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ORIGINAL ARTICLE

Temperature effect on the complex formation between tricyclic antidepressant drugs (amitriptyline or imipramine) and hydroxypropyl-β-cyclodextrin in water

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Abstract The molecular encapsulation of two tricyclic antidepressants (TCA) drugs, amitriptyline and imipramine, by a glycosidic receptor, 6-hydroxypropyl-β-cyclodextrin (HPBCD), has been carried out in water solution by means of conductometric studies at different temperatures ranging from 15 °C to 45 °C. Conductivity measurements of aqueous solutions of the drug were performed: (i) in the absence of HPBCD, as a function of drug concentration; and (ii) in the presence of HPBCD, as a function of HPBCD concentration. Both drugs, amitriptyline and imipramine, form inclusion complexes characterized by a 1:1 stoichiometry and an association constant ($K_{\mathrm{HPBCD:TCAH^+}}$) in the range of 500–1200 M^{-1}. The ionic molar conductivities at infinite dilution of the free ($\lambda^0_{\mathrm{TCAH^+}}$) and complexed ($\lambda^0_{\mathrm{HPBCD:TCAH^+}}$) drugs have been calculated from these conductivity data as well. From the dependency of the association constant on temperature, changes on the enthalpy, ΔH^0, entropy, ΔS^0, and heat capacity at constant pressure, ΔC^0_p , have been determined. This thermodynamic information, which reveals that the complexes formed by HPBCD and the antidepressant drugs, AMYTPH$^+$ and IPRH$^+$, are enthalpy driven at $T \geq 25$ °C but entropy driven at $T < 25$ °C, points to the contribution of van der Waals interactions, hydrophobic effect and solvent reorganization, as the main driven forces promoting the interaction. The analysis of these association processes was also used to elucidate the potential viability of using HPBCD as a vector of these antidepressant drugs.

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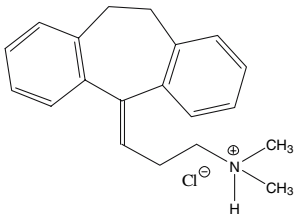
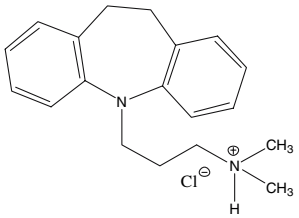
Keywords Amitriptyline · Association constant · Conductivity · Hydroxypropyl-βcyclodextrin · Imipramine · Molecular encapsulation · Temperature effect · Thermodynamics · Tricyclic antidepressant drugs

Introduction

The tricyclic antidepressants drugs (TCAs) amitriptyline (AMYTP) and imipramine (IPR) constitute an important class of neurotherapeutics. The former has a carbocyclic structure with an exocyclic double bond at C5, which is substituted with an *N*,*N*-dimethyl-1-propanamino side chain. Imipramine has the same side chain, but linked to the heteroatom of its 5*H*-dibenz[*b*,*f*]azepino skeleton (Scheme 1). The antidepressant activity of TCAs in the organism, which increases with the angle formed by the two phenyl rings, is directed to raise the endogen amines concentration levels or to promote its action. It is believed that both drugs, AMYTP and IPR, act by blocking the receptors of neurotransmitters, noradrenaline in the synapsis or serotonin in the central nervous system, which results to an increase of concentration of both molecules with a subsequent enhancement of their antidepressant potency [1]. However, TCAs suffer from several drawbacks, such as antiarrhytmic, anticholinergic, cardiovascular and/or hyperthermia side effects [1, 2], which may be reduced if the drugs are suitably vectored to the organism. The vectorization concept started as an answer to the disadvantages that appear when the drug is administered following a conventional therapeutic protocol. In this field, cyclodextrins (CDs) are considered as one of the most suitable artificial receptors for the vectorization of guest hydrophobic molecules (drugs, dyes, detergents, pesticides,



Amitriptyline Hydrochloride Molecule
(AMYTPH$^+$Cl$^-$)



Imipramine Hydrochloride Molecule
(IPRH$^+$Cl$^-$)

Scheme 1

etc) in aqueous media [3–5]. In fact, the use of CDs as a new family of pharmaceutical excipients and drug carriers has become an increasingly accepted method for many therapeutic molecules [6]. The parent cyclodextrins ares non-toxic macrocyclic sugars consisting of 6(α-CD), 7 (β-CD) or 8 (γ-CD) α(1 → 4) joined glucopyranose units, which yield a doughnut-shaped type structure with a characteristic hydrophobic surface in the internal cavity [3]. The dimensions of the β-cyclodextrin cavity are the most suitable for the molecular encapsulation of most drugs but, as it is poorly soluble in water, various substituted derivatives of β-CD, as 6-hydroxypropyl-β-cyclodextrin, with a much higher solubility, are used for industrial applications [3, 6]. A good knowledge of the molecular encapsulation process is essential for a rational design of CD:drug formulations. For example, the inclusion of the drug within cyclodextrin will only be effective if the association constant of the complex falls within the proper range [3, 6, 7]. In this sense, thermodynamic information, such as the association constant and the change of the enthalpy, ΔH^0 and entropy, ΔS^0, upon binding, is very important in order to obtain a clear picture of the driving forces governing the association process.

In this work, we present the characterization of the inclusion complexes formed by 6-hydroxypropyl-β-cyclodextrin with amitriptyline and imipramine, the two previously mentioned TCAs. The study was based on conductivity measurements at seven temperatures ranging from 15 °C to 45 °C. We expect that the results will show that the characterization of these associations from a physichochemical point of view adds light to the usual pharmacological and/or pharmacokinetic experiments, and will improve the understanding of CD:drug formulations.

Materials and methods

Materials

Hydrochlorides of amitriptyline (AMYTP.HCl) and imipramine (IPR.HCl) were purchased from Sigma. 6-Hydroxypropyl- β-cyclodextrin (HPBCD), containing an average of 0.64 hydroxypropyl groups per glucopyranose unit was from Janssen Biotech (Belgium). All of them, with 99% purity or higher, were used without further purification. Thermogravimetric analysis (TG) revealed that HPBCD consist of 2.8% of water mass content, which was taken into account in the calculations of solute concentrations. All the solutions were freshly prepared by mass using distilled and deionized water (taken from a Millipore Super-Q System, with a conductivity lower than 18 μS cm^{-1}). The homogeneity of the initial solutions was assured by sonicating them for one hour in an ultrasonic bath.

Conductivity measurements

Conductivity data were collected with a Hewlett-Packard 4263A LCR Meter, using a Metrohm electrode, whose calibration with a KCl standard solution yields a cell constant of 0.8084 cm^{-1}. Mixtures were prepared from a digital burette, whose cylinder was kept at the same constant temperature as the measuring cell. Details of the apparatuses and the experimental procedure of the fully computerized technique, were described earlier [8]. The reproducibility on the specific conductivity, κ, obtained as an average of 2400 measurements for each concentration, is believed to be higher than 0.03%. The accuracy on the molarity of the solutions is more than 1×10^{-5} M, and the temperature is held constant within ± 0.001 °C. The conductivity of the aqueous solutions was measured as a function of the drug concentration for the binary drug/water system, and as a function of HPBCD concentration, keeping constant the concentration of the drug (around 5 mM), for the ternary HPBCD/drug/water system. In the latter case, the cyclodextrin concentration ranges were chosen to guarantee a proper determination of the association constant (20–80% of the saturation curve) [9].

Results and discussion

The pH of the aqueous solutions of amitriptyline and imipramine hydrochlorides (AMYTP.HCl or IPR.HCl) has been measured as a function of drug concentration at 25 °C, using an experimental computerized procedure widely described previously [10], in order to confirm whether the amytriptylinate or imipraminate cations (AMYTPH$^+$ or IPRH$^+$), arising from the dissociation of the salts, hydrolyze in aqueous solution. Negligible changes in the pH have been observed within the concentration ranges used in all the studies reported herein, indicating that the equilibriums

$$\mathrm{AMYTPH^+ + H_2O \overset{K_a}{\rightleftarrows} AMYTP + H_3O^+}, \quad (1)$$

$$\mathrm{IPRH^+ + H_2O \overset{K'_a}{\rightleftarrows} IPR + H_3O^+}, \quad (2)$$

are almost totally shifted towards the ionized forms of the drugs, with a negligible contribution of the non-ionized forms. These experimental evidences confirm the suitability of using non-buffered solutions on the following studies at low drug concentrations.

Figure 1 reports, as an example, the values of the specific conductivity, κ, for the binary AMYTP.HCl/water solutions as a function of drug concentration at various temperatures ranging from 15 °C to 45 °C. Similar plots were obtained for the IPR.HCl/ water solutions. The specific conductivity of the solution can be expressed as a function of the ionic molar conductivities λ_i, and the concentration of the charged species, as follows,

$$\kappa = \lambda_{\mathrm{TCAH+}}[\mathrm{TCAH^+}] + \lambda_{\mathrm{Cl-}}[\mathrm{Cl^-}], \quad (3)$$

where the species $[OH^-]$ and $[H^+]$ have been excluded, since their contribution to the conductivity is negligible at the approximately neutral pH of the aqueous drug solution, compared with that of the protonated drugs $TCAH^+$ and Cl^-.

The λ_i values at low concentrations can be estimated by the Onsager relation:

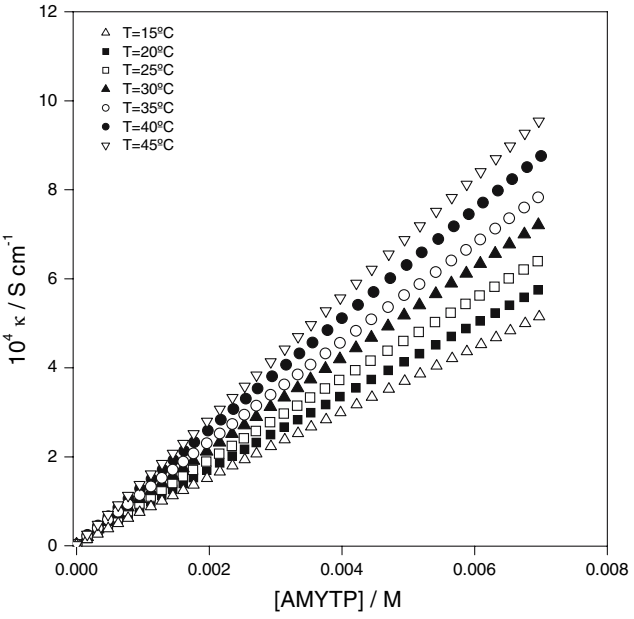


Fig. 1 Values of specific conductivity,κ, of aqueous solutions of amitriptyline hydrochloride as a function of [drug], at several temperatures ranging from 15 °C to 45 °C

$$\lambda_i = \lambda_i^0 - \frac{(\alpha + \beta\lambda_i^0)I^{1/2}}{1 + Ba_nI^{1/2}}, \quad (4)$$

where λ_i^0 represents the ionic molar conductivity at infinite dilution, a_n is the effective size of the hydrated ion, I is the ionic strength, and α, β and B are constants whose values are taken from the literature [11]. The values of $\lambda^0_{Cl^-}$ at different temperatures, shown in Table 1, were also taken from the literature as well [11, 12]. The parameter a_n of $AMYTPH^+$ (8.2 Å) and of $IPRH^+$ (8.0 Å) has been estimated from $\lambda^0_{TCAH^+}$, at 25 °C, with an empirical relation [13]. The values of $\lambda^0_{TCAH^+}$, calculated by fitting the experimental κ data to Eqs. 3 and 4 with a NLR method, are reported in Table 1 as well, and are plotted in Fig. 2 as a function of temperature. It can be noted that, at equal concentration, the specific conductivity of the AMYTP.HCl solutions (Fig. 1) is slightly lower than those of IPR.HCl (not reported), indicating that the substitution of a carbon atom by a nitrogen atom in the central ring of the molecule marginally affects the conductivity, and the values for the molar ionic conductivity of the amitriptyline is only slightly lower than those recorded for imipramine ($\lambda^0_{AMYTPH^+} \approx \lambda^0_{IPRH^+}$). Furthermore, Table 1 and Fig. 2 show an increase of these quantities with temperature for both drugs, as expected.

Figure 3 shows the plot of specific conductivity, κ, for the ternary aqueous solutions of amitriptyline hydrochloride (as an example) at a constant concentration of about 5 mM, as a function of [HPBCD], at different temperature values. A similar plot has been obtained for the ternary HPBCD/$IPRH^+$/water solutions. The formation of the inclusion complexes due to the encapsulation of the $AMYTPH^+$ moiety into the HPBCD cavity, leads to a decrease in the conductivity, κ, as long as cyclodextrin is added, since the mobility of the associated cation is expected to be less than that one of the free cation. The

Table 1 Values of ionic molar conductivities at infinite dilution of TCAs drug cations ($\lambda^0_{AMYTPH^+}$, and $\lambda^0_{IPRH^+}$), and of Cl^- ($\lambda^0_{Cl^-}$) taken from literature, in water solution at different temperatures[a]

T(K)	$\lambda^0_{Cl^-}$ (S cm^2 mol^{-1})	$\lambda^0_{AMYTPH^+}$ (S cm^2 mol^{-1})	$\lambda^0_{PRH^+}$ (S cm^2 mol^{-1})
288.15	61.4	20.4	20.5
293.15	68.9	22.5	23.4
298.15	76.4	26.4	27.1
303.15	84.2	30.4	30.9
308.15	92.2	34.3	34.6
313.15	100.4	38.2	38.7
318.15	108.9	43.8	44.5

[a] Uncertainities on $\lambda^0_{Cl^-}$, $\lambda^0_{AMYTPH^+}$, and $\lambda^0_{IPRH^+}$, are estimated to be less than ±0.2, ±0.4, and ±0.4, respectively

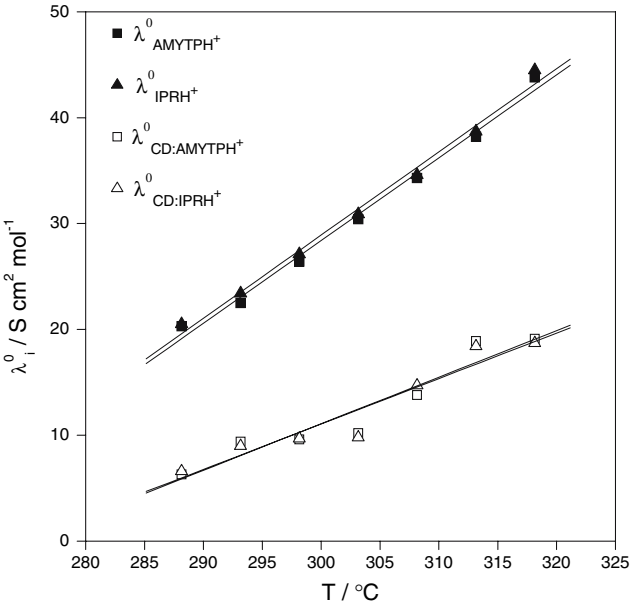


Fig. 2 Values of ionic molar conductivity at infinite dilution of TCAs drug cations, free ($\lambda^0_{AMYTPH^+}$, and $\lambda^0_{IPRH^+}$) and complexed with HPBCD ($\lambda^0_{HPBCD:AMYTPH^+}$ and $\lambda^0_{HPBCD:IPRH^+}$), as a function of temperature

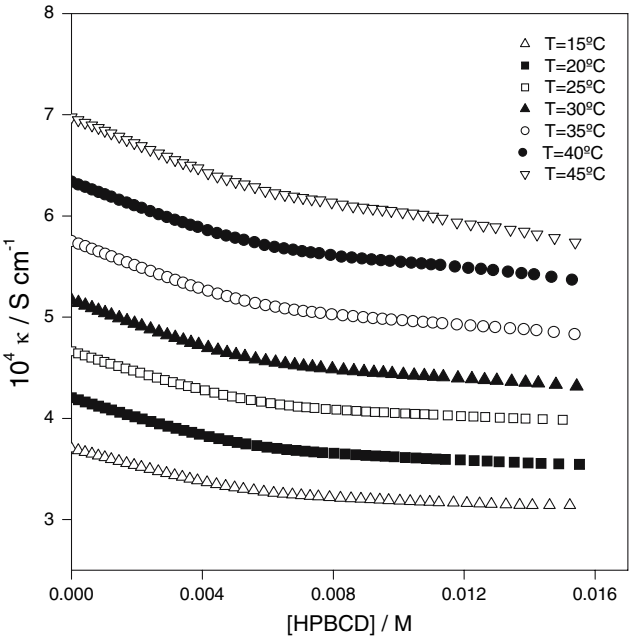


Fig. 3 Values of specific conductivity, κ, of aqueous solutions of amitriptyline hydrochloride at constant [drug] ~ 5 mM, as a function of [HPBCD], at several temperatures ranging from 15 °C to 45 °C

stoichiometry, A, of this inclusion complex has been determined as the ratio between [HPBCD] and [AMYTPH$^+$], [HPBCD] being the concentration at which two straight lines intercept at each temperature, and [AMYTPH$^+$] the initial drug concentration, kept constant during the experiment (~ 5 mM). Values of $\overline{A} = 1.02 \pm 0.03$ and $\overline{A} = 1.03 \pm 0.03$, averaged in both cases over the results obtained at all temperatures values, were obtained for HPBCD:AMYTPH$^+$ and HPBCD:IPRH$^+$, respectively. As usually encountered in most cyclodextrin/drug complexes [1, 5, 6, 14, 15], this finding demonstrates that these complexes are formed by the association of a molecule of HPBCD per each molecule of drug.

Considering this 1:1 stoichiometry, the molecular encapsulation process can be represented by:

$$TCAH^+ + HPBCD \rightleftarrows HPBCD{:}TCAH^+ \tag{5}$$

governed by the binding constant, expressed in activity terms, a_i, as:

$$K_{HPBCD:TCAH^+} = \frac{a_{HPBCD:TCAH^+}}{a_{HPBCD}a_{TCAH^+}}. \tag{6}$$

The binding constant, $K^+_{HPBCD:TCAH}$, can be calculated from the conductivity data, by using a model proposed by us [16], which is mainly based on: (i) the relation of conductivity data in terms of the complex concentration,

$$\kappa = \lambda_{Cl^-}[Cl^-] + \lambda_{TCAH^+}[TCAH^+] + \lambda_{HPBCD:TCAH^+}[HPBCD{:}TCAH^+], \tag{7}$$

(ii) the activity coefficients of the charged species, obtained through the extended Debye-Hückel theory; (iii) the ionic molar conductivities of the charged species, λ_i, related with the corresponding values at infinite dilution, λ^0_i, through the Debye-Hückel-Onsager theory; and (iv) the ionic molar conductivity at infinite dilution of TCAH$^+$, $\lambda^0_{TCAH^+}$, determined from the conductivity data of the binary system, as commented before. Thus, as widely explained elsewhere [16], Eqs. 4, 6 and 7, and the mass and charge balances have been used to fit the experimental κ data as a function of HPBCD concentrations with a nonlinear regression method, based on a nonlinear Newton-Raphson and a Marquardt algorithm. The fit coefficients, i.e., the ionic molar conductivity at infinite dilution of the complex, $\lambda^0_{HPBCD:TCAH^+}$, and the binding constant, $K_{HPBCD:TCAH^+}$, are reported in Table 2 at the seven temperature values. The ionic molar conductivities of the associated drugs, $\lambda^0_{HPBCD:AMYTPH^+}$ and $\lambda^0_{HPBCD:IPRH^+}$, decrease irrespectively of the temperature by almost 60% with respect to the value obtained for the corresponding free drug ($\lambda^0_{AMYTPH^+}$ and $\lambda^0_{IPRH^+}$) indicating, as initially observed in Fig. 3, a clear decrease in the mobility of both cations upon binding the HPBCD. In addition, the differences between ionic molar conductivities at infinite dilution of both complexes are minimal (see Table 2) at a given temperature, revealing that the mobilities of both cationic complexes are very similar, as was also found for the free drugs in water (see Table 1).

Table 2 Values of ionic molar conductivities at infinite dilution of complexed TCAs drug cations ($\lambda^0_{HPBCD:TCAH^+}$), and values of the association constants ($K_{HPBCD:TCAH^+}$), at different temperatures, for HPBCD + AMYTP.HCl + H_2O and HPBCD + IPR.HCl + H_2O ternary systems[a]

T(K)	$\lambda^0_{HPBCD:AMYTPH^+}$ (S cm^2 mol^{-1})	$K_{HPBCD:AMYTPH^+}$ (M^{-1})	$\lambda^0_{HPBCD:IPRH^+}$ (S cm^2 mol^{-1})	$K_{HPBCD:IPRH^+}$ (M^{-1})
288.15	6.3	1210	6.6	890
293.15	9.4	1140	9.0	870
298.15	9.6	1030	9.7	820
303.15	10.2	970	9.8	820
308.15	13.8	980	14.7	730
313.15	18.9	700	18.4	530
318.15	19.1	620	18.7	500

[a] Uncertainities on $\lambda^0_{HPBCD:TCAH^+}$, and $K_{HPBCD:TCAH^+}$, are estimated to be less than ±0.9, and 8%, respectively

Regarding the association constants values of the HPBCD:TCAH$^+$ complexes, reported in Table 2, several features are remarkable: (i) $K_{HPBCD:AMYTPH^+}$ ranges from 620 to 1210 M^{-1}, while $K_{HPBCD:IPR^+}$ varies from 500 to 890 M^{-1}, along the temperature range studied in this work; (ii) at all the temperatures $K_{HPBCD:AMYTPH^+} > K_{HPBCD:IPRH^+}$; and (iii) as the temperature increases, the affinity of the HPBCD for the ionized forms of the drugs decreases.

The values of the association constants obtained for both complexes are moderately high (around 10^3 M^{-1}) which is quite advantageous from a pharmaceutical point of view, since it is known [3–5, 17] that a high affinity between the drug and the HPBCD implies a troublesome delivery of the active substance to the organism, while on the other extreme (i.e. very low binding constants) there are no significant differences between the administration of the HPBCD:Drug complex and the free drug.

The fact that the formation of the HPBCD:AMYTPH$^+$ complex seems to be favoured than that with IPRH$^+$ might be due to stereoelectronic reasons; IPRH$^+$ molecule is more polar than AMYTPH$^+$ since it bears a nitrogen atom instead of a carbon atom in the central ring (see Scheme 1), and, accordingly, its inclusion in the HPBCD cavity is less favoured. The association constants for the complexes formed by β-cyclodextrin with AMYTPH$^+$ (K = 3185 M^{-1}) and with IPRH$^+$ (K = 1495 M^{-1}) reported in the literature [18], at 25 °C, are a slightly higher than the values reported in this work, which indicates that, compared with β-cyclodextrin, the presence of the hydroxypropyl chains in the HPBCD seems to hinder the entrance of a globular molecule, such as that of the TCAs, studied in this work. This behaviour is in contrast with that one observed when the encapsulated substrate is a typical elongated molecule [19–21].

An interesting thermodynamic analysis of the HPBCD:Drug association processes can be performed through a study of the influence of temperature on the K reported values. Figure 4 shows the van't Hoff plots of both association processes. A linear relationship of the Rln

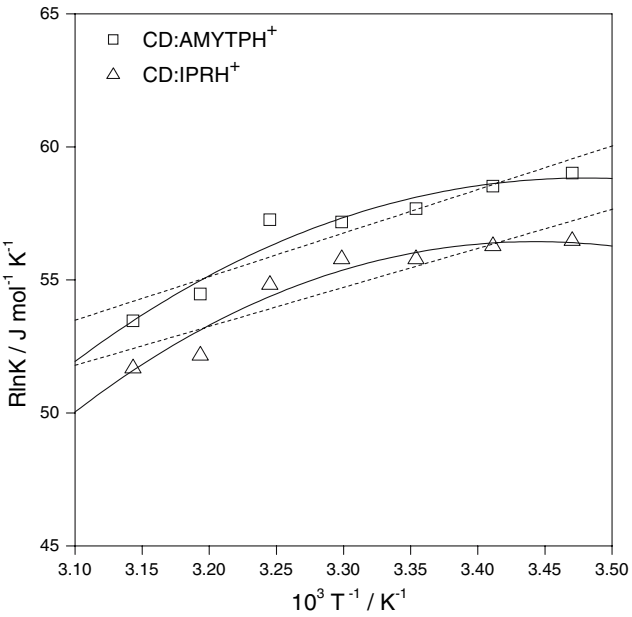


Fig. 4 van't Hoff plots for the associations of HPBCD with AMYTPH$^+$ and IPRH$^+$. Dash lines for linear fits and solid lines for nonlinear fits of Eq. 10

K vs $1/T$ data indicates the independence of ΔH^0 and ΔS^0 on T ($\Delta C^0_p \sim 0$), while the absence of such linear behavior reveals that ΔH^0 and ΔS^0 are temperature dependent, pointing to an association process with $\Delta C^0_p \neq 0$. If we assume that ΔC^0_p is temperature independent and that the dependence on temperature for ΔH and ΔS can be expressed by,

$$\Delta H = \Delta H^0 + \Delta C^0_p (T - 298.15) \quad (8)$$

$$\Delta S = \Delta S^0 + \Delta C^0_p \ln(T/298.15) \quad (9)$$

where 298.15 K has been taken as the reference temperature, the thermodynamic quantities $\Delta H^0, \Delta S^0$, and ΔC^0_p at 25 °C are related to Rln$K$ through the van't Hoff equation:

$$R\ln K = -\Delta H^0 + (T - 298.15)\Delta C_p^0]/T + \Delta C_p^0 \ln (T/298.15) + \Delta S^0 \quad (10)$$

Equation 10 can explain either the linearity or the curvature of the plots in Fig. 4. When $\Delta C_p^0 = 0$, Eq. 10 is simplified to the well-known linear relation ($R\ln K = -\Delta H^0/T + \Delta S^0$), where ΔH^0 and ΔS^0 can be estimated from the slope and intercept of the fit, respectively. On the contrary, when $\Delta C_p^0 \neq 0$, ΔH^0, ΔS^0, and ΔC_p^0 can be determined by using a nonlinear regression of the experimental K values at various temperatures. We have performed both the linear and the nonlinear van't Hoff analysis of the experimental data, and both are drawn on the van't Hoff plots of Fig. 4. Table 3 reports the results obtained for ΔH^0 and ΔS^0 in both cases, and for ΔC_p^0 in the case of the nonlinear fit. Although the uncertainty in these results is high (up to 30 %) in both the linear and the nonlinear fits, as usual for van't Hoff analysis, it can be clearly observed both from Table 3 and Fig 4 that AMYTPH$^+$ and IPRH$^+$ species bind to HPBCD following a typical non linear van't Hoff plot. Values of ΔH^0 and ΔS^0 for the HPBCD:AMYTPH$^+$ and for the HPBCD:IPRH$^+$ complexes, obtained from the slopes and the intercepts of the corresponding linear fits, support this conclusion. Accordingly, and focussing the discussion on the nonlinear analysis, data on Table 3 reveal the following: (i) ΔH, obtained with Eq. 8, is negative in both cases, (ii) ΔS, obtained with Eq. 9 is positive at T $\leq$ 25 °C and negative at higher temperatures; and, (iii) ΔC_p^0 is clearly negative. Positive ΔC_p^0 values can result from hydrophobic interactions [22], while $\Delta C_p^0 \sim 0$ may be associated to small conformational changes upon binding [23]. On the other hand, negative ΔC_p^0 values are usually found for the inclusion of non-polar solutes in cyclodextrins [24, 25] and cyclophanes [26–28], and for carbohydrates association with lectins [29, 30] in aqueous solution. In particular, ΔC_p^0 values of around –2090 J mol^{-1} K^{-1} are typical of biological associations and recognition processes where hydrogen bonds and/or polar groups are present [25–31]. Diederich et al. [26, 27], and Hayashi et al. [31], have explained these negative ΔC_p^0 values in terms of the increase with temperature of the enthalpy difference of the solvated states of the free species with respect to that of the solvated complex. A global analysis of all this information reveals that the complexes formed by HPBCD and the antidepressant drugs, AMYTPH$^+$ and IPRH$^+$, are enthalpy driven at $T \geq$ 25 °C but entropy driven at $T <$ 25 °C. This pattern is usually found in biological systems where the enthalpy governs the association process at high temperature while the entropy term does at low temperatures [32]. A combination of hydrophobic effect ($\Delta H^0 \sim 0; \Delta S^0 > 0$), van der Waals forces ($\Delta H^0 < 0; \Delta S^0 < 0$) and solvent reorganization could account for such a thermodynamic pattern. Within the uncertainty surrounding these parameters, it can be concluded that the enthalpy term is higher for the HPBCD:AMYTPH$^+$ complex than that for HPBCD:IPRH$^+$ at 25 °C, while the entropic term seems to be more favourable for the association of HPBCD with IPRH$^+$. It appears that the contribution of van der Waals interactions and hydrophobic effect could be similar in both inclusion processes, while the contribution of solvent reorganization could be the factor responsible for the difference observed between the binding of HPBCD and AMYTPH$^+$ and/or IPRH$^+$ drugs.

Thus, this physicochemical characterization of the association between a drug and a potential vector is necessary and highly recommendable. It is well known that, as long as the organism ''makes use'' of the drug, the equilibrium shown by Eq. 5 is shifted by mass action toward the release of the active ingredient, keeping and regulating its presence in the medium. The appropriate controlled release of the drug, by using suitable drug carriers, as is the case of CD's, rebound some well known advantages: (i) the adverse side effects can be substantially reduced since the quantity of drug which is really free and available in the medium may be much lower than the administered dose; (ii) the time of action of the drug can be prolonged, which in the case of most drugs is particularly important, given its well-known fast onset of action and subsequent short elimination half-life; (iii) as a consequent, the number of doses and its frequency can be reduced with the subsequent decrease of the side effects as well. It is evident that the value of the association constant of the CD/Drug complex

Table 3 Values of ΔH^o, ΔS^o, and ΔC_p^o for the association of AMYTPH$^+$ and IPRH$^+$ with HPBCD, obtained with Eq. 10 in both the linear and nonlinear forms

System		ΔH^0/ kJ mol^{-1}	ΔS^0/ J mol^{-1} K^{-1}	ΔC_p^0 / J mol^{-1} K^{-1}
HPBCD + AMYTPH$^+$	Linear	–16 ± 10	3 ± 20	–
	Nonlinear[a]	–12 ± 3	19 ± 6	–1100 ± 300
HPBCD + IPRH$^+$	Linear	–15 ± 10	4 ± 25	–
	Nonlinear[a]	–9 ± 3	25 ± 8	–1200 ± 330

[a] Obtained at a reference temperature of 298.15 K

depends on the characteristics of the CD and the drug to be encapsulated. And this overall affinity involves a particular balance between the different non covalent intermolecular forces which take place in the association process, i.e., van der Waals contacts, electrostatic and hydrophobic interactions, hydrogen bonds, solvation processes, etc. Association constant values ranging from 200 to 10,000 M^{-1} are found to be appropriate for the encapsulation of drugs by cyclodextrins, since they enable the above described controlled release of the drug. For that reason, it can be finally concluded that HPBCD could be an appropriate vector for the drugs amitriptyline and imipramine, given that the corresponding binding constants, determined in this work, fall within an optimum range.

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