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PREPARATION AND PHYSICAL CHARACTERIZATION OF FORMS II AND III OF PARACETAMOL

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Abstract

The polymorphic forms II and III of paracetamol were obtained by melting the marketed form I. Under the melting and cooling conditions used, it was possible to obtain forms I, II and III. The recrystallization conditions and the physical properties of forms II and III were investigated by means of various techniques: thermomicroscopy, DSC analysis, infrared microspectrometry and X-ray powder diffraction at room temperature and as a function of temperature. Form III was found to be very unstable. However, its formation seems to be an important intermediate step in the preparation of form II.

Keywords: paracetamol, polymorphism

Introduction

Three polymorphic forms of paracetamol are reported in the literature.

The monoclinic form (form I) is the normal marketed form. Its crystalline structure was described by Haïsa [1] and Welton [2].

In 1974, Haïsa observed a new form, form II, obtained by recrystallization from an ethanolic solution [3]. He identified form II as an orthorhombic form and calculated the lattice constants from an X-ray diffraction study. The existence of form II has been described by several other researchers, such as Kuhnert Brandstätter [4] and Bürger [5]. Nürnberg investigated the crystalline forms of paracetamol obtained when the melted crystal was cooled under different conditions [6]. With a special X-ray diffraction device, he found either a metastable form, which could be identified as the orthorhombic form II, or the monoclinic form I, depending on the quenching temperature.

A form III was mentioned by Bürger [4] as a very unstable form which cannot be studied due to its unstability.

None of these authors described the technique used to prepare the form reported on.

In the present work, we have attempted to define the best conditions for the preparation of larger quantities of forms II and III, with the idea of scaling up their

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production. This objective is justified by the better compression behaviour of form II as compared to the marketed form I [7]. In fact, the manufacturing of analgesic/antypyretic paracetamol tablets needs compaction processes. The commonly used form I is not directly compressible, so a long and relatively expensive wet granulation is required before the compression. We earlier demonstrated that the direct compression of form II is possible, due to its crystalline structure, which presents sliding planes, allowing a certain plasticity.

Experimental

Materials

Monoclinic paracetamol I:
- Fine powder < 100 μm, Rhône Poulenc, France.
- Acetaminophen USP, fine powder, Mallinckrodt, England.

Methods

Crystallization of paracetamol polymorphs

Paracetamol polymorphs II and III were prepared by melting form I. The glassy material obtained was recrystallized under different thermal conditions. In a first step, recrystallization was carried out directly on thermal analysis instruments (DSC, hot stage of thermomicroscope and X-ray camera).

In a second step, a larger quantity of form II was obtained by melting paracetamol in a glass flask in a ventilated oven (Thermosi SR 1000-Omron E5CS).

Physical characterization of paracetamol polymorphs

- Crystals were observed by optical microscopy. Thermomicroscopy was carried out with a Mettler FP 82 hot stage.
- The DSC curves were recorded on Mettler TA 3000 DSC 20 equipment (starting temperature 50°C, heating rate 10°C min^{-1}, final temperature 180°C, followed by an isothermal hold (at 180°C for 5 min). Different kinetics were used for cooling down: brutal quenching to +4°C or room temperature, or slow and progressive cooling down to room temperature within 30 to 60 min. A second heating run was then carried out to 190°C at different heating rates: 10, 1 or 0.1°C min^{-1}.
- X-ray powder diffraction was carried out at room temperature with either a Siemens X-ray diffraction device, fitted with a Guinier de Wolff camera (Nonius) (CuK_α radiation, $\lambda = 1.54178$ Å) or a Siemens D 5000 diffractometer, using CuK_α radiation (silicon was used as internal standard). A Siemens X-ray diffraction device, fitted with a Guiner Lenné camera (Nonius), was used as the temperature was scanned, at a heating rate of 3.8°C h^{-1}.
- The infrared spectra were recorded on a Brüker IFS 88 spectrometer coupled with a Brüker microscope. The working mode was transmission, the resolution was 4 cm^{-1} and 200 scans were collected. The samples were directly crystallized be-

tween a BaF_2 disk 13 mm in diameter and 1 mm in thickness and a glass cover slip in the hot stage used for thermomicroscopic studies. This material is transparent in the range of wavenumbers studied (4000–700 cm^{-1}). The analysed area had a diameter of about 25 mm when a 36× objective (magnification 720×) with a diaphragm aperture of 0.9 was used. This method allows for the analysis of a crystalline area selected by microscopic observation.

Results and discussion

Conditions to obtain forms II and III

Crystallization of form II

Although some authors refer to the orthorhombic form, the formation of this modification is discussed only by Haïsa, who wrote "The orthorhombic crystals were obtained by slow evaporation from an ethanolic solution" [3]. We were never able to prepare the orthorhombic form by crystallization from solution. So, we explored the possibilities offered by a process of melting and recrystallization. A study of the behaviour of paracetamol during heating was therefore necessary: DSC was chosen for a first trial.

Using DSC analysis, after the melting of paracetamol I at 168/169°C, a slow cooling-down at 25°C produced a glassy form. Following a new heating run, the glassy form recrystallized as form II, which melted at 157/158°C (Fig. 1). This is in agreement with literature data [3–5].

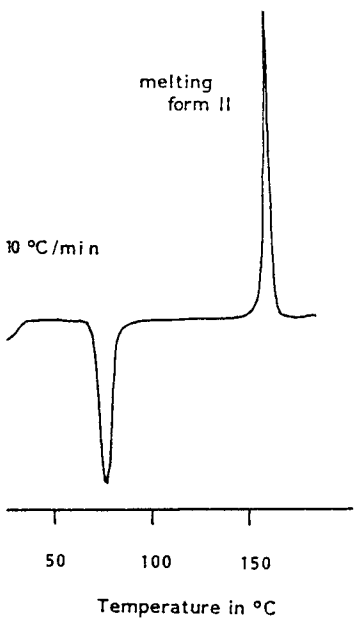

Fig. 1 DSC curve of paracetamol after melting and slow cooling in the pan in the DSC oven

The existence of form II was proved by subjecting the DSC pan content to powder X-ray diffraction: after melting, a glassy solid remained in the DSC pan. It began to recrystallize spontaneously after 30 min. The sample was then taken from the pan, and the formation of form II was confirmed by X-ray diffraction analysis at room temperature.

On the other hand, quenching of the melted mass or grinding of the glassy material promoted the recrystallization of form I.

Furthermore, the transition II→I was visualized by carrying out an X-ray diffraction *vs.* temperature study using a Guinier Lenné camera. Figure 2 reveals the melting of the monoclinic form during its first heating up to 170°C. After cooling to room temperature, the glassy form recrystallized into the orthorhombic form. During a second heating, at nearly 156°C the orthorhombic form transformed into the monoclinic form, which melted at 169°C. This is surprising because this transition from the orthorhombic into the monoclinic form was not observed in DSC experiments. In fact, there is a kinetic problem. The heating rate during the X-ray diffraction study *vs.* temperature was very low (3.8°C h^{-1}) as compared to that of 10°C min^{-1} in the DSC experiment. In a subsequent DSC experiment, carried out at 0.1°C min^{-1}, it was also possible to observe melting at 169°C.

This demonstrated that the melting of monoclinic paracetamol, followed by cooling, produces the orthorhombic form.

Crystallization of form III

Form III was first fortuitously obtained by keeping melted paracetamol for several hours, between the slide and the cover slip, at 54°C during a trial by thermomicroscopy.

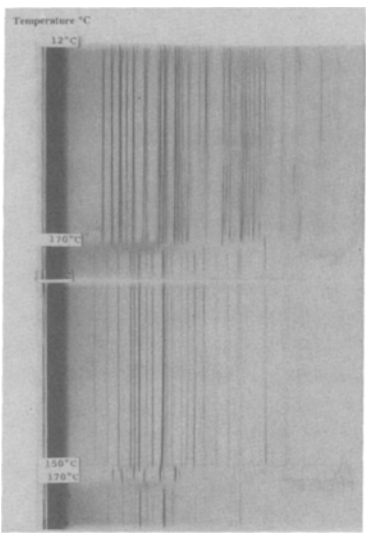

Fig. 2 Powder X-ray diffraction *vs.* temperature of paracetamol

Large transparent crystals appeared in the periphery of the melt, and at the same time some nuclei appeared in the melted mass, from which fine crystals grew radially (Fig. 3a); these fine crystals spread throughout the whole melted mass (Fig. 3b). During the second heating run, carried out at 10°C min^{-1}, a slow clear transformation was produced at nearly 70°C: the radially placed crystals turned into large transparent crystals and the transformation was achieved at nearly 120/130°C (Fig. 3c). Melting occurred at about 158°C.

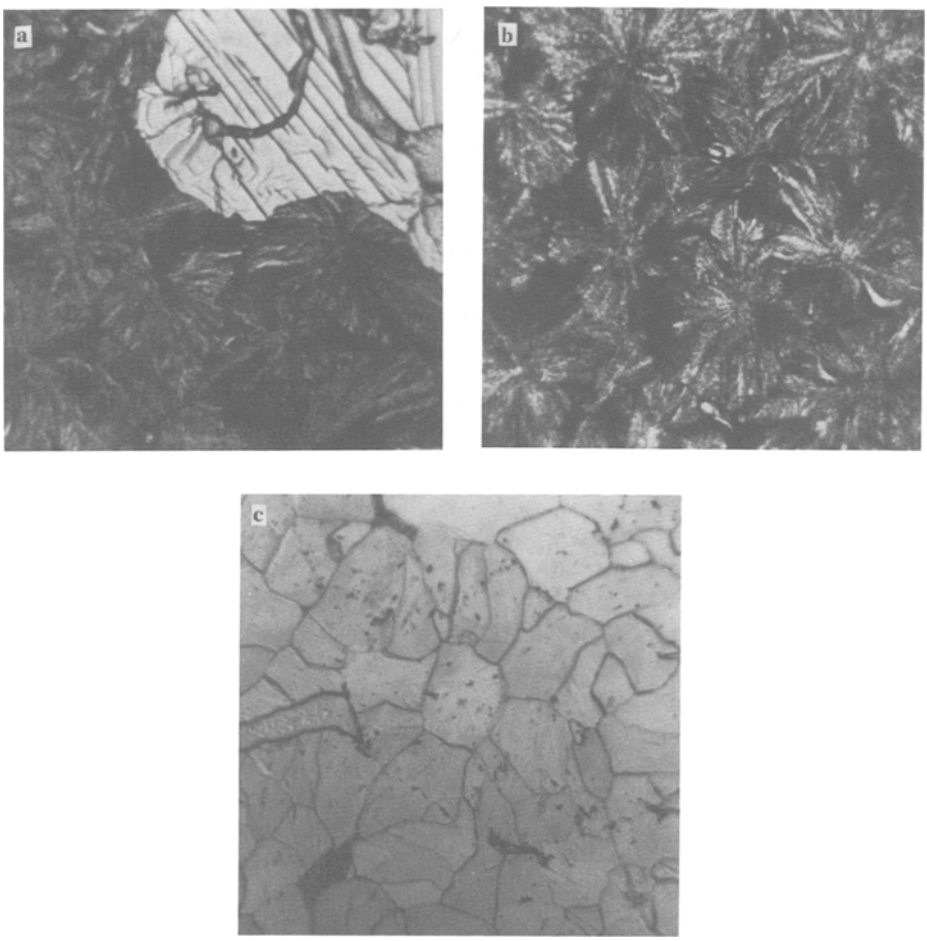

Fig. 3 Observation during thermomicroscopy experiments after melting and cooling-down at $t=54$°C (the sample is placed between the slide and the cover slip); 3a: Beginning of crystallization (form II in the periphery, form III in the inner melted mass); 3b: Crystallization of form III; 3c: Transition of form III into form II

The large transparent crystals which melted at 157°C are clearly the orthorhombic form II of paracetamol. But why should fine crystals which appear and exist at the 50°C stage subsequently turn into large form II crystals between 70 and 130°C? These observations led us to consider the existence of form III. DSC and infrared experiments corroborated this hypothesis.

Different trials were carried out in order to find the best conditions for the production of form III. In particular, the isothermal temperature was fixed within the range 45-60°C. It was observed that above 56°C and below 50°C, crystallization of form III became problematic: it was very slow from 45 to 50°C, and it was nearly impossible above 56°C. The best temperature was 54°C. The fine crystals appeared after 10 min and the crystallization was complete within 90 min.

The best conditions for the formation of form III were as follows:

– crystals of the usual form I of paracetamol were deposited between the slide and the cover slip and introduced into the hot stage;

– the temperature cycle was programmed as follows:

i. Starting temperature 54°C; heating rate 10°C min^{-1}; final temperature 170°C (melting).

ii. The temperature was allowed to return to 54°C within 10–15 min. During cooling, no recrystallization occurred.

iii. The temperature was maintained at 54°C for 90 min. During this time, nuclei of form III appeared after 10 min, crystals of this form growing slowly and radially from the nuclei.

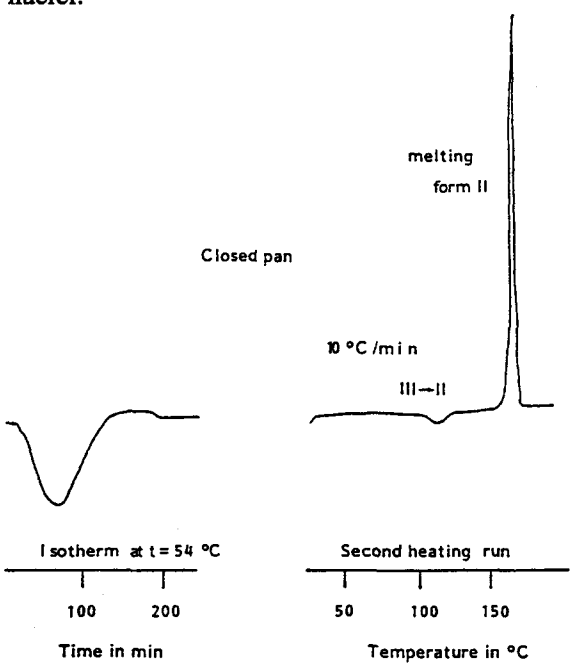

Fig. 4 DSC curve of paracetamol melted, cooled until t=54°C and reheated in a closed pan

We attempted to obtain a higher yield of form III: however, we could never identify this form III otherwise than between the slide and the cover slip during thermomicroscopy experiments, or in a closed pan during DSC analysis. This form III is stable for several months if it remains between the slide and the cover slip. If one of the two slides is removed, form III begins to transform into form II after 10 min. Transformation is complete after 1 h. The transition of form III always produces form II, and transition from form III to form I was never observed. Formation of form III could be an important step in the preparation of pure form II.

DSC experiments in a closed pan confirmed the thermomicroscopic observations. Figure 4 reveals recrystallization from the glassy mass during the isothermal stage at 54°C, and the exotherm of the transition of form III to form II during the second heating run, with the melting of form II. On the other hand, recrystallization in an open pan (Fig. 5) did not afford the exotherm of recrystallization during the second heating. The glassy state probably recrystallizes directly into form II. The necessity of very closed conditions seems to be obligatory for the formation of form III. This is the reason why the infrared trial was carried out between barium fluoride and a cover slide.

Infrared microscopy was used to record the spectra of forms I, II and III. The frequencies of the fundamentals attributed to the paracetamol molecule were calculated for all three polymorphic forms (Table 1). Since these forms are related by a polymorphism phenomenon, the fundamental attributions are nearly the same (the

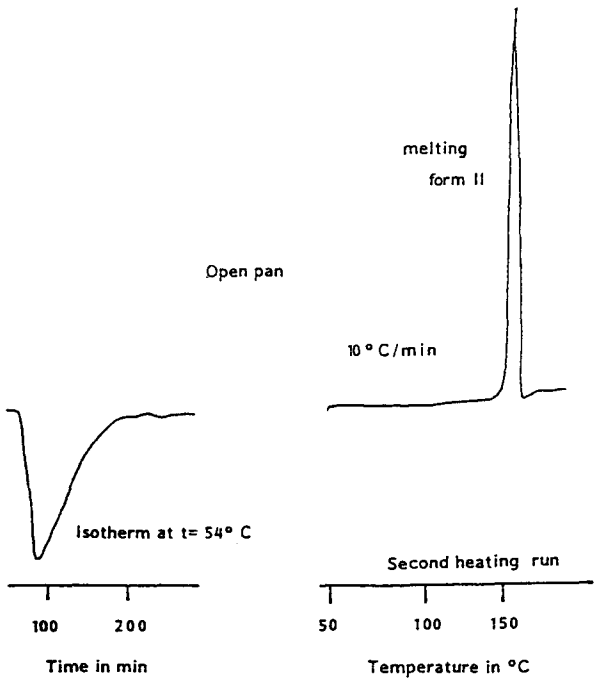

Fig. 5 DSC analysis of paracetamol melted, cooled until $t=54°C$ and reheated in an open pan

Table 1 Frequencies (cm^{-1}) of fundamental attribution for the paracetamol molecule for three polymorphic forms I, II and III

Form I	Form II	Form III	Attributions
3329	3330	3328	ν_{N-H} amidic group
1650	1673	1656	$\nu_{C=O}$ amidic group
1564	1559	1569	ν_{C-N} amidic group
1516	1510	1510	ν_{C-N} amidic group
1260	1280	1275	ν_{C-N}, ν_{N-H} amidic group
1610	1628	1614	ν_{C-C} aromatic function (1.4)
1510	1510	1510	ν_{C-C} aromatic function (1.4)
1442	1462	1462	ν_{C-C} aromatic function (1.4)
1173	1169	1173	δ_{C-H} aromatic function (1.4)
1110	1110	1110	δ_{C-H} aromatic function (1.4)

chemical structure is the same for all forms). However, a difference may be observed as far as the amidic stretching vibrations are concerned.

For form II, these are shifted to higher frequencies. Other differences are the appearance of peaks and the presence of specific peaks for each form (Fig. 6). These peaks do not correspond to the fundamental attributions, but to inter- or intramolecular interactions, dependent on the crystalline structure. These observations are essential in confirming the formation of form III.

Unfortunately, it was not possible to observe a typical diffractogram of form III by powder X-ray diffraction. The need to cover the melt to obtain form III complicates the experimental procedure considerably.

Scaling-up of form II preparation

It was obvious that form II alone could be prepared for industrial use. After studying the best kinetic conditions of preparing form II, we also attempted to obtain it in larger quantities by melting marketed monoclinic paracetamol in a ventilated oven.

First, different materials (glass, pyrex and aluminium) were tested as recipients in order to detect any possible epitaxy phenomenon. This was not observed [8].

Two types of cooling-down kinetics were applied. Brutal quenching, when the sample was taken out of the oven just after melting, leds to recrystallization of the monoclinic form. When a low regular cooling rate was applied, the sample being left in the closed oven for nearly 3 h, the orthorhombic form was generally obtained.

Experiments in an open or closed flat glass flask proved the influence of the atmospheric conditions and confirmed the necessity for the flask to be closed for better temperature control. Consequently, we chose to melt paracetamol in a closed flat flask, under pure nitrogen (to avoid oxidation of the melt), in a ventilated oven. The oven temperature was raised to 172°C. This temperature was maintained for 30 min in our experiments. Heating was then stopped and the samples were left to cool down until room temperature was attained. When the flask was taken out of the

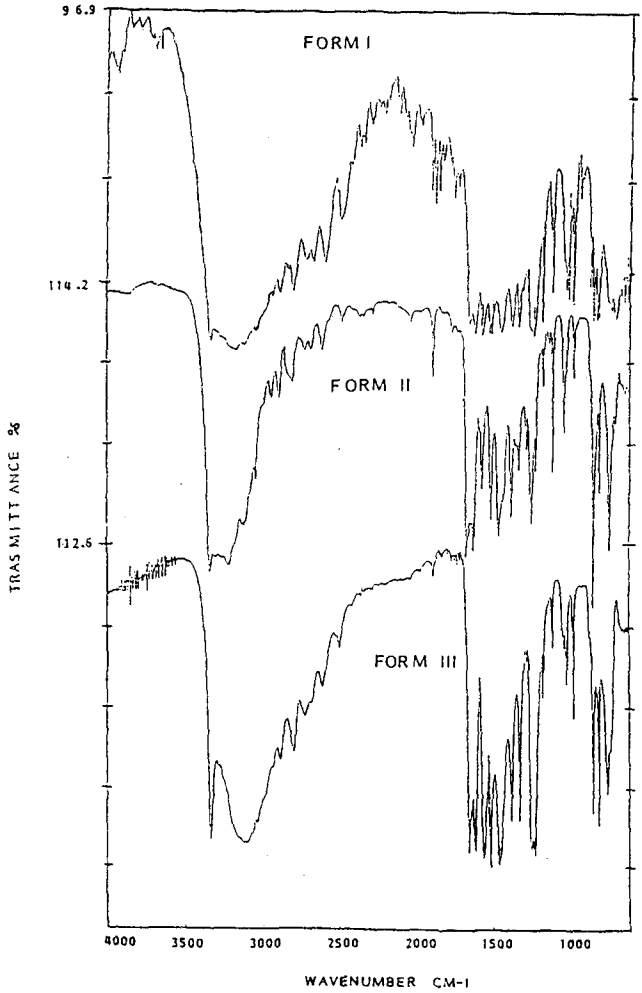

Fig. 6 Infrared spectra under a microscope of polymorphic forms I, II and III of paracetamol

oven, the solidified melt was recrystallized. This product was removed from the flask and ground in a mortar.

Physical characterization of orthorhombic form obtained in oven

The recrystallized material was studied by DSC analysis. Surprisingly, the melting occurred at the melting temperature of the monoclinic form and a transition endotherm was observed at nearly 130°C (Fig. 7). This endotherm was not observed in the other DSC experiments, in which the orthorhombic form was obtained with DSC instruments.

This result was confirmed by the powder X-ray diffraction *vs.* temperature study (Fig. 8): in the temperature range 120–140°C, transition from form II to form I was

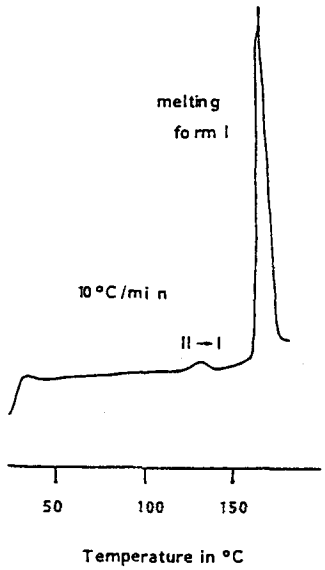

Fig. 7 DSC curve of form II obtained by melting and recrystallization in the oven

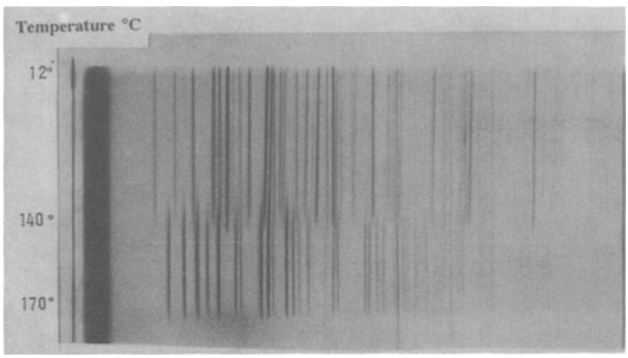

Fig. 8 Powder X-ray diffraction analysis *vs.* temperature of form II obtained in the oven

observed. The explanation for this behaviour might be that the oven material was insufficiently pure. Some nucleï of the stable monoclinic form, whose presence was not detected by the X-ray diffraction instruments, could favour the transition of form II during heating. The "impurity" of the material might be due either to incomplete melting of the monoclinic powder (the quantity placed in the oven is larger than that in the DSC pan) or to difficulty in maintaining optimal atmospheric conditions during the recrystallization of the glassy material in the oven.

For a more exact calculation of the lattice constants of form II, we used a Siemens diffractometer. The results are reported in Table 2. The very high intensity of the main reflection can be explained by the habit of the crystalline particles. These were

Table 2 X-ray data of form II calculating by the X-ray diffractometer

h k l	2Θ	*d*/Å	Rel. *I*./%
0 2 0	10.30	8.57	0.13
1 2 0	12.71	6.95	0.16
2 0 0	14.98	5.90	0.48
1 2 1	17.48	5.06	0.90
2 2 0	18.20	4.87	0.36
2 0 1	19.18	4.62	2.21
2 1 1	19.85	4.46	0.20
0 4 0	20.69	4.29	0.45
2 2 1	21.81	4.07	0.54
0 0 2	24.01	3.70	100.0
0 1 2	24.57	3.62	3.60
2 4 0	25.68	3.46	0.75
0 2 2	26.17	3.40	0.43
3 2 1	27.63	3.22	0.43
2 1 2	28.87	3.09	1.15
4 0 0	30.26	2.96	0.90
0 6 0	31.26	2.86	0.32
3 2 2	34.77	2.58	0.21
2 6 1	36.95	2.43	0.34
0 7 1	38.65	2.33	0.24
5 2 0	39.50	2.28	0.27
0 8 0	42.12	2.14	0.14
3 1 3	43.55	2.08	0.22

produced by grinding of a cooled melt of paracetamol, which has the appearance of a thin and very hard plate. This can be the reason for a preferential orientation.

The repeatability of formation of form II in the oven was verified by X-ray powder diffraction at room temperature on each batch. When traces of form I were detected, the intensities of the characteristic reflections for paracetamol I and II gave the ratio of the two forms: the sensitivity threshold detection was 2% [6].

Conclusions

It has been demonstrated that it is possible to obtain form II by melting form I. The kinetic conditions for the recrystallized glassy material have been defined. In particular, the cooling conditions represent the most critical step in the whole procedure. Figure 9 outlines the basic conditions for the formation of three forms, schematized from the thermal data.

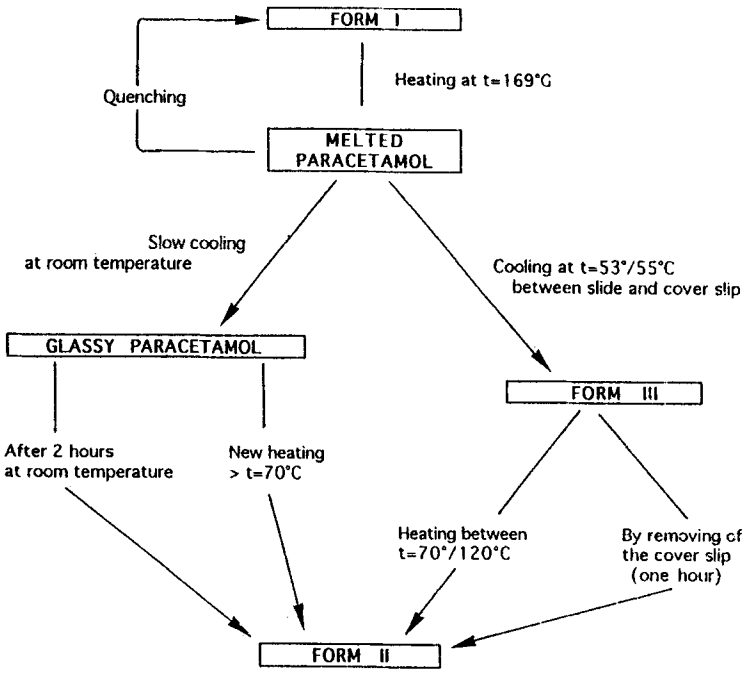

Fig. 9 Thermal analysis conditions to obtain polymorphic forms of paracetamol

A very slow cooling to room temperature and a slow recrystallization of the glassy material ensure the formation of the crystal modification form II. The intermediate form III, formation of which is favoured by very slow cooling in a controlled atmosphere, is probably very important for establishing the recrystallization balance.

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