ELSEVIER

International Journal of Pharmaceutics 198 (2000) 167–177

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Structural relationship and desolvation behavior of cromolyn, cefazolin and fenoprofen sodium hydrates

G.A. Stephenson *, B.A. Diseroad

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA

Received 16 July 1999; received in revised form 20 December 1999; accepted 21 December 1999

Abstract

The hydrated crystal structures of cromolyn, cefazolin, and fenoprofen sodium salts are reported. The former two compounds are non-stoichiometric hydrates, whereas the fenoprofen lattice maintains its stoichiometry over a broad range of relative humidity. The relationship between composition, lattice parameters, and relative humidity is studied using a combination of moisture sorption isotherms and variable humidity X-ray powder diffraction. The dehydration properties of the sodium salts are related to the ion coordination and hydrogen bonding of the water molecules in the structures. Anisotropic lattice contraction is observed during dehydration of the cromolyn and cefazolin sodium and is related to the closeness of intermolecular contacts in the hydrated structures.

Keywords: Cromolyn; Cefazolin; Fenoprofen; Hydrate; Polymorphism; Structure; X-ray diffraction

1. Introduction

Sodium salts of pharmaceuticals are often used to enhance the dissolution properties and increase the solubility of drug substances. In the last report known to the authors, this cation is responsible for 62% of the marketed salts of anionic pharmaceuticals (Berge et al., 1977). Their development poses significant development challenges due to common variability of hydration state observed in such salt forms and their extreme hygroscopicity. It has been more 29 years since the unusual solid-state behavior of cromolyn sodium was first reported (Cox et al., 1971). Studies have shown that cromolyn sodium forms a crystalline hydrated structure that contains variable quantities of water, up to nine moles per drug molecule at high relative humidity. Desolvation of the hydrated structure apparently did not result in a distinct transition to a different crystalline form or to an amorphous form, but rather a continuous transition to a similar lattice of smaller unit cell dimensions. Based on indexation of the X-ray powder diffraction pattern of cromolyn sodium and predicted molecular conformations, an 'ab initio' crystal structure was proposed. We revisit the cromolyn sodium system to resolve questions about the molecular packing arrangement pro-

* Corresponding author. Tel.: +1-317-2773841; fax: +1-317-2778387.

E-mail address: gas@lilly.com (G.A. Stephenson)

0378-5173/00/$ - see front matter
PII: S0378-5173(00)00331-8

posed in the initial report and to gain a better understanding of crystallographic systems which desolvate, yet retain the overall packing of their original lattice, that is isomorphic desolvates (Stephenson et al., 1998).

Cefazolin sodium demonstrates similar phase behavior to cromolyn sodium. It exists as a system whose lattice parameters and hydration state vary continuously as a function of relative humidity. As its hydration state is reduced, its unit cell volume reduces accordingly. Cromolyn sodium and cefazolin sodium dehydrate to an amorphous state at very low relative humidity. In the case of cefazolin sodium, the less ordered-partly dehydrated form is chemically more stable than the highly crystalline-fully hydrated form. The increased stability of the less ordered state is contraintuitive. It has been proposed that the additional water is more mobile and free to cause decomposition than the residual water that exists after partial dehydration (Rose, 1981).

In contrast to the behavior of cromolyn and cefazolin sodium salts, fenoprofen crystallizes as a highly ordered structure that undergoes a discrete phase transition to a crystalline anhydrous phase upon dehydration. The objective of the following investigation is to gain structural understanding of hydrated sodium salts of pharmaceuticals and their dehydration behavior. Through examination of the crystallographic packing, the coordination and hydrogen bonding of water molecules and arrangement of water in these three structures, a better understanding of this important class of pharmaceutical substances may be gained.

2. Materials and methods

2.1. Materials

Cromolyn sodium was purchased from Sigma Chemical Company. Initial X-ray powder diffraction studies indicated that the sample was essentially amorphous. Cromolyn sodium pentahydrate was prepared by vapor diffusion of ethanol into a saturated aqueous solution of cromolyn sodium.

Table 1
Crystallographic data for structures of sodium hydrates

	Cromolyn sodium	Cefazolin sodium	Fenoprofen sodium
Identification	9866xf	9872xf	9868xf
Empirical formula	$C_{23}H_{14}O_{11}Na_2$ 7(H_2O)	$C_{14}H_{13}N_8NaO_4S_3$ 5(H_2O)	$C_{15}H_{13}NaO_3$ 2(H_2O)
Formula weight	638.44	566.57	300.28
Temperature, K	203(2)	123(2)	293(2)
Instrument	Siemens P4, Smart 1000 CCD	Siemens P4, Smart 1000 CCD	Siemens P4, Smart 1000 CCD
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Orthorhombic	Monoclinic
Space group	P1	P2(1)2(1)2(1)	P2(1)/n
a	3.8797(8)	4.8189(4) Å	5.7835(9) Å
b	11.069(3)	28.182(2) Å	47.178(7) Å
c	15.741(4)	36.126(3) Å	6.0753(9) Å
α	92.804(4)	90°	90°
β	95.750(4)	90°	116.969(3)°
γ	94.443(5)	90°	90°
Volume	669.5(3) ,1	4906.1(7) Å^3	1477.4(4) Å^3
Z, Calculated ρ	1, 1.583 g/cm^3	8, 1.534 g/cm^3	4, 1.350 g/cm^3
Crystal size, mm	$0.05\times0.2\times0.3$	$0.05\times0.05\times0.35$	$0.10\times0.22\times0.42$
R [$I>2\sigma(I)$]	$R_1=0.0899$	$R_1=0.0814$	$R_1=0.0563$
R (all data)	$R_1=0.1531$	$R_1=0.1344$	$R_1=0.0655$
Largest diff. peak and hole, e·A^{-3}	0.157 and −0.175	0.942 and −0.976	0.206 and −0.219

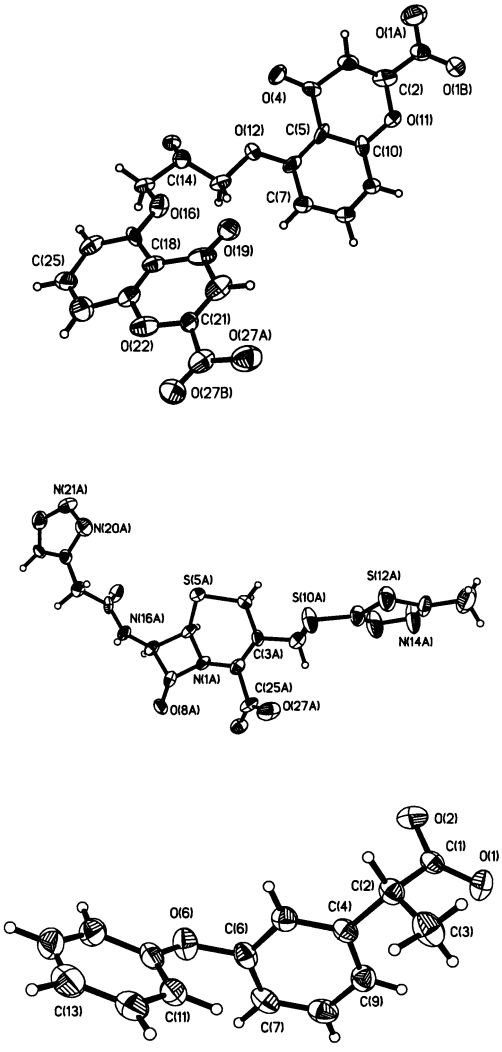

Fig. 1. The 50% thermal ellipsoid diagrams of the cromolyn, cefazolin, and fenoprofen molecules (top to bottom) showing the atomic numbering.

After a period of approximately 2 months, large crystals, $\approx 1 \times 1 \times 2$ mm, were isolated. Cromolyn 'hydrate–solvate' crystals were prepared by dropwise addition of ethanol to a saturated aqueous solution of cromolyn sodium. Cromolyn sodium 'desolvate' crystals were prepared by desolvation of cromolyn crystals (as prepared above) by exposure to ambient laboratory conditions. In a matter of minutes the crystals desolvate to a similar pattern having different interplanar spacings. Cefazolin sodium and fenoprofen sodium was acquired from Lilly Research Laboratories. The pentahydrate form of cefazolin sodium was formed by reducing the temperature of a saturated 1:2 ethanol/water solution of cefazolin sodium from 50 to 5°C at a rate of 1°C h^{-1}. The dihydrate form of fenoprofen sodium was examined as received.

2.2. Single crystal diffraction

Single crystals were mounted on a thin glass fiber and immersed in a stream of nitrogen. Data were collected using a MoK_{α} radiation source ($\lambda = 0.71073$ Å) and a P4 diffractometer equipped with a Bruker SMART 1000 CCD area detector (Madison, WI). Cell refinement and data reduction was performed using the Bruker *SAINT* program. Systemmatic conditions suggested the space group selections. The structures were solved by direct methods (Sheldrick, 1990). All atomic parameters were independently refined. The space group choice was confirmed by successful convergence of the full-matrix least-squares refinement on F^2 (Sheldrick, 1993). The details of the single crystal X-ray diffraction experiment are provided in Table 1. A full structural report is provided in the supplement.

2.3. Moisture sorption isotherms

Moisture sorption isotherms were obtained at 25°C using a VTI Vacuum Moisture Balance (model MB300G) with the following conditions: sample size 5–10 mg, drying temperature 30°C, adsorption/desorption range 0–95% relative humidity, relative humidity step 5%, and sampling interval 5 min. The partial vacuum balance was used rather than an ambient pressure system so that weight loss at relative humidity less than 5% could be measured. This is particularly important for removal of ion coordinated water.

2.4. X-ray powder diffraction

Hydrated samples were mixed with fluorophlogopite, the Nist # 675 low-angle diffraction standard, and data were collected. X-ray powder diffraction (XRD) patterns were obtained

on a Siemens D5000 X-ray powder diffractometer (now Bruker AXS of Madison, WI), equipped with a CuK_α source ($\lambda = 1.54056$ Å) operating at 50 kV and 40 mA, a scintillation detector, and a nickel filter used to reduce the K_β contribution to the X-ray signal. Each sample was scanned between 4 and 35° in 2θ with a step size of 0.02°. The patterns were collected at different relative humidities using the Sycos H gas humidifier (Endress & Hauser, Greenwood, IN). The internal standard was used to correct 2θ error arising from sample displacement that may occur during phase transitions.

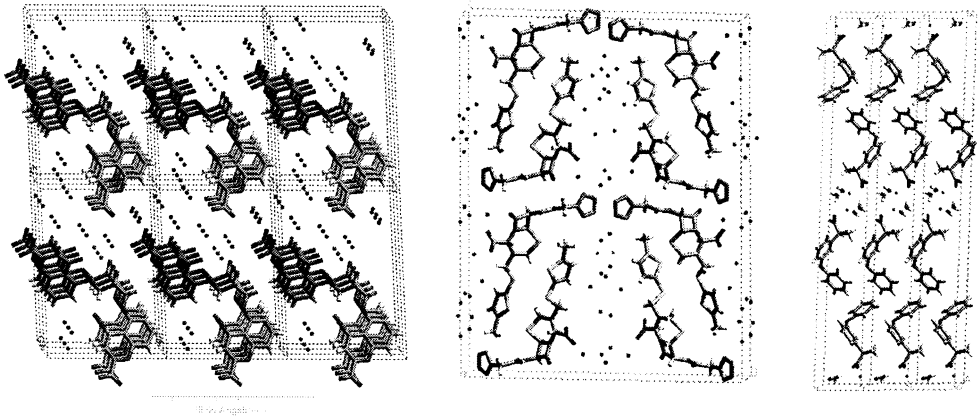

Fig. 2. Unit cell packing diagrams of cromolyn, cefazolin, and fenoprofen sodium hydrates (left to right).

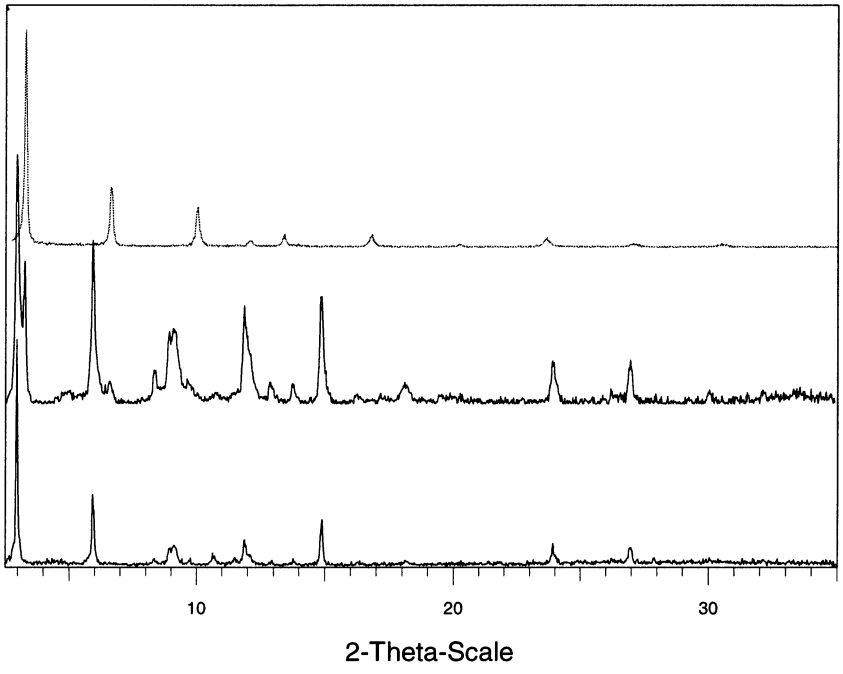

Fig. 3. Small acicular crystals of cromolyn sodium ethanolate as they desolvate (bottom to top).

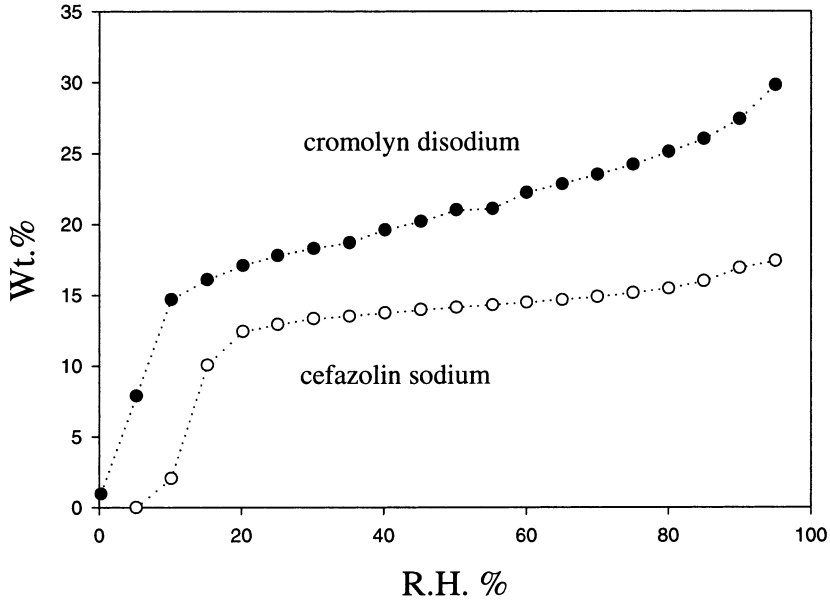

Fig. 4. Moisture desorption isotherms for cromolyn disodium salt and cefazolin sodium.

3. Results and discussion

3.1. The structure of stout crystals of cromolyn sodium 'pentahydrate'

Data were collected at low temperature to minimize sample desolvation throughout the diffraction experiment. The crystal structure was determined to be triclinic and the space group was found to be $P1$. Previous studies proposed that the molecular conformation of the cromolyn molecule is planar due to its relatively short 3.88 Å a-axis. The molecule in the structure is actually non-planar, with the angle subtended by the plane normals of the aromatic rings being 48.8°, see Fig. 1. The uniquely small a-axis of the lattice is due to very efficient packing of cromolyn molecules in successive layers of the crystal lattice.

The sodium ions and water molecules are located in large tunnels that run along the a-axis, see Fig. 2. The tunnel may be described as approximately ellipsoidal, with a major axis of 10.5 Å and a minor axis of 5.5 Å. Two sodium ions were located in the difference Fourier maps. Na1 is highly ordered and assumes a coordination number of five, forming coordinate bonds to three oxygens of the drug molecule and two well ordered water molecules. The location of the second sodium ion is less certain, it is apparently disordered among two sites bridging carboxylate groups of two adjacent drug molecules.

Seven water molecules were found in total, one being disordered among two different positions. Of the seven water molecules observed, four were in close proximity to sodium ions and three were found in the 'interstitial space' of the solvent tunnels. In the study by Cox et al. (1971) it was reported that this crystal form could accommodate as many as nine water molecules. This observation is not disputed, since there is ample space in the lattice available to accommodate additional water molecules. Since the site occupancy and/or hydration state is a function of the water activity, the composition of the crystal lattice is highly dependent upon the water activity of the solution from which the drug was recrystallized.

In the previous publication, a number of peaks were observed in the diffraction pattern that were not indexable (Cox et al., 1971). They proposed that an 'expanded lattice' was responsible for the additional lines in the pattern arising from incommensurate water molecules in the cromolyn

sodium structure. We attribute the appearance of such peaks to the presence of a different phase altogether. When crystals of 'stout' crystals are observed, there is often another phase present. This phase is composed of extremely fine needles. By extracting 'stout' crystals from ethanol/water suspensions of cromolyn sodium, a powder pattern of the 'stout' crystals is observed which is free of the 'expanded lattice lines'. On the other hand, when the needles are exposed to ambient atmosphere, they desolvate in a few minutes to a different form having a similar X-ray powder diffraction pattern to that of the parent 'fine' needles, see Fig. 3. It is this phase impurity which is typically observed in the diffraction patterns reported by Cox et al. (1971). It is possible that this is a smectic liquid crystalline phase, however the number of high angle reflections indicates additional order than we have observed with other smectic liquid crystalline phases.

3.2. Behavior of the cromolyn disodium hydrate upon desolvation

Stout needles of the hydrated phase of cromolyn sodium were shown to undergo desolvation which resulted in contraction of the crystallographic unit cell, thus resulting in a diffraction pattern which changes with the relative humidity of sample environment. Due to the authors interest in hydrated structures which retain their three dimensional order upon desolvation, that is 'isomorphic desolvates' this structure was examined by X-ray powder diffraction. Fig. 4 shows that the moisture desorption isotherm collected on the 'stout' needles of cromolyn sodium. The moisture was lost continuously down to approximately 10% relative humidity. Below this humidity, a large loss of weight with respect to humidity is observed. This behavior is consistent with obser-

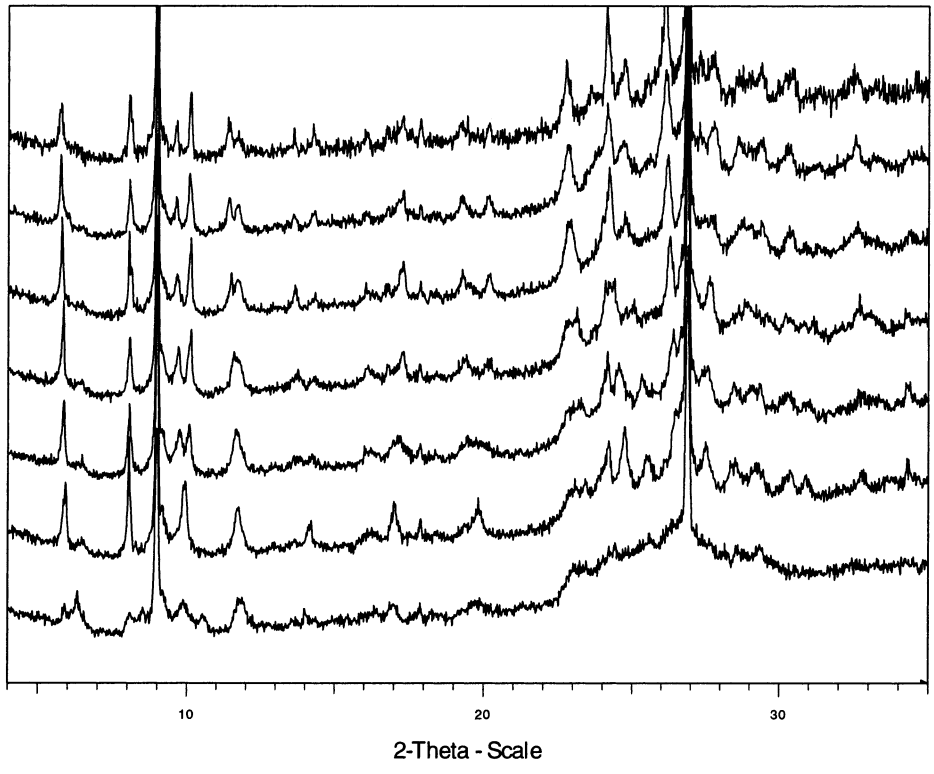

Fig. 5. X-ray powder diffraction pattern demonstrating loss of crystallinity and reduction in unit cell volume as a function of reduced relative humidity. (100, 71, 39, 24, 17, 12 and 3%, top to bottom). (NIST SRM675 peaks at 8.85 and 26.77 (supercript = o)).

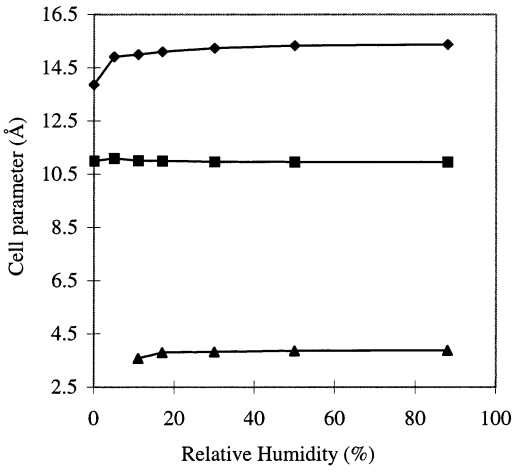

Fig. 6. The lattice contraction of the *a*, *b*, and *c* axes (in Å, bottom to top) of cromolyn sodium as a function of relative humidity (abscissa). (NIST SRM675 peaks at 8.85 (supercript = o)).

vations made on other systems that form 'isomorphic' desolvates.

Close examination of the waters of hydration indicate that the hydrate consists of two types of water molecules; metal-coordinated water and water in lattice channels (Morris and Rodriguez-Hornedo, 1993). As a result of the two separate types of water in the structure, desolvation of the lattice is non-uniform. Water is readily lost from the interstitial space, however the last four water molecules ($\approx 12\%$ water) are more reluctantly removed from coordination with the sodium ions. The removal of the ion-coordinated water causes a greater disturbance of the lattice and results in significant disturbance to the lattice at less than 5% relative humidity, see lower two traces in Fig. 5.

Shrinking of the crystal lattice during dehydration is not isotropic, as shown in Fig. 6, but rather is directionally dependent and is consistent with the molecular packing. The *c*-axis of the unit cell has more water separating adjacent molecules. As a result, anisotropic shinkage of the unit cell parameters is observed, with the *c*-axis experiencing a greater reduction in interplanar spacing as the lattice is dehydrated relative to the other two lattice parameters. The peak broadening observed with increasing diffraction angle is consistent with

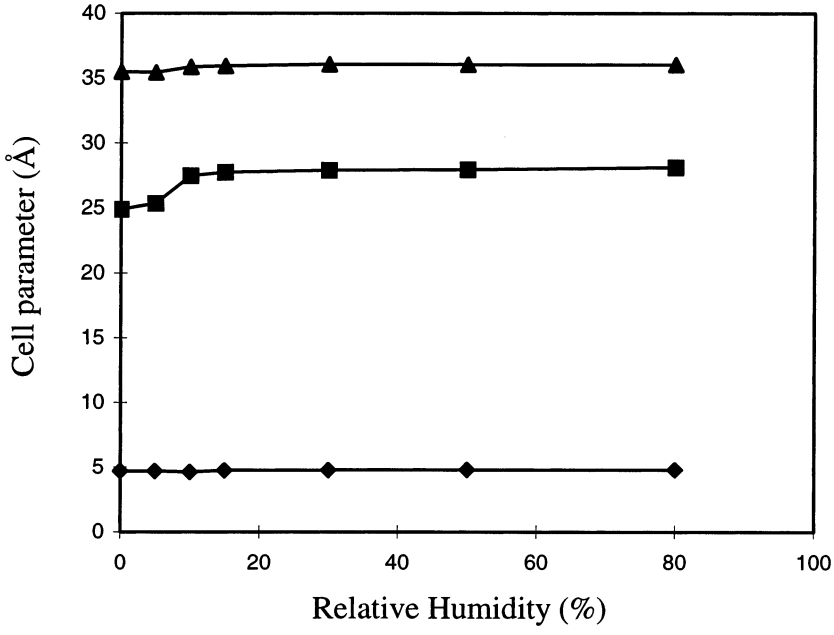

Fig. 7. The lattice contraction of the *a*, *b*, and *c* axes (in Angstroms, bottom to top) of cefazolin sodium as function of relative humidity (abscissa).

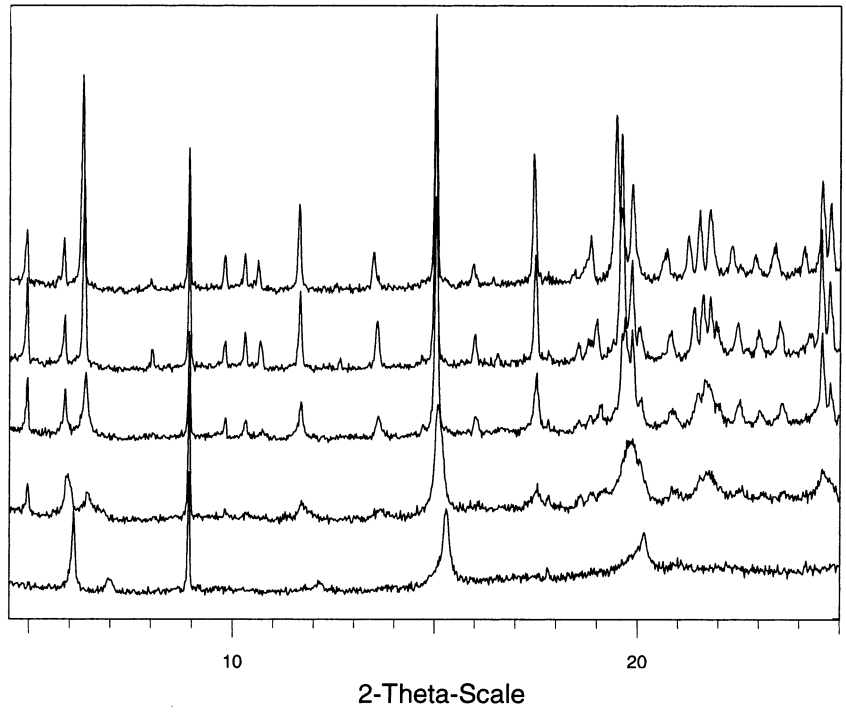

Fig. 8. The X-ray powder diffraction pattern of cefazolin sodium changes as a function of decreasing relative humidity: 80, 30, 15, 10, 5% (top to bottom).

Table 2
Description of hydrogen bonding geometry observed in fenoprofen sodium dihydrate

Donor-H	d(H..A) (Å)	<DHA (°)	d(D..A) (Å)	Acceptor
O3-H3WB	2.085	161.77	2.935	O1 [$-x,-y,-z$]
O3-H3WA	1.833	162.12	2.700	O4 [$x-1$, y, $z-1$]
O2-H2WB	1.958	167.56	2.771	O3 [$x+1$, y, z]
O2-H2WA	1.889	171.84	2.799	O1 [x, y, $z-1$]

either a reduction in particle size or increased lattice imperfection, that is microstrain (Baig et al., 1999). Microstrain is a result of crystal imperfection in which there is variability in interplanar spacing from one crystal domain to the next. In the present case, we attribute the broadening to be primarily caused by microstrain due to the reversibility of the process. As was previously reported by Cox et al., the changes in lattice parameters is completely reversible whether one proceeds from high to low relative humidity or vice-versa, little hysteresis is observed. While desolvation processes result in particle size reduction and may cause broadening of the diffraction pattern, rehydration via water vapor does not generally result in increased particle size. Since the diffraction pattern regains its original degree of line broadening upon re-exposure to relatively low levels of moisture, the broadening of the peaks at low humidity can most likely be attributed to increased lattice imperfection due to microstrain.

In our studies of the formation of isomorphic desolvates, we have shown that lattices of different crystalline pharmaceuticals contract at differ-

ent rates upon desolvation. Lattice relaxation resulting in smaller unit cell volume is proposed to be an attempt of the crystal lattice to reduce its lattice energy by achieving more efficient packing through solid-state processes. Since after desolvation drug molecules are trapped, essentially suspended in what remains of their original molecular environment, the rigidity of the lattice and the amount of disturbance imposed by the loss of the solvent plays a major role in determining relaxation kinetics.

3.3. The crystal structure of cefazolin sodium

The structure of cefazolin sodium chloride monhydrate was first solved by Professor van Meersche (van Meerssche et al., 1979) and was later modified and shown to be the cefazolin sodium pentahydrate (Martinez, 1983). The discrepancies were primarily due to the disordered state of the solvent and ionic components of the crystal lattice. We have resolved the structure of the pentahydrate and report it herein for comparison to the other sodium salts. The structure of cefazolin sodium is very similar to cromolyn sodium in many respects, see Fig. 2. As with cromolyn sodium huge solvent tunnels are found. The tunnels can be described as approximately ellipsoidal, having a long axis of 14.3 Å and a minor axis of 7.1 Å that run perpendicular to the short *a*-axis of the unit cell. There are two symmetry independent molecules, both being well ordered in the lattice. As a result of the two independent molecules in the asymmetric unit, there are ten independent water molecules and two sodium ions present in the sodium pentahydrate structure.

Again there are two general regions of water molecules, those in the large solvent tunnels and those in proximity of the sodium ions and the tetrazole moieties of the drug molecule. Both sodium ions are observed with reasonable degree of confidence. One of the sodium ions, Na1, bridges the tetrazole group of the two symmetry independent drug molecules at distances of 2.54 Å to N22A and 2.56 Å to N21B. The atom also tightly coordinates four well-defined water molecules; O1W (2.39 Å), O3W (2.38 Å), O2W

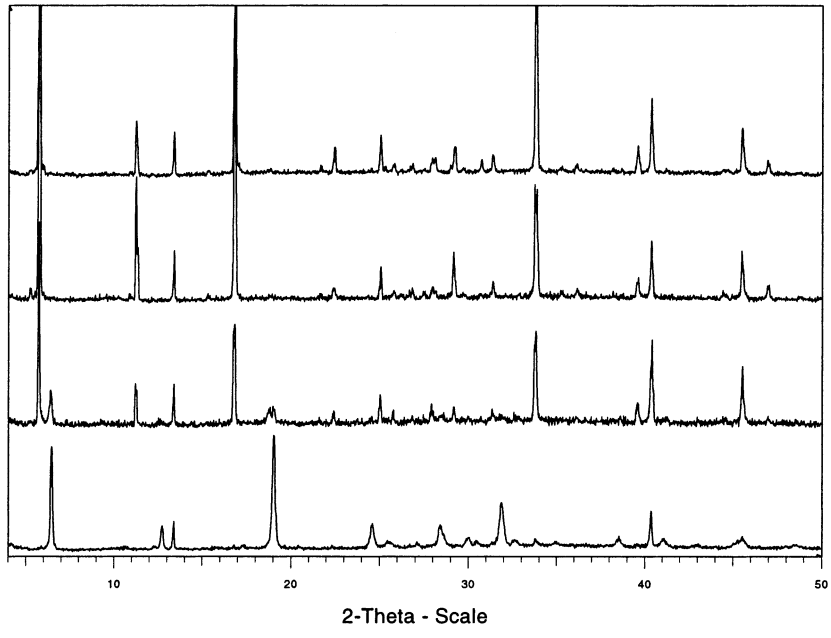

Fig. 9. The X-ray powder diffraction pattern of fenoprofen does not change until the relative humidity is less than 5%: 40%, 20%, 10%, 0% 4 h, and 0% 1 day (top to bottom).

(2.67 Å) and its symmetry equivalent molecule O2W ($x+1$, y, z) with a distance of 2.67 Å. The hydrogens on the water molecules were not observed, but the anisotropic displacement parameters indicate that these three waters are well ordered in the crystal lattice. The second sodium ion, Na2, also bridges two adjacent symmetry independent tetrazole groups; N21A at a distance of 3.02 Å and N22B at 2.98 Å. Sodium ion Na2 is also coordinated with two water molecules; however, refinement of their occupancy factors indicate that approximately one half of a water molecule exist at each location. Na2 coordinates with O9W at a distance of 2.56 Å and O10W at 2.68 Å. Five additional sites of electron density were found in the Fourier difference maps and they are of approximately unit occupancy with the exception of O8W that refined to the occupancy of 0.8.

3.4. Desolvation of cefazolin sodium

As shown in Fig. 4, the pentahydrate form of cefazolin sodium is like the hydrate of cromolyn sodium and undergoes a continuous loss of water upon exposure to low humidity. The loss of solvent from the lattice results in structural changes throughout the diffraction pattern demonstrating again a continual reduction in unit cell parameters without resulting in reorganization of molecules in the crystal lattice, see Fig. 7. Similar to cromolyn sodium, the shrinking of the lattice is anisotropic. The *b*-axis shows the greatest degree of contraction. Measurement of close contacts between molecular layers indicates that there is approximately 1.0 Å more room along the *b*-axis than along either the *a*-axis or *c*-axis. Upon desolvation, cefazolin sodium dehydrates to a poorly crystalline form (often-termed collapsed hydrate or dried α phase) (Kamat et al., 1988), see Fig. 8. Despite its reduction in crystallinity, the dried α form is chemically more stable (Rose, 1981). Apparently, the loss of the more mobile water molecules results in reduced water activity and increased chemical stability. For this reason, there is a specifcation in the USP of 6% water by Karl Fisher, a value far below that of a pentahydrate (USP, 1995).

3.5. The structure and dehydration of fenoprofen sodium dihydrate

In contrast to the structures of cromolyn sodium and cefazolin sodium, fenoprofen sodium dihydrate represents a 'well behaved' pharmaceutical. The water molecules are sufficiently ordered that even the hydrogen atoms can be found in successive difference Fourier maps. As shown in Fig. 2, the water molecules are coordinated with the sodium ions and are found in planes that run perpendicular to the *b*-axis. The sodium ion is penta-coordinated. It forms a salt bridge that coordinates with the carboxylate group of two symmetry related molecules with a distance of 2.32 Å to O1 and 2.32 Å to O2 of the adjacent molecule. The water molecules in the dihydrate structure form two hydrogen bonds and coordinate with the sodium ion. The coordination of the sodium ions and the hydrogen bonding of the water molecules are listed in Table 2. The hydrate is unusually stable for a sodium salt, maintaining its hydration state to less than 5% relative humidity before converting to an anhydrous state. Upon desolvation, the lattice undergoes a discrete phase transition to an ordered anhydrous phase, see Fig. 9. These observations are in contrast to observations where attempts to generate a crystalline anhydrate were unsuccessful (Hirsch et al., 1978). The powder diffraction pattern of the anhydrate formed therein is distinctly different from the dihydrate form and indicates that the drug molecules have undergone re-arrangement as the result of dehydration.

4. Conclusions

Despite the less than ideal structures obtained from cromolyn and cefazolin sodium hydrates, a great deal is learned from their study. First of all, the lattice shinkage upon desolvation is anisotropic and can be related to the drug-drug intermolecular separation in such structures. Water molecules in cromolyn sodium and in cefazolin sodium have both tunnel hydrate and ion-coordinated hydrate character. As a result of the tunnel hydrate character, the compounds are of non-stoi-

chiometric hydration. In contrast, fenoprofen has well defined solvent molecules, both participating in hydrogen bonding interactions and in ionic bonding with the sodium ion. Loss of the most tightly held water molecules results in substantial lattice imperfection or microstrain.

The authors have observed time and again, what does not behave well by diffraction, does not behave well as a pharmaceutical solid. The structures of cromolyn sodium and cefazolin sodium represent challenges from both crystallographic and pharmaceutical development standpoints. The drug molecules are well ordered in each of the structures of hydrated sodium salts, thereby pleasing the synthetic organic chemist. On the other hand, the water molecules and to a lesser extent the sodium ions are not as well behaved in structures having larger solvent tunnels and higher hydration states. The less ordered structures result in physical properties which make the pharmaceutical much more difficult to develop, manufacture, and control.

5. Supplementary materials

The crystallographic data is provided in supplement and will be deposited in the Cambridge Structural Database (Allen et al., 1983). Tabulations of the diffraction patterns are provided in supplement.

References

Allen, F.H., Kennard, O., Taylor, R., 1983. Systematic analysis of structural data as a research technique in organic chemistry. Acc. Chem. Res. 16, 146–153.

Berge, S.M., Bighley, L.D., Monkhouse, D.C., 1977. Pharmaceutical Salts. J. Pharm. Sci. 66 (1), 1–19.

Baig, A.A., Fox, J.L., Young, R.A., Wang, Z., Hsu, J., Higuchi, W.I., et al., 1999. Relationship among carbinated apatite solubility, crystallite size, and microstrain parameters. Calcif. Tissue Int. 64, 437–449.

Bruker AXS, Incorporated. Madison, WI, USA.

Cox, J.S.G., Woodard, G.D., McCrone, W.C., 1971. Solid-state chemistry of cromolyn sodium (disodium cromoglycate). J. Pharm. Sci. 60 (10), 1458–1465.

Kamat, M.S., Osawa, T., DeAngelis, R.J., Koyama, Y., DeLuca, P.P., 1988. Estimation of the degree of crystallinity of cefazolin sodium by X-ray and infrared methods. Pharm. Res. 5 (7), 426–429.

Hirsch, C.A., Messenger, R.J., Brannon, J.L., 1978. Fenoprofen: drug form selection and preformulation stability studies. J. Pharm. Sci. 67 (2), 231–236.

Martinez, H., 1983. Solid-State Desolvation of Cefaclor and Cefazolin Sodium. Ph.D. Thesis, Purdue University, USA.

Morris, K., Rodriguez-Hornedo, N., 1993. Hydrates. In: Swarbrick, J., Boylan, J.C. (Eds.), Encylcopedia of Pharmaceutical Technology, vol. 7. Marcel Dekker, New York.

Stephenson, G.A., Groleau, E.G., Kleemann, R.L., Xu, W., Rigsbee, D.R., 1998. Formation of isomorphic desolvates: creating a molecular vacuum. J. Pharm. Sci. 87 (5), 536–542.

Rose, H.A. Communication by internal corporate memorandum, Eli Lilly and Company, April 22, 1981.

Sheldrick, G.M., 1990. SHELXS86. Phase annealing in SHELX-90: direct methods for larger structures. Acta Cryst. A46, 467–473.

Sheldrick, G.M., 1993. SHELXS93. Program for crystal structure refinement. Institut für anorg chemie, Göttingen, Germany.

US Pharmacopeia XXIII, 1995. US Pharmacoepia Convention, Rockville, MD, 290.

van Meerssche, M., Germain, G., Declercq, J.P., Coene, B., Monreaux, C., 1979. Cephazolin sodium chloride salt. Cryst. Struct. Commun. 8, 287–288.