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Polymorphism of mefloquine hydrochloride

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Summary

The polymorphic and pseudopolymorphic forms of mefloquine hydrochloride have been characterized by use of X-ray powder diffractometry, thermal analysis, infrared spectral analysis, scanning electron microscopy, and solubility measurements. It was determined that mefloquine hydrochloride can crystallize in at least eight forms, anhydrous forms (A, B′, E and M), solvate forms (B and I) and hydrate forms (C and D). The acetone solvate (form B) and isopropanol solvate (form I) transform into forms B′ and M, respectively, when they are heated on a hot stage. Form E, which was recrystallized from ethanol, showed gradual weight loss on heating, and a small endotherm in the DSC thermogram due to desolvation. However, the X-ray powder diffraction pattern of form E after removal of virtually all the ethanol, showed almost the same pattern. This suggests that ethanol is contained in channels within the crystal lattice of form E. An X-ray powder diffraction study showed that the crystal forms of mefloquine hydrochloride in lots of commercial tablets obtained from two sources were forms E and C. When the tablets were stored at 60°C, 75% R.H., form E was transformed into form D, but form C did not undergo a significant change. A study of the effect of various excipients on the solid-state crystal transformation revealed that microcrystalline cellulose promotes the transformation from form E into form D. However, methylcellulose, hydroxyethylcellulose, β-cyclodextrin, crospovidone and hydrous lactose have no effect on the crystal transformation.

Introduction

It is well known that polymorphs and solvates of drugs exhibit different physicochemical properties including stability and solubility which, particularly in the case of compounds whose solubility in water is less than 1% w/v, can lead to differences in bioavailability (Haleblian, 1975). Furthermore, some drugs undergo transformation from a metastable form into the stable form during processing, grinding, drying or exposure to high humidity (Buxton et al., 1988; DeVilliers et al., 1991; Ando et al., 1992). Therefore, it is imperative that the physical properties of those crystal forms of active substances be determined prior to development of the final formulation.

Mefloquine hydrochloride, α-[2,8-bis(trifluoromethyl)-4-quinolyl]-α-(2-piperidyl) methanol hydrochloride (Fig. 1), is administered orally in the prophylaxis and treatment of chloroquine-resistant falciparum malaria as the *erythro* form,

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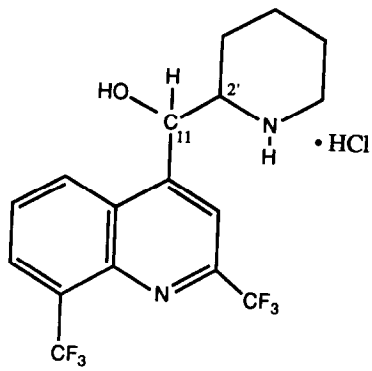

Fig. 1. Mefloquine hydrochloride.

i.e., as a racemic mixture of the (+)-(11*R*,2'*S*) and (−)-(11*S*,2'*R*) forms.

It has a different substitution pattern on the quinoline ring, and a piperidine ring substituent rather than the bulkier bicycloquinolidine ring found in the cinchona alkaloids which previously demonstrated clinical antimalarial activity against *P. falciparum.* This has led some researchers (Karle and Karle, 1991) to study the single crystal structure of mefloquine hydrochloride, and to compare the crystal structures of mefloquine salts recrystallized from various solvents with those of the cinchona alkaloids quinine and quinidine. There have also been attempts to examine the biological similarities of the compounds, including the role played by transport proteins or cellular 'effectors' of antimalarial action.

Bömches and Hardegger (1986) have identified three polymorphs and two hydrate forms of mefloquine hydrochloride obtained by recrystallization from various solvents. However, the physicochemical properties of those polymorphs and solvates have not been described in detail. In the present paper we report on the physicochemical properties of mefloquine hydrochloride polymorphs and solvates determined by use of X-ray powder diffraction, thermal analysis, infrared spectral analysis, scanning electron microscopy, and solubility determinations. In addition, we describe some aspects of the physical and chemical stability of crystals of the pure drug substance and of commercial mefloquine tablets.

Materials and Methods

Preparation of modifications

A bulk sample of mefloquine hydrochloride (later identified as form M) was obtained from Mepha Ltd (lot 01091, Aesch-Basel, Switzerland). This was used in the preparation of all the forms. Forms A, B, E, and I were prepared by recrystallization from hot (A, 70°C; others 50°C) saturated solutions. Form A was obtained from acetonitrile (HPLC Grade, EM Science); form B from acetone (Analytical Reagent, Mallinckrodt, Inc.); form E from ethanol USP (Aper Alcohol and Chemical Co.) or from methanol (suitable for HPLC, spectrophotometry, and gas chromatography, EM Science); and form I from isopropanol (Analytical Reagent, Mallinckrodt, Inc.). In each case the saturated solution was allowed to stand at room temperature, then the crystals were filtered and dried in vacuo at room temperature. Form D was prepared by suspending 2 g of the bulk sample in 20 ml of distilled water at room temperature for 12 h. The precipitate was then filtered and dried at room temperature. Form C was prepared by suspending 200 mg of bulk sample in 500 ml of distilled water at 37°C for 12 h. The precipitate was filtered and then dried at room temperature. Form B' was obtained by heating form B on a hot-stage to 190°C, followed by cooling to room temperature. Form M was obtained by heating form I on a hot-stage to 175°C, followed by cooling to room temperature.

Thermal analysis

The thermograms of the different crystal forms were recorded on a Perkin-Elmer DSC-7 Differential Scanning Calorimeter (Perkin-Elmer Corp., Norwalk, CT) equipped with a TAC 7/7 Instrument Controller and 7700 Professional Computer, and on a Perkin-Elmer Thermogravimetric Analyzer (TGA-7), similarly equipped. Calibration of the DSC was performed using ultrapure indium (99.9999%). The samples were weighed into aluminum pans (open system) and empty pans were used as the reference. A heating rate of 10°C/min was employed, and samples were analyzed under a nitrogen atmosphere.

X-ray analysis

X-ray powder diffraction patterns were collected on an automated diffractometer (Philips PW1710 (Philips Electronic Instruments Co., Mahwah, NJ), using monochromatized CuK_α (λ for $K_{\alpha 1} = 1.54060$ Å; λ for $K_{\alpha 2} = 1.54438$ Å) radiation. The diffractometer was equipped with a 2θ compensating slit and a graphite monochromator. It was calibrated to within 0.02° (2θ) using the quartz peak at 26.66° (2θ). The minimum peak/background ratio was 0.75. Samples were scanned using the powder pack technique; crystalline samples were reduced in particle size by grinding in an agate mortar. The diffractograms were recorded under the following conditions: 40 kV, 30 mA; scan speed, 0.05°/s.

Infrared spectroscopy

Infrared spectra were obtained on the Nicolet Model 5DXB (Nicolet Analytical Instruments, Madison, WI) spectrometer equipped with a deuterated triglycine sulfate (DTGS) detector, a plotter, Nicolet processor and disc drive, and operated under a dry air purge. Spectra were obtained from Nujol mulls prepared in an agate mortar.

Hot-stage microscopy

A Mettler FP-80 temperature programer and a Mettler FP-82 (Mettler Instrument Corp., Hightstown, NJ) hot-stage were used. Microscopic observations were performed with a polarized light microscope (Bausch & Lomb, Rochester, NY).

Scanning electron microscopy

Scanning electron micrographs of the samples were obtained using a scanning electron microscope (Hitachi S-2700, Hitachi Instruments, Inc., Danbury, CT) at magnifications within the range 35–4000 ×.

Solubility measurements

Solubilities of forms A, E, M and D were determined. An excess amount of sample (200 mg) was introduced into 500 ml of distilled water in a 1000 ml round-bottom flask with a plastic cap. The flask was fixed on the sample holder in a thermostatically regulated water bath maintained at 37 ± 0.5°C, and its contents were stirred by means of a paddle at 200 rpm. Aliquots (5 ml) of the solution were withdrawn at appropriate time intervals with a syringe, filtered through a 0.45 μm membrane filter (Millipore Corp., Bedford, MA) and suitably diluted with distilled water. The concentration of the drug was measured spectrophotometrically (Model 8450A, Hewlett-Packard Co., Palo Alto, CA) at 283 nm.

Gas chromatography

Residual amounts of organic solvents in the polymorphs were determined by gas chromatography (Model GC-14A, Shimadzu Scientific Instruments, Inc., Columbia, MD). The experimental conditions were as follows: detector, FID; column, G-300 (2 μm) 1.2 mm × 40 m; column temperature, 60°C; injection temperature, 150°C; carrier gas, He (25 ml/min).

Storage conditions for the stability determination

Modifications of mefloquine hydrochloride (forms E,D and C) and mefloquine hydrochloride commercial tablets (Lariam® tablets, Roche, and Mephaquin® Lactabs®, Mepha) were employed. Ground samples were put into aluminum pans (diameter, 4 cm). Physical mixtures (1 : 1 w/w) of form E and various excipients were also put into aluminum pans. These samples were placed in a desiccator containing a saturated sodium chloride (US, TAC, Mallinckrodt, Inc.) solution and the desiccator was stored in an oven (Blue M Electric Co., Blue Island, IL) at 60 ± 1°C for 2 weeks. Excipients used in this study were methylcellulose (lot MM91040721-A, Dow Chemical Co., Midland, MI); microcrystalline cellulose (lot no. 2014, FMC Corp., Philadelphia, PA); hydroxyethylcellulose (lot ccc-2725D, Union Carbide Corp., San Diego, CA), β-cyclodextrin (lot 18F-3430, Sigma Chemical Co., St. Louis, MO), crospovidone (batch no. 36–0259, BASF Fine Chemicals, Parsippany, NJ) and hydrous lactose (lot no. 24–020–524, Sheffield Products, Norwich, NY).

Thin-layer chromatography (TLC)

TLC was employed to confirm the chemical stability of the commercial mefloquine hydrochloride in tablets stored under accelerated condi-

tions according to the reported method (Karle and Karle, 1991). The chromatography system was as follows: TLC plate, pre-coated TLC plates Silica Gel 60 F-254 (E. Merck); layer thickness, 0.25 mm; developing solvents: toluene : ethanol:conc. NH_4OH (34:15:1) and isopropanol: conc. NH_4OH (9:1); detection method, UV 254 and 365 nm.

Results and Discussion

Identification of forms A, B, E and I

The IR spectra, X-ray powder diffraction patterns and thermal profiles of mefloquine hydrochloride modifications recrystallized from various solvents (acetonitrile, acetone, ethanol and isopropanol) are shown in Figs 2–4, respectively.

All these crystals exhibit characteristic patterns, and they can be distinguished from one another. Therefore, these crystals are designated form A (acetonitrile), form B (acetone), form E (ethanol), and form I (isopropanol), respectively. The IR spectra and powder X-ray diffraction patterns of forms A and E are confirmed to be the same as those reported by Bömches and Hardegger (1986).

From the results of thermal analyses, it can be concluded that form A is an anhydrous or nonsolvate form because it exhibits no weight loss or endotherm due to desolvation. On the other hand, the DSC curve of form B exhibits an endotherm

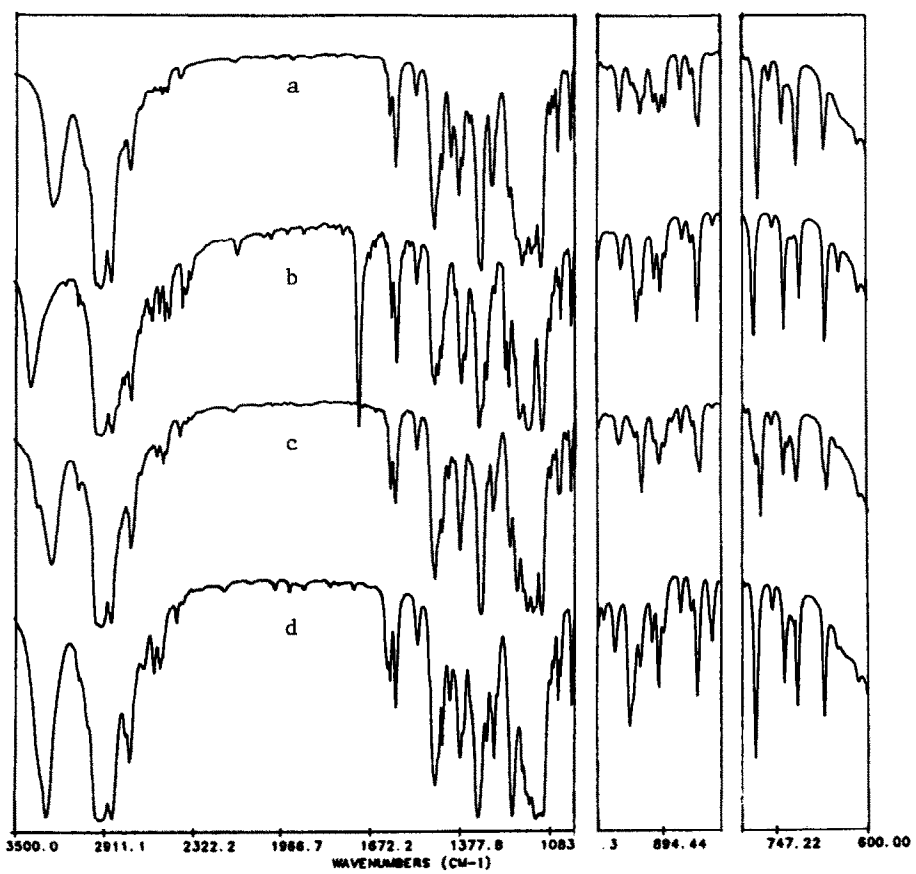

Fig. 2. Infrared spectra of mefloquine hydrochloride. (a) Form A; (b) form B; (c) form E; (d) form I.

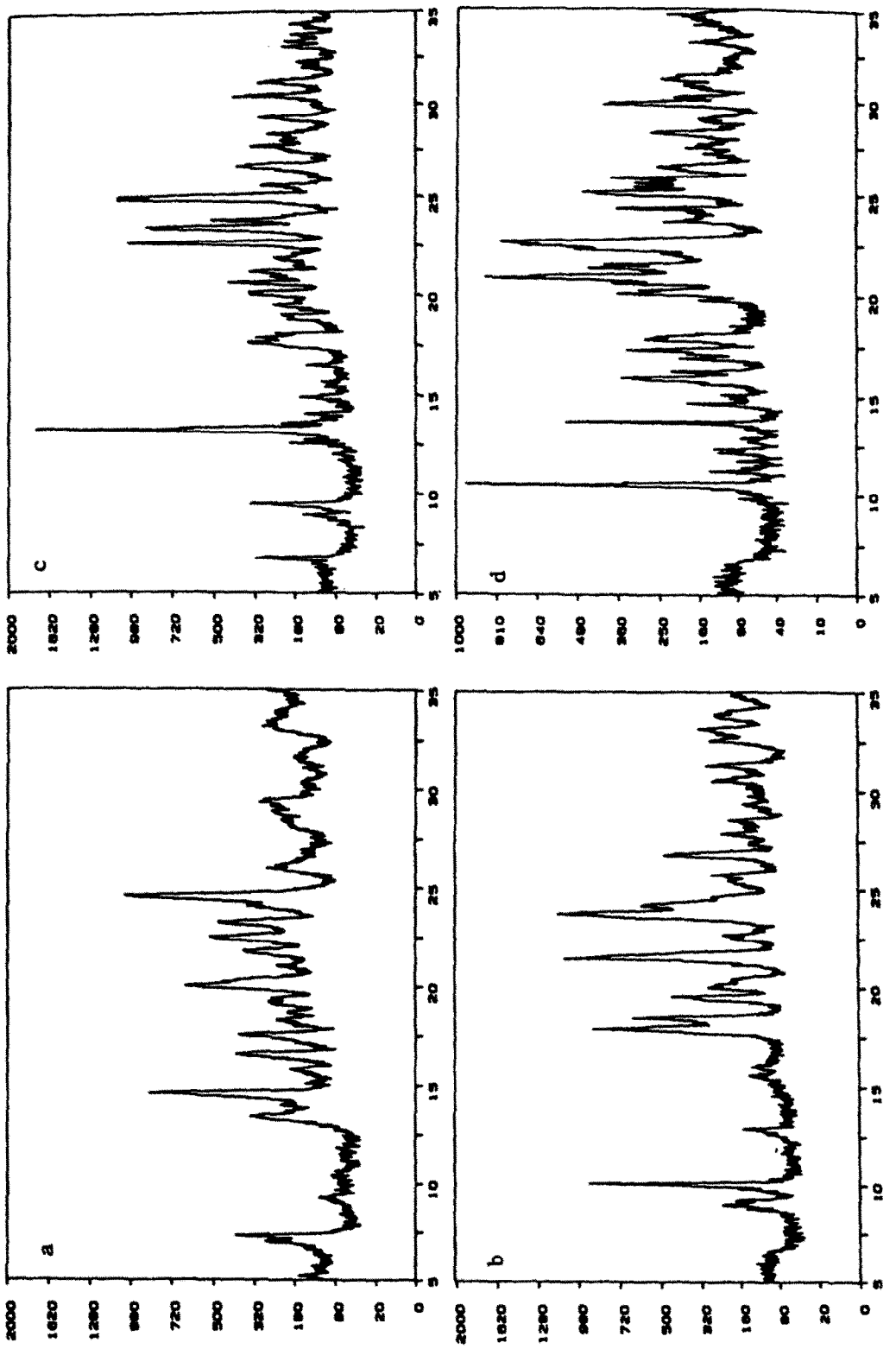

Fig. 3. X-ray powder diffraction patterns of *mefloquine* hydrochloride. (a) Form A; (b) form B; (c) form E; (d) form I.

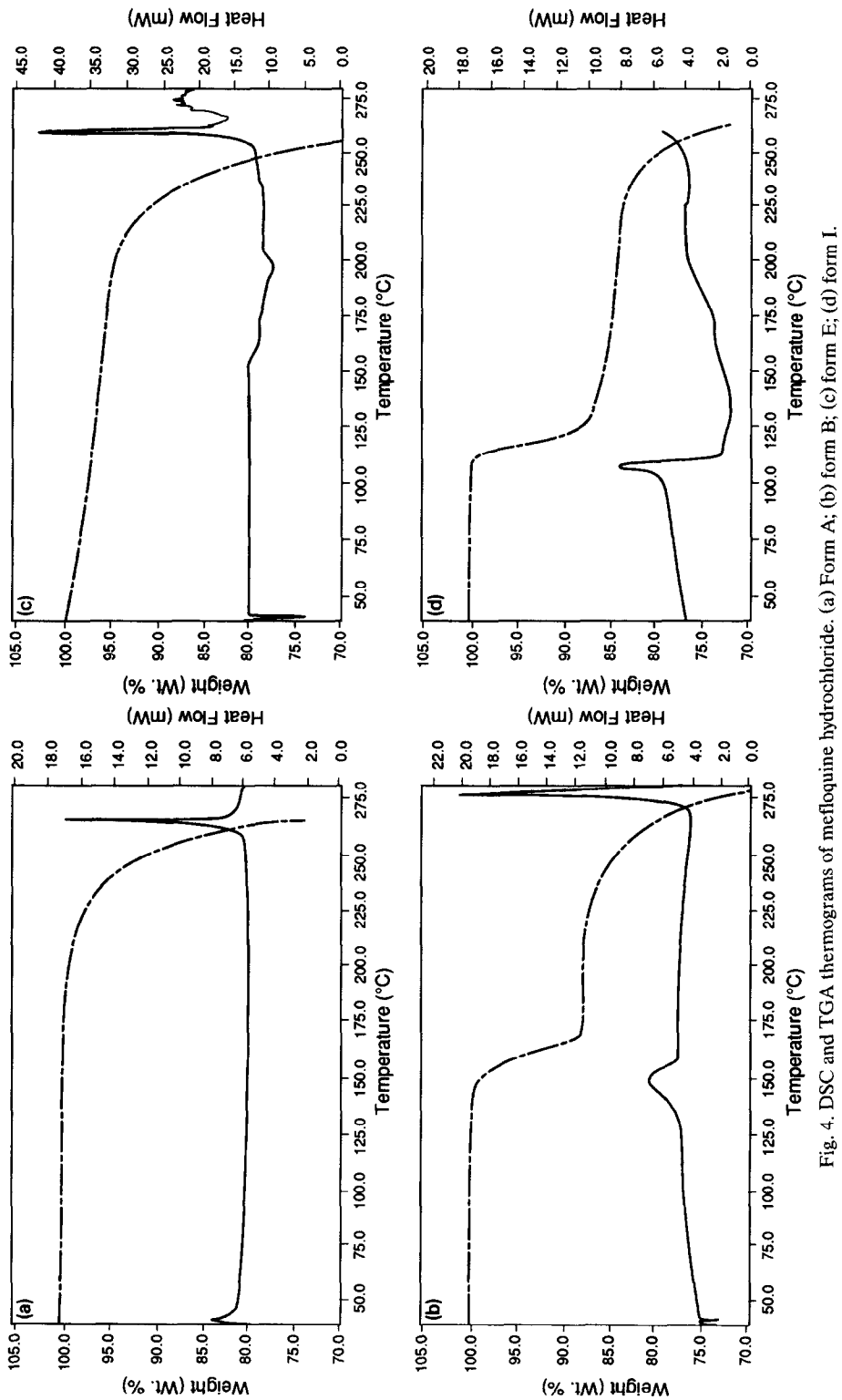

Fig. 4. DSC and TGA thermograms of mefloquine hydrochloride. (a) Form A; (b) form B; (c) form E; (d) form I.

at 120–180°C, with a corresponding weight loss in TGA of 12.2% of the total weight. This thermal behavior, as well as the IR absorption observed at 1700 cm^{-1} for form B, indicates that form B is an acetone solvate. The molecular ratio of mefloquine hydrochloride to acetone is estimated to be 1:1 (calculated amount of acetone is 12.3%) from the weight loss value obtained by TGA. The thermogram of form I also exhibits an endothermic peak at 100–150°C, and a sharp weight loss of 14.9% of the total weight, suggesting desolvation to be the cause. From the value of the weight

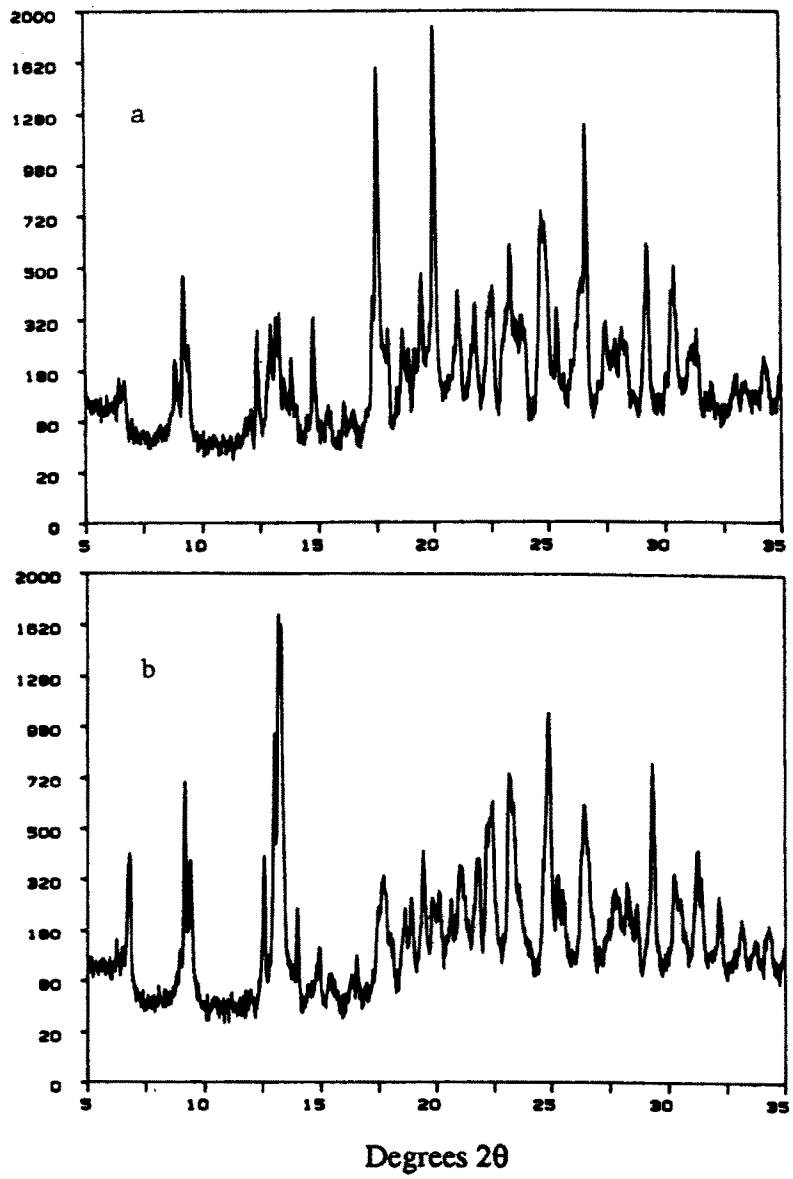

Fig. 5. X-ray powder diffraction patterns of form E before and after removal of ethanol. (a) Before removal of ethanol (ethanol content: 2.12%); (b) after removal of ethanol (ethanol content: 0.12%).

loss observed in TGA, the molecular ratio of drug to isopropanol is estimated to be 1 : 1 (calculated amount of isopropanol is 12.7%).

In contrast to forms B and I, a gradual weight loss occurring within the range from room temperature to 150°C is observed in the TGA thermogram of form E, along with a very shallow endothermic peak in the DSC from 100 to 150°C, followed by a broad, shallow, exotherm from 150 to 205°C. When the residual amount of ethanol was determined by GC, the sample was found to contain only 2.12% of ethanol. Thus, the weight loss observed below 100°C is considered largely to be due to the removal of adsorbed moisture. Following redrying of the sample at 80°C in vacuo, the amount of ethanol in the sample decreased to 0.12% as determined by GC. In the DSC thermogram for this desolvated sample the endothermic peak near 100°C disappeared and the broad exotherm became less pronounced, suggesting that the exotherm could be due to some decomposition accompanying loss of residual solvent. It should also be noted that 'melting' of mefloquine hydrochloride at 259–265°C is accompanied by sublimation and decomposition, perhaps with loss of hydrogen chloride (Figs 4 and 11).

X-ray powder diffraction patterns of these two samples, before and after removal of ethanol, were studied. The X-ray diffraction patterns of form E before and after removal of ethanol, are shown in Fig. 5.

In Fig. 5 it can be seen that while there are differences in the relative intensities of the peaks, their positions are the same in the X-ray powder diffraction patterns of the two samples. It has been reported that furosemide recrystallized from

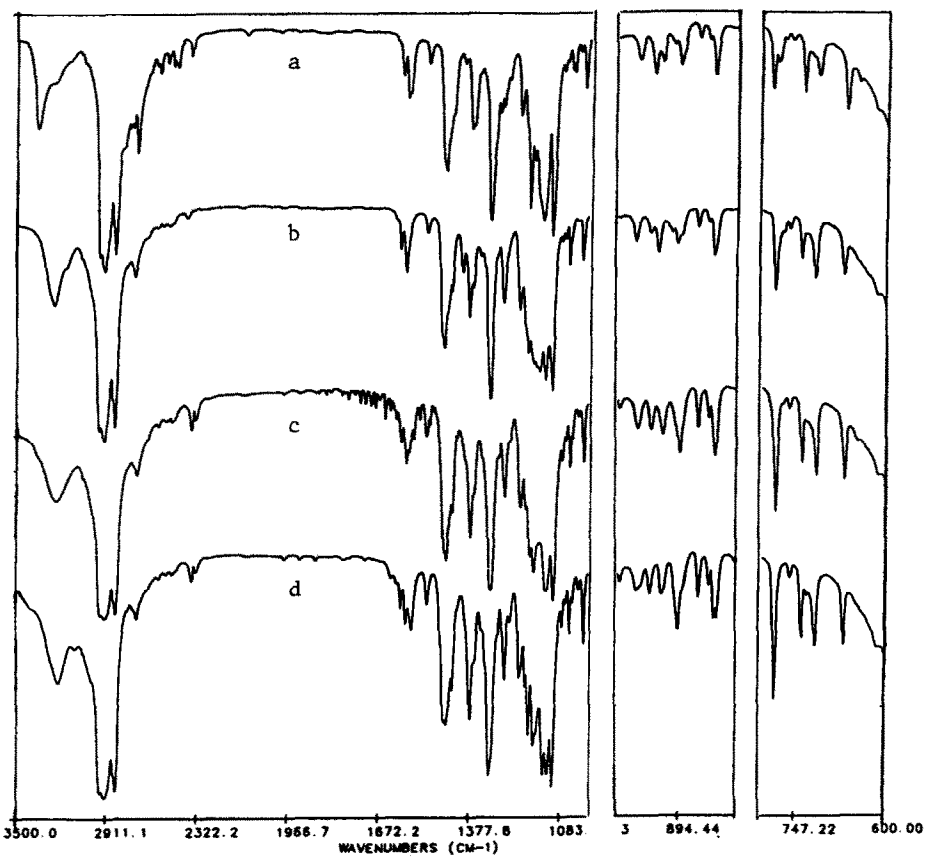

Fig 6. Infrared spectra of mefloquine hydrochloride. (a) Form B′; (b) form M, (c) form C; (d) form D.

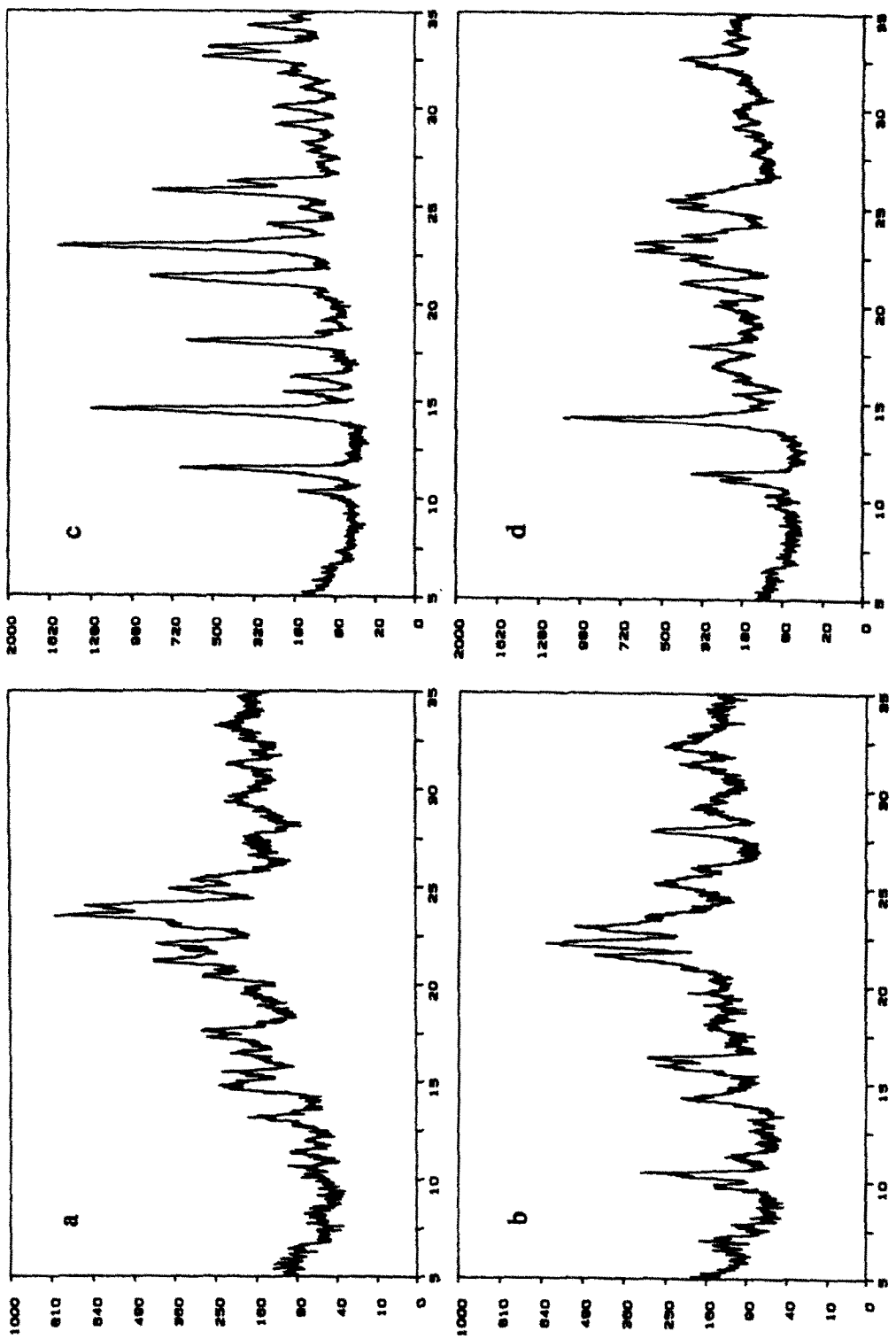

Fig. 7. X-ray powder diffraction patterns of mefloquine hydrochloride. (a) Form B′; (b) form M; (c) form C (d) form D.

acetone also includes a small amount (0.7%) of solvent, and the X-ray powder diffraction pattern of this crystal observed before and after removal of the recrystallization solvent shows no significant changes. Furthermore, complete desolvation was not attained even when the sample was stored under extreme conditions (60°C, 10–3 Torr, 16.5 h). After this exposure desolvation was still observed in the high temperature range, 100–200°C in the TGA thermogram. Therefore, the authors concluded that the molecules of acetone are entrapped nonstoichiometrically and dispersed around that portion of the crystal which has a lattice defect (Matsuda and Tatsumi, 1990).

In the case of form E, desolvation was observed to occur over a relatively high temperature range, from 100–175°C, suggesting that the crystals of form E have lattice defects similar to those found in furosemide. However, form E contains a larger amount of ethanol (about 2%), compared with the amount of solvent observed in furosemide, and most of the remaining ethanol could be removed at 80°C in vacuo. Furthermore, the amount of residual ethanol in form E was reproducible, approx. 2%.

The fact that an X-ray powder diffraction pattern of the crystal obtained from methanol exhibits the same pattern as that of form E obtained from ethanol suggests that form E also contains a channel, a layer or a cage which is large enough to accommodate a number of solvent molecules. Presently, we are obtaining a crystal structure of form E by use of a single crystal analysis. So, shortly we should be able to provide more details about the relationship between the drug and solvent molecules in form E.

Desolvation of forms B and I

Occasionally, some solvates undergo melting accompanied by desolvation, and then resolidify as the temperature rises, to give the solvent-free form. This type of behavior is exhibited by crystals of forms B and I. In order to completely remove the solvents, samples of form B and I were heated up to 190 and 175°C, respectively, at which temperature both endothermic peaks due to desolvation returned to the baseline. The IR spectra and X-ray powder diffraction patterns of these heated samples (forms B′ and M) are shown in Figs 6 (a,b) and 7 (a,b).

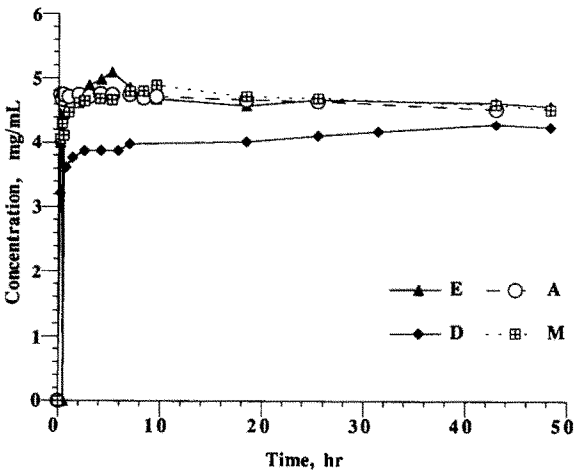

Fig. 8. The dissolution behavior of the A, D, E and M forms of mefloquine hydrochloride in water at 37°C. (○) Form A; (▲) form E; (⊞) form M; (♦) form D.

The IR and X-ray powder diffraction patterns of the heated samples of forms B and I are confirmed to be different from those of the other crystal forms. Thus, these new crystal forms are designated as forms B′ and M, respectively.

When mefloquine hydrochloride obtained from Mepha is examined, the IR and X-ray powder diffraction patterns coincide with those of form M. Forms I and M are not described by Bömches and Hardegger (1986), however, the sample obtained from Mepha is apparently produced by desolvation of form I. Furthermore, the IR spectrum of 'form B' reported by these authors was confirmed to be the same as that of form B′. This result suggests that form B in their patent is obtained by heating the acetone solvate form.

Solubility of the crystalline forms

Powder dissolution patterns of three polymorphic forms (forms A, E and M) and a hydrate form D (hemihydrate form) are shown in Fig. 8.

The sample used to obtain the dissolution pattern of form M in Fig. 8 was the powder obtained from Mepha. From Fig. 8, it can be seen that saturation was attained within 10 h. Form A reached supersaturation after approx. 5 min, form E after 5 h, and form M reached supersaturation

after 9 h, then their solubilities decreased. On comparing the supersaturated states of these samples, it can be seen that form E attained the highest concentration (≈ 5.1 mg/ml), and the other two polymorphs (forms A and M) reached similar concentrations, (≈ 4.8 and ≈ 4.9 mg/ml). Once equilibrium was attained, all polymorphs showed the same solubility (4.6 ± 0.1 mg/ml, $n = 8$), and this solubility was maintained until the experiment was terminated at 50 h.

On the other hand, the solution of form D did not reach a supersaturated state, and form D exhibited the lowest solubility (4.3 mg/ml, $n = 2$) among these samples. The form D crystals which we obtained have been identified as the hemihydrate form reported by Bömches and Hardegger. The DSC thermogram of form D exhibits a shallow endotherm from room temperature to 100°C and a 2.1% loss of weight is seen in TGA. These results suggest that the endotherm and weight loss are due to dehydration of 1/2 mol water/mol mefloquine hydrochloride (calculated percentage weight loss, 2.1%). The dissolution curves of three kinds of polymorphs in aqueous solution indicate that they undergo transformation into another crystal form. All precipitates remaining after the dissolution test were collected to identify the crystal form using X-ray powder diffraction. The crystals were identical to those of form C. Figs 6 (c,d), 7 (c,d) and 9 show the IR spectra, X-ray powder diffraction patterns, and thermograms of form C.

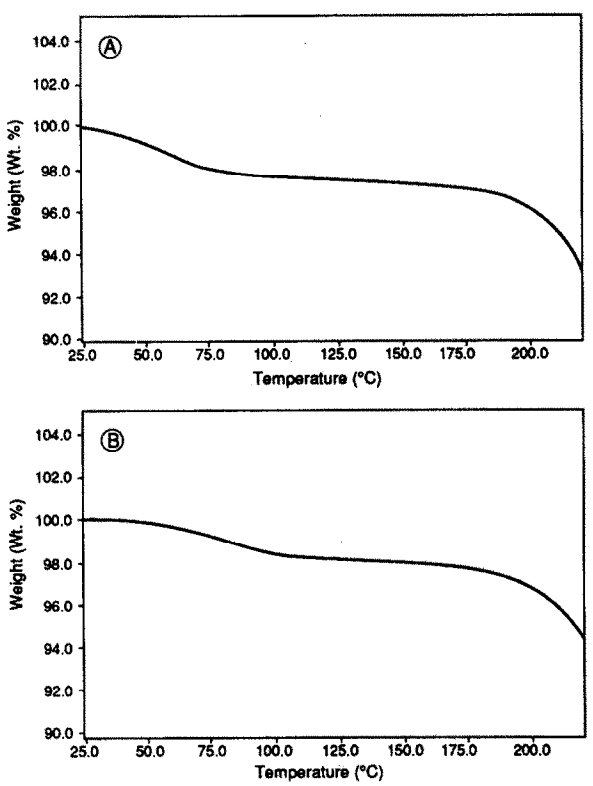

Fig. 9. TGA thermograms of mefloquine hydrochloride. (a) Form C; (b) form D.

The IR and X-ray powder diffraction patterns of the crystalline precipitate obtained after the dissolution test of form D were compared with those of a sample of form D not exposed to water. This result indicates that form D is not transformed to another crystal form under the dissolution conditions employed. On the other hand, the crystallized precipitates of polymorphs A, E and M exhibit the same IR and X-ray powder diffraction patterns, and these IR and X-ray results indicate that forms A, E and M are converted to the same crystal form on exposure to water. The thermograms of these precipitates exhibit very similar patterns to that of form D, a broad endothermic peak from room temperature to 100°C and a 2.1% loss of weight. These results suggest that polymorphs A, E and M undergo a crystallization process together with a phase transformation, not into form D, but into another hemihydrate form. This hemihydrate form is designated form C according to the report of Bömches and Hardegger (1986). However, no details regarding form C, or its crystallization process have been described. Scanning electron photographs of forms C and D, shown in Fig. 10 are quite similar, as are their IR spectra (Fig. 6c and d).

However, when the solubilities of these two hydrate forms are compared, form D is less soluble than form C. Therefore, it can be concluded that form D is thermodynamically more stable than form C at 37°C.

Stability study

From a practical point of view, it is very important to know which crystal form is present in a

tablet or capsule dosage form because occasionally, changes occur during the formulation process or under certain storage conditions. Therefore, the crystal form of mefloquine hydrochloride in commercial tablets, Lariam® (Roche) and Mephaquin® (Mepha) was studied. In order to identify the crystal form in the tablets the X-ray powder diffraction technique was used. X-ray powder diffraction patterns of mefloquine hydrochloride tablets obtained from the two commercial sources are shown in Fig. 11a and c.

In Fig. 11, it can be seen that Lariam® and Mephaquin® tablets contain forms E and C of mefloquine hydrochloride, respectively. From the

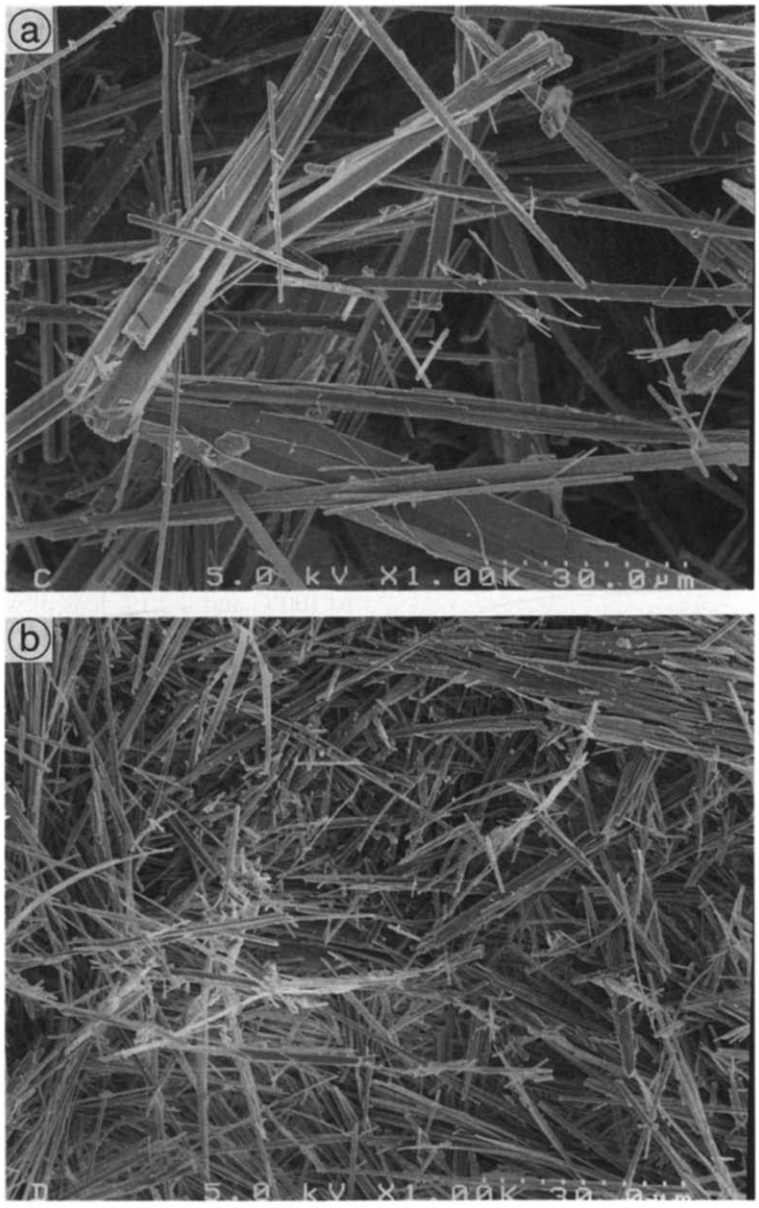

Fig. 10. Scanning electron photomicrographs of mefloquine hydrochloride. (a) Form C; (b) form D. Magnification, 1000 × (space between dots at lower right = 3 μm).

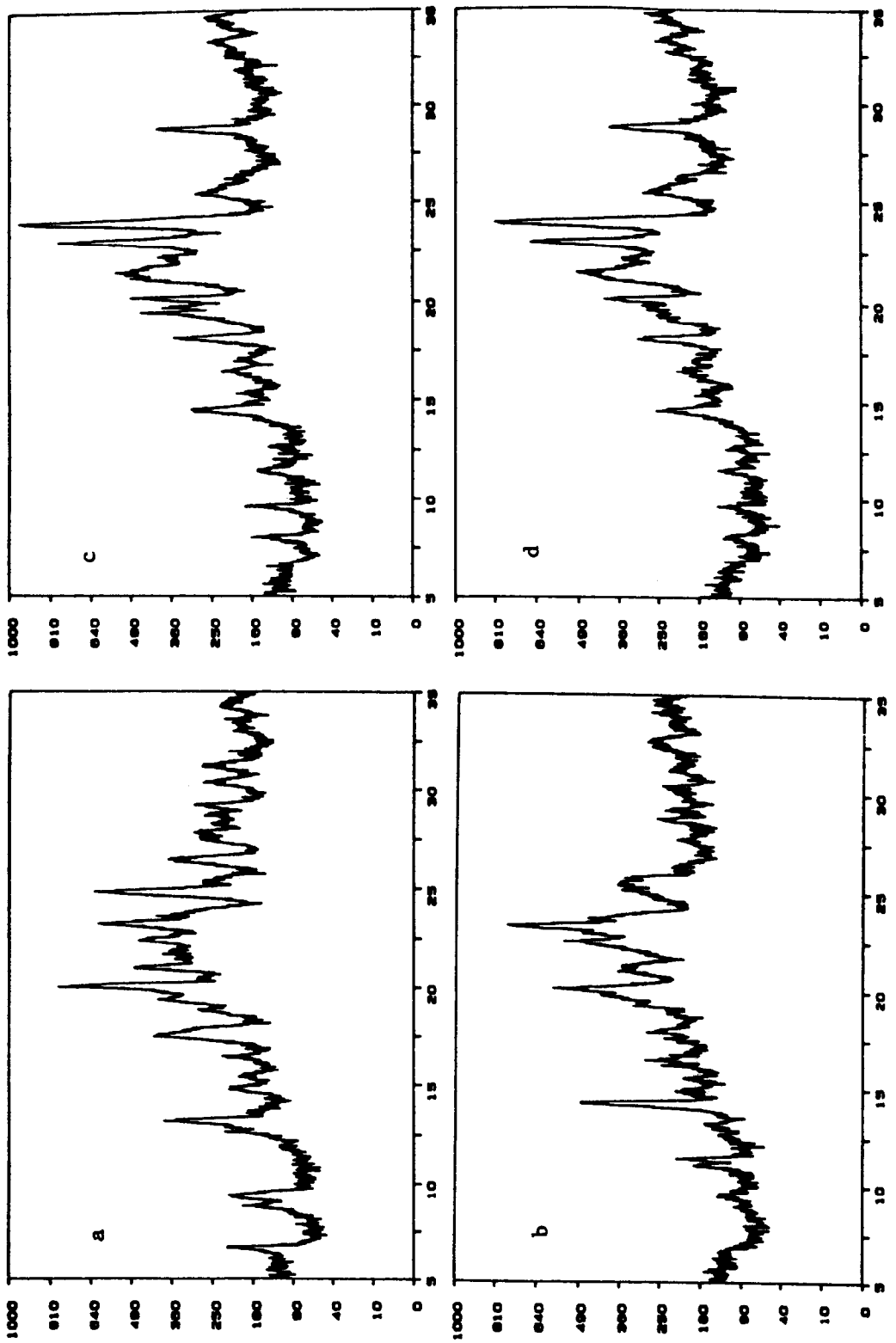

Fig. 11. X-ray powder diffraction patterns of mefloquine hydrochloride tablets. (a) Lariam® (intact); (b) Lariam® (stored at 60°C, 75% R.H. for 2 weeks); (c) Mephaquin® (intact); (d) Mephaquin® (stored at 60°C, 75% R.H. for 2 weeks).

dissolution data, forms E and M have higher solublities than forms C and D. The X-ray results suggest that mefloquine hydrochloride in Mephaquin® tablets may be changed from form M into form C during the formulation process.

After solubility, the next important factor to consider in selecting an appropriate crystal form is the physicochemical stability of the active substance in tablets. Thus, the effects of temperature and humidity on the chemical and physical stability of commercial mefloquine hydrochloride tablets were studied. X-ray powder diffraction

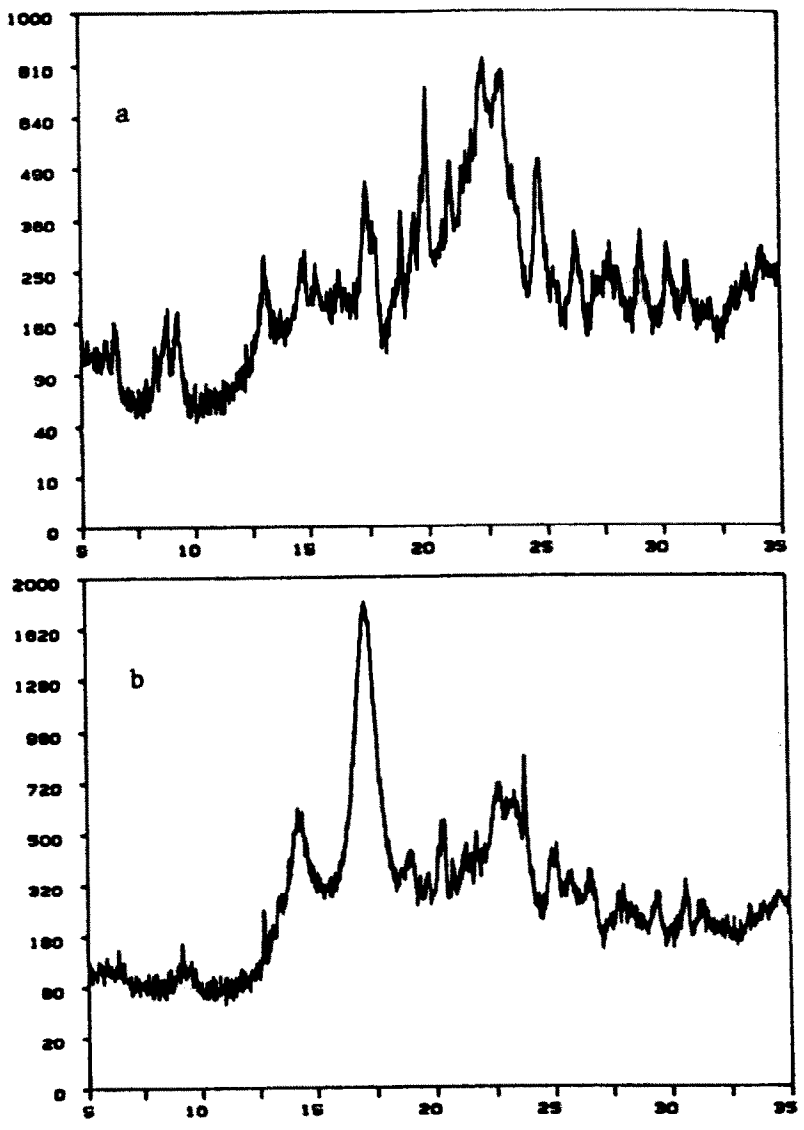

Fig. 12. X-ray powder diffraction patterns of the mixture of mefloquine hydrochloride. Form E and microcrystalline cellulose (1 : 1). (a) Intact; (b) stored at 60°C, 75% R.H. for 2 weeks.

patterns of the commercial tablets following storage at 60°C and 75% R.H. for 2 weeks are shown in Fig. 11b and d.

From these results, it is clear that the crystal structure in Lariam®, form E, changed into form D while the crystal form in Mephaquin®, form C,

TABLE 1

X-ray diffraction data

Form A (Fig. 3a)		Form B (Fig. 3b)		Form E (Fig. 3c)		Form I (Fig. 3d)	
Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)
7.31	37.78	8.99	18.7	6.78	16.2	10.49	100.0
13.49	23.21	10.13	79.8	9.47	18.3	13.71	52.3
14.6	79.87	17.95	78.7	13.19	100.0	15.87	32.2
16.61	29.69	18.52	48.0	17.57	18.8	17.31	30.3
17.51	30.41	19.59	34.7	20.14	17.9	20.86	89.5
20.06	55.38	21.51	94.4	20.59	24.1	21.01	59.9
22.35	33.42	23.81	100.0	21.17	17.9	21.38	43.4
22.53	43.27	24.21	50.2	22.59	61.8	22.68	81.4
23.25	39.01	26.75	38.5	23.31	47.6	24.36	36.2
24.56	100.0	31.27	20.1	24.79	61.4	25.92	35.4
		33.14	22.1	26.50	19.7	29.88	33.4
				27.65	19.2		
				29.27	16.2		
				30.42	21.0		
				31.17	15.8		

Form E (Fig. 5a)		Form E (Fig. 5b)		Form B′ (Fig. 7a)		Form M (Fig. 7b)	
Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)
6.70	5.5	6.82	22.8	13.16	17.3	9.72	17.7
8.86	8.6	8.96	5.3	14.58	22.3	10.46	52.2
9.21	22.5	9.17	37.0	15.54	23.4	14.27	28.2
9.45	9.2	9.42	21.6	16.49	20.1	15.85	28.7
12.38	12.6	12.59	21.4	17.27	30.0	16.00	36.4
12.96	12.4	13.02	54.0	17.61	33.2	16.39	46.8
13.17	14.3	13.18	100.0	21.15	51.8	21.59	79.2
13.32	15.2	13.31	95.5	22.08	49.6	22.05	100.0
14.77	15.6	14.95	6.3	23.52	100.0	23.04	90.7
17.54	80.0	17.72	17.8	24.02	88.4	25.21	35.8
19.45	22.7	19.43	22.1	24.91	40.5	26.12	19.4
20.02	100.0	20.14	15.7	25.36	30.9	27.93	39.9
21.05	19.7	21.00	19.3	31.36	23.8		
21.79	17.7	21.74	21.1	32.46	27.7		
22.57	19.5	22.43	34.3				
23.02	12.2	23.13	42.5				
23.34	30.2	23.35	33.7				
24.89	33.4	24.89	64.9				
25.40	16.7	25.29	18.4				
26.62	57.9	26.59	22.5				
27.44	14.6	27.70	14.9				
29.24	30.4	29.32	46.1				
30.39	22.0	30.23	18.7				
31.38	10.5	31.40	17.6				

(continued overleaf)

showed no significant changes. The ground samples of these commercial tablets also showed the same results. The chemical stabilities of these stored samples were studied by TLC. On the TLC plates, no degradation products were detected, and only the mefloquine spot was ob-

TABLE 1 (continued)

Form C (Fig. 7c)		Form D (Fig. 7d)	
Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)
10.32	8.6	11.09	20.1
11.55	41.4	11.44	30.3
14.57	84.4	14.23	100.0
15.45	11.1	16.8	19.6
16.25	9.6	17.95	27.6
18.10	40.3	20.28	18.3
21.47	51.7	21.39	25.0
22.97	100.0	22.44	30.7
24.11	15.5	22.82	51.6
25.76	54.4	23.26	52.5
26.22	25.1	23.63	30.7
32.67	34.3	25.07	32.5
33.16	32.7	25.42	37.3
		25.73	26.9
		32.65	29.3

Lariam® Intact (Fig. 11a)		Lariam® 60°C, 75% R.H. (Fig. 11b)		Mephaquin® Intact (Fig. 11c)		Mephaquin® 60°C, 75% R.H. (Fig. 11d)	
Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)
6.66 [a]	23.6	9.53	7.4	7.98	11.2	8.11	6.1
8.80	15.6	11.12 [b]	13.3	9.56	11.9	9.63	8.7
9.30 [a]	22.1	11.50 [b]	17.7	11.41 [a]	9.2	11.57 [a]	6.6
13.14 [a]	44.1	14.29 [b]	64.9	14.44	21.6	14.58	21.7
14.79	19.3	14.91	14.5	16.39	11.9	16.52	14.1
15.45	14.4	15.56	13.6	18.04 [a]	26.1	18.19 [a]	28.1
16.42	19.3	16.25	21.3	19.33	40.2	19.07	19.0
17.47	48.4	16.51 [b]	27.7	19.62	30.6	20.25	41.5
18.77	29.3	17.92 [b]	23.2	20.12	42.4	21.52 [a]	51.3
19.31	43.65	19.25	31.2	20.99	38.8	23.02 [a]	79.9
19.99	100.0	20.12	72.3	21.32 [a]	47.6	24.01	100.0
20.16 [a]	74.9	21.04 [b]	35.4	22.91 [a]	75.6	25.48 [a]	22.8
20.96	55.2	22.56 [b]	57.9	23.78	86.4	28.85	36.7
22.39 [a]	52.3	23.30 [b]	100.0	23.89	100.0	33.39	17.4
23.21	75.6	23.82 [b]	41.4	25.32 [a]	19.7		
24.78 [a]	75.6	25.48 [b]	34.0	28.75	35.0		
26.47	33.8	25.83 [b]	28.1	33.43	12.9		
29.21 [a]	23.6	26.41	8.5				
30.31 [a]	16.3	28.74	14.2				
31.15 [a]	18.2	29.27	11.3				
		30.42	10.2				
		31.19	8.7				
		32.79 [b]	13.6				

served. The R_f values were 0.40 and 0.50 for the two developing solvents used, toluene : ethanol : conc. NH_4OH (34 : 15 : 1) and isopropanol : conc NH_4OH (9 : 1), respectively. Thus, mefloquine hydrochloride in tablets was confirmed to be chemically stable under these storage conditions. Therefore, Lariam®, which contains form E should be protected from moisture to prevent a change in crystal form. It is reasonable that the commercial tablets are packed in a blister pack and sealed in aluminum foil.

Although the metastable form of a drug substance is often very useful because its solubility is higher than that of the stable form, the metastable form sometimes undergoes transformation under certain storage conditions. Consequently, many researchers have explored the possibility of employing such additives as polyvinylpyrrolidone to retard the transformation (Ebian et al., 1973). The effect of various excipients on the transformation phenomenon was investigated. The excipients employed were: methylcellulose, microcrystalline cellulose, hydroxyethylcellulose, β-cyclodextrin, crospovidone and hydrous lactose. These excipients were mixed with mefloquine hydrochloride, form E, in a ratio of 1 : 1, and the

TABLE 1 (continued)

Form E + MCC intact (Fig. 12a)		Form E + MCC 60°C, 75% R.H. (Fig. 12b)	
Angle (2θ)	Rel. intensity (%)	Angle (2θ)	Rel. intensity (%)
6.59	11.5	9.17	4.8
8.84	14.9	12.71	10.3
9.27 [a]	15.5	13.36	8.1
13.06 [a]	29.3	14.22 [b]	23.9
14.85	26.7	17.08 [b]	100.0
15.33	24.1	19.03	11.6
16.30	23.1	19.75	7.0
17.41 [a]	51.1	20.39	20.2
18.91	41.8	20.73	9.0
19.47	40.4	21.28 [b]	14.4
19.76	51.1	21.70	16.7
19.99 [a]	83.4	22.68	31.4
20.97	58.6	22.50 [b]	28.1
21.48	53.2	23.38 [b]	27.2
21.88	68.4	23.77 [b]	40.1
22.21	92.9	24.86	13.7
22.41 [a]	100.0	25.13 [b]	13.7
23.21 [a]	95.7	25.71 [b]	9.0
24.61 [a]	55.3	26.52	9.5
26.28 [a]	33.0	27.73	5.9
27.17	22.4	27.98	7.9
27.82	27.0	29.46	7.2
28.13	25.9	30.62	9.9
29.13 [a]	34.6	31.23	4.8
30.21 [a]	32.1		
31.05 [a]	25.2		
32.92	19.4		
33.54	24.8		

[a] Due to form E.
[b] Due to form D.
[c] Due to form C.

mixtures were stored at 60°C and 75% R.H. for 2 weeks. The X-ray powder diffraction patterns of the mixture of form E and microcrystalline cellulose before and after the stability study are shown in Fig. 12.

From this study, it was observed that only form E combined with microcrystalline cellulose underwent a phase transformation from form E into form D, while the other mixtures did not exhibit any changes in their X-ray powder diffraction patterns. It is also confirmed that forms E, C and D when stored alone, showed no significant changes. Therefore, it appears that microcrystalline cellulose has a unique ability to promote the transformation. Although the hygroscopicities of these excipients are different, in most cases, it is assumed that water molecules are adsorbed onto the surface of each excipient and penetrate into its pores hydrating the polar functional groups of the excipient and becoming tightly bound. In the case of microcrystalline cellulose only the amorphous regions can take up water (Zografi and Kontny, 1986). In its amorphous regions water or other hydroxylic solvents are absorbed by the cellulose, forming pools of liquid connected by crystalline bridges (Kremer and Tabb, 1990). Water in these regions is said to cause intercrystalline swelling, resulting in the rupturing of hydrogen bonds between cellulose molecules and their replacement with hydrogen bonds between a cellulose molecule or molecules and water. The region of intramolecular hydrogen bonding gives way to regions of progressive association with water which, in turn, is progressively more loosely bound to the cellulose in the disordered/amorphous area. This loosely bound water is available for the partitioning of solutes (Kremer and Tabb, 1990). It is presumably these 'pools' of water in which mefloquine hydrochloride dissolves. From these results, it appears that microcrystalline cellulose should be avoided in the formulation of mefloquine hydrochloride tablets.

Conclusions

Our results make it clear that in the development of the most appropriate formulation of a drug substance for clinical use, it is very important to consider not only polymorphism in the pure chemical substance, but also the influence of excipients on the polymorphic transformation.

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