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Dissolution rate of diazepam from polyethylene glycol 6000 solid dispersions

A.M. Rabasco, J.M. Ginés, M. Fernández-Arévalo and M.A. Holgado

Departamento de Farmacia y Tecnologia Farmaceutica, Catedra de Farmacia Galenica, Facultad de Farmacia, Universidad de Sevilla, Sevilla (Spain)

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Summary

A method for the elaboration of solid dispersions, the weight ratios of diazepam to polyethylene glycol 6000 and the particle size of drug in the solid dispersion have been investigated. The preparation method and diazepam-polyethylene glycol 6000 ratio influence the dissolution rate of the drug. It is observed that faster release characteristics were obtained with solid dispersions prepared by the fusion method and by increasing the carrier percentage. The increase in dissolution rate can be considered to result from crystal size reduction and the solubilizing effect of polyethylene glycol 6000. An intrinsic effect of the carrier also increases the dissolution rate of diazepam, since a physical mixture of the same composition dissolves more slowly than the solid dispersions. It is concluded that such a difference must be attributed to a significant reduction of the drug particle size in the carrier matrix.

Introduction

In 1961, the first approach to using solid dispersions to reduce particle size and to increase dissolution and oral absorption of poorly water-soluble drugs was reported (Sekiguchi et al., 1961).

Other factors that can contribute to the dissolution enhancement from solid dispersions are an increase in wettability (Rabinder et al., 1980) and solubility (Ford and Rubinstein, 1977), reduction in aggregation and agglomeration of hydrophobic drugs (Chiou and Riegelman, 1971) and the obtaining of polymeric forms (Collet and Kestenen, 1978).

The solid dispersions can be prepared by different methods. Melting is technically the least difficult procedure for preparing solid dispersions provided the drug and carrier are miscible in the molten state.

Polyethylene glycol 6000 (PEG 6000) has been extensively used as a water-soluble carrier for slightly soluble drugs and has been shown to increase the dissolution rate of many drugs (Ford, 1984; Ghaly and Abdallah, 1986; Sumnu, 1986; Alonso et al., 1988; Behra et al., 1988; Jafari et al., 1988).

Previous studies (Ginés et al., 1990; Sánchez-Soto et al., 1990) using differential thermal analysis (DTA) and X-ray diffraction have demon-

Correspondence: A.M. Rabasco, Departamento de Farmacia y Tecnologia Farmaceutica, Catedra de Farmacia Galenica, Facultad de Farmacia, Universidad de Sevilla, Sevilla, Spain.

strated the compatibility of drug and carrier. Based on these studies, a phase diagram for diazepam-PEG 6000 was constructed from the DTA data. It suggests that a simple eutectic is formed; the eutectic composition was found to be 13% diazepam and 87% PEG 6000. On the other hand, it was not possible to confirm the existence of a solid solution.

The present paper reports a study of the influence of the percentage and the method of solid dispersion elaboration on the dissolution characteristics of the drug and its particle size. The thermodynamic parameters of diazepam-PEG 6000 systems were also investigated.

Experimental

Materials

Commercial diazepam and PEG 6000 of pharmaceutical grade supplied by Acofar were used as starting materials. Both compounds were ground and sieved (Retsch sieve type vibro).

Preparation of solid dispersions

In a previous work (Ginés et al., 1990), solid dispersions of diazepam-PEG 6000 were prepared by melting, melting carrier and solvent methods (using ethanol as solvent) in 1 : 10, 1 : 5 and 1 : 1 w/w ratios.

Also, for comparison, physical mixtures of drug and carrier, previously sieved (250 μm), were prepared by mechanical mixing. The physical mixtures were prepared in the same ratios as the solid dispersions.

All samples were sieved and a particle size range of 50–200 μm was selected for studying the dissolution rate.

Particle size analysis

The particle size of the drug was determined using an optical microscope (Nikon type 104). Therefore, we developed a technique consisting of making a very thin film of the melt on a typical glass slide.

Solubility studies

An excess of diazepam (100 mg) was added to 25 ml of purified water or aqueous solutions of different PEG 6000 concentrations. The solutions were equilibrated by magnetical stirring at 27 and 37 °C ($\pm$0.5 °C) for 48 h. Samples were withdrawn and filtered (pore size 0.45 μm).

Molar solubilities, determined in triplicate and averaged, were obtained from a previously prepared calibration curve.

Dissolution rate determination

The dissolution rates of diazepam pure, from solid dispersions and physical mixtures with PEG 6000, were determined using the USP rotating basket dissolution apparatus at 37 $\pm$ 0.5 °C with the solution being stirred at 50 rpm. (Turu Grau model D-6).

An appropriate amount of solid dispersions containing 15 mg of diazepam was weighed (Mettler AE 50), then placed in the dissolution basket and lowered into the dissolution vessel containing 800 ml of artificial gastric medium. At different time intervals, filtered samples were withdrawn, suitably diluted and assayed (Hitachi U-2000 spectrophotometer) for drug content. The dissolution runs for all samples were performed in triplicate.

Under these experimental conditions PEG 6000 did not interfere with the spectrophotometric assay.

Results and Discussion

Particle size analysis

Comparison of the size distribution of diazepam particles into solid dispersions with the pulverized drug originally supplied is shown in Fig. 1. In this figure, it is shown that the diazepam particles in the solid dispersions obtained by the solvent method exhibit only relatively small differences.

The diazepam particles into dispersion systems obtained by the fusion methods were considerably smaller (Figs 2 and 3).

Solubility and thermodynamic parameters

In a previous article (Ginés et al., 1990), equilibrium solubility experiments were performed in

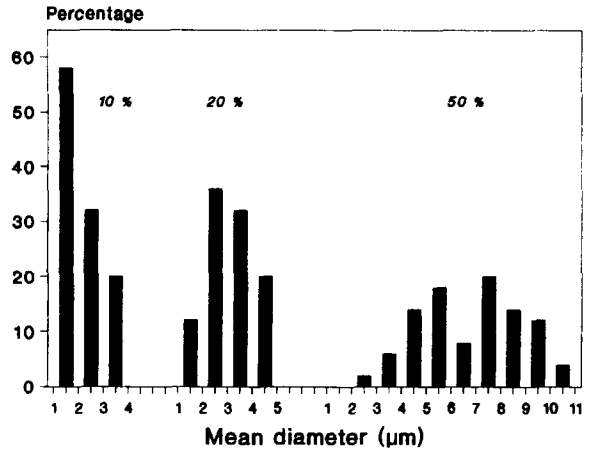

Fig. 1. Particle size distribution of diazepam (Dz) particles from the original pulverized drug and from solid dispersions (solvent method); 10, 20 and 50% w/w.

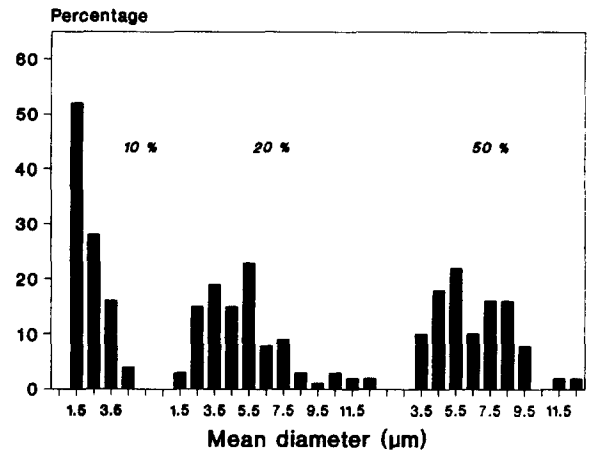

Fig. 2. Particle size distribution of diazepam particles from solid dispersion (melting method); 10, 20 and 50% w/w.

order to determine the solubilizing effect of PEG 6000 on diazepam.

A linear increase in solubility of the drug was observed with increase in PEG 6000 concentration (Fig. 4).

The thermodynamic parameters were determined for the interaction between diazepam and PEG 6000. The stability constant,

$$K = \text{slope/intercept} \cdot (1 - \text{slope})$$

was obtained from the above equation from data of the straight lines of Fig. 4.

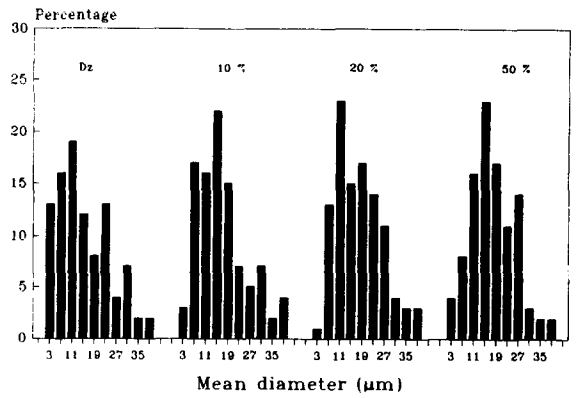

Fig. 3. Particle size distribution of diazepam particles from solid dispersion (melting carrier method); 10, 20 and 50% w/w.

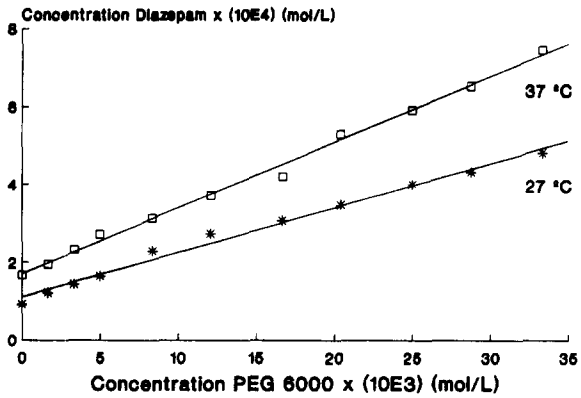

Fig. 4. Solubility of diazepam in aqueous PEG 6000 solutions at 27 and 37 °C.

The free energy change (ΔG), enthalpy change (ΔH) and entropy change (ΔS) were determined from the standard equations.

The values of the stability constants and the thermodynamic parameters are listed in Table 1.

The negative ΔG indicates a spontaneous process at these temperatures. The negative entropy

TABLE 1

Thermodynamic parameters of diazepam-PEG 6000 system

Temperature (°C)	K	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (J/mol per K)
27	124.51	−11.98	−16.00	−13.37
37	101.15	−11.85	−16.00	−13.37

change reveals the possibility of increased ordering of the species on complexation.

Dissolution rate studies

Effect of carrier weight ratio on diazepam dissolution. The percentage drug dissolved from the solid dispersions of diazepam-PEG 6000 was compared with that dissolved from an equal amount of physical mixtures and pure crystalline diazepam.

In all cases, increasing the proportion of carrier resulted in the enhancement of the dissolution rate. This extent of enhancement was markedly greater for the melted products in comparison with the coprecipitates and physical mixtures (Figs 5–7).

A higher weight ratio than 30% of diazepam leads the presence of diazepam larger crystals, confirmed by microscopical examination. This circumstance can explain the decrease observed in dissolution rate.

Effect of method of elaboration on diazepam dissolution. Melts: From Figs 5–7, it is evident that the melts of 1 : 10 and 1 : 5 w/w ratios have the fastest dissolution rates. Dissolution was greatly enhanced during the initial 5 min of the dissolution profiles. This rapid release was attributed to the presence of drug in a very fine state of subdivision.

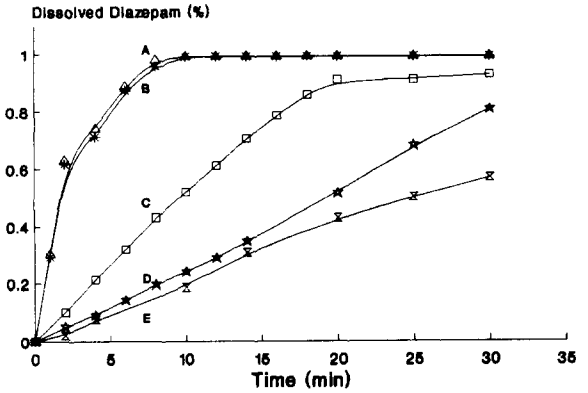

Fig. 6. Dissolution rates of the diazepam from different preparations. (A) Solid dispersion melting method, 20%; (B) solid dispersion melting carrier method, 20%; (C) solid dispersion solvent method, 20%; (D) physical mixture, 20%; (E) pure drug.

This is mainly due to the significant reduction of the drug particles size in addition to the solubilizing and wetting effect of the carrier. The solubilizing effect of PEG in the dissolution experiments is only possible in the diffusion layer due to the low concentration of the carrier.

Coprecipitates: Coprecipitates containing 1 : 10, 1 : 5 and 1 : 1 w/w ratios of diazepam-PEG 6000 exhibit slower dissolution rates than their corresponding melts. The apparently slow dissolution is due to the greater size of the diazepam particles so

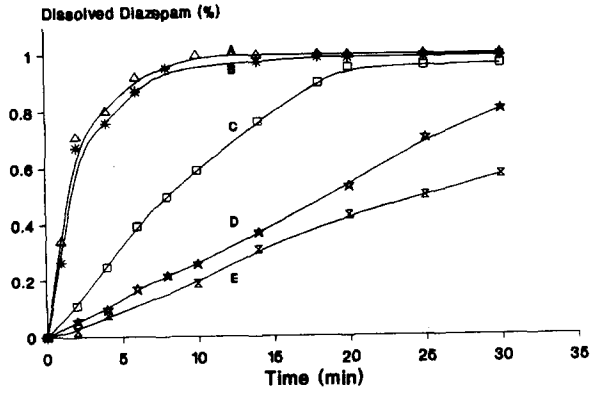

Fig. 5. Dissolution rates of the diazepam from different preparations. (A) Solid dispersion melting method, 10%; (B) solid dispersion melting carrier method, 10%; (C) solid dispersion solvent method, 10%; (D) physical mixture, 10%; (E) pure drug.

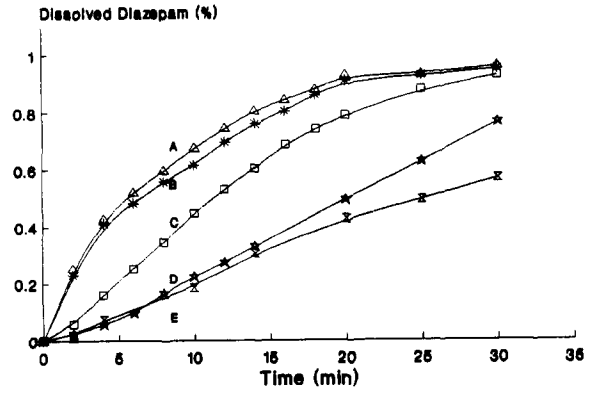

Fig. 7. Dissolution rates of the diazepam from different preparations. (A) Solid dispersion melting method, 50%; (B) solid dispersion melting carrier method, 50%; (C) solid dispersion solvent method, 50%; (D) physical mixture, 50%; (E) pure drug.

that its crystal size cannot exert a measurable effect on the dissolution rate.

Physical mixtures: The physical mixture of the diazepam with PEG 6000 dissolved more quickly than the pure drug; this can be explained by the wetting effect of the carrier.

However, physical mixtures show a slower rate of dissolution than solid dispersion systems, mainly due to their greater particle size of the drug.

The effect of particle size of drug on the dissolution rate from the solid dispersions studied here can be deduced from Figs 1–3. The role of particle size in increasing dissolution was quite apparent.

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