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Crystallization of Paracetamol from Ethanol–water Solutions in the Presence of Polymers

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Abstract

We have examined the effect of polymer nature and concentration on yield and micromeritic, melting and compression properties of paracetamol crystals obtained from ethanol–water solutions using the solvent-change technique. Agar, gelatin, polyethyleneglycol (PEG) and polyvinylpyrrolidone (PVP) were the polymers used. These four polymers have different solubility in ethanol and water.

It was found that the yield of crystallization may increase by up to 8% with agar, gelatin and PEG, polymers that are insoluble in ethanol, while the soluble PVP reduces yield by 14%. The size of crystals increased due to the addition of polymers and changed almost in parallel with the crystal yield for agar and gelatin. Gelatin resulted in the biggest crystals, agar in the most equidimensional (aspect ratio 1·45 and roundness 1·47) and PVP in the most elongated (aspect ratio 1·89 and roundness 2·13). PEG resulted in the most agglomerated crystals. Yield pressure, P_y, decreased in the following order: agar > PEG > gelatin > PVP, which is the same order for the enthalpy of fusion. Gelatin and PEG significantly decreased the elastic recovery of tablets (0·05 level), probably due to plastic deformation of crystals and fragmentation of agglomerates, respectively.

Crystallization of paracetamol in the presence of polymers by the solvent-change (ethanol–water) technique may permit increase of crystal yield, alteration of crystal shape and improvement of compression behaviour during tableting.

Crystal engineering techniques employ alternative crystallization conditions in order to obtain raw materials with improved handling properties or even suitable for direct compression (York 1992). Paracetamol exhibits poor compression ability due to excessive elastic recovery, making its tableting by direct compression impossible. To modify crystal properties of paracetamol and so improve its tableting characteristics, several studies have been reported recently employing different solvents (Nath & Khalil 1984; Fachaux et al 1993; El-Said 1995; Nichols & Frampton 1998), low level additives (Chow et al 1985; Nath & Nalwade 1987; Femi-Oyewo & Spring 1994; Garekani et al 1996), solution enhanced dispersion by supercritical fluids (Shekunov et al 1997) and cooling alteration of solutions (Shekunov et al 1996; Nichols & Frampton 1998) and of melts (Di Martino et al 1996).

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Crystallization from solution is the most widely used method for pharmaceutical substances and is achieved by evaporation or cooling or by addition of a poor solvent (solvent change). By cooling paracetamol solutions containing polymers, it has been found that the water miscibility of the solvent and the addition of polymers such as agar, gelatin, polyvinylpyrrolidone (PVP) and hydroxypropylmethyl cellulose, alter the crystal habit and improve the tableting ability (Nath & Khalil 1984; Femi-Oyewo & Spring 1994; Garekani et al 1996). Nichols & Frampton (1998) produced a more compressible orthorhombic crystal form by altering the cooling rate of paracetamol solution. Solvent change has long been used for organic compounds as a mean of speeding up the rate of crystal growth (Packter 1959). Water miscibility of the solvent as well as polymer addition frequently affect the properties of paracetamol crystals, because the interactions of solvent and solute play an important role during crystallization (Davey 1986). In this study, we have examined the combined effect of

polymer presence and solvent change (ethanol–water) on the micromeritic and compression properties of paracetamol. Crystals were prepared by adding aqueous solutions of polymers with different solubility in ethanolic paracetamol solution and applying simultaneous cooling.

Materials and Methods

Materials

Crystalline paracetamol (Monsanto, Brussels, Belgium) was used. The polymers used were a microbiological grade of agar (Bacto-agar, Difco Laboratories, USA), a research grade of gelatin (Serva Feinbiochemica, NY, USA), polyethylene glycol (PEG) of MW 4000 (laboratory reagent from BDH, Poole, UK), and polyvinylpyrrolidone (PVP) K15 MW 10 000 (Carl Roth, Karlsruhe, Germany). Other chemicals used were absolute ethanol (Merck, Darmstadt, Germany), water distilled by an all-glass apparatus, 1-bromobutane (99% purity; from Aldrich Chemie, Steinheim Germany, lot 68458-114, density 1·276 g mL^{-1} at 20°C) and dichloromethane (analytical grade from Merck Darmstadt, Germany, lot 6050·2223, density 1·320 g mL^{-1} at 20°C).

Crystallization

Crystalline paracetamol, 50 g, was dissolved in 100 g ethanol kept under constant low agitation (100 rev min^{-1}), at 50°C, inside a 1-L (10 × 30 cm) crystallization vessel (Kachrimanis et al 1998). Then, 600 mL aqueous solution of polymer (0·25–5·0‰ w/w) was added at a constant rate (3·3 mL min^{-1}), by employing a Desaga (Heidelberg, Germany) peristaltic pump. Parallel cooling was applied from 50°C down to 10°C, at a constant rate (0·22°C min^{-1}), with a Julabo PRG1 temperature controller (Julabo Labortechnik, Seelbach, Germany) connected with an external probe immersed in the crystallization liquid. Temperature of the crystallization solution was recorded by using a copper–constantan thermocouple and a Knauer chart recorder, for monitoring linearity of cooling. The crystals produced were collected by vacuum filtration immediately after the end of cooling, dried at 60°C in a vacuum oven until a constant weight was reached and kept in screw-capped amber jars.

Sixteen batches of crystals were prepared with four concentration levels of each polymer and one batch without polymer (blank or reference sample). The concentration range for each polymer was different (Table 1), selected on the basis of preliminary trials to be as high as possible but not causing great reduction in crystal yield or filtration problems due to formation of colloid dispersions.

Crystal yield was calculated from their weight expressed as the percentage of paracetamol dissolved initially in ethanol (50 g) and their properties were evaluated on the basis of size, shape and surface roughness, as well as on the basis of density, melting and compression characteristics.

Characterisation of crystals

Size, shape and surface roughness. Size was evaluated as circle equivalent diameter (CED) measured for at least 500 crystals, in four optical fields of samples dispersed in paraffin oil, by using an image processing and analysis system (Quantimet 500, Leica, Cambridge, UK). Also, the ratio of longest to shortest dimension (aspect ratio), the square of perimeter divided by 12·56-times the projection area (roundness) and the square root of projection area divided by the area of circumscribed polygon (fullness ratio) were determined. Mean values and standard deviations were calculated. The above three shape parameters assume a value of 1 for a sphere and fullness ratio is mainly related to surface smoothness, while aspect ratio to crystal elongation and roundness to both of them.

Prints of images in transmitted light of optical microscope (photomicrographs) were obtained with a laser printer connected to the image processing and analysis system and scanning electron microphotographs (SEMs) were taken, in order to evaluate differentiation in the morphology (shape and surface roughness) of crystals. A very thin coat of carbon was applied to samples of crystals before being examined in a scanning electron microscope (JSM 840A, JEOL, Japan) and microphotographs were taken at different magnifications.

Density and melting properties. True density was determined on three sieve fractions for each batch of crystals (250–500, 500–1000 and $> 1000\,\mu$m) by applying the flotation technique suggested by Duncan-Hewitt & Grant (1986) and employing liquid halogenated hydrocarbons (1-bromobutane, dichloromethane and a mixture of both in 53 : 47% w/w ratio). True density, at fixed temperature (25°C), was calculated by regression of at least nine experimental values of crystal density, D, vs temperature, T, obtained with the three liquids.

Enthalpy of fusion and point of melting onset (extrapolated onset) were determined automatically on a Shimadzu TA 50 Differential Scanning

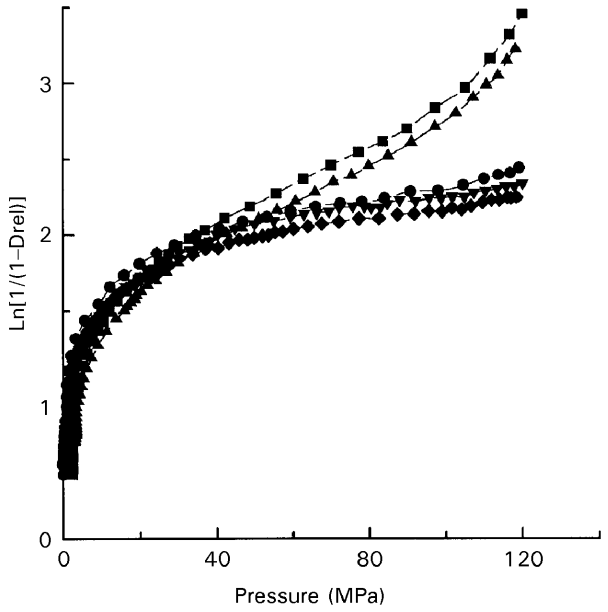

Figure 1. Heckel plots for paracetamol crystallized from ethanol–water solutions in the presence of different polymers at 1·0‰ w/w concentration in the aquatic solution added. Polymer: ▼ agar, ▲ PVP, ■ gelatin, ● PEG and ◆ none.

Calorimeter equipped with a TA-50 WSI analysis program. Samples of crystals (3–5 mg) were weighed accurately (±0·1 mg) and scanned between 30 and 200°C, at a heating rate of 2·4°C min^{-1}, in crimped aluminium pans. Mean values of four samples were calculated for each batch of crystals.

Compression properties. Compression parameters were determined on samples corresponding to a 3-mm thick tablet, at zero porosity, without any size classification of the crystals. They were weighed accurately (±0·1 mg) and compressed at pressure up to 120 MPa in an instrumented single punch tableting machine (Kachrimanis et al 1998). Profiles of log reciprocal porosity (log[1/1−Drel]) vs applied pressure were constructed according to the Heckel equation (Heckel 1961) and relative densification, D_B, at the early stages of compression, as well as yield pressure, P_y, were calculated. D_B was obtained from the difference between the packing fraction corresponding to the intercept of the extrapolated linear part of the Heckel plots and that corresponding to tapped density. The yield pressure, P_y, is the reciprocal of the slope in the linear part of the Heckel plot. Furthermore, the % elastic recovery of the compacts was evaluated from their thickness under maximum load and 24 h after ejection (Malamataris & Rees 1993). Heckel plots for paracetamol crystallized in the presence of different polymers at certain concentration (1·0‰ w/w) are shown in Figure 1. Five samples were compressed from each batch of crystals and mean values of the compression parameters were calculated.

Results and Discussion

Crystal yield and size

The results in Table 1 show that with agar, the crystal yield was higher compared with the reference sample at any concentration employed, but with PVP the yield was lower. For gelatin and PEG the crystal yield was higher at low concentration

Table 1. Crystal yield and micromeritic properties of paracetamol crystals prepared in the presence of different polymers.

Polymer		Crystal yield (%)	Circle equivalent diameter (μm) (mean ± s.d.)	Shape parameters (mean ± s.d.)		
Type	Concn (‰ w/w)			Aspect ratio	Roundness	Fullness ratio
None	0·00	54·4	33 ± 15	1·71 ± 0·73	1·66 ± 0·67	1·00 ± 0·07
Agar	0·25	60·2	34 ± 22	1·51 ± 0·64	1·59 ± 0·62	0·99 ± 0·09
	0·50	62·5	139 ± 110	1·45 ± 0·29	1·47 ± 0·37	0·92 ± 0·04
	0·75	62·8	181 ± 114	1·60 ± 0·36	1·55 ± 0·37	0·89 ± 0·06
	1·00	61·6	146 ± 105	1·55 ± 0·46	1·62 ± 0·63	0·88 ± 0·04
PVP	0·25	40·7	91 ± 64	1·89 ± 0·53	2·13 ± 1·30	0·85 ± 0·05
	0·50	40·8	48 ± 31	1·85 ± 0·63	1·99 ± 0·88	0·86 ± 0·06
	0·75	45·1	45 ± 28	1·82 ± 0·53	1·79 ± 0·71	0·88 ± 0·06
	1·00	40·9	45 ± 27	1·68 ± 0·40	1·64 ± 0·51	0·91 ± 0·05
Gelatin	1·00	62·1	379 ± 276	1·76 ± 0·42	2·03 ± 0·48	0·84 ± 0·05
	2·00	56·9	149 ± 102	1·73 ± 0·48	1·80 ± 0·72	0·87 ± 0·05
	3·00	50·3	77 ± 42	1·67 ± 0·34	1·68 ± 0·42	0·90 ± 0·04
	5·00	40·0	68 ± 44	1·65 ± 0·45	1·64 ± 0·53	0·90 ± 0·05
PEG	1·00	59·6	37 ± 22	1·50 ± 0·27	1·67 ± 0·74	0·89 ± 0·04
	2·00	56·4	60 ± 31	1·55 ± 0·33	1·63 ± 0·55	0·89 ± 0·05
	3·00	58·6	68 ± 27	1·54 ± 0·36	1·59 ± 0·50	0·89 ± 0·04
	5·00	45·9	60 ± 44	1·58 ± 0·37	1·63 ± 0·45	0·88 ± 0·03

(1·0% w/w) but at higher concentration it was becoming lower than the reference sample yield. For agar and PVP, the crystal yield was not affected by the concentration for the range employed. Analysis of variance in the crystal yield values for a two-factor experimental design with only a single replicate (Montgomery 1997) has shown that the effect of polymer nature is more significant (0·01 probability level) than that of polymer concentration (0·05 probability level).

A relation seemed to exist between the changes of crystal yield and the solubility of polymers in ethanol. PVP, which is soluble in ethanol, resulted in crystal yield reduction unaffected by the polymer concentration. The other three polymers, which were insoluble in ethanol (agar, PEG and gelatin), resulted in crystal yield increase affected greatly by the polymer concentration in a manner depending on the polymer nature.

The changes in crystal yield due to the addition of polymers were not in agreement with the reported inhibition due to viscosity and molecular movement for all the polymers. Therefore, they might be attributed to ethanol and polymer interactions occurring when the aqueous solution was added and to their effects on induction of primary heterogeneous nucleation and crystal growth.

The great inhibiting effect of ethanol-soluble PVP on crystal yield was in agreement with the observations of Femi-Oyewo & Spring (1994) for crystallization of paracetamol by cooling aqueous solution and of Simonelli et al (1970), for crystallization of sulfathiazole. It should be attributed to adsorption of PVP molecules on certain developing crystal surfaces. However, the absence of any effect of PVP concentration on crystal yield because of increases of viscosity, as has been reported for sulfathiazole with PVP of different molecular weight (Simonelli et al 1970), may be attributed to the low range of concentration employed.

The crystal size results, given in Table 1, show that the reference sample had smaller CED than crystals obtained with the addition of polymers. Also, Table 1 shows that size and crystal yield changed almost in parallel because of the concentration increase for agar and gelatin and attained maxima at similar concentration. This parallel change of yield and size may be considered as evidence of similar effects on both nucleation and growth of paracetamol crystals due to interactions of polymer, water and ethanol. With the addition of PVP and PEG, the crystal size increased slightly and yield was not affected by the concentration, except in the case of high PEG concentration (5·0‰ w/w), probably due to inhibition of crystal growth caused by the adsorption on developing crystal surfaces.

Crystal shape

The crystal shape parameters, given in Table 1, show that the reference sample had higher fullness ratio than the samples obtained with addition of polymers, meaning smoother or better-developed crystal surfaces. For the different polymers, the changes in shape parameters were the result of their concentration increase. For agar, all of the shape parameters decreased, compared with the reference sample. Also, fullness ratio decreased remarkably

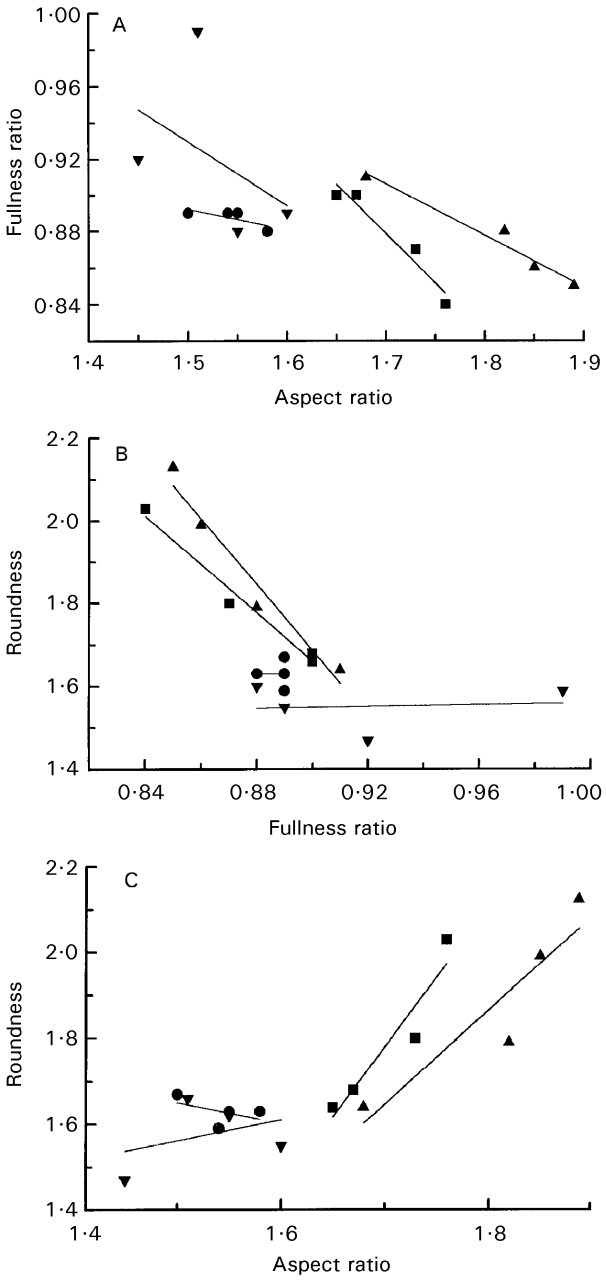

Figure 2. Relation between the shape parameters (aspect ratio, roundness and fullness ratio) for paracetamol crystallized from ethanol–water solutions in presence of different polymers. Polymer: ▼ agar, ▲ PVP, ■ gelatin, ● PEG and ◆ none.

with the concentration, while the aspect ratio and roundness did not change in a simple and general way. Addition of PVP and gelatin at low concentration resulted in an increase of aspect ratio and roundness and a decrease of fullness ratio, compared with the reference sample. With the increase of the concentration, aspect ratio and roundness were reduced while fullness ratio was increased. PEG addition contributed to a remarkable decrease of aspect ratio and fullness ratio, compared with the reference sample, while roundness remained almost unchanged. Furthermore, all of the three shape parameters were not affected by the PEG concentration.

Combined consideration of the changes in the shape parameters caused by concentration increase (Table 1) and of the general relations between them (Figure 2), may provide evidence for the similar or differential inhibition of crystal growth at different crystal faces and/or the crystal agglomeration.

For PVP and gelatin, for which the aspect ratio or the crystal shape (elongation) changed greatly due to change in concentration, the fullness ratio increased with concentration, while roundness was reduced. On the contrary, for agar and PEG, for which crystal shape is almost unchanged, the fullness ratio was either reduced (for agar, due to growth inhibition at different crystal faces), or was unchanged with concentration (for PEG, due to agglomeration).

The relation of fullness ratio with aspect ratio and roundness (Figure 2A and B) show that for PVP and gelatin the increase of fullness ratio corresponded to a reduction of aspect ratio and a great reduction of roundness. For agar and PEG, fullness ratio changed independently to roundness. Therefore, the differences in the relations between aspect ratio and roundness shown in Figure 2C, should depend on the different extent of crystal agglomeration.

Transmitted light photomicrographs and SEMs, shown in Figures 3–5, revealed greater modification in crystal shape for PVP, absence of crystal agglomerates for gelatin, and the existence of well-formed, relatively small single crystals for PEG addition and also much crystal agglomerate.

We can say that the addition of agar resulted in more equi-dimensional crystals, gelatin resulted in bigger crystals, PVP in a greater change of crystal shape (elongation), and PEG in the most agglomerated crystals.

Crystal density and melting properties

Table 2 summarizes the mean values of density for the three sieve fractions of crystals irrespective of

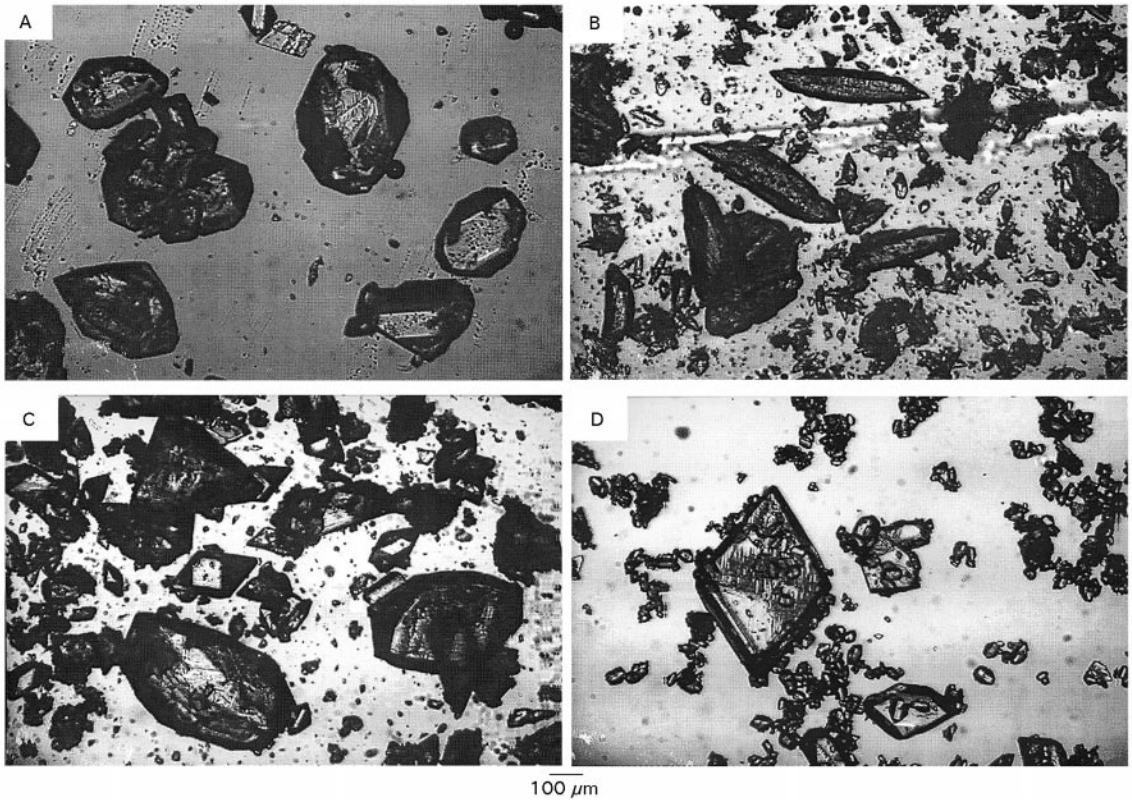

Figure 3. Transmitted light photomicrographs of paracetamol crystallized from ethanol–water solution in the presence of different polymers at the highest concentration employed in the aquatic solution added. Polymer: A, agar; B, PVP; C, gelatin; and D, PEG.

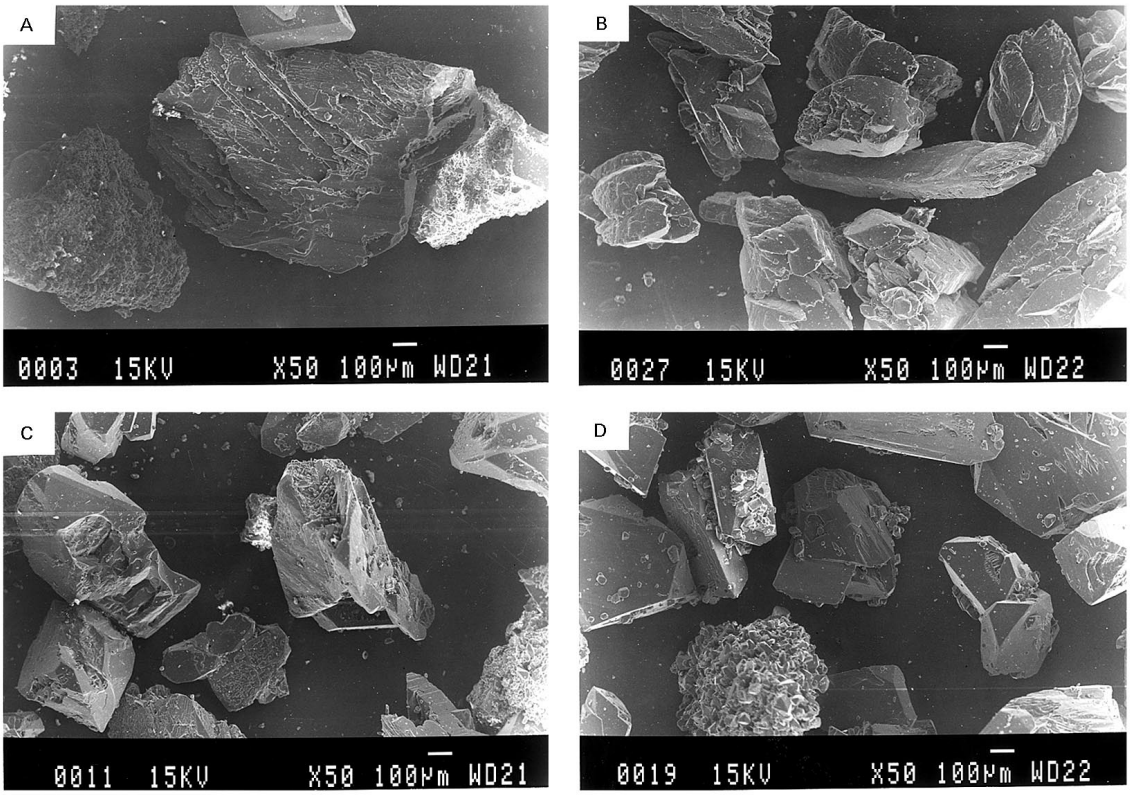

Figure 4. SEMs of paracetamol crystallized from ethanol–water solution in the presence of different polymers at the lowest concentration employed in the aquatic solution added. Polymer: A, agar; B, PVP; C, gelatin; and D, PEG.

polymer concentration, which could be compared for two reasons. Firstly, the effect of polymer concentration on crystal density was found to be insignificant, by applying analysis of variance for a three-factor full factorial experiment with no replication and with pooling the error term by combining the interactions (Table 3). Secondly, small density changes due to the polymer concentration were not detectable for the large crystals produced with the addition of agar or PEG at high concentrations (>3‰ w/w), since density measurements were done with two liquids only. The measurements with dichloromethane for the aforementioned cases were ignored, because they were leading to great reduction in the correlation coefficients of regression analysis between density and temperature.

From the mean values of density given in Table 2, it can be seen that for the large ($>1000\,\mu$m) and medium size crystals (500–1000 μm) obtained with the addition of agar and PEG, they were lower in comparison with the reference sample and all the other crystals. Therefore, the above mentioned difficulties in measurement may be attributed to low crystal density and approach of the boiling point of dichloromethane. On the contrary, for the small size fraction, 250–500 μm, no significant change in crystal density was observed due to the addition of polymers and this can be attributed to the existence of fewer defects in smaller crystals.

Regarding the melting properties (Table 4), we can say that PVP and gelatin contributed to a slight decrease, while agar and PEG contributed to a slight increase in enthalpy of fusion, compared with the reference sample. As far as the onset of melting is concerned, the extrapolated onset temperature increased slightly due to the addition of PVP and gelatin and in some cases of agar and PEG. Analysis of variance in melting parameters (four replicated determinations) has shown that for the enthalpy of fusion the effect of polymer nature is highly significant (0·01 probability level) and for melting point it is only significant (0·1 level).

Compression properties

From the results given in Table 4, no simple and general change of densification when low compression was applied (D_B) can be noticed, either due to the nature or the concentration of the polymers examined. The changes observed can be attributed to the combined effect of crystal size and shape on packing and flow of crystals. Regarding the yield pressure, P_y, results (Table 4) and taking into account that it is an indicator of plasticity, we

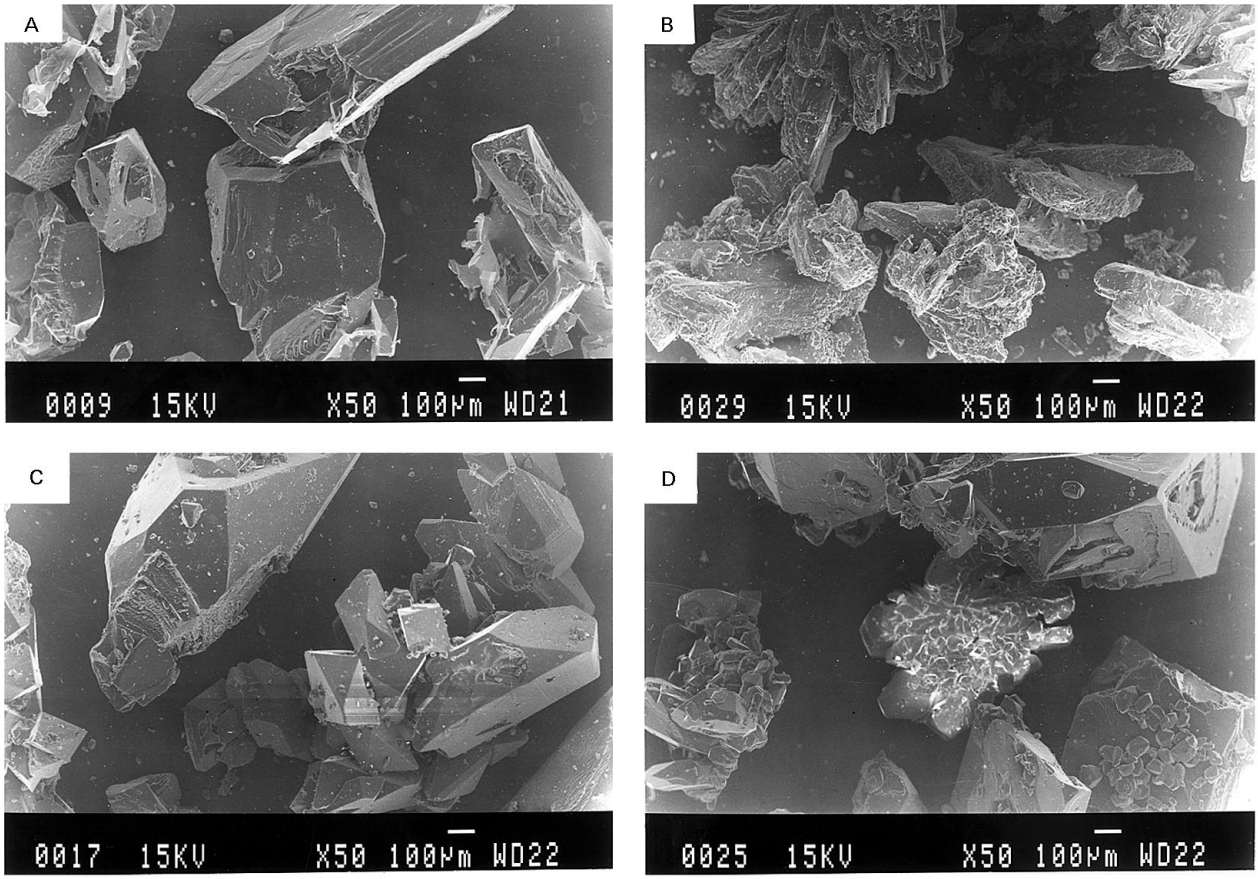

Figure 5. SEMs of paracetamol crystallized from ethanol–water solution in the presence of different polymers at the highest concentration employed in the aquatic solution added. Polymer: A, agar; B, PVP; C, gelatin; and D, PEG.

Table 2. True density, at 25°C, for three sieve fractions of paracetamol crystals prepared in the presence of different polymers.

Polymer type	Density ($g\,cm^{-3}$) for sieve fraction of crystals (mean ± s.d.)		
	$> 1000\,\mu m$	$500-1000\,\mu m$	$250-500\,\mu m$
None	1·314	1·304	1·306
Agar	1·293 ± 0·003	1·296 ± 0·003	1·305 ± 0·002
PVP	1·297 ± 0·003	1·300 ± 0·003	1·304 ± 0·001
Gelatine	1·297 ± 0·004	1·306 ± 0·005	1·307 ± 0·004
PEG	1·293 ± 0·007	1·301 ± 0·004	1·306 ± 0·008

Table 3. Analysis of variance for evaluating the effect of crystal size, polymer nature and concentration on crystal density.

Source of variation	Degrees of freedom	Mean square	F_0	Probability value
Crystal size	2	0·00446	22·809	0·0000001
Polymer nature	3	0·000067	3·43178	0·026145
Polymer concn	3	0·000018	0·9068	0·4465
Error	39	0·000020	–	–

can say that all the crystals prepared with the addition of polymers deformed more easily or plastically than the reference sample. In particular, P_y decreased in the following order: agar > PEG > gelatin > PVP. This order seems to be the same as for enthalpy of fusion. Therefore, it may reflect a possible increase of lattice defects in paracetamol crystals.

Table 4. Melting (n = 4) and compression (n = 5) properties of paracetamol crystals prepared in the presence of different polymers.

Polymer		Melting properties s		Compression properties		
Type	Concn (‰ w/w)	Enthalpy of fusion (kJ mol^{-1})	Onset melting point (°C)	Densification (D_B)	Yield pressure $P_y \pm$ s.d. (Mpa)	Elastic recovery of tablets (%)
None	0·00	23·6 ± 0·3	163·2 ± 0·3	0·384 ± 0·016	242 ± 39	6·6 ± 0·2
Agar	0·25	24·4 ± 0·1	164·7 ± 0·6	0·386 ± 0·010	184 ± 20	6·6 ± 0·1
	0·50	24·3 ± 0·3	162·9 ± 0·6	0·404 ± 0·005	169 ± 18	6·3 ± 0·1
	0·75	24·7 ± 0·4	163·2 ± 0·3	0·402 ± 0·006	234 ± 40	5·9 ± 0·3
	1·00	24·0 ± 0·3	162·6 ± 0·8	0·403 ± 0·002	223 ± 10	6·5 ± 0·1
PVP	0·25	23·4 ± 0·3	163·3 ± 0·1	0·359 ± 0·013	166 ± 20	6·2 ± 0·1
	0·50	23·4 ± 0·3	164·5 ± 0·9	0·450 ± 0·011	185 ± 17	6·2 ± 0·1
	0·75	23·1 ± 0·3	164·6 ± 0·8	0·444 ± 0·003	191 ± 11	5·8 ± 0·1
	1·00	23·1 ± 0·3	165·3 ± 0·1	0·459 ± 0·005	178 ± 8	6·5 ± 0·1
Gelatin	1·00	23·4 ± 0·3	164·5 ± 1·0	0·409 ± 0·006	174 ± 8	5·1 ± 0·1
	2·00	23·5 ± 0·3	164·0 ± 0·8	0·434 ± 0·007	181 ± 10	5·9 ± 0·1
	3·00	23·2 ± 0·2	165·5 ± 0·9	0·382 ± 0·005	168 ± 13	5·3 ± 0·1
	5·00	23·1 ± 0·3	165·9 ± 0·7	0·334 ± 0·001	161 ± 6	4·9 ± 0·1
PEG	1·00	23·9 ± 0·4	163·0 ± 0·3	0·363 ± 0·008	184 ± 22	6·2 ± 0·2
	2·00	23·7 ± 0·3	162·6 ± 0·1	0·397 ± 0·002	181 ± 12	5·2 ± 0·2
	3·00	24·5 ± 0·3	163·7 ± 0·1	0·367 ± 0·006	228 ± 37	4·9 ± 0·3
	5·00	24·1 ± 0·3	164·7 ± 0·7	0·413 ± 0·005	206 ± 13	5·3 ± 0·3

The values of elastic recovery (Table 4) also show, in general, that the addition of polymers contributed to reduction of elasticity or increase in plasticity, which was greater in the case of PEG and gelatin. Increase in plasticity can be attributed to the larger size of paracetamol crystals and the expected occurrence of more crystal defects and therefore a higher tendency for brittle fracture (Malamataris & Rees 1993). Analysis of variance has shown a significant effect of polymer nature on elastic recovery at 0·05 probability level.

The melting and compression properties changed in parallel, while there was disagreement between their changes and those of the density. Considering to be impossible the incorporation of polymers into the crystal structure under the crystallization conditions applied, a probable explanation for these controversial changes in density can be the change in water content. It has been reported to act as possible ''disrupter'' of crystal lattice (Chow et al 1985). Therefore it may have a similar effect with crystal defects on melting and compression properties but have a different influence on density. For example, a decrease in enthalpy of fusion was observed due to an increase of water content of paracetamol obtained from aqueous solutions containing different co-solvents (El-Said 1995).

In conclusion, the crystallization of paracetamol by the solvent-change (ethanol–water) technique, in the presence of polymers, may permit an increase of crystal yield, alteration of crystal shape and improvement of compression behaviour during tableting. In particular, yield may increase (up to 8%) with agar, gelatin and PEG, while it is reduced with PVP at any concentration and with 5·0‰ w/w PEG. Gelatin results in biggest crystals, agar in the most equidimensional, PVP in the most elongated and PEG in the most agglomerated crystals. Gelatin or PVP addition contributes to significant decrease of yield pressure, P_y, during compression. P_y decreases in the following order: agar > PEG > gelatin > PVP, which is the same for enthalpy of fusion. Gelatin and PEG decreases significantly the elastic recovery of tablets ($P < 0·05$), probably due to plastic deformation of crystals and fragmentation of agglomerates, respectively.

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