Solubility of Losartan Potassium in Different Pure Solvents from (293.15 to 343.15) K

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The solubility of 2-butyl-4-chloro-1-[[2′-tetrazol-5-yl)-biphenyl]-4-yl]methyl-5-(hydroxymethyl) imidazole potassium in pure methanol, ethanol, 1-propanol, 2-propanol, 1-pentanol, ethyl acetate, butyl acetate, and cyclohexane was measured by a synthetic method over the temperature range from (293.15 to 343.15) K under atmospheric pressure. The experimental data were correlated by the modified Apelblat model. The results show that the solubility of losartan potassium increases with the increasing temperature in pure methanol, ethanol, 1-propanol, and 2-propanol and decreases with the increasing temperature in 1-pentanol. It is also found that losartan potassium is sparingly soluble in ethyl acetate, butyl acetate, and cyclohexane, and the solubility in these three solvents varys little with the temperature.

Introduction

Losartan potassium is the popular name of 2-butyl-4-chloro-1-[[2′-tetrazol-5-yl)-biphenyl]-4-yl]methyl-5- (hydroxymethyl) imidazole potassium (CAS RN 124750-99-8), whose molecular structure is shown in Figure 1. It is an antagonist for the angiotensin II receptor and is widely used for treating hypertension and congestive heart failure.[1,2] To purify losartan potassium, its solubility in different solvents is needed. However, it was found that no experimental solubility data of losartan potassium were available in the literature.

In this work, the solubility of losartan potassium in pure methanol, ethanol, 1-propanol, 2-propanol, 1-pentanol, ethyl acetate, butyl acetate, and cyclohexane over the temperature range from (293.15 to 343.15) K under atmospheric pressure was experimentally determined using the synthetic method and a laser monitoring observation technique.

Experimental Section

Materials. The crude losartan potassium with a mass fraction purity of 0.96 was supplied by Huahai Pharmaceutical Co., Ltd. of China and was purified by recrystallization.[3] The crystalline losartan potassium thus obtained had a mass fraction purity of 0.995. Analytical-grade organic solvents with mass fraction purities higher than 0.995 (purchased from Tianjin Kewei Chemical Reagent Co. of China.) and distilled−deionized water were used without further purification.

Apparatus. The solubility of losartan potassium in different solvents was measured with the synthetic method,[4,5] in which the composition of a saturated solution obtained in some ways was measured or calculated according to the mass of solvent and solute having been added into the solution.

The experiments were carried out in a setup shown in Figure 2, which is similar to that described in the literature.[6,7] The equilibrium cell was a cylindrical double-jacketed glass vessel with a working volume of 50 mL. The vessel was continuously stirred with a magnetic stir bar, and the temperature was controlled by the circulating water through the outer jacket. A condenser was connected vertically to the vessel to prevent solvent evaporation. A laser monitoring system consisting of a laser generator, a photoelectric convertor, and a light intensity display was used to determine the disappearance of the last crystal in the solid + liquid mixtures. An analytical balance (Metler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.1 mg was used for the mass measurements.

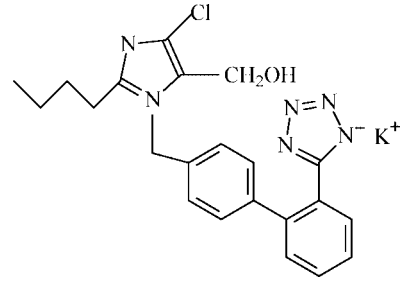

Figure 1. Structure of losartan potassium.

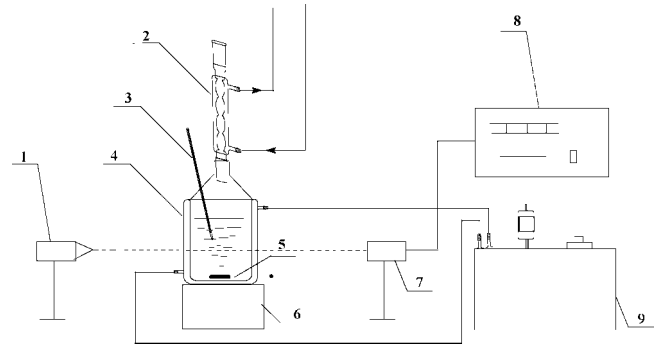

Figure 2. Schematic setup for the solubility determination: 1, laser generator; 2, condenser; 3, thermometer; 4, equilibrium vessel; 5, stir bar; 6, magnetic stirrer; 7, photoelectric convertor; 8, digital display; 9, thermostat.

Solubility Measurements. This method for solubility measurement was based on the fact that the laser intensity penetrated through the equilibrium vessel would increase with the dissolution of the solid losartan potassium when the amount of the solvent was gradually increased. For each experiment, an excess mass of losartan potassium was added to a known mass of solvent. The excess undissolved solid solute particles were

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Table 1. Solubility (x_1) of Losartan Potassium (1) in Pure Solvents (2) from T = (273.15 to 343.15) K

T/K	x_1	$((x_1 - x_1^{calcd})/x_1)\cdot 100$	T/K	x_1	$((x_1 - x_1^{calcd})/x_1)\cdot 100$
	Methanol			Ethanol	
293.15	0.02771	−5.5	293.15	0.03807	−6.1
303.15	0.03746	2.6	303.15	0.04729	−1.1
313.15	0.04449	7.5	313.15	0.05471	−1.9
323.15	0.04828	4.9	323.15	0.07022	8.7
333.15	0.05079	0.15	333.15	0.07394	1.6
343.15	0.05329	−4.3	343.15	0.07846	−4.1
	1-Propanol			2-Propanol	
293.15	0.02601	8.4	293.15	0.002704	3.7
303.15	0.02725	−2.2	303.15	0.002792	2.5
313.15	0.02985	−9.9	313.15	0.004127	3.0
323.15	0.03755	−1.6	323.15	0.005469	−4.9
333.15	0.04519	3.0	333.15	0.006965	6.8
343.15	0.04992	0.24	343.15	0.01169	5.9
	1-Pentanol			Ethyl Acetate	
293.15	0.04463	5.3	293.15	0.002509	20
303.15	0.03109	−9.2	303.15	0.001518	−18
313.15	0.02869	−0.64	313.15	0.002522	13
323.15	0.02342	−5.1	323.15	0.001381	−19
333.15	0.02051	−3.9	333.15	0.002883	15
343.15	0.02184	9.1	343.15	0.002788	5.6
	Butyl Acetate			Cyclohexane	
293.15	0.002713	2.6	293.15	3.4E−05	2.5
303.15	0.00238	12	303.15	2.87E−05	−7.4
313.15	0.000968	−13	313.15	3.05E−05	4.4
323.15	0.001206	−17	323.15	2.72E−05	−2.9
333.15	0.001933	11	333.15	2.88E−05	5.5
343.15	0.000907	−13	343.15	2.59E−05	−3.5

completely suspended in the vessel by continuous stirring for 30 min at a known temperature. Then, a known mass of additional solvent was added into the vessel through a burette. With the increase of the amount of solvent in the vessel, the solid solute gradually dissolved, and the intensity of the penetrated light increased. When the last portion of the solid solute just disappeared, the penetrated light intensity reached its maximum value. Then, the addition of solvent was stopped, and the mass of the solvent used in the experiment was recorded. Together with the mass of solute, the mole fraction solubility could be calculated by the following equation

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

where m_1 and M_1 denote the mass of losartan potassium used in the experiment and its molecular weight. m_2 and M_2 denote the mass of solvent and their molecular weight, respectively. All the experiments were repeated three times. The uncertainty in the solubility values is estimated to be 0.5 %.

Results and Discussion

Solubility Data. The solubilities of losartan potassium in pure methanol, ethanol, 1-propanol, 2-propanol, 1-pentanol, ethyl acetate, butyl acetate, and cyclohexane over the temperature range from (293.15 to 343.15) K are presented in Table 1, where T is the absolute temperature and x_1 and x_1^{calcd} denote the experimental and calculated values of the solubility, respectively.

From Table 1, it can be seen that within the temperature range of the measurements the solubility of losartan potassium in methanol, ethanol, 1-propanol, and 2-propanol increases with temperature increase. Contrarily, the solubility in 1-pentanol decreases with temperature increase. It is also shown that losartan potassium is sparingly soluble in ethyl acetate, butyl acetate, and cyclohexane, and the solubility in these three solvents varies little with temperature.

Table 2. Parameters of the Modified Apelblat Equation for Losartan Potassium in Different Solvents

solvent	A	B	C	R^2
methanol	26.653	−2019.2	−2.8691	0.909
ethanol	38.862	−2838.5	−4.4853	0.957
1-propanol	29.602	−2523.1	−3.1419	0.96
2-propanol	28.156	−4352.5	−2.239	0.956
1-pentanol	−58.493	4288.2	8.3814	0.927
ethyl acetate	−65.898	2641.5	10.135	0.969
butyl acetate	−68.7937	4857.3	9.364	0.925
cyclohexane	−85.018	4178.1	11.857	0.918

The experimental solubility values were fitted with the following semiempirical equation, namely, the modified Apelblat equation[8–11]

$$\ln(1000x_1) = A + B/(T/\mathrm{K}) + C\ln(T/\mathrm{K}) \quad (2)$$

where A, B, and C are semiempirical constants.

The temperature dependence of solubility of losartan potassium in different solvents was fitted with eq 2 by the least-squares method. The values of parameters A, B, C, and R^2 are outlined in Table 2.

It is seen that the calculated solubilities by the modified Apelblat model are in good agreement with the experimental values.

Conclusion

(1) The solubility of losartan potassium in pure methanol, ethanol, 1-propanol, and 2-propanol increased with temperature increase. The solubility of losartan potassium in different alcohol liquids is relatively high because of the compatibility between the weak electrolyte character of losartan potassium and the hydrogen bonding behavior of alcohols.

(2) The solubility of losartan potassium in 1-pentanol decreases with the temperature increase.

(3) The solubility of losartan potassium in ethyl acetate, butyl acetate, and cyclohexane is too low and varies little with temperature.

(4) The calculated solubility data by the modified Apelblat model are in good agreement with the experimental values.

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