^{14}N Nuclear Quadrupole Resonance Study of Polymorphism in Famotidine

JANKO LUŽNIK,[1,†] JANEZ PIRNAT,[1] VOJKO JAZBINŠEK,[1] ZORAN LAVRIČ,[2] VESELKO ŽAGAR,[3] STANE SRČIČ,[2] JANEZ SELIGER,[3] ZVONKO TRONTELJ[1]

[1]Institute of Mathematics, Physics and Mechanics, Ljubljana, Slovenia
[2]Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia
[3]Institute J. Stefan, Ljubljana, Slovenia

Received 19 December 2013; revised 14 February 2014; accepted 28 February 2014

Published online 25 March 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23956

ABSTRACT: ^{14}N nuclear quadrupole resonance (NQR) in two known polymorphs of famotidine was measured. At room temperature, seven quadrupolar sets of transition frequencies (ν^+, ν^-, and ν^0) corresponding to seven different nitrogen sites in the crystal structure of each of the two polymorphs were found. This confirms the expected ability of NQR to distinguish polymorph B from its analog A. NQR can also measure their ratio in a solid mixture and in the final dosage form, that is, a tablet. The NQR frequencies, line shapes, and tentative assignation to all seven molecular ^{14}N atoms were obtained. Unravelment of these two entangled NQR spectra presents a valuable contribution to the NQR database and enables studies of some possible correlations therein. Moreover, nondestructive ^{14}N NQR studies of commercial famotidine tablets can reveal some details of the drug fabrication process connected with compression. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2704–2709, 2014

Keywords: crystal structure; crystal polymorphism; spectroscopy; analysis; polymorphism; tableting; solid-state NMR; database

INTRODUCTION

The pharmaceutically active substance famotidine is used in therapy of stomach and duodenal ulcers, in reducing ulcer pain, in treatment of gastroesophageal reflux disease, and so on.

Nuclear quadrupole resonance (NQR) is a nondestructive, contactless radiofrequency (RF) spectroscopic method. Solid samples in their final form (powders, granulates, tablets, pellets, etc.) can be examined without any modification, even in their original packaging.[1] ^{14}N nuclei have spin I = 1 and thus a nonzero electric quadrupole moment. Nitrogen appears in a large number of organic and inorganic compounds, so ^{14}N NQR can be very effective in studying their structure, polymorphism, and structural dynamics. As such, the method has potential application in analysis in the areas of pharmaceutical research, quality control of manufacturing processes, and detection of counterfeit drugs.

Polymorphism in drug production is important as the various polymorphs can have different mechanical, thermal, physical, and chemical properties,[2] which in turn can have a great impact on the bioavailability, stability, and tableting processes of pharmaceutical materials.

Nuclear quadrupole resonance is based on the electric interaction between nuclei with nonzero electric quadrupole moment and the internal electric field gradient created by the surrounding electrons whose distribution is determined by the crystal structure of the solid material.

The nitrogen ^{14}N NQR frequencies are given by the expression[3,4]

$$\nu^+ = \frac{e^2qQ}{4h}(3+\eta), \quad \nu^- = \frac{e^2qQ}{4h}(3-\eta), \quad \text{and} \quad \nu^0 = \frac{e^2qQ}{2h}\eta. \quad (1)$$

Here, e^2qQ/h = QCC is the quadrupole coupling constant where eQ is the nuclear electric quadrupole moment, $eq = q_{zz}$ is the maximal principal value of the electric field gradient (EFG) tensor, e is the unit charge, h the Planck constant, and $\eta = \eta = (q_{xx} - q_{yy})/q$ is the EFG asymmetry parameter.

In the case of famotidine[5–7] (Fig. 1), there are seven nitrogen atoms per molecule, that is, seven nonequivalent positions in its monoclinic crystal structure. Seven "quadrupolar frequency sets" (QFS) of the lines ν^+, ν^-, and ν^0 appear for each polymorphic form.

Famotidine is an excellent histamine H2 receptor antagonist.[8] It crystallizes in two different polymorphic forms, stable at room temperature. Both polymorphs belong to the monoclinic crystal system with four molecules per unit cell, however, with different unit cell dimensions. For the thermodynamically more stable polymorph A, the dimensions are[6] a = 11.912 Å, b = 7.188 Å, c = 16.624 Å, and β = 100.045°; for the polymorph B, which is most often favored in crystallization kinetics, a = 16.980 Å, b = 5.285 Å, c = 17.639 Å, and β = 116.416°. Since polymorphism can influence the aqueous solubility of a pharmacologically active drug, characterization of its crystal form is of great importance.

MATERIALS

Famotidine was obtained from the pharmaceutical company Krka (Novo mesto, Slovenia). The raw material of famotidine

Abbreviations used: EFG, electric field gradient; MPSE, multipulse spin echo; NQDR, nuclear quadrupole double resonance; QCC, quadrupole coupling constant; QFS, quadrupolar frequency set (ν^+, ν^-, and ν^0).

Correspondence to: Janez Pirnat (Telephone: +386-1-4766579; Fax: +386-1-2517281; E-mail: janez.pirnat@imfm.si)
[†]Deceased.

Journal of Pharmaceutical Sciences, Vol. 103, 2704–2709 (2014)

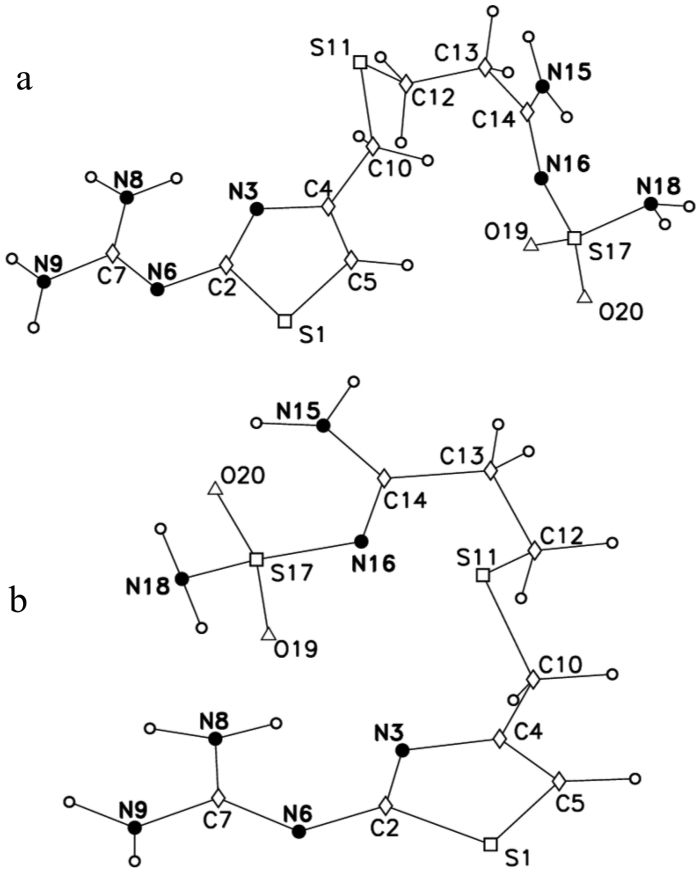

Figure 1. Famotidine molecule (2D projection): enumeration and folding of the atoms in polymorph A (panel a) and the same for polymorph B (panel b).[5,6].

was of pharmaceutical grade and the analytical methods to be described in the next sections [differential scanning calorimetry (DSC), FTIR, NQR] proved it to be of pure polymorphic form B. Therefore, this form was used for our measurements without further treatment.

Famotidine in form A was prepared by recrystalization from an aqueous solution of the raw material.[7,9] Raw famotidine (polymorph B) was dispersed in water at a concentration of 10 mg/mL. Temperature of the mixture was then increased to 80°C and kept there for a few minutes. The solution was filtered and left to cool slowly (about −50°/h) to room temperature. The suspension of precipitated polycrystals was filtered and the product—polymorph A—was dried at room temperature. Finally, the sample was analyzed as described bellow.

So, both investigated materials were easily attained in pure polymorphic forms.

Preparation of Compacts

Famotidine (form B) powder was compressed on a Killian SP300 (IMA, Cologne, Germany) eccentric single punch tablet press using round flat-faced punches (diameter 12.0 mm). The tablet press was operated in the manual mode. Compacts weighing around 600 mg were prepared at three compression forces (5, 10, and 30 kN).

ANALYTICAL METHODS

Differential Scanning Calorimetry

A DSC 1 Calorimeter from MettlerToledo was used to analyze samples in the temperature interval from 25°C to 180°C at a heating rate of 5 K/min while purging the sample compartment with a stream of nitrogen gas at 50 mL/min. Samples were placed in closed 40 μL Al pans that were lid-pierced just prior to the measurement.

Attenuated Total Reflectance–FTIR

A Nicolet Nexus FTIR spectrometer from the Nicolet Instrument Company (Madison, WI) equipped with a diamond ATR DuraSamplIR attachment from Danbury Technologies was used for IR analysis of the samples.

^{14}N Nuclear Quadrupole Resonance

We used a standard pulsed NQR spectrometer consisting of (1) a tank circuit with the sample and a preamplifier, (2) a programmable rf pulse unit (Spin Core Technologies, Gainesville, FL), (3) an rf power amplifier (Tomco Technologies, BT500 AlphaS), and (4) a homebuilt receiver. The spectrometer was operated from a PC, which was also used for data analysis.

The pulse sequence known as "MultiPulse Spin-Echo" (MPSE)—$\alpha_0 - (t\text{–}2\alpha_{90}\text{–}t\text{–})_n$—was applied.[10,11] Here, n is the number of repetitions of the basic RF pulse refocusing sequence (t–$2\alpha_{90}$–t–) in one pulse train, $2\alpha_{90}$ indicates that each refocusing pulse experiences a 90° phase shift relative to the initial α_0 pulse, and α_0 is the RF pulse width giving the optimal detected signal. The sequence of successive pulse trains including NQR echoes were repeated and accumulated at suitable intervals allowing for quadrupole spin–lattice relaxation. Finally, FFT analysis of the averaged quadrupole echo was performed to obtain the spectral lines.

RESULTS AND DISCUSSION

The commercially available form of famotidine is usually pure polymorph B, which was confirmed analytically in our case too. Although it is thermodynamically unstable, its transformation to the thermodynamically more stable form A is practically nonspontaneous.

Analysis of the form prepared in the laboratory confirmed that it was pure polymorph A. Neither DSC nor FTIR nor ^{14}N NQR measurements indicated the presence of residual polymorph B. DSC melting of the laboratory prepared form A occurred at 173°C (∼10° higher than form B). No characteristic FTIR peaks of polymorph B were observed in the FTIR spectra: in particular the locally clearly resolved peak at 3505 cm^{-1} that was used previously to determine the content of polymorph B in the mixture[5,7] was absent.

Both polymorphs were found to have a relatively long quadrupolar spin–lattice relaxation time T_1 of about 2 s at room temperature and also long effective transverse relaxation time T_2. The latter enables the use of the MPSE technique with 20 or more echoes in a single sequence,[10,11] thus multiplies the number of averages and improves the final signal-to-noise ratio.

Approximate frequencies of some of the resonance lines in famotidine A and B were found by the double resonance technique NQDR,[12–14] but because of the unfavorable experimental conditions, the NQDR signals were rather weak. Thus, to