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THERMAL DETERMINATION OF SOLID DISPERSIONS OF OXODIPINE

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ABSTRACT

In order to increase the bioavailability and the water solubility of oxodipine (a new drug for anti-arterial hypertension), solid dispersions of oxodipine in polyethylene glycol (P.E.G. 6000) were prepared and identified using differential scanning calorimetry.

INTRODUCTION

It seems appropriate here to define the term "solid dispersions" as used in this paper. The term refers to the dispersion of one or more active drugs in an inert carrier or matrix in the solid state [1].

Generally, the solid dispersions are prepared by the melting or fusion method, which was first proposed by Sekiguchi and Obi [2]. In this method the physical mixture of a drug and a water-soluble carrier is heated directly until it melts. The melted mixture is then cooled and solidified rapidly in an ice bath with vigorous stirring.

Such a technique was subsequently employed with some modification by Goldberg et al. [3–5] and Chiou and Riegelman [6] to prepare solid dispersions of some active drugs with poor water solubility.

Since the dissolution rate of a component from a surface is affected by the second component in a multiple-component mixture [7], the selection of the carries has an ultimate influence on the dissolution characteristics of the dispersed drug.

In this study, we prepared various solid dispersions of oxodipine (a new

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drug for anti-arterial hypertension) as this drug has poor water solubility and, consequently, the rate of absorption and the total bioavailability is low. We selected as matrix, polyethylene glycol of molecular weight 6000. This is a crystalline, water-soluble polymer with two parallel helices in a unit cell [8]. It is predicted that significant amounts of drug can be trapped in the helical interstitial space when polyethylene glycol–drug melts are solidified. We studied all the solid dispersions using differential scanning calorimetry.

EXPERIMENTAL

Materials

Oxodipine (purity, 99.83%) was supplied by Instituto de Química Biológica of Madrid (Spain), and was used without further purification.

Polyethylene glycol 6000 (P.E.G. 6000) was a commercial product, and was used as supplied.

Preparation of solid dispersions

We prepared nine different samples with the proportions 4, 7, 10, 15, 17.5, 20, 25, 50 and 80% of oxodipine in P.E.G. 6000 using the following procedure.

An ethanolic solution of 100 mg of oxodipine was incorporated directly into the melt of P.E.G. 6000 (obtainable below 70 °C) in the appropriate proportions with vigorous stirring. The resulting solution was set aside until the ethanol had totally evaporated.

The solidified masses of oxodipine–P.E.G. 6000 were often found to require storage of 1 day in a desiccator at room temperature for hardening and ease of powdering.

Methods

Thermal measurements were performed using a Mettler TA 3000 system with a differential scanning calorimeter (model DSC 20).

Samples of about 3 mg were used to render the degree of temperature non-uniformity within the sample insignificant. An aluminium pan was used under a dry nitrogen atmosphere at a flow rate of 10 ml min^{-1}. The scanning rate used was 5 °C min^{-1} and the instrument calibration was checked periodically with standard samples of indium (purity, 99.99%), whose heat of melting is well documented [9].

RESULTS AND DISCUSSION

The DSC results of the nine samples prepared and those obtained for oxodipine and P.E.G. 6000 are summarized in Table 1. The DSC curves for

TABLE 1

Thermal data

	Melting (°C)	ΔH melting ($J\ g^{-1}$)	Purity (%)
Oxodipine	166.8	119 ± 2.0	99.4 ± 0.5
P.E.G. 6000	60.2	225 ± 3.0	99.1 ± 0.4
4% Oxodipine + 96% P.E.G.	61.7	222 ± 2.0	98.5 ± 0.9
7% Oxodipine + 93% P.E.G.	61.2	221 ± 1.3	98.6 ± 0.6
10% Oxodipine + 90% P.E.G.	62.1	218 ± 2.1	98.9 ± 0.5
15% Oxodipine + 85% P.E.G.	61.5	197 ± 3.2	98.2 ± 1.3
17.5% Oxodipine + 82.5% P.E.G.	61.0	188 ± 1.7	98.6 ± 0.7
20% Oxodipine + 80% P.E.G.	61.1	180 ± 1.0	98.8 ± 0.6
25% Oxodipine + 75% P.E.G.	60.5	163 ± 2.3	98.6 ± 1.5
50% Oxodipine + 50% P.E.G.	60.1	260 ± 4.1	
	158.0	196 ± 2.2	
80% Oxodipine + 20% P.E.G.	56.4	256 ± 3.0	
	164.2	101 ± 1.7	

the solid dispersions of 15, 25, 50 and 80% oxodipine in P.E.G. 6000 are shown in Figs. 1–4.

The DSC curves for oxodipine and P.E.G. 6000, exhibit one endothermic peak at 166.8 and 60.2°C, respectively, which represents melting. The area under the peak was measured and ΔH melting was calculated. The calculated heat of melting for oxodipine was found to be 119 ± 2 J g^{-1}, and for P.E.G. 6000, the calculated heat of melting was found to be 225 ± 3 J g^{-1}.

We also calculated the purity of oxodipine and P.E.G. 6000 by van't Hoff's law [10,11]. The purities were found to be 99.4 ± 0.5% and 99.1 ± 0.4%, respectively. These values agree with those reported by the Instituto de Quimica Biológica for oxodipine and these obtained by HPLC.

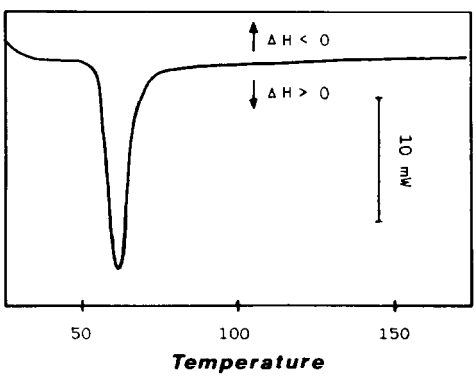

Fig. 1. DSC curve for 15% oxodipine + 85% P.E.G. 6000.

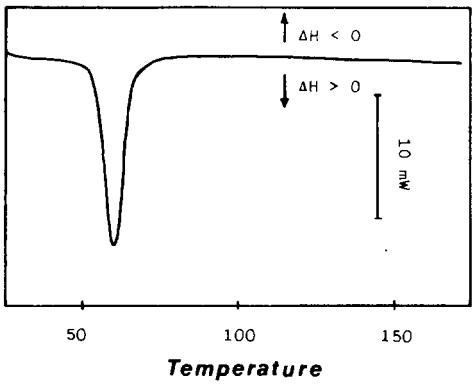

Fig. 2. DSC curve for 25% oxodipine + 75% P.E.G. 6000.

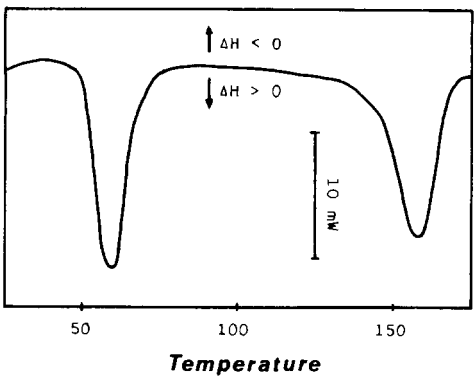

Fig. 3. DSC curve for 50% oxodipine + 50% P.E.G. 6000.

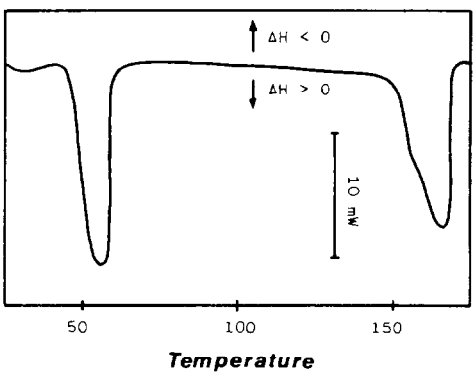

Fig. 4. DSC curve for 80% oxodipine + 20% P.E.G. 6000.

The DSC curves for the samples prepared with 4, 7, 10, 15, 17.5, 20 and 25% oxodipine in P.E.G. 6000, exhibit only one endothermic peak over 61°C (see Table 1). This endothermic process represents the melting of the samples.

The presence of only one process of melting at a greater temperature than the melting point of P.E.G. and at a lower temperature than the melting point of oxodipine, indicates the formation of a solid dispersion in these samples.

The calculated purity of these solid dispersions is over $98.5 \pm 0.5\%$, and this value reveals the limitation of the DSC method for purity determination when solid solutions are formed [12].

We can observe that a relationship exists between the calculated heat of melting of the solid dispersions, and the proportion of P.E.G. 6000 in the sample. The greater the proportion of P.E.G., the greater the heat of melting of the solid dispersion.

However, the DSC curves for the samples with 50 and 80% of oxodipine in P.E.G. 6000, exhibit two endothermic peaks. The first, at 60.1 and 56.4°C, respectively, can be attributed to the melting process of P.E.G. 6000, and the second, at 158.0 and 164.2°C, respectively, represents the melting of oxodipine. The presence of these peaks, permits us to reject the formation of solid dispersions for these samples.

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