Artículo de investigación científica

Thermodynamics of mixing of the β-adrenergic blocker propranolol-HCl in ethanol + water mixtures

Diana M. Cristancho [1], Reinaldo G. Sotomayor [2], Daniel R. Delgado [1], Asma Romdhani [3], Fleming Martínez [1*]

[1] Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Universidad Nacional de Colombia, A.A. 14490, Bogotá, D. C., Colombia.

[2] Laboratorios Procaps, Barranquilla, Colombia.

[3] Faculty of Pharmacy, University of Monastir, Tunisia.

* Corresponding Author: *E-mail: fmartinezr@unal.edu.co

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Summary

Thermodynamic functions Gibbs energy, enthalpy, and entropy of mixing of propranolol hydrochloride in ethanol + water mixtures were evaluated. Mixing quantities were calculated based on fusion calorimetric values obtained from differential scanning calorimetry measurements and equilibrium solubility values reported in the literature for this drug in these cosolvent mixtures. By means of enthalpy-entropy compensation analysis, a non-linear $\Delta_{mix}H^{\circ}$ vs. $\Delta_{mix}G^{\circ}$ plot was obtained indicating different mechanisms involved in the dissolution and mixing of this drug according to mixtures composition. Nevertheless, the molecular and ionic events involved in the dissolution of this drug in this cosolvent system are unclear.

Key words: propranolol hydrochloride, mixing process, cosolvency, ethanol, solution thermodynamics.

Resumen

Estudio termodinámico del proceso de mezcla del bloqueador β-adrenérgico propranolol-HCl en mezclas etanol + agua

En este trabajo se estudiaron las funciones termodinámicas de mezcla de propranolol clorhidrato en mezclas etanol + agua, las cuales fueron calculadas a partir de las propiedades calorimétricas de fusión y de los valores de solubilidad en equilibrio en estas mezclas cosolventes que fueron publicados en la literatura. Mediante análisis de compensación entálpica-entrópica $\Delta_{mix}H^{o}$ vs. $\Delta_{mix}G^{o}$ se obtuvo un gráfico no lineal lo que indica la presencia de diferentes mecanismos implicados en el proceso de disolución según la composición cosolvente. Sin embargo, los eventos moleculares e iónicos involucrados en el proceso de disolución de este fármaco en este sistema cosolvente no son claros.

Palabras clave: propranolol clorhidrato, proceso de mezcla, cosolvencia, etanol, termodinámica de soluciones.

Introduction

Propranolol-HCl (PPN-HCl, Fig. 1) is a non selective β-adrenergic blocker used in the treatment of many disorders including hypertension, angina pectoris, and cardiac disrhythmias (1, 2). Although PPN-HCl is widely used nowadays in therapeutics, its physicochemical information about aqueous solutions is not complete at present. Nevertheless some studies have been done in our research group which include solution thermodynamics in aqueous media for the non-protonated form (3), partitioning thermodynamics in some organic liquid/aqueous media (4), and apparent molar volumes in water at several concentrations and temperatures (5). In this way, temperature-solubility dependence allows us to carry out the respective thermodynamic analysis, which, on the other hand, also permits inside the molecular mechanisms, involved toward the solution and mixing processes (6). In this context, the main objective of this research was to evaluate the effect of the cosolvent composition on the thermodynamics of mixing of PPN-HCl in some ethanol (EtOH) + water cosolvent mixtures (7, 8). This study is based on both the calorimetric properties of fusion obtained by differential scanning calorimetry (DSC) and the van't Hoff treatment of equilibrium solubility values reported in the literature (9).

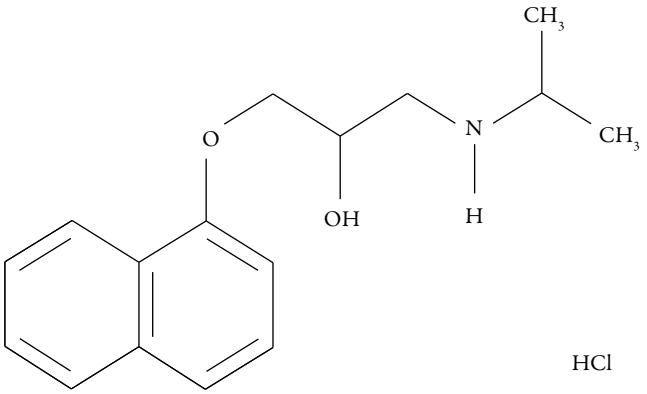

Figure 1. Molecular structure of PPN-HCl. The hydrochloride form is established by protonation of the tertiary amine group.

Materials and methods

Reagents

Propranolol-HCl (M 295.81 g mol^{-1} (*RS*)-1-[(1-Methylethyl)amino]-3-(1-naphthalenyloxy)-2-propanol hydrochloride, CAS [3506-09-0]) used was in agreement with the quality requirements indicated in the American Pharmacopeia, USP (10).

Calorimetric study

Melting point and enthalpy of fusion were determined by DSC studies (DSC 823E Mettler Toledo). Thermal analyses were performed at a heating rate of 10 K min^{-1} in a dynamic nitrogen atmosphere (60 mL min^{-1}). Nearly 1.5 mg of drug was used. The equipment was calibrated using Indium as standard.

Results and discussion

Before to show the results, it is important to consider that this drug has electrolyte behavior, and thus, it dissociates in aqueous solution interacting with the solvent by ion-dipole interactions, among other non covalent interactions; on this way, it also

could acts as a Lewis acid or base, in order to establish hydrogen bonds with proton-acceptor or donor functional groups in the solvents (–OH groups) (9).

Ideal solubility

The ideal solubility of non-electrolyte crystalline solutes in a liquid solvent can be calculated by means of Equation 1:

$$\ln x_{2-\mathrm{id}} = -\frac{\Delta_{\mathrm{fus}} H(T_{\mathrm{fus}} - T)}{R T_{\mathrm{fus}} T} + \left(\frac{\Delta C_{\mathrm{p}}}{R}\right)\left[\frac{(T_{\mathrm{fus}} - T)}{T} + \ln\left(\frac{T}{T_{\mathrm{fus}}}\right)\right] \qquad \text{(Equation 1)}$$

where $x_{2\text{-id}}$ is the ideal solubility of the solute as mole fraction, $\Delta_{\mathrm{fus}}H$ is the molar enthalpy of fusion of the pure solute, T_{fus} is the absolute melting point, T is the absolute solution temperature, R is the gas constant, and ΔC_{p} is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical supercooled liquid form (7, 8). Since ΔC_{p} cannot be easy experimentally determined it is usual assuming that it may be approximated to the entropy of fusion, calculated as $\Delta S_{\mathrm{fus}} = \Delta H_{\mathrm{fus}} / T_{\mathrm{fus}}$ as has been done earlier (7, 8). Although Eq. 1 was developed for non electrolyte compounds, it has also been used to estimate ideal solubilities of some electrolyte drugs (11). Tables 1 and 2 summarize the thermodynamic properties of fusion and the ideal solubilities of this drug as PPN-HCl and its non protonated form, PPN. Table 2 shows that ideal solubilities of PPN-HCl are lower than those reported for molecular PPN (3); as an example at 298.15 K these values are 2.164 x 10^{-2} for PPN-HCl in front to 7.57 x 10^{-2} for molecular PPN. This behavior is similar to those described for sodium naproxen and non dissociate naproxen (7). On the other hand, the experimental equilibrium solubility values for this drug in ethanol + water mixtures have been reported in the literature (9).

Table 1. Thermodynamic properties of fusion of PPN-HCl and PPN.

Drug	T_{fus} / K	$\Delta_{\mathrm{fus}}H$ / kJ mol^{-1}	$\Delta_{\mathrm{fus}}S$ / J mol^{-1} K^{-1}
PPN-HCl	435.7	36.6 (0.4)	84.0 (0.9)
PPN	364.9 [a]	38.75 [a]	106.2

[a] From Scott *et al.* (12).

Thermodynamic quantities of solution

Because the drug considered in this research is an electrolyte compound, it is important to keep in mind that in general terms, it could be stated that a strong electrolyte dissociates according to the expression, $C_{v+}A_{v-} \rightarrow v_+ C^{z+} + v_- A^{z-}$, where v_+ is the number

of cations (C^{z+}) of valence $z+$ and ν_- is the number of anions (A^{z-}) of valence $z-$ (7, 8). If the inter-ionic interactions are not considered, in a first approach the ν value could be ideally assumed as 2 for this drug, and thus this value could be used to calculate the apparent thermodynamic functions of solution (7, 8). In this way, according to van't Hoff analysis, the apparent standard enthalpy change of solution ($\Delta_{soln}H°$) for electrolytes type one-one, is obtained by using the mean harmonic temperature (T_{hm} is 295.4 K in our case) according to Eq. 2 (9), where, R is the universal gas constant.

Table 2. Ideal solubility of PPN-HCl and PPN at several temperatures.

T / K	$100\,x_{2\text{-id}}$	
	PPN-HCl	**PPN**
283.15	1.284 (0.013)	3.92
288.15	1.533 (0.015)	4.90
293.15	1.824 (0.018)	6.10
298.15	2.164 (0.022)	7.57
303.15	2.560 (0.026)	9.37
308.15	3.021 (0.030)	11.54

$$\left(\frac{\partial \ln x_{Drug}}{\partial\left(1/T - 1/T_{hm}\right)}\right)_P = -\frac{\Delta_{soln}H°}{2\cdot R} \qquad \text{(Equation 2)}$$

The apparent standard Gibbs energy change for the solution process ($\Delta_{soln}G°$) of electrolytes type one-one, considering the approach proposed by Krug *et al.* (13), is calculated at mean harmonic temperature by means of,

$$\Delta_{soln}G° = -2\cdot R\cdot T_{hm}\cdot \text{intercept} \qquad \text{(Equation 3)}$$

in which, the intercept used is the one obtained in the analysis by treatment of $\ln x_{Drug}$ as a function of $1/T - 1/T_{hm}$. Finally, the apparent standard entropic change for solution process ($\Delta_{soln}S°$) is obtained from the respective $\Delta_{soln}H°$ and $\Delta_{soln}G°$ values by using:

$$\Delta_{soln}S° = \frac{\left(\Delta_{soln}H° - \Delta_{soln}G°\right)}{T_{hm}} \qquad \text{(Equation 4)}$$

Table 3 summarizes the apparent standard thermodynamic functions for experimental solution process in all EtOH + water cosolvent mixtures. It is found that standard Gibbs energies, apparent enthalpies, and entropies of solution for this drug are positive in all cases, and therefore the dissolution processes are always endothermic and driven by the entropy of solution. With the aim to compare the relative contributions by enthalpy (ζ_H) and by entropy (ζ_{TS}) toward the solution process, equations 5 and 6 were employed, respectively (14).

$$\zeta_H = \frac{|\Delta_{soln} H^\circ|}{|\Delta_{soln} H^\circ| + |T\Delta_{soln} S^\circ|} \quad \text{(Equation 5)}$$

$$\zeta_{TS} = \frac{|T\Delta_{soln} S^\circ|}{|\Delta_{soln} H^\circ| + |T\Delta_{soln} S^\circ|} \quad \text{(Equation 6)}$$

Table 3. Apparent thermodynamic quantities relative to solution process of PPN-HCl in EtOH + water cosolvent mixtures at 295.4 K [a].

μ_{EtOH}	$\Delta_{soln}G^\circ$ / kJ mol^{-1}	$\Delta_{soln}H^\circ$ / kJ mol^{-1}	$\Delta_{soln}S^\circ$ / J mol^{-1} K^{-1}	$T\Delta_{soln}S^\circ$ / kJ mol^{-1}	ζ_H	ζ_{TS}
0.00	24.49 (0.20)	77.6 (0.8)	179.8 (2.3)	53.1 (0.7)	0.594	0.406
0.10	22.93 (0.18)	99.1 (2.3)	257.8 (6.4)	76.2 (1.9)	0.565	0.435
0.20	21.03 (0.17)	91.8 (1.6)	239.5 (4.6)	70.8 (1.4)	0.565	0.435
0.30	19.11 (0.15)	83.4 (1.4)	217.6 (4.2)	64.3 (1.2)	0.565	0.435
0.40	17.33 (0.14)	70.3 (1.0)	179.5 (3.0)	53.0 (0.9)	0.570	0.430
0.50	16.23 (0.13)	60.3 (1.1)	149.1 (3.0)	44.0 (0.9)	0.578	0.422
0.60	16.04 (0.13)	56.4 (1.4)	136.7 (3.5)	40.4 (1.0)	0.583	0.417
0.70	16.24 (0.13)	47.2 (1.1)	104.9 (2.7)	31.0 (0.8)	0.604	0.396
0.80	17.61 (0.14)	43.4 (0.8)	87.4 (1.7)	25.8 (0.5)	0.627	0.373
0.90	19.96 (0.16)	48.4 (1.0)	96.4 (2.1)	28.5 (0.6)	0.630	0.370
1.00	23.57 (0.19)	49.6 (1.1)	88.0 (2.0)	26.0 (0.6)	0.656	0.344
Ideal	9.63 (0.10)	24.8 (0.2)	50.1 (0.6)	15.2 (0.2)	0.620	0.380

[a] From Delgado and Martínez (9).

From Table 3 it follows that the main contributor to standard Gibbs energy of solution process is the enthalpy in particular in EtOH-rich mixtures indicating the relevance of the energetic factor on the dissolution processes of this drug in this cosolvent system.

Thermodynamic quantities of mixing

The solution process may be represented by the following hypothetical stages (7, 8): $Solute_{(Solid)} \rightarrow Solute_{(Liquid)} \rightarrow Solute_{(Solution)}$, where, the respective partial processes toward the solution are solute fusion and mixing at the same temperature (295.4 K), which permits to calculate the partial thermodynamic contributions to overall solution process by means of equations 7 and 8, respectively.

$$\Delta_{soln}H^{\circ} = \Delta_{fus}H^{295.4} + \Delta_{mix}H^{\circ} \qquad \text{(Equation 7)}$$

$$\Delta_{soln}S^{\circ} = \Delta_{fus}S^{295.4} + \Delta_{mix}S^{\circ} \qquad \text{(Equation 8)}$$

where, $\Delta_{fus}H^{295.4}$ and $\Delta_{fus}S^{295.4}$ represent the thermodynamic functions of fusion process at harmonic temperature (295.4 K). The $\Delta_{fus}H^{295.4}$ value was calculated from $\Delta_{fus}H^{T} = \Delta_{fus}H^{MP} - \Delta C_p(T_{fus} - T)$ by using $\Delta_{fus}S^{295.4}$ instead of ΔC_p, obtaining the value of 24.8 kJ mol^{-1}, which is coincident with the enthalpic change for the ideal solution process (Table 3). In contrast, the entropy of fusion at 295.4 K (84.0 J mol^{-1} K^{-1}) is not coincident with the entropic change of the ideal solution process at this temperature (Table 3). In this analysis $\Delta_{soln}S^{\circ\text{-id}}$ (50.1 J mol^{-1} K^{-1}) was used instead of $\Delta_{fus}S^{295.4}$ because the solution process is more adequately considered as the combination of ideal and non-ideal sub-processes (3, 15). Table 4 summarizes the thermodynamic quantities of mixing. Gibbs energy of mixing is positive in all the systems studied apparently indicating non spontaneity on the liquids mixing and the enthalpic contribution predominates in all cases.

It is found that ideal and mixing quantities are positive and therefore it could be concluded that the mixing process is driven by entropy ($\Delta_{mix}H^{\circ} > 0$ and $\Delta_{mix}S^{\circ} > 0$). The net variation in $\Delta_{mix}H^{\circ}$ values results from the contribution of several kinds of interaction. The enthalpy of cavity formation is endothermic because energy must be supplied against the cohesive forces of the solvent. This process decreases solubility. The enthalpy of solute-solvent interaction is exothermic and results mainly from ion-dipole, van der Waals and Lewis acid-base interactions. The energy of cavity formation should be lower as the proportion of EtOH increases because the polarity of the medium decreases, a fact that favors solute-solvent interactions except ion-dipole. Nevertheless, these considerations do not explain the behavior observed in water-rich mixtures where the ion-dipole interactions predominate for this electrolyte drug.

Table 4. Apparent thermodynamic quantities relative to mixing process of PPN-HCl in EtOH + water cosolvent mixtures at 295.4 K.

μ_{EtOH}	$\Delta_{mix}G°$ / kJ mol^{-1}	$\Delta_{mix}H°$ / kJ mol^{-1}	$\Delta_{mix}S°$ / J mol^{-1} K^{-1}	$T\Delta_{mix}S°$ / kJ mol^{-1}	ζ_H	ζ_{TS}
0.00	14.86 (0.22)	52.8 (0.8)	129.7 (2.4)	37.9 (0.7)	0.582	0.418
0.10	13.30 (0.21)	74.3 (2.3)	207.8 (6.4)	61.0 (1.9)	0.549	0.451
0.20	11.40 (0.19)	67.0 (1.6)	189.4 (4.7)	55.6 (1.4)	0.547	0.453
0.30	9.48 (0.18)	58.6 (1.5)	167.5 (4.2)	49.1 (1.2)	0.544	0.456
0.40	7.69 (0.17)	45.5 (1.0)	129.4 (3.0)	37.8 (0.9)	0.546	0.454
0.50	6.60 (0.16)	35.5 (1.1)	99.0 (3.0)	28.9 (0.9)	0.551	0.449
0.60	6.41 (0.16)	31.6 (1.4)	86.6 (3.6)	25.2 (1.1)	0.556	0.444
0.70	6.61 (0.16)	22.4 (1.2)	54.8 (2.8)	15.8 (0.8)	0.586	0.414
0.80	7.98 (0.17)	18.6 (0.8)	37.4 (1.8)	10.7 (0.5)	0.636	0.364
0.90	10.33 (0.19)	23.6 (1.0)	46.3 (2.2)	13.3 (0.6)	0.640	0.360
1.00	13.94 (0.21)	24.8 (1.1)	38.0 (2.1)	10.8 (0.6)	0.696	0.304

Enthalpy-Entropy compensation of mixing

Figure 2 shows fully that PPN-HCl in the EtOH + water cosolvent system present non-linear $\Delta_{mix}H°$ vs. $\Delta_{mix}G°$ compensation with negative slope in the intervals $0.00 \leq \mu_{EtOH} \leq 0.10$ and $0.60 \leq \mu_{EtOH} \leq 0.80$ and positive slope in the other intervals. Accordingly to this graph it follows that the driving function for the mixing processes of this drug is the entropy in the former cases, while in the second ones, the driving function is the enthalpy (16, 17). Nevertheless, the molecular and ionic events involved in the dissolution of this cationic drug in this cosolvent system are unclear.

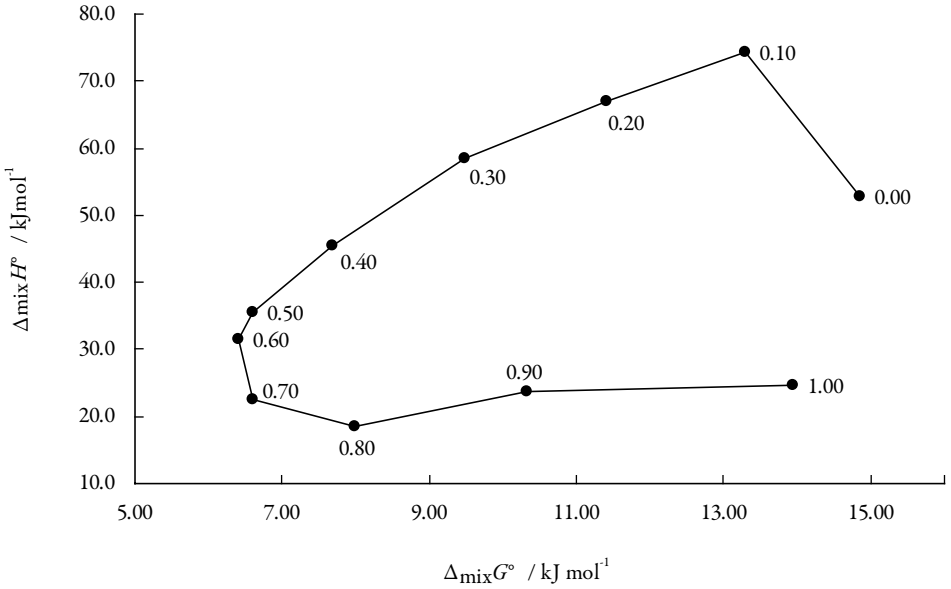

Figure 2. $\Delta_{mix}H°$ vs. $\Delta_{mix}G°$ enthalpy-entropy compensation plot of the mixing process of PPN-HCl in EtOH + water cosolvent mixtures at 295.4 K.

Conclusions

From all topics discussed previously it can be concluded that the mixing process of PPN-HCl in EtOH + water mixtures is variable depending on the cosolvent composition. Non linear enthalpy-entropy compensation was found for this drug in this cosolvent system. Similar behaviors were obtained for other electrolyte drugs studied previously (7, 8). Despite of the thermodynamic treatment made the ionic and molecular events involved in the dissolution processes of this drug are unclear. Ultimately, it can be said that the data presented in this report expand the physicochemical information about electrolyte drugs in aqueous and alcoholic solutions.

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