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Nuclear Magnetic Resonance and Infrared Spectroscopic Analysis of Nedocromil Hydrates

Linna R. Chen,[1,3] Brian E. Padden,[2] Sudha R. Vippagunta,[1] Eric J. Munson,[2] and David J. W. Grant[1,4]

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Purpose. Nedocromil sodium (NS), which is used in the treatment of reversible obstructive airway diseases, such as asthma, has been found to exist in the following solid phases: the heptahemihydrate, the trihydrate, a monohydrate, an amorphous phase, which contains variable amounts of water, and a recently discovered methanol + water (MW) solvate. Our aim was to apply ^{13}C solid-state nuclear magnetic resonance (NMR) spectroscopy and solid-state Fourier transform infrared (FTIR) spectroscopy to the study of specific interactions in the various solid forms of NS.

Methods. The ^{13}C solid-state NMR and FTIR spectra of the various solid forms of NS were obtained and were related to the crystal structures of NS, the conformations of the nedocromil anion, and the interactions of the water molecules in these crystals.

Results. The ^{13}C solid-state NMR spectrum is sensitive to the conformation of the nedocromil anion, while the solid-state FTIR spectrum is sensitive to interactions of water molecules in the solid state. In NS monohydrate, for which the crystal structure has not yet been solved, and in the amorphous phase, the information about the conformations of the nedocromil anion and the interactions of the water molecules are deduced from the ^{13}C solid-state NMR spectra and solid-state FTIR spectra, respectively.

Conclusions. ^{13}C solid-state NMR spectroscopy and solid-state FTIR spectroscopy are shown to be powerful complementary tools for probing the chemical environment of molecules in the solid state, specifically the conformation of the nedocromil anion and the interactions of water-molecules, respectively.

KEY WORDS: NMR; infrared; nedocromil; hydrates; solvate; methanol.

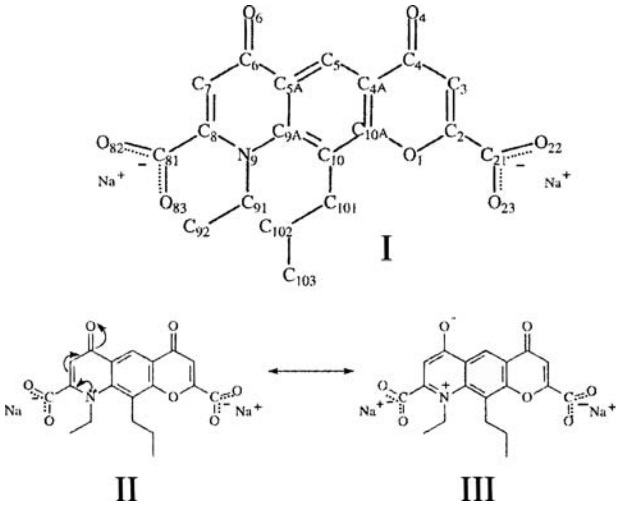
INTRODUCTION

Pharmaceutical compounds often exist as different solid phases, e.g., hydrates and polymorphs. Pharmaceutically important properties of drugs, such as stability, solubility, dissolution rate, thermal behavior, crystal color, crystal habit, compactability and flowability, often vary among different solid phases of a given drug (1,2). It is widely recognized that thorough identification and characterization of the different solid forms of a given drug are essential preformulation steps for achieving an optimum formulation (1). ^{13}C solid-state nuclear magnetic resonance (NMR) spectroscopy (3–6) and solid-state Fourier transform infrared (FTIR) spectroscopy (7) are well recognized as important tools for this purpose (8).

Solid-state NMR spectroscopy and solid-state FTIR spectroscopy are complementary techniques that can provide insights into the chemical environments of individual atoms in the solid phase and hence can reveal important structural details of the molecules. These techniques are particularly useful in instances where full X-ray crystallographic characterization of these solid phases is lacking or is impossible (4–7), as is found for the monohydrate and anhydrate phases of nedocromil sodium (9).

Nedocromil sodium (disodium 9-ethyl-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate, NS, Scheme 1, structure I) is a hydrophilic drug used in the treatment of reversible obstructive airway diseases, such as asthma (10). NS has been found to exist in the following solid phases: the heptahemihydrate (intense yellow), the trihydrate (pale yellow), a monohydrate (pale yellow), an amorphous (pale yellow) phase which contains variable amounts of water (1.5–3.0 moles per mole of NS) (9), and a recently discovered methanol + water (MW) solvate (pale yellow) (11,12). The crystal structures of the trihydrate (13), the heptahemihydrate (14), and the MW solvate (11,12) of NS have been solved, but that of the monohydrate has not yet been reported.

In this report, ^{13}C solid-state NMR spectroscopy and solid-state FTIR spectroscopy are used to probe the specific interactions in the structures of these solid phases of NS. The spectroscopic data obtained for NS heptahemihydrate, trihydrate, and MW solvate are explained in terms of their crystal structures, the conformations of the nedocromil anion, and the interactions of the water molecules in the crystals. In NS monohydrate, for which the crystal structure has not yet been solved, and in the amorphous phase, attempts are made to gain information about the conformations of the nedocromil anion and the interactions



Scheme 1. Molecular structure of nedocromil sodium showing the atomic labeling scheme (I) and the keto and enolate canonical forms (II and III).

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[1] Department of Pharmaceutics, University of Minnesota, Weaver-Densford Hall, 308 Harvard Street S.E., Minneapolis, Minnesota 55455.

[2] Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455.

[3] Present address: Parke-Davis Pharmaceutical Research, 2800 Plymouth Road, Ann Arbor, Michigan 48105.

[4] To whom correspondence should be addressed. (e-mail: grant001@tc.umn.edu)

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of water molecules from their ^{13}C solid-state NMR and solid-state FTIR spectral data.

MATERIALS AND METHODS

Materials

NS trihydrate was supplied as a pale yellow powder by Fisons plc, Pharmaceutical Division (now Astra Charnwood and Rhône-Poulenc Rorer), Loughborough, UK. Water was glass distilled in-house. 99.9% deuterated dimethylsulfoxide (DMSO) was purchased from Sigma Chemical Company (St. Louis, MO).

Preparation and Maintenance of the Various Solid Forms of Nedocromil Sodium

The intensely yellow NS heptahemihydrate was crystallized by cooling a concentrated aqueous solution of NS from 60°C to 0°C in the presence of added seed crystals. Acicular crystals of pale yellow NS trihydrate were crystallized by slowly cooling a concentrated solution of the original powder in methanol + water (v:v = 7:3, $a_w = 0.47$) (15). The pale yellow NS monohydrate was obtained by drying the trihydrate under vacuum for 1 h at 90°C, which is well below the decomposition temperature (12). This dehydration procedure was shown to be adequate by dehydration kinetic studies of the trihydrate (16).

The pale yellow MW solvate was crystallized from a suspension of the monohydrate in absolute methanol in a sealed bottle to prevent moisture sorption. Three months were sufficient to ensure complete conversion of the monohydrate to the MW solvate. The MW solvate was analyzed in the presence of a small amount of mother liquor to prevent desolvation.

The pale yellow amorphous form was prepared by rapidly evaporating a saturated absolute ethanolic solution of the trihydrate powder in a rotary film evaporator (Büchi Rotavapor, Switzerland) to complete dryness. The temperature of the water bath was kept at 80°C and a partial vacuum of 20–22 mm Hg was maintained.

To prevent any possible photodegradation, the samples were stored in vials wrapped in aluminum foil or in amber glass bottles. NS is relatively stable to light and heat, decomposing only above 250°C. The MW solvate was stored in the mother liquor in a capped bottle. The other solid forms of NS were stored at 22°C under various defined relative humidity (RH) values under which a given NS hydrate is thermodynamically stable (9): 90% RH for the heptahemihydrate; 50% (ambient) RH for the trihydrate and the amorphous form; 0% RH for the monohydrate. Powder X-ray diffractometry (PXRD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and Karl Fischer titrimetry (KFT) were performed to characterize the prepared solid phases (9,11,12).

Solid-State FTIR Spectra

Approximately 1 mg of solid sample was gently ground with a pestle in an agate mortar and was then mixed with 300 mg of ground dry potassium bromide powder (Spectra-Tech, Stamford, CT). The powder mix was loosely packed into the sample container of the FTIR spectrometer and the sample surface was leveled. The diffuse reflectance spectra of the powdered samples under dry nitrogen purge were recorded by a FTIR spectrophotometer (Nicollet Magna 750 FTIR, Nicollet Instrument Corp., Madison, WI) equipped with a deuterated triglycine sulfate (DTGS) detector and Windows-based OMNIC® software (Nicollet Instrument Corp., Madison, WI) for data collection and analysis. The spectra were recorded from 600 to 4000 cm^{-1} at 4 cm^{-1} resolution for 32 scans. A background spectrum of the potassium bromide powder without the sample was recorded under the same instrumental conditions and was subtracted from each sample spectrum. NS monohydrate is both physically and chemically stable at 100°C, as indicated by DSC, TGA, PXRD, and FTIR. The FTIR spectrum of the monohydrate was obtained at 100°C using a high temperature accessory. Because the MW solvate tends to lose some solvent under ambient conditions, the FTIR spectrum of partially desolvated MW solvate was obtained instead. Because most of the MW solvate is still intact, we can still acquire some useful information from the FTIR spectra.

Solid-State NMR Spectra

^{13}C solid-state NMR spectra were acquired at 75.4 MHz using a solid-state NMR spectrometer (Chemagnetics CMX-300, Fort Collins, CO) and a Chemagnetics 7.5 mm pencil probe. All spectra were acquired with cross polarization (CP), high power ^{1}H decoupling, and total sideband suppression (TOSS) (17,18). Samples were packed into zirconia rotors (7.5 mm o.d.) and spun at 6 kHz at the magic angle, 54.7°, with respect to the static magnetic field (magic-angle spinning, MAS) for all samples except for the MW solvate, which was spun at 3 kHz. The MW solvate was spun at a slower speed to ensure that the mother liquor did not escape from the rotor. All spectra were recorded at ambient temperature, and the chemical shifts were externally referenced to hexamethylbenzene (methyl chemical shift = 17.35 ppm). The spectral width was 30 kHz, pulse width ≤ 4 μs, contact time 1.5–5 ms, pulse delay 2.5–10 s, number of transients 1200–5400, and acquisition time 1–12 h. To ensure the physical stability of the respective phases, the MW solvate was placed in the rotors with some mother liquor, whereas the monohydrate was packed into the rotors in a glove box at 0% RH. A dipolar dephasing experiment (19), also known as an interrupted decoupling experiment, was also performed.

RESULTS AND DISCUSSION

Solid-State FTIR Spectra

The diffuse reflectance mid-IR spectra of the various solid phases of NS are given in Fig. 1. The major peaks are assigned based on published literature on related molecules (20,21). Significant differences between the IR spectra of the various solid phases of NS are observed. Therefore, a peak-by-peak comparison of the IR spectra can be used for the solid phase identification of the NS hydrates in Fig. 1. The greatest differences are observed in the OH anti-symmetric stretching region between 3000 and 3700 cm^{-1}. All solid phases of NS exhibit broad and intense peaks in this region. Because NS itself does not contain any OH groups, the observed OH stretching absorption must result from the OH of water and/or methanol molecules. The increased intensity of OH stretching peaks results from hydrogen bonding, which causes a redistribution of electron density within the OH bond that leads to a greater change in dipole

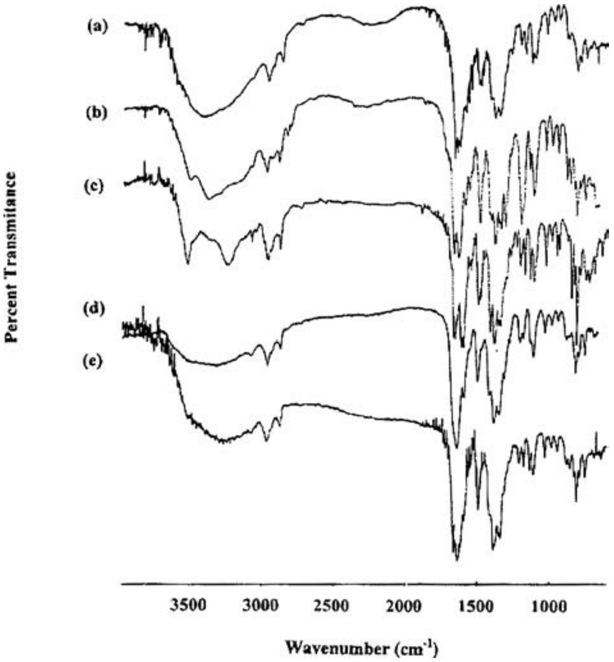

Fig. 1. Diffuse reflectance Fourier transform infrared spectra of the various solid forms of nedocromil sodium: (a) heptahemihydrate, (b) trihydrate, (c) monohydrate, (d) methanol + water solvate, and (e) amorphous phase.

moment accompanying the motion of the hydrogen atom. The broad bandwidth results mainly from the strong vibrational coupling of equivalent water molecules that are hydrogen bonded to each other. Strong coupling between stretching vibrations occurs only when there is an atom common to the two vibrations. This coupling causes each vibration of the isolated molecule to split into as many components as there are in equivalent molecules in the unit cell (22,23).

The effect of the crystalline order of the water molecules on the width of the IR absorption band (3000–3700 cm^{-1} in Fig. 1) is obscured here by the effect of vibrational coupling. There is a general trend of increasing peak intensity with increasing water content. However, the IR peak intensity (integrated area under the curve) can usually provide only a semiquantitative measurement of the water content of a crystalline hydrate. For the IR peak area to be a quantitative measure of water content, all the water molecules in the crystal lattice need to be equivalent spectroscopically and to have the same absorptivity, which may not be the case for the water molecules in the crystalline hydrate because of different bonding environments. The water molecules and the methanol molecules in the MW solvate (Fig. 1d) and the water molecules in the heptahemihydrate (Fig. 1a) and in the amorphous phase (Fig. 1e) are extensively and mutually hydrogen-bonded, as indicated by the broad band in the 3000 to 3500 cm^{-1} region. These inferences are supported by the crystallographic data for the heptahemihydrate (14) and for the MW solvate (12).

NS trihydrate (Fig. 1b) contains water molecules that are hydrogen bonded to other water molecules, as indicated by the broad diffuse OH stretching band in the 3000 to 3500 cm^{-1} region, and isolated water molecules that are not hydrogen bonded to other water molecules, as indicated by the sharper local peaks at 3241 and 3530 cm^{-1}. These results accord with the crystal structure of NS trihydrate (13). The OH stretching peak at 3241 cm^{-1} corresponds to isolated water molecules that are more tightly bound to sodium ions, while the peak at 3530 cm^{-1} corresponds to the monomer water molecules that are less tightly bound to sodium ions in the trihydrate (22,24). Coordination with metal cations is known to decrease the IR absorption frequency of the water molecule by distortion of the electron density that strengthens the dative bond donated by water molecule to the cation. The decrease in O-H stretching frequency is proportional both to the strengthening of the O-H bond and to the cation–water interaction and can approach 640 cm^{-1} (22).

The IR spectrum of the trihydrate (Fig. 1b) is consistent with the crystallographic data (13) which show that two thirds of the water molecules in the trihydrate exist as tetramers that are hydrogen-bonded to other water molecules, while one third of the water molecules exist as monomers that are bonded to sodium ions and to carboxylate oxygens only. The monohydrate contains only isolated water molecules that are not hydrogen bonded, as indicated in Fig. 1c by resolved peaks at 3251 cm^{-1} and 3530 cm^{-1} with half peak widths of approximately 100 cm^{-1} and 200 cm^{-1}, respectively. The width of the IR absorption peak suggests that these water molecules contain significant

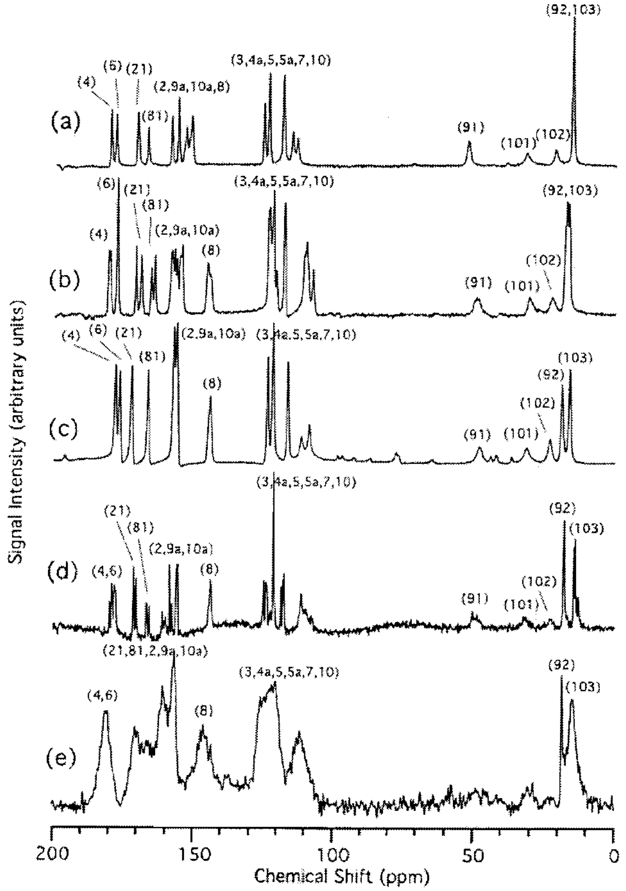

Fig. 2. ^{13}C solid-state nuclear magnetic resonance spectra of the various solid forms of nedocromil sodium: (a) heptahemihydrate, (b) trihydrate, (c) monohydrate, (d) methanol + water solvate, and (e) amorphous phase. The assignments of the ^{13}C resonances refer to Scheme 1.

Table I. Selected ^{13}C Chemical Shifts (ppm) for the Various Solid Forms of Nedocromil Sodium (NS)

	Hydrate of NS			Methanol + water solvate	Amorphous phase
Carbon nucleus	7.5 H_2O	3 H_2O	1 H_2O		
C4	180.2	180.8, 180.2	178.0	—[a]	—[a]
C6	178.3	177.6	176.6	—[a]	—[a]
C21	170.6	170.9	172.3	171.3, 170.4	~170
C81	166.9	169.0	166.4	166.7, 165.7	~166
C8	—[a]	145.3, 144.4	144.2	143.9	~144
C91	52.4	49.5	48.2	50.3, 48.7	—[b]
C101	32.0	30.7	31.5	32.4, 31.4	—[b]
C102	21.7	22.5	23.2	23.1, 22.5	—[b]
C92	15.5	17.9	19.0	18.0	~18
C103	15.5	17.4	16.3	14.6, 13.9, 12.9	~14

[a] Peak could not be differentiated from the peaks of the other carbons.
[b] Peak could not be resolved from the noise.

orientational disorder (25,26), which is not surprising considering that the monohydrate was obtained by dehydrating the trihydrate and that the IR spectrum of the monohydrate was obtained at a higher temperature, 100°C. Significant differences were also observed in the 600 to 2000 cm^{-1} region, especially in the C-O stretching region, of the IR spectra (Fig. 1) of the various solid forms of NS. However, it is impossible to differentiate between the C=O stretch of the ketone and the carboxylate, which limits the structural information that can be deduced from this region of the spectrum.

Solid-State ^{13}C NMR Spectra

The ^{13}C solid-state NMR spectra of the five solid forms of NS, shown in Fig. 2 along with the peak assignments, are distinctly different. The peaks in Fig. 2a–d for the heptahemihydrate, trihydrate, monohydrate, and MW solvate are relatively sharp suggesting high degrees of crystallinity. For the amorphous phase, all the peaks with the exception of one at 18.5 ppm are relatively broad, consistent with its amorphous nature (Fig. 2e).

Table I lists the tentative ^{13}C NMR chemical shifts for the five solid forms of NS. The peaks are assigned based on (a) the solution NMR spectrum of NS, (b) empirical structure-shift correlations, (c) a dipolar dephasing experiment (interrupted decoupling experiment), in which signals from methyl and quaternary carbons survive and those from methine and methylene carbons are suppressed (19), and (d) the molecular and crystal structures of NS.

C81 is assigned upfield of C21 (Table I), because C81 is in the vicinity of an electron donating tertiary nitrogen, while C21 is in the vicinity of an electron withdrawing ether oxygen. C6 is assigned upheld of C4, because of the enolate resonance contribution (Scheme 1, structures II and III), evident from the longer C6-O6 bond as compared with the C4-O4 bond in the heptahemihydrate, trihydrate, and MW solvate (Table II).

In all the solved crystal structures of various nedocromil salt hydrates, e.g., NS hydrates (11–14) and bivalent metal salt hydrates (27–30), the conformation of the C21 carboxylate group attached to C2 is always in plane with the tricyclic ring system. This similar conformation of C21 facilitates the assignment of C2 in Fig. 2a–e. C8 is assigned (Table I) based on the heteronuclear dipolar coupling between the carbon atom and the attached nitrogen atom, which manifests as a splitting of the resonance. The chemical shift of C8 is particularly sensitive to the conformation of the C81 carboxylate group. When the C81 carboxylate group is out of the tricyclic plane, as for NS trihydrate and the MW solvate, the chemical shift of C8 is more upfield than when it is in the tricyclic plane, as for the heptahemihydrate. The chemical shift of C8 and the orientation of the carboxylate group attached to C8 are also linked to the color of the nedocromil salts. When the carboxylate group attached to C8 is out of the tricyclic plane, the nedocromil salt has a pale yellow color (9,14,27–30). When this carboxylate group is in the tricyclic plane, the nedocromil salt assumes an intense yellow color (14).

In the ^{13}C NMR spectrum of the trihydrate (Fig. 2b), C21 and C81 display two peaks for each carbon, indicating at least two inequivalent molecules of nedocromil per asymmetric unit. The crystallographic data show that the conformations of the four nedocromil anions in the asymmetric unit are almost identical (13), suggesting that the splitting of the resonance peaks is mainly due to their different environments. Within the four

Table II. C4–O4 and C6–O6 Bond Lengths for the Heptahemihydrate, Trihydrate, and Methanol + Water Solvate of Nedocromil Sodium (NS)

	Hydrate of NS		Methanol + water solvate[c]
	7.5 H_2O[a]	3 H_2O[b]	
C4–O4 (Å)	1.240	1.224	1.2368
		1.228	1.2387
		1.222	1.2268
		1.224	
C6–O6 (Å)	1.247	1.276	1.2428
		1.259	1.2572
		1.268	1.2630
		1.252	

[a] NS heptahemihydrate has one molecule per asymmetric unit (14).
[b] NS trihydrate has four molecules per asymmetric unit (13).
[c] NS methanol + water solvate has three molecules per asymmetric unit (11,12).

molecules in the asymmetric unit of the trihydrate, two of the C21 carboxylate groups are surrounded by three sodium ions and the other two C21 carboxylate groups are surrounded by one sodium ion and one water molecule, while two of the C81 carboxylate groups are surrounded by five sodium ions and the other two C81 carboxylate groups are surrounded by one sodium ion (13).

In the ^{13}C NMR spectrum of the heptahemihydrate (Fig. 2a), all the carbons have only one resonance peak, suggesting equivalent bonding environments for all the molecules in the crystal lattice, consistent with the crystallographic finding that there is only one molecule per asymmetric unit (15). In the spectrum of the MW solvate (Fig. 2d), multiple resonance peaks are observed for most carbon atoms, indicating multiple molecules in the asymmetric unit, consistent with the finding by single crystal X-ray diffraction that there are three molecules per asymmetric unit (11,12).

For the monohydrate (Table I), the position of the C8 peak is similar to that of the trihydrate and the MW solvate, suggesting that the carboxylate group attached to C8 is out of the tricyclic plane. Only one resonance peak is observed in Fig. 2c for C4, C6, C8, C21, and C81, suggesting equivalent bonding environments of all the molecules. NS monohydrate is obtained by dehydrating the trihydrate and their PXRD patterns are similar suggesting similar packing arrangements (9). The differences in solid-state NMR spectra between the trihydrate (Fig. 2b) and the monohydrate (Fig. 2c) are probably due to a change in the hydrogen bonding environment and to slight changes in the conformation of the molecule.

CONCLUSIONS

The heptahemihydrate, trihydrate, monohydrate, the MW solvate, and the amorphous form of NS are characterized by solid-state FTIR and ^{13}C NMR spectroscopy. The spectroscopic data are related to the crystal structures of the heptahemihydrate, trihydrate and MW solvate. FTIR can detect whether or not the water molecules are isolated from, or hydrogen bonded to, other molecules and can quantitate the approximate amount of water in the solid phase. Some of the conformations of the nedocromil anion in the monohydrate and in the amorphous phase are deduced from their solid-state NMR spectra and are found to be similar to that in the trihydrate and in the MW solvate for which the carboxylate group attached to C8 is out of the tricyclic plane. FTIR spectroscopy is more useful for probing the intermolecular interactions of the water molecules, while ^{13}C NMR spectroscopy is more useful for probing the interactions and conformations of the nedocromil anion.

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