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SULPHAMETHIZOLE-CYCLODEXTRIN-HYDROXY PROPYLMETHYL CELLULOSE MULTICOMPONENT COMPLEXES

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Abstract

The effect of cyclodextrin complexation of sulphamethizole (SM) was studied. Two systems were prepared with two cyclodextrin derivatives, β-cyclodextrin (BCD) and hydroxypropyl-β-cyclodextrin (HPBCD): binary complexes and multicomponent systems (cyclodextrins and a hydroxypropylmethyl cellulose K4M). Inclusion complexes were prepared by freeze-drying and characterized by thermal analysis (DSC) and X-ray diffractometry. The presence of the polymer in the solution increases the effect of cyclodextrins – specially BCD – on the solubility of SM. In solid state, binary inclusion complexes enhance the dissolution behaviour of SM but, from the multicomponent complexes, the polymer controls the release of the drug.

Keywords: β-cyclodextrin, cyclodextrin inclusion complexes, DSC, hydroxypropyl-β-cyclodextrin, hydroxypropylmethyl cellulose, stability constant, X-ray diffractometry

Introduction

Cyclodextrins (CDs) are water-soluble, hydrophobic torus-shaped cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic central cavity. In aqueous solutions CDs are capable of forming inclusion complexes with many drugs. Because of these properties CDs can be used to improve some physicochemical properties of drug molecules such as stability or aqueous solubility [1–3].

For a variety of reasons including costs, production capabilities and toxicology, CDs can be incorporated into drug formulations in a limited amount, and therefore, it is important to develop methods that allow a reduction in the amount of CDs necessary in a particular pharmaceutical formulation [4]. Among these procedures, the use of water-soluble polymers has been extensively studied to enhance the complexing abilities of the CDs. In fact, it has been proven that various pharmaceutical polymers, such as cellulose derivatives, have a significant effect on the drug–CD complex formation because, as surfactants, they increase the solubilizing power of CDs. The in-

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teraction polymer-CD results in physical-chemical changes of the systems formed, and the solubility of the drug increases [5–7]. We have used a hydrophilic polymer, hydroxypropylmethyl cellulose (K4M) which is a well established pharmaceutical excipient, extensively used in controlled drug delivery systems. K4M has been previously reported useful in the improvement of CD complexation [8–10], but most of the studies carried out to analyse the effect of hydrophilic polymers on the complex formation with cyclodextrins were made in solution, not in solid state. Several papers have been published concerning the improvement of the solubility and bioavailability of drugs through the formation of binary and multicomponent complexes with cyclodextrins [11, 12]. Acid molecules – hydrochloric, citric or tartaric acids – were included in these multicomponent systems but not polymer molecules.

Sulphamethizole (SM) was used as a model drug. It is a short-acting sulphonamide used in the treatment of infections of the urinary tract, sometimes in combination with other antibacterial agents. It is very slightly soluble in water and this could be a drawback to formulate it in controlled release dosage forms. Its formulation as an inclusion complex either with β-cyclodextrin (BCD) or hydroxypropyl-βcyclodextrin (HPBCD) has showed a significant increase in its aqueous solubility [13].

The aim of this study was to prepare solid multicomponent systems containing cyclodextrins (BCD and HPBCD) and hydroxypropylmethyl cellulose (K4M) to be included in solid dosage forms. These systems were prepared by freeze-drying and characterized by differential scanning calorimetry and X-ray diffractometry. Drug dissolution characteristics from binary and multicomponent complexes were compared with these of the uncomplexed drug.

Experimental

Materials

Sulphamethizole was purchased from Sigma Chemical Co. (St. Louis, MO, USA). BCD and HPBCD were a gift from Laisa-Roquette (Barcelona, Spain) and Janssen Pharmaceutiche (Belgium), respectively. Hydroxypropylmethyl cellulose K4M (Methocel®) was obtained from The Dow Chemical Company (Michigan, USA). All other reagents were of analytical reagent grades.

Solubility studies

Solubility diagrams were obtained according to Higuchi and Connors methodology [14]. Excess amounts of sulphamethizole were added to water containing various concentrations of cyclodextrins. The suspensions were shaken at 37°C for seven days.

To establish the effect of the polymer on the solubility diagrams, K4M was added (0.1% *w/v*). The suspensions were autoclaved at 120°C for 20 min and equilibrated for at least 3 days at room temperature, according to Loftsson *et al.* [15].

The stability constants $K_{1:1}$ were calculated using the following relationship:

$$K_{1:1}=\frac{\text{slope}}{S_0\,(1-\text{slope})}$$

where S_0 represents the solubility of sulphamethizole in water without cyclodextrins. Drug concentration was analysed spectroscopically (Shimadzu UV-240-Graphicord) at 264 nm ($E_{1\%,1\ cm}$=577.31).

Preparation of the physical mixtures

Sulphamethizole, cyclodextrins and hydroxypropylmethyl cellulose were passed through 0.5 mm meshes, and 1:1 SM/CD ratio with 0.1 g of K4M (equal amount that is present in the inclusion complexes) were mixed in a Turbula T2C mixer for 10 min.

Preparation of the inclusion complexes

Equimolar amounts of sulphamethizole and cyclodextrins – BCD and HPBCD – were dissolved in 5% (*w/v*) aqueous ammonium hydroxide. K4M was added to obtain a final concentration of 0.1% (*w/v*), and the solution was left to stand for 24 h at 4°C. The dispersions were frozen by immersion in liquid nitrogen, and lyophilized in a Labconco Lyph-lock 6 apparatus.

Thermal analysis

Differential scanning calorimetry (DSC) was performed on a Shimadzu DSC-50 system with a DSC equipped with a computerized data station TA-5 WS/PC. General conditions: scanning rate 10°C min^{-1}, scanning temperature range 25–250°C.

X-ray

X-ray powder diffraction patterns were recorded on a Philips X-ray diffractometer (PW 1710 BASED) using CuK_α radiation. In the diffractograms the relative intensity of reflexion peaks were recorded as a function of diffraction angles 2θ°.

Dissolution studies

The dissolution behaviour of the complexes at 37°C was compared with that of pure sulphamethizole and of physical sulphamethizole-cyclodextrin mixtures using hard shell colorless gelatin capsules containing quantities of formulation equivalent to 50 mg of sulphamethizole. Capsules were placed in a stainless steel box to avoid their flotation. Tests were carried out in a USP24 Method II apparatus (Turu-Grau) using 900 mL of distilled water and a stirring speed of 50 r.p.m. All experiments were made in triplicate. At pre-specified times, 5 mL samples were extracted and filtered, and the concentration of sulphamethizole was determined spectrophotometrically at 264 nm. The resulting dissolution curves were characterized by the corresponding 0–60 min dissolution efficiency [16]. The statistical significance of differences among formula-

tions was estimated by one-way analysis of variance (one-way Anova) and the Scheffé test for multiple comparisons using SPSS for Windows (v. 10.1.3).

Results and discussion

Phase-solubility diagrams

The effect of K4M on the solubilising effect of BCD and HPBCD is shown in Table 1. Solubilities of the drug in aqueous CD solutions (S_{co}) were much higher than in water (S_0), but the introduction of small amounts of K4M to the solution medium improved the solubility even further. Thus, to obtain a significant increase of the solubility (up to 39% with BCD and 6% with HPBCD), the solutions have to be heated to 120°C for 20 min (autoclaving).

Table 1 Effect of the addition of 0.1% (*w/v*) K4M to aqueous 1%(*w/v*) HPBCD and BCD solutions on solubilization of sulphamethizole

	S_p	S_p^*	S_{co}	S_{cp}	S_{cp}^*	S_{cp}/S_{co}	S_{cp}^*/S_{co}
BCD	2.337	3.271	7.472	6.649	10.430	0.89	1.40
HPBCD	2.337	2.854	7.125	5.938	7.578	0.83	1.06

S_o: solubility of SM in aqueous solution (2.386 mM)
S_p: solubility in aqueous 0.1% (*w/v*) solution of the K4M (mM)
S_p^*: solubility in aqueous 0.1% (*w/v*) solution of the K4M with autoclaving process (mM)
S_{co}: solubility in aqueous 1% (*w/v*) CD solution (mM)
S_{cp}: solubility in aqueous solution containing both 0.1% (*w/v*) K4M and 1% (*w/v*) CD (mM)
S_{cp}^*: solubility in aqueous solution containing both 0.1% (*w/v*) K4M and 1% (*w/v*) CD with autoclaving process (mM)

Figures 1 and 2 show the phase solubility diagrams of SM in aqueous BCD and HPBCD solutions in the presence or absence of K4M. In all cases, the solubility of the drug increases linearly as a function of the CD concentration, A_L-type according to Higuchi and Connors classification. The slope of the diagrams is lower than 1, and therefore, the complex is responsible for the increase in drug solubility has a 1:1 mol:mol stoichiometry [14]. K4M enhanced significantly the solubilizing effect of CDs but did not affect the type of the phase-solubility diagram.

The apparent stability constants of SM-BCD and SM-HPBCD with and without K4M were calculated from the slopes of the phase-solubility diagrams assuming a 1:1 stoichiometry (Table 2). The stability constants of the inclusion complexes show an enhancement in the presence of K4M in the case of SM-BCD complex. This effect was not found for HPBCD systems, in fact, the effect of K4M was negligible. Similar results were found by Veiga [17] with HPBCD and HPMC, in disagreement with these obtained by other authors where the solubilization enhancement is more than simple, it is synergistic [10].

The concentration of SM dissolved was higher when an autoclaving process was carried out. During this autoclaving process, the rise in temperature caused a satura-

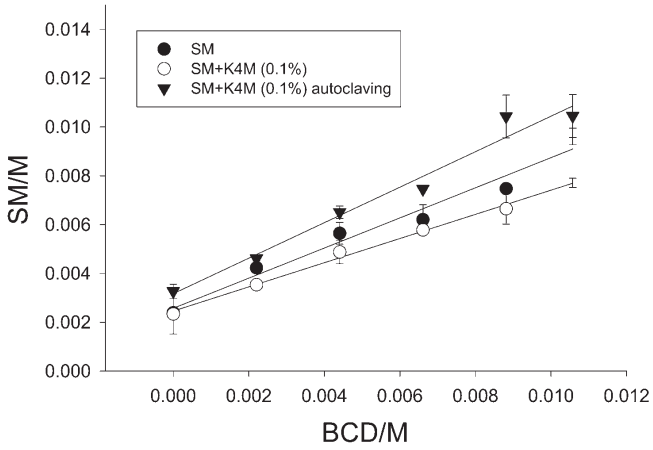

Fig. 1 Phase-solubility diagrams of SM in aqueous BCD solutions containing 0 and 0.1% K4M at 37°C

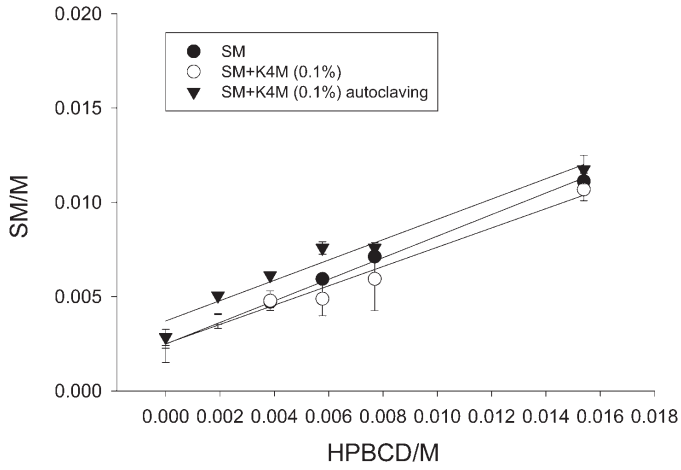

Fig. 2 Phase-solubility diagrams of SM in aqueous HPBCD solutions containing 0 and 0.1% K4M at 37°C

tion and an increase in the solubility of the drug, which could probably lead to improved interactions between SM and the CD molecules. The improved solubilization after autoclaving could be due to the various electrostatic forces involved and a facilitated fitting of the guest molecule into the cavity. For SM-HPBCD complex the increase of temperature after autoclaving could explain the lower value of the stability constant because it may well produce an overall exothermic reaction between the drug and CD [5].

Table 2 Stability constants ($K_{1:1}$) of SM complexes with HPBCD and BCD

	BCD	HPBCD
Without K4M	651.85 M^{-1} (r^2=0.9684)	563.95 M^{-1} (r^2=0.9969)
With K4M	419.93 M^{-1} (r^2=0.9948)	448.72 M^{-1} (r^2=0.9715)
With K4M and autoclaving	815.51 M^{-1} (r^2=0.9721)	409.12 M^{-1} (r^2=0.9626)

Preparation and characterization of solid inclusion complexes.

Solid inclusion complexes were obtained by freeze-drying which is a common pharmaceutical technique useful for preparing cyclodextrin inclusion complexes [18]. The drug:cyclodextrin ratio used was 1:1 mol:mol as found in the phase solubility diagrams for both CD derivatives and K4M was 0.1% *w/v* common polymer concentration [9, 15].

Differential scanning calorimetry and X-ray diffractometry were used to characterize the systems prepared.

DSC is a widely used analytical technique in the characterization of multicomponent solid systems to analyze possible changes during heating. In the case of CDs, DSC can provide a lot of information on drug/CD interactions in the solid state. Polymers can form complexes with CDs with physicochemical properties distinct from these of individual cyclodextrin molecules [19]. Figure 3 shows the DSC curves of the physical mixtures of SM and BCD as well as these of the solid binary and multicomponent complexes prepared by the freeze-dried method. BCD shows an endothermic peak from 90 to 140°C, which may be attributed to the evaporation of the adsorbed water [20]. The endothermic peak due to fusion of the drug appears at 210°C. In the freeze-dried complexes,

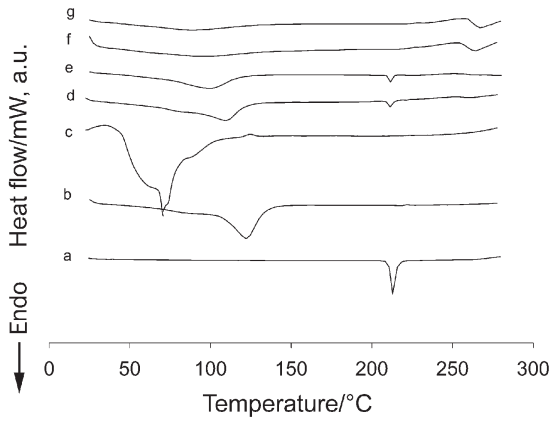

Fig. 3 DSC curves of different SM–BCD systems: a – SM, b – BCD, c – K4M, d – physical mixture SM+BCD, e – physical mixture SM+BCD/K4M, f – SM–BCD freeze-dried complex and g – SM–BCD/K4M freeze-dried complex

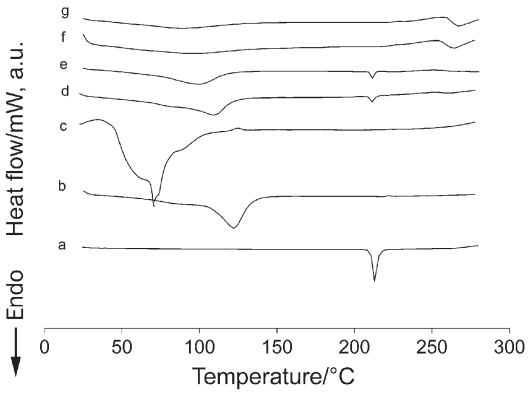

Fig. 4 DSC curves of different SM–HPBCD systems: a – SM, b – HPBCD, c – K4M, d – physical mixture SM+HPBCD, e – physical mixture SM+HPBCD/K4M, f – SM–HPBCD freeze-dried complex and g – SM-HPBCD/K4M freeze-dried complex

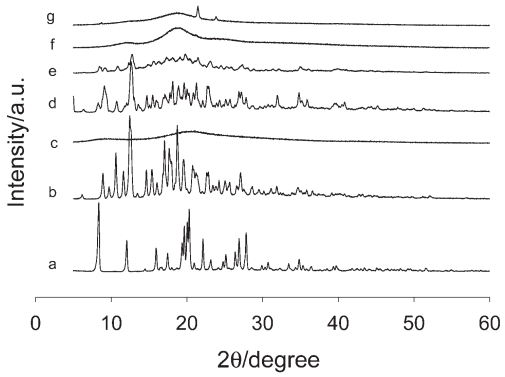

Fig. 5 X-ray diffraction patterns of different SM–BCD systems: a – SM, b – BCD, c – K4M, d – physical mixture SM+BCD, e – physical mixture SM+BCD/K4M, f – SM–BCD freeze-dried complex and g – SM-BCD/K4M freeze-dried complex

the plots show the absence of the characteristic endothermic melting peak, as compared to the physical mixtures in which this peak is clearly visible. The disappearance of the endothermic peaks of the drug is attributed to the amorphous state and the inclusion complexation of the drug inside the cavity [18].

The results of the HPBCD systems were similar to these of BCD, the peak or the drug fusion at 210°C disappeared in the binary and multicomponent complexes.

Powder X-ray diffractometry is a useful technique for the detection of CD complexation in powder or microcrystalline states. The diffraction pattern of the complex is supposed to be clearly distinct from the superposition of each component if a true complex exists.

The X-ray diffraction spectra of SM-BCD binary and multicomponent complexes in comparison with the physical mixture are shown in Fig. 5. The diffraction

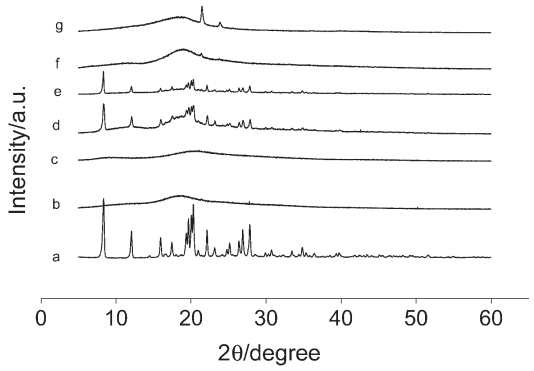

Fig. 6 X-ray diffraction patterns of different SM–HPBCD systems: a – SM, b – HPBCD, c – K4M, d – physical mixture SM+HPBCD, e – physical mixture SM+HPBCD/K4M, f – SM–HPBCD freeze-dried complex and g – SM–HPBCD/K4M freeze-dried complex

patterns of the physical mixtures correspond to the superimposed diffractograms of SM and BCD, while these of the freeze-dried complexes show fewer and less intense peaks. This indicates that all freeze-dried compounds are markedly less crystalline than the physical mixtures or the pure components.

Similarly to BCD, the X-ray diffractograms of HPBCD complexes consisted fundamentally of a single very broad band, whereas these of physical mixtures of the same compositions corresponded to superimposition of the individual components diffractograms (Fig. 6).

X-ray and DSC studies indicate the formation of amorphous binary and multi-component complexes by freeze-drying between the cyclodextrins and the drug.

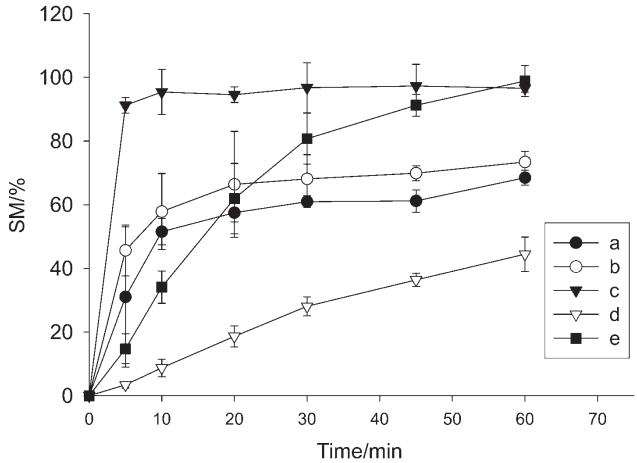

Fig. 7 Dissolution profiles of SM and different SM–BCD systems: a – SM, b – physical mixture SM+BCD, c – SM–BCD freeze-dried complex, d – physical mixture SM+BCD/K4M and e – SM–BCD/K4M freeze-dried complex

Effect of complexation on the dissolution of sulphamethizole

Figures 7 and 8 illustrate the dissolution profiles obtained with pure drug, physical mixtures and the inclusion complexes in water. In both cases, the liberation of the drug is delayed from the multicomponent system, showing the typical profile of a sustained release formulation. In fact, in spite of the stability constant of BCD being higher when the polymer is present, for the multicomponent system prepared with K4M, the dissolution rate of the drug is lower. This effect is also clear for HPBCD multicomponent complex. It seems that when the complex makes contact with the dissolution medium, K4M swells and controls the release of the drug [21].

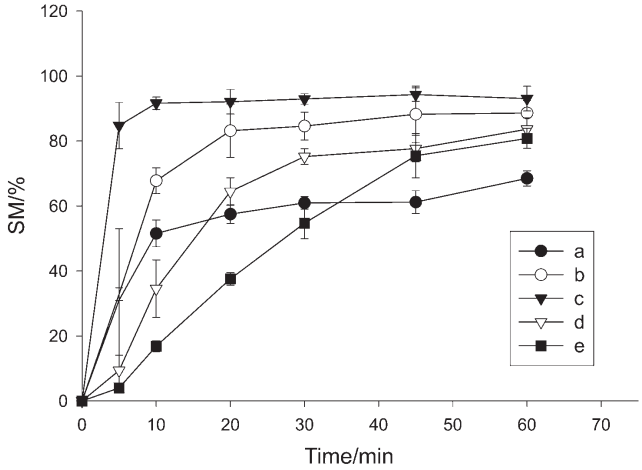

Fig. 8 Dissolution profiles of SM and different SM–HPBCD systems: a – SM, b – physical mixture SM+HPBCD, c – SM–HPBCD freeze-dried complex, d – physical mixture SM+HPBCD/K4M and e – SM-HPBCD/K4M freeze-dried complex

One-way Anova of the dissolution efficiency 0–60 min revealed significant differences between the formulations (BCD: $F_{4,10}$=74.09, α<0.05; HPBCD: $F_{4,10}$= 81.12, α<0.05). The Sheffé test grouped the formulations as follows:

BCD:

SM+BCD/K4M SM SM+BCD SM-BCD/K4M SM-BCD

HPBCD:

SM-HPBCD/K4M SM SM+HPBCD/K4M SM+HPBCD SM-HPBCD

where SM+CD are the binary physical mixtures, SM–CD the binary complexes, SM+CD/K4M the multimponent physical mixtures and SM–CD/K4M are the binary physical mixtures.

These results confirm that K4M controls the release of the drug, and in fact, the physical mixtures and inclusion complexes show, in both cases, the better dissolution profiles.

Conclusions

Our results show that K4M could enhance the complexation of SM with cyclodextrins in solution. This effect on SM solubility is only evident if an autoclaving process is included to promote the interaction between the cyclodextrin and the polymer. Solid multicomponent inclusion complexes with BCD or HPBCD and K4M can be obtained by freeze-drying and their formation has been proven using DSC and X-ray diffraction techniques. Additionally, the polymer allows to control the drug dissolution rate extending the process.

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