



# Solid state investigation of mefloquine hydrochloride

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**Abstract:** Mefloquine hydrochloride was crystallized under different conditions and the products were studied by thermal analysis, IR spectroscopy and X-ray diffraction. It was demonstrated that different conditions of crystallization resulted in different crystal structures. The  $\alpha$ - and  $\delta$ -modifications were hydrates, the  $\beta$ - and  $\gamma$ -forms were polymorphs, the  $\epsilon$ -form was an acetone solvate and  $\theta$ -mefloquine was tetrahydrofuran solvate. During long storage at room temperature, the  $\alpha$ -,  $\delta$ - and  $\theta$ -forms of mefloquine hydrochloride were transformed. By heat treatment of the  $\delta$ -,  $\epsilon$  and  $\theta$ -modifications, a new crystal structure was obtained.

**Keywords:** *Mefloquine hydrochloride; solid-state investigation; thermal analysis; polymorphism; X-ray diffraction; IR spectroscopy.*

## Introduction

Mefloquine hydrochloride (*R,S*-erythro- $\alpha$ -2-piperidyl-2,8-bis(trifluoromethyl)-4-quinoline-methanol hydrochloride) is an antimalarial drug.

The morphology and formulation of mefloquine were considered in two patents filed by Hoffmann-La Roche.

Since the physico-chemical stability, biological utilization and therapeutic activity are strongly influenced by the crystalline form of the drug [1–4], it is of great importance to elucidate the polymorphism of this compound.

Five forms of mefloquine hydrochloride are listed in the first patent cited [5]. Form A is described as an anhydrate, B is an acetone solvate while forms C, D and E are hemihydrates. In the other patent [6] the E form of mefloquine is not mentioned. The IR spectra presented (KBr technique) cannot be assigned directly to the different modifications and the intensive carbonyl stretching vibration in the IR spectrum of the acetone solvate cannot be observed; thus the conclusions in these patents are unreliable.

By evaluation of the previous publications, it was concluded that a critical investigation of the individual forms of mefloquine hydrochloride would be important. Thermal analysis, IR spectroscopy, GC and X-ray diffraction were

chosen as experimental techniques for this study. In addition the possibility of identifying the modifications of mefloquine in the final products was examined and experiments were conducted to determine if there is any chance of polymorphic transitions occurring during storage.

## Experimental

The materials used were standard samples prepared by Alkaloida Ltd; their purity was tested by a HPLC method and was found to be greater than 99.8%.

The IR spectra were recorded by a Digilab FTS — 40 Fourier transform IR spectrometer with a built-in zinc selenite single reflection prismatic cell. A room temperature DTGS detector was used with a resolution of  $2\text{ cm}^{-1}$ .

The DSC analyses were carried out in a DuPont DSC — 10 cell. Conditions: atmosphere, flowing nitrogen; heating rate,  $10^\circ\text{C min}^{-1}$ ; sample mass, about 3 mg.

Thermogravimetric curves were recorded by a DuPont 951 thermobalance. Conditions: atmosphere, flowing argon; heating rate,  $10^\circ\text{C min}^{-1}$ ; sample mass, about 5 mg.

A DuPont 916 TEA (Carle 3000) was used for detection of the evolved organic gases. Conditions: nitrogen flow,  $1.8\text{ l h}^{-1}$ ; heating rate,  $8^\circ\text{C min}^{-1}$ ; sample mass, about 3.5 mg.

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X-ray patterns were recorded with a Zeiss HZG-4 powder diffractometer. Conditions: Co tube; Fe filter; aluminium sample holder; goniometer scan-rate,  $1^\circ \text{ min}^{-1}$ .

For the identification and quantitative determination of the organic solvates, a Hewlett-Packard model 5890 GC was used with a 1.5-m Porapak Q column. Conditions: temperature, isothermal at  $150^\circ\text{C}$ ; flow rate of helium gas,  $30 \text{ cm}^3 \text{ min}^{-1}$ .

## Results and Discussion

The solvates of mefloquine hydrochloride were characterized by TG and EGA curves. The weight losses calculated from the TG curves (Fig. 1) are shown in Table 1.

For the  $\epsilon$ - and  $\theta$ -modification, the results were in good agreement with those calculated on the basis of the GC measurements.

The EGA curves demonstrated that organic compounds are formed in the case of the  $\epsilon$ - and  $\theta$ -modifications. It means that  $\alpha$ - and  $\delta$ -mefloquine hydrochloride may be regarded as hydrates whereas the  $\epsilon$ - and  $\theta$ -modifications are organic solvates. In the case of the  $\delta$ -modifications, the ratio of the first and second TG steps was not uniform for different samples. To interpret this phenomenon, it is assumed that the varying amount of the water of crystallization, which is represented by the second step, is caused by the reversible transition between the anhydrate and the hydrate forms depending on the conditions of storage. The solvents used for crystallization and the products formed are summarized in Table 2.

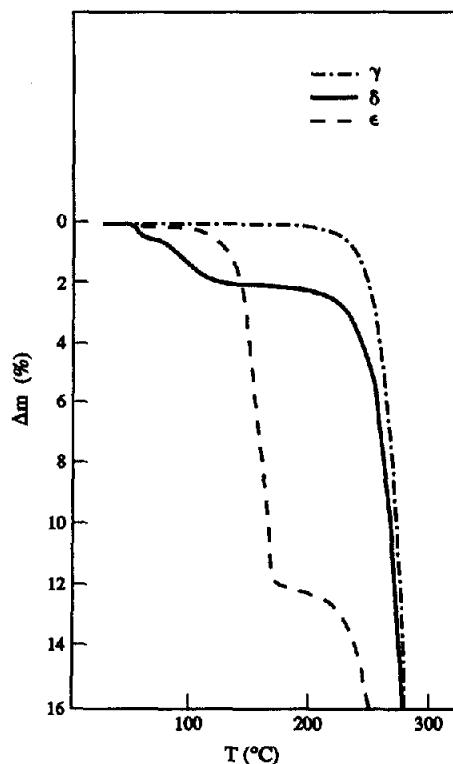
**Table 1**  
Weight loss of mefloquine hydrochloride forms

Form	$\alpha$	$\beta$	$\gamma$	$\delta^*$	$\epsilon$	$\theta$
Weight loss (%)	2	0	0	2	11.8	15.9

\* The weight loss took place in two steps between  $50$  and  $120^\circ\text{C}$ .

**Table 2**  
Solvents for crystallization and the products formed

Solvent	Products
Ethanol-water >30%	$\alpha$ (mefloquine HCl, $0.5 \text{ H}_2\text{O}$ )
Acetonitrile	$\beta$ (polymorph modification)
Dichloromethane, ethyl acetate	$\gamma$ (polymorph modification)
Ethanol-water <30%	$\delta$ (mefloquine HCl, $\times \text{H}_2\text{O}$ )
Acetone	$\epsilon$ (mefloquine HCl, $\text{Me}_2\text{CO}$ )
Tetrahydrofuran	$\theta$ (mefloquine HCl, $\text{C}_4\text{H}_8\text{O}$ )



**Figure 1**  
TG curves of the  $\gamma$ -,  $\delta$ - and  $\epsilon$ -forms of mefloquine hydrochloride.

The IR spectra were determined using a reflection technique so that the application of pressure and a matrix could be avoided. The  $1350\text{--}700 \text{ cm}^{-1}$  wave number interval proved to be the most suitable for the identification of the different modifications (Table 3). A number of differences could be observed visually as well in this region. Especially significant differences exist between  $1250$  and  $1100 \text{ cm}^{-1}$  and  $790\text{--}770 \text{ cm}^{-1}$ . The carbonyl stretching vibration band at  $1709 \text{ cm}^{-1}$  for  $\epsilon$ -mefloquine and the C—O—C asymmetrical stretching vibrational band at  $1171 \text{ cm}^{-1}$  for  $\theta$ -mefloquine hydrochloride support the hypothesis that these modifications exist in the forms of the acetone solvate and tetrahydrofuran solvate, respectively (Fig. 2).

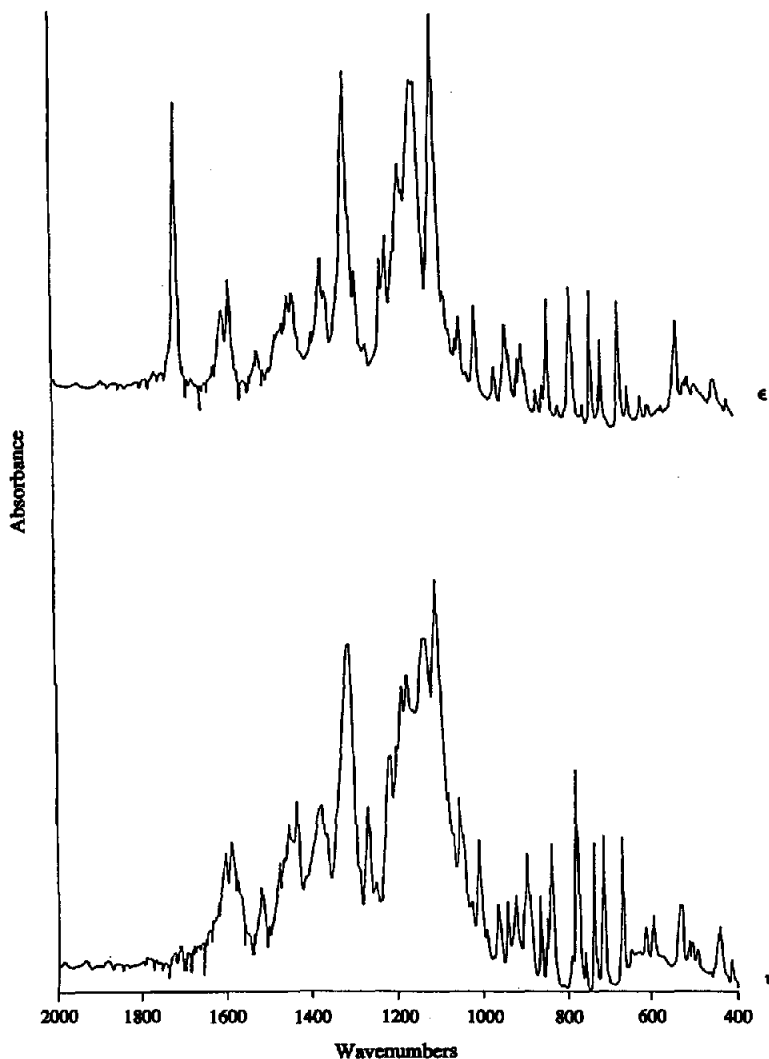


Figure 2  
IR spectra of  $\epsilon$ - and  $\theta$ -mefloquine hydrochloride.

From the DSC curves (Figs 3 and 4), the peak temperatures in Table 4 represent the melting transitions of the different modifications. For the  $\alpha$ -,  $\delta$ -,  $\epsilon$ - and  $\theta$ -forms, melting takes place in the dehydrated or desolvated structures.

The enthalpy changes associated with this transition cannot be determined because melting is accompanied by the thermal decomposition of the mefloquine hydrochloride forms.

The existence of the different forms were confirmed by the X-ray patterns of the  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ -,  $\epsilon$ - and  $\theta$ -forms. The  $d$  values and the  $I/I_0$  relative intensities are summarized in Table 5.

The crystalline samples were stored for 9 months at room temperature for stability examination. It was found that in the  $\alpha$ -

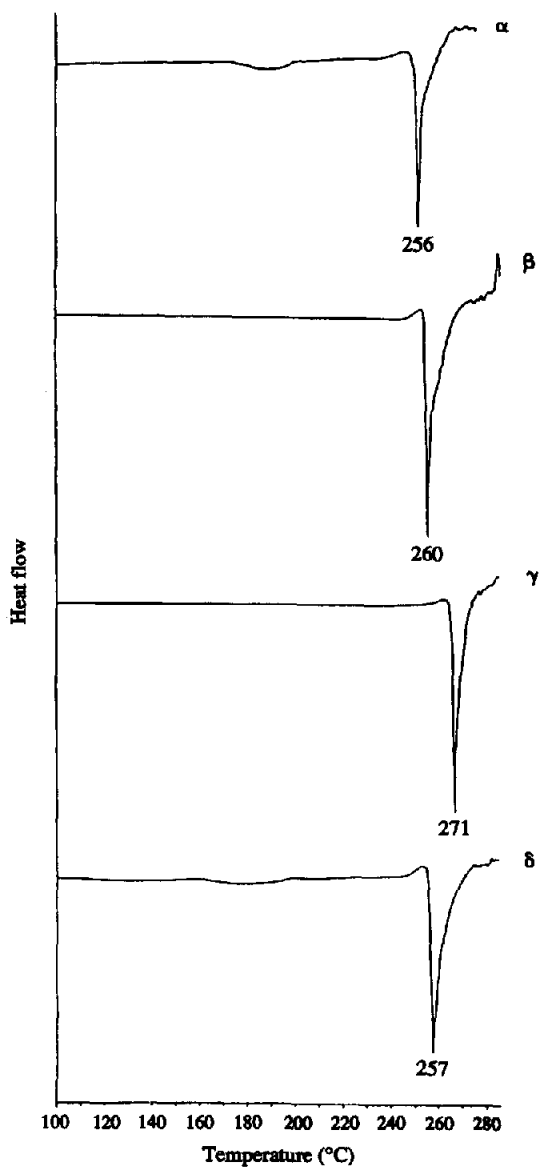
modification, a small amount of the  $\delta$ -modification had appeared. This observation is supported by the DSC and IR measurements.

In the case of the  $\delta$ -modification, new diffraction peaks appeared in the X-ray pattern representing the formation of a new modification. Accordingly, a new DSC peak was observed on the curve with the peak temperature of 263°C. In the case of  $\theta$ -mefloquine hydrochloride, the 70% decrease in the tetrahydrofuran content and a DSC peak at 263°C was observed again. On the other hand, IR studies proved that the commercial products 'Lariam' (Hoffmann-LaRoche) and 'Mephaquin' (Mepha) contain the  $\alpha$ - and  $\delta$ -hydrates of mefloquine hydrochloride, respectively.

After the heat treatment of the solvates ( $\delta$ -,  $\epsilon$ - and  $\theta$ -forms) at 167°C, X-ray diffractograms

**Table 3**  
Characteristic infrared wave numbers of mefloquine hydrochloride forms between 1300 and 700  $\text{cm}^{-1}$

$\alpha$ ( $\text{cm}^{-1}$ )	$\beta$ ( $\text{cm}^{-1}$ )	$\gamma$ ( $\text{cm}^{-1}$ )	$\delta$ ( $\text{cm}^{-1}$ )	$\epsilon$ ( $\text{cm}^{-1}$ )	$\theta$ ( $\text{cm}^{-1}$ )
1311	1312	1316	1312	1313	1308
1304	1304	1310	1306	1297	1286
1269	1267	1296	1288	1280	1266
1261	1261	1272	1264	1280	1239
1212	1217	1254	1247	1213	1212
1188	1197	1219	1217	1198	1198
1169	1187	1199	1212	1188	1186
1157	1171	1186	1187	1172	1171
1137	1161	1179	1171	1146	1130
1127	1140	1141	1162	1135	1107
1108	1128	1136	1138	1110	1069
1079	1108	1130	1123	1070	1054
1054	1078	1111	1107	1054	1030
1047	1066	1079	1077	1046	1023
1012	1054	1067	1054	1010	1008
966	1011	1046	1045	962	959
941	965	1027	1008	938	941
929	924	1008	963	924	921
892	908	960	941	897	896
881	898	937	924	891	887
865	890	924	919	855	847
839	865	906	901	849	839
834	840	896	897	840	834
772	835	890	865	836	778
736	775	864	839	788	736
729	756	839	834	779	713
715	737	786	780	753	701
713	719	753	737	736	
	714	736	714	720	
		709		714	



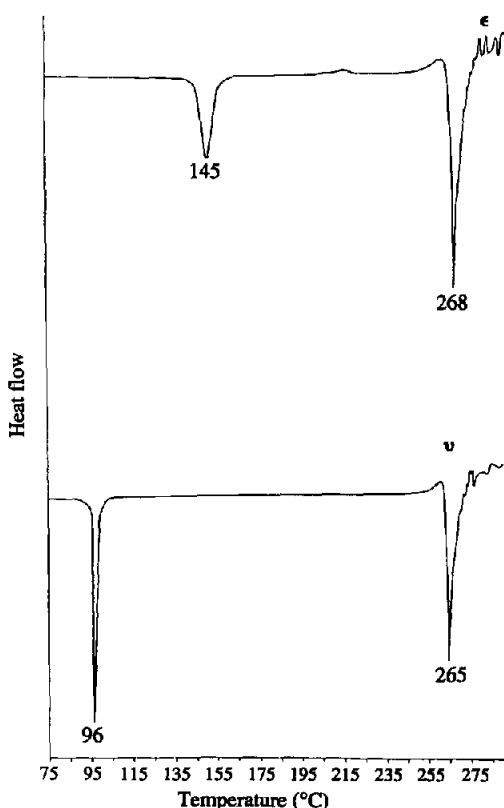
**Figure 3**  
DSC curves of  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -mefloquine hydrochloride.

**Table 4**  
Melting transitions of mefloquine hydrochloride forms

Form	$\alpha$	$\beta$	$\gamma$	$\delta$	$\epsilon$	$\theta$
Peak temperatures ( $^{\circ}\text{C}$ )	256	260	271	257	268	265

**Table 5**  
The *d* values and *I*/*I*<sub>0</sub> relative intensities of mefloquine hydrochloride forms

α		β		γ		δ		ε		θ	
<i>d</i> (Å)	(%) <i>I</i> / <i>I</i> <sub>max</sub>	<i>d</i> (Å)	(%) <i>I</i> / <i>I</i> <sub>max</sub>	<i>d</i> (Å)	(%) <i>I</i> / <i>I</i> <sub>max</sub>	<i>d</i> (Å)	(%) <i>I</i> / <i>I</i> <sub>max</sub>	<i>d</i> (Å)	(%) <i>I</i> / <i>I</i> <sub>max</sub>	<i>d</i> (Å)	(%) <i>I</i> / <i>I</i> <sub>max</sub>
13.3	(66)	16.8		11.0	(22)	16.9		9.87		17.3	
10.0		12.6	(57)	8.35	(18)	8.9		9.59	(27)	8.65	
9.47	(42)	12.05	(96)	7.38	(9)	8.49		8.78	(28)	7.73	(64)
7.14		9.56		6.30	(17)	7.95		6.91	(22)	6.12	(96)
6.9		7.50		5.99		7.72	(36)	5.66		5.49	
6.7	(100)	6.56	(61)	5.76		6.193	(100)	5.50		5.17	
5.97		6.31		5.41		5.90		4.93	(51)	4.93	(72)
5.72		6.05	(100)	5.22	(11)	5.69	(19)	4.80	(52)	4.65	
5.05	(40)	5.59		4.68	(13)	5.434		4.54		4.15	(67)
4.96		5.31	(44)	4.56	(15)	5.185		4.42		3.876	(100)
4.74		5.04	(44)	4.50		4.934	(11)	4.34		3.715	
4.59		4.84		4.273		4.720		4.12	(40)	3.481	(23)
4.42	(42)	4.75		4.20	(72)	4.588		4.07		3.41	(18)
4.34		4.62		4.07	(59)	4.44	(18)	3.928		3.068	
4.03		4.58		4.02	(47)	4.37	(17)	3.862		2.985	
4.06		4.42	(42)	3.72	(100)	4.24		3.739	(100)	2.748	
3.964		4.22		3.522	(10)	4.17	(16)	3.700	(50)	2.654	
3.883	(51)	4.07		3.358		4.00		3.656		2.404	
3.726		3.949	(51)	3.095	(13)	3.949	(27)	3.614			
3.575	(85)	3.814	(34)			3.888		3.504			
3.364		3.679				3.812	(73)	3.454			
3.247		3.614	(95)			3.752	(26)	3.320			
3.204		3.403				3.623		3.204			
3.052						3.555	(18)				
						3.504	(22)				
						3.458	(16)				



**Figure 4**  
DSC curves of ε- and θ-mefloquine hydrochloride.

were recorded. The diffraction curves of the initial and the heat-treated ε-solvate showed structural transformations. The diffraction curves of the starting and the heat-treated samples are different and also differ from the curves of the α-, β- and γ-forms, alone and together. This means that the crystal structures of the former modifications are different from the three latter forms.

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[Received for review 21 July 1993;  
revised manuscript received 18 November 1993]