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# Use of in situ FT-Raman spectroscopy to study the kinetics of the transformation of carbamazepine polymorphs

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**Abstract**

The solid-state transformation of carbamazepine from form III to form I was examined by Fourier Transform Raman spectroscopy. Using a novel environmental chamber, the isothermal conversion was monitored in situ at 130 °C, 138 °C, 140 °C and 150 °C. The rate of transformation was monitored by taking the relative intensities of peaks arising from two C–H bending modes; this approach minimised errors due to thermal artefacts and variations in power intensities or scattering efficiencies from the samples in which crystal habit changed from a characteristic prism morphology (form III) to whiskers (form I). The solid-state transformation at the different temperatures was fitted to various solid-state kinetic models of which four gave good fits, thus indicating the complexity of the process which is known to occur via a solid–gas–solid mechanism. Arrhenius plots from the kinetic models yielded activation energies from 344 kJ mol$^{-1}$ to 368 kJ mol$^{-1}$ for the transformation. The study demonstrates the value of a rapid in situ analysis of drug polymorphic type which can be of value for at-line in-process control.


*Keywords:* Carbamazepine; Polymorph; Solid-state transition; FT-Raman spectroscopy; In-process control

## 1. Introduction

Carbamazepine (Fig. 1) is an anticonvulsant drug used to treat epilepsy and to relieve trigeminal neuralgia [1]. It exhibits crystal polymorphism and several authors have investigated its anhydrous polymorphs [2–15,22] and its hydrate form [16–21]. Four well-characterised anhydrous polymorphs and a dihydrate have been described [15,17,19]. The two principal polymorphs constitute an enantiotropic pair referred to as form III and form I (although the nomenclature of β and γ, respectively has been applied to these also [22]) with the low temperature form III usually occurring in commercial material. The kinetics of the thermal interconversion between some carbamazepine polymorphs has been previously examined using off-line powder X-ray diffractometry [5].

The kinetics of solid-state transformation of drugs can be complex and so may not necessarily be described by a single kinetic equation [23], being affected by such variables as the structure of the product, imperfections within the crystal structure and sample history [24]. The ability to monitor such transformations closely by an at-line technique may allow better understanding of such reactions and so enable improved control of processes such as the isolation and drying of crystalline pharmaceutical materials. Measurement in situ avoids running the reaction separately from the analytical evaluation and having to transport the reacting sample for analysis, which may lead to error if, for example, the reaction is not properly quenched prior to transfer for analysis or potential re-organisation of fragile forms.

Thermal methods such as differential scanning calorimetry or thermogravimetric analysis can be applied to desolvation reactions [25]. Vibrational spectroscopic approaches

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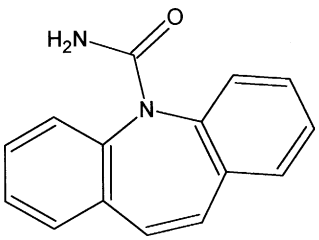


Fig. 1. Structure of carbamazepine.

[26], variable environment powder X-ray diffraction (XRD) [21] and temperature-controlled simultaneous small/wide angle X-ray scattering [22] have been used to follow crystal transformations in situ. To date there are only a limited number of reports of the application of in situ Raman spectroscopy to characterise transformations of drug polymorphs [27,28], including a study of carbamazepine crystallization [29]. If high quality spectra are obtained for the material under study, FT-Raman can scan rapidly relative to, for example, powder X-ray diffraction and therefore offers a more rapid response for at-line in-process control.

This study reports the characterisation of the conversion of carbamazepine form III to form I at elevated temperatures in situ using FT-Raman spectroscopy and a kinetic evaluation of the generated data.

## 2. Materials and methods

### 2.1. Materials

Carbamazepine polymorph III was USP grade (Diamalt, Munich, Germany), the polymorphic form being confirmed by thermal analysis and powder X-ray diffraction. Carbamazepine polymorph I was prepared by heating commercial material polymorph III at 170 °C for 2 h [7]. Quantitative conversion was confirmed by differential scanning calorimetry, comparing results with published data [10].

### 2.2. FT-Raman spectroscopy

FT-Raman spectra were obtained using a Bruker FRA 106 FT-Raman module mounted on an IFS 66 optics bench, equipped with a 750 mW Nd:YAG laser operating at 1064 nm. Solid samples (approximately 10 mg) were held in an aluminium cup (2.0 mm in diameter and 2.0 mm deep) and exposed to the focussed laser with a spot diameter of 0.1 mm. A liquid nitrogen cooled germanium detector with an extended bandwidth covered the range 3500–50 $cm^{-1}$. Band wavenumbers were calibrated against internal laser frequencies, which provided vibrational band numbers correct to $\pm 1\ cm^{-1}$.

FT-Raman heating studies were performed using a purpose built environmental chamber which allowed in situ collection of spectra under isothermal elevated temperature conditions [30]. The heating chamber was adapted from a Graseby-Specac 19930 variable temperature diffuse reflectance accessory fitted with a custom built removable polished quartz window. The orientation of the accessory was modified to permit a 90° sampling geometry. Temperature control was achieved using a Graseby-Specac 20120 series temperature programmer. Sample temperature was recorded via a thermocouple connected to the sample port and the chamber was water cooled to prevent spectral distortion caused by laser defocusing. Temperature calibration was confirmed using pure fatty acids of known melting points.

Samples were heated isothermally at 130, 138, 140 and 150 °C. Forty scans at 4 $cm^{-1}$ resolution provided sufficiently resolved spectra for a time-dependent analysis. Spectra were recorded in situ throughout the heating period and each sample was run at least in duplicate. Spectra were collected ensuring consistent scan durations and delays between scans.

## 3. Results and discussion

### 3.1. FT-Raman characterization of carbamazepine form III and form I

Analysis of carbamazepine polymorphs III and I by FT-Raman spectroscopy yielded spectra with excellent signal to noise ratios (>1000:1), with the two polymorphs exhibiting differences in peak positions and intensities. Peak positions were assigned to specific molecular vibrations by reference to published literature [31] and are reported in Table 1.

In order to evaluate the kinetics of polymorphic conversion, it was necessary to select a region within the spectrum where clear spectral differences between polymorph III and polymorph I were present. Several changes in the collected spectra were observed during the thermal transformation of carbamazepine form III to form I, with the absolute and relative intensities of a number of peaks changing. There was a clear change in the relative intensities of the two C–H bending modes at 1040 $cm^{-1}$ and 1025 $cm^{-1}$, from the ortho-substituted benzene rings of the carbamazepine molecule, as the solid-state polymorphic transformation occurred which allowed the transformation to be readily followed. The change in the relative intensities of these two C–H bending modes as the solid transition proceeded at 140 °C is illustrated in Fig. 2. The ratio of peak height at 1040 $cm^{-1}$ to peak height at 1025 $cm^{-1}$ ($I_{1040/1025}$) recorded at different time points for each temperature was used to determine the amount of polymorph III remaining. The intensity ratio was preferred as opposed to individual peak intensities, in order to compensate for potential variations in sample irradiance.

Peak intensity ratios ($I_{1040/1025}$) were converted to the fraction carbamazepine form III transformed, based on in-

Table 1
Assignment of FT-Raman bands to molecular vibrations for carbamazepine form III and form I

| Form III | Form I | Approximate description of vibrational mode | Form III | Form I | Approximate description of vibrational mode |
|---|---|---|---|---|---|
| 3071w | | $\nu$(CH) asymmetric, aromatic | 874w | 876w | $\nu$(C—N—C) |
| | 3061m | $\nu$(CH) aromatic | 853vw | 853vw | Amide V/$\delta$(C—H) aromatic |
| 3043w | | $\nu$(CH) aromatic | 723m | 720m | $\nu$(C—N—C) 3° amide |
| 3020w | 3024m | $\nu$(CH) non-aromatic | 691mw | 699w | $\delta$ aromatic, in-plane/C—H wag *cis* |
| 1624s | 1621s | $\nu$(C=C) non-aromatic | 646vw | 646vw | $\delta$(O—C—N) ring/$\delta$(C=O) |
| 1600ms | 1598s | $\delta$(N—H) amide II | 620vw | 620w | $\delta$(O—C—N) ring |
| 1588m sh | | $\nu$(C=C) aromatic | 582w | 582w | $\delta$(O—C—N) |
| 1565s | 1563s | $\nu$(C=C) aromatic | 559w | | $\delta$ aromatic, out-of-plane |
| 1489m | 1489m | $\nu$(C=C) symmetric, aromatic/$\nu$(C—N) amide III | 546w | 546w | $\delta$ aromatic, out-of-plane |
| 1460vw | 1461vw | $\delta$(CH) aromatic, in-plane | 538w sh | 537w | $\delta$ aromatic, out-of-plane |
| 1439vw | 1440vw | $\nu$(C—C) aromatic | 486vw | 481w sh | |
| 1412w | 1406w | $\nu$(C=C)/$\delta$(CH) | 469vw | 473vw | |
| 1309ms | 1305ms | $\delta$(CH) in-plane, non-aromatic | 454w | 458w | |
| 1273vw | 1271w | $\nu$(C=C) | 413w | 413w | Lattice vibration |
| 1250mw | 1253mw | $\nu$(C—N) amide III 1° amide | 390m | 394mw | Lattice vibration |
| 1221m | 1218m | $\nu$(C—N) amide III | 375mw | 371w | Lattice vibration |
| 1204w | 1206w sh | $\nu$(C—C) ring | 330w | 332w | Lattice vibration |
| 1160w | 1155w | $\nu$(C—C) ring/(C—N—C) asymmetric | 272w | 263w | Lattice vibration |
| 1130w | 1133w | $\rho(NH_2)$ | 253mw | | Lattice vibration |
| 1116w | 1110w | $\rho(NH_2)$ | 227vw | | Lattice vibration |
| 1042m | 1040m | $\delta$(C—H) aromatic, in-lane | 182ms | | Lattice vibration |
| 1025m | 1025ms | $\delta$(C—H) aromatic, in-plane | 170s | 172s | Torsion |
| 987w | 968w | $\nu$(C—N) | 120s | 116vs | Lattice vibration |
| 949w | 955vw | $\delta$(C—H) aromatic, out-of-plane | 105s | | Lattice vibration |
| 936vw | 943vw | $\delta$(C—H) aromatic, out-of-plane | | | |
| 884vw sh | 888vw sh | $\nu$(C—N—C) ring, symmetric | | | |

$\nu$: Sretch, $\delta$: bend, $\rho$: rocking, s: strong, m: medium, w: weak, v: very, sh: shoulder.

tensity ratios determined from the plateau value of the ratio during conversion of form III to form I on heating at 150 °C and the value prior to heating. Completion of this transformation was confirmed by differential scanning calorimetry.

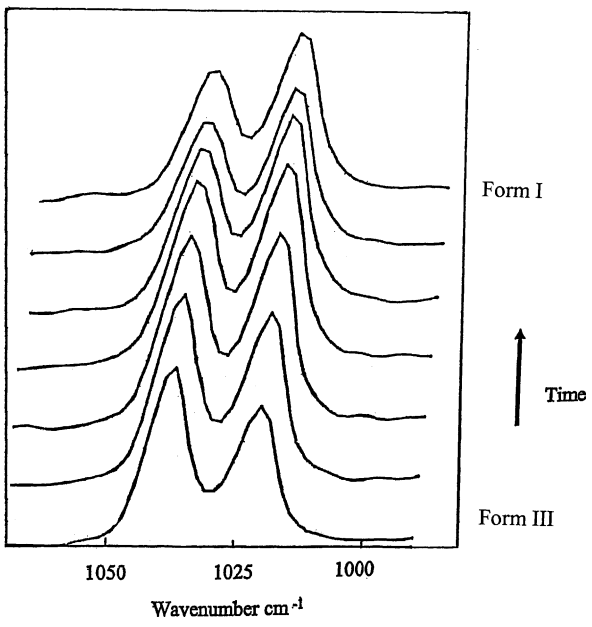


Fig. 2. FT-Raman spectra (1060–1000 $cm^{-1}$) for carbamazepine form III heated isothermally at 140 °C. Time between individual spectra is 1040 s.

### 3.2. Kinetic evaluation of carbamazepine form III to form I

The transition of carbamazepine form III to form I at the temperatures studied is via a solid-state transition [5]. There was no melt of form III material during the isothermal heating studies; these conditions parallel low heating rates in differential scanning calorimetry where the transformation of carbamazepine form III to form I was shown to be via a solid–gas–solid transformation [10]. After completion of each experiment, microscopy confirmed the habit change of carbamazepine from the prisms of form III to the whiskers of form I [32].

For each experimental temperature the intensity ratios were converted to the fraction transformed; a temperature dependent rate of reaction is evident as shown in Fig. 3.

Data in the range 0.1–0.95 fraction transformed [34] were fitted to various solid-state kinetic models [33] and the conformity of data to each model assessed by the correlation coefficient (Table 2). Several different mechanisms fitted the data with good correlation, making allocation of a single mechanism difficult. At 150 °C and 140 °C, the random nucleation process with both two ($n$ = 1/2) or three ($n$ = 1/3) dimensional growth of nuclei (Avrami–Erofeev) gave the better fit. At 130 °C and 138 °C good correlations were also obtained with both two dimensional and three dimensional phase boundary movement kinetics, as well as with one dimensional diffusional process kinetics. The phase boundary reaction kinetics

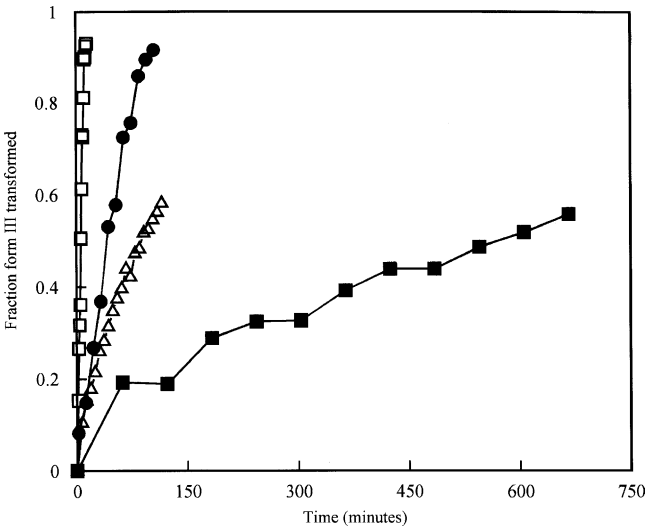


Fig. 3. Fraction of carbamazepine from III transformed to form I against time at different temperatures. Key: (□) 150 °C, (●) 140 °C, (△) 138 °C, (■) 130 °C.

also provided relatively good fit at 140 °C and 150 °C. The data may suggest that multiple mechanisms were operating simultaneously. Overall, based on correlation coefficients and inspection of regression plots (residuals analysis), the phase boundary kinetic models best described the data across the temperature range.

The ability to describe a solid-state reaction by more than one kinetic model is common, reflecting the complexity of solid:solid reactions [23]. The transformation of carbamazepine form III to form I has previously been reported to follow the two dimensional nuclear growth model (Avrami–Erofeev, $n = 1/2$) over a range of temperatures [5]. As was evident in correlation coefficients in that earlier work, in the present study data at the lower temperature studied did not fit this model as well as at higher temperatures. Plots for the Avrami–Erofeev two and three dimensional models and the two dimensional and three dimensional phase boundary models are given in Fig. 4a–d.

Table 3
Calculated activation energies for carbamazepine form III to form I transition using four kinetic models

| Kinetic model | Activation energy (kJ mol$^{-1}$) |
|---|---|
| Avrami–Erofeev ($n = 2$) | 354.8 |
| Avrami–Erofeev ($n = 3$) | 344.4 |
| Two dimensional phase boundary | 359.6 |
| Three dimensional phase boundary | 368.1 |

Arrhenius plots allowed calculation of activation energy for the carbamazepine form III to form I transition and was similar for the four best fit models, irrespective of the model selected (Table 3). The activation energy for the polymorphic transformation in this study (344–368 kJ mol$^{-1}$) is of the same order but somewhat higher than that determined in a previous study (229 kJ mol$^{-1}$) employing off-line powder X-ray diffraction [5]. Reasons for differences in the values obtained here relative to previous work might include differences in sample charactersitics (e.g., particle size) and packing in the XRD holder (where sample is tightly packed to maximize peak intensity) relative to the Raman cell (where sample was filled more loosely into the sample cup). Such a difference could lead to differences in heat transfer through the sample which might influence polymorphic conversion rates or provide conditions that constrain the solid–gas–solid transition [10] that is associated with the carbamazepine form III to form I transformation. It is suggested that the in situ method described here may be more reliable than the previously published method as there is no error associated with the need to quench the reaction, with the scanning time required in X-ray diffraction, or the need to evaluate the relative intensities of X-ray diffraction bands which can be subject to orientation effects and variation in scattering efficiencies where a change of habit occurs during scanning as is the case in this study where the prism habit of form III changes to the whisker or needle habit of form I. With suitable adaptation, perhaps using a fibre optic probe, the studies suggest that Raman spectroscopy could be used at-line, for example during drying of crystalline pharmaceuticals, to allow in-process monitoring and control of drug polymorphic form.

Table 2
Correlation coefficients calculated for carbamazepine form III to form I transformation for different kinetic models

| Kinetic model | Equation | Correlation coefficient ($r^2$) | | | |
|---|---|---|---|---|---|
| | | 150 °C | 140 °C | 138 °C | 130 °C |
| Prout–Tompkins | $\ln \alpha/(1-\alpha) = kt$ | 0.935 | 0.939 | 0.924 | 0.951 |
| Avrami–Erofeev ($n = 2$) | $[-\ln(1-\alpha)]^{1/2} = kt$ | 0.992 | 0.990 | 0.987 | 0.986 |
| Avrami–Erofeev ($n = 3$) | $[-\ln(1-\alpha)]^{1/3} = kt$ | 0.992 | 0.990 | 0.978 | 0.982 |
| First order | $-\ln(1-\alpha) = kt$ | 0.988 | 0.987 | 0.991 | 0.988 |
| One dimensional phase boundary | $1-\alpha = kt$ | 0.991 | 0.989 | 0.986 | 0.990 |
| Two dimensional phase boundary | $1-(1-\alpha)^{1/2} = kt$ | 0.988 | 0.985 | 0.997 | 0.991 |
| Three dimensional phase boundary | $1-(1-\alpha)^{1/3} = kt$ | 0.985 | 0.981 | 0.996 | 0.990 |
| One dimensional diffusion | $\alpha^2 = kt$ | 0.974 | 0.968 | 0.993 | 0.986 |
| Two dimensional diffusion | $(1-\alpha)\ln(1-\alpha) + \alpha = kt$ | 0.966 | 0.959 | 0.992 | 0.985 |
| Three dimensional diffusion | $[1-(1-\alpha)^{1/3}]^2 = kt$ | 0.947 | 0.938 | 0.988 | 0.981 |
| Ginstling–Brounshtein | $[1 = (2\alpha/3)]-(1-\alpha)^{2/3} = kt$ | 0.975 | 0.972 | 0.998 | 0.991 |

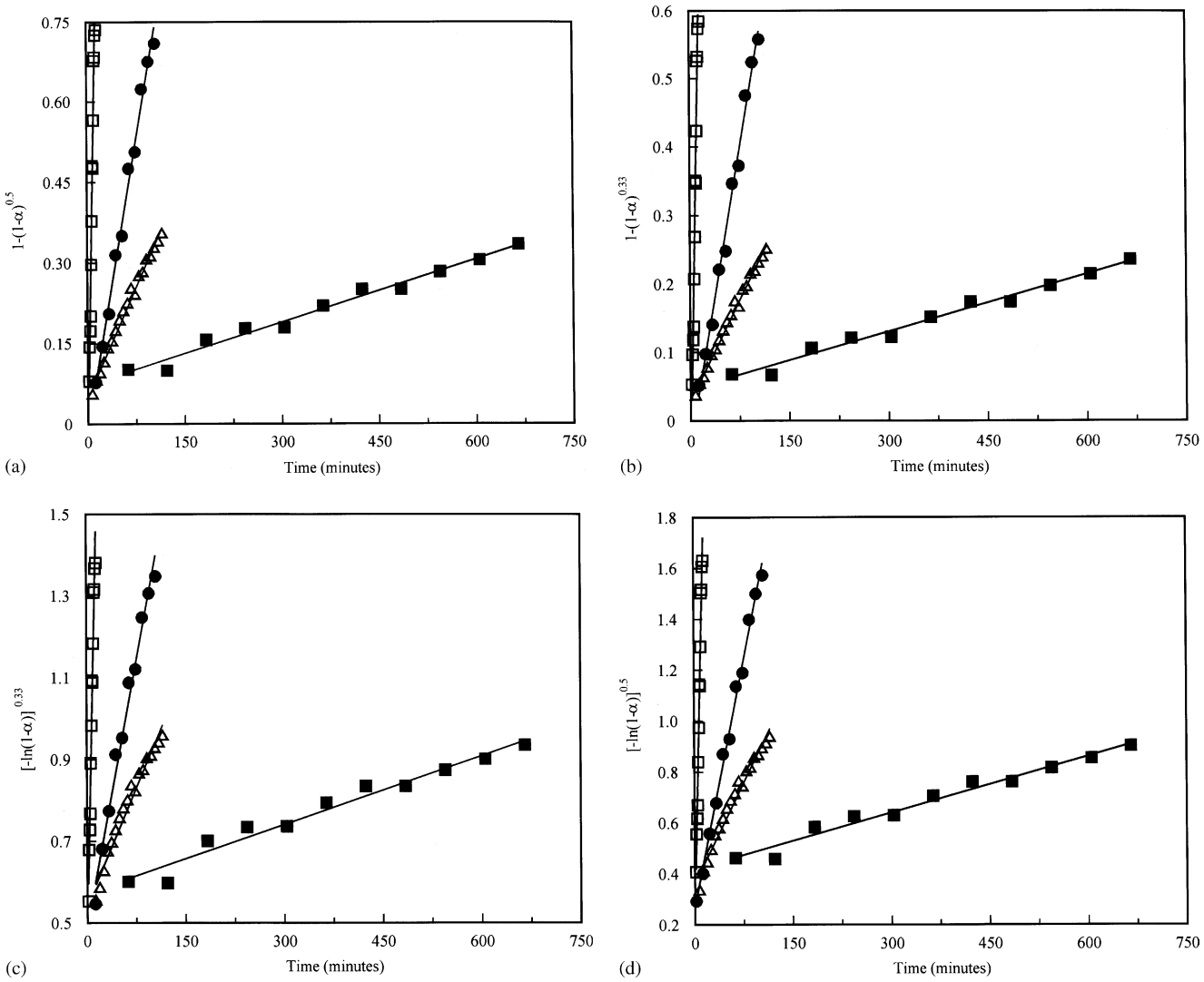


Fig. 4. Isothermal transformation of carbamzepine form III to form I: (a) two dimensional phase boundary, (b) three dimensional phase boundary, (c) three dimensional nucleation growth (Avrami–Erofeev, $n = 3$), (d) two dimensional nucleation growth (Avrami–Erofeev, $n = 2$). Key: (□) 150 °C, (●) 140 °C, (△) 138 °C, (■) 130 °C.

## 4. Conclusions

The kinetics of the solid-state transformation of carbamazepine polymorphs has been probed using in situ thermal Raman spectroscopy. The conversion fitted several solid-state models and Arrhenius analysis of the data yielded an activation energy of 344–368 kJ mol$^{-1}$ for the rearrangement. Further, the study illustrates that FT-Raman spectroscopy can be used for non-destructive in situ and at-line analysis of drug polymorphic form offering potential use for in-process control.

## References

[1] S.C. Sweetman (Ed.), Martindale, the Complete Drug Reference, 33rd ed., Pharmaceutical Press, London, 2002, p. 345.
[2] M. Kuhnert-Brandstätter, A. Kofler, A. Vlachopoulos, Sci. Pharm. 36 (1968) 164–179.
[3] J.P. Reboul, B. Cristau, J.C. Soyfer, J.P. Astier, Acta Crystallogr. Sect. B 37 (1981) 1844–1848.
[4] V.L. Himes, A.D. Mighell, W.H. De Camp, Acta Crystallogr. Sect. B 37 (1981) 2242–2245.
[5] T. Umeda, N. Ohnishi, T. Yokohama, K. Kuroda, T. Kuroda, E. Tatsumi, Y. Matsuda, Yakugaku Zasshi 104 (1984) 786–792.
[6] H. Kala, U. Haack, P. Pollandt, G. Brezesinski, Acta Pharm. Technol. 32 (1986) 72–77.
[7] C. Lefebvre, A.M. Guyot-Hermann, M. Draguet-Brughmans, R. Bouche, J.C. Guyot, Drug Dev. Ind. Pharm. 12 (1986) 1913–1927.
[8] M.M.J. Lowes, M.R. Caira, A.P. Lötter, J.G. van der Watt, J. Pharm. Sci. 76 (1987) 744–752.
[9] J.N. Lisgarten, R.A. Palmer, J.W. Saldanha, J. Crystallogr. Spectrosc. Res. 19 (1989) 641–649.
[10] R.J. Behme, D. Brooke, J. Pharm. Sci. 80 (1991) 986–990.
[11] R. Céolin, S. Toscani, M.F. Gardette, V.N. Agafonov, A.V. Dzyabchenko, B. Bachet, J. Pharm. Sci. 86 (1997) 1062–1065.
[12] Y. Kobayashi, S. Ito, S. Itai, K. Yamamoto, Int. J. Pharm. 193 (2000) 137–146.
[13] C. Rustichelli, G. Gamberini, V. Ferioli, M.C. Gamberini, R. Ficarra, S. Tommasini, J. Pharm. Biomed. Anal. 23 (2000) 41–54.

[14] M. Lang, J.W. Kampf, A.J. Matzger, J. Pharm. Sci. 91 (2002) 1186–1190.
[15] A.L. Grzesiak, M. Lang, K. Kim, A.J. Matzger, J. Pharm. Sci. 92 (2003) 2260–2271.
[16] N. Kaneniwa, T. Yamaguchi, N. Watari, M. Otsuka, Yakugaku Zasshi 104 (1984) 184–190.
[17] J. Dugué, R. Céolin, J.C. Rouland, F. Lepage, Pharm. Acta Helv. 66 (1991) 307–310.
[18] L.E. McMahon, P. Timmins, A.C. Williams, P. York, J. Pharm. Sci. 85 (1996) 1064–1069.
[19] F.U. Krahn, J.B. Mielck, Pharm. Acta Helv. 62 (1987) 247–254.
[20] G. Reck, G. Dietz, Cryst. Res. Technol. 21 (1986) 1463–1468.
[21] J. Han, R. Suryanarayanan, Int. J. Pharm. 157 (1997) 209–218.
[22] A.D. Edwards, B.Y. Shekunov, R.T. Forbes, J.G. Grossmann, P. York, J. Pharm. Sci. 90 (2001) 1106–1114.
[23] S.R. Byrn, R.R. Pfeiffer, J.G. Stowell, Solid-State Chemistry of Drugs, second ed., SSCI, West Lafayette, 1999.
[24] S.R. Byrn, R.R. Pfeiffer, G. Stephenson, D.J.W. Grant, W.B. Gleason, Chem. Mater. 6 (1994) 1148–1158.
[25] Y. Matsuda, E. Tatsumi, E. Chiba, Y. Miwa, J. Pharm. Sci. 73 (1984) 1453–1460.
[26] T. Norris, P.K. Aldridge, S.S. Sekulic, Analyst 122 (1997) 549–552.
[27] M. Szelagiewicz, C. Marcolli, S. Cianferani, A.P. Hard, A. Vit, A. Burkhard, M. von Raumer, U. Hofmeier, A. Zilian, E. Francotte, R. Schenker, J. Therm. Anal. Cal. 57 (1999) 23–43.
[28] F. Wang, J.A. Wachter, F.J. Antosz, K.A. Berglund, Org. Process Res. Dev. 4 (2000) 391–395.
[29] P.A. Anquetil, C.J.H. Brenan, C. Marcolli, I.W. Hunter, J. Pharm. Sci. 92 (2003) 149–160.
[30] H.G.M. Edwards, D.W. Farwell, J.M.C. Turner, A.C. Williams, Appl. Spectrosc. 51 (1997) 101–107.
[31] D. Lin-Vien, Handbook of Infra-red and Raman Characteristic Frequencies of Organic Molecules, Academic Press, Boston, 1991.
[32] E. Laine, V. Tuominen, P. Ilvessalo, P. Kahela, Int. J. Pharm. 20 (1984) 307–314.
[33] J.H. Sharp, G.W. Brindley, B.N.N. Achar, J. Am. Ceram. Soc. 49 (1966) 379–382.
[34] P. Jacobs, F. Tompkins, in: G. Garner (Ed.), Chemistry of the Solid State, Academic Press, New York, 1955, pp. 184–212.