

STUDY OF POLYMORPHISM FROM DSC MELTING CURVES

Polymorphs of terfenadine

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Abstract

Terfenadine samples prepared by crystallization in different media and supersaturation conditions were used to investigate the polymorphism of the substance. The study was based on DSC melting curves. An empirical parametric equation was used for modelling the experimental data. The signal recorded was resolved into the corresponding overlapping peak components by fitting analysis. Four polymorphic phases were identified.

Keywords: crystallization, peak fitting, polymorphism, terfenadine

Introduction

The impact of polymorphism in various scientific fields is well known. Among these one finds examples of pharmaceutical technology where preparation and characterisation of polymorphs of drugs are a matter of the utmost importance [1]. Indeed the structure of these substances has effects on medical and pharmaceutical properties such as, bioavailability, suitability for required formulations, structural stability and shelf-life [2–5].

Molecules as large as those of most drugs can adopt a variety of conformations. This particularity associated with specific interactions between polar groups, often present in those molecules, gives rise to solid structures, differing from each other in their space lattice type, in molecular conformation or simultaneously in both features. Therefore polymorphism for this sort of compounds is a rule rather than an exception.

The lattice energies of conformational polymorphs are very close because they correspond to different arrays of van der Waals interactions. Differences in $\Delta_{\text{trans}}H$ between 0.2 and 10.2 kJ mol⁻¹ have been reported for polymorphic transitions [1]. As a consequence of such small differences in energy and structure they exhibit similar

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properties, which makes the determination of the significant characteristics of the individual crystalline forms difficult.

The close structures presented by polymorphs favour still further the simultaneous crystallization of two or more forms, which means that the materials we are dealing with are mixtures rather than pure substances. In fact the formation of concomitant polymorphs has been reported as a consequence of the balance between the differences in Gibbs energy of nucleation of two or more crystalline forms and kinetic factors. Crystallization leads sometimes not to a unique polymorph but to a rather complex mixture of stable and metastable polymorphs, pseudopolymorphs and disordered material [6].

In the study of polymorphism one has to face sometimes the problem of identification of single crystalline forms having close properties in complex matrices. The solution to this problem is found by using experimental methods leading to good quality data, computing techniques of analysis of the results in order to obtain individual components not discriminated by instrumental methods and application of statistics to the generated data set.

A former work was published on peak fitting analysis of terfenadine fusion curves recorded by DSC. From the values obtained for T_{peak} one could ascribe three groups of polymorphic forms to terfenadine specimens, but some component curves were not identified as belonging to any group [7].

A new approach is now undertaken using an empirical equation. Thus the aim of this work is twofold: to give a contribution to the methods of identification of polymorphs through the fusion curves and updating the knowledge on the polymorphism of terfenadine.

Experimental

Preparation and characterization of terfenadine specimens

The samples used in this investigation were prepared by recrystallizing, terfenadine supplied by Sigma, from ethanol, methanol, and ethanol-water, under different experimental conditions, in order to obtain a diversity of structural forms. The terfenadine samples were separated out from the solvent media and their thermal behaviour on heating were studied by thermomicroscopy and by thermogravimetry [8]. The crystallization techniques used, the characterization of the solid phases obtained, and the transformations taking place on heating from the room temperature to the melting point, are summarized in Table 1. Depending on the nature of the solvent and on the temperature at which crystallization takes place, crystalline forms, mixtures of crystalline and amorphous states, and mixtures of solvates, amorphous and unsolvated crystalline states are obtained.

On heating, the following processes have been observed: amorphous material shows an endothermic glass transition point at about 68°C. The resulting liquid phase recrystallizes on further heating. No solid-solid transformation was observed on heat-

ing unsolvated crystalline states. However, solvates become amorphous by losing the solvent allowing recrystallization of unsolvated crystals.

Table 1 Preparation of the terfenadine specimens: methods and phase changes

Specimen	Solvent	Crystallization technique	Solid phases from solution	Phase transformations on heating at 120°C
1a	ethanol	evaporation at 60°C	crystalline	no change
1b	ethanol	evaporation at 20°C	crystalline	no change
1c	ethanol	cooling at 20°C	crystalline	no change
1d	ethanol	cooling at 3°C	crystalline+amorphous	amorphous→liquid→crystalline
1e	ethanol	cooling at -5°C	crystalline+amorphous +solvate	solvate→amorphous→ liquid→crystalline
2a	methanol	evaporation at 50°C	crystalline	no change
2b	methanol	evaporation at 20°C	crystalline+amorphous	amorphous→liquid→ crystalline
2c	methanol	cooling at 20°C	crystalline+amorphous	amorphous→liquid→ crystalline
2d	methanol	cooling at 3°C	crystalline+amorphous	amorphous→liquid→ crystalline
2e	methanol	cooling at -3°C	crystalline+amorphous +solvate	solvate→amorphous→ liquid→crystalline
1-3c	ethanol/ water (4:1 v/v)	cooling at 20°C	crystalline	no change
1-3v	ethanol/ water	water vapor diffusion in ethanol soln. at 20°C	crystalline	no change

The crystallization of the supercooled liquid is a rather slow process. However, at 120°C it is accomplished in a few minutes. In preparation of the terfenadine specimens to be studied, the precipitates obtained from the solvents were heated at 120°C for one h. X-ray diffraction study shows that in such conditions all specimens were in crystalline solid states, independent of the solvents from which they were precipitated.

DSC curves

DSC melting curves of terfenadine were recorded with a DSC-7 Perkin Elmer instrument. Details on calibration and procedure are found in previous work [7].

Experiments for selecting the most appropriate heating rate were performed and the effect on curve patterns is illustrated in Fig. 1 for terfenadine without any treatment supplied by United States Pharmacopeia. 1°C min⁻¹ was the selected rate and the curves recorded for all the terfenadine specimens are shown in Fig. 2.

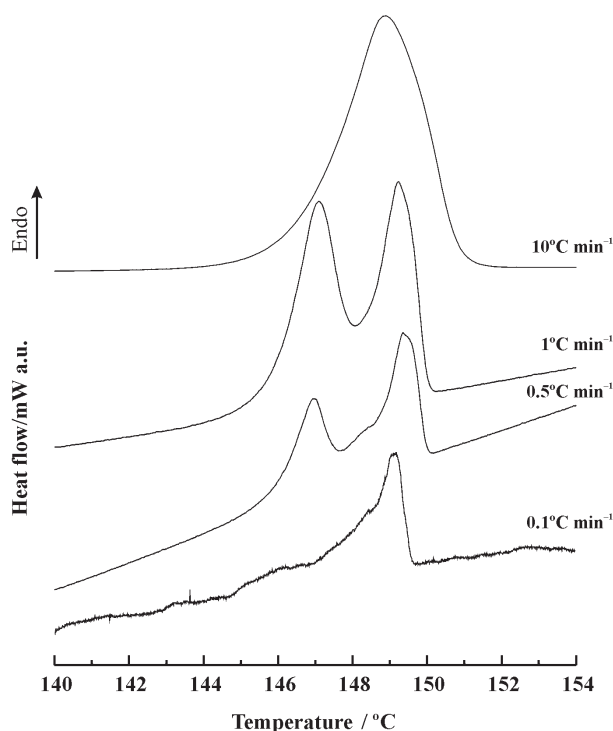


Fig. 1 Effect of the heating rate on DSC melting curve patterns for USP terfenadine

The data quoted for T_{ons} and T_{peak} are means of five replicates of a given batch. Test regarding the variability between batches were preformed. The uncertainty for the repeatability and for the reproducibility were always less than 0.1°C.

X-ray powder diffraction

X-ray powder diffractogram for each terfenadine specimen was recorded between 3 and 63°2 θ with Philips 1830 instrument. A nickel filtered CuK $_{\alpha}$ radiation at 40 kV and 30 mA was used. Powder samples of particle size below 300 μm were packed into a 16 mm diameter stainless holder and gently pressed. The scanning was performed with 0.02°2 θ . Counting was detected using a 1.25 s time constant. The X-ray diffraction patterns for some terfenadine specimens are shown in Fig. 3.

Peak fitting analysis of the DSC melting curves

DSC curves of terfenadine specimens give evidence for the existence of fusion composite peaks except for those obtained from ethanol-water (Fig. 2: 1–3c and 1–3v) which are single component systems. A curve fitting analysis was carried out in order to determine the overlapping peak positions and areas.

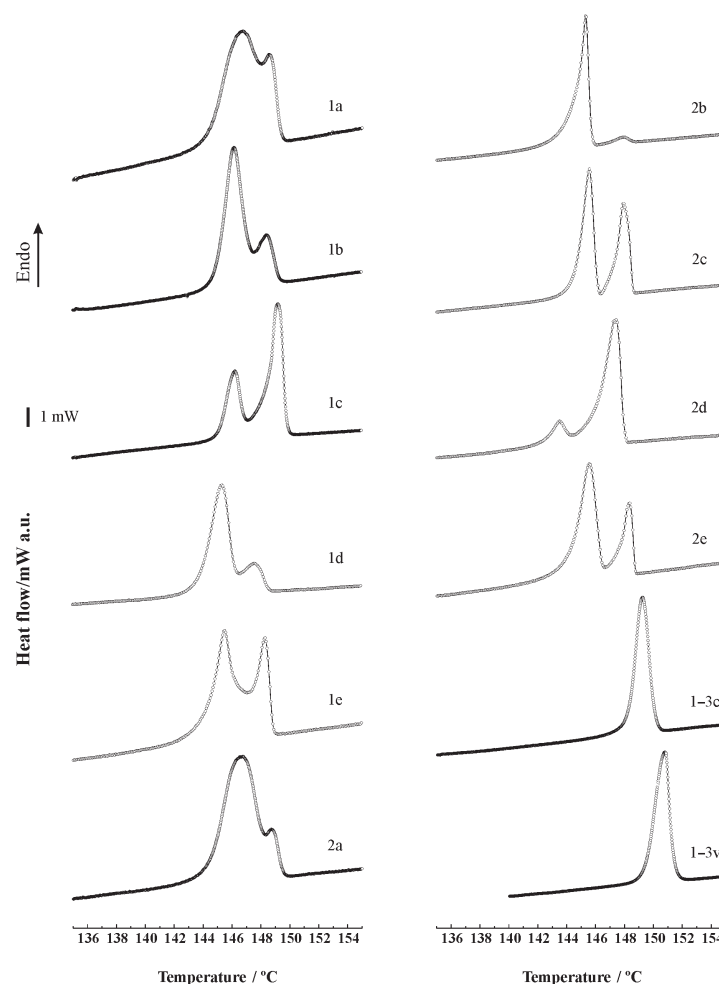


Fig. 2 DSC melting curves for terfenadine specimens recorded at $1^{\circ}\text{C min}^{-1}$

The deconvolution of DSC curves has been matter of much concern. Various types of functions have been used long since to resolve superimposed peaks [9, 10]. Software providing DSC peak analysis, in general or applied to specific systems, are developed by calorimetry equipment manufacturers. Attempts to set up unified mathematical functions for describing DSC signals have also been published [11–14]. However, these approaches are still waiting for confirmation about how far they can be generalised to different instrumental features, sample characteristics, and type of phase transformations. The deconvolution of a DSC signal into individual curves with physical meaning is still an open question.

The equation used in the present work for the fitting of the peaks was obtained by simulation of the experimental data got from DSC fusion curve of the single polymorphic

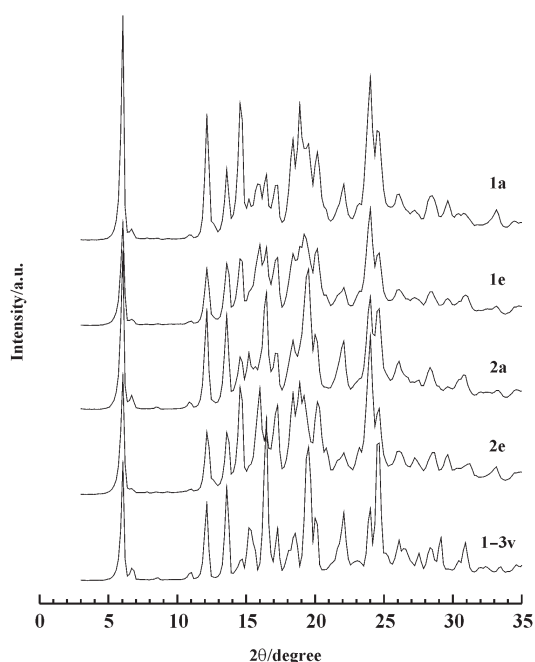


Fig. 3 X-ray powder patterns of terfenadine specimens

form. As the signal obtained for terfenadine specimens crystallized from ethanol–water do not exhibit any separation into components when they are recorded at different scanning rates, they are considered as a single structural form. Specimen 1–3v was selected as a standard. The equation is presented in the Appendix and is called hereafter as empirical equation or empirical function. The peaks are characterized by T_{ons} and T_{peak} .

For determining T_{ons} , the inflexion point of the function rising line is to be found, being the claimed value given by the interception of the tangent to the curve at the inflexion point with the baseline. From Eq. (1) in Appendix one obtains,

$$t_{\text{ons}} = x_{\text{inf}} \left(\frac{\partial \eta(x_{\text{inf}})}{\partial x} \right)^{-1} \eta(x_{\text{inf}}) \quad (1)$$

x_{inf} is the temperature at the inflexion point and $\eta(x_{\text{inf}})$ is the expected value for heat flux at this particular temperature.

Among the parameters of the empirical equation deserving particular attention are those related with peak asymmetry. In fact, this equation can be applied allowing θ_3/θ_5 as a variable factor (flexible profile function) or ascribing to this ratio the value determined from five replicas of the standard specimen (fixed profile). In the first version, the asymmetry of the individual polymorphic curves is allowed to vary and in the second it is admitted that the overlapping curves have the same asymmetry factor whose value is just that determined for the reference sample. On the mathematical point of view the first

version gives always a more accurate fitting, but this can be reached by defilement of the peak profile in particular for less abundant components. The choice between the two options should be taken by comparison of the results generated by them.

In Fig. 4b it is shown the deconvolution of DSC curve for 1c specimen of terfenadine into three peaks by using flexible (b1) and fixed (b2) profile equation. The value taken for the asymmetry factor in the latter procedure is that quoted from 1-3v ($\theta_3/\theta_5=2.05$). As one can see from the figure both procedures give identical values for T_{ons} and T_{peak} . However, the profile given for the component present in less amount is more real for the fixed profile than for the flexible profile version. We must conclude that in the present case the fixed profile equation is more adequate to describe the system we are dealing with. In other words the DSC curves for the polymorphs of terfenadine are identical on respect of the asymmetry factor.

For comparison, a Gaussian function was also used for fitting the set of DSC curves. The program used is an addition module to Origin 6.1 purchased from Jandel Scientific GmbH, Germany. It allows the calculation of relevant features of the curves as, top centre, peak height, width at half maximum and the area fraction under the peaks. From Gaussian function properties, T_{ons} is given by

$$T_{\text{ons}} = T_{\text{peak}} - \Delta T_{\text{w}1/2} \quad (2)$$

$\Delta T_{\text{w}1/2}$ is the temperature interval corresponding to the curve width at half height maximum.

The inadequateness of Gaussian function for a detailed analysis of DSC fusion curves is illustrated in Fig. 4a which shows the curve obtained for 2c specimen fitted by Gaussians. The peak decomposition in two curves is a rough solution. When three peaks are inscribed, besides the poor accuracy observed for the fitting, the intermediate peak cannot be identified as that of a pure component. The resolution into four Gaussian curves leads to two peaks not distinct from the two others.

An identical conclusion is reached from the comparison of the results originated by the three equations under discussion. Figure 4b, mentioned above in discussing the two versions of the empirical equation, shows the same curve analysed by the three functions. Indeed, Gaussian is a poor solution as compared with that given by the proposed function.

Table 2 contains the values determined for T_{ons} and T_{peak} obtained by using empirical and Gaussian functions in the deconvolution of the melting curve of each terfenadine specimen recorded at 1°C min^{-1} . The values of T_{ons} and T_{peak} for all specimens under consideration were submitted to the pattern recognition technique using K neighbour algorithm proposed by Bratchell for allocation into distinct groups [15]. Four clusters were defined and the values assigned to the characteristic temperatures are quoted in Table 3. Each cluster corresponds to a distinct structural modification, that is, to a polymorph.

Fitting analysis, besides the characterization of polymorphic forms through temperature, allows the determination of the area fraction under each overlapping curve. From these areas the quantification of the composition of the specimens can be determined provide the molar enthalpy of the components is known. As the proposed

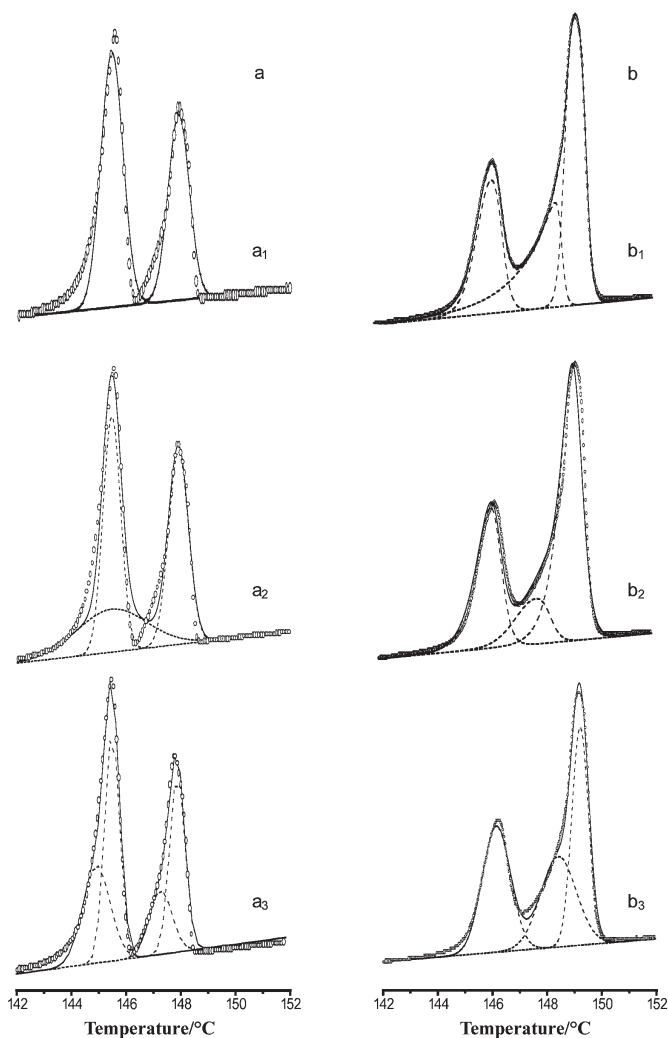


Fig. 4 a – Peak fitting analysis of DSC melting curve for 2c terfenadine: Gaussian function; b – Fitting analysis of DSC melting curve for 1c terfenadine: b₁ – flexible profile; b₂ – fixed profile; b₃ – Gaussian function

equation is obtained empirically the areas have to be calculated by numerical integration. The areas for each specimen calculated from the flexible and from the fixed profile are presented in Table 4. As expected from what was said, the area is more dependent on the equation adopted than the temperature. No values for the areas of Gaussian peaks were presented because in some specimens the curves generated have no physical meaning.

Table 2 Values for T_{ons} and T_{peak} obtained for terfenadine specimens from peak fitting analysis

Terfenadine	$T_{\text{ons}}/^{\circ}\text{C}$		$T_{\text{peak}}/^{\circ}\text{C}$				
	Flexible profile						
1a	148.3	145.3		149.8	147.7		
1b	147.9	146.0		150.3	147.4		
1c	149.7	148.0	145.6	150.3	149.6	147.2	
1d	147.1	144.9		148.7	146.4		
1e	148.3	145.9	144.7	149.4	147.2	146.4	
2a	149.1	145.4		149.9	147.7		
2b	147.6	145.7	143.7	149.2	146.4	145.6	
2c	148.0	145.6		149.1	146.6		
2d	147.2	145.0	143.4	148.6	148.1	144.6	
2e	148.5	145.5	143.3	149.4	146.6	145.4	
1-3c	149.4			150.5			
1-3v	150.5			151.8			
	Fixed profile						
1a	147.9	145.4		149.6	147.7		
1b	147.2	145.9		149.4	147.3		
1c	149.3	147.4	146.2	150.3	149.0	147.3	
1d	146.8	144.8		148.6	146.4		
1e	148.3	145.6	144.2	149.3	147.7	146.2	
2a	148.0	145.5		149.7	147.8		
2b	148.0	145.3	143	149.1	147.9	146.3	
2c	148.1	145.6		149.1	146.6		
2d	147.4	145.2	143.3	148.4	147.2	144.6	
2e	148.3	145.3	143.2	149.3	146.7	145.1	
1-3c	149.4			150.5			
1-3v	150.5			151.8			
	Gaussian						
1a	147.8	143.7		148.6	146.7		
1b	147.1	144.6		148.3	146.2		
1c	148.5	147.1	144.9	149.2	148.4	146.1	
1d	146.3	143.6		147.5	145.2		
1e	147.6	145.9	144.4	142.1	148.2	147.4	145.4
2a	148.1	143.9		148.8	146.5		
2b	146.5	144.7	143.0	147.7	145.3	144.6	
2c	147.3	146.4	144.9	143.7	147.4	145.5	145.0
2d	146.6	145.1	140.7	147.4	146.6	143.7	
2e	147.8	146.9	144.5	142.2	148.3	147.6	145.5
1-3c	148.0			149.2			
1-3v	149.4			150.6			

Table 3 Values for T_{ons} and T_{peak} ascribed to polymorphs of terfenadine from cluster analysis

Cluster	$T_{\text{ons}}/^{\circ}\text{C}$	$T_{\text{peak}}/^{\circ}\text{C}$
Flexible profile		
I	149.7±0.6	150.8±0.7
II	147.9±0.5	149.3±0.5
III	145.6±0.3	147.1±0.6
IV	144.0±0.7	145.2±0.6
Fixed profile		
I	149.1±0.9	150.9±0.8
II	147.2±0.5	149.1±0.4
III	145.3±0.3	147.1±0.6
IV	143.5±0.4	144.8±0.4
Gaussian		
I	148.5±0.7	149.8±0.7
II	146.8±0.4	148.4±0.3
III	144.9±0.4	147.2±0.5
IV	143.1±0.9	145.2±0.67

From the results presented so far it is possible to draw conclusions about the method followed for the study of polymorphism and about the system under consideration. The method used allows the thermal characterization of four polymorphic forms of terfenadine, a system which gives rise to structural forms similar in energy. Identical values are obtained for any of the versions of the empirical equation we are dealing with. However differences between the methods should be pointed out. The values for T_{ons} given by flexible profile equation are systematically about 0.5°C higher than those obtained by the fixed profile one. No significant differences were observed between T_{peak} obtained by both equations. The decision about the choice between the solution given by the flexible or by the fixed profile version is taken after the results they generate. In the present system the latter gives more real peaks than the former.

When the polymorphs have different peak asymmetry it is believed that flexible profile is a more correct solution.

Gaussian can only be used in preliminary studies. Besides leading to less accurate results for T_{ons} and T_{peak} tends to originate no real peaks when a more refined data analysis is intended.

Polymorphism of terfenadine

Among the terfenadine specimens prepared as described above four polymorphic structural modifications have been identified. The values assigned to the melting temperature are given in Table 3 for the fixed profile functions. Only terfenadine pre-

pared from ethanol–water media is a single crystalline structure; all the others are mixtures of two, or in some cases, three polymorphs.

The composition of each specimen is found in Table 4 (fixed profile). Polymorph III and polymorph II are the forms more often present. We can see that crystallization at high temperature tends to produce high melting polymorphic forms whereas low temperature leads to low melting ones. The solvent also affects the structure of the solid formed. Ethanol-water gives rise to the highest melting under a single form, whereas ethanol favours the precipitation of mixtures of higher melting polymorphic forms relatively to methanol.

Table 4 Composition of terfenadine specimens in percentage

Specimen	I	II	III	IV
Flexible profile				
1a		26.3	73.7	
1b		30.4	69.6	
1c	43.1	29.8	27.1	
1d		20.8		79.2
1e		29.5	29.8	40.7
2a	8.7		91.3	
2b		5.1	56.4	38.5
2c		40.8	59.2	
2d		59.1	30.8	10.1
2e		27.4	54.2	18.4
1–3c	100.0			
1–3v	100.0			
Fixed profile				
1a		37.5	62.5	
1b		34.1	65.9	
1c	55.5	13.1	31.4	
1d		23.4	76.6	
1e	33.9	29.0	37.1	
2a	21.8		78.2	
2b	4.6		75.7	19.7
2c	41.7		58.3	
2d		61.8	22.7	15.5
2e		27.4	61.5	11.1
1–3c	100.0			
1–3v	100.0			

Some terfenadine specimens are formed by crystals coming from solvent and from the melt. As these specimens are the only mixtures that contain the polymorph IV, one could conclude that this form would result from the melt. It was observed previously that the relative contribution of those sources for the solid is favourable to the melt as the temperature of crystallization in solution decreases. As no relationship is observed between the molar fraction of that polymorphs and the temperature of crystallization, solidification of the melt does not give rise to a new structural form.

Table 5 Scattering angles, interplanar distances and relative intensities for X-ray powder diffraction of 1-3v terfenadine specimen

$2\theta/\text{degree}$	$d/\text{\AA}$	$I/I_{\text{max}}/\%$
6.180	14.2901	100.0
6.875	12.8470	11.7
8.645	10.2453	1.3
11.085	7.9754	3.7
12.290	7.1960	27.8
13.750	6.4351	33.1
14.690	6.0253	7.4
15.360	5.7640	18.3
15.685	5.6453	10.9
16.565	5.3473	45.7
16.825	5.2652	7.4
17.385	5.0969	13.6
18.150	4.8837	7.8
18.455	4.8155	11.3
18.730	4.7338	10.2
19.420	4.5671	32.1
19.705	4.5017	26.2
20.170	4.3990	15.9
21.715	4.0894	7.4
22.190	4.0029	13.6
22.935	3.8745	3.4
24.045	3.6981	14.3
24.610	3.6145	33.2
25.210	3.5298	5.2
26.160	3.4037	6.6
26.550	3.3546	5.4
...

The small difference between the melting point of the polymorphs of terfenadine indicates a small energy difference between the modifications adopted by the structure of the terfenadine. Apparently, they differ one from another in the arrays of van der Waals interactions arising from different molecular conformations. This conclusion is in agreement with differences of 1.2 kJ mol^{-1} found for the enthalpy of solution of terfenadine specimen in ethanol and in methanol [16].

No reliable data for X-ray diffraction of terfenadine polymorphic forms were published. Hence it is not possible at this stage to use this technique for identifying polymorphs of this substance. However, important information on several aspects can be drawn from it on the structural point of view.

X-ray powder diffraction patterns of all specimens exhibit sharp peaks what means that they are crystalline state phases. This conclusion is important since original material was in unsolvated crystalline, amorphous and solvated states.

Among the polymorphs identified by DSC in the present work the only one prepared in single crystalline phase was the one with the highest melting point (polymorph I). X-ray powder diffraction patterns given in Fig. 3 are of great analytical interest. This is a valuable method of identification of this structural form. In Table 5 crystallographic data obtained for this polymorph are given.

The comparison of X-ray patterns got for polymorph I and for the other specimens gives evidence for small differences between the crystal lattice of the polymorphic forms of terfenadine. This conclusions are not surprising attending to the close values obtained for their melting points. However, differences in values of the scattering angles and of relative intensities accounting into differences in composition are observed.

Conclusions

The information contained in the melting curves of organic compounds obtained by DSC can be detailed enough for discriminating mixtures of polymorphs with close lattice energies. The separation of the overlapped peaks was achieved by optimising the conditions of tracing DSC curves and by computational analysis of the experimental data. Statistical analysis applied to the data obtained for T_{peak} allows the characterization of the polymorphic forms.

A multiparametric equation developed especially for describing a DSC peak was used to assign the parameter values related with the peak shape determined from a single polymorphic form of terfenadine.

Among the twelve terfenadine specimens under consideration only two of them are single crystalline forms. All of the others are mixtures of two or three polymorphs and an estimation of their composition was made from the deconvoluted peak areas.

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The authors acknowledge the financial support from 'Fundação para a Ciência e a Tecnologia', FCT, Lisboa, the (PRAXIS/P/QUI/10137/1998).

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Appendix

A DSC curve corresponding to the fusion of a single structural form of a compound is defined by an increasing temperature function accounting to the heat required for the phase transition and a decreasing one corresponding to the energy supplied to restore the thermal equilibrium. In order to find adequate equations for describing these ascending and descending lines, several attempts were performed on the data obtained for the fusion of a single polymorphic form of terfenadine, 1–3v: linearization of normalised data, data simulation, and characterization of goodness-of-fit for empirical functions. The following equation was then obtained for describing the DSC signal for single peak fusion

$$\eta(x_i) = \frac{\theta_1 \exp\left(\frac{x_i - \theta_2}{\theta_3}\right)}{1 + \exp\left(\frac{x_i - \theta_2}{\theta_3}\right)} x - \frac{1}{1 + \exp\left(\frac{x_i - \theta_4}{\theta_5}\right)} + \theta_6 x_i + \theta_7 \quad (1)$$

x_i is the independent variable (T), $\eta(x_i)$ is the dependent variable (predicted value for the heat flux) and θ_1 to θ_7 are empirical parameters related to the curve features: θ_1 , height of the peak maximum, θ_2 and θ_4 , the peak position, θ_3 and θ_5 , the peak asymmetry, θ_6 and θ_7 , the background correction.

The first two terms of the second member of Eq. (1) are concerned with the front and terminal line of the fusion curve, respectively. The background, assumed to be a straight line, is given by the two last parcels of this equation.

Equation (1) is adequate to fit symmetric, back, and front tailed curves by varying θ_3/θ_5 ratio. To show the effect of this ratio, peaks were generated using different values for θ_3/θ_5 which are depicted in Fig. 1.

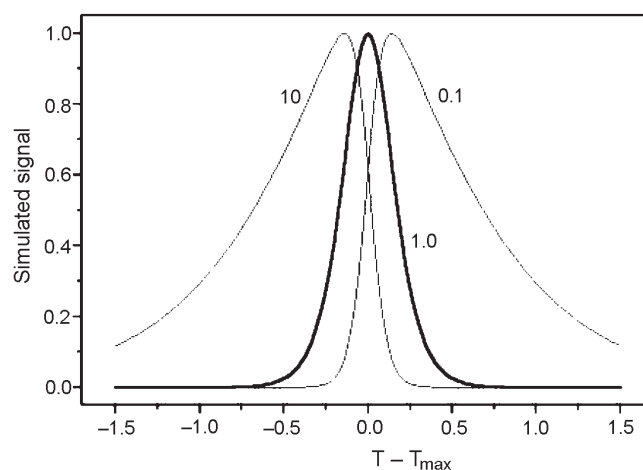


Fig. 1 Simulated DSC curves generated by the empirical function for different θ_3/θ_5 value

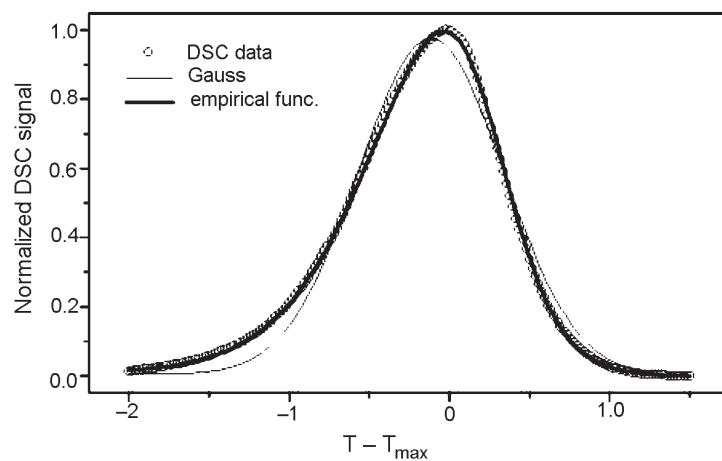


Fig. 2 DSC data fit using the Gaussian and the empirical function

Equation (1) was tested successfully, against the data obtained for the fusion curve of cyclohexane and benzoic acid.

In Fig. 2 one can observe the fitting of DSC signal obtained for 1–3v terfenadine peak fusion. The Gaussian function fitted to the experimental data was also represented in Fig. 2, to compare the adjustments achieved.

The performance of both functions is given by the statistical parameters presented in Table 1.

Table 1 Comparison of performance in DSC signal modelling using Gaussian function and empirical equation

Fitting function	Corr	Bias ($\cdot 10^6$)	σ^2 ($\cdot 10^3$)	Skew	Kurt
Gaussian	0.99271	7717.49	1.7207	0.2739	1.793
Empirical	0.99989	0.0158	0.0246	0.08772	3.413