*Journal of Thermal Analysis, Vol. 47 (1996) 1743-1753*

# THERMAL INVESTIGATION OF PEG 4000 – OXAZEPAM BINARY SYSTEM

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(Received September 1, 1995; in revised form January 5, 1996)

## Abstract

A thermal study using DSC and Hot Stage Microscopy (HSM) was carried out to investigate the interaction in solid state of the binary system PEG 4000 – oxazepam, and to establish their phase diagram. The eutectic composition, which melting occurs at lower temperature as compared with the pure components, has been determined. The results obtained by DSC and HSM have indicated that PEG 4000 – oxazepam mixtures displays no obvious incompatibilities, and that the system shows a typical eutectic behaviour. However because of the closeness of the melting of PEG 4000 to the eutectic temperature, it was difficult to determine precisely the eutectic composition and temperature on the basis of DSC measurements alone. The use of heats of fusion corresponding to physical mixtures allowed an estimation of the eutectic composition at 6% w/w oxazepam. Additional information of temperature (57.6°C) and composition (5–10% w/w oxazepam) of the eutectic was obtained by HSM using the contact method. This low melting temperature in this range of compositions offers advantages in terms of drug stability and easy manufacture.

**Keywords:** DSC, HSM, oxazepam, PEG 4000, solid dispersion

## Introduction

The incorporation of drugs into solid hydrophilic carriers, by solid dispersion techniques, has frequently been reported to result in an increase in the drug dissolution rate [1–4]. The structure of the resultant solid dispersion may be represented by one or more of the following phase interactions: simple eutectic mixtures, solid solutions, glass solutions or suspensions, amorphous precipita-

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*0368–4466/96/ $ 5.00*

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tions or complex formation [5, 6]. Several methods are commonly used to analyse the phase interactions of organic compounds. Thermoanalytical methods such as DSC and Hot Stage Microscopy (HSM) have proved to be powerful tools in evaluating the interactions in binary systems [7].

In this paper, a thermal study of the binary system containing oxazepam, a hypnotic and sedative benzodiazepine, and polyethyleneglycol 4000 (PEG 4000), polymer obtained by polycondensation of ethylene oxide, molecular weight fraction 4000, has been carried out using DSC. HSM was further applied as a complementary thermal technique to examine the physicochemical interactions of these two components because of its ability to detect the early melting of products. From these results, the binary phase diagram has been proposed.

## Experimental

### *Materials*

Oxazepam was supplied by Boehringer-Ingelheim (Germany) and PEG 4000 by Acofarma (Tarrasa, Spain). Both samples were of adequate purity guaranteed by the suppliers.

### *Preparation of the samples*

Physical mixtures were prepared by simple intensive mixing of the two components previously sieved (under 270 mesh) in 2–90% w/w compositions.

### *DSC curves*

Samples of 10 mg were exactly weighted (±0.1 mg) after being finely powdered and encapsulated in flat-bottoned aluminium pans of 45 μL crimped-on lids. The thermograms were obtained in air on a Mettler DSC equipment (model FP85), by heating from 30 to 300°C at 10°C $min^{-1}$.

Heats of fusion were determined following calibration with indium using integration of the areas under the melting DSC endotherms.

### *HSM determinations*

The component of higher melting point (oxazepam) was placed on a glass slide at the edge of the cover-slip and heated to complete melting using a hot stage device attached to the microscope (Mettler model FP83HT). After solidification, recrystallized oxazepam occupied about half the free space. PEG 4000 was then placed at the still free edge of the above coverslip and heated until it melts. In the contact zone, the second product, after melting would dissolve a little amount of the first one. Both of them have the possibility of further reaction being thus detected by this technique [8].

Upon reheating, samples examined using polarized light with crossed nicols, allowed to differentiate between eutectic, formation of molecular compounds, mixed crystals, etc.

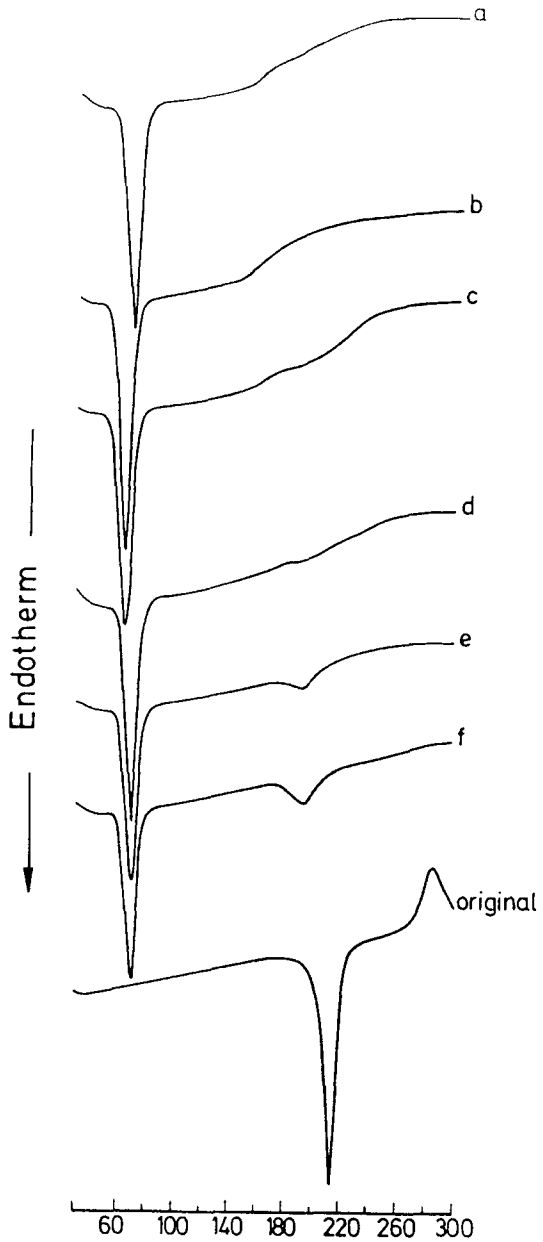


**Fig. 1** DSC diagrams of PEG 4000 (a), physical mixture 2% (b), 5% (c), 10% (d), 20% (e), and 30% (f) w/w in oxazepam. Original is oxazepam

## Results and discussion

### *Thermal analysis by DSC*

Figures 1 and 2 show the DSC diagrams of PEG 4000, oxazepam and PEG 4000 – oxazepam physical mixtures. The DSC curves of each component gave a single endothermal peak. PEG 4000 shows an endothermic peak at 60.4°C (melting point) with a fusion enthalpy value of 234 J $g^{-1}$, and a weak inflection or endothermic change in their base line is detected at ca. 160°C. Oxazepam exhibits also a unique endothermal peak at 210°C with a fusion en-

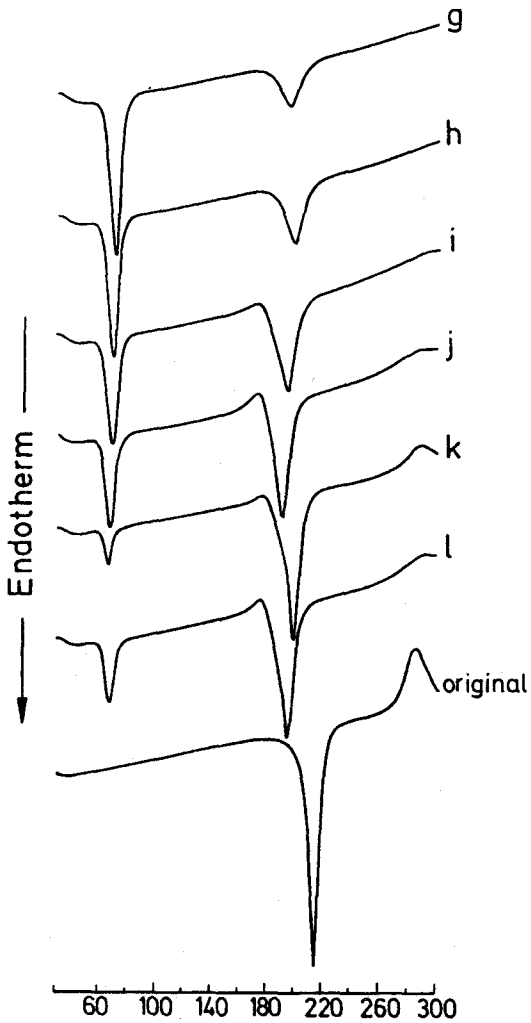


**Fig. 2** DSC diagrams of physical mixture 40% (g), 50% (h), 60% (i), 70% (j), 80% (k), and 90% (l) w/w in oxazepam. Original is oxazepam

thalpy value of 253 J $g^{-1}$, and an exothermal peak at 270°C due to their decomposition upon heating.

One or two endothermal peaks were obtained from physical mixtures, depending on the proportion of the drug into polymer. It can be observed that up to 10% w/w of oxazepam, the DSC curves show only a single endothermic effect associated to the melting of the eutectic component.

Above of 20% w/w oxazepam, the DSC curves showed two clear endothermal peaks: the low temperature peak, reflected melting of eutectic, is accompanied by another endotherm due to excess of oxazepam. This second peak is shifted progressively as increasing the proportion of the drug in the binary mixture. It is clear that with the increasing of oxazepam content, the second endothermic peak approaches to that of pure oxazepam, and consequently, its area increases keeping constant the sample weight for DSC runs.

## Tamman's triangle

In a binary system, one can determine the composition of the eutectic point using Tamman's triangle [9]. The diagram, (Fig. 3), is constructed by studying the relationship between the area of the DSC peak considered and the composition of the system. Newly, the formation of a eutectic system can be inferred, as pointed out above.

## Heats of fusion

DSC has been alternatively used as a possible method of estimating the eutectic composition based on the heats of fusion of the pure components, the eutectic and the products present in excess compared to the eutectic [10].

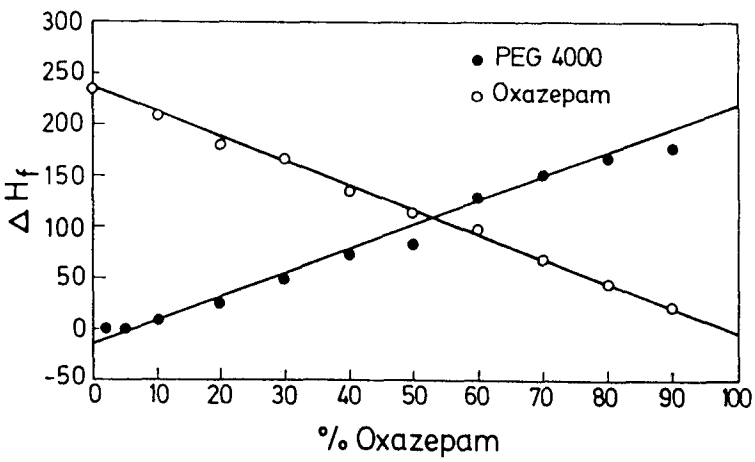


**Fig. 3** Relationship between the composition of the PEG 4000 – oxazepam system and the areas ($\Delta H_f$) of the first endothermic DSC peak

Heats of fusion for isolated PEG 4000 and oxazepam were 234 and 253 J $g^{-1}$, respectively, and were used together with the heats of transition of the eutectic and excess component to determine the eutectic composition.

In the present case, a linear relationship between the composition and heats of fusion corresponding to oxazepam and the eutectic component (Fig. 4) is deduced plotting the experimental values.

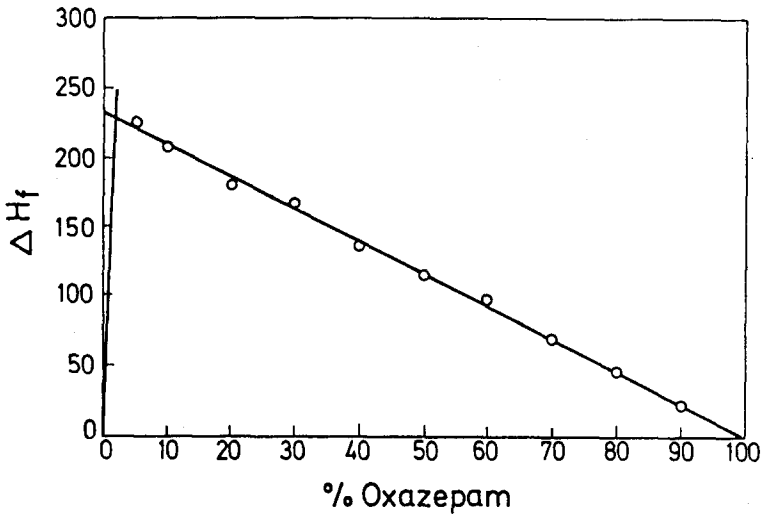


**Fig. 4** Heats of fusion of ($\Delta H_f$) PEG 4000 – oxazepam physical mixtures (derived from DSC data) plotted as a function of oxazepam content (see the text)

The equation describing the relationship for the excess of oxazepam is:

$$-\Delta H_{(oxa)} = ax + b \tag{1}$$

where, $\Delta H_{(oxa)}$=heat of fusion due to the excess oxazepam component, $x$=percentage of oxazepam.

The values of intercept ($b$) and slope ($a$) where calculated by lineal regression ($r$=0.9863), resulting $a$=2.34 and $b$=−13.85.

At the eutectic composition, the heat of fusion due to excess of oxazepam is zero. By substitution in Eq. (1), gives an eutectic composition of 5.9% oxazepam.

The regression equation derived corresponding to the eutectic component is:

$$\Delta H_{(eut)} = a'x + b' \tag{2}$$

where, $\Delta H_{(eut)}$=the heat of fusion to the eutectic component, $x$=percentage of oxazepam.

The values of intercept ($b'$) and slope ($a'$) where calculated by lineal regression ($r=0.9967$), resulting $a'=-2.4$ and $b'=237$.

Substituting the obtained eutectic composition (5.9% oxazepam) in Eq. (2), gives a heat of fusion for the pure eutectic of 222 J $g^{-1}$.

## Phase diagram

From DSC results, a tentative phase diagram of PEG 4000 – oxazepam was included in Fig. 5. The eutectic composition was difficult to quantify because of the similarities with the melting point of pure PEG 4000, and its determination by extrapolation of the liquidus line to the pure PEG 4000 is only tentative. The phase diagram appears as a monotectic system. One of the liquid branches has disappear, and the branch indicating the component of lower melting point (PEG 4000) has been replaced with the eutectic compound in samples containing up to 20% w/w oxazepam. Similar results have been obtained by different authors employing this thermal technique (DSC), and studying PEG and several drugs [11–12].

However, HSM data have allow construct a more precise phase diagram (Fig. 3) with a correct eutectic determination. Using this technique is possible to determine the liquidus line up to 2% w/w oxazepam, as opposite using DSC data. It is clear from the proposed phase diagram by HSM that the eutectic composition must be in the range 5–10% w/w oxazepam, which is in accordance with the estimation of eutectic composition by heats of fusion (Fig. 4).

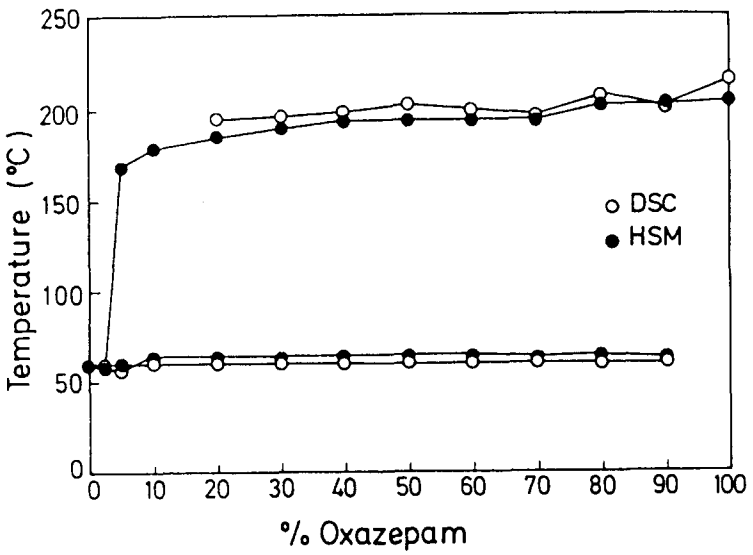


**Fig. 5** Proposed phase diagram of the PEG 4000 – oxazepam binary system

The disappearance of endothermal DSC peak of oxazepam in this system with low drug percentages (below 20% w/w) can be explained on the basis of the change of oxazepam state. This takes place with very low energetic change, and is not detected by DSC under our experimental conditions. The DSC technique is not enough to explain the interaction between PEG 4000 and oxazepam. It is necessary a complementary thermal technique, such as thermomicroscopy for a correct interpretation of the results obtained by DSC.

### *Thermal analysis by the contact method (HSM)*

Figure 6 shows HSM micrographs of pure substances. Original micronized oxazepam (Fig. 6a) is characterized by the presence of orthorhombic flat crystals.

The micrographs of commercial PEG 4000 revealed crystals irregularly shaped (Fig. 6b). After fusion and solidification, oxazepam crystals remained

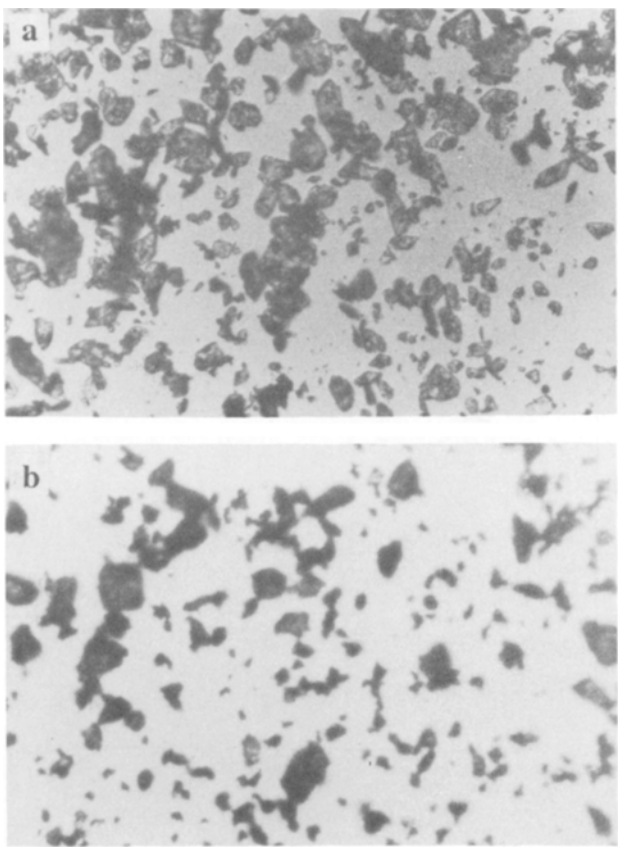


**Fig. 6** HSM micrographs of pure substances: a) oxazepam, b) PEG 4000

unaltered (Fig. 7a), while PEG 4000 crystallized, forming spherical structures with fine radiating branches called spherulites (Fig.7b) [13].

Figure 8a shows the HSM micrographs of the system oxazepam – PEG 4000 prepared by the contact method at room temperature. Upon reheating, when a certain temperature is reached (57.6°C), the first liquid formation is detected in the contact zone between the two substances. Under polarized light, a continuous black streak can be observed (Fig. 8b), being indicative of the fluid formed during melting. This fact can be attributed to the formation of an eutectic between the two pure substances. The temperature of 57.6°C is then the true eutectic temperature, or temperature of lower melting of the binary system PEG 4000 – oxazepam. This low melting temperature offers advantages in terms of drug stability and easy manufacture.

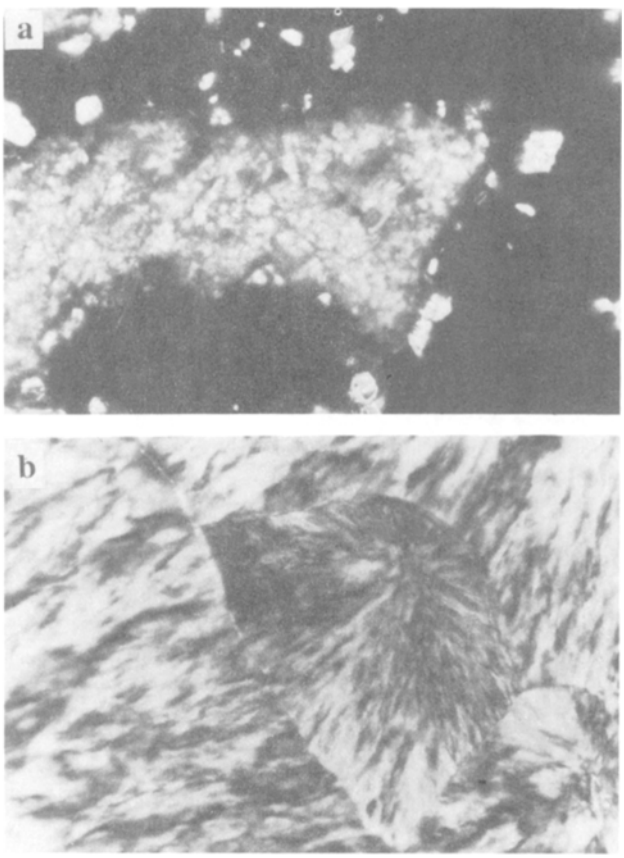


**Fig. 7** HSM micrographs of recrystallized substances: a) oxazepam, b) PEG 4000

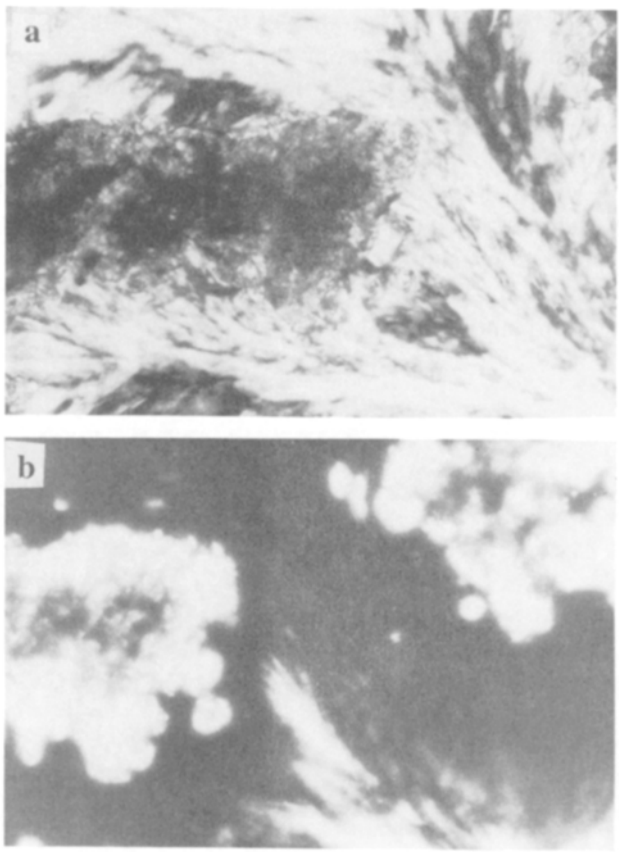


**Fig. 8** HSM micrographs obtained under polarized light of the system oxazepam – PEG 4000 prepared by the contact method: a) room temperature, b) eutectic temperature (57.6°C)

## Conclusions

The DSC technique is not enough to explain the interaction between PEG 4000 and oxazepam. It is necessary a complementary thermal technique as thermomicroscopy for a correct interpretation of the results obtained by DSC. The binary phase diagram has been proposed on the basis of HSM and DSC results. The use of heats of fusion and HSM allowed an estimation of the composition (6% w/w oxazepam) and temperature (57.6°C), of the eutectic. This low temperature advantages in terms of drug stability and easy manufacture.

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