Solubility of Valsartan in Ethyl Acetate + Hexane Binary Mixtures from (278.15 to 313.15) K

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The solubility of valsartan in ethyl acetate + hexane binary mixtures was measured by a synthetic method over the temperature range from (278.15 to 313.15) K at atmosphere pressure. The results show that the solubility of valsartan increases with increasing temperature and the increasing mole fraction of ethyl acetate of 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]

Valsartan was extracted from the reaction mixture by ethyl acetate at the end of synthesis process.[2] Therefore, the ethyl acetate was used as the preferred solvent for the recrystallization of valsartan. However, it has been observed that the crystallization of valsartan using ethyl acetate results in low yield, slow filtration, and prolonged drying. The hexane can be used as the proper antisolvent to minimize and eliminate the above problems.[3] The solubility of valsartan in the ethyl acetate + hexane binary mixtures is the crucial data for designing and controlling the dilution crystallization process. However, no experimental solubility data of valsartan in the ethyl acetate + hexane binary mixtures were found in the literature.

In this work, the solubility data of valsartan in the ethyl acetate + hexane binary mixtures at temperatures ranging from (278.15 to 313.15) K under 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 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 of China.

Apparatus and Procedures. The solubility of valsartan in ethyl acetate + hexane binary mixtures was measured with a synthetic method.[4−7] The apparatus for the measurement is shown in Figure 2, which is similar to that described in the literature.[8] 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 that 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 an uncertainty of ± 0.1 mg was used for the mass measurements.

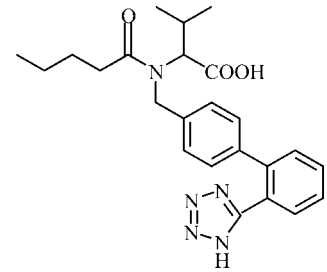

Figure 1. Structure of valsartan.

At the beginning, a predetermined known mass of valsartan and pure solvent were added to the jacketed vessel. The amount of solute was slightly in excess. The contents of the vessel were continuously stirred for 30 min at a fixed temperature. Then, a known mass about 50 mg of additional solvent was introduced to 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 ethyl acetate + hexane binary mixtures can be calculated by the following eq 1; the composition of the binary ethyl acetate + hexane 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 ethyl acetate + hexane binary mixtures system, m_A, m_B, and m_C represent the mass of valsartan, ethyl acetate, and

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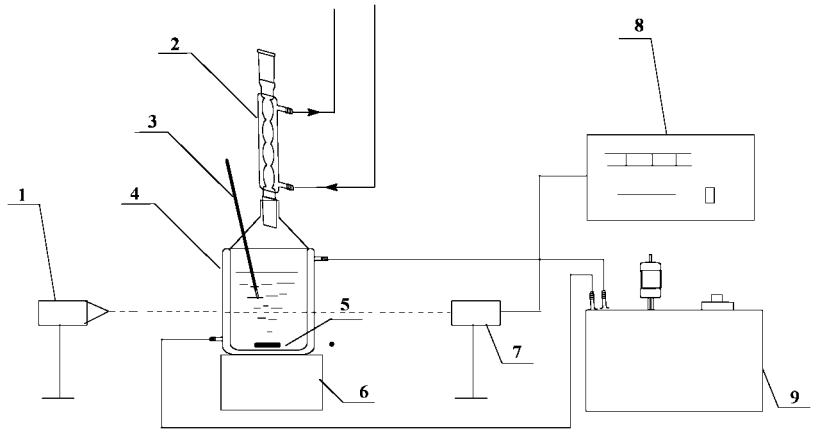

Figure 2. Schematic setup for the solubility determination: 1, laser generator; 2, condenser; 3, thermometer; 4, equilibrium vessel; 5, stir bar; 6, magnetic stirrer; 7, photoelectric convertor; 8, digital display; 9, thermostat.

hexane. M_A, M_B, and M_C are the molecular weights of valsartan, ethyl acetate, and hexane, respectively. All of the 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 ethyl acetate + hexane binary mixtures at the different temperature are listed in Table 1 and are shown in Figure 3. From Table 1 and Figure 3, it can be seen that within the temperature range of the measurements, the solubility of valsartan increased with increasing temperature and increasing mole fraction of ethyl acetate.

In the crystallization process of valsartan by pure ethyl acetate, for the strong molecular interaction, the valsartan forms the sticky swollen gel, which leads to slow filtration and prolonged drying. Moreover, the wide metastable zone of valsartan causes the long operation cycle and low yield. To raise the refining yield, lower temperature is needed, but the increasing operation cost is incurred, too. As the valsartan is undissolved in hexane, the hexane can be used as antisolvent in the isolation process. According to the solubility data of valsartan in the ethyl acetate + hexane binary mixtures, the operation parameters of dilution crystallization can be determined.

The temperature dependence solubility of valsartan was correlated by the following semiempirical eq 3[9−11]

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

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 ethyl acetate + hexane binary mixtures are listed in Table 2.

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

$$\mathrm{rmsd} = \sqrt{\frac{\sum_{i=1}^{N}(x_A^{\mathrm{exptl}} - x_A^{\mathrm{calcd}})^2}{N}} \qquad (4)$$

where N is the number of experimental points and x_A^{exptl} and x_A^{exptl} represent the experimental and calculated values of the solubility, respectively. The rmsd values of ethyl acetate + hexane binary mixtures are also listed in Table 2.

Table 1. Solubility of Valsartan in Ethyl Acetate (1) + Hexane (2) Binary Mixtures from (278.15 to 313.15) K

T/K	$10^4 x_A$	$10^2(x_A^{\mathrm{exptl}} - x_A^{\mathrm{calcd}})/x_A$	T/K	$10^4 x_A$	$10^2(x_A^{\mathrm{exptl}} - x_A^{\mathrm{calcd}})/x_A$
	$x_1 = 1.0000$			$x_1 = 0.9081$	
278.15	24.7	3.83	278.15	16.5	5.65
283.15	33.4	2.05	283.15	23.6	7.61
288.15	44.3	−0.97	288.15	30.7	0.88
293.15	59.6	−1.40	293.15	40.6	−2.99
298.15	80.4	−0.63	298.15	55.7	−2.37
303.15	108.0	0.57	303.15	77.4	0.48
308.15	141.4	0.05	308.15	103.0	−0.16
313.15	184.7	0.06	313.15	137.3	0.31
	$x_1 = 0.8726$			$x_1 = 0.8547$	
278.15	13.2	3.38	278.15	11.7	1.31
283.15	18.5	2.01	283.15	16.6	1.10
288.15	26.7	4.54	288.15	23.6	1.47
293.15	35.2	−0.86	293.15	33.1	1.73
298.15	47.7	−2.52	298.15	44.1	−2.02
303.15	66.3	−0.70	303.15	61.6	−0.18
308.15	90.5	0.32	308.15	83.6	−0.21
313.15	121.1	0.22	313.15	112.9	0.25
	$x_1 = 0.7953$			$x_1 = 0.7455$	
278.15	9.6	2.38	278.15	8.4	2.56
283.15	13.4	2.17	283.15	11.5	4.53
288.15	18.7	3.30	288.15	14.4	−2.34
293.15	25.4	2.90	293.15	19.9	1.86
298.15	32.4	−3.22	298.15	25.2	−1.94
303.15	43.9	−2.64	303.15	33.4	−0.47
308.15	60.9	1.36	308.15	43.6	−0.11
313.15	79.6	0.19	313.15	56.6	0.41
	$x_1 = 0.6969$			$x_1 = 0.6624$	
278.15	7.6	0.34	278.15	6.4	0.06
283.15	9.8	0.45	283.15	8.3	0.05
288.15	12.3	−1.65	288.15	10.7	1.35
293.15	16.0	−0.17	293.15	13.1	−2.22
298.15	20.5	0.57	298.15	17.2	1.12
303.15	25.8	0.22	303.15	21.3	−0.88
308.15	32.2	−0.66	308.15	27.0	0.06
313.15	40.6	0.26	313.15	33.8	−0.09
	$x_1 = 0.5967$			$x_1 = 0.4944$	
278.15	5.0	−0.01	278.15	3.2	3.44
283.15	6.4	0.84	283.15	4.0	0.30
288.15	8.0	−0.44	288.15	5.2	1.32
293.15	10.3	0.90	293.15	6.6	0.25
298.15	12.9	0.12	298.15	8.2	−2.71
303.15	16.1	−0.42	303.15	10.8	0.54
308.15	20.3	−0.19	308.15	13.9	1.01
313.15	25.5	0.09	313.15	17.4	−0.13

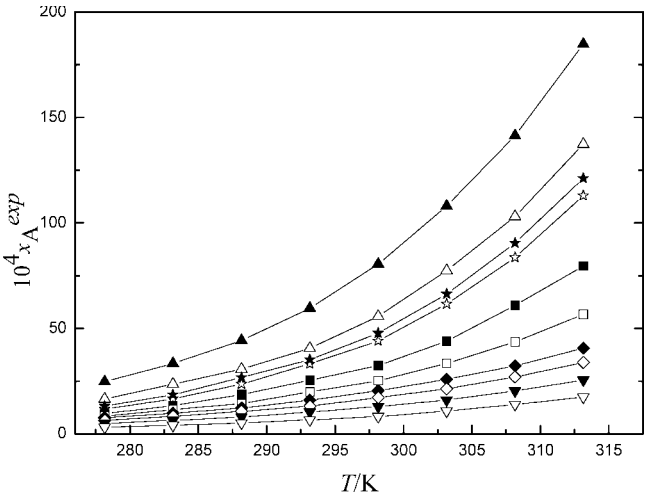

Figure 3. Experimental mole fraction solubility of valsartan in ethyl acetate (1) + hexane (2) binary mixtures: ▲, $x_1 = 1.0000$; △, $x_1 = 0.9081$; ★, $x_1 = 0.8726$; ☆, $x_1 = 0.8547$; ■, $x_1 = 0.7953$; □, $x_1 = 0.7455$; ◆, $x_1 = 0.6969$; ◇, $x_1 = 0.6624$; ▼, $x_1 = 0.5967$; ▽, $x_1 = 0.4944$.

Table 2. Parameters of the Modified Apelblat Equation for Valsartan in Different Compositions of Ethyl Acetate (1) + Hexane (2) Binary Mixtures

composition	*A*	*B*	*C*	10^4rmsd
$x_1 = 1.0000$	−1.84	−4071.1	3.49	0.60
$x_1 = 0.9081$	1.37	−4497.0	3.12	0.98
$x_1 = 0.8726$	1.37	−4660.6	3.19	0.68
$x_1 = 0.8547$	0.71	−4698.7	3.31	0.42
$x_1 = 0.7953$	−16.22	−3660.7	5.62	0.72
$x_1 = 0.7455$	−32.08	−2538.3	7.69	0.33
$x_1 = 0.6969$	−47.67	−1332.8	9.68	0.12
$x_1 = 0.6624$	−81.38	197.7	14.66	0.15
$x_1 = 0.5967$	−114.36	1712.7	19.51	0.05
$x_1 = 0.4944$	−114.49	1476.7	19.60	0.11

Conclusions

(1) The solubility of valsartan increased with an increase in temperature and the increasing mole fraction of ethyl acetate in the binary mixtures. (2) The hexane can be used as an effective antisolvent in the valsartan crystallization process using ethyl acetate. (3) The calculated solubility data by the semiempirical equation are in good agreement with the experimental values.

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