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Characterization of famotidine polymorphic forms

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Abstract

Famotidine, crystallized from different solvents and solvent mixtures, was found to exist in three crystal forms, A, B, and C, depending on the solvent system used. This was confirmed by differential scanning calormimetry (DSC), infra-red (IR) spectroscopy, X-ray powder diffraction, thermomicroscopy, scanning electron microscopy and equilibrium solubility. The A, B, and C forms which melt at 171.3°C, 166.4°C and 160.9°C, respectively, were obtained in pure form by crystallization, as indicated from their DSC thermograms. The B form, which is the commercial form of famotidine, is probably the most stable and has therefore the lowest aqueous solubility (0.55 mg/ml). The solubility of the A form (0.82 mg/ml) is comparable to that of the C form (0.85 mg/ml). © 1997 Elsevier Science B.V.

Keywords: Famotidine; Polymorphic form; Preparation; Characterization

1. Introduction

Famotidine is an H_2-receptor antagonist that is a high potent inhibitor of gastric and acid secretion in humans (Campoli-Richards and Clissold, 1986). Structurally, famotidine contains a thiazole ring rather than the imidazole ring of cimitidine or the furan ring of ranitidine. The latter two H_2-receptor antagonists were demonstrated to exhibit polymorphism and/or pseudopolymorphism. Cimitidine was found to exist in four crystalline forms, three anhydrous and a monohydrate (Shibata et al., 1983). The dissolution rate constant for the monohydrate was 1.29–1.90 times greater than those measured for anhydrous forms. On the other hand, ranitidine hydrochloride was reported to occur in two polymorphic forms (Cholerton et al., 1985).

Since polymorphism may have a great impact on aqueous solubility and hence the bioavailability of a pharmacologically active drug (Haleblian, 1975), isolation and characterization of the crystal forms of such drug is highly significant. In analogy to cimitidine and ranitidine two polymorphic

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modifications of famotidine were reported (Belahegedus et al., 1989). The objective of this work was to investigate the possibility for the existence of other polymorphic forms. This was achieved by crystallizing the drug from different organic solvents or mixtures under variable conditions. The isolated crystal forms were characterized by determining their melting points, IR spectra, X-ray powder diffraction patterns, thermal behavior, microscopic techniques and equilibrium solubility.

2. Materials and methods

2.1. Materials

Famotidine, pharmaceutical grade, was kindly provided as a gift by Dar Al-Dawa Development and Investment Co., Na'ur, Jordan. Methanol (Gainland Chemicals, Clwyd, England), ethanol, benzene, acetonitrile and diethyl ether (BDH chemicals, Poole, England), tetrahydrofuran (THF), toluene and *n*-hexane (Sigma, St Louis, MO). Water was double distilled from an all-glass still.

2.2. Methods

2.2.1. Preparation of famotidine polymorphic forms

- A Form: To 0.5 g of famotidine, 50 ml of boiling acetonitrile was added with stirring. The suspension was brought to boiling and filtered, while hot. The filtrate was kept in a refrigerator until crystallization was complete. The crystals were collected, dried under vaccum and kept in a desicator over silica gel until used.
- B Form: 1.0 g of famotidine was dissolved in 50 ml of boiling methanol, filtered while hot, and the filtrate was allowed to cool at room temperature. The crystals, were collected and treated as above. This polymorphic form (B) was also obtained from a number of binary solvent systems: water/methanol (5:1), methanol/diethyl ether (1:1), acetonitrile/diethyl ether (1:1), THF/diethyl ether (2:1), THF/*n*-hexane (5:3), methanol/benzene (2:4) and methanol/toluene (2:4).
- C Form: To 0.5 g of famotidine, 100 ml of boiling THF was added with stirring, and brought to boiling. The suspension was filtered and 450 ml of diethyl ether was added. The solution was kept in the refrigerator until crystallization was complete. The crystals was collected and treated as in form A.

2.2.2. Thermal analysis

The thermal curves were recorded on a simultaneous differential scanning calorimetry (DSC) thermogravimetry (TG) thermal analyzer (Model 785, Stanton Redcroft, England) in an open pan system under static conditions as previously described (Hassan et al., 1990). The analyzer is equipped with a data acquisition station with a capability to obtain the first derivative of DSC. Alumina was used as the inert reference. The heating rate was 10°C min^{-1}. As preliminary runs showed no changes in the DSC and TG curves below 100°C, the samples were heated from this temperature to 190°C.

2.2.3. IR spectra

The IR spectra were recorded on a double-beam spectrometer (Model IR-435 Shimadzu, Japan) using the potassium bromide disk technique. No polymorphic changes were observed to be induced by grinding or compressing famotidine raw material for sample preparation.

2.2.4. X-ray powder diffraction analysis.

The X-ray diffraction patterns were recorded on an X-ray diffractometer (Model PPW 1729, Philips, Holland) with Cu Kα radiation (= 1.79025 A).

2.2.5. Hot-stage microscopy

Thermomicroscope (Reichert–Jung, Germany) equipped with a Koffler hot stage and a camera system (Kam ESZ, Reichert–Jung, Germany) was used for determining the melting points and crystal habits.

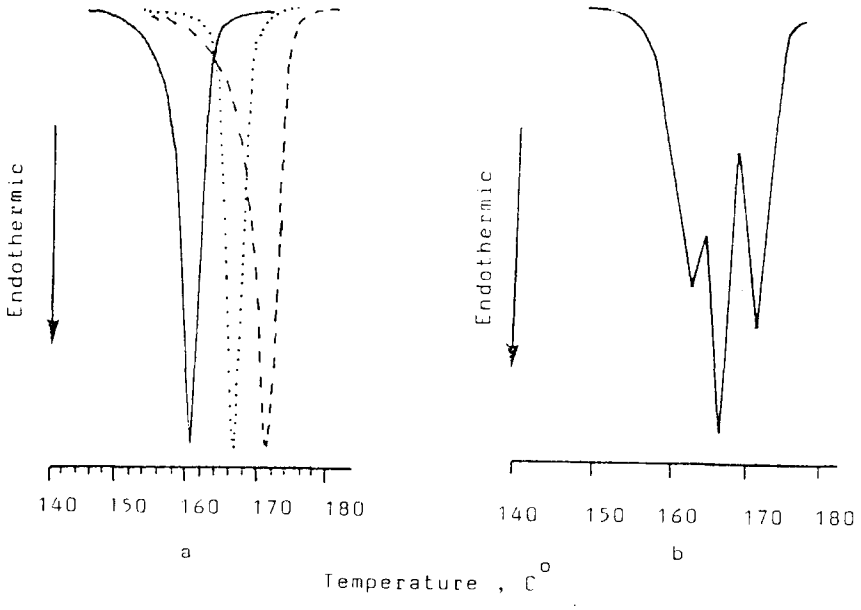

Fig. 1. (a) DSC curves of polymorphs A (- - -), B(· · ·), and C(——). (b) DSC curve of a mixture of polymorphs A, B, and C.

2.2.6. Scanning electron microscope

Samples were prepared by coating with gold using (Polaron E 6100 vaccum coater, UK), and examined by scanning electron microscope (Cameca SU30, Semprobe, France).

2.2.7. Solubility measurment

The solubility of each polymorphic form was determined as follows: an excess amount of each form (100 mg) and 25 ml of distilled water were placed in a 100 ml Erlenmeyer flask with a glass stopper. The flasks were placed in a thermostatic water bath maintained at 37°C and mechanically shaken at a rate of 80 strokes min^{-1} for 20 h. An aliquot (3 ml) of each solution was withdrawn and filtered through a 0.45 μm Millipore filter. The solubility of each polymorphic form was determined by measurement of the absorbance at 280 nm using a UV spectrophotometer (Model UV-240, Shimadzu, Japan) and with reference to a suitably-constructed calibration curve. No degradation of the drug was observed as demonstrated by TLC and HPLC under these conditions.

3. Results and discussion

3.1. Thermal analysis

The TG curves of all crystal forms of famotidine did not show any weight changes over the temperature range 100–190°C which indicates that the forms are nonsolvated forms.

The DSC curves of the three crystal forms of famotidine are shown in Fig. 1a. The DSC curve of the B form, which is obtained by crystallization from methanol exhibits a single sharp endotherm at 166.4°C corresponding to its melting point. Heating of the B form at 50°C for 1 h, or compression at 686 MNm^{-2} for 0.5 h, or suspension in water for 4 days did not induce any polymorphic transformation as shown by the abscence of additional peaks in the DSC curves. This indicates that this form is a relatively stable form.

It was also noted that famotidine samples obtained by crystallization from water/methanol (5:1), methanol/diethyl ether (1:1), acetonitrile/diethyl ether (1:1), THF/diethyl ether (2:1), THF/*n*-hexane (5:3), methanol/benzene (2:4), methanol/toluene (2:4), and a sample of the com-

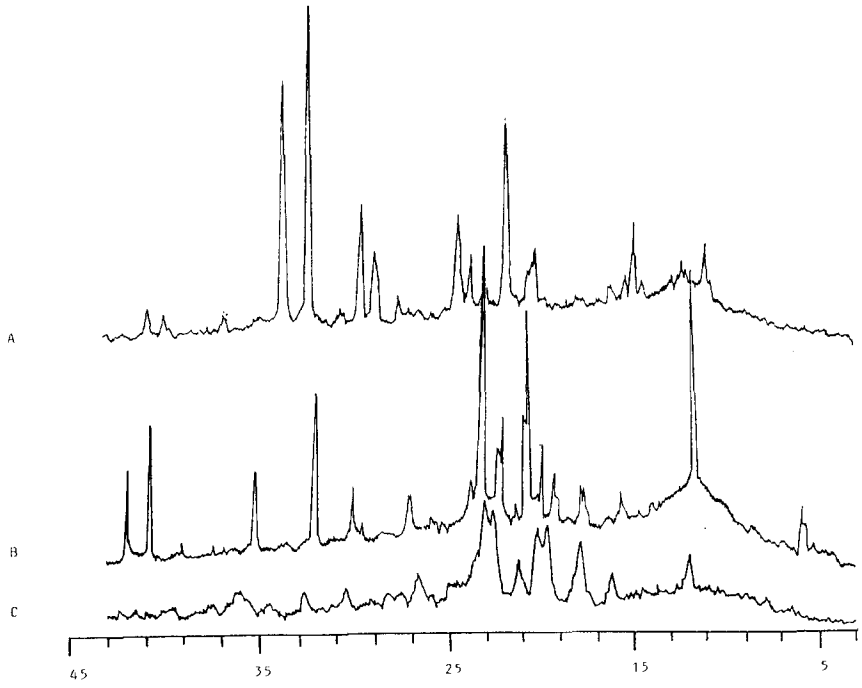

Fig. 2. X-ray diffraction patterns of polymorphs A, B, and C.

mercially available famotidine raw material showed a DSC pattern similar to that of the B Form.

The DSC curve of the famotidine sample crystallized from acetonitrile shows one endothermic peak at 171.3°C. Mixing this sample with a sample of the B form resulted in a DSC curve with two well resolved and sharp endotherms of almost the same height and area. This suggests that the first peak corresponds to the B form, while the second may correspond to a different crystal form, designated here as the A form. Heating of form A at 50°C for 3 days resulted in the decrease of the peak occurring at 171.3°C and the appearance of a peak corresponding to the B form which indicates transformation of the A form to the B form.

The DSC curve of the famotidine sample crystallized from THF/ether shows an endothermic peak at 160.9°C. The DSC curve of a mixture of this sample and the samples from the A and B forms showed three resolved peaks (Fig. 1b). These observations indicate that wherease the first and second peaks correspond to the B and A forms, respectively, the third peak corresponds to a different crystal form, i.e. the C form.

The purity of the three forms were tested using a stability indicating HPLC method reported by Suleiman et al. (1989). Additional evidence for the purity was achieved by thin layer chromatography using two differnt solvent systems, butanol/water/acetic acid (4:2:1) and methanol/chloroform (2:8). The three forms showed only one spot with the same R_f value.

3.2. X-ray diffraction

The X-ray diffraction patterns of the crystal forms are shown in Fig. 2. The diffractograms are quite different with respect to both the position and intensity of the diffractions. The spectrum of the B form shows more diffractions than those of the other two crystal forms. Further, the diffractions exhibited by the B form are more intense than the corresponding diffractions of the samples crystallized from acetonitrile or THF/ether. Based

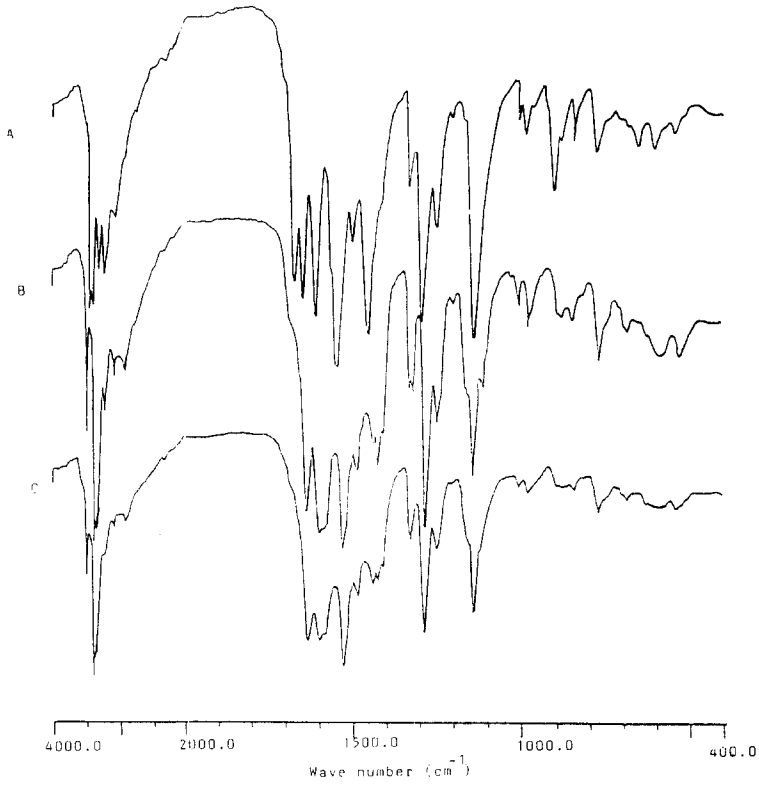

Fig. 3. IR spectra of forms A, B, and C.

on the number and intensity of diffractions, the samples obtained from acetonitrile (form A) and methanol (form B) are more crystalline than the sample obtained from THF/ether (form C).

3.3. IR spectroscopy

The IR spectra of the three crystal forms are presented in Fig. 3. Significant differences exist between the sample obtained from acetonitrile (A form) and the samples obtained from THF/ether or methanol. An additional peak at, 1672 cm^{-1} observed with the sample obtained from acetonitrile (form A) which is lacking in the B and C forms. Two peaks in the spectra of B and C at positions 3506 and 1490 cm^{-1} are lacking in form A. Further, many peaks which are distinct with the B form (2948, 1440, 1320, 1164, 1116 cm^{-1}) are only rudimentary with the C form. However, no differences were observed between the two samples in the number and position of peaks.

3.4. Scanning electron microscopy (SEM)

Fig. 4 shows the SEM photographs of the three polymorphic forms of famotidine. The figure clearly demonstrates the difference in the crystalline nature in these forms. Form B exhibits a rod like cubical crystals, form C in contrast, exhibits an obvious amorphous nature, form A however appears to be of an intermediate nature exhibiting a needle like particles. The cluster like shape of form C could be due to the high interfacial free energy of the particles which would lead to the particle aggregation in an attempt by the particles to reduce such energy and attain thermodynamic stability.

3.5. Equilibrium solubility

The equilibrium solubility values of the three forms A, B and C were 0.82, 0.55 and 0.85 mg/ml,

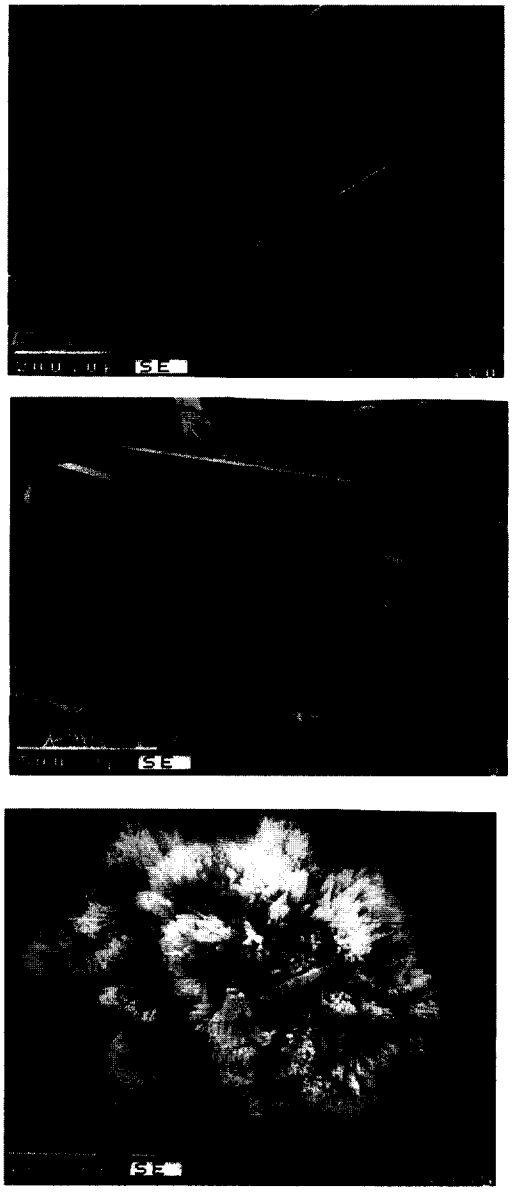

Fig. 4. SEM photographs of A, B, and C crystal forms.

respectively. The difference in solubility of the three forms could be attributed to the difference in their polymorphic and crystalline nature. As indicated by the SEM photographs, form B exhibits the most crystalline state and therefore the most stable and hence least soluble form in contrast, form C exhibits the most amorphous and therefore most energetic and hence most soluble form. Form A exhibits a less crystalline needle like particles and therefore has a higher solubility than form B and close to that of C.

In conclusion, famotidine was found to exist in three polymorphic forms A, B and C. The B form has the highest stability and the lowest solubility. The existence of these polymorphic forms may affect the bioavailability of the drug.

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