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Crystallization conditions and formation of orthorhombic paracetamol from ethanolic solution

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Abstract

Orthorhombic paracetamol exhibits far better tabletability than the monoclinic form and its bulk crystallization from solution attracts much interest. In this study, temperature changes in supersaturated ethanolic solution have been recorded after seeding with orthorhombic crystals under different cooling temperatures (T_C) and agitation rates (AR). Average cooling rate (CR), time for maximum temperature deviation (t_{max}) and area confined between curves of measured and reference temperature plots (AUC) were calculated and correlated with crystal yield (Y). The micromeritic (size and shape) and the compression properties, the density and the orthorhombic content of the crystalline product were evaluated and related to the main crystallization conditions applied (T_C and AR). Conditions for optimal crystal yield and orthorhombic content were elucidated. It was found that crystal yield (Y) increased with AR and decreased with T_C. The ratio t_{max}/CR provided good prediction of crystal yield ($Y = 58.92 - 1.386\ t_{max}/CR$, $r^2 = 0.964$ and $P = 0.0001$). T_C and AR linearly affected crystal size and the size distribution, probably due to alterations in supersaturation, but they did not affect the crystal shape significantly. Density and compression properties (yield pressure and elastic recovery) were determined by the content of the orthorhombic form, which increased linearly with AR ($P = 0.009$) and with T_C ($P = 0.039$) when agitation was between 300 and 500 rev min^{-1}, while t_{max} decreased. At 700 rev min^{-1} orthorhombic content was maximized and became independent to T_C. Higher orthorhombic content and crystal yield was expected for lower T_C and for lower t_{max}, which corresponded to higher AR and might have also been affected by alteration of seeding and harvesting procedure.

Introduction

Monoclinic paracetamol is produced in large quantities and is used as high-dose tablets (300–500 mg) exhibiting very poor compression ability. However, paracetamol with improved compactability has been prepared in laboratory-scale by modifying the crystallization process (Fachaux et al 1995a, b), by crystallization in the presence of polymers (Nath & Nalwade 1987; Femi-Oyewo & Spring 1994; Kachrimanis & Malamataris 1999; Garekani et al 2000a, b) or by changing the crystallization solvent (Nath & Khalil 1984; El-Said 1995; Shekunov et al 1997; Garekani et al 1999). However, the improvement has been limited because it came only from changes in the shape (habit) instead of in the lattice of crystals. Therefore, mixtures of paracetamol with polyvinylpyrrolidone (PVP), gelatine or starch derivatives have been manufactured for direct compression (Bolhuis & Chowan 1995). The considerable efforts made by investigators for the preparation of pure

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paracetamol suitable for direct compression are justified (Di Martino et al 1996, 1997; Nichols & Frampton 1998).

In the literature, three polymorphs of paracetamol have been reported. The monoclinic form, form I, the orthorhombic, form II, and a very unstable form III (Haisa et al 1974, 1976; Di Martino et al 1997). The monoclinic lacks slip planes in its crystal structure, which is a prerequisite for plastic deformation upon compaction. In contrast, orthorhombic paracetamol (form II) has well-developed slip planes in its crystal structure and, as a result, it undergoes plastic deformation upon compaction (Joiris et al 1998). Consequently, the ability to produce form II in quantity has attracted much interest.

Up until now, the only method that has been reported for the bulk preparation of form II has been to grow it as polycrystalline material from fused form I in a nonoxidizing atmosphere (Di Martino et al 1996, 1997). However, the scaling up of this method, to suit the industrial process, seems difficult because of the high oxidability of melted paracetamol and the overlap of the two forms' transition phases (De Wet et al 1998). Nichols & Frampton (1998) developed a laboratory-scale method of crystallization from solution for form II, by nucleation of a supersaturated solution of industrial methylated spirit with seeds of form II (obtained from melt-crystallized paracetamol). Unfortunately the yield was low (less than 30%); to increase the yield for commercial production of form II, the crystallization and recovery process would need to be optimized.

In this study we have attempted to make a detailed investigation on the method originally reported by Nichols & Frampton (1998). Temperature changes in supersaturated ethanolic solution of paracetamol, crystal yield, polymorphic purity, micromeritic properties and compression behaviour of the crystalline product were measured as a function of the main crystallization conditions i.e. cooling temperature (T_C) and agitation rate (AR).

Materials and Methods

Materials

Monoclinic microcrystalline paracetamol (Eu.Ph. grade, from Boehringer Ingelheim, Germany, supplied by Boehringer Ingelheim, Athens, Greece), double distilled ethanol (96%, b.p. 79°C) and spectroscopic grade potassium bromide (Uvasol, Merck, Darmstadt, Germany) were used.

Preparation of orthorhombic seed-crystals from melt

The method suggested by Sohn (1990) was applied. Approximately 5 mg monoclinic paracetamol powder was completely melted on a glass microscopic slide, at 190°C, using a controlled temperature hot plate (Stuart Scientific, SH1D, UK). The slide was then rapidly cooled by placing it on a metallic block, at room temperature, and covered with a Petri dish to avoid contamination. After complete crystallization, FT-IR spectroscopic analysis was performed on 2 mg of the crystallized melt, as a quick and simple method to ensure the existence of the pure orthorhombic form (Al-Zoubi et al 2000). The remaining melt on the slide was kept in a desiccator over phosphorus pentoxide until required for seeding.

Crystallization of orthorhombic paracetamol from solution

A 1000-mL crystallizer was used. It was a cylindrical (7 × 30 cm) glass-vessel with a jacketed wall connected with double valves to refrigerated and heated circulators, for flexible change and better cooling control. The temperature inside the crystallizing liquid was monitored by a Pt 100 thermistor connected to an electronic polymeter (Handyscope, Tie Pie Engineering, The Netherlands) and to a computer.

For the crystallization, 150 g monoclinic paracetamol was dissolved in 500 mL ethanol kept under agitation, at a constant temperature of 50°C, in a 1-L beaker, until a clear solution was obtained. The solution was then carefully transferred, with a long-neck glass funnel, into the crystallization vessel, also thermostated at 50°C by circulating warm water through the jacketed wall. The solution was not agitated and its clarity was checked again. The circulation of the warm (50°C) water was then stopped, allowing the content of the jacketed wall and tubes to drain, and cooling was commenced by circulating cold fluid (mixture of water with anti-freeze solution) at −10, 0 or +10°C. After cooling for exactly 10 min, the crystallization solution was seeded, by gently scrapping the surface of the recrystallized paracetamol-melt that remained on the slide with a blade, adding approximately 0.5 mg seed-crystals, and agitation was commenced at 300, 500 or 700 rev min^{-1}. Twenty minutes after seeding, the crystals produced were harvested by filtration under vacuum and dried.

The drying equipment consisted of a 100-μm sieve placed under another of 10 μm on a metallic base having a side opening (air inlet). The harvested crystals were spread on the 100-μm sieve already placed on the base

and the top sieve was fitted (allowing escape of air and preventing loss of crystals). Then air was blown, at room temperature, for 1 h; the 100-μm sieve with the crystals was subsequently removed and left in the open-air for 24 h for evaporation of any remaining traces of ethanol. This procedure did not involve heating, minimized drying time and therefore the risk of transformation. Finally, the crystals were collected, weighed and kept in plastic bottles until required for examination.

Temperature change of crystallization liquid

Temperature of the crystallization liquid was measured through the cooling period with an accuracy of ± 0.01°C. Data for approximately 900 points were collected and graphs were plotted with and without paracetamol (reference). The temperature at which the angle between the tangents of the two plots became greatest, T_m, was determined. Then the extrapolated point, T_d, was obtained as the intersection of the vertical passing from T_m and the reference plot (Nikolakakis et al 2000). T_d was the ideal cooling temperature that corresponded to the maximum rate of temperature deviation in the crystallization solution and was considered as an indication of maximum crystallization rate. The time, t_{max}, from seeding to maximum crystallization rate was further determined. The area confined between the curves of the measured and reference plots (AUC) was calculated by using the trapezoidal rule. Average cooling rate from the time of seeding to the end of each crystallization run was calculated as the difference between corresponding temperatures divided by the duration (20 min). Finally, the crystal yield (Y) was calculated from the weight of crystals expressed as percentage of paracetamol dissolved initially (150 g).

Characterization of crystalline product

Content of the orthorhombic form (% w/w) and true density were selected as composition parameters. The micromeritic properties of size and shape were evaluated also. The yield pressure and the elastic recovery of compacted crystalline product were selected as parameters of compression behaviour.

For the determination of the orthorhombic content, KBr disks (1% w/w) were analysed, using a Perkin Elmer FT-IR 1605 spectrophotometer, following a purposely-developed method (Al-Zoubi et al 2000), which was validated by XRD and FT-Raman spectroscopy. Three determinations were made and the mean and standard deviation were calculated. The true density of the crystals was determined with a Beckman, model 930, air comparison pycnometer using samples of 20 g and taking the mean of five measurements.

The circle equivalent diameter (CED) of single crystals was measured using an image processing and analysis system (Quantimet 500, Leica, Cambrige, UK). At least 500 crystals were measured in four optical fields of samples dispersed in paraffin oil. Mean diameter by number and standard deviation was calculated. The size data were fitted into the three-parameter Gaussian equation and the coefficient of determination (r^2) was obtained by applying non-linear regression analysis (SigmaPlot 5.0). r^2 was taken as a measure of the goodness of fit or of the closeness of size distribution to normal. The aspect ratio and the roundness were determined as described by Nikolakakis et al (2000).

Parameters of compression behaviour of crystals were obtained, without any size classification, from compression tests on an instrumented tablet machine (Kachrimanis et al 1998). Logarithm of reciprocal porosity was plotted against applied pressure (Heckel 1961) and yield pressure was calculated as the reciprocal of the slope in the linear part of the plot. Elastic recovery (%) of the compacts was evaluated from their thickness under maximum load and 24 h after ejection (Malamataris & Rees 1993). Five samples from each batch were compressed and mean values and standard deviations were calculated.

Experimental design and statistical analysis

A full factorial experimental design was followed with two factors or independent variables (agitation rate, AR, and cooling temperature, T_C), at three equally spaced levels (0 ± 10°C and 500 ± 200 rev min^{-1}) and one replicated central point (Montgomery 1997). The experimental data were fitted to a second-order polynomial equation by applying multiple linear regression. Analysis of variance (F-test) was subsequently used to evaluate the statistical significance of the polynomials and of the effects of the main crystallization factors (linear and quadratic terms) and of their interaction. Methodology of contour plots was applied to visualize the effects of the crystallization factors and elucidate the conditions for optimal crystal yield and orthorhombic content. For statistical analysis the program SPSS 9.0 (Inc. Chicago, IL) was used.

Results and Discussion

The results of the parameters of temperature change in the crystallization liquid are given in Table 1 together with crystal yield, the content of orthorhombic form

Table 1 Parameters of temperature change in the crystallization liquid, crystal yield and composition properties of crystalline product obtained under different agitation rates and cooling temperatures.

Agitation rate (rev min^{-1})	Cooling temperature T_c (°C)	Average cooling rate (°C min^{-1})	t_{max} (min)	Crystal yield (%)	AUC (°C min)	Orthorhombic content (%)	Crystal density* (g mL^{-1})
300	−10	0.96	17.4	29.0	13.8	38.6±5.1	1.309
300	0	0.62	16.1	23.0	8.3	56.3±4.7	1.311
300	10	0.44	18.0	2.1	6.3	100.0±2.0	1.339
500	−10	0.76	12.5	39.6	8.5	85.4±6.4	1.321
500	0	0.72	10.2	38.9	10.4	89.1±5.6	1.322
500	10	0.48	8.7	37.7	7.4	90.1±3.2	1.333
700	−10	0.83	6.2	47.9	16.8	100.0±2.0	1.338
700	0	0.68	6.0	46.5	12.5	100.0±2.0	1.339
700	10	0.49	6.3	37.7	11.0	100.0±2.0	1.340
500	0	0.66	8.9	42.7	8.6	82.1±4.4	1.325

*Mean±0.001.

Table 2 Circle equivalent diameter and compression parameters for crystals obtained under different agitation rates and cooling temperatures.

Agitation rate (rev min^{-1})	Cooling temperature (°C)	Circle equivalent diameter			Yield pressure (MPa) (mean±s.d.)	% Elastic recovery (mean±s.d.)
		(μm) mean±s.d.	Gaussian fit (r^2) and (p)			
300	−10	91±55	0.606	0.061	83.7±2.9	5.6±0.3
300	0	100±59	0.529	0.072	82.4±3.4	6.6±0.2
300	10	217±127	0.079	0.519	69.3±2.1	3.0±0.1
500	−10	66±29	0.782	0.102	72.0±2.5	3.4±0.2
500	0	96±57	0.698	0.001	69.8±2.2	3.8±0.2
500	10	130±88	0.432	0.014	73.6±3.4	3.1±0.2
700	−10	61±29	0.771	0.229	71.9±2.8	3.1±0.2
700	0	106±62	0.767	< 0.001	71.0±3.7	3.3±0.3
700	10	79±39	0.888	0.004	70.6±1.9	2.3±0.2
500	0	108±61	0.571	0.009	70.1±1.7	3.4±0.2

and the true density. In Table 2 the micromeritic properties are summarized together with the compression parameters for all the crystalline products.

Temperature change in the crystallization liquid

From Table 1 it can be seen that average cooling rate decreased with increasing cooling temperature, as expected. It seemed to be affected by the agitation in a different way for each cooling temperature applied. Regression analysis applied to the data irrespective of agitation showed a direct linear relationship between the average cooling rate (CR) and the cooling temperature (r^2 = 0.893 for n = 10). This meant that the degree of supersaturation was determined mainly by cooling temperature (T_C).

The values of time for maximum crystallization rate, t_{max} in Table 1, decreased with increasing agitation rate, as expected. t_{max} was a parameter expressing the speed of crystallization. Regression analysis between t_{max} and agitation rate gave a straight line of a very high correlation coefficient (r^2 = 0.911, for n = 10).

Crystal yield

The values of crystal yield (Y) in Table 1 and in Figure 1 (presented as contour plots) generally increased with agitation rate (AR) and decreased with cooling tem-

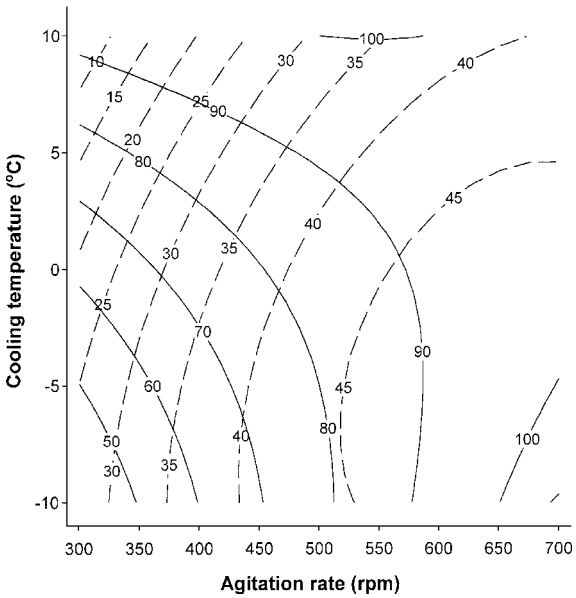

Figure 1 Superimposed contour plots of crystal yield (dashed line) and orthorhombic content (solid line) for the crystallization conditions applied.

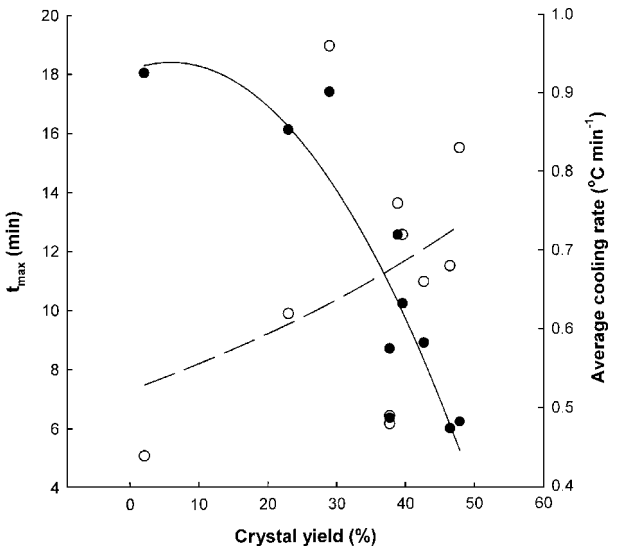

Figure 2 Plots of crystal yield with t_{max} (solid line, closed symbols) and average cooling rate (dashed line, open symbols).

perature (T_C). The polynomial equation expressing the relationship was:

$$Y\% = -40.78 + 0.26AR - 1.69T_C + 2.09 \times 10^{-3}(AR) \times (T_C) - 2.00 \times 10^{-4}(AR)^2 - 4.11 \times 10^{-2}(T_C)^2 \quad (1)$$
$$(r^2 = 0.933)$$

Analysis of variance for equation 1 gave F = 11.23 and $P = 0.018$, for df = 5, 4, while the test for lack of fit was not significant, showing that it fitted the data adequately. Analysis of variance for the effects of the factors under examination, given in Table 3, showed that the linear T_C term was significant ($P = 0.039$), whereas for AR the linear and the quadratic terms were significant ($P = 0.004$ and 0.081, respectively). This last effect can be

Table 3 Analysis of variance (F and *P* values) for crystal yield, size and parameters of composition and compression behaviour.

Results	Agitation rate				Cooling temperature				Interaction	
	Linear		Quadratic		Linear		Quadratic		F	*P*
	F	*P*	F	*P*	F	*P*	F	*P*		
Crystal yield	36.54	0.004	5.39	0.081	9.13	0.039	1.42	0.300	2.51	0.188
Mean diameter	6.00	0.050	0.15	0.722	6.82	0.059	0.13	0.739	2.53	0.187
Diameter s.d.	6.22	0.067	0.06	0.818	10.04	0.034	0.0	0.942	2.91	0.163
Gaussian fit	26.89	0.007	0.01	0.926	10.57	0.031	0.57	0.492	11.39	0.028
Orthorhombic content	23.23	0.009	0.73	0.442	9.19	0.039	0.63	0.471	11.89	0.026
Crystal density	31.45	0.005	1.35	0.310	18.10	0.013	3.56	0.132	10.99	0.029
Yield pressure	5.26	0.084	1.89	0.241	2.18	0.214	0.02	0.885	2.82	0.168
Elastic recovery	11.80	0.026	2.03	0.227	3.82	0.122	3.74	0.125	1.36	0.309

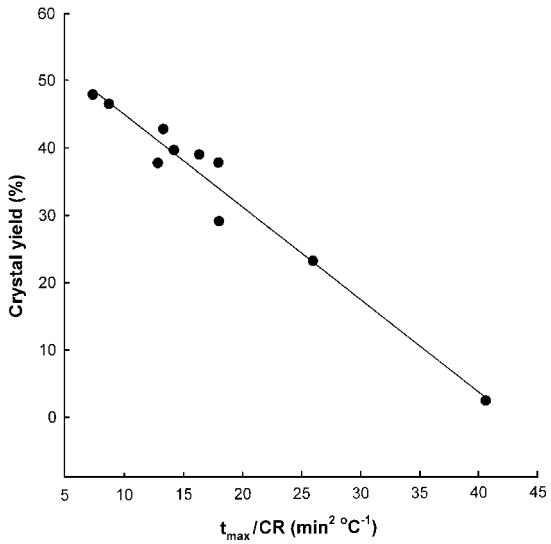

Figure 3 Crystal yield vs the ratio of time for the maximum crystallization rate after seeding to average cooling rate (t_{max}/CR).

possibly explained by the dissolving effect at high agitation, which suppressed nucleation rate and crystal growth. Since short harvesting time was used as a precaution to avoid transformation of crystal form (Nichols & Frampton 1998) and since t_{max} expressed the speed, and presumably the completion of crystallization, a relationship was expected between crystal yield and t_{max}. Figure 2 shows plots of crystal yield, Y, with t_{max} and average cooling rate. It can be seen that Y decreased with t_{max} and increased with cooling rate, probably due to an increase of supersaturation. Taking into account the effects of t_{max} and cooling rate (CR) on yield (Y) and plotting it against the ratio t_{max}/CR (Figure 3), a direct straight line of excellent fit was obtained ($r^2 = 0.964$, $n = 10$), which could be used for predictions and was expressed by equation 2:

$$Y = 58.92 - 1.386 t_{max}/CR \quad (2)$$

This equation showed that the highest possible crystal yield was 58.92%, which was approximately 10% higher than the achieved maximum value under the applied experimental conditions. Therefore, further optimization was justified.

A relation between crystal yield and AUC was also expected, since AUC represented the heat evolved due to crystallization. From Table 1 it can be seen that AUC increased with average cooling rate or that it depended on the degree of supersaturation. Furthermore, the average value of AUC for the crystallization experiments carried out under certain agitation rates showed remarkable increases for the high agitation rate. The average value of AUC at 700 rev min^{-1} was 13.4 compared with 8.7 and 9.5°C min for 500 and 300 rev min^{-1}, respectively. Regression analysis showed that a relationship between crystal yield and AUC could be found only after involvement of agitation rate (AR) as well as cooling rate (CR):

$$Y = 4.103AUC - 290.51AUC/(CR \times AR) \quad (3)$$

However, the correlation coeffi cient for equation 3 ($r^2 = 0.919$, $n = 10$) was lower than that for equation 2 including t_{max}. Therefore t_{max} provided a simpler and better correlation with yield.

Micromeritic properties

From Table 2 it can be seen that mean diameter and standard deviation (s.d.) of mean diameter increased with cooling temperature, except for the cases of 700 rev min^{-1} and decrease with agitation. The effect of agitation was more pronounced at the high level of cooling temperature (+10°C). This might have been due to the reduction in the degree of supersaturation. Analysis of variance (Table 3) showed that the effect of cooling temperature and agitation was mainly linear ($P = 0.059$ and 0.034 for cooling and $P = 0.050$ and 0.067 for agitation on mean diameter and diameter s.d., respectively).

The results of the goodness of fit for the Gaussian equation (Table 2) showed that size distribution became closer to normal (r^2 increased) as the agitation rate increased and deviated from normal (r^2 decreased) as cooling temperature increased, with the exception for the cases of high agitation rate (700 rev min^{-1}). The effect of cooling became negligible at high agitation. Therefore, the general effect of cooling was smaller than that of agitation. Analysis of variance (Table 3) showed that the effect of cooling temperature and agitation was mainly linear ($P = 0.031$ for cooling and $P = 0.007$ for agitation). The effect of agitation was greater at high cooling temperature, implying interaction between the two factors ($P = 0.028$).

As far as crystal shape was concerned, the parameters evaluated did not show any general and characteristic change related to the alteration of the crystallization conditions (AR and T_C). This may be because the factors known to greatly affect the crystal shape, such as solvent type (El Said 1995; Garekani et al 1999), presence of polymers (Kachrimanis & Malamataris 1999), and impurities (Chow & Grant 1989), are not involved in the applied experimental design. Another possible explanation for the absence of characteristic change might have been the predominance of size and crystal form changes over those in growth rate of the different crystal

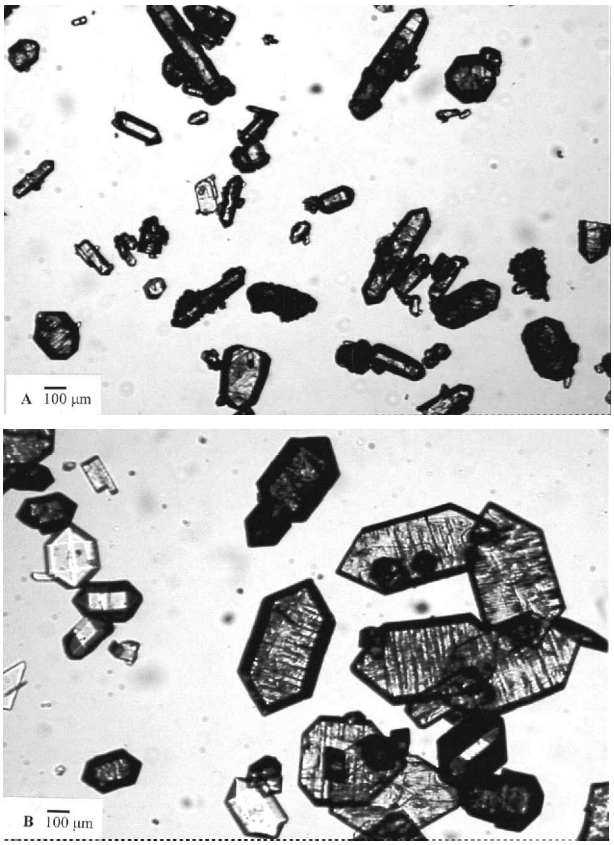

Figure 4 Microphotographs of crystals with great difference in orthorhombic content prepared at certain agitation (300 rev min^{-1}) but under different cooling temperature: A, −10°C; and B, +10°C.

faces. Figure 4 shows microphotographs of crystals with great differences in orthorhombic content prepared at certain agitation rates (300 rev min^{-1}) but under different cooling temperatures.

Composition and compression properties

The results of orthorhombic content and density (Table 1) showed that the effects of agitation and cooling temperature were similar for both, and this was also indicated in Table 3 by the terms of similar significance. This was attributed to the difference in crystal density between the two forms (1.29 g cm^{-3} for monoclinic and 1.34 g cm^{-3} for orthorhombic) and to the linear relation between crystal density and orthorhombic content for all the crystalline products examined (density = 0.052 orthorhombic content $\times 10^{-2} + 1.284$, $r^2 = 0.842$, n = 10).

The yield pressure and elastic recovery (Table 2) seemed to decrease with agitation rate and this was the

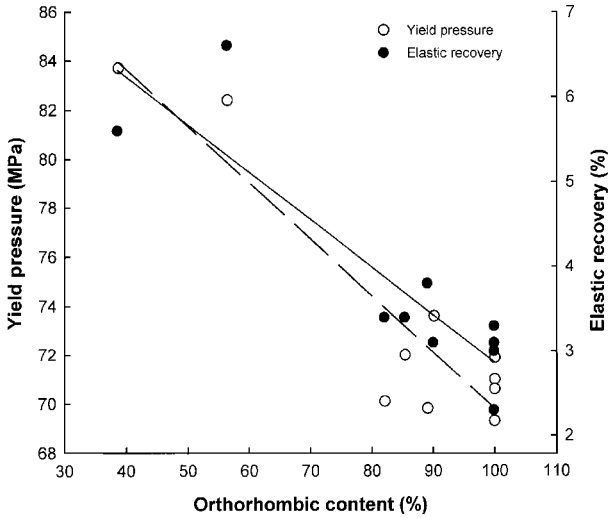

Figure 5 Plots of yield pressure (dashed line) and elastic recovery (solid line) of compact vs the content of orthorhombic form.

only significant effect due to the crystallization conditions examined, as analysis of variance showed (Table 3). It should be attributed to change in crystal form, because it is known that the crystal form of paracetamol affects yield pressure and elastic recovery (Joiris et al 1998; Nichols & Frampton 1998). Plots of compression parameters vs the orthorhombic content (Figure 5), show that they decreased linearly with orthorhombic content ($r^2 = 0.920$ and 0.791, n = 10, for yield pressure and elastic recovery, respectively). This confirmed that orthorhombic paracetamol could be tableted by direct compression. We observed that intact tablets were always formed when the orthorhombic content was higher than 80%. At the lower contents (38.6 and 56.3%), however, a number of compression trials had to be made to produce intact tablets.

The content of the orthorhombic form (Table 1) seemed to be affected by the agitation rate and the cooling temperature applied. The changes in the orthorhombic content with the crystallization conditions are shown in Figure 1, and show that higher orthorhombic content was obtained at higher agitation rates and cooling temperatures. The polynomial expressing the change was:

$$\text{orthorhombic content \%} = 9.45 + 0.21\text{AR} + 4.94T_C - 7.68\times10^{-3}(\text{AR}) \times (T_C) - 1.24\times10^{-4}(\text{AR})^2 + 4.64\times10^{-2}(T_C)^2 \quad (4)$$

($r^2 = 0.919$)

Analysis of variance for equation 4 gave F = 9.10 and $P = 0.026$, for df = 5, 4, while the test for lack of fit was

not significant, showing that it fitted the data adequately. Analysis of variance for the effects of the factors under examination (Table 3) showed that the linear terms for T_C and AR ($P = 0.039$ and 0.009, respectively) were significant. Table 3 shows that there was significant interaction ($P = 0.026$) between the two factors (T_C and AR). The dependence of the cooling effect on the orthorhombic content from agitation can be seen from the values in Table 1. The increase of the orthorhombic content with cooling temperature took place for agitation at 300 and 500 rev min^{-1}, but not for 700 rev min^{-1}. A similar increase took place with agitation but only for cooling at -10 and 0°C.

The increase of the orthorhombic content with cooling temperature and agitation rate should be related to the kinetics of crystallization and of instability for the orthorhombic form. The orthorhombic form, which is thermodynamically less stable than the monoclinic, should crystallize initially because of the lower energy requirement. Later, the orthorhombic nuclei or crystals transform to monoclinic resulting in the decrease of the orthorhombic content observed. Therefore, a higher orthorhombic content was expected for a higher cooling temperature (lower supersaturation rate) and for quicker completion of the crystallization or shorter t_{max}, which corresponded to higher agitation as already mentioned. However, the higher cooling temperature reduced the crystal yield and might have accelerated transformation of the orthorhombic form. Cooling temperature and agitation rate for optimum crystal yield and orthorhombic content could be found by superimposing the corresponding contour plots (Figure 1). This was at approximately 650 rev min^{-1} and -5°C and further experiments are needed for exact determination and achievement of yield closer to the theoretical ($\sim 59\%$). Furthermore, the seeding and harvesting procedure (seeding temperature and crystallization time) might have affected yield and orthorhombic content but in this experimental design they were unchanged.

It can be concluded that for the crystallization of paracetamol from an ethanolic solution by seeding, the crystal yield increased with agitation rate and decreased with cooling temperature. Among the parameters examined for temperature change in the crystallization liquid (CR, t_{max} and AUC), the ratio t_{max}/CR provided a simpler and better correlation with crystal yield ($Y = 58.92 - 1.386 t_{max}/CR$, $r^2 = 0.964$ for $n = 10$). Cooling temperature and agitation linearly affected the crystal size (mean diameter) and the size distribution, probably due to alterations in the degree of supersaturation. Crystal shape did not show any general characteristic change probably due to the predominance of size and crystal form changes. Density, yield pressure and elastic recovery were determined by the proportion of the orthorhombic form, which increased linearly with agitation rate ($P = 0.009$) and with cooling temperature ($P = 0.039$), but only for agitation in the range of 300 to 500 rev min^{-1}. Orthorhombic content was maximized and became independent to cooling temperature for agitation at 700 rev min^{-1}. However, orthorhombic content increased for shorter t_{max}, which corresponded to higher agitation and for higher cooling temperature that reduced the crystal yield and possibly the stability of the orthorhombic form.

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