Solubility of Oxymatrine in Supercritical Carbon Dioxide

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The solubility of oxymatrine in supercritical carbon dioxide over the pressures ranging from (11 to 21) MPa and at the temperatures of (308.15, 318.15, and 328.15) K was measured using a continuous flow-type apparatus. The measured solubilities were correlated using a semiempirical model proposed by Bartle.

Introduction

Oxymatrine is one of the quinolizidine alkaloids extracted primarily from the root of traditional Chinese herbal medicine *Sophora japonica* (*kushen*) but also from *Sophora subprostrata* (*shandougen*) and from the aboveground portion of *Sophora alopecuroides*. The chemical structure of oxymatrine is shown in Figure 1. It has been reported that oxymatrine plays important roles in antiarrhythmic, immunity regulation, antitumors, and so on.[1,2]

Generally, oxymatrine is obtained by extraction using organic solvent which produces serious environmental pollution. Therefore, an alternative method with better selectivity and efficiency is highly desirable. Since supercritical carbon dioxide ($SCCO_2$) is nontoxic, inexpensive, and relatively nonpolluting, supercritical fluid extraction (SFE) becomes attractive. To build the SFE method, the data of the solubility of oxymatrine in $SCCO_2$ are necessary.

In this work, the solubility of oxymatrine in supercritical carbon dioxide was determined over the pressures ranging from (11 to 21) MPa and at the temperatures of (308.15, 318.15, and 328.15) K using a continuous flow-type apparatus equipped with a high-pressure UV−vis detector. The experimental solubility data were correlated using a semiempirical model proposed by Bartle.

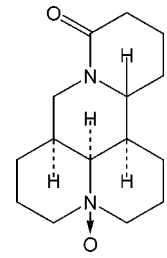

Figure 1. Chemical structure of oxymatrine.

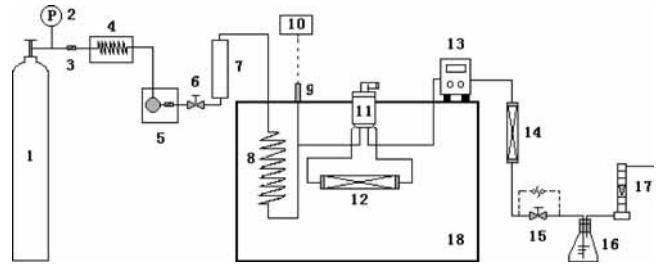

Figure 2. Schematic diagram of experimental apparatus: 1, CO_2 cylinder; 2, pressure gauge; 3, filter; 4, cooling bath; 5, pump; 6, check valve; 7, surge tank; 8, preheating coil; 9, pressure transducer; 10, pressure display; 11, six-way valve; 12, saturation cell; 13, high-pressure UV detector; 14,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

Experimental Section

Materials. Carbon dioxide (99.995 % purity) purchased from Shanghai Praxair-Baosteel, Inc. was used in all experiments. Oxymatrine (more than 98 % purity) was supplied by China Aroma Chemical Co., Ltd. (Hangzhou, China) and used without further purification. HPLC grade acetonitrile (99.95 % purity) was obtained from Tedia Company, Inc. (Fairfield, OH).

Apparatus and Procedure. The schematic diagram of a flow-type apparatus is presented in Figure 2, which had been described by Xing[3] and Bao.[4] In this study, this apparatus has been used to determine the solubility of oxymatrine in $SCCO_2$, and it is described as follows again for convenience. The gaseous CO_2 from a cylinder (1) was first cooled with a cooling bath (4) and liquefied, and then it was pressurized above its critical pressure with a high-pressure pump (5). Pressurized CO_2 was introduced into the saturation cell (12) through a 2 m preheating coil (8), where the solvent was heated to the temperature of the thermostat. A commercially available empty HPLC column (150 mm × 4.6 mm) with sintered stainless steel frits of 2 μm at both ends was used as the saturation cell. The saturation cell was connected to a Rheodyne six-port valve (11), which enables the cell to be switched in or out of the flow path. Approximately 0.5 g of oxymatrine was mixed well with clean sand and packed into the saturation cell. A high-pressure UV−vis detector (13) (OTECH model 200) was used to detect solute concentration in $SCCO_2$, and the UV cell was equipped with a water jacket which maintained the cell's temperature as a thermobath. The pressure and temperature of the system were controlled to accuracies of ± 0.05 MPa and ± 0.1 K, respectively. To avoid potential blockage, a column (14) packed with silica gel was used to adsorb oxymatrine behind the detector, and the valve at the outlet was heated to 353.15 K. The gas exiting from the outlet valve was expanded to atmospheric pressure, and its volumetric flow was measured by a rotameter (17).

The detector wavelength is set to 225 nm for the solubility measurements. Initially, the Rheodyne six-port valve was switched to direct the CO_2 flow along a bypass line and through a high-pressure flow cell, also allowing solute-free CO_2 to clean

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Table 1. Solubility of Oxymatrine in $SCCO_2$

T/K	P/MPa	ρ/g·L^{-1}	10^7x/mol fraction
308.15	11.10	748.1	6.81
	13.00	787.1	8.92
	15.05	816.9	11.50
	17.05	839.6	13.20
	19.10	858.9	13.50
	21.03	874.7	14.20
318.15	11.05	607.5	8.87
	12.91	692.2	11.10
	15.05	744.1	15.40
	17.00	776.5	20.40
	19.02	802.6	21.00
	21.07	824.3	21.50
328.15	11.04	422.5	7.27
	12.99	572.6	11.80
	14.99	654.5	18.90
	16.95	703.8	23.80
	18.94	739.6	24.20
	21.00	768.4	24.60

and flush the tubing and flow cell. Once a UV response baseline was established in the detector, the saturation cell was brought online, allowing the $SCCO_2$ to saturate with oxymatrine. Equilibrium was typically established within (5 to 7) min when the plateau of the elution profile occurred and maintained this state for about 15 min. Then the pressure was increased in sequential steps, and equilibrium was established to each pressure. The net oxymatrine UV response was determined by subtracting the average baseline signal of neat CO_2 from the average UV response plateau of CO_2 saturated with oxymatrine.

To calculate the solubility data from the elution profile, the UV−vis detector was calibrated as follows. For calibration, the saturation cell was substituted by a 20 μL sample injection loop filled with standard solution of oxymatrine in acetonitrile. Initially, the sample injection loop was switched out of the flow path to establish a zero baseline response. Then, the sample injection loop was brought online, and a typical response for each calibration was recorded until the signal returned to the baseline. The response factor K was calculated at each temperature and pressure by eq 1, and the mole fraction solubility x at the employed experimental pressures and temperatures was calculated by eq 2[4]

$$K = \frac{F_0 A_0}{m_0} \tag{1}$$

$$x = \frac{H_i M_C}{K \rho M_O} \tag{2}$$

where F_0 is the $SCCO_2$ flow rate (L·S^{-1}); A_0 is the elution area of an amount of m_0 solute (mV·S); m_0 is the amount of the solute injected into the sample loop (g); H_i is the average UV response plateau (mV); ρ is the density of $SCCO_2$ (g·L^{-1});

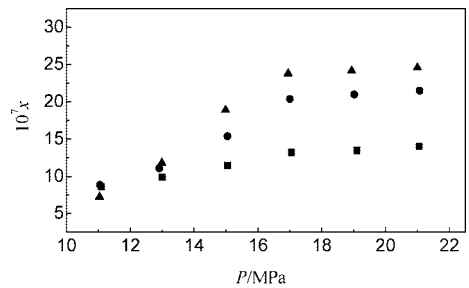

Figure 3. Solubility of oxymatrine in supercritical carbon dioxide. ■, 308.15 K; ●, 318.15 K; ▲, 328.15 K.

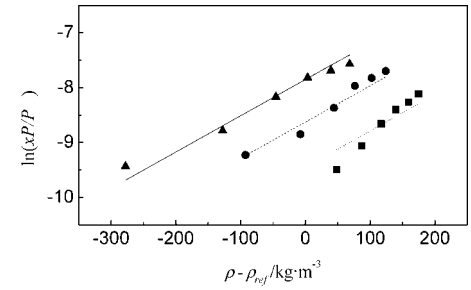

Figure 4. Plots of $\ln(xP/P_{ref})$ vs $(\rho - \rho_{ref})$ for oxymatrine at various temperatures. ■, 308.15 K; ●, 318.15 K; ▲, 328.15 K. The lines represent Bartle's regression fit.

Table 2. Constants in Equation 5 Obtained from Data Correlation[a,b]

a	b/K	C/m^3·kg^{-1}	AARD %
16.753	−8074.5	0.00661	12.7

[a] $\ln(xP/P_{ref}) = 16.753 - 8074.5/T + 0.00661(\rho - \rho_{ref})$. [b] AARD % $= 1/n\Sigma|(x_{i,calcd} - x_{i,exptl})/x_{i,exptl}|\cdot 100$ %, $i = 1$ to 15.

M_O is the molecular weight of oxymatrine (g·mol^{-1}); and M_C is the molecular weight of CO_2.

Results and Discussion

The solubility of oxymatrine in carbon dioxide was determined over the pressures ranging from (11 to 21) MPa and at the temperatures of (308.15, 318.15, and 328.15) K (Figure 3). To confirm that the equilibrium saturation of oxymatrine and $SCCO_2$ was achieved, experiments were performed under a relatively low flow rate of CO_2 (approximately 30 mL·min^{-1}) according to Xing[3] and Bao.[4] Experimental solubility data were listed in Table 1 in terms of oxymatrine mole fraction x (the ratio of the number of moles of solute divided by the number of moles of carbon dioxide) and also plotted in Figure 4 as a function of pressure. The reproducibility of most of the experimental data was within 5.0 %, besides the data at low densities. As respected, it was observed that the solubility of oxymatrine increases with the increase of pressure, and a crossover of solubility isotherms occurs at around 12 MPa as reported previously.[5]

The experimental solubility data were correlated using the following semiempirical equations first proposed by Bartle[6–8]

$$\ln(xP/P_{ref}) = a + b/T + C(\rho - \rho_{ref}) \tag{3}$$

where x is the mole fraction of the solute in $SCCO_2$; P is the pressure (MPa); P_{ref} is 0.1 MPa; T is the absolute temperature (K); ρ is the density (approximaly taken as the density of pure carbon dioxide); ρ_{ref} is 700 g·L^{-1}, and a, b, and C are constants. $a + b/T$ arises from the equation of the vapor pressure (fugacity) of the solute. C results physically from the solvation by the fluid, and it is assumed to be constant over the temperature range.

By performing a multiple linear regression on $\ln(xP/P_{ref})$ as a function of $1/T$ and $(\rho - \rho_{ref})$, the experimental data were correlated by eq 3, and the results are presented in Table 2. Then the values of a, b, and C were used to predict solubility from eq 3. Figure 4 compares the calculated solubility with the experimental data. The average absolute relative deviation was obtained with AARD % $= 1/n\Sigma|(x_{i,calcd} - x_{i,exptl})/x_{i,exptl}|\cdot 100$ %, where n is the number of experimental points and $x_{i,calcd}$ and $x_{i,exptl}$ are the calculated and experimental data, respectively. The value of AARD % is 12.7 %.

The parameter b is approximately related to the enthalpy of sublimation $\Delta_{vap}H$ of the solid solutes by

$$\Delta_{vap} = -Rb \quad (4)$$

where R is the gas constant. The validity of eq 4 relies on the assumption that the enhancement factor $\ln(xP/P_v)$, where P_v is the vapor pressure of the solute, is independent of temperature, which is found to be approximately true in practice.[7] For oxymatrine, the calculated value of $\Delta_{vap}H$ from eq 4 is 67 $kJ \cdot mol^{-1}$.

Conclusions

The solubility of oxymatrine in carbon dioxide was determined over the pressures ranging from (11 to 21) MPa and at the temperatures of (308.15, 318.15, and 328.15) K. The determined solubility was in the range of (6.81 to 24.6)$\cdot 10^{-7}$ mole fraction in all experimental conditions. The solubility increased with rising pressure at constant temperature, and the crossover pressure was found to locate at around 12 MPa among three solubility isotherms. The experimental data were fitted by a three-parameter semiempirical model supposed by Bartle, which leads to an AARD % of 12.7 %.

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