International Journal of Pharmaceutics 398 (2010) 50–60

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Further study of (±)-mefloquinium chloride solvates. Crystal structures of the hemihydrate and monohydrate of (±)-mefloquinium chloride, from data collected at 120 K

Altivo Pitaluga Jr.[a], Lívia D. Prado[a], Rafael Seiceira[a], James L. Wardell[b,c], Solange M.S.V. Wardell[a,*]

[a] Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos – Farmanguinhos, R. Sizenando Nabuco, 100, Manguinhos, 21041-250, Rio de Janeiro, RJ, Brazil
[b] Department of Chemistry, University of Aberdeen, Meston Walk, Old Aberdeen, AB24 3UE, Scotland, United Kingdom
[c] Centro de Desenvolvimento Tecnológico em Saúde (CDTS), Fundação Oswaldo Cruz (FIOCRUZ), Casa Amarela, Campus de Manguinhos, Av. Brasil 4365, 21040-900, Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 20 January 2010
Received in revised form 13 July 2010
Accepted 15 July 2010
Available online 30 July 2010

Keywords:
Mefloquine
Solvates
Hydrates
Crystal structures
Near IR
Powder diffraction patterns
DSC

ABSTRACT

The crystal structure of a monohydrate of (±)-mefloquinium chloride, (±)-**[MEFHCl·(H_2O)]**, has been obtained from data collected at 120 K. Further details of the crystal structure of a hemihydrate, (±)-**[MEFHCl·½(H_2O)]**, previously determined at room temperature, are also reported from data collected at 120 K. The structural data, along with X-ray powder patterns, infrared spectra (both mid and near IR ranges) and DSC data, provide definitive evidence for the two hydrates. Further attempts to completely resolve the crystal structure of a tetragonal solvated phase failed due to the considerable disorder, involving the solvates, either water or methanol, even at 120 K, however X-ray powder pattern and infrared spectral and DSC data for this phase are also reported. Comparisons of the data obtained for the hydrates in this study, with X-ray powder patterns and mid-infrared spectra of previously reported forms of (±)-mefloquinium chloride have highlighted erroneous assignments and allowed structural identification of previously and differently designated forms.

1. Introduction

Malaria is currently one of the world's major health problems accounting for more than two millions death each year. In South and Central Americas, 50% of the reported cases are in the Brazilian Amazon rain Forest. (R*, S*)-(±)-α-2-piperidinyl-2,8-bis (trifluoromethyl)-4-quinolinemethanol hydrochloride or (±)-mefloquinium hydrochloride, was a particularly effective antimalarial agent, when first introduced in 1971, and, because of its long half-life, was a good prophylactic. However, due to the increasing resistance by the parasites involved in malaria, mefloquine hydrochloride is now been used combined with other agents in fixed-dose combination (Newton and White, 1999; Wilairatana et al., 2002; Kremsner and Krishna, 2004).

Mefloquine base has two chiral centres and thus has four stereoisomers. The commercial drug substance, orally administered as the hydrochloride salt, is a racemic mixture of the *erythro* isomers (see Fig. 1). Both enantiomers have been shown to be active (Karle and Karle, 2002).

Being an important drug substance, much investigation has been carried out on the polymorphs and solvates of (±)-mefloquinium chloride. This is so since physical–chemical stability, biological utilization and therapeutic activity are strongly influenced by the crystalline form of a drug substance. A number of polymorphic and solvated forms of (±)-mefloquinium chloride have been cited, using, in the main, evidence collected from powder diffraction, DSC and infrared spectroscopic data. However different notation systems, e.g., A, B, C, etc. or α, β, γ, etc., have been employed by different authors for (±)-mefloquinium chloride forms, obtained by different procedures from studies using combinations of using thermal analysis, IR, and X-ray powder diffraction and other techniques.

In a 1986 patent (Bömches and Hardegger, 1986), five forms were indicated: A (anhydrous), B (acetone solvate), C, D and E (hydrates), while in an earlier patent (Bömches and Hardegger, 1985), the E-form was not mentioned at all. Kitamura et al. (1994) listed eight forms: A, B′, and M (all anhydrous), E (ethanol solvate), B (acetone solvate), I (isopropanol solvate), and C and D (hydrate). A further patent in 2005 (Sinden et al., 2005.) indicated the following forms: A, B and C (obtained from aqueous ethanol), G (methyl ethyl ketone solvate), D (a desolvated ethyl methyl ketone solvate), E (acetone solvate) and F (THF solvate). Kiss et al. (1994), reported formation of the following forms: α and δ (hydrates), β and γ

* Corresponding author.
E-mail address: solangewardell@yahoo.co.uk (S.M.S.V. Wardell).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.07.034

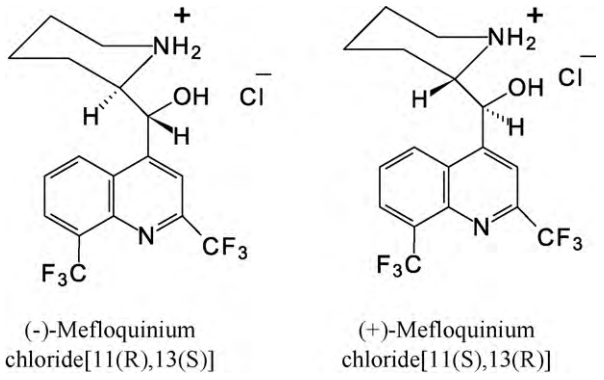


Fig. 1. *erythro* isomers of mefloquinium chloride.

(anhydrous), ε (acetone solvate) and θ (THF solvate). Furthermore, heating the δ, ε or θ forms led to further forms.

It is particularly confusing when similar procedures are quoted as providing differently notated species having different physical properties. The unreliability of some of interpretations is shown when, for example, the intensive carbonyl stretching vibration cannot be observed in the infrared spectrum of a form assigned as an acetone solvate. Indeed, the evidence is far from convincing that a notated form is indeed a unique and pure form. Of some interest was the report by Kitamura et al. (1994) that their ethanol solvate had the same powder diffraction pattern as that of a sample grown from methanol. Interestingly, also, are the statements, in the 2005 Patent (Sinden et al., 2005), that no classical hydrates can be formed from aqueous solvents and that the 1/4 hydrate, reported by Karle and Karle (2002), see later, is explained by residual water in channels within the crystal lattice.

A technique which could resolve assignments of structure is single crystal X-ray diffraction. The only X-ray crystal structures reported for mefloquinium chloride samples are for (i) an orthorhombic form of (−)-mefloquinium chloride·(1/4)H_2O from data collected at room temperature (Karle and Karle, 2002: space group $P2_12_12_1$), (ii) a monoclinic monohydrate form of (±)-mefloquinium chloride, solved from data collected at room temperature (Skórska et al., 2006: space group $C2/c$) and (iii) a tetragonal species, assumed to be a methanol solvate of (±)-mefloquinium chloride (Karle and Karle, 1991: space group $P4_2/n$) also from data collected at room temperature.

In the work presented here, we have looked at (±)-mefloquinium chloride samples obtained by crystallisation from methanol, ethanol, isopropanol, ethyl acetate, acetone or acetonitrile solutions, with an emphasis on single crystal X-ray studies.

From single crystal X-ray diffraction data collected at 120 K, we have obtained evidence for three distinct phases, two of which coincide with those previously reported by Skórska et al. (2006) and Karle and Karle (1991). The third phase is a hemihydrate, whose structures has not previously been determined by single crystallography. The structures solved from the 120 K data are discussed with the structures obtained at room temperature.

X-ray powder patterns, DSC data and infrared spectra have been obtained for the authenticated phases and compared with data for phases reported in the literature.

2. Results and discussion

2.1. Crystal preparation

Samples of (±)-*erythro*-mefloquinium chloride from the same industrial batch were recrystallised from different solvents under two different sets of conditions: (i) a saturated solution at near reflux temperatures was allowed to cool and crystallise with limited contact with air and (ii) dilute solutions were allowed to slowly evaporate at 5 °C again with limited contact with air. Table 1 lists the systems which produced single crystals and the space groups subsequently determined by X-ray crystallography at 120 K. Solvents had been previously dried using published procedures.

All recrystallisations from concentrated solutions allowed to cool from near reflux temperatures gave the (±)-monohydrate-form, regardless of the solvent used [MeOH, EtOH or EtOAc]. The structure of this (±)-monohydrate-form [space group space group $C2/c$] had been previously solved from room temperature data (Skórska et al., 2006). We have used (±)-**[MEFHCl·(H_2O)]** to designate this hydrate. From the 120 K data, we have managed to extract more details of the hydrogen bonding and the supramolecular arrangements. The crystals for Skórska et al.'s sample had been obtained from a solution containing mefloquine hydrochloride and $CoCl_2·6H_2O$. The water solvate in our samples apparent came from ingress of moisture to the recrystallation media. The finding of the formation of the monohydrate using MeOH, EtOH or EtOAc, is in contrast with those in several of the earlier publications.

The samples recrystallised by slow evaporation of non-saturated solutions in isopropanol or acetone at room temperature produced the (±)-hemihydrate-form, designated as (±)-**[MEFHCl·½(H_2O)]**. The hemihydrate form was also isolated from a reaction mixture containing **MEFHCl** and hydrated copper acetate in methanol. No previous crystal structure of this form has been reported.

The tetragonal ($P4_2/n$), crystals obtained from a 1:1 acetonitrile/methanol solution at room temperature, were found to be the same as a solvate solved by Karle and Karle (1991), from data collected at room temperature. Karle and Karle (1991) had some reservations regarding the particular solvate present. In the abstract of their 1991 article, entitled "Structure of the antimalarial (±)-mefloquine hydrochloride", it was reported that the structure reported was that of a ½ methanol solvate. However, doubts about whether or not the solvate was indeed methanol, or water, were made apparent in the article. The solvate, whatever it may or may not have been, resided in channels of the structure. A further indication of doubt was provided by the cif-file's lack of mention of any solvate. Our synchrotron120 K data, unfortunately, did not improve on the earlier room temperature solution, due both to the considerable disordered of the solvate molecules and to the less than ideal crystals. Hence the nature of the solvate thus still remains unsolved.

Table 1
Samples used in the single crystal X-ray structure determinations.

Sample	Solvent of crystallisation	[g/ml]	Form obtained	Structure space group.
A	Methanol	Saturated[a]	Monohydrate	Monoclinic/$C2/c$
B	Ethyl acetate	Saturated[a]	Monohydrate	Monoclinic/$C2/c$
C	Ethanol	Saturated[a]	Monohydrate	Monoclinic/$C2/c$
D	Isopropanol	0.037[b]	Hemihydrate	Triclinic/$P-1$
E	Acetone	0.004[b]	Hemihydrate	Triclinic/$P-1$
F	Acetonitrile/methanol(1:1)	0.005[b]	Solvate	Tetragonal/$P42/n$

[a] Hot saturated solution allowed to stand at room temperature with limited access to the atmosphere.
[b] Dilute solution lowly evaporated at 5 °C with limited contact with air.

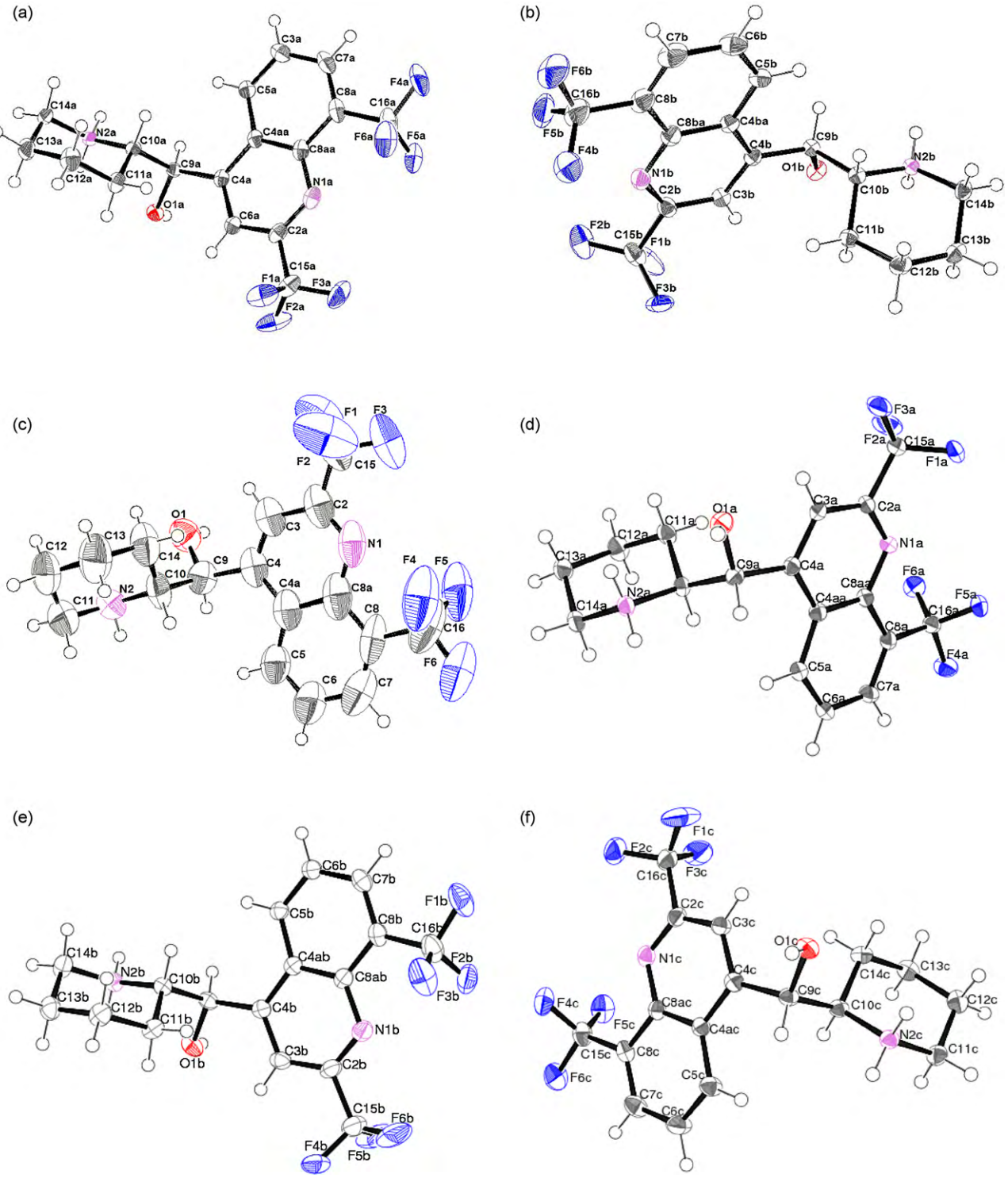


Fig. 2. Atom arrangements, numbering schemes and intramolecular H-bonds for (a) and (b) cation A and cation B of (±)-**[MEFHCl·½(H$_2$O)]**; (c) cation tetragonal solvated of (±)-**[MEFHCl]**, (d)–(f) cations a, b, and c of (±)-**[MEFHCl·(H$_2$O)]**. Probability ellipsoids are drawn at the 50% level. Hydrogen atoms are drawn as spheres of arbitrary radius.

Apart from changes in the cell dimensions resulting from the different temperatures used to collect data, there are no discrepancies between the data. Where we have need to refer to this phase, we have used the notation tetragonal-solvated-(±)-**[MEFHCl]**. It is of some interest that the simulated powder pattern from our diffraction data, using the MERCURY program, essentially concurred with that reported for a hydrated phase, C, reported by Kitamura et al. (1994), see later.

2.2. Crystal structures

2.2.1. General

The species, (±)-**[MEFHCl·½(H$_2$O)]**, crystallises in the non-chiral space group, $P\bar{1}$, with an asymmetric unit consisting of two mefloquinium cations, two chloride ions and one water molecule. The two cations are enantiomers, differing slightly in their conformations and in their hydrogen bonding arrangements, see later. As

Table 2
Hydrogen bonding parameters (Å,°), for (±)-**[MEFHCl·½(H$_2$O)]**.

D–H···A	Symmetry operation	D–H	H···A	D···A	D–H···A
O1A–H1A···Cl2	$x,1+y,z$	0.84	2.28	3.0995(12)	164
O1B–H1B···Cl1	$1-x,1-y,1-z$	0.84	2.26	3.0870(12)	170
N2A–H2A···Cl2	$1+x,y,z$	0.959(19)	2.197(19)	3.0679(15)	150.5(15)
N2B–H2B···Cl1	$-x,1-y,1-z$	0.844(19)	2.529(18)	3.2210(15)	140.0(16)
N2A–H2C···Cl1		0.916(18)	2.344(18)	3.1819(14)	152.0(15)
N2A–H2C···O1A		0.916(18)	2.441(18)	2.7792(17)	102.0(13)
N2B–H2D···Cl2		0.934(18)	2.369(18)	3.2134(15)	150.2(15)
N2B–H2D···O1B		0.934(18)	2.327(18)	2.7052(17)	103.7(13)
OW1–HW1···OW1	$-x,2-y,1-z$	0.85(2)	1.11(4)	1.867(4)	144(6)
N2B–H2B···OW1	$-x,1-y,1-z$	0.844(19)	2.370(19)	2.935(3)	124.9(15)
C3B–H3B···O1B		0.95	2.41	2.7518(19)	101
C6A–H6A···O1A		0.95	2.44	2.776(2)	101
C11A–H11B···O1A		0.99	2.59	2.930(2)	100
C5A–H5A···Cl2	$1+x,y,z$	0.95	2.82	3.7608(18)	173
C14A–H14B···O1A	$1+x,y,z$	0.99	2.43	3.374(2)	160
C14B–H14C···O1B	$-1+x,y,z$	0.99	2.44	3.385(2)	160

Table 3
Hydrogen bonding parameters (Å,°), for (±)-**[MEFHCl·(H$_2$O)]**.

D–H···A	Symmetry operation	D–H	H···A	D···A	D–H···A
N2–H2A···Cl1		0.90(3)	2.39(2)	3.193(2)	149(2)
N2A–H2AA···O1C		0.90(3)	2.56(3)	3.080(3)	117(2)
N2B–H2BB···Cl3		0.88(3)	2.24(3)	3.114(2)	172(3)
N2B–H2BB···Cl2	$1-x,1+y,1/2-z$	0.99(3)	2.25(3)	3.169(2)	155(2)
N2C–HCA···Cl1		0.92(3)	2.20(3)	3.098(2)	164(3)
N2C–HCB···Cl2	$x,1+y,z$	0.99(3)	2.12(3)	3.098(2)	172(3)
O1–H1···Cl3	$1-x,y,1/2-z$	0.84	2.26	3.0934(18)	170
O1B–H1B···Cl1	$1-x,y,1/2-z$	0.84	2.24	3.070(2)	170
O1C–H1C···Cl3	$1-x,y,1/2-z$	0.84	2.30	3.1277(18)	172
N2A–H2AB···OW1		0.97(3)	1.80(3)	2.733(3)	159(3)
OW1–HW1A···Cl2		0.855(12)	2.319(12)	3.172(2)	174(2)
OW1–HW1B···OW2		0.85(2)	1.965(18)	2.802(3)	168(3)
OW2–HW2A···Cl3	$1-x,y,1/2-z$	0.86(3)	2.55(3)	3.315(3)	150(3)
OW4–HW4A···Cl3	$3/2-x,3/2-y,1-z$	0.85(6)	2.67(6)	3.408(6)	147(6)
OW4–HW4B···Cl3		0.85(6)	2.39(7)	3.203(6)	160(6)
C3A–H3A···O1A		0.95	2.35	2.714(3)	102
C5A–H5A···Cl1		0.95	2.56	3.491(2)	168
C7A–H7A···Cl1	$1-x,y,1/2-z$	0.95	2.83	3.495(2)	128
C3B–H3B···O1B		0.95	2.37	2.726(3)	102
C3C–H3C···O1C		0.95	2.49	2.816(3)	100
C5C–H5C···Cl2	$x,1+y,z$	0.95	2.80	3.740(3)	172

found by Skórska et al., the asymmetric unit of (±)-**[MEFHCl·(H$_2$O)]** is composed of three mefloquinium cations [two of one hand and one of the other], three chloride ions and three water molecules. Again as this crystallises in the non-chiral space group, *C*2/*c*, an equal number of each enantiomer must be present in the crystalline bulk.

PLATON analyses (Spek, 2003) were generally used to obtain parameters for hydrogen bonding and other interactions. These are

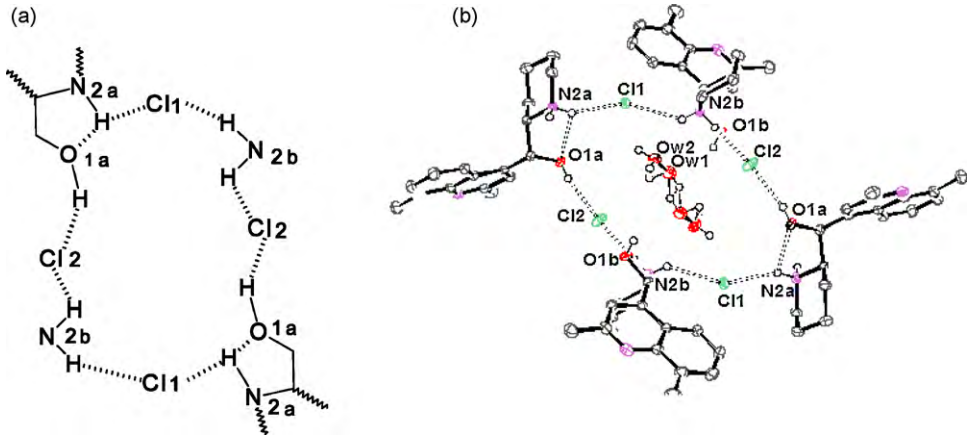


Fig. 3. (±)-**[MEFHCl·½(H$_2$O)]**. (a) Schematic of the ring formed from O1A–H1A···Cl2, N2B–H2B···Cl1, N2A–H2C···Cl1, N2A–H2C···O1A and N2B–H2D···Cl2 hydrogen bonds, (b) view looking down the cavity generated for the linked rings showing the encaged disordered water molecules: NB O1b is involved in linking rings and not forming rings, the CF_3 groups and selected hydrogens have been removed for clarity. Symmetry operations are listed in Table 2.

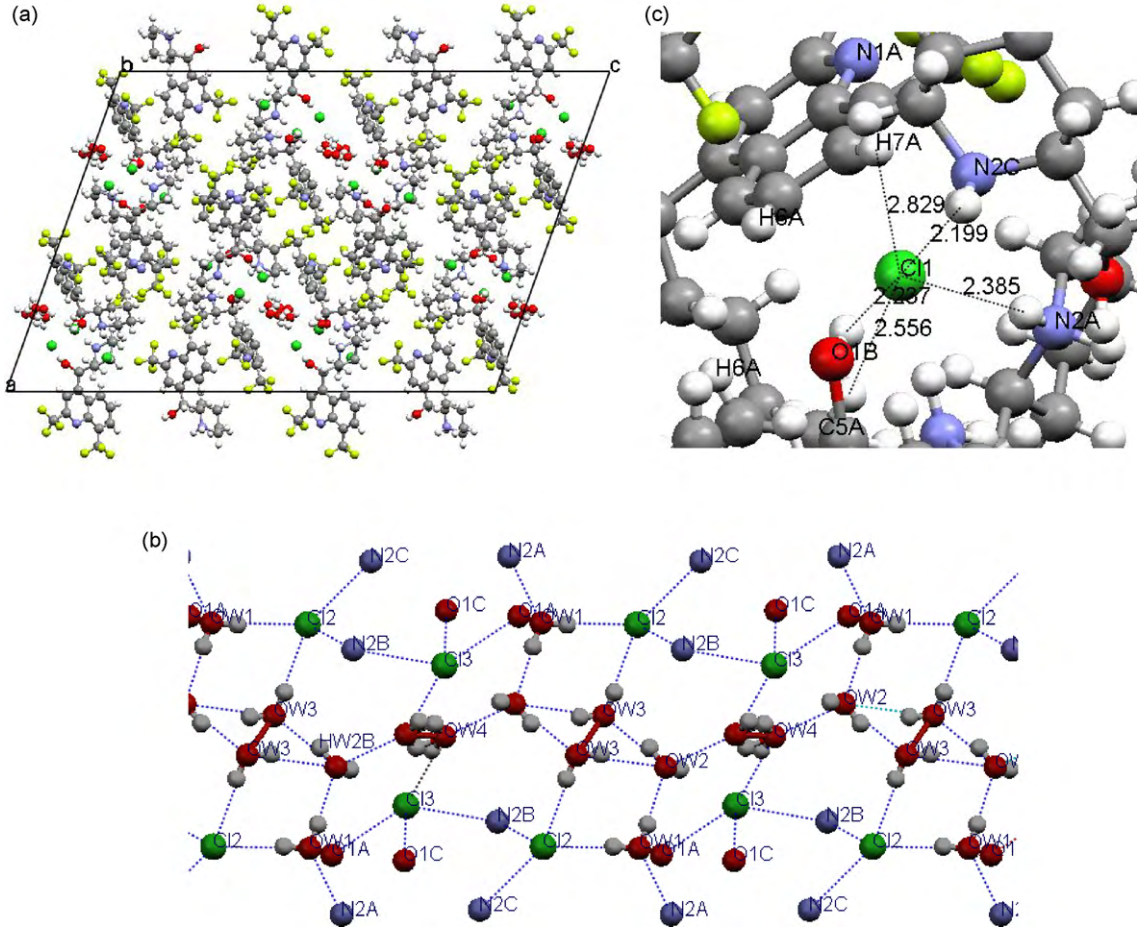


Fig. 4. (±)-**[MEFHCl·(H$_2$O)]**. (a) Packing looking down b. (b) The arrangements of hydrogen bonds looking down a. Only the atoms of the mefloquinium cations actively involved in hydrogen bonding are indicated: NB no Cl1 ions are visible in this view; (c) the arrangements around Cl1: dotted lines indicated hydrogen bonds and distances, in Å, are values for Cl···H distances obtained using the MERCURY program.

listed in appropriate tables. Generally the weaker C–H···O hydrogen bonds are not further discussed.

2.2.2. Cation geometries

The atom arrangements and numbering schemes for cations in (±)-**[MEFHCl·½(H$_2$O)]** and (±)-**[MEFHCl·(H$_2$O)]** are shown in Fig. 2. As stated by Karle and Karle (2002) and Skórska et al. (2006), the conformation of *erythro* isomers adopted by the mefloquine moiety, despite having flexible bonds, has been found to be the essentially the same in the free base and in salts, and in either hand. This is confirmed in this study. The cation of the tetragonal-solvated-(±)-**[MEFHCl]** is also shown.

The piperazinyl ring in each cation has a near perfect chair-shaped conformation with the alkyl substituents on the nitrogen atoms in the equatorial sites. As protonation of mefloquine base occurs at the piperidinyl nitrogen to give the mefloquinium salts, the proximity of the protonated piperidinyl nitrogen to the hydroxyl group results in a polar/hydrophilic area of the molecule in contrast to the hydrophobic area around the F_3C substituents in the quinoline ring (see Fig. 1). In all the cations, the torsion angles, C4–C9–C10–N2 are close to 180°, which indicate that the piperidinyl nitrogens are sited almost as far from the quinoline ring as possible.

All bond lengths and angles in the cations of (±)-**[MEFHCl·½(H$_2$O)]** and (±)-**[MEFHCl·(H$_2$O)]**, as are those in tetragonal-solvated-(±)-**[MEFHCl]**, are in the expected regions and are not discussed further. As commonly reported, fluorine atoms in trifluoromethyl groups attached to the 2 and 8 positions of quinoline rings (Karle and Bhattacharjee, 1996) exhibit disorder: this is evident in our study, e.g., with F2b and F3b in cation B of (±)-**[MEFHCl·½(H$_2$O)]**.

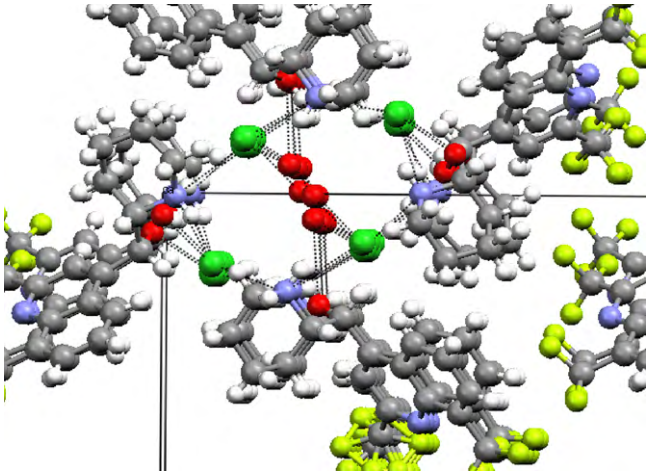
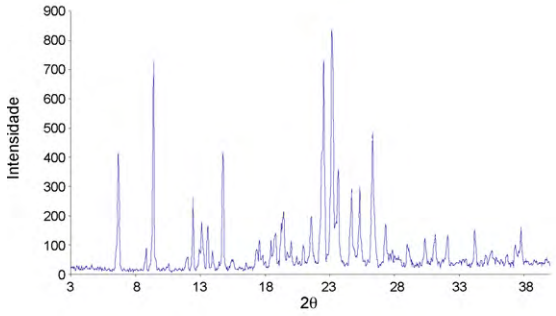
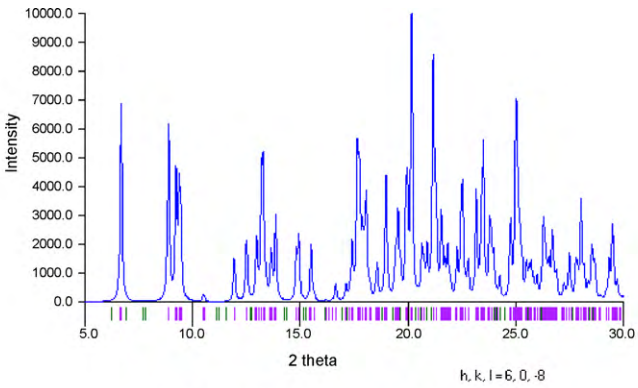


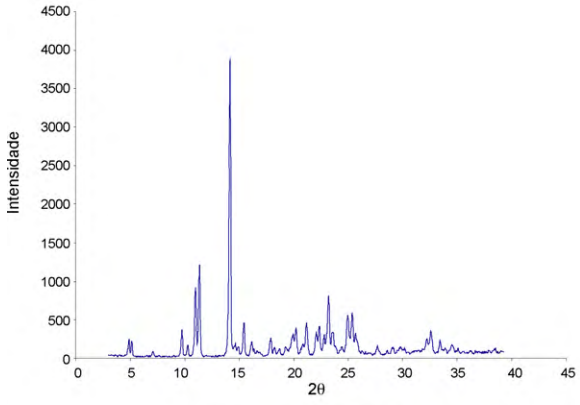
Fig. 5. View of the disordered quarter water solvate molecules in (−)-**[MEFHCl·(1/4)(H$_2$O)]** (Karle and Karle, 2002) inside a channel formed from tetrameric arrays of chloride ions (green) and mefloquinium cations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)



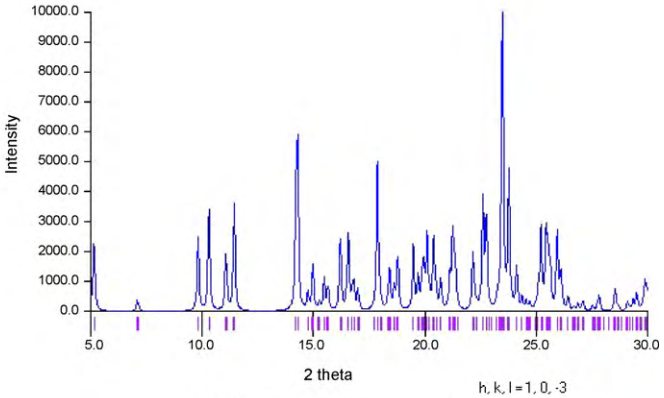
(a) Experimental diffractogram for (±)-**[MEFHCl. (H_2O)]**



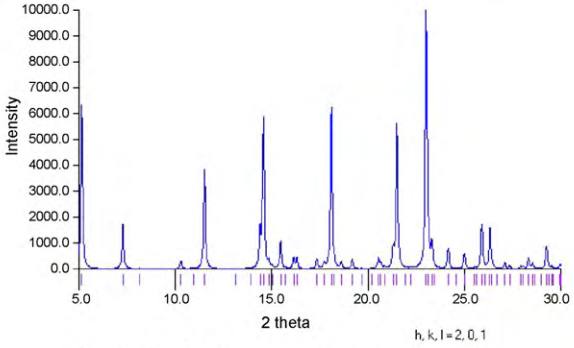
(b) Simulated diffractogram from single crystal determination for (±)-**[MEFHCl. (H_2O)]**



(c) Experimental diffractogram for (±)-**[MEFHCl. ½(H_2O)]**

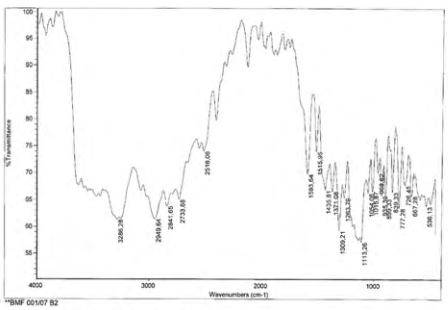


(d) Simulated diffractogram from single crystal determination for (±)-**[MEFHCl. ½(H_2O)]**

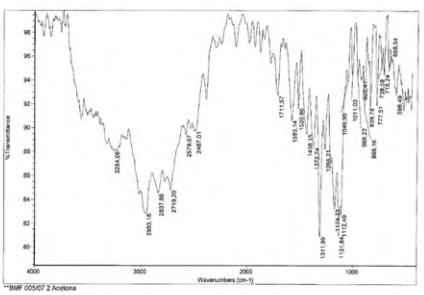


(e) Simulated diffractogram from single crystal determination for tetragonal-solvated (±)-**[MEFHCl]**

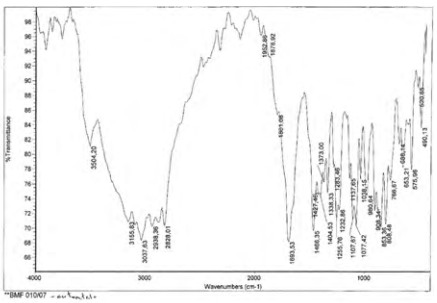
Fig. 6. X-ray powder patterns for forms in this study.



(a) (±)-**[MEFHCl. (H_2O)]**



(b) (±)-**[MEFHCl. ½(H_2O]**



(c) tetragonal.solvated-(±)-**[MEFHCl]**

Fig. 7. IR spectra in region from 4000 to 400 cm^{-1}.

Table 4
Comparison of calculated *d* spacings (Å).

(a)

(±)-**[MEFHCl·(H$_2$O)]** (this study)			E-form (Kitamura et al., 1994)	α-Form (Kiss et al., 1994)	E-form (Bömches and Hardegger, 1986)
h,k,l	2*θ*	*d* (Å)	*d* (Å)	*d* (Å)	*d* (Å)
2,0,−2	6.71	13.16	13.04	13.3	13.3
1,1,−2	9.47	9.33	9.33	9.47	9.35
2,0,−6	13.17	6.71	6.71	6.7	6.70
2,2,−1	17.61	5.03	5.04	5.05	505
6,0,−6	20.14	4.41	4.41	4.42	4.41
4,0,9	20.58	4.31	4.31	4.34	
2,2,−6	21.15	4.19	4.19		4.21
0,0,10	23.20	3.83	3.82	3.83	3.84
7,1,0	24.79	3.59	3.59	3.58	3.57
2,0,−12	26.40	3.37	3.36	3.36	3.36
2,2,−10	27.51	3.24	3.23	3.24	3.18
1,3,6	29.32	3.04	3.05	3.05	3.05
4,0,10	30.57	2.92	2.93		2.93
4,2,8	31.19	2.86	2.87		2.86

(b)

(±)-**[MEFHCl·½(H$_2$O)]** (this study)			δ-Form (Kiss et al., 1994)	D-form (Kitamura et al., 1994)
h,k,l	2*θ*	*d* (Å)	*d* (Å)	*d* (Å)
0,0,2	9.82	9.00	8.90	–
0,1,2	11.11	7.96	7.95	7.97
0,2,−1	11.40	7.76	7.72	7.74
				5.28
0,2,2	14.27	6.20	6.19	6.22
1,2,−1	17.85	4.96	4.93	4.93
1,−1,−2	20.10	4.41	4.44	4.38
0,1,4	20.40	4.35	4.37	
0,4,1	21.30	4.16	4.17	4.15
1,−2,−2	22.58	3.93	3.95	3.90, 3.96
1,1,4	23.59	3.78	3.81	3.77, 3.80, 3.83
0,3,4	25.17	3.53	3.56	3.51
0,4,−3	25.44	3.50	3.50	3.46

(c)

Tetragonal-solvated-(±)-**[MEFHCl]** (this study)		C-form (Kitamura et al., 1994)
2*θ*	*d* (Å)	*d* (Å)
10.25	8.42	8.58
11.46	7.71	7.76
14.59	6.06	6.08
15.49	5.71	5.73
16.20	5.47	5.45
18.12	4.94	4.90
21.45	4.12	4.14
23.06	3.85	3.87
24.18	3.68	3.69
25.89	3.44	3.46
32.84	2.72	2.74
33.16	2.70	2.70

2.2.3. Supramolecular arrangements

*2.2.3.1. (±)-**[MEFHCl·½(H$_2$O)]**.* Tetrameric units of mefloquinium chloride of (±)-**[MEFHCl·½(H$_2$O)]** are linked into rings via hydrogen bonds, O1A–H1A···Cl2, N2B–H2B···Cl, N2A–H2C···Cl, N2A–H2C···O1A and N2B–H2D···Cl2, see Table 2 for list of hydrogen bonds and symmetry codes. The rings contain alternating cations A and B, i.e. alternating enantiomeric units. Coupled with the intra-cation hydrogen bonds, N2A–H2C···O1A, a set of three rings is obtained, see Fig. 3a, which shows a schematic of the ring system. The rings are linked to rings in adjacent layers by N2A–H2A···Cl2, O1B–H1B···Cl1 and N2B–H2D···O1B hydrogen bonds, thus forming a channel, see Table 2 for symmetry codes. Fig. 3b shows a view of the arrangement looking down the rings with the disordered water solvates encaged in the channel. It is noteworthy that the hydroxyl oxygens in the two enatiomeric cations play different roles: O1A is involved in ring formation while O1B is involved in linking the rings, thus. The disordered water solvates are linked to the atoms forming the cavity by N2B–H2B···OW1 hydrogen bonds, while OW1–HW1···OW1 link the water solvates.

*2.2.3.2. (±)-**[MEFHCl·(H$_2$O)]**.* The involvement of the water solvate molecules in (±)-**[MEFHCl·(H$_2$O)]** is quite different from that in (±)-**[MEFHCl·½(H$_2$O)]**. In (±)-**[MEFHCl·(H$_2$O)]**, the water molecules have a much greater influence on the packing and interaction of the species. These and the chloride ions are involved in linking the three different cations, A, B and C, and are not hidden away in channels as in (±)-**[MEFHCl·½(H$_2$O)]**. Fig. 4a shows the packing of the compound. A view of the linking of the mefloquinium cations, via water molecules and chloride ions, looking down the *a* axis, is shown in Fig. 4b: only the donor and acceptor atoms in the hydrogen bonds are drawn. All three different mefloquinium cations are indicated in

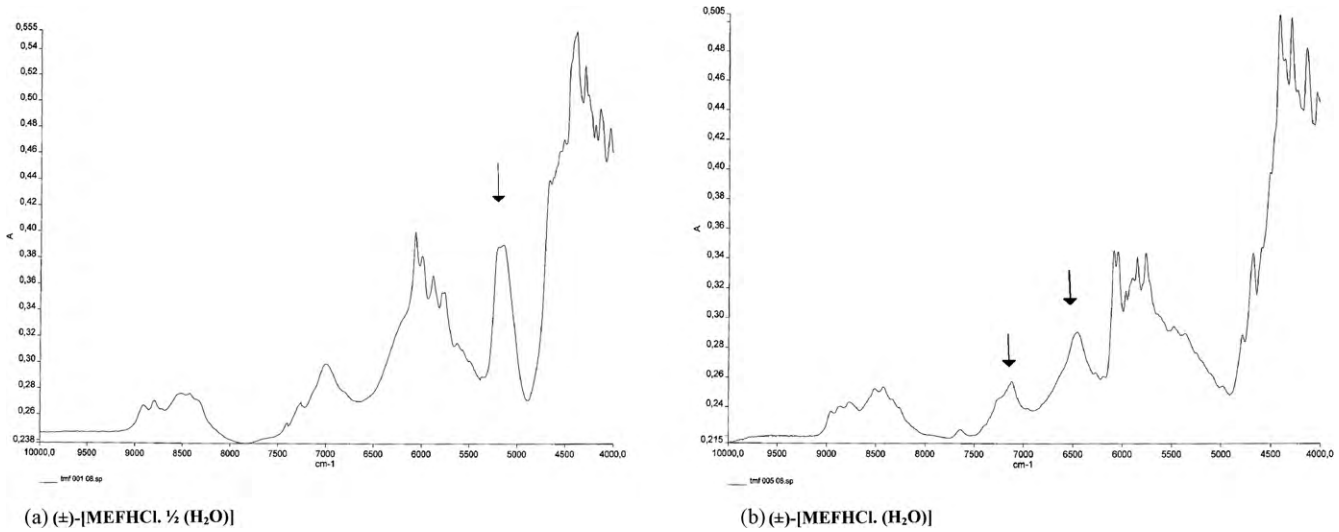


Fig. 8. Near infrared spectra of (a) (±)-**[MEFHCl·½(H$_2$O)]** and (b) (±)-**[MEFHCl·(H$_2$O)]**.

this view, but interestingly not Cl(1). Arrangements about Cl(1) are shown in Fig. 4c. Each chloride ion has its own set of neighbouring atoms. Table 3 lists the hydrogen bonds present.

Of interest, the crystal structures of the quarter hydrate of (−)-mefloquinium chloride, (−)-**[MEFHCl·(1/4)(H$_2$O)]** (Karle and Karle, 2002) and (±)-mefloquine, (±)-**[MEF]** (Skórska et al., 2006) have also been reported. In (−)-**[MEFHCl·(1/4)(H$_2$O)]**, again the water solvate appears to be encaged in channels formed from tetrameric arrays of (−)-mefloquinium and chloride ions, see Fig. 6, while in the free base, (±)-**[MEF]**, cyclic tetramers of mefloquine molecules are present (Fig. 5).

2.3. X-ray powder patterns, infrared spectra, DC and other data

X-ray powder patterns, infrared spectra and DSC data have been obtained for the three phases studied in this paper. The X-ray powder patterns, simulated using the MERCURY program from the single crystal data for all three forms and directly using a powder diffractometer for the two hydrates, are shown in Fig. 6. The *d* values, shown in Table 4, were calculated using the Bragg equation, Eq. (1):

$$d = \frac{\lambda}{2\sin\theta} \quad (1)$$

where λ is the wavelength of incident radiation, d is the spacing between the planes in the lattice, and θ is the angle between the incident ray and the scattering planes.

The IR spectra are shown in the region from 4000 to 400 cm^{-1}, Fig. 7, for all three forms. And in the near infrared region, 8000–5000 cm^{-1}, for (±)-**[MEFHCl·½(H$_2$O)]** and (±)-**[MEFHCl·(H$_2$O)]**. The near infrared region is a far superior region to use as a complementary technique for identifying polymorphs and pseudopolymorphs as the relevant bands are better separated (see for example Blanco et al., 2005, 2006; Aaltonen et al., 2003, 2007). As indicated by the arrows in Fig. 8, there are clear distinctions in the frequencies exhibited by (±)-**[MEFHCl·½(H$_2$O)]** and (±)-**[MEFHCl·(H$_2$O)]** in this selected region of the vibrational spectrum and thus can be used diagnostically.

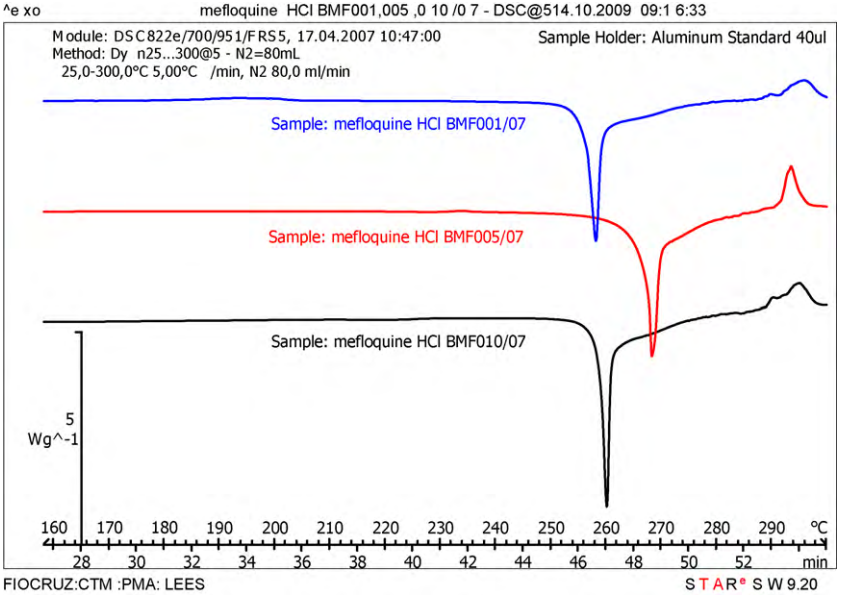


Fig. 9. DSC data for the three solvates: top (blue) is (±)-**[MEFHCl·(H$_2$O)]**, middle (red) is (±)-**[MEFHCl·½(H$_2$O)]** and bottom (black) is tetragonal-solvated (±)-**[MEFHCl]**. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

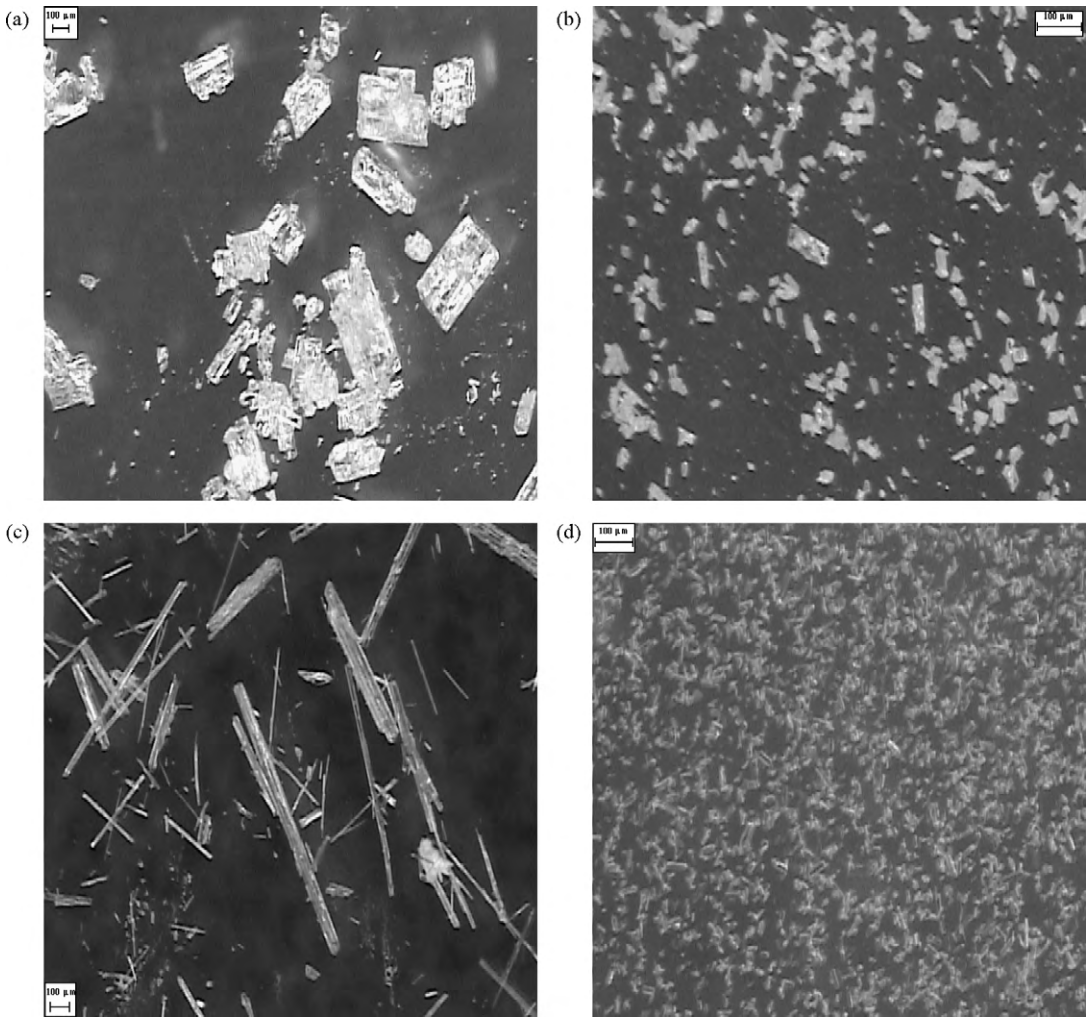


Fig. 10. Photomicrographs of samples (a) (±)-**[MEFHCl·(H_2O)]**, recrystallised from methanol, (b) (±)-**[MEFHCl·(H_2O)]**, recrystallised from ethyl acetate, (c) (±)-**[MEFHCl·½(H_2O)]**, recrystallised from isopropanol and (d) raw material.

The DSC results shown in Fig. 9 indicate small differences in the melting points of the three forms studied. The temperature of the endothermic peak associated to the melting transition of tetragonal-solvated-(±)-**[MEFHCl]** is higher than those of the other two. The form, (±)-**[MEFHCl·½(H_2O)]**, appears to be the thermodynamically most stable form.

The morphology and particle size of samples of (±)-**[MEFHCl·(H_2O)]**, (±)-**[MEFHCl·½(H_2O)]** are shown in Fig. 10. These can be compared wit those of the bulk material used to obtain the hydrated phases (see Fig. 10d). Samples of (±)-**[MEFHCl·(H_2O)]**, are obtained as plates, whether isolated from moist acetone or ethyl acetate solutions. In contrast, a needle form is apparent for (±)-**[MEFHCl·½(H_2O)]**.

2.3.1. Summary of data for particular forms

*2.3.1.1. Form (±)-**[MEFHCl·(H_2O)]**.* From a comparison of *d* values from the diffraction studies, it is clear that the phase we designated as (±)-**[MEFHCl·(H_2O)]** is the same as the E-form in both Kitamura et al. (1994) and Bömches and Hardegger (1985, 1986), as well as the α-form of Kiss et al. (1994) (see Table 4a). Kiss et al. (1994) used ethanol–water >30% for recrystallisation of their α-form, which they considered to be a ½ hydrate. Furthermore, Kitamura et al. (1994) considered their E-form, obtained by crystallisation from a saturated ethanol solution, to have EtOH present in the channels within the crystal lattice and not a hydrate at all, as we have determined in this study. Similarities are found between the IR spectra of our (±)-**[MEFHCl·(H_2O)]** species and that of the E-form of Kitamura et al. (1994) throughout the 3500–600 cm^{-1} region. However the absence of a list of frequencies makes the comparison a qualitative one. Kiss et al. (1994) did provide such a list for the 1400–4000 cm^{-1} region and here agreement is good.

*2.3.1.2. Form **[MEFHCl·½(H_2O)]**.* A comparison of *d* values indicates that the phase we designated as (±)-**[MEFHCl·½(H_2O)]** is the same as the D-form of Kitamura et al. (1994) and the hemihydrate in Bömches and Hardegger (1986), as well as the δ-form of Kiss et al. (1994) (see Table 4b).

Kitamura et al. (1994) obtained their D-form by suspending 2 g of a bulk sample in water (20 ml) at RT for 12 h. Bömches and Hardegger (1985, 1986) obtained their hemihydrate from ethanol or methanol solutions, containing less than 30% water, while, Kiss et al. (1994) obtained their δ-form from recrystallisation from ethanol–water <30%.

The IR spectrum of the δ-form of Kiss et al. (1994) and the frequency list for the hemihydrate of Bömches and Hardegger (1985, 1986) show similarities with our spectrum for (±)-**[MEFHCl·½(H_2O)]**; however slight differences are observed.

*2.3.1.3. Form tetragonal, solvated (±)-**[MEFHCl]**.* In a comparison of *d* values, it is clear that the phase we designated as tetragonal-solvated-(±)-**[MEFHCl]** is very similar, at least, to the C-form of

Table 5
Crystal data and structure refinement.

	(±)-**[MEFHCl·X]**	(±)-**[MEFHCl·½(H_2O)]**	(±)-**[MEFHCl·(H_2O)]**
Empirical formula		$C_{17}H_{18}ClF_6N_2O_{1.50}$	$C_{17}H_{19}ClF_6N_2O_2$
Formula weight	430.80	423.78	432.79
Temperature, K	120(2)	120(2)	120(2)
Wavelength, Å	0.6941	0.71073	0.71073
Crystal system	Tetragonal	Triclinic	Monoclinic
Space group	*P*42/*n*	*P*−1	*C*2/*c*
Unit cell dimensions			
a, Å	24.298(6)	6.0491(5)	28.3091(5)
b, Å	24.298(6)	17.388(2)	10.7446(2)
c, Å	6.3571(16)	18.112(2)	40.6940(5)
α,°	90	89.300(5)	90
β,°	90	83.838(7)	109.7140(10)
δ,°	90	80.732(6)	90
Volume, Å^3	3753.2(16)	1869.3(3)	11,652.4
Z	8	4	24
Density (calculated), mg/m^3	1.525	1.506	1.480
Absorption coefficient, mm^{-1}	0.275	0.274	0.267
F(0 0 0)	1768	868	5328
Crystal size, mm	0.04 × 0.04 × 0.002	0.48 × 0.38 × 0.16	0.32 × 0.20 × 0.20
θ range for data collection,°	2.32–20.33	3.27–27.58	2.98–27.52
Index ranges	−24 ≤ h ≤ 24; −24 ≤ k ≤ 24; −6 ≤ l ≤ 6	−7 ≤ h ≤ 7; −22 ≤ k ≤ 22; −23 ≤ l ≤ 23	−36 ≤ h ≤ 36; −13 ≤ k ≤ 13; −52 ≤ l ≤ 52
Reflections collected	17,318	31,882	57,256
Independent reflections	1968 [*R*(int) = 0.0629]	8584 [*R*(int) = 0.0405]	13,333 [*R*(int) = 0.0813]
Reflections obsd. (>2sigma)	1536	6620	9745
Data completeness	0.995	0.992	0.995
Absorption correction	None	None	None
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	1968/0/252	8584/0/553	13,333/12/813
Goodness-of-fit on F^2	1.138	1.039	1.037
Final *R* indices [*I* > 2sigma(I)]	R_1 = 0.1102 wR_2 = 0.2335	R_1 = 0.0397 wR_2 = 0.0941	R_1 = 0.0537 wR_2 = 0.1377
R indices (all data)	R_1 = 0.1307 wR_2 = 0.2438	R_1 = 0.0580 wR_2 = 0.1026	R_1 = 0.0798 wR_2 = 0.1525
Largest diff. peak and hole, e Å^{-3}	0.452 and −0.289	0.359 and −0.401	0.482 and −0.363
CCDC no.	762442	762403	762402

Kitamura et al. (1994) (see Table 4c). Form C of Kitamura et al. (1994) was obtained on exposure of their form E, among other forms, to water. They indicate that it is a hemihydrate, but different from their form D.

3. Conclusions

In summary, this study has structurally identified two hydrates of (±)-**[MEFHCl]**, namely (±)-**[MEFHCl·½(H_2O)]** and (±)-**[MEFHCl·(H_2O)]**, as well provide some further information of a tetragonal solvated phase, whose powder patterns had been reported previously and, in so doing, we have corrected erroneous assumptions regarding these phases. An example being Kitamura et al.'s (1994) report of a anhydrous phase (their form E), obtained from a hot saturated ethanol solution, as an anhydrous phase (with the possibility of residual alcohol molecules held in channels), while we, in this paper, indicate this to be (±)-**[MEFHCl·(H_2O)]**. Clearly the formation of hydrates in our studies arises from the presence of small quantities of water.

We stress that our aim in this study was to obtain definitive structural and other evidence for forms and solvates of mefloquinium chloride, which could be then be used as standards. We did not search for specific forms, but did intentionally use solvent systems previously adopted by other research groups. As mentioned earlier, the isolation of such solvates of mefloquine, as the acetone and isopropanol solvates, have been indicated by different groups. It is apparent that a form containing acetone, designated B (Kitamura et al., 1994), E (Sinden et al., 2005) and *ε* (Kiss et al., 1994), has been produced as the IR spectra showed the required *υ*(C=O) value and TGA, where carried out, indicated the correct mass loss for acetone. The acetone solvate was described as being produced on recrystallisation from acetone solutions, for example, Kiss et al. (1994) indicate that they used saturated solutions initially at 70 °C, before cooling to RT. In our study, slow recrystallisation from dilute acetone solution led to the isolation of (±)-**[MEFHCl·½(H_2O)]**. Our prime concern was the attainment of the best crystals possible yields, or even species, were not considerations. Slow recrystallisation over days may well lead to the formation of the most thermodynically stable form as well as to allow the continuing ingress of moisture, while faster recrystallisation could lead to the isolation of the bulk material from solution. This further illustrates the importance of the procedure and motives for forming the crystalline phase. Clearly for powder diffraction study, any non-amorphous material can be used, but for single crystal diffraction studies only well-formed crystals are suitable. For single crystal studies, bulk formation is far from a requirement, but it may be of prime importance in other studies.

Much remains still to be resolved for the complete characterization of other phases. Finally, we emphasize the value of single crystal X-ray studies, but, as indicated by the findings with the tetragonal-solvated (±)-**[MEFHCl]**, good crystals and crystals free of disorder at low temperatures are vital.

4. Experimental

4.1. X-ray

Intensity data for tetragonal-solvated-(±)-**[MEFHCl]** were obtained at 120 K with synchrotron radiation by means of a Bruker SMART APEX2 CCD diffractometer, based at Daresbury SRS station 9.8. The data collection was controlled by the program APEX2 (Bruker AXS Inc., 2004) and data reduction and unit cell refinement were achieved with the SAINT (Bruker AXS Inc., 2004). Corrections for absorption, by comparison of the intensities of equivalent

reflections, were applied using the program SADABS (Sheldrick, 2003). Intensity data for tetragonal-solvated-(±)-**[MEFHCl]** were obtained at 120 K with synchrotron radiation by means of a Bruker SMART APEX2 CCD diffractometer, based at Daresbury SRS station 9.8. The data collection was controlled by the program APEX2 (Bruker AXS Inc., 2004) and data reduction and unit cell refinement were achieved with the SAINT (Bruker AXS Inc., 2004). Corrections for absorption, by comparison of the intensities of equivalent reflections, were applied using the program SADABS (Sheldrick, 2003). Intensity data for (±)-**[MEFHCl·½(H$_2$O)]** and (±)-**[MEFHCl·(H$_2$O)]** were collected at 120 K with Mo-Kα radiation using the κ-goniostat Bruker–Nonius CCD camera of the EPSRC crystallographic service, based at the University of Southampton, UK. Data collection was carried using the program COLLECT (Hooft, 1998) and data reduction and unit cell refinement were achieved with the COLLECT (Hooft, 1998) and DENZO programs (Otwinowski and Minor, 1997). Corrections for absorption, by comparison of the intensities of equivalent reflections, were applied using the program SADABS (Sheldrick, 2003). The structures were solved by direct methods using SHELXS-97 and refined against F^2 with SHELXL-97 (Sheldrick, 1997a,b). The hydrogen atoms of the N–H groups of tetragonal-solvated-(±)-**[MEFHCl]** were refined with N–H = 1.05 (1) and H···H = 1.65 (5). The hydrogen atoms of the N–H groups in (±)-**[MEFHCl·½(H$_2$O)]** were located from difference maps and freely refined. The water-bound hydrogen atoms in (±)-**[MEFHCl·½(H$_2$O)]** were refined with O–H = 0.85(1) and H···H = 1.40(5) Å, giving 6 restraints. All the other hydrogen atoms were placed in calculated positions and refined as riding. The program ORTEP-3 for Windows (Farrugia, 1999) was used in the preparation of figures and PLATON (Spek, 2003) in the calculation of molecular geometry. Crystal data and structure refinement details are listed in Table 5.

4.2. Powder diffraction study

This was carried out using a Bruker AXS DS advanced LDRX powder diffractometer, based at Universidade Federal Fluminense, Niteroi, Rio de Janeiro.

4.3. DSC analysis

The DSC measurements were performed using an 822^{e}Mettler Toledo. Calibration was carried out using indium and zinc as reference materials. Samples weighing approximately 3 mg were analyzed in aluminium pans with pierced lids, from 25 °C to 300 °C using a heating rate of 5 °C/min under a nitrogen purge.

4.4. Infrared

Mid-infrared spectra were recorded using a Thermo Nicolet Nexus 670 spectrometer with diffuse reflectance accessory. A Perkin-Elmer Spectrum One FT-NIR spectrometer was used to collect the near infrared spectra.

4.5. Optical microscopy

Samples were examined under an Optical Microscope Olympus BX50.

Supplementary material

Structural data in cif format have been deposited with the Cambridge Crystallographic Data Centre with deposition numbers 762403 for (±)-**[MEFHCl·½(H$_2$O)]**, 762402 for (±)-**[MEFHCl·(H$_2$O)]** and 762442 for tetragonal-solvated (±)-**[MEFHCl]**. Copies of these can be obtained free of charge on written application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033); on request by e-mail to deposit@ccdc.cam.ac.uk or by access to http://www.ccdc.cam.ac.uk.

Acknowledgements

The use of the EPSRC X-ray crystallographic service at the University of Southampton, England and the valuable assistance of the staff are gratefully acknowledged. We acknowledge Prof. William Clegg and the Synchrotron Component, Daresbury, of the EPSRC National Crystallography Service, based at the University of Southampton. S.M.S.V.W., L.D.P., and J.L.W. acknowledge support from CNPq, FAPERJ and CAPES, respectively.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2010.07.034.

References

Aaltonen, J., Strachan, C., Pollanen, K., Yliruusi, J., Rantanen, J., 2007. Hyphenated spectroscopy as a polymorph screening tool. J. Pharm. Biomed. Acta 44, 477–483.
Aaltonen, J., Rantanen, J., Siiriä, S., Karjalainen, M., Jørgensen, A., Laitinen, N., Savolainen, M., Seitavuopio, P., Louhi-Kultanen, M., Yliruus, J., 2003. Polymorph screening using near-infrared spectroscopy. Anal. Chem. 75, 5267–5273.
APEX2, 2004. Bruker AXS Inc., Madison, USA.
Blanco, M., Valdes, D., Llorente, I., Bayod, M., 2005. Application of NIR spectroscopy in polymorphic analysis: study of pseudo-polymorphs stability. J. Pharm. Sci. 94, 1336–1342.
Blanco, M., Alcalá, M., González, J.M., Torras, E., 2006. Near infrared spectroscopy in the study of polymorphic transformations. Anal. Chim. Acta 567, 262–268.
Bömches, H., Hardegger, B., 1985. USP 4 507 482.
Bömches, H., Hardegger, B., 1986. USP 4 579 855.
Farrugia, L.J.J., 1999. ORTEP-3 for Windows—a version of ORTEP-III with a graphical user interface. J. Appl. Crystallogr. 32, 837–883.
Hooft, R.W.W., 1998. COLLECT, Data Collection Software. Nonius BV, Delft, The Netherlands.
Karle, J.M., Bhattacharjee, A.K., 1996. Trifluoromethyl group disorder in crystalline 2,8-bis(trifluoromethyl)-4-hydroxymethylquinoline. J. Chem. Crystallogr. 26, 615–619.
Karle, J.M., Karle, I.L., 1991. Structure of the antimalarial (±) mefloquine hydrochloride. Acta Crystallogr. C 47, 2391–2395.
Karle, J.M., Karle, I.L., 2002. Crystal structure of (−) mefloquine hydrochloride reveals consistency of configuration with biological activity. Antimicrob. Agents Chemother., 1529–1534.
Kiss, A., Répási, J., Salamon, Z., Novák, Cs., Pokol, G., Tomor, K., 1994. Solid state investigation of mefloquine hydrochloride. J. Pharm. Biomed. Anal. 12, 889–893.
Kitamura, S., Chang, L.-C., Guillory, J.K., 1994. Polymorphism of mefloquine hydrochloride. Int. J. Pharm. 101, 127–144.
Kremsner, P.G., Krishna, S., 2004. Antimalarial combinations. Lancet 364, 285–294.
Newton, P., White, N., 1999. Malaria: new developments in treatment and prevention. Ann. Rev. Med. 50, 179–192.
Otwinowski, Z., Minor, W., 1997. Processing of X-ray diffraction data collected in oscillation mode. Methods in enzymology. In: Carter Jr., C.W., Sweet, R.M. (Eds.), Macromolecular Crystallography, Part A, vol. 276. Academic Press, New York, pp. 307–326.
SAINT, 2004. Bruker AXS Inc., Madison, USA.
Sheldrick, G.M., 2003. SADABS. Version 2.10. Bruker AXS Inc., Madison, WI, USA.
Sheldrick, G.M., 1997a. SHELXL-97. Program for Crystal Structure Refinement. University of Göttingen, Germany.
Sheldrick, G.M., 1997b. SHELXS-97. Program for the Solution of Crystal Structures. University of Göttingen, Germany.
Sinden, K.W., Baxter, A.D., Szelagiewicz, M., Hilfiker, R., 2005. WO 2005/058872.
Skórska, A., Śliwiński, J., Oleksyn, B.J., 2006. Conformation stability and organization of mefloquine molecules in different environments. Bioorg. Med. Chem. Lett. 16, 850–853.
Spek, A.L., 2003. Single-crystal structure validation with the program PLATON. J. Appl. Crystallogr. 36, 7–13.
Wilairatana, P., Krudsood, S., Treeprasertsuk, S., Chalermrut, K., Looareesuwan, S., 2002. The future outlook of antimalarial drugs and recent work on the treatment of malaria. Arch. Med. Res. 33, 416–421.