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Calorimetric study of polymorphic forms of terfenadine

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Abstract

Terfenadine polymorphic forms have been prepared by crystallization from ethanol and methanol solutions. The two polymorphs were studied by differential scanning calorimetry (DSC) and thermogravimetry (TG) in a temperature range between 233 and 443 K. From DSC data, structural differences between both forms were pointed out. Enthalpies for solution processes of the polymorphs in ethanol and in methanol were determined. Differences between both solid forms as well as between the solvent behaviour are well noted from the standard solution enthalpy values and from the variation of the enthalpy with concentration.

Keywords: DSC; Polymorphism; Solution calorimetry; Terfenadine; TG

1. Introduction

Terfenadine, α-[4-(1,1-dimethylethyl) phenyl]-4-(hydroxydiphenylmethyl)-1-piperidine butanol, is a non-sedating antihistaminic drug widely used in therapeutical practice. It has been claimed that terfenadine gives rise to different polymorphic forms according to solvents that it is crystallized from [1–4]. A higher and a lower melting form have been described and characterized by different methods. For instances, crystallization from ethanol leads to the higher melting form while from methanol the lower melting one is obtained [1,4]. The solid sample obtained from methanol is also described as a solvate [4].

Polymorphism is an important property on the pharmaceutical point of view and on that account a study on terfenadine leading to physical and chemical characterization of different forms was undertaken. In this paper, we present some calorimetric results for terfenadine samples prepared by crystallization from ethanol and methanol solutions. Differential scanning calorimetry, thermogravimetry and solution calorimetry were the techniques used in this work.

2. Experimental

Terfenadine was purchased from Sigma and purified by crystallization from ethanol. No impurities were detected by IR spectroscopy. Two samples were prepared, one from recovering the solid terfenadine from ethanol solution (Form I) and the other recovering the solid phase from methanol solution (Form II). The procedure followed in both cases are similar to that described somewhere and consisted of a slow evaporation of the solvents at room temperature and drying the solid at 35°C under vacuum for 48 h [3,4].

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DSC curves were obtained with DSC 7 Perkin–Elmer instrument. Calibration and experimental details were presented in a previous work [5].

Thermogravimetric studies were performed with STA Rheometric Scientific instrument between 303 to 443 K at heating rate 10.0 K min^{-1} using nitrogen as purge gas.

Solution calorimetric determinations were carried out with a Setaram C 80 mixing calorimeter. A standard reversal mixing cell supplied by the manufacturer was used. The upper limit for the concentration range studied for each system was determined by the solubility. Calibration of the calorimeter was accomplished by Joule effect and from the value tabled for the heat of solution of KCl. The figures obtained by the two methods show no significant differences.

3. Results

DSC study of every sample was started by increasing the temperature from 293 to 443 K. Then several cooling and heating runs were performed between 443 and 233 K. The only difference shown by the two forms of terfenadine lies on the first heating process. Fig. 1 contains DSC curves of Form I and Form II during the first heating process and Table 1 the respective thermodynamic data. Form I shows no phase transition but fusion, while Form II gives an endothermic peak at 347.0 and an exothermic one at 373.5 K before fusion occurs.

Liquid terfenadine obtained by fusion of either Form I or Form II gives a glass transition in the temperature range from 326 to 321 K. On heating, devitrification occurs at a temperature between 327

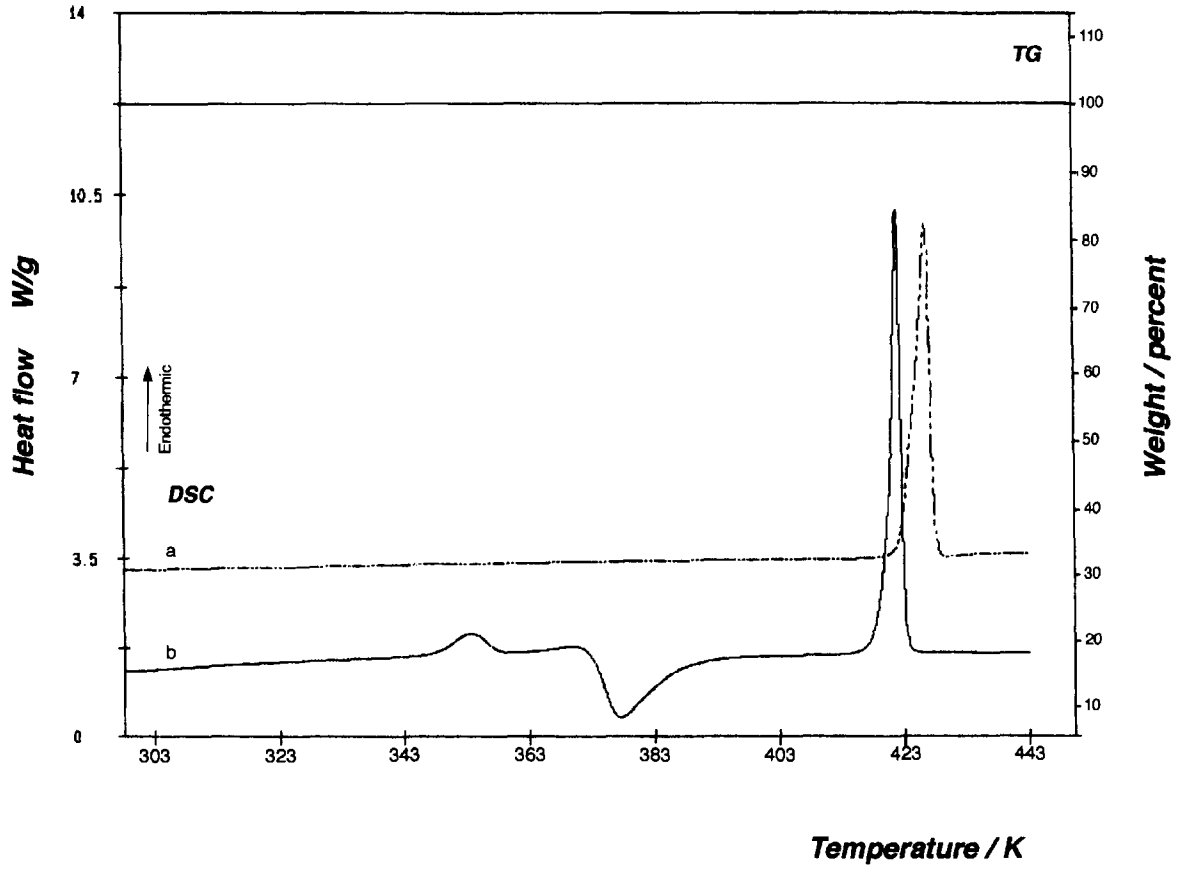

Fig. 1. DSC and TG curves of terfenadine. DSC curves: Heating runs. (a) Form 1; (b) Form II; $\beta = 10.0$ K min^{-1}. TG curve: Form I and Form II; $\beta = 10.0$ K min^{-1}.

Table 1
Thermodynamic data obtained from DSC curves of terfenadine polymorphic forms. First heating run

Polymorph	T_{trs} (K)	$\Delta_{trs}H$ (kJ mol^{-1})	T_{fus} (K)	$\Delta_{fus}H$ (kJ mol^{-1})
Form I			423.8±0.36	55.7±0.54
Form II	347.0±0.81	6.3±0.60	422±1.8	52.9±0.39
	374±1.3	−39±3.2		

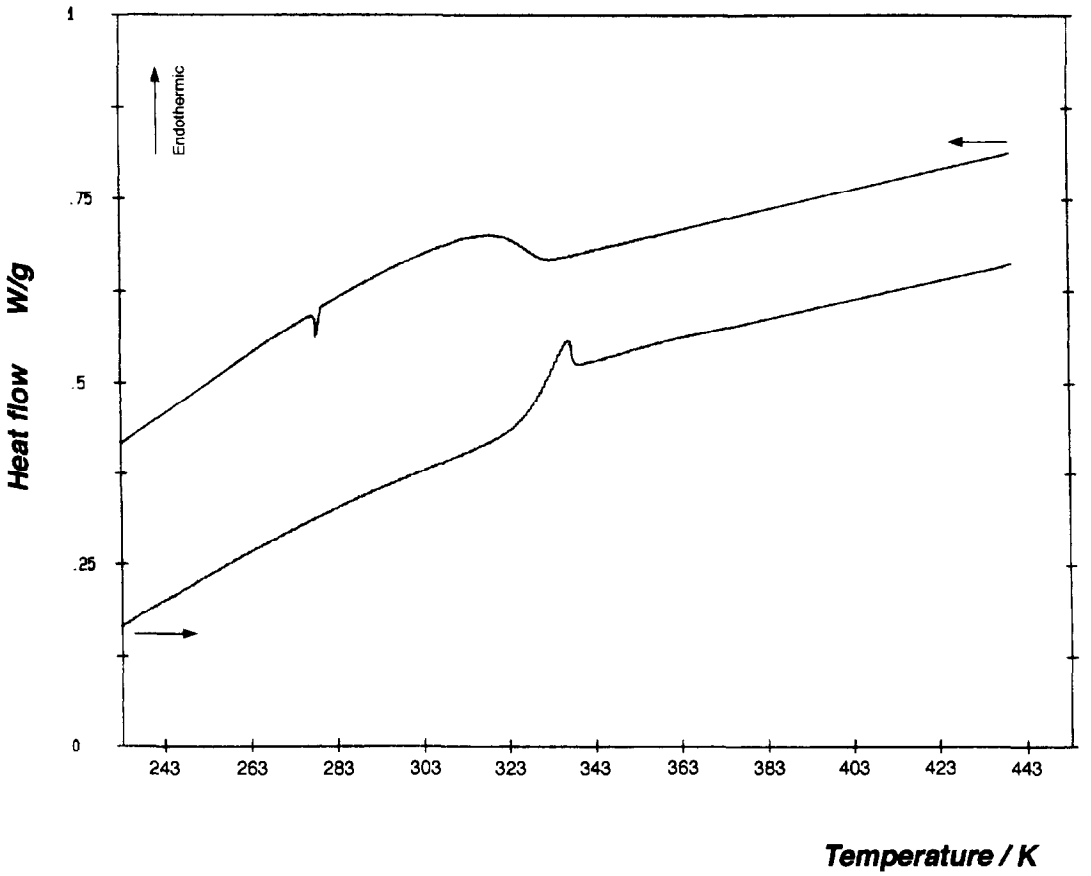

Fig. 2. DSC curves of terfenadine after fusion. Cooling/heating cycles. β=10.0 K min^{-1}. Cooling run: T_o=335–333 K; T_g=326–321 K; ΔC_p=0.43 J g^{-1} K^{-1}. Heating run: T_o=329–331 K; T_g=327–332 K; T_p=334–336 K; ΔC_p=0.47 J g^{-1} K^{-1}; ΔH=0.91–0.95 J g^{-1}.

and 332 K showing a glass transition with an endothermal enthalpy relaxation peak. The behaviour just described has been exhibited in successive heating and cooling runs of glassy terfenadine.

Fig. 2 contains typical DSC curves for liquid terfenadine corresponding to successive cooling and heating runs carried out between 443 and 233 K.

The glass transition is characterized by typical parameters, namely, extrapolated onset temperature, T_o, glass transition temperature, T_g, maximum temperature of the relaxation peak, T_p, heat capacity change, ΔC_p, and relaxation enthalpy, ΔH. The values obtained for these parameters are given in Fig. 2.

Thermogravimetric experiments show no weight loss by heating the sample from room temperature to fusion.

The results obtained for the enthalpy of solution, $\Delta_{sol}H$, of the terfenadine solid forms in ethanol and

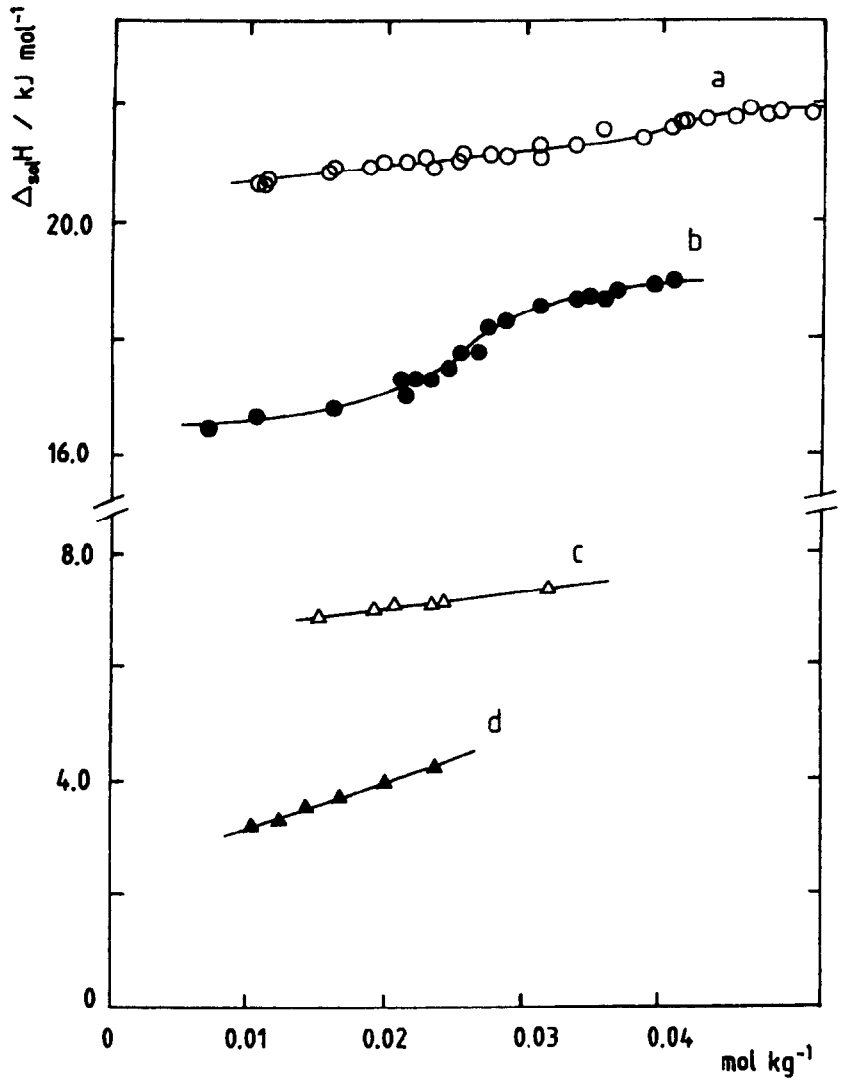

Fig. 3. Enthalpy of solution of polymorphic terfenadine forms in ethanol and methanol as a function of concentration. (a) Form I in ethanol (b) Form I in methanol (c) Form II in ethanol (d) Form II in methanol.

Table 2
Standard enthalpy of solution for terfenadine polymorphic forms in methanol and ethanol at 298.15 K

Polymorph	$\Delta_{sol}H^\circ$ (kJ mol^{-1})	
	Methanol	Ethanol
Form I	15.4±0.59	20.2±0.19
Form II	2.3±0.31	6.6±0.16

methanol are represented in Fig. 3. From the values of $\Delta_{sol}H$ got for different concentrations, the limiting values for zero concentration, $\Delta_{sol}H^\circ$, were calculated, as it can be found in Table 2.

4. Discussion

Phase transitions observed on the first heating run before fusion for Form II play an important role in understanding structural differences between the solid forms recovered from ethanol and methanol. It should be stressed that the exothermic transition corresponds

to a structural transformation which occurs as a consequence of the endothermic one. In fact if the heating process is interrupted at 363 K, just after the endothermic transition taking place, the exothermic peak is observed. Stopping the first heating run at 403 K, just after recording the exothermic peak, and cooling the sample to 293 K and heating again, no transition occurs before melting.

Thermogravimetry gives valuable information. Once no weight variation takes place in the temperature range studied, the existence of a solvate should be ruled out.

DSC data can be interpreted admitting that while Form I is a stable crystalline solid phase from room temperature to fusion, Form II is stable up to the temperature of 347.0 K, then a structure disruption occurs which gives rise to a new structure by crystallization. These phase transitions correspond to an increase in crystallinity of the solid obtained from the methanolic solution, which could be followed by the authors through the variation of the OH vibration frequency in this temperature range.

An important point regards the structure formed after this solid-phase transition taking place is whether this structure is the same as that of Form I or a different one. The difference found for the melting point indicates that even at the temperature above 403 K the two forms have different structures.

DSC curves prove that different structural forms can be obtained by crystallizing terfenadine from different solvents. The structure of these forms depends on the solvent but may depend also on the method used in the crystallization process.

The enthalpy values obtained for the solution processes provide information about the structural differences between the polymorphic forms and about solute/solvent interaction. For interpreting solvation data it is useful to consider the process as taking place into two steps: transport of the solute molecule from the solid to the gas phase (sublimation) followed by the transport from gas to the solution (solvation). Enthalpy of solution, $\Delta_{sol}H$, can then be related to enthalpy of sublimation, $\Delta_{sub}H$, and to enthalpy of solvation, $\Delta_{solv}H$, by the following expression

$$\Delta_{sol}H = \Delta_{sub}H + \Delta_{solv}H$$

$\Delta_{sub}H$ gives a positive contribution and its value is solid structure dependent, whereas $\Delta_{solv}H$ is negative and depends on solute/solvent interaction and on the solvent's own structure. In so far the positive figures are obtained for $\Delta_{sol}H$ it should be concluded that $\Delta_{sub}H$ is always higher than $\Delta_{solv}H$.

The comparison of the values obtained for $\Delta_{sol}H^\circ$ of the two terfenadine forms in both solvents shows that intermolecular forces in Form I are stronger than in Form II. Indeed the difference between the values for $\Delta_{sol}H^\circ$ of the two forms either in ethanol or methanol is approximately 13 kJ mol^{-1}.

The comparison of the behaviour between both solvents towards terfenadine shows that methanol may give stronger solute/solvent interaction than ethanol. In fact for any solid form of terfenadine $\Delta_{sol}H^\circ$ in methanol is about 4 kJ mol^{-1} lower than in ethanol. These results indicate that polar groups in the terfenadine molecule play an important role in solute/solvent interaction in hydrogen bonding polar liquids. Higher values of dipole moment and of hydrogen bond donor power (Taft and Kamlet parameter) given for methanol relatively to those of ethanol can account for these differences between $\Delta_{sol}H^\circ$ of the solvents [6–8].

Some important information can also be drawn from $\Delta_{sol}H$ vs. concentration curves. For any solution it is observed that solution enthalpy increases as concentration increases. Very likely solute molecular association takes place even in a very low concentration region. The association of terfenadine molecules in solution is followed by a reduction in the number of solvent molecules in the solvation envelop giving rise to a decrease of $\Delta_{solv}H$ but to an increase of $\Delta_{solv}S$. As the contribution of the last term to the Gibbs energy overcomes that corresponding to the enthalpy, molecular self association occurs. This effect, resembling that observed for non-electrolytes in water solutions, is sometimes called solvaphobic interaction which, in the present case, as in many others, is entropy driven [9].

Concerning self association of terfenadine, differences between the polymorphic forms and between the solvents can be pointed out. The slope of $\Delta_{sol}H$ vs. concentration curves of Form I increases as the concentration reaches 0.035 mol kg^{-1} in ethanol and 0.020 mol kg^{-1} in methanol. These circumstances give to the curves a well-noted sigmoid shape particularly in methanol. Likely at these concentration values nucleus of solute molecular aggregation are

formed. For Form II, $\Delta_{sol}H$ vs. concentration curves show almost constant slopes although the value observed in methanol is higher than that in ethanol.

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