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The methanol disolvate and the dihydrate of fexofenadine, an antihistamine drug

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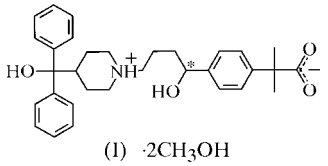
Fexofenadine [systematic name: (±)-(4-{1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidinium-1-yl]-butyl}phenyl)-2-methylpropionate], crystallizes in two forms, *viz*. as the methanol disolvate, $C_{32}H_{39}NO_4\cdot 2CH_4O$, and as the dihydrate, $C_{32}H_{39}NO_4\cdot 2H_2O$. It exists in the two structures as a zwitterion, which self-assembles as dimers sustained by a pair of charged-assisted N—H···OOC hydrogen bonds. In the methanol disolvate, the supramolecular organization consists of discrete fexofenadine dimers solvated by four molecules of methanol. The dihydrate structure is sustained by a more extended hydrogen-bonding scheme, wherein the hydrated dimeric entities are interlinked by additional hydrogen bonds. The fexofenadine molecule adopts different and differently disordered conformations of the 1-hydroxybutyl residue in the two structures.

Comment

We have been investigating the structural chemistry and pseudo-polymorphism of a series of pharmaceutical compounds (Tessler & Goldberg, 2004*a*,*b*, 2005*a*,*b*). Fexofenadine is an antihistamine used to relieve hay fever and allergy symptoms. The drug is administered orally in its hydrochloride form as the active ingredient. Fexofenadine was approved by the US Food and Drug Administration in July 1995. It works by preventing the activation of H1-receptor-containing cells by histamine, a chemical which is released in the body by other cells. Fexofenadine (*L*) contains several functional groups



(I) ·2CH_3OH
(II) ·2H_2O

with hydrogen-bonding capacity, and normally exists as a zwitterion. Therefore, not surprisingly, it forms sizeable single crystals more readily in a solvated (with polar and protic solvents) rather than a pure form, as co-crystallization with protic solvents allows for better (strain free) optimization of the hydrogen-bonding potential (Etter, 1991).

The conformational flexibility of *L* aids in the formation of pseudo-polymorphic crystals of this compound. In this context, we were able to crystallize and analyze (at *ca* 110 K) the structures of the methanol disolvate, (I), and the dihydrate, (II), of *L*. The corresponding molecular structures are illustrated in Fig. 1, showing the different conformations of the molecular framework.

The main conformational degrees of freedom of the fexofenadine framework are about the C7—C14 and C26—C29 single bonds, and atoms C19–C22 in the central aliphatic chain (Tables 1 and 2). Inspection of the torsion angles indicates a minor difference between the two structures in the conformation about the C7—C14 bond. More significant variation is associated with the rotation of the α,α-dimethylacetic acid residue with respect to the adjacent benzene ring in (I) and (II), in order to optimize the corresponding intermolecular interaction scheme (see below). However, the most distinct flexibility is apparent in the N1—C19—C20—C21 and C19—C20—C21—C22 torsion angles (Tables 1 and 3). They impart a bent molecular framework structure in (I), as opposed to a more extended conformation in (II). The disorder of the O2—H functions, with C20—C21—C22—O2*A* torsion angles of 59.4 (3)° in (I) and 60.6 (4)° in (II) at the major site, but with

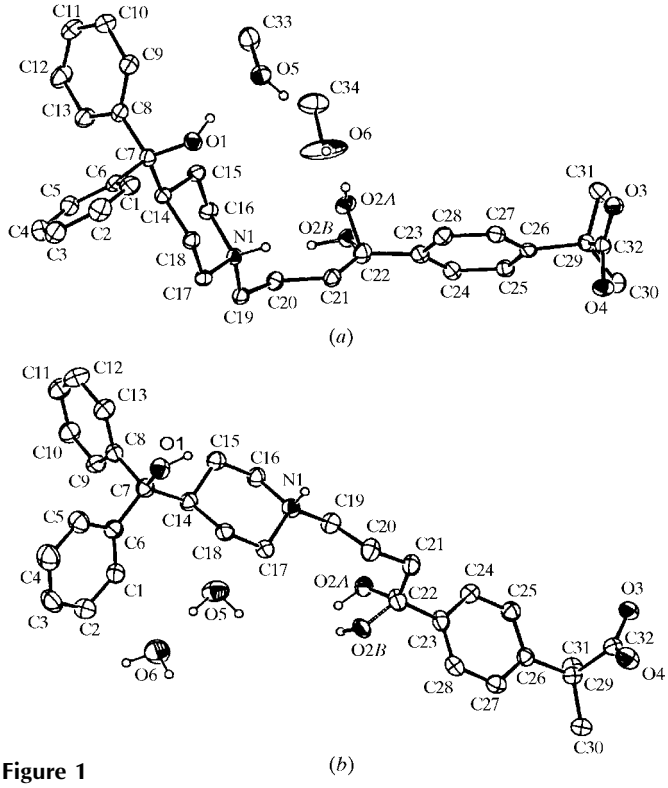


Figure 1
The molecular structure of (*a*) (I) and (*b*) (II), showing the atom-labelling schemes. Displacement ellipsoids are drawn at the 50% probability level at *ca* 110 K. Both of the disordered positions for atom O2 are shown (O2*A* and O2*B*). H atoms bound to N and O atoms are involved in the hydrogen bonding and are shown; all other H atoms have been omitted for clarity.

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C20—C21—C22—O2*B* torsion angles of −5.6 (7)° in (I) and −28.8 (4)° in (II) at the minor site, further attests to the conformational flexibility of *L*.

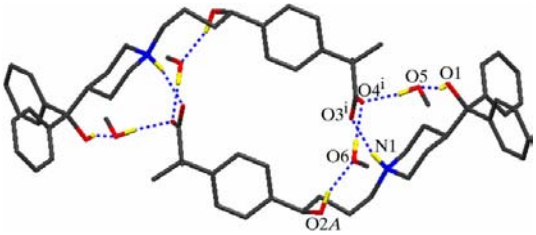

Figure 2
The hydrogen-bonding assembly mode in (I), showing the fexofenadine dimer solvated by four molecules of methanol. The dimer consists of molecules related by inversion at $(\frac{1}{2}, \frac{1}{2}, 1)$. Only the major disordered site (O2*A*) is shown. H atoms have been omitted for clarity, except for those attached to N and O atoms that are involved in the hydrogen bonding. Hydrogen bonds are denoted by dashed lines. [Symmetry code: (i) $1-x$, $1-y$, $2-z$.]

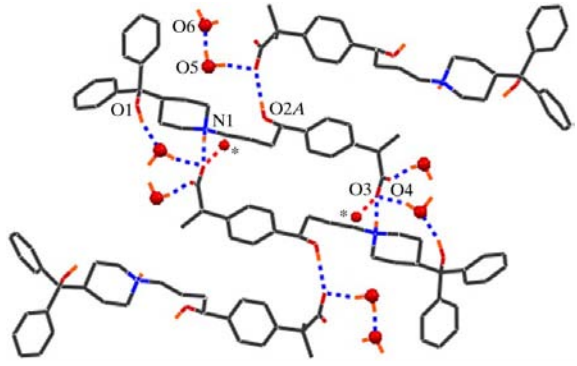

Figure 3
The hydrogen-bonding assembly mode in (II), showing the fexofenadine dimer solvated by molecules of water (shown as small spheres), and further hydrogen bonding of this dimer to neighbouring molecules through atoms O2 and O3 [only the major disordered site (O2*A*) is shown; see also Table 4]. The dimer consists of molecules related by inversion at $(1, 0, \frac{1}{2})$. H atoms have been omitted for clarity, except for those attached to N and O atoms that are involved in the hydrogen bonding. Hydrogen bonds are denoted by dashed lines. The spheres marked with an asterisk (without H atoms attached to them) mark the O2*A* sites of two additional molecules of fexofenadine hydrogen bonded to the carboxylate groups of the central dimer.

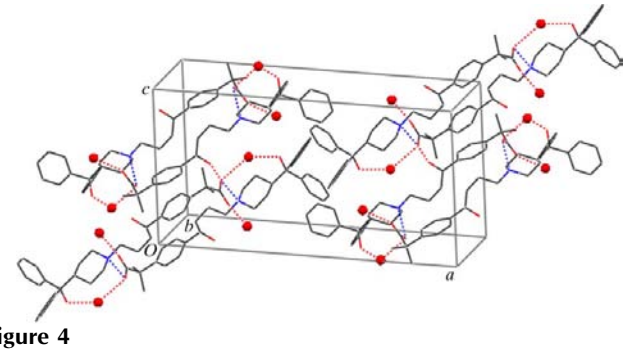

Figure 4
The crystal packing of (II), showing four fexofenadine dimers and the solvent water molecules (small spheres). Hydrogen bonds are denoted by dashed lines. H atoms have been omitted for clarity. The dimeric entities are distributed between two different continuously hydrogen-bonded layers formed in the crystal which are centered at $x = 0$ and $x = 1$. At the interface between the layers (at $x = \frac{1}{2}$), the diphenylmethyl embraces provide the stabilizing van der Waals interaction.

The above conformational details (Tables 1 and 2) are closely related to the intermolecular interaction patterns revealed by the two crystals. The most dominant intermolecular interaction in both structures is the charge-assisted hydrogen-bonding attraction between the NH^+ and the COO^- sites of adjacent molecules (Jeffrey, 1997). This leads to the formation of dimeric entities paired by two $NH^+\cdots COO^-$ hydrogen bonds between molecules related to each other by crystallographic inversion (Tables 3 and 4).

In (I), the two methanol molecules incorporated into the lattice provide the solvation environment as H-atom acceptors for the two hydroxylic acid functions O1—H and O2—H (disordered as O2*A* and O2*B*), which point to the concave side of the paired molecules, by hydrogen bonding (Table 2). Each methanol species also solvates the carboxylate function by donating its H atom to the second carboxylate O atom (O4). The hydrogen-bonded clusters in this structure consist of two molecules of fexofenadine and four molecules of methanol, and have an oval shape (Fig. 2 and Table 3). The crystal packing of these discrete hydrogen-bonded clusters in (I) is stabilized by common dispersion between their lipophilic C—H lined surfaces.

While similar $NH^+\cdots COO^-$ bound dimers form in structure (II) around inversion centres, the different conformation of the fexofenadine framework causes the O2—H site to point outward and be exposed on the periphery of the dimeric entities to hydrogen-bonding interaction with neighbouring dimers (Fig. 3). This results in the formation of an extended hydrogen-bonding pattern that propagates continuously throughout the crystal within molecular layers perpendicular to the *a* axis and centered at $x = 0$ (Fig. 4). The water molecules incorporated into (II) take part in the solvation of one of the hydroxylic acid functions (O1—H) and of the carboxylate anion. In this structure, the fexofenadine dimers are interlinked with neighbouring dimeric entities by four additional hydrogen bonds, utilizing to this end the disordered O2—H H-atom donors and the COO^- H-atom acceptors (Table 4). The crystal packing of the hydrogen-bonded layers in (II) is illustrated in Fig. 4.

All bond lengths and angles are in normal ranges (Cambridge Structural Database, Version 5.26, update of November 2004; Allen, 2002), including indication of partial delocalization of the electron density within the C32—O3 and C32—O4 bonds of the carboxylate group, which is consistent with the zwitterionic nature of *L*. To our knowledge, this is the first crystallographic report of the fexofenadine structure (Allen, 2002).

Experimental

Crude fexofenadine powder was obtained from Teva Pharmaceutical Industries Ltd. Compound (I) was crystallized by slow evaporation from methanol. Compound (II) was crystallized by slow evaporation from wet acetonitrile. Thermal analyses of both compounds confirmed their chemical purity. In both cases, the crystals obtained were characterized by relatively high mosaicity, which is most probably affected by the conformational disorder of the fexofenadine compound, and yielded generally weak diffraction. Correspondingly,

the crystallographic refinements were based on data sets containing a high percentage of weak reflections and they concluded in relatively high R values. Attempts to crystallize unsolvated fexofenadine were not successful.

Compound (I)

Crystal data

$C_{32}H_{39}NO_4\cdot 2CH_4O$
$M_r = 565.73$
Monoclinic, $P2_1/c$
$a = 20.8661$ (3) Å
$b = 9.6138$ (2) Å
$c = 16.0702$ (5) Å
$\beta = 107.8870$ (8)°
$V = 3067.90$ (12) Å^3
$Z = 4$
$D_x = 1.225$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6836 reflections
$\theta = 2.1$–27.9°
$\mu = 0.08$ mm^{-1}
$T = 110$ (2) K
Prism, colourless
0.30 × 0.25 × 0.25 mm

Data collection

Nonius KappaCCD area-detector diffractometer
0.8° φ and ω scans
22588 measured reflections
7172 independent reflections
4405 reflections with $I > 2\sigma(I)$
$R_{int} = 0.072$
$\theta_{max} = 27.9°$
$h = -27 \rightarrow 25$
$k = -11 \rightarrow 11$
$l = -21 \rightarrow 21$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.064$
$wR(F^2) = 0.168$
$S = 1.00$
7172 reflections
396 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0734P)^2 + 1.5166P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.007$
$\Delta\rho_{max} = 0.42$ e Å^{-3}
$\Delta\rho_{min} = -0.41$ e Å^{-3}

Table 1
Selected torsion angles (°) for (I).

O1—C7—C14—C15	−64.3 (2)	C20—C21—C22—O2*A*	59.4 (3)
O1—C7—C14—C18	58.0 (2)	C20—C21—C22—C23	−173.0 (2)
N1—C19—C20—C21	71.4 (2)	C25—C26—C29—C32	−154.8 (2)
C19—C20—C21—C22	−168.4 (2)	C27—C26—C29—C32	30.4 (3)
C20—C21—C22—O2*B*	−5.6 (7)		

Table 2
Selected torsion angles (°) for (II).

O1—C7—C14—C15	−72.1 (3)	C20—C21—C22—O2*B*	−28.8 (4)
O1—C7—C14—C18	50.9 (3)	C20—C21—C22—C23	−167.5 (3)
N1—C19—C20—C21	−179.0 (3)	C25—C26—C29—C32	65.1 (3)
C19—C20—C21—C22	−65.2 (4)	C27—C26—C29—C32	−114.4 (3)
C20—C21—C22—O2*A*	60.6 (4)		

Compound (II)

Crystal data

$C_{32}H_{39}NO_4\cdot 2H_2O$
$M_r = 537.67$
Monoclinic, $P2_1/c$
$a = 23.8180$ (9) Å
$b = 9.8444$ (3) Å
$c = 12.3959$ (4) Å
$\beta = 93.1770$ (12)°
$V = 2902.05$ (17) Å^3
$Z = 4$
$D_x = 1.231$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 5703 reflections
$\theta = 2.2$–27.9°
$\mu = 0.08$ mm^{-1}
$T = 110$ (2) K
Chunk, colourless
0.25 × 0.15 × 0.15 mm

Data collection

Nonius KappaCCD area-detector diffractometer
0.4° φ scans
19430 measured reflections
6860 independent reflections
3243 reflections with $I > 2\sigma(I)$
$R_{int} = 0.082$
$\theta_{max} = 27.9°$
$h = -31 \rightarrow 31$
$k = -12 \rightarrow 12$
$l = -15 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.073$
$wR(F^2) = 0.214$
$S = 0.99$
6860 reflections
373 parameters
H atom: as for (I)
$w = 1/[\sigma^2(F_o^2) + (0.0992P)^2 + 0.8167P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.004$
$\Delta\rho_{max} = 0.37$ e Å^{-3}
$\Delta\rho_{min} = -0.26$ e Å^{-3}

Table 3
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O5	0.93 (3)	1.86 (3)	2.763 (2)	163 (3)
O2*A*—H2O*A*···O6	0.92	1.80	2.680 (3)	162
N1—H1N···O3^{i}	0.92 (3)	1.88 (3)	2.772 (2)	163 (2)
O5—H5O···O4^{i}	0.88 (3)	1.90 (3)	2.756 (3)	166 (3)
O6—H6O···O4^{i}	0.93 (4)	1.74 (4)	2.666 (3)	175 (4)

Symmetry code: (i) $-x+1, -y+1, -z+2$.

Table 4
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O5^{i}	0.86 (5)	2.00 (5)	2.822 (3)	160 (4)
O2*A*—H2O*A*···O3^{ii}	0.92	1.85	2.758 (3)	168
O2*B*—H2O*B*···O3^{ii}	0.84	2.05	2.897 (3)	180
N1—H1N···O3^{iii}	0.96 (3)	1.81 (3)	2.768 (3)	174 (3)
O5—H5*A*O···O3^{ii}	1.00	1.89	2.868 (3)	164
O5—H5*B*O···O6	0.97	1.81	2.776 (3)	174
O6—H6*B*O···O4^{iv}	0.95	1.80	2.741 (3)	172

Symmetry codes: (i) $x, -y+\frac{1}{2}, z-\frac{1}{2}$; (ii) $-x+2, y+\frac{1}{2}, -z+\frac{3}{2}$; (iii) $-x+2, -y, -z+1$; (iv) $-x+2, -y+1, -z+1$.

Both compounds reveal structural disorder, which results in two posssible positions for the central O2—H group in each structure. In the refined structural models, the relative occupancies of these positions refined to 0.867 (5) (O2*A*) and 0.133 (5) (O2*B*) in (I), and 0.573 (5) (O2*A*) and O.427 (5) (O2*B*) in (II), while the bond lengths for C22—O2*A* and C22—O2*B* were restrained to be similar. In both structures, the methyl H atoms were constrained to an ideal geometry, with C—H = 0.98 Å and U_{iso}(H) = 1.5U_{eq}(C), but were allowed to rotate freely about the parent C—C bonds. All other H atoms bound to C atoms were placed in idealized positions and were constrained to ride on their parent atoms, with C—H distances in the range 0.95–0.99 Å and with U_{iso}(H) = 1.2U_{eq}(C). In (I), H atoms attached to N and O atoms (except for the minor O2*B* site) were located in difference Fourier maps and their parameters were refined freely (except for the H atom attached to O2*A*, which did not refine well and was fixed in its initial position). The H atom attached to atom O2*B* was fixed in an initially calculated position, with U_{iso}(H) = 1.2U_{eq}(O2*B*). In (II), only H atoms bound to atoms O1 and N1 were located in a difference Fourier map and their parameters were refined freely. The H atoms attached to the disordered O2*A* and O2*B* sites, as well as water H atoms, were placed in calculated positions by taking into account the most probable hydrogen-bonding interactions, as indicated by O···O intermolecular distances < 3.0 Å. These H atoms did not refine well and were

subsequently held fixed in their initial positions. The U_{iso}(H) parameters were refined for the water H atoms, while the H atoms on O2*A* and O2*B* were assigned $U_{iso}(H) = 1.2U_{eq}(O)$.

For both compounds, data collection: *COLLECT* (Nonius, 1999); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *DENZO*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *MERCURY* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1187). Services for accessing these data are described at the back of the journal.

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