

Application of Hot Stage Microscopy (HSM) to the thermal study of two binary systems of pharmaceutical interest: Triamterene-Polyethyleneglycol (PEG) 6000 and Triamterene- β -Cyclodextrin

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Hot Stage Microscopy (HSM) is an analytical technique to perform a solid-state physical characterization of materials as a function of temperature. The formulations of poorly water soluble drugs (Triamterene) with hydrophilic carriers (PEG 6000 or β -Cyclodextrin) to obtain solid dispersions or inclusion complex, respectively, have been frequently used to improve their dissolution rate. In order to explain the drug – carrier interactions, the binary systems Triamterene-PEG 6000 and Triamterene- β -Cyclodextrin were studied using HSM and Differential Scanning Calorimetry (DSC).

The results obtained by the HSM study show that although during the elaboration process partial or total dissolution of the drug in melted PEG 6000 was produced, this interaction are not detected by DSC. In consequence, a solid dispersion with low drug proportion would be defined as “solid solution”. The DSC thermogram of Triamterene- β -Cyclodextrin inclusion complex obtained by co-grinding shows a curve with various exothermic and endothermic peaks. The use of HSM as complementary thermal technique aided to explain the nature of these thermal effects.

Keywords: Hot Stage Microscopy; solid dispersions; Triamterene; PEG 6000; β -Cyclodextrin; inclusion compounds; thermal analysis

1. Introduction

A solid dispersion was defined as a dispersion of one or more active ingredients in a carrier or matrix at solid state prepared by the melting, solvent or melting-solvent method [1]. The fusion process is technically the less difficult method of preparing solid dispersions provided the drug and carrier are miscible in the molten state. In this method a mixture of drug and carrier are directly heated to form a co-melt and subsequently cooled. As both drug and carrier are due completely melted, potential problems such as thermal degradation, sublimation, polymorphic transformation, etc. of the drug or vehicle may be occurred when the drug shows a high melting point. In this case, the fusion carrier method can be employed [2, 3]. This is the case of Triamterene.

Basically, the solid dispersions systems obtained can be divided in six major groups: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitation in a crystalline carrier, compound or complex formation and combinations. The physicochemical structure obtained depends of elaboration conditions and plays an important role in controlling the drug release [4-7]. Many methods can be employed to obtain information of the physicochemical nature of a solid dispersion system (DSC, HSM, TG, DRX, IR, RMN) [8, 9]. On most cases, combinations of several methods are required. Moreover, the thermal techniques (DSC and HSM) are frequently employed to establish the phase diagrams, very used in the investigations of the melting properties of the solid dispersions. These diagrams usually indicate the presence of eutectics, monotectics, solid solutions or glasses [10, 11].

The increased dissolution rates from solid dispersions were attributed to different causes. The reduction of particle size of the drug was considered the principal. The particle size reduction to the minimum level (the molecular state) is the most desirable since when the carrier dissolves the drug must go into solution. Molecular dispersion of the drug is obtained in solid and glass solutions and probably in amorphous dispersions. In this last case, the degree of crystallinity (and hence amorphousness) will control dissolution rates. In other cases, the formation of metastable polymorphs form of drug, can be the justification of the increase dissolution rates. Another factor contributing to the increase dissolution from solid dispersions is increase wettability and/or solubility of drug by the hydrophilic or surfactant carriers [12].

Many of the advantages claimed with the solid dispersions derive from their rapid dissolution rate, for example the increase in absorption rates and extents of absorptions, that could be used to decrease the dose of drug administrated. The increased dissolution and associated rapid absorption may reduce the proportion of drug metabolized presystemically. Other advantages claimed for the solid dispersions are probably due to the specific action of carrier, for example the PEGs may protect certain drugs [1, 12].

Cyclodextrins have been extensively applied to improve the solubility, dissolution, stability and bioavailability of poorly soluble drugs. Cyclodextrins are known to form inclusion complexes with a variety of guest molecules in solution and in the solid state, since their inherent annular structure exists stable in both phases [13, 14]. It is known that different methods can be employed for preparing solid drug-cyclodextrin complexes (kneading, co-precipitation, freeze

drying, spray drying, co-grinding and sealed heating), and the choice of the most efficacious one should be carefully evaluated case by case [15, 16].

2. Materials and methods

2.1 Materials

Micronized Triamterene (2, 4, 7-triamino-6-phenyl-pteridine) was provided from 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.

2.2 Preparation of solid dispersions

Triamterene-PEG 6000 solid dispersion was prepared by melting the carrier and adding amounts of Triamterene corresponding to 10 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 obtained melt was homogeneous, the melted mixture was cooled and solidified rapidly by placing the dish on an ice-water. After cooling, the obtained solid was ground and sieved. The fraction under 270 mesh was selected for further study.

2.3 Preparation of inclusion complex

The preparation of Triamterene- β -CD solid complexes (molar ratio 1:1) was performed by grinding. Co-grinding was performed by using an oscillating mill (Herzog HSM 100). The volume of the mill was 300 cm³ and the grinding time 5 minutes.

2.4 Differential Scanning Calorimetry (DSC)

DSC thermograms were obtained in air on Mettler DSC equipment (model Mettler FP85), by heating from 30 °C to a 360 °C at 10 °C/min. Samples of 10 mg were exactly weighed (\pm 0.1 mg) and encapsulated in flat-bottomed aluminum pans of 45 μ L with crimped-on lids.

2.5 Hot Stage Microscopy (HSM)

Different observations were made during heating using a hot stage microscope (HSM Mettler model FP82HT). Approximately 0.1 mg of samples (solid dispersion and inclusion complex) were placed on glass slides with coverglass and heated at 5 °C/min.

3. Results and discussion

3.1 Triamterene - PEG 6000 solid dispersion

Pure Triamterene and PEG 6000 melt at 342.6 and 77.8 °C (peak temperature), respectively, using a heating rate of 10°C/min (data not show). It can be observed the DSC diagrams of solid dispersion in Figure 1. This figure shows only a single endothermic effect associated to the melting of the carrier, since no additional endothermal effects were detected. If the drug is crystalline, the absence of the typical endothermal peak of fusion into the DSC thermogram was interpreted as "solid solution" formation of drug into the vehicle [1, 12].

The complementary study of these systems by HSM showed that after dynamic heating at 60 °C, the carrier melts and small and larger vesicles are observed. This process produces that the crystalline particles of drug can be easily detected by microscopy. Heating at high temperatures as 120 °C produces a partial dissolution of the crystals entrapped inside the liquid vesicles. This dissolution process is broader as temperature increases, as observed by HSM producing a single liquid phase enriched in Triamterene. The results evidence that really a solid dispersion was obtained and not a "solid solution", because the drug is in the solid state.

These results can be interpreted on the basis that the dissolution process of Triamterene into the melted carrier, exhibits a low enthalpy change and occurs in a wide range of temperature. So, the DSC apparatus could not detect the process. As it is well-known, DSC is a very useful technique to study solid dispersions; the obtained data are useful for preparing the phase diagram and to detect the presence and the composition of eutectics. However, in binary systems in which a process of dissolution occurs, this technique can be misleading, requiring, therefore, another complementary technique as the HSM.

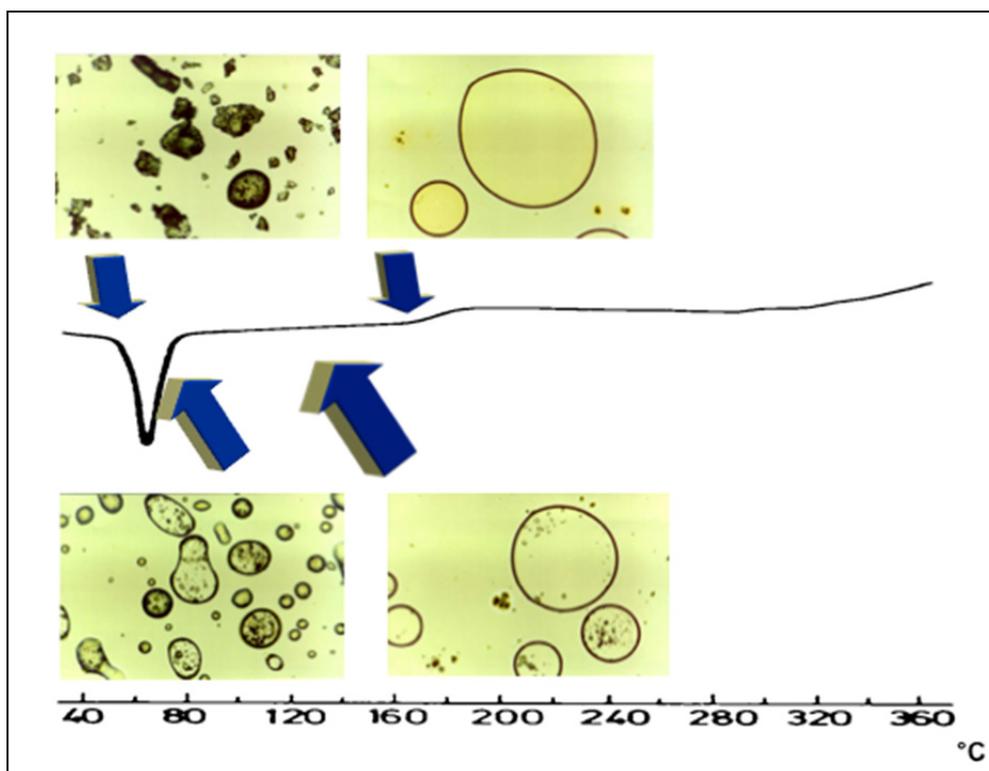


Fig. 1 DSC curve and thermophotomicrographs of 10% w/w Triamterene-PEG 6000 solid dispersion.

3.2 Triamterene- β -CD inclusion complex

Figure 2 shows the thermogram of Triamterene- β -CD inclusion complex obtained by co-grinding. The thermogram shows a broad asymmetric endothermic effect at ≈ 80 °C, which is attributed to β -CD dehydration process. This fact can be clearly corroborated by the HSM study. The product is treated on the microscope slide with 1 or 2 drops of silicone oil, covered with the cover-slip, and heated. The dehydration process can be seen microscopically or even macroscopically, by the formation of bubbles of gas above 90 °C. Also, in the DSC thermogram it is clearly observed the presence of an intense exothermic effect, situated at 265 °C.

This effect may be assigned to any thermal event to be exothermic: crystallization, oxidation, polymerization, etc., but the recrystallization of an amorphous form, obtained during the mechanical treatment of the sample (grinding) is the one most likely to occur. Taking into account at this consideration, there are three possible reasons to explain the exothermic effect obtained in to DSC thermogram: crystallization of triamterene, crystallization of β -CD or the formation of a complex including its crystallization. In our case, we have not observed this circumstance in the raw materials treated in separate. According to the other authors [17], and taking into account the chemical nature of the components, the third possibility seems to be here the most probable. The photomicrograph revealed that during the DSC heating, the amorphous product obtained after grinding, recrystallizes into the more stable crystalline form of higher melting temperature. Also, it was observed a weak endotherm peak at 290 °C, which may be ascribed to the melt of this recrystallized complex. The recrystallization and fusion process was confirmed by HSM study. Finally, a very intense endothermic peak is detected into DSC thermogram at 330 °C; the HSM photomicrographs revealed that this endothermic effect is due to the fusion process of β -CD not complexed.

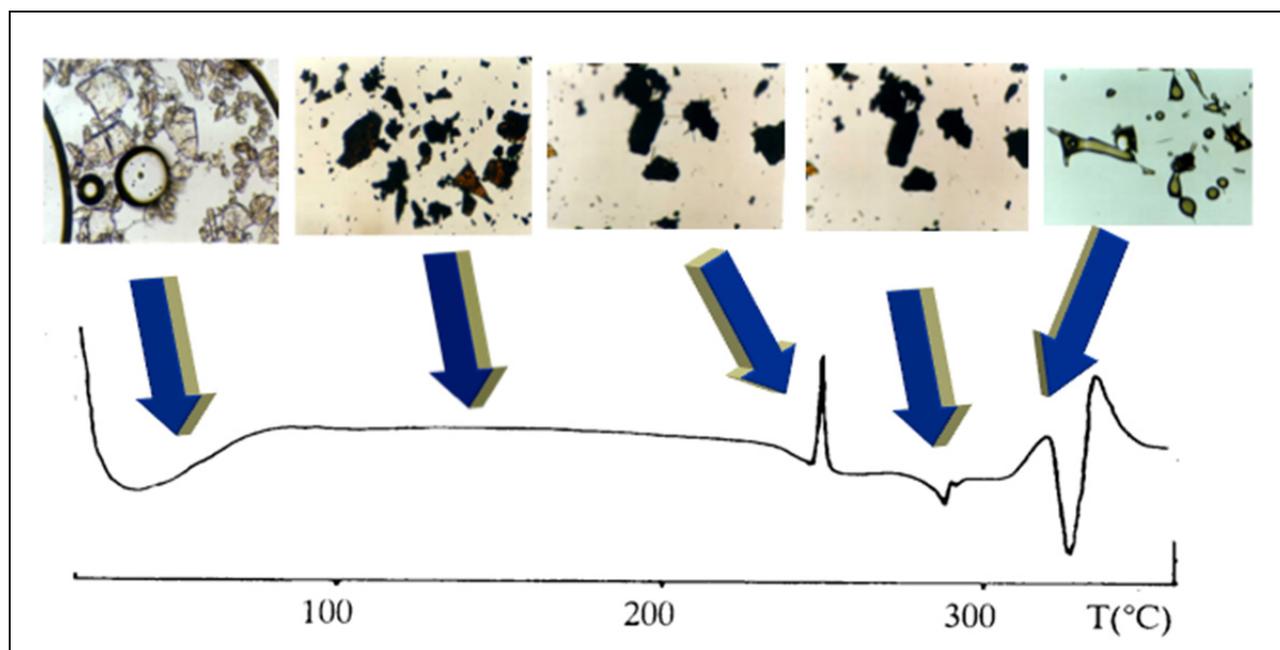


Fig. 2 DSC curve and thermophotomicrographs of 1:1 Triamterene- β -Cyclodextrin inclusion complex obtained by co-grinding.

4. Conclusions

Thermal analysis by DSC has been widely used in the pharmaceutical technology to the determination of solid-liquid equilibrium, 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 T-PEG 6000, because there is a partial dissolution process of Triamterene in the vehicle detected by HSM, which is not detected by using DSC. Then, HSM is a complementary technique to investigate the thermal behavior 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. The DSC thermogram of Triamterene- β -Cyclodextrin shows an intense exothermic effect that after HSM observation could be attributed to the recrystallization phenomenon of the amorphous complex.

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