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Highly compressible paracetamol — II. Compression properties

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Abstract

Paracetamol particles crystallized in the presence of polyvinylpyrrolidone (PVP) exhibited an obvious improvement in their compression properties compared to untreated paracetamol. Paracetamol particles crystallized in the presence of 0.5% w/v PVP 10 000 or PVP 50 000 produced tablets with improved crushing strength with no tendency to cap even at high compression speeds. The very low values of strain rate sensitivity (SRS) and the lack of reduction in crushing strength with increasing compression speed for these particles, were indicative of a high degree of fragmentation during compression. The results of elastic recoveries and elastic energies of tablets were indicative of much less elastic behaviour of these particles than untreated paracetamol. The low elastic energy/plastic energy (EE/PE) ratio for paracetamol crystallized in the presence of PVP indicated that, contrary to untreated paracetamol, a minor portion of compression energy was utilized as elastic energy.

Keywords: Paracetamol; Polyvinylpyrrolidone; Agglomerated particles; Compression force; Compression speed; Crushing strength; Elastic recovery; Elastic energy/plastic energy ratio

1. Introduction

There are several reports in the pharmaceutical literature of attempts to change the morphology of drug crystals using alternative crystallization procedures to improve their compression properties. Examples include spherical crystallization, which transforms crystalline drugs into agglomerated forms (Morishima et al., 1994; Gordon and Chowhan 1990; Guillaume et al., 1993), crystallization from different solvents to produce different crystal habit (Gordon and Amin 1984) and incorporation of additives by co-precipitation (Kaul et al., 1992).

In recent years some attempts have been made to modify the paracetamol crystals using different

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crystallization techniques, to improve its compression properties (Fachaux et al., 1993; Di Martino et al., 1996; Abdelillah et al., 1995). Garekani et al., (1999) produced a modified form of paracetamol crystals (thin plate-like crystals), but this form did not exhibit any improvement in the compression properties compared to polyhedral crystals, which is the dominant form of paracetamol crystals. In the previous study (Garekani et al., 2000) paracetamol was crystallized by a watering-out method in the presence of different grades of PVP. It was found that PVP was an effective additive during crystallization of paracetamol and significantly influenced the crystallization process and changed the crystal habit. The paracetamol particles obtained in the presence of 0.5% PVP had near spherical structure and consisted of numerous rod shape microcrystals which had agglomerated together. The aim of this study was to investigate the compression properties of paracetamol particles crystallized in the presence of different grades of PVP.

2. Materials and methods

Paracetamol particles crystallized in the presence of 0.1, 0.3 or 0.5% w/v of PVP of molecular weight 2000, 10 000 or 50 000, as described in our previous study (Garekani et al., 2000), were used. Several batches of each crystals were combined prior to study. Untreated paracetamol, obtained from Sterling Organics, Northumberland, UK, was also used for this study.

2.1. Particle size fractions

Sieved fractions of paracetamol particles crystallized in the presence of 0.5% w/v of different grades of PVP (<90 μm) and untreated paracetamol crystals (<90 μm) were obtained by sieving the materials through test sieves (Endecotts Ltd., London, UK) on a mechanical sieve shaker (Pascall Ltd, Sussex, England). However, particles crystallized in the presence of 0.1 or 0.3% w/v of different grades of PVP were used unsieved as harvested from crystallization medium.

2.2. Compression

All the paracetamol samples were dried in an oven at 55°C for 24 h and then stored in tightly closed jars before compression. Compression was carried out using a high speed compaction simulator as detailed by Garekani et al. (1999). Four tablets, each 400 mg, were prepared at compression speeds of 10, 50, 100 or 250 mm s^{-1} up to a maximum compression force of 30 kN.

2.3. Crushing strength and capping tendency of tablets

The crushing strength of tablets were determined 24 h after compression, from the force required to fracture tablets by diametral compression on a motorized tablet hardness tester (Schleuniger, Model 2E, Switzerland). Tablets were assessed visually for capping by observation of the final tablets for horizontal striations. The tablets were divided into four groups depending on their capping tendencies: no capping ($-$), low capping ($+$), high capping ($++$) and very high capping ($+++$).

2.4. Analyses of compression data

Analyses of the compression data according to the Heckel equation, and determination of elastic recoveries and plastic (net compression) and elastic energies were carried out as previously detailed by Garekani et al. (1999).

3. Results and discussion

The influence of compression force on the crushing strength of tablets made from paracetamol particles crystallized in the presence of different amounts of PVP of molecular weight 2000, 10 000 or 50 000 are shown in Fig. 1, respectively. The tendency of tablets made from these particles to cap are presented in Table 1. The tablets made from untreated paracetamol were very weak with no measurable crushing strength and had a high tendency to cap. These data show a amjor improvement in the compression properties of

paracetamol particles crystallized in the presence of PVP. The crushing strengths of the tablets increased with increasing molecular weight and/or the concentration of PVP present in the crystals.

The paracetamol particles obtained in the presence of 0.5% w/v of each grade of PVP exhibited improved compression properties than the samples obtained in the presence of 0.1 or 0.3% w/v of PVP. Therefore, paracetamol particles crystallized in the presence of 0.5% w/v of different grades of PVP chosen for further studies.

Data in Fig. 1 and Table 1 demonstrate that particles crystallized in the presence of 0.5% w/v PVP 10 000 or PVP 50 000 produced tablets with excellent crushing strength and lack of tendency to cap. However, particles obtained in the presence of PVP 2000 showed little improvement in their compression properties. The high crushing strengths of the tablets are indicative of stronger interparticulate bondings between the particles crystallized in presence of PVP compared to the untreated paracetamol.

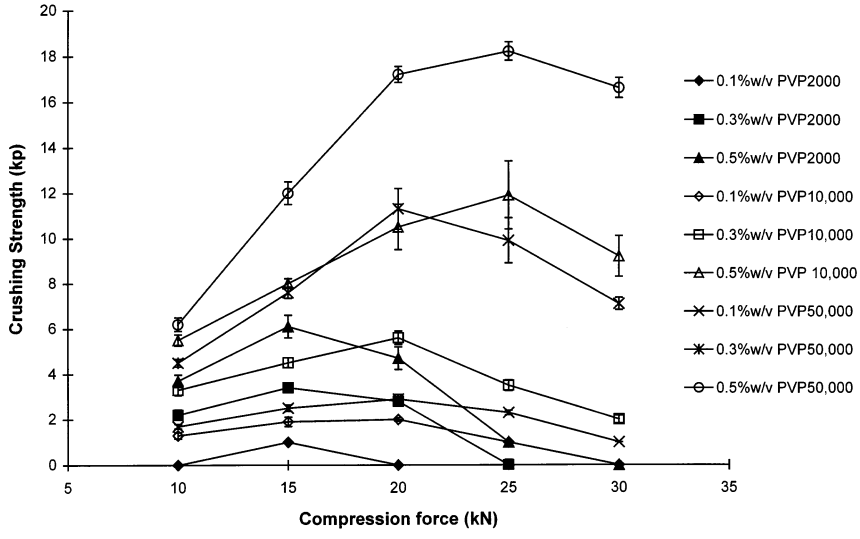

Fig. 1. Effect of compression force on the crushing strengths of tablets prepared from paracetamol crystallized in the presence of: 0.1, 0.3 or 0.5% w/v of PVP 2000, PVP 10 000 or PVP 50 000 at a compression speed of 10 mm s^{-1} ($n = 4$; ± SD).

Table 1
Effect of compression force on the capping tendency of tablets made from paracetamol crystallized in the presence of 0.1, 0.3 or 0.5% w/v of different grades of PVP, at a compression speed of 10 mm s^{-1}

Compression force (kN)	Particles crystallized in the presence of:								
	PVP 2000 (%w/v)			PVP 10 000 (%w/v)			PVP 50 000 (%w/v)		
	0.1	0.3	0.5	0.1	0.3	0.5	0.1	0.3	0.5
10	+++[a]	++	+	++	−	−	+	−	−
15	+++	++	+	++	−	−	+	−	−
20	+++	++	++	++	−	−	+	−	−
25	+++	+++	++	+++	+	−	++	+	−
30	+++	+++	++	+++	++	−	+++	+	−

[a] −, +, ++ and +++ as defined in Section 2.3.

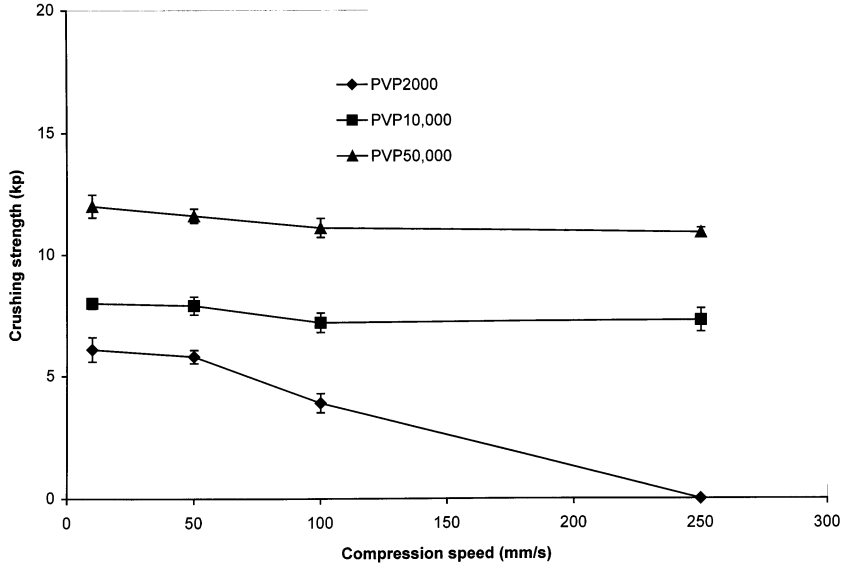

Fig. 2. Effect of compression speed on the crushing strengths of tablets prepared from paracetamol crystallized in the presence of 0.5% w/v of: PVP 2000, PVP 10 000 or PVP 50 000, at a compression force of 15 kN ($n = 4$; $\pm$ SD).

Table 2
Effect of compression speed on the capping tendency of tablets made from paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP, at a compression force of 15 kN

Compression speed (mm s^{-1})	Particles crystallized in presence of 0.5% w/v of:		
	PVP 2000	PVP 10 000	PVP 50 000
10	+[a]	−	−
50	+	−	−
100	++	−	−
250	++	−	−

[a] −, +, ++ and +++ as defined in Section 2.3.

The influence of compression speed on the crushing strengths and capping tendencies of tablets made from paracetamol crystallized in the presence of 0.5% w/v PVP is shown in Fig. 2 and Table 2. Tablets made from particles obtained in the presence of PVP 10 000 or PVP 50 000 exhibited good crushing strength with no tendency to cap, even at the highest compression speed (250 mm s^{-1}). The lack of reduction in crushing strength with increasing compression speed may be attributed to fragmentation of the particles under the applied load. The crushing strengths of tablets made from materials such as xylitol or dicalcium phosphate dihydrate (Emcompress®) which consolidate by a dominant fragmentation mechanism were independent of compression speed (David and Augsburger, 1977; Garr and Rubinstein, 1990; Garr, 1992). Emcompress consists of aggregates of smaller primary particles. These aggregates are extensively fragmented during compression (Duberg and Nystrom, 1982). Paracetamol crystallized in the presence of 0.5% w/v of PVP 10 000 or PVP 50 000 had an agglomerated structure which consisted of numerous fine microcrystals which had stuck together (Garekani et al. 2000). It is reasonable to assume

therefore, that these agglomerates undergo fragmentation during compression. However, for tablets made from particles crystallized in the presence of PVP 2000, PVP 2000a dramatic decrease in crushing strength occurred with increasing compression speed.

The effects of compression speed on the mean yield pressure (MYP) of untreated paracetamol and paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP were investigated (Table 3). Two way analysis of variance showed that there were no significant differences ($p > 0.05$) between the mean yield pressures of particles obtained in the presence of PVP 10 000 and PVP 50 000. However, differences between paracetamol obtained in the presence of PVP 2000 and those obtained in the presence of PVP 10 000 or 50 000 were significant (Table 3). As the compression speed increased, the MYP for all samples generally increased. However, particles crystallized in the presence of the higher molecular weight of PVP (10 000 or 50 000) were less sensitive to changes in compression speed. The changes of MYP with different compression speeds were quantified as strain rate sensitivity (SRS), which was described previously (Garekani et al., 1999). The values of SRS for particles crystallized in the presence of PVP 2000, PVP 10 000 or PVP 50 000 and untreated paracetamol were 5.9, 8.4, 14.9 or 13.6%, respectively. It has been reported that the mean yield pressures increase with increasing punch velocity for plastic materials which consequently show higher values of SRS (Roberts and Rowe, 1985, 1986, 1987). The lower values of SRS for paracetamol crystallized in the presence of PVP 10 000 or PVP 50 000 indicate that these particles were less sensitive to compression speed, again suggesting that a high degree of fragmentation occurred during compression. It has been reported that materials which consolidate by fragmentation show no obvious change in mean yield pressure with increasing compression speed and therefore exhibit a low SRS (Roberts and Rowe, 1985; Garr, 1992). Paracetamol crystallized in the presence of PVP 10 000 or PVP 50 000 consisted of numerous fine microcrystals and therefore, it may be expected that these particles underwent a greater fragmentation during compression.

The effect of compression force on the elastic recoveries in the die of tablets made from paracetamol crystallized in the presence of 0.5% w/v of PVP and untreated paracetamol is shown in Fig. 3. Tablets made from particles crystallized in the presence of PVP exhibited lower elastic recoveries than untreated paracetamol. Tablets made from particles obtained in the presence of PVP 10 000 or PVP 50 000 exhibited lower elastic recoveries than those obtained in the presence of PVP 2000 following the removal of compression pressure.

The data of crushing strengths and elastic recoveries indicated that the interparticulate bondings between particles crystallized in the presence of PVP should be much stronger than untreated paracetamol. Particles crystallized in the presence of PVP were consisted of numerous microcrystals agglomerated together. Fragmentation of each particle under load will produce numerous fresh and clean surfaces which can probably form

Table 3
Effect of compression speed on the mean yield pressure of paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP ($n = 4$; $\pm$ SD)

Compression speed (mm s^{-1})	Mean yield pressure $\pm$ SD (MPa)			
	Particles crystallized in presence of:			Untreated paracetamol
	PVP 2000	PVP 10 000	PVP 50 000	
10	48.9 ± 1.2	56.8 ± 1.7	59.4 ± 2.2	44.5 ± 1.5
50	53.7 ± 2.7	59.5 ± 0.6	61.5 ± 2.3	44.8 ± 1.2
100	55.8 ± 1.3	61.5 ± 1.4	64.3 ± 1.9	48.7 ± 1.5
250	57.5 ± 1.1	62.0 ± 2.0	63.1 ± 1.3	51.5 ± 2.7

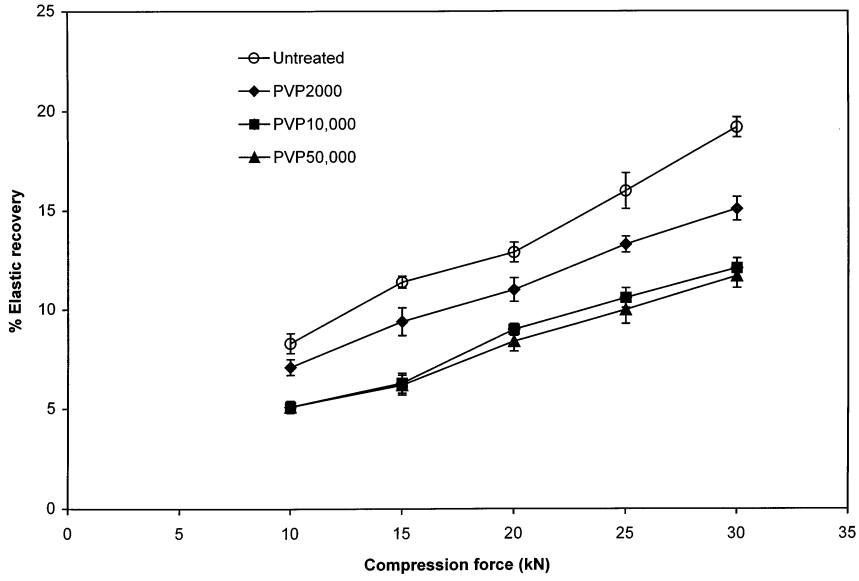

Fig. 3. Effect of compression force on the elastic recovery in the die of tablets made from: untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of: PVP 2000, PVP 10 000 or PVP 50 000, at a compression speed of 10 mm s^{-1} ($n = 4$; $\pm$ SD).

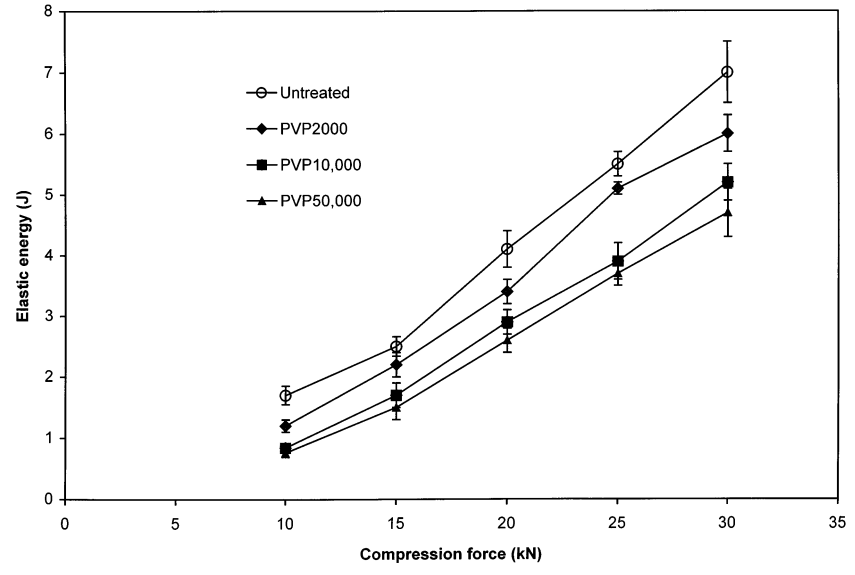

Fig. 4. Effect of compression force on the elastic energies of tablets made from: untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of: PVP 2000, PVP 10 000 or PVP 50 000, at a compression speed of 10 mm s^{-1} ($n = 4$; $\pm$ SD).

bonds between each other. The adsorbed PVP in the paracetamol crystals may also increase the interparticulate bonding between the particles, even at low concentrations.

The effects of compression force or compression speed on the elastic energies of tablets made from untreated paracetamol and paracetamol crystallized in the presence of 0.5% w/v PVP are

illustrated in Figs. 4 and 5. These figures indicate that, at different compression forces or speeds, the elastic energies of tablets made from particles crystallized in the presence of PVP were less than that of the untreated paracetamol. These figures also reveal that the elastic energies of tablets made from particles crystallized in the presence of higher molecular weight PVP were less than for particles obtained in presence of lower molecular weight PVP. However, Tukey's test showed that there were no significant differences ($p > 0.05$) between the elastic energies of samples obtained in the presence of PVP 10 000 or PVP 50 000 at all compression forces, and also at 10 or 50 mm s^{-1} compression speeds. These results indicated that particles crystallized in the presence of PVP showed less elastic behaviour than the untreated paracetamol.

The effects of compression force or compression speed on the plastic energies of tablets made from untreated paracetamol and paracetamol crystallized in the presence of 0.5% w/v of PVP are illustrated in Figs. 6 and 7. These figures clearly indicate that the plastic energies of tablets made from particles crystallized in the presence of PVP were much higher than for untreated particles. These data also indicate that the plastic energies increased as the molecular weight of PVP increased. Tukey's test revealed that the differences between the plastic energies of paracetamol crystallized in the presence of PVP 10 000 or PVP 50 000 were not significant at 20 kN compression force, and also at 50, 100 and 250 mm s^{-1} compression speeds. The increases in plastic energy of tablets made from particles crystallized in the presence of PVP may be attributed to the energy required for fragmentation of these particles and most importantly to the formation of bonds between the particles during compression. The high crushing strengths of the tablets made from these particles indicated strong interparticulate bonding.

Tables 4 and 5 show the effect of compression force or compression speed on the elastic energy/plastic energy ratios (EE/PE) of tablets made from untreated paracetamol and paracetamol crystallized in the presence of 0.5% w/v PVP. The ratios of EE/PE for particles crystallized in the presence of PVP were much lower than for untreated crystals. These results indicate that for untreated particles the major portion of compres-

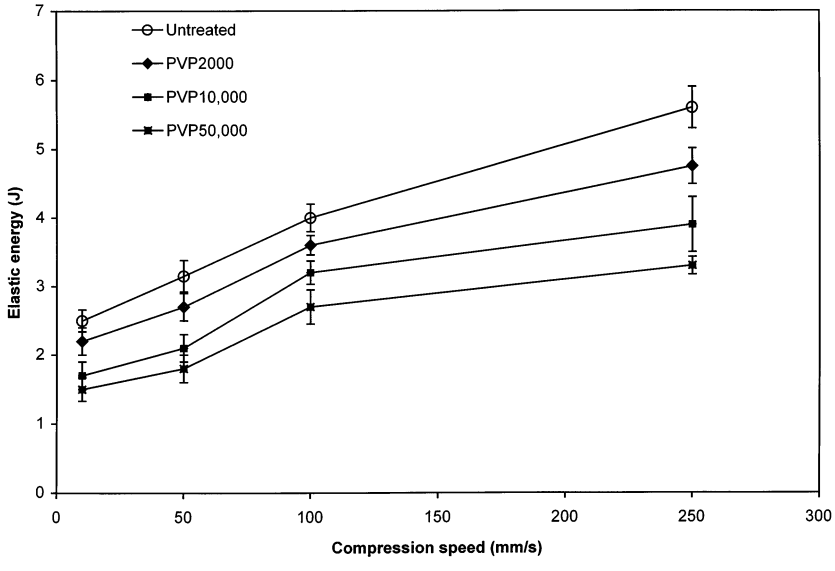

Fig. 5. Effect of compression speed on the elastic energies of tablets made from: untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of: PVP 2000, PVP 10 000 or PVP 50 000, at a compression force of 15 kN ($n = 4$; $\pm$ SD).

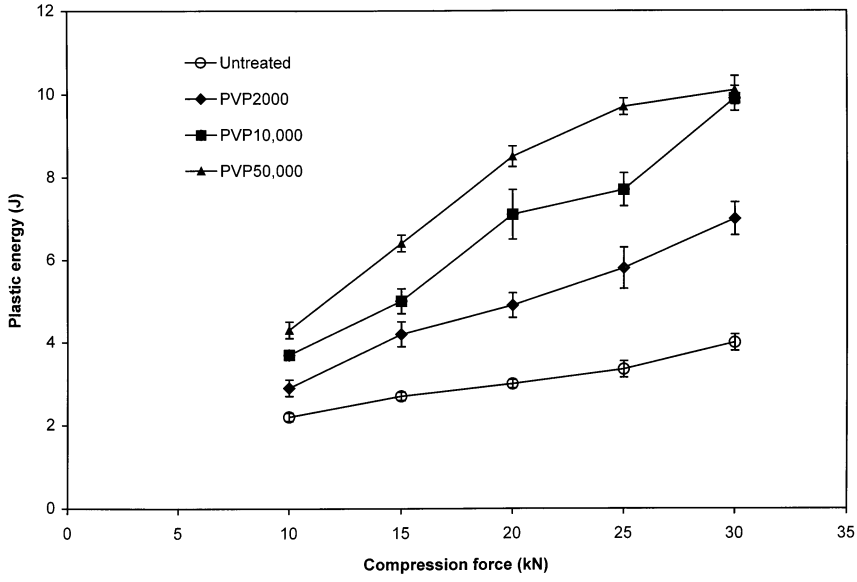

Fig. 6. Effect of compression force on the plastic energies of tablets made from: untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of: PVP 2000, PVP 10 000 or PVP 50 000, at a compression speed of 10 mm s^{-1} ($n = 4$; $\pm$ SD).

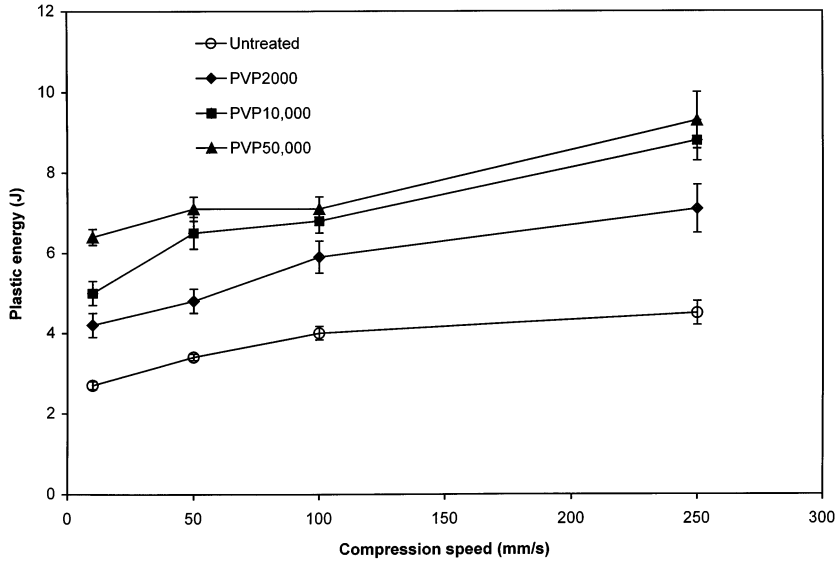

Fig. 7. Effect of compression speed on the plastic energies of tablets made from: untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of: PVP 2000, PVP 10 000 or PVP 50 000, at a compression force of 15 kN ($n = 4$; $\pm$ SD).

sion energy is utilised as elastic energy, while for particles obtained in the presence of PVP a minor portion is used as elastic energy. Tables 4 and 5 also indicate that paracetamol crystallized in the presence of higher molecular weight of PVP (10 000 or 50 000) exhibited lower EE/PE ratios than those obtained in the presence of PVP 2000. However, Tukey's test revealed that there were no

Table 4
Effect of compression force on the ratio of elastic energy/plastic energy of tablets made from paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP, at a compression speed of 10 mm s^{-1} ($n = 4$; ± SD)

Compression force (kN)	Elastic energy/plastic energy ratio ± SD			
	Particles crystallized in presence of:			Untreated paracetamol
	PVP 2000	PVP 10 000	PVP 50 000	
10	0.41 ± 0.04	0.23 ± 0.02	0.18 ± 0.01	0.74 ± 0.06
15	0.52 ± 0.05	0.34 ± 0.05	0.23 ± 0.03	0.91 ± 0.04
20	0.75 ± 0.07	0.47 ± 0.05	0.38 ± 0.03	1.36 ± 0.14
25	1.00 ± 0.07	0.59 ± 0.09	0.44 ± 0.06	1.73 ± 0.11
30	1.10 ± 0.15	0.66 ± 0.09	0.52 ± 0.07	1.78 ± 0.17

Table 5
Effect of compression speed on the ratio of elastic energy/plastic energy of tablets made from paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP, at a compression force of 15 kN ($n = 4$; ± SD)

Compression speed (mm s^{-1})	Elastic energy/plastic energy ratio ± SD			
	Particles crystallized in presence of:			Untreated paracetamol
	PVP 2000	PVP 10 000	PVP 50 000	
10	0.52 ± 0.05	0.34 ± 0.05	0.23 ± 0.03	0.91 ± 0.04
50	0.56 ± 0.09	0.32 ± 0.05	0.26 ± 0.04	0.92 ± 0.08
100	0.62 ± 0.04	0.47 ± 0.05	0.38 ± 0.03	1.00 ± 0.06
250	0.67 ± 0.04	0.44 ± 0.06	0.36 ± 0.03	1.24 ± 0.10

significant differences ($p > 0.05$) between the EE/PE ratios for particles crystallized in the presence of PVP 10 000 or PVP 50 000 at compression speeds of 50 and 250 mm s^{-1}, and also at a compression force of 30 kN. It has been reported that the relative high EE/PE ratio is indicating that the majority of energy involved during compression, is utilised as elastic energy due to high elastic deformation of paracetamol particles. This is an important factor in capping and failure of paracetamol tablets during compression (Garr and Rubinstein, 1991; Garekani, 1996).

4. Conclusions

Crystallization of paracetamol in the presence of PVP significantly improved its compression properties as compared to untreated paracetamol. Particles crystallized in the presence of 0.5% w/v PVP 10 000 or PVP 50 000 produced tablets with excellent crushing strength with no tendency to cap even at high compression speeds. However, particles crystallized in the presence of PVP 2000 exhibited less improvement in their compression properties.

It was found that particles crystallized in the presence of PVP 10 000 or PVP 50 000 underwent a high degree of fragmentation during compression resulting in the formation of numerous fresh and clean surfaces for particle/particle bondings.

The results of elastic recovery, elastic energy and elastic energy/plastic energy ratios, revealed that particles crystallized in the presence of PVP exhibited much less elastic behaviour under pressure, as compared to untreated paracetamol particles.

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