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Solubility and Kinetic Release Studies of Naproxen and Ibuprofen in Soluble Epichlorohydrin-β-cyclodextrin Polymer

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Naproxen (NAP) and ibuprofen (IBU) are poor water soluble anti-inflammatory drugs. A water-soluble epichlorohydrin-β-cyclodextrin polymer (β-CDEPI) was synthesized in a highly basic aqueous solution and at a molar ratio β-CD/EPI of 1:12. Drug solubility and kinetic release of NAP and IBU from the inclusion complexes they form with β-CDEPI as host was studied. Water solubility for both drugs in the presence of this polymer increased (NAP 0.28 mmol and IBU 0.40 mmol per gram of β-CDEPI). The apparent inclusion constants for both drugs in β-CDEPI were calculated from the solubility-phase diagrams with K_{incl} values of 4300 ± 100 $L.mol^{-1}$ for NAP and 5100 ± 300 $L.mol^{-1}$ for IBU. Kinetic release of Ibuprofen gave a pure Fick trend ($t^{1/2}$) behavior. However, for Naproxen a zero order was obtained (t). These results indicate that the nature and bulkiness of the drugs are ruling these kinetic behaviors in the environment of a highly branched polymer.

Keywords: Inclusion complex; Cyclodextrin polymer; Drug delivery; Ibuprofen; Naproxen

INTRODUCTION

Naproxen (NAP) and ibuprofen (IBU) are non-steroidal anti-inflammatory drugs. The low water solubility of these drugs can be enhanced by the formation of inclusion complex with native and chemically modified cyclodextrins [1,2] Cyclodextrins (CDs) are a class of cyclic oligosaccharides composed of α(1–4)-linked D-glucopyranose units containing a hydrophobic central cavity and external hydrophilic surface. Such structure allows them to form stable inclusion complexes with a wide variety of guests containing a hydrophobic moiety [3]. Natural and modified CDs are widely used in drug formulations. The formation of inclusion complexes with CDs can enhance drug water-solubility. Simultaneously, the CDs cavity protects the drug from reactions with the environment and can also mask undesirable odors and flavors [4]. In solid drug formulations CDs can serve as drug carriers in immediate release or delayed release formulations [5].

Several CD-containing polymers have been used as matrixes for potential drug delivery of anti-tumoral [6] and anti-inflammatory compounds [7], for gene delivery [8] or as temperature sensitive polymers [9]. Special attention must be paid to the kinetic and thermodynamic considerations involved in this kind of release system. The polymeric network may alter the behavior of the drug by inducing changes in the solubility and diffusivity.

The aim of the present paper is to obtain a water-soluble epichlorohydrin-β-cyclodextrin polymer (β-CDEPI) able to increase the solubility of NAP and IBU and modulate the kinetic release of both included drugs.

RESULTS AND DISCUSSION

The synthesis of the β-CDEPI polymer was performed taking into consideration previous reports in order to achieve a non-linear polycondensation with specific structural features that could favor drug release purposes [10].

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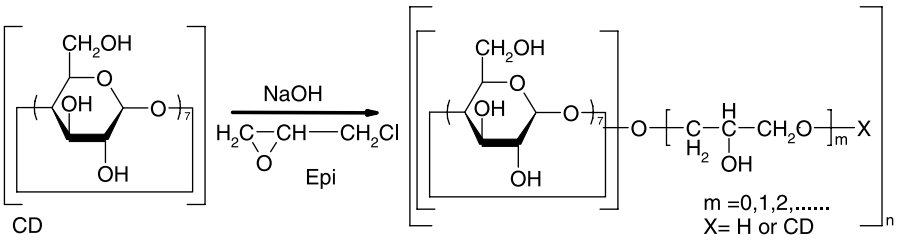

SCHEME 1 Schematic reaction of the polymerization process.

The polymerization reaction depends mainly on the proportion in which NaOH, β-CD and epichlorohydrin (EPI) and reaction time is employed. Generally, β-CD/EPI molar ratios from 1/1 to 1/15 and hydroxide concentration from 10% to 50% are used. Low branched soluble polymers of low Mw are obtained when 10% NaOH and a β-CD/EPI = 1/10 molar ratio are employed. If NaOH concentration is increased (10–20%), with short reaction periods medium branched polymers of low molecular weights (Mw) are obtained. For higher hydroxide concentrations (20–30%) or longer reaction times hyperbranched polymers with high Mw are obtained. If an external cross-linking in high Mw polymers is achieved gel formation can take place. These considerations open the question about the contribution of the polymer structure to the inclusion of drugs and supramolecular interactions in other sites than β-CD cavities.

The aim of the used synthetic procedure was to select reaction parameters appropriate to obtain a polymeric matrix most adequate for the best modulation of the drug release process, as will be discussed below. The hydroxide concentration used in the polymerization reaction (16%) should lead to a molar ratio between both monomers in the composition of the polymer similar to the amounts used in the reaction mixture (β-CD/EPI = 1/12) which can be considered an intermediate value. A schematic representation of this reaction is presented in Scheme 1.

The degree of substitution of EPI per β-CD unit was determined by integrating the ^{1}H-NMR signals of the anomeric protons. The molar ratio EPI/β-CD = 11,37 found this way is similar to the proportion of the reagents used. The incorporation of EPI substituents at both rims of β-CD was confirmed by the corresponding ^{13}C-NMR spectrum (Fig. 1). The signals at 79, 77, and 70 ppm correspond to substituted C-2, C-3 and C-6 carbon atoms, respectively. The signals assigned as 8, 8″, 9, 9″ correspond to the hydroxypropyl- or epoxypropyl-terminal groups of the branches. The presence of these latter signals indicates that these terminal groups did not participate in any crosslinking reaction. The other signals (8′ and 9′) were assigned to the hydroxypropyl ether segments that contribute to the chain formation with long branches.

The Mw of the different fractions of the obtained polymer were determined by Size Exclusion Chromatography. A high polydispersion was observed at low Mw (8000–36000 Da) including

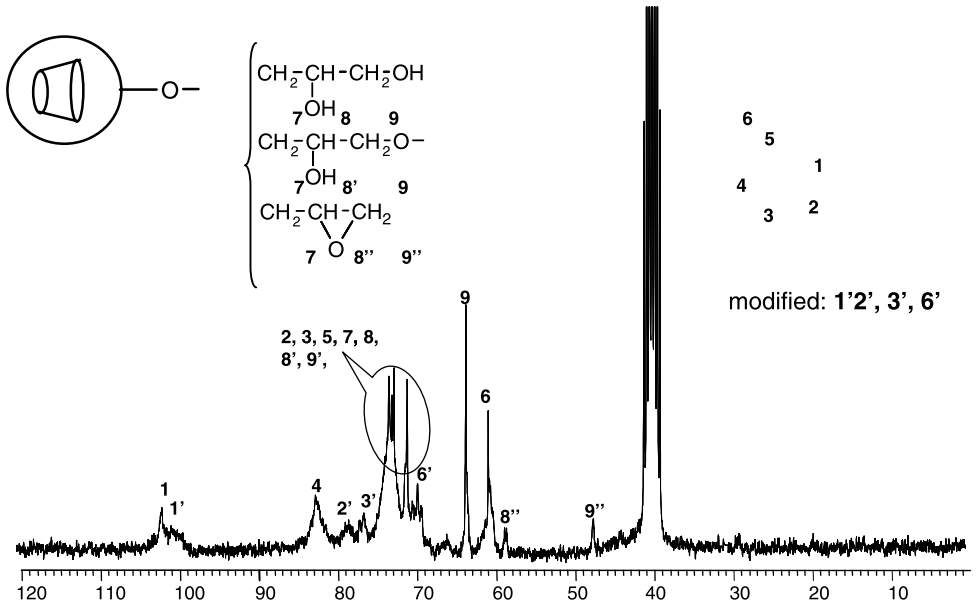

FIGURE 1 ^{13}C-NMR spectrum of the β-CDEPI polymer.

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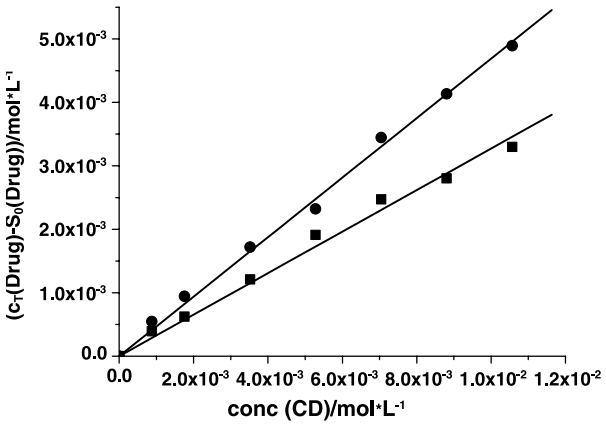

FIGURE 2 Phase-solubility diagram of naproxen (■) and ibuprofen (•) with β-CD EPI. Data correspond to one set of the three experiments carried out.

long chains, characteristic of a polycondensation polymerization. These results are in agreement with those reported by Renard [10]. The host-guest interactions were studied in terms of the apparent inclusion constants of both drugs (NAP and IBU) in β-CDEPI, which were determined by the slopes of the corresponding A_L-type phase-solubility diagram (as in Fig. 2) in triplicate experiments (Table I).

For NAP, the obtained apparent inclusion constant value with β-CDEPI at 300 K ($K_{incl} = 4300\ L.mol^{-1}$) was higher than that reported for β-CD ($K_{incl} = 1600\ L.mol^{-1}$) [2] and also for its hydroxypropyl- and hydroxyethyl-derivatives ($K_{incl} = 2300\ L.mol^{-1}$ and $2600\ L.mol^{-1}$, respectively) [1] but lower than that corresponding methyl-derivatives, which are the best hosts for NAP (K_{incl} values of 6200 and 6800 for dimethyl- and randomly methylated-β-CD, respectively). The solubilization of the drugs in the presence of β-CD or its derivatives is accepted to be mainly due to the formation of inclusion complexes, but in some cases non-inclusion association has also been suggested [11]. For a β-CDEPI polymer the host-guest interactions can be even more complex due to the spatial structure of the polymer. The value of the inclusion complex of NAP reported by Mura et al. was $K_{incl} = 2800\ L.mol^{-1}$, but using a β-CDEPI polymer obtained under apparently different experimental conditions [1]. These two different values of K_{incl} ($2800\ L.mol^{-1}$ and $4300\ L.mol^{-1}$) for the same type of polymer and guest indicate that the degree of substitution in the polymeric network is determining the host-guest interaction (Scheme 2). The structure of a hyperbranched polymeric network should also take part in the inclusion process due to the nanometric dimensions of the microvoids it has. This effect is also expressed in the reported inclusion constants of NAP in β-CD-containing polymers of dextran ($K_{incl} = 2580\ L.mol^{-1}$) and mannan ($K_{incl} = 4050\ L.mol^{-1}$) [7].

In the case of IBU the value of the obtained inclusion constant was greater ($5100\ L.mol^{-1}$) than for NAP. The lower value of the constant for NAP should be related to the larger size (due to an additional aromatic ring) of this guest respect to the β-CD cavity. Therefore, a weaker interaction due to steric hindrance inside the cavity should take place. On the other hand, the relatively smaller size of IBU enables its stronger host-guest interaction with the β-CD cavity.

The water-solubility of both drugs increases considerably in the presence of β-CDEPI. The loading capacity of β-CDEPI is 0.28 mmol of NAP and 0.40 mmol of IBU per gram of polymer. The ratio between these two values differs from that of the obtained inclusion constants and indicates that the polymeric network also plays a role in the solubilization of both drugs (Scheme 2). Therefore, this factor should also be expressed when studying the kinetic release of the drugs from β-CDEPI.

The expected different kinetic release behavior between both drugs was observed. A typical zero order ($n = 1$) behavior was observed in the case of NAP (Fig. 3) according to Eq. (1), where $\mathbf{c_t}$ and $\mathbf{c_{t\infty}}$ are the concentrations of the drug released at time **t** and at infinite time, respectively, **k** is a constant and **n** can vary depending on the type of diffusion.

$$\frac{\mathbf{c_t}}{\mathbf{c_{t_\infty}}} = \mathbf{kt^n} \tag{1}$$

In the case of IBU a Fickian trend was observed ($n = 1/2$, Fig. 4) indicating a true Fickian diffusion of the drug.

The mechanism accepted for the release of drugs from β-CD polymers involves the drug jumping from one β-CD cavity to another through the polymeric network, the whole process being kinetically controlled by the characteristics of the latter. This can explain the effect of the size of the drug on the kinetic release behavior. Since IBU is smaller than NAP its diffusion within the polymeric network should not be as much hindered by the polymer

TABLE I Inclusion constants values calculated from the A_L-type phase-solubility diagram for the three experiments carried out

	Naproxen			Ibuprofen		
Experiment	1	2	3	1	2	3
Slope	0.33	0.32	0.33	0.47	0.47	0.46
$S_0/10^{-4}\ L.mol^{-1}$	1.17	1.10	1.12	1.79	1.75	1.56
$K_{incl}/10^3\ L.mol^{-1}$	4.2	4.3	4.4	4.9	5.0	5.4
$K_{incl}/10^3\ L.mol^{-1}$		4.3 ± 0.1			5.1 ± 0.2	

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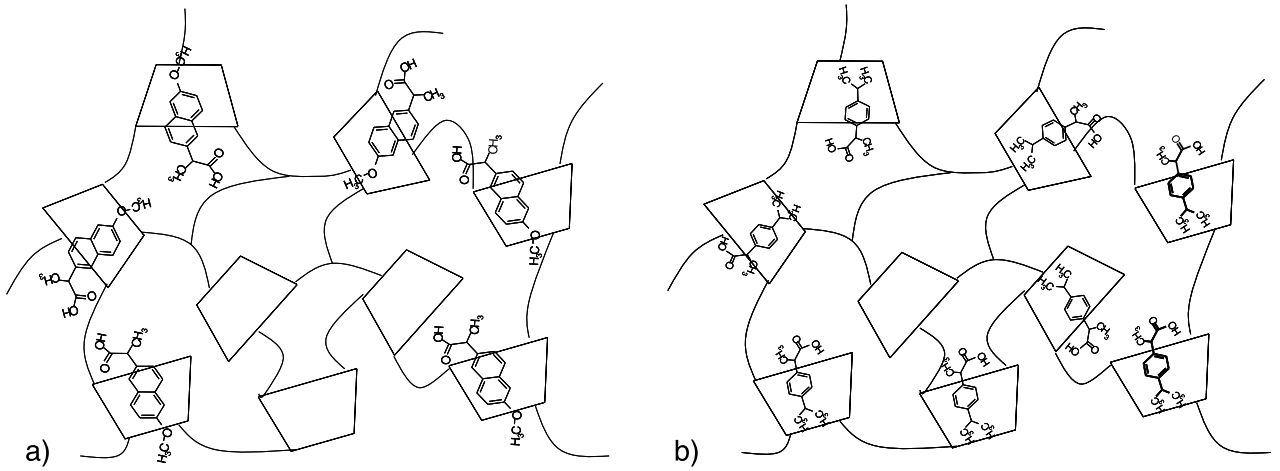

SCHEME 2 Schematic representation of the polymer-drug interaction. a) Naproxen-β-CDEPI and b) Ibuprofen-β-CDEPI.

segment mobility as for NAP. Thus, it seems that the same structural features are governing the inclusion/release thermodynamics and kinetic behaviors of both drugs, but with a strong dependence on their steric characteristics.

CONCLUSIONS

A water-soluble highly dispersed epichlorohydrin-β-cyclodextrin polymer (β-CDEPI) was synthesized through a polycondensation polymerization reactions, with EPI substituted on both rims of β-CD. This polymer served to include both NAP and IBU in the β-CD and also in the formed microvoids.

NAP is larger in size than IBU which permits a better fit of the latter in the β-CD cavity. For that reason the obtained inclusion constant for IBU is higher than that of NAP. For the same reason the observed increase in water solubility when interacting with the polymer is higher for IBU. A difference in the kinetic release behavior of both drugs was also observed and attributed to the restrictions imposed by the dimensions of the microvoids of the polymer for the diffusion of the drugs with different steric characteristics.

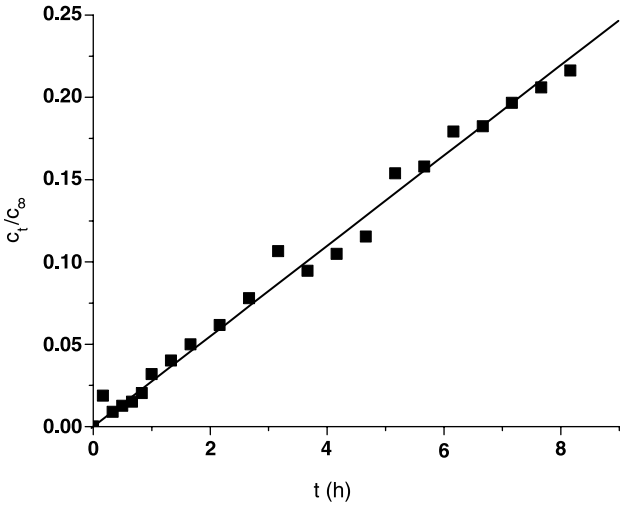

FIGURE 3 Kinetic behavior of the release of Naproxen included in β-CD EPI.

EXPERIMENTAL

Naproxen and ibuprofen were purchased from Riedel-de-Haën. β-cyclodextrin, epichlorohydrin and other chemical reagents were purchased from Sigma-Aldrich and used without further purification.

Spectrophotometric determinations were performed on a UV–Vis Ultrospect 2100 Pro (Amersham-Bioscience) spectrophotometer. ^{13}C-NMR spectrum was recorded in D_2O on a Bruker AC250F spectrometer. ^{1}H-NMR spectrum was recorded in D_2O on a Varian-Inova 500 MHz spectrometer.

Soluble β-cyclodextrin-epichlorohydrin polymer, β-CDEPI, was synthesized by dissolving 3.75 g (3.3 mmol) of β-cyclodextrin in 5 mL of NaOH 16% aqueous solution and stirring overnight. 3 mL (39 mmol) of epichlorohydrin were then added rapidly and the mixture was stirred at 300 rpm for 4 hours at room temperature. The solution was adjusted to pH 8 with hydrochloric acid 6 M, poured into a dialysis membrane (cut-off 5000–7000) and dialyzed for 72 h against distilled water. The dialyzed polymer was precipitated in acetone and dried under vacuum.

Size Exclusion Chromatography was carried out in a low pressure chromatographic system (Gradifrac System Pharmacia). Sepharose CL6B in a column of 3 × 70 cm was used as stationary phase and a solution of NaCl 0.2% as eluent and 0.3 mL/min flow rate. The Mw distribution was determined by the phenol–sulphuric acid method at 490 nm [12].

Polymer loading was achieved by adding 200 mg of β-CDEPI polymer to a saturated drug solution and stirred for 24 h. The kinetic release studies were

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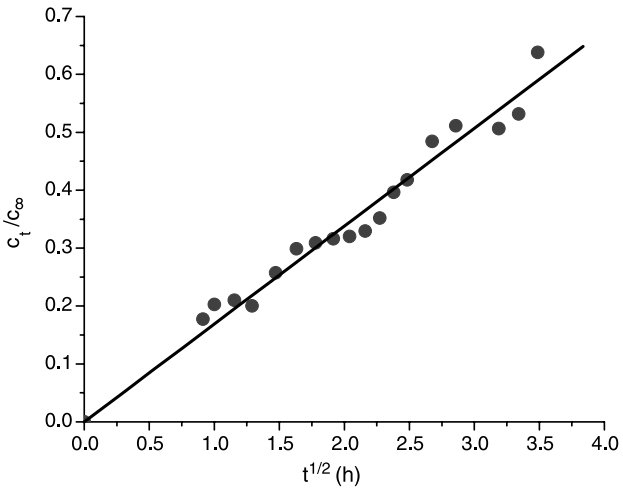

FIGURE 4 Kinetic behavior of the release of Ibuprofen included in β-CD EPI.

carried out using 5 mL of the loaded polymer solution which was poured into a Spectrapore dialysis membrane (cut-off 5000–7000 Da) sealed and dipped in 400 ml of water at 30 ± 0.5°C. An appropriate aliquot was collected at different intervals and measured spectrophotometrically at 230 and 222 nm for NAP and IBU, respectively.

The apparent inclusion constants were determined from the phase-solubility diagram. For this 25 mg of drug were added to water or aqueous solution of β-CDEPI (10 mL), in the 0–120 mg mass range, in a sealed glass container which was magnetically stirred at 30 ± 0.5°C until the equilibrium was reached (24 h). The solutions were centrifuged and the concentration was determined spectrophotometrically at 230 and 222 nm for NAP and IBU, respectively. The apparent inclusion constant of the drug-β-CDEPI complex was calculated from the slope and intercept of the phase solubility diagram according to Eq. (2) [11].

$$K_{incl} = \frac{\text{slope}}{So(1 - \text{slope})} \tag{2}$$

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