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EFFECT OF HYDROXYPROPYLMETHYL CELLULOSE ON THE COMPLEXATION OF DICLOFENAC WITH CYCLODEXTRINS

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Abstract

The effect of a hydrophilic polymer, hydroxypropylmethyl cellulose K4M, on the complexation of diclofenac sodium with β- and hydroxypropyl-β-cyclodextrins has been studied. Multicomponent systems were prepared with the drug, both cyclodextrin and the polymer. Phase solubility diagrams revealed the positive effect of the polymer on the complexation of the drug but this effect was found after autoclaving the solutions. Solid inclusion complexes were prepared by freeze-drying and characterized by thermal analysis (DSC) and X-ray diffractometry. In solid state, binary inclusion complexes enhance the dissolution behaviour of diclofenac but, from the β-cyclodextrin multicomponent complex, the polymer controls the release of the drug. In the case of hydroxypropyl-β-cyclodextrin multicomponent system, the solubility of the drugs increases significantly compared with the binary complex.

Keywords: β-cyclodextrin, cyclodextrin inclusion complexes, differential scanning calorimetry, dissolution, hydroxypropyl-β-cyclodextrin, hydroxypropylmethyl cellulose, sodium diclofenac, stability constant, X-ray diffractometry

Introduction

Aqueous solubility becomes, for many drugs, the main drawback for its formulation either in a liquid dosage form or in a controlled release one. Multiple technological alternatives have been used to overcome this problem – inclusion in colloidal systems such as liposomes, preparation of salts, etc. Among all of them, cyclodextrin complexation has seemed to the most promising one. Cyclodextrins (CDs) are cyclic α-(1,4)-linked oligomers of *D*-glucopyranose, which have been previously used in drug development to increase the water solubility of lipophilic compounds [1]. For several reasons, including toxicology, dosage and cost, the amount of cyclodextrins used in most of the formulations must be limited. Therefore, it is important to develop strategies to increase the effectiveness of cyclodextrin complexation that could be reflected in a reduction in the amount of CD necessary in a particular drug formulation.

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With this aim the use of water-soluble polymers [2], the preparation of drug/CD/hydroxy acid multicomponent systems [3] or the formation of CD complexes of salts of acidic drugs have been described [4]. The use of polymers has been extensively used in the recent years but the exact nature of the polymer: CD interaction is not known yet [5]. Among these polymers, hydrypropylmethyl cellulose K4M is one of the most frequently used for this purpose [6]. This cellulose derivative is a hydrophilic polymer which is well established like pharmaceutical excipient and it has been extensively used in controlled drug delivery systems.

The interaction polymer–CD has been tested in solution but solid complex has not been prepared. In a previous work [7] we analyzed the effect of HPMC–CD interaction on the solubility of sulphamethizole – a slightly water soluble and non ionic drug. Our results showed that, for this particular drug, the polymer increases the solubilizing effect of the CD but, when the solid complex was prepared, the solubility of the drug decreases compared with the binary complex drug–CD. In this particular case, the polymer allows to control the drug dissolution rate.

The aim of this study was to analyze the effect of hydroxypropylmethyl cellulose (K4M) on the complexation of diclofenac with two cyclodextrins, β-cyclodextrin (BCD) and hydroxypropyl-β-cyclodextrin (HPBCD). Diclofenac, has been selected as a model ionic drug which is widely used as nonsteroidal anti-inflammatory and analgesic. Its solubility in water is low, specially in gastric juice (about 15 μg mL^{-1}) and, it is unstable in aqueous solution [8]. This limited solubility in acidic medium seems to be a problem in its oral bioavailability and it is a drawback in its formulation in controlled release devices. This drug forms inclusion complexes with both cyclodextrins and the complexation increases its solubility [9–11].

Solid inclusion complexes containing diclofenac, cyclodextrins and HPMC 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 those of the uncomplexed drug.

Experimental

Materials

Sodium diclofenac (2-[(2,6-dichlophenyl) amino]benzeneacetic acid monosodium salt) was purchased from Sigma Chemical Co. (St. Louis, MO, USA). β-cyclodextrin and hydroxypropyl-β-cyclodextrin (D.S. 4.6) were a gift from Laisa-Roquette (Barcelona, Spain) and Janssen Pharmaceutiche (Belgium), respectively. Hydroxypropylmethyl cellulose K4M-Methocel® was purchased 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 [12]. Excess amounts of diclofenac were added to artificial gastric juice (USP 24 Ed.)

containing various concentrations of cyclodextrins. The suspensions were shaken at 37ºC for seven days.

To establish the effect of the polymer on the solubility diagrams, K4M was added (0.1 mass/vol%). The suspensions were autoclaved at 120ºC for 20 min and equilibrated for at least 3 days at room temperature, according to Loftsson *et al*. [13] .

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 diclofenac in simulated gastric juice without cyclodextrins. Drug concentration was analysed spectroscopically (Shimadzu UV-240-Graphicord) at 276 nm ($E_{1\%,1\ cm}$=283.85).

Preparation of the physical mixtures

Diclofenac, cyclodextrins and hydroxypropylmethyl cellulose were passed through 0.5 mm meshes and mixed in a Turbula T2C mixer for 10 min. Another sort of systems were prepared by adding K4M in the same concentration that in the inclusion complexes studied.

Preparation of the inclusion complexes

Equimolar amounts of diclofenac and cyclodextrins - BCD and HPBCD - were dissolved in 5% (mass/vol) aqueous ammonium hydroxide. K4M was added to obtain a final concentration of 0.1% (mass/vol), and the solution was let to stand for 24 h at 4ºC to left the system swollen. 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 25–250ºC.

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 behaviour of diclofenac in dissolution was compared not only in the physical mixtures but also in the inclusion complexes, and all of them with the pure drug.

Hard shell colorless gelatin capsules were employed to carry out these studies. Each capsule was filled with the quantity of formulation that contained 50 mg of drug. 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 artificial gastric juice and at 37ºC with a stirring speed of 50 rpm all experiments were made in triplicate. Samples of 5 mL were taken at pre-defined times and once they were filtered the drug was determined spectrophotometrically at 276 nm.

The resulting dissolution curves were characterized by the corresponding 0–180 min dissolution efficiency [14]. The statistical significance of differences among formulations 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).

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 higher than in simulated gastric juice (S_0). The introduction of small amounts of K4M in the solution medium did not improve the solubility just as a physical mixture. To obtain a significant increase of the solubility, the solutions had to be heated to 120ºC for 20 min (autoclaving).

Table 1 Effect of the addition of 0.1 mass/vol% K4M to 1 mass/vol% HPBCD and BCD solutions in artificial gastric juice on solubilization of diclofenac; S_0 – solubility of diclofenac in artificial gastric juice (mM); S_p – solubility in artificial juice 0.1 mass/vol% solution of the K4M with autoclaving process (mM); S_{co} – solubility in artificial gastric juice 1 mass/vol% CD solution (mM); S_{cp} – solubility in artificial gastric juice solution containing both 0.1 mass/vol% K4M and 1 mass/vol% CD (mM); S^*_{cp} – solubility in artificial gastric juice solution containing both 0.1 mass/vol% K4M and 1 mass/vol% CD with autoclaving process (mM)

	S_p	S^*_p	S_{co}	S_{cp}	S^*_{cp}	S_{cp}/S_{co}	S^*_{cp}/S_{co}
BCD	0.0157	0.0597	0.0698	0.0583	0.1369	0.8360	1.5086
HPBCD	0.0157	0.0597	0.1146	0.0838	0.1046	0.7309	0.9126

S_0=0.01638

Phase solubility diagrams of diclofenac in aqueous BCD and HPBCD solutions in the presence or absence of K4M are shown in Figs 1 and 2. In all cases, the diagrams can be included in the A_L-type according to Higuchi and Connors classification. The slope of the diagrams is lower than 1, and therefore, the complex responsible of the increase in drug solubility has a 1:1 mol:mol stoichiometry [12] K4M enhanced significantly the solubilizing effect of CDs but did not affect the type of the phase-solubility diagram.

The apparent stability constants of diclofenac-BCD and diclofenac-HPBCD with and without K4M were calculated from the slopes of the phase-solubility dia-

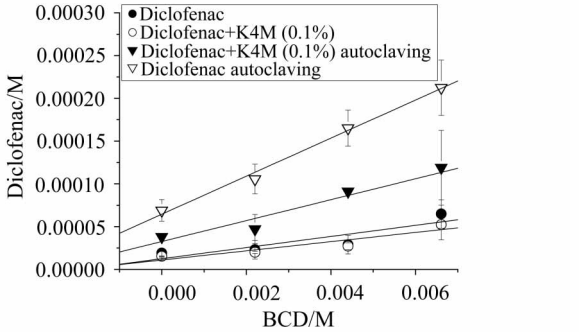

Fig. 1 Phase-solubility diagrams of diclofenac in artificial gastric juice BCD solutions containing different BCD solutions with 0 and 0.1% K4M at 37ºC

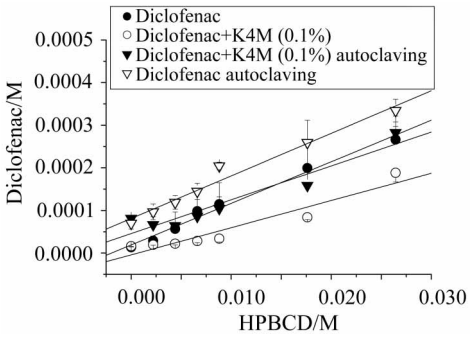

Fig. 2 Phase-solubility diagrams of diclofenac in artificial gastric juice HPBCD solutions containing different HPBCD solutions with 0 and 0.1% K4M at 37ºC

grams assuming a 1:1 stoichiometry (Table 2). The stability constants of the inclusion complexes show, in both cases, an enhancement in the presence of K4M. The effect has been found higher after autoclaving which makes this process necessary to obtain a good interaction between the cyclodextrin and the polymer. During this autoclaving process, the rise in temperature caused a saturation and an increase in the solubility of the drug, this fact could probably lead to improve interactions between diclofenac, the CD molecules and the polymer. The improved solubilization after autoclaving could be due to the several electrostatic forces involved and a facilitated fitting of the guest molecule into the cavity. The fact of heating the CD systems also shows a posi-

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

	BCD	HPBCD
Without K4M	100.60 M^{-1} (r^2=0.9684)	115.80 M^{-1} (r^2=0.9969)
With K4M	330.46 M^{-1} (r^2=0.9255)	392.03 M^{-1} (r^2=0.9545)
With K4M and autoclaving	777.17 M^{-1} (r^2=0.9846)	488.88 M^{-1} (r^2=0.9540)
Without K4M and autoclaving	1393.44 M^{-1} (r^2=0.9963)	630.11 M^{-1} (r^2=0.9855)

tive effect on diclofenac complexation. This methods has been extensively used to the preparation of solid inclusion complexes [15, 16].

Preparation and characterization of solid inclusion complexes

Freeze-drying was chosen as the method of preparation of solid inclusion complexes. It is a common technique that allows the preparation of cyclodextrin inclusion complexes with a high yield [17]. The complexes were prepared with a 1:1 drug:cyclodextrin molar ratio, according to the phase solubility diagrams for both CD. The polymer K4M was incorporated in a 0.1 mass/vol% ratio [6, 13]. The solid inclusion complexes were characterized using differential scanning calorimetry (DSC) and X-ray diffractometry.

DSC can provide a lot of information on drug/CD interactions in the solid state. The presence of hydrophilic polymer in multicomponent complexes could show different physicochemical properties from the individual cyclodextrin molecules or binary systems [18–21]. Figure 3 shows the DSC curves of the physical mixtures of Diclofenac 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 140ºC, which may be attributed to the evaporation of the adsorbed water. The drug does not have any significant peak in the temperature range analyzed because the melting and decomposition point is 283–285ºC (not shown). The peaks of the evaporation of water appeared in the temperature range of 50–150ºC. A physical mixture prepared with freeze-dried diclofenac and freeze-dried cyclodextrin was analysed. The system shows a similar behaviour to the physical mixture prepared without freeze-drying the compounds. In the freeze-dried complexes, the plots show the absence of the characteristic endothermic melting peak, while in the physical mixtures in which this peak is clearly visible. The disappear-

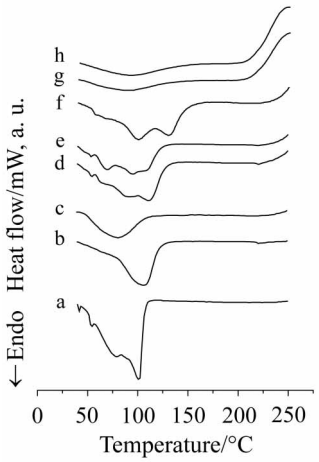

Fig. 3 DSC curves of different diclofenac-BCD systems: a – diclofenac; b – BCD; c – K4M; d – physical mixture diclofenac+BCD; e – physical mixture diclofenac+BCD/K4M; f – physical mixture freeze-dried diclofenac+freeze-dried BCD; g – diclofenac-BCD freeze-dried complex and h – diclofenac -BCD/K4M freeze-dried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

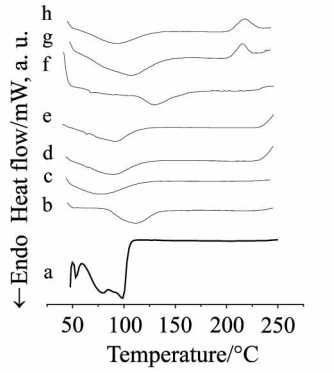

Fig. 4 DSC curves of different diclofenac-HPBCD systems: a – diclofenac; b – HPBCD; c – K4M; d – physical mixture diclofenac+HPBCD; e – physical mixture diclofenac+HPBCD/K4M; f – physical mixture freeze-dried diclofenac+freeze-dried HPBCD; g – diclofenac-HPBCD freeze-dried complex and h – diclofenac-HPBCD/K4M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

ance 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 (Fig. 4).

Figure 5 shows the X-ray diffraction spectra of diclofenac-BCD binary and multicomponent complexes in comparison with the physical mixture. The physical mixtures show diffraction patterns that correspond to the superimposed diffractograms of diclofenac and BCD, while the ones of the freeze-dried complexes show fewer and less intense peaks. All of this indicates that all freeze-dried compounds are markedly less crystalline than the physical mixtures or the pure components.

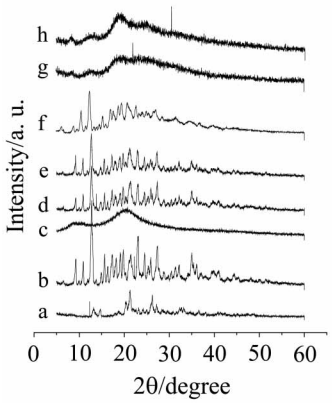

Fig. 5 X-ray diffraction patterns of different diclofenac-BCD systems: a – diclofenac; b – BCD; c – K4M; d – physical mixture diclofenac+BCD; e – physical mixture diclofenac+BCD/K4M; f – physical mixture freeze-dried diclofenac+freeze-dried BCD; g – diclofenac-BCD freeze-dried complex and h – diclofenac-BCD/K4M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

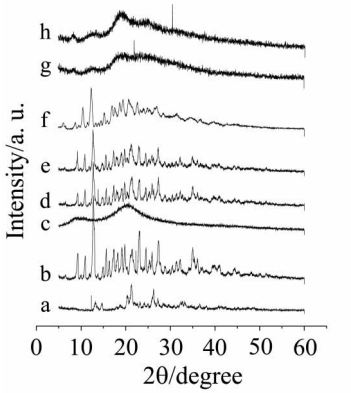

Fig. 6 X-ray diffraction patterns of different diclofenac-HPBCD systems: a – DIC; b – HPBCD; c – K4M; d – physical mixture diclofenac+HPBCD; e – physical mixture diclofenac+HPBCD/K4M; f – physical mixture freeze-dried diclofenac+freeze-dried HPBCD; g – diclofenac-HPBCD freeze-dried complex and h – diclofenac-HPBCD/K4M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

In the same way of 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 multicomponent complexes by freeze-drying bcetween the cyclodextrins and the drug.

Effect of complexation on the dissolution of diclofenac

The dissolution profiles corresponding to the pure drug, physical mixtures and the inclusion complexes (binary and multicomponent systems) in simulated gastric juice are shown in Figs 7 and 8.

One-way ANOVA of the dissolution efficiency 0–180 min revealed significant differences between the formulations (BCD: $F_{4,10}$=88.45, α<0.05; HPBCD:

BCD:
diclofenac diclofenac–BCD/K4M diclofenac+BCD/K4M diclofenac–BCD diclofenac+BCD

HPBCD:
diclofenac diclofenac+HPBCD diclofenac–HPBCD diclofenac+HPBCD/K4M diclofenac–HPBCD/K4M

$F_{4,10}$=96.49, α<0.05). The Sheffé test grouped the formulations as follows:
where Diclofenac+CD are the binary physical mixtures, Diclofenac–CD the binary complexes, Diclofenac+CD/K4M the multicomponent physical mixtures and Diclofenac–CD/K4M are the multicomponent complexes.

The effect of the polymer in the complex depends on the cyclodextrin used. In the case of BCD, the liberation of the drug is delayed from the multicomponent system, showing the typical profile of a sustained release formulation. In fact, although

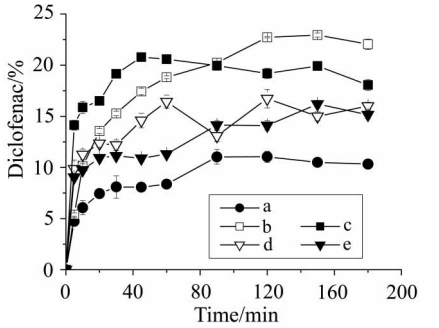

Fig. 7 Dissolution profiles of DIC and different DIC-BCD systems: a – DIC; b – physical mixture DIC+BCD; c – DIC-BCD freeze-dried complex; d – physical mixture DIC+BCD/K4M and e – DIC-BCD/K4M freeze-dried complex

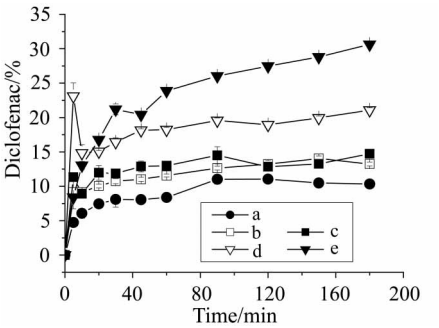

Fig. 8 Dissolution profiles of DIC and different DIC-HPBCD systems: a – DIC; b – physical mixture DIC+HPBCD; c – DIC-HPBCD freeze-dried complex; d – physical mixture DIC+HPBCD/K4M and e – DIC-HPBCD/K4M freeze-dried complex

the stability constant of BCD is higher when the polymer is present, for the multicomponent system prepared with K4M, the dissolution rate of the drug is lower compared with the binary system. It seems when the complex makes contact with the dissolution medium, K4M swells and controls the release of the drug [22] and, therefore, the effect of the CD complexation disappears. A similar behaviour has been found with both CDs in the case of a non-ionic drug such as sulphamethizole [6]. Nevertheless, HPBCD multicomponent complex significantly increases the solubility of the drug compare to the binary complex.

Conclusions

Our results show that K4M could enhance the complexation of diclofenac with cyclodextrins in solution. This effect on diclofenac 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 probed by

using DSC and X-ray diffraction techniques. The solid diclofenac-BCD multicomponent systems do not improve the solubility effect of the cyclodextrin, in fact, the polymer allows to control the drug dissolution rate extending the process. Nevertheless, the polymer increases the solubilizing effect of HPBCD not only in solution but also from a solid system.

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