Solubility of Scutellarin in Methanol, Water, Ethanol, and Ethanol + Water Binary Mixtures from (293.2 to 333.2) K

Lian-Jun Luan, Yun Zhou, Yong-Jiang Wu, Xue-Song Liu, and Long-Hu Wang*

Department of Chinese Medicine Sciences & Engineering, Zhejiang University, Hangzhou, 310058, China

The solubility of scutellarin in methanol, ethanol, water, and ethanol + water binary mixtures was measured over the temperature range of (293.2 to 333.2) K. The solubility of scutellarin in those solvents increases with increasing temperature. The solubility data were correlated with a modified Apelblat equation.

Introduction

Scutellarin, with its chemical name 7-(β-D-glucopyranurono-syloxy)-5,6-dihydroxy-2-(4-hydroxyphenyl)-1-benzopyran-4-one ($C_{21}H_{18}O_{12}$, CAS RN 27740-0-8, Figure 1) is one of the most important active constitutes in *Erigeron breviscapus* (Vant.) Hand-Mazz, which has been used in China over centuries for preventing blood coagulation, enhancing blood circulation, and dilating brain blood vessels.[1] It has been evidenced by its clinical application in the treatment of cerebral infarction, myocardial ischemia, and coronary arteriosclerosis,[2,3] especially as a long-range therapeutic drug with no evident side effects.

Although chemical synthesis has been applied to obtain scutellarin,[4] extraction from plants and crystallization from the solution is still the most common and efficient way to get commercial scutellarin, as much as tons,[5] and in this process methanol, water, or ethanol + water binary mixtures are used commonly. Therefore, it is necessary to determine the solubility of scutellarin in those solvents to optimize the operating conditions in the processes for extraction or purification. Unfortunately, there are no solubility data published of scutellarin for solvent selection.

In this work, the solubility of scutellarin in several common solvents as methanol, water, ethanol, and ethanol + water binary mixtures was measured over the temperature range from (293.2 to 333.2) K. The temperature dependence of the solubility in those solvents was described by a semiempirical equation.

Experimental Section

Reagents and Apparatus. Scutellarin was supplied by Kunming Longjin Pharmaceutical Co. (Yunnan, China) with a minimum purity of 99.0 % and dried in a DZF-6021 vacuum dryer produced by Jinghong Laboratorial Equipment Factory (Shanghai, China) at (105 to 110) °C for 2 h before used. All organic solvents used were analytical purity grade and obtained from Gaojing Reagent Factory (Hangzhou, China). Redistilled deionized water was used throughout. The methanol used as solvent of the mobile phase was purchased from Merck for high-performance liquid chromatography (HPLC) analysis. A THZ-C shaker was supplied by Taicang Laboratorial Equipment Factory (Hangzhou, China), a DFY thermostatic bath supplied by Yingyujinghua Laboratorial Equipment Factory (Gongyi, China), and an HPLC instrument (Agilent 1200) coupled with a UV detector used for analysis of the samples.

* To whom correspondence may be addressed. E-mail: wang2000@zju.edu.cn.

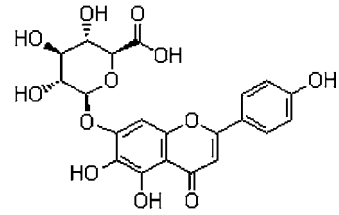

Figure 1. Molecular structure of scutellarein.

Sample Preparation. Excess amounts of scutellarin were added in a specially designed sealed dual-wall flask. Between the outer and the inner walls of the flask, water at constant temperature was circulated. The temperature of the circulating water was controlled by a thermostat within ± 0.1 K. The solution was constantly stirred using a magnet stirrer for 12 h to make sure the solution attains equilibrium, and the stirrer was turned off to let the solution settle for 2 h. Then the upper portion was taken and poured into a suitable volumetric flask (the upper portion of methanol was poured into a 50 mL volumetric flask, water was poured into a 2 mL volumetric flask, ethanol and ethanol + water binary mixtures were poured into a 10 mL volumetric flask). For preparing the solutions for HPLC analysis, the solutions were diluted to a suitable volume with methanol.

Sample Analysis. To determine the scutellarin concentration in the solution, the HPLC system mentioned above was used. All determinations were performed at 40 °C using an Agilent SB-C_{18} column (4.6 mm × 250 mm, 4 μm). Chromatographic separation was conducted with two solvent compositions: 0.4 % (V/V) orthophosphoric acid water solution (solvent A) and methanol solution (solvent B) with a volume fraction of 0.65 methanol and at a flow rate of 1.0 mL·min^{-1}. The elution was monitored by a UV detector at the wavelength of 335 nm, the injection volume being 10 μL. The calibration curve for the estimation of scutellarin was established by using the standard solutions in the appropriate concentration range (4.25 to 212.6) mg·L^{-1}.

Each measurement was repeated three times. The measuring relative expanded uncertainty (U_{rel}) is 2 % with a 95 % confidence level.

Results and Discussion

The solubility data of scutellarin in methanol, water, and ethanol at different temperatures are presented in Table 1. The

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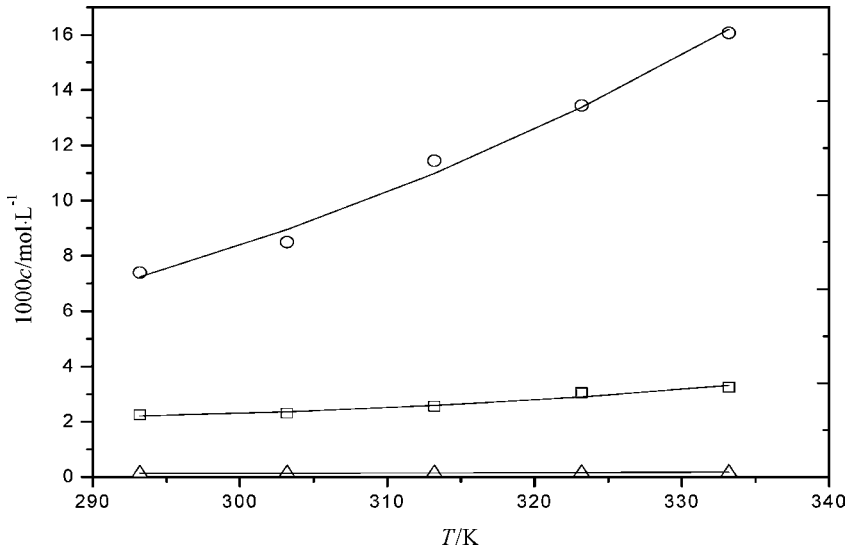

Figure 2. Solubility of scutellarein at different temperatures in three solvents: ○, methanol; □, ethanol; △, water; −−, calculated by eq 2.

Table 1. Solubility (c/mol·L^{-1}) of Scutellarin in Methanol (1), Water (2), and Ethanol (3) from (293.2 to 333.2) K

T/K	$10^3\ c_1$	$((c_1 - c_1^{calc})/c_1)$	$10^3\ c_2$	$((c_2 - c_2^{calc})/c_2)$	$10^3\ c_3$	$((c_3 - c_3^{calc})/c_3)$
293.2	7.39	0.020	0.145	−0.002	2.250	0.017
303.2	8.49	−0.054	0.146	0.004	2.322	−0.022
313.2	11.44	0.039	0.148	−0.005	2.558	−0.012
323.2	13.44	0.004	0.157	0.008	3.052	0.049
333.2	16.07	−0.008	0.167	0.003	3.254	−0.019

Table 2. Solubility (c/mol·L^{-1}) of Scutellarin in Different Compositions of Ethanol (1) + Water (2) Binary Mixtures from (293.2 to 333.2) K

T/K	$10^3\ c$	$((c - c^{calc})/c)$	T/K	$10^3\ c$	$((c - c^{calc})/c)$
	$x_1 = 0.8544$			$x_1 = 0.2360$	
293.2	0.501	0.013	293.2	0.207	0.021
303.2	0.584	−0.038	303.2	0.265	−0.029
313.2	0.779	0.024	313.2	0.352	−0.033
323.2	0.976	0.003	323.2	0.517	0.075
333.2	1.258	−0.009	333.2	0.604	−0.034
	$x_1 = 0.4188$			$x_1 = 0.1169$	
293.2	0.284	−0.030	293.2	0.155	0.008
303.2	0.373	0.023	303.2	0.158	−0.022
313.2	0.442	−0.079	313.2	0.174	0.002
323.2	0.667	0.019	323.2	0.194	0.016
333.2	0.912	−0.025	333.2	0.212	−0.013

solubility of scutellarin in methanol is higher than in water and ethanol. The solubility of scutellarin in water is the lowest. Figure 2 shows the calculated solubility of scutellarin at different temperatures with the experimental values. The composition of the binary ethanol + water solvent mixtures, x_1, is defined as eq 1[6]

$$x1 = \frac{m_B/M_B}{m_B/M_B + m_C/M_C} \qquad (1)$$

In the binary mixtures system, m_B and m_C represented the mass of ethanol and water. M_B and M_C were the molecular weight of ethanol and water. The solubility data of scutellarin in binary ethanol + water mixtures are listed in Table 2 and shown in Figure 3.

The experimental data show that the solubility of scutellarin in methanol, ethanol, water, and ethanol + water binary mixtures increases with the increase in temperature. The temperature

Table 3. Parameters of the Equation for Scutellarin in the Three Solvents

solvent	A	B	C	10^4 rmsd
methanol	−35.6	−237	5.54	3.043
water	−168.9	7122	23.90	0.008
ethanol	−195.9	7956	28.64	0.796

Table 4. Parameters of the Equation for Scutellarin in Different Compositions of Ethanol (1) + Water (2) Binary Mixtures

composition	A	B	C	10^4 rmsd
$x_1 = 0.8544$	−234.7	8579	34.82	0.143
$x_1 = 0.4188$	−424.3	16880	63.12	0.203
$x_1 = 0.2360$	−52.7	−268	7.93	0.207
$x_1 = 0.1169$	−188.4	7636	27.04	0.025

dependence of scutellarin solubility in those solvents can be described by the modified Apelblat equation[7–10]

$$\ln(c/\text{mol}\cdot\text{L}^{-1}) = A + B/(T/\text{K}) + C\ln(T/\text{K}) \qquad (2)$$

where c is the solubility of scutellarin; T is the absolute temperature; and A, B, and C are parameters. The data of relative differences between the calculated and the experimental solubility of scutellarin are also shown in Tables 1 and 2. The values of parameters A, B, C and the root-mean-square deviations (rmsd) are listed in Tables 3 and 4. The rmsd is defined as

$$\text{rmsd} = \sqrt{\frac{\sum_{i=1}^{N}(c_i^{calc} - c_i)^2}{N}} \qquad (3)$$

where N is the number of experimental points, c_i^{calc} and c_i represent the solubility calculated and the experimental solubility values, respectively.

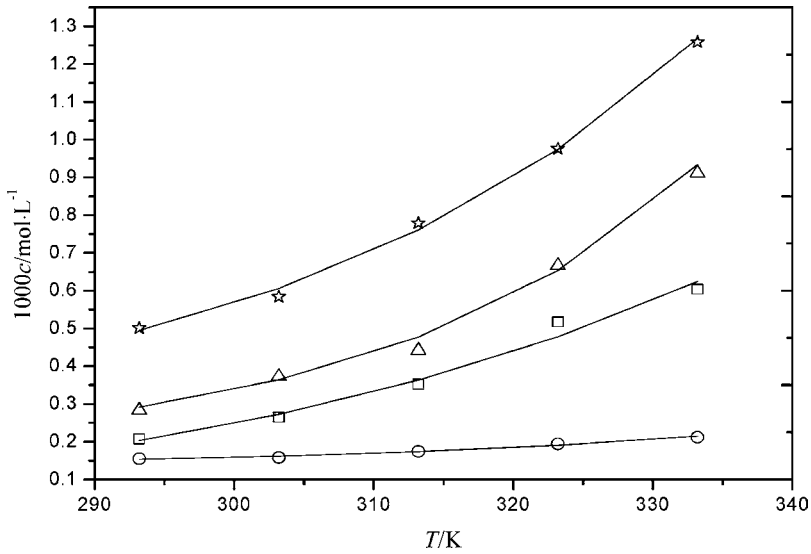

Figure 3. Solubility of scutellarein at different temperatures in ethanol (1) + water (2) binary mixtures: ☆, $x_1 = 0.8544$; △, $x_1 = 0.4188$; □, $x_1 = 0.2360$; ○, $x_1 = 0.1169$; —, calculated by eq 2.

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