Solubility of Artemisinin in Ethanol + Water from (278.2 to 343.2) K

Long-Hu Wang, Yan-Ting Song, Yong Chen, and Yi-Yu Cheng*

Department of Chinese Medicine Sciences & Engineering, Zhejiang University, Hangzhou, 310027, China

The solubility of artemisinin in ethanol + water was measured at several concentrations and over the temperature range of (278.2 to 343.2) K. The solubility of artemisinin in ethanol and water mixture increases with the increase in temperature and with ethanol concentration. The solubility data were correlated with a modified Apelblat equation.

Introduction

Artemisinin (Figure 1), [$C_{15}H_{22}O_5$, CASRN 63968-64-9] also known by the Chinese name Qinghaosu, is a promising drug in the treatment of cerebral malaria. It was first found by Chinese researchers in the plant of *Artemisia annua* L.,[1] which had been used for many centuries in traditional Chinese medicine for the treatment of fever and malaria. A total synthesis of artemisinin has been achieved,[2] but it is not economically feasible as a large-scale production yet. Nowadays, the main source for artemisinin is extraction from *A. annua* leaves, during which the organic solvents such as toluene, hexane, or petroleum ether are widely applied.[3,4] Because of the use of hazardous solvents and its low recovery yield, alternative extraction techniques with better selectivity and efficiency such as supercritical fluid extraction with carbon dioxide are highly desirable.[5,6] Through an extraction process, whether liquid solvent extraction or supercritical fluid extraction, the artemisinin is obtained only as a raw product or an extract, which is not as pure as that for dosage and has to be purified further by crystallization at least once. Alcohol solutions are the most common solvent used for artemisinin purification because it is permitted in the food and pharmacological industry. It has been known that water added to alcohol can change the solubility of artemisinin. Therefore, it is necessary to determine the solubility of artemisinin in different ethanol + water mixtures in order to optimize the operating conditions in the processes for purification. Unfortunately, there are no published solubility data for artemisinin in such a system.

Recently, the solubility of artemisinin in supercritical CO_2 has been measured and correlated so as to make use of supercritical fluid technologies and processes.[6,7] Furthermore, in this work, the solubility of artemisinin in ethanol + water solvents was determined at several concentrations and over the temperature range of (278.2 to 343.2) K. The temperature dependence of artemisinin solubility in ethanol + water is described by a semi-empirical equation. The results obtained are useful to increase the recovery yield of this drug.

Experimental Section

Materials. The artemisinin sample (CAS 63968-64-9) was supplied by Sigma Chemical (USA) with minimum purities of 99.0 %. Other reagents used such as ethanol were of analytical purity grade and provided by Zhejiang Chemical Reagent Plant (China). Redistilled deionized water was used throughout.

Sample Preparation. Binary (water + ethanol) mixtures were prepared by mass with an uncertainty of ± 0.1 mg. An excess amount of crystal artemisinin was added to the binary solvents in a specially designed sealed 30 mL dual-wall flask. Between the outer and 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. After attaining equilibrium, the stirrer was turned off to let the solution settle for 2 h. Then the upper portion was taken, filtered, and poured into a 50 mL volumetric flask. For preparing the solutions for HPLC analysis, the solutions were diluted to 50 mL volume with double-distilled water.

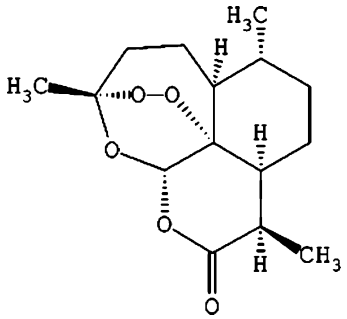

Figure 1. Molecular structure of artemisinin (Qinghaosu).

Sample Analysis. A HPLC instrument coupled with a UV detector was used for analysis of samples and detecting the composition of stock solutions for (artemisinin + ethanol + water) mixtures. Artemisinin in the samples was converted into a UV-absorbing compound (Q_{260}) by being treated with 0.2 % (mass fraction) NaOH solution for 0.5 h and then with 0.08 mol·L^{-1} acetic acid.[8] A reversed-phase C-18 silica column (4.6 × 250 mm, 5 μm) was selected as a fixed phase, and the mobile phase was 45/10/45 (by volume) of methanol/acetonitrile/0.9 mmol·L^{-1} Na_2HPO_4−3.6 mmol·L^{-1} NaH_2PO_4 buffer (pH 7.76). The flow rate was 0.5 mL·min^{-1}, and the detection wavelength was 260 nm. The HPLC instrument was calibrated by using the standard solutions in the appropriate concentration range from (0.040 to 0.20) mg·mL^{-1}.

The saturated solubility of the solute (x_A) in ethanol + water solvent mixtures was measured three times. The uncertainty of the experimental solubility values is about 0.5 %.

Results and Discussion

The solubility data of artemisinin in ethanol + water at different temperatures are presented in Table 1. During this experimental investigation, it was noticed that artemisinin decomposed slightly in the solution at 343.2 K after 2 h, and it

* Corresponding author. E-mail: chengyy@zju.edu.cn.

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Table 1. Solubility of Artemisinin (x_A) in Water (B) + Ethanol (C) from (278.2 to 343.2) K

T	$x_C = 0.138$		$x_C = 0.273$		$x_C = 0.467$		$x_C = 0.771$		$x_C = 1.000$	
K	$10^4 x_A$	$10^4 x_A^{calc}$	$10^4 x_A$	$10^4 x_A^{calc}$	$10^4 x_A$	$10^4 x_A^{calc}$	$10^4 x_A$	$10^4 x_A^{calc}$	$10^4 x_A$	$10^4 x_A^{calc}$
278.2	0.408 ± 0.002	0.468	0.987 ± 0.003	1.080	4.17 ± 0.02	4.34	7.00 ± 0.03	7.75	9.98 ± 0.04	10.97
286.2	0.719 ± 0.003	0.661	1.728 ± 0.008	1.663	7.02 ± 0.03	6.71	14.59 ± 0.05	11.20	18.11 ± 0.08	15.75
303.2	1.483 ± 0.006	1.332	3.55 ± 0.01	3.73	14.22 ± 0.05	15.70	21.40 ± 0.10	23.91	29.73 ± 0.12	32.12
313.2	2.32 ± 0.01	2.00	5.33 ± 0.01	5.64	24.70 ± 0.08	24.86	35.88 ± 0.12	37.14	45.67 ± 0.15	48.80
323.2	3.16 ± 0.01	2.88	8.84 ± 0.02	8.33	42.09 ± 0.08	38.32	60.63 ± 0.22	57.25	80.06 ± 0.22	73.65
343.2	5.38 ± 0.01	5.93	16.44 ± 0.05	16.62	82.10 ± 0.20	84.78	127.8 ± 0.5	133.4	158.8 ± 0.5	163.5

Table 2. Curve-Fitting Parameters of Artemisinin in Ethanol + Water Solvents from (278.2 to 343.2) K

x_C	A	B	C	10^4 rmsd
0.138	−73.36	−215	11.4	0.292
0.273	55.15	−6299	−7.397	0.274
0.467	−3.028	−3862	1.629	1.98
0.771	−135.12	2373	21.22	3.23
1.000	−123.96	2041	19.51	4.01

would be serious at a temperature higher. Thus, no experimental data were obtained at temperatures higher than 343.2 K. The experimental data show that the solubility of artemisinin in the binary (water + ethanol) mixtures increases with an increase in ethanol concentration and with an increase in temperature. The temperature dependence of artemisinin solubility in binary solvents can be described by the modified Apelblat equation:[9−12]

$$\ln(x_A) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \quad (1)$$

where x is the mole fraction solubility of artemisinin; T is the absolute temperature; and A, B, and C are the parameters. The calculated solubility values of artemisinin x_A^{calc} are also given in Table 1. The values of parameters A, B, and C are listed in Table 2 together with the root-mean-square deviations (rmsd):

$$\mathrm{rmsd} = \sqrt{\frac{\sum_{i=1}^{N} (x_{A,i}^{calc} - x_{A,i})^2}{N}} \quad (2)$$

where N is the number of experimental points, $x_{A,i}^{calc}$ represents the solubility calculated, and $x_{A,i}$ represents the experimental solubility values. Figure 2 shows both the experimental solubility values and those calculated by the semi-empirical equation.

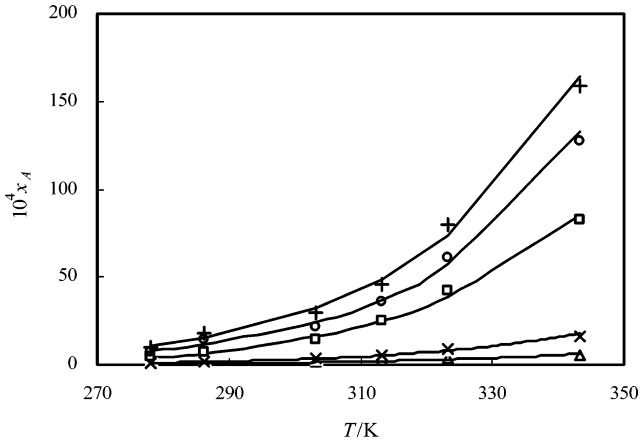

Figure 2. Solubility of artemisinin in binary system of ethanol + water mixture along temperature: △, $x_C = 0.138$; ×, $x_C = 0.273$; □, $x_C = 0.467$; ○, $x_C = 0.771$; +, $x_C = 1.000$; —, calculated by eq 1.

From Table 1 and Figure 2, the following conclusions can be drawn: (i) The solubility of artemisinin in binary ethanol + water solvent mixtures is a function of temperature, and solubility increases with an increase of temperature. (ii) The solubility increases with the increasing molar fraction of ethanol in the solvent mixture.

From the data listed in Table 2, it can be seen that the calculated solubilities show some agreement with the experimental values, indicating that the Apelblat equation is fit to correlate the solubility of artemisinin in ethanol + water mixtures. Both the experimental solubility and correlation equation in this work can be used for the purification process or crystallization of this anti-malarial drug.

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