Journal of Thermal Analysis, Vol. 54 (1998) 139-149

MELTING CURVES OF TERFENADINE CRYSTALLIZED FROM DIFFERENT SOLVENTS

J. Canotilho[1], *F. S. Costa*[1], *A. T. Sousa*[1], *J. S. Redinha*[2] *and M. L. P. Leitão*[2*]

[1]Faculdade de Farmácia, Universidade de Coimbra, 3000 Coimbra
[2]Departamento de Química, Faculdade de Ciencias e Tecnologia, Universidade de Coimbra 3000 Coimbra, Portugal

Abstract

Several samples of terfenadine prepared by crystallization from different solvents under different experimental conditions were studied. The DSC curves obtained at a heating rate of $1°C\ min^{-1}$ afforded the temperature of melting and the mole fractions of the components of each sample. Certain of the samples were composed of two solid phases mixed in molar ratios varying between nearly one and a single structural form. Three polymorphic forms were identified.

Keywords: crystallization, DSC, melting curves, peak-fitting, polymorphism, terfenadine

Introduction

Terfenadine, α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol, is used in medical practice as an antihistaminic drug. It has been claimed by several authors that terfenadine can occur in polymorphic forms. However, in spite of the number of papers published on this field, the polymorphism of terfenadine remains an open question.

Processes relating to the preparation of a high and a low-melting form were mentioned in some patent applications [1–4]. However, in the USP [5], no reference is made to the existence of polymorphs.

The melting point is by rule one of the reference physical properties in the characterization of terfenadine polymorphs. In the literature, the disagreement of the data on terfenadine is a common feature. Indeed, while some authors [6] claimed to have identified three polymorphic forms, I (*m.p.* 149–152°C), II (*m.p.* 146–148°C) and III (*m.p.* 142–144°C), others [7] suggested that the diversity of the melting points observed for terfenadine were due to the existence of a high

* Author to whom all correspondence should be addressed.

1418–2874/98/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

and a low-melting form and a mixture of the two. The melting points reported for the polymorphs also vary considerably from one author to another.

Besides a high and a low-melting form, Hakanen *et al.* [8] identified a solvate obtained by crystallization from methanol solution. Following the same experimental procedure, the authors of the present work [9] proved that no solvate is formed and that the endotherm observed in the DSC traces, attributed by Hakanen to a solvate, reflects instead a transition from a metastable phase into a more stable one.

The misunderstanding increases still further when a specific polymorphic form is assigned to a certain solvent. It has been stated [8, 9] that terfenadine prepared from ethanol does not participate in any solid-phase transition but fusion. Nevertheless, in a recent publication [10], it was concluded that *n*-alkanols, with the exception of methanol and ethanol, produce stable polymorphs. These two alcohols, and also *iso*-alkanols, give rise to solvates.

No comparison of the data determined for the polymorphs by means of different techniques is possible [6, 8, 11–13].

A more systematic study seems essential to prove the existence of polymorphs of terfenadine, to establish methods of their preparation and to tabulate their properties. Such a study has been undertaken by the authors for some time, and the present paper reports data on the melting curves of terfenadine prepared by crystallization from different solvents under different experimental conditions.

Chemicals and methods

Since it has been proven that the solvents influence the properties of terfenadine obtained by crystallization, one way to prepare a wide diversity of forms is to employ different solvents and follow several procedures. Methanol, ethanol, acetone, cyclohexane and ethanol-water were the solvents used. Saturated solutions of terfenadine in these solvents were prepared and the solid phases were obtained by evaporating the solvent or by lowering the temperature. The solid obtained from each of the crystallization processes was dried at 40°C under vacuum for 24 h and kept in a desiccator.

Terfenadine was supplied by Sigma Chemical Co. The infrared spectrum, X-ray diffractogram and DSC trace were similar to those obtained for the USP Reference Standard. The solvents were of the best grade available commercially.

Table 1 lists the solvents, and the processes employed in the preparation of the various samples.

DSC curves were produced with a power-compensated Perkin-Elmer DSC 7 calorimeter equipped with a CCA 7 controlled cooling device. The calorimeter was calibrated for temperature with indium and cyclohexane, and for heat with indium. The expected accuracy is ±0.28°C for T and ±0.06 J g^{-1} for ΔH. The experiments were carried out under dry nitrogen in the temperature range between –40 and 170°C. TGA with an STA Rheometric Scientific instrument revealed no loss in mass in the temperature range between 25 and 170°C.

Table 1 Processes of preparation of terfenadine samples by crystallization from different solvents

Sample	Solvent	Initial conditions	Crystallization process	
		saturated solution at/	solvent evaporated at/	crystal growth at/
		°C	°C	
1a	ethanol	60	60	
1b			20	
1c				20
1d				3
1e				–3
2a	methanol	50	50	
2b			20	
2c				20
2d				3
2e				–3
3	acetone	40		3
4	cyclohexane	60		3
5	ethanol/water (7:3, v/v)	60		20

Results and discussion

Two types of DSC curves were recorded by heating terfenadine samples from 25 to 170°C. One exhibits no phase transition except fusion, while the other reveals an endotherm followed by an exotherm transition before melting takes place, as reported by some authors [8, 9]. The first group includes samples 1a, 1b, 1c, 2a, 3 and 5, and the second group samples 1d, 1e, 2b, 2c, 2d and 2e. Sample 4 gives a smaller premelting peak than the above substances.

Table 2 presents results obtained on the temperature and enthalpy of fusion. Each value is the mean of data from five experiments. The uncertainties are twice the standard deviations.

Table 2 involves some features which are worthy of mention. Both the nature of the solvent and the method of preparation play a role in the characteristics of the samples and hence the fusion curves. The melting points, T_{onset}, lie in the temperature range between 143.8 and 149.8°C. The sample obtained from cyclohexane gives the lowest melting point and that obtained from the ethanol-water solution the highest one. The samples obtained from ethanol, methanol and acetone have values of T_{onset} or T_{peak} in a range of 2–3°C.

Differences in $\Delta_{fus}H$ can also be observed, which are apparently related to the existence or co-existence of premelting phase transitions. The values found for

Table 2 Temperatures and enthalpies of fusion of terfenadine samples determined from DSC curves recorded at 10°C min^{-1}

Sample	T_{onset}/ °C	T_{peak}/ °C	$\Delta_{fus}H$/ kJ mol^{-1}	Remarks
1a	146.7±0.63	151.2±0.55	53.6±0.22	
1b	146.1±0.47	149.4±0.55	53.8±0.75	second max. at 150.3±0.40
1c	145.8±0.06	151.0±0.15	54.2±0.22	second max. at 148.2±0.15
1d	145.9±0.13	149.1±0.14	53.4±0.52	slightly asymmetric curve
1e	144.6±0.20	147.8±0.17	44.2±0.15	second max. at 150.2±0.16
2a	146.3±0.28	150.5±0.40	54.3±0.15	
2b	147.4±0.58	149.2±0.49	52.9±0.84	
2c	146.5±0.08	148.5±0.07	51.8±0.60	
2d	146.8±0.50	148.6±0.44	35.3±0.39	second max. at 150.9±0.39
2e	145.0±0.16	148.2±0.17	39.5±0.42	shoulder at 150.5±0.28
3	146.5±0.29	151.2±0.37	54.4±0.33	second max. at 149.2±0.28
4	143.8±0.23	145.6±0.17	48.5±0.99	slightly asymmetric curve
5	149.8±0.39	153.4±0.75	54.5±0.15	

$\Delta_{fus}H$ of the samples exhibiting no solid-phase transition lie around 53 kJ mol^{-1}, while the others display smaller values, with significant differences between samples.

As pointed out in the remarks on Table 2, some fusion peaks are slightly asymmetric or present shoulders or even two maxima, features that may indicate the presence of more than one pure crystalline form. As concerns the differences in T_{peak} and $\Delta_{fus}H$ between samples, the structures involved should be similar, which makes terfenadine a very complex system to be studied.

To acquire a deeper insight into these systems, DSC curves were recorded at heating rates of 10, 5, 3 and 1°C min^{-1} for samples examined without interruption of the heating, or after subjecting the samples to 130°C for 1 or 30 min. The results obtained on sample 2b, as an example, are shown in Fig. 1.

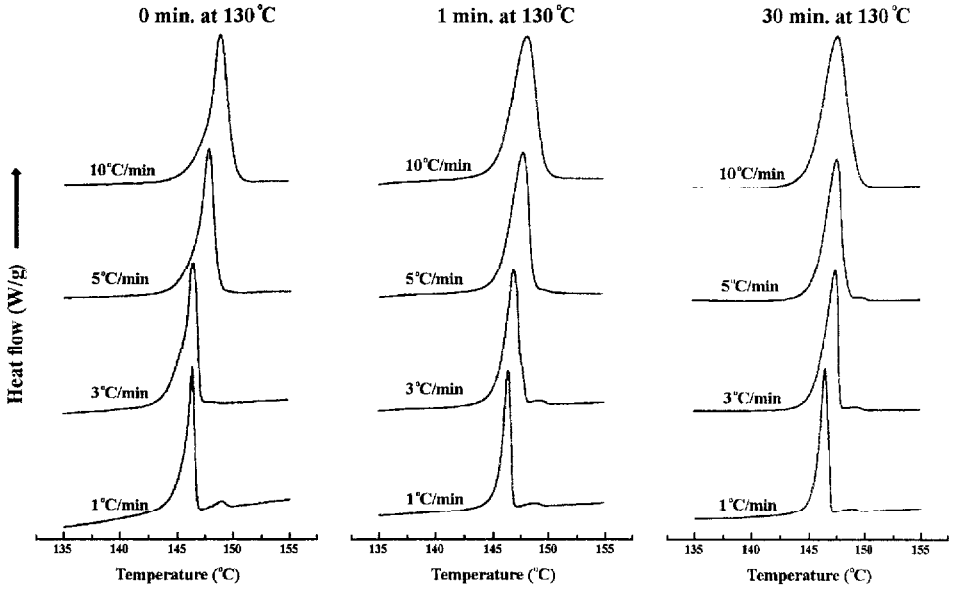

Fig. 1 DSC curves for sample 2b at different heating rates and different heating times at 130°C

Heating the samples for a certain time at a temperature near the melting point improved the resolution and a shift in T_{peak} towards a constant value was observed. However, the DSC traces at lower heating rates do not depend on whether or not the samples had any prior thermal treatment. At 1°C min^{-1}, T_{peak} and $\Delta_{fus}H$ have the same values, no matter what the history of the sample. Before these conclusions, DSC curves were recorded at 1°C min^{-1} for all samples and the results are presented in Table 3.

For all curves except sample 5, two peaks are observed, but with great diversity as concerns the degree of overlapping and the peak areas.

The values obtained for $\Delta_{fus}H$ allow the differentiation of two groups of samples. The first comprises the samples obtained from ethanol-water, acetone and ethanol at temperatures between 60 and 3°C, and from methanol at 50°C, which have $\Delta_{fus}H$ values between 53 and 52 kJ mol^{-1}. The second involves the samples obtained from ethanol and methanol at lower temperature, and from cyclohexane, which give a lower and broader range for $\Delta_{fus}H$.

The effect of the temperature of crystallization on $\Delta_{fus}H$ is well illustrated by the example of methanol. A gradual decrease of the temperature gives rise to a gradual decrease in enthalpy.

The analysis of the peaks can be further refined by mathematical means. This was done by using the Peak Fit Program of Jandel Scientific GmbH, Germany. This program allows determination of the maxima and the areas of overlapping

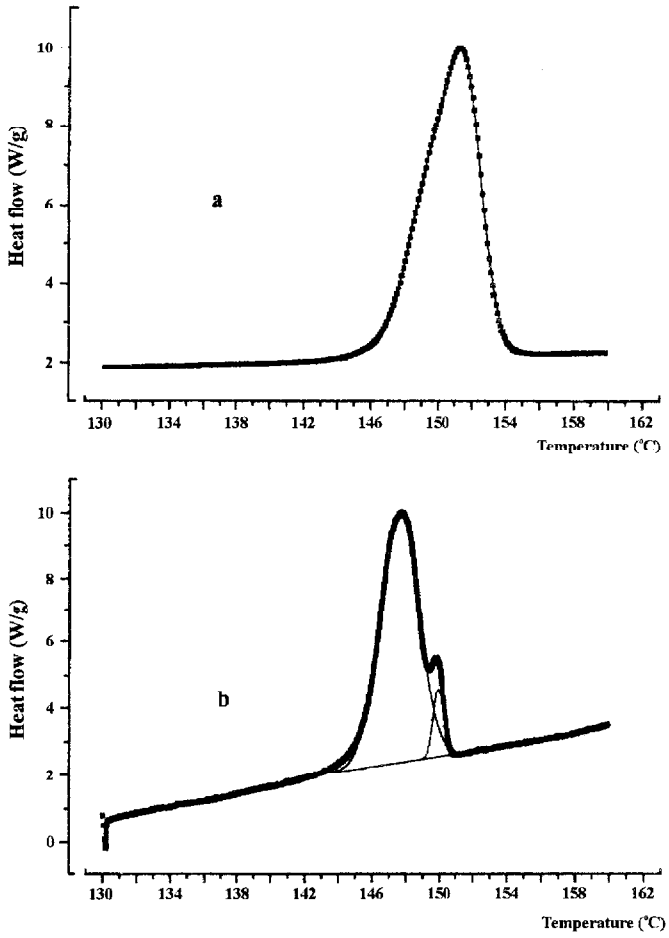

Fig. 2 DSC curves for sample 2a. a) Heating rate 10°C min^{-1} . b) Heating rate 1°C min^{-1}; the two peaks determined by peak-fitting analysis are shown

Table 3 Temperatures and enthalpies of fusion of terfenadine samples determined from DSC curves recorded at 1°C min^{-1}

Sample	T_{onset}/	T_{peak}/		$\Delta_{fus}H$/
	°C			kJ mol^{-1}
1a	145.5±0.19	147.8±0.02	149.7±0.08	52.0±0.30
1b	146.1±0.09	147.5±0.21	149.1±0.36	52.2±0.95
1c	146.1±0.35	147.0±0.41	150.0±0.41	53.3±0.58
1d	145.3±0.53	146.5±0.21	148.7±0.13	52.2±0.61
1e	145.3±0.08	146.5±0.06	149.3±0.05	48.3±0.36
2a	145.6±0.05	147.7±0.14	149.6±0.30	51.9±0.70
2b	145.4±0.53	146.2±0.50	148.6±0.56	50.7±0.12
2c	144.4±0.04	146.5±0.04	148.9±0.03	50.3±0.74
2d	144.2±0.30	146.0±0.30	148.9±0.40	49.7±0.61
2e	145.3±0.06	146.6±0.01	149.3±0.02	49.6±0.29
3	146.5±0.81	147.7±0.78	150.0±0.70	52.1±0.55
4	143.9±0.30	146.3±0.10	149.4±0.13	46.8±0.47
5	149.4±0.09	150.5±0.19		53.2±0.58

curves, often observed in analytical work. A Gaussian function was found to give accurate fittings to the DSC peaks and this function was therefore used in this analysis. Figure 2 shows the fitting analysis for sample 2a.

Table 4 Fitting of DSC curves obtained at a heating rate of 1°C min^{-1}

Sample	T_{peak}/°C	ΔH_i/kJ	α_i
1a	147.8	45.6	0.88
	149.7	6.5	0.12
1b	147.2	40.9	0.77
	149.4	12.4	0.23
1c	147.3	22.0	0.41
	150.2	31.4	0.59
1d	146.3	42.8	0.82
	148.6	9.3	0.18
1e	146.6	34.6	0.71
	149.2	14.1	0.29
2a	147.6	48.8	0.93
	149.9	3.5	0.07
2b	146.2	49.5	0.97
	148.9	1.4	0.03
2c	146.5	29.8	0.59
	149.0	21.1	0.41
2d	146.0	21.4	0.59
	148.9	27.7	0.41
2e	146.5	36.5	0.74
	149.3	12.7	0.26
3	147.5	33.1	0.63
	149.6	19.5	0.37
4	145.9	40.8	0.87
	149.2	5.9	0.13
5	150.3	53.6	1.0

Table 4 lists the values obtained for T_{peak} and for the areas of the individual curves for each sample. These areas reflect the contributions, ΔH_i, of the components to $\Delta_{fus}H$ of the samples, and their ratios would give the mole fractions provided that the molar enthalpies of all components have the same value. Although this requirement is not entirely fulfilled, the variations observed for $\Delta_{fus}H$ are not large, and at least for a majority of the samples, taking the ratios of areas as mole

fractions is a reasonable approach. The mole fractions thus calculated are included in Table 4 and denoted by α_i.

From the values determined for T_{peak} resulting from the fitting of the DSC patterns recorded at 1°C min^{-1}, four temperature ranges can be defined. The first range, temperatures slightly above 150°C, contains the peaks of samples 5 and 1c; the second, between 149.7 and 148.6°C, includes many peaks which correspond to relatively small fractions of the respective samples; the third, between 147.8 and 147.3°C, involved five peaks, some corresponding to almost pure forms; finally, the fourth range, between 146.6 and 145.9°C, contains seven peaks, some of which are also due to almost pure forms. Figure 3 depicts the distribution of the peaks, where the four groups can be observed.

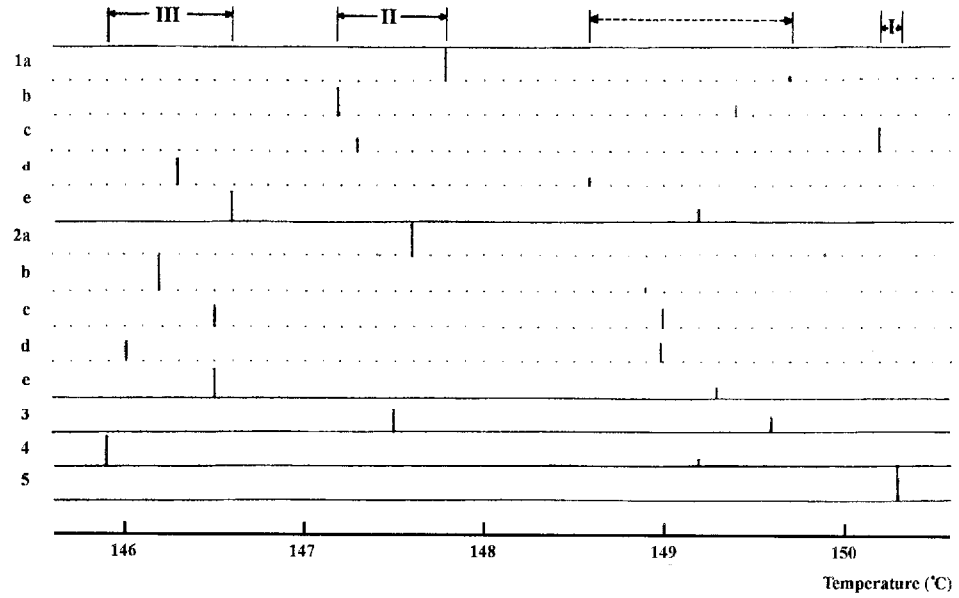

Fig. 3 Distribution of T_{peak} of the different forms of terfenadine. The ordinate is the mole fraction of each of the components in each of the samples

Omitting a discussion relating to the definition of polymorphism [14], in this work a polymorph is taken to be a well-defined structural form of terfenadine which can be prepared by well-defined methods. The distribution of T_{peak} in narrow temperature ranges in which we can find pure or almost pure forms lends support to the assignment of these ranges to polymorphs. From the limits of the temperature ranges defined by the simple phases, the most probable values for the melting points of polymorphs can be determined. Thus, the three polymorphic forms of terfenadine are as follows: form I: *m.p.* 150.2±0.1°C; form II: *m.p.* 147.5±0.3°C; and form III: *m.p.* 146.2±0.4°C. Identical values are found if the

m.p. of the purest sample included in the respective range is taken for the polymorph. The peaks in the range between 149.7 and 148.6°C are generally small. More data, especially on the thermodynamics of the solid phases involved, are necessary for their interpretations.

Examples of these three polymorphs may be mentioned. Form I: sample 5; form II: sample 2a; and form III: sample 2b. The methods used in their preparation are those followed to obtain the three types of forms.

Conclusions

The data reported on the preparation and characterization of terfenadine in this work are worthy of emphasis because of the interest in terfenadine itself, and also in polymorphism in general.

Thermal analysis is one of the techniques available for the examination of polymorphs. When research is based on phase transitions, a detailed program is required, as otherwise erroneous conclusions may be drawn, in particular for more complex systems. In this work, it would be an incorrect procedure to assign the values obtained for T_{peak} in the DSC curves run at 10°C min^{-1} to polymorphic forms. Indeed, the information provided by the curves recorded at a low heating rate, complemented by those obtained from a peak-fitting analysis, lead to the conclusion that in most of the examined samples, besides a single structural form, there are two polymorphs mixed in a wide range of proportions.

Crystallization is a common method of obtaining polymorphs. The properties of the products prepared with this technique depend on the nature of the solvent and on the experimental conditions. It may be incorrect to assign a certain polymorph to a form crystallizing from a specific solvent.

The crystallization of terfenadine often leads to multiphase systems of different compositions. However, if the solvent and experimental conditions are appropriately selected, polymorphs can be obtained. Indeed, the polymorph with *m.p.* 150.2°C can be prepared from the ethanol-water system at 20°C; the polymorph with *m.p.* 147.5°C is obtained from ethanol or methanol by evaporation of the solvent at high temperature; and the polymorph with *m.p.* 146.2°C is formed in methanol medium at 20°C.

References

1 US Patent 4, 742, 175, May 3, 1988.
2 European patent 0 346 765 A2, Bulletin 89/51.
3 European patent 0 385 375 A1, Bulletin 90/36.
4 F European patent 0 396 100 A1, Bulletin 90/45.
5 US Pharmacopoeia 23-NF 18 (1995) 1494.
6 A. A. Badwan, H. N. Al-Kaisy, L. B. Owais, M. S. Salem and T. A. Arafat, in Anal. Profile Drug Subst., Vol. 19, K. Florey Ed., Academic Press, London 1990, p. 627.

7 R. E. Homan and F. Desantis, Drug Dev. Ind. Pharm., 18 (1992) 861.
8 A. Hakanen and E. Laine, Thermochim. Acta, 248 (1995) 217.
9 J. Canotilho, F. S. Costa, A. T. Sousa, J. S. Redinha and M. L. P. Leitão, Thermochim. Acta, 283 (1997) 1.
10 M. S. Salem, G. K. Pillai, L. Nabulsi, H. N. Al-Kaysi, T. A. Arafat, A. A. Malooh, M. Saleh and A. A. Badwan, Int. J. Pharm., 141 (1996) 257.
11 N. M. Sanghavi, R. Mayekar and M. Fruitwala, Drug. Dev. Ind. Pharm., 21 (1995) 375.
12 P. Girenchedi, R. Stefli, L. Maggi, M. Setti and U. Conte, STP Pharma Sciences, 6 (1996) 307.
13 A. A. Badwan, A. A. Malooh, L. B. Owais, M. S. Salem, H. N. Al-Kaysi and T. A. Arafat, Eur. J. Pharm. Biopharm., 37 (1991) 166.
14 T. L. Trelfall, Analyst, 120 (1995) 2435 and references therein.