ELSEVIER

Thermochimica Acta 321 (1998) 33–41

thermochimica acta

Study by DSC and HSM of the oxazepam–PEG 6000 and oxazepam–D-mannitol systems: Application to the preparation of solid dispersions

M.J. Arias[1,*], J.R. Moyano, J.M. Ginés

Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, 41012-Seville, Spain

Received 28 February 1997; accepted 20 March 1998

Abstract

Oxazepam is a drug characterised by its marked hydrophobicity and unsatisfactory wettability on contact with water. These properties lead to incomplete absorption of the drug from the gastrointestinal tract when the pharmaceutical dosage form is not adequately formulated. For this reason, it is of interest to optimise its dissolution properties. For this purpose, the preparation of solid dispersions with hydrophilic carriers has been often employed. In this paper, the possibility of employing two hydrophilic substances (PEG 6000 and D-mannitol) as carriers for solid dispersions, prepared by the co-fusion or the fusion carrier methods, were evaluated by DSC and HSM. The results show, in terms of the miscibility of molten oxazepam in the fused vehicle, that PEG 6000 is the only suitable carrier. D-mannitol yielded non-homogeneous systems. © 1998 Elsevier Science B.V.

Keywords: D-mannitol; DSC; HSM; Oxazepam; PEG 6000; Solid dispersion

1. Introduction

Solid dispersions play an important role in increasing the solubility, dissolution rate, absorption and therapeutic efficacy of many drugs, especially those which are poorly water-soluble. In a solid dispersion, the drug particles or drug molecules are homogenously distributed in a matrix (carrier). The selection of the carrier and the preparative method play a key role on the properties of the final solid dispersion.

Many substances can be employed as carriers to prepare solid dispersions. Polymers such as polyethyleneglycols (PEGs) have been extensively used as vehicles for solid dispersions, due to their low melting point, rapid solidification rate, capability of forming interstitial solid solutions, low toxicity and economic cost [1–4]. Also, some sugars, e.g. D-mannitol, have been recommended and employed as carriers for solid dispersions due to their negligible toxicity, high aqueous solubility and physiological acceptance [5–7]. Moreover, the temperature of decomposition of D-mannitol is above 250°C. It also has good flow and compression properties.

The co-fusion method (co-melting of drug and vehicle) is technologically the easiest method to prepare solid dispersions, provided the drug and carrier are miscible in the molten state. An alternative when the drug decomposes immediately after its fusion is the melting carrier method.

*Corresponding author. Tel.: +34-5-455-66-18; fax: +34-5-455-67-26; e-mail: mjarias@fafar.us.es

[1]Present address: C/Duero, 15 Valencina de la Concepción, 41907 Sevilla, Spain.

PII: S0040-6031(98)00437-7

The physicochemical nature of the solid dispersion plays an important role in drug release. Although various systems have been described as representative of interactions between drugs and carriers, the term 'solid dispersion' includes at least one of the following: eutectics, solid solutions, glass solutions or suspensions and amorphous precipitation in a crystalline carrier or compound or complex formation [8].

Many methods are available for determining the physical nature of solid dispersions. Thermal analysis, whether DTA or DSC, has proved to be a powerful tool in evaluating the drug–carrier interactions [9–11]. However, since solid dispersion often contain amorphous or molecularly dispersed drugs, the complementary thermal techniques such as HSM may help in the interpretation of the DSC results [12–14].

In the present paper, a preliminary study of the binary systems (poorly water-soluble benzodiazepine Oxazepam [15]) with PEG 6000 or D-mannitol has been carried out using DSC and HSM. The physicochemical interactions of these two components were examined with regard to the suitability of employing solid dispersions formed by the melting carrier method. Solubility assays were also performed to study the drug–carrier interactions in aqueous solutions.

2. Experimental

2.1. Materials

Oxazepam was supplied by Boehringer-Ingelheim (Germany). Acofarma (Tarrasa, Spain) provided PEG 6000 (<0.1% insoluble matter) and D-mannitol (98% purity).

2.2. Preparation of the samples

Physical mixtures were prepared by simple mixing (30 min) of the two components previously sieved (50–270 μ) compositions ranging from 5–90% w/w.

2.3. Phase-solubility studies

Phase-solubility studies were carried out by adding excess of drug (30 mg) in Erlenmeyer flasks containing 10 ml of purified water on aqueous solutions of different PEG 6000 or D-mannitol concentrations. The solutions were continuously shaken in a water bath at 25 or 37°C for seven days. The solutions were filtered through 1.2 μm cellulose nitrate membrane filters. The filtrates were analysed, spectrophotometrically (Hitachi U-2000), for the dissolved drug at 230 nm. All assays were performed in triplicate.

2.4. DSC scans

Finely powdered samples 10±0.1 mg were weighed and encapsulated in flat-bottomed aluminium pans with crimped-on lids. The scans were obtained in an air atmosphere using a Mettler model FP85 DSC, by heating from 30° to 300°C at a rate of 10°C/min. Runs were performed in triplicate. The apparatus, following calibration with indium, automatically calculated heats of fusion, by integration of the areas under the melting DSC endotherms.

2.5. HSM

Amounts, ≈0.1 mg, of the samples were placed on glass slides with cover glass and heated at the rate of 5°C/min. Observations were made during heating using a Mettler FP82HT hot stage microscope. Temperatures at which melting started and at which complete melting was reached, were determined by visual observation.

3. Results and discussion

3.1. Phase-solubility studies

Fig. 1 represents the effect of temperature on the solubility of oxazepam in the presence of PEG 6000 (Fig. 1(a)) and D-mannitol (Fig. 1(b)). The apparent stability constants (K_a) and thermodynamic parameters derived from Fig. 1 are shown in Table 1. The straight lines were adjusted by the least-squares method. The results show that in both cases, the solubility of oxazepam increased with increasing temperature and carrier concentration.

The free energy changes were composed of negative enthalpy and positive entropy changes. The contribution of ΔH to the whole ΔG value confirms that

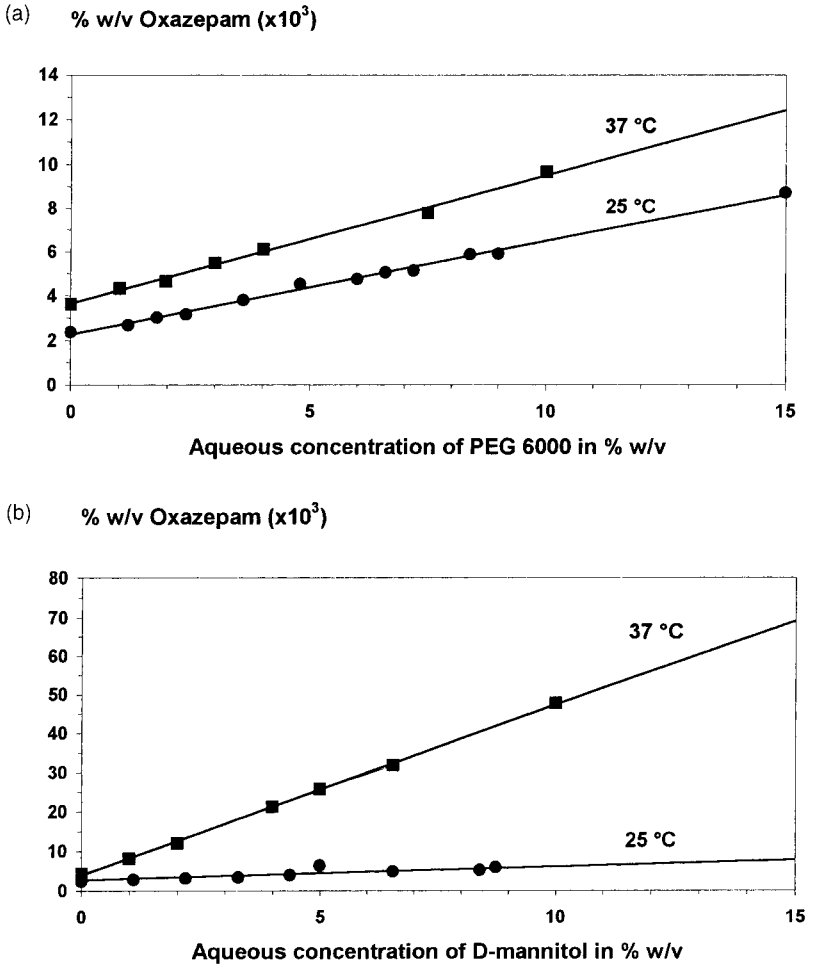

Fig. 1. Solubility of oxazepam (g/100 ml) in aqueous solutions of (a) PEG 6000 (b) and D-mannitol in water at 25° and 37°C.

Table 1
Thermodynamic parameters of oxazepam–PEG 6000 and oxazepam–D-mannitol interactions

	T (°C)	Intercept (M)	Slope	K_a [a] (M^{-1})	ΔG [b] (kJ/mol)	ΔH [c] (kJ/mol)	ΔS (J/mol K)
PEG 6000	25	7.819×10^{-5}	8.852×10^{-3}	114.2	−11.7	−11.3	1.4
	37	1.295×10^{-4}	1.234×10^{-2}	96.5	−11.8	−11.3	1.4
D-mannitol	25	9.229×10^{-5}	2.110×10^{-3}	22.9	−7.8	−6.1	5.7
	37	1.332×10^{-4}	2.768×10^{-3}	20.8	−7.8	−6.1	5.7

[a] 1 : 1 complex apparent stability constant (K_a=slope/intercept (1-slope)), where slope and intercept are obtained from Fig. 1.
[b] Free Gibbs energy, calculated from: $\Delta G=-Rt \ln K_a$, being R=8.314 J/mol K.
[c] Enthalpy change calculated from van't Hoff equation.

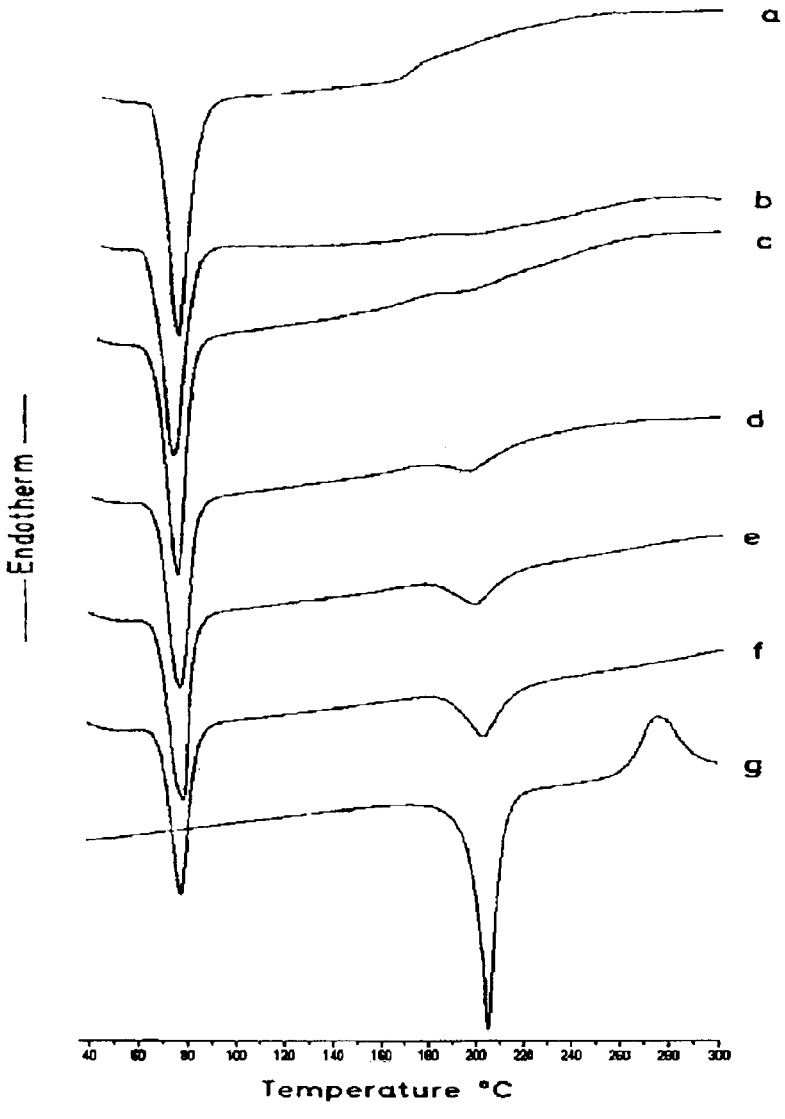

Fig. 2. (a) DSC curves of PEG 6000, (b) oxazepam-PEG 6000 physical mixtures of 5% w/w drug, (c) 10% w/w drug, (d) 20% w/w drug, (e) 30% w/w drug, (f) 40% w/w drug, and (g) oxazepam.

this type of interactions is enthalpic rather than entropic driven.

3.2. Thermal analysis by DSC

Fig. 2 shows the DSC scans of oxazepam, PEG 6000 and oxazepam–PEG 6000 physical mixtures. Table 2 summarises the onset and peak temperatures and the enthalpy values for each thermal event. PEG 6000 showed an endothermic peak at 73.2±0.1°C (peak temperature) with a fusion enthalpy of 284.0±3.7 J/g, and a weak inflection or exothermic change in its base line at ≈160°C. This effect, demonstrated by other authors for PEGs with different molecular weights [16], is related to the oxidation of the PEG at this temperature. The former authors have observed that the exotherms disappeared when the samples were recorded under nitrogen. On the

Table 2
Thermal evaluation of the melting effects observed for the indicated systems

	w/w%	Carrier melting effect			Drug melting effect		
		T_{onset} (°C)	T_{peak} (°C)	ΔH_f (J/g)	T_{onset} (°C)	T_{peak} (°C)	ΔH_f (J/g)
Oxazepam		—	—	—	194.1	205.3	−250.3
Oxazepam–PEG 6000 physical mixtures	5%	55.6	70.4	−236.6	—	—	—
	10%	62.3	74.5	−208.9	—	—	—
	20%	65.5	78.1	−180.2	176.3	195.1	−20.4
	30%	65.7	78.3	−167.4	178.6	199.3	−48.5
	40%	66.8	78.6	−136.7	183.3	202.6	−73.5
PEG 6000		52.8	73.2	−284.0	—	—	—
Oxazepam–D-mannitol physical mixtures	5%	166.6	180.6	−189.2	—	198.1	−3.2
	10%	168.4	182.9	−178.4	195.2	199.5	−9.1
	20%	169.1	184.1	−169.1	195.5	201.7	−36.8
	30%	169.1	184.5	−145.0	196.1	202.3	−50.7
	40%	169.5	184.6	−133.2	195.1	204.6	−69.0
D-mannitol		165.2	176.9	−192.1	—	—	—

contrary, when PEGs were run in air, this condition lead to the oxidation of the polymer.

Oxazepam exhibits an endothermic peak at 205.3± 0.05°C with a fusion enthalpy of 250.3±0.6 J/g, and an exothermic peak at ca. 275°C ($\Delta H \approx 120$ J/g), attributed to its decomposition on heating.

One or two endothermic peaks were obtained from the physical mixtures, depending on the drug : polymer ratio. Physical mixtures of 5 and 10% w/w oxazepam–PEG 6000 showed a single endothermic effect associated with the melting of the polymer. Above 20% w/w oxazepam, the scans displayed two endothermic peaks: the lower temperature peak reflects the melting of the PEG 6000, and the second endothermic effect the melting of the drug. In the 20% w/w physical mixture, the drug melting peak appeared as a weak and broad peak centred at 195°C. Increasing the drug ratio of oxazepam into the PEGs resulted in a slight displacement of the peaks to higher temperatures.

Fig. 3 shows the DSC plots of oxazepam, D-mannitol and oxazepam–D-mannitol physical mixtures. Table 2 displays the evaluation of the melting effects for such systems. Pure D-mannitol displayed an endothermic peak at 176.9±0.1°C (melting point) with a melting enthalpy of 184±2.7 J/g. DSC scans of the physical mixtures showed two endothermic peaks for all compositions. The lower one corresponded to the melting of D-mannitol whereas the other belonged to the melting of oxazepam. Both peaks were progressively shifted to lower temperatures with decrease in the drug ratio in the binary mixture. The second peak is clearly appreciable for all the compositions, except for the 5% w/w drug : carrier physical mixture, where the fusion peak appeared as a little shoulder, close to the melting of D-mannitol.

As the melting peak of oxazepam disappeared in systems with PEG 6000 containing low drug percentages (<20% w/w), it is evident that the DSC technique alone is not enough to explain the interaction between the polymer and oxazepam. It is necessary to use a complementary thermal technique, such as thermomicroscopy for a suitable interpretation of the results obtained by DSC.

3.3. Hot stage microscopy

The oxazepam–PEG 6000 physical mixture containing 10% w/w drug was studied by HSM. Selected photomicrographs are shown in Fig. 4. After dynamic

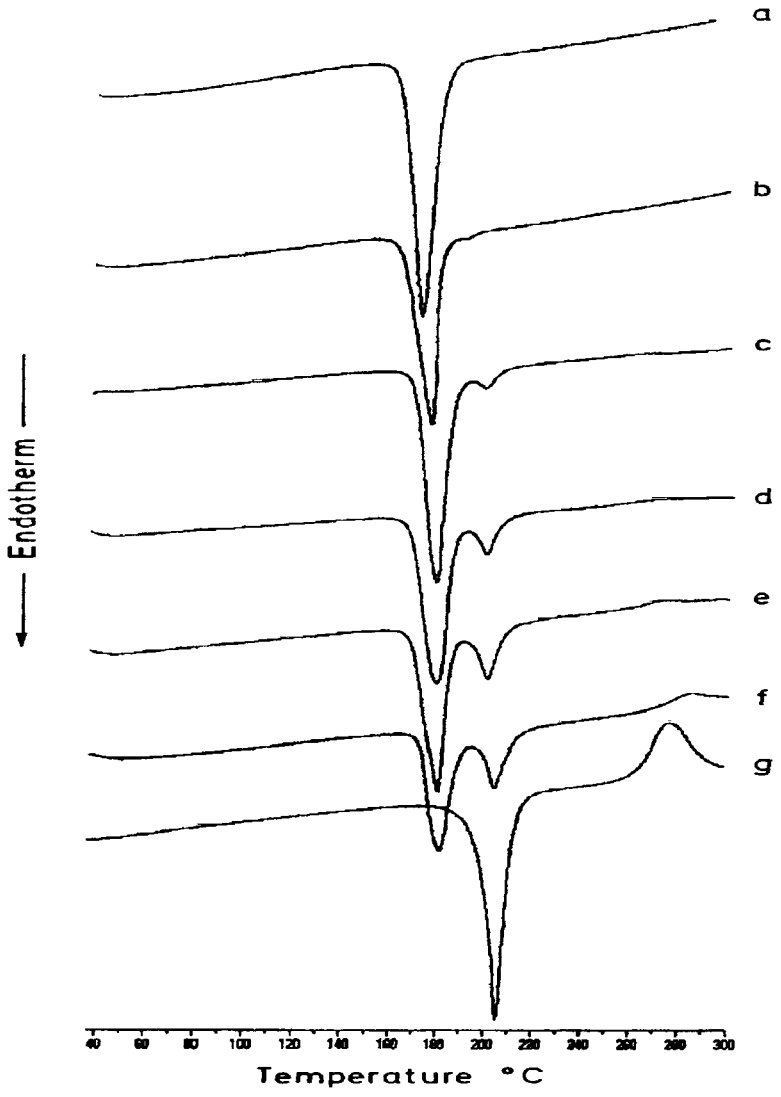

Fig. 3. (a) DSC curves of D-mannitol, (b) oxazepam-D-mannitol physical mixtures of 5% w/w drug, (c) 10% w/w drug, (d) 20% w/w drug, (e) 30% w/w drug, (f) 40% w/w drug, and (g) oxazepam.

heating to 100°C, the carrier melts and different-sized vesicles containing solid drug particles are observed (Fig. 4(a)). On heating to a higher temperature (160°C) (Fig. 4(b)) a mixing of the crystals entrapped inside the liquid vesicles was observed, this phenomena being complete at 180°C (Fig. 4(c)).

At larger drug ratios in the oxazepam–PEG 6000 physical mixtures (such as 40% w/w drug), the miscibility process is slower. Fig. 5(a) displays the system at 100°C, and at 175°C crystalline particles of unmixed drug can be visualised (Fig. 5(b)). The drug completely mixed at 183°C. These results demonstrated that oxazepam and PEG 6000 are miscible in the molten state. Thus, one can predict this property as providing uniform systems by the fusion method, from the point of view of drug distribution. Similar results were obtained for oxazepam–PEG 4000 system [17].

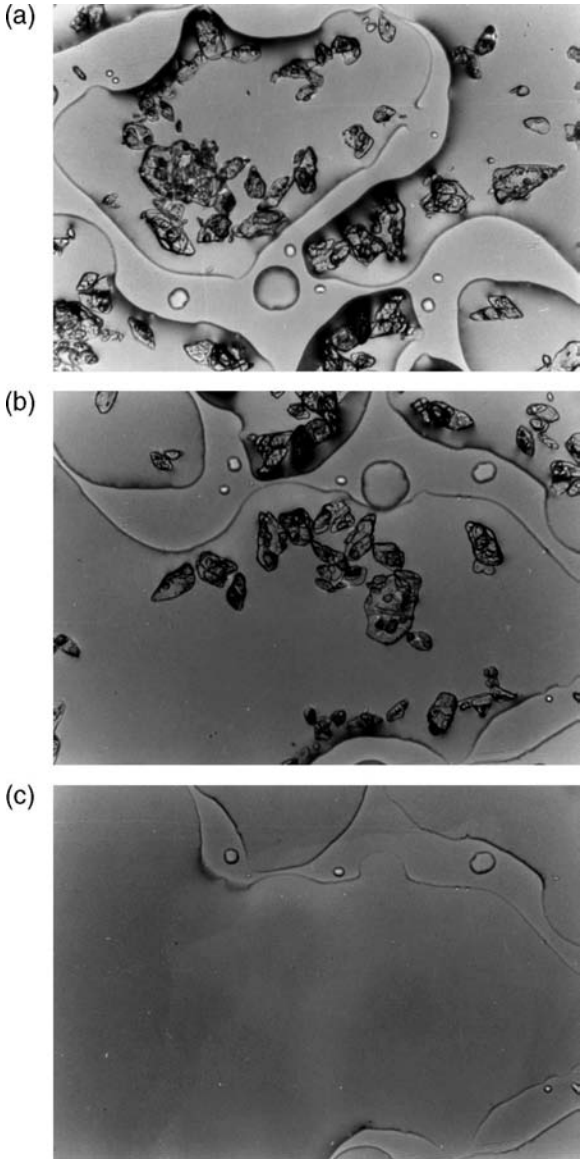

Fig. 4. HSM photomicrographs of an oxazepam-PEG 6000 physical mixture at 10% w/w drug at (a) 100°C, (b) 160°C, and (c) 175°C.

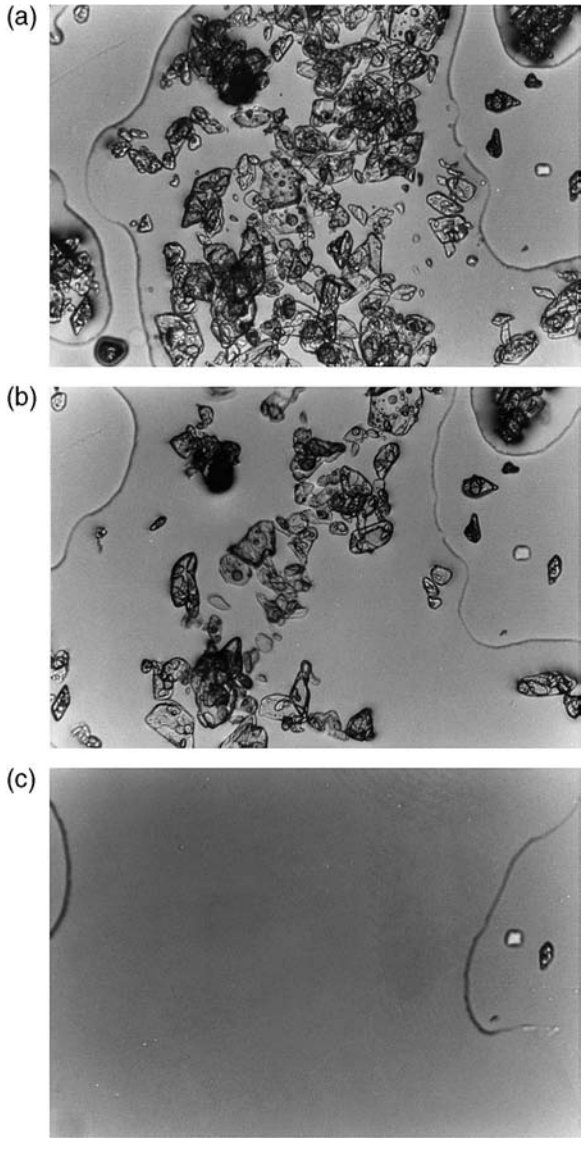

Fig. 5. HSM photomicrographs of an oxazepam-PEG 6000 physical mixture at 40% w/w drug at (a) 100°C, (b) 175°C, and (c) 183°C.

Although the thermal behaviour is complex, these results are in accordance with the DSC diagrams (see Fig. 2). The disappearance of the endothermic peak corresponding to the melting of oxazepam in low drug concentrations systems is associated to its complete miscibility in the molten PEG 6000. At higher drug ratios, only a partial miscibility is reached, and the drug remains as a solid until 180°C, temperature at which it starts to melt. The molten drug rapidly mixes with the molten PEG, fact that aids the fusion of the remaining drug. This process is detected in the scan as a pronounced endothermic peak.

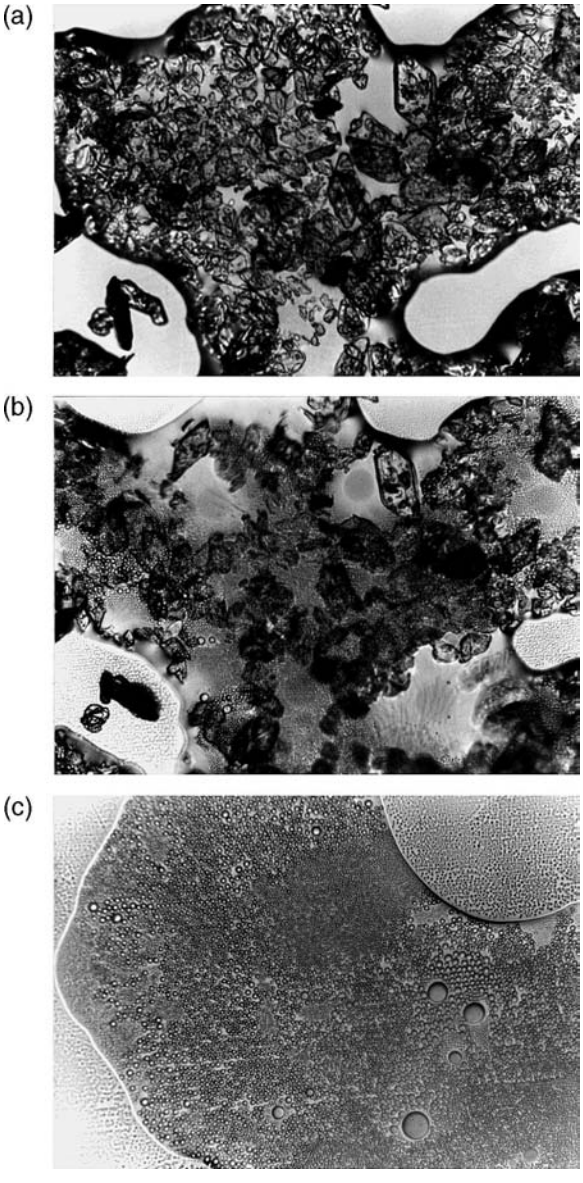

Fig. 6. HSM photomicrographs of an oxazepam-D-mannitol physical mixture at 10% w/w drug at (a) 180°C, (b) 193°C, and (c) 200°C.

In the case of the 10% w/w oxazepam–D-mannitol physical mixture, the results are different. After dynamic heating to 180°C, the carrier melts (Fig. 6(a)), but heating at higher temperatures (≈193°C) did not produce the miscibility of the crystals entrapped inside the liquid vesicles (Fig. 6(b)), but only the melt of the drug. At 200°C, the molten drug gives rise to an immiscible liquid phase with the molten carrier (Fig. 5(b)). Other authors obtained similar results when studying the interaction of D-mannitol with several drugs, such as sulphonamides [18], tolbutamide [19] and isopropylantipyrin [20].

From these results, it is clear that it is impossible to reach a homogeneous system by using D-mannitol. This behaviour is opposite to that recorded for triamterene with the same carrier [21,22].

4. Conclusions

We have observed that oxazepam is miscible at the molten state with PEG 6000 but immiscible with D-mannitol. The results from this preliminary screening indicate that D-mannitol is not adequate for the preparation of solid dispersions with oxazepam by the fusion method, because it leads to heterogeneous melts.

References

[1] C. Chemtob, S.T.P. Pharma 6 (1985) 531.
[2] S.M. Chatham, S.T.P. Pharma 3 (1987) 575.
[3] M.J. Arias, J.M. Ginés, J.R. Moyano, A.M. Rabasco, Pharm. Acta Helv. 71 (1996) 229.
[4] D.Q.M. Craig, Drug Dev. Ind. Pharm. 16 (1990) 2501.
[5] M.J. Arias, J.M. Ginés, J.R. Moyano, A.M. Rabasco, J. Drug Targ. 2 (1994) 45.
[6] A.S. Geneidi, H. Hamacher, Pharm. Ind. 42 (1980) 401.
[7] M.A. Attia, F.S. Habib, Drug Dev. Ind. Pharm. 11 (1985) 1957.
[8] J.L. Ford, Pharm. Acta Helv. 61 (1986) 69.
[9] J.L. Ford, P. Timmins, Pharmaceutical Thermal Analysis, Ellis Horwood Ltd., Chichester, 1989, Chap. 2.
[10] J. Masse, A. Chauvet, G. de Maury, A. Terol, Thermochimica Acta 96 (1985) 189.
[11] J.M. Ginés, M.J. Arias, J.R. Moyano, P.J. Sanchez-Soto, Int. J. Pharm. 143 (1996) 247.
[12] M.D. Veiga, M.J. Bernanrd, C. Escobar, Int. J. Pharm. 89 (1993) 119.
[13] P.J. Sánchez-Soto, J.M. Ginés, A.M. Rabasco, A. Justo, J.L. Pérez-Rodríguez, Thermochimica Acta 158 (1990) 225.
[14] A. Chauvet, J. Masse, Thermochimica Acta 66 (1983) 25.
[15] K. Florey, Analytical Profiles of Drug Substances, vol. 3, edn., Academic Press, New York, 1974, pp. 441–464.

[16] S. Anguiano-Igea, F.J. Otero-Espinar, J.L. Vila-Jato, J. Blanco-Méndez, Pharm. Acta Helv. 70 (1995) 57.
[17] J.M. Ginés, M.J. Arias, J.R. Moyano, C. Novak, G. Pokol, P.J. Sánchez-Soto, J. Thermal. Anal. 47 (1996) 1743.
[18] J.L. Kaning, J. Pharm. Sci. 53 (1964) 188.
[19] H.M. El-Banna, N.A. Daabis, L.M. Mortada, S. Abd-Elfattah, Pharmazie 30 (1975) 788.
[20] S. Bobdanova, P. Gentcheva, R. Shekerdjiiski, B. Piskjulev, E. Minkov, Labo-Pharma Probl. Tech. 32 (1984) 835.
[21] J.M. Ginés, M.J. Arias, A.M. Rabasco, P.J. Sánchez-Soto, J. Thermal. Anal. 42 (1994) 143.
[22] M.J. Arias, J.M. Ginés, J.R. Moyano, J.I. Pérez-Martínez, A.M. Rabasco, Int. J. Pharm. 123 (1995) 25.