

# APPARENT MOLAR VOLUMES OF THE BETA-ADRENERGIC BLOCKER PROPRANOLOL-HCl IN AQUEOUS MEDIA AT SEVERAL TEMPERATURES

## VOLÚMENES MOLARES APARENTES DEL AGENTE BETA-BLOQUEADOR PROPRANOLOL-HCl EN MEDIOS ACUOSOS A DIFERENTES TEMPERATURAS

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### ABSTRACT

Propranolol-HCl is a non selective  $\beta$ -adrenergic blocker widely used in the treatment of several cardiovascular diseases; nevertheless, the physicochemical information about its volumetric behavior and other aqueous properties is not complete at present. In this context, densities of aqueous solutions of propranolol-HCl have been measured in this research as a function of concentration (from 0.0500 to 0.2500) mol  $\text{kg}^{-1}$  at several temperatures, i.e. (278.15, 283.15, 288.15, 293.15, 298.15, 303.15, 308.15 and 313.15) K. These values have not been reported earlier in the literature. The apparent molar volumes and partial molar volumes at infinite dilution for the electrolyte drug were calculated. Otherwise, the partial molar volumes at infinite dilution and the partial molar expansibilities for the drug as molecular form were also calculated. The dependence of these properties on temperature is presented. The results are interpreted in terms of several solute-solvent interactions. Ultimately, the reported information can be useful to understand the intermolecular events exhibited by this drug in pharmaceutical and biological systems.

**Keywords:** Propranolol, apparent molar volume, molar expansibility, dissolution, chemical thermodynamics.

### RESUMEN

El Propranolol-HCl es un agente bloqueador  $\beta$ -adrenérgico no selectivo ampliamente usado en el tratamiento de varias enfermedades cardiovasculares; sin embargo, la información fisicoquímica acerca de su comportamiento volumétrico, así como de otras propiedades fisicoquímicas, aún es incompleta en la actualidad. Por esta razón, en este artículo se presentan los valores de densidad de algunas soluciones acuosas de este fármaco en función de la concentración (desde 0,0500 hasta 0,2500) mol  $\text{kg}^{-1}$  a diferentes temperaturas (278,15, 283,15, 288,15, 293,15, 298,15, 303,15, 308,15 y 313,15) K. Estos valores no habían sido reportados previamente en la literatura. Asimismo, se presentan los volúmenes molares aparentes y volúmenes molares parciales a dilución infinita del fármaco como electrolito, y de otro lado, los volúmenes molares parciales a dilución infinita del fármaco molecular y las expansibilidades molares, los cuales fueron calculados a partir de los valores de densidad y composición de las mezclas. Los resultados obtenidos se interpretaron en términos de interacciones soluto-solvente. Finalmente, se tiene que la información

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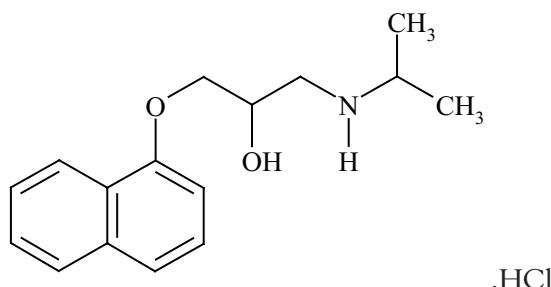
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presentada en este trabajo podría ser utilizada para el entendimiento de algunos eventos moleculares exhibidos por este fármaco en sistemas farmacéuticos y biológicos.

**Palabras clave:** Propranolol, volumen molar aparente, expansibilidad molar, disolución, termodinámica química.

## INTRODUCTION

Propranolol-HCl (PPN-HCl, which molecular structure is presented in figure 1) is a non selective  $\beta$ -adrenergic blocker widely used in the treatment of hypertension, angina pectoris, and cardiac dysrhythmias (1, 2). Although PPN-HCl is widely used nowadays in therapeutics, its physicochemical information about volumetric behavior and other aqueous properties is not complete at present. Furthermore, it is well known that the pharmaceutical and biopharmaceutical behavior of drugs is strongly dependent on their physicochemical properties, especially, those of thermodynamic character (3). Thus, the solution thermodynamics in aqueous media for the molecular form has been presented in the literature (4), and the thermodynamics of the transfer between organic solvents with different hydrogen-bonding capability and aqueous media has also been presented (5). In this context, the study of molar volumes of pharmaceutical relevant compounds has been carried out to facilitate the design process of dosage forms, and for explaining the transfer mechanisms of drugs across biological membranes (6).



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

For these reasons, as a contribution to the generation and systematization of physicochemical information about the aqueous behavior of drugs, the main goal of this study was to evaluate the effect of concentration and temperature on the apparent molar volume of PPN-HCl in water. Taking into

account such purpose, an interpretation in terms of solute-solvent interactions based on the corresponding volumetric behavior was developed.

## MATERIALS AND METHODS

### Chemicals

Propranolol-HCl of USP quality (7) from Shenzhen Sunrising Industry Co., Ltd., China (drug purity near to 0.999 in mass fraction) and distilled water (conductivity  $< 2 \mu\text{S cm}^{-1}$ ) were used in this research.

### Preparation of PPN-HCl aqueous solutions

All PPN-HCl aqueous solutions were prepared by mass in quantities of 30.00 g using a Ohaus Pioneer TM PA214 analytical balance with a sensitivity of  $\pm 0.1$  mg, in drug concentrations from 0.0500 mol kg $^{-1}$  to 0.2500 mol kg $^{-1}$  in order to study nine solutions. This procedure implied an uncertainty value of  $\pm 2 \times 10^{-5}$  in molality.

### Density determination

Density was determined at temperatures of 278.15, 283.15, 288.15, 293.15, 298.15, 303.15, 308.15 and 313.15 K by using a DMA 45 Anton Paar digital density meter connected to a Neslab RTE 10 Digital Plus (Thermo Electron Company) recirculating thermostatic water bath according to a procedure previously described (6). The equipment was calibrated according to the Instruction Manual using air and water at the different temperatures studied (8). Volumes near to 3.0 cm $^3$  were employed in all the density determinations. All volumetric properties were calculated from the experimental density values and solution compositions according to the equations presented earlier (6).

## RESULTS AND DISCUSSION

The experimental densities of PPN-HCl in water at the range of 278.15 to 313.15 K are shown in table 1. The apparent molar volumes ( $\phi_V$ ) were calculated by using equation 1.

$$\phi_V = \frac{M_2}{\rho} + \frac{1000 \cdot (\rho_0 - \rho)}{\rho_0 \cdot \rho \cdot m}$$

**Equation 1.**

In this equation,  $M_2$  is the molecular mass of the solute;  $\rho_0$  and  $\rho$  are the densities of solvent and solution respectively, and  $m$  is the solution concentration expressed as molality.

Table 1 summarizes the results of the apparent molar volumes of PPN-HCl, their molal concentrations and their uncertainties. Uncertainty values were calculated according to the law of propagation of uncertainties (9). It is clear that  $\phi_V$  values decrease as the temperature increases for the same drug concentration. Moreover,  $\phi_V$  values decrease as the drug concentration increases at almost all temperatures except at 278.15 K.

**Table 1.** Density of PPN-HCl aqueous solutions and apparent molar volumes of PPN-HCl at several drug concentrations and temperatures.

| $m / \text{mol kg}^{-1}$ | $\rho / \text{g cm}^{-3}$ | $\phi_V / \text{cm}^3 \text{mol}^{-1}$ | $\sigma(\phi_V) / \text{cm}^3 \text{mol}^{-1}$ | $m / \text{mol kg}^{-1}$ | $\rho / \text{g cm}^{-3}$ | $\phi_V / \text{cm}^3 \text{mol}^{-1}$ | $\sigma(\phi_V) / \text{cm}^3 \text{mol}^{-1}$ |
|--------------------------|---------------------------|--|--|--------------------------|---------------------------|--|--|
| 278.15 K                 |                           |  |  | 298.15 K                 |                           |  |  |
| 0.05000                  | 1.0024                    | 241.2                                  | 2.0  | 0.05000                  | 0.9981                    | 248.1                                  | 2.0  |
| 0.07500                  | 1.0037                    | 241.6                                  | 1.3  | 0.07500                  | 0.9992                    | 249.1                                  | 1.4  |
| 0.10000                  | 1.0049                    | 242.6                                  | 1.0  | 0.10000                  | 1.0004                    | 248.5                                  | 1.0  |
| 0.12500                  | 1.0062                    | 242.3                                  | 0.8  | 0.12500                  | 1.0015                    | 248.8                                  | 0.8  |
| 0.15000                  | 1.0074                    | 242.7                                  | 0.7  | 0.15000                  | 1.0027                    | 248.3                                  | 0.7  |
| 0.17500                  | 1.0086                    | 242.8                                  | 0.6  | 0.17500                  | 1.0038                    | 248.4                                  | 0.6  |
| 0.20000                  | 1.0098                    | 242.9                                  | 0.5  | 0.20000                  | 1.0050                    | 247.9                                  | 0.5  |
| 0.22500                  | 1.0111                    | 242.4                                  | 0.5  | 0.22500                  | 1.0061                    | 247.9                                  | 0.5  |
| 0.25000                  | 1.0122                    | 242.8                                  | 0.4  | 0.25000                  | 1.0072                    | 247.8                                  | 0.4  |
| 283.15 K                 |                           |  |  | 303.15 K                 |                           |  |  |
| 0.05000                  | 1.0016                    | 245.4                                  | 2.0  | 0.05000                  | 0.9964                    | 248.4                                  | 2.0  |
| 0.07500                  | 1.0029                    | 244.4                                  | 1.3  | 0.07500                  | 0.9975                    | 249.5                                  | 1.4  |
| 0.10000                  | 1.0041                    | 244.8                                  | 1.0  | 0.10000                  | 0.9987                    | 248.8                                  | 1.0  |
| 0.12500                  | 1.0053                    | 244.9                                  | 0.8  | 0.12500                  | 0.9998                    | 249.2                                  | 0.8  |
| 0.15000                  | 1.0067                    | 243.5                                  | 0.7  | 0.15000                  | 1.0009                    | 249.3                                  | 0.7  |
| 0.17500                  | 1.0078                    | 244.1                                  | 0.6  | 0.17500                  | 1.0020                    | 249.3                                  | 0.6  |
| 0.20000                  | 1.0091                    | 243.5                                  | 0.5  | 0.20000                  | 1.0032                    | 248.7                                  | 0.5  |
| 0.22500                  | 1.0103                    | 243.5                                  | 0.5  | 0.22500                  | 1.0042                    | 249.1                                  | 0.5  |
| 0.25000                  | 1.0114                    | 243.8                                  | 0.4  | 0.25000                  | 1.0053                    | 249.0                                  | 0.4  |
| 288.15 K                 |                           |  |  | 308.15 K                 |                           |  |  |
| 0.05000                  | 1.0007                    | 245.5                                  | 2.0  | 0.05000                  | 0.9944                    | 252.9                                  | 2.0  |
| 0.07500                  | 1.0019                    | 245.9                                  | 1.3  | 0.07500                  | 0.9955                    | 252.6                                  | 1.4  |
| 0.10000                  | 1.0032                    | 244.9                                  | 1.0  | 0.10000                  | 0.9966                    | 252.3                                  | 1.0  |
| 0.12500                  | 1.0043                    | 245.9                                  | 0.8  | 0.12500                  | 0.9978                    | 251.2                                  | 0.8  |
| 0.15000                  | 1.0055                    | 245.7                                  | 0.7  | 0.15000                  | 0.9989                    | 251.1                                  | 0.7  |
| 0.17500                  | 1.0067                    | 245.5                                  | 0.6  | 0.17500                  | 1.0000                    | 250.9                                  | 0.6  |
| 0.20000                  | 1.0079                    | 245.3                                  | 0.5  | 0.20000                  | 1.0011                    | 250.7                                  | 0.5  |
| 0.22500                  | 1.0091                    | 245.0                                  | 0.5  | 0.22500                  | 1.0023                    | 250.0                                  | 0.5  |
| 0.25000                  | 1.0102                    | 245.2                                  | 0.4  | 0.25000                  | 1.0033                    | 250.2                                  | 0.4  |
| 293.15 K                 |                           |  |  | 313.15 K                 |                           |  |  |
| 0.05000                  | 0.9995                    | 245.8                                  | 2.0  | 0.05000                  | 0.9924                    | 253.3                                  | 2.1  |
| 0.07500                  | 1.0007                    | 246.1                                  | 1.4  | 0.07500                  | 0.9934                    | 254.4                                  | 1.4  |
| 0.10000                  | 1.0018                    | 247.2                                  | 1.0  | 0.10000                  | 0.9946                    | 252.7                                  | 1.0  |
| 0.12500                  | 1.0031                    | 246.1                                  | 0.8  | 0.12500                  | 0.9957                    | 252.5                                  | 0.8  |
| 0.15000                  | 1.0043                    | 245.9                                  | 0.7  | 0.15000                  | 0.9968                    | 252.2                                  | 0.7  |
| 0.17500                  | 1.0054                    | 246.3                                  | 0.6  | 0.17500                  | 0.9979                    | 251.9                                  | 0.6  |
| 0.20000                  | 1.0065                    | 246.6                                  | 0.5  | 0.20000                  | 0.9990                    | 251.6                                  | 0.5  |
| 0.22500                  | 1.0078                    | 245.7                                  | 0.5  | 0.22500                  | 1.0002                    | 250.9                                  | 0.5  |
| 0.25000                  | 1.0089                    | 245.9                                  | 0.4  | 0.25000                  | 1.0013                    | 250.6                                  | 0.4  |

The  $\phi_V$  dependence regarding the drug molal concentration (at all the temperatures studied) was fitted to equations of the following type (10):

$$\phi_V = \phi_V^0 + S_V m^{1/2} \quad \text{Equation 2.}$$

In equation 2,  $\phi_V^0 = \bar{V}_2^0$  is the apparent molar volume at infinite dilution (equal to the partial molar volume at infinite dilution);  $S_V$  is an experimental parameter (related to the water-structure promotion or disruption), and  $m$  is the molality once again. Values of  $\bar{V}_2^0$  (for PPN-HCl) and  $S_V$  were obtained by means of weighted least-squares, and the numerical values together with their uncertainties are shown in table 2.

**Table 2.** Partial molar volumes of PPN-HCl at infinite dilution and the  $S_V$  parameter at several temperatures.

| T / K  | $\bar{V}_2^0$<br>(PPN-HCl) / $\text{cm}^3 \text{mol}^{-1}$ | $\sigma(\bar{V}_2^0)$<br>(PPN-HCl) / $\text{cm}^3 \text{mol}^{-1}$ | $S_V / \text{cm}^3 \text{kg}^{1/2} \text{mol}^{-3/2}$ | $\sigma(S_V)$ / $\text{cm}^3 \text{kg}^{1/2} \text{mol}^{-3/2}$ |
|--------|--|--|---|---|
| 278.15 | 241.4  | 0.7  | 2.9   | 1.5   |
| 283.15 | 246.1  | 0.9  | -5.0  | 2.0   |
| 288.15 | 246.5  | 0.6  | -2.6  | 1.3   |
| 293.15 | 247.3  | 0.9  | -2.8  | 2.0   |
| 298.15 | 250.2  | 0.5  | -4.8  | 1.1   |
| 303.15 | 249.3  | 0.6  | -0.5  | 1.3   |
| 308.15 | 255.1  | 0.6  | -10.2   | 1.4   |
| 313.15 | 257.2  | 0.6  | -13.1   | 1.4   |

Using the principle of volume additivity, the apparent molar volume at infinite dilution of PPN-HCl can be separated into individual ionic contributions according to the following equation (11, 12):

$$\bar{V}_{\text{PPN-HCl}}^0 = \bar{V}_{\text{PPN}}^0 + \bar{V}_{\text{HCl}}^0 \quad \text{Equation 3.}$$

In such equation,  $\bar{V}_{\text{PPN}}^0$  and  $\bar{V}_{\text{HCl}}^0$  are the partial molar volumes of free base and HCl, respectively.

Data of  $\bar{V}_{\text{HCl}}^0$  were taken from the literature (13).

Values of  $\bar{V}_{\text{PPN}}^0$  (for the molecular form) obtained from equation 3 at each temperature studied are shown in table 3.  $\bar{V}_{\text{PPN}}^0$  values calculated from the literature data are also shown in this table.

**Table 3.** Partial molar volumes of PPN at infinite dilution at several temperatures.

| T / K  | $\bar{V}_2^0$<br>(PPN) / $\text{cm}^3 \text{mol}^{-1}$ | $\sigma(\bar{V}_2^0)$<br>(PPN) / $\text{cm}^3 \text{mol}^{-1}$ | $\bar{V}_2^0$<br>(PPN) / $\text{cm}^3 \text{mol}^{-1}$ |
|--------|--|--|--|
| 278.15 | 225.1  | 0.7  |  |
| 283.15 | 229.4  | 0.9  |  |
| 288.15 | 229.4  | 0.6  | 239.8 <sup>a</sup>                                     |
| 293.15 | 229.8  | 0.9  | 227.34 <sup>b</sup> ; 240.0 <sup>a</sup>               |
| 298.15 | 232.5  | 0.5  | 240.0 <sup>a</sup>                                     |
| 303.15 | 231.4  | 0.6  | 239.9 <sup>a</sup>                                     |
| 308.15 | 237.1  | 0.6  | 231.09 <sup>c</sup> ; 240.7 <sup>a</sup>               |
| 313.15 | 239.1  | 0.6  | 244.3 <sup>a</sup>                                     |

<sup>a</sup> Reported by Russo *et al.*, 2004 (14)

<sup>b</sup> Reported by Iqbal and Verral, 1989 (15)

<sup>c</sup> Reported by Iqbal *et al.*, 1994 (12)

The variation of  $\bar{V}_{\text{PPN}}^0$  with regard to the temperature was adjusted by the method of weighted least squares according to the following linear empiric equation (with  $r^2$  equal to 0.87):

$$\bar{V}_{\text{PPN}}^0 = 129(\pm 9) + 0.346(\pm 0.029) \cdot T \quad \text{Equation 4.}$$

In this equation,  $T$  is the temperature in Kelvin.

Figure 2 shows the dependence of  $\bar{V}_{\text{PPN}}^0$  on  $T$ . Furthermore, the partial molar expansibility at infinite dilution ( $E_\phi^0$ ) can be calculated from Equation 4 by differentiating it according to the temperature as follows:  $E_\phi^0 = \partial \bar{V}_{\text{PPN}}^0 / \partial T$ .

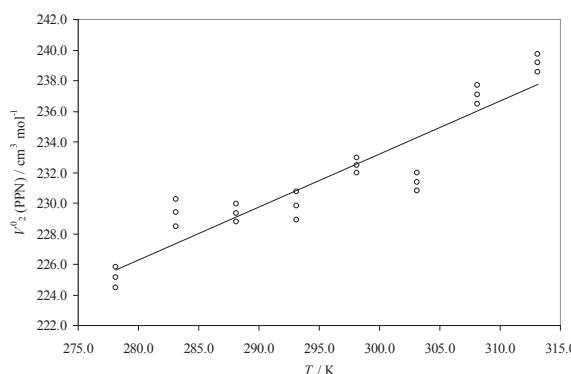
The value of  $E_\phi^0$  is  $0.346 \pm 0.029 \text{ cm}^3 \text{mol}^{-1} \text{K}^{-1}$ .

According to table 3, the data reported by Russo *et al.* (14) show significant differences in  $\bar{V}_{\text{PPN}}^0$  compared with the data obtained in this study. However, significant similarity was found with the  $\bar{V}_{\text{PPN}}^0$  values reported by Iqbal *et al.*, 1994, 1989 (12, 15) at 298.15 and 308.15 K. Nevertheless, we cannot explain the differences found between data reported in this study and the one of Iqbal *et al.*, 1994, 1989 (12, 15) regarding the data reported by Russo *et al.*, 2004 (14).

The sign of the  $S_V$  parameter in equation 2 can be associated with the influence of the solute upon water. This structural influence can be described in terms of structure promotion or structure-breaking effects of the solute on the surrounding water medium (16, 17). Negative  $S_V$  values were found for some solutes such as tetraalkylammonium salts, which are typical ionic surfactants, characterized by their water-structure promotion effect (17-20). In this type of solutes, the hydrophobic effect becomes dominant compared with the hydrophilic effect;

therefore, solvation around of the ionic moiety decreases. According to table 3, the  $S_V$  value is negative for all temperatures, except at 278.15 K. These observations can be interpreted in terms of the structure promotion effect of PPN on the water-structure at temperatures above 278.15 K.

In figure 2, it can be seen the tendency in which  $\bar{V}_{PPN}^0$  increases when the temperature increases. This result could be attributed to the breakage of the solvent structure, which causes an increase in the structural molar volume (19). As it was already stated,  $E_\phi^0$  is positive and this can be explained according to the formation of “clathrate-like” structures as described by Wen and Saito, 1964 (17). Thus, when the concentration of PPN-HCl increases, the water cluster surrounding the ions tends to join their neighbors and form flickering cages, forcing the ions to get inside these cages. If these structures are heated, they would breakdown, leading to the expansion of the complete system (20).



**Figure 2.** Partial molar volume of PPN at infinite dilution as a function of temperature.

## CONCLUSION

From all previously discussed topics, it can be concluded that the volumetric behavior of PPN-HCl in aqueous media is dependent on both concentration and temperature. Based on the negative sign of the  $S_V$  term obtained, it can be proposed that this drug acts as a water-structure promoter due to hydrophobic effect around its non-polar moieties. Ultimately, the data presented in this report fulfills the purpose of expanding the physicochemical information about electrolyte drugs in aqueous solutions.

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