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Studies on paracetamol crystals produced by growth in aqueous solutions

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Abstract

Paracetamol (P) crystals were grown from pure aqueous solutions containing varying concentrations (0.1–0.7% w/w of different additives. The additives were agar, gelatin, polyvinylpyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC). The presence of the additives significantly modified the crystal habit from polygonal prismatic habit without additive, to rectangular/rod-shaped with gelatin, triangular/wing-shaped crystals with agar and rod-shaped/cllipsoidal/spherical crystals with PVP. The P crystal size and yield also decreased and were concentration (additive) dependent. However, PVP and HPMC showed a very high degree of crystal growth inhibition producing microcrystals with very low yield. The presence of additives also reduced the residual moisture content of P crystals, while gelatin improved the crystal flow rate. Stronger P crystals are produced with gelatin as indicated by the force at major fracture, whereas crystallization in agar solutions resulted in weaker crystals. P crystals produced from growth in aqueous solutions with and without the additives, agar or gelatin (0.1–0.7% w/w), were compressed into compacts. Crystallization of P improved its compressibility producing compacts without capping. The presence of additives in the growth medium increased the hardness and disintegration times of the compacts and these properties were also concentration dependent. Compacts of P crystals produced from the agar system had much longer disintegration times than those with gelatin as additive. Dissolution rates, as determined from the t_{50} values, were in the order gelatin > no additive > agar.

Keywords: Paracetamol crystal; Additive effect; Crystal properties; Crystal habit; Crystal size; Crystal strength; Crystal flow rate; Compaction

1. Introduction

Growth of crystals from solvent is the most widely used method of crystal preparation. Crystallization by the solvent exchange method has long been used in organic chemistry for producing chemicals in a pure form (Packter, 1959). Crystal engineering of pharmaceuticals provides an enormous potential for preparing powdered materials with preferred chemical, physical and/or mechanical properties (Marshall and

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York, 1987). Several recent studies have used alternative solvents (Garti and Tibika, 1980; Berkovitch-Yellin, 1985; Marshall, 1986; Marshall and York, 1987) or low level additives (Al-Meshal and York, 1984; Chow et al., 1985a; Chow and Grant, 1988) in attempts to modify crystal properties.

Paracetamol (acetaminophen) is a widely used analgesic and antipyretic drug but with poor compaction behaviour. The nature of the water miscible solvent used in the solvent exchange method of crystallization has been reported to alter the habit of paracetamol crystals (Nath and Khalil, 1984). While Chow et al. (1985b) reported the modification of acetaminophen crystals from growth in aqueous solutions in the presence of *p*-acetoxyacetanilide – a proposed pro-drug and synthetic impurity of acetaminophen. The use of agar in crystallization has been reported by Wong and Aulton (1987) for growing single crystals of α-lactose monohydrate. It is hoped that the modification of paracetamol crystals would produce crystals with improved compaction properties.

In the present work, the effect of agar, gelatin, hydroxypropylmethyl cellulose (HPMC) and polyvinylpyrrolidone (PVP) in the growth medium is reported.

While few crystalline drugs, such as methanamine, aspirin, chlorides and bromides of sodium and potassium can be directly compressed into good tablets, others such as paracetamol, phenacetin and hexamine resist compression.

Paracetamol, a widely used analgesic and antipyretic drug, has been reported to exhibit poor compaction behaviour with the tablets capping and laminating extensively during decompression and ejection from the die (Danielson et al., 1983; Duncan-Hewitt and Weatherly, 1989).

According to York (1983), crystal habit (i.e., shape) and crystal imperfections (e.g., point defect and dislocations) arise during and/or after crystallization and could play important roles in the processability of pharmaceutical raw materials as well as the efficacy and performance of the final solid dosage forms. Thus, modification of the crystal structure of P to give crystals suitable for direct compression becomes highly necessary and desirable.

2. Materials and methods

2.1. Materials

Paracetamol (acetaminophen) was obtained from Sigma (Poole, U.K.). Gelatin (Fisons Scientific Apparatus Ltd, Loughborough, U.K.), Plasdone K-29–32, PVP (GAF Corp., New York) and Methocel-15, hydroxypropylmethyl cellulose (HPMC), obtained from Colorcon Ltd, Dow Chemical Co., U.K., were each used as additives.

2.2. Methods

2.2.1. Preparation of P crystals

Single crystals of P were produced by batch crystallization from water.

Paracetamol (15 g) was dissolved in 500 ml of distilled water at 70°C to form a clear solution. The solution was cooled by immersing the beaker containing the solution in a water bath containing warm water (45°C) to slow down the cooling rate of the solution. The crystals formed were allowed to grow for 24 h, filtered and dried in an oven at 70°C for 2 h and then packed in screw-capped amber bottles.

The above procedure was repeated with the required amount of additive added to the hot P solution before making up to volume (500 ml) and cooling.

Nutrient agar was added in the powder form and the solution stirred until the agar had dissolved; the required amounts of the respective aqueous solutions were used for the other additives. The additives were used at concentrations from 0.1 to 0.7% w/w. The P seed when used was added to the solution at 60°C just before nucleation.

2.2.2. Determination of physicochemical properties of P crystals

The melting point of the crystal was determined by using a Gallenkamp melting point apparatus. Size measurement of crystals was determined by optical microscopy, by measuring the size of 20 randomly sampled crystals from each batch using an optical microscope equipped with a calibrated eye-piece. The length (longest di-

mension), width (shortest dimension) and thickness of the crystals were measured whenever possible.

2.2.3. Preparation of compacts of P crystals

Crystals were ground using a pestle and mortar to achieve a similar particle size distribution for each batch. Compacts were prepared directly from the ground crystals, using 13 mm flat-faced punches on a hydraulic press (Beckman, U.K.). The compaction surfaces were lubricated with 4% w/v magnesium stearate in carbon tetrachloride solution before each compaction. The materials for each tablet (500 mg) was weighed and introduced into the die and compacted at a load of 800 kg. The compacts were then held under load for 30 s, released and stored in screw-capped sample bottle for 24 h before use to allow for possibly hardening and elastic recovery.

2.2.4. Evaluation of compacts

Compact hardness was measured by stressing a compact to failure between two parallel platerns, one of which was attached to a 50 N load cell. The other platern was driven at a rate of 1.47 mm/min, the output from the load cell was amplified and recorded. The mean of five determinations was taken as the batch hardness. The disintegration time of the compacts was determined by using the British Pharmacopoeia disin-

Table 1
Effect of additive type and concentration on the properties of paracetamol crystals

Concentration of additive (% w/v)		Crystal characteristics					
		Mean Size (mm)			Distance between wing tips (mm)	Shape	Angle
		Length	Width	Thickness			
None		4.28	3.12	2.2	–	polygonal	–
None	(s)	2.68	2.2	1.22	–	prismatic	–
0.1 agar		9.44	1.98	1.54	8.06	triangular	119.5
0.2		13.90	1.76	1.46	12.28	winged	130
0.5		25.90	1.83	1.93	22.9	winged	137
0.7		18.10	1.38	1.65	17.3	winged	136
0.1 agar	(s)	8.54	2.10	1.36	7.34	triangular	119
0.2	(s)	10.16	1.74	1.40	9.02	winged	122.5
0.5	(s)	8.76	1.23	1.13	7.78	winged	124.5
0.7	(s)	4.65	0.90	0.95	4.15	winged	119
0.1 gelatin		2.98	2.32	1.14	–	rectangular/	
0.2		2.64	1.44	1.44	–	block	
0.5		4.4	2.1	2.1	–	shaped	
0.7		1.98	0.4	0.24	–	rod	
0.1 HPMC		0.3	0.17			rods	
0.2		0.35	0.17			in	
0.5		0.38	0.18			clusters	
0.7		0.42	0.18				
0.1 PVP		0.86	0.16			rod	
0.5		0.88	0.2			rod	
0.7		0.9	0.3			rod	
0.1 PVP		mean diameter		0.5		rounded	
0.2		mean diameter		0.4		rounded	
0.5		mean diameter		0.4		rounded	
0.7		mean diameter		0.43		rounded	

(s) Seeded.

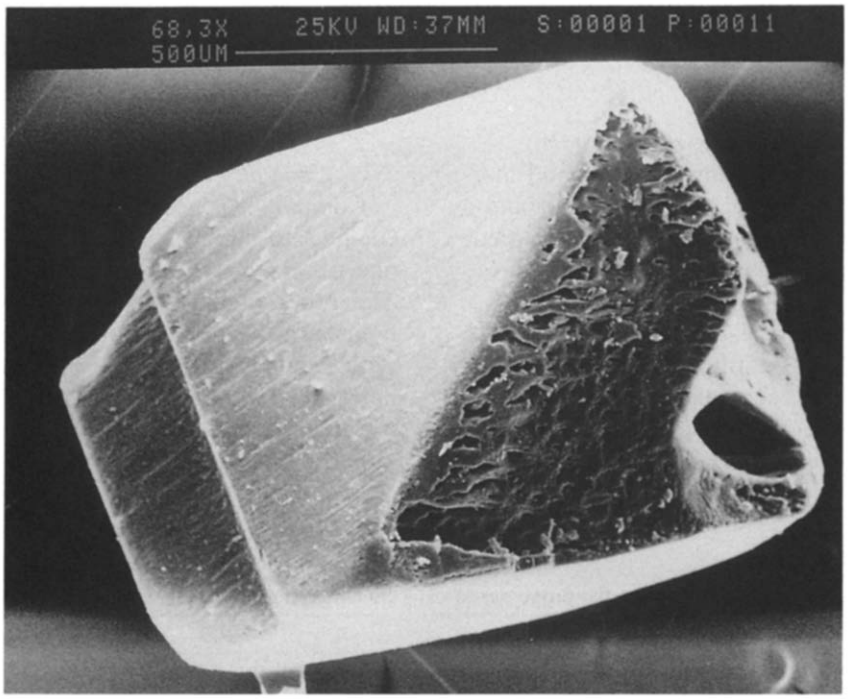

Fig. 1. Scanning electron micrograph of the surfaces of paracetamol crystals grown in water.

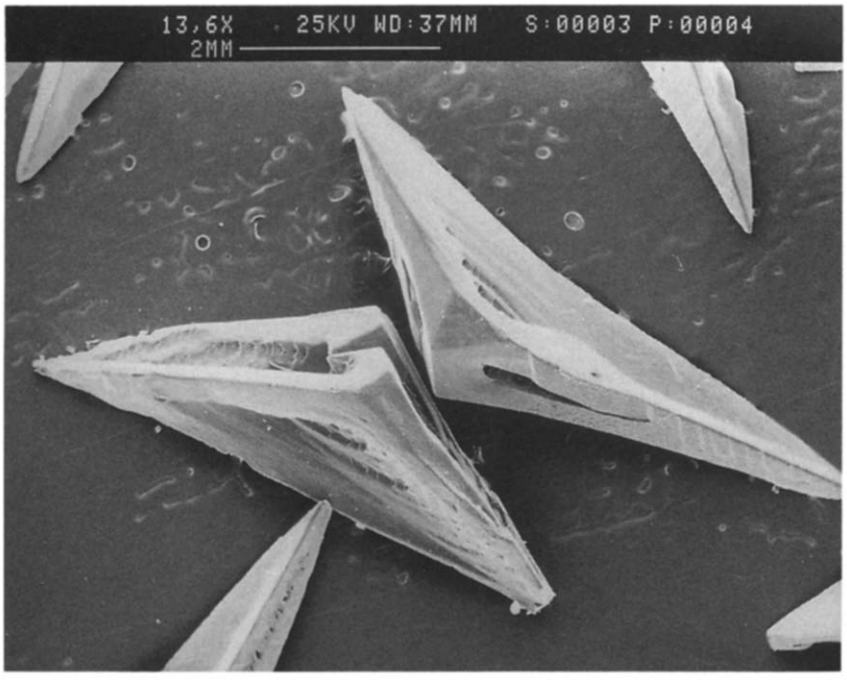

Fig. 2. Scanning electron micrograph of the surfaces of paracetamol crystals grown in water containing agar 0.2% w/v.

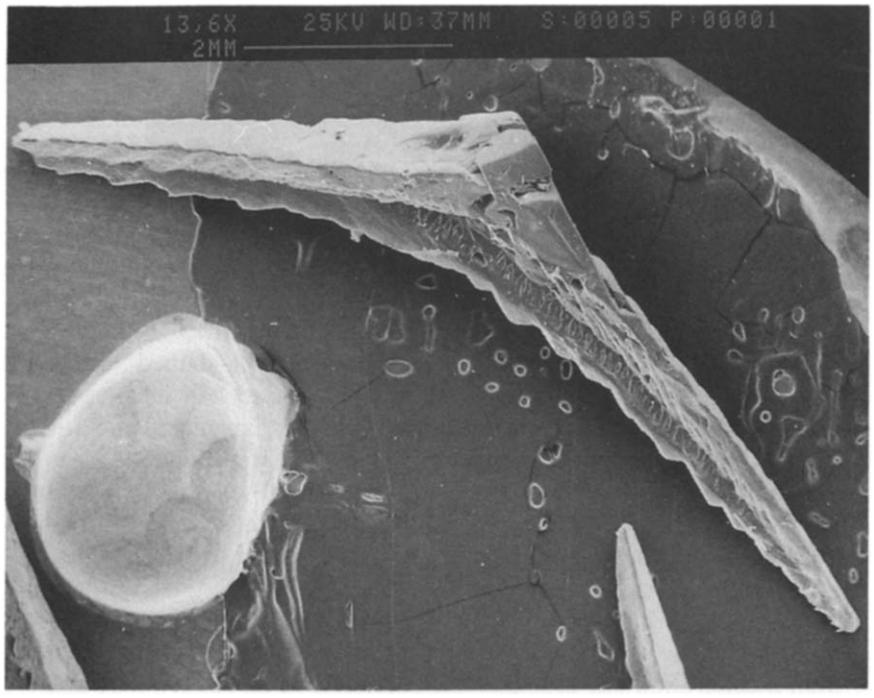

Fig. 3. Scanning electron micrograph of the surfaces of paracetamol crystals grown in water containing agar 0.5% w/v.

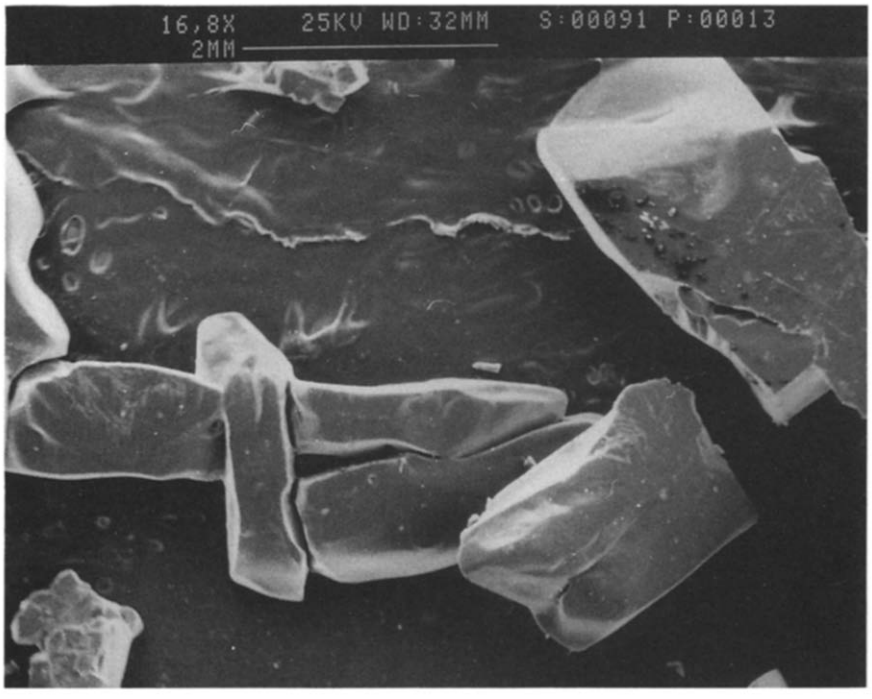

Fig. 4. Scanning electron micrograph of the surfaces of paracetamol crystals grown in water containing gelatin 0.5% w/v.

tegration apparatus (Erweka, Germany) on five individual compacts, with the mean taken as the disintegration time of the batch. A micrometer was used to measure the compact thickness.

The dissolution of the compacts was determined by using a Caleva 8ST dissolution apparatus with 1000 ml distilled water at 37 ± 0.2°C as the dissolution medium and a stirrer speed of 100 rpm. Samples (5 ml) were taken at fixed times for a period of 160 min and replaced by an equivalent amount of distilled water maintained at the same temperature. Samples were removed at a point halfway up the beaker beneath the liquid surface to minimise error due to possible variation in concentration of the solute within the vessel. The samples were diluted, passed through a Millipore/syringe assembly (Millipore 0.2 mm pore size, 25 mm diameter) and assayed for paracetamol by using a UV spectrophotometer (CE 202 Cecil Instruments Ltd, Cambridge, U.K.) at λ 243 nm. The concentration of the dissolved P was then determined from a calibration curve.

3. Results and discussion

3.1. Crystal morphology / size

The presence of the additives, which are pharmaceutical binders/hydrocolloids, in the solution growth medium affected the morphology and size of the P crystals (Table 1 and Fig. 1–4). These properties were also influenced by the concentration of the additives. The crystal shape which was originally block-shaped (or polygonal prismatic habit) from growth in aqueous solution (Fig. 1) assumed a triangular shape at 0.2% and a winged shape with well defined edges and groves 0.5% agar (Fig. 2, 3 and 6). The obtuse angle formed by the crystal wings and also in the triangular crystals was found to be between 119 and 137°, depending on the concentration of agar (Table 1) irrespective of the size of the crystals. Triangular crystals were also present in the P obtained from Sigma (Fig. 5). It should be noted that this obtuse

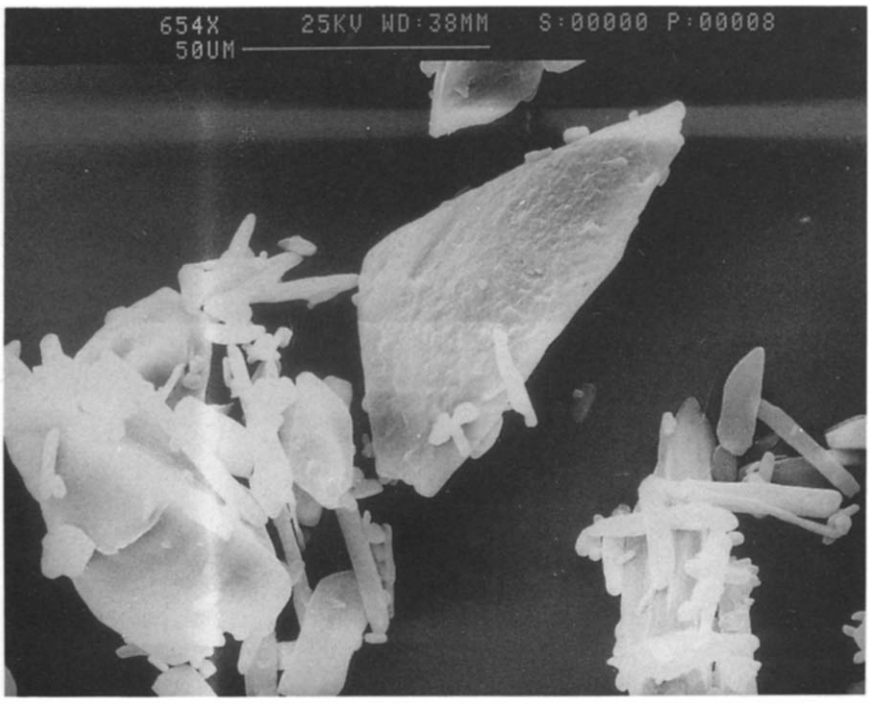

Fig. 5. Scanning electron micrograph of the surfaces of paracetamol crystals used as starting material.

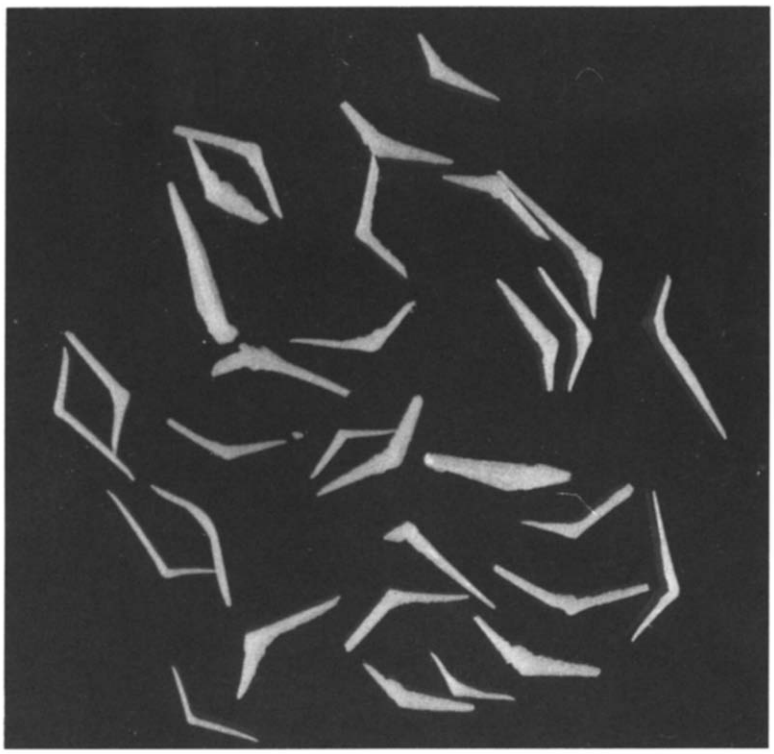

Fig. 6. Wing-shaped paracetamol crystals obtained by crystallization in the presence of agar 0.5%.

angle is also found within the polygonal-prismatic crystals.

In the presence of gelatin, the crystals became rectangular block/tabular to rod-shaped (at the highest concentration) with distinct edges (Fig. 4), whereas micro-crystals, which were mainly in clusters, were formed with HPMC or PVP with the crystals assuming the habit of a rod for HPMC and spherical, ellipsoidal/rod for PVP. In fact, these two binders/hydrocolloids, especially PVP, almost completely inhibited the growth of P crystals as can be seen by the values of both the crystal size (Table 1) and crystal yield (Table 2) produced in their presence.

The change in crystal shape can be explained on the basis of modified growth rates of crystal faces of different polarity, due to the nature of the hydrocolloids used, as well as their viscous effect on the medium. The preferential growth of certain crystal faces in the presence of agar would

Table 2
Crystal yield (in g) obtained with four polymeric additives

Additive concentration (% w/v)	Agar	Gelatin	HPMC	PVP	Seeded agar
0	8.5	8.5	8.5	8.5	5.3
0.1	4.35	6.75	3.4	0.15	2.6
0.2	5.5	6.9	2.6	0.1	3.8
0.5	6.0	6.95	2.8	0.15	5.7
0.7	5.05	5.25	0.75	0.5	3.7

have resulted in the triangular and finally wing-shaped crystals observed as the agar concentration is increased.

The size of P crystals generally decreased with the presence of gelatin, HPMC or PVP, with the last two showing a very high degree of crystal growth inhibition. However, with agar, comparison is difficult due to the difference in crystal habit. Nevertheless, there was elongation of the wings, thus producing longer crystals than the aqueous or water system alone, while crystal width and thickness were both reduced by the presence of agar (Table 1).

Increasing concentrations of the additives, however, increased the crystal size which reached a maximum at 0.5% w/v concentration and then decreased at 0.7% w/v for both agar and gelatin. This concentration (0.5% w/v) also produced the highest crystal yield for these two additives (Table 2). Increasing concentrations of the additives had variable effects on the crystal yield.

Similar inhibition of crystal growth of some pharmaceutical drugs by PVP has been reported by Simonelli et al. (1970) and Nath and Nalwade (1987).

The effect of heterogeneous nucleation (seeding) produced smaller crystals (Table 1). Seeds from both the agar system and water-system were added separately to saturated paracetamol solutions set in agar (0.5% w/v) system. The type of seeds used did not affect the shape/type of crystals produced.

The surfaces of the P crystals using SEM were seen to be smooth on some sides and rough in some (Fig. 1–4) with some well defined groves, ridges and serrated edges in the triangular and wing-shaped crystals (Fig. 2 and 3).

The X-ray powder diffraction performed on crystals (two) from the agar system showed both the monoclinic and orthorhombic forms of P crystals, while a crystal from the gelatin-system was found to be monoclinic. Both the monoclinic and orthorhombic forms of P crystals have been reported (Haisa et al., 1974; Welton and McCarthy, 1988).

3.2. Moisture content

The crystals formed in the absence of additive, had a light, pink colour while white crystals were produced with the additives. Determination of the moisture contents showed that the moisture content of the crystals from the water system alone was twice (0.6%) that of the gelatin (0.2–0.3%) or agar (0.3%) system crystals. It is possible that the water-system crystals, probably en-

Table 3
Properties of paracetamol crystals and their compacts

[Additive] (% w/v)	Properties				
	Crystals		Compacts		
	$F_{maj.}$ (kg force)	Flow rate (g/s)	Mean hardness (kg force)	Mean thickness (mm)	Disintegration time (h)
0	0.572	2.5	0.70	3.34	1.00
Agar					
0.1	0.262	[b]	0.78	3.35	1.38
0.2	0.370	[b]	1.02	3.39	1.58
0.5	0.894	[b]	1.12	3.38	2.53
0.7	0.520	[b]	1.01	3.37	2.00
Gelatin					
0.1	1.268	3.3	1.19	3.32	1.36
0.2	1.678	4.0	1.21	3.34	1.33
0.5	2.032	4.8	1.28	3.37	1.31
0.7	[a]	5.0	1.09	3.35	0.98

[a] Cystals too small to measure.
[b] No flow due to crystal shape.

trapped more water molecules into their structure which gave a pinkish colour on refraction of light rays. The viscous/gel-like nature of the other systems could have reduced their affinity for water molecules.

3.3. Flow rate

The flow rate of P crystals was increased by the presence of gelatin in the growth solution medium (Table 3). The shape of crystals from the agar system (wing-shaped) made it impossible for this test to be performed on their crystals. The increased flow rate of P crystals from the gelatin system is probably due to the smaller size of the crystals.

3.4. The force at major fracture (Fmaj.) of crystals

The $F_{maj.}$ results of the P crystals are listed in Table 3. For the gelatin-system crystals, the presence of gelatin increased the force required to produce fracture in the crystals, that is, the crystal strength. This ($F_{maj.}$) increased with increase in concentration of gelatin, whereas for the agar-system crystals, the strength ($F_{maj.}$) was decreased by the presence of agar in the growth medium except at the 0.5% w/v agar concentration which also gave the optimum crystal size. This test could not be performed on crystals of PVP and HPMC systems because of their micro-size. Thus, it can be seen that the presence of gelatin in the growth medium produced stronger crystals, while agar weakened the crystal except at 0.5% w/v concentration at which maximum crystal growth was obtained.

These observed effects may be due to the differences in the shape and crystal imperfections of the crystals. Thus, the block/polygonal prismatic/rectangular forms of P crystals are stronger than the triangular/winged forms.

3.5. Properties of compacts

The properties of the compacts of P crystals and the relevant crystal properties are given in Table 3. The various crystal batches produced compacts without capping. An attempt made to prepare compacts from the original P crystalline powder produced compacts which were prone to capping and lamination giving a 45% capping for the sample. Thus, the degree of capping of P tablets during compression is reduced by using the ground P crystals.

The presence of additives (agar and gelatin) in the growth medium of P crystals affected the properties of their compacts. The compact hardness generally increased in the presence of these additives and with increasing concentration. The increasing compact hardness with additive concentration is also consistent with force at major fracture, $F_{maj.}$, of the crystal, which also tends to increase with increasing additive concentration.

The disintegration time of the compact is also generally increased by the presence of both the agar and the gelatin in the growth medium (Table 3). Irrespective of the additive concentration, compacts of crystals produced from the agar systems are thicker and with longer disintegration times despite their much lower crystal fracture force, $F_{maj.}$, than their gelatin counterparts (Table 3). Thus, other factors such as differences in crystal shape/habit, differences in polarity of the

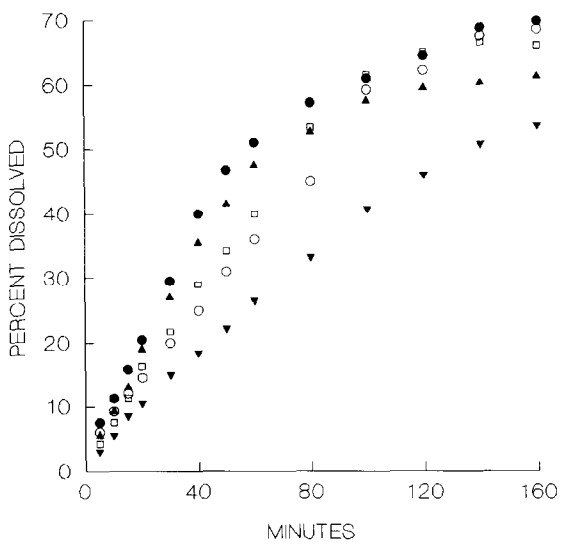

Fig. 7. Intrinsic dissolution time profiles for paracetamol compacts prepared from crystals grown in the presence of agar. (●) Water, (▲) 0.1% agar, (□) 0.2% agar, (▼) 0.5% agar, (○) 0.7% agar.

different crystal surfaces brought about by the differential inhibition of growth at the different faces by agar and gelatin, rather than the crystal strength could account for the differences in their disintegration times.

The intrinsic dissolution time profiles of the compacts produced from the various crystal batches with and without gelatin or agar in their growth medium are shown in Fig. 1 and 2. The results showed a marked difference in dissolution behaviour of the compacts of P crystals. The amount of P released is greatly reduced by the presence of agar in the growth medium (Fig. 7) while gelatin showed an opposite effect, giving compacts with slightly higher dissolution rates than compacts from the water-system crystal, i.e., without any additive (Fig. 8). These results are consistent with the t_{50} results – i.e., the time taken for 50% of the drug, P, to be released as shown in Table 4.

Increasing concentrations of the additive also have variable effects on the t_{50} of the compacts. While t_{50} decreased from 56 to 48 min for the gelatin system compacts – a trend observed also for the compact disintegration time, increase in t_{50} with additive concentration was observed for the agar-system compacts, ranging from 68 to 138 min with the 0.5% w/v concentration giving the maximum value.

Table 4
Effect of additive concentration on t_{50} for compacts of paracetamol

Additive concentration (% w/v)	t_{50} (min)	
	Agar	Gelatin
0	58	58
0.1	68	56
0.2	75	54
0.5	138	52
0.7	90	48.5

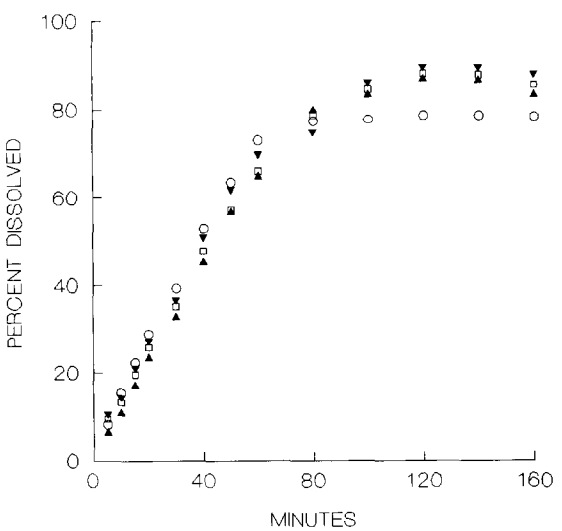

Fig. 8. Intrinsic dissolution time profiles for paracetamol compacts prepared from crystals grown in the presence of gelatin. (▲) 0.1% gelatin, (□) 0.2% gelatin, (▼) 0.5% gelatin, (○) 0.7% gelatin.

Thus, compacts produced from the blocked or polygonal prismatic habit, or rectangular/rod-like crystals from the water and gelatin – systems consistently demonstrate much higher intrinsic dissolution rates and lower t_{50} values than those of the wing-shaped/triangular crystals obtained from the agar system.

Crystal habit and closely related properties, such as anisotropy, defects, and hydrodynamic conditions during dissolution are known to influence the dissolution time profile (of both the crystals and their tablets). These differences in dissolution rates have been reported for nickel sulphate α-hexahydrate (Burt and Mitchell, 1979, 1980), acetylsalicylic acid (Watanabe et al., 1982), paracetamol crystals and tablets (Nath and Khalil, 1984; Chow et al., 1985a,b). The observed effects have been attributed to the different intrinsic dissolution rates of the different crystal faces whose relative areas differ from habit to habit and also on their interaction with the solvent involved. With water as the solvent, the polar crystal faces will tend to dissolve faster than the less polar ones.

Thus, for the compacts, the overall dissolution rate is a function of the relative contribution of the individual faces possessing different polarities within the compact. Since the difference in surface area of the compacts can be said to be very

little or negligible, then the large differences in their dissolution rates may probably be due to differences in their crystal habit and shape related hydrodynamic conditions during dissolution. The crystal water content may also be a contributing factor. The residual moisture content of the crystals is affected by the crystallization conditions and was found to be in the order of water $\gg$ gelatin > agar.

While Chow and Grant (1988) found lower water contents of crystals to favour faster dissolution rate which is consistent with the results of the gelatin system compacts, compacts of agar system with crystals of lower moisture content had much lower dissolution rates. This implies that there is a relative dominance of other factors such as the formation of less polar crystal faces brought about by differential inhibition of growth at different faces by agar and hence less favourable hydrodynamic conditions for aqueous dissolution. These factors are also concentration related as implied from the compact dissolution rates and t_{50}.

It is possible that the presence of agar in the crystal growth medium may block the growth of the higher energy sites of the crystal surfaces, making them less available for active dissolution as suggested by Chow et al. (1985a,b). This may have resulted in the production of the unique wing-shaped/triangular P crystals by this additive.

Tablets of P crystals, made from crystals obtained using the solvent exchange method of crystallization, prepared by the wet granulation method and by direct compression with diluent and lubricant have been reported to show differences in their compressibility and dissolution behaviour (Nath and Khalil, 1984).

The flow rate of P crystals increased with the presence of gelatin in the growth medium and with increasing gelatin concentration (Table 3). Many drugs are not directly compressible because of their poor flow properties and compressibility. Thus crystal engineering of pharmaceuticals may serve to render a drug substance free-flowing and improve the compressibility of the drug as observed in the improved flow rate of P crystals in the presence of gelatin.

4. Conclusion

The presence of additives in the aqueous growth medium of paracetamol modified significantly the crystal properties.

The crystal shape changed from polygonal-prismatic without an additive to rectangular/rod-shaped with gelatin, triangular/wing-shaped crystals with agar or rod-shaped/ellipsoidal/spherical with PVP.

The crystal size and yield also decreased, with PVP and HPMC showing a very high degree of crystal growth inhibition giving microcrystals with very low yield. The residual moisture content of the P crystals was reduced by the additives, while gelatin improved the crystal flow rate.

The presence of agar generally weakened the P crystals, as indicated by the force at major fracture; stronger P crystals were produced with gelatin. Crystallization of paracetamol improved its compressibility producting compacts without capping.

The presence of additive (agar or gelatin) in the growth medium of paracetamol crystals affected the properties of their compacts. The compact hardness and disintegration times increased and these were concentration dependent with the compacts of the agar system having much longer disintegration times.

While faster drug release was obtained from compacts of P crystals in the gelatin system, those of the agar system gave slower drug release than compacts of P crystals grown in the absence of additive.

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