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Sorption of pindolol and related compounds by a β-cyclodextrin polymer: Isosteric heat of sorption

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Abstract

The possibility of using cyclodextrin polymers in drug delivery makes it necessary an investigation of their mechanisms of interaction with different solutes. In this sense, the sorption of pindolol, propranolol, indole and 4-methoxyindole on a crosslinked polymer containing β-cyclodextrin has been studied. The similar rapid kinetic profiles obtained for the four solutes can be related to the high swelling capacity of the polymer, which enables the expansion of its network and the diffusion process. The differences detected in the sorption capacities of the solutes are associated to their ability to form inclusion complexes within the cyclodextrin cavities. The sorption isosteric heats determined evidence the heterogeneity of the polymer, with the cyclodextrin cavity being the most favourable adsorption site.

Keywords: Cyclodextrin polymers; Sorption; Pindolol; Propranolol; Isosteric heat

1. Introduction

Cyclodextrins (CDs) are torus shaped cyclic oligosaccharides consisting of α-(1,4) linked glucose units. The most common cyclodextrins are α, β and γ-cyclodextrin, which contain six, seven and eight glucose units, respectively. A characteristic feature of these compounds is the presence of an internal hydrophobic cavity with a remarkable capacity to form inclusion complexes whose stability constants depend on the polarity, size and shape of the guest molecule included (Connors, 1997; Szejtli & Osa, 1996).

Compounds consisting of two or more covalently linked cyclodextrin rings are called cyclodextrin polymers. Insoluble β-CD polymers can be obtained by crosslinking with bi or multifunctional reagents. The application fields of these materials are in continuous development as new cyclodextrin polymers are being synthesised (Crini & Morcellet, 2002). For example, they have been used as heterogeneous systems to sorb industrial waste water pollutants. In this sense, Crini (2003) proposed the use of insoluble β-CD polymers for the removal of various dyes from aqueous solutions and also for the sorption of some benzene derivatives which are often present as organic pollutants in waste water (Crini et al., 1998). In both cases, high sorption capacities were reported for these polymers, which were related to a mechanism of sorption involving both physical adsorption in the polymer network and the formation of inclusion complexes with the cyclodextrin units.

The applications of cyclodextrins in the pharmaceutical sector have been extensively reported, although there is limited evidence in the literature about the use of cyclodextrin polymers in drug release. Gerlóczy, Fónagy, Fenyvesi, and Szejtli (1985) studied the use of an insoluble crosslinked β-cyclodextrin polymer as tablet disintegrating agent and they concluded that it could not be absorbed from the gastrointestinal tract. The potential use of these polymers for controlled drug release needs further investigations both in the way of synthesising new polymers and in the way of analysing the behaviour of different drugs in the presence of these polymers. In relation to the synthesis of new polymers, it

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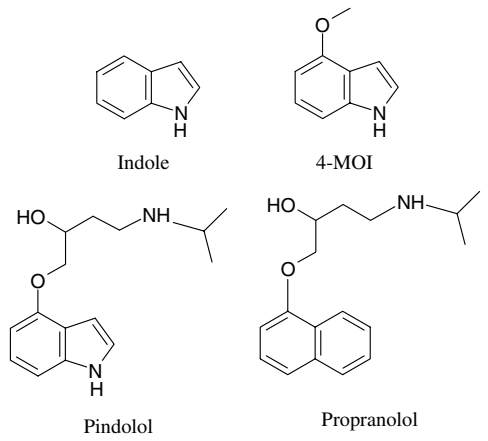

Fig. 1. Chemical structures of the solutes.

must be taken into account that when epichlorohydrin is used as crosslinking agent, the excess must be carefully eliminated from the polymer because it is considered an hazardous compound (Mlejnek & Kolman, 1999).

Friedman and West (1988) reported the applications of cyclodextrin containing polymers in the food and pharmaceutical industries. A recent study evaluates the use of novel β-cyclodextrin polymers as drug carrier systems (Li, Xiao, Li, & Zhong, 2004c).

The aim of this work was to investigate the sorption of different solutes on an insoluble β-CD polymer. Taking into account that the complexation of pindolol, 4-methoxyindole and indole with β-cyclodextrin had been evidenced in our previous studies (Gazpio et al., 2005, 2003), these compounds were selected for the sorption investigations. The β-blocker pindolol was chosen in the first place and, considering that its chemical structure (Fig. 1) bears an indole ring with an ether substitution in C4, the parent indole ring and 4-methoxyindole were selected as well for comparison purposes. In addition, it appeared to us interesting to study the sorption of propranolol, another β-blocker whose structure presents the aliphatic chain of pindolol attached to a naphthalene ring. The comparison of the sorption of both β-blockers would evidence the differences associated to the presence of each aromatic ring i.e. indole and naphthalene.

The present paper is framed on a wider study of the mechanisms of retention of different solutes on cyclodextrin polymers in order to find applications in different fields such as drug release and removal of contaminants. In this sense, an analysis of the sorption of dibenzofuran derivatives on a β-CD polymer has been recently reported (Romo, Peñas, & Isasi, 2004).

2. Experimental

2.1. Materials

Pindolol, propranolol hydrochloride, 4-methoxyindole and indole were purchased from Sigma–Aldrich, and the β-cyclodextrin polymer (β-CDP) from Cyclolab (Hungary). The polymer was in the shape of spherical beads with sizes ranging from 0.100 to 0.300 mm, the cyclodextrin content was 55% wt. and its swelling capacity was approximately 5 mL/g in water. The Brunauer-Emmet-Teller (BET) surface area of the beads was 0.11 m^2/g, it was determined by nitrogen adsorption/desorption isotherms at 77 K using a Micromeritics ASAP-2000 analyser. Water was deionised at 18 MΩ using a Wasserlab ultra-pure water system.

2.2. Methods

2.2.1. Kinetic studies

The kinetic adsorption tests have been performed in unbuffered water (pH 6.5) at 17, 20, 25 and 30 °C; these temperature values had been chosen in our previous studies of complexation with β-CD (Gazpio et al., 2003). Aqueous 7.91×10^{-5} M solutions of the compounds tested were stirred at 150 rpm in the presence of 1.12 g of the polymer, this amount corresponds to a 30:1 CD-solute molar ratio. The initial concentration was the same for all the compounds studied and it was conditioned by the low aqueous solubility of pindolol in water. Samples were taken from the supernatant and the residual concentrations of the solutes were determined spectrophotometrically at 264 nm using a HP 8452 A diode array spectrophotometer.

The same experimental conditions have been used to assay the adsorption of pindolol on a polymer of sucrose crosslinked with epichlorohydrin (Su67EF) that was synthesised in our laboratory (García-Zubiri, González-Gaitano, & Isasi, 2007).

2.2.2. Sorption measurements

The adsorption isotherms have been obtained in unbuffered water (pH 6.5) at 17, 20, 25 and 30 °C. Batch adsorption tests have been carried out in flasks containing 50 mL of 7.74×10^{-5} M solutions of the compounds tested and different amounts of β-CDP. After stirring during 1 h, equilibrium was reached and the amount of solute remaining in solution was determined spectrophotometrically at 264 nm.

3. Results and discussion

3.1. Sorption kinetic studies

The sorption capacities of the β-CD polymer versus the stirring time towards the different solutes in water at 20 °C are shown in Fig. 2. There is a rapid increase during the first 10 min and the maximum capacity is obtained after 20 min stirring. The similar kinetic profiles obtained for the four solutes indicate that diffusion within the polymer is a rapid process scarcely influenced by the differences in their chemical structures; this fact is probably due to the high swelling capacity of the polymer, which enables the expansion of its network and the diffusion of the solutes. Due to the complexity of the crosslinked CD polymer

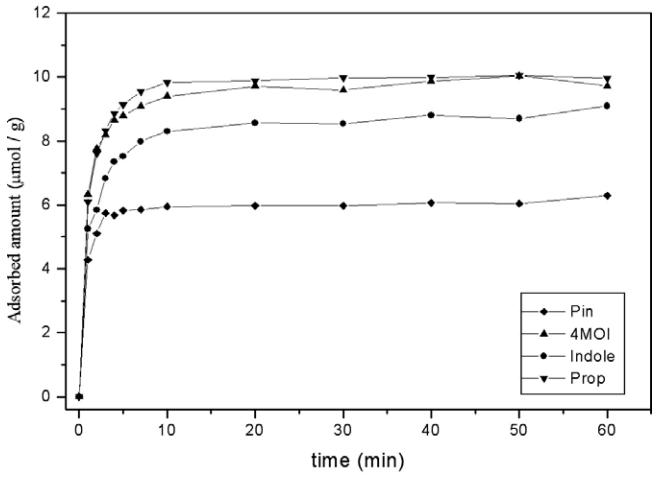

Fig. 2. Amount of pindolol, 4-methoxyindole, indole and propranolol adsorbed by β-CDP as a function of time in water at 20 °C.

and its specific characteristics, the sorption mechanism is different from those of other conventional adsorbents. In general, physical adsorption and diffusion do not play a significant role in the interaction between crosslinked polysaccharide-based beads and organic compounds because the beads have a small surface area (Crini, 2005).

The highest sorption is found for propranolol followed by 4-methoxyindole and indole and the lowest sorption value is that of pindolol. Taking into account that pindolol and propranolol bear the same chain, the presence of a naphthalene instead of an indole ring seems of great importance in the sorption process. If we tried to explain these results on the basis of physical sorption, it seems that the interactions of an indole ring with the polymer network would be more intense than those of a naphthalene ring, due to the presence of an electronegative atom which would increase the electrostatic interactions and could form H-bonds. Therefore, as it was said before, a mere physical sorption does not explain the differences detected in the sorption behaviour of both compounds.

It is well known that crosslinked cyclodextrin polymers show specific sorption characteristics compared to those of epichlorohydrin crosslinked linear dextrans, this effect can be explained by complex formation (Romo et al., 2004). As it was said before, inclusion complexation is a complicated process that depends on different properties of the guest molecule, such as the polarity, size and ability to closely fit within the cavity, together with various interactions involving van der Waals, dispersive forces, dipole–dipole interactions, electrostatic forces and hydrogen bonding. In this sense, the formation constants for the inclusion complexes of indole and naphthalene with β-CD at 25 °C are 184 (Örstan & Ross, 1987) and 676 M^{-1} (Guo, Zheng, Ruan, Luo, & Liu, 1996), respectively. These differences in the association constants would be in accordance with the sorption values obtained, therefore, it appears that the inclusion phenomena play an important role in the sorption mechanism.

With respect to the indolic derivatives studied, despite the presence of a chain with groups capable of H-bonding in pindolol, this solute exhibits the lowest sorption value, which may be explained by the steric hindrance induced by a bulky substituent during the inclusion process. In relation to this, the previously reported values of the apparent stability constants for the β-CD complexes with pindolol and 4-methoxyindole in water at 25 °C, being 51 and 163 M^{-1}, respectively (Gazpio et al., 2005), allowed a relationship with their respective sorption values to be established.

A correlation between stability constants and sorption capacity is not always obtained. Although the stability constant of indole is slightly higher than that of 4-methoxyindole, the amount of indole retained in the polymer is lower. Crini et al. (1998) reported lower sorption capacities for solutes with higher association constants that were attributed to other interactions such as physical sorption, hydrogen bond interactions with the crosslinked agent and hydrophobic guest–guest interactions.

The inclusional nature of the interaction with the β-CD polymer is borne out by an assay of adsorption of pindolol on a carbohydrate polymer of sucrose crosslinked with epichlorohydrin (Su67EP) synthesised in our laboratory (García-Zubiri et al., 2007). The fact that the adsorption of pindolol on this sucrose polymer was negligible supports the idea that inclusion is the main contribution to sorption in the cyclodextrin polymer. Nevertheless, an aggregation mechanism due to solute–solute interactions might be possible in the cases of pindolol and propranolol due to the presence of a bulky chain bearing groups capable of H-bonding which, once the aromatic ring has been included in the CD cavity, could interact either with the polymer network or with other solute molecules.

The kinetic data of the solutes were tested for agreement with the Elovich equation and also with the intraparticle diffusion model by plotting q (μmol/g) versus $\ln t$ and versus $t^{0.5}$, respectively (Chang & Juang, 2005). The best fittings were obtained for the Elovich equation, with linear regression coefficients of determination (R^2) between 0.93 and 0.99. This model has been successfully applied to adsorption on heterogeneous surfaces, as would be the case for our cyclodextrin polymer.

With respect to the effect of temperature, it would be expected that the adsorption rate increased at high temperatures due to improved diffusion phenomena. However, the kinetic profiles at different temperatures are similar, as can be observed in Fig. 3, which shows the kinetic profiles of 4-methoxyindole, as an example. This suggests that the sorption mechanism is mainly due to the formation of an inclusion complex through host–guest interactions.

3.2. Sorption isotherms and isosteric heat of sorption

A common way to represent sorption data is the adsorption isotherm, which represents the equilibrium uptake

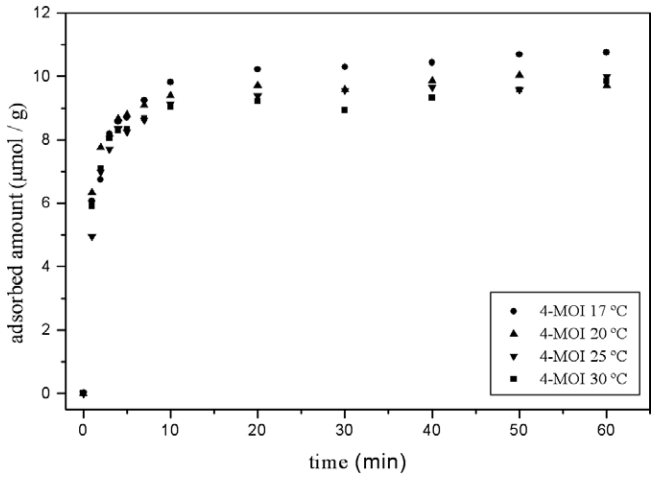

Fig. 3. Amount of 4-methoxyindole adsorbed by β-CDP as a function of time in water at 17, 20, 25 and 30 °C.

(amount adsorbed per gram of sorbent) versus the free solute concentration at a constant temperature. The Langmuir and Freundlich isotherms are the most frequently used equations for adsorption of solutes by solids (Rubin & Mercer, 1981, chap. 8). The Langmuir isotherm assumes the formation of a monolayer on a homogeneous surface while the Freundlich type is empirical and it is suitable for multilayer heterogeneous adsorption sites with different adsorption heats (Umpleby et al., 2004). The Freundlich equation has been selected in this study because the β-CD polymer exhibits a heterogeneous surface with the possibility of interacting both with the cavity of the cyclodextrin and with the polymer network.

The experimental data in the intermediate portions of the isotherms fit the Freundlich equation, but the experimental values at low equilibrium concentrations deviate from it. It is well known that this equation fails to predict the adsorption behaviour at low concentrations and also the saturation of the monolayer at high concentrations (Rubin & Mercer, 1981, chap. 8).

The sorption isotherms at different temperatures are depicted in Fig. 4. The Freundlich parameters K_F and n have been determined and they are shown in Table 1. The amount adsorbed (q) has been calculated in moles of solute per gram of polymer (q) and the solute equilibrium concentration is given in mol/L. As occurs for the inclusion process, sorption by β-CDP is exothermic, the amounts sorbed decrease at high temperatures, but the isotherm of pindolol at 25 °C seems to deviate from this behaviour.

The temperature dependence of the Freundlich isotherms of pindolol and propranolol is different from that of indole and 4-methoxyindole in the way that the former tend to converge to a value at high uptakes, suggesting a maximum coverage of the polymer network. This could be attributed to the fact that, once the aromatic rings of

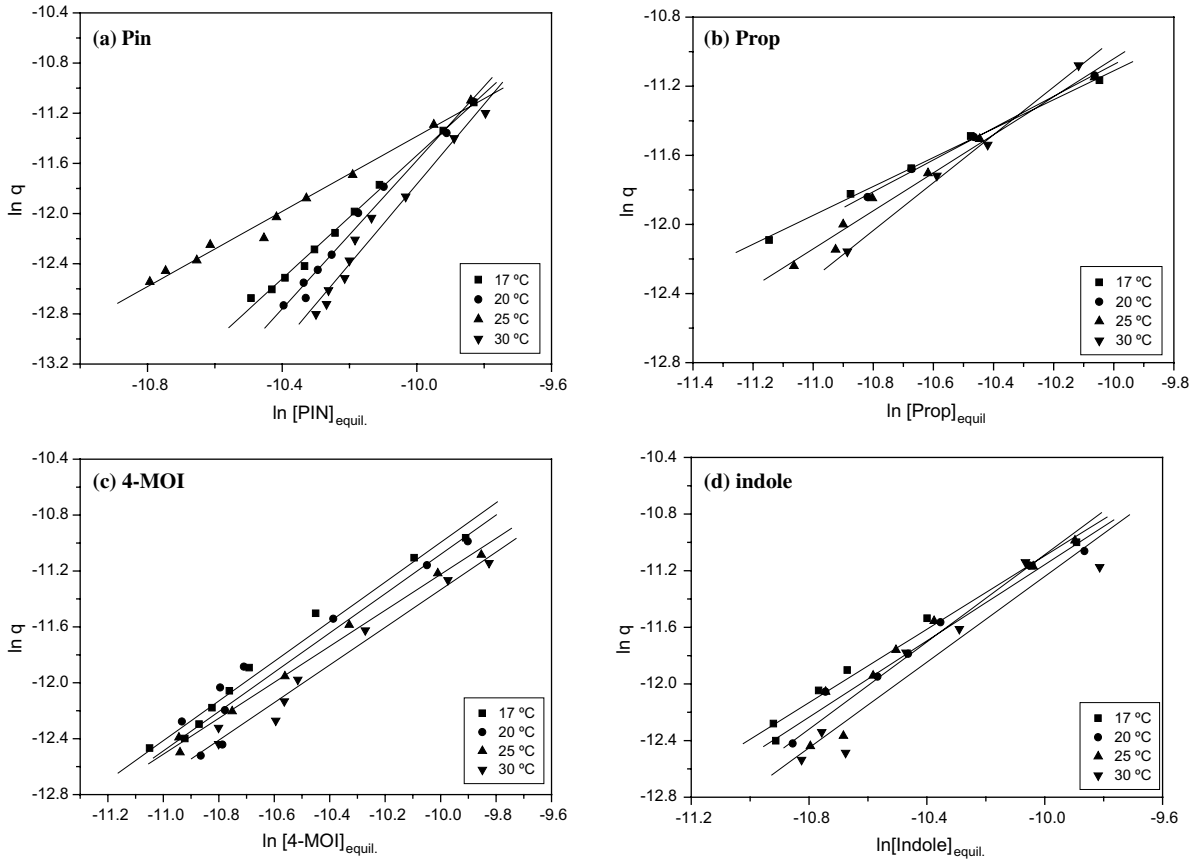

Fig. 4. Freundlich isotherms at 17, 20, 25 and 30 °C for (a) pindolol, (b) propranolol, (c) 4-methoxyindole and (d) indole. The amount adsorbed (q) is represented in mol/g and the equilibrium concentration in mol/L.

Table 1
Fitting parameters of the Freundlich isotherms K_F and n (capacity and affinity constants) and correlation coefficient for pindolol, indole, 4-methoxyindole and propranolol in water

T (K)	Freundlich isotherm $\ln q = \ln K_F + n \ln C_e$		
	$\ln K_F$	n	r
Pindolol			
290	13.06 ± 0.60	2.46 ± 0.06	0.998
293	17.99 ± 1.26	2.96 ± 0.12	0.994
298	3.60 ± 0.61	1.50 ± 0.06	0.994
303	20.12 ± 1.93	3.19 ± 0.19	0.990
Indole			
290	1.86 ± 0.78	1.30 ± 0.07	0.992
293	2.31 ± 1.07	1.35 ± 0.10	0.990
298	4.32 ± 1.75	1.54 ± 0.17	0.970
303	3.89 ± 2.11	1.51 ± 0.20	0.960
4-Methoxyindole			
290	3.19 ± 0.80	1.42 ± 0.08	0.990
293	2.98 ± 1.69	1.41 ± 0.16	0.960
298	1.65 ± 0.51	1.29 ± 0.05	0.999
303	2.13 ± 0.89	1.35 ± 0.09	0.990
Propranolol			
290	−2.74 ± 0.28	0.84 ± 0.03	0.999
293	−1.87 ± 0.29	0.92 ± 0.03	0.999
298	−0.04 ± 0.75	1.10 ± 0.07	0.990
303	2.92 ± 0.55	1.39 ± 0.05	0.999

The amount adsorbed (q) is represented in mol/g and the equilibrium concentration (C_e) in mol/L.

pindolol and propranolol have been included within the CD cavities, their bulky chains can interact with the polymer network resulting in an increased coverage.

The relationship between the sorbate equilibrium concentration and the temperature at a constant equilibrium uptake is represented by the adsorption isostere. The determination of sorption isosteric heats is an interesting approach for the study of heterogeneous adsorbents. The Freundlich model, although empirical, can be derived by assuming that the adsorption heat decreases exponentially with surface coverage. However, the Langmuir model assumes equal interaction energies for every adsorption site so it is only applicable to homogeneous surfaces (Adamson & Gast, 1997).

The isosteric adsorption enthalpies have been determined at a given equilibrium uptake from the slope of the plot of $\ln C_e$ versus T^{-1}, where C_e is the concentration of free solute in the equilibrium (Li, Jiao, Xu, Shi, & He, 2004a; Li, Xu, Shi, & He, 2004b). The plot has been constructed giving values to the respective equations of the Freundlich isotherm in the range of coverages studied. The values of ΔH are obtained from these plots for each equilibrium uptake or fractional surface coverage (θ), which is proportional to the moles of sorbate retained per unit mass of sorbent (q). The data fit straight line equations with R^2 values ranging from 0.85 to 0.99. The isosteric heats Q_{isost} of the sorption process are readily determined from these plots as Q_{isost} is defined as $-\Delta H$.

Fig. 5 shows the isosteric heats at different uptakes for the compounds studied. In all the cases except for 4-methoxyindole, the isosteric heat is higher at low θ, probably because the sites with higher interaction energies are filled first. In the cyclodextrin polymers these sites are the cyclodextrin cavities, because all the solutes studied present aromatic rings capable of forming inclusion compounds, as it was said before. The isosteric heats of propranolol at high uptakes become negative, probably due to the repulsive forces induced by the aliphatic chain. This is not so in the case of pindolol, as its adsorption is lower and probably such high coverages are not achieved.

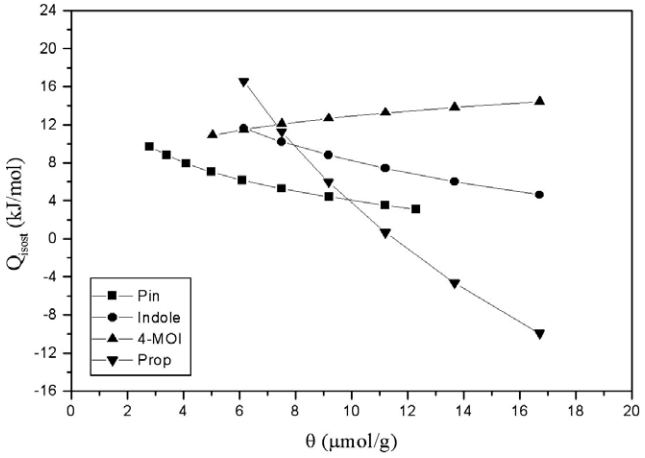

Fig. 5. Isosteric heat of pindolol, indole, 4-methoxyindole and propranolol as a function of the surface coverage.

The range of coverage (θ) from 6 to 12 μmol/g has been taken as reference for comparing the behaviour of the four solutes because all of them present experimental values in this interval. The higher isosteric heat (16.6 kJ/mol) obtained for propranolol at low uptakes (6.1 μmol/g) can be attributed to a more favourable inclusion of naphthalene compared to indolic derivatives. Indole and 4-methoxyindole present very similar isosteric heats (11.5 and 11.6 kJ/mol, respectively, for 6.1 μmol/g) which would be in accordance with their similar chemical structures. However, the isosteric heat of pindolol at the same coverage becomes much lower, being 6.15 kJ/mol, probably due to the steric hindrance induced by its bulky chain during the inclusion process (Gazpio et al., 2005).

3.3. Influence of pH

The influence of pH and ionic strength has been investigated only in the case of pindolol because we had carried out previous investigations of the effect of pH on the complexation of this drug with β-CD.

The sorption measurements were carried out using a constant amount of polymer (0.250 g) and a constant concentration of pindolol (7.74×10^{-5} M) in the presence of increasing concentrations of NaCl. The results obtained are shown in Fig. 6. The retention of pindolol by the polymer decreased with increasing salt concentrations, probably due to a predominance of the solvation forces over the inter-

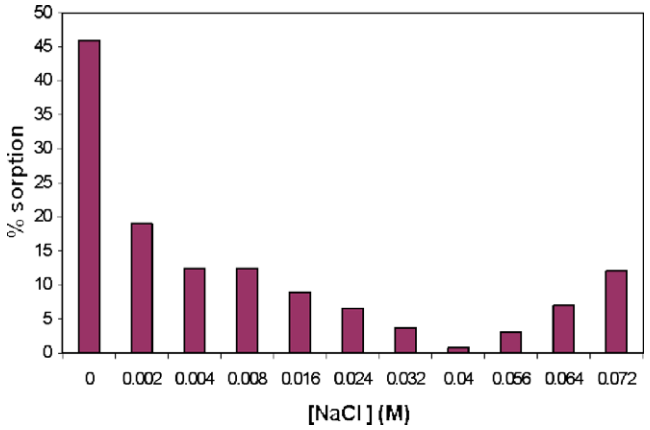

Fig. 6. Influence of salt concentration on the retention of pindolol by β-CDP.

actions with the cyclodextrin cavities. In general, salts may have two main functions in the adsorption phenomena, on the one hand, they may screen the electrostatic interactions of opposite charges in adsorbent and solute molecules, and on the other hand, they may enhance the degree of dissociation of the solutes. The first one involves a decrease of the amount adsorbed in the presence of increasing salt concentrations while the increased dissociation of the solute would, in general, enhance the amount adsorbed. The β-CD polymer is not charged in unbuffered aqueous solution, so the main effect associated to the increase of salt concentration will be an increase of the dissociation of pindolol and also an enhanced aqueous solubility. In contrast to what is usual in other type of adsorbents, this fact is unfavourable for the sorption process, because it has a negative effect on the driving forces of inclusion complexation, which are based on the stabilisation of a non polar solute in aqueous solution upon inclusion in the cyclodextrin cavity.

With respect to the influence of pH, taking into account that pindolol is a weak base with $pK_a = 9.4$, its amine group is protonated in water while it is neutral in pH 12 aqueous solution. The sorption values of neutral pindolol have been determined in pH 12 buffer solution and they have been compared with those determined in an aqueous solution containing the same ionic strength as the pH 12 buffer, the values obtained are higher for the neutral form of the drug, in accordance with its more favourable inclusion in the β-CD cavity detected in our previous studies (Gazpio et al., 2005).

The pK_a of β-CD is 12.20, so the polymer is neutral in water and partially ionised at pH 12. Despite the presence of some negative charges in the polymer at this pH value, electrostatic interactions do not seem to contribute significantly to a higher retention of pindolol by the polymer, because, as it was said before, the inclusion of the non polar parts of the solute in the CD cavities play the main role in the adsorption process. In order to clarify this point, an experiment of adsorption of 4-methoxyindole in pH 12 aqueous solution has been carried out and the results have been compared with those obtained in water, being found that the amounts adsorbed in both media are equivalent. Taking into account that 4-methoxyindole is neutral in both media, the presence of charges in the polymer at pH 12 does not seem to affect the amount of solute adsorbed, supporting the main role of inclusion in the sorption process.

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