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ELABORATION AND CHARACTERIZATION OF THE DIAZEPAM-POLYETHYLENEGLYCOL 6000 SOLID DISPERSIONS

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ABSTRACT

Diazepam - polyethyleneglycol 6000 solid dispersions systems were prepared by melting and solvent methods. These dispersions were characterized using D.T.A., X-Ray diffraction and microscopy. The phase diagram has shown that this system is characterized as a simple eutectic mixture with a eutectic composition of 87 % diazepam and 13 % P.E.G. 6000. Solubility studies showed a linear increase in drug solubility with the increase of P.E.G. 6000 concentration.

INTRODUCTION

The bioavailabilities of many poorly water-soluble drugs are limited by their dissolution rates which are in turn controlled by the surface area that they present for dissolution. Consequently, the reduction of the particle size can very often increase the rate of absorption and the amount of absorbed drug.

Particle size reduction of drugs is generally achieved by mechanical micronization processes, but the resultant micronized particles can have disadvantages. Aggregations and agglomerations can occur due to the increased surface energy and poor wettability in water is observed.

SEKIGUCHI and OBI [1] first proposed the use of solid dispersions as a novel method for reducing particles size and demonstrated the potential of solid dispersion in increasing the bioavailability of poorly water-soluble drugs, to increase the dissolution and oral absorption. Moreover the carrier can increase the aqueous solubility of the drug. The mechanism of enhacement solubility of insoluble or slightly soluble drugs via solid dispersion techniques is extensively reviewed by CHIOU and RIEGELMAN [2] and very recently by FORD [3].

Diazepam, a poorly water-soluble benzodiazepine, has been shown to be irregulary absorption after oral administration because of its low solubility [4, 5].

Many substances have been examined for their carrier properties. Polyethyleneglycols are the most commonly used carriers [6]; P.E.G. 6000 has been most extensively studied [7 - 13].

The present work deals with physicochemical properties of diazepam-P.E.G. 6000 solid dispersions. The purpose of this study is to characterized the solid dispersions systems prepared by fusion and solvent method and to determine how the solubility and size of particle of drug is modified when a solid dispersion is done.

The physicochemical structure of the solid dispersion play an important role in controlling their drug release. The phase equilibria between drugs and carriers may be examined using thermal analysis, X-ray diffraction, microscopic, spectroscopic, thermodynamic techniques and by dissolution rates data [2].

EXPERIMENTAL

Materials

Commercial diazepam and polyethyleneglycol-6000 of pharmaceutical grade supplied by Acofar, were used as starting materials. Both compounds were ground and sieved (Retsch sieve type vibro). For solid dispersion preparation, the 50 - 200 µm fraction was selected.

Preparation of Solid Dispersions Diazepam-PEG 6000

A) Melting method

Physical mixtures of diazepam and P.E.G. 6000 were weighted from the range 5 to 80 %. Then, they were gradually heated up to 150 °C, with constant stirring, employing a magnetic stirrer heater Selecta Agimatic, S-243 model. This temperature is lightly higher than the melting point of diazepam.

When the obtained melt was clear and homogeneous, the dispersion was rapidly quenched in an ice-bath.

After cooling, the obtained solid was ground and sieved. The fraction of 270 mesh was selected.

B) Solvent method

Diazepam solid dispersions in P.E.G. 6000 were prepared by the solvent method using ethanol as a solvent in 1:10, 1:5 and 1:1 w/w ratios.

Weighted quantities of two components were dissolved in a minimum volume of ethanol.

The solvent was then removed by evaporation in vacuum at room temperature using a magnetic stirrer.

The obtained viscous liquids were allowed to solidify at room temperature in a glass desiccator.

After 24 hours of standing in the glass desiccator the solid masses were powdered and the 270 mesh fraction was selected.

C) Physical mixtures

The physical mixtures were prepared by simple mixing of the two components previously sieved (270 mesh) in 1:10, 1:5 and 1:1 w/w ratios.

The physical mixtures were used for comparation with solid dispersions.

Stability Studies

Thermal and X-ray diffraction methods were used to evidence chemical stability of drug after elaboration of solid dispersions.

Differential Thermal Analysis

Differential thermal analysis (DTA) experiments were carried out in static air with an automatic

thermal analyzer system Rigaku, PTC-10 A model. The data processing system DPS-1 and the plotter Watanabe Miplot were connected to the thermal analyzer. Samples of 20 mg in weight were packed loosely into a platinum cylindrical holder and heated from 20 °C to a maximum of 200 °C (Pt/Pt-Rh 13 % thermocouple). The heating rates were 10 and 5 degrees/min. Calcined alumina was used as a reference material. For calibration, KNO_3 Merck was employed. The sensitivity range in DTA was ± 25 μV and the chart speed 2.5 mm/min.

X-Ray Diffraction

X-ray diagrams were obtained in a Siemens Kristalloflex D-500 diffractometer with Ni-filtered Cu Kα radiation at a goniometer speed of 1° (2 Θ)/min and a chart speed of 1 cm/min.

Solubility Study

An excess of diazepam (100 mg) was added to 25 mL of purified water in a erlenmeyer flask, containing 0 - 20 % of P.E.G. 6000.

The flask were equilibrated by magnetical stirring at 37 ± 0.5 °C for 48 hours, time that was found enough to reach equilibrium.

At the end of this period, the solution were then withdrawn by a syringe fitted with a membrane filter (pore size 0.45 μm), suitably diluted and assayed spectrophotometrically at 241 nm.

Microscopy of Solid Dispersions

A) Scanning electron microscopy

Samples deposited in a Cu holder, were coated with a thin film of Au to make them conducting and examined

under a scanning electron microscope ISI model SS-40 at 20 Kv.

B) Optical microscopy

Initially, we got some difficulties to identificate the diazepam into solid dispersions by using this technique. So, we developed another technique consisting in making a very thin film of the melt on a typical slide-glass.

Due to formation of a very thin film at cooling of P.E.G. 6000, the diazepam particles can be easily identified by using a microscope Nikon type 104 with a camera attachment. Selected microphotographs of several visual fields were performed.

RESULTS AND DISCUSSION

Stability Studies

A) Pure diazepam

The thermal stability of diazepam (m.p. 131 - 135 °C) was demonstrated by DTA.

Analogous thermograms were reached for diazepam untreated, melt-resolidified (melted) and diazepam obtained by evaporation of its ethanolic solution sample (solvated) (fig. 1).

Neither alteration nor shifts in U.V. spectra were noted between original and treated diazepam.

The X-ray diffraction spectra of the three samples evidence that this treatment did not influence the crystallinity of the drug; moreover the lack of additional diffraction peaks indicated that no degradation had occurred (fig. 2).

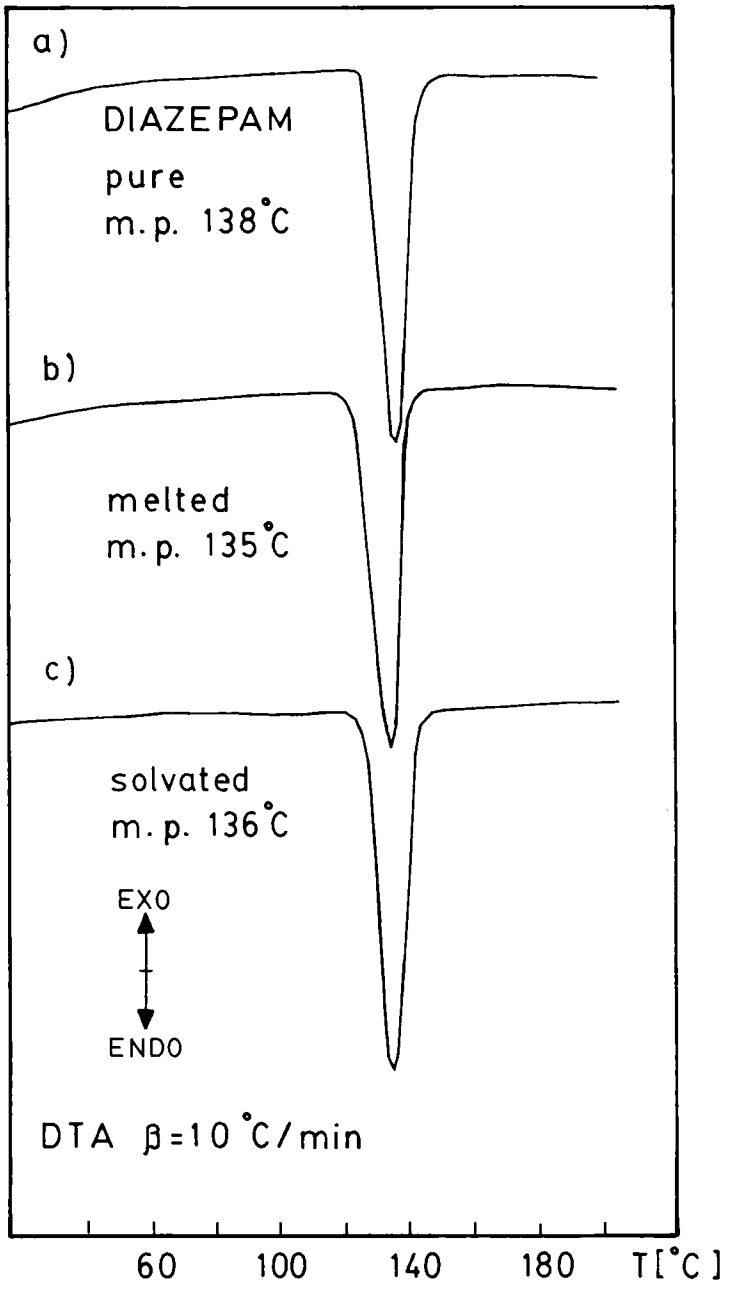

FIGURE 1
DTA thermograms of: a)Untreated diazepam b)Melt resolidified diazepam c)Solvated diazepam

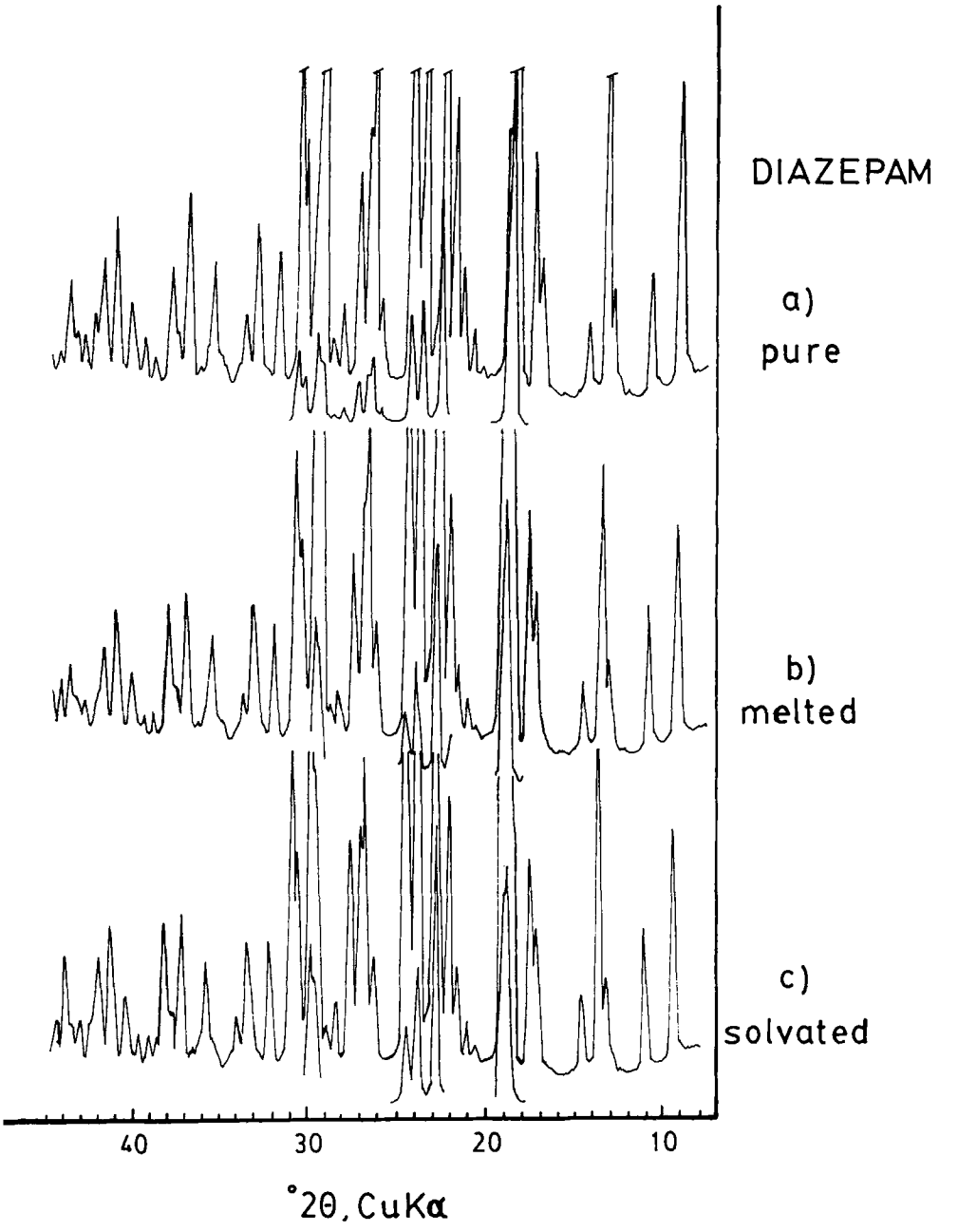

FIGURE 2
X-ray diffraction patterns of: a)pure diazepam b)melted diazepam c)solvated diazepam

B) Solid dispersions

Diazepam dispersed in P.E.G. 6000 prepared by fusion and solvent method showed same U.V. spectra to that of untreated diazepam.

Differential Thermal Analysis

The DTA thermograms of diazepam-PEG 6000 "solidified-melts" and pure compounds, obtained heating up to 200 °C, are depicted in figure 3.

In general, endothermic DTA effects that result from melting are observed, and endothermic effects corresponding to melting of a simple eutectic system also appear. From these curves, it is clear that with increasing diazepam content, the second DTA-endothermic peak is closer to that of pure diazepam compound. Note than the two-endothermics DTA effects disappear at 20 % w/w composition, and a single endothermic effect of the solid dispersion is obtained.

In connection with this fact, increasing PEG 6000 leads to a decrease of melting point, as well as the DTA endothermic areas remarkably increase. This endothermic peak is very close to that of the pure compound.

Phase Diagram

The phase diagram for diazepam-PEG 6000 compositions, determined by the DTA data is shown in figure 3.

Thermal analysis suggest that a simple eutectic is formed close to the melting point of pure PEG 6000. According to these results, the phase diagram diazepam-P.E.G. 6000 is proposed, although the precise determination of the eutectic point is tentative, as in

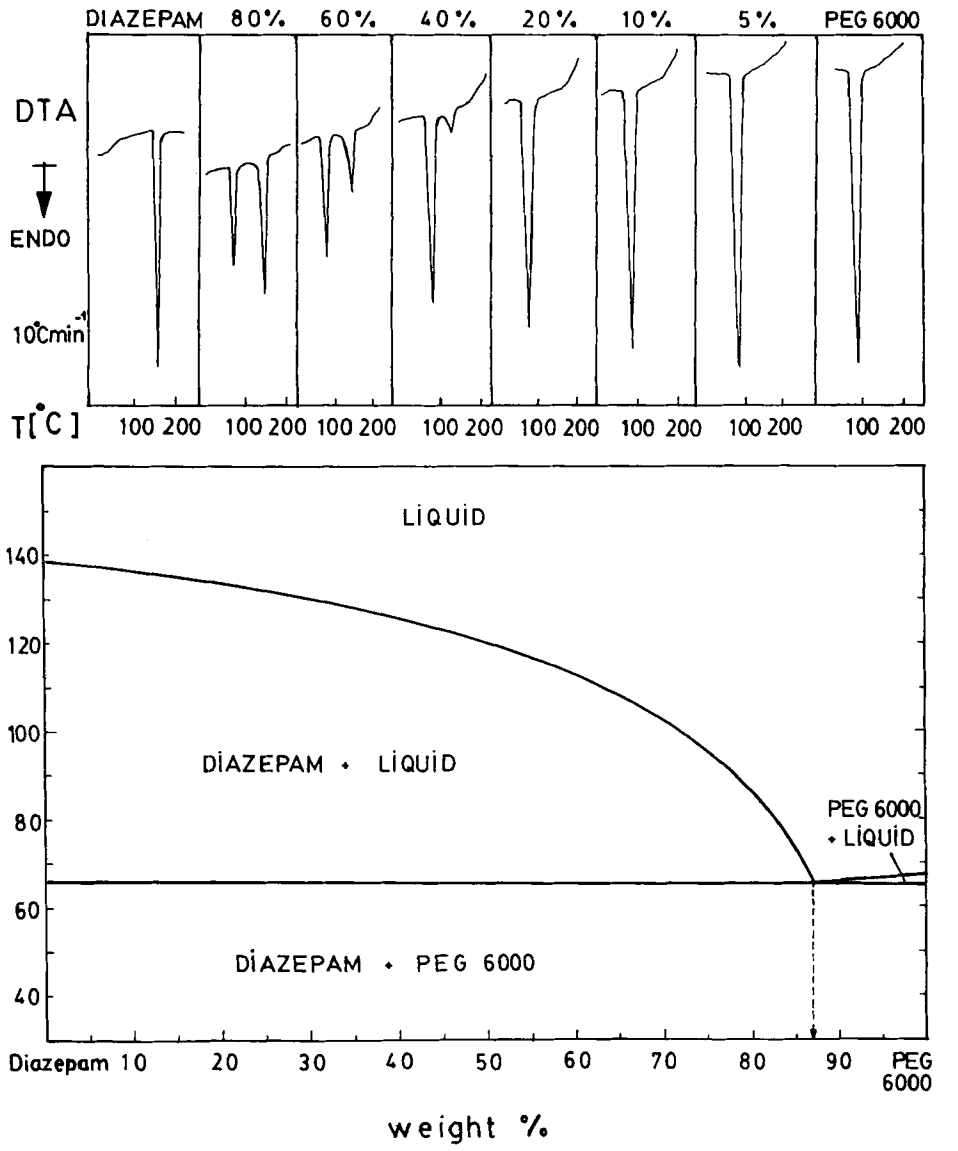

FIGURE 3

DTA diagrams of diazepam (Dz), P.E.G. 6000 and solid dispersions (melting method). Heating rate 10ºC/min; and phase diagram proposed of the diazepam-P.E.G. 6000 binary system.

other solid dispersions systems. The extrapolated values are 87 % of PEG 6000 and 13 % of the drug (w/w).

X-Ray Diffraction

The X-ray difraction patterns of the pure diazepam and pure P.E.G. 6000 and patterns of solid dispersions of 10 % diazepam prepared by melting and solvent method and physical mixtures of 10 % are shown in figure 4.

No additional new difraction lines were detected, indicating that no degradation or new compounds formation had ocurred. Minor changes in the intensity of some peaks were observed. However, this was probably due to change in preferred orientation rather than any alteration in the physicochemical properties of the drug.

Spectra indicate that the diazepam and P.E.G. 6000 in the solid dispersions show the same patterns that in the pure compounds.

X-ray difraction data also show that dispersed systems of diazepam in PEG 6000 should be clasified as a simple eutectic mixture, as found by DTA studies.

Solubility Study

The solubility study was performed to determine the solubilizing effect of P.E.G. 6000 on diazepam.

The equilibrium solubility data of diazepam in purified water, containing different carrier concentration at two temperatures are shown in figure 5. A linear increase in the solubility of the drugs was observed with the increase of P.E.G. 6000 concentration.

Similar reports about the solubilizing effect of P.E.G. on another drugs have been published [14, 15]

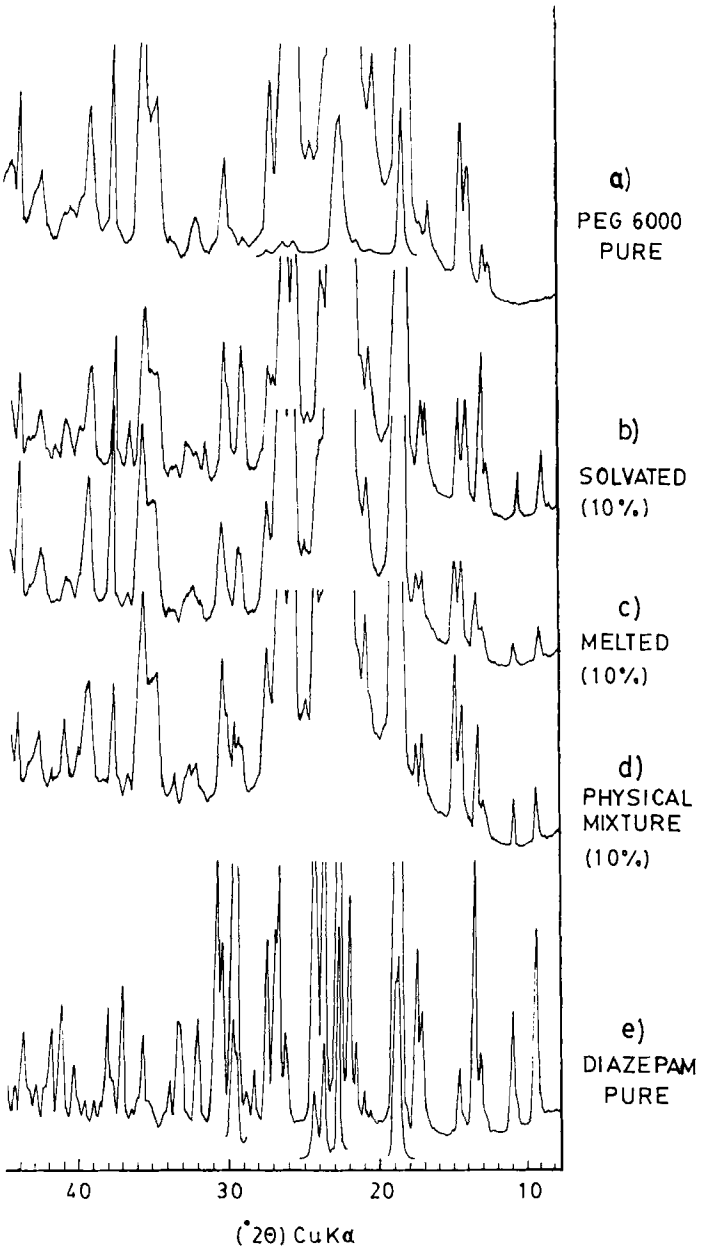

FIGURE 4
X-ray diffraction patterns of: a)pure - P.E.G. 6000, b)solid dispersion of 10% - diazepam (solvent method) c)solid dispersion of 10% diazepam (melting method d) physical mixtures of 10% diazepam e)pure diazepam.

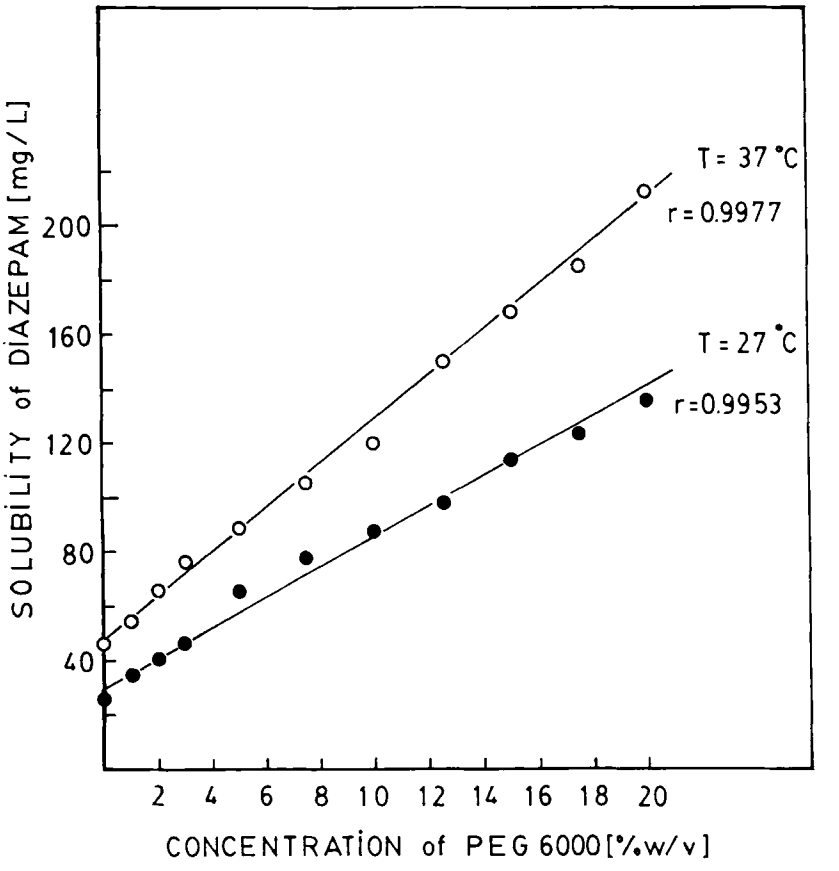

FIGURE 5
Solubility of diazepam in aqueous P.E.G. 6000 solutions at 37ºC and 27ºC.

and attributed to the formation of a soluble complex. However, it should be a very weak complex with a high dissociation constant, since X-ray difraction studies did not show the existence of any complexation between the two components in their solid state.

Microscopy Study

A) Electron microscopy

Figures 6 and 7 show the original products, diazepam and P.E.G. 6000 respectively. The solid

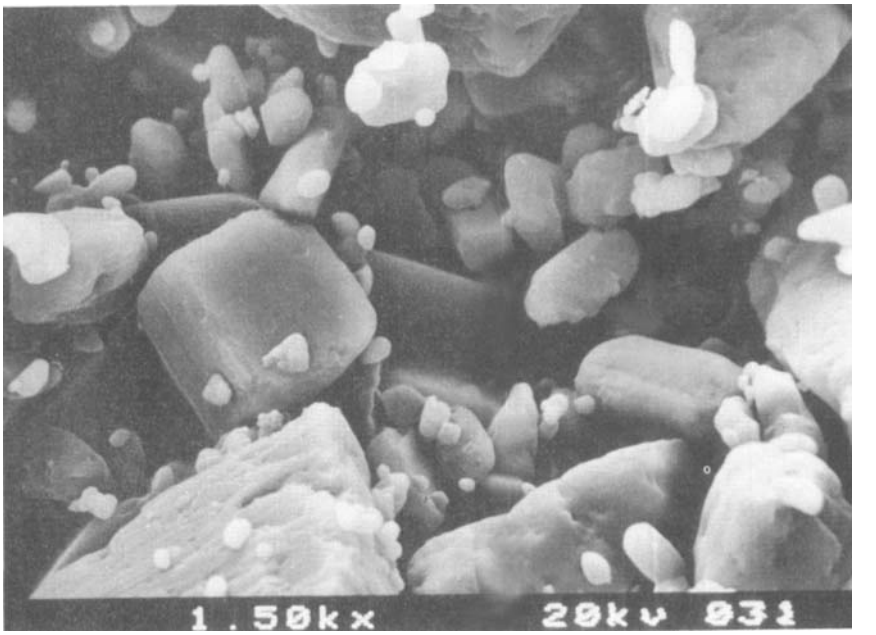

FIGURE 6
Scanning electron micrograph of pure diazepam

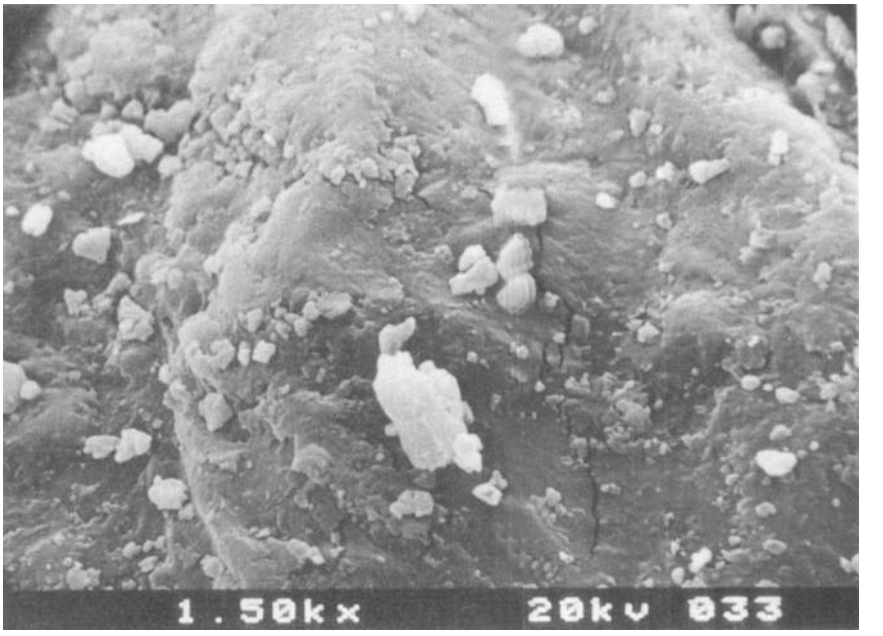

FIGURE 7
Scanning electron micrograph of pure PEG 6000

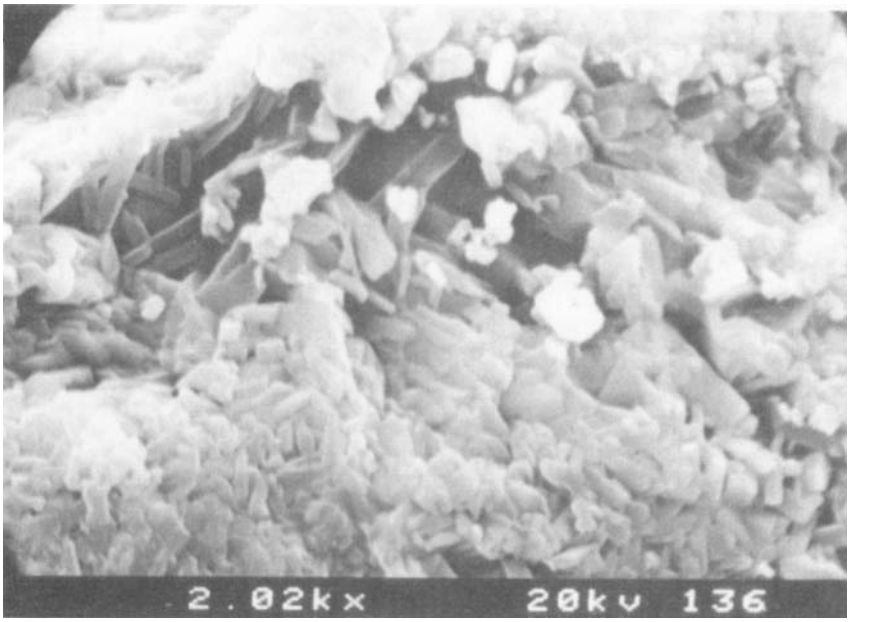

FIGURE 8
Scanning electron micrograph of solid dispersion 10 % diazepam (melting method)

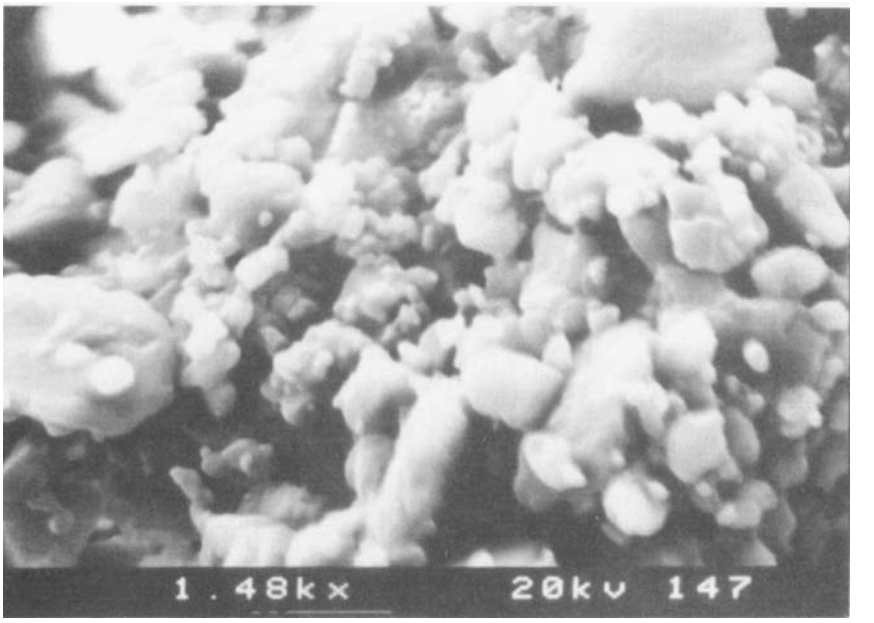

FIGURE 9
Scanning electron micrograph of solid dispersion 20 % diazepam (solvent method)

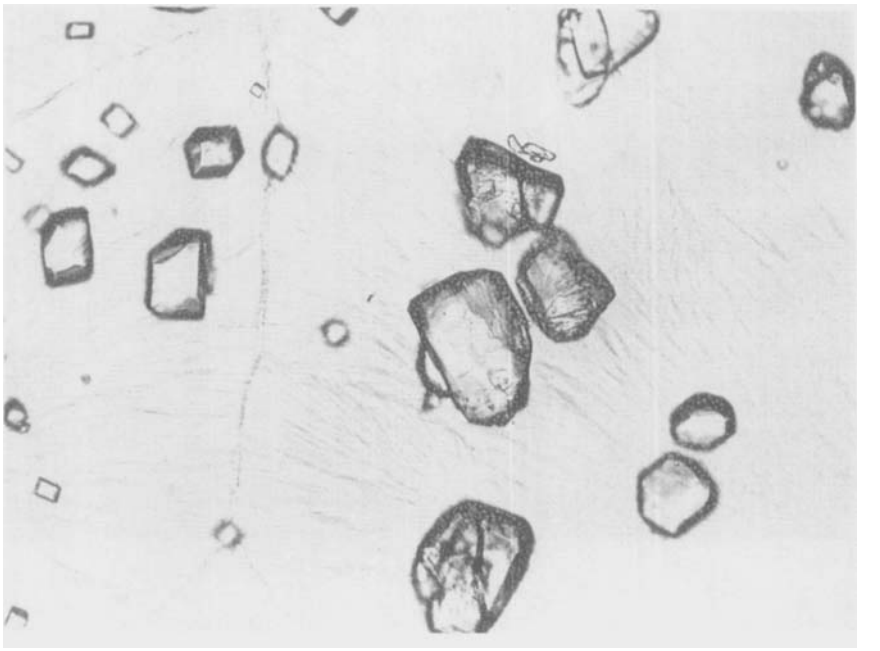

FIGURE 10
Microphotograph of "coevaporate" 20 % diazepam (x 100) after solidification

dispersions of 10 % w/w melting method and 20 % w/w solvent method are shown in figures 8 and 9.

The identification of particles of the drug into the solid dispersion was not possible by electron microscopy because the carrier masked them.

B) Optical microscopy

Figure 10 shows the microphotograph of "coprecipitate" of 20 %, prepared as indicated previously. The solvent method did not reduce significantly the particle size of pulverized drug.

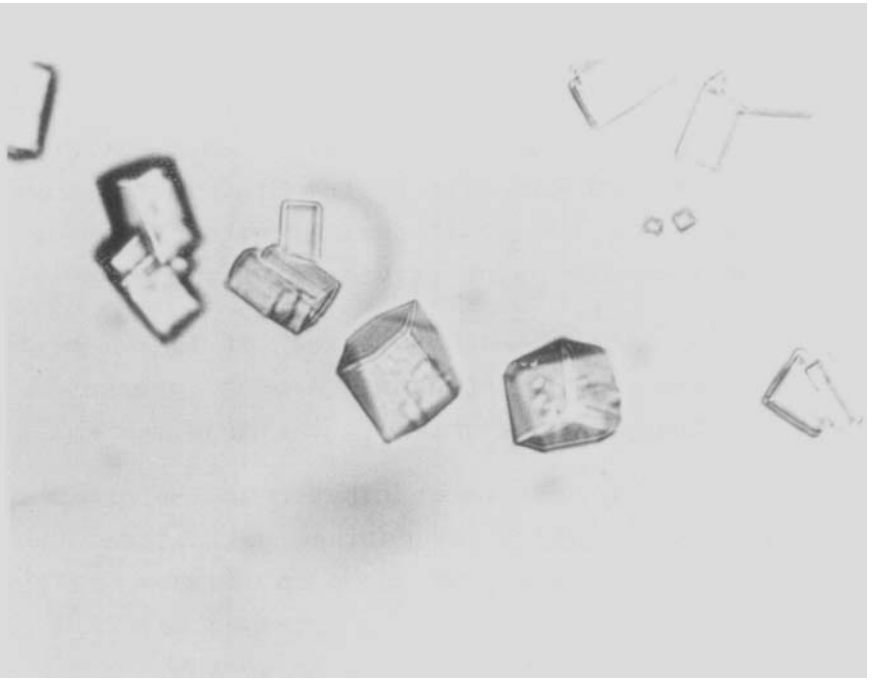

FIGURE 11
Microphotograph of "melt-resolidified"
20 % diazepam (x 1000)

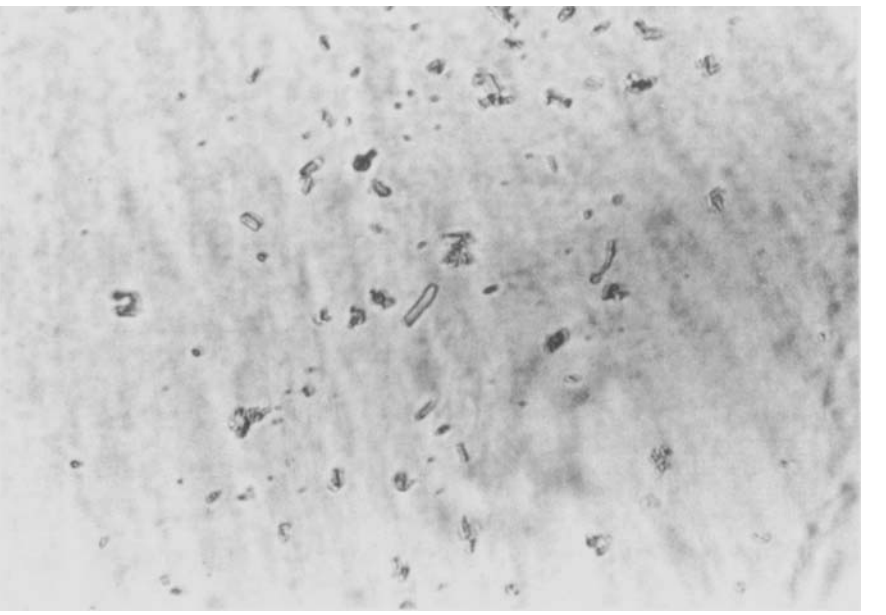

FIGURE 12
Microphotograph of "melt-resolidified"
10 % diazepam (x 400)

In the solid dispersion of 20 %, as it is show in figure 11, the particle size of the drug is considerably reduced when we use the fusion method, which is interesting from the point of view of solid dispersion.

Moreover, the solid dispersion of 10 % (melting method), shows the homogeneous aspect presented in figure 12. The particle size of the drug is smaller.

Usually, this fact is attributed to the formation of very fine drug particles during solidification of the eutectic melt [16], as shown in figure 12. The above result confirms the data obtained for 10 % w/w solid dispersions by X-Ray Diffraction and the suggested phase diagram (figures 3 and 4).

REFERENCES

1.- K. SEKIGUCHI, N. OBI: Chem. Pharm. Bull., 9, 866 (1961).

2.- W. L. CHIOU, S. RIEGELMAN: J. Pharm. Sci., 60, 1281 (1971).

3.- J. L. FORD: Pharm. Acta Helv., 61, 69 (1986).

4.- V. D. STEINBACH, E. WEBER, C. PIPER, H. MÖLLER, W. STÜBER: Pharm. Ztg., 125, 1297 (1980).

5.- V. D. STEINBACH, E. WEBER, C. PIPER, H. MÖLLER, W. STÜBER: Pharm. Ztg., 125, 1343 (1980).

6.- C. CHEMTOB: S.T.P. Pharma, 1, 531 (1985).

7.- J. L. DUBOIS, J. L. FORD: J. Pharm. Pharmacol., 37, 494 (1985).

8.- S. STAVCHANSKY, G. W. GOWAN: J. Pharm. Sci., 73, 733 (1984).

9.- J. L. VILA-JATO, M. J. ALONSO, J. BLANCO: Drug Dev. Ind. Pharm., 12, 1545 (1986).

10.- J. L. DUBOIS, J. C. CHAUMEIL, J. L. FORD: S.T.P. Pharma, 1, 711 (1985).

11.- J. L. FORD: Pharm. Acta Helv., 59, 280 (1984).

12.- J. M. GINES: Tesis de Licenciatura. Universidad de Sevilla, 1988

13.- G. M. GHALY, O. ABDALLAH: S.T.P. Pharma, 2, 209 (1986).

14.- P. MURA, A. LIGUORI, G. BRAMANTI: Farmaco Ed. Pr., 42, 149 (1987).

15.- H. M. EL-BANNA, O. ABDALLAH: Pharm. Acta Helv., 55, 256 (1980).

16.- M. SUMNU: S.T.P. Pharma, 2, 214 (1986).