Carbohydrate Polymers 87 (2012) 2024–2030

Contents lists available at SciVerse ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

β-Cyclodextrin hydrogels as potential drug delivery systems

Rubén Machín, José Ramón Isasi, Itziar Vélaz*

Department of Chemistry and Soil Science, Faculty of Sciences, University of Navarra, C/Irunlarrea s/n, Pamplona, 31080 Navarra, Spain

ARTICLE INFO

Article history:
Received 9 June 2011
Received in revised form 23 August 2011
Accepted 6 October 2011
Available online 18 October 2011

Keywords:
β-cyclodextrin hydrogels
Diffusion coefficients
Release profiles
Drug delivery

ABSTRACT

β-cyclodextrins (βCD) are cyclic oligosaccharides which have been widely employed for pharmaceutical applications. Discs of insoluble polymers were synthesized by crosslinking β-cyclodextrins with the reagent epichlorohydrin. In this work, the possibility of employing a polymer containing 60 ± 3% βCD for drug delivery of two antiinflammatory (naproxen and nabumetone) and two antifungal drugs (naftifine and terbinafine) has been investigated. The interaction of Naproxen with the polymers was evidenced by X-ray diffractometry, FTIR spectroscopy and differential thermal analysis. Drug release kinetics were carried out at physiological conditions of pH and temperature, and kinetic and diffusion constants were calculated by fitting 60% of the release profile according to the Korsmeyer–Peppas equation. Also, diffusion coefficients were calculated according to the simplified Higuchi model. The drug release followed a simple Fickian diffusion mechanism for all the model drugs. This study suggests that these hydrogel matrices are potentially suitable as sustained release systems.

1. Introduction

β-cyclodextrin (βCD), a natural molecule derived from starch, is a torus-shaped cyclic oligosaccharide with a relatively hydrophobic cavity (Szejtli, 1998). It is well known that this structure gives rise to a remarkable capacity to form inclusion complexes with organic molecules, through host–guest interactions (Dodziuk, 2006). A great variety of applications for CDs has been described: water purification, analytical separations, food and pharmaceutical industry uses (Skold, Thyne, Drexler, & McCray, 2009; Szejtli & Osa, 1996; Szente & Szejtli, 2004). Numerous studies have revealed that CDs are capable of improving the solubility and bioavailability of poorly soluble drugs (Loftsson & Masson, 2004; Szejtli & Osa, 1996).

The efficiency and applicability of cyclodextrins can be increased if they are incorporated into a polymeric structure (i.e. an insoluble three-dimensional network) (Cesteros, Ramírez, Peciña, & Katime, 2006, Cesteros, Ramírez, Peciña, & Katime, 2007; García-Zubiri, González-Gaitano, & Isasi, 2007; Renard, Deratani, Volet, & Sebille, 1997). In the last 20 years, the pharmaceutical research studies have been focussed on obtaining new compounds useful for drug controlled release. Hydrogels are three dimensional high molecular weight networks which have acquired great importance because of their potential applications (Hoffman, 2002; Liu, Fan, Hu, & Tang, 2004; Lowman, 2000; Pasparakis & Bouropoulos, 2006; Peppas & Klier, 1991).

β-cyclodextrin insoluble polymers using epichlorohydrin as a crosslinking agent can be obtained as reported previously (Fig. 1) (Crini & Morcellet, 2002). The high capacity of retaining water for these polymers suggests the possibility of using them as carriers of drugs for controlled release (Peppas & Ende, 1997). The controlled release allows keeping dosage of drugs within the therapeutic level. This fact reduces the administration frequency, toxicity and potential side effects.

Once the polymers have been obtained it is important to know the predominant mechanism of drug release (Lin & Metters, 2006). Incorporation of CDs into polymeric systems can influence these mechanisms (Liu et al., 2004; Pariot, Edwards-Levy, Andry, & Levy, 2002). The quantitative analysis of the physical, chemical and potentially biological phenomena, which are involved in the control of drug release, offers another fundamental advantage: the underlying drug release mechanisms can be elucidated (Siepmann & Siepmann, 2008).

Mechanistic mathematical theories are based on real phenomena, such as diffusion, dissolution, swelling, erosion, precipitation and/or degradation. This type of models allows for the determination of system specific parameters that can offer a deeper insight into the underlying drug release behaviour. For instance, the relative importance of several processes that are involved (e.g. drug diffusion and polymer swelling) can be estimated.

The aim of this work is the synthesis and characterization of novel β-cyclodextrin polymers (βCDP) as well as to study their applicability as drug carriers for drug release. The mechanisms involved in the process have been studied using four different model drugs (naproxen, NAP; nabumetone, NAB; naftifine, NF and terbinafine, TB; Fig. 2). Naproxen and the prodrug nabumetone

* Corresponding author. Tel.: +34 948425600; fax: +34 948425740.
E-mail address: itzvelaz@unav.es (I. Vélaz).

0144-8617/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2011.10.024

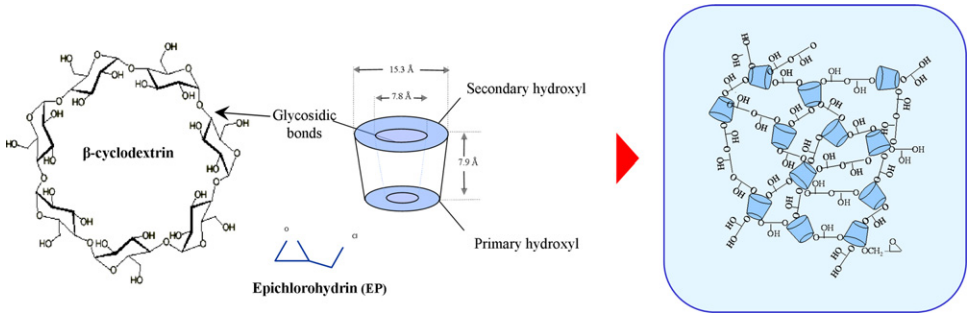

Fig. 1. βCD, epichlorohydrin and polymer network structures.

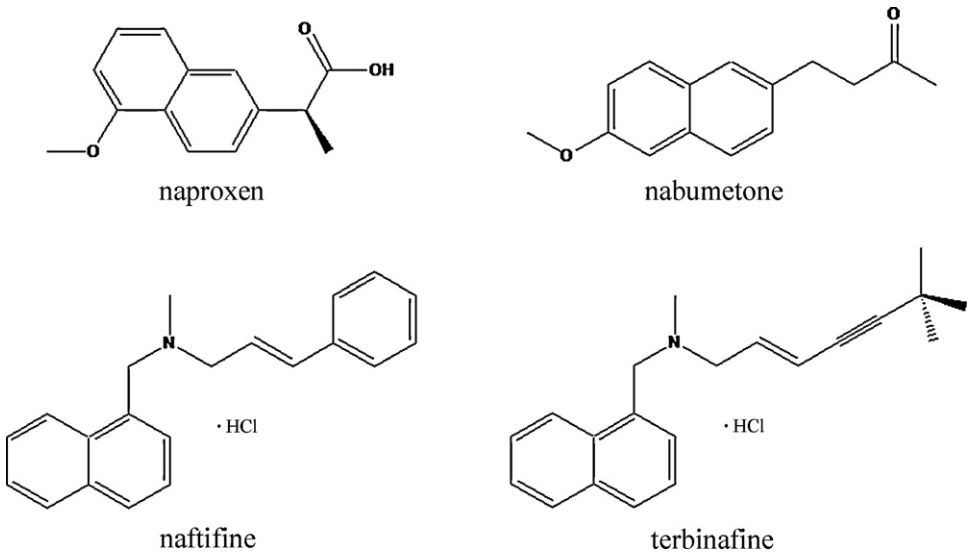

Fig. 2. Chemical structures of the drugs.

have anti-inflammatory effects in the symptomatic treatment of diseases such as osteoarthritis and rheumatoid arthritis. The allylamines naftifine (NF) and terbinafine (TB) are two antifungal drugs, whose mechanism involves inhibition of squalene epoxidation, an earlier stage in the ergosterol pathway.

Previous works have demonstrated the ability of cyclodextrins to retain the model drugs selected. The interaction between naproxen (Vélaz, Sánchez, Martín, Martínez-Ohárriz, & Zornoza, 1997; Vélaz et al., 2007) and nabumetone (Chen, Chang, & Gilson, 2004; Goyenechea et al., 2001, 2002) with β-cyclodextrin molecules has been extensively studied. More recent studies, carried out in our laboratory, have proved the formation of the inclusion complexes between β-cyclodextrin and the two antifungal drugs used as models (Uzqueda et al., 2006, 2009, 2010).

2. Experimental

2.1. Materials

β-cyclodextrin was purchased from Wacker (water content 12 ± 1%). Naproxen ((+)-6-methoxy-α-methyl-2-naphtaleneacetic acid; $C_{14}H_{14}O_3$; molecular weight: 230.3 g/mol; melting point: 156 °C) was obtained from Syntex-Latino. Nabumetone (4-(6-methoxy-2-naphthyl)-2-butanone; $C_{15}H_{16}O_2$; molecular weight: 228.3 g/mol; melting point: 80 °C) was from SmithKline-Beecham pharmaceuticals. Naftifine ((*E*)-N-methyl-N-(1-naphthylmethyl)-3-phenyl-2-propen-1-amine-hydrochloride; $C_{21}H_{22}NCl$; molecular weight: 323.5 g/mol; melting point: 177–179 °C) was kindly supplied by Schering. Terbinafine ((*E*)–N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethylamine-hydrochloride; $C_{21}H_{26}NCl$; molecular weight: 327.9 g/mol; melting point: 203–207 °C) was kindly supplied by Novartis. Reagents epichlorohydrin (EP) (Aldrich), $NaBH_4$ and NaOH (Panreac, analytical grade) were used as received. Release media were prepared using: HCl, Na_2HPO_4 and KH_2PO_4 (Panreac). All other reagents and solvents were from Panreac.

2.2. Synthesis and characterization of the cyclodextrin polymers

2.2.1. Polymer synthesis

β-cyclodextrin insoluble polymers (βCDP) were synthesized using the reagent epichlorohydrin. The EP: CD ratio was 11:1, and the synthesis temperature ranged between 25 and 60 °C. The procedure was previously detailed by García-Zubiri, González-Gaitano, & Isasi (2006) based on that of Crini et al. (1998).

In order to synthesize the cyclodextrin polymer, 12 g βCD were dissolved in 12 mL H_2O in a thermostated reactor vessel containing $NaBH_4$ (30 mg), that prevents oxidation of βCD. After homogenizing the mixture, an excess of NaOH 40% (w/w) (13 mL) was added. NaOH deprotonates the hydroxyl groups in the βCD, allowing them to react with EP. Epichlorohydrin was added slowly and with constant stirring at a constant temperature. Stirring continued until there was only a single homogeneous phase (see Table 1 for approximate gelation times); then the mixture was carefully transferred into a template using a syringe. Templates were made of two silanized glass squares (treated with a 4% solution of dichloromethylsilane in toluene) and a Teflon® ring, forming a cylindrical cavity (diameter 76 mm, thickness 3 mm). The samples

Table 1
Percentage of cyclodextrin, gelation times, and average size and weight of discs[a], for different synthesized polymers.

Polymer	% Cyclodextrin	Gelation time (min)	Diameter (mm)	Thickness (mm)	Dry weight (mg)
1125	64 ± 3	250–300	12.3 ± 0.1	2.9 ± 0.1	174 ± 2
1135	61 ± 3	120–150	12.7 ± 0.2	2.9 ± 0.1	179 ± 2
1150	60 ± 3	45–60	13.5 ± 0.3	3.3 ± 0.1	156 ± 8
1160	58 ± 3	25–30	14.2 ± 0.1	3.6 ± 0.1	133 ± 2

[a] Standard errors are indicated.

were introduced in an oven at the synthesis temperature, until complete gelation. Subsequently, moulds were carefully removed and the gels were cut with a cork borer (diameter 13 mm) to obtain smaller discs.

Once the polymers have been cut into small discs, they were washed twice: water was replaced after 2–3 h and the discs were left immersed overnight (ca. 12 h) to remove reaction residues (NaOH, reagents) and small polymer particles, which sometimes remain attached to the disc surface. After washing, discs were frozen at −80 °C, in their equilibrium swollen state, and freeze-dried (*Telstar Cryodos Lyophilizator*) at −50 °C (4 h).

2.2.2. Characterization of the polymers

The percentage of cyclodextrin present in each type of polymer was studied by elemental analysis of ground powdered samples (ca. 0.180 g) using a *LECO CHN-2000 analyzer* (García-Zubiri et al., 2006). The average of three measurements for the polymers is shown in Table 1. This method has been also reported by other authors (Gao & Zhao, 2004). In our particular case, we realized that consistency is excellent when the humidity of the sample is also considered in the stoichiometry of the material. Other methods have been proposed in the literature, based on the determination of reducing sugars (Crini et al., 1998). In our previous works, we concluded that elemental analysis yields reproducible results while the hydrolysis of the cyclodextrin materials can be somewhat problematic.

Swelling assays were carried out for dried polymers synthesized at four temperatures: 25, 35, 50 and 60 °C according to standard procedures (Cesteros et al., 2006). The results revealed that, at 30 °C, the polymers are able to retain 65, 65, 73 and 78% of water, respectively.

2.3. Drug loading

Freeze-dried discs synthesized at 50 °C were loaded with the drugs from ethanol/water solutions. Due to the different solubility of each drug, 40/60 (v/v) ethanol/water solutions were used for the anti-inflammatory drugs (NAP: 5.2×10^{-3} M; NAB: 3.5×10^{-3} M), and 30/70 (v/v) ethanol/water solutions were used in the case of the antifungal drugs loading (3.7×10^{-3} M). The loading assays were carried out at 25.0 ± 0.1 °C in a shaking thermostated bath (50 osc/min). Each disc was immersed in 50 mL of loading solution for 48 h. The loading solutions were changed after 24 h.

To determine the loaded amount, some discs were placed in a medium that allowed them to release all the drug loaded. The total amount of drug loaded was estimated spectrofluorimetrically (*Perkin Elmer LS-50B spectrofluorimeter*; excitation/emission: 272/353 nm for NAP and NAB; 256/325 nm for NF; 284/325 nm for TB). The assays for the quantification of the amount of drug loaded were performed in triplicate.

2.4. Interactions between naproxen and βCDP

Solid state studies were carried out only for NAP, due to its higher amount of drug loaded compared with NAB, NF and TB. The formation of the complex was evidenced by X-ray diffractometry, IR spectroscopy and differential thermal analysis, by comparison with the NAP/βCDP physical mixture with the same molar ratio. X-ray powder diffraction patterns were collected on a *Bruker D8 Advance diffractometer* (Karlsruhe, Germany), with a $CuK_{\alpha 1}$ radiation, at a 40 kV voltage and a 30 mA current (2–40°). The IR spectra were recorded over the range 600–4000 cm^{-1} with a *Nicolet-FTIR Avatar 360 spectrometer* (WI, USA), using a MKII Golden Gate ATR device, with OMNIC E.S.P. software (128 scans, resolution 2 cm^{-1}). The thermal analysis was performed with a simultaneous *TGA/sDTA 851 Mettler Toledo thermoanalyzer* (Schwerzenbach, Switzerland). The thermal behaviour was studied by heating about 10 mg of the sample at a scan rate of 5 °C/min in a pierced aluminium crucible under static air atmosphere from 25 to 250 °C.

2.5. Drug release kinetics

In vitro drug release experiments were carried out using loaded and dried discs. According to the swelling kinetics, sorption and mechanical properties, the discs synthesized at 50 °C were selected for these assays. Two different release media were used: pH 7.0 phosphate buffer (simulated intestinal pH) and pH 1.2 HCl solution (simulated gastric pH). The dissolution tests were performed using the USP paddle method at 50 rpm with a *Sotax AT7 smart* (Sotax, Basel, Switzerland). All assays were carried out according to sink conditions. Each loaded disc was placed into a vessel containing 900 mL of release medium at 37.0 ± 0.2 °C. Aliquots of 3 mL were withdrawn and replaced with fresh medium to keep constant volume. The amount of drug delivered from discs was determined spectrofluorimetrically. Kinetic and diffusion constants were calculated by fitting the release data corresponding to 60% of drug released according to Korsmeyer–Peppas equation (Lin & Metters, 2006):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where t is the release time (min), M_t is the amount of drug delivered at time t, M_α is the total amount of drug delivered, k is a kinetic constant related to the network structure and n is a diffusion constant which indicates the mechanism of release. Due to the similar diffusion constants obtained in all the release assays, no other mathematical models were applied [Higuchi, First order or Zero order kinetics (Costa, Manuel, & Lobo, 2001)].

Diffusion coefficients were determined for all the assays, according to the simplified Higuchi model (Pitarresi et al., 2002):

$$q = 2\,C_0 \left(\frac{Dt}{\pi}\right)^{1/2} \quad (2)$$

where q is the amount of drug released into the medium per unit area of exposure (mg/cm^2), C_0 is the amount of drug loaded per unit volume of disc (mg/cm^3), D is the apparent diffusion coefficient of each drug (cm^2/s) and t represents the time elapsed since the start of drug release. Values of D were calculated from the slope of the linear regression of q versus $t^{1/2}$.

Table 2
Amount loaded[a] of NAP in 1125, 1135, 1150 and 1160 polymer discs.

Polymer type	Amount loaded (mg/disc)	Amount loaded (mg/g dry polymer)
1125	9 ± 2	50 ± 1
1135	16 ± 3	90 ± 2
1150	23 ± 1	156 ± 3
1160	18 ± 1	130 ± 1

[a] Standard errors are indicated.

3. Results and discussion

3.1. Synthesis and characterization of the cyclodextrin polymers

Several batches of CD polymer were synthesized at different temperatures (25, 35, 50 and 60 °C). These polymers were named 1125, 1135, 1150 and 1160, respectively, the first two digits referring to the EP: CD molar ratio used, and the last two digits to the temperature at which each synthesis was carried out.

Samples of each polymer were characterized by elemental analysis (Table 1). It can be observed that the amount of cyclodextrin in the polymer is higher at a lower temperature of synthesis. It can be due to the fact that higher temperatures promote the self-reaction of epichlorohydrin so the average distance between the cyclodextrin molecules is increased. Gelation times also depend on synthesis temperature (Table 1). The average yield of the synthesis was about 51%. The main characteristics of the discs obtained from the different polymer types are listed in Table 1.

3.2. Drug loading

A comparative assay was performed by loading lyophilized discs of the four polymer types using the same drug (NAP) in all tests. The results show that 1150 polymer discs were able to retain a higher amount of NAP (Table 2). Moreover, they showed higher resistance to breakage than the others; therefore, 1150 polymer discs were selected as the most suitable ones for the controlled release kinetics.

The amount of drug loaded (average of at least 3 discs) was successfully quantified in 1150 polymer discs. The results are shown in Table 3. The sorption capacity is related to the formation of inclusion complexes with the cyclodextrin units and to physical adsorption in the polymer network (Gazpio et al., 2008). NAP showed the highest amount loaded probably due to the higher value of NAP-βCD complex stability constant (Goyenechea et al., 2001; Uzqueda et al., 2009; Vélaz et al., 1997); although complex stability constants studied were obtained by different techniques in aqueous solutions, NAP presents a stronger interaction with βCD in the loading solution.

3.3. Interactions between naproxen and βCDP

The diffraction patterns are shown in Fig. 3. The physical mixture pattern was a superposition of both single components. Main naproxen peaks between $2\theta = 5^\circ$ to 30° can be observed, suggesting the presence of free drug in this sample. In contrast, in the loaded polymer pattern, NAP peaks could not be observed, probably because the drug inclusion within CD cavities and its sorption into polymer network prevent its crystallization.

Table 3
Amount loaded[a] of model drugs in 1150 polymer discs.

Drug	Amount loaded (mg/disc)	Amount loaded (mg/g dry polymer)
Naproxen	22.6 ± 0.4	156 ± 3
Nabumetone	2.0 ± 0.6	14 ± 4
Naftifine	1.8 ± 0.2	11 ± 1
Terbinafine	1.8 ± 0.3	12 ± 2

[a] Standard errors are indicated.

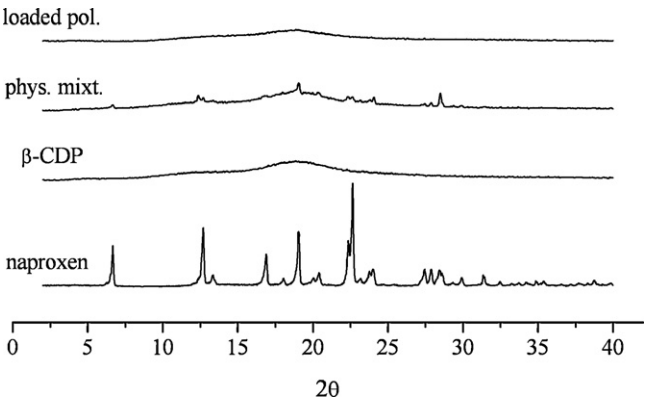

Fig. 3. X-ray diffraction patterns of NAP, βCDP, physical mixture and loaded polymer.

Differential thermal analysis of NAP showed an endothermic peak at 158–160 °C, corresponding to the melting point of the drug (Fig. 4). This peak was also detected in the physical mixture, but it disappeared in the loaded polymer. This fact can be considered as an evidence of complex formation between NAP and βCDP, in agreement with the X-ray diffraction study shown in Fig. 3.

Fig. 5 shows the FTIR spectra of solid dispersions. The vibration modes detected at 1026 and 857 cm^{-1} correspond to C–O–C bonds in naproxen. The band at 1726 cm^{-1} is attributed to C=O stretching vibration. Fig. 5a shows the C–O–C naproxen bands in the case of the physical mixture, but not for the loaded polymer. Moreover, the band at 1726 cm^{-1}, corresponding to the carbonyl stretching region (Fig. 5b), is observed in the physical mixture and also for the loaded polymer, the presence of NAP in both polymer samples. It can be inferred that the interaction between the drug and the polymer occurs; probably through the methoxy group of naproxen.

Moreover, βCDP presents an intense band located at 1650 cm^{-1}, corresponding to the δ-HOH bending of water molecules attached to βCD (Netto-Ferreira, Ilharco, García, & Ferreira, 2000). This band has been shifted to lower frequencies for the spectrum corresponding to the loaded polymer. This effect could be attributed to naproxen molecules replacing water molecules in the cyclodextrin cavities as previously shown for other systems (García-Zubiri et al., 2006).

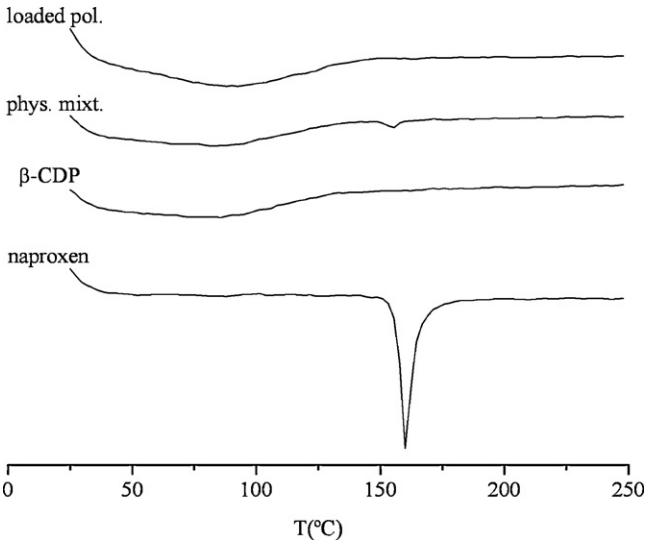

Fig. 4. DTA thermograms of NAP, βCDP, physical mixture and loaded polymer.

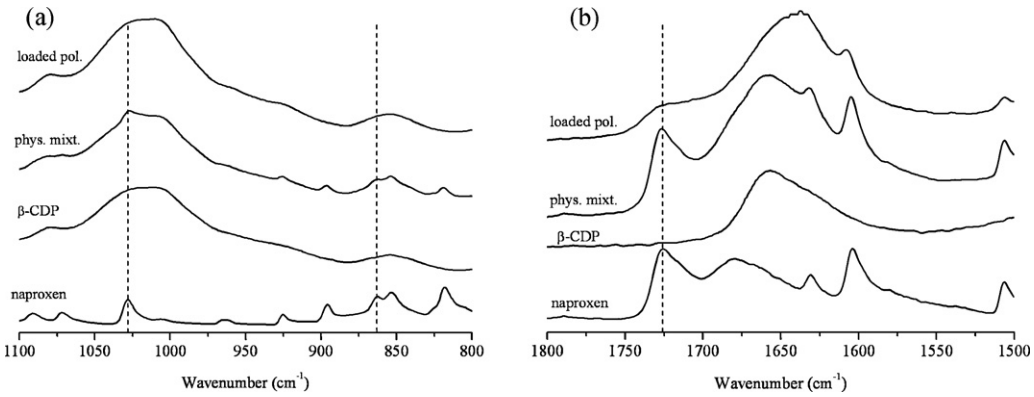

Fig. 5. FTIR spectra of NAP, βCD polymer, physical mixture and loaded polymer, in (a) the 1100–800 cm^{-1} region (broken lines: modes at 857 cm^{-1} and 1026 cm^{-1}) and (b) the carbonyl stretching region (broken line: mode at 1726 cm^{-1}).

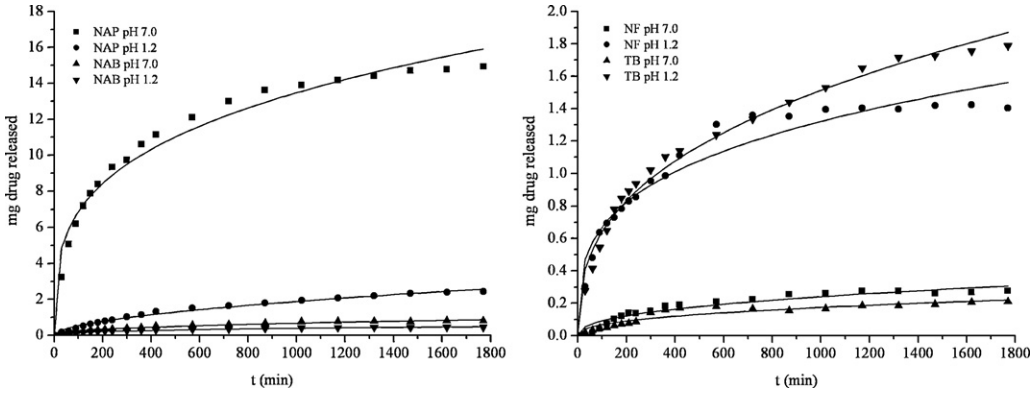

Fig. 6. Release profiles of model drugs at pH 7.0 and pH 1.2, at 37 °C.

3.4. Controlled release kinetics

All the release experiments were carried out at 37 °C in pH 1.2 and 7.0. The percentages released were calculated taking into account the amounts loaded. The amount of NAP released at pH 7.0 (64 ± 10% of the amount loaded) was higher than that delivered in the acidic medium (11 ± 1%). This is a reasonable result taking into account that NAP is an acidic drug (pK_a = 4.2), so at pH 7.0 it is in its ionized form. In these conditions, the solubility of the drug is 250 ± 10 mg/L eight-fold higher than at pH 1.2 (31 ± 6 mg/L) at 25 °C. NAB, however, presents similar behaviours at both pH values (slightly higher at pH 7.0 (38 ± 3%) than at pH 1.2 (21 ± 2%)), in accordance with the absence of ionizable groups (Fig. 2). NF and TB present a low solubility at pH 7.0 (NF: 11 ± 1 mg/L; TB: 5 ± 2 mg/L) (Uzqueda et al., 2006; Uzqueda, Martín, Zornoza, Sánchez, & Vélaz, 2010). For this reason, the amounts released were much higher in acidic media (NF: 77 ± 2%; TB: 96 ± 6%) than at pH 7.0 (NF: 15 ± 2%; TB: 10 ± 3%) for both drugs.

The drug release profiles obtained at 37 °C are compiled in Fig. 6. Table 4 shows the kinetic and diffusion constants calculated according to Eq. (1). NAP kinetic constant at pH 7.0 is higher than pH 1.2 because of its acidic nature. In contrast, kinetic constants are similar for NAB at both media; this is consistent with the ketonic nature of the drug. In the case of the two allylamines, the kinetic parameters obtained (Table 4) can be related to the chemical structure of the drug and to the stability constants of their inclusion complexes with βCD [NF: 830 M^{-1}; TB: 1400 M^{-1} at 25 °C (Uzqueda et al., 2009)]. The higher kinetic constant of NF compared to that of TB can be associated to its lower stability constant, which leads to a poorer entrapment of the drug in the polymer. Constants

Table 4
Kinetic and diffusion constants[a] at 37 °C.

Drug	pH	r^2	$k \times 10^2$	n
Naproxen	7.0	0.995	4.9 ± 0.6	0.47 ± 0.03
	1.2	0.995	1.9 ± 0.2	0.53 ± 0.01
Nabumetone	7.0	0.995	2.2 ± 0.2	0.54 ± 0.02
	1.2	0.990	2.8 ± 0.5	0.53 ± 0.03
Naftifine	1.2	0.991	5.2 ± 0.9	0.45 ± 0.03
Terbinafine	1.2	0.990	3.0 ± 0.4	0.52 ± 0.03

[a] Standard errors are indicated.

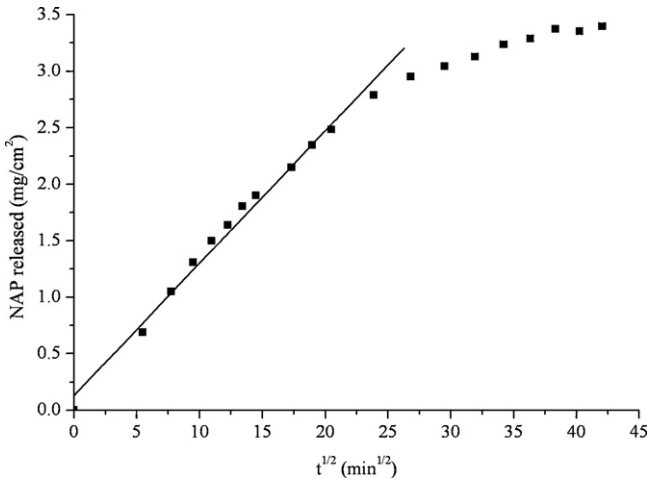

Fig. 7. Amount of NAP released per unit area of exposure at pH 7.0 as a function of the square root of time.

Table 5
Drug diffusion coefficients (D, cm^2/s) at 37 °C.

Drug	pH	r	$D \times 10^8$ (cm^2/s)
Naproxen	7.0	0.994	7.6
	1.2	0.986	0.1
Nabumetone	7.0	0.997	2.3
	1.2	0.992	0.9
Naftifine	1.2	0.992	13.5
Terbinafine	1.2	0.988	15.3

could not be determined at pH 7.0 for the antifungal drugs, due to its extremely low solubility in this medium, yielding a negligible amount released and a greater experimental error.

According to n values, a delivery system can be classified into three different types (Namazi & Kanani, 2009): (a) n values near 0.5 refer to a simple Fickian diffusion mechanism; (b) a value of n of about 1.0 means a Case II transport, that reflects the influence of polymer relaxation on guest molecules movement in the matrix; (c) if n takes a value between 0.5 and 1.0 this indicates a non-Fickian or anomalous behaviour, when the Fickian transport and polymer relaxation occur simultaneously and their rates are comparable (Ritger & Peppas, 1987a,b). Values of n close to 0.5 in all the assays point to a simple Fickian diffusion (Case I diffusion).

In order to determine diffusion coefficients, at least three assays for each drug and medium were plotted using Eq. (2) (Fig. 7), obtaining a good linear relationship ($r > 0.98$). Linearity is kept only for the first 60% of released drug data in all the assays, which confirms the decision of fitting release data to Eq. (1) up to that time. Table 5 shows that apparent diffusion coefficients are much higher for each drug in its most favourable release medium; these results are consistent with kinetic constants shown in Table 4.

4. Concluding remarks

Cyclodextrin–epichlorohydrin insoluble polymers have been used widely in our group for sorption and release studies of different substances, not only drugs but also pollutants (Fernández et al., 2011; García-Zubiri, González-Gaitano, Sánchez, & Isasi, 2003; García-Zubiri et al., 2006, 2007; Gazpio et al., 2008; Maddens et al., 2011; Uzqueda et al., 2011; Vélaz et al., 2007). In this work, we propose a novel polymeric hydrogel synthesized with a controlled geometry, as a drug carrier for controlled release. The interest of a controlled geometry system lies in the possibility to obtain kinetic parameters by fitting experimental data to mathematical models for drug release (Lin & Metters, 2006), and to obtain diffusion coefficients according to the contact surface of the polymeric matrix. It has been demonstrated that solute transport in swellable hydrophilic polymers is affected by a variety of structural and physical characteristics of the crosslinked polymers and by the nature of the solutes used (Brazel & Peppas, 1999, 2000). Knowing kinetic parameters and diffusion coefficients of a particular drug delivery system allows us to achieve progress in the design of new polymeric matrices, by using either different crosslinking agents or other cyclodextrins, according to the structure of the selected model drugs.

Acknowledgements

The authors wish to thank to Universidad de Navarra (PIUNA) and Ministerio de Ciencia y Tecnología (project no. MAT2007-65752) for the financial aid and to Gobierno de Navarra for R. Machín grant.

References

Brazel, C. S. & Peppas, N. A. (1999). Mechanisms of solute and drug transport in relaxing, swellable, hydrophilic glassy polymers. *Polymer*, *40*, 3383–3398.
Brazel, C. S. & Peppas, N. A. (2000). Modeling of drug release from swellable polymers. *European Journal of Pharmaceutics and Biopharmaceutics*, *49*, 47–58.
Cesteros, L. C., Ramírez, C., Peciña, A. & Katime, I. (2006). Poly(ethylene glycol-beta-cyclodextrin) gels: Synthesis and properties. *Journal of Applied Polymer Science*, *102*(2), 1162–1166.
Cesteros, L. C., Ramírez, C., Peciña, A. & Katime, I. (2007). Synthesis and properties of hydrophilic networks based on poly(ethylene glycol) and beta-cyclodextrin. *Macromolecular Chemistry and Physics*, *208*(16), 1764–1772.
Chen, W., Chang, C. & Gilson, M. (2004). Calculation of cyclodextrin binding affinities: Energy, entropy, and implications for drug design. *Biophysical Journal*, *87*(5), 3035–3049.
Costa, P., Manuel, J. & Lobo, S. (2001). Modeling and comparison of dissolution profiles. *European Journal of Pharmaceutical Sciences*, *13*(2), 123–133.
Crini, G., Cosentino, C., Bertini, S., Naggi, A., Torri, G. & Vecchi, C. (1998). Solid state NMR spectroscopy study of molecular motion in cyclomaltoheptaose (beta-cyclodextrin) crosslinked with epichlorohydrin. *Carbohydrate Research*, *308*(1–2), 37–45.
Crini, G. & Morcellet, M. (2002). Synthesis and applications of adsorbents containing cyclodextrins. *Journal of Separation Science*, *25*(13), 789–813.
Dodziuk, H. (2006). *Cyclodextrins and their complexes: Chemistry, analytical methods, applications*. Weinheim: Wiley VCH.
Fernández, L., Machín, R., Zornoza, A., Vélaz, I., Martín, C. & Martínez-Ohárriz, C. (2011). Mechanism of sorption and release of a weak acid from beta-cyclodextrin polymers. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, *69*, 411–415.
Gao, Z. & Zhao, X. (2004). Two roles of guest and crosslinked degree on hydrosoluble β-cyclodextrin polymer electrorheological fluids. *Polymer*, *45*(5), 1609–1615.
García-Zubiri, I., González-Gaitano, G., Sánchez, M. & Isasi, J. R. (2003). FTIR study of dibenzofuran-2-carboxylic acid and its complexes with beta-cyclodextrin. *Vibrational Spectroscopy*, *33*(1–2), 205–213.
García-Zubiri, I., González-Gaitano, G. & Isasi, J. R. (2006). Thermal stability of solid dispersions of naphthalene derivatives with beta-cyclodextrin and beta-cyclodextrin polymers. *Thermochimica Acta*, *444*(1), 57–64.
García-Zubiri, I., González-Gaitano, G. & Isasi, J. R. (2007). Isosteric heats of sorption of 1-naphthol and phenol from aqueous solutions by beta-cyclodextrin polymers. *Journal of Colloid and Interface Science*, *307*(1), 64–70.
Gazpio, C., Sánchez, M., Isasi, J. R., Vélaz, I., Martín, C. & Martínez-Ohárriz, C. (2008). Sorption of pindolol and related compounds by a beta-cyclodextrin polymer: Isosteric heat of sorption. *Carbohydrate Polymers*, *71*(1), 140–146.
Goyenechea, N., Sánchez, M., Vélaz, I., Martín, C., Martínez-Ohárriz, C. & Zornoza, A. (2002). Interactions of nabumetone with cyclodextrins in solution and in the solid state. *Journal of Inclusion Phenomena and Molecular Recognition in Chemistry*, *44*(1–4), 283–287.
Goyenechea, N., Sánchez, M., Vélaz, I., Martín, C., Martínez-Ohárriz, M. & González-Gaitano, G. (2001). Inclusion complexes of nabumetone with beta-cyclodextrins: Thermodynamics and molecular modelling studies influence of sodium perchlorate. *Luminescence*, *16*(2), 117–127.
Hoffman, A. S. (2002). Hydrogels for biomedical applications. *Advanced Drug Delivery Reviews*, *54*(1), 3–12.
Lin, C. & Metters, A. (2006). Hydrogels in controlled release formulations: Network design and mathematical modeling. *Advanced Drug Delivery Reviews*, *58*(12–13), 1379–1408.
Liu, Y., Fan, X., Hu, H. & Tang, Z. (2004). Release of chlorambucil from poly(N-isopropylacrylamide) hydrogels with beta-cyclodextrin moieties. *Macromolecular Bioscience*, *4*(8), 729–736.
Loftsson, T. & Masson, M. (2004). The effects of water-soluble polymers on cyclodextrins and cyclodextrin solubilization of drugs. *S.T.P. Pharma Sciences*, *14*(1), 35–43.
Lowman, A. M. (2000). *Complexing polymers in drug delivery* (pp. 89–98). In D. L. Wise (Ed.), *Handbook of pharmaceutical controlled release technology*.
Maddens, T., Vélaz, I., Machín, R., Isasi, J. R., Martín, C., Martínez-Ohárriz, M. C., et al. (2011). Complexation of ebastine with beta-cyclodextrin derivatives. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*.
Namazi, H. & Kanani, A. (2009). Investigation diffusion mechanism of beta-lactam conjugated telechelic polymers of PEG and beta-cyclodextrin as the new nano-sized drug carrier devices. *Carbohydrate Polymers*, *76*(1), 46–50.
Netto-Ferreira, J. C., Ilharco, L. M., García, A. R. & Ferreira, L. F. V. (2000). Characterization of solid complexes between aromatic ketones and beta-cyclodextrin using diffuse reflectance infrared Fourier transform spectroscopy. *Langmuir*, *16*(26), 10392–10397.
Pariot, N., Edwards-Levy, F., Andry, M. & Levy, M. (2002). Cross-linked beta-cyclodextrin microcapsules. II. Retarding effect on drug release through semi-permeable membranes. *International Journal of Pharmaceutics*, *232*(1–2), 175–181.
Pasparakis, G. & Bouropoulos, N. (2006). Swelling studies and in vitro release of verapamil from calcium alginate and calcium alginate-chitosan beads. *International Journal of Pharmaceutics*, *323*(1–2), 34–42.
Peppas, N. & Ende, D. (1997). Controlled release of perfumes from polymers. II. Incorporation and release of essential oils from glassy polymers. *Journal of Applied Polymer Science*, *66*(3), 509–513.
Peppas, N. & Klier, J. (1991). Controlled release by using poly (methacrylic acid-g-ethylene glycol) hydrogels. *Journal of Controlled Release*, *16*(1–2), 203–214.

Pitarresi, G., Cavallaro, G., Giammona, G., De Guidi, G., Salemi, M. & Sortino, S. (2002). New hydrogel matrices containing an anti-inflammatory agent evaluation of in vitro release and photoprotective activity. *Biomaterials*, *23*(2), 537–550.

Renard, E., Deratani, A., Volet, G. & Sebille, B. (1997). Preparation and characterization of water soluble high molecular weight beta-cyclodextrin-epichlorohydrin polymers. *European Polymer Journal*, *33*(1), 49–57.

Ritger, P. & Peppas, N. (1987a). A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *Journal of Controlled Release*, *5*(1), 23–36.

Ritger, P. & Peppas, N. (1987b). A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. *Journal of Controlled Release*, *5*(1), 37–42.

Siepmann, J. & Siepmann, F. (2008). Mathematical modeling of drug delivery. *International Journal of Pharmaceutics*, *364*(2), 328–343.

Skold, M., Thyne, G., Drexler, J. & McCray, J. (2009). Solubility enhancement of seven metal contaminants using carboxymethyl-beta-cyclodextrin (CMCD). *Journal of Contaminant Hydrology*, *107*(3–4), 108–113.

Szejtli, J., & Osa, T. (Eds.). (1996). *Cyclodextrins, comprehensive supramolecular chemistry*. Oxford, UK: Pergamon.

Szejtli, J. (1998). Introduction and general overview of cyclodextrin chemistry. *Chemical Reviews*, *98*(5), 1743–1753.

Szente, L. & Szejtli, J. (2004). Cyclodextrins as food ingredients. *Trends in Food Science Technology*, *15*(3–4), 137–142.

Uzqueda, M., González-Gaitano, G., Wouessidjewe, D., Zornoza, A., Sánchez, M., Martín, C., et al. (2009). Spectroscopic characterisation of the inclusion complexes between the antifungal drugs naftifine and terbinafine and cyclodextrins. *Supramolecular Chemistry*, *21*(8), 759–769.

Uzqueda, M., Martín, C., Zornoza, A., Sánchez, M., Martínez-Oharriz, M. & Vélaz, I. (2006). Characterization of complexes between naftifine and cyclodextrins in solution and in the solid state. *Pharmaceutical Research*, *23*(5), 980–988.

Uzqueda, M., Martín, C., Zornoza, A., Sánchez, M. & Vélaz, I. (2010). Physicochemical characterization of terbinafine-cyclodextrin complexes in solution and in the solid state. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, *66*(3–4), 393–402.

Uzqueda, M., Zornoza, A., Isasi, J. R., Martín, C., Sánchez, M. & Vélaz, I. (2011). Interactions of terbinafine with beta-cyclodextrin polymers: Sorption and release studies. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, *69*, 469–474.

Vélaz, I., Sánchez, M., Martín, C., Martínez-Oharriz, M. C. & Zornoza, A. (1997). Interactions of naproxen with vinylpyrrolidone and β-cyclodextrin: A fluorimetric study. *International Journal of Pharmaceutics*, *153*(2), 211–217.

Vélaz, I., Machín, R., Zornoza, A., Safont, B., Martínez-Oharriz, M.C., González-Gaitano, G., et al. New drug delivery systems based on beta-cyclodextrin polymers. Optimising drug therapy: An imperative for World Health, Amsterdam, 2007 (e-book of abstracts: DD-W-105).