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Effect of PVP K-25 on the formation of the naproxen:β-ciclodextrin complex

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Abstract

The aim of this study was to investigate the effects of the presence of the water-soluble polymer polyvinylpyrrolidone K-25 (MW = 24,000 g/mol) on the complexation of the AINE naproxen, in its sodium salt form, with the β-cyclodextrin.

The data revealed that the polyvinylpyrrolidone K-25 interacts with the drug as well as with the drug:β-cyclodextrin inclusion complex. The polymer shows more affinity for the inclusion complex, $K = (6.67 \pm 0.292) \times 10^{-5}\,M^{-1}$ than for the free drug, $(2.08 \pm 0.208) \times 10^{-5}\,M^{-1}$.

The presence of different proportions of polymer, in a range 0–1% (w/w) of polyvinylpyrrolidone, does not increase the ability of drug–cyclodextrin complexation but important changes in the driving force of complex formation were detected, depending on the percentage of polyvinylpyrrolidone K-25 present. At low polymer concentrations, the complexation process is driven entropically, while at higher PVP proportions it is enthalpically favored.

In the ternary system, polyvinylpyrrolidone K-25 partially or totally coats the drug:β-cyclodextrin inclusion complex interacting with the β-cyclodextrin (through hydrogen bonds), and with the naproxen.

Keywords: Naproxen; Inclusion complex; Polyvinylpyrrolidone; Ultraviolet-visible absorption and emission spectroscopy; Fourier transform infrared spectroscopy

1. Introduction

Naproxen (represented in Scheme 1 as sodium salt) is a non-steroidal anti-inflammatory drug with analgesic and antipyretic effects that is used for the treatment of rheumatoid arthritis, osteoarthritis and traumatic contusions. However, it has been associated with gastrointestinal side-effects and different types of adverse cutaneous photosensitive reactions (Moore and Chappuis, 1988; Boscá and Miranda, 1988).

These problems can be minimized through the use of suitable drug carriers. In this sense, the interaction of drugs with supramolecular aggregates and cyclodextrins is an important feature in the pharmaceutical field since these systems can bind drugs, modifying their chemical stability as well as other properties such as solubility, dissolution rate, bioavailability, etc. Several studies on the complexation of naproxen with different cyclodextrins have reported clear proof of these advantages (Mura et al., 2001; Partyka et al., 2001; Erden and Çelebi, 1988).

The addition of a third component such as alcohol, alkylsufates or amino acids can dramatically alter the apparent association constants between CDs and different compounds (Van Stam et al., 1996; Yang and Bohne, 1996). Little attention has been focused on the use of third components, such as water-soluble

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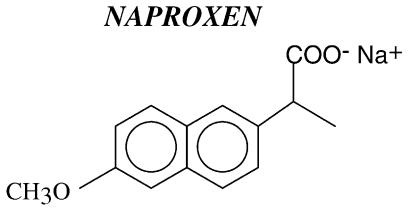


(S) 6-methoxy-α-methyl)-2-naphthaleneacetic acid, sodium salt

Scheme 1.

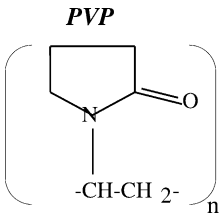
polymers, for improving the properties of drug:CD complexes. Water-soluble polymers are widely used in pharmaceutical excipients, as coating materials and builders, and in controlled-release dosage formulations.

Polymers are known to interact with CDs (Hladon and Cwiertinia, 1994), although the exact nature of the polymer:CD interaction is still not known. It has also been shown that at low concentrations, polymers increase the complexing abilities of CDs (Loftsson et al., 1994; Ganzerli et al., 1996) and enhance drug availability in aqueous CD solutions (Sigurðardóttir and Loftsson, 1995).

Polyvinylpyrrolidone (PVP), a synthetic polymer made up of linear groups of 1-vinyl-2-pyrrolidone monomers (Scheme 2) forms molecular adducts with many substances and is frequently used in pharmaceutical formulations involving anti-inflammatory non-steroidal drugs.

The favorable effect of PVP on the solubility and dissolution rate of naproxen (in its molecular form) has been demonstrated previously (Bettinetti and Mura, 1994). Other authors have studied the interactions of naproxen with the VP monomer and β-cyclodextrin (Vélaz et al., 1997).

All the above studies have addressed the effect of the addition of PVP on the solubility of drugs. However,



Scheme 2.

the precise chemical structure of drug:CD:polymer complexes is not known. In addition, no studies have addressed the effect of PVP or other polymers on the complexation of naproxen in its anionic form—naproxen Na. It therefore seemed of interest to focus our investigations on the effect of PVP on naproxen Na:β-CD complex formation. Absorption steady-state fluorescence and infrared spectroscopic methods were used to study the ternary system.

2. Material and methods

2.1. Materials

Naproxen Na, 2-(6-methoxy-α-methyl-2-naphthyl) propionic acid sodium salt was purchased from Sigma. β-Cyclodextrin (β-CD) was obtained from Sigma. The samples of PVP K-25 (Fluka) had molecular weight of 24,000 g/mol, stated by the manufacturers. These reagents were considered sufficiently well characterized 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 Na/H_2O; prepared by weight and stirred.
(2) Naproxen Na/PVP/H_2O; prepared by weight of the required amount of PVP, using the aqueous drug solution (1), as solvent.
(3) Naproxen Na/β-CD/PVP/H_2O; prepared by weight of the required amount of β-CD, using the aqueous drug/polymer solution (2) as solvent.

Solutions with variable PVP concentrations were obtained by successive dilution of (2) with (1). Solutions with variable β-CD concentrations, and different PVP content, were obtained by successive dilution of (3) with (2). All measurements were carried out at 25.0 °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 (Velázquez et al., 1995; Valero et al., 2000). Measurements of the refractive index were carried out using an Atago Abbè Refractometer, model DR-A1.

Infrared absorption spectra were recorded on a Perkin-Elmer 1730 FT-IR spectrophotometer. A spectral range of 4000–1000 cm^{-1} and an effective resolution of 2 cm^{-1} were used. In order to obtain good quality spectra, a minimum of 15 scans were accumulated. Solid dispersions of the different systems were obtained by solvent evaporation of the corresponding aqueous solutions. Residual solvent was removed by drying under a vacuum at room temperature for several days. The corresponding residue was mixed with dry KBr to form pellets. The pellets were dried again under vacuum at room temperature.

3. Results and discussion

3.1. UV-Vis study

3.1.1. Drug–PVP interaction

The possibility of specific interactions between naproxen Na and the PVP polymer K-25 was investigated using absorption and emission spectroscopic techniques. The absorption and emission spectra of naproxen Na change following the addition of PVP K-25 (range 0–1% (w/w)). It was observed that upon the addition of PVP, the fluorescence intensity decreased while that of absorption increased, indicating the existence of some interaction between the drug and the polymer. Also, no broad excimer-like emission was observed, indicating than no more than one drug molecule was bound by the polymer.

Based on this, from the emission and absorption data, and considering a 1:1 complex, a binding constant of naproxen Na:PVP was determined using either Eq. (1) or (2) (Valero et al., 1996, 1999):

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

$$A = \frac{A_D + A_B K[CD]}{1 + K[CD]} \quad (2)$$

where F_D and F_B represent the molar fluorescence intensity at the maximum of the emission band (355 nm), of the free and complexed drug, respectively, and [CD] is the analytical cyclodextrin concentration. A_D and A_B represent the absorbance at one maximum of the absorption spectra (in our case at 317 nm), of the free and complexed drug, respectively.

The best fitting parameters of the experimental data (Fig. 1A) gave a binding constant value of $(1.92 \pm 0.104) \times 10^{-5}\ M^{-1}$ from the emission data, in good agreement with that obtained with the absorption data, i.e. $(2.33 \pm 0.208) \times 10^{-5}\ M^{-1}$.

The drug was quenched by the polymer with a Stern–Volmer constant of $1.27 \times 10^{-6}\ M^{-1}$ (Fig. 1A, inset). As a consequence, an important decrease of around 35% was observed in the quantum yield of fluorescence of the free drug.

In aqueous solution, a decrease in quantum yield has been detected for naproxen Na (Velázquez et al., 1995) and other naphthalene derivatives when solubilized in protic solvents (Chakrabarti and Ware, 1971). The reason for this behavior has been attributed to solute–solvent intermolecular hydrogen bond formation. This type of interaction has been described for the indomethacine:PVP complex (Taylor and Zografi, 1997; Matsumoto and Zografi, 1999) but in this case—the naproxen Na and PVP—this type of bond may be not involved. Therefore, the possible existence of an ion–dipole interaction could be invoked, as proposed

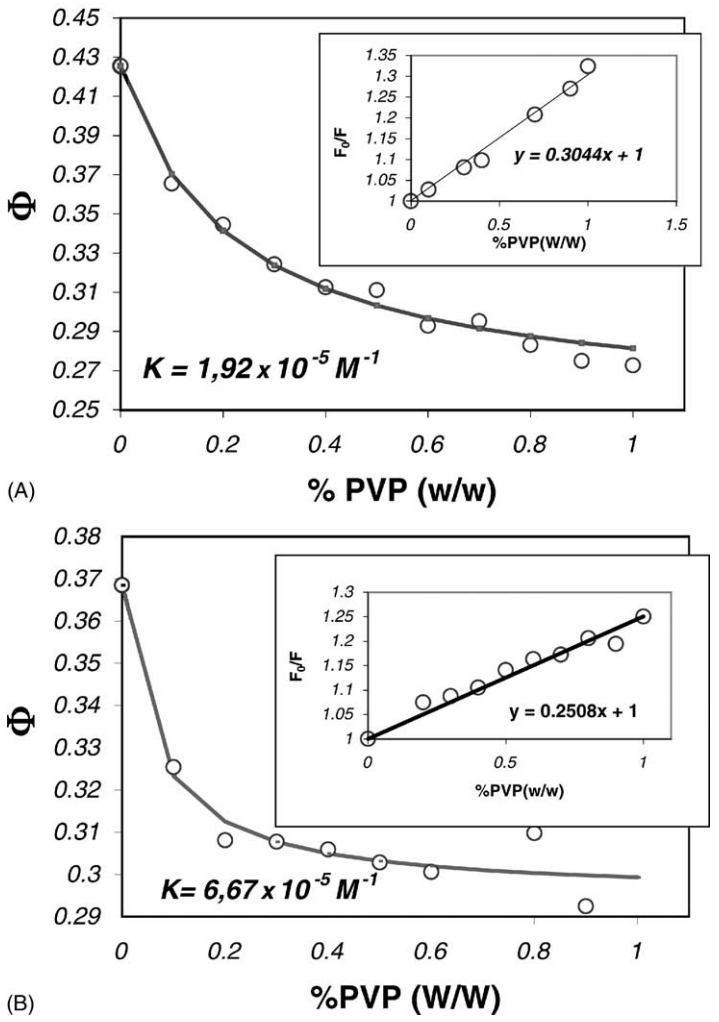


Fig. 1. Effect of PVP concentration on: (A) the quantum yield of naproxen Na (4×10^{-5} M) at 25 °C. Inset: Stern–Volmer fit of the quenching data. (B) The quantum yield of naproxen Na:β-CD inclusion complex. Inset: Stern–Volmer fit of the quenching data.

for the interaction of another drug having a carboxylate group and PVP (Khougaz and Clas, 2000).

3.1.2. *Drug:β-CD complex–PVP interaction*

Addition of β-CD to aqueous naproxen Na solution containing a fixed PVP concentration, also resulted in appreciable spectral changes.

It was observed that in the whole range of % PVP studied, the absorption wavelength was red-shifted when increasing amounts of β-CD were added (Fig. 2A). A similar bathochromic effect has been detected in weakly polar solvents (Velázquez et al., 1995). These changes clearly indicate the inclusion of the drug within the apolar cavity of the cyclodextrin. The formation of the inclusion complex also produced a hyperchromic effect on the absorption and emission spectra (Fig. 2B). 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 Na:β-CD inclusion complex is formed at all the PVP percentages studied.

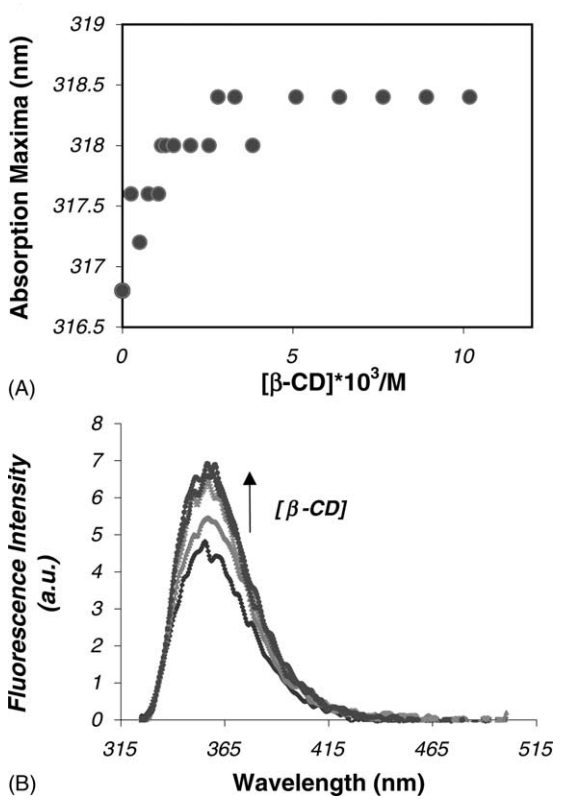


Fig. 2. Effect of β-CD addition on aqueous naproxen Na:PVP solutions (A) on the absorption maxima position; (B) on the emission spectra.

For investigating the interaction between the naproxen Na:β-CD complex and PVP, the effect of the addition of increasing amounts of PVP to a fixed concentration of drug:β-CD solution (with the drug totally complexed) were studied spectroscopically.

Absorption intensity was slightly increased by the presence of PVP, whereas the position of the maxima remains constant, indicating that the drug had remained in the same environment as in the absence of PVP; that is, inside the cyclodextrin.

The emission intensity was also modified by the presence of the polymer, but not the wavelength of the maximum. The presence of increasing amounts of PVP produced a quenching of fluorescence (Fig. 1B), as observed for the non-complexed drug, indicating that PVP also interacts with naproxen Na when it forms the inclusion complex. These changes indicate that PVP interacts with the drug:β-CD complex to form a ternary complex. A binding constant of the polymer to the drug:β-CD complex of $(6.67 \pm 0.292) \times 10^{-5}\,M^{-1}$ is obtained by fitting the quantum yield of fluorescence versus the PVP concentration. The obtained value reveals that PVP shows more affinity for the complex than for the free drug. In this case, the drug was also quenched by the PVP with a lower Stern–Volmer constant (Fig. 2B, inset) than for the non-complexed drug, $K_{SV} = 1.04 \times 10^{-6}\,M^{-1}$. This means that the fluorophore was protected from the quencher. The quantum yield of the complexed drug decreased as the PVP concentration increased, but in this case the decrease was around 10%, in the range of PVP studied, in good agreement with the K_{SV} value. This fact, together with the lower K_{SV}, suggests that the PVP partially or wholly coats the drug:CD complex in the ternary complex, but it does not form inclusion with it.

3.1.3. Naproxen Na:β-CD complexation in the presence of PVP

The values of the binding constant, K, of the inclusion complex formed between naproxen Na and β-CD in the presence of PVP at different concentrations (between 0 and 1% (w/w)) were determined using the fluorescence intensity and absorption data at 355 and 317 nm, respectively, by fitting to the well-known binding isotherms (Eqs. (1) and (2)). The binding constants obtained for the formation of the naproxen Na:β-CD inclusion complex at different PVP percentages are presented in Table 1. In all cases, a good agreement between the experimental data and

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

% PVP (w/w)	K (M^{-1})[a]	K (M^{-1})[b]
1	1115 ± 45	–
0.5	1100 ± 80	980 ± 70
0.2	1125 ± 57	910 ± 40
0.1	595 ± 15	630 ± 45
0.08	700 ± 45	635 ± 53
0.05	600 ± 35	600 ± 54
0	1100 ± 66[c]	845 ± 30[d]

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

those calculated using the fitting parameters shown in Table 1 was observed. Therefore, the presence of the polymer does not seem to change the stoichiometry of the complex formed; that is, 1:1 in the PVP range studied, as happens in the absence of polymer (Valero et al., 1999).

The binding constants obtained show that no increase in the naproxen Na:β-CD complexation ability is produced due to the presence of PVP. This behavior differs from that of the molecular form of the drug—naproxen—when complexed with HP-β-CD in the presence of PVP (Mura et al., 2001), but is in good agreement with the data obtained for other drugs in the presence of different polymers (Loftsson and Friðriksdóttir, 1998), where K values were only modified after certain types of treatment. On the other hand, the drug:CD binding constant increases as [PVP] increases.

These results show an undefined trend. The interaction between naproxen Na and PVP competes initially with the formation of the drug:β-CD inclusion complex, decreasing the drug:β-CD binding constant, but at higher [PVP] concentrations, with also higher concentrations of drug:PVP species, the binding of the drug to the cyclodextrin is favored. Therefore, at high PVP concentrations, the interaction between the polymer and the drug:β-CD complex, as previously shown, must be favorable to the formation of the inclusion complex. The thermodynamic parameters of the inclusion process in presence of different PVP percentages, were determined from the temperature dependence of the binding constant K using the Van't Hoff expression.

In all cases (Fig. 3), a good fit was obtained where it can be seen that, as temperature increases, the affinity of the cyclodextrin for the drug follows two different trends. The thermodynamic parameters obtained for naproxen Na:β-CD complexation in the presence of different percentages of PVP, Table 2, shows that the driving force of the process changes, in value and sign, with PVP concentration.

Thus, at low polymer concentrations drug complexation is mainly driven by a favorable change in entropy while at high [PVP] (>0.2% (w/w)) the complexation process is exothermic and enthalpy-driven ($|\Delta H^\circ| > T|\Delta S^\circ|$), as is the case in the absence of polymer (Valero et al., 1999). These changes clearly show that the initial and final thermodynamic states

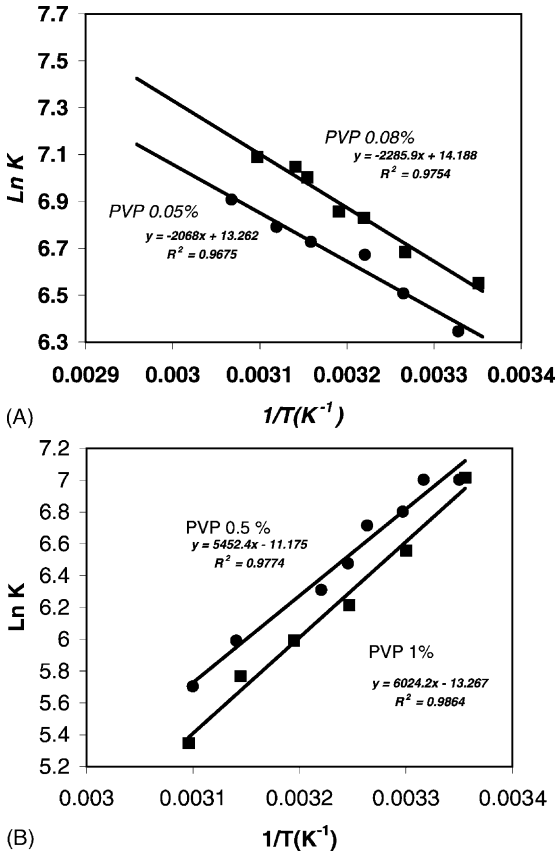


Fig. 3. Van't Hoff plots for the formation of naproxen Na:β-CD complex in presence of 0.05, 0.08 (A) and 0.5, 1 (B) % PVP (w/w).

Table 2
ΔH° and ΔS°, the formation of the 1:1 complexes with β-CD at different PVP percentages

% PVP (w/w)	ΔH° (kJ/mol)	ΔS° (J/mol K)	ΔG° (kcal/mol) (298.15 K)
1	−50.1 ± 1.1	−110.3 ± 3.3	−17.2 ± 0.3
0.5	−45.1 ± 1.3	−92.9 ± 2.8	−17.4 ± 0.3
0.2	−29.7 ± 0.9	−33.7 ±1.2	−19.6 ± 0.5
0.1	20.7 ± 0.8	122.1 ± 4.0	−15.7 ± 0.4
0.08	19.0 ± 0.5	118.0 ± 3.2	−16.2 ± 0.4
0.05	16.5 ± 0.8	108.1 ± 3.0	−15.7 ± 0.2
0.0	−22.0 ± 0.6[a]	−15.7 ± 0.6[a]	−16.8 ± 0.1[a]

[a] Valero et al. (1999).

of the system (before and after β-CD complexation, respectively) are different, depending on [PVP].

Complexation of the naproxen Na with β-CD at [PVP] < 0.2% is accompanied by a positive ΔH° and ΔS° values. This means that the system takes more energy on breaking the interactions of the drug in the PVP aqueous solution than on losing them from the new interactions that occur in the inclusion complex formed. Also the complexation state is a more disordered than the drug:PVP one. This behavior clearly differs from that previously reported for the drug in the absence of polymer (Valero et al., 1999), which indicates that the process involves the breaking of drug:PVP bonds, with the formation of a less bonded and more disordered inclusion complex.

A different behavior is observed when [PVP] > 0.2% (w/w). In this case, the negative ΔH° value in the complex can be ascribed to the stronger binding between the complexing agent and the drug, while the negative ΔS° value can be ascribed to greater structural restraints as a consequence of complexation. Both this type of thermodynamic behavior and the interaction detected with fluorescence data between PVP and the complexed drug seem to indicate that the inclusion complex, naproxen Na:CD, must be partially or totally coated by the polymer, as described for naproxen:HP-β-CD:PVP (Mura et al., 2001). The changes in free Gibb's energy corresponding to the association process are the same order of magnitude as in the absence of polymer (Valero et al., 1999) in good agreement with the binding constant values obtained.

A linear correlation between ΔH° and ΔS° was observed at all PVP concentrations, including [PVP] = 0. The compensation behavior can be seen as an evidence in favor of a single mechanism throughout the correlated series (Linert et al., 1989; Liu and Guo, 2002; Connors, 1997) and has been shown to be very sensitive to changes of the final form of the complex. In our case, a good correlation was also obtained when the data corresponding to naproxen Na and nabumetone (another naphthalene derivative) with β- and HP-β-CD in the absence of polymer were included (Valero et al., 1999). This implies that the geometry of the inclusion complex obtained in the presence of PVP does not differ from those found in β-CD or HP-β-CD in the absence of polymer. Accordingly, the drug will enter the cavity through the methoxy side, the carboxylate group protruding into the water. This scenario agrees with the deactivating interaction of PVP with the drug observed in the ternary complex.

3.2. Infrared spectroscopy study

In this section, the analysis of the infrared spectra of the naproxen Na:PVP and naproxen Na:β-CD binary systems as well as the naproxen Na:β-CD:PVP ternary system is carried out. The results have been in all cases interpreted following two steps:

(i) Observation of the spectral changes due to the addition of the different compounds.
(ii) Deconvolution of the most representative bands of the spectra.

Initially, the FT-IR spectra of aqueous residues of pure compounds were obtained (Fig. 4). The assignments of the individual bands (Bellamy, 1975; Szejtly, 1982) are included in Table 3.

3.2.1. Naproxen Na–β-CD inclusion complex

The naproxen Na and β-CD FT-IR spectra are shown in Fig. 4A and B, respectively. Some typical bands of these compounds are offered in Table 3.

3.2.1.1. Binary system spectra. The inclusion complex spectrum displays the characteristic bands of the cyclodextrin (Table 3).

The presence of naproxen Na produces some changes in the relative intensity of the OH deformation and C–O stretching bands of the glycosidic bonds. The sensitivity of these absorptions to structural changes is known, marked variations in intensity and/or position of the maxima being observed (Bellamy, 1975). The A_{1029}/A_{1158} ratio decreases by 22% when drug is added (1.7 and 1.4 in the absence and presence of drug, respectively) whereas A_{1029}/A_{2924} remains unaltered. This means that it is the intensity of the band of glycosidic bonds centered at 1158 cm^{-1}, which is increased by the presence of naproxen Na. Considering the low drug concentration, this effect indicates a strong interaction between the drug and this part of the cyclodextrin, therefore leading to the inclusion complex formation and therefore formation of the inclusion complex.

The OH stretching region can be seen in the infrared spectrum as a very broad band characteristic of

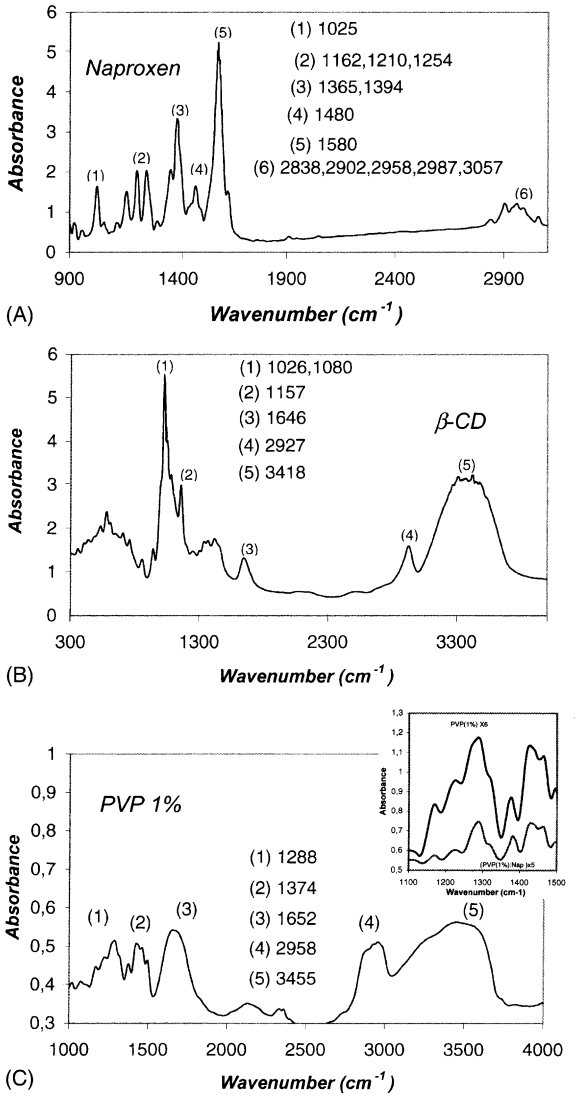


Fig. 4. IR spectra of (A) naproxen Na; (B) β-CD; (C) PVP (1% (w/w)). Inset: naproxen Na:PVP (1% (w/w)).

different hydrogen-bonded hydroxyl groups (Bellamy, 1975). The deconvolution process is extremely sensitive for detecting overlapping bands under the spectral contour, and has been successfully used for the spectral resolution of complex mixtures. A more detailed study of the OH stretching band in the β-CD and drug:β-CD inclusion complex was carried out after the deconvolution procedure. The strong band centered around 2927 cm^{-1} corresponding to the glucose units C–H stretching modes was also deconvoluted.

3.2.1.2. Deconvolution of bands centered around 3000 cm^{-1}. The Gaussian band parameters (Fig. 5A), that best account for the spectral contour are shown in Table 4.

The OH stretching band of the cyclodextrin may be deconvoluted in three Gaussians, centered at 3252, 3480 and 3620 cm^{-1}, respectively. It is known that intermolecular hydrogen-bonded alcohols result in a shift to lower frequencies and hence these bands can be assigned to two different types of hydrogen-bonded and free hydroxyl groups, respectively. The band centered at 3252 cm^{-1} was assigned to the O–H stretch of the intermolecular polymeric hydrogen-bonded hydroxyl groups. The 3478 cm^{-1} band was assigned to the same type of vibration of single intermolecular hydrogen-bonded alcohols (Bellamy, 1975).

Formation of the inclusion complex (Fig. 5B) produces an important blue shift to the bands corresponding to the hydrogen-bonded alcohols and the disappearance of the bands corresponding to the free ones (Table 4). The frequency of the bonded OH is a direct measure of the strength of the hydrogen bond, with a consequent large low-frequency shift (Bellamy, 1975). On this basis, the results clearly show the formation of strong hydrogen bonds between naproxen Na and β-CD after complexation.

No changes were observed (Table 4) in the C–H stretching band of the cyclodextrin after formation of the inclusion complex.

3.2.2. Naproxen Na:PVP interaction

3.2.2.1. Binary system spectra. Fig. 4C shows the FT-IR spectrum of the aqueous residue of 1% PVP (w/w); the assignments of the bands are included in Table 3.

The naproxen Na:PVP interaction should be reflected by shifts in either the PVP carbonyl or C–N vibrations, depending on the site of interaction.

At all PVP concentrations studied, the presence of naproxen Na changed the form and position (a slight shift to longer wavenumbers) of the two systems of bands centered at 1400 and 1500 cm^{-1} (Fig. 4C, inset) of the PVP spectrum. The most important change was observed in the pyrrole stretching band centered at 1374 cm^{-1}, which was shifted to 1384 cm^{-1} and its relative intensity was clearly increased following

Table 3
Assignment bands of IR spectrum of pure compounds, binary systems naproxen Na:β-CD and naproxen Na:PVP and ternary ones naproxen Na:β-CD:PVP, expressed in cm^{-1}

Naproxen	β-CD	Naproxen:β-CD[a]		Assignment
	1026	1029		CO stretching primary OH
	1080	1081		CO stretching secondary OH
	1157	1158		CO stretching glucosidic bond
1210				C–O– stretching ether
1254				C–O stretching acid
1394–1365				CH_3 bending
1480				Anti-symmetrical COO^- stretching
1580				Symmetrical COO^- stretching
1628				C–C aromatic skeletal stretching
	1646			O–H bending H_2O
	2927	2924		C–H aliphatic stretch
3057, 2838				Ar–H stretch
	3418	3382		OH stretching (H-bonded)
PVP	PVP:naproxen Na			
	% PVP			Assignment
	0.05	0.1	1	
1288	1290	1291	1291	C–N stretch and C–H bend
1374	1384	1384	1384	Pyrrole ring stretch
1652	1653	1653	1653	Amide I band
2958	2923	2957	2957	C–H aliphatic stretch
3455	3446	3445	3446	C–H stretch of pyrrole
	Naproxen Na:β-CD:PVP			
	% PVP			Assignment
	0.05	0.1	1	
	1028	1028	1029	CO stretching primary OH
	1081	1081	1081	CO stretching secondary OH
	1158	1158	1158	CO stretch glucosidic bond
	1652	1652	1653	Amide I band, O–H bend of H_2O
	2925	2925	2925	C–H aliphatic stretch
	3392	3392	3407	OH stretching (H-bonded)

[a] Assignment from Szejtly (1982).

naproxen Na addition. These changes suggest that the drug interacts with the nitrogen.

In our case, the naproxen Na:PVP interaction did not modify the position of the maximum of the carbonyl absorption band, although the carbonyl group of PVP is considered the most favorable site for interactions due to steric hindrance on the nitrogen (Molyneux, 1983). In order to better study the interaction in this case, the band centered around 3000 cm^{-1} as well as the carbonyl band were deconvoluted.

3.2.2.2. Deconvolution of bands.

3.2.2.2.1. Carbonyl band deconvolution. The deconvolution of the carbonyl band for the PVP and naproxen Na:PVP (at 0, 0.05, 0.1 and 1% of PVP) residue was carried out. The fitting parameters are shown in Table 5.

As can be seen, in all cases the carbonyl band can be fitted to three Gaussians (Fig. 6). The main component appearing around 1645 cm^{-1} is characteristic of the

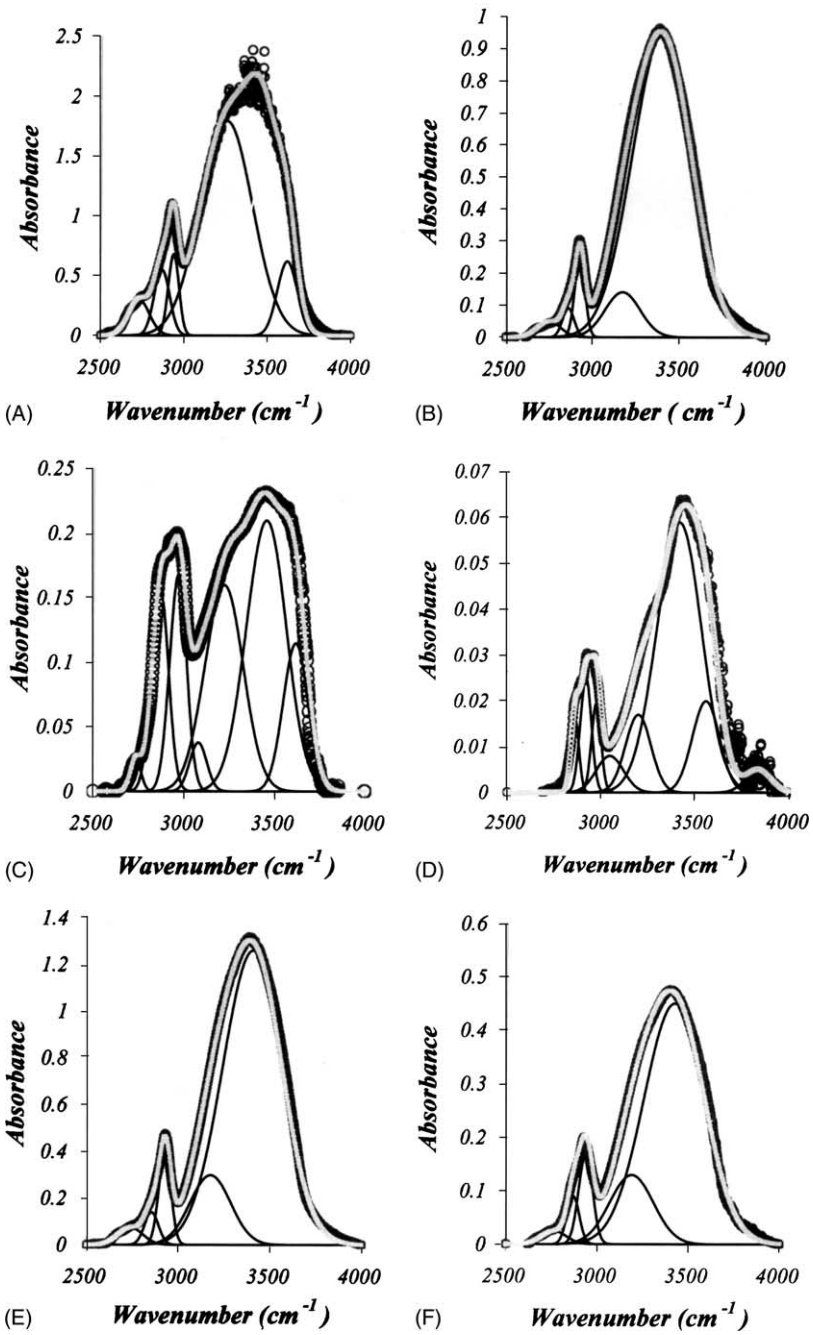


Fig. 5. Deconvolution into Gaussians of the band centered around 3000 cm^{-1} of (A) β-CD; (B) naproxen Na:β-CD complex; (C) PVP (1% (w/w)); (D) naproxen Na:PVP (1% (w/w)); (E) naproxen Na:β-CD:PVP (0.1% (w/w)) (F) naproxen Na:β-CD:PVP (1% (w/w)).

Table 4
Decovolution into Gaussian bands of the IR bands centered around 3000 cm^{-1} of PVP 1% and binary systems naproxen Na:PVP and naproxen Na:β-CD

	PVP	Naproxen:PVP				β-CD	Naproxen:β-CD
	% PVP	% PVP					
	1	0.05	0.1	0.5	1		
A	0.025	0.013	0.012	0.03	0.016	0.3	0.05
ν (cm^{-1})	2735	2860	2863	2855	2863	2730	2750
δ (cm^{-1})	35	25	25	30	25	75	80
A	0.155	0.022	0.022	0.045	0.025	0.55	0.09
ν (cm^{-1})	2868	2922	2920	2920	2920	2868	2862
δ (cm^{-1})	55	35	35	40	35	55	40
A	0.168	0.012	0.0155	0.028	0.0195	0.68	0.25
ν (cm^{-1})	2967	2981	2975	2976	2976	2939	2928
δ (cm^{-1})	55	27	30	30	30	40	35
A	0.038	0.0026	0.004	0.014	0.008	–	–
ν (cm^{-1})	3080	3050	3049	3049	3049	–	–
δ (cm^{-1})	55	85	85	85	85	–	–
A	0.16	0.025	0.016	0.024	0.017	1.8	0.14
ν (cm^{-1})	3220	3261	3220	3200	3200	3252	3175
δ (cm^{-1})	125	130	110	80	80	185	120
A	0.21	0.044	0.052	0.098	0.059	1.4	0.94
ν (cm^{-1})	3452	3456	3442	3425	3415	3480	3397
δ (cm^{-1})	130	105	130	145	140	120	200
A	0.115	0.02	0.015	0.024	0.02	0.62	–
ν (cm^{-1})	3615	3598	3592	3570	3560	3620	–
δ (cm^{-1})	80	80	80	85	85	70	–
A	–	0.0055	0.005	0.004	0.003	–	
ν (cm^{-1})	–	3810	3840	3840	3840	–	–
δ (cm^{-1})	–	80	80	80	80	–	–

Table 5
Decovolution into Gaussian bands of the IR band centered around 1600 cm^{-1} of pure compounds and binary systems, naproxen Na:PVP

	PVP	Naproxen Na:PVP			
	% PVP	% PVP			
	1	0.05	0.1	0.5	1
A	0.013	0.0035	0.007	0.003	0.006
ν (cm^{-1})	1600	1572	1570	1570	1570
δ (cm^{-1})	15	10	10	15	13
A	0.152	0.041	0.075	0.074	0.06
ν (cm^{-1})	1645	1648	1660	1649	1659
δ (cm^{-1})	50	42	43	43	44
A	0.098	0.011	0.01	0.029	0.008
ν (cm^{-1})	1720	1710	1725	1709	1715
δ (cm^{-1})	42	40	40	43	40

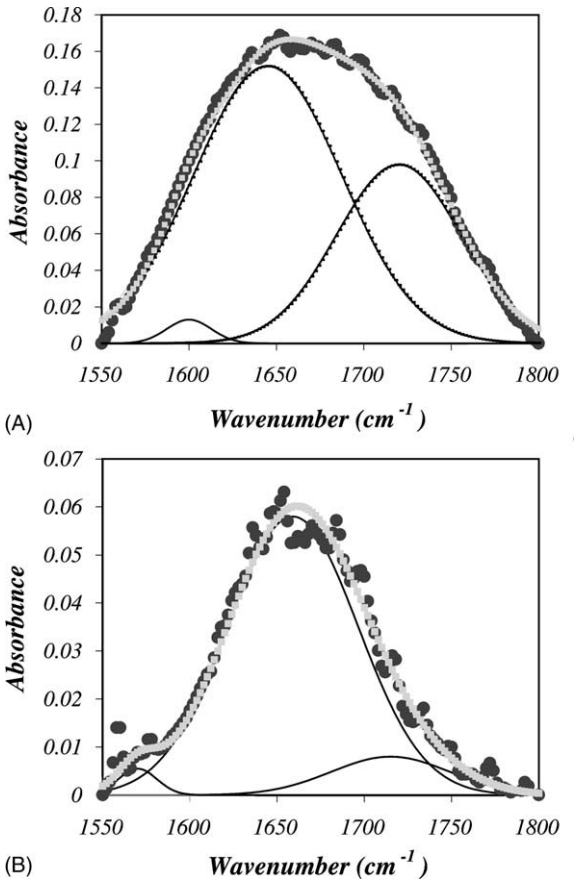


Fig. 6. Deconvolution into Gaussians of the band centered around 1600 cm^{-1} of (A) PVP (1% (w/w)); (B) naproxen Na:PVP (1% (w/w)).

amide I band of tertiary amides (Khougaz and Clas, 2000; Bellamy, 1975). There is some evidence that in tertiary amides the carbonyl band may be single or double, depending on the possibility of one or two preferred conformations, respectively (Bellamy, 1975). On this basis, the bands appearing around 1660 and 1720 cm^{-1} were assigned to different conformations of the tertiary amide. The other Gaussian appearing around 1570 cm^{-1} must correspond to the third band of the ring breathing band on the pyrrole (Bellamy, 1975).

The results show that the presence of the drug does not modify the position of these bands (Table 5), indicating that this group of the polymer is not directly involved in the drug interaction. However, the drug:PVP interaction clearly changes the intramolecular interactions in the polymer, as may be inferred by the change in the proportion of the two preferred conformations of the tertiary amide (Fig. 6).

3.2.2.2.2. 3000 cm^{-1} band deconvolution. The bands appearing around 2700 and 3400 cm^{-1} were also deconvoluted. The results obtained are included in Table 4 and Fig. 5C and D. The bands that constitute the spectral contour of the band centered around 3400 cm^{-1} cannot be assigned with any certainty, and hence in these cases this part of the band will not be discussed.

The band centered around 2700 cm^{-1} can be fitted to three bands. The position and intensity of these Gaussian bands (2735, 2868 and 2967 cm^{-1} for PVP in the absence of drug) allowed them to be assigned to the C–H stretching and symmetric and asymmetric $–CH_2$ stretching modes of PVP, respectively. The frequencies of these bands are sensitive to the gauche/trans conformer ratio of the methylene chains. The gauche conformation is the higher energy conformation with respect to the trans conformation. The order of the structure in which CH_2 groups are included varies the gauche/trans conformer ratio; the frequency decreases when the methylene chain is in a more ordered structure and the gauche/trans conformer ratio decreases (Bhat and Gaikar, 1999).

In the presence of naproxen Na, both the –CH– and CH_2 stretching bands are strongly shifted to a higher frequency region: 2863, 2920 and 2976 cm^{-1}, respectively. This increase therefore implies that the PVP methylene chain is in (a) more disordered structure, confirming that intramolecular interactions are diminished by the presence of the drug, in good agreement with the behavior of the carbonyl band.

PVP can only act as proton acceptor (through either the O or N atoms of the pyrrole ring). Therefore, hydrogen bonds cannot be formed between PVP and the drug. Additionally, amides do not enolise although there is a good deal of resonance towards a dipolar form. The results therefore seem to indicate that the interaction between naproxen Na and PVP occurs by means of the carboxylate group of the drug and the nitrogen atom of the polymer via of an ion–dipole interaction, as described for the PVP–polyacrylic acid system (Florence and Attwood, 1986).

3.2.3. Naproxen Na:β-CD–PVP interaction

3.2.3.1. Ternary system spectra. Finally, the naproxen Na:β-CD inclusion complex formed in the presence of 0.05, 0.1 and 1% (w/w) of PVP was studied. The IR spectra of these ternary systems clearly correspond to that of the major component of the mixture; i.e. β-CD (Table 3). Therefore, the spectra of the ternary systems were compared with the corresponding ones of the β-CD and naproxen Na:β-CD inclusion complex.

In the ternary complex spectra, the A_{1026}/A_{1158} ratio does not change with the presence of increased amounts of PVP, being 1.36, 1.36 and 1.35 for 0.05, 0.1 and 1% PVP, respectively. Furthermore, this ratio is the same as that seen in the naproxen Na:β-CD complex formed in the absence of PVP. This indicates that only the drug penetrates into the β-CD cavity.

3.2.3.2. Deconvolution of bands.

3.2.3.2.1. 3000 cm^{-1} band deconvolution. The broad band corresponding to hydroxyl group absorption does not have a defined maximum, such that the deconvolution of this band was carried out (Fig. 5E and F). The spectral contour can be decomposed into two Gaussian bands, as for the naproxen Na:β-CD complex. The bands were red-shifted as the PVP concentration increased (Fig. 5F), and the contribution of each band to the total envelope contour changed (Table 6). Thus, as the PVP percentage increased, the proportion (obtained as a ratio between the area of the Gaussian and the total area of the band A_i/A_t) of the two bands changes. The observed trend was for the one corresponding to the intermolecular hydrogen polymeric-bonded species to increase (6, 10, 13% at 0, 0.1 and 1% PVP, respectively) and the single-bonded one to decrease (90, 85, 82% at 0, 0.1 and 1% PVP, respectively).

The results seem to confirm the notion that in the ternary system the PVP coats the naproxen Na:β-CD inclusion complex and interacts with the cyclodextrin by means of multiple intermolecular hydrogen bonds. This situation is in good agreement with the more disordered structure of the polymer as reflected by the CH bands.

Table 6
Decovolution into Gaussian bands of the IR bands centered around 3000 cm^{-1} of the ternary system naproxen Na:β-CD:PVP at different PVP percentages

	Naproxen Na:β-CD:PVP		
	% PVP		
	0.05	0.1	1
A	0.065	0.075	0.025
ν (cm^{-1})	2725	2740	2765
δ (cm^{-1})	80	80	80
A	0.11	0.14	0.09
ν (cm^{-1})	2860	2855	2870
δ (cm^{-1})	55	45	40
A	0.23	0.4	0.17
ν (cm^{-1})	2927	2927	2938
δ (cm^{-1})	37	39	45
A	0.05	0.3	0.13
ν (cm^{-1})	3170	3175	3190
δ (cm^{-1})	94	130	140
A	0.93	1.26	0.45
ν (cm^{-1})	3395	3399	3420
δ (cm^{-1})	245	190	195

4. Conclusions

Free naproxen Na and the naproxen Na:β-CD inclusion complex interact with PVP in aqueous solution. PVP shows more affinity for the complex—$K = (6.67 \pm 0.292) \times 10^{-5}\,M^{-1}$—than for the free drug—$(2.08 \pm 0.208) \times 10^{-5}\,M^{-1}$.

In general, the presence of PVP either decreases or fails to modify the drug:CD binding constant.

The thermodynamic study shows that the driving force responsible for complex formation changes with the percentage of PVP. At low polymer concentrations, the complexation process is driven entropically, while at higher PVP proportions it is enthalpically favored.

Finally, the IR study points to some evidence that naproxen Na interacts with the nitrogen atom of the PVP, whereas no change is observed in the carbonyl band of the tertiary amide. On this basis, and considering that amides do not enolise but that there is a good deal of resonance towards a dipolar form, an ion–dipole interaction is proposed to account for the drug:PVP interaction. The interaction of PVP with the drug in the ternary complex was also observed.

In the ternary complex only the drug penetrates into the β-CD cavity. The interaction occurs through intermolecular polymeric hydrogen bond formation between β-CD and PVP.

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