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# Complexation of the Non-steroidal Anti-inflammatory Drug *Nabumetone* with Modified and Unmodified Cyclodextrins

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**Abstract.** The inclusion of the anti-inflammatory drug, *Nabumetone*, in $\alpha$-, $\beta$- and hydroxypropyl-$\beta$-cyclodextrin (CDs) is studied using UV-VIS absorption and steady-state fluorescence emission. Binding constants and thermodynamic parameters of complex formation are determined by spectrofluorimetry. The inclusion phenomena of *Nabumetone* with the three cyclodextrins is compared with that of the well known similar anti-inflammatory drug *Naproxen*. In the case of *Nabumetone* pronounced differences are observed in the complexation process with each cyclodextrin whereas the respective *Naproxen* complexes are nearly identical. $^1$H-NMR experiments show that the inclusion process in *Nabumetone* can occur either through the substituents in the -2 (butanone) or -6 (methoxy) positions in the naphthalene ring.

**Key words:** *Nabumetone*, *Naproxen*, cyclodextrin, UV-absorption spectroscopy, fluorescence spectroscopy, thermodynamics, proton NMR.

## 1. Introduction

Cyclodextrins (CDs) are popular host molecules and their complexation with a variety of compounds has been described over the last decade [1–3]. Three distinct CDs are commonly available consisting of six ($\alpha$-CD) , seven ($\beta$-CD) or eight ($\gamma$-CD) sugar units all of which have a doughnut shaped hydrophobic cavity. Hydroxyl groups, on the rim cavities, can be easily modified by derivatization, as in hydroxypropyl $\beta$-cyclodextrin (HP$\beta$-CD), where the hydrogens of the primary hydroxyls of the different glucose units are substituted. A more extended modification often results in CDs with more desirable properties as host molecules than the unmodified ones [4, 5]. Encapsulation of drugs by means of monomolecular inclusion complex formation offers a new form of dosage and its importance in pharmaceutical formulation has been fully realised [6–9].

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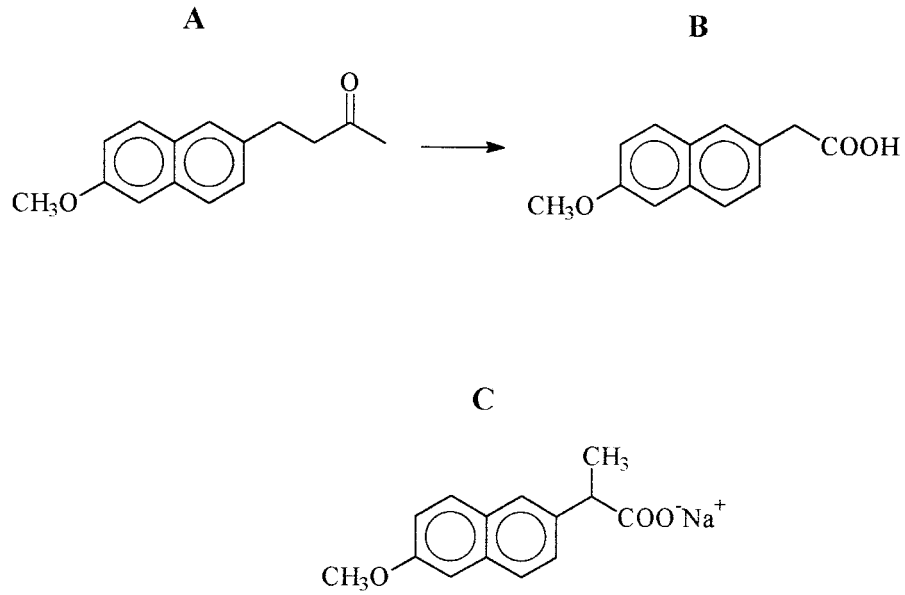



*Scheme 1.* The chemical structure of *Nabumetone* (A), its active metabolite (B) and *Naproxen* (C).

Non-steroidal anti-inflammatory and analgesic drugs are suitable for inclusion as guests within some cyclodextrins [1, 2]. It has been proposed that the well known deleterious effects of non-steroidal anti-inflammatory drugs on the epithelium of the gastro-intestinal tract may be improved by their inclusion within a cyclodextrin molecule, resulting in a reduced concentration of free drug in the gastro-intestinal tract [10]. Presently, the pharmaceutical industry is not searching for new drugs with higher anti-inflammatory power but rather it is looking for drugs with a lower incidence of undesirable effects, which in most cases make the use of the drug impossible. In this connection, a new non-steroidal anti-inflammatory drug *Nabumetone*, (4-[6-methoxy-2-naphthyl]-2-butanone) was released recently which produces, by metabolic reactions, the active molecule 6-methoxy-2-naphthylacetic acid (Scheme I). This active metabolite has practically the same structure as *Naproxen* (Scheme I) which itself is an anti-inflammatory drug widely used for therapeutic purposes. The chemical structures of *Nabumetone* and *Naproxen* differ on the substituent chain of the naphthalene moiety, butanone, in the case of *Nabumetone*, and 2 methyl acetic acid sodium salt in *Naproxen*. In the former, the presence of butanone reduces strongly the anti-inflammatory capacity but has the advantage of decreasing also some undesirable effects when compared with *Naproxen* [11–13].

The incorporation within a cyclodextrin will be effective in reducing the concentration of free drug if the inclusion complex stability constant is sufficiently large as was pointed out by Habon et al. [14]. Previous studies have reported $\alpha$-

and $\beta$-cyclodextrin inclusion complexes of *Naproxen* [15–17] with stability constants determined by UV-VIS and NMR spectroscopic techniques. However, data for *Nabumetone* is very scarce and the stability constant reported for the inclusion of this drug in $\beta$-cyclodextrin is very high [18].

Using a more sensitive optical technique, fluorescence emission, this work was directed at discovering the stoichiometry, equilibrium constants and thermodynamic parameters of the inclusion complexes formed between the anti-inflammatory *Nabumetone* and $\alpha$-, $\beta$- and hydroxypropyl-$\beta$-cyclodextrins. For comparative purposes a parallel study with *Naproxen* was also carried out.

Proton NMR spectroscopy was also used to obtain information on the inclusion process, in particular regarding the entry of the aliphatic substituent of *Nabumetone* inside the CD cavities.

## 2. Experimental

### 2.1. MATERIALS

*Nabumetone*, *Naproxen* and $\alpha$-, $\beta$-, and hydroxypropyl $\beta$-cyclodextrins ($\alpha$-CD, $\beta$-CD and HP$\beta$-CD), were purchased from Sigma. Bidistilled water was used for preparation of all aqueous solutions. Spectroquality deuterium oxide (min 99.8%) was purchased from Merck (Uvasol grade) and used without any further purification.

The solubilization of *Nabumetone* in aqueous and cyclodextrin aqueous solution was carried out as follows: appropriate volumes of a given concentration of the drug in methanol were placed into a volumetric flask and the solvent was evaporated by slow passage of $N_2$. The water or cyclodextrin solution was added to the evaporated residue and the resulting solution was stirred until the drug was solubilized. Aqueous solutions of cyclodextrins were prepared by weight. The final *Nabumetone* and *Naproxen* concentrations were 50 $\mu$M and 40 $\mu$M respectively. In all the solutions the pH was around 6. At this pH the ionic *Naproxen* species is always predominant, pKa = 3.5 [19].

### 2.2. APPARATUS

Absorption spectra were recorded with a JASCO V-560 UV/VIS spectrophotometer. Steady-state emission measurements were recorded with a Perkin Elmer LS 50B spectrofluorimeter with the sample holder thermostated. The instrumental response at each wavelength was corrected by means of a curve obtained using appropriate fluorescence standards (up to 400 nm) together with the one provided with the apparatus.

The emission spectra were recorded in the range 340–450 nm with excitation at 330 nm and 2 nm slit widths.

In order to obtain the thermodynamic parameters of the inclusion processes the association constants were determined at seven temperatures in the range 15–45 °C.

The $^1$H-NMR experiments were performed on a Varian Unity spectrometer operating at 300 MHz. *tert*-Butanol (1.3 ppm per TMS) was added to the $D_2O$ solutions as internal reference for proton chemical shifts.

For the NMR studies the guest to host ratio was maintained at 1 : 1 in the case of *Naproxen* with $\beta$-, and HP$\beta$-CD; 1 : 8 with $\alpha$-CD. For *Nabumetone* the ratio was the highest allowed by the drug solubility; 1 : 10 for $\beta$-, and HP$\beta$-CD; and 1 : 80 for $\alpha$-CD. In all cases the cyclodextrin concentration was high enough to ensure the total drug complexation in solution. All solutions were prepared in $D_2O$.

### 2.3. ANALYSIS OF BINDING DATA

The detection of hyperchromic effects in the fluorescence spectra of a given molecule induced upon the addition of cyclodextrins provides a way of determining the binding constants. A simple 1 : 1 scheme for the binding ligand, L, to the drug molecule, D, with a binding constant K, can be used to describe the interaction adequately. Some different stoichiometry of the complexes has been observed in the case of Naproxen with $\alpha$- and $\gamma$-cyclodextrins, but these complexes were formed in drug saturated solutions [20].

$$D + L \rightarrow DL \tag{1}$$

$$K = [DL]/[D][L].$$

Considering that there are two species in solution emitting light, the free and complexed drug, the total fluorescence intensity is the sum of the contribution of the free and complexed drug. Taking into account the corresponding mass balances and the equilibrium conditions, the apparent fluorescence intensity at a given wavelength is given by:

$$I_F = (I_D + I_B K[CD])/(1 + K[CD]), \tag{2}$$

where $I_D$ and $I_B$ represent the molar fluorescence intensity of the free and complexed drug respectively and [CD] is the analytical cyclodextrin concentration. In this equation, the equilibrium concentration of free CD is considered to be equal to the analytical CD concentration, since the former is much larger than that of the drug. The fluorescence intensity $I_B$ can be experimentally measured for complexes of either drug with $\beta$-CDs. The variation of the fluorescence intensity with the cyclodextrin concentration was fitted to Equation (2) allowing evaluation of the association constant K. In studies of *Nabumetone* and *Naproxen*-$\alpha$-CD complexation processes, solubility restrictions of this cyclodextrin prevented the experimental measurement of $I_B$. Then the complete fit of the data to Equation (2) could only be achieved with $I_B$ as an adjustable parameter and only the upper limit of the binding constant was calculated. To fit experimental results to Equation 2 a non-linear least squares method was used. A similar relationship with the absorbance

data could be applied but the changes observed after complexation are so small that fluorescence measurements are preferable to study the inclusion process. The fluorescence intensity was measured at the maximum of the emission spectra which was 355 nm in both cases.

## 3. Results and Discussion

### 3.1. ELECTRONIC SPECTRA

The absorption spectrum of *Nabumetone* and *Naproxen* in water is typical of 2-substituted naphthalene compounds [10]. They present a three band system centered around 220 nm ($^1A_{1g} \rightarrow {}^1B_b$), 240–280 nm ($^1A_{1g} \rightarrow {}^1L_a$) and 310–330 nm ($^1A_{1g} \rightarrow {}^1L_b$). The vibronic structure of the latter two bands is clearly observed in *Nabumetone* (Figure 1) and in *Naproxen* [21]. The fluorescence spectra of both drugs in water are rather broad and centered around 355 nm.

Upon inclusion of the molecule within a cyclodextrin cavity, the UV-Visible spectrum usually changes since the solvation shell of the molecule is partly or totally replaced by the cyclodextrin molecule, leading to altered solute/environment interactions [1, 22, 23]. For *Naproxen* no changes were observed in the absorption and emission maxima upon addition of cyclodextrins [21] but some variations were detected in the absorptivity and emission intensity. The presence of $\alpha$-CD produces a very weak effect on the spectroscopic features of the *Naproxen*. The effect of the two $\beta$-CDs studied is stronger but, there is no difference between them. In the case of *Nabumetone*, each of the three cyclodextrins ($\alpha$-, $\beta$-, and HP$\beta$-CD) produced different effects on both absorption and emission drug spectra (Figure 2).

When $\alpha$-CD is added to an aqueous solution containing *Nabumetone* significant changes in the position and intensity of both the absorption and emission spectra are observed. The position of the maximum corresponding to the absorption spectrum is red shifted by 9 nm, and the absorptivity increased. On the other hand, the shape of the fluorescence spectrum is substantially changed upon complexation and a vibrational structure appears with two maxima centered around 350 and 361 nm.

Conversely, the effect of the addition of $\beta$-CD and its derivative HP$\beta$-CD on the emissive optical properties of *Nabumetone* is not so pronounced. The shape of the spectra in both complexes remains unaltered. The position of the maxima of the absorption spectra are slightly red shifted whereas the position of the drug emission maximum does not change after inclusion. The complexation effect on the molar absorptivity is different: it increases upon inclusion with $\beta$-CD and decreases with HP$\beta$-CD. As may be seen in Figure 2 the increase of emission intensity is greater in HP$\beta$-CD than in $\beta$-CD.

For comparative purposes the fluorescence spectra of naphthalene dissolved in hexane and in the presence of $\alpha$- and $\beta$-CD were also recorded. Results are presented in Figure 3. As can be seen in the figure, significant similarities between the shape of these spectra are observed. This fact seems to indicate that the species

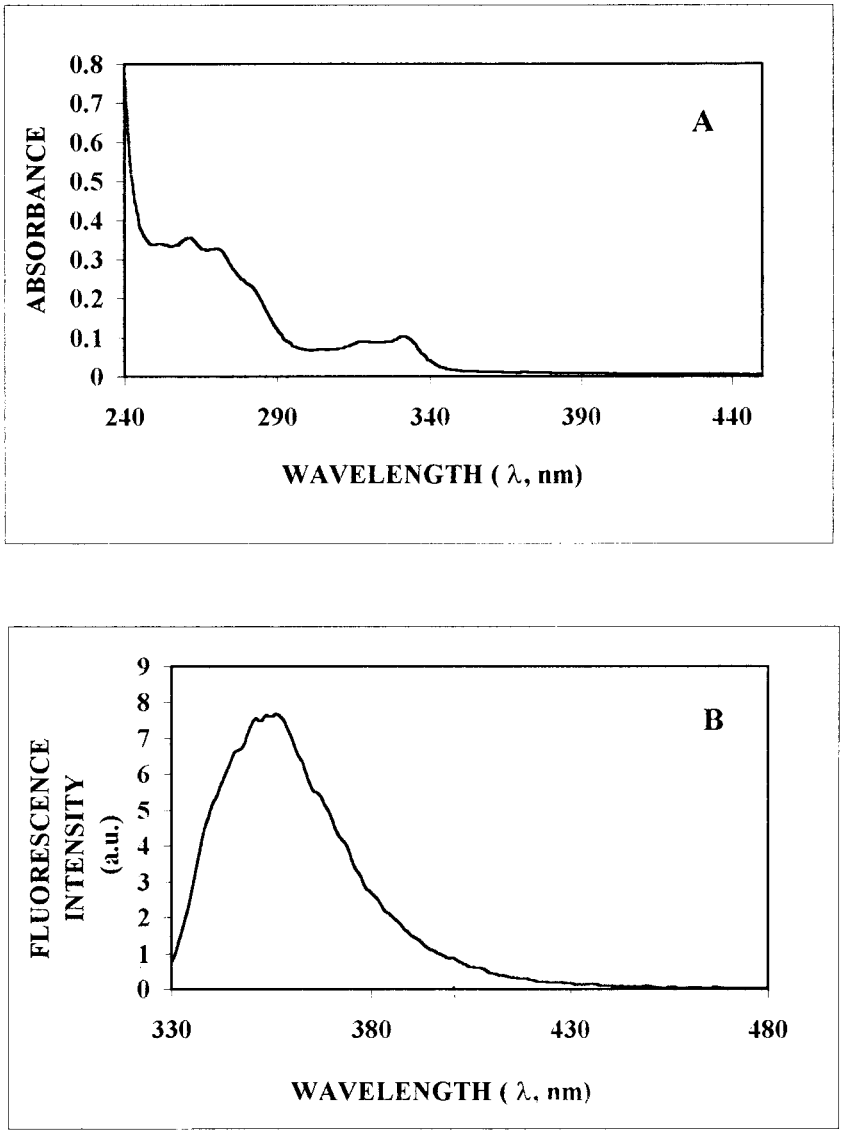



*Figure 1.* Absorption (A) and emission spectra (B) of *Nabumetone* aqueous solution, $C_{NAB} = 4.89 \times 10^{-5}$ M, at 20 °C.

responsible for the fluorescence emission of *Nabumetone* complexed with $\alpha$-CD is similar to that of naphthalene and different to those of free *Nabumetone* or *Nabumetone* complexed with $\beta$- and HP$\beta$-CD. We can make a naive interpretation of this behavior in terms of differences in the group responsible for the inclusion. In the case of $\alpha$-CD, the substituent of *Nabumetone*, 2-butanone, can be included into the cyclodextrin cavity. This fact could minimize the effect of substitution resulting

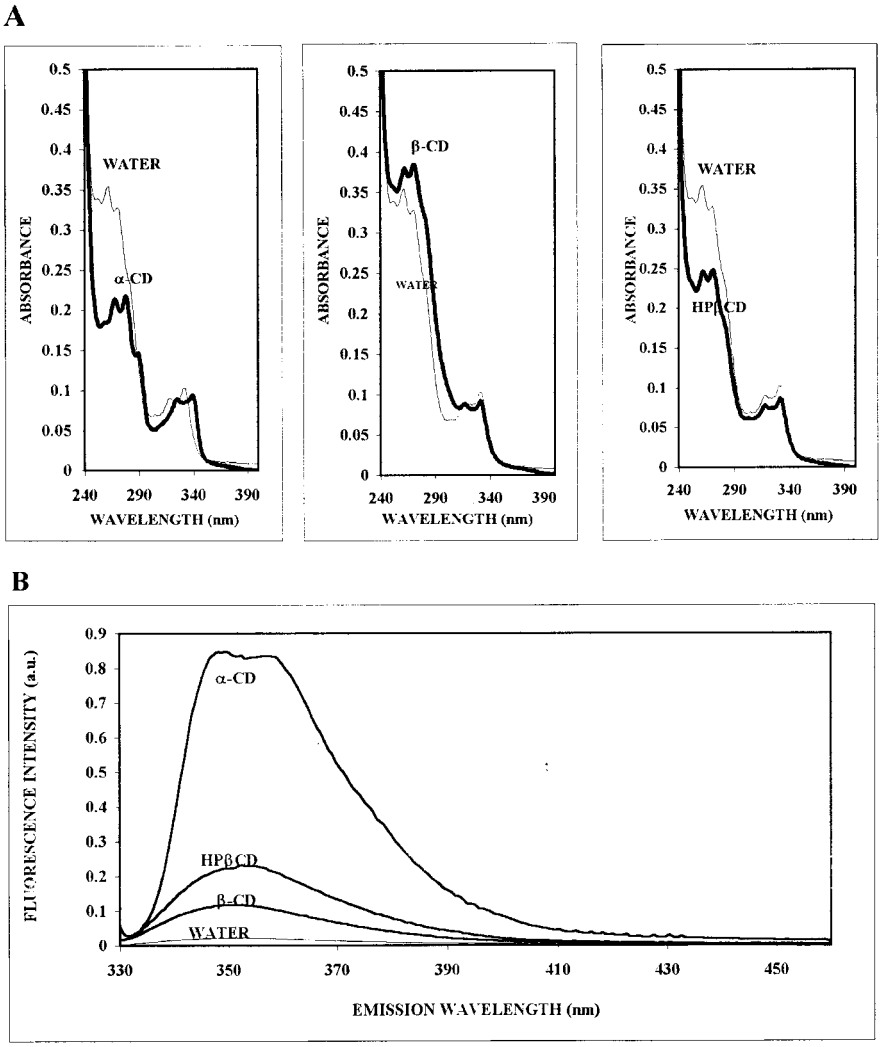
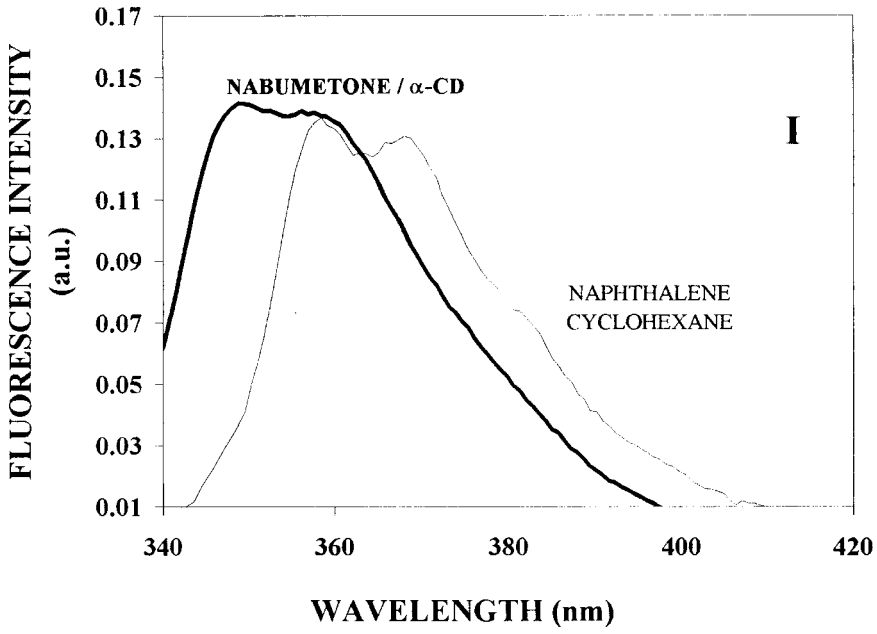



*Figure 2.* Absorption (A) and emission (B) spectra of *Nabumetone* aqueous solution $C_{Nab} = 4.89 \times 10^{-5}$ M free (– – –) and complexed (———) with $\alpha$-CD, $\beta$-CD and HP$\beta$-CD, at 20 °C.

in the naphthalene spectrum. In order to confirm this assumption the proton NMR spectra of the free and complexed drug were recorded. Results will be discussed later in Section 3.4.

## 3.2. BINDING CONSTANTS

Values of the binding constant, K, of the inclusion complex formed between *Nabumetone*, or *Naproxen* and $\alpha$-, $\beta$- or HP$\beta$-CD were determined using the



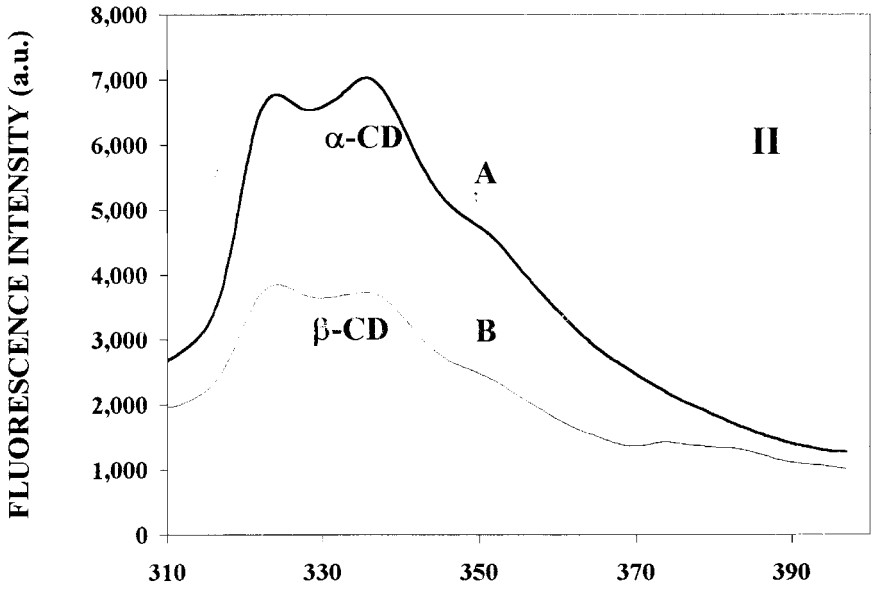




*Figure 3.* I: Emission spectra of aqueous *Nabumetone* – $\alpha$-CD complex and naphthalene in cyclohexane. II: Effect of addition of $\alpha$-CD (A) and $\beta$-CD (B) to an aqueous solution of naphthalene, at 20 °C.

*Table I.* Binding parameters of complexation of aqueous anti-inflammatory drug solutions with cyclodextrins at 20 °C

| Cyclodextrin | Nabumetone K ($M^{-1}$) | Naproxen K ($M^{-1}$) |
|---|---|---|
| $\alpha$-CD | $42.8 \pm 3$[a] | $<15$[a] |
| $\beta$-CD | $2864 \pm 143$ | $1100 \pm 66$ |
| HP$\beta$-CD | $3048 \pm 122$ | $1062 \pm 53$ |

[a] $I_B$ (Equation (2)) obtained by fitting.

fluorescence intensity changes in emission maxima which were large enough to allow satisfactory fitting. The best fitting parameters of the experimental data to Equation (2) are presented in Table I (see Section 2.3). Figure 4 shows that there is excellent agreement between the fluorescence intensity and Equation (2) using the fitting parameters of Table I. Furthermore, it confirms the fact that a simple 1 : 1 complexation scheme is enough to account for the observed behaviour. The binding constant of Naproxen to $\alpha$-CD is very small in good agreement with earlier findings [15] and that with $\beta$-CD also agrees with recent reports using UV-VIS spectroscopy [16] and $^1$H NMR [17].

The binding constant values in Table I show that:

(a) they follow a monotonic trend, as expected from their increasing cavity size. In all cases the drugs have higher affinity for $\beta$-CDs than for $\alpha$-CD. These results indicate that the size of the cyclodextrin cavity plays an important role in the complex formation. On the basis of size considerations, the best fit would be achieved with $\beta$-CDs whereas in $\alpha$-CD the drugs are too big to fit into the cavity as observed with naphthalene [9] and with *Naproxen* by examination of the Corey–Paulig–Koultum (CPK) space filling molecular models [15]. Consequently, in this case, the association with $\alpha$-CD could be carried out by the inclusion of *Nabumetone* substituents.

(b) the binding constants for complexation with $\beta$-CD and HP$\beta$-CD are the same, as expected, since the size of the cavity of these two cyclodextrins is the same.

(c) in all cases the binding constants of *Nabumetone* are 2 or 3 times larger than those of *Naproxen*.

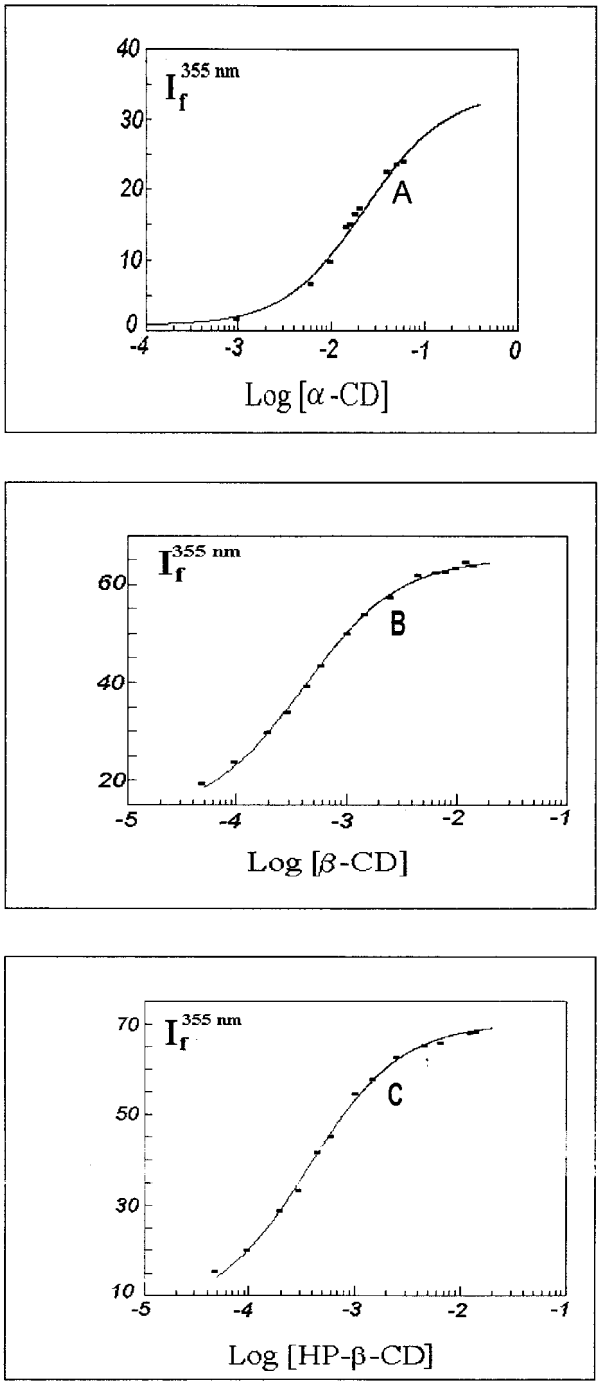



*Figure 4.* Changes in fluorescence intensity at 355 nm, of aqueous *Nabumetone* plotted vs free $\alpha$-CD (A), $\beta$-CD (B) and HP$\beta$-CD (C) at 20 °C. The fittings were calculated using Equation (2) and K values of Table I.

*Table II.* Thermodynamic parameters of complexation of Nabumetone and Naproxen with $\alpha$-, $\beta$ - and HP$\beta$-CD

| Nabumetone | $\Delta$H (kJ/mol) | $\Delta$S (J/mol K) | $\Delta$G (kJ/mol) 293.16 K |
|---|---|---|---|
| $\alpha$-CD | $-25.0 \pm 0.3$ | $-54.9 \pm 1.2$ | $-8.9 \pm 0.2$ |
| $\beta$-CD | $-28.8 \pm 0.8$ | $-32.8 \pm 0.8$ | $-19.2 \pm 0.7$ |
| HP$\beta$-CD | $-16.7 \pm 0.4$ | $9.8 \pm 0.4$ | $-19.6 \pm 0.4$ |
| Naproxen | $\Delta$H (kJ/mol) | $\Delta$S (J/mol K) | $\Delta$G (kJ/mol) 295.16 K |
| $\alpha$-CD | – | – | – |
| $\beta$-CD | $-22 \pm 0.2$ | $-15.7 \pm 0.6$ | $-18.1 \pm 0.3$ |
| HP$\beta$-CD | $-20 \pm 0.1$ | $-11.0 \pm 0.4$ | $-16.8 \pm 0.3$ |

### 3.3. THERMODYNAMIC STUDY

The thermodynamic parameters of the inclusion processes were determined from the temperature dependence of the association constant K using the van t'Hoff relation.

In the case of *Naproxen* it was not possible to obtain the thermodynamic parameters of the inclusion in $\alpha$-CD because it is only possible to calculate the upper limit for the binding constant due to ligand solubility restrictions, as explained in the experimental section.

The thermodynamic parameters of the different complexation processes are presented in Table II.

In view of the values shown in Table II it can be noted: (a) the change of free energy corresponding to the association processes are of the same order of magnitude in all the complexes studied, except in the case of $\alpha$-CD. If it is considered that the complexation is due to the inclusion of butanone into the cavity of $\alpha$-CD, the change of free energy for each methylene group included in $\alpha$-CD is around 2.9 kJ/mol at 25 °C and these values agree very well with those obtained by Tee [24]; (b) the change of entropy is also more negative in this process; this behavior can be explained considering that the complexation through the butanone group decreases the translational and rotational degrees of freedom of the complexed drug molecule as compared with the free one. These facts seem to indicate that the complexation of *Nabumetone* with $\alpha$-CD is carried out preferably by the inclusion of butanone into the cavity; (c) the change of free energy corresponding to the complexation with $\beta$-CDs is always more negative in *Nabumetone* than in *Naproxen* as expected from the higher solvation [25] of the latter as compared with that of the former; d) there is an approximately linear correlation between $\Delta$H and $\Delta$S in the case of complexation with $\beta$-CDs, but the point corresponding to the *Nabumetone*-$\alpha$-CD complex falls outside of the correlation (Figure 5). Compensation behaviour has been observed in a related series of reactions or processes. In the cyclodextrin

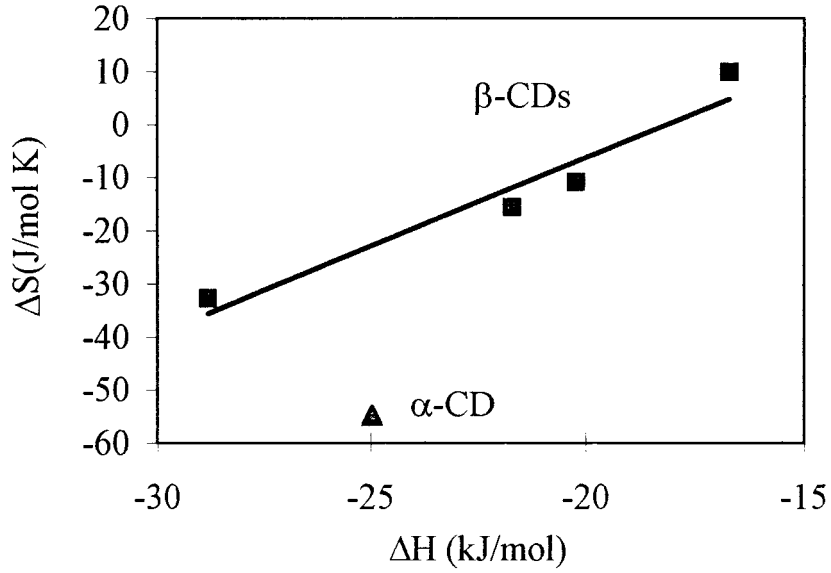



*Figure 5.* Enthalpy – entropy compensation of the complexes formed by *Nabumetone* and *Naproxen* with the three CDs (■, $\beta$-CD; ▲, $\alpha$-CD).

field, several studies [26–28] have gathered a large amount of data covering a wide variety of molecular structures to examine in some depth the universality of the compensation effect. The conclusion reached was that the compensation behavior can be looked at as evidence that a single mechanism is responsible throughout the correlated series [29].

The thermodynamic parameters of *Nabumetone* inclusion in HP$\beta$-CD differ considerably from those of inclusion in $\beta$-CD, whereas this difference is not detected with *Naproxen*.

In the latter case the inclusion complex obtained with either CD will enter always through the methoxy side. However, the drug *Nabumetone* has the possibility of entering through both the methoxy or butanone sides. The respective complexes formed will be the same with $\beta$-CD, as pictured in Figure 6, (III) and (IV) but with HP$\beta$CD different ones will be obtained, Figure 6 (I) and (II). Since the complexes formed between *Naproxen* and both cyclodextrins present the same thermodynamic behavior, the presence of the hydroxylpropyl groups does not seem to explain the large difference observed in the case of *Nabumetone* complexes with these two $\beta$-CDs. A possible explanation may then reside in the fact that the inclusion in HP$\beta$-CD proceeds in such a way that the naphthalene moiety is included in the cavity, but the 2-butanone group remains outside in a hydrophobic environment provided by the hydrocarbon chains of the hydroxypropyl group, contributing to a less negative $\Delta$H and a positive $\Delta$S.

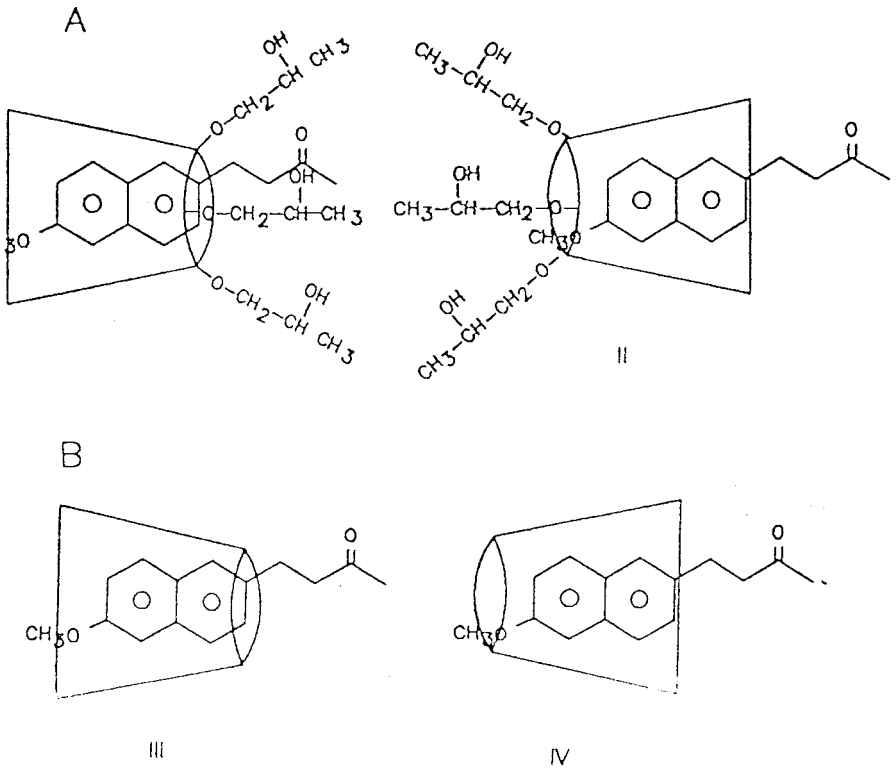



*Figure 6.* Resulting complexes of *Nabumetone* with HP$\beta$-CD (A: I and II) and $\beta$-CD (B: III and IV) viewed from the side of drug entrance (methoxy or 2-butanone group). Here it is assumed that the cyclodextrins penetrate through the secondary hydroxyl side.

### 3.4. PROTON NMR STUDIES

Proton NMR spectroscopy was employed in an effort to provide further evidence for the inclusion of *Nabumetone* inside the $\alpha$-, $\beta$- and HP$\beta$-CD cavity, as well as to gain information about the geometry and orientation of the incorporated drug molecule. Examination of cycloamylose induced chemical shifts in the $^1$H NMR spectra of the aromatic substrate provides a convenient method of determining the substrate penetration in the cavity. The complete set of differences in chemical shifts between the free state and the host-guest system are reported in Table III.

The aromatic protons of *Naproxen* are practically unaffected in the presence of $\alpha$-CD (1:8) indicating that there is no inclusion of this group as expected. After complexation with $\beta$- and HP$\beta$-CD all the aromatic protons are shifted confirming the inclusion of the whole naphthalene moiety inside the cavity of both [17].

In the case of *Nabumetone*, due to the low solubility of the drug in water, the proton spectrum at 300 MHz was obtained from a very diluted solution in $D_2O$ prepared by addition of 4 drops of $CD_3OD$ in $D_2O$. The largest differences in chemical shifts appear for $\alpha$-CD, as found with the other techniques used (Table III). The

*Table III.* Differences of chemical shifts (ppm) of the protons of *Nabumetone*. $\Delta\delta_{CD} = \delta_{free} - \delta_{host-guestsystem}$

| Proton | $\Delta\delta_{\alpha\text{-CD}}$ | $\Delta\delta_{\beta\text{-CD}}$ | $\Delta\delta_{HP\beta\text{-CD}}$ |
|---|---|---|---|
| 1 | −0.25 | 0.13 | 0.08 |
| 3 | −0.32 | 0.010 | 0.01 |
| 4 | −0.06 | 0.12 | 0.04 |
| 5 | 0.42 | 0.15 | 0.10 |
| 7 | −0.23 | −0.06 | −0.05 |
| 8 | −0.21 | 0.05 | 0.01 |
| $(\alpha)CH_2$ | −0.16 | 0.07 | 0.09 |
| $(\beta)CH_2$ | −0.33 | −0.04 | −0.01 |

methylenic protons of the 2-butanone chain are strongly affected. The shifts are also strong for the aromatic protons 1, 3 and 5, 7, 8 but not for the proton 4. This may be explained considering that both substituents in the 2- and 6-positions can enter the cavity and therefore affect also the neighbouring aromatic protons. By contrast, when *Nabumetone* is complexed with $\beta$-CD or HP$\beta$-CD the methylenic protons are hardly shifted but the aromatic protons are, confirming that the naphthalene is included (likewise in the *Naproxen* case) in the $\beta$-CDs cavities but the substituent chain remains outside.

## 4. Conclusions

The results described show clearly that the cavity of both cycloheptamyloses ($\beta$- and HP$\beta$-CD) are suitable to include the naphthalene moiety, but $\alpha$-CD is too small. Therefore high stability constants are found for $\beta$- and HP$\beta$-CD complexes whereas for $\alpha$-CD a very small binding constant is obtained. The complex stoichiometry is 1 : 1 for the three cases.

$^1$H NMR results show that the inclusion of $\alpha$-CD may happen through the 2-butanone group and the methoxy group of *Nabumetone*. The complexation by inclusion of these groups introduces a loss of motional freedom of the guest. As a consequence, a large decrease in entropy is produced by complex formation with a strong enhancement of the optical absorption and emission intensity as compared with *Nabumetone* in water. $^1$H NMR spectra also show that the naphthalene group is responsible for the complexation of this drug to $\beta$-cyclodextrins.

The modification of the substituent in the 2 position of naphthalene in *Nabumetone* enhances the interaction of this drug with the three cyclodextrins studied, as compared with *Naproxen* with the same CDs.

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