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An investigation of flurbiprofen polymorphism by thermoanalytical and spectroscopic methods and a study of its interactions with poly-(ethylene glycol) 6000 by differential scanning calorimetry and modelling

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Abstract

The polymorphism of flurbiprofen was investigated. The flurbiprofen-PEG 6000 phase diagram was constructed and compared with the modelling diagram in order to examine interactions between the two compounds. Thermoanalytical (differential scanning calorimetry, transparency measure, thermomicroscopy) and spectral methods (infrared spectroscopy and X-ray diffraction) were used to identify the polymorphic forms and to construct the phase diagram. Thermodynamic data were used to model the flurbiprofen-PEG 6000 system. Two polymorphic forms were identified ($T_{fI} = 112.8 \pm 0.2$°C, $\Delta H_I = 108.1 \pm 3.2$ J/g and $T_{fII} = 97.0 \pm 0.2$°C) along with a probable enantiotropic transition of form II into form I at 60°C. The construction of the flurbiprofen-PEG 6000 phase diagram showed the existence of a stable invariant characterized by $(X_E)\text{exp} = 67\%$ of PEG 6000 (w/w) and $(T_{fE})\text{exp} = 48.0 \pm 0.2$°C. Modelling confirmed these results with $(X_E)\text{exp} = 67\%$ of PEG 6000 (w/w) and $(T_{fE})\text{th} = 53.3 \pm 0.2$°C and was used to evaluate $\chi = -2.67$. The Flory–Huggins parameter 'χ' was evaluated from the model. Its value confirms the existence of interactions due to hydrogen bonds. © 1997 Elsevier Science B.V.

Keywords: Flurbiprofen; Poly-(ethylene glycol) 6000; Polymorphism; Thermal analysis; X-ray diffractometry; Phase diagram

1. Introduction

Flurbiprofen (FB) is a non-steroidal anti-inflammatory drug that is slightly water soluble (Martindale, 1989). It is used routinely in the

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treatment of rheumatoid arthritis (Dallas et al., 1987).

Crystal polymorphism of pharmaceutical molecules has been a source of interest for many years, as evidenced by the numerous reports in the literature on steroids, sulfonamides and barbiturates (Byrn, 1982). The understanding of the polymorphism of a compound can be critical to the development of a drug, the performance of a solid dosage form and ultimately the success or failure of a pharmaceutical product. Indeed, polymorphs have been demonstrated to have different physical properties such as apparent solubility, physical and chemical stability. The current study examines aspects of the polymorphism and crystallization behavior of flurbiprofen.

For a drug to produce optimal activity, it is necessary to deliver the drug into the body and target its site of action as efficiently as possible. The biodisponibility of slightly water-soluble drugs is limited by the dissolution process in the gastrointestinal tract. The dissolution rate may be enhanced by the formulation of an eutectic mixture of a slightly water-soluble drug with a freely water-soluble and physiologically inert carrier (Chiou and Riegelman, 1971). Poly-(ethylene glycols) are usually used extensively as carriers because of their favourable solution properties, low melting point and low toxicity. Firstly, solid–solid interactions between flurbiprofen and poly-(ethylene glycol) 6000 (PEG 6000) were studied by the construction of a phase diagram obtained from physical mixtures. This provided information about the eutectic composition, invariant point whose physical characteristics, particularly the dissolution kinetics or solubility, are improved in comparison with the drug in isolation (Burger and Ramburger, 1979; Goldberg et al., 1966; Sekiguchi et al., 1963).

Then thermodynamic rules were used to produce a model of the FB-PEG 6000 system (Prigogine and Defay, 1946) and to quantify interactions by calculating 'χ' the Flory–Huggins interaction parameter. The Flory–Huggins theory (Flory, 1942; Huggins, 1942) is used to describe interactions between molecules which differ greatly in size, e.g., polymers and organic solvents. Thus, a polymer solution is considered to be non ideal ($\Delta Hm \neq 0$, ΔHm is the enthalpy of the mixture). We have attempted to apply the Flory-Huggins theory to the FB-PEG 6000 system with the following hypothesis: the flurbiprofen powder is considered to be the solvent and the FB-PEG 6000 mixture is slightly diluted in comparison with a polymer solution.

2. Materials and methods

2.1. Materials

Flurbiprofen (2-[2 fluoro-4-biphenyl] propionic acid) is a non-steroidal anti-inflammatory drug that is slightly water soluble. It was provided by Sigma (batches 64H3334 and 111H3342, Saint Quentin Fallavier, France) and has a molecular weight of 244.3 g.

Poly-(ethylene glycol) 6000 (PEG 6000) is a macromolecule obtained by the polymerization of ethylene oxide. It was supplied by Merck (Merck Schuchardt art. 807491 batch 7239412) and has a molecular weight of 5400–6000 (Handbook of Pharmaceutical Excipient, 1986). Its melting point can vary from 55 to 63°C (Flory, 1978).

2.2. Methods

2.2.1. Recrystallization methods

Different methods were tested to recrystallize flurbiprofen: recrystallization by quenching which consists of hot dissolution of the drug followed by rapid cooling in a freezer, recrystallization by elimination of solvent, i.e. evaporation at reduced pressure using a rotavapor (1 mmHg), recrystallization using a water-bath: hot dissolution and evaporation of solvent at 90°C.

The following solvents were used: dichloromethane, chloroform, acetone, ethyl acetate, acetonitrile, dioxane, methanol, propanol, cyclohexane, hexane and pentane.

2.2.2. Preparation of the physical mixtures

To construct the phase diagram, physical mixtures (PM) of drug and polymer (between 3 and 97% of PEG 6000, w/w) were obtained by grinding the mixture in an agate mortar with a pestle for 5 min.

2.2.3. Differential scanning calorimetry

The DSC profiles of the different polymorphic forms and physical mixtures were recorded on a Mettler FP800 thermal analyzer fitted with a Mettler FP 85 DSC cell and an Epson HX 20 programmer connected to a Mettler GA11 recorder. Thermal behavior was studied under normal conditions with perforated and sealed pans and with a nitrogen gas flow of 10 ml/min. The samples (2–4 mg) were heated at a rate of 2;5 or 10°C/min over a temperature range of 30–140°C. The apparatus was calibrated using a pure sample reference material. Onset temperatures (temperatures at the equilibrium between phases) and enthalpies were determined by calculating the mean of three measurements. The thermal behavior of the polymorphic forms was examined by heating and cooling cycles of 5°C/min: the sample was heated at 5°C/min and then cooled rapidly at 25°C/min. A special process was used to explain the polymorphism of flurbiprofen, i.e. the addition of thermally and chemically stable silicone oil to the powder. Roman numerals were assigned to the different polymorph forms (form I corresponds to the more stable form).

2.2.4. Thermomicroscopic investigation

A Leitz SM POL microscope connected to a Mettler FP52 hot stage and a Mettler FP5 temperature controller was used for microscopic investigations. Observations were videotaped with a Leica recorder and a Sony color video camera DXC-101 P directly attached to the microscope. The crystals were heated at a rate of 5°C/min. Silicone oil was added to the powder between the slide and the cover-slip to render visible the polymorphism of flurbiprofen and the possible existence of solvates. Physical mixtures similar to the composition of eutectic were studied by a technique called 'contact process' (Kuhnert-Branstätetter, 1971).

2.2.5. Transparency measurement

The profiles of the different polymorphic forms of flurbiprofen were recorded on a Mettler FP 800 thermal analyzer fitted with a Mettler FP 81 DSC cell connected to a HX20 programmer and a Mettler GA17 recorder. The samples placed in capillaries were heated at a rate of 2, 5 or 10°C/min. Melting temperatures were determined by calculating the mean of three graphical measurements (Vergnon and Drevon, 1974). The transparency measurements show only the melting or the recrystallization of a substance.

2.2.6. Powder X-ray diffractometry

Powder X-ray Diffraction patterns were measured using a Philips PW 1730 powder diffractometer fitted with a CGR goniometer (type C, horizontal), employing monochromatized CuKα radiation ($\lambda = 1.54051$ Å), a voltage of 40 kV and a current of 20 mA. The gently crushed samples were mounted on a glass plate. The transformation rate of the forms was given by the intensity variation of the peaks characterizing each form.

2.2.7. Infrared spectroscopy (IR)

IR spectra were obtained on a Perkin-Elmer 983G spectrometer from potassium bromide (KBr) pellets with a pressure of 10 tonnes. Spectra were recorded over 4000–400 cm^{-1}. DSC was used to confirm that the pressure has no effect on powder polymorphism.

3. Results and discussion

3.1. Polymorphism of flurbiprofen

3.1.1. Thermomicroscopy

When heated at 5°C/min, flurbiprofen began to melt at 110°C and completed its melting phase at 115°C. The melted substance rapidly cooled at room temperature solidifies to form a glass.

When this mixture was heated a second time at the same rate, forms I (small coloured needles) and II (large grey prisms) crystallize. Form II grows between 40 and 60°C. Then at 70°C, the larger of form II transformed into form I which, in this case, showed a colored prismatic appearance.

At $T_{fII} = 90$°C, non-transformed form II melted and the form I prisms continued to grow in the melt up to 100°C. Form I melted at $T_{fI} = 113$°C. The visualization of form II was improved by the use of silicone oil.

3.1.2. Differential scanning calorimetry

The thermal behavior of flurbiprofen was investigated by four heating and cooling cycles at 5°C/min (Fig. 1a, b, c, d and e) to show the reproducibility of the process. During the first heating, the DSC tracing (Fig. 1a and Fig. 2b) showed an endothermic peak at $T_{fI} = 112.8 \pm 0.2$°C with $\Delta H_{fI} = 108.1 \pm 3.2$ J/g, temperature and melting enthalpy of form I; at 2°C/min, $T_{fI} = 112.4 \pm 0.2$°C and $\Delta H_{fI} = 111.4 \pm 3.3$ J/g (Fig. 2a); at 10°C/min, $T_{fI} = 112.8 \pm 0.2$°C and $\Delta H_{fI} = 113.2 \pm 3.4$ J/g (Fig. 2c). The DSC tracing of the melt after rapid cooling and heating showed a complex exothermic process constituted by two peaks at $T_{rec} = 44.6 \pm 0.2$°C and 60.0 ± 0.2°C and an endothermic process at $T_{fI} = 112.8 \pm 0.2$°C (melting of form I). The DSC tracing obtained in the presence of silicone oil is presented in Fig. 3. It shows two exothermic processes corresponding to the melting of form II and form I ($T_{fII} = 83.3 \pm 0.2$°C and $T_{fI} = 106.7 \pm 0.2$°C) and to an exothermic process concerning the recrystallization of form I from the melt of form II.

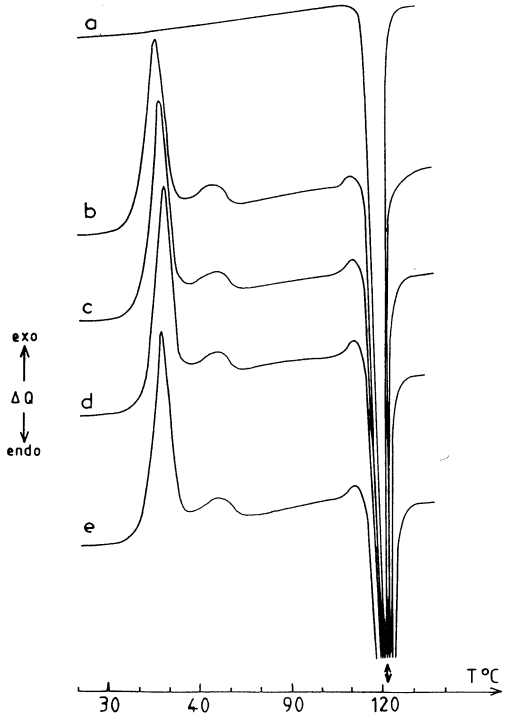

Fig. 1. DSC tracings of flurbiprofen at a rate of 5°C/min; (a) first heating; (b) second heating after rapid cooling; (c), (d), (e), heating-cooling cycles.

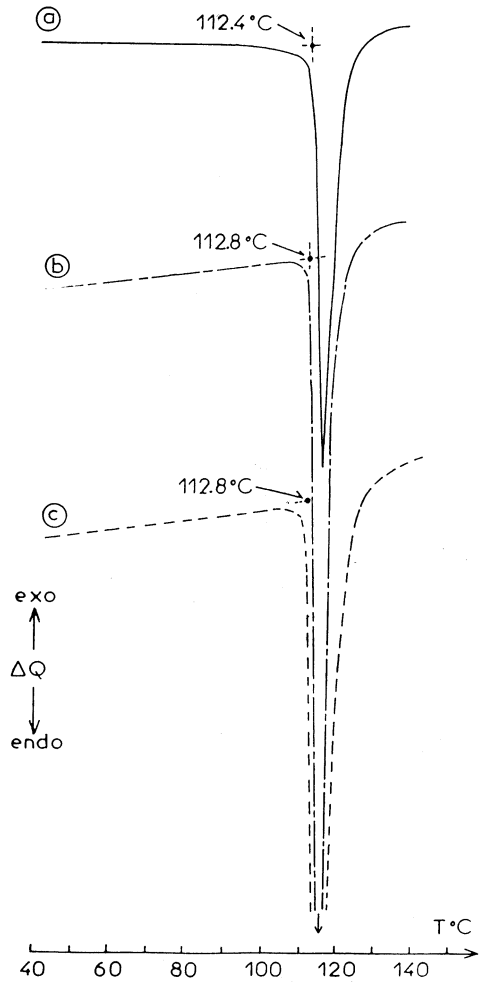

Fig. 2. DSC tracings of flurbiprofen; (a) v = 2°C/min; (b) v = 5°C/min; (c) v = 10°C/min.

3.1.3. Transparency measurement

The cycles conducted at 5°C/min determined the recrystallization (T_{rec}) and melting (T_{fI}) temperatures at 49.7 ± 0.5°C and 117.5 ± 0.5°C respectively. At the rate of 2 and 10°C/min, melting temperatures were $T_{fI} = 116.3 \pm 0.5$°C and $T_{fI} = 119.4 \pm 0.5$°C.

Thermomicroscopy can explain the results obtained using DSC during the heating and cooling cycles (Fig. 1). The first exothermic process corre-

sponded to the recrystallization of form II. The second exothermic process corresponded to the solid↔solid transformation of form II into form I and at the same time the recrystallization of form I. However, we are unable to determine whether the transformation is exothermic (monotropic transition) or endothermic (enantiotropic transition) because the process is complex and the transformation rate is probably very slow. By its very principle, the transparency measurements confirm that a recrystallization process is present but cannot determine whether form I and form II recrystallize together or if only form I recrystallizes after the first heating and cooling cycle. When using DSC, the results of the melting-recrystallization-melting process conducted in the presence of silicone oil (Fig. 3) permit us to consider the transformation of form II into form I as an enantiotropic transition. Form II could not have melted at 90°C because it was totally transformed at 60°C. Silicone oil by limiting contacts between the two forms can be used to show the melting of form II.

The recrystallization of form II was observed by thermomicroscopy when the thickness of the melt between the slide and the cover-slip was very small. Such conditions could not be created when using DSC.

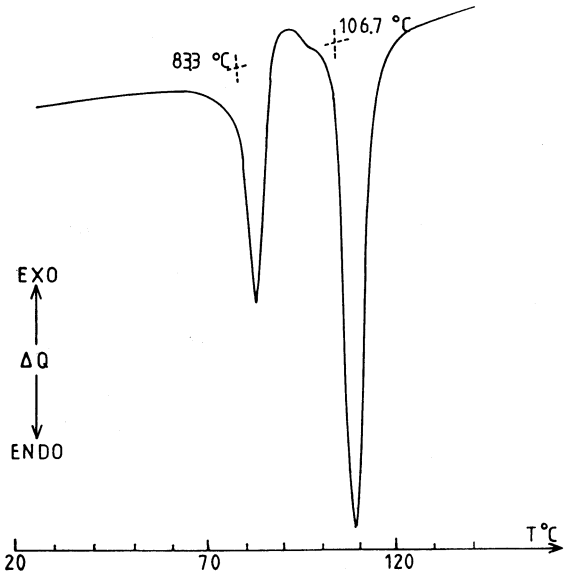

Fig. 3. DSC tracing of flurbiprofen at a rate of 5°C/min in the presence of silicone oil.

The recrystallizations in different solvents were unable to isolate form II. However, a mixture of the two forms was obtained by quenching recrystallization in heptane, though only a small amount was produced, and in a non-reproducible manner. When tested by DSC, the melting temperature of form II in the mixture was noted to be 94°C (graphical determination).

3.1.4. X-ray diffraction

ln order to follow the transformation of form II into form I by X-ray diffraction, the powder was melted on a glass plate and a limited part of the spectrum between 3.00 and 6.00°θ (where modifications are visible) was recorded from the beginning of its recrystallization (Fig. 4). A peak not visible in the initial spectrum of flurbiprofen appeared at 4.60°θ. This peak decreased in intensity during the recrystallization phase and at the same time, two other peaks appeared at 3.66 and 5.48°θ. These are present in the spectrum of the powder confirming the transformation of form II into form I over a period of time. The transformation rate of form II into form I were studied (Fig. 5). A plateau was reached after 800 min, this point corresponding to the end of the recrystallization of the form I.

3.1.5. Infrared spectroscopy

The spectrum of the powder recrystallized in heptane (Fig. 6b) was studied and compared to that of the initial powder (Fig. 6a). Significant shifts in the absorption bands are visible. From the mixture spectrum, it can be seen that the carbonyl stretching band of the FB powder at 1700 cm^{-1} (Fig. 6a) has shifted to a higher frequency, i.e. 1711 cm^{-1} (Fig. 6b) and that the OH out-of-plane deformation band at 958 cm^{-1} has disappeared (Fig. 6b).

3.2. Experimental flurbiprofen-PEG 6000 phase diagram

A flurbiprofen-PEG 6000 phase diagram (Chiou and Riegelman, 1971) was constructed by DSC (Fig. 7). We verified that the energy due to

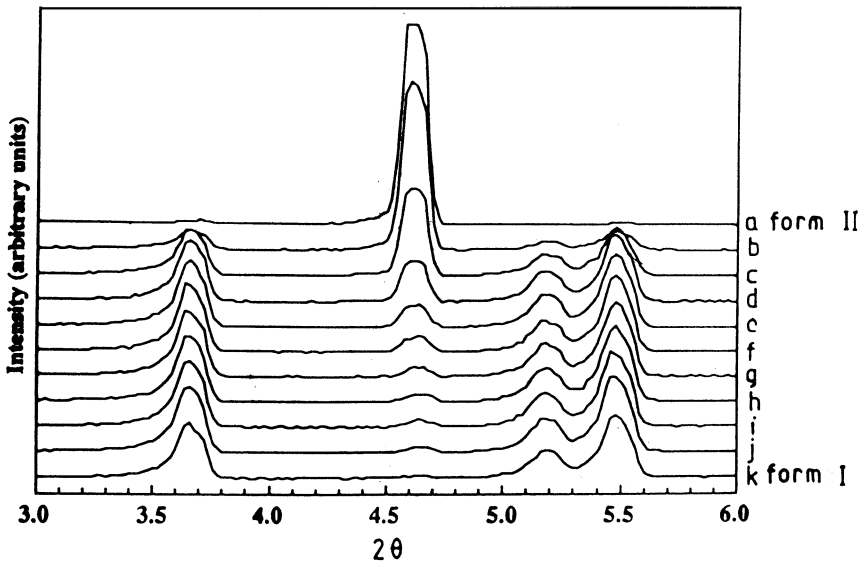

Fig. 4. Study of the transformation by X-ray diffractometry; (a) 0 min; (b) 62.5 min; (c) 125 min; (d) 187.5 min; (e) 250 min; (f) 312.5 min; (g) 625 min; (h) 937.5 min; (i) 1250 min; (j) 1875; (k) 3037.5 min.

crushing has no effect on the polymorphism of PEG 6000 or on the thermograms of the mixtures of different composition. The results obtained by DSC and thermomicroscopy are presented in Table 1. The mixtures show two endothermic processes but not for the compositions near the eutectic composition (67 and 70%). The first corresponds to the melting of the eutectic composition and the second to the end of the melting process. The diagram (Fig. 8a) shows a stable invariant for all compositions from 3 to 97% PEG 6000 (w/w) (excluding the formation of solid solution) with the following characteristics:

'Eutectic': flurbiprofen + PEG 6000 → eutectic liquid,

$(X_E)_{exp} = 67\%$ (w/w) of PEG 6000,

$(T_{fE})_{exp} = 48.0 \pm 0.2°C = 321.0 \pm 0.2K$,

$(\Delta H_{fE})_{exp} = 143.3 \pm 4.3$ J/g

$(X_E)_{exp}$, $(T_{fE})_{exp}$ and $(\Delta H_{fE})_{exp}$ are the experimental eutectic composition, the experimental temperature and the enthalpy of the eutectic melting, respectively.

The $(\Delta H_{fE})_{exp}$ values obtained for each composition were used to construct a Tammann diagram (Fig. 8b) (Tammann, 1924). This gave the position of the eutectic at $(X_E)_{exp} = 70\%$ of PEG 6000 (w/w). The thermomicroscopic examination was conducted in dispersions containing 3–97% of PEG 6000 (w/w). The temperature of the end of the melting was higher than that obtained in DSC as this technique indicates the temperature at which all the crystals have melted. (In DSC, it corresponds to the temperature at the top of the peak).

The contact process, when the drug and the polymer were placed side by side, showed a continuous black streak at the eutectic melting temperature (Chauvet and Masse, 1983). When the drug and mixtures of different composition were placed side by side, this technique specified the eutectic composition by the absence of this streak.

The two large peaks in the X-ray spectrum of PEG 6000 (a high proportion of which is present in the PEG 6000-flurbiprofen mixture) can mask characteristic peaks of the eutectic mixture. The X-ray diffractometry could not confirm the existence of the stable invariant.

Comparison to the infrared spectra (Fig. 6a, c and d) shows that flurbiprofen (Fig. 6a) and PEG 6000 (Fig. 6c) peaks are present in the spectrum of the physical mixture (Fig. 6d). The two compounds may be linked by hydrogen bonds, but these may be too weak to modify the spectrum.

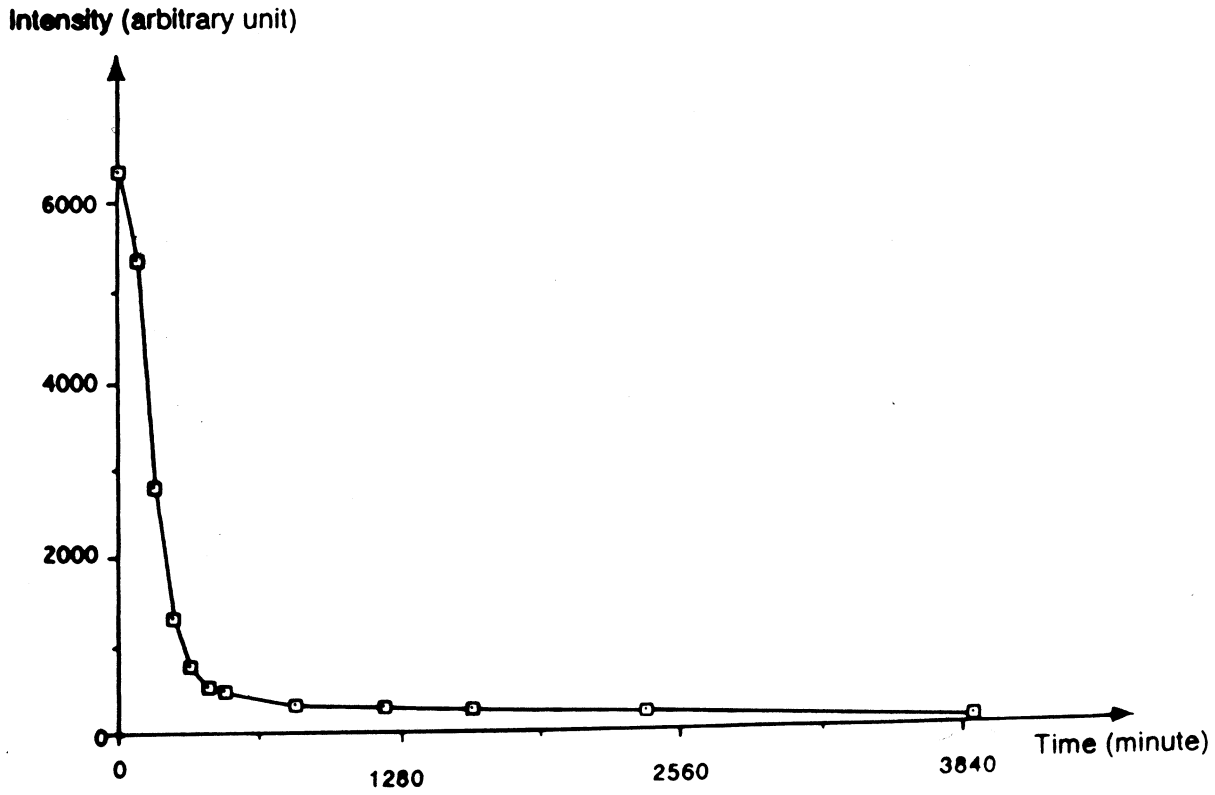

Fig. 5. Tracing of the transformation kinetic using X-ray diffractometry.

3.3. Theorical flurbiprofen-PEG 6000 phase diagram (modelling)

3.3.1. Thermodynamic approach

To construct the phase diagram, each physical mixture was heated to produce a homogeneous mixture of the components in the liquid phase. The thermodynamic requirement for the formation of a two compounds solution is that the Gibbs free energy G_{ij} of the mixture must be lower than the sum of free energies G_i and G_j of the pure components in isolation (Young and Lovell, 1991).

$$\Delta G_m = G_{ij} - (G_i - G_j) \quad (1)$$

$\Delta G_m < 0$ for a solution to form. ΔG_m is the Gibbs free enthalpy of mixing:

$$\Delta G_m = \Delta H_m - T\Delta S_m \quad (2)$$

where ΔH_m is the heat (or enthalpy) of mixing and ΔS_m is the entropy of mixing.

Since the eutectic composition is a simple mixture of two components and if we neglect the change of heat capacity, then $(\Delta H_{mE})_{exp}$ corresponds to the difference between experimental heat of eutectic melting $(\Delta H_{fE})_{exp}$ and the theoretical heat of melting $(\Delta H_{fE})_{th}$ (Rai et al., 1989; Rai and Mandal, 1990):

$$(\Delta H_{mE})_{exp} = (\Delta H_{fE})_{exp} - (\Delta H_{fE})_{th} \quad (3)$$

$$(\Delta H_{fE})_{th} = X_{iE}\Delta H_{fi} + X_{jE}\Delta H_{fj} \quad (4)$$

$X_{i,j,E}$ and $\Delta H_{fi,j}$ are the mole fraction and the melting enthalpy of each phase, 'E' means 'eutectic'.

In the case of ideal solutions (Huggins, 1942), the energy of interaction between a pair of solvent molecules, a pair of solute molecules and a sol-

vent–solute pair must be the same so that $(\Delta H_{mE})_{exp} = 0$.

When the excipient is composed of a molecule of polymer, the size and the conformation of which differ from those of small molecules, the Flory–Huggins model is suitable to describe the deviations from ideality and the interactions between the two substances. In the Flory–Huggins theory (Flory, 1942; Huggins, 1942), the polymer molecules are considered to be chains of segments, each segment being equal in size to a solvent molecule (here the solvent is replaced by the drug).

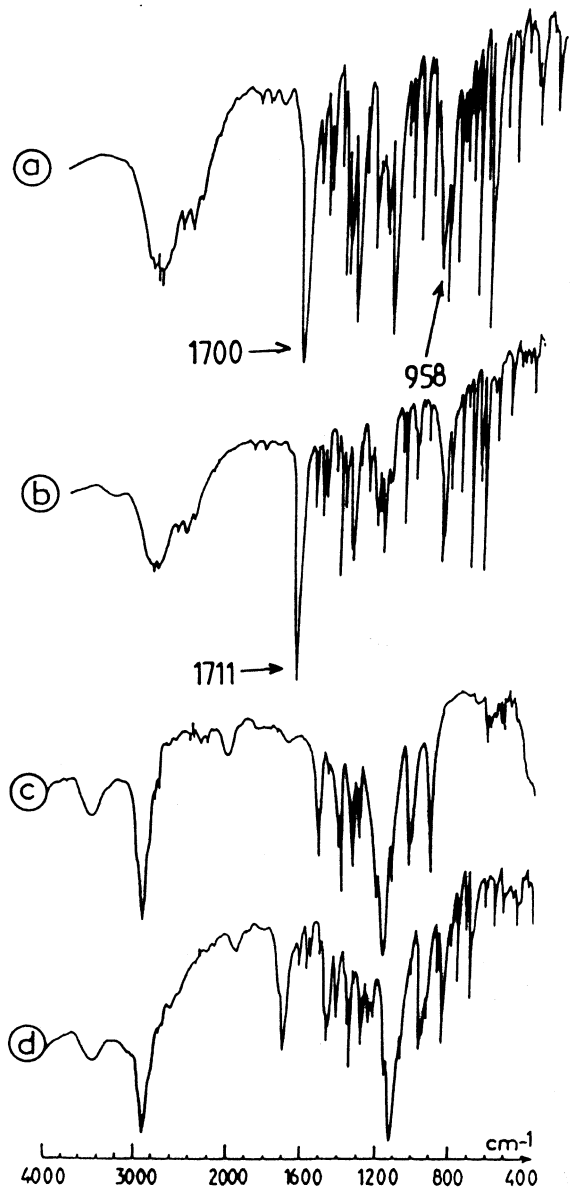

Fig. 6. Infrared spectra; (a) flurbiprofen; (b) flurbiprofen recrystallized in heptane; (c) PEG 6000; (d) physical mixture of FB-PEG 6000 (67%, of PEG 6000, w/w).

The mole fraction X is converted to the volume fraction ϕ:

$$\phi_i = \frac{n_i V_i}{n_i V_i + n_j V_j} = \frac{1}{1 + \frac{X_j \sigma_i}{X_i \sigma_j}}; \quad \phi_j = \frac{n_j V_j}{n_i V_i + n_j V_j} = \frac{1}{1 + \frac{X_i \sigma_j}{X_j \sigma_i}} \tag{5}$$

$n_{i,j}$; $V_{i,j}$; $X_{i,j}$ and $\sigma_{i,j}$ are the number of moles at the eutectic composition, the mole volume, the weight fraction, and the density (of melted compounds) of each component.

In a monomer–polymer equlibrium, ΔS_m (the mixture entropy) can be replaced by ΔS_{conf} (configurational entropy change) because each molecule in a pure amorphous polymer can adopt many different conformations; there are no changes in the rotational vibrational or translational entropies of the components upon mixing. ΔS_{conf} depends on the volume fraction (Young and Lovell, 1991):

$$\Delta S_m = \Delta S_{conf} = -R(n_i \ln \phi_i + n_j \ln \phi_j) \tag{6}$$

The enthalpy of mixing is given below:

$$\Delta H_m = (Z-2) n_i \phi_j \Delta \omega_{ij} = n_i \phi_j \Delta w_{ij} = RT n_i \phi_j \chi \tag{7}$$

with $\Delta w_{ij} = (Z-2)\Delta \omega_{ij}$ and where Z, N_i, Δw_{ij} correspond to the site number, the solvent molecule and the total interaction energy per macromolecular volume element (Wunderlich, 1990). 'χ' is called the Flory–Huggins interaction parameter: it is zero for athermal mixtures, negative for exothermic mixing and positive for endothermic mixing.

According to Eq. 6 and Eq. 7, the Gibbs free energy of mixing (ΔG_m) becomes

$$\Delta G_m = RT(n_i \ln \phi_i + n_j \ln \phi_j) + n_i \phi_j \Delta W_{ij} \tag{8}$$

$$\Delta G_m = RT(n_i \ln \phi_i + n_j \ln \phi_j + n_i \phi_j \chi) \tag{9}$$

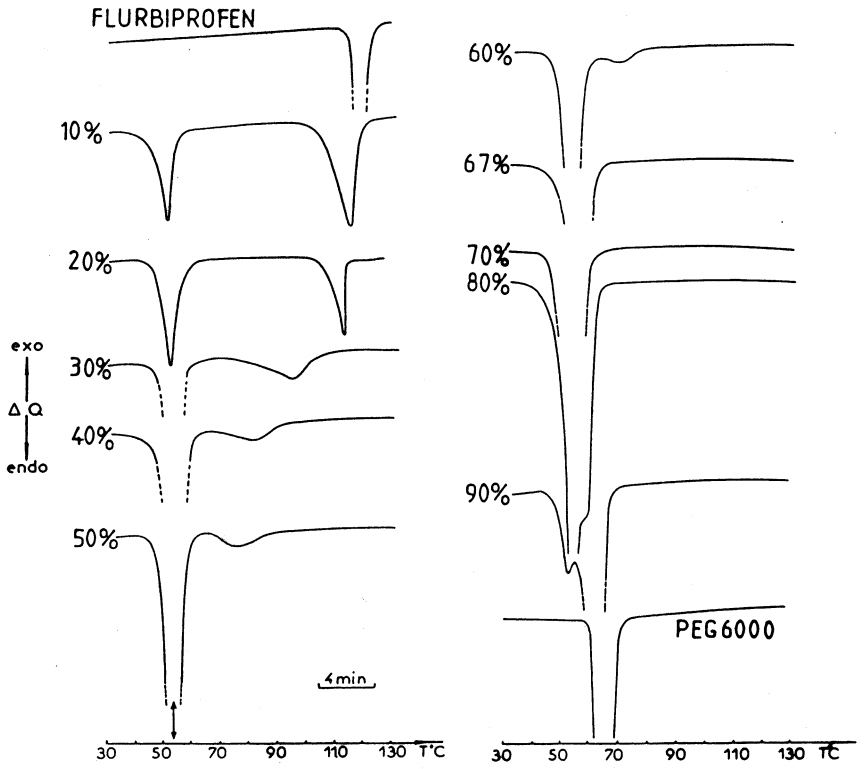

Fig. 7. DSC tracings obtained after heating physical mixtures of FB-PEG 6000 (10–90%, of PEG 6000, w/w) at a rate of 5°C/min.

In an equilibrium between two phases, the chemical potential (μ) must be equal in both phases (liquid 'ℓ' and solid 's') for all compounds ($\mu_{i(\ell)} = \mu_{i(s)}$ and $\mu_{j(\ell)} = \mu_{j(s)}$) and it can be related to its activity 'a' by the phase standard thermodynamic rules:

$$\mu_{i(\ell)} = \mu^{\circ}_{i(\ell)} + RT \ln a_{i(\ell)} \tag{10}$$

$$\mu_{j(\ell)} = \mu^{\circ}_{j(\ell)} + RT \ln a_{j(\ell)} \tag{11}$$

where $\mu^{\circ}_{i,j(\ell)}$ is the standard chemical potential of pure components.

$$RT \ln a_{i(\ell)} = (\delta \Delta G/\delta n_i)_{T,P,nj} = RT \ln \phi_i + RT\, \phi_j \left(1 - \frac{V_i}{V_j}\right) + \Delta W_{ij} \phi_j^2 \tag{12}$$

$$RT \ln a_{j(\ell)} = (\delta \Delta G/\delta n_j)_{T,P,ni} = RT \ln \phi_j + RT\, \phi_i \left(1 - \frac{V_j}{V_i}\right) + \Delta W_{ij} \phi_i^2 \tag{13}$$

If the two components are not miscible in the solid phase,

$$\mu_{i(s)} = \mu^{\circ}_{i(s)}$$

$$\mu_{j(s)} = \mu^{\circ}_{j(s)} \tag{14}$$

If we consider that $C^{\circ}_{P}(\ell)$ is equal to $C^{\circ}_{P}(s)$ then:

$$\Delta C_P = 0 \text{ and } \mu_{i(\ell)} - \mu_{i(s)} = \Delta H_{fi} \left(1 - \frac{T}{T_{fi}}\right) \tag{15}$$

where C_P is the heat capacity at constant pressure.

Table 1
Differential scanning calorimetry (DSC) and thermomicroscopy (TM) of physical mixtures FB-PEG 6000 at a rate of 5°C/min

PEG 6000 % (w/w)	Eutectic level			End of melting			Flurbiprofen % (w/w)
	Enthalpy (J/g)	DSC ± 0.2°C	TM (°C)	Enthalpy (J/g)	DSC ± 0.2°C	TM (°C)	
0	—	—	—	108.1(3.2)	112.8	115	100
3	6.5(0.2)	—	50	98.4(2.9)	110.8	115	97
10	20.4(0.6)	46.6	49	70.3(1.8)	108.5	112	90
20	35.4(1.1)	46.7	50	38.5(1.2)	102.3	111	80
30	62.8(1.9)	47.7	48	30.9(0.9)	91.5	98	70
40	86.2(2.6)	47.7	47	—	80.0	87	60
50	104.9(3.1)	48.0	46	—	72.6	84	50
55	120.2(3.6)	47.0	47	Shoulder	66.1	75	45
60	128.9(3.9)	48.0	46	Shoulder	65.0	70	40
67	143.3(4.3)	48.0	46	—	—	—	33
70	Shoulder	46.8	47	Shoulder	—	—	30
75	Shoulder	47.5	46	Shoulder	—	57	25
80	111.9(3.4)	47.3	46	32.4(1.0)	56.0	58	20
85	70.5(2.1)	47.2	47	135.9(4.1)	56.4	58	15
90	52.8(1.6)	46.7	46	147.0(4.4)	56.5	60	10
97	—	—	—	181.7(5.4)	58.0	60	3
100	—	—	—	198.1 (5.5)	59.5	60	0

(): Relative error.

The relation between the melting heat of each component and the temperature (T) of the liquidus is given below where R is the gas constant:

$$\Delta H_{fi}\left(1-\frac{T}{T_{fi}}\right) = -RT\left[\ln\phi_i+\phi_j\left(1-\frac{V_i}{V_j}\right)\right]-\Delta W_{ij}\phi_j^2 \quad (16)$$

$$\Delta H_{fi}\left(1-\frac{T}{T_{fi}}\right) = -RT\left[\ln\phi_j+\phi_i\left(1-\frac{V_j}{V_i}\right)\right]-\Delta W_{ij}\phi_i^2 \quad (17)$$

3.3.2. Application to the FB-PEG 6000 system at the eutectic composition

A model of the equilibrium between phases was constructed by assuming that the drug and the polymer are not soluble in the solid state. The experimental data used were the temperature of the liquidus and the thermodynamic properties determined by DSC (Table 2) $(\Delta H_{fE})_{th}$ is calculated from Eq. (4) by replaced $X_{i,j}$ by $\phi_{i,j}$; $(\Delta H_{mE})_{exp}$ is obtained from Eq. (3). If 1 ($i=1$) and 2 ($j=2$) are drug and polymer indices from the equation, liquidus temperature can be calculated: when $X_1 < X_E$, then

$$T=\frac{\Delta H_{f1}+\Delta W_{12}\phi_2^2}{\frac{\Delta H_{f1}}{T_{f1}}-R\left[\ln(1-\phi_2)+\phi_2\left(1-\frac{V_1}{V_2}\right)\right]} \quad (18)$$

when $X_1 > X_E$, then

$$T=\frac{\Delta H_{f2}+\Delta W_{12}(1-\phi_2)^2}{\frac{\Delta H_{f2}}{T_{f2}}-R\left[\ln\phi_2+(1-\phi_2)\left(1-\frac{V_2}{V_1}\right)\right]} \quad (19)$$

At the eutectic point the two equations are equivalent so that we can obtain ΔW_{12}

$$\Delta W_{12}=\left[\Delta H_{f1}\left[\frac{\Delta H_{f2}}{T_{f2}}-R\left[\ln\phi_2+(1-\phi_2)\left(1-\frac{V_2}{V_1}\right)\right]\right]-\Delta H_{f2}\left[\frac{\Delta H_{f1}}{T_{f1}}-R\left[\ln(1-\phi_2)+\phi_2\left(1-\frac{V_1}{V_2}\right)\right]\right]\right]\Big/\left[\phi_2^2\left[\frac{\Delta H_{f2}}{T_{f2}}-R\left[\ln\phi_2+(1-\phi_2)\left(1-\frac{V_2}{V_1}\right)\right]\right]\right]$$

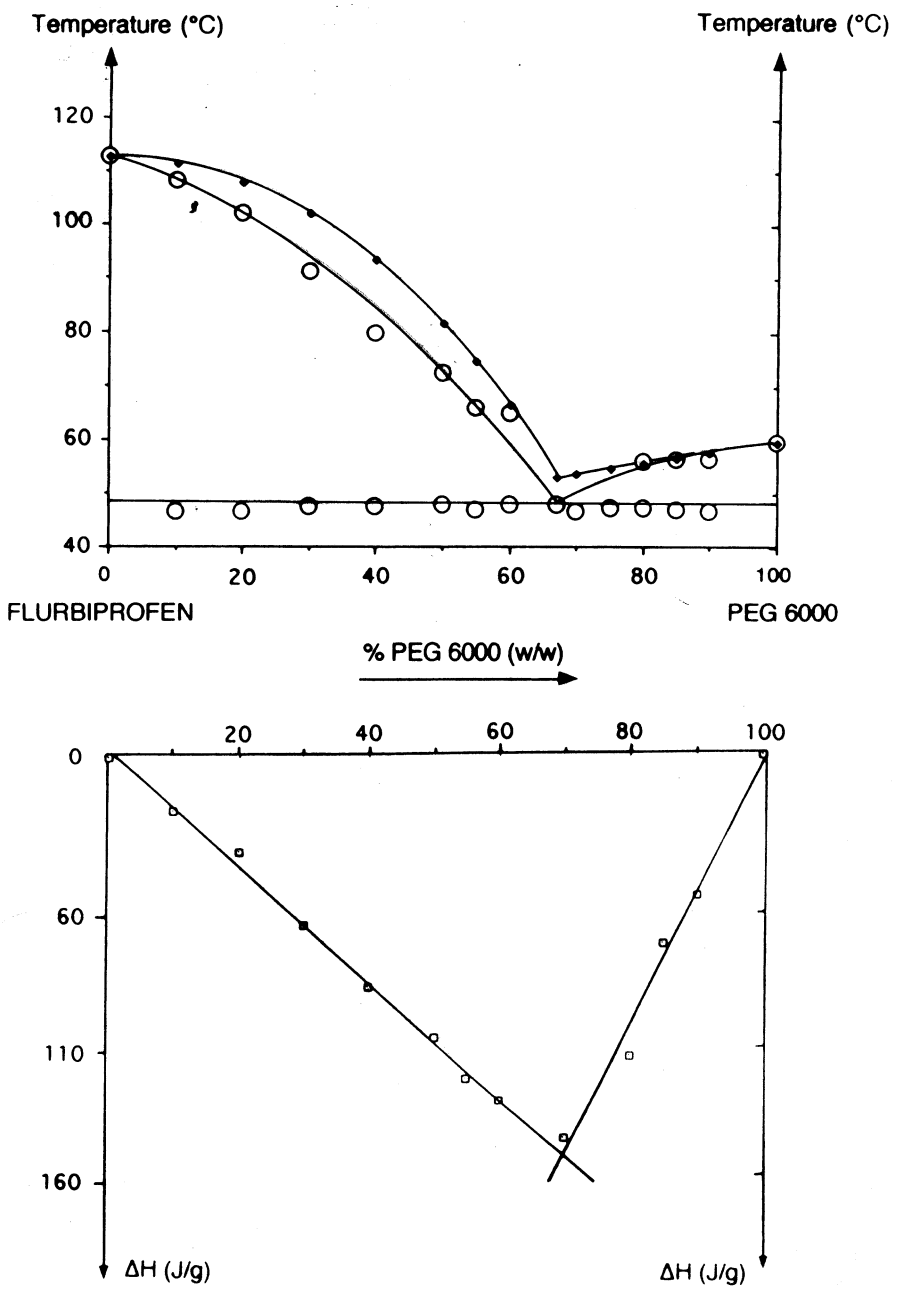

Fig. 8. Phase diagram; (a) ○ obtained experimentally by DSC, ● obtained by modelling; (b) □ Tammann diagram.

$$+(1-\phi_2)^2\left[\frac{\Delta H_{f1}}{T_{f1}}-R\left[\ln(1-\phi_2)+\phi_2\left(1-\frac{V_1}{V_2}\right)\right]\right]\right] \quad (20)$$

The phase diagram (Fig. 8a) was constructed from Eq. (18) and Eq. (19). Modelling the system gives the following results: 'Eutectic' = flurbiprofen + PEG 6000 → eutectic liquid, $(X_E)_{th} = (X_E)_{exp} = 67\%$ of PEG 6000 (w/w), $(T_{fE})_{th} =$

Table 2
Melting enthalpy $(\Delta H_m)_{exp}$ of FB-PEG 6000 physical mixtures

PEG 6000 % (w/w)	$(\Delta H_{fE})_{exp}$ (a) (J/g)	$(\Delta H_{EM})^{a}_{exp}$(b) (J/g)	$(\Delta H_f)_{exp}$ = (a)+(b) (J/g)	$(\Delta H_f)_{th}$ (J/g)	$(\Delta H_m)_{exp}$ (J/g)
10	20.4	70.3	90.7	116.1	−25.4
20	35.4	38.5	73.9	124.2	−50.3
30	62.8	30.9	93.7	135.6	−41.9
67	143.3	– –	143.3	165.7	−22.4
80	111.9	32.4	144.3	178.1	−33.8
90	52.8	147.0	199.8	187.9	−11.9

[a] EM: end of melting.

$53.3 \pm 0.2°C = 326.3 \pm 0.2$ K.

Calculation of the 'χ' parameter and of $(\Delta H_{mE})_{th}$ at the eutectic composition: $M_{sample} = 2.70$ mg; $M_1 = 244.3$ g; $M_2 = 5700$ g; $T_{f1} = 385.8$ K; $T_{f2} = 332.5$ K; $\Delta H_{f1} = 108.1$ J/g; $\Delta H_{f2} = 198.1$ J/g; $\rho_1 = 0.9366$ (density of the melted compound); $\rho_2 = 1.07$ (density of the melted compound); $\phi_{1E} = 0.36$; $\phi_{2E} = 0.64$; $V_1/V_2 = 0.049$; $n_{1E} = 3.647.10^{-6}$ mol.

Eq. (20) gives $\Delta W_{12} = -7222.54$ J/mol.

The formula (Eq. (7)) is used to calculate 'χ':

$$\chi = \frac{\Delta W_{12}}{R(T_{fE})_{th}} = -2.67$$

Eq. (7) gives the value of the mixing enthalpy:

$$(\Delta H_{mE})_{th} = n_{1E}\phi_{2E}\Delta W_{12} = -0.01686 \text{ J} = -6.24 \text{ J/g}$$

4. Conclusion

Thermoanalytical and spectral methods were used to identify two polymorphic forms of flurbiprofen ($T_{fI} = 112.8 \pm 0.2°C$, $\Delta H_I = 108.1 \pm 3.2$ J/g and $T_{fII} = 97.0 \pm 0.2°C$) and the probable enantiotropic transition of one into the other.

Construction of the flurbiprofen-PEG 6000 phase diagram revealed the existence of the stable invariant characterized by $(X_E)_{exp} = 67\%$ PEG 6000 and $(T_{fE})_{exp} = 48.0 \pm 0.2°C$.

Modelling the system produced a diagram similar to the experimental binary system and interactions between the two components were estimated. The theoretical value for $(\Delta H_{mE})_{th}$ was close to ideality whereas the experimental value $(\Delta H_{mE})_{exp}$ deviated from this.

The negative value of 'χ' (when the polymer is associated with an organic solvent, 'χ' is often within a range of $-1 < \chi < 2.5$) indicates that the mixture is exothermic and that interactions occur between flurbiprofen and PEG 6000, corresponding to hydrogen bonding between the hydroxyl group of each component. These bondings which reach a maximum in number at the eutectic composition are responsible for the increased solubility of the mixture in comparison with the drug in isolation.

In order to explain the 'χ' value and to determine the nature of the interactions, other physical mixtures with PEG 6000 of different molecular weights should be prepared and other spectroscopic methods used. This will constitute our next task.

'χ' and $(\Delta H_{mE})_{th}$ were calculated for slightly diluted solutions prepared by mixing melted substances (different from a liquid solution) and therefore possesed a specific viscosity. This therefore requires the consideration of other energies than these present in the calculation of 'χ'.

Modelling is of prime importance as it has permitted us to describe the characteristic properties of the stable invariant and by consequence the solubility increase at this point, an interesting fact for the pharmaceutical industry when choosing a carrier to manufacture medicines.

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