International Journal of Pharmaceutics, 59 (1990) 281–286
Elsevier

IJP 02023

Study of the polymorphism of 3-(((3-(2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl)((3-(dimethylamino-3-oxopropyl)thio)methyl)-thio)propanoic acid (MK571) by DSC, TG, XRPD and solubility measurements

Samir Ghodbane and James A. McCauley

Analytical Research Department, Merck Sharp & Dohme Research Laboratories, R80L-106, Rahway, NJ 07065 (U.S.A.)

(Received 18 August 1989)
(Modified version received 27 October 1989)
(Accepted 2 November 1989)

Key words: Antagonist, MK571; Leukotriene D_4-specific antagonist; Polymorphism; Solubility; X-ray powder diffraction; DSC

Summary

Two polymorphs of the free acid of MK571 have been characterized unambiguously by differential scanning calorimetry (DSC), thermal gravimetric analysis (TG), X-ray powder diffraction (XRPD) and solubility measurements. These two species are designated forms I and II, respectively. The solubilities of the two crystal forms of MK571 were determined at several temperatures (5–55 °C) in isopropyl alcohol (IPA) and methyl ethyl ketone (MEK). In all cases, Form II shows higher solubility than Form I which indicates that the latter is the thermodynamically stable form in this temperature range. The melting point of Form I (164 °C) is higher than that of Form II (152 °C), indicating that Form I is the more stable polymorph in the high temperature range. These data suggest that the two forms are monotropic polymorphs.

Introduction

When the same chemical substance exists in more than one crystal structure, the phenomenon is termed polymorphism while the different crystal structures are called forms, polymorphs or polymorphic modifications (Verma et al., 1966). In general, the crystal structures and the properties of the polymorph of a given chemical substance are as distinct as those belonging to different chemical species. Polymorphism, although not generally predictable, occurs frequently in pharmaceutical compounds. Consequently, investigation of polymorphism has become a requirement in the pharmaceutical industry (Lord, 1988) because the physical properties and bioavailabilities of crystalline drugs depend on their polymorphic form (Halebian et al., 1969; Yang et al., 1972; Halebian, 1975; Byrn, 1982).

MK571 (Fig. 1) is a potent selective, orally active, specific leukotriene D_4 (LTD_4) antagonist (Young et al., 1987) and is currently being evaluated as a potential therapy for bronchial

Correspondence: S. Ghodbane, Analytical Research Department, Merck Sharp & Dohme Research Laboratories, R80L-106, Rahway, NJ 07065, U.S.A.

0378-5173/90/$03.50 © 1990 Elsevier Science Publishers B.V. (Biomedical Division)

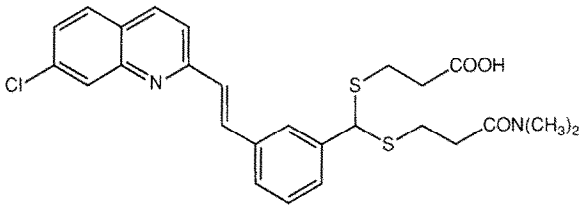

Fig. 1. Structure of MK571.

asthma. In the crystalline state, it appears to exist in at least two polymorphic forms, designated Forms I and II. In the present study, the physical properties of the polymorphs were investigated by DSC, XRPD and solubility measurements and the thermodynamic relationship between the two forms established.

Materials and Methods

Materials

MK571 is synthesized via a four-step procedure (McNamara et al., 1989) starting from 7-chloroquinaldine (Leir, 1977). MK571 is then recrystallized from MEK or ethanol.

Apparatus and procedures

The DSC curves were obtained in open pans under a nitrogen atmosphere (about 30 ml/min) at heating rates of 2 and 20 °C/min with a Dupont 910 Thermal Analyzer. The sample size ranged from 2 to 6 mg.

Weight loss determinations were made under a nitrogen flow (30 ml/min) at a heating rate of 10 °C/min up to 100 °C and 2 °C/min from 100 to 190 °C with a Perkin-Elmer TGA 7 system.

X – ray powder patterns were acquired with a Phillips APD 1700 automated powder diffraction instrument using Cu-Kα radiation.

The solubility of each form was determined at several temperatures in MEK and IPA. Saturated solutions of both forms were prepared by suspending weighed amounts of the samples in 2 ml of solvent in a borosilicate glass tube (13 × 100 mm). The tubes were then sealed and the saturated solutions equilibrated overnight and/or for 3 days by means of a vibromixer in an RTE-8 Endocal refrigerated circulating water bath. After this equilibration period, the solid was allowed to settle by rapid centrifugation, the glass tube broken open and the mother liquor recovered. The latter was usually diluted with the corresponding solvent prior to analysis by UV spectrophotometry. A Perkin Elmer Lambda 5 UV/VIS spectrophotometer coupled to a 3600 Data Station was used. For each form and solvent, two unsaturated standard solutions containing 1 and 2 mg in 100 ml were prepared and their absorbance values determined.

Results and Discussion

Recrystallization of MK571 from ethanol and MEK yields Forms I and II, respectively. The

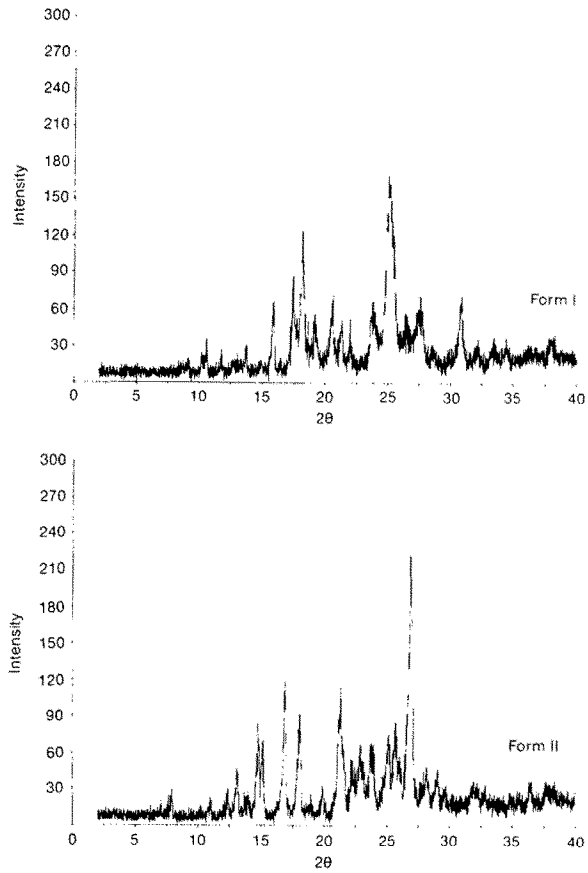

Fig. 2. X-ray powder diffraction patterns of the two polymorphs.

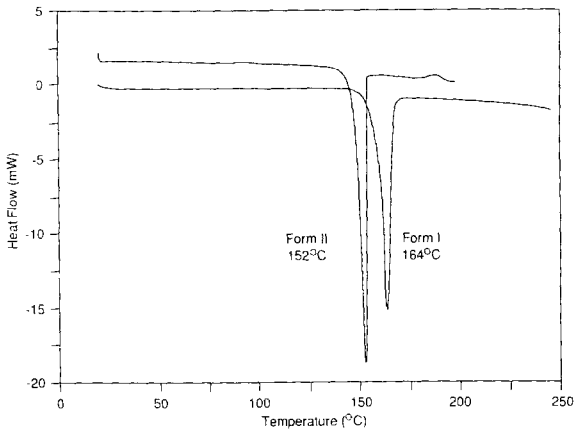

Fig. 3. Superimposed DSC traces of the two polymorphs of MK571.

XRPD patterns obtained for Forms I and II are reproduced in Fig. 2. The powder patterns are clearly different and reveal that MK571 exists in two different crystalline structures. No significant weight loss was observed by TG for either form implying that no solvation occurs.

The DSC curves, recorded at 2°C/min, of Forms I and II, respectively, are superimposed in Fig. 3. Form II melts at 152°C, 12°C lower than Form I (164°C). The melting temperatures are virtually independent of heating rate. The heat of fusion of Form I is 12.9 kcal/mol, with that of Form II being 11.7 kcal/mol. The higher melting point for Form I indicates that it is the more thermodynamically stable polymorph in the temperature region of the melting points. The higher heat of fusion also supports this contention, although it is not absolutely conclusive.

The solubility (S_i) of either polymorph in both solvents increases with rising temperature (Tables 1 and 2) and is independent of the equilibration time. The uncertainty in the solubility data is the standard deviation of measurements taken on a minimum of two saturated solutions at three different wavelengths. XRPD and/or DSC did not indicate any conversion of the polymorphs during the equilibration period. Moreover, there was no chemical change in the solid or liquid phase for MK571 as determined by HPLC. The solubility of Form II is higher than that of Form I in IPA ($S_2/S_1 \approx 1.7$) and MEK ($S_2/S_1 \approx 1.9$). The solubility ratio reflects the relative thermodynamic stability of the two polymorphs, i.e., the relative Gibbs free energy, ΔG, of the two forms. Let us consider the following transformation of Form II to Form I:

TABLE 1

Solubilities (in mg/ml) of MK571 in IPA

T (°C)	S_1	S_2	S_2/S_1
5	0.057±0.003	0.092±0.001	1.6
15	0.113±0.001	0.192±0.001	1.7
25	0.228±0.007	0.390±0.006	1.7
36	0.531±0.002	0.87 ±0.06	1.6
45	0.968±0.007	1.78 ±0.01	1.8
55	1.51 ±0.02	4.01 ±0.06	2.8

$$\text{MK571(s,II)} \rightarrow \text{MK571(s,I)} \quad (1)$$

where s represents pure solid.

If we can determine the sign of the ΔG for Eqn. 1, the more stable form can be identified. Since the Gibbs free energy is a state function, its value does not depend on the path by which the final product is reached. Therefore, Eqn. 1 can be rewritten as the sum of the following equations:

$$\text{MK571(s,II)} \rightarrow \text{MK571(sol},S_2) \quad (2)$$

$$\text{MK571(sol},S_2) \rightarrow \text{MK571(sol},S_1) \quad (3)$$

$$\text{MK571(sol},S_1) \rightarrow \text{MK571(s,I)} \quad (4)$$

where sol denotes solution and S_i the solubility of Form i (i = I,II). Since the steps represented by Eqns 2 and 4 are equilibria, their Gibbs free energy change is equal to zero. The standard state of the compound in solution is taken as the usual thermochemical one, namely, the hypothetical

TABLE 2

Solubilities (in mg/ml) of MK571 in MEK

T (°C)	S_1	S_2	S_2/S_1
15	0.73±0.02	1.39±0.04	1.9
25	1.24±0.08	2.40±0.05	1.9
35	2.20±0.02	4.3 ±0.4	1.9
45	3.34±0.03	7.2 ±0.1	2.1

ideal solution at unit molality (Wagman et al., 1982). If it is assumed that the saturated solutions are ideal (a good assumption considering the low solubility – 10^{-3} mole fraction), the free energy change for Eqn. 3 and consequently for the transformation of II to I is given by:

$$\Delta G(1) = \Delta G(3) = RT \ln(S_1/S_2) \quad (5)$$

where R is the gas constant in cal/mol per K.

Since the ratio S_1/S_2 is always less than unity (see Tables 1 and 2), $\Delta G(1)$ is always negative, i.e., the reaction is spontaneous. In other words, Form I is thermodynamically the more stable form in the temperature range of the solubility experiments.

Another straightforward thermodynamic (Prausnitz, 1969) argument can be used to determine the standard integral heat ($\Delta H^{\circ}_{\mathrm{sol}i}$) and entropy ($\Delta S^{\circ}_{\mathrm{sol}i}$) of saturated solution, respectively, for Form i (i = I,II). The integral heat of saturated solution corresponds to the heat absorbed or evolved while the integral entropy of saturated solution is a measure of the randomness (or ordering) which takes place when a saturated solution of Form i is made. The change in the standard Gibbs free energy, $\Delta G^{\circ}_{\mathrm{sol}i}$ of saturated solution is given by the following equation (for the sake of simplicity in the subsequent text, the superscript ° will be omitted):

$$\Delta G_{\mathrm{sol}i} = \Delta H_{\mathrm{sol}i} - T\Delta S_{\mathrm{sol}i} = -RT \ln(a_i/a_{si}) \quad (6)$$

where a_i is the activity of MK571 in solution and a_{si} that of Form i in the solid phase. Since the standard state in the solid phase is taken as the pure solid phase at the corresponding temperature, a_{si} is always equal or very close to unity.

Since MK571 is not very soluble in both solvents (i.e., dilute solution), it can be assumed that the activity coefficient is equal to unity and the activity can be equated to the mole fraction:

$$a_i = x_i \approx n_i/n_{\mathrm{svt}} = (m_i M_{\mathrm{svt}})/(m_{\mathrm{svt}} M_i) \quad (7)$$

where n denotes the number of moles, m is the mass, M is the molecular weight, and the subscripts i and svt refer to Form i and solvent, respectively.

Since the solubility S is defined as the mass of compound dissolved per unit volume of solvent:

$$S_i = m_i/V_{\mathrm{svt}} \quad (8)$$

and the solvent density d as:

$$d = m_{\mathrm{svt}}/V_{\mathrm{svt}} \quad (9)$$

x_i can be rewritten as follows:

$$x_i = S_i(M_{\mathrm{svt}}/(M_i d)) \quad (10)$$

Combining and rearranging Eqns 6 and 10 lead to the following expression:

$$\log(S_i) + \log(M_{\mathrm{svt}}/\{M_i d\}) =$$

$$-\Delta H_{\mathrm{sol}i}/(2.303RT) + \Delta S_{\mathrm{sol}i}/(2.303R) \quad (11)$$

The solubility as a function of temperature, in a given solvent, is fitted to the following equation:

$$\log(S_i[\mathrm{mg/ml}]) = B_i - A_i/T \quad (12)$$

where A_i and B_i are the linear least-squares parameters of the $\log(S_i)$ vs $1000/T$ fit (Table 3). The experimental results are plotted in Figs 4 (IPA) and 5 (MEK) with correlation coefficients

TABLE 3

Linear least-squares parameters and integral heats of saturated solution

	IPA		MEK	
	Form I	Form II	Form I	Form II
A	2.678	2.821	2.044	2.193
B	8.37	9.09	6.96	7.75
r^2	0.997	0.997	0.998	0.993
ΔH_{sol} [c]	12.2 ± 0.3	12.9 ± 0.4	9.3 ± 0.3	10.0 ± 0.2
ΔH_{melt} [c]	12.9 ± 0.6	11.7 ± 0.6		
ΔS_{sol} [d]	34.5 ± 0.1 [a]	37.8 ± 0.1 [a]	28.4 ± 0.1 [b]	32.0 ± 0.1 [b]

[a] d^{25} = 0.782 mg/ml; M = 60.1 g/mol.
[b] d^{25} = 0.802 mg/ml; M = 72.1 g/mol.
[c] kcal/mol.
[d] cal/mol per K.

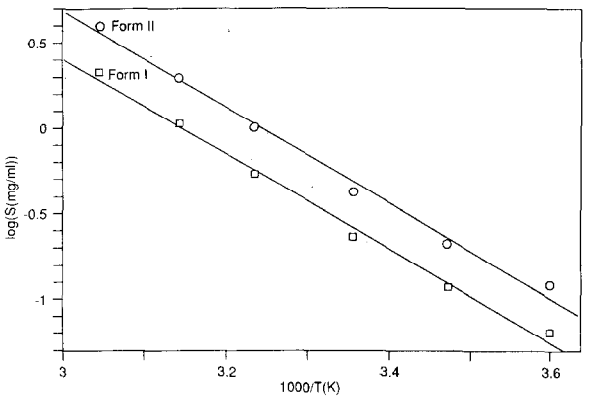

Fig. 4. Plot of $\log(S_i)$ vs $1000/T$ in IPA (i = I or II).

of the linear least-squares fits all in excess of 0.99 (Table 3).

Comparison of Eqns 11 and 12 leads to the determination of the integral heat:

$$\Delta H_{\mathrm{sol}i}(\mathrm{kcal/mol}) = 2.303RA_i \qquad (13)$$

and entropy of saturated solution:

$$\Delta S_{\mathrm{sol}i}(\mathrm{cal/mol\ per\ K}) = 2.303R\left\{B_i + \log\left[M_{\mathrm{svt}}/(M_i d)\right]\right\} \qquad (14)$$

For a given polymorph, in IPA, $\Delta H_{\mathrm{sol}i}$ is equal, within the limits of experimental error, to the corresponding heat of fusion (see Table 3). In MEK, this equality no longer exists. These trends

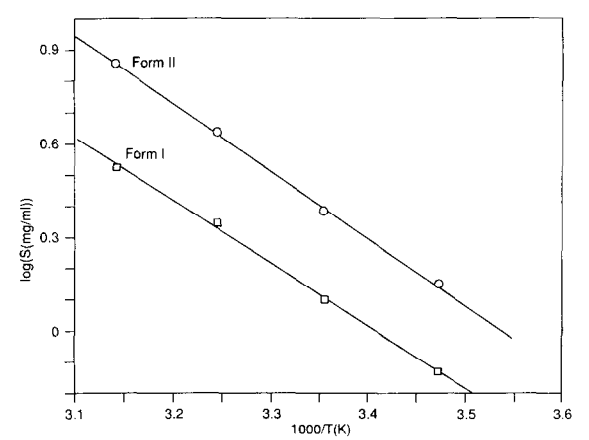

Fig. 5. Plot of $\log(S_i)$ vs $1000/T$ in MEK (i = I or II).

seem to indicate that the assumption of ideality for the solution is a good approximation in IPA but some non-ideality exists in MEK. Determination of the entropy changes should shed more light on the degree of ideality of the solutions. The integral entropy is a function of the solvent density (Eqn. 14). To a first approximation, some insight into the ordering of the solutions is gained by calculation of the entropies assuming that the solvent densities remain constant within the temperature range investigated. The results are listed in Table 3. The integral entropies are consistently higher for IPA. This implies that the saturated IPA solutions are more disordered than the corresponding MEK solutions, thus indicating stronger MK571-MEK interactions. These latter results corroborate those determined for the enthalpy regarding the relative idealities of the saturated solutions.

The ΔS_{sol} values are always smaller for Form I inrespective of the solvent (3.3 and 3.6 cal/mol per K in IPA and MEK, respectively). These values, which are identical within experimental error, correspond to the standard entropy difference $\Delta S°$, for the transformation of Form II to I (see Eqn. 1). The integral heat of saturated solution of Form II is 0.7 kcal/mol higher than that of Form I regardless of the solvent. This corresponds to the 0.7 kcal/mol standard enthalpy change for Eqn. 1. The standard free energy change for the transformation of II to I can then be calculated at 25°C from the following equation:

$$\Delta G° = \Delta H° - T\Delta S° \qquad (15)$$

The value obtained is negative in sign, −0.3 kcal/mol, confirming that Form I is the thermodynamically stable form at 25°C.

Conclusion

MK571 exists in two non-solvated crystal forms. From the solubility and DSC measurements, it is evident that the two forms are related as monotropic crystal forms with Form I being the more stable polymorph.

From the thermodynamic evaluation of the solubility data, it is clearly demonstrated that solute-solvent interactions are stronger in MEK than in IPA. Additional work is required at the molecular level (solution IR and NMR) in order to shed more light on this matter. Finally, the two forms should also be investigated in the solid state (solid-state NMR and IR, single-crystal X-ray diffraction) to determine the nature of their differences.

References

Byrn, S.R., *Solid State Chemistry of Drugs*, Academic Press, New York, 1982, p. 79.

Haleblian, J.K., Characterization of habits and crystalline modification of solids and their pharmaceutical applications. *J. Pharm. Sci.*, 64 (1975) 1269–1288.

Haleblian, J.K. and McCrone, W.J., Pharmaceutical applications of drugs. *Pharm. Sci.*, 58 (1969) 911–929.

Ip, D.P., Brenner, G.S., Stevenson, J.M., Lindenbaum, S., Douglas, A. W., Klein, S.D. and McCauley, J.A., High resolution spectroscopic evidence and solution calorimetry studies on the polymorphs of enalapril maleate. *Int. J. Pharm.*, 28 (1986) 183–191.

Leir, C.M., *J. Org. Chem.*, 42 (1977) 911–913.

Lord, A.G., BPC's and cGMP's. *Pharm. Eng.*, 8 (1988) 30–35.

McNamara, J.M., Leazer, J.L., Bhupathy, M., Amato, J.S., Reamer, R.A., Reider, P.J. and Grabowski, E.J.J., *J. Org. Chem.*, 54 (1989) 3718–3721.

Prausnitz J.M., *Molecular Thermodynamics of Fluid Phase Equilibria*, Prentice-Hall, Englewood Cliffs, NJ, 1969, pp. 391–395.

Verma, A.R. and Krishna P., *Polymorphism and Polytypism in Crystals*, Wiley, New York, 1966, pp. 7–60.

Wagman et al., The NBS tables of Chem. Therm. Properties, *J. Phys. Chem. Ref. Data*, Suppl. 2 (1982).

Yang, S.S. and Guillory, J.K., *J. Pharm. Sci.*, 61 (1972) 26–40.

Young, R.N., Zamboni, R. and Leger, S., *European Patent Application* no. 2190377, November 18, 1987.