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A new pure paracetamol for direct compression: the orthorhombic form

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Abstract

The poor compression ability of paracetamol is well known. The paracetamols for direct compression that can be found on the market are all compounds of paracetamol with gelatin, PVP, starch or starch derivatives. A pure paracetamol for direct compression, in keeping with the Pharmacopoeïa monograph would be particularly convenient. In a previous paper, we reported the preparation of a new pure paracetamol for direct compression: it was recrystallized from a dioxane solution and its crystals exhibited a sintered-like texture favourable to compression. The disadvantage of this paracetamol was the difficulty in obtaining complete elimination of residual solvent. In this work we have investigated the polymorphs of paracetamol. The usual form is the monoclinic form. The arrangement of the molecules inside the crystal presents a stiff construction, consequently its compression ability is poor. We prepared form II which crystallizes in the orthorhombic system. Its physical structure contains possible sliding planes. This is the reason why this polymorph exhibits good compression ability. We investigated this new form as far as its physical, technological and stability properties are concerned, using X-ray powder diffraction, thermal analysis, and an instrumented tablet machine. Tablets were formulated and their mechanical, biopharmaceutical and stability properties were studied.

Keywords: Paracetamol; Direct compression; Polymorphism

1. Introduction

Two polymorphic forms of paracetamol are generally mentioned in publications: (1) form I which crystallizes in the monoclinic system. Powder X-ray data have been proposed by several researchers (Haïsa et al., 1976; Nürnberg and Hopp, 1982; Welton and McCarthy, 1988). This is the usual commercial form, although its poor compression ability is quite well known. (2) form II which crystallizes in the orthorhombic system. Its physical structure was elucidated by Haïsa et al. (1974). This form was sometimes empirically

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observed by other researchers (Nürnberg and Hopp, 1982; Sohn, 1990), who had not, however, identified its crystalline structure as being orthorhombic. In these cases, form II was called 'metastable modification'.

In addition to these two forms, Bürger (1982) quoted a third modification, the instability of which is so high that it was not possible to investigate its structure and its physical properties.

In our study, the three polymorphic forms of paracetamol were prepared and their physical properties investigated using thermomicroscopy, DSC, infra-red spectroscopy and X-ray powder diffraction. Results will be reported in a future publication (Di Martino, Guyot-Hermann, Conflant and Bouché, unpublished).

The observation of the crystalline structure of form II from Haïsa's data shows that a sliding plane can be found in this structure, thus leading us to think that a certain plasticity may exist under compression. This property could allow for tablet preparation by direct compression. A trial preparation of this form II was carried out by Sohn (1990) in Korea. However, it seems that the material he obtained was slightly unstable. Stability under compression was improved by adding certain excipients.

The aim of this work was to try to prepare form II, to characterize it, and to investigate its technological properties and its stability.

2. Materials

2.1. Form I of paracetamol

(Monoclinic system): fine powder (mean diameter: $\leq$ 100 μm) Rhône Poulenc France and coarse powder (mean diameter: 313 μm) Rhône Poulenc France.

2.2. Form II of paracetamol

Form II (orthorhombic system) was prepared by melting form I in a stoppered flat-sided glass flask at 170°C in an anhydrous nitrogen atmosphere. After a slow cooling-down to room temperature, the solidified material was taken out of the flask and ground into a mortar. The 100–400 μm sieved fraction was recovered.

The raw material was a mixture of several batches. The polymorphic form of each batch was controlled by X-ray powder diffraction.

2.3. Excipients for tablet formulation

Maize starch (Roquette Fréres, Lestrem, France) Sorbitol (Roquette Fréres, France) Talc (Cooper Pharmaceutique, Melun, France) Avicel PH102® (SEPPIC, Paris, France) Sterotex® (Karlshamns).

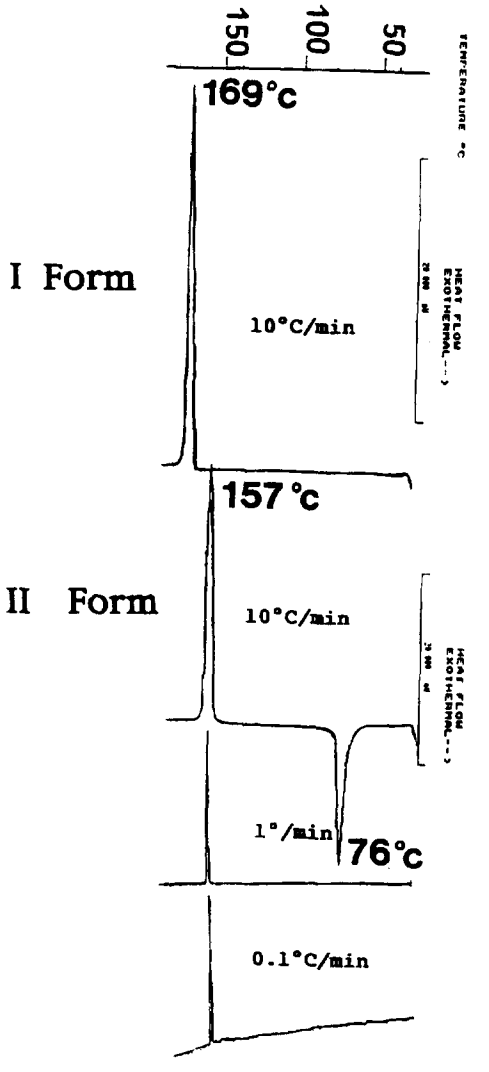

Fig. 1. DSC curves of forms I and II of paracetamol.

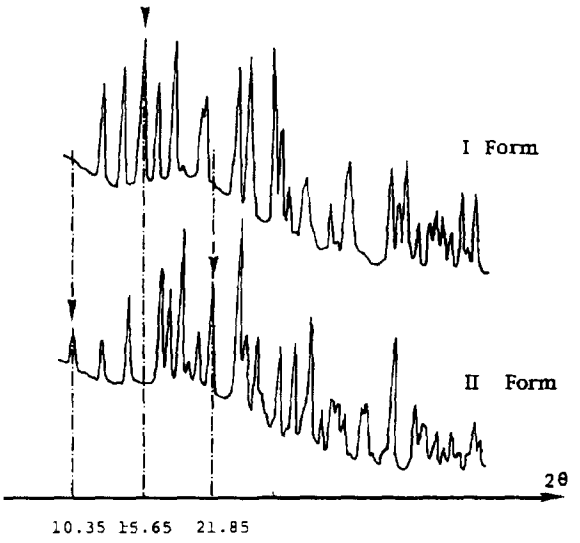

Fig. 2. Powder X-ray diffraction patterns of the polymorphic forms I and II of paracetamol. The arrows point to the characteristic reflection of each form of paracetamol, allowing for its quantitative evaluation.

3. Methods

3.1. Study of the crystals of form II of paracetamol

3.1.1. Thermal analysis

DSC measurements were performed using a Mettler TA 3000 DSC 20 differential scanning calorimeter. The weight of the samples was nearly 5 mg in closed aluminium pans. Heating rates were 0.1°C/min, 1°C/min and 10°C/min.

3.1.2. X-ray powder diffractometry

X-ray powder diffraction was carried out, at room temperature, using a Siemens X-ray diffraction device, fitted with a Guinier de Wolff Camera (Nonius) (Cu K$\bar{\alpha}$ radiation, $\lambda = 1.54178$ Å).

Densitograms were recorded with a Hoeger scanning densitometer.

3.1.3. Compression ability

Because some samples were very small, the 1 CP method was used on an instrumented alternative tablet machine (Lefebvre et al., 1991). Tablets

Table 1
Compression ability data of paracetamol II

	Y_1 (da N)	Y_2 (da N)	Y_2/Y_1	Crushing strength (da N)	Cohesion index
Batch 1	648	590	0.91	1.5	231.5
	647	584	0.90	1.8	278.2
	1610	1460	0.91	4.1	254.7
	2321	2099	0.90	4.5	193.9
	2572	2378	0.92	5.8	225.5
Batch 2	635	570	0.90	1.9	299.2
	639	574	0.90	2.3	359.9
	764	686	0.90	2.0	261.8
	1317	1182	0.90	3.5	250.6
	2078	1890	0.91	4.7	226.2
	2548	2319	0.91	4.7	184.5
Batch 3	537	484	0.90	1.3	242.1
	854	766	0.90	2.7	316.2
	1421	1284	0.90	3.0	211.1
	1523	1388	0.91	4.3	282.3
	2144	2099	0.98	4.9	228.5
	2501	2230	0.92	5.0	199.9
	2539	2323	0.91	5.6	220.6

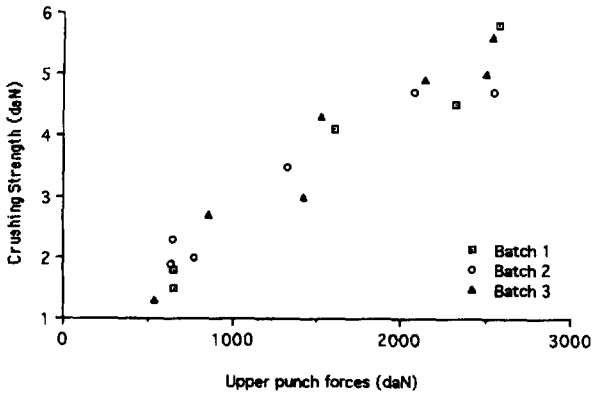

Fig. 3. Evaluation of crushing strength versus Y_1 force on the upper punch (three batches).

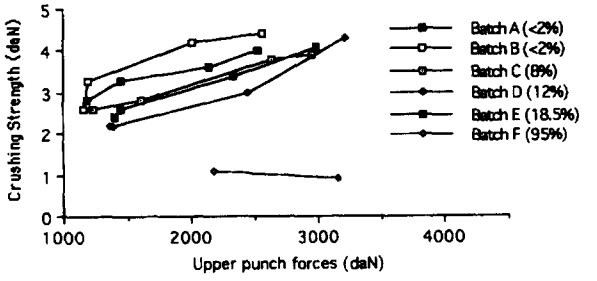

Fig. 4. Evaluation of crushing strength versus Y_1 force on the upper punch: batches containing different amounts of form I.

were produced one after another, in standardized conditions by introducing powder samples manually into the prelubricated die. The Y_1 force affecting the upper punch and the Y_2 force affecting the lower punch were noted. Different adjustments of the upper punch displacements were made to obtain different compression forces (Y_1). The Y_2/Y_1 ratio is indicative of the transmission forces through the powder. Crushing strength was measured with a Schleuniger hardness tester.

The ratio crushing strength/Y_1 is indicative of compression ability: it is multiplied by 10^5 for easier use and represents the 'Cohesion index': the higher this Cohesion index, the better the compressibility (Guyot et al., 1992).

3.1.4. Dissolution study

We investigated the dissolution properties of the orthorhombic form in comparison with those of the monoclinic form. Dissolution was carried out in continuous flow cells (Merle et al., 1977) in hydrochlorhydric acid 0.1 N at 37°C. At regular intervals, samples were taken, the concentration of paracetamol in each sample was determined, based on absorbance at $\lambda = 245$ nm. For each polymorphic form of paracetamol, we used fine and coarse crystals.

3.2. Study of tablets containing form II of paracetamol

3.2.1. Formulation, preparation and compression investigation

The formulation for one tablet was as follows:

II Paracetamol	500 mg
Maize starch	50 mg
Avicel PH 102	30 mg
Talc	17.5 mg
Sterotex®	17.5 mg
Sorbitol	30 mg
Total weight	645 mg

The weight was nearly the same as those of equivalent tablets on the market.

Mixtures were obtained in a Turbula mixer. They were compressed with the same instrumented alternative tablet machine as the one used for the study of paracetamol II, fitted with the same punches. Several adjustments were made to vary the compression force. The maximum forces on the upper and lower punches were noted during compression.

3.2.2. Study of tablet properties

Tablet crushing strength was measured using the Schleuniger hardness tester. Disintegration time was determined in water at 37°C according to the test in the European Pharmacopoeïa.

Dissolution studies were carried out in 800 ml of artificial gastric USP liquid without enzymes at 37°C using the paddle device of the European Pharmacopoeïa. The rotation speed was 100 rev./min. Samples were taken at intervals of 5 min.

Table 2
Influence of granulometric size on paracetamol powder dissolution rate

II Paracetamol fine crystals (86 μm)			II Paracetamol coarse crystals (192 μm)			I Paracetamol fine crystals (< 100 μm)			I Paracetamol coarse crystals (313 μm)		
m	S.D.	V.C.	*m*	S.D.	V.C.	*m*	S.D.	V.C.	*m*	S.D.	V.C.
58%	11.5	19.8%	78%	8.4	10.8%	84%	7.0	8.3%	75%	7.2	9.6%
75%	10.0	13.3%	88%	5.8	6.6%	91%	7.6	8.4%	79%	6.3	8.0%
96%	2.5	2.6%	98%	2.7	2.8%	94%	4.5	4.8%	85%	2.1	2.6%
98%	1.4	1.4%	98%	1.9	1.9%	95%	4.9	5.2%	87%	1.2	1.4%
99%	0.95	0.96%	98%	2.5	2.6%	98%	2.2	2.2%	89%	2.5	2.6%

Table 3
Compression ability and disintegration time of the formulated tablets

Y_1 (da N)	Y_2 (da N)	Y_2/Y_1	Crushing strength (da N)		Cohesion index	Disintegration time
			m	S.D.		
1521	1227	0.81	5.3	0.98	348	11 s
1615	1343	0.83	6.1	1.80	378	12 s

Table 4
Dissolution rate of paracetamol from formulated tablets compared with commercial tablets

	Form II paracetamol tablets						Commercial tablets		
	0 Time			9 months					
Time	*m*	S.D.	V.C.	*m*	S.D.	V.C.	*m*	S.D.	V.C.
7.5 min	95.0%	0.8	0.8%	92.0%	5.7	6.2%	98.6%	1.6	1.6%
15 min	98.0%	1.5	1.5%	96.0%	4.5	4.5%	99.6%	1.2	1.2%
30 min	98.7%	1.1	1.1%	99.5%	1.5	3.2%	100.0%	0.6	0.6%
45 min	99.2%	1.0	1.0%						

The concentration of paracetamol in each filtered sample was determined, based on absorbance at $\lambda = 245$ nm.

3.3. Stability study

The stability of paracetamol II was tested on the ground raw material using X-ray powder diffractometry. Forms I and II of paracetamol each exhibit characteristic reflections which make it possible to differentiate one from the other quite easily (Di Martino, Guyot-Hermann, Conflant and Bouché, unpublished). Each film contains the diffractograms of four samples. After recording the densitograms of the four samples on each film, the heights of the most characteristic diffraction peaks of the two forms were measured on each densitogram. Consequently, it was possible to express the proportion of form I in the form II sample. For a more precise result, it is also possible to use form II as a second reference.

The characteristic reflections were as follows:

Table 5
Stability of paracetamol II powder under compression and during storage at room temperature (% of paracetemol I)

	Batch	0 Time	4 Months	8 Months	11 Months
Pure II paracetamol	Powder	< 2%		< 2%	7%
	A				
	After compression	< 2%	< 2%	< 2%	6%
	Powder	< 2%	< 2%	< 2%	< 5%
	B				
	After compression				
	Powder	< 2%	< 2%	< 2%	
	C				
	After compression				
	Powder	< 2%			
	G				
	After compression	< 2%			10%
'Mixed' II paracetamol	Powder	> 85%		> 85%	> 85%
	D				
	After compression				
	Powder	68%			68%
	E				
	After compression	75.5%			80%
	Powder	8%	9%		
	F				
	After compression				

Table 6
Stability of the F batch, during storage at different relatives humidities levels (% of paracetamol I)

	0 Time	R.H.	2 Months	8 Months
Powder		22%		7%
	8%	55%	11%	8%
		86%	10%	8%
Mixture for compression		22%	9.5%	10%
	9.5%	55%	13%	10.5%
		86%	13%	12%
Tablet		22%	10.5%	15%
	9%	55%	12.5%	18.5%
		86%	20%	20%

form I: $2\theta = 15.65$
form II: $2\theta = 21.85$

Reflections do not exist in the same place for both forms. The ratio of the intensities of a characteristic reflection of form I ($2\theta = 15.65$) on a characteristic reflection of form II ($2\theta = 21.85$) allows for the calculation of the proportion of form I in form II after internal standardization.

3.3.1. Stability of form II in paracetamol powder

The samples to be investigated were stored at room temperature at different relative humidity levels.

The stability of several batches of paracetamol II was investigated:

— 'Pure paracetamol II', which was a paracetamol II without any trace of the polymorphic form I by using powder X-ray diffraction. The limit of detection of form I in form II is < 2% (three batches A, B and C).

— 'Mixed paracetamol II' which was a paracetamol II containing different percentages of form I, calculated from the powder X-ray diffraction patterns (three batches: D, E and F containing at 0 time 20, 37 and 68% of form I.

Stability during grinding was automatically controlled for each sample: as a matter of fact, samples are always ground before exposed to an X-ray beam.

Stability during compression was studied on ground tablet fragments resulting from the powder compression test.

3.3.2. Stability of paracetamol II in formulated tablets

The study was carried out after storage at room temperature at different relative levels of humidity.

4. Results

4.1. Study of the crystals of form II of paracetamol

Fig. 1 shows the DSC curves of forms I and II of paracetamol. We can observe an endothermic peak at 169°C for the monoclinic form, at 157°C for the orthorhombic form. These endotherms correspond to the melting point.

For form II, with fast heating rate (10°C/min), an exothermic peak can be detected. It corresponds to recrystallization of the remaining amorphous paracetamol.

It must be noted that the DSC curve of a sample of form II of paracetamol, containing traces of form I, is a curve of paracetamol I. This was the case for all batches prepared in a thermostated oven, even if no reflection of form I was detected in the X-ray powder pattern (the detection limit by X-ray diffraction is 2%).

X-ray powder diffraction patterns are depicted in Fig. 2. They are characteristic of each form. The characteristic reflection which does not exist in the other form is pointed out.

The compression ability data are compiled in Table 1. It can be observed that the orthorhombic form II of paracetamol exhibits relatively good behaviour under compression.

Fig. 3 presents crushing strength versus compression force Y_1. Good linearity can be noted up to Y_1: 2500 da N.

Further studies have shown that reasonable compression ability making direct compression feasible after formulation is maintained up to a 20% amount of form I in form II powder (Fig. 4). In contrast, no tablet is obtained from the monoclinic form I.

Dissolution study data are compiled in Table 2: results are seen to be similar for the two forms.

4.2. Study of formulated tablets

Compression data, tablet crushing strengths and disintegration times are compiled in Table 3. As we can see, the compression data of the formulation tested are good. Transmission force Y_2/Y_1 through the powder bed is good, crushing strengths and cohesion indexes are correct. Disintegrating times are very fast; 2000 da N force was selected for tablet manufacturing.

Dissolution rates are displayed in Table 4. By way of comparison, data of commercial paracetamol tablets are given. We can see that the dissolution rate of formulated tablets made with paracetamol II is similar to that of commercial tablets.

4.3. Stability study

Stability data are compiled in Table 5 and Table 6.

4.3.1. Stability of the paracetamol II powder during storage

It seems that form II is relatively stable after 11 months. Storage in conditions of different relative levels of humidity shows relatively good stability.

4.3.2. Stability of paracetamol II under grinding and compression

Stability during grinding was automatically controlled for each sample as is usually done. The stability of paracetamol II powder under compression seems to be good, as can be seen in Table 6. After storage of the compacts, it was observed that the II to I transition in the resulting compact seems to have similar kinetics to those of the non-compressed powder.

4.3.3. Stability of paracetamol II in formulated tablets

Tablets, the mixture for compression containing the same compounds, and the corresponding 'paracetamol II' were stored at different relative levels of humidity for 8 months. It can be noted that humidity does not seem to lead to a II/I transition, even if it is as high as 86% H.R. (Table 6). A dissolution study of the tablets after 9 months at room temperature confirms this observation (Table 4).

5. Conclusion

It seems that the orthorhombic form II of paracetamol is a paracetamol for direct compression. Its great advantage is that it contains no adjuvant and no recrystallization solvent can be found in this raw material.

However, the atmosphere, the time and the melting temperature have to be strictly controlled for an industrial process. The consequence of the eventual transition mentioned in the text would be important only on the compression level: direct compression is possible for an amount of up to 20% of form I in form II. In contrast, the dissolution rates are similar for the two forms and so possible transition of the form II to form I in tablets during storage is without consequence on bioavailability.

Current techniques of industrial crystallization by melting and solidifying should make it possible to prepare this very interesting polymorph of the usual monoclinic paracetamol.

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References

Bürger, A., Zur Interpretation von Polymorphie-Untersuchungen. *Acta Pharm. Technol.*, 28 (1982) 1–20.

Guyot, J-C., Tete, L., Tak Tak, S. and Delacourte, A., Practical interest of the Cohesion Index for the technological formulation of tablets. *6è Congrès International de Technologie Pharmaceutique*, Association de Pharmacie Galeinique Industrielle, Paris, in proceeding, 3 (1992) 246–254.

Haïsa, M., Kashino, S. and Maeda, H., The Orthorhombic form of *p*-Hydroxyacetanilide. *Acta Cryst.*, B30 (1974) 2510–2512.

Haïsa, M., Kashino, S., Kawai, R. and Maeda, H., The monoclinic form of *p*-Hydroxyacetanilide. *Acta Cryst.*, B32 (1976) 1283–1285.

Lefebvre, C., Guillaume, F., Bouché, R., Bouaziz, R. and Guyot, J-C., Etude de différentes formes polymorphes du méprobamate. *Pharm. Acta Helv.*, 66 (1991) 90–96.

Merle, C., Mangin, C. and Guyot-Hermann, A-M., Essai d'un appareil de dissolution à flux continu. Application à l'étude de l'influence du tassage des poudres dans les gélules. *Bull. Soc. Pharm. Lille*, 2 (1977) 87–94.

Nürnberg, E. and Hopp, A., Galenisch relevante Untersuchungen von Paracetamol. *Pharm. Ind.*, 44 (1982) 1081–1084.

Welton, J-M. and McCarthy, J.G., X Ray powder data for Acetaminophen. *Powder Diffraction*, 3 (1988) 102–103.

Sohn, Y.T., Study on the Polymorphism of Acetaminophen. *J. Kor. Pharm. Sci.*, 20 (1990) 97–104.