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Investigation of the triamterene–β-cyclodextrin system prepared by co-grinding

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Abstract

Complex formation of triamterene and β-cyclodextrin in solution was studied by phase solubility and spectral shift methods. The value of the apparent stability constant, K_c, calculated by these techniques, were 340 and 470 M^{-1}, respectively. Binary systems of triamterene and β-CD were prepared using the dry co-grinding method. Their characterization was performed by Fourier transform infrared spectroscopy and scanning electron microscopy. The main conclusion arising from these studies has been a high interaction between drug and carrier, linked to a clear increase in the amorphous nature of the drug in these systems. Finally, as expected, the 1 min co-ground system presented a notable improvement in its dissolution rate: up to five fold dissolution efficiency over the first 60 min over free drug. This might be attributed to the amorphous state, the increased wettability of the drug and the inclusion complex formation at the liquid state. © 1997 Elsevier Science B.V.

Keywords: Triamterene; β-cyclodextrin; Grinding; FTIR; SEM; Dissolution rate

1. Introduction

Grinding is often used as a technique to reduce the particle size of powders in order to enhance the bioavailability of poorly water-soluble drugs, because the particle size and physicochemical properties of powdered drugs affect their dissolution rates. The method is also simple and easy to carry out. However, sometimes, not only desired changes in physical properties, such as specific area and shape, but reduction in drug stability or polymorphic transformations may also occur (Takahashi et al., 1985; Miyamae et al., 1994). Besides, grinding is not effective if the obtained fine powder forms aggregates. This problem is often dealt with grinding in the presence of different additives (cyclodextrins, surfactants, polymers, etc.) (Boullay, 1987; Rubinstein and Gould, 1987). Many studies report that co-grind-

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ing with an additive, such as cyclodextrins (CDs), enhances the solubility, dissolution rate and bioavailability of poorly water-soluble drugs. Moreover, this treatment may increase the molecular interaction between drugs and additives in the ground mixtures, often providing complex formation and changes in crystalline state of the drug into amorphous state, with improvements on the dissolution properties (Uekama et al., 1983; Çelebi and Nagai, 1987; Nakai et al., 1991; Arias et al., 1996b).

β-CD is a cyclic oligosaccharide containing 7 $\alpha \rightarrow$(1,4)-linked glucopyranose units, which delimit a relatively apolar cavity. Among the cyclodextrins commercially available, β-CD is the most useful to be applied as drug carrier, on the basis of its lower price and higher stability.

On the other hand, triamterene is a potassium-sparing diuretic drug practically insoluble in water. Its limited aqueous solubility creates variation in its dissolution rate and, consequently, in its bioavailability (Pruitt et al., 1977). For this reason, triamterene may benefit from formulation with hydrosoluble carriers. Surprisingly, to date, only a few formulations have been proposed (Arias et al., 1994a,b,c, 1995, 1996a; Ginés et al., 1994, 1995).

The aim of this work has been to study the dispersion state of triamterene in β-CD in ground mixtures, evaluating the influence of the grinding time in the dissolution performance of the drug from the formulations. For this purpose, the molecular state of triamterene in the co-ground systems has been investigated using Fourier transform infrared spectroscopy (FTIR) and the surface and shape of the particles by scanning electron microscopy (SEM). Moreover, complex formation of the drug with the β-CD in solution has been investigated by phase solubility and spectral shift methods. The value of the obtained stability constant has been also correlated with the dissolution behaviour of the binary systems.

2. Materials

Micronized triamterene (2,4,7-triamino-6-phenyl-pteridine) was purchased by courtesy of Laboratories Miquel S.A. (Barcelona, Spain) and β-CD was provided by Roquette (Lestrem, France). These chemicals were of pharmaceutical purity guaranteed by the suppliers.

3. Methods

3.1. Preliminary studies

3.1.1. Phase solubility studies

The solubility studies were performed according to the method reported by Higuchi and Connors (1965). Triamterene, in amounts that exceeded its aqueous solubility (50 mg), were accurately weighed in each 50 ml Erlenmeyer flasks to which were added 25 ml of water containing various concentrations of β-CD (0.002–0.016 M). These flasks were sealed and shaken at 20°C for one week, time considered enough to reach the equilibrium. The samples were then filtered with syringe through a 1.2 μm Sartorius cellulose nitrate membrane filter and properly diluted. Samples were analyzed spectrophotometrically (Hitachi U-2000) at 357 nm. The presence of trace amounts of β-CD did not interfere with the assay.

The apparent 1:1 stability constant K_c was calculated from the initial straight line portion of the phase solubility diagram, following the equation:

$$K_c = \frac{\text{slope}}{\text{intercept}\,(1 - \text{slope})}$$

3.1.2. Spectroscopic studies

Complex formation between triamterene and β-CD was also studied by the spectral shift method (Connors and Mollica, 1966). The concentration of the drug in these studies was 1.58×10^{-6} M, whereas the CD concentration was increased from 8×10^{-4} to 1×10^{-2} M and the UV spectra of triamterene were recorded on a Hitachi U-2000 UV–VIS spectrophotometer. The change in absorbance of the substrate (triamterene) by the addition of various concentrations of the ligand (β-CD) was measured at 357 nm to evaluate the stability constant of the complex. The blanks were prepared in the same concentrations of β-CD in water, in order to cancel any absorbance coming from the CD molecules.

3.2. Preparation of the ground mixtures

The ground mixtures of triamterene with β-CD in 1:1 molar ratio were prepared by co-grinding using an oscillating mill (Herzog HSM-100), the volume of the mill being 300 ml. After grinding, the samples were withdrawn at selected time intervals (0.5, 1.0 and 5.0 min) for further examination and sieved under 270 mesh. Moreover, the raw materials were separately ground for 1 min, and a physical mixture of the two components (mechanical mixing 15 min) was prepared. Both of these were used as reference samples.

3.3. Characterization techniques

3.3.1. FTIR

The infrared spectra of the binary systems were obtained using a Bio-Rad FTS-7 IR instrument. The samples were prepared by elaborating compressed KBr disks. The selected wavenumber ranged between 400 and 4000 cm^{-1}, over 64 scans and a spectrum resolution of 4 cm^{-1}.

3.3.2. SEM

The morphological features of the raw materials (commercial and ground samples) were compared with those of the obtained products (physical mixtures and co-ground systems) by examination under SEM (Philips XL-30). The samples were previously coated with Au to make them conductors (Edwars Auto 306). Magnifications selected were 1000–2000 $\times$ since it is enough to appreciate, in detail, the general morphology of the powders under study.

3.3.3. Dissolution rate study

The dissolution rate studies were performed according to the USP 23 paddle method using a Turu Grau equipment, model D-6. The dissolution medium was USP 23 artificial gastric medium without enzymes (1000 ml), the stirring speed 50 rpm and the temperature 37 $\pm$ 0.5°C. The samples (3 ml) were withdrawn at various time intervals using a syringe and analyzed spectrophotometrically at 357 nm in a Hitachi U-2000 spectrophotometer.

4. Results and discussion

4.1. Phase solubility studies

The phase solubility diagram for triamterene and β-CD is presented in Fig. 1. This plot shows that the aqueous solubility of the drug increases linearly as a function of β-CD concentration. It is clearly observed that the solubility diagram of triamterene in the presence of β-CD can be classified as A_L type of Higuchi. The linear relationship may be ascribed to the formation of a soluble 1:1 (triamterene:β-CD) complex. Because the phase solubility diagram was of the A_L type, solid complexes could not be prepared by coprecipitation, which is only possible for complexes showing a B_S type phase solubility diagram. Moreover, among the multiple techniques known to prepare inclusion complexes, co-grinding has already proven to be specially useful in their preparation (Ahmed et al., 1990; Çelebi and Erden, 1992), presenting the advantage of rapid preparation.

The apparent stability constant (K_c) can be estimated from the initial line portion of the solubility diagram, according to the above mentioned equation (Higuchi and Connors, 1965). K_c was calculated using the linear regression analysis method, and was found to be 340 M^{-1}. This value of K_c was included in the range of 200 and 5000 M^{-1}, considered by various authors ade-

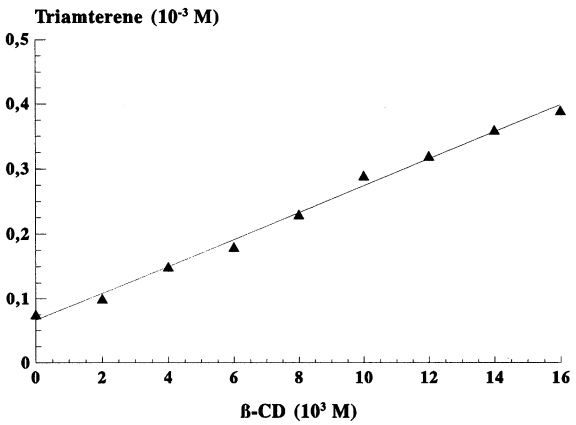

Fig. 1. Phase-solubility diagram of triamterene–β-CD system at 20°C.

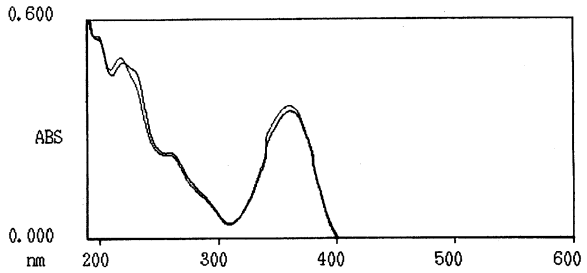

Fig. 2. Effect of β-CD concentration on UV absorption spectra of triamterene in water. The concentration of drug was 1.85×10^{-6} M: (a) drug alone; (b) drug in presence of 1.60×10^{-3} M concentration of β-CD.

quate for the formation of an inclusion complex, which may contribute to improved bioavailability of poorly water-soluble drugs (Blanco et al., 1991).

4.2. Spectral shift method

The effect of different molar concentrations of β-CD on the absorption spectrum of triamterene is given in the Fig. 2. It appears as a bathochromic effect in the absorption maxima of the drug, with a diminution of the absorbance. These induced changes in absorbance are attributed, primarily, to the formation of a inclusion complex in the liquid state. The changes in the intensity of the peak are assumed to result from changes in the solvent microenvironment upon inclusion of the solute. The observed reduction in peak intensity may be the result of the transference of guest molecules from water to the CD cavity. This is reasonable in the light of fact that there are no proton donating groups inside cavity of the CD molecule (Ismail, 1991).

The spectral data were analyzed by the double reciprocal plot as shown in Fig. 3. The plot of $1/\Delta A$ vs $1/[\mathrm{CD}]$ is linear, indicating the presence of 1:1 complex.

The apparent 1:1 stability constant was determined by the Benesi–Hildebrand equation (Benesi and Hildebrand, 1949):

$$\frac{1}{\Delta A} = \frac{1}{[\mathrm{D}]K_c\Delta\varepsilon}\frac{1}{[\mathrm{CD}]} + \frac{1}{[\mathrm{D}]\Delta\varepsilon}$$

where ΔA is the difference of absorbance at 230 nm, [CD] is the CD concentration, [D] is the total drug concentration (constant) and $\Delta\epsilon$ is the difference of molar absorptivities between the complexed and free drug. The stability constant, K_c, was obtained from the intercept/slope ratio and this value was 470 M^{-1}, that is approximately of the same order of value calculated by solubility studies.

4.3. FTIR

Fig. 4 shows the FTIR spectra of the samples under study. IR spectrum of triamterene (Fig. 4a) is characterized by the absorption of the NH_2 group, located in the bands at 3475, 3371, 3291 and 3196 cm^{-1}. The first two bands are assigned to asymmetric and symmetric stretching vibrations of the free NH_2 groups in the molecule of the pure drug. The rest of the bands at 3291 and 3126 cm^{-1} are caused by the amino-groups bonded by intermolecular hydrogen bonds. Deformation vibrations of $-NH_2$ groups are observed at 1677 cm^{-1}. The large shift of these vibrations to higher wavenumbers as compared with usual wavenumbers of the amino groups (1620–1640 cm^{-1} region) proves the hydrogen-bonded state of the amino groups. Finally, wavenumbers observed at 1609 and 1425 cm^{-1} may be assigned to the C=N and C–N bonds,

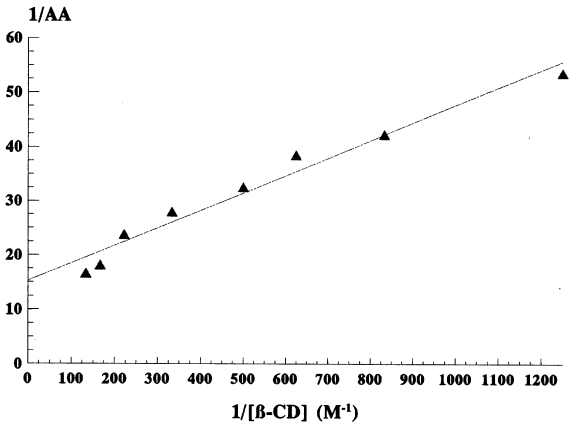

Fig. 3. Benesi–Hildebrand plot for the triamterene–β-CD system (ΔA displays the change of absorbance at $\lambda_{max} = 357$ nm and [CD] the cyclodextrin concentration).

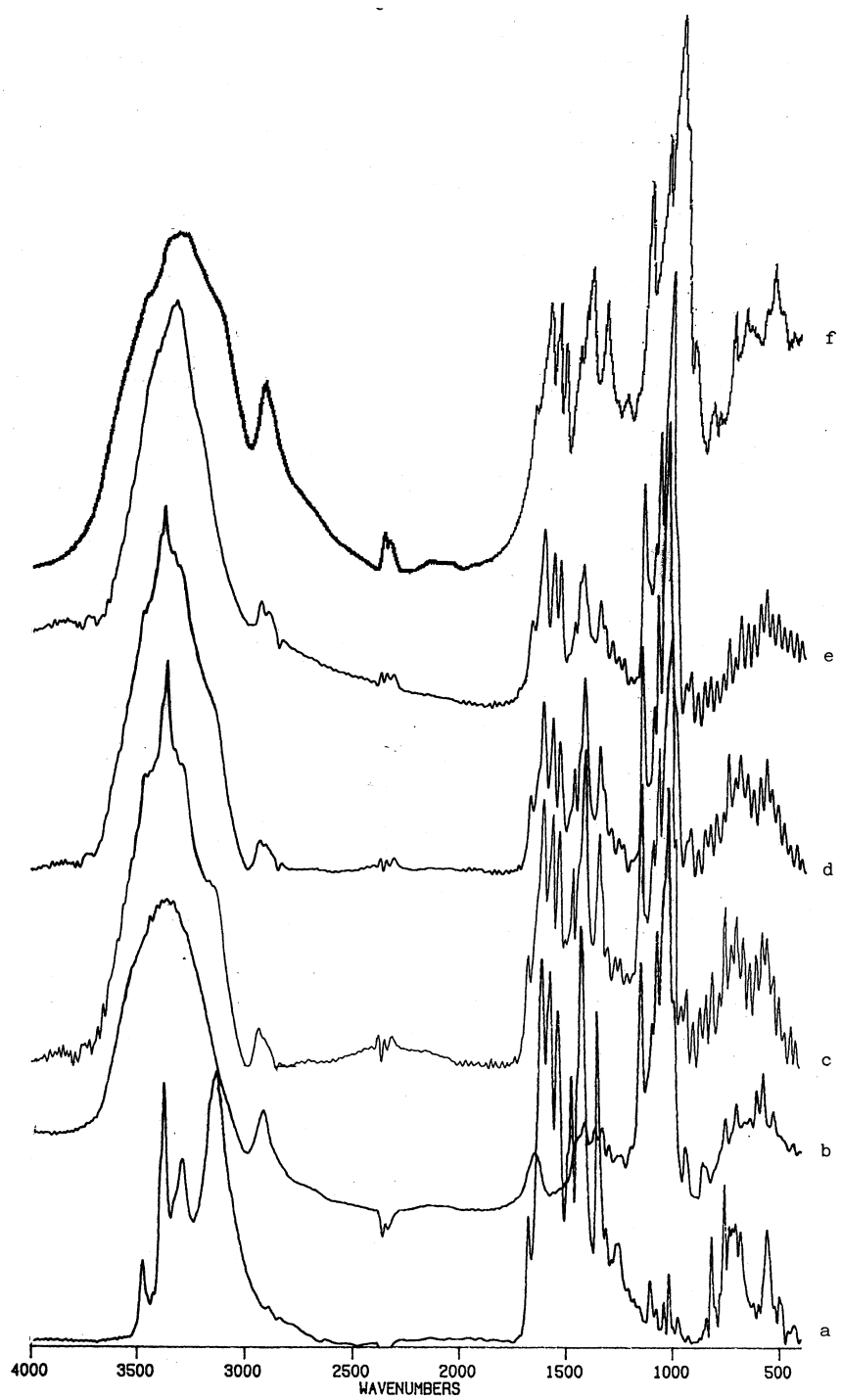

Fig. 4. FTIR spectra for the triamterene–β-CD systems: (a) triamterene; (b) β-CD; (c) physical mixture; (d) co-ground for 0.5 min; (e) co-ground for 1 min; and (f) co-ground for 5 min.

respectively, and which is typical for condensed cyclic hydrogen-containing systems.

The IR spectrum of β-CD (Fig. 4b) is characterized by intense bands at 3500–3300 cm^{-1}, associated with the absorption of hydrogen-bonded –OH groups of the CD. The vibrations of the –CH and $-CH_2$ groups appear in the 2800–2950 cm^{-1} region. Several sharp and intense bands in 1030–1160 cm^{-1} may be assigned to the stretching vibrations of the primary or secondary C–OH groups. It should be noted that the CD contain some moisture, which is characterized by the band at 1640 cm^{-1}.

The observed changes in the infrared spectra of the binary systems may be explained by the different preparation methods. As can be seen in the spectral pattern of the physical mixture (Fig. 4c), it corresponds simply to the superposition of the IR spectra of the two components. However, in the co-ground system for 1 min (Fig. 4e), it is appreciated the almost total smoothing of the band situated at 3200–3500 cm^{-1}, accompanied by the disappearance of the band at 1677 cm^{-1}, which was assigned to the deformation vibration of the amino groups. Moreover, the vibrations of C=N and C–N groups are shifted to 1621 and 1439 cm^{-1}, respectively, and reduced in their intensities. Thus, as spectral changes always concern $-NH_2$, C=N and C–N groups of the triamterene and the –OH groups of the CD, it should be suggested that the host–guest interactions are dominated by hydrogen bonds among the above mentioned groups.

4.4. SEM

The gradual reduction in size and associated morphological changes which occur during the grinding process are revealed by the SEM study. Some selected photographs are shown. After grinding triamterene for 1 min, a wide agglomeration process was detected (Fig. 5a). This agglomeration process occurs naturally in powders, because of adhesion forces that always act between the fine particles obtained by grinding. It also produces a coating effect of crystalline products by the amorphous phase, these observations being consistent with the XRD results (Ginés et al., 1995). The bonding mechanisms have been discussed in detail by some authors (Rumpf and Schubert, 1978).

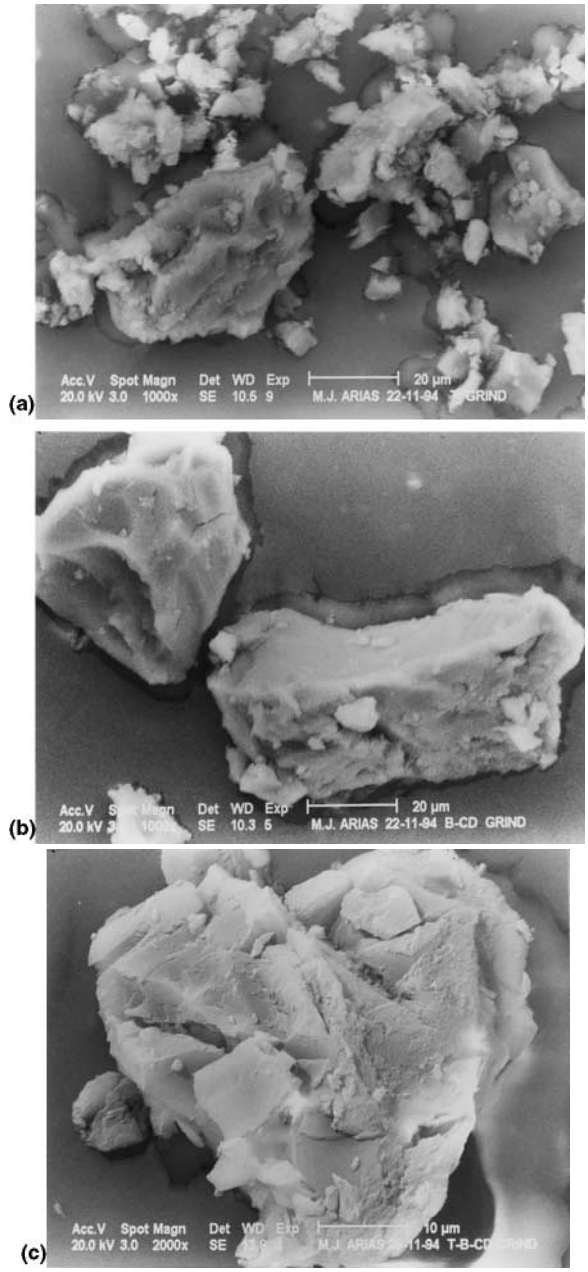

Fig. 5. SEMs of (a) ground triamterene for 1 min, (b) ground β-CD for 1 min and (c) co-ground 1:1 triamterene-β-CD for 1 min.

Microscopic examination revealed also striking differences in the morphology of the ground β-

CD with respect to the commercial one. The ground β-CD appears as irregular-size pieces of rough and porous surface (Fig. 5b), thus revealing its amorphous nature.

SEM photographs of the co-ground sample for 1 min (Fig. 5c) indicated that the drug particles were mechanically covered with a film of CD during their co-grinding, appearing now as only one type of granule. Previous SEM/EDX studies helped us to elucidate the dispersion state of triamterene formulated by spray–drying with β-CD (Arias et al., 1994c). Similar studies have been performed for the systems under study with the same results.

4.5. Dissolution rate studies

The dissolution rates of the co-ground samples (Fig. 6) were compared with those of the physical mixture and pure and ground drug, in terms of dissolution percentage and dissolution efficiency over the first 60 min (DP_{60} and DE_{60} respectively). The release profile of commercial triamterene compared with that found from ground drug alone was not significantly modified, as observed from their respective DP_{60} and DE_{60} values (Table 1). It must be taken into account that grinding does not provide an extensive amorphous state of the pure drug and that, on the contrary, it produces aggregation and aglomeration of drug particles to some extent.

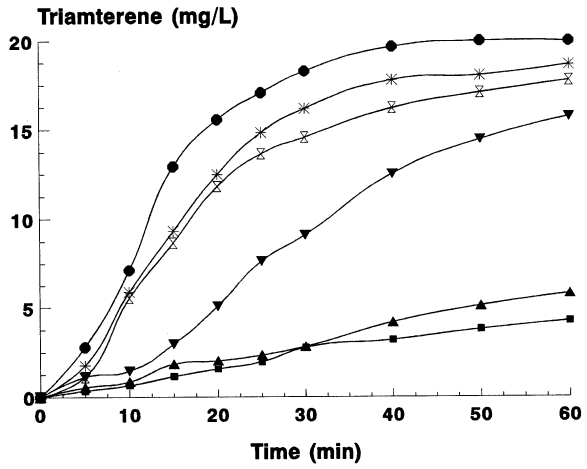

Fig. 6. In vitro dissolution rate profiles corresponding to triamterene–β-cyclodextrin binary systems processed by co-grinding (▲, commercial drug; ▩, ground drug for 1 min; ▼, physical mixture; *, co-ground for 0.5 min; ●, co-ground for 1 min and ⧖, co-ground for 5 min).

Table 1
Dissolution percentage and dissolution efficiency over the first 60 min (DP_{60} and DE_{60}) corresponding to the binary systems triamterene–β-cyclodextrin processed by co-grinding

Binary systems	Elaboration method	DP_{60}	DE_{60}
Triamterene–β-CD	Physical mixture	78.70	0.423
	Co-ground 0.5 min	93.30	0.662
	Co-ground 1 min	100.00	0.759
	Co-ground 5 min	88.90	0.613
Commercial triamterene		29.00	0.151
Triamterene ground 1 min		21.20	0.117

The increase in dissolution rate recorded for the physical mixture may be explained on the basis of the solubility of the drug in aqueous β-CD solutions. Since the β-CD dissolves more rapidly in the dissolution medium than the pure drug, it can be assumed that, in early stages of the dissolution process, the β-CD molecule will operate locally on the hydrodynamic layer surrounding the particles of the drug, this action resulting in an in situ inclusion process, which produces a rapid increase of the amount of dissolved drug. This situation has been similarly described by other authors (Ling et al., 1991). The marked increase in the dissolution rate of physical mixtures could be also due, although to a lesser extent, to the hydrophilic effect of β-CD, which can reduce the interfacial tension between water-insoluble drugs and the dissolution medium, thus leading to a higher dissolution rate.

It is evident that triamterene dissolves faster from ground mixtures with β-CD than from physical mixtures (Fig. 6). This enhancement in the dissolution rate may be attributed not only to the dispersion of triamterene in the β-CD after co-grinding, but also to the nearly amorphous state of such system. This assumption has been

confirmed by XRD, DTA (Ginés et al., 1995), FTIR and SEM.

Moreover, it must be pointed out the faster dissolution rate was recorded for the binary system co-ground for 1 min with respect to the one co-ground for 5 min. This fact may be explained by the formation of aggregated and agglomerated particles during a relatively prolongated grinding time. The existence of a practical limit to grinding has been already demonstrated (El-Gendy et al., 1986; Nakai et al., 1991; Nozawa et al., 1994) and determined to be due mainly to the tendency of the product to re-aggregate and to establish a physical equilibrium between the fragmentation and the size reduction. This fact results in an aggregation process, with the subsequent decrease in specific surface area. Also, the solid residues from co-grinding become cemented together by highly reactive amorphous material that acts as coating as co-grinding progressed (Papirer and Roland, 1981). These circumstances produce a diminution of triamterene dissolution rate and, surely, in its bioavailability.

5. Conclusion

The apparent K_c for triamterene and β-cyclodextrin in solution calculated by phase solubility and spectral shift methods was 340 and 470 M^{-1}, respectively. This value, although it indicates only a limited affinity of the drug for the CD cavity, is considered enough to increase the drug solubility in water.

The dry co-grinding method, used for preparing triamterene–β-CD binary systems, has yield products, characterized by their rapid dissolution rate. The optimal co-grinding time found has been 1 min. Less time lead to poorly dispersed and not fully amorphous systems and more grinding time leads to agglomeration of the particles as well as a contamination from the mill. The good dissolution performance of the 1 min co-ground system has been attributed to the amorphization of the drug during the grinding treatment, the high dispersion state (that supposes an increased wettability of triamterene) and to the mere presence of the CD—which increases water solubility of the drug. Finally, it is important to remark the utility of the co-grinding process to produce systems presenting a very rapid amorphization of the drug, much more rapid than simple grinding of the drug alone.

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