Solubility of Artemisinin in Supercritical Carbon Dioxide

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Thesolubility of artemisinin in supercritical carbon dioxide was measured in a pressure range (10 to 27) MPa and from (310.1 to 338.1) K by using a flow-type apparatus equipped with a high-pressure UV detector. A four-parameter semiempirical model leads to a good agreement with the experimental values.

Introduction

Artemisinin (Qinghaosu) is a promising drug against chloroquine-resistant strains of *Plasmodium falciparum* and in the treatment of cerebral malaria.[1] In parts of Southeast Asia, artemisinin is now the only effective treatment for malaria. This compound is an endoperoxide sesquiterpene lactone (Figure 1) found in the plant of *Artemisia annua L.*, which had been used for many centuries in traditional Chinese medicine for the treatment of fever and malaria. Although a total synthesis of artemisinin has been achieved,[2] its product is not competitive in price with the natural product. Liquid solvent extraction with toluene, hexane, or petroleum ether is the most currently applied technique.[3] However, these procedures exhaust a large amount of potentially hazardous solvents to the environment, and its recovery yield is low. Therefore, alternative extraction techniques with better selectivity and efficiency are highly desirable. In view of its properties already described in the literature,[4] supercritical fluid extraction with carbon dioxide is an interesting alternative to conventional liquid solvent extraction methods. To evaluate the possibility of SFE, the knowledge of the solubility of artemisinin in supercritical carbon dioxide ($SC-CO_2$) is needed.

In this work, the solubility of artemisinin in $SC-CO_2$ over the pressure range (10 to 27) MPa and from (310.1 to 338.1) K was determined by using a flow-type apparatus equipped with a high-pressure UV detector. No published data of solubility for artemisinin in $SC-CO_2$ was found.

Experimental Section

Materials. CO_2 with a stated purity of 99.95% was used. Crystalline artemisinin with a purity of 99% was obtained from Yunnan Phytopharmaceutical Co., LTD (China).

Experimental Apparatus. A modification of the previously applied flow-type apparatus was used.[5,6] The schematic diagram of the modified apparatus is presented in Figure 2. The CO_2 was cooled with a cooling bath, and then it was pressurized above its critical pressure with a pump. Pressurized CO_2 was introduced into the saturation cell through a 2-m preheating coil (stainless steel tubing), where the solvent was heated to the temperature of the thermostat. A commercially available empty HPLC column (200 mm × 4.6 mm) with sintered stainless steel frits of 0.5 μm at both ends was used as the saturation cell, which

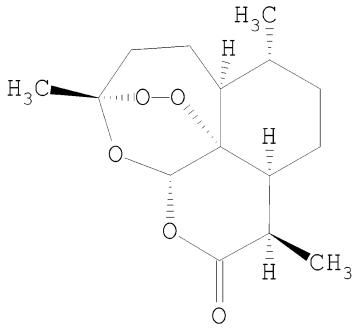

Figure 1. Structure of artemisinin.

was filled with artemisinin mixed with clean sands. A high-pressure UV detector (OTECH Model 9550-0150) was used to detect solute concentration in $SC-CO_2$, and the UV cell was equipped with a water jacket which maintained the cell's temperature as thermobath. To avoid potential blockage of the tubing, a column packed with silica gel was used to adsorb artemisinin behind the detector. At the inlet of the saturation cell, a pressure transducer was used to monitor the equilibrium pressure of the system. The pressure of the system was maintained with a heated valve. The gas exiting from the valve was expanded to atmospheric pressure and its volumetric flow was measured by a rotameter.

Method. A typical artemisinin solubility profile was shown in Figure 3. The detector wavelength was set to 210 nm for the solubility measurements. A UV absorbance baseline was established by collecting data while bypassing the saturation cell, allowing solute-free CO_2 to flow through the detector. Once baseline was reached in the detector, the flow was switched to the saturation cell allowing the $SC-CO_2$ to be saturated with artemisinin. Equilibrium typically occurred within 5 to 7 min, and maintained this state about 12 min. Then the pressure was increased in sequential steps, and equilibrium was established to each pressure.

Calibration of the UV detector was performed by weighing approximately 10 to 15 mg of artemisinin into the saturation cell followed by elution of the solute at every temperature and pressure. The UV detection response was recorded until the signal returned to baseline. The response factor (K) of the UV detector at each temperature and pressure could be calculated by

$$K = \frac{F_0 A_0}{W_0} \tag{1}$$

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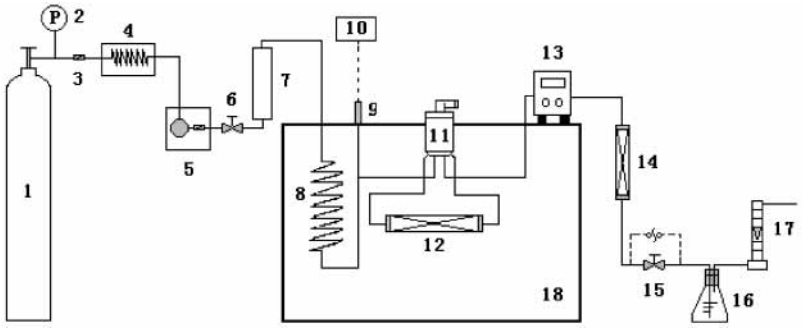

Figure 2. Schematic diagram of experimental apparatus: (1) CO_2 cylinder; (2) pressure gauge; (3) filter; (4) cooling bath; (5) pump; (6) check valve; (7) surge tank; (8) preheating coil; (9) pressure transducer; (10) pressure display; (11) six-way valve; (12) saturation cell; (13) high-pressure UV detector; (14) adsorption column; (15) heated valve; (16) water flask; (17) rotameter; (18) thermobath.

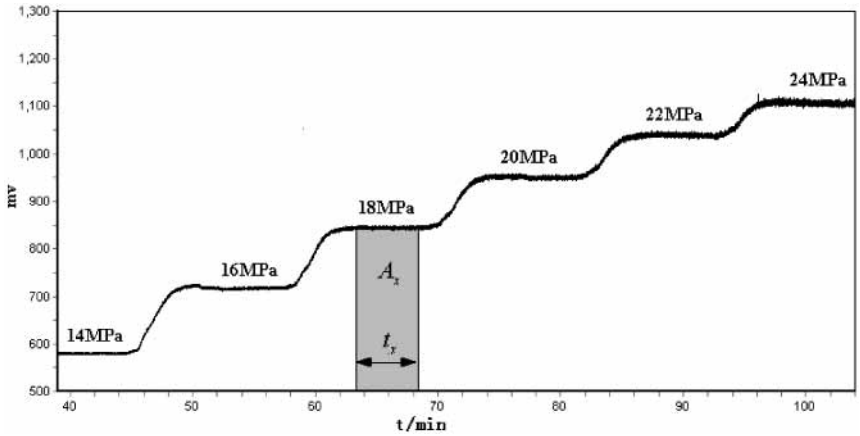

Figure 3. UV response versus pressure for artemisinin at 318.1 K.

where F_0 is the SC−CO_2 flow rate ($m^3 \cdot s^{-1}$), W_0 is the amount of artemisinin weighed into the saturation cell (kg), and A_0 is the elution area of W_0 artemisinin (mv·s).

The response of UV detector as a function of artemisinin concentration was examined and found to obey Beer's law. Hence, Solubility was calculated by

$$c = \frac{H_x}{K} = \frac{A_x}{Kt_x} \tag{2}$$

where c is the concentration of artemisnin in SC−CO_2 ($kg \cdot m^{-3}$), H_x is the average response of UV detector (mv), t_x is the width of the plateau-peak of the UV response (*s*), and A_x is the area of plateau-peak (mv·s).

The accuracy of the developed measurement procedure was analyzed as below. The temperature was measured by a thermocouple with an accuracy of 0.1 K, and the system temperature was controlled within ±0.1 K. The pressure was measured by a pressure transducer (KYB18, Kangyu Control System Co. Ltd.) with an accuracy of 0.1 MPa, and the pressure fluctuation was controlled within ±0.1 MPa. The main source of error is the response of the UV detector. For the fluctuation of the pressure and the baseline noise, the response fluctuated within 5 mv. In our experiment, the overall uncertainty of solubility was lower than 4×10^{-5} (molar fraction).

Results and Discussion

To check that the solvent flow in a desirable range to maintain CO_2 saturated with artemisinin, the flow range for which the solubility did not change was determined. As show in Figure 4, the solubility of artemisinin is not affected within (10 to 320) $mL \cdot min^{-1}$ (CO_2 gaseous flow, 293 K, 0.1 MPa). To prevent entrainment of the solutes by the supercritical fluid flow, the CO_2 flow rate was adjusted to relatively low values (approximately 30 $mL \cdot min^{-1}$) in the experiment.

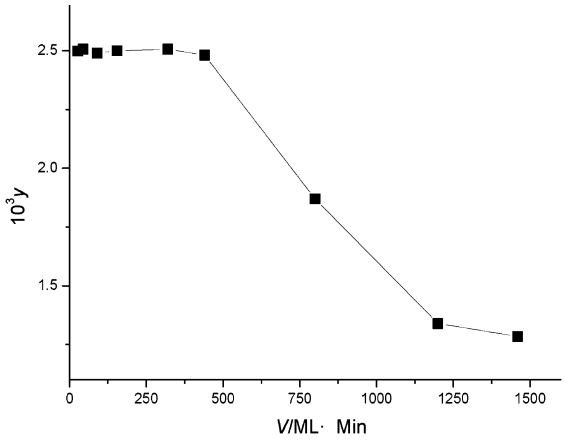

Figure 4. Effect of CO_2 flow rate on the solubility determination (24 Mpa, 338 K).

The solubility of artemisinin in SC−CO_2 is summarized in Table 1. The reproducibility of most of data was within 3.2%, besides the data at low densities. The experimental results are also presented in Figure 5 as a function of pressure. It can be observed that the solubility increases with pressure under all studied conditions. However, the effect of temperature on solubility is complex. As shown in Figure 5, it is noted that the crossover of solubility isotherms occurs when pressure is used as a variable. The phenomenon is a consequence of two competitive effects: the density of SC−CO_2 and the vapor pressure of artemisinin. As the temperature increases, the vapor pressure increases too, which enhances the solubility; but the

Table 1. Solubility of Artemisinin in SC−CO_2 (Molar Fraction × 10^3)

	y*10^3			
P/MPa	*T* = 310.1 K	*T* = 318.1 K	*T* = 328.1 K	*T* = 338.1 K
10.0 ± 0.1	0.663	0.342	0.099	
10.1 ± 0.1				0.098
12.0 ± 0.1	0.903[a]	0.768[a]	0.502	0.307
14.0 ± 0.1	1.139	1.060	0.810	0.642
16.0 ± 0.1	1.346	1.337	1.242	0.990
18.0 ± 0.1	1.629	1.587	1.591	1.437
20.0 ± 0.1	1.734	1.799	1.893	1.868
22.0 ± 0.1	1.864	1.983	2.169	2.238
24.0 ± 0.1	1.982	2.120	2.375	2.501
26.0 ± 0.1	_	2.226	2.519	2.659
27.0 ± 0.1	2.125			

[a] Average of four measurements. Other data are average of two measurements.

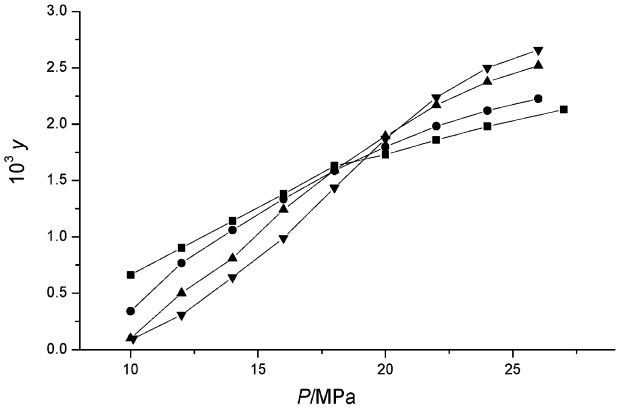

Figure 5. Relationship between solubility and pressure at different temperatures: ■, 310.1 K; ●, 318.1 K; ▲, 328.1 K; ▼, 338.1 K.

density and the CO_2 solvent power decrease, which resulted in a decrease of solubility. At pressures from (10 to 19) MPa, solubility decreases as temperature increases for the effect of the density is dominant. At pressures over 19 MPa, the vapor pressure of artemisinin becomes a dominant factor, and the solubility increases with the temperature.

Data Correlation

Most of the models describing the solubility of solid in a supercritical fluid were based on thermodynamic considerations. To correlate and predict solubility from these models by using equations of state requires tedious computational effort and physical property values that are often difficult to obtain. Therefore, it is easier to predict solubility with a semiempirical model[5,7] based on chemical association

$$\ln y = a \ln(\rho T) + b\rho + c/T + d \qquad (3)$$

where *a* is the association number and *b*, *c*, and *d* are equation parameters. By linear least-squares fitting, the experimental data were correlated by eq 3, and the results are presented in Figure 6 and Table 2. It can be seen that the average absolute relative deviation (AARD %) of eq 3 is 4.24%, and the fitting of the results is very good even at temperatures close to the critical point of carbon dioxide.

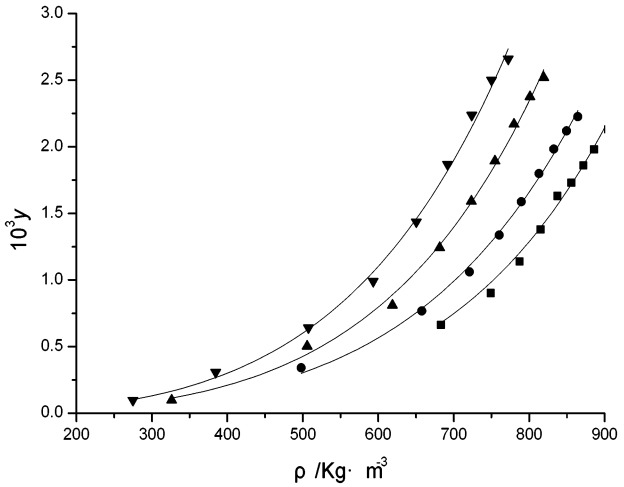

Figure 6. Relationship between solubility and density at different temperatures: ■, 310.1 K; ●, 318.1 K; ▲, 328.1 K; ▼, 338.1 K; —, eq 3.

Table 2. Regression Analysis of eq 3 for Artemisinin in SC−CO_2

a	*b*	*c*	*d*	AARD %[a]
2.162	0.002238	−2795.485	−26.311	4.24

[a] AARD% = 100/36 $\sum_{i=1}^{36} (y_{exp} - y_{cal}/y_{exp})$; $i = 1-36$.

Conclusions

The solubility of artemisinin in SC−CO_2 was determined over an extended range of temperatures and pressures. It can be affirmed that, at a pressure above 19 MPa, the solubility increases as temperature or pressure increase. At pressures from (10 to 19) MPa, the solubility increases with pressure and decreases with increasing temperature.

The four-parameter semiempirical model leads to a good agreement with the experimental values. Given the solubility of artemisinin, supercritical carbon dioxide extraction of artemisinin from *Artemisia annua L.* is a feasible method as an alternative technique to conventional liquid solvent extraction.

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