Physicochemical Characterization of the Orthorhombic Polymorph of Paracetamol Crystallized from Solution

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Abstract □ This paper describes a method for the laboratory-scale crystallization of the orthorhombic polymorph (form II) of paracetamol (acetaminophen) from solution. Its structure has been determined by single-crystal X-ray crystallography at 298 K (to confirm the results of data published in 1974) and at 123 K (to improve the overall accuracy of the structure determination). Despite considerable effort by many investigators, the crystallization of form II from solution, using the method given in the 1974 structure report, has been elusive. The incentive for this effort is that form II, unlike commercial paracetamol (form I), undergoes plastic deformation and is suitable for direct compression. Consequently, the ability to produce form II in quantity has attracted much interest because of the potential commercial benefits to be gained by not using binders during the manufacture of tablets. However, until now, the only method that has been reported for the bulk preparation of form II has been to grow it as polycrystalline material from fused form I. This study also compares the solid-state properties of form II with those of form I, with particular emphasis on the crystallography (both X-ray and optical), crystal morphology, thermal behavior, and compaction properties.

Introduction

This paper reports the results of an investigation that was initiated by the repeated failure of researchers to crystallize the orthorhombic polymorph (form II) of paracetamol from solution using the method described in 1974 by Haisa et al.[1] Since the initial results of this current work were first published,[2] the potential commercial significance of the findings became evident. Therefore, additional studies have subsequently been conducted (1) to develop a laboratory-scale crystallization method and (2) to characterize the physicochemical properties of form II in comparison with those of form I.

Paracetamol (acetaminophen) is an analgesic drug that is used worldwide in the manufacture of many millions of tablets and other dosage forms every year. The crystal structures for the two known crystal modifications of paracetamol (monoclinic and orthorhombic) have already been published.[1,3] Monoclinic paracetamol is the thermodynamically stable modification at room temperature with respect to the orthorhombic modification. Evidence has also been published which indicates that a third modification exists.[4,5] However, this third polymorph (form III) has only been observed during fusion experiments and is reported to be so unstable that, as yet, no crystals have been isolated to enable its structure or physicochemical properties to be determined.

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Monoclinic paracetamol (form I), which is the commercially used form, is not suitable for direct compression into tablets. This is because it lacks slip planes in its crystal structure, which are a prerequisite for plastic deformation upon compaction. Consequently, form I has to be mixed with binding agents before tabletting, which is costly in both time and materials. However, directly compressible form I has been prepared by modifying the crystallization process; for example, by the desolvation of a hemisolvate to produce sintered-like crystals[6,7] and by crystallization in the presence of 0.5% of PVP 10000 or 50000.[8] In contrast, orthorhombic paracetamol (form II) has well-developed slip planes in its crystal structure and, as a result, it undergoes plastic deformation upon compaction.[9] For this reason, it has been postulated that the orthorhombic form of paracetamol may have distinct processing advantages over the monoclinic form.[9] In addition to the commercial benefit of direct compression, there is evidence to suggest that form II, which is the metastable polymorph, may also be slightly more soluble than form I.[10]

Despite considerable efforts to crystallize the orthorhombic polymorph by slow evaporation from an ethanol solution, as described by Haisa et al.,[1] this method of producing it has eluded subsequent researchers.[5,10] The only method that has been reported for the reproducible bulk production of polymorphically pure orthorhombic paracetamol powder is by crystallization from melted monoclinic paracetamol in a nonoxidizing atmosphere.[5] Consequently, studies into the pharmaceutical and mechanical properties of form II have been performed using milled, polycrystalline material. However, crystallization of form II from a solution would be a more desirable and controllable manufacturing process for industrial scale-up purposes. Monoclinic paracetamol, on the other hand, is readily produced from aqueous solution[3] and many other solvents.[10,11]

To crystallize form II from solution, a supersaturated solution of paracetamol was nucleated with seeds of form II (from melt-crystallized paracetamol) while the crystallization was observed by light microscopy. The crystallization of form II was successful and this paper describes a laboratory-scale method that has been developed from the microscale to crystallize orthorhombic paracetamol from solution. The identity of form II has been confirmed by single-crystal X-ray analysis and powder X-ray diffraction. Single-crystal structure analyses of both forms I and II have been determined at 298 K (+25 °C) to confirm the results of Haisa et al.[1,3] and at 123 K (−150 °C) to improve the overall accuracy of the structure determination. The results of the 123 K data collections are presented here because these supplement and enhance the existing structural data. The unit cell parameters for both forms I and II at room temperature are also reported and are compared with previously published data.

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In addition to the confirmation of the crystal structures of forms I and II, the morphologies of forms I and II have been simulated and the predicted models are compared with the morphologies of the experimentally grown crystals. Also, the compaction properties of forms I and II (both crystallized from solution) have been determined using a compaction simulator. To our knowledge, the diagnostic optical properties of form II have never been fully characterized and published. For completeness, therefore, the principal refractive indices for form II were determined and compared with those for form I.

Experimental Section

Materials—Paracetamol (4-acetamidophenol) (Sigma Chemical Co., Poole, Dorset, England) was used for the preparation of form II. This material was confirmed as being form I by powder X-ray diffraction. The solvent used to crystallize form II was BP (British Pharmacopeia) grade industrial methylated spirits (IMS) which is ethanol with approximately 4% methanol (by volume). Benzyl alcohol (Aldrich Chemical Co., Gillingham, Dorset, England) was used for the preparation of single crystals of form II.

Preparation of Form II Seed Crystals—Polycrystalline form II is readily prepared by the fusion of form I.[10] About 5 mg of form I was melted on a glass microscope slide over a spirit lamp. The melt was vitrified by rapid cooling to room temperature after placing the slide on an aluminum block. Within 30 min of cooling, the glass had started to crystallize as form II. Seeds were collected by gently scraping the top surface of the crystallized melt with a microspatula. Due to the simplicity of this method to grow seeds of pure form II, new seeds were grown for every solvent crystallization experiment.

Crystallization of Orthorhombic Paracetamol from Solution—Two different methods were used to crystallize form II for the single-crystal X-ray analysis (Method 1) and for all other experiments (Method 2).

Method 1—For the isolation of well-formed crystals that are suitable for single-crystal X-ray analysis, crystallization from a supersaturated, high-boiling point solvent has been suggested by McCrone.[12] Benzyl alcohol, which boils at 205 °C, has been used successfully to grow crystals of form II using the following microcrystallization method, which requires the use of a transmitted light compound microscope (magnification of about 40×) to observe the development of the crystals and to enable the single crystals to be manipulated and harvested. A single drop of a benzyl alcohol (about 1 mL) on a microscope slide was warmed to about 50 °C on a hot plate and paracetamol was added until no more would dissolve. The drop was then warmed to about 80 °C to ensure complete dissolution of the paracetamol. The microscope slide was then rapidly chilled, to achieve a supersaturated solution, by placing it on an aluminum block that had been prechilled to 0 °C on ice. The chilled drop was seeded with a few micrograms of form II (prepared from a recrystallized melt) and was left uncovered. The microscope slide was maintained at 0 °C and was examined periodically, using the light microscope, to monitor the growth of needle-shaped form II crystals. After about 15 min, the largest crystals (between 100 and 200 μm long) were isolated from the drop using a steel needle probe and dried with a piece of filter paper that had been cut to a sharp point.

Method 2—Attempts to crystallize form II by cooling supersaturated IMS solutions (without seeding) at different temperatures (22 °C, 4 °C, −34 °C, and −75 °C) always resulted in the growth of form I. However, as described later, subambient temperatures did sometimes favor the growth of form II, provided that the crystals were harvested soon after the onset of crystallization.

The next approach was to nucleate the supersaturated solution using seeds of form II that had been prepared from a crystallized melt. This nucleation method was successful, so a simple and repeatable method for the laboratory-scale preparation of orthorhombic paracetamol from IMS was developed, as described below.

The amounts of paracetamol (form I) needed to give saturated solutions in IMS at room temperature (22 °C) and at 0 °C were found to be 6.75 g in 50 mL (0.135 g/mL) and 5.00 g in 50 mL (0.1 g/mL), respectively. These values were used as a guide to prepare supersaturated solutions for the crystallization experiments.

A supersaturated solution of paracetamol was prepared by dissolving 9.3 g of form I in 50 mL of IMS at about 50 °C in a stoppered 150 mL conical flask. This solution was agitated until the paracetamol was completely dissolved. The warm solution was carefully transferred (using a funnel to prevent splashing) into a second, clean, dry, 150 mL conical flask that had been prechilled in an ice bath at 0 °C. After cooling for about 10 min, the solution was seeded with a small amount (about 50 μg) of the powdered, melt-crystallized form II.

The seeded solution was left to stand at 0 °C, with occasional mixing by gentle swirling. Precipitation and growth of form II crystals occurred rapidly (usually within 10 min of seeding). After 15−20 min from seeding, the precipitated crystals of form II were harvested by rapid suction filtration onto a paper filter and then air-dried. It is very important that the form II crystals are completely dried as quickly as possible. This is because residual solvent can induce a partial conversion of form II to form I during storage (via a solvent-mediated transformation as discussed later).

It was observed that if the precipitation was allowed to continue for more than a few minutes (in an attempt to increase the yield of form II), crystals of form I began to grow. For the purpose of these laboratory-scale experiments, the yield was not of prime importance. Generally, the yield of pure form II was low (typically less than 30%); therefore, to increase the yield for commercial production of form II, the crystallization and recovery process would need to be optimized.

Analysis and Characterization—A combination of analytical techniques was used to characterize and compare the physicochemical properties of the orthorhombic and monoclinic polymorphs of paracetamol.

Single-Crystal X-ray Diffraction—Single crystals of form I were grown from an ethanol solution and crystals of form II were grown from benzyl alcohol. Diffraction data were collected at temperatures of 298 and 123 K on a Rigaku AFC7R diffractometer equipped with a graphite monochromator, using Mo Kα radiation.

An Oxford Cryosystems cryostream cooler[13] (Oxford Cryosystems, Long Hanborough, Oxford, England) was used to cool the crystals to 123 K during the collection of the data. The intensities were collected in the $\omega-2\theta$ scan mode. The recorded reflections were corrected for Lorentz and polarization effects. No absorption correction was applied since preliminary ψ-scan measurements revealed no significant absorption effects. Three orientation and intensity standards were monitored after every 150 reflections recorded; no significant variation was observed for either sample.

The structures were solved by direct methods, followed by full-matrix least-squares refinement on F^2. All non-hydrogen atoms were refined with anisotropic temperature factors. All hydrogen atoms were located in subsequent difference maps and freely refined with isotropic temperature factors with convergence at $\Delta/\sigma_{max.} < 0.005$. Programs used for the structure determination were teXsan, version 1.6 (Molecular Structure Corp., The Woodlands, TX) and SHELXTL (Sheldrick, G. M., *Program for crystal structure refinement*; University of Göttingen, Germany, 1996).

Powder X-ray Diffraction (PXRD)—The powder X-ray diffraction patterns for forms I and II were acquired at room temperature on a Siemens D5000 diffractometer using Cu Kα radiation (tube operated at 40kV, 40mA), a $\theta-\theta$ goniometer, automatic divergence and receiving slits, a graphite secondary monochromator, and a scintillation counter. The data were collected over an angular range from 2° to 55° 2θ in continuous scan mode using a step size of 0.02° 2θ and a step time of 5 s.

Form I (Sigma) and form II (grown from IMS solution) were prepared as flat plate specimens using powder that had been sieved, without grinding, to less than 90 μm using a 170 mesh screen. The powders were packed into 12 mm diameter, 0.5 mm deep cavities cut into polished, zero-background silicon wafers (The Gem Dugout, 1652 Princeton Drive, Pennsylvania State College, PA). All specimens were rotated in their own plane during analysis. Silicon powder (approximately 15% w/w) was used as an internal standard to correct for peak displacement.

The diffraction data are reported using Cu Kα_1 ($\lambda = 1.5406$ Å) after the Kα_2 component had been stripped using the Siemens Eva software.

Differential Scanning Calorimetry (DSC)—The thermal behaviors above ambient of forms I and II were recorded using a Perkin-Elmer DSC Series 7 differential scanning calorimeter equipped with an automatic sample changer. Approximately 3 mg of each

sample was heated at 10 °C/min from 30 to 190 °C in perforated, crimped aluminum pans while being purged with dry nitrogen.

Thermomicroscopy—Thermally induced events were observed using a Nikon Labophot transmitted light microscope equipped with a Mettler FP5 controller and FP52 microscope heating stage. A few crystals were scattered dry between a coverglass and microscope slide and these were heated at 5 °C/min from room temperature to 175 °C.

Optical Crystallography—Despite a careful literature search, no reference to the optical properties of the orthorhombic polymorph of paracetamol could be found. Only one reference for the monoclinic form, giving minimal optical data, was found.[14] Consequently, the optical properties for both the orthorhombic and monoclinic polymorphs were determined and are reported in this paper.

A Nikon Optiphot POL polarizing light microscope, fitted with a rotating specimen stage, was used for the full optical characterizations of both forms I and II. Orthoscopic and conoscopic observations were made at magnifications from 40× to 1000×. Fresh, certified Cargille refractive index liquids (R. P. Cargille Co., Cedar Grove, NJ) were used to measure the three principal refractive indices ($n\alpha$, $n\beta$, and $n\gamma$) for both polymorphs by the immersion method.[15] The refractive index values were determined using monochromatic light ($\lambda = 589$ nm) and were corrected to 25 °C.

Scanning Electron Microscopy (SEM)—An Amray 1820T scanning electron microscope was used to examine the crystal habits of forms I and II. The powders were mounted onto 13 mm diameter aluminum stubs using double-sided adhesive tape and were sputter-coated with gold. The scanning electron microscope was operated with a beam accelerating potential of 3kV, and images were collected in secondary electron mode.

Crystal Morphology—Crystal morphology modeling was performed using Cerius^2, version 3.0 (Molecular Simulations Ltd., Cambridge, England) to compare the predicted crystal habits of forms I and II with those grown experimentally. For both polymorphs, two simulated models were calculated: (i) the Bravais-Friedel and Donnay-Harker (BFDH) model (which is calculated using the crystal lattice geometry) and (ii) the attachment energy (AE) model (which is calculated from the energy released as a growth slice attaches onto a specific surface on the crystal).[16] For the attachment energy calculations, the Dreiding 2.21 force field was used.

Compaction Studies—Previous studies on the compressibility of form II powder derived from melt crystallization have shown that it can be directly compressed without the need for binding agents.[9] To establish if form II grown from solution is also suitable for direct compression, exploratory controlled-compaction studies were performed in triplicate using the method of Heckel.[17,18] For comparison, the compaction properties of form I (grown from IMS solution) were also determined under the same conditions. The particle sizes of form I and form II used for the compaction experiments were similar and were measured (using light microscopy) to be less than 100 μm across, typically between 25 and 50 μm.

The yield pressures of forms I and II were determined using an ESH compaction simulator (ESH Testing Ltd., Briefly Hill, West Midlands, England). Flat-faced, 8 mm diameter punches were used to compact the powders at velocities of 2 and 220 mm s^{-1}. The punch and die faces were lubricated with a 5% w/v suspension of magnesium stearate in methanol. The fill weights were calculated (using the density values calculated from the X-ray analyses) from the amount of material required to give compacts that would theoretically be 3 mm thick at zero porosity. For each experiment, a single compaction was provided using a V-shaped profile.

Results

Single-Crystal X-ray Diffraction—The molecular structures of forms I and II determined at 123 K are shown in Figures 1 and 2, respectively. Both structures have similar, planar conformations and these agree with the structures reported by Haisa et al.[1,3] This low-temperature data enhances the previously published results because the overall accuracy has been improved. A summary of the single-crystal data acquired at 123 K for both forms I and II is given in Table 1.

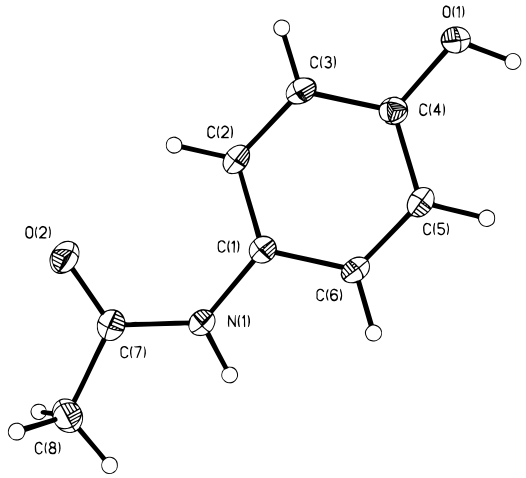

Figure 1—Molecular structure for monoclinic paracetamol (form I) determined using single crystal X-ray diffraction at 123 K. Ellipsoids are drawn at the 50% probability level.

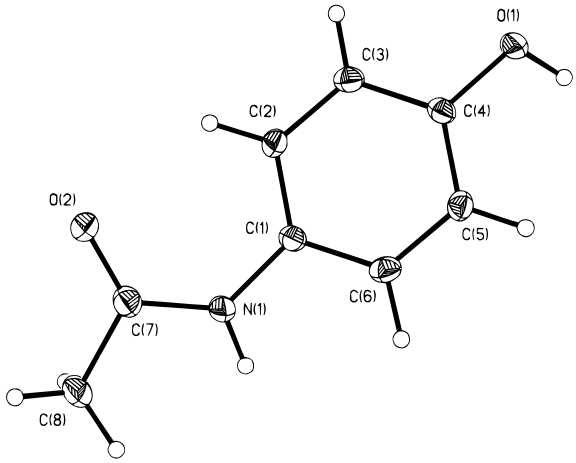

Figure 2—Molecular structure for orthorhombic paracetamol (form II) determined using single-crystal X-ray diffraction at 123 K. Ellipsoids are drawn at the 50% probability level.

Form II has been confirmed as orthorhombic and is assigned to the space group *Pbca*, which agrees with the data of Haisa et al.[1] Form I has also been confirmed as monoclinic, but this study has resulted in the choice of the $P2_1/n$ space group. This is in agreement with the work of Welton and McCarthy[19] and Wilson et al.[20] but differs from the assignment of the $P2_1/a$ space group by Haisa et al.[1]

The room-temperature unit cell parameters for forms I and II are in accord with those determined by Haisa et al.[1,3] and are summarized in Table 2.

Powder X-ray Diffraction—Forms I and II have different crystal structures and can be distinguished from each other by PXRD. Figures 3 and 4 show the patterns that have been acquired from forms I and II, respectively.

PXRD data for the first 30 peaks for forms I and II, which have relative integrated intensities (expressed as a percentage of the strongest peak) of 1% or greater, are listed in Table 3. The peaks for both polymorphs were indexed using Cerius^2. The powder data for form I agrees with that given by Welton and McCarthy.[19] In contrast, the PXRD pattern for form II grown from solution is very different from the pattern from melt-crystallized material.[5] The latter has a very intense main reflection and many weak reflections due to the effects of preferred orientation.

Table 1—Summary of Results for the Single Crystal X-ray Analyses of Paracetamol Forms I and II Performed at 123 K

	form I	form II
chemical formula	$C_8H_9NO_2$	$C_8H_9NO_2$
formula weight	151.16	151.16
temperature (K)	123	123
wavelength (Å)	0.71069	0.71069
crystal system	monoclinic	orthorhombic
space group	$P2_1/n$	$Pbca$
unit cell dimensions		
a (Å)	7.0941 (12)	17.1657 (12)
b (Å)	9.2322 (11)	11.7773 (11)
c (Å)	11.6196 (10)	7.212 (2)
β °	97.821 (10)	90.000
volume (Å^3)	753.9 (2)	1458.1 (4)
no. of reflct used for cell deter. (deg θ ranges)	25 ($17.30 \leq \theta \leq 19.90$)°	20 ($9.55 \leq \theta \leq 11.25$)°
Z	4	8
D_c (g/cm^3)	1.332	1.377
μ(Mo Kα) (mm^{-1})	0.097	0.100
F(000)	320	640
crystal dimen (mm)	$0.30 \times 0.30 \times 0.15$	$0.28 \times 0.25 \times 0.15$
index ranges		
h	0–9	0–21
k	0–11	0–15
l	–14 to 14	0–9
θ range for data collect. (deg)	2.83–26.99	2.94–26.99
no. of reflct collected	1771	1588
no. of unique reflct	1642	1588
R_{int}	0.0143	no equiv reflct measured
no. with $I \geq 2\sigma(I)$	1423	955
no. of parameters	137	137
weighting scheme (A, B)[a]		
wR^2 (all data)	0.0975	0.1144
R_1 ($I \geq 2\sigma(I)$)	0.0333	0.0423
extinction coefficient (x)[b]	0.0189 (43)	0.0027 (7)
goodness of fit	1.013	1.020
residual density (e Å^3)	0.289 and –0.192	0.230 and –0.202

[a] $w^{-1} = \sigma^2(F_o^2) + (AP)^2 + BP$, where $P = (F_o^2 + 2F_c^2)/3$. [b] $F_c^* = kF_c[1 + 0.001xF_c^2\lambda^3/\sin(2\theta)]^{-1/4}$.

Differential Scanning Calorimetry—The thermogram for form I shows a single endothermic event (Figure 5). This sharp peak is due to the melting of form I at about 171 °C (onset = 169 °C; enthalpy = 186 J g^{-1}).

Form II gave a thermogram with three endothermic events, as shown in Figure 6. The first event, which is broad and weak, occurs over the temperature range 115 to 128 °C and is centered at about 122 °C (onset = 115 °C; enthalpy = 2 J g^{-1}). The second event is a weak but sharp peak at about 157 °C (onset = 157 °C; enthalpy = 1 J g^{-1}). The third endotherm is a strong, sharp peak at about 171 °C (onset = 169 °C; enthalpy = 185 J g^{-1}).

The thermally induced events for form II have been interpreted as (in order of increasing temperature) a solid-state conversion of form II to form I, followed by the melting of nonconverted form II, and finally, the melting of form I. This interpretation was confirmed by thermomicroscopy (see below).

Interestingly, the thermal behavior of form II that has been crystallized from solution is different to that of form II crystallized from the melt. Melt-crystallized paracetamol has a single strong endothermic event, due to melting, at about 157 °C.[5,10] This suggests that melt-crystallized form II is polymorphically pure, whereas solution grown form I may have a low level of form I present that is not detected by PXRD. Alternatively, crystals of form II that precipitated rapidly from solution may contain many structural defects that could promote the thermally induced conversion of form II to form I.

Table 2—Summary of the Crystal Morphology, Unit Cell Parameters, and Crystal Optics for Paracetamol Forms I and II Determined at Room Temperature

	form I	form II
	Crystal Morphology	
crystal system	monoclinic	orthorhombic
habit	prisms and plates elongated parallel to $\{10\bar{1}\}$	prisms elongated parallel to c-axis
cleavage	moderate; parallel to 010	perfect; parallel to 001
	Unit Cell Parameters	
temperature (K)	298	298
space group	$P2_1/n$	$Pbca$
a (Å)	7.106(2)	17.156(6)
b (Å)	9.382(3)	11.831(4)
c (Å)	11.704(3)	7.405(3)
axial ratio (a:b:c)	0.757:1:1.247	1.450:1:0.626
β angle	97.36(2)°	90.00°
cell volume (Å^3)	774	1503
molecules per unit cell (Z)	4	8
density (calcd) g/cm^3	1.297	1.336
	Crystal Optics	
refractive indices (n^{25}_D):		
$n\alpha$	1.580(±0.001)	1.491(±0.001)
$n\beta$	1.643(±0.001)	1.667(±0.001)
$n\gamma$	1.704(±0.001)	1.840(±0.002)
extinction	inclined and dispersed: $\gamma \wedge 10\bar{1} = 36.2°$	straight for prisms, and symmetrical in rhomb-shaped (001) cleavage fragments

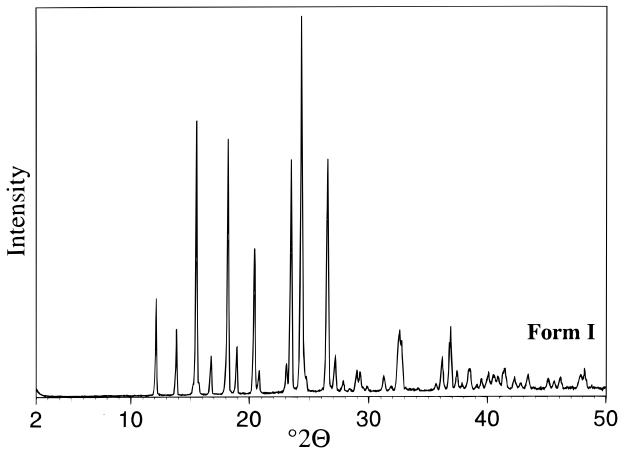

Figure 3—Experimental powder X-ray diffraction pattern for monoclinic paracetamol (form I).

This study suggests that DSC is unlikely to be a reliable method for the routine quality control of form II grown from solution, because the major thermal event is the melting of form I that results from the thermally induced solid-state conversion of form II to form I.

Thermomicroscopy—From about 60 °C, individual crystals of form II converted in the solid-state to form I. This solid-state conversion was a slow and gradual process that was observed in discrete crystals. The conversion did speed up slightly from 120 to 135 °C. Between 157 and 158 °C, residual crystals of form II melted. Where the melt was in direct contact with those crystals that had already converted to form I, it recrystallized as form I. Melt that was not in contact with crystals of form I did not recrystallize and remained molten. Finally, all the form I crystals melted, without decomposition, between 170 and 171 °C.

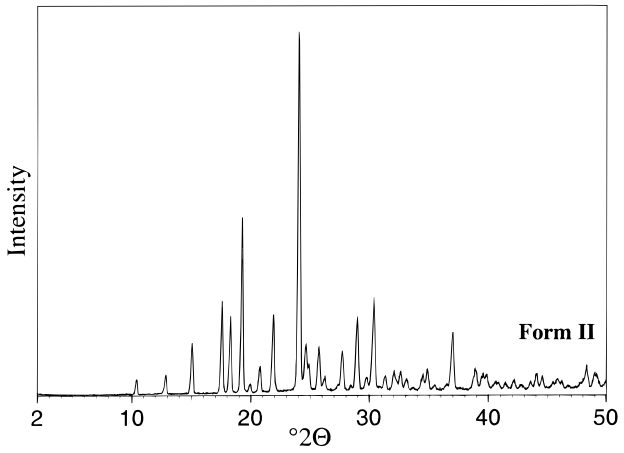

Figure 4—Experimental powder X-ray diffraction pattern for orthorhombic paracetamol (form II).

Table 3—Experimental Powder X-ray Diffraction Data for Paracetamol Forms I and II

form I				form II			
hkl	*d* (Å)	°2Θ	I/I_{max} (%)	*hkl*	*d* (Å)	°2Θ	I/I_{max} (%)
01$\bar{1}$	7.301	12.112	26	200	8.562	10.323	4
10$\bar{1}$	6.398	13.830	18	210	6.935	12.755	5
002	5.809	15.240	3	020	5.907	14.986	14
101	5.709	15.508	72	211	5.061	17.508	26
1$\bar{1}$0	5.640	15.700	4	220	4.862	18.232	22
11$\bar{1}$	5.294	16.732	11	021	4.618	19.203	49
111	4.877	18.175	68	121	4.463	19.878	3
020	4.690	18.905	13	400	4.284	20.716	9
02$\bar{1}$	4.355	20.376	39	221	4.066	21.844	22
11$\bar{2}$	4.276	20.756	7	002	3.699	24.038	100
1$\bar{1}$2	3.849	23.087	9	102	3.616	24.597	14
12$\bar{1}$	3.785	23.483	62	230	3.579	24.855	9
02$\bar{2}$	3.650	24.367	100	420/112	3.464	25.700	13
10$\bar{3}$	3.596	24.741	5	131/202	3.401	26.177	5
12$\bar{2}$	3.355	26.545	62	231	3.222	27.663	12
21$\bar{1}$	3.280	27.165	11	022	3.139	28.407	3
20$\bar{2}$	3.201	27.847	4	122	3.084	28.931	21
122	3.140	28.403	2	312	3.006	29.700	5
211	3.075	29.012	7	222	2.945	30.325	27
113	3.048	29.273	6	600	2.857	31.280	5
023	2.987	29.887	3	240	2.792	32.026	7
12$\bar{3}$	2.858	31.273	5	322	2.747	32.572	6
22$\bar{1}$	2.805	31.877	3	141/431	2.706	33.081	4
032/131	2.747	32.575	17	132	2.662	33.639	2
13$\bar{2}$	2.622	34.173	2	611	2.600	34.462	5
132	2.513	35.706	3	232	2.573	34.840	7
114	2.480	36.193	10	422	2.530	35.454	3
033	2.434	36.904	18	512	2.461	36.486	3
20$\bar{4}$/22$\bar{3}$	2.398	37.466	7	440/621	2.431	36.955	17
213	2.372	37.896	4	630	2.314	38.891	7

The solid-state conversion of form II to form I was readily monitored between crossed polarizers. Form II crystals at their extinction position (i.e. black when they are parallel with one of the polarizers), became bright as they converted to the monoclinic form I (which has inclined extinction when viewed along the *b*-axis).

Optical Crystallography—The solid-state optical properties of a specific compound, such as refractive index, birefringence, and extinction angle,[15] are controlled by its molecular structure and are therefore a physical constant for that compound. The optical properties for both the monoclinic and orthorhombic forms of paracetamol are given in Table 2. The polymorphs of a compound have unique molecular structures and chemical properties and, as a consequence, each has unique and diagnostic optical properties. These optical properties can be used to distinguish between the polymorphs of paracetamol.

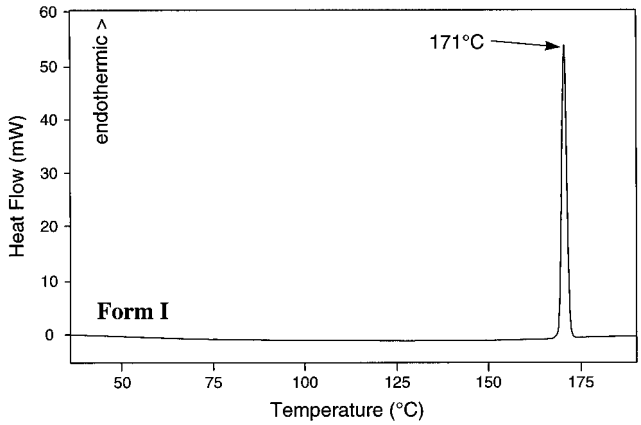

Figure 5—DSC thermogram for monoclinic paracetamol (form I).

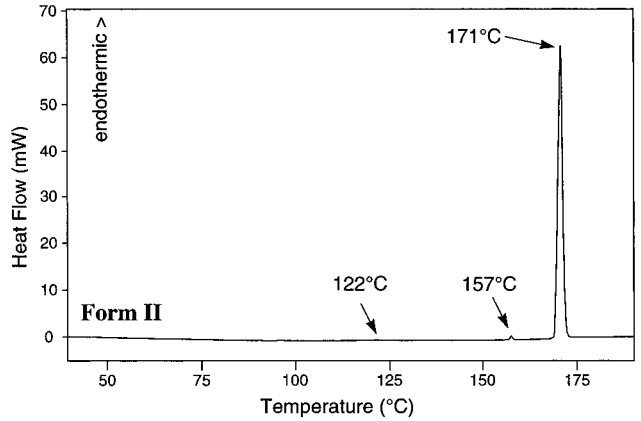

Figure 6—DSC thermogram for orthorhombic paracetamol (form II).

Comparison of the optical properties for forms I and II shows that they are quite different from each other. As a consequence, form II can be readily distinguished from form I for analytical purposes by determining and comparing their respective optical properties. The principal refractive indices determined for form I are consistent with those previously reported by Jordan.[14] The results of a complete optical characterization for both form I and form II will be published elsewhere.

The most striking optical difference between the two polymorphs is seen when they are rotated between crossed polarizers. Crystals of form II show complete extinction every 90° during rotation of the microscope stage. However, when form I is orientated so that it is viewed along the *b*-axis, it shows incomplete and dispersed extinction with a distinctive change in interference color from yellow to blue as it passes through the extinction position.

As a rapid screening tool, polarized light microscopy was used to confirm that form II had been isolated in preference to form I during the crystallization experiments. The dispersed extinction displayed by form I was of practical use during the experiments to prepare form II from solution. This microscopical screening method is very sensitive and it was possible to identify trace amounts of form I in samples that were analyzed as "polymorphically pure" form II by powder X-ray diffraction.

When gently crushed between a microscope slide and coverglass, forms I and II fracture in distinctly different ways. Form I usually fractured into irregular fragments together with some polygonal cleavage plates that were parallel to (010). Form II, on the other hand, gave many thin, diamond-shaped plates that were parallel to (001).

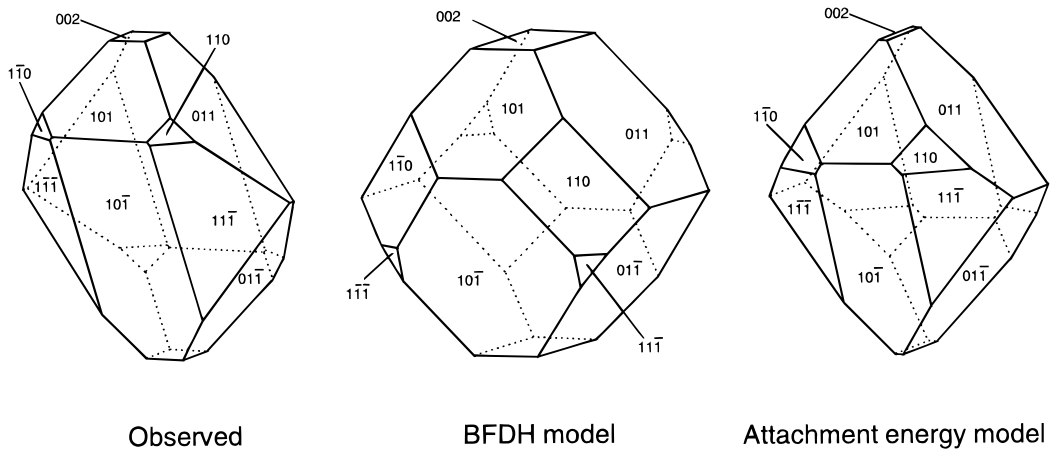

Figure 7—Comparison of the observed morphology (grown from supersaturated IMS solution) and the predicted morphologies (BFDH and attachment energy models) for monoclinic paracetamol (form I).

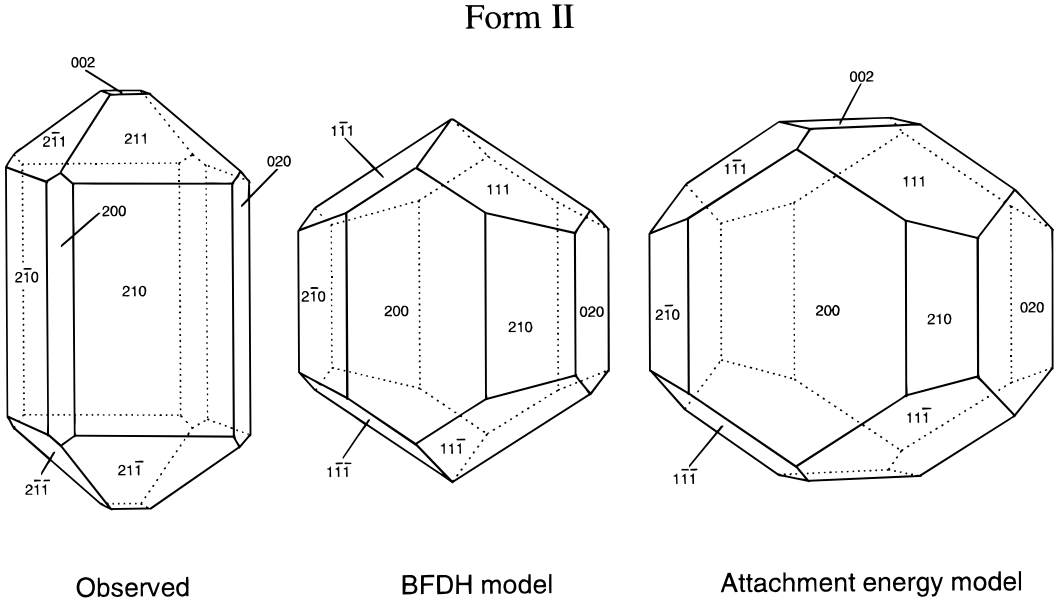

Figure 8—Comparison of the observed morphology (grown from supersaturated IMS solution) and the predicted morphologies (BFDH and attachment energy models) for orthorhombic paracetamol (form II).

Crystal Morphology—Figures 7 and 8 show the observed morphologies compared with the predicted BFDH and attachment energy models for forms I and II, respectively. The drawings of observed morphology were constructed and indexed by modifying the predicted models to match the habits of the crystals that were grown experimentally.

Form I—Form I crystallizes from IMS with a prismatic to platy habit that is elongated in the direction of the *c*-axis, but parallel with the {101} faces. Mature crystals (i.e. the larger ones that had been growing for the longest time) show the development of the pinacoids {10$\bar{1}$} and {101} and the prisms {011} and {110} as the dominant forms. Some immature crystals also show pinacoids {001} and prisms {111}, which are the fast growing faces. The morphology of form I, as observed by scanning electron microscopy, is shown in Figure 9.

There is reasonably good agreement between the observed morphology of form I and its predicted attachment energy model. However, there is less similarity between the observed and predicted BFDH morphologies. The BFDH model tends to over emphasize the {110} faces and under emphasizes the {11$\bar{1}$} faces.

Form II—Form II crystallizes from IMS as prisms that are elongated along the *c*-axis. The dominant forms in mature crystals are prisms {210} and bipyramids {211}. Immature crystals sometimes show the pinacoids {100}, {010}, and {001} which are the fast growing faces. The morphology of form II, as observed by scanning electron microscopy, is shown in Figure 10.

In contrast to form I, the observed morphology of form II shows poor agreement with both the BFDH and attachment energy models. The attachment energy model predicts an equant, squat prismatic habit, while the BFDH model predicts a habit that is slightly elongated along the *c*-axis direction. For both of the predicted models, the {111}, {200}, and {020} faces are dominant, whereas the observed morphology is dominated by the {210} and {211} faces.

The dissimilarity between the observed morphology and the predicted morphologies for form II is in contrast to the similarity between the observed and predicted morpholo-

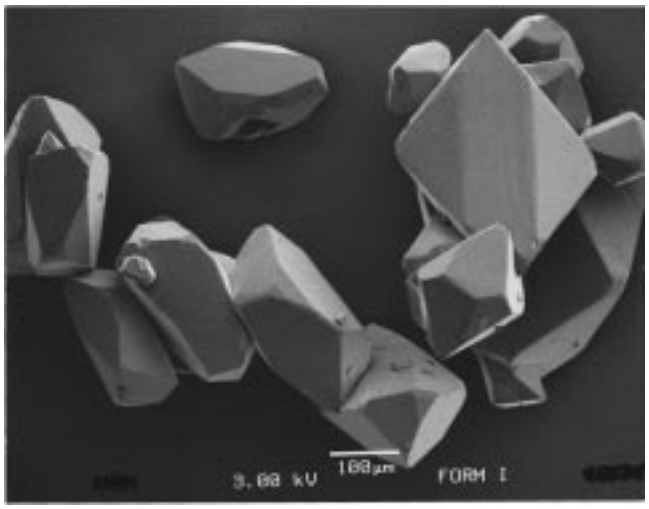

Figure 9—Scanning electronmicrograph showing the crystal habit of paracetamol (form I) grown from supersaturated IMS solution. Scale bar = 100 μm.

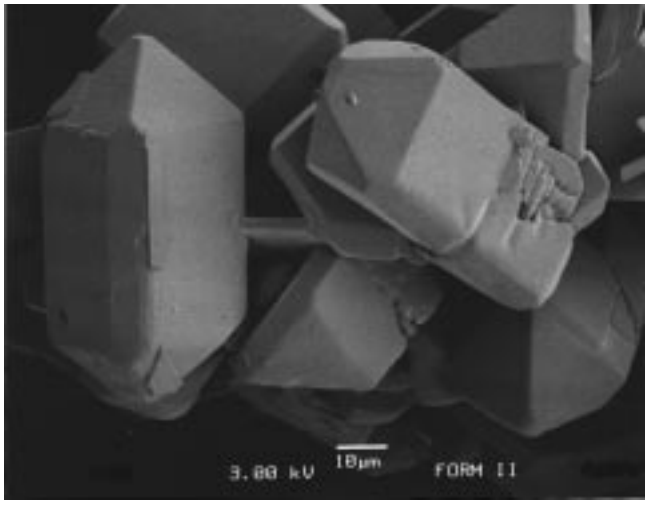

Figure 10—Scanning electronmicrograph showing the crystal habit of paracetamol (form II) grown from supersaturated IMS solution. Scale bar = 10 μm.

gies for form I. One reason for the dissimilarity shown by form II could be the effect of solvent, which is known to have a profound influence on the shapes of paracetamol crystals.[21] However, the most likely reason for the difference between observed and predicted morphologies is due to the rate of crystal growth (probably due to the degree of supersaturation) during the preparation of the two polymorphs. Differences in the morphology of form I, due to the effect of supersaturation during crystallization, have also been observed by other workers.[22,23] Form I was grown slowly over a period of several hours, so it had time to achieve a dynamic equilibrium with its solution, whereas form II was precipitated rapidly and, as a result, the crystals did not achieve a dynamic equilibrium. This suggests that the observed morphology of form II is a consequence of its rapid growth rate. Form II crystals grown under less stressful conditions may adopt a morphology that is more like the equant, squat prismatic habit that is predicted by the attachment energy model. However, as this present investigation has shown, the isolation of form II from a supersaturated solution relies upon rapid growth and so, fully developed crystals such as those predicted may rarely be observed using the crystallization conditions described.

Table 4—Results from the Compaction Simulator Experiments Conducted on Paracetamol Forms I and II with Punch Velocities of 2 and 220 mm s^{-1}

sample	1st run (MPa)	2nd run (MPa)	3rd run (MPa)	mean (MPa)	standard deviation	strain rate sensitivity (%)
2 mm s^{-1}						
form I	70.06	72.30	72.92	71.76	1.23	
form II	48.42	43.67	42.52	44.87	2.55	
220 mm s^{-1}						
form I	76.59	79.28	79.88	78.58	1.43	9.5
form II	53.87	56.53	56.87	55.76	1.34	24.3

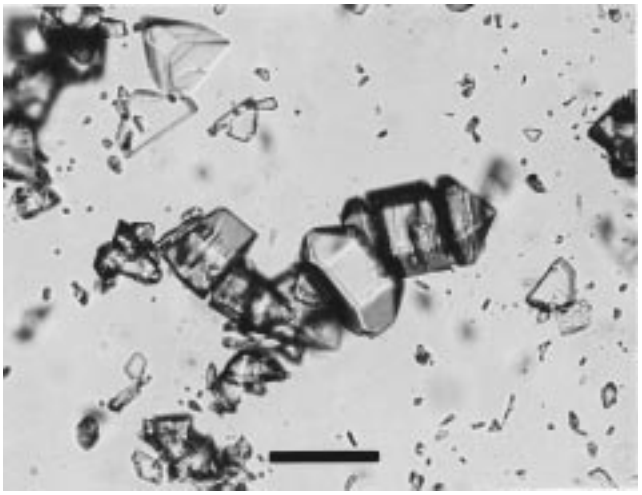

Figure 11—Photomicrograph showing pressure-induced multiple cleavages along slip planes in a prismatic crystal (to the right of center) of orthorhombic paracetamol (form II). Scale bar = 50 μm.

Compaction Studies—The results of the compaction experiments are given in Table 4. The yield pressure values for form I are in reasonable agreement with a range of literature values as given from 79 to 127 MPa.[24] When compared with form I, the data for form II suggests that it has a low yield pressure, which is indicative of plastic deformation. Also, a comparison of the strain rate sensitivity values for forms I and II (which describe the percentage increase in yield pressure over the two punch velocities[24]) indicates that form II has the greater increase in yield pressure. This increase is consistent with plastic deformation, so of the two polymorphs, form II should be suitable for direct compression. After compaction, the pellets of form I disintegrated, while those made from form II remained intact and have not crumbled, even after storage for several months.

As mentioned in the Introduction, a significant commercial advantage may be gained by using orthorhombic paracetamol in preference to the monoclinic form. This is because it undergoes plastic deformation upon compaction and could be directly compressed into tablets without the need for binding agents. Form I, the commercial form, is unsuitable for direct compression because it does not deform plastically but breaks by brittle fracture and, therefore, tablets require binding agents.

Figure 11 is a photomicrograph showing some crystals of form II (that are immersed in silicone oil between a microscope slide and coverglass) that have been fractured by applying pressure to the top of the coverglass with a steel needle. Note that one crystal shows multiple cleavages perpendicular to its length (i.e. parallel with {001}). The observation of these cleavages confirms the existence of a well-developed slip system which is attributed to the existence of two-dimensional molecular sheets that lie in the plane containing the *a*- and *b*-axes, as identified by

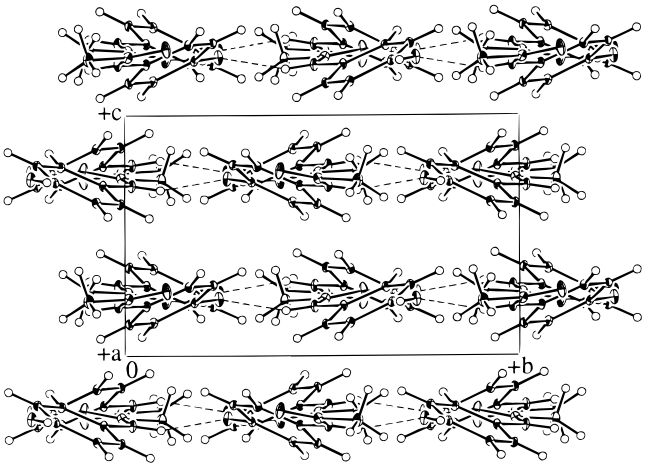

Figure 12—Projection of the crystal structure of form II (down the *a*-axis) showing the hydrogen-bonded molecular sheets that lie in the plane of the *a*- and *b*-axes (H-bonds are shown as dashed lines).

Haisa et al.[1] Figure 12 is a molecular diagram (constructed using data from this investigation) showing these sheets in the direction of the *c*-axis and they are held together by hydrogen bonds. Adjacent sheets are weakly bonded (there are no intersheet H-bonds) and it is because of this that form II has slip planes and can undergo plastic deformation.

Discussion

This paper has reported that the growth of the orthorhombic polymorph of paracetamol from solution is a relatively simple procedure. Indeed, 3−5 g of polymorphically pure form II (as determined by PXRD) have been grown in less than 1 h. So, why has the crystallization of form II from solution been so elusive since 1974 when Haisa et al.[1] first grew it and determined its structure? As this investigation has demonstrated, it is a matter of harvesting the crystals from the mother liquor soon after the crystals have begun to grow. Indeed, if the crystals of form II are left in contact with the mother liquor for too long, they will convert to the more stable polymorph, form I.

Throughout this investigation, observations were made about the thermodynamic stability of form II relative to form I. These observations are reported below.

Solution-Phase Conversion of Form II to Form I—The first indication that form II can be grown from solution was the microscopical observation of a solution phase polymorphic conversion of form II to form I. During the early stages of this investigation, light microscopy was used to study and gain an understanding of the crystallization process of paracetamol at room temperature.

Single drops of a saturated solution of paracetamol in benzyl alcohol were examined after they had been seeded with form II powder. It was noted that the first crystals to grow were needles of form II. However, within 15 min at room temperature, prismatic and platy crystals of form I began to grow as the needles of form II dissolved. Figure 13 shows this solution-phase conversion with two photomicrographs of the same field of view, taken 30 min apart. Note that the crystals of form I increase in size at the expense of the form II crystals.

Later in the investigation, the same polymorphic transformation process was noted in larger volumes of solutions of paracetamol in IMS. Depending upon the time allowed for the growth of crystals once the precipitation has occurred, either pure form II, pure form I, or a mixture of

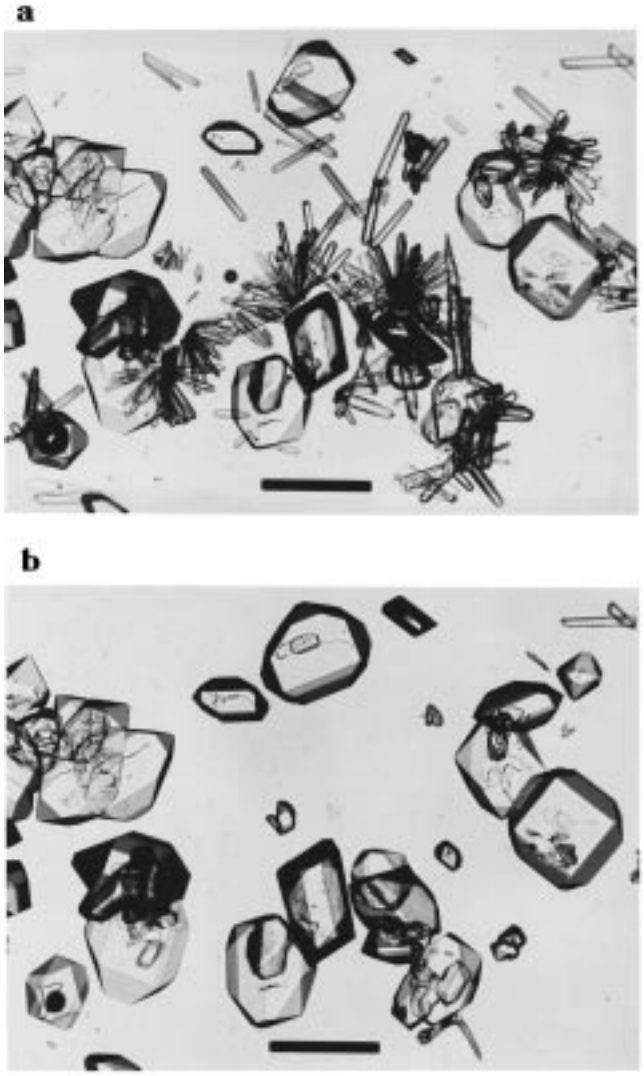

Figure 13—Photomicrographs showing the solution phase polymorphic conversion of orthorhombic paracetamol (needles) to monoclinic paracetamol (prisms and plates) at room temperature in saturated benzyl alcohol. Micrograph a was taken at $t = 0$ and b was taken at $t = 30$ min. Scale bars = 250 μm.

the two will result. These observations indicated that the crystallization of paracetamol from solution had undergone a solvent-mediated transformation in accordance with Ostwald's law of stages.[25]

A nonseeded, supersaturated solution in IMS held at −75 °C in a stoppered flask took about 7 days to begin to crystallize. After 21 days, the crystals were confirmed as being form II using polarized light microscopy. However, after 43 days at −75 °C, the form II crystals had converted to form I.

An experiment was performed to monitor the conversion of form II to form I in an IMS solution as a function of time at 0 °C. Form II was prepared in a flask using the seeding method described previously and polarized light microscopy was used to examine the crystals at specific time intervals. The solution was gently agitated intermittently during this experiment. The results are summarized in Table 5.

Therefore, the most likely reason that form II crystallized from solution has been elusive to so many other researchers is that the precipitates formed have not been harvested quickly enough. The conversion of form II to form I seems to be quite rapid and this is probably due to the fact that the solubility of form II is similar to that of form I.[9] If the crystals of form II are collected soon after they have formed,

Table 5—Summary of the Microscopical Observations during the Solution-Phase Polymorphic Conversion of Paracetamol Form II to Form I in a Seeded, Supersaturated IMS Solution at 0 °C over a Period of 6 h

time from seeding	observations
10 min	well-formed prismatic crystals of form II; form I not found
1 h	well-formed prismatic crystals of form II, but showing signs of dissolution
2 h	form II crystals undergoing extensive dissolution; a few, small, well-formed form I crystals observed
3 h	form II crystals are extensively eroded; form I crystals growing larger
4 h	well-formed platy form I crystals are dominant; a few ragged form II crystals remain
6 h	all crystals are form I

they are unlikely to have had chance to transform to form I. By conducting the crystallization at subambient temperature (ideally below 5 °C), the conversion rate of II → I is retarded and the yield and polymorphic purity of the product will be enhanced. This is not a unique phenomenon and similar saturation-temperature-dependent polymorph interconversions have been reported for other compounds.[26]

To develop this laboratory-scale crystallization of form II into a commercially viable industrial-scale process would require extensive optimization. This optimization should account for the rapid conversion of form II to form I, so rapid precipitation and rapid harvesting will be essential.

Residual Solvent—As described earlier, it is most important to fully dry the form II crystals because traces of residual mother liquor can induce a solvent-mediated polymorphic transformation during storage. It may transpire that bulk production of form II, free from form I, may be exceedingly difficult if all of the solvent cannot be removed rapidly by filtration before it begins to convert to form I. This observation emphasizes the importance of complete drying of form II prior to storage to ensure polymorphic purity.

Prolonged Storage at Room Temperature—Inspection of the phase diagram for the paracetamol system shows that at temperatures above about −30 °C, form I is the thermodynamically stable form.[4] This implies that form II is metastable at room temperature and, as a consequence, could undergo a conversion to form I during processing or storage. However, samples of form II that have been fully dried and stored in stoppered vials at room-temperature had not converted to form I after 6 months.

Effect of Compression—Approximately 100 mg of form II was compressed at 5 tons for 1 min in a 13 mm diameter die-set using a laboratory infrared press. The pellet was pulverized with a spatula and gently ground to a fine powder using an agate pestle and mortar. Analysis by powder X-ray diffraction showed that it had not converted to form I.

Effect of Grinding—Approximately 100 mg of form II was vigorously ground to a fine powder with an agate pestle and mortar for 1 min. When compared with the starting material using PXRD, it was found that the grinding had not converted it form I.

Conclusions

This investigation has shown that the elusive orthorhombic polymorph of paracetamol (form II) can be crystallized from a supersaturated solution of IMS by nucleation with seeds of form II. Form II undergoes a solution-phase conversion to form I which has been monitored using light microscopy. It has been demonstrated that in order to ensure that form II is recovered in preference to form I, it is important to conduct the crystallization at a low temperature (0 °C) and to harvest the crystals within 1 h after the onset of nucleation. In addition, this investigation has highlighted the value of light microscopy in the early stages of a crystallization experiment to observe the microscale crystallization process so that a successful laboratory method can be developed.

The crystal structures of forms II and I have been determined at both room temperature and low temperature by X-ray crystallography.[27] These analyses confirm the structures that were published in 1974[1] and 1976,[3] respectively, and in addition, the low-temperature experiments improve the overall accuracy of the earlier determinations. Differences in the crystal structures between forms I and II are also reflected in their optical characteristics. Therefore, forms I and II can be differentiated by X-ray diffraction and optical crystallography.

The thermal behavior of solution grown form II precludes the use of differential scanning calorimetry as an analytical method to confirm its identity. This is because it slowly converts to form I in the solid state and melts as form I.

The compaction properties of form II have been determined, and when compared with those of form I, form II has been shown to undergo plastic deformation. This confirms that form II could be directly compressed into tablets. Observations on the relative stability of form II suggest that it does not readily convert to form I upon storage for several months or if it is mechanically stressed.

Although form II has been crystallized in small (several grams) quantities at the laboratory-scale, further studies would be needed to establish the feasibility of scaling-up the crystallization for commercial purposes.

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