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Highly compressible paracetamol: I: crystallization and characterization

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Abstract

It was found that polyvinylpyrrolidone (PVP) is an effective additive during crystallization of paracetamol and significantly influenced the crystallization and crystal habit of paracetamol. These effects were attributed to adsorption of PVP onto the surfaces of growing crystals. It was found that the higher molecular weights of PVP (PVP 10 000 and PVP 50 000) were more effective additives than lower molecular weight PVP (PVP 2000). Paracetamol particles obtained in the presence of 0.5% w/v of PVP 10 000 or PVP 50 000 had near spherical structure and consisted of numerous rod-shaped microcrystals which had agglomerated together. Particles obtained in the presence of PVP 2000 consisted of fewer microcrystals. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XPD) experiments showed that paracetamol particles, crystallized in the presence of PVP, did not undergo structural modifications. By increasing the molecular weight and/or the concentration of PVP in the crystallization medium the amount of PVP incorporated into the paracetamol particles increased. The maximum amount of PVP in the particles was 4.32% w/w.

Keywords: Paracetamol; Polyvinylpyrrolidone; Crystallization; Crystal habit; Crystal structure; Differential scanning calorimetry; X-ray powder diffraction

1. Introduction

It is well known that paracetamol exhibits poor compressibility during compaction, often resulting in weak and unacceptable tablets with a high tendency to cap (Krycer et al., 1982). It is desirable to produce drug crystals with improved compaction properties and suitable for direct compression. There are a limited number of examples of attempts to deliberately alter the physico-mechanical properties of crystals by alternative crystallization procedures. In recent years some attempts have been made to modify the properties of paracetamol crystals using different crystallization techniques in order to improve the

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compaction properties of unmodified crystals. Fachaux et al. (1993) prepared a sintered form of paracetamol crystals by crystallization from dioxane followed by a controlled drying process. These crystals induced plasticity and improved the compressibility of paracetamol. One limitation of this form of this method was the difficulty in the complete elimination of residual solvent from the final product. Di Martino et al. (1996) prepared a polymorph of paracetamol (orthorhombic form) by melting the drug at 170°C in an anhydrous nitrogen atmosphere. After slow cooling to room temperature, the solidified material was ground. The obtained crystals exhibited better compressibility than untreated crystals. The disadvantage of this work was that a high temperature was required and therefore the atmosphere and time have to be strictly controlled. Abdelillah et al. (1995) prepared agglomerated particles of paracetamol using a spherical crystallization technique. The agglomerated particles were obtained by adding a paracetamol solution in tetrahydrofuran into either hexane or a hexane/chloroform mixture. The agglomerated particles exhibited good compressibility compared to untreated paracetamol. The most obvious limitation of this method was that a relatively high tetrahydrofuran content remained in the final agglomerates even after drying.

One of the most common causes of habit modification is the presence of impurities in the crystallizing solution. The presence of small amounts of an effective additive in the crystallization medium can dramatically change the crystal size and shape (Davey, 1982). The additives used in crystallization procedures may be classified into several groups: Surface active agents, low molecular weight organic or inorganic substances, long chain polymeric materials and proteinaceous substances (Mullin, 1993). There are several reports of attempts to change the crystal habit of a particular substance in the presence of additives during crystallization processes. For example, the crystal habit of adipic acid was modified in the presence of anionic or cationic surfactants (Michaels & Colville, 1960), or in the presence of alkanols or alkanoic acids (Fairbrother & Grant, 1978, 1979). Habit modification of paracetamol crystals in the presence of *p*-acetoxy-acetanillide, or in the presence of agar or gelatin was reported by Chow et al. (1985) and Femi-Oyewo and Spring (1994), respectively. Mackellar et al. (1994a,b) demonstrated that the use of poloxamer 188 (a surfactant) during crystallization of ethyl *p*-hydroxybenzene, modified the size and habit of the obtained crystals.

Those additives which influence the crystallization processes are those that can be adsorbed on to the crystal surfaces (Davey, 1982). The degree of adsorption between additives and the crystal surfaces depends on their chemical and structural properties such as the presence of anionic or cationic groups, or the possibility of the formation of hydrogen bonds (Khamskii, 1976; Davey, 1982). It has been reported that polyvinylpyrrolidone (PVP) can interact with paracetamol in their aqueous solution and that they can bind together via formation of hydrogen bonding (Garekani, 1996; Sekikawa et al., 1979; Horn & Ditter, 1982). It has been also demonstrated that PVP is a strong crystal growth inhibitor for paracetamol by adsorption on to the surfaces of paracetamol crystals (Garekani, 1996; Ziller & Rupprecht, 1988).

The crystallization of paracetamol by a 'watering-out' method from its ethanolic solution at low temperature caused marked modification to the crystal habit and produced thin plate-like crystals (Garekani et al., 1999). However these crystals did not exhibit any improvement in their compaction properties compared to untreated paracetamol. The aim of this work was to investigate the effects of small amounts of different grades of PVP during crystallization of paracetamol, by the watering-out method.

2. Materials and methods

Paracetamol powder, was obtained from Sterling Organics, Northumberland,UK. Absolute ethanol BP, containing not less than 99.5% v/v of C_2H_5OH, was obtained from Hayman Ltd, Witham, Essex, UK. Soluble grades of polyvinylpyrrolidone (PVP) were obtained from BASF, Aktiengesellscaft, 67056 Ludwigshafen,

Germany, as trade names Kollidon 12PF, Kollidon 17PF and Kollidon 30 with average molecular weights of 2000, 10 000 and 50 000, respectively. Iodine, potassium iodide and citric acid anhydrous, were obtained from BDH Chemicals Ltd, Poole, UK.

2.1. Crystallization procedures

The crystallization process used in this study was similar to method which was introduced in previous study as the watering-out method (Garekani et al., 1999). Samples of paracetamol (5 g) were dissolved in 12 ml of ethanol at 75°C. The temperature of the solutions were allowed to fall to 65°C. Then the solutions were added rapidly to 50 ml quantities of cold water at 3°C containing 0, 0.1, 0.3 or 0.5% w/v PVP of molecular weights of 2000, 10 000 or 50 000. The resultant solutions were thoroughly mixed with a glass rod and maintained at 3 ± 1°C in an ice-water bath with no agitation for 5 min. After 10 min, the precipitated crystals were collected by filtration, using a sintered glass funnel No. 3 under vacuum. The crystals were spread on glass petri dishes and dried for 24 h at 55°C. The dried crystals were stored in a desiccator, over silica gel, at room temperature before use.

2.2. Quantitive determination of PVP in crystals

The amount of PVP present in the paracetamol crystals was determined by photometric analysis (using a Philips spectrophotometer, Cambridge, UK) of the PVP-iodine complex (Levy & Fergus, 1953). 30 mg of each sample was dissolved in 50 ml of water and then mixed with 25 ml of aqueous 0.2 M citric acid solution and 10 ml of 0.006 N iodine solution (0.81 g of freshly sublimed iodine and 1.44 g of potassium iodide dissolved in 1000 ml of water). The intensity of the colour of the solution, which depended on the concentration of PVP-iodine complex, was measured by determination of the absorbance of solution against a blank solution (50 ml water + 25 ml of 0.2 M citric acid + 10 ml 0.006 N iodine solution) at 470 nm. The PVP contents were determined from calibration curves previously obtained for the relevant grades of PVP. The colour intensity was dependent on the molecular weight of PVP (Levy & Fergus, 1953), for this reason calibration curves were produced for each grades of PVP.

2.3. Scanning electron microscopy

Electron-micrographs of crystals were obtained using a scanning electron microscope (Jeol model JSM T200, Tokyo, Japan). The specimens were mounted on a metal stub with double sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation.

2.4. Particle size measurements

Particle size of crystals (diameters of the agglomerates) were measured using the scanning electron-micrographs. Each determination was carried out on a minimum of 60 crystals and their distribution was reported.

2.5. Differential scanning calorimetry (DSC)

A differential scanning calorimeter model DSC7 (Perkin Elmer, Baconsfield, UK), controlled by a Perkin Elmer TAC7, was used. The equipment was calibrated using indium and zinc. Paracetamol samples (2–4 mg) were heated at 10°C min^{-1} in crimped aluminium pans under nitrogen atmosphere. The onsets of the melting points and enthalpies of fusion of samples were automatically calculated by the instrument.

2.6. X-ray powder diffraction (XPD)

X-ray diffraction spectra of paracetamol samples were obtained using a Phillips PW 1729 X-ray generator fixed with PW 1710 diffractometer (Phillips, Almelo, Netherland). The cavity of the metal sample holder was filled with the ground sample powder and then smoothed with a spatula. Scanning rate of 0.04° 2θ s^{-1} over the range of 10° to 70° 2θ was used to produce each spectrum.

3. Results and discussion

Following the addition of the ethanolic solution of paracetamol to cold water containing different concentrations of PVP, the time taken for appearance of the first visible particles (induction time) depended on the molecular weight and/or concentration of PVP in the solution (Fig. 1). With increasing molecular weight and/or concentration of PVP, the induction time increased. In the absence of PVP, crystals were observed within 15–20 s, whilst in the presence of 0.5% w/v of PVP 50000 this time was 115 s.

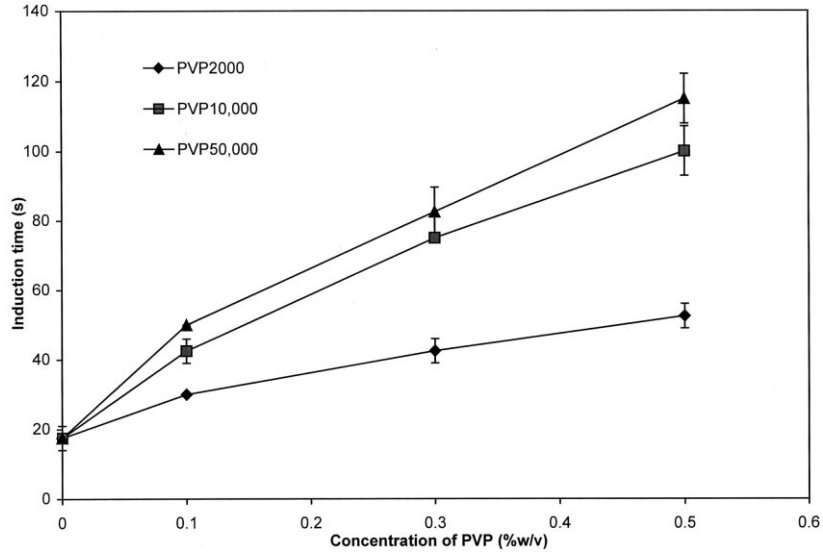


Fig. 1. Induction time of crystallization as a function of concentration of: PVP2000, PVP10 000 or PVP50 000 ($n = 3$; $\pm$SD).

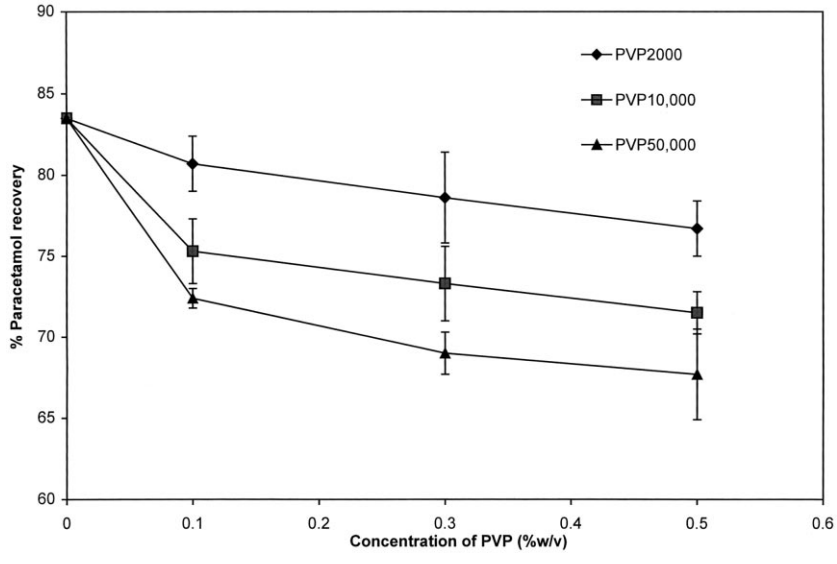


Fig. 2. Paracetamol recovery as a function of concentration of: PVP2000, PVP 10 000 or PVP50 000 ($n = 3$; $\pm$SD).

Table 1
The percentage (%w/w) of PVP adsorbed onto paracetamol particles crystallized in the presence of different concentrations of various grades of PVP ($n = 3$; $\pm$ SD)

Concentration of PVP incrystallisation medium (%w/w)	Amount of adsorbed PVP onto paracetamol crystals (%w/w)		
	PVP 2000	PVP 10 000	PVP 50 000
0.1	0.55 ± 0.05	0.89 ± 0.05	0.98 ± 0.04
0.3	2.13 ± 0.09	3.21 ± 0.07	3.48 ± 0.07
0.5	3.23 ± 0.14	3.96 ± 0.06	4.32 ± 0.19

The % recovery of paracetamol during crystallization in the presence of PVP is illustrated in Fig. 2. The % recovery of paracetamol decreased as the molecular weight and/or the concentration of PVP in the crystallization medium increased. The% recovery in the absence of PVP was 83.5% whilst in the presence of 0.5% w/v of PVP 50 000 was 67.5%.

The amount of PVP taken up by paracetamol particles crystallized from media containing different concentrations of various grades of PVP is presented in Table 1. According to these results, by increasing the molecular weight and/or the concentration of PVP in the crystallization medium, the amount of PVP adsorbed onto the particles increased.

Fig. 3 shows paracetamol particles crystallized in the absence of PVP. These crystals are very thin and flaky. These crystals were also described in our previous paper (Garekani et al., 1999). Figs. 4 and 5 and Fig. 6 illustrate paracetamol particles crystallized from media containing different amounts of PVP 2000, PVP 10 000 or PVP 50 000, respectively. These figures clearly indicate that the use of PVP in the crystallization media, had a major effect on the morphology of paracetamol crystals as compared to particles obtained in the absence of PVP. Paracetamol crystals obtained in absence of PVP were very thin and flaky, whereas those obtained in the presence of 0.3 or 0.5% w/v of PVP 10 000 or PVP 50 000 were near spherical in structure (Fig. 5b, c and Fig. 6b, c). With higher magnification, the spherical particles obtained in the presence of 0.5% w/v of PVP 10 000 or PVP 50 000 (Fig. 7b and c) seem to be agglomerates (clusters) of numerous fine finger-like (rod-shape) microcrystals which had stuck together. The particles obtained in the presence of PVP 2000 even at highest concentration of PVP (0.5% w/v) consisted of a fewer microcrystals which had stuck together (Fig. 7a).

It has been reported that effective additives influence the crystallization process and produce crystals of a different shape to those formed from a pure solution. Furthermore, these additives increase the induction time and also reduce the crystal growth and yield. These effects are attributed to the adsorption of additives onto the surfaces of growing crystals (Davey, 1982). In the present study the observed changes in crystal habit of paracetamol (Figs. 3–5 and Fig. 6), the delay in the appearance of crystals (Fig. 1), reduction in the yield (Fig. 2) and sorption of PVP by paracetamol crystals (Table 1), are indicative that PVP is an effective additive during the crystallization of paracetamol. It appeared that the highest

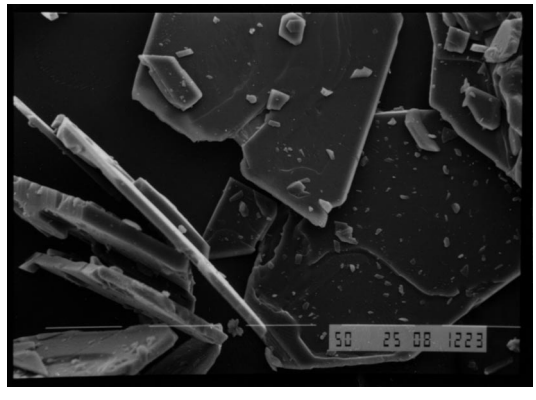


Fig. 3. Micrographs of paracetamol particles crystallized by watering-out method in absence of PVP (magnification × 200).

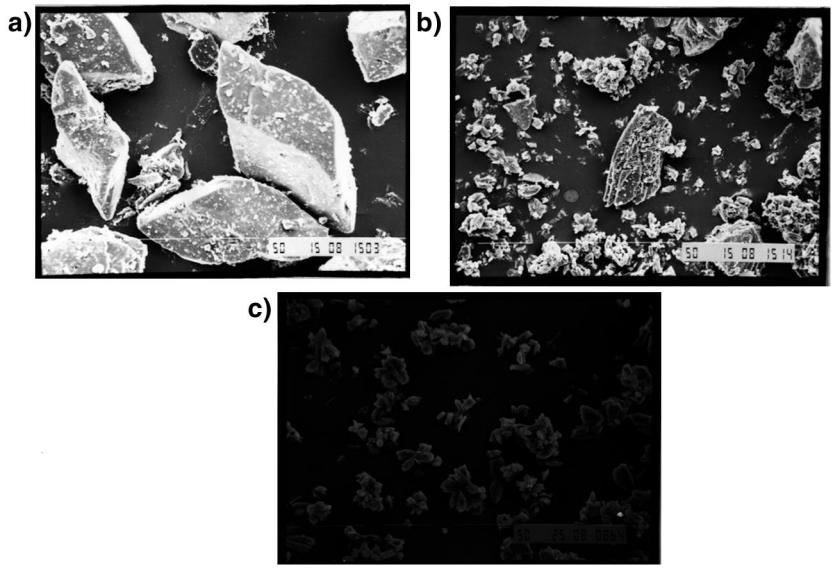


Fig. 4. Micrographs of paracetamol particles crystallized in the presence of: (a) 0.1; (b) 0.3 or (c) 0.5% w/v of PVP2000 (magnification × 200).

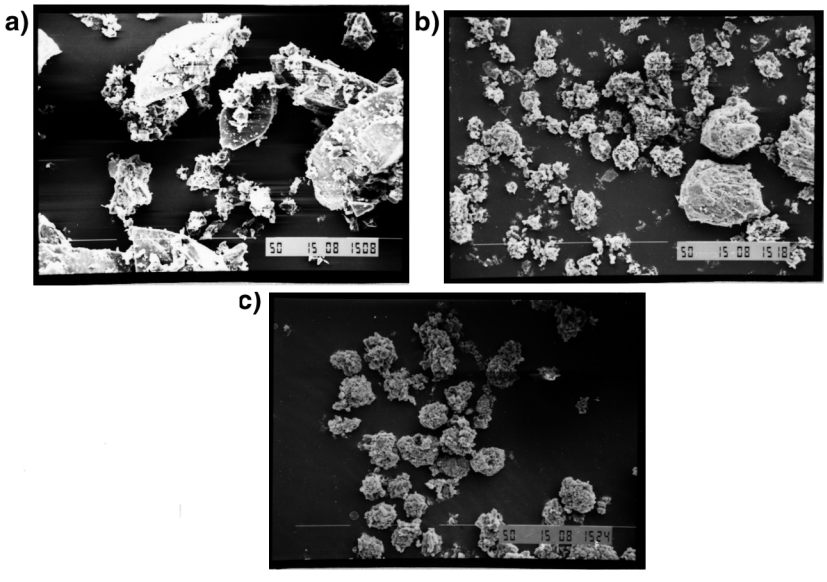


Fig. 5. Micrographs of paracetamol particles crystallized in the presence of: (a) 0.1; (b) 0.3 or (c) 0.5% w/v of PVP10 000 (magnification × 200).

molecular weight of PVP was the most effective additive. The relative effectiveness of the three grades of PVP, as considered by the parameters mentioned above, followed the order PVP 50 000 > PVP 10 000 > PVP 2000. The observed effects of PVP during the crystallization of paracetamol are attributed to the adsorption of PVP onto the surfaces of growing crystals. Uptake of

PVP by paracetamol particles (Table 1) is also indicative of adsorption of PVP onto the paracetamol particles. It has been suggested that PVP binds to paracetamol via hydrogen bonding (Garekani, 1996). It has been reported that PVP has a strong inhibitory effect on the crystallization of paracetamol from its solution which was attributed to the its adsorption onto the paracetamol nuclei (Garekani, 1996; Ziller & Rupprecht, 1988).

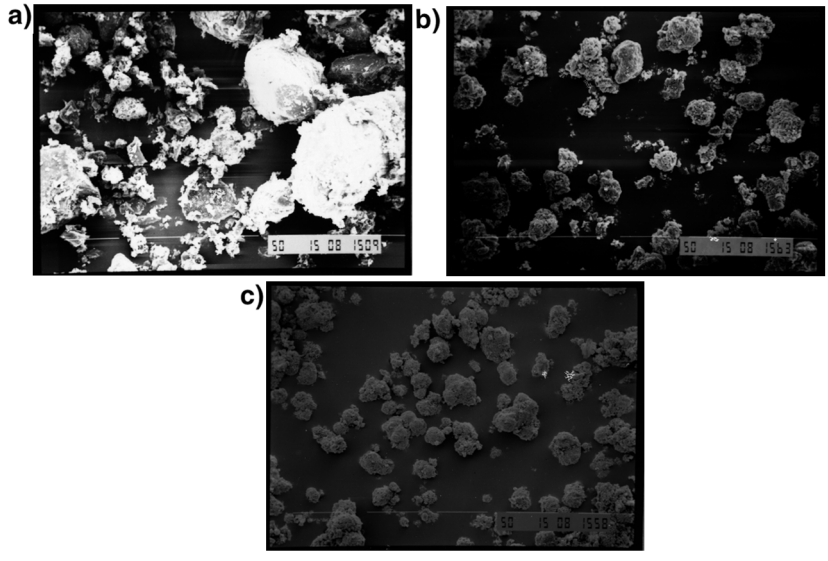


Fig. 6. Micrographs of paracetamol particles crystallized in the presence of: (a) 0.1; (b) 0.3 or (c) 0.5% w/v of PVP50 000 (magnification × 200).

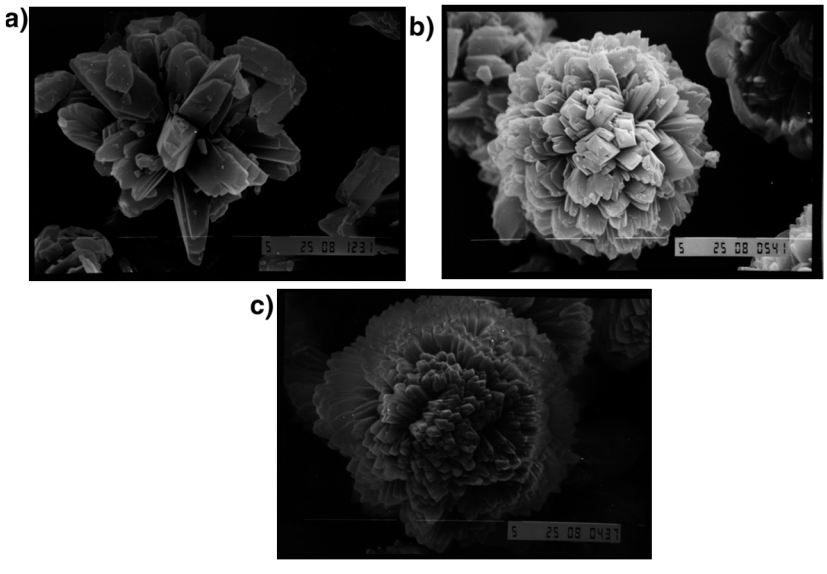


Fig. 7. Micrographs of paracetamol particles crystallized from media containing 0.5%w/v of: (a) PVP 2000; (b) PVP10 000 or (c) PVP50 000 (magnification × 1500).

Table 2
The onset of melting point (T_m) and enthalpy of fusion (ΔH_f) for untreated paracetamol and particles crystallized in the presence of 0.5% w/v of different grades of PVP ($n = 3$; $\pm$ SD)

Paracetamol crystallized in presence of PVP	Onset of $T_m \pm$ SD (°C)	$\Delta H_f \pm$ SD (J g^{-1})
2000	171.4 ± 0.3	155.1 ± 3.3
10 000	171.2 ± 0.3	148.5 ± 5.7
50 000	170.9 ± 0.2	138.3 ± 4.3
Untreated paracetamol	171.6 ± 0.2	176.1 ± 2.2

Table 3
The onset of melting point (T_m) and enthalpy of fusion (ΔH_f) for physical mixtures of paracetamol and PVP of molecular weight 50 000 ($n = 3$; $\pm$ SD)

Concentration of PVP (%w/w)	Onset of $T_m \pm$ SD (°C)	$\Delta H_f \pm$ SD (J g^{-1})
Pure paracetamol	171.6 ± 0.2	176.1 ± 2.2
3	171.5 ± 0.2	150.0 ± 2.4
5	170.9 ± 0.1	134.6 ± 4.5
7	170.8 ± 0.7	126.1 ± 3.2
10	170.5 ± 0.3	104.7 ± 3.6

Chow and Hsia (1991), Gordon and Chow (1992) and Chow et al. (1995) reported that crystallization of phenytoin in the presence of three different ester homologues of diphenylhydantoin changed the crystal habit and caused a drastic reduction in crystal yield. These effects were attributed to the adsorption of additive onto the crystal faces of phenytoin. It was also suggested that the most effective additive was the one which changed habit at the lowest concentration and caused the most reduction in crystal yield. It has been reported that crystallization of paracetamol from water in the presence of agar or gelatin, changed the crystal habit of paracetamol and caused a decrease in crystal yield (Femi-Oyewo & Spring, 1994).

The size distribution of diameter of agglomerated particles crystallized in the presence of 0.5% w/v of different grades of PVP is illustrated in Fig. 8. The diameter of majority of these particles was between 10–40 μm. Fig. 7b and c indicate that each agglomerated particle crystallized in the presence of 0.5% w/v of PVP 10 000 or 50 000 consisted of hundreds of rod-shaped microcrystals which had agglomerated together. The thickness of these microcrystals was about 1–2 μm.

The X-ray powder diffraction spectra of untreated paracetamol and samples crystallized from media containing 0.5% w/v of different grades of PVP (Fig. 9) exhibited essentially similar diffraction patterns (2θ values), suggesting that particles crystallized in the presence of PVP did not undergo structural modifications. However, the differences in the relative intensities of their peaks, may be attributed to differences in the crystal sizes and habits of the samples (El-Said, 1995; Marshall & York, 1989).

Differential scanning calorimetry of untreated paracetamol and samples crystallized from media containing 0.5% w/v of different grades of PVP were carried out. The mean values of the onsets of melting points and enthalpies of fusion for untreated paracetamol and samples obtained from media containing different grades of PVP are presented in Table 2. All samples showed a sharp melting point with flat baseline which indicated that no events such as hydration, solvation or polymorphic transition had occurred during crystallization of the particles. However, Table 2 indicates that the onsets of melting point and enthalpies of fusion of paracetamol crystallized in the presence of PVP decreased by 0.2–0.7°C and 21–38 J g^{-1}, as compared to the untreated samples. These reductions in enthalpy of fusion and melting point onset, may be attributed to the presence of amorphous regions in the crystals, or due to weakening and disruption of the crystal lattice and order, or in this case, may be attributed to an interaction between paracetamol and PVP in the crystals.

The DSC was also carried out for physical mixtures of paracetamol and PVP and their melting point onsets and enthalpies of fusion are given in Table 3. These data (Table 3) clearly indicated that the enthalpies of fusion of paracetamol decreased as the proportion of PVP in the physical mixtures increased. According to Table 1 the crystals of paracetamol formed in the presence of PVP 50 000 contained 4.3% of PVP. The values of enthalpy and onset temperature for these particles

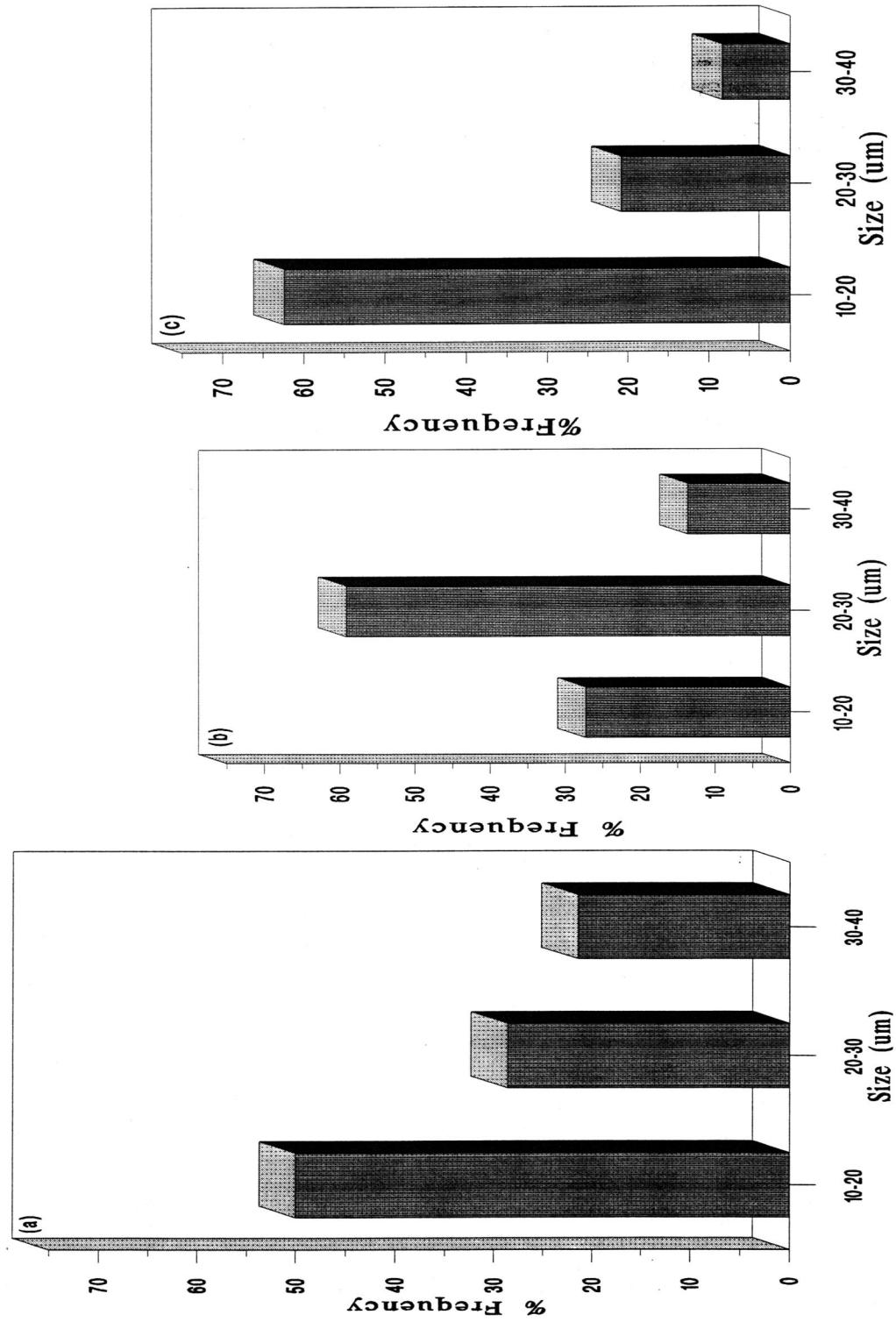


Fig. 8. The size distribution of diameter of agglomerated particles crystallized in the presence of 0.5% w/v of: (a) PVP2000; (b) PVP10 000 or (c) PVP50 000.

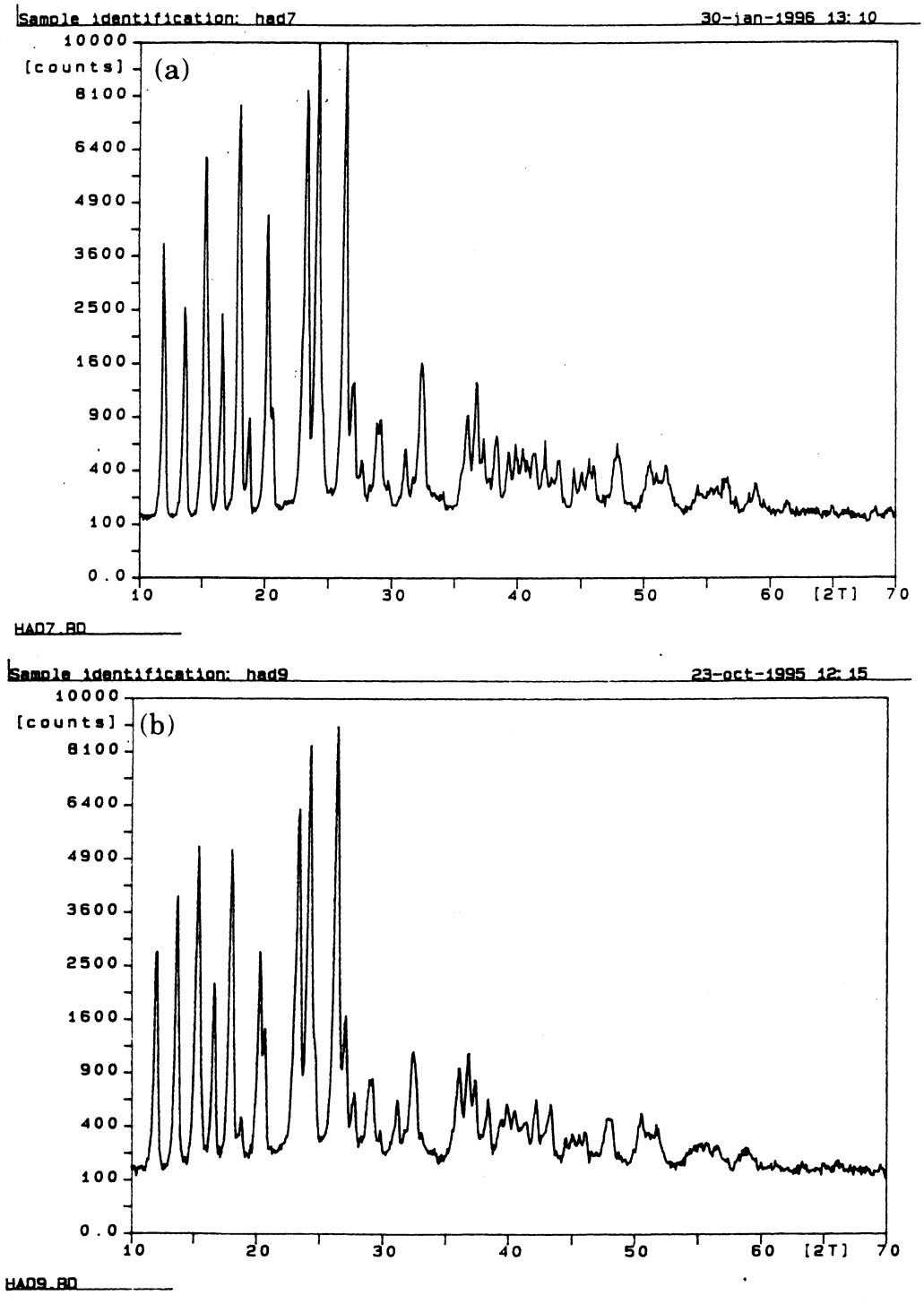
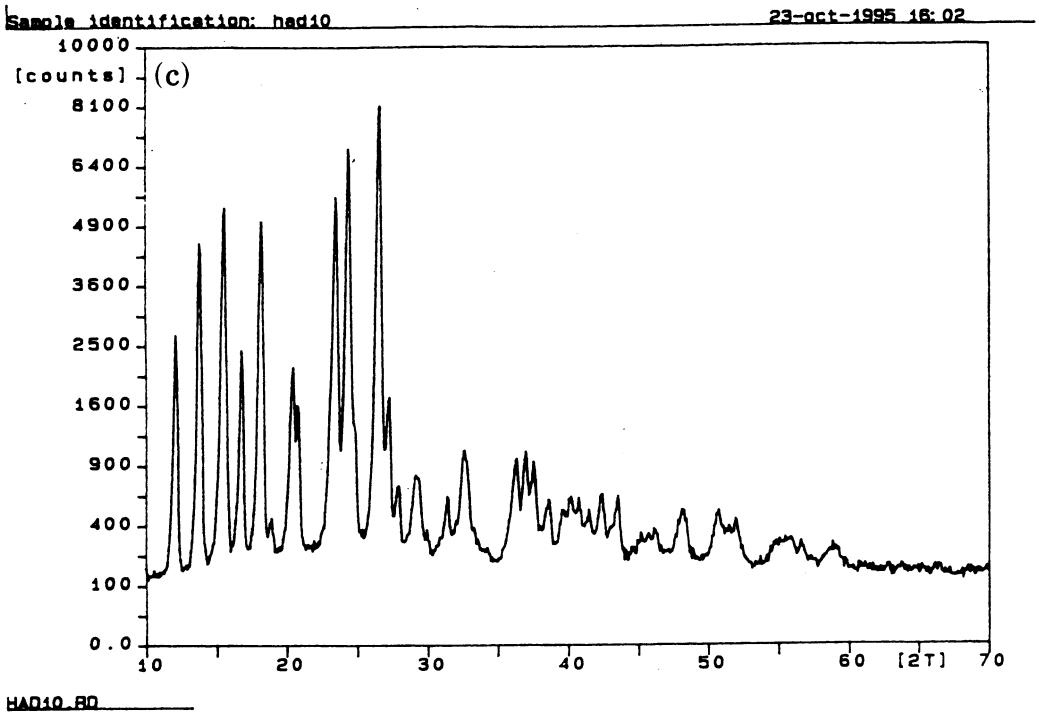


Fig. 9. The XPD spectra of: (a) untreated paracetamol particles, and paracetamol crystallized in the presence of 0.5% w/v of (b) PVP2000; (c) PVP10 000 or (d) PVP50 000.



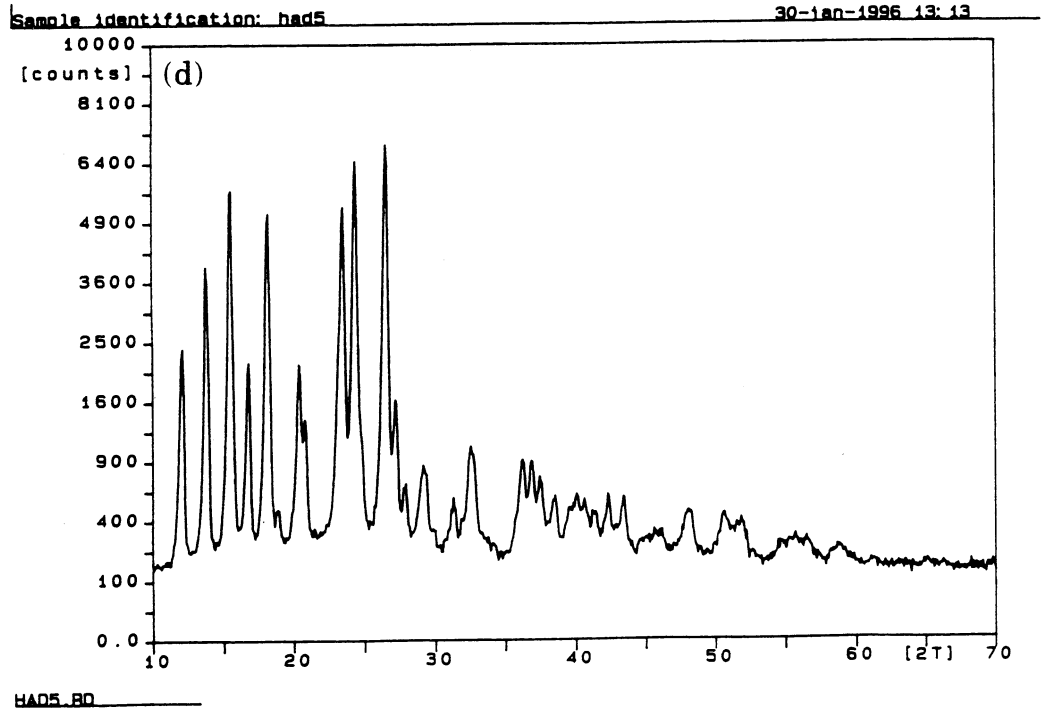


Fig. 9. (*Continued*)

(Table 2) are similar to those of the physical mixture containing 5% PVP 50 000 (Table 3). It is therefore possible that the low enthalpies of fusion for paracetamol crystallized in the presence of PVP (Table 2) are not due to amorphous regions or crystal disruption but due to presence of PVP in the crystals. Additionally X-ray powder diffraction data also confirmed that no structural modifications occurred in the samples crystallized in the presence of PVP.

4. Conclusions

It was found that PVP is an effective additive during crystallization of paracetamol and significantly influenced the crystallization process and changed the crystal habit. These effects were attributed to adsorption of PVP onto the surfaces of growing crystals. It was found that the higher molecular weights of PVP (PVP 10 000 and PVP 50 000) were more effective additives than lower molecular weight PVP (PVP 2000).

Paracetamol particles obtained in the presence of 0.5% w/v of PVP 10 000 or PVP 50 000 had near spherical agglomerated structure and consisted of numerous rod-shape microcrystals which had stuck together. Particles obtained in the presence of PVP 2000 consisted of fewer microcrystals.

DSC and XPD experiments showed that paracetamol particles crystallized in the presence of PVP, did not undergo structural modifications compared to untreated paracetamol crystals.

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