International Journal of Pharmaceutics 232 (2002) 23–33

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Crystal structure and thermal behavior of nedocromil nickel octahydrate

Haijian (Jim) Zhu [a,*], Victor G. Young Jr [b], David J.W. Grant [c]

[a] *Pharmaceutics Department, GlaxoSmithKline Inc., Five Moore Drive, Research Triangle Park, NC 27709, USA*
[b] *Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA*
[c] *Department of Pharmaceutics, University of Minnesota, Minneapolis, MN 55455, USA*

Received 22 March 2001; received in revised form 22 August 2001; accepted 21 September 2001

Abstract

The hydration behavior of a salt depends on the nature of the cation and the anion and on the molecular packing. A transition metal salt (nickel) of nedocromil was prepared and its crystal structure was elucidated in an attempt to study the influence of the nature of the bivalent cation on the structure, water interactions and molecular packing. Crystal data: nedocromil nickel octahydrate (NNi), orthorhombic, $Pca2_1$, $a = 29.5446(1)$ Å, $b = 25.0444(1)$ Å, $c = 13.3767(2)$ Å, $Z = 16$. The Ni^{2+}, has octahedral coordination, but the coordination environments of the cations and the bonding environments of the water molecules differ. NNi contains four Ni^{2+} ions in the asymmetric unit, two of which are each octahedrally coordinated to five water molecules and to a carboxyl oxygen. The two remaining Ni^{2+} ions are linked in a $Ni_2(H_2O)_{10}^{+4}$ species. Thermal analytical data for NNi show that the water molecules in this hydrate are lost in a single step dehydration, which may be attributed to the fairly continuous water layer in the *ac* plane of the crystal lattice. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Nedocromil; Hydrate; Thermal analysis; Powder X-ray diffraction, Single crystal X-ray; Crystal structure; Dehydration

---

1. Introduction

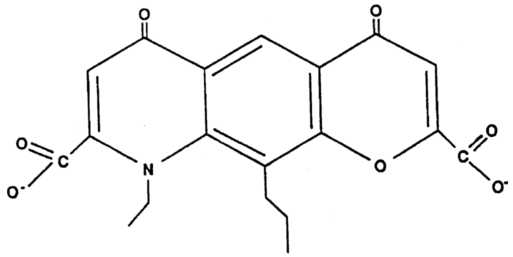
The sodium salt of nedocromil (9-ethyl-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate, Scheme 1), is used in the treatment of reversible obstructive airways diseases such as asthma (Cairns et al., 1985). The physicochemical, mechanical and biological characteristics of nedocromil sodium can be altered by its conversion to other salt forms (Hirsch et al., 1978; Forbes et al., 1992; Zhu et al., 1996, 1997a,b; Zhu, 1997). Since the nature and stability of a salt hydrate are known to vary with a change of the counterion, knowledge of the stoichiometry, stability, and crystal structure of salt hydrates is essential for optimum salt selection. In a preliminary study, Khankari (1993) has investigated the influence of differences in the metal ion and crystallization conditions on the physical chemical properties of nedocromil salt hydrates. The crystal structure and physical chemical properties of ne-

---

* Corresponding author. Tel.: +1-919-483-7927; fax: +1-919-483-5652.

E-mail address: hjz40534@gsk.com (H.J. Zhu).

PII: S0378-5173(01)00911-5



Scheme 1. Molecular structure of the nedocromil anion.

docromil zinc (Ojala et al., 1996), magnesium (Ojala et al., 1996), and calcium (Zhu et al., 1997b) have been previously described. This paper compares nedocromil nickel octahydrate dehydration behavior with its crystal structure.

2. Materials and methods

2.1. Materials

Nedocromil sodium trihydrate was supplied by Fison, plc., Pharmaceutical Division, Loughborough, UK (now AstraZeneca). Nickel nitrate hexahydrate was supplied by Mallinckrodt, Paris, KY.

2.2. Preparation and crystallization of hydrates

The nickel salt of nedocromil (abbreviated as NNi) was prepared by adding, in equimolar quantities, a 2.55 M aqueous solution of nickel nitrate hexahydrate to a 0.255 M aqueous solution of nedocromil sodium. The washed precipitate of the nickel salt of nedocromil was dissolved in distilled water at room temperature (23 °C) to provide a saturated solution (~1 mg/ml) into which acetone vapor was allowed to diffuse slowly (Jones, 1981). After 6 months, crystals were filtered off and air-dried at 23 °C. The water content of the salt, determined by Karl Fischer titrimetry using a Moisture Meter (Mitsubishi CA-05, Mitsubishi Chemical Industries Ltd, Tokyo, Japan), corresponded to NNi octahydrate.

2.3. Thermogravimetric analysis (TGA)

A DuPont 951 thermogravimetric analyzer (TA Instruments, New Castle, DE) linked to a data station (Thermal Analyst 2000, TA Instruments, New Castle, DE) was used in the TGA mode and derivative (dTGA) mode. Crystals (2–4 mg) in open pans were heated at 10 °C/min under nitrogen purge.

2.4. Differential scanning calorimetry (DSC)

A DuPont 910 differential scanning calorimeter (TA Instruments, New Castle, DE) equipped with a data station (Thermal Analyst 2000, TA Instrument, New Castle, DE) was used to determine the DSC curves. The equipment was calibrated with indium. Crystals (2–4 mg) in open or crimped aluminum pans were heated at 10 °C/min under nitrogen purge.

2.5. Powder X-ray diffraction (PXRD)

The PXRD patterns of these nedocromil salt hydrates were determined at ambient temperature and atmosphere using a diffractometer (Siemens D-500, Germany) with CuKα radiation at 30 mA and 45 kV. Counts were measured using a scintil-

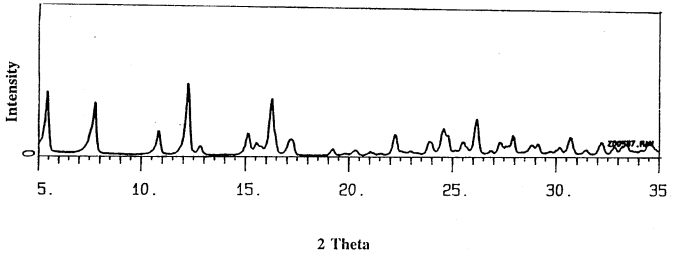


Fig. 1. Powder X-ray diffraction pattern of nedocromil nickel octahydrate.

Table 1
Crystallographic data, data collection, solution, and refinement for nedocromil nickel octahydrate

Crystal data	NNi
Empirical formula	$C_{19}H_{31}NNiO_{15}$
Crystal habit, color	Plate, light-green
Crystal size	$0.25 \times 0.08 \times 0.015$ mm
Crystal system	Orthorhombic
Space group	$Pca2_1$
Cell constant	$a = 29.3446(1)$ Å $b = 25.0444(1)$ Å $c = 13.3767(2)$ Å
Volume	9897.8(2) $Å^3$
Z	16
Formula weight	572.16
Density (calculated)	1.536 g/cm^3
Absorption coefficient	0.859/mm
$F(000)$	4800
Data Collection	
Diffractometer	Siemens SMART Platform CCD
Wavelength	0.71073 Å
Temperature	173(2) K
θ range for data collection	0.81–24.99°
Index ranges	$0 \leq h \leq 5$, $0 \leq k \leq 29$, $-15 \leq l \leq 13$
Reflections collected	49 812
Independent reflections	16 454 ($R_{int} = 0.0377$)
Solution and refinement	
System used	SHELXTL-V5.0
Solution	Direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting scheme	$w = [\sigma^2(F_o^2) + (AP)^2 + (BP)]^{-1}$,
Max/min transmission	1.000 and 0.863
Absolute structure parameter	0.341(12)
Data/restraints/parameters	16 454/1/1306
R indices ($I > 2\sigma(I)$)	$R_1 = 0.0539$, $wR_2 = 0.1172$
R indices (all data)	$R_1 = 0.0740$, $wR_2 = 0.1269$
Goodness of fit on F^2	1.020
Largest difference peak and hole	1.281 and $-0.587/eÅ^3$

lation counter. Samples were packed into an aluminum holder and scanned with the diffraction angle, 2θ, increasing from 5 to 35°, at a step size of 0.05° with a counting time of 1 s. The experimental PXRD pattern of NNi is in Fig. 1.

2.6. Structural determination and refinement

The crystallographic data and refinement parameters for the NNi are listed in Tables 1 and 2. The data collection technique employed is generally known as a hemisphere collection. A randomly oriented region of reciprocal space is surveyed to the extent of about 1.3 hemispheres to a resolution of 0.84 Å. Three major swaths of frames are collected with 0.30° steps in ω.

A successful direct-method solution (SHELXTL-PlusV5.0, 1996) was calculated and provided most non-hydrogen atoms from the E-map. Several full-matrix least squares/difference Fourier cycles were performed which located the remainder of the non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with individual (or group, if appropriate) isotropic displacement parameters.

3. Results and discussion

3.1. Thermal behavior

DSC of NNi in open-pans showed a large dehydration endotherm, with peak maximum at 80 °C. The multiple ill-defined endotherms in DSC (Fig. 2a) at 120–200 °C were due to decomposition as continuous weight loss was observed in TGA (Fig. 3). The DSC curve (Fig. 2a) is approximately mirror images about a horizontal axis of the corresponding derivative TGA (dTGA) curve (Fig. 3). The dehydration behaviors in crimped (Fig. 2b) and open pan DSC (Fig. 2a) differ for the NNi. The peak maximum for dehydration shifted from 80 °C (Fig. 2a) in an open pan to 110 °C (Fig. 2b) in a crimped pan. In crimped pan the water pressure built up inside the pan changed the dehydration behavior of nedocromil salt hydrates (Zhu et al., 1997a,b; Zhu, 1997).

To measure the sensitivity of the water of hydration in the NNi to increasing temperature, the temperature T_t at which 2% of the total water content was lost from each salt was employed. This approach was introduced by Byrn (1982) to study the dehydration behavior of thymine hydrate, caffeine hydrate and theophylline hydrate and was also used by Forbes et al. (1992) to study the stability of *p*-aminosalicylic acid salt hydrates. The T_t for the nedocromil cobalt heptahydrate (NCo) and the nedocromil manganese pentahydrate (NMn) (Zhu, 1997) was also determined and compared with the NNi octahydrate. The rank order of T_t for the three bivalent metal salts was as follows: NCo (40 °C) < NMn (55 °C) < NNi (57 °C), indicating increasing order of hydrate stability. Byrn (1982) identified crystal packing, defects as nuclei and hydrogen bonding as factors that could influence the solid-state desolvation reaction.

3.2. Crystal structure

3.2.1. Unit cell parameters

NNi crystallized in the orthorhombic space group $Pca2_1$. This space group is polar and the one restraint is the polar axis restraint. The specimen is also a racemic twin in a 0.66:0.34 ratio. The asymmetric unit contains four NNi molecules associated with 32 water molecules. The bonding motifs, including the molecular conformations of the nedocromil anions, the coordination environments of the metal ions, and the bonding environments of the water molecules, are described below.

3.2.2. Molecular conformation of the nedocromil anions

The thermal ellipsoid diagram of the NNi (Fig. 4) includes the atomic labeling scheme, while the stereo packing diagram of its unit cell is shown in Fig. 5. The molecular conformation of the nedocromil anion in the NNi is compared by reference to the dihedral angles between the various least-squares planes in Table 3.

In NNi, two different conformations of the nedocromil molecules are observed. For molecules 1 and 2 in the asymmetric unit (Fig. 4a), the carboxylate group at C2 lies nearly in the plane of the tricyclic ring structure, while the carboxylate group at C8 is almost perpendicular to the tricyclic plane. The propyl and ethyl groups are both twisted out of the tricyclic plane. For molecules 3 and 4 in the asymmetric unit (Fig. 4b), the dihedral angles between the plane of the tricyclic ring structure and plane of the two carboxylate groups show that both carboxylate groups at C2 and C8 lie nearly in the plane of the tricyclic ring structure. The propyl and ethyl groups are both twisted out of the tricyclic plane.

The conformation of nedocromil on the dehydration behavior of its salt hydrate is not well understood. However, our studies (Khankari, 1993; Zhu et al., 1997a,b; Zhu, 1997) showed the environment of nedocromil anion could affect the deepness of the color of its salt hydrates. In general, as the orientation of the carboxylate group becomes increasingly aligned with the tricyclic plane, the more intensely colored the solid becomes.

Table 2
Comparison of selected dihedral angles bewteen various least-squares planes in nedocromil nickel octahydrate

Least-squares planes		Dihedral angle (°)			
Plane	Plane	NNi[a]			
		Molecule 1	Molecule 2	Molecule 3	Molecule 4
1[b]	2[c]	7.8	5.1	9.6	4.9
1	3[d]	101.0	98.8	26.1	29.8
1	4[e]	88.3	87.6	101.6	104.7
1	5[f]	73.6	72.5	73.2	74.0

[a] Four molecules per asymmetric unit.

[b] Atoms defining planes 1 = O(1)–C(2)–C(3)–C(4)–C(4a)–C(5)–C(5a)–C(6)–C(7)–C(8)–N(9)–C(9a)–C(10)–C(10a).

[c] Atoms defining planes 2 = O(22)–C(21)–O(23).

[d] Atoms defining planes 3 = O(82)–C(81)–O(83).

[e] Atoms defining planes 4 = O(101)–C(102)–O(103).

[f] Atoms defining planes 5 = N(9)–C(91)–O(92).

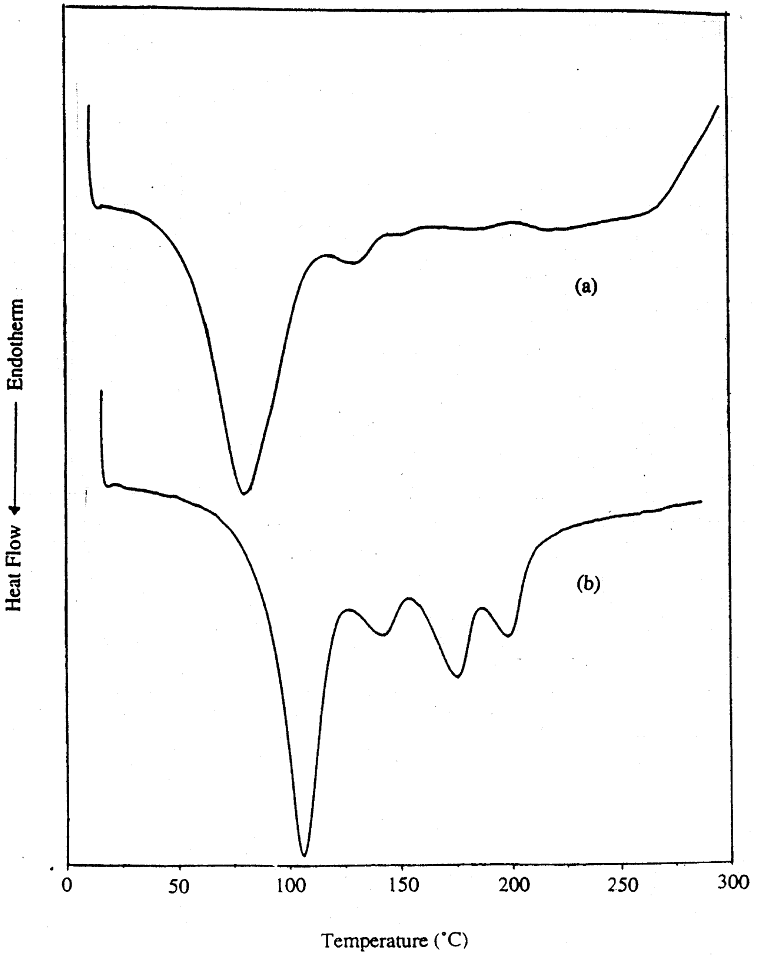


Fig. 2. Differential scanning calorimetric curves nedocromil nickel octahydarate (a) open pan; (b) crimped pan.

The pale yellow color of nedocromil sodium trihydrate, like those of nedocromil calcium 8/3 hydrate and nedocromil magnesium pentahydrate may be attributed to the less extended conjugation arising from the out-of plane conformation of the carboxylate group at C8. However, for the intensely yellow, highly hydrated crystalline salt, nedocromil sodium heptahydrate, nedocromil calcium pentahydrate and nedocromil zinc octahydrate, the carboxylate group at C8 is oriented in the tricyclic plane, giving rise to a more extended conjugation and a more intense yellow color.

3.2.3. Coordination environment of the metal ions

For the four nickel ions in the asymmetric unit of NNi, two nickel ions (Ni1 and Ni2) each link to five water molecules and to a carboxyl oxygen in an octahedral coordination (Fig. 4a). The two remaining nickel ions join together to form a $Ni_2(H_2O)_{10}^{+4}$ species (Fig. 4b). No carboxylate oxygens are incorporated into this +4 species. The octahedral coordination of the Ni^{+2} (Ni3 and Ni4) is maintained by bridging the Ni^{2+} ions (Fig. 4b).

The mean bond distances, metal ion-to-water oxygen for NNi (2.1 Å in Table 3) are similar to the salt hydrates previously reported (2.2 Å for nedocromil magnesium pentahydrate and 2.1 Å for nedocromil zinc heptahydrate (Ojala et al., 1996)), indicating similar ion-dipole interactions

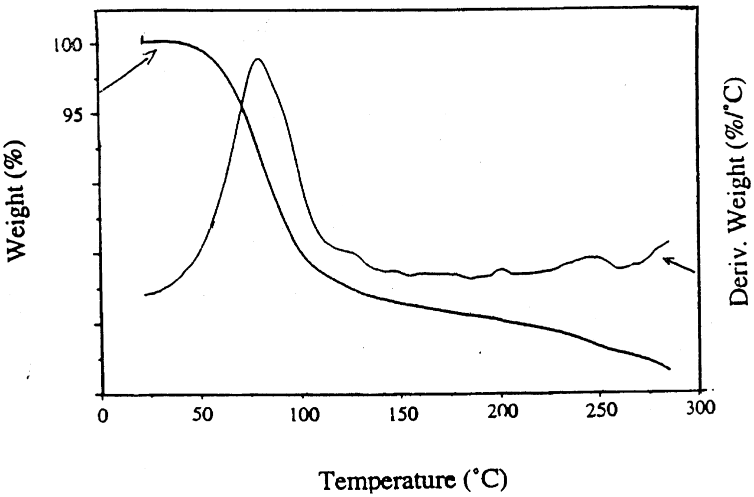


Fig. 3. Thermogravimetric curves and derivative thermogravimetric curves of the nedocromil nickel octahydrate.

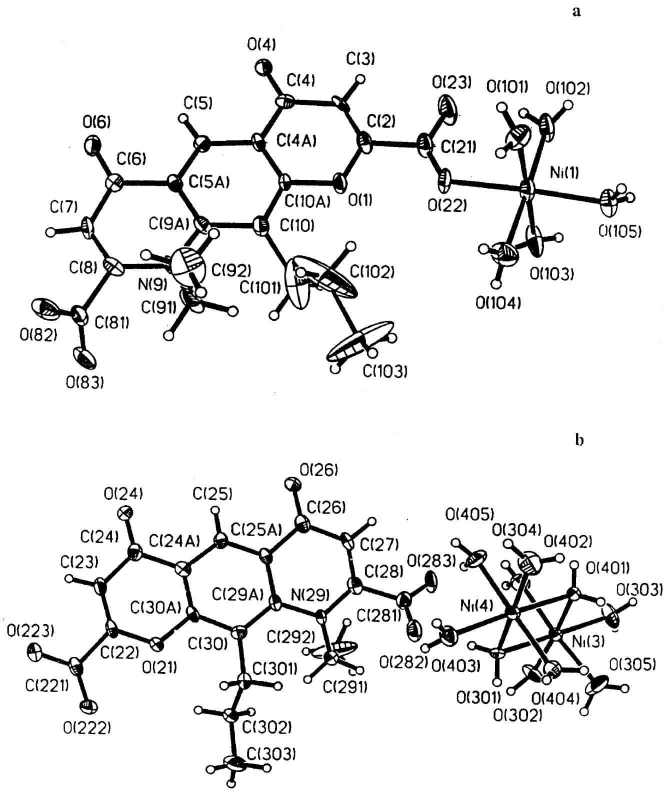


Fig. 4. Thermal ellipsoid diagrams of four nedocromil nickel octahydrate molecules in the asymmetric unit at 50% probability, showing the atomic numbering scheme. (a) Molecule 1 or 2; (b) molecule 3 or 4.

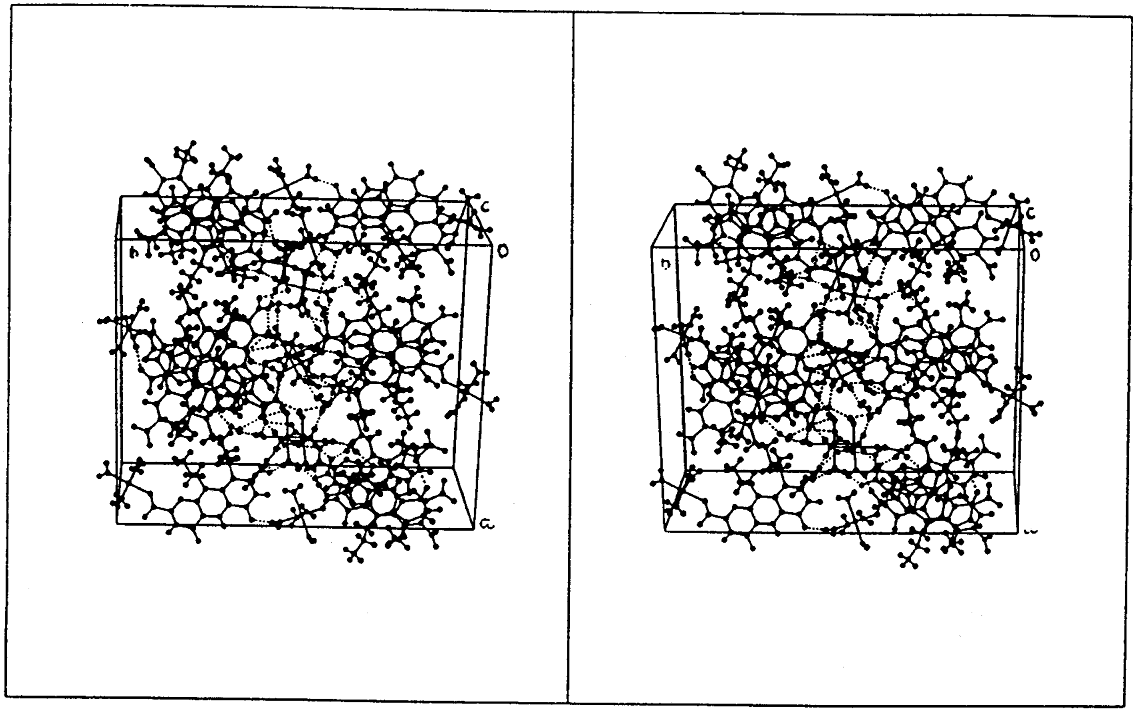


Fig. 5. Stereoscopic views of the crystal packing of nedocromil nickel octahydrate, NNi, looking down the *c*-axis.

in the crystal structures. Though the water molecules in a salt hydrate are bound to the ions by ion–dipole interactions, the strength of the metal ion–water dipolar interactions cannot explain the thermal stability of the salt hydrates.

3.2.4. Bonding environments of the water molecules

For NNi, the asymmetric unit contains four NNi molecules associated with thirty two water molecules (Figs. 4 and 5, Table 4). Of the ten water molecules in the coordination sphere of the Ni1 and Ni2 ions, O101 and O203 are each linked to Ni^{2+} and are hydrogen-bonded to a carboxyl oxygen. O102, O103 and O204 are isolated water molecules and are not linked to any other ligands. O104, O201 and O202 are the only water molecules, which are hydrogen-bonded to other water molecules. Water molecules, O105 and O205, link the Ni^{2+} ion to a carbonyl oxygen and a carboxylate oxygen and are present in a tetrahedral environment.

Of the ten water molecules in the coordination spheres of the Ni3 and Ni4 ions, O303, O305, O402, O403 and O404 are each hydrogen-bonded to a carboxylate oxygen and to a water molecule, whereas O301, O302, O304, O401 and O405 are hydrogen bonded to two carboxylate oxygens.

Twelve water molecules are located in the asymmetric unit in addition to the twenty water molecules coordinated by nickel ions. O501, O502 and O505 are each hydrogen-bonded to one water molecule and form dimers. O506 and O507 are hydrogen-bonded to three water molecules and form three-dimensional water networks. O503 and O510 are hydrogen-bonded to two water molecules and one carboxylate oxygen in a tetrahedral environment. O508 is not linked to any other water and is hydrogen-bonded only to carboxylate oxygen. O509 is hydrogen-bonded to a carbonyl oxygen. O511 and O512 are present in the tetrahedral environment comprising a water molecule, a carboxylate oxygen and a carbonyl oxygen as its ligands. O504 is present in a free water molecule and is not linked to any ligand.

The structure of NNi has a hydrophobic region and a hydrophilic region. The hydrophobic region is composed of π^- stacks of nedocromil groups roughly centered on the central tricyclic ring. The hydrophilic region is composed of $Ni_2(H_2O)_{10}^{+4}$ species and hydrogen-bonded water molecules (Fig. 6). The layer of water molecules is evident at the heart of the hydrophilic region and appears to be fairly continuous in the *ac* plane.

The single step dehydration of NNi (Fig. 3) is explained by the fact that all the water molecules are connected together in the hydrophilic layer (Table 4). Since most of water molecules are mutually linked by hydrogen bonds in NNi, loss of one molecule would be expected to destabilize the other water molecules and to produce a continuous dehydration.

Table 3
Metal coordination distance (S.D. = ± 0.002 Å), in nedocromil nickel octahydrate

Metal ion	Water oxygens	Carboxylate oxygen	Carbonyl oxygen
Ni1	O101 2.103	O22 2.085	
	O102 2.031		
	O103 2.054		
	O104 2.072		
	O105 2.059		
Ni2	O201 2.014	O122 2.080	
	O202 2.056		
	O203 2.074		
	O204 2.080		
	O205 2.055		
Ni3	O301 2.106		
	O302 2.034		
	O303 2.034		
	O304 2.014		
	O305 2.034		
	O401 2.125		
Ni4	O3012.110		
	O401 2.128		
	O402 2.034		
	O403 2.042		
	O404 2.028		
	O405 2.047		

Four nickel ions per asymmetric unit.

3.2.5. Effect of ionic radius on the hydration states

The hydration behavior of metal salts is expected to depend on the nature of the cation, the anion, and the molecular packing. The tendency of a cation to become hydrates is greater the larger its charge and/or the smaller its ionic radius. Table 5 lists the ionic radii of the bivalent metal cations and the stoichiometries of the solved crystal structures of nedocromil salt hydrates determined by single crystal XRD (Zhu et al., 1997b; Zhu, 1997; Ojala et al., 1996). For the alkaline earth metals (magnesium, calcium), the ionic radius increases with increasing atomic number for a given octahedral coordination (coordination number of six). However, for the metals of first transition series (manganese, cobalt, nickel and zinc) the ionic radius decreases with increasing atomic number. Thus the general trend that the hydration state of the cation to become hydrated is greater the smaller the ionic radius is reflected in the bivalent metal salts of nedocromil, such that the number of moles water associated with the salts increases as the ionic radius decreases. A similar generalization has been reported for ionic solid (Forbes et al., 1992). However, the practical usefulness of such generalization to predict the predict the hydration stoichiometries and behavior of series of metal salts is limited, because a given salt may form several stoichiometric hydrates with different amounts of water, depending on the crystallization conditions.

4. Conclusions

The thermal behavior and crystal structure of NNi have been studied. Water is associated with nedocromil nickel in the solid state, but its bonding environments differ. NNi contains four Ni^{2+} ions in the asymmetric unit, two of which are each octahedrally coordinated to five water molecules and to a carboxyl oxygen. A single step dehydration of NNi in TGA can be explained by the fact that all the water molecules are connected together in the hydrophilic layer. Since most of water molecules are mutually linked by hydrogen bonds in NNi, loss of one molecule would be

Table 4
Intermolecular and nickel–water distances (S.D. = ± 40.002 Å) involving the 32 water molecules in nedocromil nickel octahydrate

OW	Ni	OW	Carboxylate oxygen	Carbonyl oxygen
O101	(1) 2.103		(223) 2.880	
O102	(1) 2.031			
O103	(1) 2.054			
O104	(1) 2.072	(503) 2.803		
O105	(1) 2.059		(283) 2.866	(6) 2.756
O201	(2) 2.014	(506) 2.658		
O202	(2) 2.056	(507) 2.692		
O203	(2) 2.074		(323) 2.661	
O204	(2) 2.080			
O205	(2) 2.055		(383) 2.781	(16) 2.649
O301	(3) 2.106		(182) 2.626 (282) 2.663	
O302	(3) 2.034		(183) 2.789 (322) 2.813	
O303	(3) 2.034	(511) 2.746	(322) 2.761	
O304	(3) 2.014		(83) 2.657 (283) 2.704	
O305	(3) 2.034	(506) 2.761	(123) 2.722	
O401	(4) 2.128		(82) 2.619 (382) 2.667	
O402	(4) 2.034	(501) 2.745	(222) 2.812	
O403	(4) 2.042	(512) 2.734	(222) 2.753	
O404	(4) 2.028	(507) 2.780	(383) 2.691	
O405	(4) 2.047		(23) 2.705 (223) 2.692	
O501		(402) 2.745		
O502		(503) 2.734		
O503		(104) 2.803 (502) 2.734	(283) 2.880	
O504				
O505		(507) 2.667		
O506		(201) 2.658 (305) 2.761 (203) 2.811		
O507		(404) 2.780 (202) 2.692 (505) 2.667		
O508			(83) 2.703	
O509				(26) 2.688
O510		(201) 2.740 (507) 2.861	(182) 2.899	
O511		(303) 2.746	(382) 2.784	(14) 2.881
O512		(403) 2.734	(282) 2.756	(4) 2.863

The numbers in parentheses refer to the numbering scheme of the atoms in Fig. 4.

expected to destabilize the other water molecules and to produce a continuous dehydration. The thermal behavior of the NNi, as determined by TGA and DSC correlate well with the crystal structure data.

Acknowledgements

We thank Fison, plc (now AstraZeneca), for a gift of nedocromil sodium. We also thank Lihua Zhang for help in preparing this manuscript.

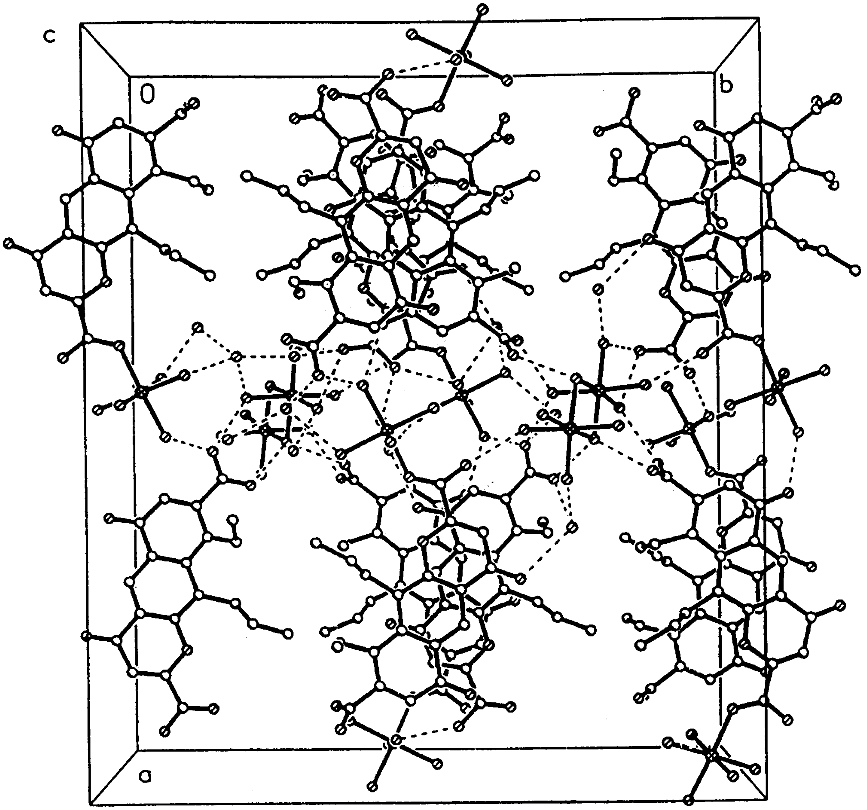


Fig. 6. Molecular packing diagram of nedocromil nickel octahydrate, NNi, looking down the *b*-axis, showing the hydrophilic layer in the *ac* plane.

Table 5
Electronic configurations, ionic radii, hydration states and space groups of bivalent metal salts of nedocromil

Cation	Periodic group	Outer electronic configuration	Ionic radius (Å)[a]	Water stoichiometry from single crystal XRD[b]	Space group from single crystal XRD[b]
Mg	IIA (2)	$3s^2$	0.86	5[c]	$P1$
Ca	IIA (2)	$4s^2$	1.14	8/3[d]	$P1$
Mn	VIIB (7)	$4s^23d^5$	0.97	5	$P1$
Co	VII (9)	$4s^23d^7$	0.89	7	$P2_1$
Ni	VIII(10)	$4s^23d^8$	0.83	8[e]	$Pca2_1$
Zn	IIB (12)	$4s^23d^{10}$	0.88	7	$P2_1$

[a] For coordination number 6.

[b] X-ray diffraction.

[c] From reference: Ojala et al., 1996.

[d] From reference: Zhu et al., 1997b.

[e] From reference: Zhu, 1997.

References

Byrn, S.R., 1982. Solid-State Chemistry of Drugs. Academic Press, New York, NY, pp. 178–179.

Cairns, H., Cox, D., Gould, K.J., Ingall, A.H., Suschitzky, J.L., 1985. New antiallergic pyrano[3,2-g]quinoline-2,8 dicarboxylic acids with potential for the tropical treatment of asthma. J. Med. Chem. 28, 1832–1842.

Forbes, R.T., York, P., Fawcett, V., Shields, L., 1992. Physicochemical properties of salts of *p*-aminosalicylic acid. I. Correlation of crystal structure and hydrate stability. Pharm. Res. 9, 1428–1435.

Hirsch, C.A., Messenger, R.J., Brannon, J.L., 1978. Fenoprofen: drug form selection and prefomulation stability studies. J. Pharm. Sci. 67, 231–236.

Jones, P.G., 1981. Chem. Br. 117, 222–225.

Khankari, R.K., 1993. Physicochemical Characterization and Thermodynamic Properties of Nedocromil Salt Hydrates, Ph.D. Thesis, University of Minnesota, Minneapolis, MN, pp. 40–148.

Ojala, W.H., Khankari, R.K., Grand, D.J.W., Gleason, W.B., 1996. Crystal structures and physical chemical properties of nedocromil zinc heptahydrate and nedocromil magnesium pentahydrate. J. Chem. Crystallogr. 26, 167–178.

SHELXTL-PlusV5.0, 1996. Siemems Industrial Automation, Inc, Madison, WI, USA.

Zhu, H., 1997 Physicochemical Properties and Crystal Structures of Some Pharmaceutical Hydrates, Ph.D. Thesis, University of Minnesota, Minneapolis, MN, pp. 222–255.

Zhu, H., Khankari, R.K., Padden, B.E., Munson, E.J., Gleason, W.B., Grant, D.J.W., 1996. Physicochemical characterization of nedocromil bivalent metal salt hydrates: 1. Nedocromil magnesium. J. Pharm. Sci. 85, 1026–1034.

Zhu, H., Padden, B.E., Munson, E.J., Grant, D.J.W., 1997a. Physicochemical characterization of nedocromil bivalent metal salt hydrates 2. Nedocromil zinc. J. Pharm. Sci. 86, 418–429.

Zhu, H., Halfen, J.A., Young, V.G. Jr, Padden, B.E., Munson, E.J., Grant, D.J.W., 1997b. Physicochemical characterization of nedocromil bivalent metal salt hydrates 3. Nedocromil calcium. J. Pharm. Sci. 86, 1439–1447.