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Effect of pressure on the polymorphic forms of famotidine

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Abstract

In order to study the effect of pressure on famotidine, 3-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]tio]-*N*-(aminosulfonyl)propanimidamide, two polymorphs already known, A (m.p. = 169.4 °C), and B (m.p. = 161.8 °C) were submitted to pressures of 200, 400, 600, 800 and 1000 MPa. Thermophysical study of the behavior, as a function of the temperature, of the fresh and treated samples was carried out by differential scanning calorimetry in the temperature interval between 20 and 180 °C.

Keywords: Famotidine; Pressure modifications; Polymorphism; Differential scanning calorimetry

1. Introduction

Polymorphism is the property of some substances to crystallize in more than one distinct crystal form, the different solid forms of a same compound being called polymorphs. Haleblian [1,2] suggested that almost all organic compounds could show in different polymorphic states. A list of the most important reviews related with this subject has recently been published by Giron [3].

The structure adopted by a given compound upon crystallization can deeply affect several physical solid-state properties [4] of this compound as a consequence of differences in the dimensions, shape, symmetry and number of molecules in its unit cell. Furthermore, differences in thermodynamic and kinetic properties are of great importance for the pharmaceutical industry, especially if bioavailability depends on compound solubility. For these reasons investigation of the polymorphic behavior of drugs and excipients is an important part of the preformulation work. Differential scanning calorimetry (DSC) analysis is a useful tool for studying solid-state changes such as phase transitions, structural conversions, decomposition reactions or desolvation processes [5], and consequently has become the most widely used method of thermal analysis for the pharmaceutical industry. A general chapter concerning DSC can be found in the United States Pharmacopoeia [6].

Famotidine, 3-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]tio]-*N*-(aminosulfonyl)propanimidamide, is a drug with an effect histamine H_2 receptor antagonist, and consequently is a very potent inhibitor of gastric secretion (Fig. 1).

In the patents [7–9] describing its synthesis no mention was made of the morphological aspects of the substance. In 1988 and 1989 two different polymorphic forms, named A and B, were described by Bod et al. [10] and Hegedüs et al. [11]. The melting points for the named modifications (or polymorphs) A and B were determined by DSC as the maximum of the fusion peaks obtained. The values, lying between

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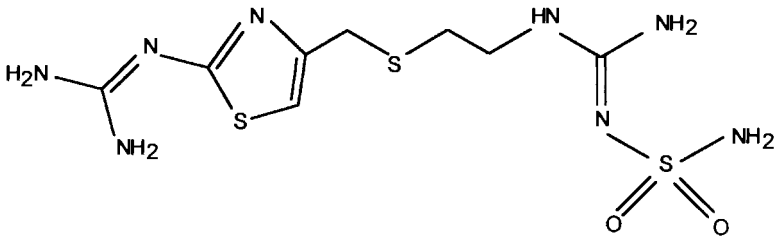

Fig. 1. Famotidine.

158.9–173.2 and 155.2–164.8 °C for A and B, respectively, were obtained from several experiments at temperature rates between 0.25 and 10 °C min^{-1}. For a heating rate of 5 °C min^{-1} the values obtained for the maximum of the fusion peak and enthalpy of fusion were 171.8 °C and 153.8 J g^{-1} for the modification A and 163.7 °C and 145.5 J g^{-1} for the modification B. Was also observed that modification B turned into modification A quantitatively, while modification A was stable under the experimental conditions.

In 1997 the results of the recrystallization of famotidine from different solvent and solvents mixtures were described by Hassan et al. [12], three crystal forms, A, B, and C appearing, depending on the solvent system used. DSC and other techniques confirmed this. The melting points of the three polymorphic forms A, B and C, taken of the maximum of the fusion peaks at heating rate 10 °C min^{-1}, were given as 171.3, 166.4 and 160.9 °C, respectively. The corresponding equilibrium solubilities were 0.82, 0.55 and 0.85 mg ml^{-1}, for the polymorphic forms A, B and C. It was also shown that the polymorphic form A converts into polymorphic form B when it is subjected to a temperature of 50 °C for 3 days.

In 2000 a new study, concerning the polymorphic behavior of famotidine, was reported by Ferenczy et al. [13]. They found the same two different polymorphic forms already described early [11], A (m.p. = 167–169 °C) and B (m.p. = 159–161 °C), with substantially different molecular conformations: an elongated S form (A) vs. a folded “hairpin” shape (B) polymorph, A being thermodynamically more stable, while modification B was kinetically favored.

In the same way that some polymorphic compounds can undergo transformations as a function of the temperature, transformations can be produced by pressure changes as well [14,15], since conformational changes can be associated to phase changes. In order to promote a reactive conformation, which could be important for the pharmaceutical industry, we report in this work a DSC study of the effect of the pressure on the two polymorphic stable forms of famotidine.

2. Experimental procedure

A differential scanning calorimeter (Perkin Elmer, Pyris 1) equipped with an intra-cooler unit was used. Its temperature and power scales were calibrated [16,17] at heating rates of 2.5, 5 and 10 °C min^{-1}. Its temperature scale was calibrated by measuring the melting temperature of the recommended high-purity reference materials: benzoic acid, tin, and indium [17]. The power scale was calibrated with high-purity indium (mass fraction: >0.99999) as reference material [17]. Benzoic acid was NIST standard reference material sample 39j. Indium and tin reference materials were supplied by Perkin-Elmer. All the measurements were made under N_2 atmosphere. The samples were studied in hermetically sealed volatile aluminum pans and they were weighed with a Mettler AT21 microbalance. All the pans were also weighed after the experiments in order to confirm that no product leakage had occurred. The estimated errors were ±0.5 °C and about 1% for temperature and enthalpy determinations, respectively.

Samples of famotidine characterized as polymorphs A and B were used in this work. Preliminary runs showed no changes in famotidine samples for temperatures below 140 °C, and consequently all the experiments were made in the temperature interval of 140–180 °C. Before studying the effects of pressure, experiments at atmospheric pressure were made in order to determine the best experimental conditions for the DSC experiments. Several runs at heating rates

between 2.5 and 10 °C min^{-1} were made with mixtures of fresh samples of polymorphic forms A and B of famotidine in order to determine the conditions under which a larger separation between the fusion peaks could be observed. A heating rate of 5 °C min^{-1} was found to be the best one, and consequently all the experiments were made at this heating rate.

For pressure studies, samples of polymorphic forms A and B of famotidine were separately ground into an agate mortar, and only samples of polymorphic form B of famotidine were compressed for 15 min in a Perkin-Elmer Infrared press at 200, 400, 600, 800 and 1000 MPa.

3. Results

In Table 1 the temperatures and enthalpies of fusion of the two polymorphic forms A and B of famotidine are given. The onset temperatures of the fusion peaks obtained were taken as the temperatures of fusion. For comparison with the results obtained for other authors [11–13], the temperatures obtained for the maximum of the peaks are also given. The results are the mean values and standard deviations of four experiments made with fresh samples.

Table 1
Melting temperatures and enthalpies of fusion of two polymorphic forms of famotidine

Polymorphic form	t_{peak} [a] (°C)	t_{fus} [b] (°C)	$\Delta_{fus}h$ (J g^{-1})
A	173.1 ± 0.2	169.4 ± 0.3	150.0 ± 2.4
B	165.0 ± 0.2	161.8 ± 0.2	143.8 ± 1.3

[a] Taken as maximum.
[b] Taken as onset.

Samples of the two polymorphic forms A and B of famotidine were ground in an agate mortar. After this

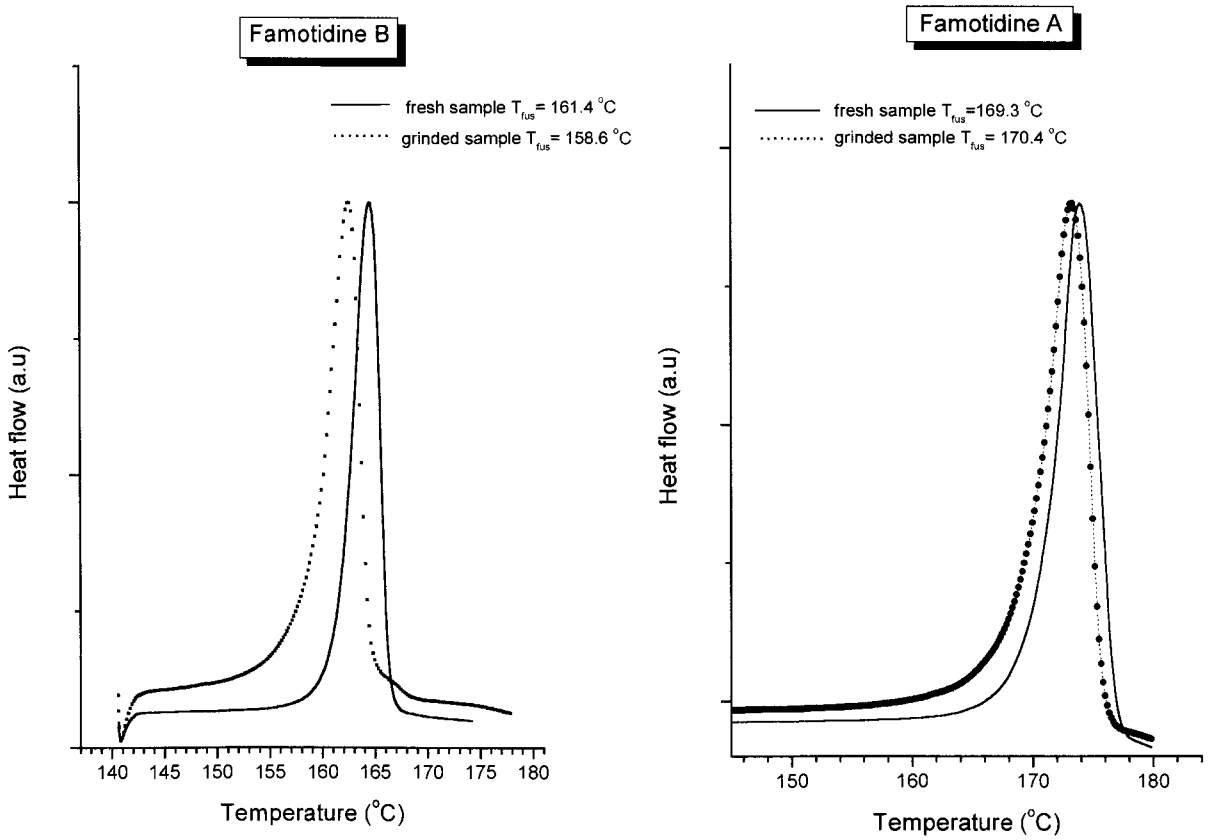

Fig. 2. Effect of grinding in polymorphic forms B and A of famotidine.

treatment the samples were scanned in the DSC, and the curves are given in Fig. 2 together with those ones obtained with fresh samples.

Comparison of the DSC scans of the fresh and compressed polymorphic form B shows that the fusion peak of the fresh form B becomes broader after grinding, and its melting point decreases, from 161.4 to 158.6 °C. This modification was confirmed with several scans of different samples obtained in the same conditions. Scans of famotidine B obtained 10 days after grinding showed the same behavior, which suggests that grinding produces stable changes in famotidine B.

A different behavior was observed when samples of polymorphic form A of famotidine were ground in the agate mortar. No significant changes in the DSC curves behavior could be observed (Fig. 2) suggesting that grinding produces no changes in famotidine A.

Fig. 3 shows the DSC scans of samples of polymorphic form B of famotidine subjected to pressures of 200, 400, 600, 800 and 1000 MPa for 15 min, and also the DSC scan of the same unpressed polymorphic form.

It can be observed that pressure produces different modifications in the behavior of famotidine B samples. Samples subjected to a pressure of 200 MPa show

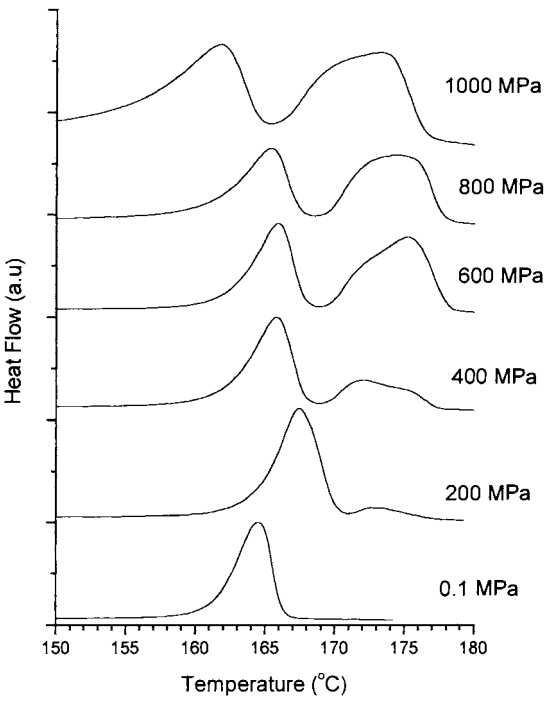

Fig. 3. Effect to pressure in polymorphic form B of famotidine.

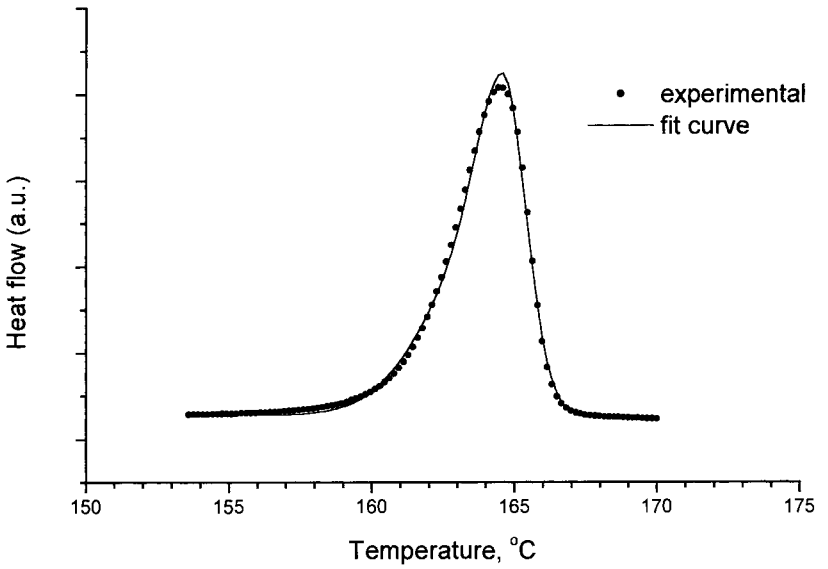

Fig. 4. Fit to a Gaussian–Lorenzian type curve of polymorphic form B of famotidine (0.1 MPa).

Table 2
Effect of pressure in the polymorphic form B of famotidine

p (MPa)	*t* (°C)	Area (%)	*t* (°C)	Area (%)	*t* (°C)	Area (%)	*t* (°C)	Area (%)	*t* (°C)	Area (%)	*t* (°C)	Area (%)
0.1			161.8	100								
200			163.4	88.5			169.9	11.9				
400			162.5	49.5			169.2	21.0			172.7	29.5
600			161.1	50.9			168.7	16.9	171.6	13.3	173.7	18.9
800			162.6	15.6			168.8	16.5			172.3	67.9
1000	155.1	53.1			166.1	22.9	168.1	14.5	171.0	9.5		
Ground in mortar	158.8	96.7	163.3	3.3								

an increase of their melting temperature, appearing as well a second broader and smaller peak with a temperature of 169.9 °C. With pressures between 400 and 800 MPa a progressive evolution of these peaks occurs: the first one retains the onset and peak temperatures and shape of the fresh sample, while the second one changes progressively. The DSC scan of the sample subjected to a pressure of 1000 MPa shows some differences in comparison with those subjected to lower pressures. A broad peak appears at lower temperatures, between 144.8 and 165.3 °C with an onset temperature of 155.1 °C followed by a second peak, with several shoulders, between 166.0 and 178.7 °C.

The curves were fitted to a Gaussian–Lorenzian type curve that yielded the best fit of the curve obtained with a fresh sample of the polymorphic form B of famotidine at atmospheric pressure (see Fig. 4).

The results of a deconvolution study of the DSC curves of samples previously subjected to different pressures are given in Table 2; the temperatures of the peaks and their relative percentages are given. It can be seen that the peaks corresponding to transformations with high temperatures increase with increasing pressure, which is in agreement with the knowledge that pressure promotes conformational changes associated with phase changes.

The comparison of the deconvolution study of the sample subjected to a pressure of 1000 MPa (Fig. 5) with those of the sample ground in an agate mortar are interesting.

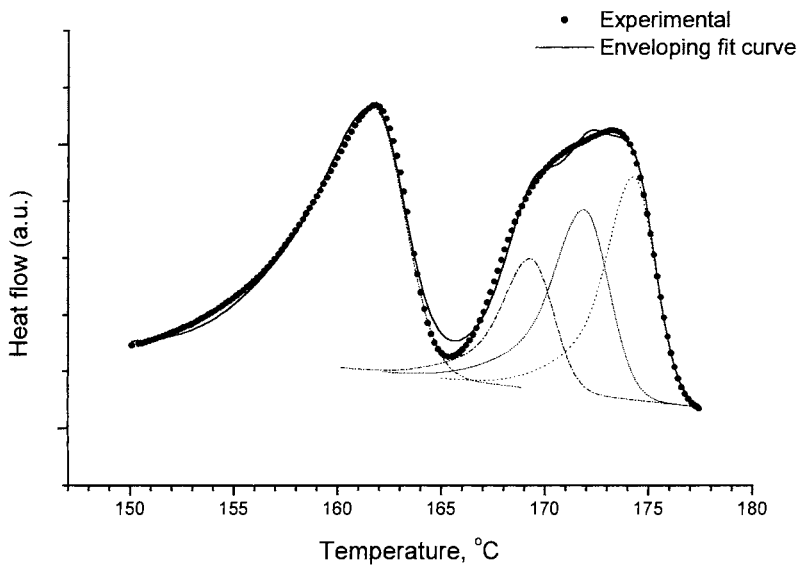

Fig. 5. Fit to a Gaussian–Lorenzian type curves of polymorphic form B of famotidine (1000 MPa).

In the two cases a polymorphic form with a lower temperature peak appears, although this transformation is 96.7% in ground famotidine vs. 53.1% in famotidine previously subjected to 1000 MPa. It is remarkable that in the last case the polymorphic form B of famotidine has been completely converted into other forms with different transition temperatures.

Experiments made on samples 10 days after they were subjected to high pressures show a decrease in the peaks which appeared at temperatures of 168–169 °C and higher, indicating that the transformations are not stable. On the contrary, the transition of the ground famotidine was stable over the same time period.

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