

# Transformation of Metastable Forms of Acetaminophen Studied by Thermal Fourier Transform Infrared (FT-IR) Microspectroscopy

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**A novel Fourier transform infrared (FT-IR) microspectroscopy equipped with a micro hot stage (thermal FT-IR microscopic system) was used to quickly study the phase transformation of acetaminophen polymorphs by a one-step process. Acetaminophen was sealed in KBr disc on the first and second heating processes under this system. The results indicate that the contour IR profile of form I acetaminophen in the first heating process changed dramatically only near 165 °C, but in the re-heating process exhibited a considerable alteration in peak intensity, band width and position near the temperatures at 85, 118 and 153 °C. A glassy form of acetaminophen was obtained after rapidly cooling the melted acetaminophen from 200 to 25 °C. The glassy acetaminophen was recrystallized at 85 °C to transform to the form III of acetaminophen in the reheating process, and then transformed to its form II near 118 °C. The thermal FT-IR microscopic system is a simple, quick and timesaving tool for investigation of the thermo-dependent molecular structure of acetaminophen polymorphs in the processes of recrystallization and polymorphic transition.**

**Key words** acetaminophen; polymorphs; thermal FT-IR microscopic system; transformation

Acetaminophen is still worldwide used for analgesic and antipyretic therapy by millions of tablets and other dosage forms. Two polymorphs of acetaminophen have been published: form I is a monoclinic crystal and form II is an orthorhombic crystal. Form I (the usual form) is more stable at room temperature than form II.<sup>1–4</sup> Form I has poor binding and densification properties,<sup>5,6</sup> and is not suitable for direct compression into tablet. The preparation for monoclinic acetaminophen tablets therefore needs a series of time- and material consuming processes and excipients, and the size of the tablets cannot be enlarged. On the other hand, the orthorhombic acetaminophen not only has a sliding plane for good compression but also shows a faster dissolution rate than the monoclinic form.<sup>6–8</sup> Therefore, many studies have focused on how to prepare the orthorhombic form of acetaminophen.<sup>8–10</sup> An unstable third modification of acetaminophen (form III) has been found after different crystallization methods and the cooling rates, but the ambiguous explanations due to various differential scanning calorimetry (DSC) curves obtained have caused argument.<sup>8–11</sup> In the present study, a simple, quick and timesaving tool of Fourier transform infrared (FT-IR) microspectroscopy equipped with a micro hot stage (thermal FT-IR microscopic system) was used to readily and exactly explain the phase transition of metastable forms of acetaminophen by one-step process, as compared with different DSC thermograms of acetaminophen polymorphs prepared by different methods.

## Experimental

**Materials** Acetaminophen was of pharmaceutical grade, purchased from Seven Star Pharm. Co., Ltd. Taiwan, ROC. It was first recrystallized from aqueous solution, and then stored at 25 °C, 75% relative humidity (RH) for further use. KBr crystal was of analytical IR grade, purchased from Jasco Co., Tokyo, Japan.

**Thermal FT-IR Microspectroscopic Study** The acetaminophen powder was sandwiched between two KBr pieces by a hydraulic press to form a disc. This sample disc was directly put on a micro hot stage (DSC microscopy cell, FP 84, Mettler, Switzerland). The cell was then set on the stage of the microscope installed in the FT-IR microscopic spectrophotometer (Micro FTIR-200, Jasco, Tokyo, Japan) with an MCT detector. The sys-

tem was operated in the transmission mode. The desired sample size for determination was selected and defined by means of an Aperture Through Optical System (ATOS) using microscope. The temperature of DSC microscopy cell was monitored with a central processor (FT80HT, Mettler, Switzerland). The heating rate of DSC assembly was controlled at 3 °C/min in ambient conditions. The sample disc was previously equilibrated at the starting temperature (25 °C) for about 3 min and then heated to 200 °C. The thermal-responsive IR spectra were recorded with respect to the temperature. After the first heating process, the sample disc was cooled to 25 °C and then re-heated from 25 to 200 °C in the same conditions.

**Preparation and Determination of Different Acetaminophen Samples by Thermal Analyzer** (1) Sample 2: Raw powder of acetaminophen (sample 1) was first heated to 180 °C by a differential scanning calorimetry (DSC-910, TA Instruments Inc., U.S.A.) at a heating rate of 3 °C/min in an aluminum pan, maintained isothermally for 5 min, and then cooled to 25 °C using a cooling system (DSC refrigerated cooling system, TA Instruments Inc., U.S.A.) at a cooling rate of 15 °C/min to obtain the solidified melts. The process was carried out in an anhydrous nitrogen atmosphere.

(2) Sample 3: The solidified melts of sample 2 was pre-heated to 80 °C by a DSC system at a heating rate of 3 °C/min in an aluminum pan, and then cooled to 25 °C using a cooling system at a cooling rate of 10 °C/min. The process was carried out in an anhydrous nitrogen atmosphere.

(3) Sample 4: The solidified melts of sample 2 was pre-heated to 135 °C by a DSC system at a heating rate of 3 °C/min in an aluminum pan, and then cooled to 25 °C using a cooling system at a cooling rate of 10 °C/min. The process was carried out in an anhydrous nitrogen atmosphere.

All the test samples were respectively examined by using a DSC analysis to determine the polymorphic properties. The DSC cell was calibrated with indium.

## Results and Discussion

In the present study, acetaminophen was confirmed as being form I by FT-IR and DSC analyses, which was consistent with the IR spectra of acetaminophen determined by Nujol method<sup>12</sup> and its DSC curve.<sup>4,6,10</sup> This suggests that there was no physical stability problem of acetaminophen after compression of making a KBr disc. Three-dimensional plots of FT-IR spectra of acetaminophen on first-heating (A) and second-heating (B) with respect to the temperature are shown in Fig. 1. Obviously, the contour IR profile of acetaminophen on first-heating changed dramatically near 165 °C (Fig. 1A), which was close to the melting point (168–170 °C) of acetaminophen.<sup>4,6,10,13</sup> The acetaminophen was

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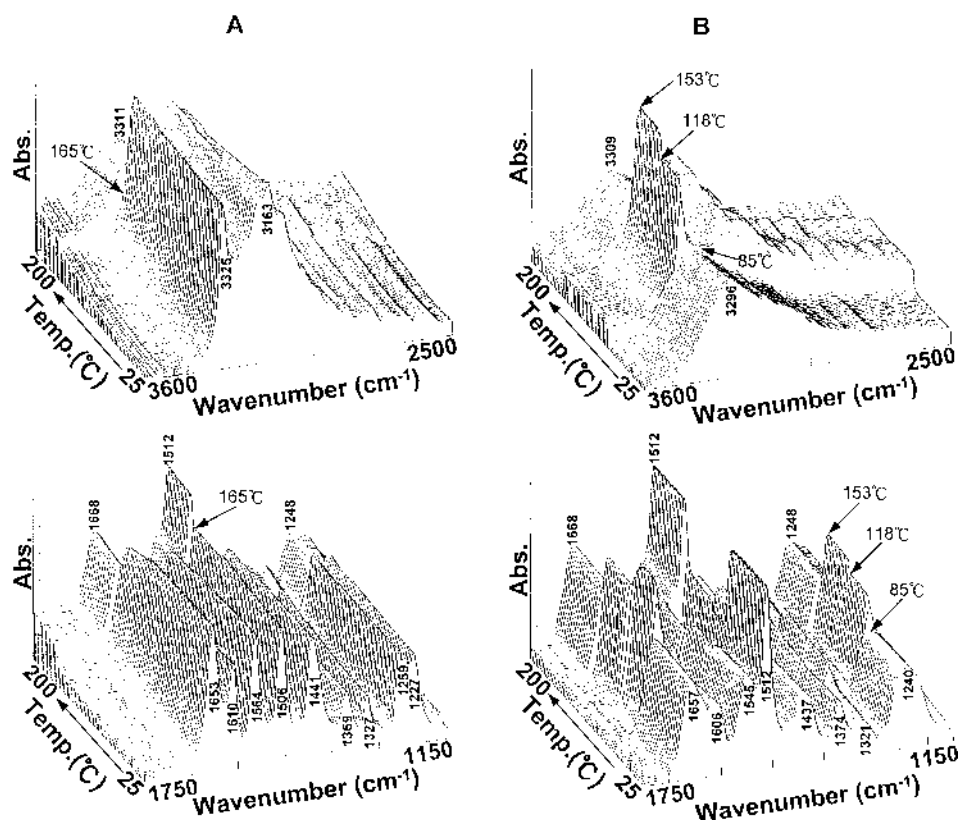


Fig. 1. Three-Dimensional Plots of FT-IR Spectra of Acetaminophen on First-Heating (A) and Second-Heating (B) with Respect to the Temperature

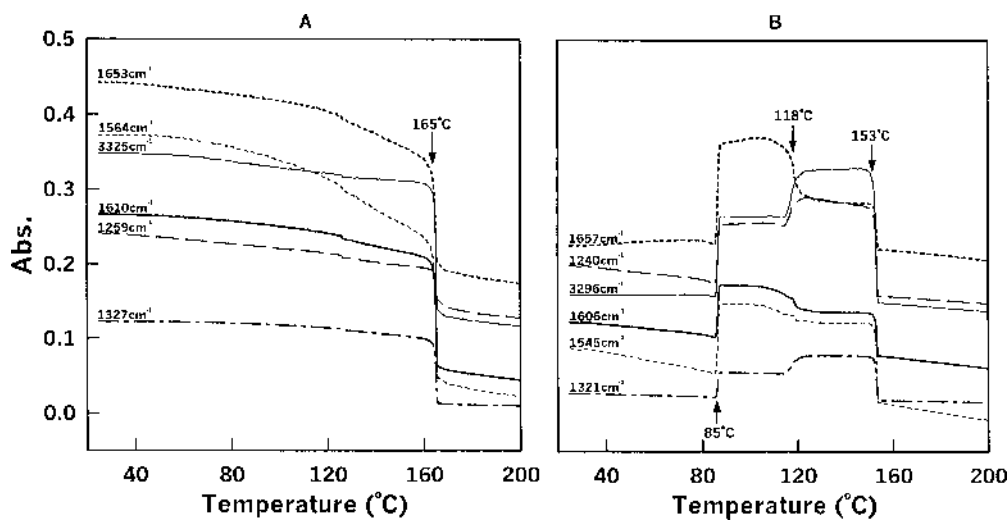


Fig. 2. Temperature-Dependent Changes of the Specified Peak Intensity of Acetaminophen

Key: (A) first-heating process; (B) second-heating process.

liquidated above 165 °C, leading to the less sharp intensity in the liquid state as compared with the solid state.<sup>14)</sup> The assignment of each peak in the solid state is as follows: 3325  $\text{cm}^{-1}$ : the N–H stretching vibration; 3163  $\text{cm}^{-1}$ : the hydrogen-bonded OH stretching vibration plus other combination bands; 1653  $\text{cm}^{-1}$ : the C=O stretching vibration; 1564  $\text{cm}^{-1}$ : the N–H in-plane bending; 1610, 1506 and 1441  $\text{cm}^{-1}$ : the aromatic ring mode; 1327  $\text{cm}^{-1}$ : the O–H bending vibration (the disappearance of 1564 and 1327  $\text{cm}^{-1}$  in  $\text{D}_2\text{O}$  solution might be used to explain its assignment); and 1259–1227  $\text{cm}^{-1}$ : the C–O and/or C–N stretching vibrations, re-

spectively. The above representative IR bands decreased its peak intensity slightly with the increase of temperature up to 165 °C (Fig. 2A), since the atoms or molecules occupied the fixed site with very little vibrational motion in the solid state. Once beyond 165 °C, however, the peak intensity of these specific IR bands decreased dramatically because acetaminophen changed from solid state to liquid state.<sup>14)</sup> Moreover, the peak positions of the C=O stretching and N–H bending bands for acetaminophen shifted to a much higher or lower wavenumber when temperature was >165 °C, respectively. The shift from 1653 to 1668  $\text{cm}^{-1}$  for C=O stretching

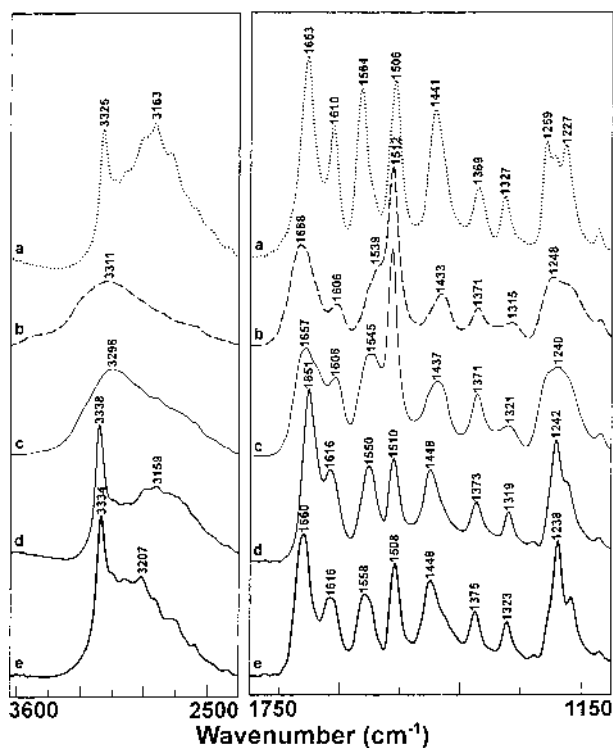


Fig. 3. Comparisons of Different IR Spectra of the Acetaminophen after Various Heating Treatments

Key: a, native acetaminophen powder at 25 °C; b, native acetaminophen powder after heating to 175 °C; c, b sample after rapidly cooling to 25 °C; d, c sample after reheating to 100 °C; e, c sample after continuously reheating to 130 °C.

band and from 1564 to about 1539  $\text{cm}^{-1}$  for N–H bending band was attributable to the gradual breaking of intermolecular hydrogen bonds between acetaminophen molecules induced by the increase of temperature. A sharp peak at 1512  $\text{cm}^{-1}$  shifted from 1506  $\text{cm}^{-1}$  was also observed, might be intensified by the N–H bending band of 1539  $\text{cm}^{-1}$ .

It is surprising to find that the peak intensity of acetaminophen changed a lot in re-heating process in several specific temperature ranges (Figs. 1B, 2B), for examples, 85, 118 and 153 °C, as compared with the slight change in temperature in the first-heating process (Figs. 1A, 2A). In order to investigate these intensive changes, the IR spectra at each specific temperature are isolated in Fig. 3. The transformation of acetaminophen from solid to liquid states might broaden the IR spectrum. Moreover, the shift of the C=O stretching and N–H bending bands in acetaminophen molecule also indicated the weakness of intermolecular hydrogen bonding in the liquid state (Fig. 3a→Fig. 3b). Once the liquefied acetaminophen was cooled to 25 °C to form a solidified melt, several specific peaks at higher frequencies (3311, 1668  $\text{cm}^{-1}$ ) shifted to lower frequencies (3296, 1657  $\text{cm}^{-1}$ ), implying that the intermolecular interaction in the solidified acetaminophen became slightly stronger (Fig. 3b→Fig. 3c). However, the IR spectrum of the solidified acetaminophen was broad and similar to that of the liquefied acetaminophen, suggesting the crystal form of the solidified acetaminophen was still irregular and might be defined as a glassy form.<sup>10</sup> Reheating the glassy form of acetaminophen from 25 to 100 °C could obtain a sharp IR spectrum. The shift from 3296, 1657, 1606, 1545 and 1437  $\text{cm}^{-1}$  to 3338, 1651, 1616,

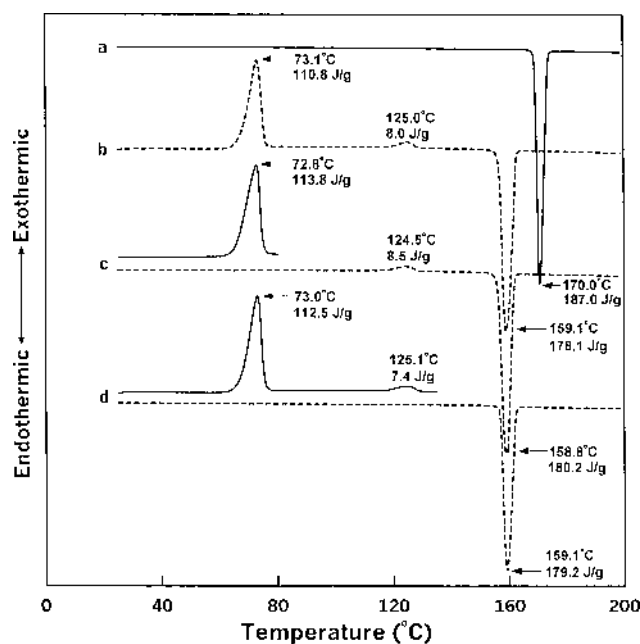


Fig. 4. DSC Thermograms of Different Samples of Acetaminophen

Key: a, sample 1: native acetaminophen; b, sample 2: preheated to 180 °C and then quickly cooled to 25 °C; c, sample 3: preheated to 80 °C and then cooled to 25 °C; d, sample 4: preheated to 135 °C and then cooled to 25 °C. Solid line: first heating; dotted line: second heating.

1550 and 1448  $\text{cm}^{-1}$  (Fig. 3c→Fig. 3d) indicates that over 85 °C the irregular crystal form of the glassy acetaminophen was transformed to the regular crystal form. 85 °C was the temperature for recrystallization of the glassy acetaminophen.

Once the sample was continuously reheated from 100 to 130 °C (Fig. 3d→Fig. 3e), its IR spectrum was still so sharp and had shifting behavior at several frequencies. The peaks at 3338  $\text{cm}^{-1}$  assigned to N–H stretching, at 1651  $\text{cm}^{-1}$  due to the C=O stretching, at 1550  $\text{cm}^{-1}$  corresponding to N–H bending, and at 1319  $\text{cm}^{-1}$  assigned to O–H bending shifted to 3334, 1660, 1558 and 1323  $\text{cm}^{-1}$ , respectively. Because the IR spectra for 100 °C-heated and 130 °C-heated samples were so sharp and different from each other, they should be of a different polymorph. The thermal change near 118 °C might be due to the polymorphic phase transition. Since the reheated acetaminophen in KBr disc showed a melting point at 153 °C determined by thermal FT-IR microscopic study, near the melting point (159 °C) of form II acetaminophen determined by DSC analysis (Fig. 4), we supposed that the 130 °C-heated sample in KBr disc should be the form II acetaminophen with a melting point at 153 °C (Figs. 1B, 2B). On the other hand, the 100 °C-heated sample might be due to the form III acetaminophen. The DSC thermograms in Fig. 4 also confirmed this supposition. Acetaminophen has been reported with two types of intermolecular hydrogen bonding (Chart 1) which was important to control the stability of different polymorphs. According to the X-ray crystallographic data,<sup>1,2,7,8</sup> the form I acetaminophen exhibited a stronger hydrogen bonding than form II. The distance of NH···O assigned to the type A hydrogen bonding and OH···O assigned to the type B hydrogen bonding in acetaminophen crystal is 2.91 and 2.65 Å for form I and 2.97 and 2.72 Å for form II, respectively. The short distance caused the strong intermolecular interaction in form I crystal to have a higher melting

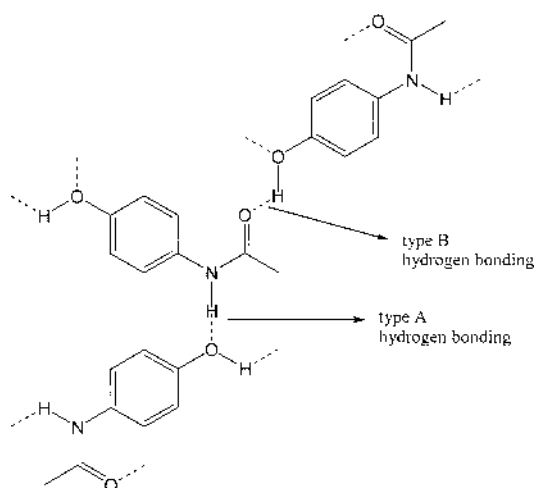


Chart 1. The Hydrogen Bonding Structure of Acetaminophen

point of 170 °C than that of 159 °C for form II (Fig. 4). In the present study, the results of FT-IR spectra were similar to the conclusion of X-ray crystallographic data. The N–H and C=O stretching modes were located at lower frequencies for form I acetaminophen (3325, 1653  $\text{cm}^{-1}$ ) but at higher frequencies (3334, 1660  $\text{cm}^{-1}$ ) for form II. The N–H bending mode at 1564  $\text{cm}^{-1}$  for form I and at 1558  $\text{cm}^{-1}$  for form II also showed the same result. As compared with the FT-IR spectra of different polymorphs in Figs. 3d and e, form III showed a stronger type B hydrogen bonding than form II since the C=O stretching mode was 1651  $\text{cm}^{-1}$  for form III but 1660  $\text{cm}^{-1}$  for form II. On the other hand, the type A hydrogen bonding in form II was stronger than in form III since the N–H stretch mode of Form II (3334  $\text{cm}^{-1}$ ) was less frequent than form III (3338  $\text{cm}^{-1}$ ).

As seen from the DSC curve in Fig. 4a, a native acetaminophen (sample 1) showed an endothermic peak near 170 °C with an enthalpy of 187 J/g, and should be confirmed as form I acetaminophen.<sup>6,10</sup> However, the DSC curve of the sample 2 indicated two exothermic peaks near 73 °C (110 J/g) and 125 °C (8 J/g), and one endothermic peak at 159 °C (178 J/g), respectively (Fig. 4b). The exothermic peak at 73 °C might be due to the recrystallization of glassy form of solidified acetaminophen melt, which was consistent with other reports.<sup>4,6,9,10</sup> However, the interpretations of the exothermic peak at 125 °C were controversial, including habit transformation and solid state conversion from form II to form I,<sup>8,10</sup> although our thermal FT-IR microscopic results failed to support these explanations. From the above FT-IR spectral evidence, we regarded this exothermic peak at 125 °C as a result of polymorphic phase transition from form III to form II, also consistent with Martino's study.<sup>9</sup> The endothermic peak at 159 °C was attributed to the melting point of form II acetaminophen, which was confirmed by DSC

curves of other samples (Figs. 4c, d) and other studies.<sup>4,6,9,10</sup> However, the enthalpy difference of the phase transition from form III to form II is quite small (8 J/g) since the form II had strong type A hydrogen bonding but form III had strong type B hydrogen bonding. The compensation between them might cause the transformation only with a lower enthalpy of 8 J/g at 125 °C. Thus, entropy was the predominant factor of the transformation from form III to form II. Since the temperature of recrystallization and phase transition was strongly dependent on the environmental factors, different results were obtained with different cooling rates, conditions and methods, leading to different temperature of recrystallization (72 versus 85 °C) and phase transition (125 versus 118 °C) by using DSC analysis and thermal FT-IR microscopic study.

To most compounds, it is difficult to obtain a single crystal of metastable form. In this study, we could obtain the bonding information of acetaminophen at various temperatures in different polymorphs by FT-IR spectra, as in the X-ray crystallographic study. The macroscopic viewpoint of DSC analysis was impossible to obtain this kind of information. This strongly suggests that the thermal FT-IR microscopic system was a powerful tool for the determination of the phase transition of drug.

## Conclusions

A novel thermal FT-IR microscopic system was used to easily investigate the phase transformation of acetaminophen polymorphs by a one-step continuous process. A glassy form of acetaminophen was obtained after rapidly cooling the melted acetaminophen from 200 to 25 °C. The glassy acetaminophen was recrystallized at 85 °C to form III, and then transformed to form II near 118 °C by determination of this thermal FT-IR microscopic system.

## References

- 1) Haisa M., Kashino S., Maeda H., *Acta Cryst.*, **B30**, 2510–2513 (1974).
- 2) Haisa M., Kashino S., Kawai R., Maeda H., *Acta Cryst.*, **B32**, 1283–1285 (1976).
- 3) Sohn Y. T., *J. Korea. Pharm. Sci.*, **20**, 97–104 (1990).
- 4) Lin S. Y., Perng R. I., *Chin. Pharm. J.*, **44**, 133–139 (1992).
- 5) Duberg M., Nystrom C., *Powder Technol.*, **46**, 67–75 (1994).
- 6) Martino P. D., Guyot-Hermann A. M., Conflant P., Drache M., Guyot J. C., *Int. J. Pharm.*, **128**, 1–8 (1996).
- 7) Joiris E., Martino P. D., Berneron C., Guyot-Hermann A. M., Guyot J. C., *Pharm. Res.*, **15**, 1122–1130 (1998).
- 8) Nichols G., Frampton C. S., *J. Pharm. Sci.*, **87**, 684–693 (1998).
- 9) Martino P. D., Conflant P., Drache M., Huvenne J. P., Guyot-Hermann A. M., *J. Thermal Anal.*, **48**, 447–458 (1997).
- 10) de Wet F. N., Gerber J. J., Lotter A. P., van der Watt J. G., Dekker T. G., *Drug Devel. Indus. Pharm.*, **224**, 447–453 (1998).
- 11) Burger A., *Acta Pharm. Technol.*, **28**, 1–20 (1982).
- 12) Acetaminophen monograph in JP IX, p. C-70.
- 13) Lin S. Y., Perng R. I., *J. Inclusion Phenom. Mol. Reg. Chem.*, **14**, 149–156 (1992).
- 14) Lin S. Y., Wang S. L., Cheng Y. D., *J. Phys. Chem. Solids*, **61**, 1889–1893 (2000).