Drug Development and Industrial Pharmacy, 24(5), 447–453 (1998)

RESEARCH PAPER

A Study of the Changes During Heating of Paracetamol

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ABSTRACT

The orthorhombic form of paracetamol has been shown to exhibit greater compressibility and faster dissolution than the monoclinic form. The orthorhombic form is produced by melting of monoclinic crystals of paracetamol followed by cooling at specific rates. Cooling rate, although a very important factor, is not the only factor influencing the formation of either of the two morphs. To study the cooling rate required for production of form II, paracetamol samples were melted in a differential scanning calorimeter, cooled at three specific rates, and melted again. In all of the samples, cooling resulted in the glassy form followed by recrystallization and the melting of form II. On the hot-stage microscope both forms were produced in one sample. Standardizing conditions for prediction of the resulting form remains a problem. There seems to be a great deal of overlap of the two forms' transition phases, which would make it difficult to force the crystallization of one form by keeping the solution or melt at a specific temperature. The thermal behavior of paracetamol during the heating and cooling phases must be understood in order to manipulate the process. A video camera mounted on a hot-stage microscope was used to follow the changes during heating and cooling of both forms. Nucleation, crystal growth, habit transformation, sublimation, and the final melt are shown on snap shots taken from the video.

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INTRODUCTION

The polymorphic forms of paracetamol have been studied by several researchers and described by several authors (1–7). Crystallization is a very complex process, embodying at least three causally linked processes, i.e., nucleation, growth of the crystals, and the so-called ripening of the suspension. As soon as stable crystal nuclei are formed in saturated solutions or in the melt, they begin to grow (8).

It was shown by Martino et al. (7) that it is possible to obtain paracetamol tablets by direct compression of form II (orthorhombic form) and that form II shows a dissolution rate twice as fast as form I (monoclinic form). Preparation of form II remains a problem as shown by the different methods of preparation used by the authors mentioned below.

Nürnberg and Hopp (4) prepared the orthorhombic form by cooling a melt of commercial paracetamol. Conflant and Guyot-Hermann (6) used x-ray powder diffraction to observe the changes in crystal form during heating and cooling. During the first heating phase melting of the monoclinic form was observed. Quenching of the sample gave the glassy form which transformed into the orthorhombic form during cooling. During a second heating phase they observed transition of the orthorhombic to the monoclinic form, and finally, melting of the monoclinic form was observed. In a study of solid dispersions, Ford (9) chilled samples rapidly after fusion, resulting in the monoclinic form. Martino et al. (7) showed that by slow cooling of a melt of paracetamol it is possible to produce the orthorhombic form as described by Haisa (2) (Table 1).

Although the mentioned authors used specific rates of cooling of melted paracetamol to obtain the orthorhombic form, the cooling rates that they used differed from each other. The cooling rate of the melt has an effect on the crystal form obtained, but it is probably not the determining factor. In this study we tried to determine the changes in the crystal appearance/structure of paracetamol during heating and cooling. Hot-stage microscopy combined with video photography was found to be ideally suitable for observing the changes while they were taking place.

MATERIALS AND METHODS

Materials

Paracetamol obtained from Fine Chemicals Corp. (Eppindust, South Africa) was used.

Methods

To study the cooling rate required for production of form II, the differential scanning calorimeter (DSC) was used. In the first experiment nine paracetamol samples were melted and cooled at three specific rates.

Another set of DSC runs was done by repeated heating and cooling of one paracetamol sample. Cooling rates were the same as in the first experiment. Results were similar to those of the experiments above. All of the thermograms showed the melt of orthorhombic paracetamol.

To identify the changes accounting for the exotherms, the hot-stage microscope was used. Kuhnert-Brandstätter (1) reported sublimation of grains, hexagonal prisms, and rhomboids from 140°C. Residual crystals grew into hexagonal and polyhedral grains and prisms. The melt of paracetamol solidified to a glass, which gave unstable columnar aggregates at 110°C on which rectangular plates and prisms of the stable form were induced from about 140°C.

In the third experiment paracetamol raw material was placed between two glass plates and melted on the hot-stage microscope while recording was done with a video camera. Another sample was prepared by placing three heaps of paracetamol crystals on the plate with no cover

Table 1

Methods for the Preparation of Orthorhombic Paracetamol Described in Literature

Author	Method of Crystallization	Rate
Kuhnert-Brandstätter, 1971	Melt	Thermomicroscope
Haisa, 1974	Ethanol	Slow cooling
Nürnberg and Hopp, 1982	Melt	Cooling at different rates
Bürger, 1982	Melt	Thermomicroscope
Conflant and Guyot-Hermann, 1994	Melt	Quenching
Martino et al., 1995	Melt	Slow cooling

slide. The sample was heated and left to cool after melting at ±167°C.

Cooling Conditions for the Production of Form II

Paracetamol powder samples (4.0 mg) were sealed in aluminum pans and melted in a Shimadzu DSC by heating to 200°C. The samples were kept at this temperature for 5 min to ensure a complete melt. The melts were subsequently cooled at three different rates: a very slow rate (200–25°C in 2.5 hr), a fast rate (200–25°C in 15 min), and quenching (200–5°C). This procedure was repeated three times with the different samples at each cooling rate. After each cooling, a DSC analysis was done to determine the polymorphic properties.

Differential Scanning Calorimetry (DSC)

A Shimadzu DSC-50 was used to obtain DSC traces of the different samples. Samples with a mass not exceeding 4.0 mg were sealed in aluminum pans. A similar sealed empty pan was used as a reference. DSC curves were obtained under nitrogen purge of 35 ml/min at a heating rate of 10°C. Samples were heated and maintained at 200°C for 5 min before being cooled at different rates.

Although this was a quick and easy method, the use of DSC is very limited when used on its own and can create more problems than it solves (10). It is also difficult to observe transitions that exhibit very weak energy, and for this reason, Conflant and Guyot-Hermann (6) used x-ray powder diffraction to study the changes during melting.

Hot-Stage Microscopy and Video Attachment

A Panasonic® WC-CL 502 video camera was mounted onto a Leitz (Laborlux K) hot-stage microscope. Recordings were made on Philips HG 180 min VHS cassettes and the timer reading was noted for the entire temperature range.

RESULTS AND DISCUSSION

The DSC thermograms of paracetamol raw material and one of the samples are given in Fig. 1, and the exo- and endotherms of the different samples at the corresponding cooling rates are shown in Table 2.

The first trace in Fig. 1 is that of the paracetamol raw material showing the melting endotherm of the monoclinic form. The second trace is that of a glass showing a recrystallization exotherm and a melting endotherm of the orthorhombic form.

Almost all of the thermograms showed an exotherm and one endotherm. The exotherms corresponded to the recrystallization of paracetamol from the glassy form. These exotherms were in the region of 76–79°C, which represents quite a large temperature range. This could be explained by the number of nuclei that formed dur-

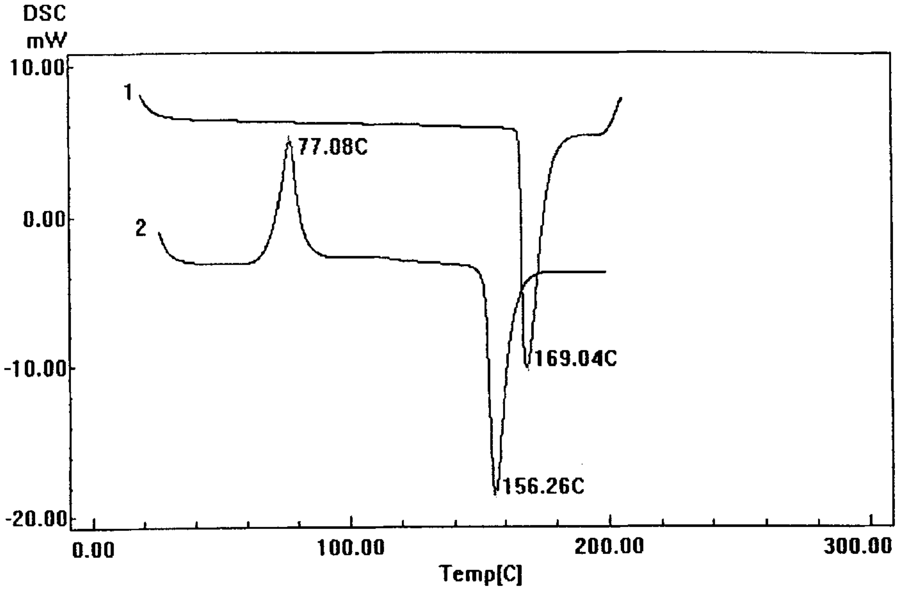

Figure 1. DSC thermograms of paracetamol. (1) Paracetamol raw material. (2) Glassy paracetamol.

Table 2

Exo- and Endotherms on DSC Thermograms After Heating of Glassy Paracetamol Samples

Run No.	Exotherm	Endotherm
Cooling Rate 1: Quenching to ±5°C (Immediately)		
1	79.23	155.33
2	78.06	156.46
3	78.84	156.22
Cooling Rate 2: Fast Cooling to 25°C (15 min)		
1	77.38	155.62
2	78.17	155.54
3		156.59
Cooling Rate 3: Very Slow Cooling to 25°C (2.5 hr)		
1		156.15
2	77.08	156.26
3	76.73	155.98

ing cooling/reheating. The more nuclei present, the faster crystal growth would take place and would be represented by the exotherms in the lower part of the first exotherm region. Two samples did not show exotherms at all. It is possible that for these samples crystallization took place during the cooling phase. A set of very small exotherms could be seen in the region of 120°C. These exotherms were not present on all of the thermograms and could not be explained from the DSC thermograms alone. An endotherm representing the melt of form II could be seen.

The effect of aging of glassy paracetamol was seen in a sample that was stored for 2 days and melted again. The thermogram of this run showed endotherms for both the orthorhombic and the monoclinic forms of paracetamol, as can be seen in Fig. 2. It is possible that upon storage of the sample a transition from the orthorhombic form to the monoclinic form took place. Cooling and reheating of this sample resulted only in the melting of the orthorhombic form.

The trace is that of a glass, again showing the recrystallization exotherm but showing the endotherms of both the monoclinic and the orthorhombic forms. This experiment suggests that the rate of cooling was not the determining factor in the formation of a specific form.

Figure 3 shows the melting of the raw material at ±167°C.

Upon slow cooling, the melt solidified to a glass. Upon reheating, nucleus formation was seen as a small dot at ±60°C (Fig. 4) and progressed into the crystal growth phase that ended at ±83°C (Fig. 5). Upon further heating it is possible that a habit transformation took place between 115 and 126°C (Fig. 6).

At ±135°C sublimation could be seen as the formation of small bubbles followed by the movement of air between the top glass plate and the crystals. If the slide

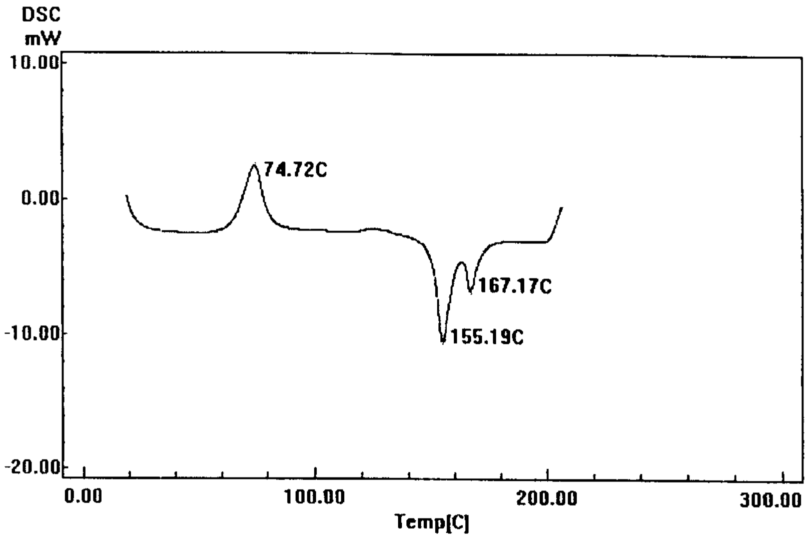

Figure 2. DSC thermogram of a paracetamol sample showing the melting of two forms of paracetamol.

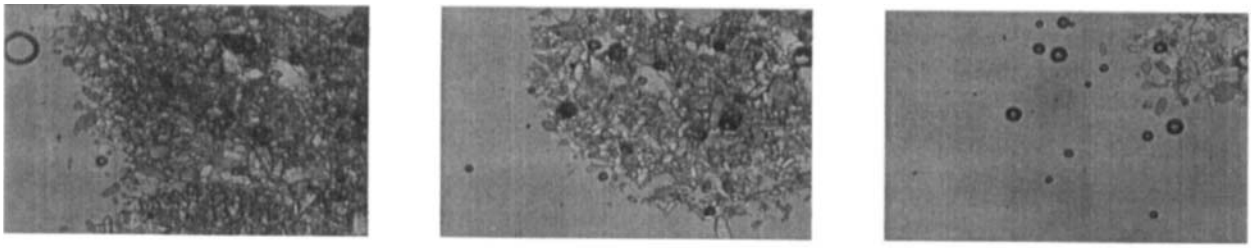

Figure 3. Melting of paracetamol raw material at ±167°C.

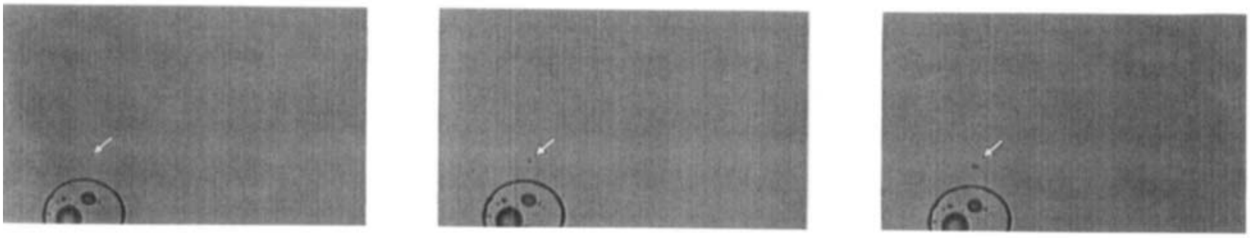

Figure 4. Nucleus formation of glassy paracetamol at ±60°C.

Figure 5. Crystal growth of paracetamol at ±60–83°C.

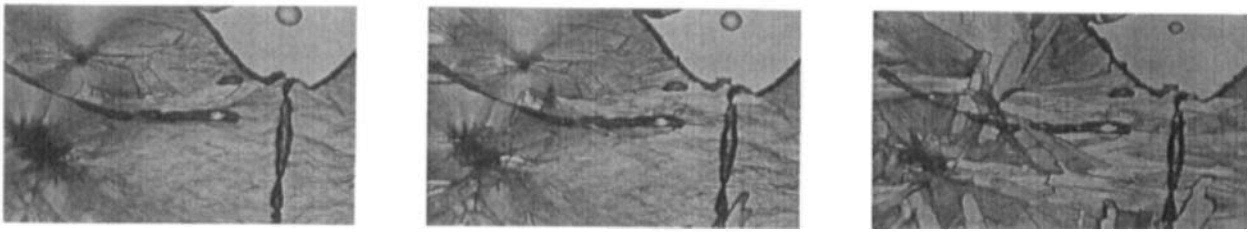

Figure 6. Habit transformation of paracetamol at ±115–126°C.

was not covered, sublimation led to the formation of single crystals on the glass plate between the hot stage and the microscope lens (Fig. 7).

The melt of paracetamol could be observed at ±167°C (Fig. 8).

The sample used above was left to cool to room temperature, after which it was heated again. During the cooling a glass formed with some remaining crystals trapped within the glass. With this heating the sample showed the same transformations as mentioned above except that the melting of the crystals was at ±154°C.

The next sample was prepared by placing three heaps of paracetamol crystals on the plate with no cover slide. The sample was heated and left to cool after melting at

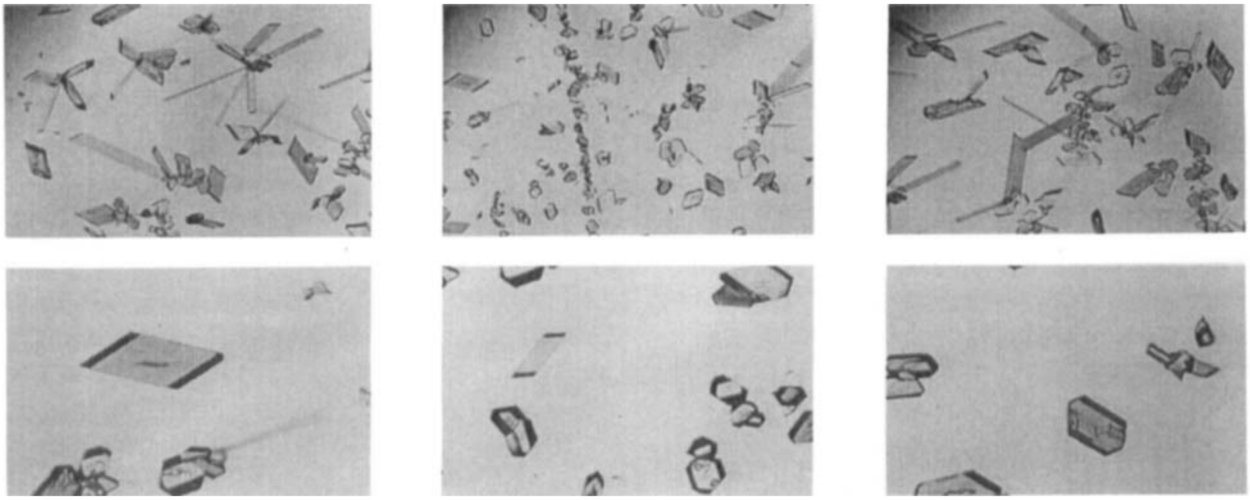

Figure 7. Single crystals of different habits following sublimation at ±135°C.

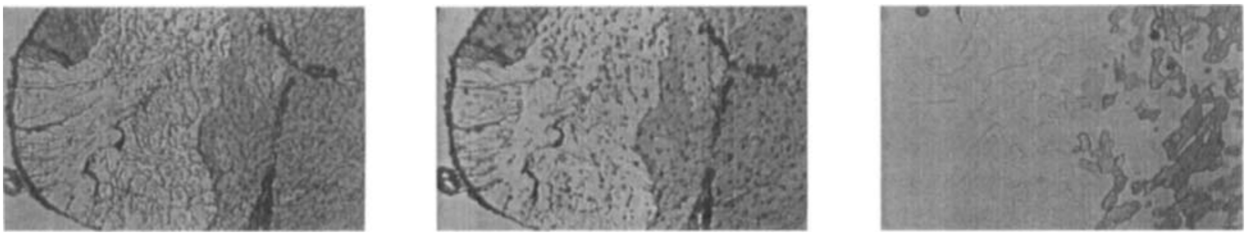

Figure 8. Melting of monoclinic paracetamol at ±167°C.

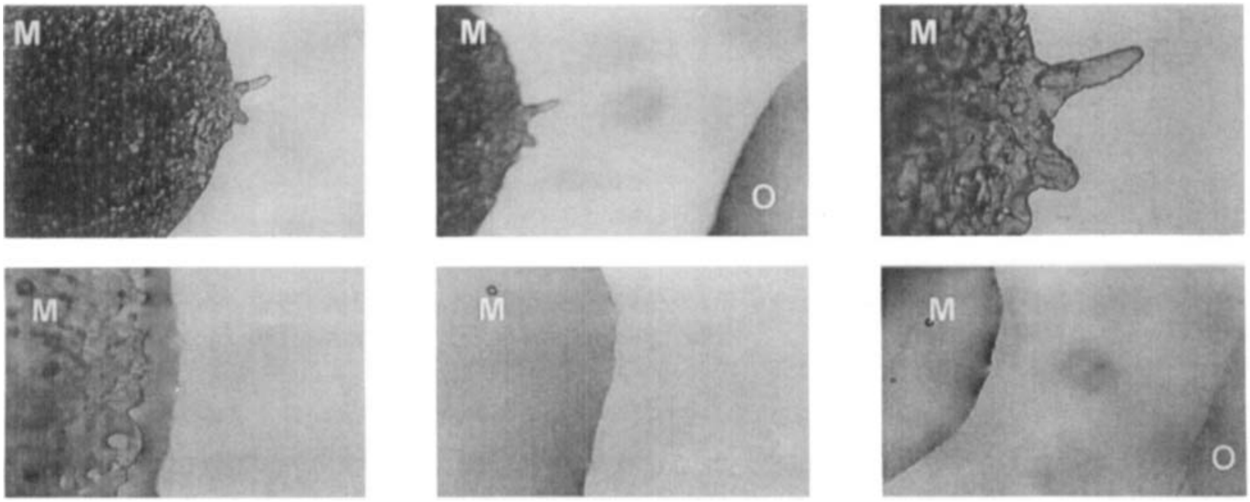

Figure 9. Melting of two forms of paracetamol at ±158°C and at ±168°C, prepared at the same time. M = monoclinic; O = orthorhombic.

±167°C. All three of the melts solidified to a glass. Upon reheating, all three glass samples transformed into crystals. Two of the three melted at ±158°C and the last sample melted at ±168°C (Fig. 9).

It is clear that there was a difference in melting temperature of ±10°C between the lower and the higher melting points. This suggests that both forms of paracetamol formed after being cooled under the same conditions. It is possible that the temperature distribution in the hot stage was not even, but a difference of 10°C in the melting of the bulk crystals is large enough to differentiate between the two melting points. The small projection from the sample with the higher melting point started melting at ±162°C. This projection should have melted if the melting point of these crystals was at 158°C.

CONCLUSION

To produce either one of the two forms of paracetamol it was suggested by many authors that the rate of cooling was the important factor. Although a very important factor, this is not the only factor influencing the formation of either of the two morphs. The use of video confirmed the DSC results and the changes responsible for the different exo- and endotherms could be seen. Video images served as a useful tool in clarifying problems created by the use of DSC alone. There seems to be a great deal of overlap of the two forms' transition phases, which would make it difficult to force the crystallization of one form by keeping the solution or melt at a specific temperature. A better approach to the problem would be the crystallization from a solution or a melt by means of seeding of the preparation.

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