Available online at www.sciencedirect.com
SCIENCE DIRECT®
Thermochimica Acta 430 (2005) 35–41
thermochimica acta
www.elsevier.com/locate/tca

Pressurization effects on the polymorphic forms of famotidine

Zoltán Német[a], Béla Hegedűs[b,*], Csaba Szántay Jr.[b], Janisz Sztatisz[a], György Pokol[a]

[a] *Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*
[b] *Gedeon Richter Ltd., Spectroscopic Research, Diosgyori utca 21, P.O. Box 27, H-1475 Budapest, Hungary*

Received 14 September 2004; received in revised form 17 December 2004; accepted 21 December 2004
Available online 20 January 2005

Abstract

The effects of high static pressure on the polymorphic modifications A and B of famotidine were examined by differential scanning calorimetry, infrared and Raman spectroscopy, and X-ray powder diffractometry. The obtained effects appeared to differ significantly depending on whether they were monitored by DSC or any of the other above techniques. In particular, DSC measurements tend to deceptively amplify a tendency of the pure modification B to turn into the more stable form A under pressurization, while the spectroscopic methods and XRPD exhibit no essential change in the crystal structure of the metastable form B. The apparent morphological transformation in the pressed samples stems from the nature of the DSC method itself.

Keywords: Famotidine; Polymorphism; Pressurization; Differential scanning calorimetry; Complex analytical approach

1. Introduction

Famotidine (3[[[2-[(amino-iminomethyl)amino]-4-thiazolyl]-methyl]thio]-*N*-(aminosulfonyl)-propanimidamide) is a widely used histamine H_2-receptor antagonist which was invented by the Japanese firm Yamanouchi in 1979. Famotidine exhibits two major crystalline polymorphs B and A, where B is the metastable form [1]. A detailed physical characterization (DSC, IR, XRPD) of these modifications was reported by Hegedűs et al. [2], while a comparison of their energetic and conformational features, based on single-crystal X-ray and quantum mechanical studies, was published by Ferenczy et al. [3].

Recently the effect of pressurization and grinding on the polymorphism of famotidine was discussed by Roux et al. [4]. The two pure modifications A and B were, on the one hand, subjected to different pressures of 200–1000 MPa in a high pressure press, and on the other hand they were ground in a mortar. The resulting effects were examined only by DSC which was the basis of the conclusions formed by the authors: they state that grinding produces no changes in modification A, but reduces the melting point of form B. On the other hand high pressure affected on famotidine B results in the appearance of some new entities, called "modifications" by the authors, which were characterized only through the observation that their melting points differ from that of the original B form; however, the identity of those "modifications" was not discussed.

Based on these data we became interested in exploring any potentially new polymorphic modifications of famotidine that may be formed under such extreme conditions. In this article we report our results obtained upon attempting to reproduce the investigations of Roux et al. [4]. Because of the difficulties in reproducibly controlling the grinding procedure as well as in adequately separating the complex and simultaneously occurring local and global influences (particle size reduction, mechanical pressing and shearing effects, sample warming) herein we focus only on the better-quantifiable effects of pressurization. (Our observations in that regard will serve as a sound basis for discussing the influences of grinding in a subsequent publication).

* Corresponding author. Tel.: +36 1 431 4951; fax: +36 1 432 6003.
E-mail address: b.hegedus@richter.hu (B. Hegedűs).

0040-6031/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.tca.2004.12.009

We have approached the pressurization problem through a complex analytical examination (DSC, IR, Raman, XRPD) rather than just using one method and our conclusions are somewhat different from those reported by Roux et al. [4].

2. Experimental

2.1. Sample preparation

Famotidine samples were taken from the manufacturing plant of Gedeon Richter Ltd. The chemical purity of the investigated samples was about 99.5% and they had no initially detectable morphological cross contamination.

Pressurization was carried out in a Graseby/Specac electro hydraulic press normally used for the preparation of the 13 mm KBr pellets for the FT-IR examinations. Famotidine samples (100 mg) were placed into the equipment as a flat layer and were pressed with preset different forces for 15 min. The applied pressing forces were about 13.3, 26.6, 53.2, 106.4 kN (1.3, 2.7, 5.4 and 10.8 t set on the press); considering that the surface of a pellet is 1.33 cm^2, this is equal to 100, 200, 400 and 800 MPa pressures. The obtained famotidine pellets were examined by different techniques. Except for the IR measurement, whole pellets or pieces of pellets were analyzed so as to avoid the simultaneous effect of grinding and pressure on the sample.

2.2. FT-infrared spectroscopy

IR spectra were recorded in KBr pellets on a Perkin-Elmer Spectrum 1000 spectrophotometer equipped with DTGS detector. An amount of 2 mg of famotidine was gently ground with 200 mg of KBr for 30 s in an agate mortar and then subjected to 800 MPa pressure in a high pressure press for 20 s. The applied scan number was 10 and the spectral resolution was 4 cm^{-1}.

2.3. FT-Raman spectroscopy

FT-Raman investigations were performed on a Perkin-Elmer Spectrum 2000 spectrophotometer equipped with a Nd:YAG laser. The power of the irradiating beam was set to 300 mW; the applied scan number was 30.

2.4. X-ray powder diffraction

XRPD examinations were carried out on a Philips PW 1729 model on the wavelength of the Cu Kα radiation, with 40 mA anode current and 40 kV accelerating voltage at a scanning rate of 3° 2Θ min^{-1}.

2.5. Differential scanning calorimetry

DSC measurements were carried out on a TA Instruments 2920 Modulated DSC equipment. Calibration was done with indium standard. Hermetically sealed aluminum pans were applied without purging gas flow. Mass of samples varied in 1.750–3.670 mg range. Similarly to the published experiments [4], the heating rate was 5 °C min^{-1} and was started from 140 °C.

3. Results

3.1. Preliminary investigation of non-pressed modifications

Because of the monotropic character of famotidine it is reasonable to formulate the initial expectation that high pressures may to some extent transform the metastable form B into the more stable form A. In anticipation of that process, we first conducted experiments aimed at gaining some initial insight into the analytical capabilities of the aforementioned methods regarding the pure, non-pressed A and B forms and their homogeneous model mixtures (in this sense "homogeneous" means well admixed). The following observations constitute a brief preliminary summary of those aspects of that study that are required for the interpretation of the subsequent pressurization experiments (a more detailed account will be reported elsewhere).

XRPD proved to have a limit of detection (LOD) of about 5–10% in model A/B mixtures, and the diffraction pattern of modification A is less repeatable in spite of the fact that it consists of tabular, while form B of acicular crystals (form A has a greater particle size possibly leading to a preferred orientation effect, which may be responsible for this decreased repeatability in the case of form A).

Similarly to XRPD, Raman spectroscopic examination also has the advantage that it does not require sample preparation prior to measurement, on the other hand it has a much better LOD: about 2% in the case of both modifications.

By IR spectroscopy the LOD of modification B in A is about 0.5%, however, the LOD of form A in B is higher than 10%. It should be pointed out that IR spectroscopic measurements using KBr pellets may involve the potential risk of polymorphic transformation (most likely that of the B → A kind) during sample preparation. A comparison of the IR spectra of the model A/B mixtures indicated that the pure B form undergoes no *detectable* amount of B → A transition during sample preparation; nevertheless some amount of such transformation cannot be ruled out in light of the relatively high LOD for A in B. For the sake of correctness, in the following we will regard the IR spectra obtained from the pure A and B forms as those of the "non-pressed" sample, relative to which the effects of high pressures on the IR spectra will be discussed below. (Diffuse reflectance IR spectroscopy which would in principle circumvent the problem of unintended pressurization during sample preparation was not included in our study).

By means of an appropriate choice of the measurement conditions DSC has the best LOD, allowing the detection

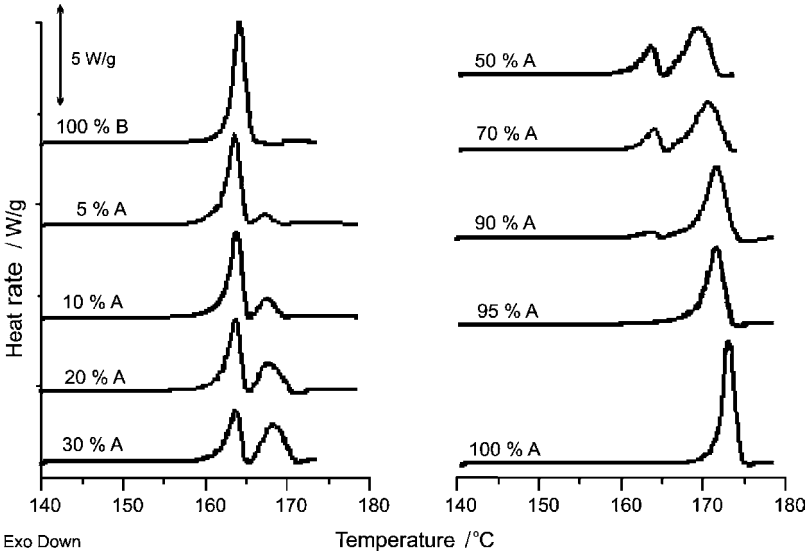

Fig. 1. DSC curves of homogeneous mixtures of the famotidine A and B forms. Percentages indicate the prepared composition of the mixtures.

of 0.5% of modification A in B. The quantitative measurement, however, is affected by the decomposition of famotidine during melting as well as by the length of time the sample is kept below the melting point. Another disadvantage of the method is a certain systematic error in measuring the melting enthalpies in homogeneous morphological mixtures. In particular, measurements based on the melting enthalpies tend to overestimate form A, and this error increases with the amount of A (Fig. 1). (Suitable calibration, coupled with validated sample preparation and measurement parameters can circumvent this problem).

Table 1 shows the melting characteristics of the pure polymorphic forms of famotidine: the endothermic peak maximum, the temperature of fusion (onset of the melting peak) and enthalpy of fusion, as measured by DSC prior to pressurization.

3.2. Pressurization of modification A

In the case of the pure modification A, pressurization did not result in any significant change in the melting characteristics (Table 2).

Similarly, no appreciable difference was detected in the IR and Raman spectra upon pressurization. However, there were significant changes in the relative intensities of the diffraction lines in the XRPD pattern (Fig. 5).

3.3. Pressurization of modification B

Pressurization of form B resulted in the appearance of a new endothermic DSC peak at higher temperatures (about 167 °C) whose peak intensity increased when the applied pressure had been increased. The sample pressed with 800 MPa exhibited a strong endothermic peak at about 170 °C (Table 3, Fig. 2) besides a small residual peak at about 163 °C (Table 3, Fig. 2), which is consistent with the initial modification B (Table 1). We could not reproduce the DSC curves presented by Roux et al. [4]; in particular, the monotonic growth and broadening of the peak above 172 °C was missing. The temperature of fusion of the residual B form decreased significantly by increasing the pressure; this tendency is clearly related to the decrease of the apparent amount of form B.

It is noted that the large estimated uncertainty of the fusion enthalpies is not due to measurement variation since the measuring conditions in the DSC cell were well controlled and repeatable. The intensity change of the endothermic peaks is not a monotonic function of the pressing force (Fig. 3). A similar tendency manifested itself when the sample had been pressed with 800 MPa. Consequently we may assume that the pressure distribution might have been inhomogeneous on the sample surface during the pressurization. This inhomogeneity in the local effect of the pressing force may be explained by the lumpy character of famotidine B.

Table 1
Melting characteristics of the B and A polymorphic forms of famotidine[a]

Form	T_{peak} (°C)	T_{fus} (°C)	ΔH_{fus} (J g^{-1})
B	164.1 ± 0.4	162.9 ± 0.3	151.7 ± 4.6
A	172.3 ± 0.2	170.6 ± 0.2	164.2 ± 2.0

[a] The results are averages of four non-consecutive measurements; the uncertainty is estimated as standard deviation.

Table 2
Melting characteristics of the pressurized A modification[a]

No.	T_{peak} (°C)	T_{fus} (°C)	ΔH_{fus} (J g^{-1})
1	171.7	170.7	158.9
2	171.6	170.9	155.5

[a] Results from two DSC measurements of modification A that had been subjected to a pressure of 800 MPa for 15 min.

Table 3
Melting characteristics of the pressurized B modification[a]

p (MPa)	T_{peak} (°C)		T_{fus} (°C)		ΔH_{fus} (J g^{-1})	
100[b]	164.6 ± 0.4	–[c]	163.9 ± 0.1	–	149.1 ± 5.7	6.0 ± 5.7
200[b]	164.8 ± 0.2	168.1 ± 0.1	163.4 ± 0.5	–	139.5 ± 3.7	13.8 ± 8.1
400[d]	164.0 ± 0.4	169.1 ± 1.1	161.5 ± 1.2	166.8 ± 1.2	71.3 ± 41.7	86.9 ± 43.3
800[d]	163.1 ± 0.5	170.4 ± 0.2	159.9 ± 0.5	167.8 ± 0.2	25.8 ± 29.7	134.8 ± 29.8

[a] The uncertainty is estimated as standard deviation.
[b] Calculated from two measurements.
[c] There is no definite peak at higher temperature.
[d] Calculated from four measurements.

Although the higher-temperature peak (about 168–170 °C, Table 1) is not specifically characteristic of modification A, in comparing the DSC curves of the pressed samples with those of the artificially prepared morphological mixtures of A and B, the similarity is obvious (Fig. 1). Clearly the melting temperature of modification A is dependent on the morphological cross contamination so that the presence of modification B reduces the melting range of form A (Fig. 1). In that light the higher-temperature peaks can safely be assigned to the A form (Table 1).

To our initial surprise, in contrast to the DSC results almost no change was observed in the FT-IR and FT-Raman spectra of the pressurized B form with respect to those of the pure, non-pressed B form, and practically no sign of the presence of the A modification was observed. Only slight broadenings on the spectral bands could be detected (Fig. 4).

However, the relative intensities of the characteristic lines exhibited appreciable changes in the XRPD pattern. It is reasonable to assume that the pressurization-incurred changes in the sample's particle size as well as in the properties of the analyzed surface have a small effect on the Raman scattering [5,6]. The same effects however may influence much more heavily the relative intensities of the X-ray diffraction lines [7]. XRPD measurements were performed on the flat layer of pellets made by the electro hydraulic press, so that the pellet was fixed to the glass plate of the sample holder. Due to slight variations in the positions of the sample pellets the positions of the diffraction lines shifted by 0.2–0.5° 2Θ values. It is interesting to note that the alteration of the relative intensities

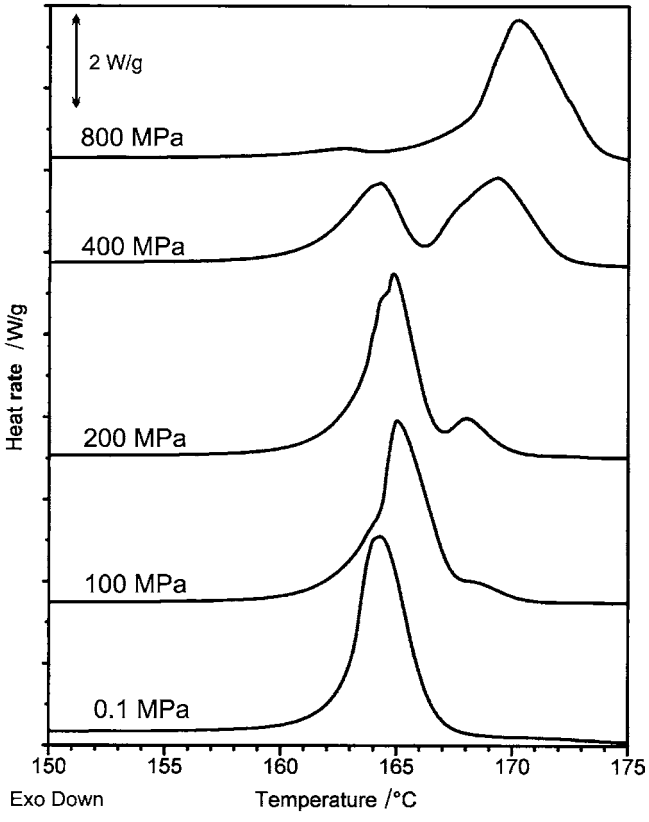

Fig. 2. DSC curves of pressurized modification B of famotidine.

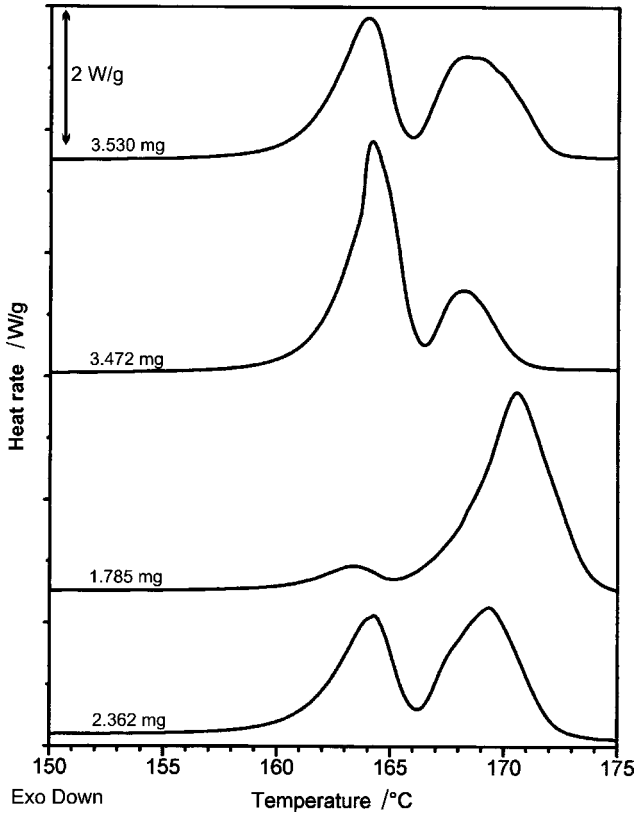

Fig. 3. DSC curves of four consecutive measurements for a pellet pressed with 400 MPa for 15 min.

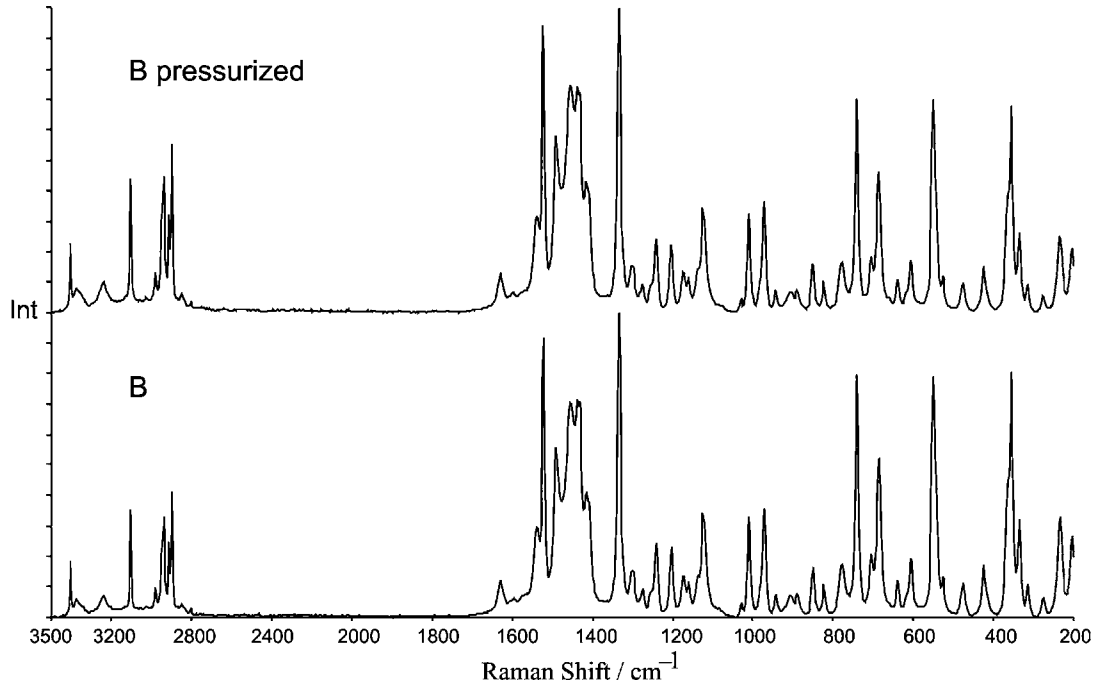

Fig. 4. Effect of pressurization on the Raman spectrum of modification B: intact sample (bottom) and sample pressurized with 800 MPa for 15 min (top).

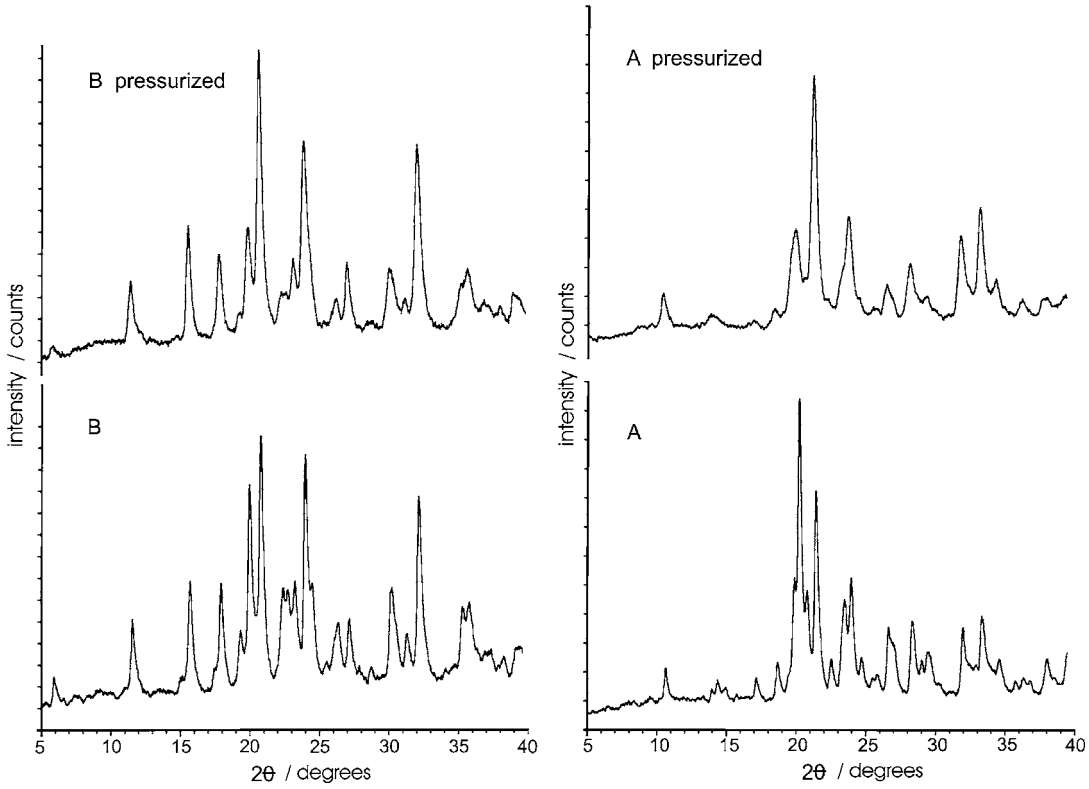

Fig. 5. Effect of pressurization on the XRPD pattern of modifications B and A, respectively: intact samples (bottom) and samples pressurized with 800 MPa for 15 min (top).

was more significant in the diffraction pattern of modification A. The diffraction pattern of the pressurized samples of both modifications was less informative because of an ensuing line broadening, whereby less intense lines merged with the background; characteristic lines of modification A were not detectable (Fig. 5).

4. Discussion

An important conclusion that can be established from the above results is that high pressure does not induce a B → A transformation to the extent that this would be detectable by IR, Raman or X-ray diffraction measurements. In contrast, the DSC method is clearly indicative of such a transformation. Considering the above discussed B → A transformation observed during the DSC measurement (Fig. 1), this contradiction can be resolved by assuming that, although pressurization itself may not produce any appreciable B → A transformation, nevertheless it can "sensitize" the sample (see below) to such transition during heating.

The B → A transformation in the DSC measuring cell was verified also by the IR examination of form B previously pressed with 800 MPa pressure for 15 min. The pieces of pellet were heated to different temperatures near the melting point in the DSC cell in four consecutive attempts, and thereafter their IR spectra were taken in KBr pellets. The growth of the characteristic spectral bands of form A (e.g. 3453 and 1672 cm^{-1}) is distinctly visible while the bands due to form B (e.g. 3506 cm^{-1}) disappear (Fig. 6).

As for rationalizing this effect of the B form being "sensitized" to B → A transformation following high pressure, we note that the B → A conversion, as is indicated by the melting enthalpies in intact mixtures, was not observable in inhomogeneous A/B mixtures, when for instance the two forms were present side by side in the pan during the DSC measurement. Presumably a direct B-to-A contact is needed for the morphological change to occur and, as is widely known in the case of solid-state reactions, mechanochemical activation produced by high pressure can effectively promote the transformation.

As a result of this activation, high pressure may produce some amorphous modification X of famotidine, the amount of which may increase by increasing the pressing force; the B → A transformation may then be mediated by this amorphous form (B → X → A).

Another possible interpretation is that the free energy content of the metastable state B increases due to pressurization, thus decreasing the kinetic energy barrier for the direct (B → A) transformation.

With the knowledge that there is a possibility of formation of the kinetically unfavoured modification during the formation of the solid-state, the presence of nuclei (or aggregates) of the A modification cannot be ruled out in the crystal lattice of a practically homogeneous B form. A real crystal cannot be perfect and in addition to structural defects there are often inclusions, which may cause chemical or morphological inhomogeneity. Consequently the level of homogeneity of a given sample is basically defined by the applied analytical method's limit of detection for a given contamination. The investigation of the behavior of mixtures of famotidine

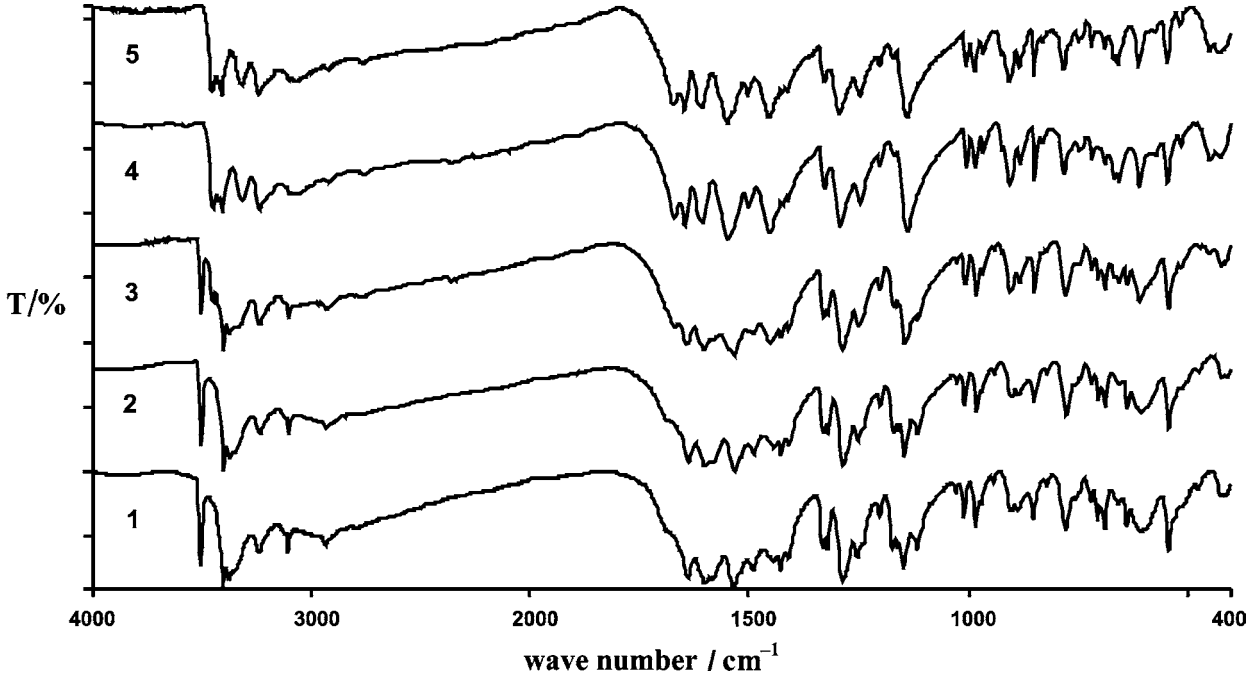

Fig. 6. Transformation of modification B into A as monitored by IR spectroscopy – 1: form B, 2: form B pressurized with 800 MPa, 3: pressurized B form heated to 150 °C, 4: pressurized B form heated to 164 °C, 5: form A.

polymorphic forms under the effect of pressurization may serve with useful information about the mechanism of transformation. Assuming the presence of modification A in the apparently homogeneous form B, a small quantity of A may induce the transformation produced by heating in samples previously treated under such extreme circumstances.

A better understanding of the transformations taking place during DSC measurements requires further investigations into the behavior of homogenized morphological mixtures under high pressure, as well as the exploration of the aforementioned hypothetical amorphous modification.

5. Summary

Our investigation of the effect of high static pressure on the pure forms of famotidine has verified that there is an apparent pressure-induced transformation of the B form in the DSC measurements in accordance with previous findings [4]. However, our DSC results indicated that form B transforms only into one main entity as opposed to the new "modifications" reported by Roux et al. [4]. A comprehensive comparison of the DSC, IR, Raman and XRPD data of the non-pressed and pressed A and B forms leads us to conclude that: (1) The transformation seen in the DSC curve of the pressurized B form is due to a B → A conversion; (2) from an analytical standpoint the DSC result is misleading in that pressurization itself does not actually result in any significant B → A transformation; (3) pressurization however greatly "sensitizes" the B form to showing a more pronounced, heat induced B → A transformation during the DSC measurement – this effect may stem from mechanochemical activation caused by high pressure.

Since famotidine is an active pharmaceutical ingredient produced on an industrial scale and as such may be exposed to significant mechanical influences during the manufacturing procedure, one has to be careful with the exclusive application of DSC in the morphological control of the product. A complex analytical approach to this problem is needed, keeping in view all the effects which the sample may be exposed to and which can modify its characteristics in an analytical assay.

Acknowledgements

We thank Dr. Katalin Berki for supplying the famotidine samples and Dr. Márta Bálint for her support with the XRPD measurements at Gedeon Richter Ltd. Zoltán Német thanks for a student sponsorship from Gedeon Richter Ltd.

References

[1] European Patent 0,256,747.
[2] B. Hegedűs, P. Bod, K. Harsányi, I. Péter, A. Kálmán, L. Párkányi, J. Pharm. Biomed. Anal. 7 (1989) 563–569.
[3] G. Ferenczy, L. Párkányi, J.G. Ángyán, A. Kálmán, B. Hegedűs, J. Mol. Struct. (Theochem.) 503 (2000) 73–79.
[4] M.V. Roux, J.Z. Dávalos, P. Jiménez, Thermochim. Acta 394 (2002) 19–24.
[5] P. Kubelka, F. Munk, Z. Tech. Physik 11a (1931) 593–601.
[6] M.V. Pellow-Jarman, P.J. Hendra, R.J. Lehnert, Vibr. Spectrosc. 12 (1996) 257–261.
[7] H.P. Klug, L.E. Alexander, X-ray Diffraction Procedures for Polycrystalline and Amorphous Materials, 2nd ed., Wiley, New York, 1974.