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Hydration of drug molecules: cavity-inclusion of water in crystals of loperamide hydrochloride tetrahydrate

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Single crystal X-ray determination of the hydration sites in loperamide hydrochloride tetrahydrate reveals that both ordered and disordered water molecules are entrapped in cavities formed by the packing of drug molecules around threefold crystallographic axes. The compound was obtained by recrystallization of loperamide HCl from ethanol and crystallizes in the trigonal system, space group R3, with a = 22.497(3), c = 16.719(6)Å, Z = 9 and D_c = 1.194g cm^{-3}; final R = 0.070 for 2029 observed data collected at 294K. The cation adopts an extended conformation in the crystal and there is extensive hydrogen bonding involving water molecules, chloride ions and the cation O-H and N$^+$-H groups. The compound was also characterized by hot-stage microscopy, thermogravimetry, differential scanning calorimetry and X-ray powder diffraction (XRD).

INTRODUCTION

Loperamide hydrochloride, [4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl-αα-diphenyl-1-piperidinebutanamine monohydrochloride], is a widely used, specific, long-acting antidiarrhoeal which is reported to occur in two polymorphic forms as well as a tetrahydrate.[1] A crystallographic study of the monohydrate of the free base, loperamide, has been reported,[2] but no X-ray structures of the hydrochloride salt or its modifications have been documented. A large number of drugs and other biologically-active molecules occur with water of crystallization. Byrn has listed over one hundred drug hydrates which have been identified.[3] These species are important in the pharmaceutical industry because the loss of water can alter the dissolution rate, bioavailability and stability of the drug. The extent to which water is 'ordered' by the host drug molecule is important in the study of solvent influences in drug-receptor interaction and it has been noted that crystalline multihydrated drug molecules provide excellent models for the study of water arrangements[4]. Our studies of multihydrated drugs show that water may aggregate in channels in the host structure as in e.g. urapidil pentahydrate[5] or in distinct layers separating host molecules as in e.g. diclofenac sodium tetrahydrate.[6,7] In this paper, we describe the entrapment of ordered and disordered water molecules in a cage formed by the host drug molecules.

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EXPERIMENTAL

Crystal preparation and preliminary characterization

The raw material, loperamide HCl, was supplied by Premier Pharmaceuticals, Bryanston, South Africa. Crystals of the title compound were obtained by recrystallization from absolute ethanol. The crystals are large, colorless prisms with distorted hexagonal cross-section. Preliminary characterization of the crystals included thermogravimetry (TG), differential scanning calorimetry (DSC), hot-stage microscopy, X-ray powder diffraction and elemental analysis. For thermal analysis, a Perkin-Elmer TGA 7 balance and a Perkin-Elmer DSC 7 instrument calibrated with indium and zinc were used. For both methods, sample heating rates were in the range 5-20°C min^{-1} in the temperature range 25-250°C. The X-ray powder pattern was recorded with a Philips PW1050/80 vertical goniometer with Ni-filtered CuKα X-rays. A step scan of 0.02° 2θ over the 2θ-range 6-36° was used. The calculated X-ray powder pattern was obtained using program LAZY PULVERIX[8] with the unit cell data, space group and atomic coordinate data obtained from the single crystal X-ray analysis as input.

Elemental analyses were carried out in quadruplicate on a Carlo Erba Elemental Analyser Model 1106.

Single crystal X-ray analysis

Examination of the crystals under the polarizing microscope revealed a uniaxial interference figure which, together with the morphology, suggested the trigonal or hexagonal crystal system. Preliminary X-ray de Jong-Bouman photographs indicated the trigonal system (Laue group $\bar{3}$) with reflections present only for $-h+k+l = 3n$ (referred to a hexagonal cell). These conditions indicate space group R3 or R$\bar{3}$.

Intensity data were collected at 294K on an Enraf-Nonius CAD4 diffractometer with MoKα-radiation ($\lambda = 0.71069$Å). Accurate cell parameters were determined by least-squares analysis of the setting angles of 24 reflections in the θ-range 16-17°. Reflections with index range h:0, 26; k:0, 26; l:-19, 19 and $1° < \theta < 25°$ were collected by the ω-2θ scan mode using a variable scan speed depending on I and σ(I) with a maximum time of 40 s per reflection. Intensity control was performed every hour and orientation control every 200 measured reflections. For a total exposure time of 26.7 h, the overall intensity of the standard reflections decreased by 2.6% only, indicating crystal stability. Data were corrected for Lp-effects and for absorption[9] using the program EAC of the Enraf-Nonius Structure Determination Package.[10] Crystal data, data-collection parameters and details of structure refinements are listed in Table 1. Intensity statistics showed an acentric distribution confirming the space group as R3. The structure was solved by direct methods.[11] The E-map yielded the positions of the Cl^- ion, the non-hydrogen atoms of the cation and several water molecules. Only the cation and anion were initially inserted for isotropic, and subsequently anisotropic, refinement[12] which yielded R = 0.157. Water molecules were sought in subsequent difference electron-density (Δρ) syntheses. Location and inclusion of water oxygen atoms were performed carefully using several successive least-squares refinements followed by Δρ maps. New additions were continually inspected to ensure that reasonable hydrogen bonding distances resulted. Since water location was an important feature of the analysis, some details follow. Initially, atoms O(1), O(2) and O(3) in general positions with Δρ in the range 1.7-2.1 $eÅ^{-3}$ were inserted and refined isotropically. Refined U_{iso} values were in the range 0.14-0.19$Å^2$. A fourth peak in a general position with $\Delta\rho = 1.1 eÅ^{-3}$ was inserted as O(4A). Refinement yielded $U_{iso} = 0.35Å^2$ suggesting disorder. The U_{iso} value was fixed at 0.17$Å^2$ (the average for O(1), O(2), O(3)) and the site-occupancy factor (s.o.f.) varied. A fifth peak with $\Delta\rho = 1.1 eÅ^{-3}$, located on the threefold axis, was assigned as oxygen O(4B) and was treated similarly to O(4A). After refinement of the s.o.f.s, the final model corresponded to 4.02 water molecules per asymmetric unit. Only the positions of the water O atoms were then allowed to vary while many of the H atoms of the cation, including that on atom N(11) of the piperidine ring, were located and inserted in idealized positions (C-H, N-H 1.00Å) with a common variable U_{iso} which refined to 0.083$Å^2$. The H atom of the cation hydroxyl group was not located and no attempt was made to place water H atoms. Full-matrix least-squares refinement involved minimization of $\Sigma w(|F_o|-|kF_c|)^2$ with $w = [\sigma^2(F_o) + 0.005F_o^2]^{-1}$, chosen to minimize the variation in $\Sigma w(\Delta F)^2$ with sinθ and $(F_o/F_{max})^{1/2}$. Five reflections were omitted as they suffered from secondary extinction. Refinement of the model with the reversed polarity was also performed but application of the Hamilton R-ratio test showed it could be rejected at the 0.005 level.[13] Complex neutral atomic scattering factors were used.[14] Program PARST[15] was used to calculate molecular parameters. Table 2 lists refined atomic coordinates, U_{iso} values for water O atoms, and equivalent isotropic thermal parameters ($U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i.a_j$) for all other non-hydrogen atoms.

Table 1 Crystal data, details of data-collection and refinement

Formula	$C_{29}H_{33}N_2O_2Cl.HCl.4H_2O$
M_r	585.57
a/Å	22.497(3)
c/Å	16.719(6)
V/$Å^3$	7328(3)
Z	9
Space group	R3
μ(MoKα)/cm^{-1}	2.37
F(000)	2808
D_c/g cm^{-3}	1.194
Crystal size/mm	0.3 × 0.4 × 0.5
Absorption correction factor range	0.9450–0.9997
Scan width in ω/deg	.85 + .35 tanθ
Vertical aperture/mm	4
Aperture width/mm	1.12 + 1.05 tanθ
Reflections measured	3111
Unique reflections	2683
R_{int}	0.00
Observed reflections, $I > 2\sigma(I)$	2029
Parameters refined	338
Max Δ/σ	0.02
R	0.070
R_w	0.074
S	1.366
Δρ/e$Å^{-3}$,min,max	−.37,.47

RESULTS AND DISCUSSION

Preliminary characterization

It was important to reconcile the modelled crystal structure with an independent analytical determination of the crystal water content. Initial assay was based on TG analysis which showed a one-step weight loss of 14.8% (average of 5 measurements) in the temperature range 30-130°C. This yields a loperamide HCl:H_2O ratio of

Table 2 Fractional atomic coordinates (× 10^4) and equivalent isotropic thermal parameters (Å^2 × 10^3) for non-hydrogen atoms with e.s.d.s in parentheses

Atom	*x/a*	*y/b*	*z/c*	U_{eq}/U_{iso}*
Cl(1)	2339(1)	−92(1)	2644	85(1)
C(2)	3453(4)	545(5)	1712(5)	61(4)
C(3)	4079(4)	666(5)	1432(5)	59(4)
C(4)	4371(4)	294(4)	1682(5)	46(3)
C(5)	4021(5)	−206(5)	2240(7)	76(5)
C(6)	3389(5)	−334(5)	2537(7)	76(5)
C(7)	3124(4)	47(4)	2249(5)	53(3)
C(8)	5058(4)	418(4)	1357(5)	53(4)
C(9)	4989(4)	−198(4)	917(5)	52(4)
C(10)	5662(4)	−121(5)	657(5)	53(4)
N(11)	6141(3)	41(3)	1350(4)	45(2)
C(12)	6249(4)	686(5)	1747(7)	73(5)
C(13)	5578(4)	608(5)	2037(6)	64(4)
O(14)	5342(4)	983(4)	806(5)	96(4)
C(15)	6799(4)	93(4)	1082(5)	51(3)
C(16)	7257(3)	165(4)	1776(4)	46(3)
C(17)	7899(4)	87(4)	1559(4)	43(3)
C(18)	8422(4)	747(4)	1126(5)	48(3)
O(19)	8272(3)	1187(3)	973(5)	68(3)
N(20)	9042(3)	851(3)	928(4)	57(3)
C(21)	9535(5)	1492(5)	528(6)	74(4)
C(22)	9304(4)	376(5)	1113(7)	76(5)
C(23)	7644(4)	−561(4)	1048(5)	45(4)
C(24)	7143(4)	−1191(4)	1374(6)	58(4)
C(25)	6886(5)	−1782(4)	897(8)	80(5)
C(26)	7087(6)	−1755(6)	156(8)	82(7)
C(27)	7580(6)	−1120(7)	−186(6)	79(6)
C(28)	7840(4)	−537(4)	272(5)	54(4)
C(29)	8222(4)	53(4)	2377(5)	47(3)
C(30)	8301(4)	−487(4)	2605(5)	56(4)
C(31)	8599(6)	−482(5)	3328(7)	79(6)
C(32)	8835(6)	66(5)	3829(6)	76(5)
C(33)	8766(6)	624(6)	3606(6)	78(6)
C(34)	8470(5)	620(5)	2883(5)	62(4)
Cl(35)	5396(2)	−1099(2)	2541(3)	108(2)
O(1)	7745(6)	2064(6)	670(7)	139(4)*
O(2)	5434(7)	1128(8)	−836(9)	174(5)*
O(3)	7711(9)	3222(9)	1314(10)	190(6)*
O(4A)[a]	5407(10)	2289(10)	−1231(11)	170*
O(4B)[b]	6667	3333	582(20)	170*

[a]s.o.f. = 0.77 [b]s.o.f. = 0.25

1:4.8, assuming that only water is lost upon heating. However, elemental analysis of the crystals, which were not pre-dried, yielded %C 59.3, %H 7.2, %N 4.6 (average of 4 determinations) which is consistent with calculated values of 59.5, 7.2 and 4.8% respectively for a tetrahydrate. (A pentahydrate, for example, would require a significantly lower %C, namely 57.7). It is pertinent to note that an authoritative review[1] of the properties of loperamide hydrochloride cites two polymorphs of the drug as well as a 'tetrahydrate' form, the latter yielding 14.5% weight loss on heating, attributed to the evaporation of solvated water. A possible explanation for the high TG estimate is that minor drug decomposition accompanies water loss. We have relied on the elemental analysis in formulating the species studied as a tetrahydrate and this was later found to be consistent with the X-ray analysis. It is also noteworthy that the water content of the crystals remained unchanged even after storage in a glass vial for two years. On the hot-stage, the behaviour of the crystals was complex. They turned opaque at 68°C, and at 115°C gave the appearance of melting, only liquid remaining at 155°C. Further heating revealed recrystallization at 193°C and a final melt at 228°C. In contrast to the TGA traces which were invariant in appearance, DSC traces tended to vary considerably with heating rate. At a rate of 20°C min^{-1}, the DSC yielded two unresolved endotherms in the range 85-130°C corresponding to dehydration, indicating that this process is complex. A final fusion endotherm with onset temperature 222°C was also observed. The reported melting point of polymorph I of loperamide HCl is 224.4°C. As a final check on the identity of the material with that documented as the tetrahydrate,[1] the single crystal X-ray data described below were used to generate the powder pattern shown in Fig 1. This pattern was compared with the published pattern.[1] With one exception, all of the peaks shown in Fig 1 have counterparts with comparable intensities in the published pattern at corresponding 2θ-values, leaving no doubt of the identity of these two phases. The exception is a peak in the published pattern at 2θ = 11.25° which is absent from Fig 1 and also absent from our experimental pattern. The close match between our calculated and measured XRD patterns proves that there is no change in phase when the title compound is triturated. Fig 1, based on the single crystal data, may be regarded as the most reliable reference pattern for the title compound.[16] Recrystallization of loperamide HCl from ethanol-hexane mixtures yielded crystals with the same XRD trace as that shown.

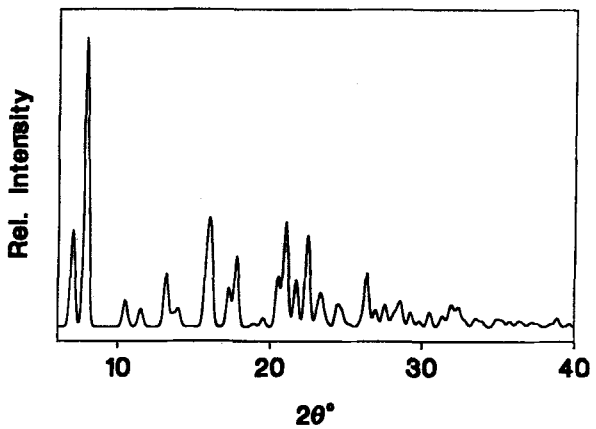

Figure 1 X-ray powder pattern for loperamide hydrochloride tetrahydrate calculated from the single crystal X-ray data.

Single crystal X-ray analysis

The structure of the formula unit is shown in Fig. 2. It consists of a discrete organic cation, a chloride ion and the equivalent of four water molecules. Each of O(1), O(2) and O(3) is in a general position with s.o.f. unity while the fourth water oxygen atom is disordered over

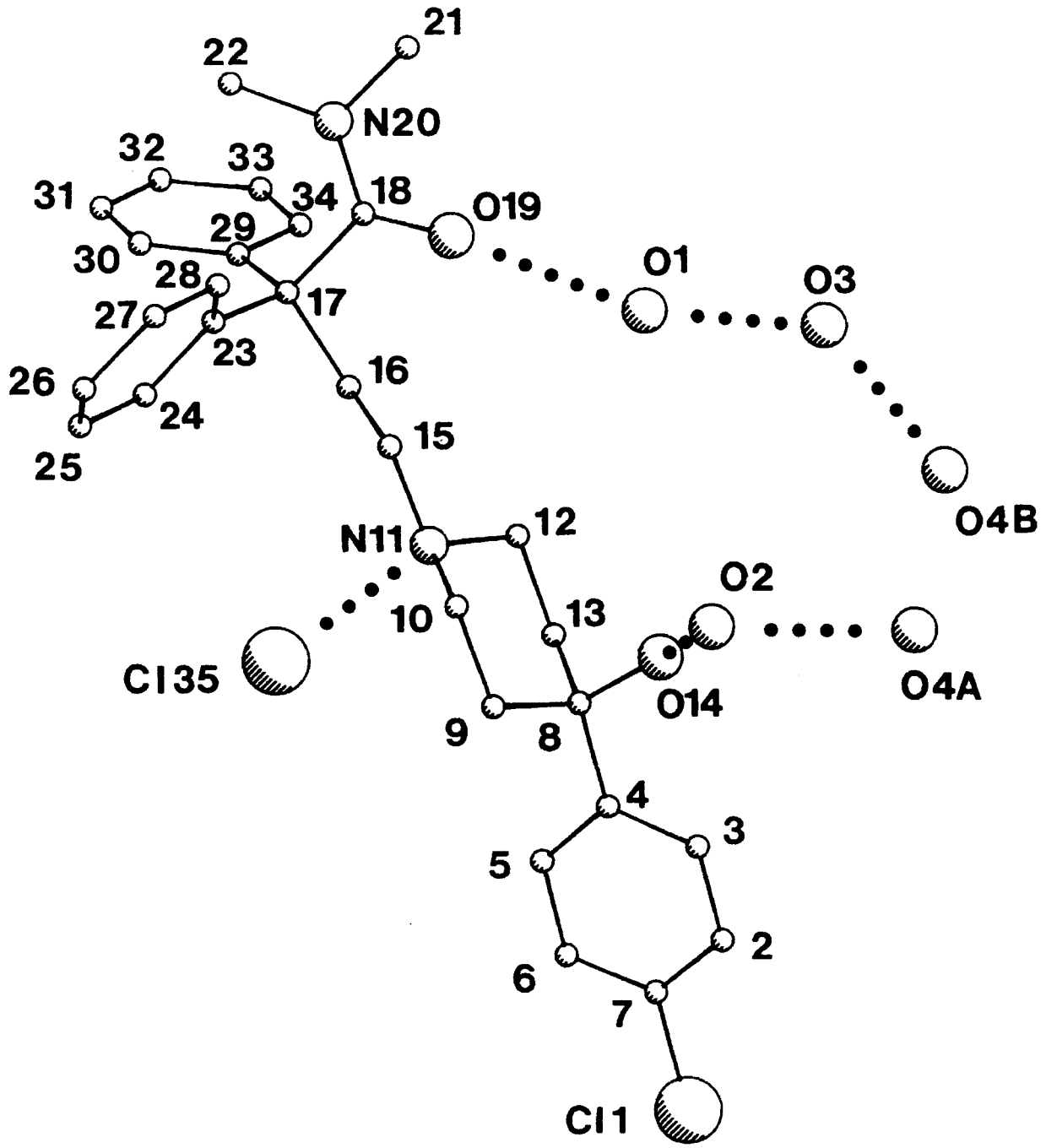

Figure 2 The conformation of the cation and hydrogen bonds (dotted lines) between atoms in the asymmetric unit. H atoms omitted for clarity.

two sites: O(4A) in a general position with refined s.o.f. 0.77 and O(4B) on a threefold axis with refined s.o.f. 0.25. This accounts for 4.0 water molecules per drug molecule in accordance with the microanalytical data.

Bond distances and bond angles appear in Table 3. In the cation, whose overall conformation is described by the torsion angles in Table 4, the piperidinium ring adopts a chair conformation with N(11) protonated and hydrogen bonded to the chloride ion, Cl(35). All bond distances agree with those reported for loperamide hydrate.[2] Hydrogen bonds associated with the asymmetric unit are indicated in Fig 2 and a complete list of O...O, N...Cl^- and O...Cl^- distances from which hydrogen bonding was inferred appears in Table 5. These distances are all reasonable, providing further support of adequate modelling of the water in the crystal structure.

A stereoview of the crystal packing around one of the threefold axes is shown in Fig 3. The cations pack with

Table 3 Bond lengths (Å) and bond angles (°); e.s.d.s are 0.01Å and 1°

Cl(1)	– C(7)	1.76	
C(2)	– C(3)	1.38	
C(2)	– C(7)	1.33	
C(3)	– C(4)	1.36	
C(4)	– C(5)	1.37	
C(4)	– C(8)	1.53	
C(5)	– C(6)	1.39	
C(6)	– C(7)	1.35	
C(8)	– C(9)	1.51	
C(8)	– C(13)	1.53	
C(8)	– O(14)	1.44	
C(9)	– C(10)	1.50	
C(10)	– N(11)	1.50	
N(11)	– C(12)	1.50	
N(11)	– C(15)	1.49	
C(12)	– C(13)	1.51	
C(15)	– C(16)	1.51	
C(16)	– C(17)	1.58	
C(17)	– C(18)	1.54	
C(17)	– C(23)	1.53	
C(17)	– C(29)	1.57	
C(18)	– O(19)	1.22	
C(18)	– N(20)	1.33	
N(20)	– C(21)	1.47	
N(20)	– C(22)	1.49	
C(23)	– C(24)	1.41	
C(23)	– C(28)	1.36	
C(24)	– C(25)	1.40	
C(25)	– C(26)	1.31	
C(26)	– C(27)	1.42	
C(27)	– C(28)	1.37	
C(29)	– C(30)	1.37	
C(29)	– C(34)	1.39	
C(30)	– C(31)	1.38	
C(31)	– C(32)	1.36	
C(32)	– C(33)	1.39	
C(33)	– C(34)	1.38	
C(3)	– C(2)	– C(7)	119
C(2)	– C(3)	– C(4)	122
C(3)	– C(4)	– C(8)	122
C(3)	– C(4)	– C(5)	117
C(5)	– C(4)	– C(8)	120
C(4)	– C(5)	– C(6)	121
C(5)	– C(6)	– C(7)	118
C(2)	– C(7)	– C(6)	122
Cl(1)	– C(7)	– C(6)	118
Cl(1)	– C(7)	– C(2)	119
C(4)	– C(8)	– O(14)	111
C(4)	– C(8)	– C(13)	110
C(4)	– C(8)	– C(9)	112
C(13)	– C(8)	– O(14)	107
C(9)	– C(8)	– O(14)	107
C(9)	– C(8)	– C(13)	109
C(8)	– C(9)	– C(10)	114
C(9)	– C(10)	– N(11)	111
C(10)	– N(11)	– C(15)	111
C(10)	– N(11)	– C(12)	109
C(12)	– N(11)	– C(15)	112
N(11)	– C(12)	– C(13)	111
C(8)	– C(13)	– C(12)	112
N(11)	– C(15)	– C(16)	112
C(15)	– C(16)	– C(17)	115
C(16)	– C(17)	– C(29)	106
C(16)	– C(17)	– C(23)	108
C(16)	– C(17)	– C(18)	108
C(23)	– C(17)	– C(29)	114
C(18)	– C(17)	– C(29)	108
C(18)	– C(17)	– C(23)	113
C(17)	– C(18)	– N(20)	121
C(17)	– C(18)	– O(19)	120
O(19)	– C(18)	– N(20)	119
C(18)	– N(20)	– C(22)	125
C(18)	– N(20)	– C(21)	120
C(21)	– N(20)	– C(22)	115
C(17)	– C(23)	– C(28)	122
C(17)	– C(23)	– C(24)	118
C(24)	– C(23)	– C(28)	119
C(23)	– C(24)	– C(25)	119
C(24)	– C(25)	– C(26)	122
C(25)	– C(26)	– C(27)	120
C(26)	– C(27)	– C(28)	119
C(23)	– C(28)	– C(27)	121
C(17)	– C(29)	– C(34)	118
C(17)	– C(29)	– C(30)	124
C(30)	– C(29)	– C(34)	118
C(29)	– C(30)	– C(31)	121
C(30)	– C(31)	– C(32)	121
C(31)	– C(32)	– C(33)	119
C(32)	– C(33)	– C(34)	120
C(29)	– C(34)	– C(33)	121

their long molecular axes nearly parallel to the crystal xy-plane. Their arrangement around the threefold axis generates a large cavity in which the water molecules and chloride ions are located. Within the cavity, extensive hydrogen bonding occurs between water molecules and between the drug molecules by mediation of water molecules. The topology of the cavity was studied using program MOLMAP.[17] The unit cell was sectioned at intervals of 0.05 (0.83Å) along the c-axis and the intersections of all atoms (represented with van der Waals radii) with each level were inspected. This revealed that the cavity spans a range z = 0.40 to 1.05 (10.9Å) while the range for the entrapped water molecules is z = 0.45 to

Table 4 Selected torsion angles (°)[a]

C(3)	– C(4)	– C(8)	– C(9)	−117
C(3)	– C(4)	– C(8)	– O(14)	3
C(4)	– C(8)	– C(9)	– C(10)	−175
C(8)	– C(9)	– C(10)	– N(11)	56
C(9)	– C(10)	– N(11)	– C(12)	−58
C(10)	– N(11)	– C(12)	– C(13)	59
N(11)	– C(12)	– C(13)	– C(8)	−57
C(9)	– C(8)	– C(13)	– C(12)	52
C(13)	– C(8)	– C(9)	– C(10)	−52
C(9)	– C(10)	– N(11)	– C(15)	178
C(10)	– N(11)	– C(15)	– C(16)	−173
N(11)	– C(15)	– C(16)	– C(17)	169
C(15)	– C(16)	– C(17)	– C(18)	74
C(15)	– C(16)	– C(17)	– C(23)	−48
C(15)	– C(16)	– C(17)	– C(29)	−171
C(16)	– C(17)	– C(18)	– N(20)	174
C(16)	– C(17)	– C(23)	– C(24)	−59
C(16)	– C(17)	– C(29)	– C(30)	121

[a]Average e.s.d. 1°

Table 5 Hydrogen bond distances (Å); e.s.d.s in parentheses

N(11)...Cl(35)	3.009(7)	O(3)...O(4B)	2.77(3)
O(14)...O(2)	2.76(2)	O(14)...O(3)^{i}	2.89(2)
O(19)...O(1)	2.81(2)	Cl(35)...O(1)^{ii}	3.11(1)
O(1)...O(3)	2.86(3)	Cl(35)...O(2)^{ii}	3.01(2)
O(2)...O(4A)	2.72(3)		

(i) = 1 − x + y, 1 − x, z (ii) = (2/3) − y, −(2/3) + x − y, (1/3) + z

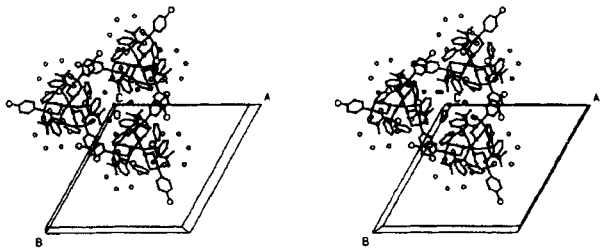

Figure 3 Stereoview showing the packing arrangement around the threefold axis. Entrapped water molecules are indicated as filled circles.

0.85 (6.7Å). As evident from Fig 3, the cavity is closed off at both ends along the c-axis by the sterically bulky N,N-dimethyl and α,α-diphenyl residues of three drug cations related by the rotation axis parallel to z. At z = 0.70, the cavity area in the xy-plane is a maximum with an approximate area 140Å^2 i.e. about one-third of the unit cell area. This section of the unit cell is shown in Fig 4.

The host drug molecule possesses structural features which could be conducive to inclusion of small guest molecules, namely steric bulk at one end, separated from hydrogen bonding functions (O-H, N$^+$-H) by a dimethylene chain and piperidinium ring 'spacer'. The propensity for hydrate formation is evident from the fact that the title compound was obtained by recrystallization of loperamide hydrochloride from absolute ethanol or from ethanol-hexane mixtures. Further studies of the potential of the anhydrous material for inclusion are being investigated using rigorously dry solvents.

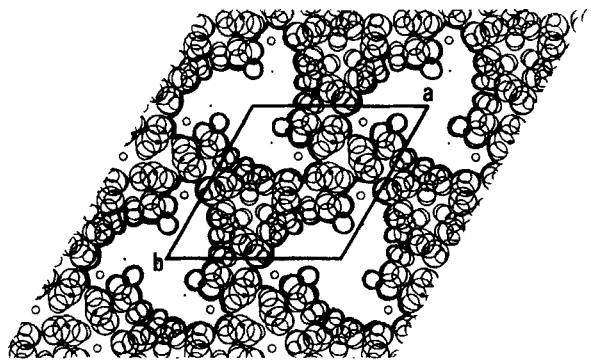

Figure 4 Section of the unit cell at z = 0.70 showing cavity area (unshaded). Water molecules have been omitted and host atoms are represented with van der Waals radii.

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