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ENTHALPY OF SOLUTION OF TERFENADINE IN DIFFERENT SOLVENTS

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Abstract

Enthalpies of solution of various terfenadine samples in methanol and in ethanol were measured. Samples were prepared by crystallization in different solvents. The calorimetric results give important information on crystal structure of the terfenadine forms and on the solute/solvent interactions of this compound with the solvents.

Keywords: crystallization, polymorphism, solution calorimetry, terfenadine

Introduction

Terfenadine, α-[4-(1,1-dimethylethyl) phenyl]-4-(hydroxydiphenylmethyl)-1-piperidine butanol, is used as an antihistaminic drug. It is a general belief that terfenadine gives rise to different polymorphic forms. Values for the melting point of this substance between 144 and 153°C have been reported [1–5]. Some polymorphs have been assigned but no agreement has been reached as to the properties for their identification, even contradictory results are found [6–10].

It has been observed by the authors of the present work that terfenadine prepared by crystallization from different solvents in identical experimental conditions exhibits different properties. Also, different experimental conditions of crystallization from a specific solvent yield solid phases with different properties.

Data obtained from solution calorimetry can be useful to understand the role of the solvent on the stucture of samples of terfenadine prepared by different crystallization processes and to identify different polymorphs.

In a previous publication some preliminary data on the enthalpy of solution of terfenadine in ethanol and in methanol were given by the authors [11]. In this paper a more complete set of experimental results is presented allowing a deeper interpretation of the data.

Polymorphism is a common characteristic of organic compounds which has great importance in pharmacy [12]. There are two main points which we are looking for:

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identification of polymorphic forms by the enthalpy of solution and understanding the role of the solvent in the preparation of the polymorphs by crystallization in solution.

Preparation of terfenadine samples and experimental methods

Terfenadine was purchased from Sigma Chemical Co. Infrared spectrum and melting point show similar patterns as a standard sample supplied by US Pharmacopeia.

High grade ethanol and methanol free from water were used in crystallization and in solution processes.

The samples of terfenadine studied were prepared by crystallization either by evaporation of the solvent or by lowering the temperature. The selection of the samples for the study undertaken in this work was made keeping in mind to cover the melting temperature range observed for the whole set prepared using various solvents and techniques. In Table 1 the methods used for the preparation of the samples which through out the text are denoted by A_1, A_2, B and C are given briefly.

Table 1 Methods of preparation of terfenadine samples by crystallization

Sample	Solvent	Procedure	Drying
A_1	Methanol at 50°C	Evaporation of the solvent at 20°C	20°C
A_2	Methanol at 50°C	Evaporation of the solvent at 20°C	100°C for 60 min
B	Methanol at 50°C	Evaporation of the solvent at 50°C	100°C for 60 min
C	Ethano/water (7:3, v/v) at 60°C	Crystallization at 20°C	100°C for 60 min

Sample A_1 when examined by differential scanning calorimetry at a heating rate of 10°C min^{-1} exhibits an endothermic peak at about 75°C and an exothermic one at a temperature around 90°C. After this, no other phase transitions are observed until fusion. A_2 was prepared as A_1 but as it was subjected to a temperature above that at which the pre-melting phase transitions take place, only the fusion peak was observed for this sample. For B and C no phase transition occurs but fusion.

The solid phase transitions occurring in sample A_1 and X-ray powder diffraction patterns reveal that this sample is a mixture of crystalline and poor crystalline or even amorphous phase.

A_2, B and C exhibit different X-ray diffraction patterns and they have different melting points. The deconvolution of the fusion peaks shows that they are almost single structural forms.

The onset and the peak temperatures of fusion were determined by DSC recorded at 1°C min^{-1}. DSC 7 Perkin Elmer instrument was used and experimental details were published before [11].

The measurements of the enthalpy of solution were carried out with a Setaram C 80 solution calorimeter and experimental details were described elsewhere [11]. The experiments were carried out at 25°C.

Results and discussion

In Fig. 1 the results obtained for $\Delta_{sol}H$ *vs.* concentration for terfenadine in ethanol and in methanol solutions are represented. By extrapolating the results to null concentration the limiting values, $\Delta_{sol}H^o$, were determined. The values so obtained are given in Table 2.

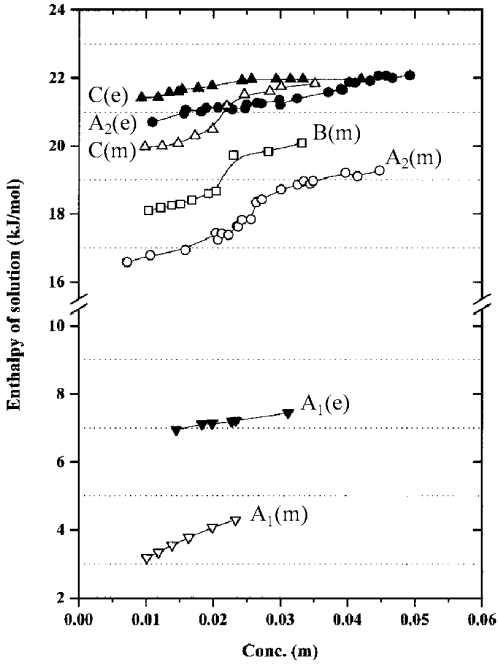

Fig. 1 Enthalpy of solution as a function of concentration for polymorphs of terfenadine in ethanol and methanol solutions. Capital letters are for the polymorphic form (Table 1) and lower case letters stand for the solvent: ethanol (e) and methanol (m)

Table 2 Standard enthalpy of solution of terfenadine in ethanol and in methanol

Sample	$\Delta_{sol}H^o$/kJ mol^{-1}	
	Ethanol	Methanol
A_1	6.6±0.16	2.3±0.31
A_2	20.2±0.19	16.5±0.25
B	–	17.6±0.02
C	21.1±0.28	19.8±0.13

Table 3 contains the temperatures and the enthalpies of fusion for the terfenadine samples used in this study.

Table 3 Melting point and enthalpy of fusion of several terfenadine forms

Sample	T_{onset}/°C	T_{peak}/°C	$\Delta_{fus}H$/kJ mol^{-1}
A_2	145.4±0.16	146.2±0.16	50.7±0.12
B	145.6±0.10	147.7±0.14	51.9±0.70
C	149.4±0.10	150.5±0.19	53.2±0.58

The thermodynamic property more closely related to solute/solvent interactions is solvation (solute in ideal gas → solution at infinite dilution) as in the initial state no intermolecular forces are involved. For a solid, the enthalpy of solvation, $\Delta_{solv}H$, is commonly calculated from the knowledge of the enthalpy of solution, $\Delta_{sol}H$, and from the enthalpy of sublimation, $\Delta_{sub}H$, according to the following thermodynamic cycle

$$\Delta_{solv}H + \Delta_{sub}H - \Delta_{sol}H = 0 \quad (1)$$

No data are available for $\Delta_{sub}H$ of terfenadine and so the study of the solution processes undertaken in the present work have to be limited to the discussion of $\Delta_{sol}H$ values. The conclusions are more qualitative in nature than would be based on $\Delta_{solv}H$, nevertheless some valuable information can be drawn from this property.

The values obtained for $\Delta_{sol}H$ of all systems are positive. Bearing in mind that sublimation gives positive contributions to the enthalpy and to the entropy and that the solvation process will give a negative contribution to these thermodynamic functions, a positive result for $\Delta_{sol}H$ means that $\Delta_{sub}H$ overcomes the absolute value of $\Delta_{solv}H$. As $\Delta_{sol}H$ becomes unfavourable to the dissolution of terfenadine, the solubility observed is due to entropy. That is, the sublimation and solvation processes on the whole give the dissolution of terfenadine an unfavourable enthalpy but a favourable entropy. The solubility observed indicates then that apparently sublimation and solvation are more unlike in the entropic than in the enthalpic terms. A low value for the entropy of crystalline terfenadine is to be expected because, besides the depression arising from holding the molecules together, we have to account for orientational order imposed by specific interactions involving polar groups in particular hydrogen bonds.

From the differences observed for $\Delta_{sol}H^o$ between ethanol and methanol some inferences can be made on the prevailing solute/solvent interactions of terfenadine with these alcohols. Any terfenadine sample gives a higher value of $\Delta_{sol}H^o$ in ethanol than in methanol. As the former alcohol has a higher electrical dipole moment than the latter and in turn ethanol has a higher polarizability than methanol, the relative values of $\Delta_{sol}H^o$ observed for these two solvents indicate that the more important solute/solvent interactions are due to polar rather than to dispersion forces.

Another important point which must be referred regards the variation of $\Delta_{sol}H$ with concentration. It is observed that the enthalpy increases as concentration increases both in methanol and in ethanol solution. Such a behaviour shows that solute/solute interactions take place even at very low concentrations. Since these inter-

actions give rise to an increase of entropy, a straightforward interpretation is that in the molecular association of terfenadine in these solutions the entropy loss due to solute/solute holding forces is overcome by the entropy gain due to the freedom of the solvent molecules which were bonded to the terfenadine by solute/solvent forces.

$\Delta_{sol}H$ *vs.* concentration pointed out a striking difference between ethanol and methanol solutions. If A_1 is excluded because it is structurally different from the others, as will be explained ahead, methanol solutions show a sudden increase of $\Delta_{sol}H$ as concentration reaches a value around 0.025 m. In methanol solution the solute/solute interaction gives rise to oligomers of low aggregation number. As the concentration reaches a critical value of 0.025 m the oligomers become nucleus of *n*-mer aggregates which, in its turn, grow giving rise to the solid phase. In ethanol, solute association of monomers or oligomers to form a *n*-mer aggregate is not a single step one. In this solvent ethanol only a slight trend for increasing the slope of the enthalpy *vs.* concentration curves is observed. The enthalpy jump observed in methanol is a manifestation of solute molecular aggregation. That is, as concentration reaches a certain level the molecular association seen at lower concentration gives rise to molecular aggregates. This tendency of methanol to induce formation of aggregates explains the lower solubility of terfenadine in this solvent relatively to that observed in ethanol in spite of the stronger solute/solvent interactions with the former alcohol.

The results observed for $\Delta_{sol}H^o$ prove that this property is useful for characterizing polymorphic forms of terfenadine. The differences between $\Delta_{sol}H^o$ for a certain solvent are ordered according to the enthalpy of fusion of the terfenadine forms. This finding should be expected because both properties are, in principle, indications of strong molecular interactions in the crystal phase.

Furthermore it should be underlined that the enthalpy of solution is very sensitive to structural differences.

Based on the study of the solid phase transitions observed in the DSC curves the authors of the present work admitted that sample A_1 is a mixture of two polymorphs with different crystallinity. As pointed out by Etter *et al*. [13] sometimes more than one polymorph are nucleated in the same solution. The crystallization of polymorphes are controlled by kinetic and thermodynamic factors. It is clear that seeding with a pure form or a mixture of polymorphs of a given substance is playing an important role in the crystallization. However, decisive factor of the crystallization route is the Gibbs free energy functions of all the polymorphic forms involved. These functions as shown by Marti et al., in the laboratory of Ciba Geigy Ltd., Basel, already in 1974, determine also the vapour pressure and solubility curves and are the base for the driving forces of crystallization [14, 15]. The less ordered phase is not stable at temperatures above 75°C giving rise to a crystalline structure by heating. This interpretation is in agreement with the results obtained for $\Delta_{sol}H^o$ for this sample. Indeed, the more disordered phase will give a lower enthalpy of solution considering the weaker intermolecular interactions in this phase. Hence, the lower values obtained for $\Delta_{sol}H^o$, compared with those obtained for more crystalline samples.

A special pattern observed for the experimental curves (Fig. 2) corresponding to the solution process reinforce the idea that A_1 is, in fact, a two phase system being

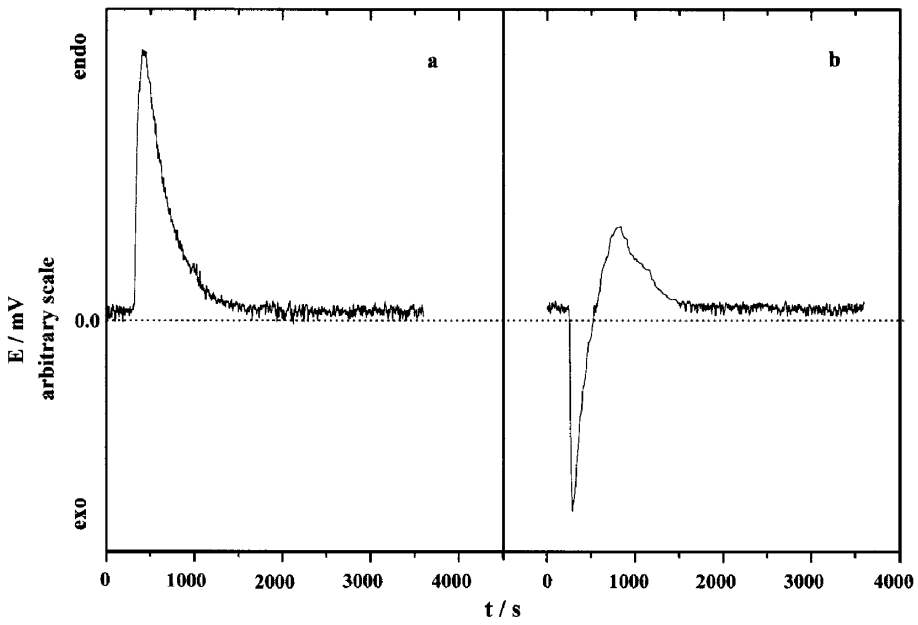

Fig. 2 Solution calorimetric curve patterns; a – all systems, except A_1, in methanol; b – A_1 in methanol

one of them a poorly crystalline phase. Whereas for all other samples solute/solvent mixing gives endothermic peaks, for A_1 an exothermic peak is observed in a first stage and an endothermic one in a second. The less crystalline form is of course more permeable to the solvent than the more crystalline one. Hence the rate of solution is higher while the former phase is present and a negative enthalpy of solution is observed; then, the more crystalline phase becomes predominant and a positive enthalpy is observed.

The molecular aggregates arising in solution as the concentration of terfenadine reaches a certain level have great importance because it is admitted that nucleation is due to the same type of intermolecular interactions [16]. The structure of organic crystals prepared by crystallization in solution will be dependent on the type of the molecular aggregates.

For terfenadine, methanol favours the formation of aggregates, which is in agreement with the difference in behaviour shown by the two alcohols as crystallization media.

Conclusions

Enthalpy of solution is shown to be a useful property for characterizing structural differences in organic crystals namely, for the discrimination of polymorphs of terfenadine.

From the limiting values of the enthalpy of solution, information on intermolecular interactions in solid phase and in solution can be inferred.

Finally, the variation of enthalpy of solution with concentration provides data on the role of the solvent when used in the preparation of terfenadine by crystallization in solution.

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