# Solubility of Valsartan in Different Organic Solvents and Ethanol + Water Binary Mixtures from (278.15 to 313.15) K

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The solubility of valsartan in pure methyl acetate, *n*-butyl acetate, acetonitrile, *N*,*N*-dimethylformamide, dichloromethane, chloroform, and ethanol + water binary mixtures was measured by a synthetic method over the temperature range (278.15 to 313.15) K at atmospheric pressure. The results show that the solubility of valsartan increases with increasing temperature in all six pure solvents and ethanol + water binary mixtures, and it increases with increasing mole fraction of ethanol in the binary mixtures. The experimental data were correlated using the modified Apelblat model, and the agreement with the experimental data was very good.

## Introduction

Valsartan (CAS No. 137862-53-4, Figure 1), with the chemical name (*S*)-*N*-(1-carboxy-2-methyl-1-yl)-*N*-pentanoyl-*N*-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl methyl]-amine, is an orally active specific angiotensin II antagonist acting on AT1 receptor. Valsartan with high pharmaceutical activity is prescribed for the treatment of hypertension.[1]

In addition, several crystal forms of valsartan can be obtained when different solvents and solvent mixtures were used in the crystallization process.[2] So the solubility of valsartan in different solvents and solvent mixtures is critical for controlling and designing the refining process. However, no experimental solubility data of valsartan in different pure solvents and solvent mixtures were found in the literature.

In this work, the solubility data of valsartan in pure methyl acetate, *n*-butyl acetate, acetonitrile, *N*,*N*-dimethylformamide, dichloromethane, chloroform, and ethanol + water binary mixtures over the temperature range (278.15 to 313.15) K at atmospheric pressure were experimentally determined using a synthetic method and a laser monitoring observation technique.

## Experimental Section

***Materials.*** The valsartan with a mass fraction purity of 0.95 was supplied by Huahai Pharmaceutical Co. Ltd. of China. After refining treatment, the valsartan with mass fraction purity of 0.99 (detected by HPLC) can be obtained. Analytical-grade organic solvents with mass fraction higher than 0.995 and distilled−deionized water were purchased from Tianjin Kewei Chemical Reagent Co. Ltd. of China.

***Apparatus and Procedures.*** The solubility of valsartan in six pure solvents and ethanol + water binary mixtures was measured with a synthetic method.[3,4] The apparatus for the measurement is similar to that described in the literature.[5] A cylindrical double-jacketed glass vessel with a working volume of 100 $cm^3$ was used as the equilibrium cell. A magnetic bar was used for continuous stirring. The temperature, with an uncertainty of ± 0.05 K, was controlled by circulating water through the outer jacket. A condenser was used to prevent solvent evaporation. A laser monitoring system which consisted of a laser generator, a photoelectric convertor, and a light intensity display was used to determine the disappearance of the last crystal in the mixtures. An analytical balance (Metler Toledo AB204-N, Switzerland) with uncertainty of ± 0.1 mg was used for the mass measurements.

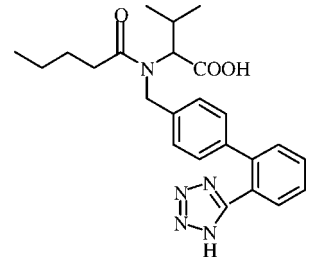


**Figure 1.** Structure of valsartan.

At the beginning, a predetermined known mass of valsartan and pure solvent were added to the jacketed vessel. The amount of solute was a little in excess. The contents of the vessel were stirred continuously for 30 min at a fixed temperature. Then, a known mass of additional solvent was introduced into the vessel by an injector. When the last solute just disappeared, the penetrated light intensity reached its maximum value. The mass of the solvent consumed in the experiment would be recorded. Together with the mass of solute, the solubility would be obtained. The saturated mole fraction of the valsartan $x_A$ in different pure solvents and ethanol + water binary mixtures can be calculated by the following eq 1, and the composition of the binary ethanol + water solvent mixtures $x_1$ is defined as eq 2

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \quad (1)$$

$$x_1 = \frac{m_B/M_B}{m_B/M_B + m_C/M_C} \quad (2)$$

In the ethanol + water binary mixtures system, $m_A$, $m_B$, and $m_C$ represented the mass of valsartan, ethanol, and water. $M_A$, $M_B$, and $M_C$ were the molecular weight of valsartan, ethanol, and water, respectively. In the pure solvent system, $m_A$ and $m_B$ represented the mass of solute and solvent; $M_A$ and $M_B$ are the molecular weight of solute and solvent; and $m_C = 0$. All the

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**Table 1. Solubility of Valsartan in Methyl Acetate, *n*-Butyl Acetate, *N*,*N*-Dimethylformamide, Acetonitrile, Dichloromethane, and Chloroform from (278.15 to 313.15) K**

| $T$/K | $10^4 x_A$ | $10^2(x_A^{exp} - x_A^{cal})/x_A$ | $T$/K | $10^4 x_A$ | $10^2(x_A^{exp} - x_A^{cal})/x_A$ |
|---|---|---|---|---|---|
| Methyl Acetate | | | *n*-Butyl Acetate | | |
| 278.15 | 30.75 | −0.21 | 278.15 | 14.9 | 6.78 |
| 283.15 | 44.6 | 1.71 | 283.15 | 20.35 | 5.21 |
| 288.15 | 61.0 | −0.87 | 288.15 | 27.3 | 3.00 |
| 293.15 | 85.7 | 0.22 | 293.15 | 36.7 | 1.92 |
| 298.15 | 118.6 | 0.72 | 298.15 | 47.3 | −2.47 |
| 303.15 | 158.6 | −1.13 | 303.15 | 64.0 | −0.94 |
| 308.15 | 217.3 | 0.34 | 308.15 | 83.05 | −2.96 |
| 313.15 | 289.7 | 0.02 | 313.15 | 114.2 | 1.72 |
| *N*,*N*-Dimethylformamide | | | Acetonitrile | | |
| 278.15 | 68.7 | 4.21 | 278.15 | 39.6 | 1.08 |
| 283.15 | 86.2 | −1.67 | 283.15 | 54.2 | −2.03 |
| 288.15 | 115.3 | −0.42 | 288.15 | 76.2 | −1.30 |
| 293.15 | 154.7 | 1.88 | 293.15 | 107.3 | 0.81 |
| 298.15 | 196.3 | −0.49 | 298.15 | 145.5 | 0.10 |
| 303.15 | 253.0 | −0.58 | 303.15 | 197.0 | 0.24 |
| 308.15 | 324.5 | −0.41 | 308.15 | 263.5 | 0.13 |
| 313.15 | 416.5 | 0.50 | 313.15 | 348.8 | −0.11 |
| Dichloromethane | | | Chloroform | | |
| 278.15 | 8.73 | 2.62 | 278.15 | 5.9 | −4.78 |
| 283.15 | 12.8 | 1.53 | 283.15 | 10.8 | 5.91 |
| 288.15 | 19.0 | 3.27 | 288.15 | 15.4 | −7.14 |
| 293.15 | 26.0 | −1.61 | 293.15 | 25.6 | −2.25 |
| 298.15 | 38.1 | 1.01 | 298.15 | 42.4 | 3.02 |
| 303.15 | 52.4 | −1.59 | 303.15 | 62.75 | −1.27 |
| 308.15 | 74.3 | 0.01 | 308.15 | 97.8 | 0.78 |
| 313.15 | 103.0 | 0.21 | 313.15 | 145.6 | −0.20 |

**Table 2. Solubility of Valsartan in Ethanol (1) + Water (2) Binary Mixtures from (278.15 to 313.15) K**

| $T$/K | $10^4 x_A$ | $10^2(x_A^{exp} - x_A^{cal})/x_A$ | $T$/K | $10^4 x_A$ | $10^2(x_A^{exp} - x_A^{cal})/x_A$ |
|---|---|---|---|---|---|
| $x_1 = 0.6991$ | | | $x_1 = 0.6006$ | | |
| 278.15 | 30.0 | −6.58 | 278.15 | 17.4 | −2.04 |
| 283.15 | 48.0 | −3.41 | 283.15 | 26.3 | 0.59 |
| 288.15 | 78.5 | 3.45 | 288.15 | 36.5 | −3.92 |
| 293.15 | 113.6 | −0.48 | 293.15 | 55.4 | 1.74 |
| 298.15 | 169.9 | 0.15 | 298.15 | 77.8 | 0.89 |
| 303.15 | 248.4 | −0.20 | 303.15 | 107.6 | −0.38 |
| 308.15 | 361.8 | 0.23 | 308.15 | 149.9 | 0.10 |
| 313.15 | 517.2 | −0.07 | 313.15 | 205.5 | −0.05 |
| $x_1 = 0.4992$ | | | $x_1 = 0.4000$ | | |
| 278.15 | 13.8 | 1.20 | 278.15 | 10.5 | −4.73 |
| 283.15 | 20.8 | 4.88 | 283.15 | 16.35 | 2.46 |
| 288.15 | 27.9 | −1.97 | 288.15 | 22.7 | −0.97 |
| 293.15 | 40.3 | −0.26 | 293.15 | 32.25 | −0.98 |
| 298.15 | 57.0 | 0.34 | 298.15 | 46.1 | 0.69 |
| 303.15 | 78.8 | −0.23 | 303.15 | 63.65 | 0.17 |
| 308.15 | 108.5 | −0.21 | 308.15 | 87.6 | 0.21 |
| 313.15 | 148.8 | 0.25 | 313.15 | 118.8 | −0.16 |
| $x_1 = 0.2991$ | | | $x_1 = 0.1998$ | | |
| 278.15 | 8.3 | −5.69 | 278.15 | 0.505 | −2.32 |
| 283.15 | 13.0 | −0.47 | 283.15 | 1.0 | 4.90 |
| 288.15 | 19.3 | 0.63 | 288.15 | 1.7 | −3.74 |
| 293.15 | 27.9 | 0.67 | 293.15 | 3.1 | 1.65 |
| 298.15 | 39.3 | −0.53 | 298.15 | 5.1 | −4.16 |
| 303.15 | 56.05 | 0.40 | 303.15 | 9.2 | −0.26 |
| 308.15 | 78.1 | 0.11 | 308.15 | 15.9 | 1.43 |
| 313.15 | 107.7 | −0.11 | 313.15 | 26.3 | −0.36 |

experiments were repeated three times, and the solubility data were the average of experimental results. Considering other factors, the uncertainty of experimental solubility values is estimated to be 0.5 %.

## Results and Discussion

The solubility data of valsartan in pure methyl acetate, *n*-butyl acetate, acetonitrile, *N*,*N*-dimethylformamide, dichloromethane, and chloroform at the different temperatures were listed in Table 1 and shown in Figure 2, and the solubility data of valsartan in binary ethanol + water mixtures were listed in Table 2 and shown in Figure 3.

From Table 1 and Figure 2, it can be seen that within the temperature range of the measurements the solubility of valsartan increased with an increase in temperature in all six pure solvents. Table 2 and Figure 3 have shown that the solubility of valsartan in ethanol + water binary mixtures increased with the increasing temperature and the mole fraction of ethanol. Water was used as antisolvent in the ethanol−water mixed solvent dilution crystallization process. As valsartan is not dissolved in aqueous solution, water may be added into other solvent systems to improve the yield.

It is known that the solvent used in the crystallization process determines the crystal form of the product. To obtain the required crystal form of valsartan, different solvents would be used. According to the dissolution characteristics of valsartan in different solvents, different crystallization methods will be established. From Figure 2, it can be seen that the solubility of valsartan obviously varied with the temperature change in

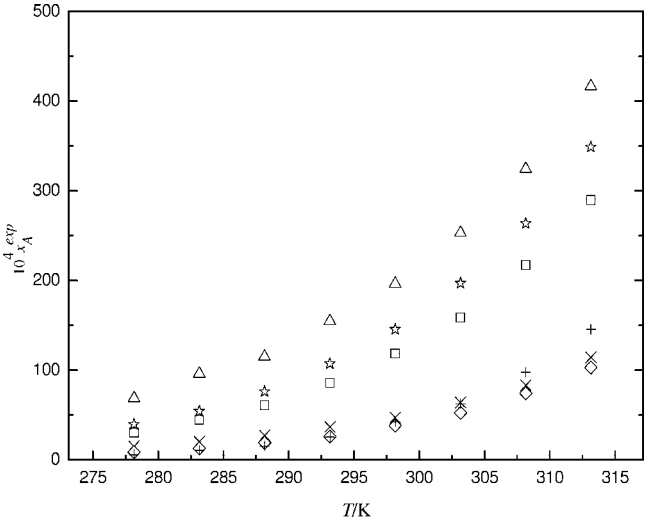


**Figure 2.** Experimental mole fraction solubility of valsartan in different solvents: □, Methyl acetate; ×, *n*-butyl acetate; △, *N*,*N*-dimethylformamide; ☆, acetonitrile; ◇, dichloromethane; +, chloroform.

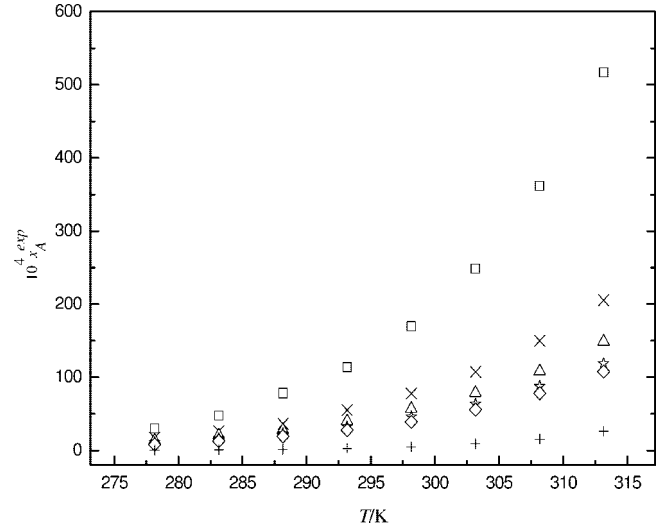


**Figure 3.** Experimental mole fraction solubility of valsartan in ethanol (1) + water (2) binary mixtures: □, $x_1 = 0.6991$; ×, $x_1 = 0.6006$; △, $x_1 = 0.4992$; ☆, $x_1 = 0.4000$; ◇, $x_1 = 0.2991$; +, $x_1 = 0.1998$.

**Table 3. Parameters of the Modified Apelblat Equation for Valsartan in Different Pure Solvents**

| solvent | *A* | *B* | *C* | $10^4$rmsd |
|---|---|---|---|---|
| methyl acetate | 4.94 | −4758.9 | 2.77 | 0.82 |
| *n*-butyl acetate | 1.50 | −4322.4 | 2.96 | 1.37 |
| *N*,*N*-dimethylformamide | −4.91 | −3453.7 | 3.82 | 1.88 |
| acetonitrile | 15.00 | −5079.1 | 1.23 | 0.68 |
| dichloromethane | 2.565 | −5236.8 | 3.27 | 0.44 |
| chloroform | 18.22 | −7343.1 | 1.78 | 0.79 |

**Table 4. Parameters of the Modified Apelblat Equation for Valsartan in Different Composition of Ethanol (1) + Water (2) Binary Mixtures**

| composition | *A* | *B* | *C* | $10^4$rmsd |
|---|---|---|---|---|
| $x_1 = 0.6991$ | 16.94 | −6422.7 | 1.71 | 1.38 |
| $x_1 = 0.6006$ | 14.2 | −5623.2 | 1.58 | 0.69 |
| $x_1 = 0.4992$ | −5.42 | −4639.2 | 4.39 | 0.45 |
| $x_1 = 0.4000$ | 15.52 | −5573.9 | 1.23 | 0.30 |
| $x_1 = 0.2991$ | 16.2 | −5861.5 | 1.25 | 0.22 |
| $x_1 = 0.1998$ | −52.30 | −5957.8 | 12.98 | 0.12 |

methyl acetate, *n*-butyl acetate, acetonitrile, *N*,*N*-dimethylformamide, dichloromethane, and chloroform, so the cooling crystallization is a good choice. However, the solubility of valsartan in *N*,*N*-dimethylformamide at 278.15 K is still large. To raise the refining yield, lower temperature is needed, but the increasing operation cost is incurred too. Adding an amount of water into the mother liquor may be an effective method.

The temperature dependence solubility of valsartan was correlated by the following semiempirical eq 3.[6−8]

$$\ln(10^4 x_A) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \quad (3)$$

where $x_A$ is the mole fraction solubility of valsartan; $T$ is the absolute temperature; and $A$, $B$, and $C$ are empirical constants. The correlated values of $A$, $B$, and $C$ of different pure solvents and ethanol + water binary mixtures were listed in Table 3 and Table 4.

The root-mean-square deviation (rmsd) is defined as follows:

$$\mathrm{RMSD} = \sqrt{\frac{\sum_{i=1}^{N} (x_A^{exp} - x_A^{cal})^2}{N}} \quad (4)$$

where $N$ is the number of experimental points, and $x_A^{exp}$ and $x_A^{cal}$represent the experimental and calculated values of the solubility, respectively. The rmsd of different pure solvents and ethanol + water binary mixtures were also listed in Table 3 and Table 4.

## Conclusion

(1) The solubility of valsartan increased with an increase of temperature in the pure methyl acetate, *n*-butyl acetate, acetonitrile, *N*,*N*-dimethylformamide, dichloromethane, chloroform, and ethanol + water binary mixtures.

(2) The solubility of valsartan in ethanol + water binary mixtures increased with the increasing mole fraction of ethanol.

(3) The water can be used as an effective antisolvent in the crystallization process.

(4) The calculated solubility data by the semiempirical equation are in good agreement with the experimental values.

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