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Ternary naproxen:β-cyclodextrin:polyethylene glycol complex formation

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Abstract

The aim of this study was to investigate the effect of the presence of the water-soluble polymer polyethylene glycol (PEG)—MW = 35000 g/mol—on the complexation of the phototoxic anti-inflammatory drug naproxen, in its sodium salt form, with β-cyclodextrin (β-CD). The data revealed that the polymer does not interact with the uncomplexed naproxen whereas it does with the β-CD.

The presence of different proportions of PEG, in the 0–1% (w/w) range, systematically lowers K_{app} of the formation of the naproxen:β-CD inclusion complex. The reason for the decrease in the complexed drug is the presence of other competing equilibria, the first one is an interaction of the polymer with the β-CD, which in turn reduces the amount of free CD available for including the naproxen, and the second is the formation of a naproxen:β-CD:PEG ternary complex with lower affinity than the binary complex. The binding constant of these processes are $K_2 = (4.5 \pm 1.0) \times 10^5\,M^{-1}$ and $K_3 = 870 \pm 19\,M^{-1}$, respectively.

In addition the presence of the PEG produces an important change in the driving force of the complex formation. In this case the process is enthalpically unfavoured and entropically favoured; these are typical characteristics of processes governed by hydrophobic interactions.

Keywords: Naproxen; β-Cyclodextrin; Polyethylene glycol

1. Introduction

Naproxen, (+)-6-methoxy-α-methyl-2-naphthaleneacetic sodium salt (Scheme 1), is a non-steroidal anti-inflammatory drug typically used to treat rheumatoid and gouty arthritis. However, it can be associated with gastrointestinal side-effects, drowsiness, dizziness (Delgado and Remers, 1998) and different types of adverse cutaneous photosensitive reactions (Moore and Chappuis, 1988; Boscá and Miranda, 1988). These problems can be minimised through the use of suitable drug carriers. In this sense, a usual procedure is the inclusion complex formation of the drug with different cyclodextrins (CDs, Mura et al., 2001; Partyka et al., 2001).

For a variety of reasons including cost, production capability and toxicology, the amount that can be incorporated into drug formulations is limited (Loftsson, 1998). It is therefore important to develop methods which can be applied in order to enhance the efficiency of drug:CD complexation. Typical pharmaceutical preparations are complex mixtures of drugs and excipients which may include anti-microbial agents, surfactants, polymers, etc. (Loftsson and Järvinem, 1999; Chan et al., 2000). Polymers are

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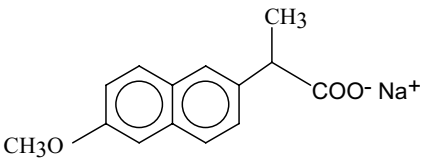

Scheme 1. The chemical structure of naproxen.

used widely in pharmaceutical systems as adjuvants, as suspending and emulsifying agents, as flocculating agents, adhesives, packaging and coating materials. Surfactants have been widely studied as third party components in the drug:CD systems (Skiba et al., 1996a,b; Veiga and Ahsan, 1997, 1998) however, little attention has been focused on the use of polymers as a third component. Polymers are known to interact with CDs (Hladon and Cwiertinia, 1994), enhancing drug availability in aqueous solutions (Sigurðardóttir and Loftsson, 1995). The favourable effect of polyvinylpyrrolidone K25 (PVP) (Bettinetti and Mura, 1994) and polyethylene glycol (PEG) (Vélaz et al., 1998) on the solubility and dissolution rate of naproxen (in its molecular form) has been demonstrated previously.

However, the effect of the polymers on complexation capacity of CDs, has been scarcely studied, and the conclusions reached are different depending on the system. So, Loftsson (1998) concluded that the simple addition of polymers without further treatment of the system does not produce any effect on the capacity of CDs to complex drugs. On the other hand, Mura et al. (2001), indicate that a strong increase in the naproxen:hydroxypropyl-β-CD binding constant is observed when 0.1% of PVP is added.

In addition, previous works realised in our laboratory have shown that the presence of PVP in the system containing naproxen:β-CD produces a different effect on the binding constant depending on the polymer concentration (Valero et al., 2003). To date, the literature contains no reference to the effect of the presence of PEG in the CD complexation of the naproxen or other drugs. PEG (Scheme 2) is a hydrophilic polymer commonly used in the preparation

$$HO\{\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}O\text{-}\}_n\text{-}H$$

Scheme 2. The chemical structure of PEG.

of solid dispersions. The presence of the PEG has been shown to improve the solubility and the dissolution rate of many anti-inflammatory drugs (Mura et al., 1987; Fernández et al., 1993; Margarit et al., 1994) including naproxen, in its molecular form (Vélaz et al., 1998) formulated as solid dispersions, but neither the effect on the complexation ability with CDs nor the structure of the complexes formed in its presence are known.

Therefore and taking into account that in the real formulations naproxen will be exposed to "third-party" components that may improve or decrease its binding to the CD, we decided to undertake a detailed absorption and steady-state emission study of the binding of the drug to β-CD in the presence of increased amounts of PEG, 35.000.

2. Material and methods

2.1. Materials

Naproxen, 2-(6-methoxy-α-methyl-2-naphthyl) propionic acid sodium salt was purchased from Sigma Chemical Co. β-Cyclodextrin (β-CD) was obtained from Sigma. The samples of PEG K25 (Fluka) had weight of 35,000, stated by the manufacturers. These reagents were considered sufficiently well characterised by the manufacturer to be used without further purification. Water was treated with a Milli-Q system from Millipore.

2.2. Methods

Three concentrated aqueous solutions were initially prepared:

(1) 4.0×10^{-5} M naproxen/H_2O; prepared by weight and stirred;
(2) naproxen/PEG/H_2O; prepared by weight of the required amount of PEG, using the aqueous drug solution (1), as solvent;
(3) naproxen/β-CD/PEG/H_2O: prepared by weight of the required amount of β-CD, using the aqueous drug/polymer solution (2) as solvent.

Solutions with variable PEG concentrations were obtained by successive dilution of (2) with (1). Solutions with variable β-CD concentrations, and constant

PEG content, were obtained by successive dilution of (3) with (2). All measurements were carried out at 25 °C and at least 24 h after sample preparation to ensure that the equilibrium had been reached.

2.3. Spectroscopy

UV-Vis absorption spectra were recorded on a Hitachi UV-Vis spectrophotometer, model 150-20. Fluorescence emission spectra were recorded on a Perkin-Elmer LS 50B Spectrofluorimeter. The instrumental response at each wavelength was corrected by means of a curve provided by the apparatus. Emission spectra were obtained in the $\lambda_{em} = 325$–450 nm range, with excitation at $\lambda_{exc} = 317.0$ nm. The spectral slits used were 2.5 and <2 nm (this value corresponds to the minimum possible width, which remains constant for any particular instrument). The fluorescence quantum yield, Φ, was determined using an expression described in previous works (Valero et al., 2000; Velázquez et al., 1995).

Measurements of the refractive index were carried out using an Atago Abbè Refractometer, model DR-A1.

3. Results and discussion

3.1. Complexation of naproxen with β-CD in the presence of PEG

The possibility of specific interactions between naproxen and the PEG was initially investigated using absorption and emission spectroscopic techniques.

Fluorescence and absorption measurements were made from 4×10^{-5} M of the drug in the form of sodium salt in aqueous solutions so, the drug will be in the anionic deprotonated form.

The spectroscopic parameters of naproxen does not change following the addition of PEG (range 0–1% (w/w)). The maxima absorption position, 317.2 and 330.0 nm, and the quantum yield, 0.365, remain constant when increased amount of PEG are added. This situation indicates that there was no interaction between the drug and the PEG, as described previously for several NSAIDs and this polymer (Vélaz et al., 1998; Margarit et al., 1994; Najib and Suleiman, 1989; Fernández et al., 1992).

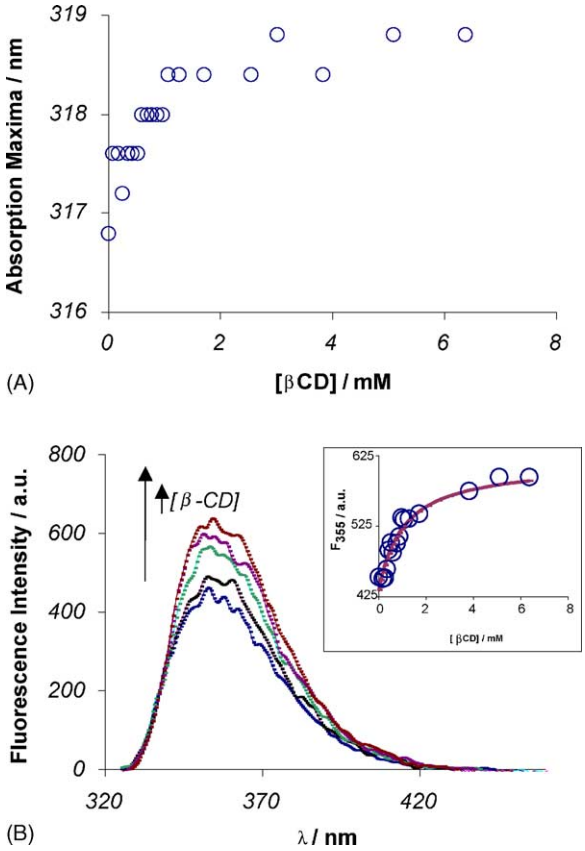

Fig. 1. Effect of β-CD addition on the naproxen aqueous solutions (A) on the absorption maxima position, (B) on the emission spectra, in the presence of PEG.

By contrast, addition of β-CD to naproxen aqueous solution containing a fixed PEG concentration, resulted in appreciable spectral changes.

It was observed that in the whole range of PEG studied, the absorption wavelength was red-shifted when increasing amounts of β-CD were added (Fig. 1A). As can be observed, this property reaches a plateau value, indicating that most drug molecules are included in a different microenvironment. A similar bathochromic effect has been detected in weakly polar solvents (Velázquez et al., 1995) and when the drug is included in the hydrophobic region of *N*-acetyl-*N*,*N*,*N*-trimethyl-ammoniumbromide-CTAB-micelles (Valero et al., 2002) and β-CD (Valero et al., 2003). These changes clearly indicate that naproxen is changing from the polar water solution to a more hydrophobic media in good agreement with the inclusion

of the drug within the apolar cavity of the CD. In addition a hyperchromic effect is also produced on the absorption and emission spectra (Fig. 1B). It is well known that the enhancement of the luminescent processes of luminophores partially or wholly encapsulated by the CD cavity is a result of the better protection from quenching and other processes that occur in the bulk solvent. Thus, the spectroscopic data show that a naproxen:β-CD inclusion complex is formed at all the PEG percentages studied.

When the fluorescence intensity (Fig. 1B, inset) or absorbance (data not shown) values are plotted as a function of [β-CD] a typical binding isotherm (Connors, 1987) is observed.

According to the literature on the binding of the naphthalene derivatives (Van Stam et al., 1996) including naproxen (Valero et al., 1996, 2003) to β-CD, it is expected that the naproxen:β-CD complex is a so called 1:1 complex formed via the equilibrium process:

$$\text{naproxen} + \beta\text{-CD} \Leftrightarrow \text{naproxen} : \beta\text{-CD}, \quad K_1 \qquad (1)$$

The treatment for extracting the value of K from the binding isotherm has been described previously (Valero et al., 1996, 1999, 2003). Essentially the binding isotherm data are fit by the model (Eqs. (2) and (3)), for the emission and adsorption data, respectively:

$$F = \frac{(F_D + F_B K[CD])}{(1 + K[CD])} \qquad (2)$$

and

$$A = \frac{(A_D + A_B K[CD])}{(1 + K[CD])} \qquad (3)$$

The values of the binding constant, K, of the inclusion complex formed between naproxen and β-CD in the presence of PEG at different concentrations (between 0 and 1% (w/w)) were determined using the fluorescence intensity and absorption data at 355 and 317 nm, respectively. Fig. 1B (inset), shows no linear regression fits of Eq. (2), to the binding isotherm data for the aqueous systems in the presence of 0.02% PEG; similar plots were obtained for the other systems examined, by both techniques.

The binding constants obtained for the formation of the naproxen:β-CD inclusion complex at different PEG percentages are presented in Table 1. In all cases, a good agreement between the experimental data and those calculated using the fitting parameters shown in Table 1 was observed (Fig. 1B, inset). Therefore, the presence of the polymer does not change the stoichiometry of the complex formed; that is, 1:1 in the PEG range studied, as it was observed in the absence of the PEG (Valero et al., 1996, 1999) and in the presence of other polymers (Valero et al., 2003). Taking into account the small change observed in the absorbance, the discussion has been made considering the binding constant values obtained from fluorescence data.

Table 1
Binding constant of complexation of aqueous naproxen Na with β-CD in the presence of PEG

% PEG (w/w)	K_{app} (M^{-1})[a]	K_{app} (M^{-1})[b]
0	1100 ± 66[c]	845 ± 30[d]
0.02	880 ± 53	900 ± 54
0.05	800 ± 48	950 ± 57
0.1	950 ± 57	850 ± 21
0.5	800 ± 65	925 ± 56
1.0	900 ± 54	900 ± 54

[a] From fluorescence data.
[b] From UV-Vis absorption data.
[c] Valero et al. (1999).
[d] Valero et al. (1996).

The binding constant values show that the presence of PEG, produces a decrease in the affinity of the β-CD to the naproxen, but the trend is not clear. Water-soluble fluorescence quenchers have often been used to gain insight into the relative distribution of a guest between aqueous and CD environments (Van Stam et al., 1996; Evans et al., 2000). KI is a good choice of fluorescence quencher in this context. Iodide salts are often used to quench excited singlet states (Kalyanasundaram, 1987; Murov et al., 1993) and has at most very weak association with β-CD cavity.

On this basis, we performed a series of experiments in which we used KI to quench the fluorescence of naproxen in the presence of varying [PEG] in the absence and presence of β-CD. In the last case, the [β-CD] is enough to ensure that all the drug is complexed. Stern-Volmer plots (F_0/F_q versus [KI]) were measured up to 50 mM KI. Under these conditions the plots are linear (Fig. 2) in all cases and the resulting Stern-Volmer constants, K_{SV}, are presented in Table 2. In the absence of β-CD, i.e. when the drug is free in aqueous solution, the K_{SV} remains unaltered with the

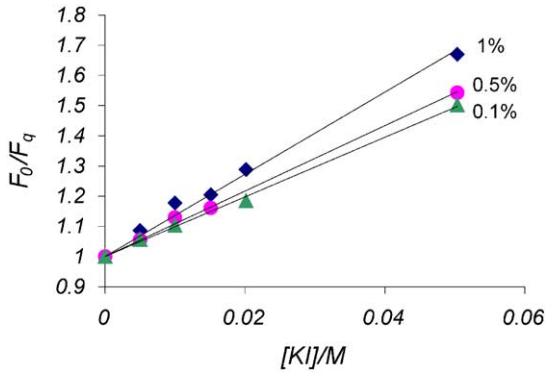

Fig. 2. Stern-Volmer plots of naproxen:β-CD with different [PEG] with KI.

increased amounts of PEG, confirming no interaction between the drug and the polymer occurs as pointed out by the electronic spectra. In the presence of β-CD and in the absence of PEG there is a strong reduction of the K_{SV} which indicates that the encapsulation of the naproxen by the β-CD, thereby partially isolating it from the primarily aqueous phase KI quencher. In the presence of β-CD and PEG there is a gradual increase of K_{SV} as the [PEG] is increased, which clearly indicates that the polymer forces the drug to reside in the aqueous environment where it is more readily quenched than in the β-CD environment. The trend in the K_{SV} is consistent with the decrease in the naproxen:β-CD binding constant observed by fluorescence. The results of our fluorescence experiments clearly indicate that PEG weaken the association between naproxen and the β-CD cavity.

A similar effect has been reported for the influence of the presence of other additives such as alcohols (Partyka et al., 2001; Van Stam et al., 1996; Evans et al., 2000) and sodium *n*-alkyl sulfate surfactants on naphthalene (Evans et al., 2000) and 2-naphthol (Van Stam et al., 1996) binding to β-CD. This is usually interpreted as reflecting the reduction in the concentration of free CD when the additive is present which, in turn, inhibits binding of the drug to the CD cavity (Van Stam et al., 1996; Evans et al., 2000).

Table 2
Stern-Volmer constant values for aqueous naproxen Na and complexed with β-CD, in the presence of PEG

% PEG (w/w)	K_{SV} (M^{-1}) free drug	K_{SV} (M^{-1}) drug complexed with β-CD
0.1	26.2 ± 0.453	9.88 ± 0.249
0.5	27.6 ± 0.998	10.8 ± 0.320
1.0	27.6 ± 0.938	13.6 ± 0.656

Recently, we have reported that the presence of PVP K25 elicits the formation of a ternary complex with the naproxen:β-CD system (Valero et al., 2003). No studies have addressed the interaction between the PEG and CDs or their inclusion complexes. For these reasons, initially two possible causes for the decrease in the binding constant must be taken into account: (1) exclusion of drug from CD cavity, due to the occupation of the internal space by the PEG molecules, as observed for 2-naphthol complexes (Liao and Bohne, 1996); and/or (2) ternary complex formation between CD, PEG and naproxen with a lower binding constant than that of the binary system.

In any case, in both situations the binding constant values obtained (Table 1) correspond to an apparent binding constant, K_{app}, related to the equilibrium constant of the processes involved; accordingly, the K_{app} values estimated at different PEG concentrations can be used to obtain the equilibrium constant of these processes.

In our case, and taking into account that the drug does not interact with the polymer, two additional equilibria must also be considered:

$$\text{PEG} + \beta\text{-CD} \Leftrightarrow \beta\text{-CD} : \text{PEG}, \quad K_2 \tag{4}$$

$$\text{PEG} + \text{naproxen} : \beta\text{-CD} \Leftrightarrow \text{naproxen} : \beta\text{-CD} : \text{PEG}, \quad K_3 \tag{5}$$

If we suppose that the decrease in the binding constant is due exclusively to (1), the system represents two ligands competing for the binding to the CD and hence only equilibria (1) and (4) must be considered. In this case, the K_{app} of naproxen to β-CD in the presence of PEG is related with K_1 and K_2 via the following equation (Cadenas, 1978):

$$K_{app} = K_1 \left[\frac{1}{(1 + K_2[\text{PEG}])} \right] \tag{6}$$

It is not possible to fit the K_{app} data shown in Table 1 to this equation, which means that the interaction between PEG and β-CD is not the only cause of the decrease in the naproxen:β-CD binding constant.

Therefore, the three possible equilibria involved—(1), (4) and (5)—each described by its respective

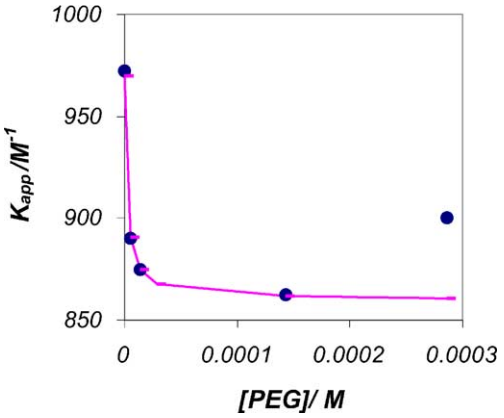

Fig. 3. Fitting of K_{app} (Table 1) to Eq. (7).

equilibrium constant: K_1, K_2 and K_3, must be considered. The relation between K_{app} and these three equilibrium constant is given by the following equation (Van Stam et al., 1996; Liao and Bohne, 1996; Mrozek et al., 2002):

$$K_{app} = \frac{K_1 + K_2 K_3[\text{PEG}]}{1 + K_2[\text{PEG}]} \quad (7)$$

As can be seen in Fig. 3, a good fitting of the data to Eq. (7) is obtained, clearly pointing to the formation of the ternary complex in addition to the PEG:β-CD interaction. The equilibrium constants obtained from the fit were $K_1 = 970 \pm 33\,M^{-1}$, $K_2 = (4.5 \pm 1.0) \times 10^5\,M^{-1}$ and $K_3 = 825 \pm 19\,M^{-1}$. In the absence of the added PEG, the value of K_{app} corresponds to that of K_1. The K_1 value obtained in this study corresponds closely to the value of 845 ± 30 (Valero et al., 1996) and 1100 ± 66 (Valero et al., 1999) reported previously. The results of our modelling procedures support the view that the PEG interacts with the β-CD to form binary—PEG:β-CD—and ternary, naproxen:β-CD:PEG, complexes.

Further information about the ternary complex formation was obtained investigating the interaction between the naproxen:β-CD complex with PEG. To this end, the effect of the addition of increasing amounts of PEG at a fixed concentration of drug:β-CD solution (with the drug totally complexed) was studied spectroscopically. The addition of PEG to the naproxen:β-CD inclusion complex produced a decrease in the quantum yield (Table 3) of the drug complexed, in good agreement with the binding constant values.

Table 3
Spectroscopic parameters of the naproxen complexed with β-CD in the presence of increased amounts of PEG

% PEG (w/w)	Absorption maxima position (nm)	Φ
1.0	318.4	0.358
0.6	318.0	0.392
0.3	318.4	0.400
0.1	318.4	0.409
0.07	318.8	0.416
0.04	318.4	0.409
0	318.8	0.439

The position of the absorption maximum is red-shifted from the 317.2 nm, when the drug was free in water, to 318.8 nm when it was complexed with β-CD. No changes in the position of this maximum were observed when PEG was added. All the data showed that at all PEG concentrations studied, the microenvironment of the drug remains unaltered but inside the CD.

Therefore these data seem to indicate that in the ternary complex, the PEG is not inside the CD cavity but interacting with the external sides of it. Taking into account the corresponding structures, the most probable is that the interaction occurs via hydrogen bond formation between the β-CD and the PEG.

3.2. Thermodynamic study of the complexation process

The thermodynamic parameters of the inclusion process, in the presence of different PEG percentages, were determined from the temperature dependence of the association constant K using the van't Hoff expression.

In all cases, Fig. 4, a good fit was obtained of the experimental data and it can be seen that, as temperature increases, the affinity of the CD for the drug increases. The thermodynamic parameters obtained for naproxen:β-CD complexation in the presence of different percentages of PEG are included in Table 4.

The data clearly show that different forces and/or mechanisms are involved in the complex formation, depending on the presence or the absence of PEG.

Naproxen:β-CD complexation in the absence of any additive, was characterised by a negative enthalpy and entropy values (Valero et al., 1999), as reported

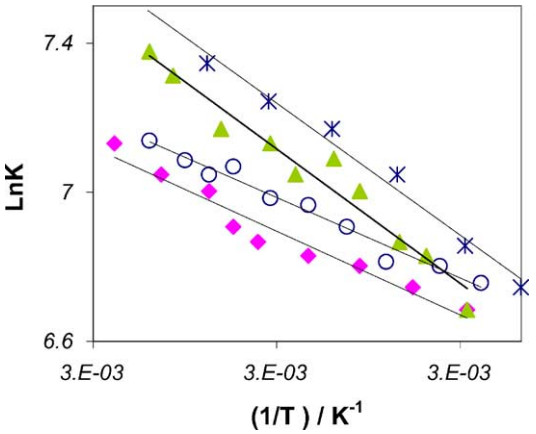

Fig. 4. van't Hoff plots for the formation of naproxen:β-CD complex in the presence of 0.02 (○), 0.05 (pink diamond), 0.5 (green triangle) and 1% (✳) PEG (w/w). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in most experimental data concerning the molecular recognition of CDs (Rekharsky and Inoue, 1998). However, in the presence of PEG the thermodynamic behaviour changed, and at all polymer concentrations studied the complexation process was characterized by a large positive, favourable, entropy change and a positive, unfavourable enthalpy change. The only possible source of the positive entropy was hydrophobic interaction and hence this type of interaction must be the driving force for the formation of the naproxen:β-CD complex in the presence of the PEG. The hydrophobic effect relies on the redistribution of the cavity of CD water molecules and the interaction between the solute and water. Taking into account that non-complexed naproxen does not interact with the polymer and that in the ternary complex the PEG is not inside the CD cavity, the effect of the additive must be on the hydrophobic surface exposed to water in the ternary complex. A similar kind of behaviour has been observed in capped CDs, where the hydrophobic surface of the complexed ligand in contact with water is reduced by capping one end of the pore via covalent linkages (Kalyanasundaram, 1987). As a result, an increase in the binding constant is observed. In our case, the binding constant of the naproxen to β-CD decreased owing to the presence of the PEG, suggesting that the hydrophobic surface of the drug inside the complex is more exposed to water. The formation of strong hydrogen bonds between naproxen and β-CD, after complexation, has been described previously (Valero et al., 2003). If these bonds were broken by the PEG, the hydroxyl groups of the CD would become removed from the carboxylate group of the drug, and the naphthalene ring would be in closer contact with water than in the absence of PEG. This situation is clearly in agreement with the structure suggested by the spectroscopic data and with the change in the driving force, since the presence of other types of interactions between ligand:CD, changes the thermodynamic parameters characteristics of hydrophobic interactions, which are clearly observed when only this type of interaction is involved (Liu, 2002).

The changes in Gibbs's free energy corresponding to the association process are the same order of magnitude as in the absence of polymer (Valero et al., 1999) indicating that the stability of the complex formed does not change by its presence in good agreement with the binding constant values obtained.

A linear correlation between ΔH° and ΔS° was observed at all PEG concentrations studied, including [PEG] = 0. A good correlation was also obtained when the data corresponding to naproxen and

Table 4
ΔH° and ΔS° in the formation of naproxen:β-CD complex formation at different PEG percentages

% PVP (w/w)	ΔH° (kJ/mol)	ΔS° (J/mol K)	ΔG° (kcal/mol) (298.15 K)
0.0	−22.1 ± 0.6[a]	−15.7 ± 0.6[a]	−16.8 ± 0.1[a]
0.02	11.97 ± 0.6749	96.37 ± 2.173	−16.77 ± 0.0173
0.05	12.43 ± 1.039	97.12 ± 3.333	−16.52 ± 0.036
0.1	19.63 ± 1.332	123.0 ± 4.376	−17.04 ± 0.015
0.5	19.98 ± 1.483	123.1 ± 4.786	−16.72 ± 0.036
1.0	12.04 ± 0.7573	96.78 ± 2.462	−16.82 ± 0.017

[a] Valero et al. (1999).

nabumetone (another naphthalene derivative) with β- and HPβ-CD in water and in the presence of PVP were included (Valero et al., 1999, 2003). This implies that in the inclusion complex obtained in the presence of PEG, the drug will enter the cavity through the methoxy side, with the carboxylate group protruding into the water as observed for the related complexes (Valero et al., 1999).

The thermodynamic behaviour observed, support some evidence about the structure of the ternary complex suggested on the basis of the spectroscopic data in which the inclusion complex naproxen:β-CD is total or partially recovered by the polymer interacting exclusively with the CD.

4. Conclusions

PEG does not interact with the free naproxen whereas it interacts with the naproxen:β-CD inclusion complex. The experimental data show that a naproxen:β-CD inclusion complex is formed at all the PEG percentages studied with 1:1 stoichiometry. The presence of PEG produces a decrease in the affinity of β-CD for naproxen. Quenching of fluorescence of the drug with KI shows that the β-CD cavity protects it from this aqueous phase quencher, although the presence of PEG partially inhibits this protective effect.

The decrease in the apparent binding constant is due to the simultaneous formation of binary naproxen:β-CD and ternary naproxen:β-CD:PEG complex, in addition to the PEG:β-CD interaction. The equilibrium constant obtained for these processes are $K_1 = 970 \pm 33\,M^{-1}$, $K_2 = (4.5 \pm 1.0) \times 10^5\,M^{-1}$ and $K_3 = 825 \pm 19\,M^{-1}$.

The thermodynamic parameters showed that in the presence of PEG different forces and/or mechanisms are involved in the formation of the complex; the thermodynamic behavior is characterised by a large positive, favourable, entropy change, showing that the hydrophobic interaction is the driving force of complexation.

References

Bettinetti, G.P., Mura, P., 1994. Dissolution properties of naproxen in combinations with polyvinylpyrrolidone. Drug Dev. Ind. Pharm. 20, 1353–1366.

Boscá, F., Miranda, M.A., 1988. Photosensitizing drugs containing the benzophenone chromophore. J. Photochem. Photobiol. B: Biol. 43, 1–26.

Cadenas, E., 1978. Enzimas alostéricas. H. Blume Ediciones.

Chan, L.W., Kurup, Y.R.R., Muthaiah, A., Thenmozhiyal, J.C., 2000. Interaction of *p*-hydroxybenzoic esters with β-cyclodextrins. Int. J. Pharm. 195, 71–79.

Connors, K.A., 1987. Binding Constants. Wiley, New York.

Delgado, J.N., Remers, W.A. (Eds.), 1998. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 10th ed. Lippincott-Raven, New York.

Evans, C.H., Partyka, M., van Stam, J., 2000. Naphthalene complexation by β-cyclodextrin: influence of added short chain branched and linear alcohols. J. Incl. Phenom. 38, 381–396.

Fernández, M., Rodríguez, I.C., Margarit, V., Cerezo, A., 1992. Characterization of solid dispersions of piroxicam/polyethylene glycol 4000. Int. J. Pharm. 84, 197–202.

Fernández, M., Margarit, M.V., Rodríguez, I.C., Cerezo, A., 1993. Dissolution kinetics of piroxicam in solid dispersions with polyethylene glycol 4000. Int. J. Pharm. 98, 29–35.

Hladon, T., Cwiertinia, B., 1994. Physical and chemical interactions between cellulose ethers and β-cyclodextrin. Pharmazie 49, 497–500.

Kalyanasundaram, K., 1987. Photochemistry in Microheterogeneous Systems. Academic Press, New York.

Liao, Y., Bohne, C., 1996. Alcohol effect on equilibrium constants and dissociation dynamics of xanthone-cyclodextrin complexes. J. Phys. Chem. 100, 734–743.

Liu, L., Guo, Q.-X., 2002. The driving forces in the inclusion complexation of cyclodextrins. J. Incl. Phenom. 42, 1–14.

Loftsson, T., 1998. Increasing the cyclodextrin complexation of drugs and drug bioavailability through addition of water-soluble polymers. Pharmazie 53, 733–740.

Loftsson, T., Järvinem, T., 1999. Cyclodextrins in ophthalmic drug delivery. Adv. Drug Deliv. Rev. 36, 59–79.

Margarit, M.V., Rodríguez, I.C., Cerezo, A., 1994. Physical characteristics and dissolution kinetics of solid dispersions of ketoprofen and polyethylene glycol 6000. Int. J. Pharm. 108, 101–107.

Moore, D.E., Chappuis, P.P., 1988. A comparative study of photochemistry of the non-steroidal antiinflammatory drugs, naproxen, benoxaprofen and indomethacin. Photochem. Photobiol. 47, 173–180.

Mrozek, J., Guzow, K., Szabelski, M., Karolczak, J., Wiczk, W., 2002. Influence of methanol and cyclodextrins cavity size on stoichiometry and binding constant of 3-[2-(9-anthryl) benzoxazol-5-yl]-ine. J. Photochem. Photobiol. A: Chem. 153, 121–128.

Mura, P., Liguori, A., Bramanti, G., 1987. Preparation and dissolution characteristics of solid dispersions of ibuprofen in various polyethylene glycols indomethacin from solid dispersions. Il Fármaco 42, 149–156.

Mura, P., Faucci, M.T.M.T., Bettinetti, G.P., 2001. The influence of the polyvinylpyrrolidone on naproxen complexation with hydroxypropyl β-cyclodextrin. Eur. J. Pharm. Sci. 13, 187–194.

Murov, S.L., Carmicheal, I., Hug, G.L., 1993. Handbook of Photochemistry, 2nd ed. Marcel Decker, New York.

Najib, N.M., Suleiman, M.S., 1989. Characterization of a diffusional polyethylene glycol solid dispersion system. Int. J. Pharm. 51, 225–232.

Partyka, M., Ha Au, B., Evans, C.H., 2001. Cyclodextrins as phototoxicity inhibitors in drugs formulation; studies on model systems involving naproxen and β-cyclodextrin. J. Photochem. Photobiol. A: Chem. 140, 67–74.

Rekharsky, M.V., Inoue, Y., 1998. Complexation thermodynamics of cyclodextrins. Chem. Rev. 98, 1875–1880.

Sigurðardóttir, A.M., Loftsson, T., 1995. The effect of polyvinylpyrrolidone on cyclodextrin complexation of hydrocortisone and its diffusion through hairless mouse skin. Int. J. Pharm. 126, 73–78.

Skiba, M., Nemati, F., Puisieux, F., Duchêne, D., Wouessidjewe, D., 1996a. Spontaneous formation of drug-containing amphiphilic beta-cyclodextrin nanocapsules. Int. J. Pharm. 145, 241–245.

Skiba, M., Duchêne, D., Puisieux, F., Wouessidjewe, D., 1996b. Development of a new colloidal drug carrier from chemically-modified cyclodextrins:nanospheres and influence of physicochemical and technological factors on particle size. Int. J. Pharm. 129, 113–121.

Valero, M., Rodríguez, L.J., Velázquez, M.M., 1996. Inclusion of a non-steroidal anti-inflammatory agents into aqueous cyclodextrins: a UV-absorption spectroscopic study. Il Fármaco 51, 525–533.

Valero, M., Costa, S.M.B., Ascenso, J.R., Velázquez, M.M., Rodríguez, L.J., 1999. Complexation of the non-steroidal anti-inflammatory drug nabumetone with modified and unmodified cyclodextrins. J. Incl. Phenom. Macrocycl. Chem. 35, 663–677.

Valero, M., Costa, S.M.B., Santos, M.A., 2000. Conformations of a non-steroidal anti-inflammatory drug nabumetone in aqueous environment. J. Photochem. Photobiol. A: Chem. 132, 67–74.

Valero, M., del Arco, A., Rodríguez, L.J., 2002. New insight into the structure of CTAB micelles in the presence of cyclodextrins, using non-steroidic anti-inflammatory agents nabumetone, naproxen as fluorescent probes. J. Incl. Phenom. Macrocycl. Chem. 42, 121–130.

Valero, M., Pérez, B.I., Rodríguez, L.J., 2003. Effect of PVP K-25 on formation of naproxen:β-cyclodextrin complex. Int. J. Pharm. 253, 97–110.

Van Stam, J., De Feyter, S., De Schryver, F.C., Evans, C.H., 1996. 2-Naphthol complexation by β-cyclodextrin: influence of added short linear alcohols. J. Phys. Chem. 100, 19959–19996.

Veiga, M.D., Ahsan, F., 1997. Study of surfactants/beta-cyclodextrin interactions over mequitazine dissolution. Drug Dev. Ind. Pharm. 23, 721–725.

Veiga, M.D., Ahsan, F., 1998. Solubility study of tolbutamide in monocomponent and dicomponent solutions of water. Int. J. Pharm. 160, 43–49.

Vélaz, I., Sánchez, M., Martín, C., Martínez-Ohárriz, M.C., 1998. Effect of PEG 4000 on the dissolution rate of naproxen. J. Drug Metab. Pharm. 23, 103–108.

Velázquez, M.M., Valero, M., Rodríguez, L.J., Costa, S.M.B., Santos, M.A., 1995. Hydrogen bonding in a non-steroidal anti-inflammatory drug naproxen. J. Photochem. Photobiol. B: Biol. 29, 23–31.