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THERMAL STUDY OF THE POLYETHYLENEGLYCOL 6000-TRIAMTERENE SYSTEM

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This paper examines binary polyethyleneglycol (molecular weight 6000)-Triamterene (PEG 6000-T) solid dispersions (5–40 w/w% of T) prepared by the fusion carrirer method, and physical mixtures (5–90 w/w% of T) are studied using DSC and Hot Stage Microscopy (HSM). The use of these combined techniques allows to explain the thermal behaviour on the basis of dissolution of T in the liquid carrier according to the progressive disappearance of the original crystals over a wide range of temperatures (ca. 100°C). The above fact, and possibly the sublimation of T, also could explain that at low T content (≤ 30 w/w%), DSC curves exhibited only a single endothermic peak and/or weak endothermic peaks. On the basis of DSC data, a tentative phase diagram of this system is proposed.

Keywords: DSC, phase diagram, Hot Stage Microscopy, polyethyleneglycol 6000–triamterene system

Introduction

Triamterene (T) is a pteridine derivate, potassium-sparing diuretic with melting point of 327°C. It is practically insoluble in water (45 μg/ml) and very slightly soluble in alcohol [1]. This limited aqueous solubility in gastrointestinal fluids may create variations in its dissolution rate, and consequently in its bioavailability [2]. For all these reasons, new processing methods to increase the

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solubility and dissolution rate of this kind of hydrophobic drug have been proposed in the pharmaceutical literature. The preparation of drugs as inclusion compounds (using cyclodextrins) [3] and solid dispersion techniques [4–6] has been proposed. Solid dispersion systems are formed by both, one or several active principles dispersed in one or several water-soluble inert carriers that act as excipients. In a solid dispersion the drug particles or drug molecules are homogeneously distributed in a matrix by a special preparation technique. The selection of the carrier and the method of preparation plays a key role in determining the properties of the resultant solid dispersion. The fusion process (cofusion of drug and vehicle or carrier), is technologically the least difficult method to prepare dispersions provided the drug and carrier are miscible in the molten state. When the drug shows a high melting point, such as T [7], the fusion carrier method is the most indicated. In this case, the vehicle is melted before the drug is additioned. Thus the degradation of vehicle by thermal treatment is avoided.

On the other hand, many substances can be applied as carriers to prepare solid dispersions. Polymers as polyethyleneglycols (PEGs) have been extensively used as carriers for solid dispersions due to their low melting point, rapid solidification rates, capability of formation of interstitial solid solutions, low toxicity and low cost [8].

In the present paper, a preliminary study on the binary system PEG 6000-T has been carried out using DSC and HSM. The use of these combined techniques has allowed to examine their physicochemical interactions. Using the DSC data, a tentative phase diagram of this system has been proposed. These results are of great interest in the pharmaceutical technology, in the preparation of solid dispersions, and in the further processing of this drug.

Experimental

Materials and procedure

Micronized T (2,4,7-triamino-6-phenyl-pteridine) was provided by Laboratories Miquel S. A. (Barcelona, Spain) and used as received. Commercial PEG 6000 was supplied by Acofar (Barcelona, Spain). Both compounds were of pharmaceutical grade.

PEG 6000-T solid dispersions were prepared by melting the carrier and adding amounts of T corresponding to 5–40 w/w%. PEG 6000 was gradually heated up to 70°C in a small porcelain cup, with constant stirring, employing a magnetic stirrer heater (Selecta Agimatic S-243 model). When the carrier appeared completely melted, the drug was added. Once the melt was homogeneous, the melted mixture

was cooled and solidified rapidly by placing the dish on ice-water. After cooling, the solid was ground and sieved. The fraction under 270 mesh was selected for further study. It was only possible to prepare PEG 6000-T solid dispersions up to 40% w/w because of the lack of homogeneity of the dispersions observed over this percentage.

Physical mixtures were prepared by simple intensive mechanical mixing of the two components previously sieved (under 270 mesh) in 5–90% w/w compositions. These physical mixtures were tested for comparison with solid dispersions.

Methods

DSC curves were obtained in air on a Mettler DSC equipment (model Mettler FP85), by heating from 30° to 360°C at 10 deg·min^{-1}. Finely powdered samples of 10 mg were weighed (± 0.1 mg and encapsulated in flat-bottomed aluminium pans of 45 µl volume with crimped-on lids. Heats of fusion were determined following calibration with indium (28.4 J/g) using integration of the areas under the DSC endothermal peaks of melting.

Different observations were made during heating using a hot stage microscope (HSM Mettler model FP82HT). Approximately 0.1 mg of samples (solid dispersions and physical mixtures) were placed on glass slides with coverglass and heated at 5 deg·min^{-1}.

Results and discussion

Figure 1 shows the DSC curves of PEG 6000-T solid dispersions up to 40 w/w% T. The DSC curves corresponding to physical mixtures (5–90 w/w%) are shown in Fig. 2. Pure T and PEG 6000 melt at 342.6° and 77.8°C (peak temperature), respectively, using a heating rate of 10 deg·min^{-1}. It can be observed that up to 30% w/w of T, both sets of DSC curves show only a single endothermic effect associated with the melting of the composition since no additional endothermal effects were detected. A variation in peak temperature is observed, starting from 77.8°C (Pure PEG 6000) and decreasing to 72.4°C in solid dispersions and 74.1°C in physical mixtures, both at 40% w/w T. The lowest melting point of these compositions is 63°C at 95% w/w T. At the same time, the intensity of this thermal event decreases progressively with increasing T content. In the zone 40–60% w/w T (physical mixtures), the first endothermic DSC effect is accompanied by a weak effect detected at ca. 308°C at 40%. This effect becomes more intense and centered at 316°C when the amount of T is 60%.

It is interesting to point out that a weak inflection or endothermic change in the base line is detected at ca. 160°C in pure PEG and at different compositions

up to 60% T. Furthermore, when the T content is 70%, an exothermic DSC effect is detected at 180°C, with no weight loss indicated by TG, close to the temperature region where the above thermal event is observed. This result can be interpreted in terms of a reaction between the polymeric chains of PEG 6000 and the triamterene molecule producing a complex, its formation being only observed at high T content (over 60%). It has already been reported that drug molecules interacted with repeating units of $-CH_2-CH_2-O-$ in the PEG molecule [9].

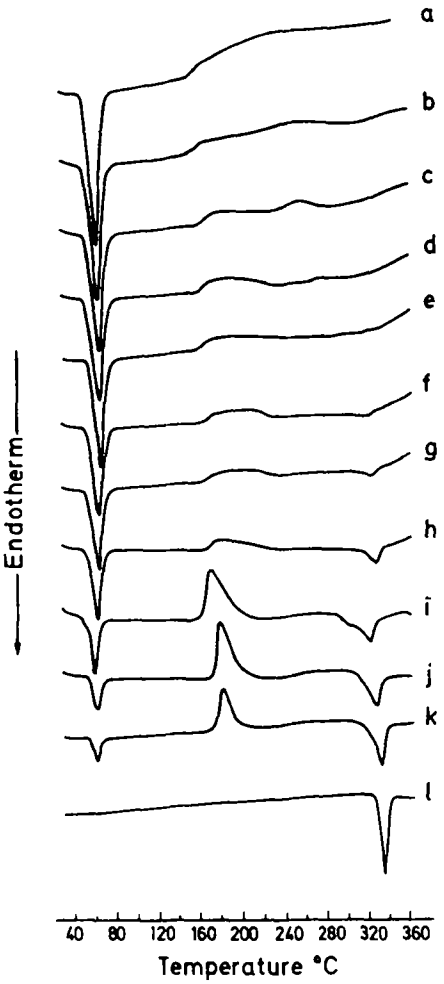

Fig. 1 DSC curves of PEG 6000 (a), solid dispersions of 5% (b), 10% (c), 20% (d), 30% (e) and 40% w/w triamterene (f), and pure triamterene (g)

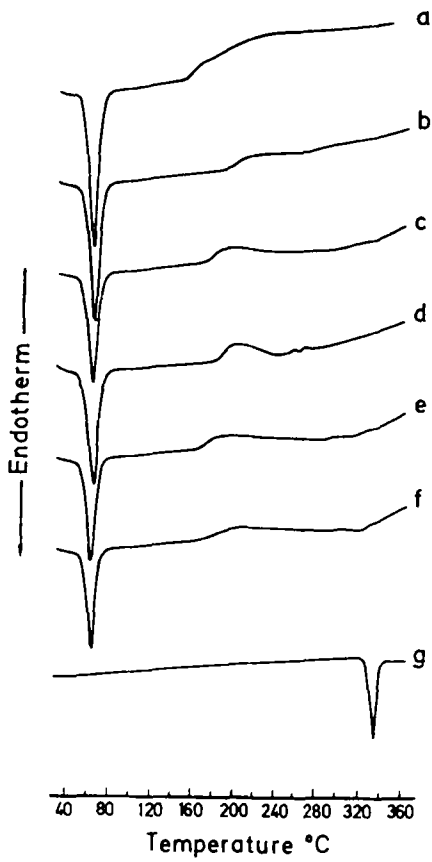

Fig. 2 DSC curves of PEG 6000 (a), physical mixtures of 5% (b), 10% (c), 20% (d), 30% (e), 40% (f), 50% (g), 60% (h), 70% (i), 80% (j), 90% w/w triamterene (k), and pure triamterene (l)

An endothermic DSC effect centered at 323°C close to the melting point of T is observed from 90% to 40% T (the last centered at 308°C), being an indication of the existence of a liquidus zone between T and PEG 6000 at high T content. This effect is accompanied by a shoulder detected at 70% T and centered at ca. 300°C.

It is worth noting that no important differences in DSC curves can be observed between solid dispersions (up to 40% T) and physical mixtures despite the former being previously prepared by a fusion method at temperature slightly higher than the melting point of pure PEG 6000. This processing method produces apparently a better homogeneity and dispersion of the drug particles in the vehicle than the

simple mechanical mixing. However, a lack of homogeneity was observed visually when the preparation of solid dispersions over 40% w/w T was attempted.

Figure 3 shows a plot of heats of fusion corresponding to excess of PEG 6000 (first endothermic DSC effect in solid dispersions and physical mixtures) as a function of composition. Scattered values of heats of fusion were found in the case of solid dispersions. An inverse linear relationship between both parameters was obtained in the case of physical mixtures with a good correlation coefficient ($r = 0.9946$). A similar representation of heats of fusion corresponding to the thermal events detected in the zone 280°–360°C, however, did not show a similar linear relation.

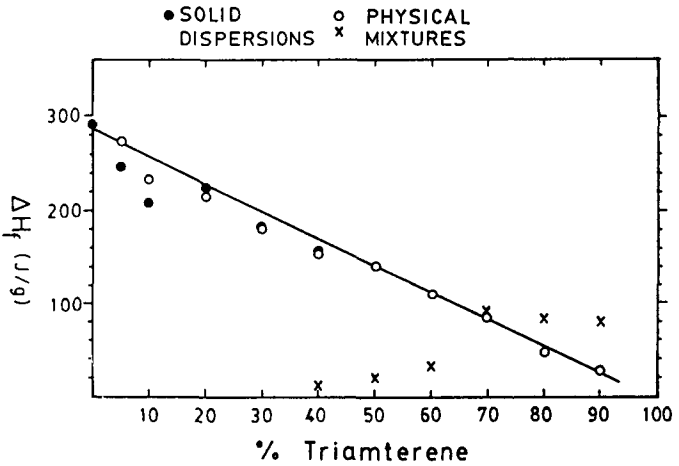

Fig. 3 Heats of fusion of PEG 6000–triamterene solid dispersions and physical mixtures (from DSC data) plotted as a function of triamterene content

Different compositions were studied by HSM, although only selected results will be presented here. HSM micrographs of solid dispersion 5% and 40% w/w triamterene are shown in Fig. 4 and 5, respectively. Initially, the identification of drug particles in the solid dispersions was not possible by optical microscopy because they are strongly masked by the unmelted carrier. After dynamic heating at 60°C, the carrier melts and small and larger vesicles are observed (Fig. 4a). This process allows the crystalline particles (T) to be easily detected by microscopy. Heating at temperatures higher than 120°C (Fig. 4b) produces a partial dissolution of the crystals entrapped inside the liquid vesicles. This dissolution process is broader as the temperature increases, as observed by HSM (Fig. 4c), producing a single liquid phase enriched in T.

For greater drug proportion (40%), the dissolution process is partial because at temperature near 250°C the vesicles of melted carrier were observed progres-

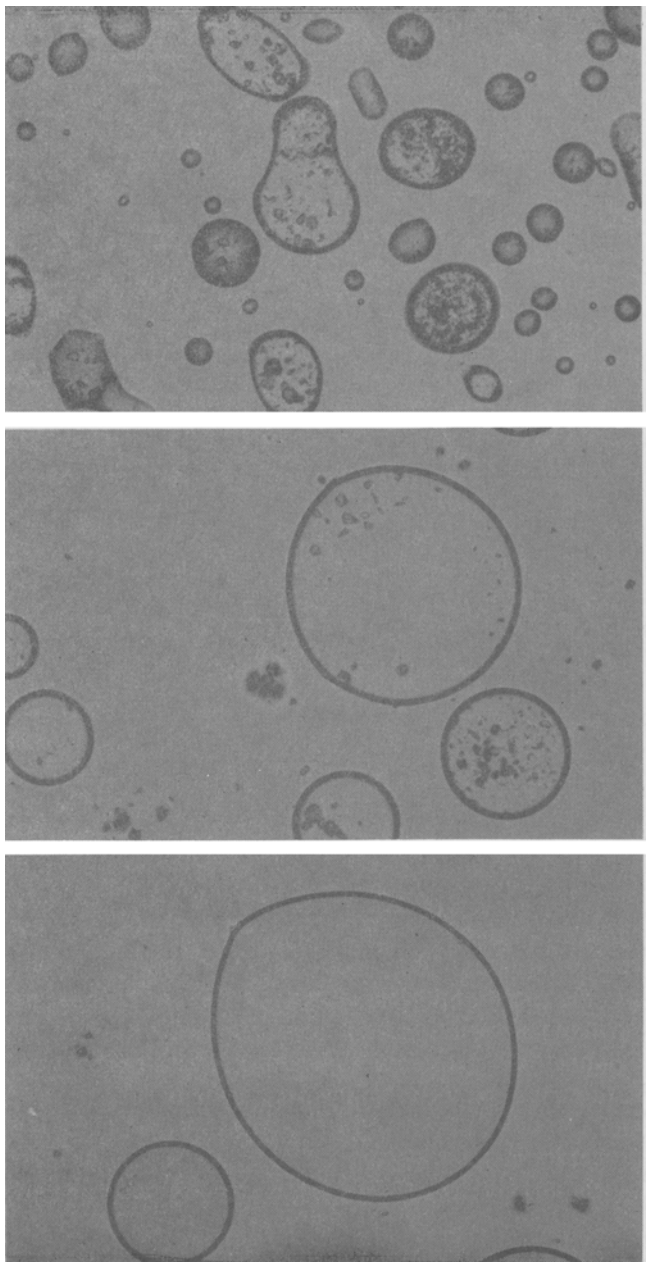

Fig. 4 HSM micrographs of 5% w/w triamterene solid dispersion after heating at 60°C (a), 120°C (b) and 200°C (c)

sively to darken (Fig. 5). This fact is attributed to the degradation of the polymer on heating. Then, the dissolution process seems to be hindered and crystals of T are detected up to the melting point. In addition, it was observed using a microscope slide without cover glass that pure T undergoes partial sublimation in the zone around the melting temperature, in accordance with literature data [10].

Although the thermal behaviour is complex, the above results seem to be in accordance with the DSC curves of solid dispersions (Figs 1 and 2), which showed several thermal effects associated with a partial melting process detected by HSM and the uncertainty of the eutectic. This behaviour also could explain the trend observed in the heat of fusion values as a function of T content (Fig. 3).

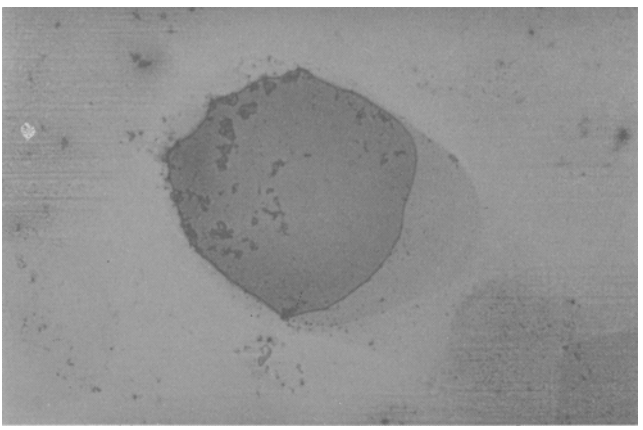

Fig. 5 HSM micrographs of 40% w/w triamterene solid dispersion after heating at 250°C

According to DSC results, a tentative phase diagram of the binary system T-PEG 6000 is included in Fig. 6. In this diagram, all the compositions show a melting point approximately constant in the range 78°–63°C, corresponding to the first endothermic DSC peak (Fig. 2). The liquidus temperatures increase as the proportion of drug increases. However, the exact position of the eutectic (temperature and composition) remains uncertain.

In a previous study [10], it has been proposed on the basis of DTA and HSM results that the phase diagram of PEG 6000–T solid dispersions shows a monotectic. However, solidus temperatures were determined by DTA (the upper temperature of DTA runs was reported as 170°C), and liquidus temperatures by HSM, showing no variations in temperature at decreasing T content. The results reported here by DSC up to 360°C studying physical mixtures indicate that there is a slight decrease in liquidus temperatures in this particular binary system.

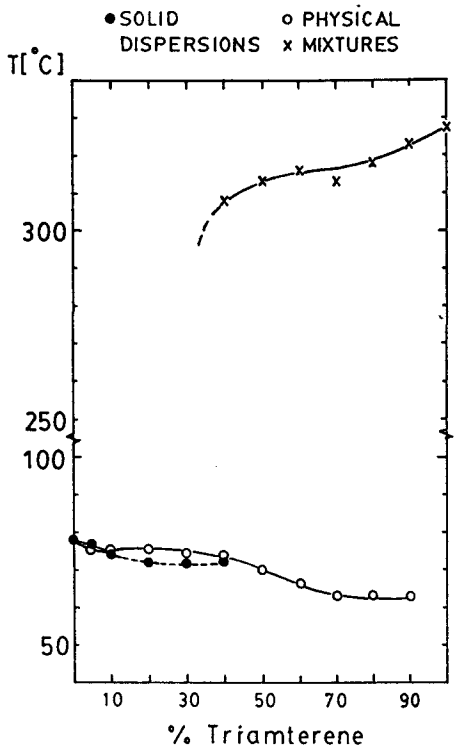

Fig. 6 Phase diagram of the PEG 6000–triamterene binary system

Concluding remarks

Thermal analysis by DSC has been widely used in the pharmaceutical technology to the determination of solid-liquid equilibria, and in many other studies (solid solutions, solid dispersions, purity determinations, interactions, etc). However, there are systems where the thermal information provided by DSC must be considered with special attention. This is the case of the binary system PEG 6000–T, because there is a partial dissolution process of T in the vehicle detected by HSM, which is not detected using DSC. Thus HSM is a complementary technique to investigate the thermal behaviour in these kinds of systems and to know the dissolution phenomena of drugs in vehicles, but the phase diagrams obtained using this technique are to be carefully established.

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Zusammenfassung — Es werden binäre Polyethylenglycol-(Molekülgewicht 6000)-Triamteren (PEG 6000-T)-Feststoffdispersionen (5–40 m% T) im Schmelz-Carrier-Verfahren hergestellt und physikalische Gemische (5–90 m% T) mittels DSC und Hot Stage Mikroskopie untersucht. Die Anwendung dieser kombinierten Techniken erlaubt die Erklärung des thermischen Verhaltens auf der Grundlage des Auflösens von T im flüssigen Carriermaterial, entsprechend dem progressiven Verschwinden der Originalkristalle in einem breiten Temperaturbereich (ca. 100°C). Diese Tatsache sowie möglicherweise auch die Sublimation von T kann eine Erklärung dafür bieten, daß DSC-Kurven bei niedrigem T-Gehalt (30 m%) nur einen einzigen endothermen Peak und/oder schwache endotherme Peaks aufweisen. Ausgehend von den DSC-Angaben wurde ein vorläufiges Phasendiagramm dieses Systemes erstellt.