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Comparison of the polymorphic modifications of famotidine

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Abstract: The polymorphic modifications of famotidine are described and characterized by their spectroscopic (infrared, X-ray) and some physico-chemical data. In addition to the standard physico-chemical data (melting point, solubility, bulk density) some further properties influencing its use in pharmaceutical technology are also characterized. The methods used to prepare the morphologically homogeneous modifications are also given.

Keywords: *Famotidine modifications; polymorphism; FT-IR, DSC and X-ray data; morphological stability; physico-chemical properties.*

Introduction

Famotidine is known as a drug with excellent histamine H_2 receptor blocking effect. In the patents [1, 2] describing its preparation no mention is made on the morphological aspects of the material. Its share in the market of anti-ulcerogenic agents seems to be comparable with those of cimetidine and ranitidine, so it seems to be advisable to also examine the morphological aspects of famotidine. This is of great importance, because the characteristics of the modifications of famotidine are rather different.

As we are the first to describe the modifications, we will call the modification of higher melting point, **A**, and that of lower melting point, **B**. The reason for this is given under Morphological Stability.

Experimental

The materials used were prepared according to the patent application of Gedeon Richter Ltd [3]. The essence of the method is that the kinetics of crystallization should be properly chosen. When preparing modification **A**, famotidine is dissolved in hot water, and allowed to cool very slowly. When preparing modification **B**, a similar aqueous solution is prepared and poured on ice, or oversaturated very rapidly by outer ice cooling.

Infrared (IR) spectra

Spectra presented here were recorded on a NICOLET 7000 type FT-IR spectrometer in KBr pellets. The resolution of the spectra is 1 cm^{-1}.

X-ray diffraction

The structure determination of both modifications by X-ray diffraction was carried out on an Enraf Nonius CAD-4 diffractometer. The powder diffractograms were recorded on a Philips equipment, and the simulated powder diffraction data were calculated from the data of the single crystal analysis with the help of the program PULVERIX.

Differential scanning calorimetry

The measurements were performed on a METTLER TA 3000 S instrument under N_2 atmosphere with various heating rates.

Morphological stability

In order to determine the morphological stabilities of the two modifications of famotidine in aqueous medium, model mixtures were prepared consisting of 95% of one and 5% of the other modification, respectively. The crystal mixtures were stirred in water of 5-fold quantity, thermostatted at about 60°C for 1 day. Then the crystals were filtered and analysed by IR spectroscopy.

Dynamic solubility

Ten milligrams of each modifications were weighed into 100 ml of distilled water with stirring. The system was thermostatted at 26°C. At pre-defined times samples were taken from the system, and after filtration and appropriate dilution the amount of dissolved famotidine was determined by ultraviolet (UV) spectroscopy.

Bulk density

The weight/volume ratio was determined with the use of a calibrated measuring cylinder first without compaction, and later with compaction. Compaction was achieved with a hand-vibrator for 5 min.

Rolling angle and arching tendency

The modification to be tested was filled into a funnel provided with a tube of 5 mm dia, then the funnel was set into a position so that its flow-out hole stood 10 cm high above the plane of the bench. The basic angles of the cones formed by the flowing-through grains were determined.

The behaviour of the modifications in the funnel was also observed from the point of view of arching tendency and adhesiveness.

Deformation ratio

The deformation ratio is considered as the ratio of the longitudinal axis and the greatest diameter of crystal.

The measurement was performed on a KONTRON IBAS 1000 equipment using 250–250 grains for the averaging.

Electrostatic charging

Into a glass dish of 120 mm dia, 37 g of one of the forms was transferred and the

sample was stirred for 1 min, rubbing with a flattened-end glass rod. Then the content of the dish was poured without shaking, and the amount of the electrostatically held material was measured on a balance. Following this the dish was knocked 10 times and the measurement was repeated.

Results

Infrared spectra

Since famotidine has not been registered in any pharmacopoeia, and the data published in the patents [1, 2] are of poor reliability, it was considered advisable to present both the spectra and the detailed peaklist (Table 1).

Infrared spectroscopy is a good method for detecting the cross-contamination of the modifications; 1–2% of modification **B** can be detected in modification **A** with the help of the absorption band at 3506 cm^{-1} (Figs 1 and 2).

X-ray diffraction

Both modifications have $P2_1/c$ space group. Basic parameters of the cell are given in Table 2.

To show the main differences between structures, the torsion angles of the chain are given in Table 3. The numbering of the atoms can be seen in Fig. 3.

The configurations of the modifications are shown in Fig. 4. The projections are presented in the plane of the thiazole ring. When comparing the calculated and the measured powder diffractograms no significant difference was found.

Since the reproducibility of X-ray powder diffractograms is not very good, especially if reflection intensities are concerned, only the strongest reflections are listed, providing

Table 1
Peaklists of the IR spectra of the modifications

Famotidine **A**	Famotidine **B**	Famotidine **A**	Famotidine **B**
3452 s	3506 s	987 m	1125 w
3428 w	3401 s	967 m	1116 m
3409 s	3377 m	926 w	1028 w
3314 s	3237 m	907 s	1010 m
3101 w	3105 m	883 m	983 m
3070 b	2937 w	850 s	970 w
2934 w	2897 w	831 w	941 w
2918 w	1639 s	783 m	903 m
2756 b	1601 s	749 w	887 m
1671 s	1534 s	740 w	853 m
1647 s	1519 w	719 w	821 w
1606 s	1490 s	690 m	777 s
1548 s	1444 m	667 m	756 w
1502 m	1428 s	658 m	744 w
1453 s	1411 m	611 s	721 w
1423 w	1332 m	575 w	705 m
1412 w	1321 m	547 s	689 m
1329 m	1287 s	517 w	657 w
1294 s	1277 m	451 m	639 m
1246 m	1253 m	430 m	606 b
1202 w	1201 w		544 s
1170 w	1172 w		476 w
1140 s	1161 w		426 w
1006 m	1148 s		

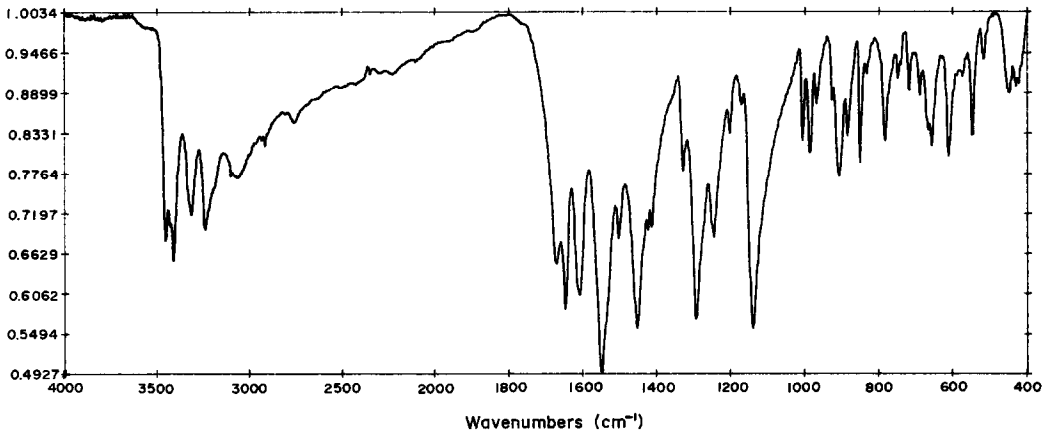

Figure 1
Infrared spectrum of famotidine **A**.

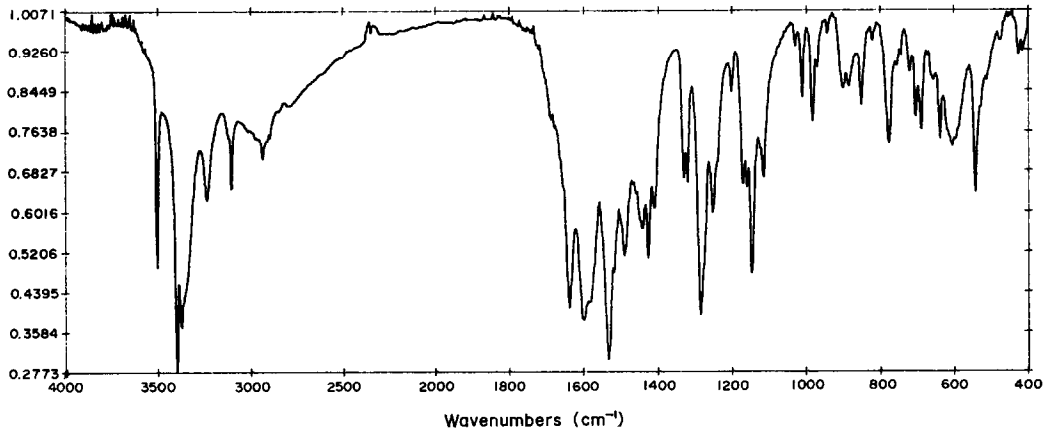

Figure 2
Infrared spectrum of famotidine **B**.

Table 2
Cell parameters

Parameter	Modification **A**	Modification **B**
a (Å)	11.978	17.762
b (Å)	7.196	5.329
c (Å)	16.812	18.307
β (°Å)	99.8	123.6
D_c (Mg m^{-3})	1.57	1.55

the layer distances in Table 4. The details of the results of the single crystal analyses are to be published elsewhere.

Differential scanning calorimetry

In the case of famotidine, some uncertainties were observed in the melting point data.

Table 3
Relevant torsion angles

Bonding atoms	Modification A	Modification B
N(3)—C(4)—C(10)—S(11)	79.3°	56.6°
C(4)—C(10)—S(11)—C(12)	72.9°	62.6°
C(10)—S(11)—C(12)—C(13)	89.5°	−170.8°
S(11)—C(12)—C(13)—C(14)	−68.4°	68.3°
C(12)—C(13)—C(14)—N(16)	−77.0°	51.1°
C(13)—C(14)—N(16)—S(17)	172.3°	177.6°

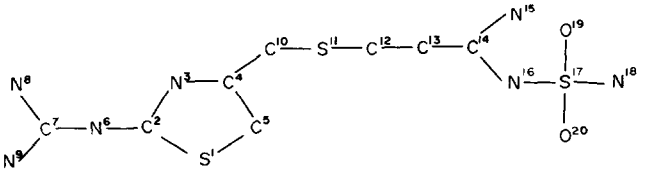

Figure 3
Numbering of the skeleton.

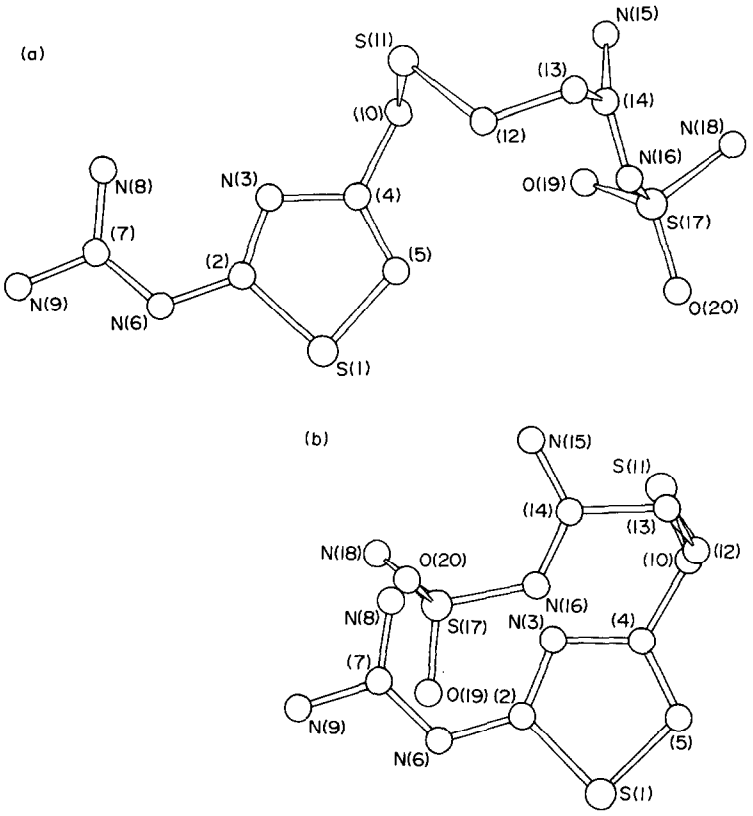

Figure 4
Projection of the modifications in the plane of the thiazole ring. (a) Modification **A**; (b) Modification **B**.

Table 4
Significant powder diffraction data of modifications (Å)

Modification **A**	Modification **B**
8.23; 6.29; 5.13; 4.78; 4.44; 4.30; 4.24; 3.79; 3.43; 2.790; 2.657	14.03; 7.47; 5.79; 5.52; 4.85; 4.38; 3.66; 2.950; 2.755

Table 5
DSC data of modifications

Heating rate (°C min^{-1})	Modification **B** Max (°C)	Enthalpy (J g^{-1})	Modification **A** Max (°C)	Enthalpy (J g^{-1})
10	164.8	148.9	173.2	152.0
5	163.7	145.5	171.8	153.8
2.5	162.2	141.9	169.6	150.6
1	159.5	136.0	165.1	150.3
0.5	157.5	129.3	161.5	146.5
0.25	155.2	126.8	158.9	132.8

These measurements were performed to clear up the background of the phenomena. The results are presented in Table 5.

The results suggest that before melting, decomposition starts, the products of which cause the melting point depression observed at lower heating rates.

Morphological stability

It was found that modification **B** turned into modification **A**, quantitatively, while modification **A** proved to be stable under the conditions of the experiments. This is why the modification of higher melting point is declared as modification **A**.

Dynamic solubility

The rate of dissolution for the two forms is shown in Fig. 5.

Bulk density

	Modification **A**	Modification **B**
Without compaction	695 g l^{-1}	340 g l^{-1}
With compaction	960 g l^{-1}	505 g l^{-1}
Compaction ratio	1.38	1.47

Rolling angle

In the case of modification **A**, it was possible to measure a reproducible angle with the method described in the Experimental. Modification **A** does not arch and is not adhesive. Its behaviour is similar to that of sand. The value of the rolling angle of modification **A** is 41–42°.

In the case of modification **B**, it was not possible to measure the correct data for the rolling angle because the material was heavily arched in the funnel and agglutinated into nodes, and passing the tube of the funnel, the sample piled up with a 80–85° slope and the 1–2 mm coagulates lose the wall. The given data correspond to this observation, as the rolling angle of modification **B** is more than 55°.

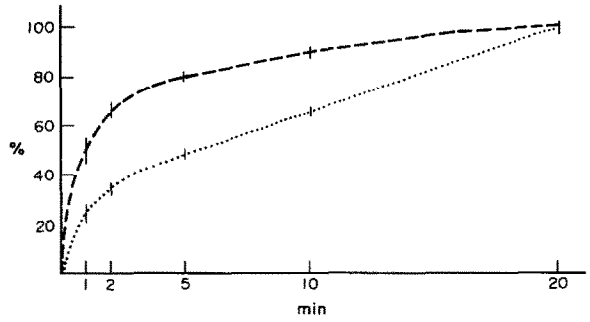

Figure 5
Solubility of modifications. . . ., Modification **A**; – – –, modification **B**.

Deformation ratio

Modification **A**	Modification **B**
1.40	4.70

Electrostatic charging

The electrostatically held material was weighed and the results are demonstrated below:

	Modification **A**	Modification **B**
Without knocking	2.8 g	13.0 g
After knocking	0.5 g	10.0 g

Discussion

From the data given one can see clearly that there is a significant difference between the two modifications of famotidine. The most significant differences are in the field of physical properties, especially in arching capability, electrostatic charging, deformation ratio and rolling angle. From the point of view of pharmaceutical technology, these data suggest the need of morphological purity of the substance to be formulated.

References

[1] USA Pat. 4 283 408.
[2] Eur. Pat. 128 736.
[3] Hung. Pat. Applic. 3370/86.

[*Manuscript received for review 28 January 1988*]