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THERMAL STUDY OF COMPLEX FORMATION OF TRIAMTERENE WITH β-CYCLODEXTRIN BY SPRAY-DRYING AND CO-GRINDING

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Abstract

The formation of crystalline inclusion complex of triamterene with β-cyclodextrin (β-CD) was studied, evaluating the thermal behaviour and dispersion state of this drug in different types of binary systems. Spray-drying and co-grinding (oscillating mill) mixtures of triamterene with β-CD were prepared in 1:1 molar ratio. The changes of crystalline properties of original (untreated) triamterene, β-CD, and composites obtained by co-grinding and spray-drying were investigated in comparison with those produced in simple physical mixtures. The thermal behaviour of the different samples was investigated using DTA. X-ray diffraction was applied as a complementary technique. The results have been explained by formation of amorphous drug particles on spray-drying samples and co-grinding or alternatively by means of a solid dispersion formation or a combination of these two. A contamination effect by grinding media was also observed as increasing grinding time.

Keywords: β-cyclodextrin, complex formation, DTA, triamterene, X-ray

Introduction

A number of so-called "solid dispersion" techniques are known to enhance the dissolution and the absorption rate of drugs [1]. As carriers in such solid dispersions, polyvinylpyrrolidone, polyethylene glycol, microcrystalline cellulose and cyclodextrins (CDs) are generally used. In particular, cyclodextrins form inclusion compounds with various drug molecules, and the complexation with cyclodextrins is widespread used in the pharmaceutical field.

CDs have been extensively applied to improve the solubility, dissolution, stability and bioavailability of poorly soluble drugs. CDs are known to form inclu-

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sion complexes with a variety of guest molecules in solution and in the solid state, since their inherent annular structure exists stable in both phases [2]. Several methods have been employed to obtain the cyclodextrins complexes, including kneading, co-precipitation, freeze drying, spray-drying, co-grinding and sealed heating.

Triamterene is a diuretic practically insoluble in water with a low bioavailability. In a previous paper [3], the authors studied the thermal behaviour of solid dispersions triamterene-polyethyleneglycol by thermal methods (DSC and Hot Stage Microscopy). However it would be also interesting to improve its solubility and dissolution rate by complexation with CDs.

The objective of the present work was to study the interaction of triamterene with β-CD and to evaluate the thermal behaviour and dispersion state of this drug in the two types of binary systems. Spray-drying and ground mixtures of triamterene with β-CD were prepared in 1:1 molar ratio. The changes of crystalline properties of triamterene by grinding with CDs were investigated in comparison with those produced in the spray-drying process. The physicochemical properties of the different samples have been investigated using DTA. Preliminary data on the thermal behaviour of this system is reported. Other techniques, as X-ray Diffraction (XRD) were applied for identification purposes.

Experimental

Micronized triamterene (2,4,7-triamino-6-phenyl-pteridine) was provided from Laboratories Miquel S.A. (Barcelona, Spain) and β-CD by Roquette (Lestrem, France).

The preparation of solid complexes triamterene–β-CD (molar ratio 1:1) was performed by two techniques: grinding and spray-drying. Furthermore, the raw materials were separately grinding and spray-dried. We have also prepared a physical mixture of the two components in order to serve as reference.

Grinding and co-grinding were performed by using an oscillating mill (Herzog HSM 100), the volume of the mill 300 cm^3 during 1 and 5 min.

Spray-drying was performed in a Büchi 190M miniSpray-Dryer. Triamterene was dissolved in 400 ml of 96 vol% ethanol. The required amount of β-CD was dissolved in 400 ml of purified water. Next, the solutions were mixed for 20 min by sonication to produce a clear solution, which was spray-dried. The drying conditions were: 1000 ml/h flow rate, 168°C inlet temperature, 90°C outlet temperature, 400 Nl/h air flow rate.

The DTA runs were carried out in inert atmosphere (99.999% nitrogen) to prevent the effect of degradation of cyclodextrins which takes place at the same temperature range of the drug melting point. A Setaram high-temperature apparatus (model 92, 16-18) was used. A nitrogen flow of 16 $cm^3 \cdot min^{-1}$ was hold during the runs up to 600°C. Calcined alumina was used as a reference material and open Pt crucibles as sample holders.

The XRD diagrams were performed by using CuK_α Ni filtered radiation in a Siemens (D-501 model) powder diffractometer.

Results and discussion

DTA studies

The DTA curves of original triamterene, spray-dried and ground during 1 min are shown in Fig. 1. In all cases, the triamterene exhibits a characteristic endothermic fusion peak at 327°C. The DTA curves of β-CD (Fig. 2), shows a

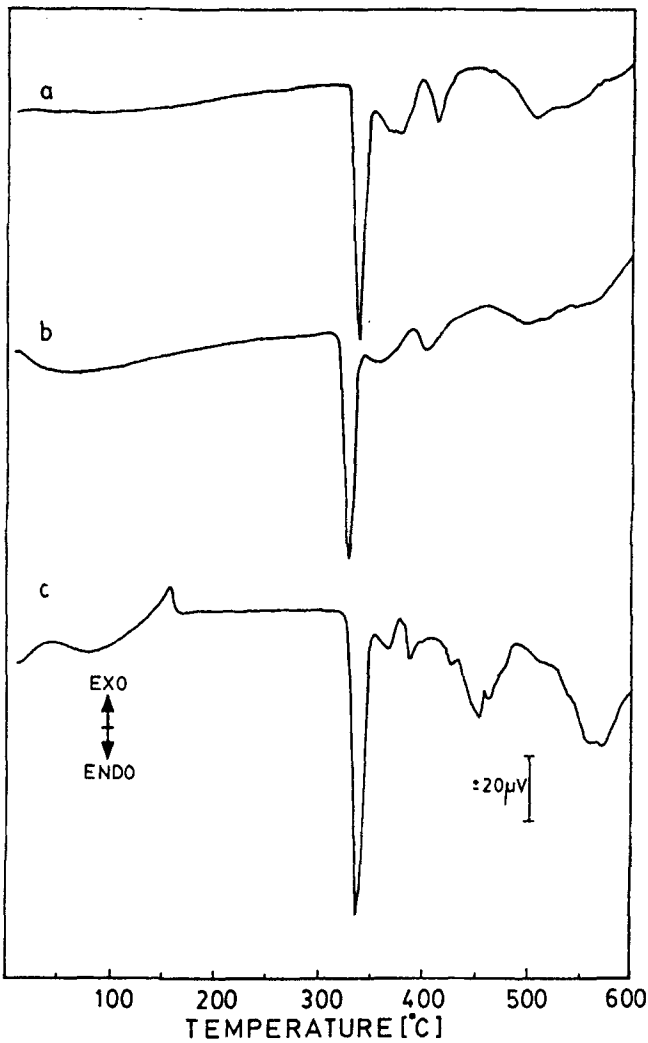

Fig. 1 DTA curves of triamterene: a) untreated, b) spray-dried and c) ground (1 min)

broad asymmetric endothermic effect at ≈ 100°C, which is attributed to a dehydration process. This effect is very intense in the pure β-CD [4], and broader and smoother for β-CD after spray-drying (Fig. 2b) and grinding during 1 min (Fig. 2c), both appearing at lower temperatures.

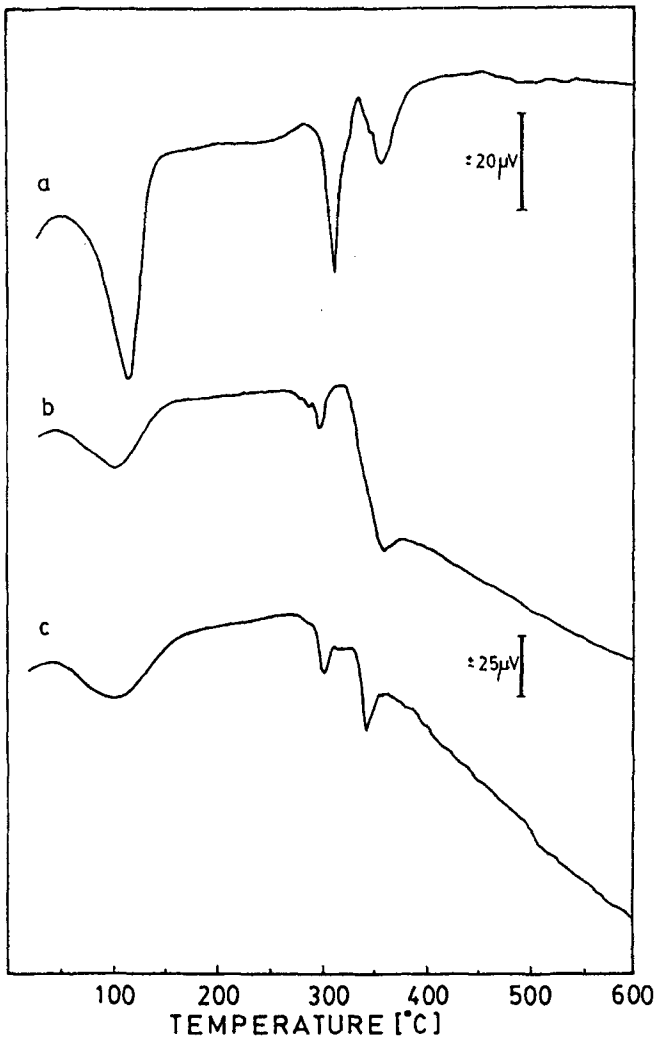

Fig. 2 DTA curves of β-CD: a) untreated, b) spray-dried and c) ground (1 min)

The DTA curves of binary systems (Fig. 3) show a first endothermic effect around 100–150°C corresponding to the dehydration process, being more intense in the physical mixture, but appearing at lower temperatures in the other cases.

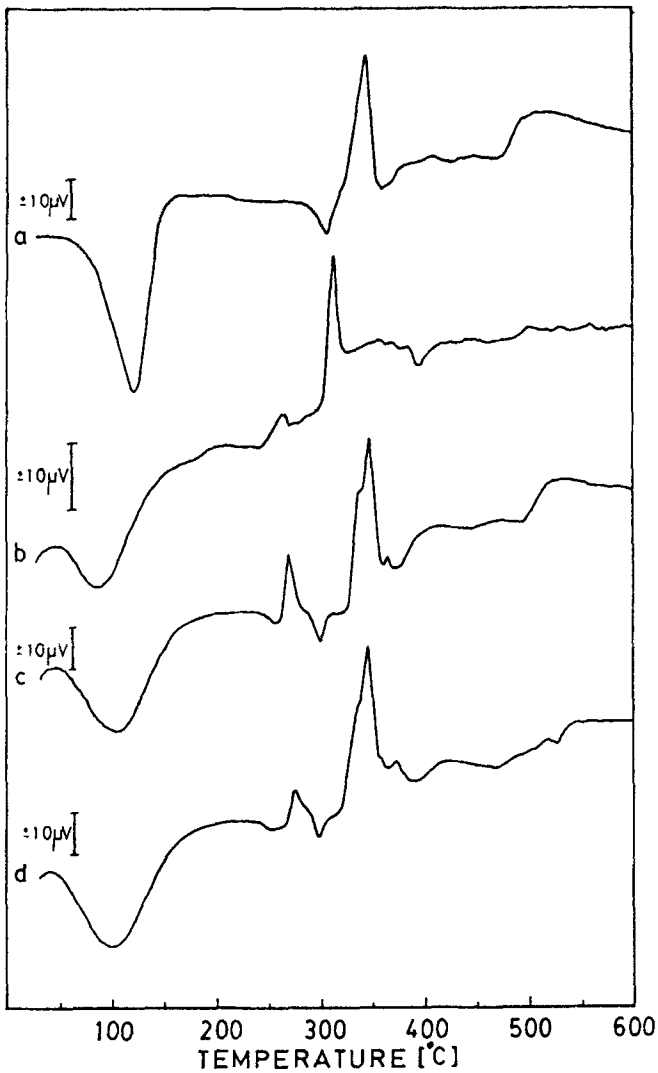

Fig. 3 DTA curves of 1:1 triamterene–β-CD binary system: a) physical mixture, b) spray-dried, c) ground (1 min) and d) ground (5 min)

The spray-dried and ground samples (Figs 3b, 3c, and 3d) show exothermic effects at 260, 269 and 275°C respectively, accompanied by an endothermic effect. Finally, very intense exothermic peaks are detected in all the cases, appearing at lower temperatures in the spray-dried samples. There are three possible reasons to explain the first exothermic effects: crystallization of triamterene, crystallization of β-CD or the formation of a complex including its crystallization. Taking into account the chemical nature of the components, the

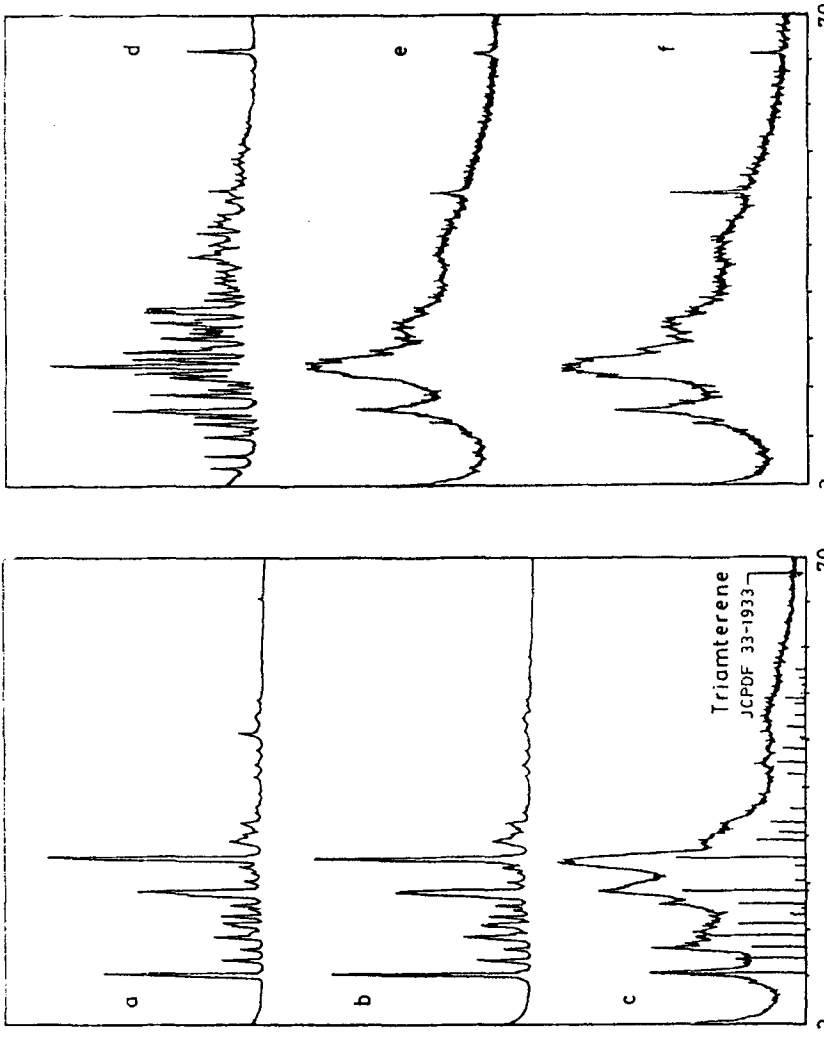

Fig. 4 XRD diffractograms of the raw materials: a) triamterene, b) triamterene spray-dried, c) triamterene ground (1 min), d) β-CD, e) β-CD spray-dried and f) β-CD ground (1 min)

third possibility seems here the most probable. As the exothermic temperature of this effect is lower than the triamterene melting point, it cannot be due to the drug crystallization alone. On the other hand, the DTA curve of β-CD spray-dried and ground samples did not show any exothermic effect in this temperature range. According to these considerations, the crystallization of a complex seems the most probable reason of this behaviour. Figure 3 also shows the changes in DTA curve with the progress of grinding. It is evident that the temperature of crystallization also increases as increasing the grinding time. Similar results have been obtained by other authors [5].

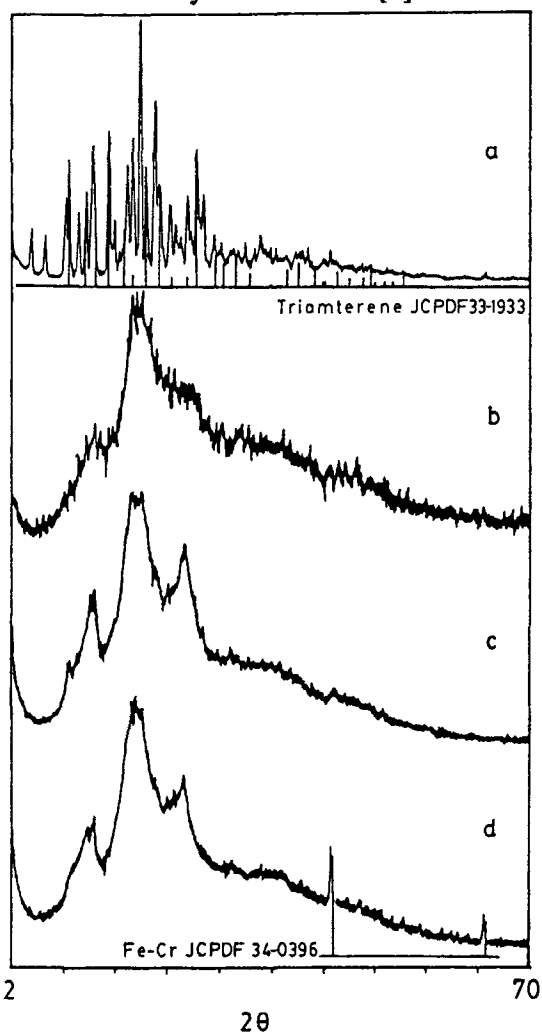

Fig. 5 XRD diffractograms of 1:1 triamterene–β-CD binary system: a) physical mixture, b) spray-dried, c) ground (1 min) and d) ground (5 min)

X-ray diffraction studies

Figure 4 shows the X-ray powder diffraction diagrams of pure components, after spray-drying and grinding. It is evident that these treatments produced a decrease in crystallinity of β-CD, because the X-ray diffraction patterns of original crystals disappeared partially (case of triamterene) or completely (β-CD) and the diffractogram changed to an amorphous halo pattern. Moreover, the XRD diagram of triamterene spray-dried did not show an amorphization process as intense as β-CD, which is in accordance with the behaviour of solids after intensive mechanical treatment by grinding. Note that grinding produces also a contamination effect (Figs 4 and 5). In this case, Fe–Cr alloy impurities coming from the grinding media is incorporated into the ground sample.

The X-ray diffraction patterns for the triamterene–β-CD physical mixture, after spray-drying and co-grinding are presented in Fig. 5. The diffraction pattern of physical mixture show the sum of each pure component, indicating the presence of triamterene in crystalline state. In contrast, the grinding and spray-dried systems exhibit a great diminution of the diffraction peaks, revealing that these are in fact, less crystalline than that in the physical mixture. The above results suggest that triamterene–β-CD form an inclusion complex in the solid state. Alternatively, the data could be explained under terms of the formation of amorphous drug particles on spray-drying samples, or even by means of a solid dispersion formation.

These facts must be taken into account when co-grinding of triamterene and β-CD is performed under similar experimental conditions to enhancing the dissolution rate.

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Zusammenfassung — Mittels Auswertung des thermischen Verhaltens und des Dispersionszustandes der Droge bei verschiedenen Typen binärer Systeme wurde die Bildung kristalliner Einschlußkomplexe von Triamteren mit β-Cyclodextrin (β-CD) untersucht. In einem Molverhältnis von 1:1 wurden sprühgetrocknete und kogemahlene (Oszillationsmühlen) Gemische von triamteren mit β-CD angefertigt. Die Änderungen der kristallinen Eigenschaften von Original-Triamteren (unbehandelt), β-CD und von Substanzen, die durch Komahlen und Sprühtrocknen erhalten wurden, wurden im Vergleich zu jenen in einfachen physikalischen Gemischen untersucht. Das thermische Verhalten der verschiedenen Proben wurde mittels DTA untersucht. Röntgendiffraktion wurde als eine zusätzliche Technik eingesetzt. Die Ergebnisse wurden mit der Bildung amorpher Drogenpartikel bei sprühgetrockneten Proben und mit Komahlen oder alternativ mit der Bildung einer festen Dispersion oder einer Kombination beider erklärt. Ein Verschmutzungseffekt beim Mahlen wurde ebenfalls beobachtet wie steigende Mahlzeit.