Drug Development and Industrial Pharmacy, 2009; 35(10): 1264–1270

informa
healthcare

ORIGINAL ARTICLE

Influence of soluble and insoluble cyclodextrin polymers on drug release from hydroxypropyl methylcellulose tablets

Maria Esther Zugasti[1], Arantza Zornoza[2], María del Mar Goñi[1], José Ramón Isasi[2], Itziar Vélaz[2], Carmen Martín[2], Miguel Sánchez[2] and María Cristina Martínez-Ohárriz[2]

[1]*Department of Pharmacy and Pharmaceutical Technology, University of Navarra, Pamplona, Spain and* [2]*Department of Chemistry and Soil Science, University of Navarra, Pamplona, Spain*

Abstract

Background: The influence of β-cyclodextrin (β-CD) polymers on drug release from hydroxypropyl methylcellulose (HPMC) matrices has not been reported in the literature. *Aim*: The influence of monomeric β-CD and both soluble and insoluble β-CD polymers on drug release from tablets containing either 30% or 50% hydroxypropyl methylcellulose has been studied using diflunisal (DF) as model drug. *Method*: The DF-β-CD inclusion complex (1:1 M) was prepared by coevaporation and characterised using X-ray diffraction, differential thermal analysis, and IR spectroscopy. The dissolution assays were performed according to the USP paddle method. *Results*: The incorporation of β-CD in the complexed form increases drug release from hydroxypropyl methylcellulose tablets in comparison with the physical mixture because of the better solubilization of the drug. The soluble polymer promotes drug release to a higher extent than the physical mixture with monomeric β-CD, but the insoluble polymer, which is itself a hydrogel, gives rise to the most retarded release profile, probably by retention of the drug in its structure. The formulations containing physical mixtures with either β-CD or the soluble polymer present an optimum adjustment to zero-order release kinetics, and the inclusion complex followed non-Fickian diffusion according to the Korsmeyer–Peppas model. *Conclusion*: The release profile of DF from a HPMC matrix can be modulated in different ways by the use of either monomeric or polymeric β-CD.

Key words: *β-Cyclodextrin; drug release; HPMC; solid state; soluble and insoluble β-cyclodextrin polymers*

Introduction

Hydrophilic polymers have been extensively used in the preparation of oral controlled drug delivery systems, as they are advantageous both from the economic and the technologic points of view. Hydroxypropyl methylcellulose (HPMC) is one of the most employed carrier material for pharmaceutical applications[1]. This polymer displays good compression nature, can accommodate high levels of drug loading, and it is considered nontoxic and exhibits a high swelling capacity[2]. Upon contact with water, HPMC hydrates rapidly, leading to a transition from the glassy to the rubbery state, which results in the formation of a gel layer with a significant effect on the release kinetics of an incorporated drug[3].

Drug release from HPMC matrices is a complex process which is determined by different mechanisms such as polymer swelling and relaxation, drug dissolution, and diffusion and polymer erosion[4–6].

The profiles of drug release from HPMC matrices can be modified using different common excipients such as lactose, microcrystalline cellulose, and starch[7] and also in the presence of cyclodextrins (CDs)[8]. CDs are cyclic oligosaccharides made up of linked glucopyranose units; their more characteristic feature is the presence of a cavity that exhibits a hydrophobic character, while the outside of the molecule is hydrophilic[9].

Address for correspondence: Dr. María Cristina Martínez-Ohárriz, Departamento de Química y Edafología, Facultad de Ciencias, Universidad de Navarra, Irunlarrea s/n, Pamplona 31080, Spain. Fax: +34 948 425 649. E-mail: moharriz@unav.es

(Received 12 Sep 2008; accepted 10 Mar 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040902882306

This relatively nonpolar cavity can form inclusion compounds that have been widely used to improve the solubility, bioavailability, and stability of pharmaceuticals[10].

The influence of monomeric CDs on drug release from HPMC matrices has been reported previously, but to our knowledge, the influence of β-cyclodextrin polymers (β-CDPs) on drug release from HPMC matrices has not been reported in the literature, and this is the main novelty of this work.

Complexation with monomeric CDs can either enhance or retard drug release from HPMC matrices depending on the characteristics of the system such as drug solubility, drug loading, and diffusivity of the complexes formed. The effect of β- and hydroxypropyl-β-CD on the release of sulfamethizole and diclofenac sodium from HPMC tablets was found to be a balance between the increase in dissolution rate and the decrease in diffusion rate[11]. Complexation with β-CD increased carbamazepine, ketoprofen, and naproxen release from HPMC matrices because of the solubility enhancements[12–14]. In addition, the release of vinpocetine from HPMC tablets was improved significantly in the presence of β-CD and sulfobutylether-β-CD as a result of complexation[15], but in the case of ibuprofen[16], the incorporation of β-CD as diluent led to a small increase.

CDs can be linked by covalent bonds giving rise to CDPs. Both soluble and insoluble β-CDPs can be obtained by cross-linking with bifunctional or multifunctional reagents. The application fields of these materials are in continuous development as new CDPs are being synthesized. There is limited evidence in the literature about the use of CDPs for the enhancement of drug release. A β-CDP was studied as a controlled release system based on pH-dependent inclusion complexation using methyl orange as model compound[17]. Water-soluble cationic β-CDPs were proposed as drug carrier systems with better hemolytic activity than β-CD[18]. In addition, the cross-linking of hydroxypropyl-β-CD with ethyleneglycol diglycidyl ether yielded a hydrogel with good controlled release ability and high drug loadings[19,20].

As it was said before, the main novelty of our work is the incorporation of both soluble and insoluble β-CDPs cross-linked with epichlorohydrin to HPMC matrices. The aim of this article was to investigate the possible use of these polymers of CDs to modulate, either to enhance or to retard, the release of a model drug from HPMC matrices. Diflunisal (DF), 5-(2,4-difluorophenyl)-2-hydroxy benzoic acid, a nonsteroidal anti-inflammatory drug, was chosen as a model compound because previous studies had shown that the inclusion of DF in the cavity of β-CD was very favorable[21]. Therefore, this work compares the release of DF from HPMC tablets containing either monomeric β-CD or β-CD-soluble and β-CD-insoluble polymers.

Materials and methods

Materials

DF (MW 250.2) was supplied by Merck Sharp and Dohme (Madrid, Spain), and HPMC K4M was obtained from Colorcon (Orpington, UK). β-CD (MW 1135) was kindly donated by Roquette (Lestrem, France), and the β-CD-soluble polymer (batch no. CYL-265) was purchased from Cyclolab (Budapest, Hungary). The insoluble polymer of β-CD cross-linked with epichlorohydrin (50CD69EP) was synthesized by bulk polymerization in our laboratory as described by García-Zubiri et al.[22]

Preparation and characterization of DF-β-CD inclusion complex

The inclusion complex between DF and β-CD in 1:1 molar ratio has been prepared by the coevaporation method using ammonium aqueous solution (pH 12). DF (150 mg) and β-CD (750 mg) were dissolved in aqueous solution (pH 12), and the solvent was eliminated by vacuum evaporation (Buchi-R144) at 60°C.

The formation of the complex was evidenced by X-ray diffractometry (Bruker axs D8 ADVANCE, CuK_{α}, 40 kV, 30 mA), IR spectroscopy (Nicolet FTIR spectrometer), and differential thermal analysis (DTA/TGA 851 Mettler Toledo) in comparison with the DF-β-CD physical mixture in the same molar ratio.

Preparation of HPMC matrix tablets

The polymers were incorporated to the formulation by simple physical mixture, while the influence of monomeric β-CD has been analyzed both in the complexed form and physically mixed.

The formulations (Table 1) contained either 30% HPMC or 50% HPMC, and the tablet weights were 132 and 182 mg, respectively. In addition, these formulations contained either 69.5% or 49.5% of the following components: DF-β-CD physical mixture (PM30, PM50), inclusion complex (C30, C50), and DF physical mixture with soluble β-CDP (SP30, SP50) and with insoluble

Table 1. Matrix tablet composition (%).

	Formulation							
Component	PM30	PM50	C30	C50	SP30	SP50	IP30	IP50
Diflunisal	11.4	8.2	11.4	8.2	11.4	8.2	11.4	8.2
HPMC	30	50	30	50	30	50	30	50
β-CD	58.1	41.3	58.1	41.3	—	—	—	—
Soluble polymer	—	—	—	—	58.1	41.3	—	—
Insoluble polymer	—	—	—	—	—	—	58.1	41.3
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

β-CDP (IP30, IP50). All the mixtures contained 15 mg of DF and 0.5% of magnesium stearate. HPMC matrix tablets were obtained by direct compression of the formulation mixtures using a Manesty B3B rotative machine.

Dissolution studies

The dissolution rate assays were performed according to the USP 28 paddle method in a Sotax AT7 Smart with automated UV-vis spectrophotometric determination of drug concentration at 252 nm. The dissolution medium was 900 mL of phosphate buffer solutions (pH 5) maintained at 37 ± 0.1°C and stirred at 100 rpm.

A mathematical comparison of the dissolution profiles was carried out using a model-independent pairwise procedure based on the determination of difference (f_1) and similarity (f_2) factors[23,24].

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\},$$

where n is the number of time points, R_t is the dissolution value of the reference formulation at time t, and T_t is the dissolution value of the test formulation at time t. In the comparison of a pair of profiles, the formulation with the more rapid release was always taken as reference.

The release profiles of the different matrices were tested for correspondence with different kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas using experimental data of drug release from 5% to 65–70%[23,24].

Studies of retention of diflunisal by a β-CD-insoluble polymer

An aqueous 4×10^{-5} M solution (pH 5, 50 mL) of DF was stirred at 150 rpm in the presence of 0.3 g of the insoluble polymer. Samples were taken from the supernatant until the sorption equilibrium was reached (1 hour), and the residual concentrations of DF were determined spectrophotometrically at 252 nm using a HP 8452 A diode array spectrophotometer.

Results and discussion

Evidence of complex formation between DF and β-CD in the solid state

The formation of an inclusion complex between DF and β-CD has been evidenced in solution[21], but complexation in the solid state has not been reported in the literature. Therefore, as a previous step before the preparation of tablets C30 and C50, an inclusion complex between DF and β-CD in the solid state has been obtained and characterized. The complex, with 1:1 stoichiometry, was prepared by the coevaporation method[9] and subsequently analyzed using X-ray diffraction, IR spectroscopy, and differential thermal analysis by comparison with the corresponding physical mixture.

The diffraction pattern of the physical mixture (Figure 1) was simply a superposition of both components, whereas in the diffraction pattern of the complex, the peak of pure DF at $2\theta = 14.6°$ (form II)[25] disappeared and new reflections appeared, especially between $2\theta = 16°$ and 22°, suggesting the formation of a new solid phase which was markedly less crystalline than the mixture of pure components.

The differential thermal analysis of DF showed a sharp endothermic peak at 212°C, which corresponded to the melting of the drug (Figure 2). This endothermic peak was detected in the physical mixture, but it disappeared in the coevaporated system. This fact can be considered evidence of complex formation between DF and β-CD in the solid state.

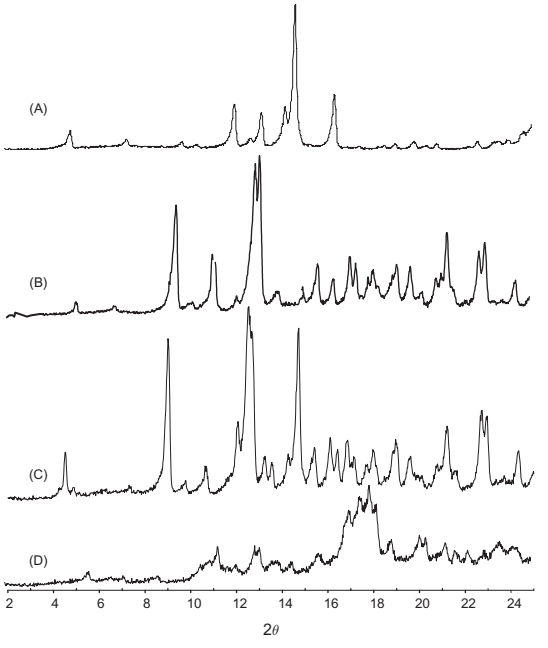

Figure 1. X-ray diffraction patterns of diflunisal (A), β-CD (B), physical mixture (C), and inclusion complex DF-β-CD (D).

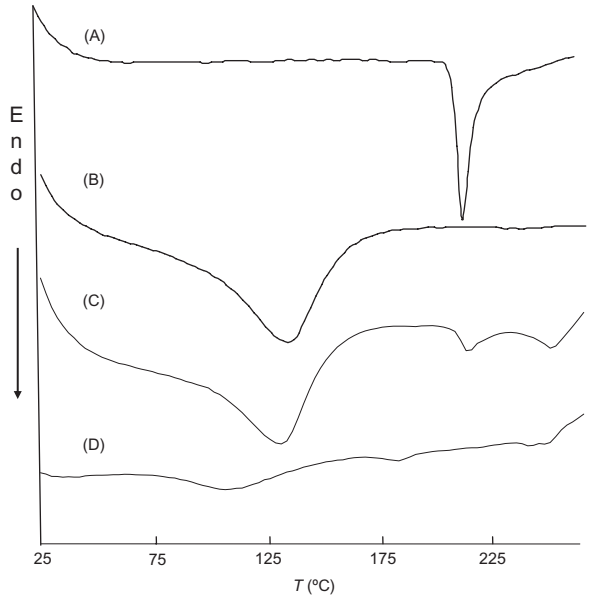

Figure 2. DTA curves of diflunisal (A), β-CD (B), physical mixture (C), and inclusion complex DF-β-CD (D).

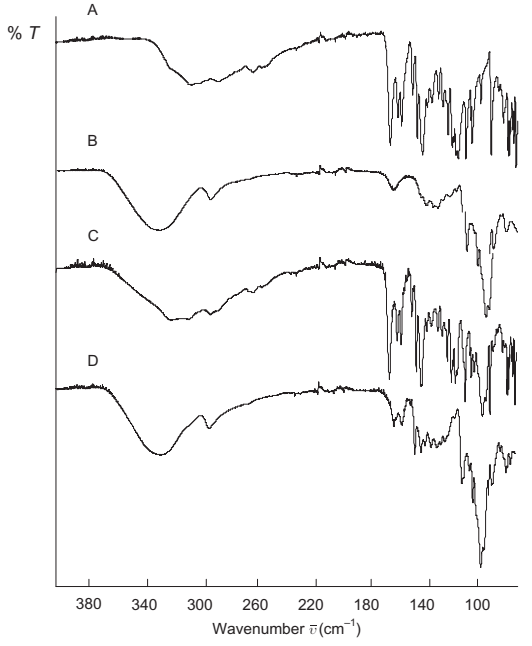

Figure 3. IR spectra of diflunisal (A), β-CD (B), physical mixture (C), and inclusion complex DF-β-CD (D).

The most significant changes in the IR spectra between the physical mixture and the complex (Figure 3) were found in the characteristic frequencies of the carbonyl (1670–1640 cm^{-1}), phenyl (1600–1580 cm^{-1}), and fluorine (1400–1300 cm^{-1}) groups, which are implicated in the formation of hydrogen bonds among the DF molecules. In addition, marked differences were detected between both systems in the fingerprint region.

Dissolution studies

The drug/HPMC ratio is one of the most important parameters that determine drug release from HPMC matrices[26]. The dissolution profiles of the matrices containing 30% HPMC in aqueous solution (pH 5) exhibited DF extended release during a period of more than 12 hours, and the formulations with 50% HPMC prolonged DF release up to 18–24 hours. This extended release is associated with the swelling of the hydrophilic HPMC tablets in contact with the dissolution medium, which results in a gel layer with a longer diffusional path at higher polymer concentration.

Figure 4 shows the dissolution profiles of the different HPMC tablets in aqueous solution (pH 5). As can be seen, significant differences have been obtained among the formulations tested. The most rapid release was obtained for the complex with β-CD, followed by the physical mixtures with both soluble polymeric and monomeric β-CD, whereas the lowest release rate was that of the formulations containing the insoluble β-CDP.

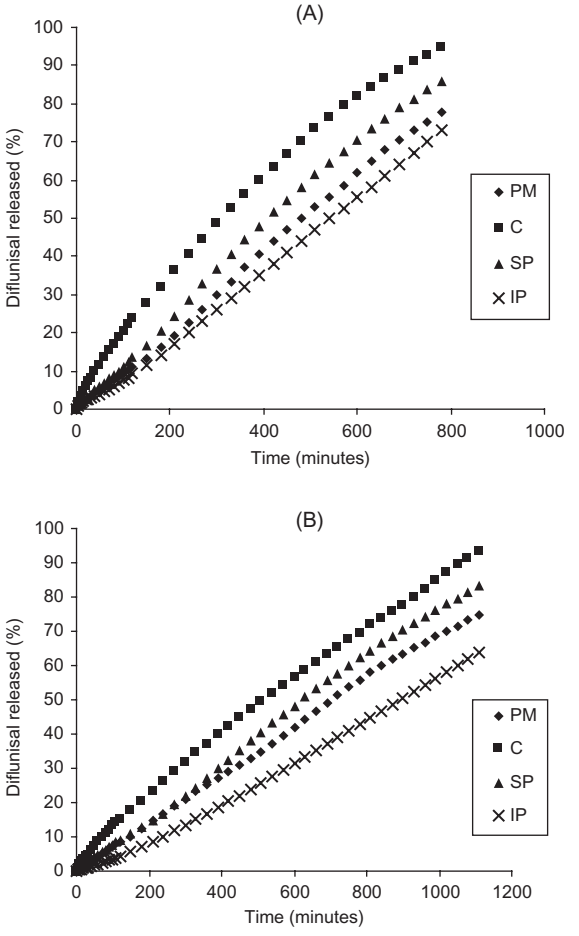

Figure 4. Dissolution profiles of formulations containing 30% HPMC (A) and 50% HPMC (B). Key: physical mixture (PM) and inclusion compound (IC) with β-CD, soluble β-CD polymer (SP),w and insoluble β-CD polymer (IP).

Table 2. Values of f_1 and f_2 in the pairwise comparison.

	30% HPMC		50% HPMC	
Comparisons	f_1	f_2	f_1	f_2
Complex/soluble polymer	23.3	47.9	17.1	54.5
Soluble polymer/physical mixture	15.7	59.9	10.2	65.4
Physical mixture/insoluble polymer	12.4	68.4	23.7	50.0
Complex/physical mixture	35.4	38.5	25.6	45.4
Soluble polymer/insoluble polymer	35.4	38.5	33.5	42.4

To compare the dissolution profiles obtained, a model-independent pairwise procedure based on the determination of difference (f_1) and similarity (f_2) factors[27] has been applied, and the results are summarized in Table 2. It was possible to calculate these values using the mean percent dissolved of each pair of curves, because the dispersion associated with each dissolution profile was markedly low, with variation coefficients below 5% in all the experimental determinations of percent dissolved. In general, values of f_1 up to 15 and values of f_2 higher than 50 indicate sameness of the two curves[28]. Significant differences were obtained between the complex and the physical mixture and also between the use of either soluble or insoluble polymers at both 30% and 50% HPMC contents. The dissolution profiles of the tablets containing physical mixtures with either monomeric β-CD (PM30, PM50) or soluble polymer (SP30, SP50) have been found to be similar in terms of f_1 and f_2 values although the polymer exhibits higher release rates at both 30% and 50% HPMC contents. The difference between the formulations containing the physical mixture with β-CD and the insoluble polymer was evidenced by the f_1 and f_2 values only in the case of 50% HPMC matrices.

For a better analysis of the release mechanisms, it is important to take into account some characteristics of the drug[29]. It has to be considered that the drug is poorly soluble in aqueous solution (pH 5) and also that the carboxylic group of DF (pK_a 3.3) is partially ionized at this pH value while the phenolic group is neutral (pK_a 14). In relation to this, it seems that the incorporation of the drug in the complexed form to the HPMC matrix results in an improved solubilization, which leads to a more rapid release compared with the physical mixture with β-CD. It is well known that drug solubility plays an important role in the mechanism of release from a hydrophilic matrix. In general, and simplifying all the processes implicated, it can be stated that the predominant mechanism for soluble drugs is diffusion through the hydrogel, often with first-order kinetics, while insoluble drugs are more frequently released by matrix erosion with zero-order kinetics[4].

The release mechanism from each formulation was evaluated according to several kinetic mathematical models[23,24]: zero-order, first-order, Higuchi, and Korsmeyer–Peppas. Table 3 summarizes the parameters of the fittings obtained for each formulation. The well-known equation that describes the Korsmeyer–Peppas kinetic mathematical model is the power law $M_t/M_\infty = kt^n$, where M_t and M_∞ are the drug released amounts at time t and at an infinite time, respectively, k is a kinetic constant, t is the release time, and n is the exponent that can be associated with the drug transport mechanism. For cylindrical matrices, like those prepared in this work, n values of 0.45 indicate diffusion-controlled drug release and n values of 0.89 correspond to swelling-controlled release, while intermediate values between 0.45 and 0.89 indicate a superposition of both mechanisms[30].

In relation to the Higuchi model, a good correlation between the cumulative amount of drug released and the square root of time is indicative of diffusion-controlled drug release. The fact that none of the formulations studied fitted the Higuchi equation with a good correlation points out that the mechanism of drug release is not only diffusional, but there are also other processes implicated.

The formulations containing physical mixtures of DF with either β-CD or soluble β-CDP (PM30, PM50, SP30, and SP50) exhibited similar behaviors, they fitted the zero-order model ($M_t/M_\infty = kt$). This type of profile involves the release of the same amount of drug per unit of time, a very interesting behavior for an extended release

Table 3. Fitting results of the experimental diflunisal release data for several formulations to different kinetic equations.

	Zero-order ($Q_t = Q_0 + k_0 t$)		First-order ($Q_t = Q_\infty (1 - e^{-kt})$		Higuchi ($Q_t = k_H t^{1/2}$)		Korsmeyer–Peppas ($M_t/M_\infty = kt^n$)		
Formulation	k_0 (% min^{-1})	R^2	k_1 (min^{-1})	R^2	k_H (mg/min$^{1/2}$)	R^2	k_{KP} (min^{-n})	n	R^2
PM30	0.1010	**0.998**	0.0018	0.9852	0.4904	0.9545	0.0008	1.04	0.9979
C30	0.1200	0.9824	0.0024	**0.9929**	0.5615	0.9866	0.0056	0.78	0.9996
SP30	0.1172	**0.9983**	0.0024	0.9888	0.5034	0.9539	0.0014	1.02	0.9972
IP30	0.0573	**0.9968**	0.0017	0.9862	0.4132	0.9331	0.0004	1.13	0.9993
PM50	0.0673	**0.9978**	0.0013	0.9733	0.3949	0.9633	0.0007	1.00	0.9995
C50	0.0831	**0.9949**	0.0015	0.9917	0.4341	0.9760	0.0030	0.82	0.9997
SP50	0.0770	**0.9985**	0.0015	0.9866	0.4339	0.9591	0.0007	1.01	0.9968
IP50	0.0591	**0.9984**	0.0011	0.9675	0.3499	0.9280	0.0001	1.21	0.9989

Best results in bold face; R^2 is the coefficient of determination.

pharmaceutical dosage form. Similar results were obtained for the physical mixture carbamazepine-β-CD incorporated to a HPMC matrix, which also exhibited zero-order release kinetics, unlike the system incorporating the previously complexed carbamazepine[14]. Both monomeric β-CD and the soluble polymer incorporated to the matrix by physical mixture can act as channeling agents and also as in situ complexing agents[12]. The relatively higher release associated with the polymer could be related to an increasing porosity of the system during the release process because of its higher molecular weight and also because of its higher aqueous solubility, compared with monomeric β-CD.

The formulation that incorporated the complex of DF with β-CD (C30, C50) presented the most rapid release kinetics. They followed non-Fickian diffusion with n = 0.78 and 0.82, respectively. As it was said before, it is common that water-soluble drugs follow a diffusion-controlled release with first-order kinetics, whereas insoluble drugs are released mainly by erosion with zero-order kinetics[4]. The experimental results obtained followed this trend, as the increased release of the complexed drug, associated with its higher solubility, involved an approximation to first-order kinetics while the physical mixtures fitted to zero-order kinetics.

Finally, the formulation containing the insoluble β-CDP presented a $n > 1.0$ exponent that corresponds to a Super Case II transport, which can be associated with structural changes in the polymeric matrix involving an increased plasticization at the relaxing boundary[31]. This behavior could be explained by the fact that the insoluble polymer is itself a hydrogel which can swell, giving rise to distortions in the HPMC gel structure. In addition, this formulation exhibits the slowest release of DF. Taking into account that the insoluble polymer cannot diffuse through the HPMC matrix, it can retard DF release due to the fact that part of the drug can be retained by sorption in the polymeric structure. Our previous studies of different molecular interactions with CDPs suggested that sorption in the polymeric structure results from inclusion within the CD cavities together with interaction with the polymeric network[32]. In the case of DF, a study of retention by the β-CD-insoluble polymer has been carried out in aqueous solution (pH 5) at 37°C, experimental conditions similar to those of the dissolution rate assays. It was determined that 88 ± 1% of a 4×10^{-5} M solution of DF was retained by 300 mg of polymer. This evidence of drug retention by the polymer might be an explanation for the retarded drug release in formulations IP30 and IP50.

Conclusions

The release profile of DF from a HPMC matrix can be modulated by the use of either monomeric or polymeric β-CD in different ways. First, the incorporation of DF previously complexed with β-CD enhances the release of the drug in comparison with the simple physical mixture. In addition, it is possible to modify drug release from HPMC matrices by incorporating β-CDPs with different solubility, as soluble polymers promote drug release while insoluble polymers are able to retain the drug mainly by inclusion within the CD cavities present in the polymeric structure.

Acknowledgments

The authors acknowledge the University of Navarra (PIUNA) and the Ministerio de Ciencia e Innovación (MAT2007-65752) for financial support.

Declaration of interest: The authors report no conflicts of interest.

References

1. Siepmann J, Peppas NA. (2001). Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev, 48:139–57.
2. Fu XC, Wang GP, Liang WQ, Chow MSS. (2004). Prediction of drug release from HPMC matrices: Effect of physicochemical properties of drug and polymer concentration. J Control Release, 95:209–16.
3. Conti S, Maggi L, Segale L, Ochoa Machiste E, Conte U, Grenier P, et al. (2007). Matrices containing NaCMC and HPMC 1. Dissolution performance characterization. Int J Pharm, 333:136–42.
4. Bettini R, Catellani PL, Santi P, Massimo G, Peppas NA, Colombo P. (2001). Translocation of drug particles in HPMC matrix gel layer: Effect of drug solubility and influence on release rate. J Control Release, 70:383–91.
5. Siepmann J, Streubel A, Peppas NA. (2002). Understanding and predicting drug delivery from hydrophilic matrix tablets using the 'sequential layer' model. Pharm Res, 19:306–14.
6. Miranda A, Millán M, Caraballo I. (2006). Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery. Int J Pharm, 311:75–81.
7. Levina M, Rajabi-Siahboomi AR. (2004). The influence of excipients on drug release from hydroxypropyl methylcellulose matrices. J Pharm Sci, 93:2746–54.
8. Bibby DC, Davies NM, Tucker IG. (2000). Mechanisms by which cyclodextrins modify drug release from polymeric drug delivery systems. Int J Pharm, 197:1–11.
9. Szejtli J, Osa T. (1996). Cyclodextrins, comprehensive supramolecular chemistry, vol. 3. Oxford (UK): Pergamon.
10. Loftsson T, Duchêne D. (2007). Cyclodextrins and their pharmaceutical applications. Int J Pharm, 329:1–11.
11. Pose-Vilarnovo B, Rodríguez-Tenreiro C, Rosa dos Santos JF, Vázquez-Doval J, Concheiro A, Alvarez-Lorenzo C. (2004). Modulating drug release with cyclodextrins in hydroxypropyl methylcellulose gels and tablets. J Control Release, 94:351–63.
12. Koester LS, Clarissa RX, Mayorga P, Bassani VL. (2003). Influence of β-cyclodextrin complexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets. Eur J Pharm Biopharm, 55:85–91.
13. Sangalli ME, Zema L, Maroni A, Foppoli A, Giordano F, Gazzaniga A. (2001). Influence of betacyclodextrin on the release of poorly soluble drugs from inert and hydrophilic heterogeneous polymeric matrices. Biomaterials, 22:2647–51.

14. Koester LS, Ortega GG, Mayorga P, Bassani VL. (2004). Mathematical evaluation of in vitro release profiles of hydroxypropylmethylcellulose matrix tablets containing carbamazepine associated to β-cyclodextrin. Eur J Pharm Biopharm, 58:177–9.
15. Ribeiro L, Ferreira DC, Veiga FJB. (2005). In vitro controlled release of vinpocetine-cyclodextrin-tartaric acid multicomponent complexes from HPMC swellable tablets. J Control Release, 103:325–39.
16. Vueba ML, Batista de Carvalho LA, Veiga F, Sousa JJ, Pina ME. (2005). Role of cellulose ether polymers on ibuprofen release from matrix tablets. Drug Dev Ind Pharm, 31:653–65.
17. Liu YY, Fan XD, Kang T, Sun L. (2004). A cyclodextrin microgel for controlled release driven by inclusion effects. Macromol Rapid Commun, 25:1912–6.
18. Li J, Xiao H, Li J, Zhong YP. (2004). Drug carrier systems based on water-soluble cationic β-cyclodextrin polymers. Int J Pharm, 278:329–42.
19. Rodriguez-Tenreiro C, Alvarez-Lorenzo C, Rodriguez-Perez A, Concheiro A, Torres-Labandeira JJ. (2006). New cyclodextrin hydrogels cross-linked with diglycidylethers with a high drug loading and controlled release ability. Pharm Res, 23:121–30.
20. Rodriguez-Tenreiro C, Alvarez-Lorenzo C, Rodriguez-Perez A, Concheiro A, Torres-Labandeira JJ. (2007). Estradiol sustained release from high affinity cyclodextrin hydrogels. Eur J Pharm Biopharm, 66:55–62.
21. Zornoza A, Sánchez M, Vélaz I, Fernandez L. (1999). Diflunisal and its complexation with cyclodextrins. A fluorimetric study. Biomed Chromatogr, 13:111–2.
22. García-Zubiri IX, González-Gaitano G, Isasi JR. (2007). Isosteric heats of sorption of 1-naphthol and phenol from aqueous solutions by cyclodextrin polymers. J Colloid Interface Sci, 307:64–70.
23. Costa P, Sousa Lobo JM. (2001). Modeling and comparison of dissolution profiles. Eur J Pharm Sci, 13:123–33.
24. Costa FO, Sousa JJS, Pais AACC, Formosinho SJ. (2003). Comparison of dissolution profiles of ibuprofen pellets. J Control Release, 89:199–212.
25. Martínez-Oharriz MC, Martín C, Goñi MM, Rodríguez-Espinosa C, Tros de Ilarduya-Apaolaza MC, Sánchez M. (1994). Polymorphism of diflunisal: Isolation and characteristics of a new crystal form. J Pharm Sci, 83:174–7.
26. Velasco MV, Ford JL, Rowe P, Rajabi-Siahboomi AR. (1999). Influence of drug:hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. J Control Release, 57:75–85.
27. Moore JW, Flanner HH. (1996). Mathematical comparison of dissolution profiles. Pharm Tech, 20:64–74.
28. FDA. (1977). Guidance for industry: Dissolution testing of immediate release solid oral dosage forms. Rockville (MD): FDA Center for Drug Evaluation and Research. http://www.fda.gov/cder/guidance.htm [accessed August 25, 1997].
29. Cotton M, Hux R. (1985). Diflunisal. In: Florey K, ed. Analytical profiles of drug substances. London: Academic Press, Inc., 491–526.
30. Peppas NA. (1985). Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv, 60:110–1.
31. Ferrero C, Muñoz-Ruiz A, Jiménez-Castellanos MR. (1985). Fronts movement as a useful tool for hydrophilic matrix release mechanism elucidation. Int J Pharm, 202:21–8.
32. Gazpio C, Sánchez M, Isasi JR, Vélaz I, Martín C, Martínez-Oharriz C, Zornoza A. (2008). Sorption of pindolol and related compounds by a beta-cyclodextrin polymer. Isosteric heat of sorption. Carbohydr Polym, 71:140–6.