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Dedicated to Professor Lisa Heller-Kallai on the occasion of her 65th birthday

THERMAL ANALYSIS OF THE SYSTEM TRIAMTERENE–*D*-MANNITOL

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Abstract

Thermal analysis (DSC and HSM), and equilibrium solubility determinations were carried out to elucidate the mechanism of interaction at the solid state in the binary system triamterene–*D*-mannitol. Physical mixtures (5–90% w/w triamterene) and solid dispersions (5 up to 40% w/w triamterene) were prepared and studied.

From DSC and HSM results, the thermal changes were associated with the variations in composition of the binary mixture, being more pronounced in the range 20–50% w/w. The binary phase diagram was proposed, although the exact position of the eutectic was uncertain. This is in accordance with a partial dissolution process detected by HSM.

A linear increase in the solubility of triamterene with increasing aqueous mannitol concentration was obtained. The thermodynamic parameters of the solution properties were calculated, with an activation energy value of 96.081 kJ/mole. The solubilization increase was associated with complexation processes and hydrogen bonding formation.

Keywords: DSC, DTA, Hot Stage Microscopy, thermodynamic parameters, triamterene–*D*-mannitol

Introduction

Solid dispersions play an important role in increasing the solubility, dissolution rate, absorption and therapeutic efficacy of many drugs, especially those poorly soluble in water [1]. 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 have an

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important influence on the properties of the resultant solid dispersion. The fusion process is technically the least difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. However, when the drug shows a high melting point, the fusion carrier method is the most feasible. This is the case of triamterene [2].

Triamterene is a pteridine derivate, potassium-sparing diuretic. It is practically insoluble in water (45 μg/ml) and very slightly soluble in alcohol [3]. This limited aqueous solubility in gastrointestinal fluids may create variation in its dissolution rate, and consequently in its bioavailability [3]. For all these reasons, triamterene is an adequate drug for manufacturing as a solid dispersion system.

Many substances have been recommended as carriers for solid dispersions. One of these is *D*-mannitol, a vehicle often employed due to its low toxicity, high aqueous solubility and physiological tolerance. Additionally, its good flow and compression properties make this a very suitable vehicle for formulations into dosage forms [5].

Several thermal methods are available for determining the physical nature of solid dispersion systems. Thermal analyses by DTA, DSC and Hot Stage Microscopy (HSM) have proved to be powerful tools in evaluating the drug – vehicle interactions [6–8].

In this paper, a preliminary study of the binary system triamterene–mannitol has been carried out using DSC and HSM, examining the physicochemical interactions of these two components. Since it is of interest to know the solubilizing effects of carriers, the solubility of triamterene in aqueous mannitol solutions was also studied in order to evaluate the role of solubilization in the enhancement of drug dissolution. The stability constants and the thermodynamic parameters of this process were thus calculated.

Experimental

Materials

Micronized triamterene (2,4,7-triamino-6-phenyl-pteridine) was provided from Laboratories Miquel S. A. (Barcelona, Spain) and used without further purification. Commercial *D*-mannitol of pharmaceutical grade was supplied by Acofar (Barcelona, Spain).

Preparation of the samples

Triamterene–mannitol solid dispersions were prepared by melting the carrier and adding amounts of triamterene corresponding to 5, 10, 15, 20 and

40% w/w. *D*-Mannitol was gradually heated up to 165°C (this temperature is slightly higher than the reported melting point of the compound) 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 obtained melt was homogeneous, the melted mixture was cooled and solidified rapidly by placing the dish in ice-water. After cooling, the obtained solid was ground and sieved. The fraction under 270 mesh was selected.

It was only possible to prepare triamterene-mannitol solid dispersions up to 40% w/w because of the lack of homogeneity of the dispersions above this concentration.

Mechanical mixtures (thereafter "physical mixtures") were prepared by simple intensive 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.

Thermal analysis

The chemical stability of the drug after elaboration of solid dispersions and the physical nature of solid–solid interactions were tested by DSC and HSM. This information was used to construct the corresponding phase diagram. Thus, HSM was used as a complementary technique in the present study.

Differential scanning calorimetry

Samples of 10 mg were exactly weighed (±0.1 mg) after being finely powdered and encapsulated in flat-bottomed aluminium pans of 45 µl with crimped-on lids. The DSC curves were obtained in air on a Mettler DSC equipment (model Mettler FP85), by heating from 120 to a 360°C at 10 deg·min^{-1}.

Heats of fusion were determined following calibration with indium using integration of the areas under the melting DSC endotherms.

Hot Stage Microscopy

Approximately 0.1 mg of samples (triamterene, *D*-mannitol solid dispersions and physical mixtures) were placed on glass slides with coverglass and heated at the rate of 5 deg·min^{-1}.

Different observations were made during heating using a hot stage microscope (Model Mettler FP82HT). Thus, the temperature at which melting started (thaw point) and the temperature at which complete melting was affected (melting point), were determined by visual observation. These two temperatures

were used to define the melting point range of different samples. Runs were made in triplicate.

Solubility studies

Solubility studies were performed to determine the extent of interaction between triamterene and *D*-mannitol in aqueous solution, and to calculate the thermodynamic parameters (stability constants, free energy change, activation energy and entropy change).

For this purpose, an excess of triamterene was placed in glass Erlenmeyer flasks containing 20 ml of deionized water or aqueous solutions of different concentrations of *D*-mannitol. The solutions, in stoppered glass Erlenmeyer flasks, were continuously shaken in a water bath at 25 and 37°C for 4 days. After this period, the solutions were filtered through Pyrex number 4 sintered glass. The filtrate was analyzed spectrophotometrically (Spectrophotometer Hitachi model U-2000) to determine the amount of dissolved drug (wavelength: 357 nm). A calibration was performed previously.

Results and discussion

Differential scanning calorimetry curves

Figure 1 shows the DSC curves of triamterene–mannitol solid dispersions up to 40% w/w triamterene prepared according to the procedure described in the experimental section.

Pure triamterene and mannitol melt at 342.6 and 183°C, respectively, under our experimental conditions (heating rate 10 deg·min^{-1}). Solid dispersions of 5–15% w/w triamterene show several weak endothermal effects in the 320–360°C zone. These effects become a single weak endothermal effect at 20% w/w triamterene, i.e., as mannitol content decreases. Thus, at 40% w/w that effect disappears, and a new broad weak endothermal effect begins to be detected centered at ca. 250°C. The absence of such a thermal effect at 40% w/w triamterene and the formation of a small broad endotherm centered at 250°C may indicate an interaction between both kinds of compounds, one with different $-NH_2$ groups (triamterene) and the other one with several –OH groups [5].

However, it is interesting to point out that no variations are observed in the first melting peak of these solid dispersions. That effect is close to the melting DSC effect of pure mannitol, and its intensity (as peak areas) seems to decrease as triamterene content increases.

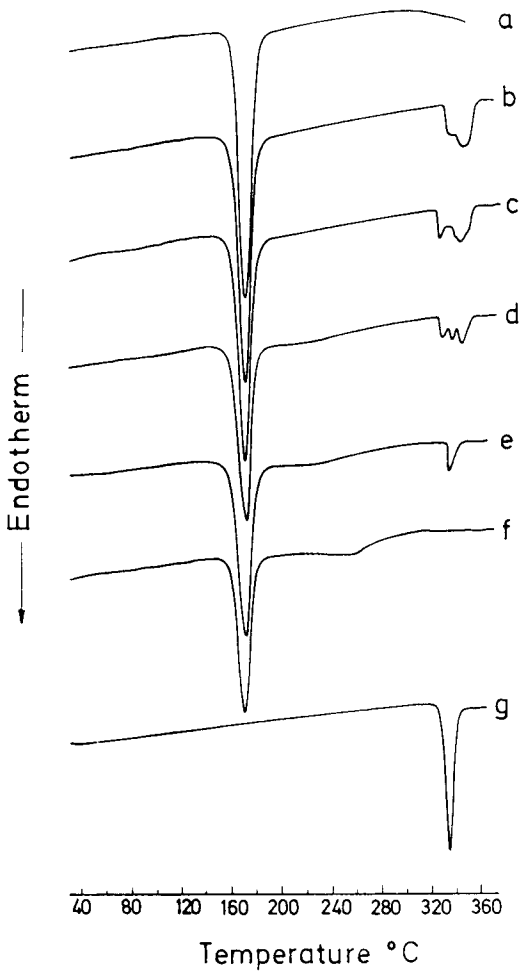

Fig. 1 DSC curves of mannitol (a), solid dispersions of 5% (b), 10% (c), 15% (d), 20% (e) and 40% w/w triamterene (f) and pure triamterene (g)

The DSC set of curves corresponding to physical mixtures triamterene–mannitol is shown in Fig. 2. As compared with the DSC curves of Fig. 1, some variations are observed up to 40% w/w triamterene. Thus, weak endothermal effects also appear in the 320–360°C zone, although more overlapped in DSC curves of physical mixtures. Two effects are detected at 20% w/w triamterene, in contrast with that observed at the same concentration as a solid dispersion. These differences can be attributed to the fact that the solid dispersions were prepared according to a fusion method at temperatures slightly higher than the melting point of mannitol. When this compound appeared to be completely

melted, triamterene was added. This processing method produces a better homogeneity and dispersion of drug particles in the vehicle that the simplest mixing by mechanical physical methods. In this sense, pure mannitol exhibits a sharp melting endotherm, as shown in Fig. 1, and no apparent decomposition up to at least 300°C can be observed. This is beneficial because the melting points of carbohydrates commonly used as drug carriers, are not usually sharp and undergo decomposition reactions [9].

Returning to Fig. 2, a weak DSC endotherm is detected at 40% w/w triamterene physical mixture, in accordance with the analogous thermoanalytical curves of a solid dispersion (Fig. 1). That thermal effect increases in intensity and peak temperature as triamterene content increases, and becomes greater in intensity at 90% w/w.

It is also detected a variation in the temperature position (peak maximum) of the thermal effect corresponding to the first endothermic DSC effect (first appearance of liquid), and a decrease in its intensity, both with increasing triamterene content. It is difficult to explain the variation observed in peak temperature. Mannitol is stable above its melting point up to temperatures in excess of 300°C. Nevertheless, some differences in melting temperatures have been reported [10].

In the same sense, the interaction of –OH structural groups present in mannitol with the $-NH_2$ groups of triamterene could be influencing the thermal behaviour of the solid dispersions, especially with increasing triamterene content. The drug particles are assumed to be well distributed homogeneously in the carrier matrix.

From the above DSC results, it is clear that thermal changes are associated with the variations in composition of the binary mixture. The most important thermal variations are observed in the range of 20–50% w/w triamterene.

Heats of fusion

The endotherm areas of DSC curves (Figs 1 and 2) were used to calculate the heats of fusion of the triamterene-mannitol binary mixtures.

An inverse linear relationship between heats of fusion corresponding to an excess of mannitol (first endothermic DSC effect) as a function of composition was obtained, as shown in Fig. 3. A good correlation coefficient was obtained ($r = 0.9969$).

A similar representation of heats of fusion corresponding to the thermal effects detected in the 240–360°C zone, however, did not show a similar linear variation. The experimental points are dispersed. Several explanations can justify this behaviour. First of all, the heats of fusion correspond to different thermal effects that were neglected in the calculations, in contrast with those

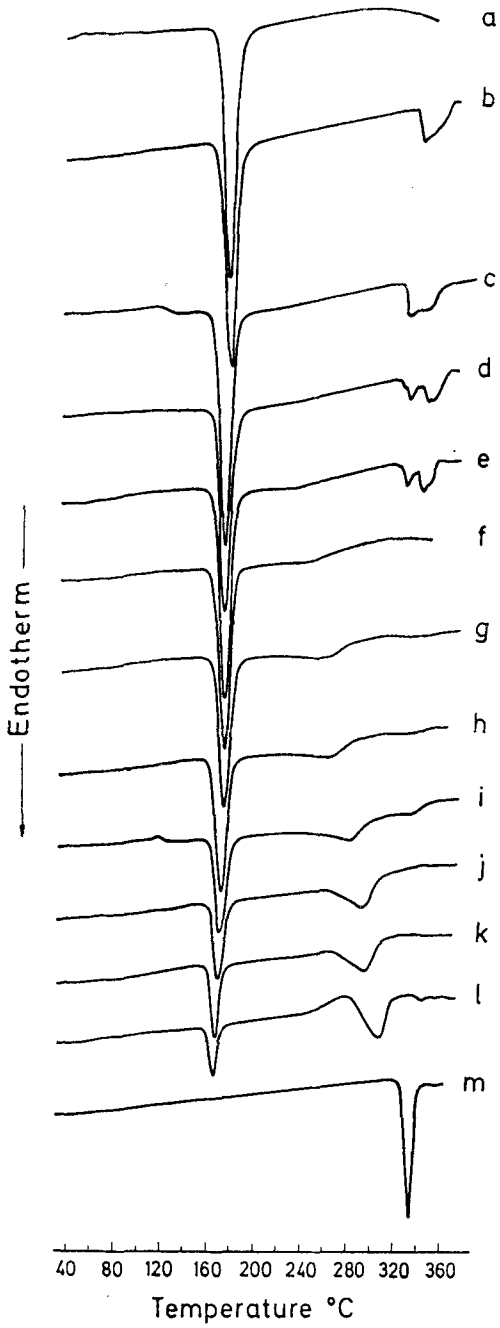

Fig. 2 DSC curves of mannitol (a), physical mixtures of 5% (b), 10% (c), 15% (d), 20% (e), 30% (f), 40% (g), 50% (h), 60% (i), 70% (j), 80% (k), 90% w/w triamterene (l); and pure triamterene (m)

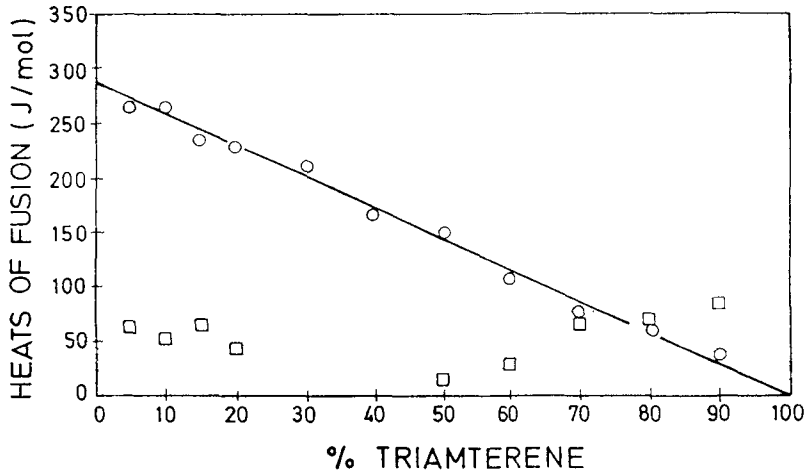

Fig. 3 Heats of fusion of triamterene–mannitol physical mixtures (derived from DSC data) plotted as a function of triamterene content

calculated from the first single endothermic effect. Secondly, these effects are broader than those corresponding to excess mannitol, making it difficult to determine accurate peak areas. In the same sense, the exact position of the eutectic is uncertain. Consequently, HSM technique was used to obtain more information about the thermal behaviour of this binary system.

Hot Stage Microscopy

Although different compositions were studied by HSM, only selected results will be presented in this section. Figure 4 shows a micrograph corresponding to original micronized triamterene particles (as received) unmelted. The average particle size of this powdered material is low, and crystalline appearance is observed.

Solid dispersion 20% w/w triamterene HSM micrographs are shown in Figs 5 and 6. 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 (Fig. 5a), in contrast with the results showed in Fig. 4. After dynamic heating at 200°C, the carrier melts and both small and larger vesicles are observed (Fig. 5b), probably originated by a surface tension phenomenon. This process enables the crystalline particles (triamterene) to be easily detected by microscopy. At this point, the crystalline particle size is slightly smaller compared to the original product (Fig. 4). The vesicles contain liquid and crystalline particles inside which seem to be of larger particle size when compared with that observed initially (Fig. 4).

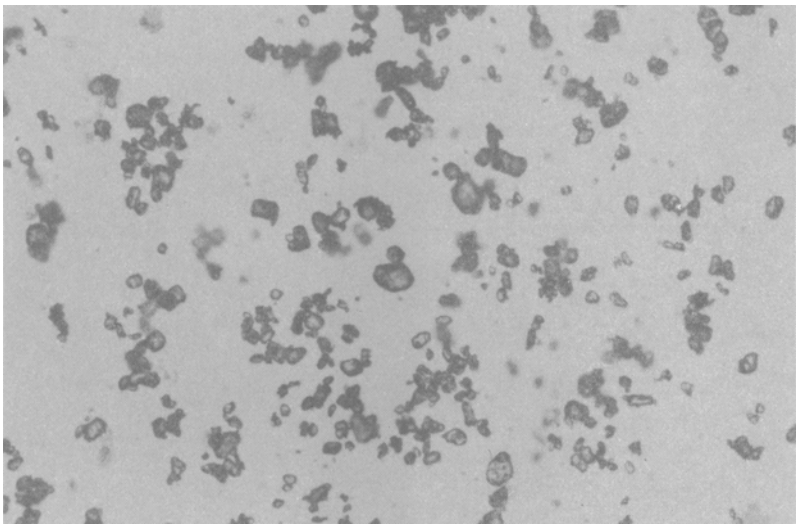

Fig. 4 Micrograph of original triamterene particles (as received)

Heating at higher temperatures (Fig. 6a) produces a partial dissolution of the crystals entrapped inside the liquid vesicles, and liquid viscosity presumably decreases. This dissolution process is broader as temperature increases, as observed by HSM (Fig. 6b), producing a single liquid phase rich in triamterene. Few of crystals are observed outside the vesicles containing liquid (Fig. 6b). Similar observations were made at different solid dispersion compositions.

Although the thermal behaviour is complex, the above results are in accordance with solid dispersion DSC curves (Fig. 1), which show several thermal effects associated with partial melting processes detected by HSM and the uncertainty of the eutectic. This behaviour also may explain the evolution observed in heat of fusion values as a function of triamterene content, the only linear zone corresponding to mannitol excess.

No important differences were observed studying physical mixtures by HSM.

Phase diagrams

According to DSC and HSM results, a tentative phase diagram of the binary system triamterene–mannitol is shown in Fig. 7.

In this diagram, all the compositions show a melting point approximately constant in the range of 183–170°C, corresponding to the first endothermic DSC peak (Fig. 2) and the first appearance of liquid by microscopical observa-

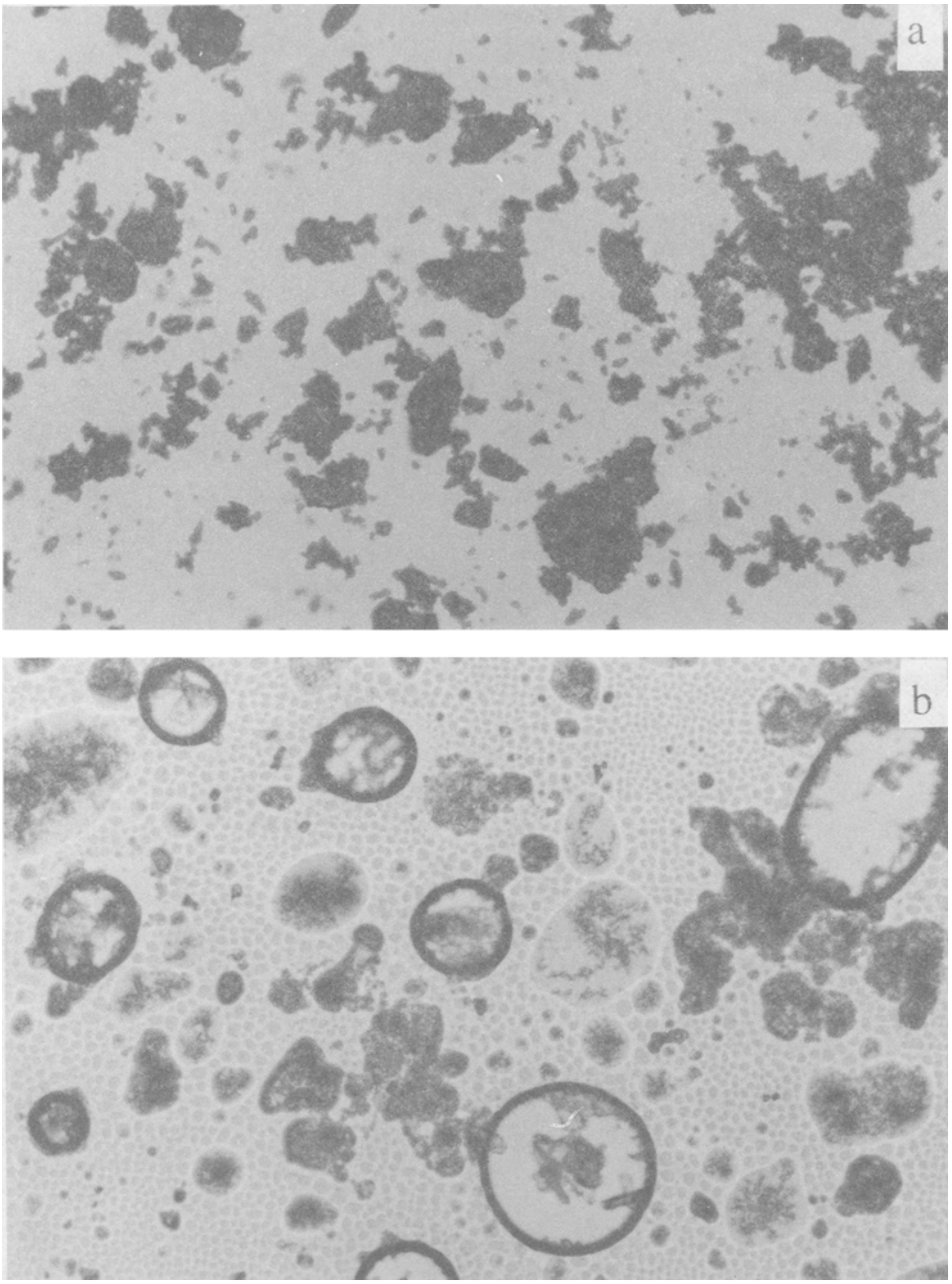

Fig. 5 HSM photos of 20% w/w triamterene solid dispersion at 150°C (a), and 200°C (b)

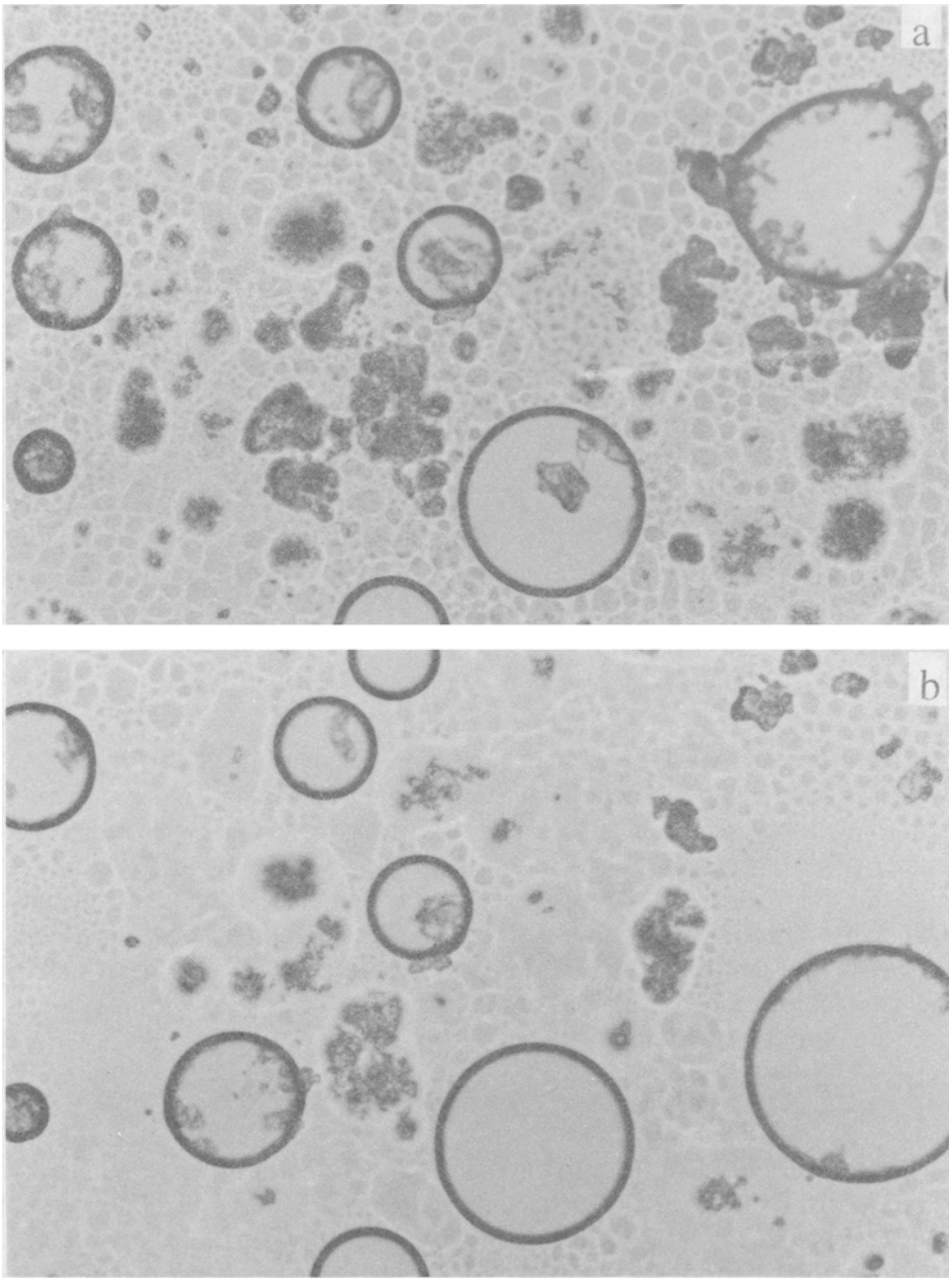

Fig. 6 HSM photos of 20% w/w triamterene solid dispersion at 225°C (a), and 235°C (b)

tion (Fig. 5). The liquidus point, defined as the temperature above which no more crystals are visible by HSM, increases, as the proportion of drug increases.

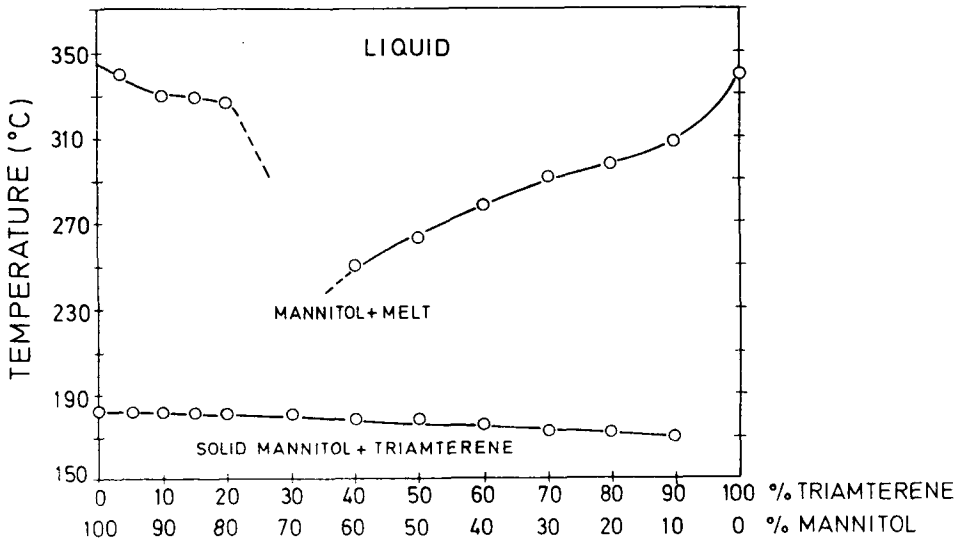

Fig. 7 Phase diagram of the triamterene–mannitol binary system

Two different zones can be distinguished in the phase diagram: (i) zone up to 20% w/w triamterene, with slight diminution of liquidus temperature with increasing triamterene content, and (ii) zone from 40% w/w triamterene, with an increasing of liquidus temperature from 250°C, as shown by the DSC curves (Fig. 2). The exact position of the eutectic (temperature and composition) remains uncertain. However, the eutectic zone is around 20–40% w/w triamterene because of the formation of a single DSC peak at 30% w/w (Figs 1 and 2) and the lack of a line of liquidus at 40% w/w, in accordance with that found studying other binary systems [11].

Solubility study

In order to elucidate the participation of the different thermodynamic parameters in the solubilization of triamterene by aqueous mannitol solutions, and to determine the extent of interaction between both compounds, two solubilization tests were performed at 25 and 37°C. Figure 8 shows the experimental data. Some kind of interaction is evident from the linear increase in the solubility of triamterene when mannitol concentration is increased in aqueous solutions, appreciated as indicated by the increase of aqueous solubility. It is also

clear that solubilization of triamterene in different aqueous mannitol concentrations increases significantly when the carrier concentration and the temperature of the experiment is increased.

The straight lines were adjusted by the least squares method. The linear correlation coefficients were 0.9757 at 25°C and 0.9860 at 37°C valid above 0.1 mol/l mannitol.

The slope, stability constant (K_a) of a 1:1 complex between triamterene and mannitol, and the thermodynamic parameters of interaction are given in Table 1. The results at 25°C indicate that the solution process is not spontaneous, being controlled by the enthalpy, which is positive and is accompanied by a positive entropy. Firstly, this suggests that solubility is achieved primarily in mannitol solutions through a mechanism of water-structure disordering, as proposed previously in analogous binary systems [12]. Secondly, the negative ΔG value at 37°C reveals a spontaneous process. However, the stability constants (K_a values, Table 1) show that complexation also plays a role in the promotion of increased solubility of triamterene under our experimental conditions. Thus, increasing temperature from 25 to 37°C leads to an increase of more than four times the value of K_a, and a negative value of ΔG.

Table 1 Thermodynamic parameters of triamterene–*D*-mannitol interactions

Temperature/ °C	Slope×10^{-6}	K_a*	ΔG^x/ kJ·mol^{-1}	$\Delta H^\#$ / kJ·mol^{-1}	ΔS^+ / kJ·mol^{-1}·K^{-1}
25	35.80	0.380	2.383	96.081	0.314
37	88.14	1.718	−1.389	96.081	0.305

*1:1 complex association constant, [13] or stability constant K_a = slope/intercept ×(1-slope), where slope and intercept are obtained from Fig. 8, as described in Ref. [13].

^{x}From $\Delta G = -RT \ln K_a$

$^\#$Activation energy calculated from the equation $\ln K_a(T_2)/K_a(T_1) = \Delta H/R[(T_2 - T_1)/T_2T_1]$, where T_1=298 K, T_2=310 K and R=8.28 J·mol^{-1}·K^{-1}.

$^+$Entropy change calculated according to the standard equation $\Delta G = \Delta H - T\Delta S$.

The positive entropy and activation energy (enthalpy change) are in accordance with the assumption that the enhancement of dissolution of hydrophobic compounds in aqueous mannitol solutions is accomplished by the breaking of the water structure by mannitol due to competitive reactions between solute and solvent molecules [14, 15]. The increase in entropy produced in this process makes the association of non-polar molecules by hydrophobic bonding thermodynamically less favourable. As assumed in similar binary systems [15], the increase of both mannitol concentration and temperature results in an increase of water structure breaking, and creates an energetically more favourable environ-

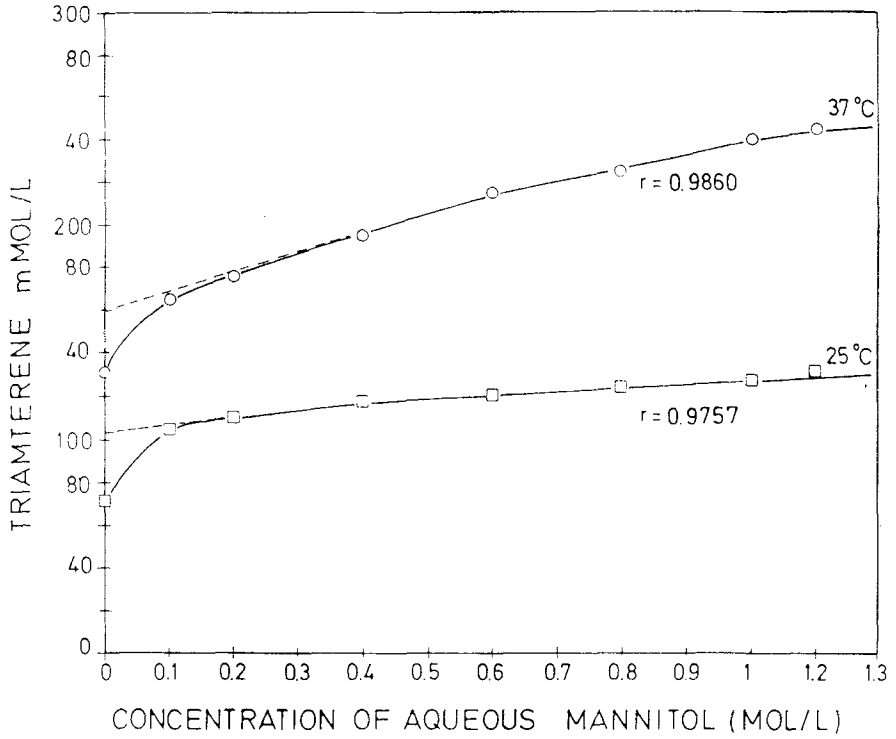

Fig. 8 Solubility of triamterene in aqueous mannitol solutions at 25 and 37°C

ment for hydrophobic solutes, such as triamterene. Note that this drug is practically insoluble in water (45 μg/ml) [3].

The enthalpy of formation of a hydrogen bond is between 12 and 20 kJ/mol. The enthalpy value obtained for the triamterene-mannitol interaction (estimated as 96 kJ/mol) favours the fact that complexation between triamterene and mannitol in water involves hydrogen bond formation. This fact is in accordance with the molecular characteristics of mannitol, with several –OH groups in its structure capable of participating in hydrogen bonding with water and other molecules.

Summary and conclusions

Thermal analysis (DSC and HSM) and equilibrium solubility determinations were used in an attempt to elucidate the mechanism of interaction in the solid state and in solution into the binary system triamterene–mannitol. Physical mixtures (up to 90% w/w) and solid dispersions (40% w/w triamterene) were prepared, the latter by the fusion process. From the DSC results, it was concluded

that the thermal changes were associated with the variations in composition of the binary mixture, being more important in the range of 20–50% w/w triamterene. A linear relationship between heats of fusion, corresponding to an excess of mannitol, as a function of composition was obtained. HSM was used as a complementary technique in this thermal study and also provided information on the thermal behaviour of the system. A partial dissolution process was detected by this technique.

Taking into account the above results, a tentative phase diagram of the binary system triamterene–*D*-mannitol was proposed. However, the exact position of the eutectic is uncertain, although it is assumed to be around 20–40% w/w triamterene because of the formation of a single DSC endothermal effect at 30% w/w, and the consequent lack of a liquidus line at 40% w/w.

A linear increase in the solubility of triamterene in aqueous mannitol solutions was found at 25°C, but it increased at higher temperatures (37°C). The thermodynamic parameters of this interaction in solution were also obtained, showing an energy of activation value (enthalpy change) of 96.081 kJ/mol. The increase in solubilization was associated to processes of complexation and hydrogen bonding formation.

All the above results are of interest to the pharmaceutical technology, and in further processing of triamterene–*D*-mannitol formulations.

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Zusammenfassung — Zur Bestimmung des Mechanismus der Wechselwirkung im festen Zustand des binären Systemes Triamteren–*D*-Mannitol wurden die Thermoanalyse (DSC und HSM) sowie Bestimmungen der Gleichgewichtslöslichkeit herangezogen. Dafür wurden physikalische Gemenge (5–90 Gew.% Triamteren) und feste Dispersionen (5–40 Gew.% Triamteren) hergestellt und untersucht.

Anhand der DSC- und HSM-Daten wurden die thermischen Veränderungen mit den unterschiedlichen Zusammensetzungen des binären Gemisches in Zusammenhang gebracht, die im Bereich 20–50 Gew.% besonders betont sind. Es wurde ein Phasendiagramm vorgeschlagen, obwohl die exakte Position des Eutektikums unsicher ist. Dies steht in Übereinstimmung mit dem durch HSM nachgewiesenen partiellen Lösungsprozeß.

Mit zunehmender Mannitol-Konzentration erhält man ein lineares Ansteigen der Löslichkeit von Triamteren. Die thermodynamischen Parameter der Lösungseigenschaften wurden mit einer Aktivierungsenergie von 96.081 kJ/mol berechnet. Das Ansteigen der Solubilisierung wird Komplexbildungsprozessen und der Bildung von Wasserstoffbrückenbindungen zugeschrieben.