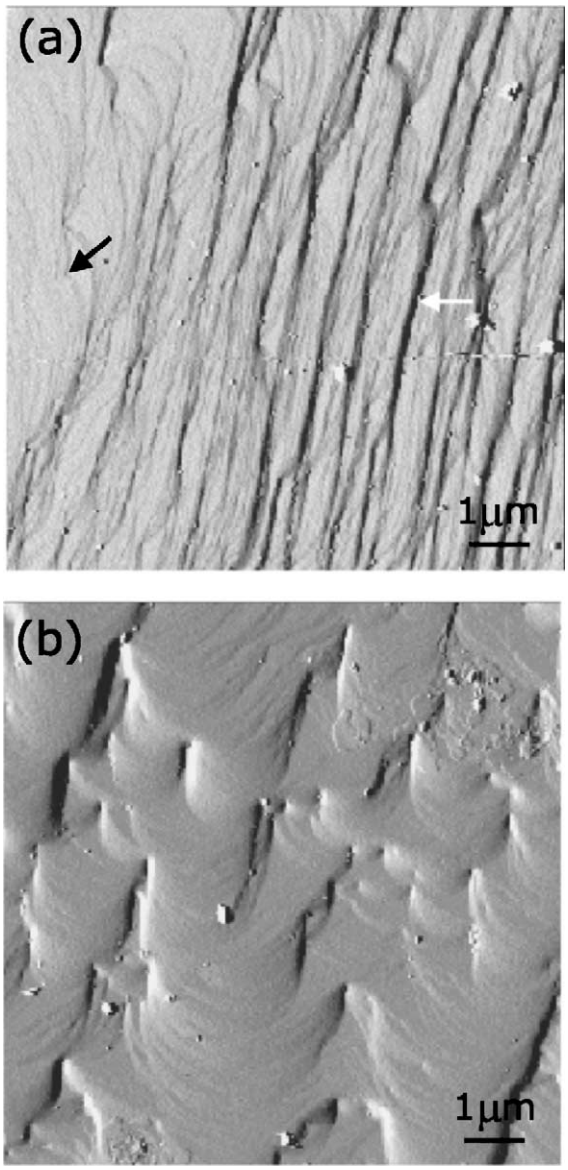

Fig. 5. 10 μm × 10 μm AFM images of the surface of a paracetamol crystal acquired in air. Image (a) illustrates the appearance of both small, curved steps (black arrow) and larger, straight-edged steps (white arrow) on the surface of the crystal. Image (b) highlights the small steps visible on the surface. Both (a) and (b) are deflection images.

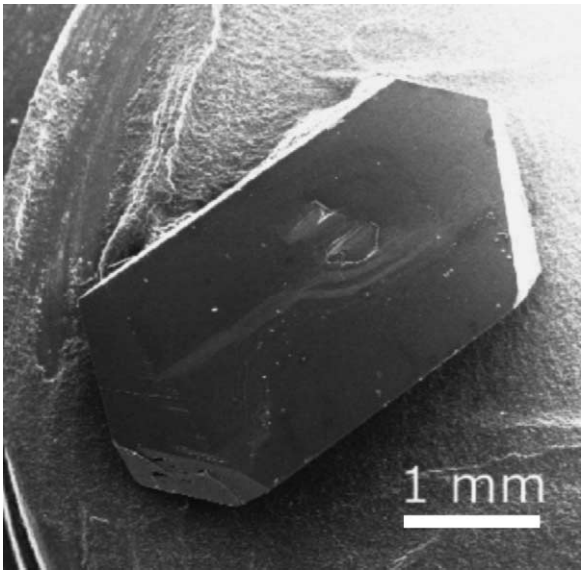

Fig. 6. An SEM image of a paracetamol crystal grown in the presence of 4 mol% acetanilide. This image is at magnification 17.2×.

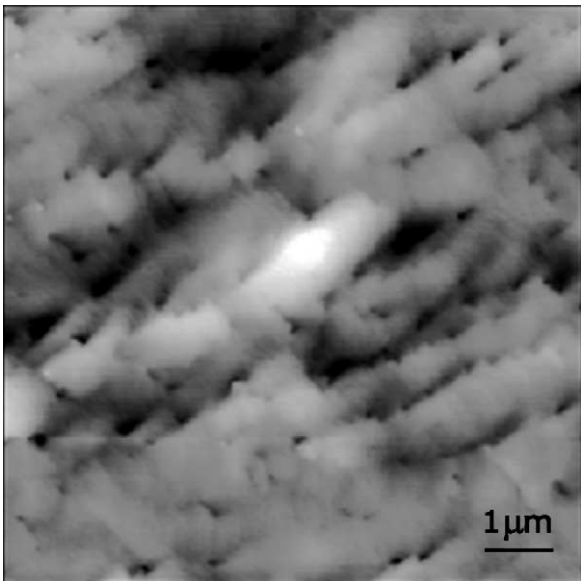

Fig. 7. A 10 μm × 10 μm AFM topographical image of the surface of a paracetamol crystal grown in the presence of 4 mol% acetanilide.

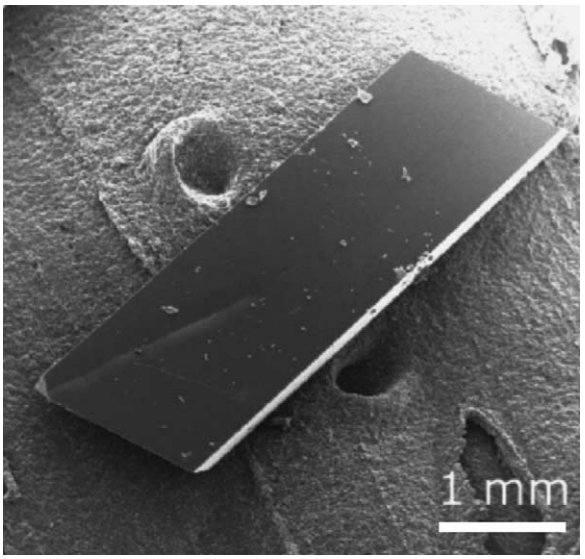

Fig. 8. A typical SEM image of a paracetamol crystal grown in the presence of 4 mol% metacetamol. This image is at magnification 16.4×.

Fig. 9 shows a typical AFM image of the surface of a PM crystal. This image depicts steps of approximately 15 nm in height interspersed with holes in the surface. A defect is also evident in the centre of the image. It is apparent from this image that metacetamol considerably increases the defect density of the (0 0 1) face of paracetamol crystals. These data suggest that the crystal lattice is significantly disrupted by metacetamol molecules during growth.

3.2. Growth on the (0 0 1) face of a paracetamol crystal in solutions of pure paracetamol, and those containing acetanilide or metacetamol

The sequence of images in Fig. 10 illustrate the growth of steps on the (0 0 1) face of a paracetamol crystal during incubation in a pure solution, where $\sigma = 0.29$. The steps range from 95 to 588 nm in height, and hence are macrosteps. The steps are curved in appearance, indicating that they are growing via the dislocation mechanism (Burton et al., 1951). These data are consistent with previous studies which have shown that all of the major faces of paracetamol ($\{1\,1\,0\}$, $\{0\,0\,1\}$, and $\{-2\,0\,1\}$) grow via a dislocation mechanism (Shekunov and Grant, 1997). The rate of growth of the observed steps ranges from 26.4 to 76.2 nm/s,

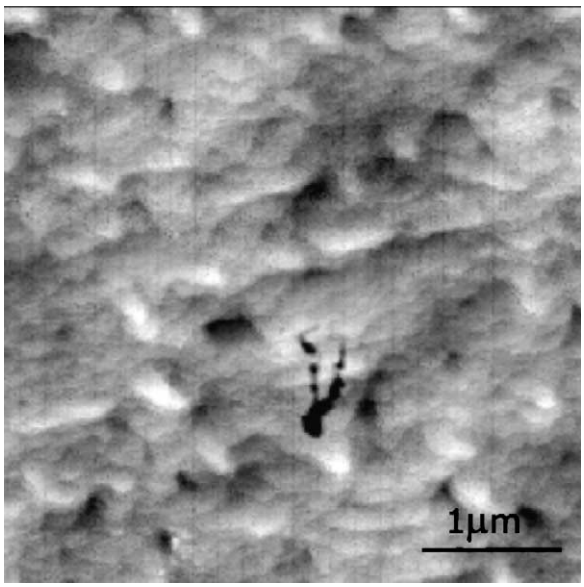

Fig. 9. A 5 μm × 5 μm AFM topographical image of the surface of a paracetamol crystal grown in the presence of 4 mol% metacetamol.

and decreases with increasing step height. The steps are observed to grow in the [−1 0 0] direction.

The images shown in Fig. 11 portray the (0 0 1) face of a paracetamol crystal during incubation in paracetamol/4 mol% acetanilide solution. The supersaturation of the solution is 0.29, with respect to paracetamol. From these images it is clear that dissolution is occurring on the face. Prior to incubation in paracetamol/4 mol% acetanilide solution, the surface of the crystal exhibited features comparable to those shown in Fig. 5. However, after 11.5 min of incubation, shown in Fig. 11(a), holes emerged in the surface. One such hole is highlighted by an arrow in Fig. 11(a), and its dissolution is followed by an arrow in subsequent images. These holes may originate from defects in the crystal surface. The steps, which range from 13 to 45 nm in height, are observed to dissolve at rates between 1.3 and 2.7 nm/s, in the [1 0 0] direction. The dissolution rate of the steps decreases with increasing step height. The holes or clefts in the surface are also observed to deepen over time, indicating that dissolution is taking place towards the crystal core as well as laterally.

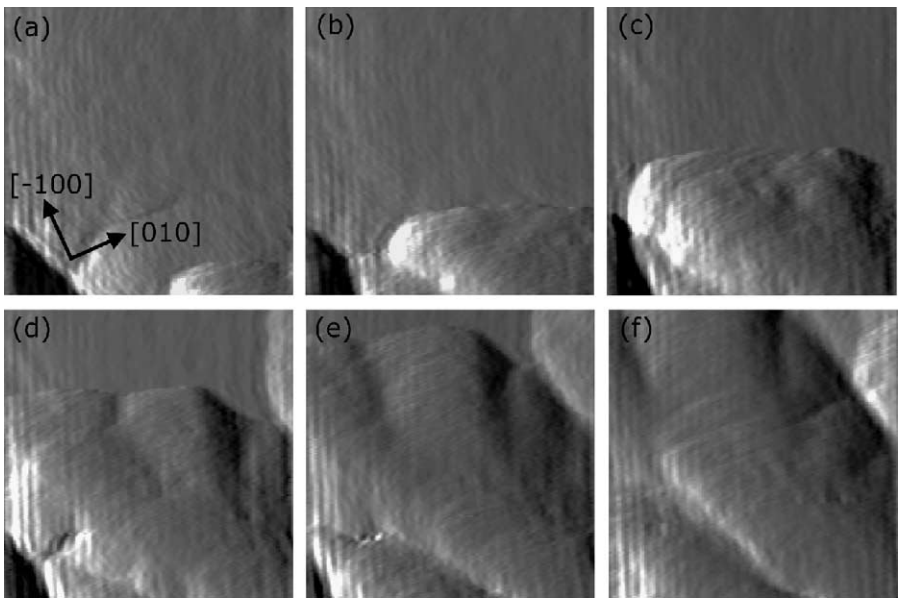

Fig. 10. A sequence of 10 μm × 10 μm AFM images of the (0 0 1) face of a paracetamol crystal during incubation in paracetamol solution of supersaturation 0.29. In image (a) time $t = 0$ s, (b) $t = 60$ s, (c) $t = 118$ s, (d) $t = 176$ s, (e) $t = 234$ s, and (f) $t = 292$ s. All images are deflection images.

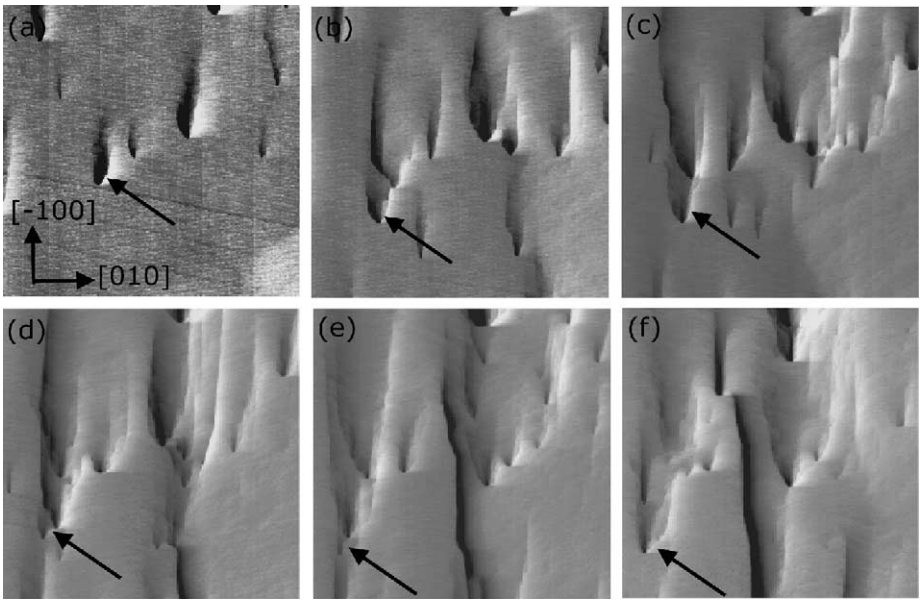

Fig. 11. A sequence of 10 μm × 10 μm AFM images of the (0 0 1) face of a paracetamol crystal during incubation in paracetamol/4 mol% acetanilide solution. The supersaturation of the solution is 0.29, with respect to paracetamol. The dissolution of one step is followed by a black arrow on each image. Image (a) is taken 11.5 min after addition of paracetamol/4 mol% acetanilide solution. Images (b–f) are taken at the following times after image (a): (b) $t = 146$ s, (c) $t = 290$ s, (d) $t = 436$ s, (e) $t = 582$ s, and (f) $t = 728$ s. All images are deflection images.

As previously mentioned, the presence of additive molecules increases the solubility of paracetamol, which may induce the dissolution demonstrated here. However, we cannot assume that dissolution is ubiquitous over the crystal, as the remaining faces may be influenced to different degrees by the additive molecules. Further studies must be undertaken to evaluate the affect of such levels of acetanilide on the other faces of paracetamol crystals. These studies should allow a more precise determination of the extent to which acetanilide inhibits paracetamol crystal growth.

Fig. 12 shows a sequence of AFM images of the (0 0 1) face of a paracetamol crystal during incubation in paracetamol/4 mol% metacetamol solution. The supersaturation of the solution is again 0.29, with respect to paracetamol. A black and a white arrow follow the movement of two steps on the surface. From these images, it is apparent that steps are growing in the [−1 0 0] direction. The steps range from 4 to 21 nm in height, and their calculated growth rates range from 19.0 to 37.8 nm/s, with no relation between step height and growth rate. From the AFM images alone, it is evident that the progression of steps is hindered by metacetamol. Those images showing growth during incubation in pure paracetamol solution, Fig. 10, illustrate that in such an environment, the face grows via the dislocation mechanisms of macrosteps. However, the images shown in Fig. 12 portray significantly smaller steps which are pointed in appearance, implying that "pinning" is taking place. As previously stated, pinning occurs when additives adsorb onto step or terrace regions of the growing crystal, and thus, the steps must bend in order to squeeze through the impurity "fence". Here, the steps acquire a pointed appearance. These characteristic pointed, and thus pinned, steps have been observed using AFM in other crystal-additive systems (Land et al., 1999; Nakada et al., 1999; Mauri and Moret, 2000).

The presence of metacetamol molecules not only alters the morphology of the growing steps, it also reduces their growth rates from an average of 49.5–27.1 nm/s in the [−1 0 0] direction. These data are also consistent with previous AFM studies on

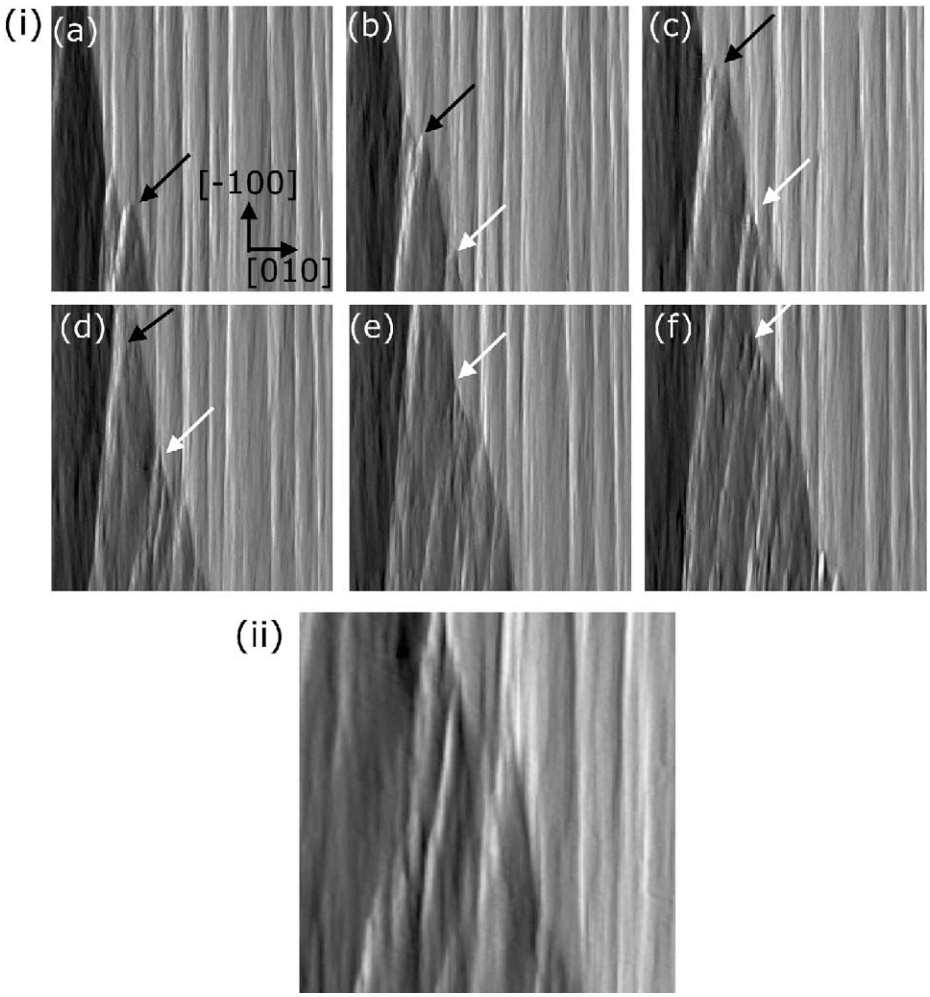

Fig. 12. (i) A sequence of 10 μm × 10 μm AFM images of the (0 0 1) face of a paracetamol crystal during incubation in paracetamol/4 mol% metacetamol solution. The supersaturation of the solution is 0.29, with respect to paracetamol. A black and a white arrow follow the movement of two steps on the surface. In image (a) time $t = 0$ s, (b) $t = 90$ s, (c) $t = 182$ s, (d) $t = 272$ s, (e) $t = 364$ s, and (f) $t = 454$ s. (ii) A 4.8 μm × 4.8 μm image showing a portion of image (i), (d) at higher magnification, to highlight the pointed steps. All images are deflection images.

additive effects on growth interfaces, which show a considerable retardation in step velocity in the presence of additive molecules (Land et al., 1999; Nakada et al., 1999; Mauri and Moret, 2000). It is evident, therefore, that metacetamol induces considerable inhibition of growth on the (0 0 1) face of paracetamol at this level (4 mol%).

Fig. 1 illustrates the molecular structure of paracetamol on the (0 0 1) face of the crystal. From this diagram, it is evident that the groups protruding from the surface in the direction of growth, [−1 0 0], are OH and $NHCOCH_3$. Both of these groups allow the perpetuation of the hydrogen bonding network within the crystal, via attachment of molecules to the OH and CO groups. The only difference between paracetamol and metacetamol is the *p*- and *m*-position of their OH group, respectively. Hence, metacetamol could for example readily attach to the protruding OH groups of the crystal surface via its CO group, which is equivalent to that of paracetamol, but its OH group, which

resides juxtaposed to that of paracetamol, would distort the hydrogen bonding network for subsequently bound molecules. It appears therefore that metacetamol molecules could attach to the (0 0 1) face of paracetamol crystals and induce the degree of inhibition detected here. Again, we cannot assume that the same degree of inhibition would be observed on the other faces of the crystal, and hence further studies are required to assess the metacetamol-induced inhibition on the remaining faces. These studies may reveal the mechanisms by which metacetamol modifies the habit of paracetamol from tabular to columnar (Figs. 3 and 8, respectively).

4. Conclusions

The use of AFM and SEM has permitted the investigation of the effects of the additives acetanilide and metacetamol on the morphology and the growth on the (0 0 1) face of paracetamol crystals. SEM images showed the characteristic tabular habit of pure paracetamol crystals was only moderately altered by the presence of acetanilide, but the crystals adopted a columnar habit when grown in the presence of metacetamol.

On a microscopic level, AFM revealed that the surface features of pure paracetamol crystals were steps ranging from 1 to 21 nm in height. On the contrary, crystals grown with acetanilide possessed thin, branched steps of approximately 20 nm in height. We suspect that the branched appearance of the steps is due to the adsorption of acetanilide molecules onto terraces or steps during growth, causing pinning and bending of the growing steps. The presence of metacetamol during growth resulted in steps of approximately 15 nm in height interspersed with holes, and also induced the formation of defects in the crystal surface. These data suggest that the crystal lattice, and hence the hydrogen bonding network, were considerably disrupted by metacetamol during growth.

Growth on the (0 0 1) face of paracetamol crystals in the presence and absence of acetanilide or metacetamol was monitored via AFM. In the absence of any additive, growth was observed to occur by a dislocation mechanism. The rate of growth of the steps ranged from 26.4 to 76.2 nm/s, and all steps were observed to grow in the [−1 0 0] direction.

In the presence of acetanilide, holes, which may have originated from defects, emerged in the surface during incubation. Steps emanated from these holes and dissolved at rates between 1.3 and 2.7 nm/s, in the [1 0 0] direction. The holes were observed to deepen over time, indicating that dissolution was occurring into the crystal core as well as laterally. The presence of additives is known to increase the solubility of paracetamol, which may have induced such dissolution. However, we cannot assume that dissolution was ubiquitous over the crystal, as each of the faces may have been influenced to different degrees by the additive molecules, and some may have grown under these conditions. Nonetheless, the presence of acetanilide in the growth medium caused dissolution in the [1 0 0] direction, whereas a pure paracetamol solution of the same σ facilitated growth of macrosteps in the [−1 0 0] direction.

The presence of metacetamol resulted in the growth of steps at rates of 19.0 to 37.8 nm/s in the [−1 0 0] direction. The steps were pointed in appearance and significantly smaller than those observed in the absence of metacetamol, suggesting that the additive molecules pinned the steps. The average growth rates in the absence and presence of metacetamol were 49.5 and 27.1 nm/s, respectively. Hence, metacetamol dramatically altered not only the morphology, but also the rate of the growing steps. AFM enabled the observation of the effects of metacetamol on the growing interface on a micrometre scale. However, we could not establish, at this resolution, whether additive adsorption occurred at step edges or on terraces, as both generate the formation of pointed, pinned steps (Mauri and Moret, 2000). Nonetheless, pinning of steps and reduction in growth rates were observed, in accordance with the Cabrera and Vermilyea model.

The functional groups that protrude from the (0 0 1) face, in the [−1 0 0] direction, are $NHCOCH_3$ and OH. These groups may enable attachment of metacetamol molecules via their CO group, which is equivalent to that of paracetamol, or their OH group, which is located juxtaposed to that of paracetamol. In either case, the hydrogen bonding network of the crystal would be largely preserved. Hence, metacetamol may bind with relative ease to this face and induce the degree of inhibition observed.

We suggest that further similar experiments should be carried out using each of the structurally related

additives, not only on the (0 0 1) face, but on all other faces of the crystal. These investigations would help to achieve a ranking order of the inhibitory effects of the additives on each of the crystal faces. Particular attention should be paid to the inhibitory activities on the {1 1 0} faces. These are considered to be morphologically the most influential, because their growth rates and mechanisms change with increasing σ, altering the habit of the crystal from columnar to tabular (Finnie et al., 1999; Prasad et al., 2001; Ristic et al., 2001). Once the degree of inhibition of these additives has been established for each face of paracetamol, they could, individually or as a mixture, be employed to control the habit of paracetamol crystals, their chemical properties, and perhaps their problematic compaction behaviour.

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