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THERMAL STUDY OF DIAZEPAM–POLY(ETHYLENE GLYCOL) 6000 SOLID DISPERSIONS

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ABSTRACT

Solid dispersions of the binary system Diazepam–poly(ethylene glycol) 6000 have been prepared and studied by means of DTA and optical microscopy.

Thermal analysis suggests that a simple eutectic is formed close to the melting point of pure poly(ethylene glycol) 6000. A Diazepam–poly(ethylene glycol) 6000 phase diagram is proposed, although the precise determination of the eutectic point is tentative, as in other solid dispersion systems. The extrapolated values are 87 wt.% poly(ethylene glycol) 6000 and 13 wt.% of the drug. This is in accordance with Tamman's triangle, which is constructed and discussed.

The microscopic study of the system has shown how the drug becomes very finely dispersed by the formation of very fine particles during solidification of the melt.

All these results are of great pharmacological interest in further studies on dissolution processes.

INTRODUCTION

Solid dispersions were introduced into the pharmaceutical industry in 1961 by Sekiguchi and Obi [1] with the aim of improving the solubility and rate of dissolution of the active principles. Subsequent publications have considerably developed this interesting area of research [2–6]. These systems are formed by both, one or several poorly soluble active principles dispersed in one or several water-soluble inert carriers that act as excipients.

Chiou and Riegelman [2] have defined solid dispersions as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid state

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prepared by the melting (fusion), solvent or melting-solvent methods". The fusion process is technologically the least difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state (in French, "cofondus"). For this purpose, the molecular size of the carrier should be considerably greater than that of the active principle, and consequently, polymers such as poly(ethylene glycol) or poly(vinylpyrrolidone) have been investigated and are commonly used. The high molecular weight of poly(ethylene glycol) facilitates the formation of interstitial solid solutions with drugs. Therefore, a better bioavailability of the active principles is obtained, and their sustained or controlled release can also be achieved [3].

Thermoanalytical methods have been successfully applied to the determination of solid–liquid equilibrium and to binary systems of organic compounds [7–9]. Pharmaceuticals, in particular, have received considerable attention [10–13], and thermal analysis has been applied in many solid dispersions studies [5].

As pointed out by Ford [5], the study of a solid dispersion system involves the knowledge of its phase diagram, constructed from DTA data, and of the influence of the carrier on drug solubility and on dissolution rates. In this paper, we have investigated the thermal behaviour of the solid dispersion Diazepam–poly(ethylene glycol) (molecular weight 6000), because of the great pharmacological interest in this drug, also well-known commercially as Valium. This study is the first part of a research programme on this system.

EXPERIMENTAL

The starting materials were commercial Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one), m.p. 131–135 °C, and poly(ethylene glycol) 6000 (polymer made by the condensation of ethylene oxide, molecular weight fraction 6000, m.p. 65 °C) both of pharmaceutical grade supplied by Acofar.

Both compounds were ground in a Braun mill and sieved (Retsch sieve, vibro type). For solid dispersion preparation, the 50–200 μm fraction was selected.

Preparation of the solid dispersion

Solid dispersions of Diazepam–poly(ethylene glycol) 6000 were prepared according to the fusion method [1–3]. For this purpose, Diazepam (Dz) and poly(ethylene glycol) 6000 (PEG 6000) were mixed in the composition range of 5–80 wt.% of the drug and gradually heated at 10 °C min^{-1} in a bath up to 150 °C, with continuous agitation, using a magnetic stirrer and heater, Selecta Agimatic model S-243. The temperature was slightly above the melting point of Diazepam.

Apparatus

Differential thermal analysis

DTA experiments were carried out in static air with an automatic thermal analyser system, (RigaKu, model PTC-10 A). The data processing system DPS-1 and the Watanabe Miplot plotter were connected to the thermal analyser. 20 mg samples were loosely packed into a cylindrical platinum holder and heated from 20 °C to a maximum of 200 °C (Pt/Pt–Rh(13%) thermocouple). The heating rates were 10 °C min^{-1} and 5 °C min^{-1}. Calcined alumina was used as a reference material. Merck KNO_3 was used for calibration. The DTA sensitivity range was ± 25 μV and the chart speed was 2.5 mm min^{-1}.

The areas under the experimental curves were determined by tracing them onto drawing paper of uniform weight and cutting out the inscribed area. The weights of the cut-outs were subsequently determined on an analytical balance.

Microscopical study of solid dispersion

Additional information on the thermal behaviour of these solid dispersions was obtained by visual identification using an optical microscope. The identification of particles of the drug (Dz) in the solid dispersion is not possible by optical microscopy because they are masked by the carrier. Therefore, a technique was developed in which a very thin film of the melt was made on a glass slide, analogous to the oriented samples prepared for X-ray diffraction.

The Diazepam particles form a very thin film on cooling and can be easily identified using a Nikon Microscope type 104. Selected microphotographs of several visual fields were made.

RESULTS AND DISCUSSION

Figure 1 shows the DTA curves of pure compounds and solid dispersions obtained on heating up to 200 °C. As indicated in the figure, the temperatures, shapes and magnitudes of the thermal effects are a function of the composition of the solid dispersions under study. In general, the endothermic DTA effects that result from melting are observed, together with the endothermic effects corresponding to melting of a simple eutectic system. From these curves, it is clear that with increasing Diazepam content, the second endothermic DTA peak approaches that of pure Diazepam and its area increases. At 20 wt.% Diazepam, the two peaks disappear and a single endothermic effect of the solid dispersion is obtained. In connection with this, increasing the PEG 6000 content leads to a lowering of the melting point, as well as to a considerable increase in the DTA endothermic peak areas. This endothermic peak is very close to that of the pure compound.

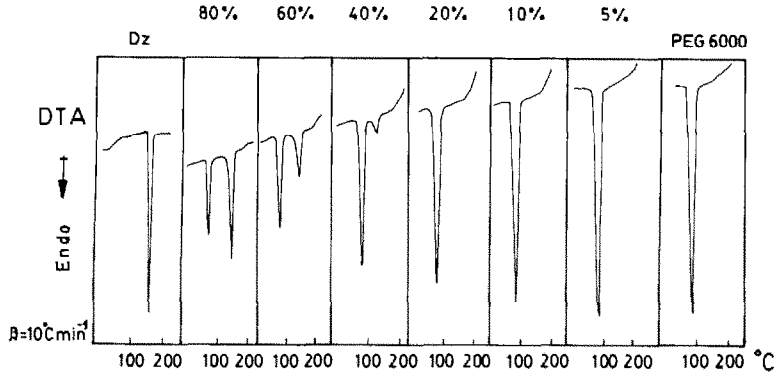

Fig. 1. DTA curves for Diazepam (Dz), poly(ethylene glycol) 6000 (PEG 6000) and solid dispersions prepared according to the fusion method. Heating rate, 10 °C min^{-1}.

In a recent paper, Ford [5] reported a complete study on the thermal behaviour of pure PEG 6000, and our results are in good agreement with this. A complete interpretation is complex, but we may infer that the melting point of the polymer probably corresponds to fusion of folded chain crystals and this is related to the molecular weight.

The processed data enable the amplification of temperature ranges of interest. Some selected results are shown in Fig. 2. The increase in area of the first endothermic peak and the progressive disappearance of the second are clearly visible, and a better resolution of the experimental curves is attained.

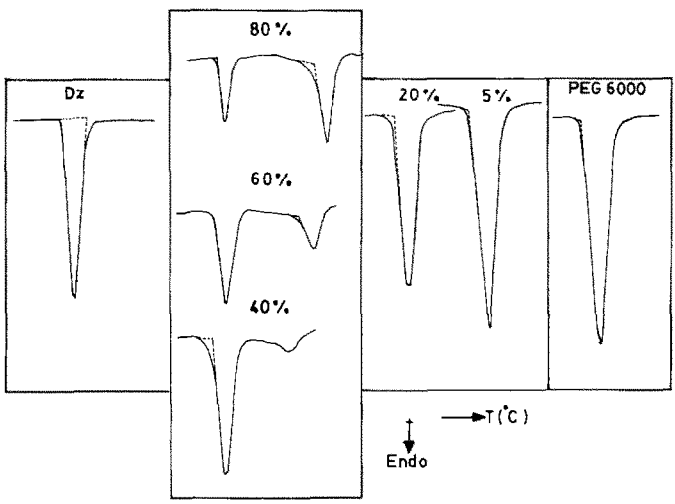

Fig. 2. DTA curves for Diazepam (Dz), poly(ethylene glycol) 6000 (PEG 6000) and solid dispersions prepared according to the fusion method. Results obtained from DTA data processed by the system DPS-1 and plotted. Heating rate, 10 °C min^{-1}.

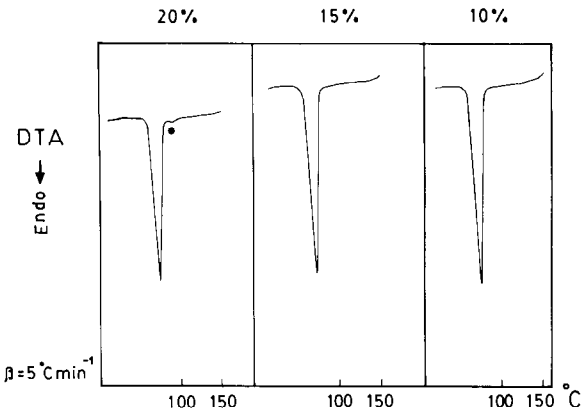

Fig. 3. DTA curves for 20, 15 and 10 wt.% Diazepam solid dispersions. Heating rate, 5 °C min^{-1}.

For a more thorough investigation, solid dispersions of selected compositions were heated at a slower heating rate (5 °C min^{-1}). Figure 3 shows the results obtained for 20 wt.%, 15 wt.% and 10 wt.% solid dispersions. The DTA curve for 20 wt.% shows a small endothermic effect close to the principal one. This small effect disappeared in mixtures having a lower Diazepam content, when the PEG 6000 level increased. Thus, the eutectic composition is close to 20 wt.% Diazepam.

From the data presented above, a simple interpretation of the phase diagram based on the DTA curves is shown in Fig. 4.

The precise determination of the eutectic point is tentative, because it is very close to pure PEG 6000, and the melting temperature is only a few

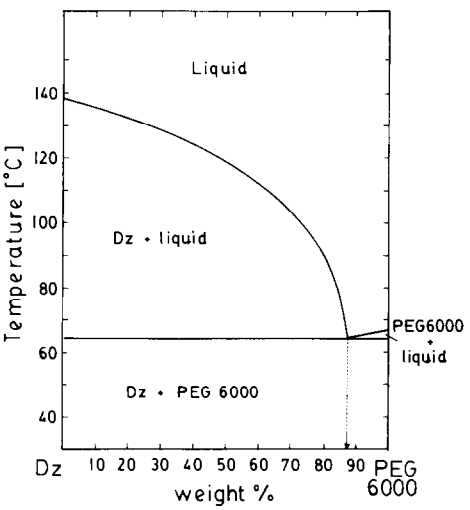

Fig. 4. Proposed phase diagram of the Diazepam–poly(ethylene glycol) 6000 binary system.

degrees lower. However, extrapolation of the liquidus line to the PEG 6000 zone gave us an estimated eutectic composition of 87 wt.% PEG 6000 and 13 wt.% of the drug.

In the case of solid dispersions prepared from the same drug and another poly(ethylene glycol) (PEG 4000), Henry et al. [14] have reported that the eutectic point lies at 53° C, i.e. practically the melting point of the pure PEG 4000 compound, and with a composition of 17 wt.% Diazepam and 83 wt.% PEG 4000, also very close to pure PEG 4000 as is the case in the present research.

In general, several important factors influence this behaviour, e.g. the physical characteristics of the drug itself, the configuration of the PEG molecules within the PEG matrix, solid solutions, retardation of crystallisation and other factors that may be mobilised in these systems. At the same time, care must be taken when constructing phase diagrams from DTA data, because erroneous results can originate from metastable states [9].

For instance, the molecular weight of the PEG influences the results because polymers of higher molecular weight may form more viscous solutions, thus reducing further crystallisation of the drug and increasingly favouring its incorporation in solid solutions. On the other hand, they form flakes more readily during posterior dissolution [3].

The phase diagram obtained is analogous to the Phenacetine–PEG 6000 solid dispersion. In this system, extrapolation of the liquidus line gave an estimated eutectic composition of 8 wt.% of the drug, also very close to pure PEG 6000 [5].

In binary systems, one can determine the composition of the eutectic point using Tamman's triangles [15]. The diagram is constructed by studying the relationships between the area of the DTA peak considered and the composition of the system. This empirical rule, established by Tamman, has been discussed in a recent paper by Mills and Coyle [16], and has also been successfully applied for the determination of the eutectic composition in systems in which one of the components is unstable in the vicinity of the melting temperature of the eutectic [17].

Figure 5 shows the area of the first endothermic DTA peak plotted against the composition. A linear relationship between areas and temperature is observed, but the exact and precise determination of the eutectic composition is not possible, as shown above. However, the linear relation holds for up to 90 wt.% PEG 6000, or 10 wt.% Diazepam, in good agreement with the extrapolated values of 87 and 13 wt.% of PEG 6000 and drug, respectively, in accordance with the suggested phase diagram (Fig. 4). In fact, a true Tamman's triangle cannot be constructed because of the narrow range of temperatures between the eutectic point and the melting point of PEG 6000.

Figure 6 shows the original Diazepam particles selected as the starting material for this study. For comparison, Fig. 7 shows the microphotograph

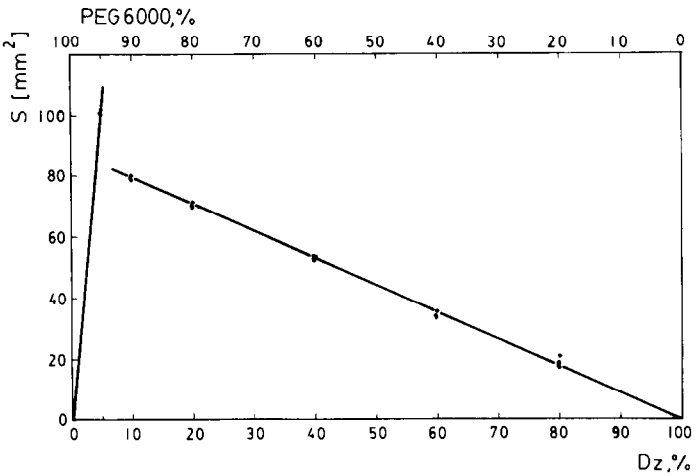

Fig. 5. Relationship between the composition of the Diazepam–poly(ethylene glycol) 6000 system and the areas of the first endothermic peak observed in DTA.

of the 50 wt.% solid dispersion prepared as indicated above. The same microscopic field is photographed during fusion and after solidification. It is clear from in Fig. 7 that the particle size of the drug has been considerably reduced, which is interesting from the point of view of solid dispersions.

The solid dispersion of 10 wt.% has a homogeneous aspect, shown in Fig. 8. The particle size of the drug is smaller, which is interesting because of the

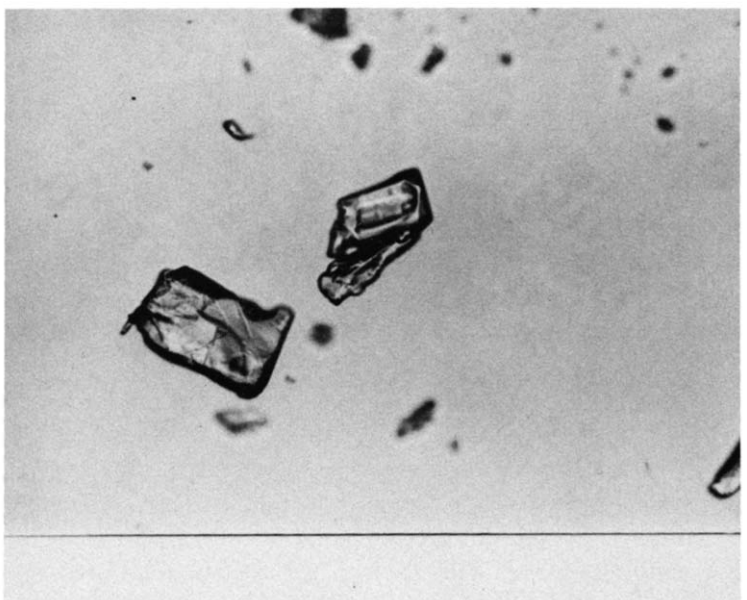

Fig. 6. Microphotograph of original Diazepam particles (×100).

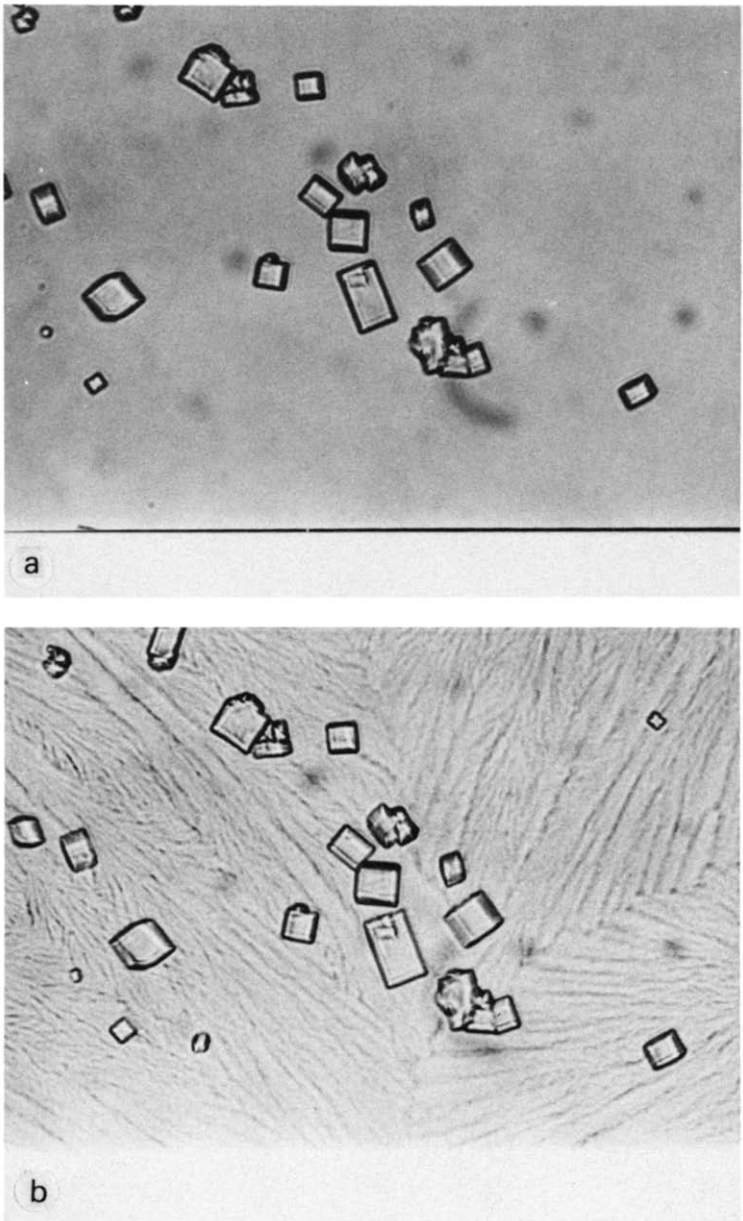

Fig. 7. Microphotographs of solid dispersion of 50 wt.% Diazepam–poly(ethylene glycol) 6000: a, fusion (×400); b, solidification (×400).

rapid dissolution of the active principle, poorly soluble in water, by solid dispersion in an easily soluble carrier. This fact, in general, is attributed to the formation of very fine drug particles during solidification of the eutectic melt [4], as shown in Fig. 8. The above result confirms the data obtained for

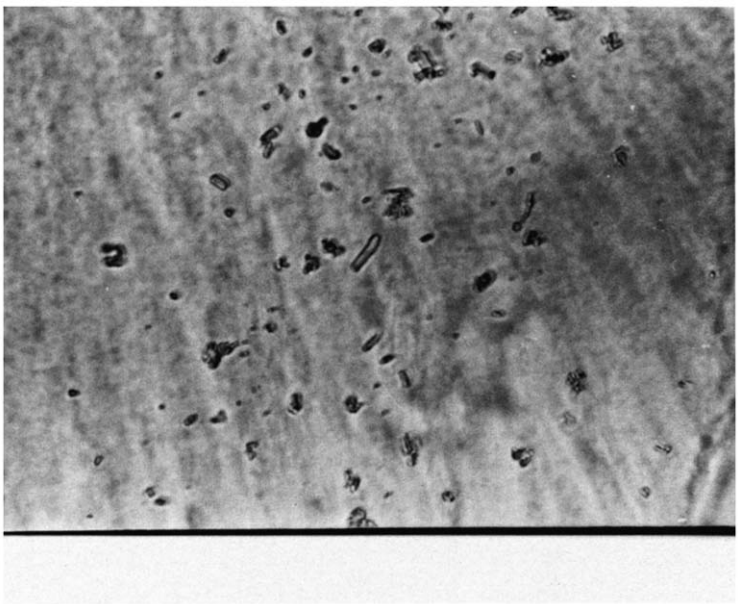

Fig. 8. Microphotograph of 10 wt.% solid dispersion of Diazepam after solidification ($\times 400$ for comparison).

10 wt.% Diazepam by using Tamman's triangle (Fig. 5) and the suggested phase diagram (Fig. 4).

Further experimental work is being performed on the dissolution processes of this solid dispersion, which are of great pharmocological interest.

CONCLUSIONS

Thermal analysis of solid dispersions of the Diazepam–poly(ethylene glycol) 6000 system suggested that a simple eutectic is formed close to the melting point of pure poly(ethylene glycol) 6000. From these results, a DZ–PEG 6000 phase diagram was proposed, although the determination of the eutectic point could not be precise. The extrapolated values are 87 wt.% PEG 6000 and 13 wt.% of the drug. This is in accordance with the Tamman's triangle constructed from the DTA data.

The drug becomes very finely dispersed due to the formation of very fine particles during solidification of the melt, as demonstrated in the microscopic study.

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