Solubilization of Oxymatrine in Water-in-Supercritical Carbon Dioxide Microemulsions

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The solubilization amount of oxymatrine in ammonium carboxylate perfluoropolyether (PFPE-NH_4) water-in-supercritical carbon dioxide microemulsions with a water-to-surfactant molar ratio of (10.2, 14.8, and 21.0) was determined at temperatures of (308.15, 313.15, 318.15, 323.15, and 328.15) K and a density of 0.822 g·mL^{-1} using a static apparatus with a sampling part. The determined solubilization amount of oxymatrine was 2 orders of magnitude higher than the solubility of oxymatrine in supercritical carbon dioxide and about 1/6 to 1/5 of the solubility of oxymatrine in bulk water. It was indicated that the solubilization amount of oxymatrine increased with an increase of the water-to-surfactant molar ratio and temperature in all experimental conditions.

Introduction

Supercritical carbon dioxide ($scCO_2$) is the most frequently used solvent in supercritical fluid technology because it offers the transport and tunability properties of a supercritical fluid in an economic, environmentally benign form.[1] However, $scCO_2$ is a poor solvent for a wide range of hydrophiles and polar substances because of its low permittivity. This disadvantage has limited the application of $scCO_2$ to chemical processes such as separation, reaction, and material formation. One of the most promising approaches for enhancing the solubility is to use water-in-$scCO_2$ (W/C) microemulsions.[2,3] A W/C microemulsion is formed as the polar chemicals of small diameter droplets dispersed in CO_2. The aqueous phase especially disperses as nanosized (nm) droplets surrounded by a monolayer of surfactant molecules in the continuous CO_2-rich phase of the W/C microemulsion.[4] Using supercritical CO_2 to create a W/C microemulsion may be advantageous in some chemical processes, such as extraction, cleaning, nanoparticle synthesis, and chemical reactions. Knowledge of the solubilization amount is therefore essential for the application of these processes based on W/C microemulsions.

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.[5,6]

In this work, we measured the solubilization amount of oxymatrine in W/C microemulsions formed by ammonium carboxylate perfluoropolyether (PFPE-NH_4) and studied the effects of water-to-surfactant molar ratio (W_0) and temperature on the solubilization amount.

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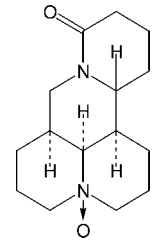

Figure 1. Chemical structure of oxymatrine.

Experimental Section

Materials. Carbon dioxide (99.995 % purity) purchased from Shanghai Praxair-Baosteel Inc. was used. Oxymatrine (more than 98.0 % purity) was supplied by the China Aroma Chemical Co. Ltd. and used without further purification. Perfluoropolyether (PFPE) with an average molecular weight of 2500 Da was purchased from DuPont. Water with a resistance of more than 16.0 MΩ was purified by a Nanopure system (Waters, USA). Ammonia, methanol, phosphoric acid, and triethylamine were analytically pure grade.

Apparatus and Methods. PFPE-NH_4 was prepared by conversion of the acid form of PFPE with an excess amount of ammonia. In a typical experiment, 35 mL of ammonia was stirred with 10 g of PFPE dropping into it very slowly at room temperature. Then the ammonia was decanted off, replaced by fresh ammonia, and stirred for about 24 h. The waxy product was washed with deionized water and dried by an oil vacuum pump at 333.15 K overnight. FTIR was used to monitor the conversion of the acid to the ammonium salt according to Frank and Marr.[7] The peak $\gamma(COONH_4) = 1655$ cm^{-1} of the totally converted PFPE-NH_4 appeared and displaced the peak $\gamma(COOH) = 1776$ cm^{-1} of the PFPE.

A static apparatus connected with a sampling part was built to determine the solubilization amount of oxymatrine in W/C microemulsions and is shown in Figure 2. A 39.68 mL Autoclave (7) is the core equipment which can operate at pressures up to 40 MPa and temperatures below 343.15 K. The sampling part consists of two high-pressure valves (13, 14) and

10.1021/je700719r CCC: $40.75
Published on Web 06/26/2008

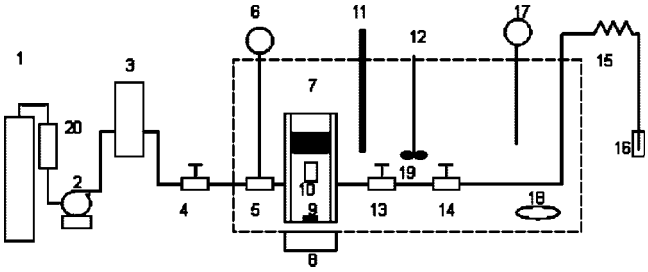

Figure 2. Schematic diagram of the experimental apparatus for measuring the solubilization amount. 1, CO_2 cylinder; 2, high pressure pump; 3, buffer tank; 4, 13, 14, high-pressure valve; 5, three-way connector; 6, pressure transducer; 7, autoclave; 8, magnetic stirrer; 9, stirring bar; 10, sample basket; 11, thermometer; 12, stirrer; 15, capillary; 16, collection bottle; 17, thermocouple; 18, heat coil; 19, sampling pipe; 20, cooling bath.

Table 1. Results of Blank Experiments

materials in autoclave	solubility
oxymatrine/$scCO_2$	$\sim 10^{-3}$ mg·mL^{-1}
oxymatrine/PFPE-NH_4/$scCO_2$	$\sim 10^{-3}$ mg·mL^{-1}
oxymatrine/water/$scCO_2$	$\sim 10^{-3}$ mg·mL^{-1}
oxymatrine/PFPE-NH_4/water/$scCO_2$	$\sim 10^{-1}$ mg·mL^{-1}

Table 2. Solubilization Amount of Oxymatrine in W/C Microemusions

W_0	T/K	P/MPa	S/mg·mL^{-1}
10.2	308.15	14.99	0.462
	313.15	16.92	0.893
	318.15	18.61	1.215
	323.15	20.47	1.577
	328.15	21.78	2.073
14.8	308.15	15.81	1.481
	313.15	17.78	1.791
	318.15	19.52	1.954
	323.15	21.31	2.162
	328.15	22.81	2.466
21.0	308.15	15.40	1.763
	313.15	17.20	2.275
	318.15	18.72	2.990
	323.15	19.94	3.288
	328.15	21.42	3.938

a (74.89 or 82.67) μL sampling pipe (19). An excessive amount of oxymatrine was placed into a sample basket (10), and a given amount of PFPE-NH_4, water, and a stirring bar (9) were loaded into the autoclave. CO_2 was then pumped into the sealed autoclave to a target pressure. The system was stirred by a magnetic stirrer (8). Temperature variation was controlled within $\pm$ 0.1 K. Equilibrium was reached when the oxymatrine concentration in the autoclave did not change further. It often takes about (15 to 20) h for equilibrium as proved by sample analysis. Samples were carefully obtained using the sampling part after equilibrium was attained.

Oxymatine in the sample was dissolved in methanol and quantified by HPLC. The chromatographic analysis was carried out on a Symmetry C18 column (150 mm $\times$ 4.6 mm, 5 μm, Waters) at a flowrate of 0.3 mL·min^{-1} at 303.15 K. The mobile phase was methanol−water−triethylamine (55:45:0.2, V:V:V), which was adjusted to pH 7.0 by phosphoric acid. The detection wavelength was set at 254 nm.

The static apparatus was evaluate through measuring the solubility of naphthalene in $scCO_2$ at 308.15 K and comparing the obtained results with the data from Tsekhanskaya[8] and Hansen.[9] There is a satisfying agreement of $\pm$ 5 %.

Results and Discussion

Blank Experiments. Blank experiments were undertaken to prove that the solubility of oxymatrine in $scCO_2$ was enhanced by W/C microemulsions. At 328.25 K and 30.0 MPa, the solubility of oxymatrine in $scCO_2$, PFPE-NH_4/$scCO_2$, and water/$scCO_2$ was determined and compared. to the solubility of oxymatrine in PFPE-NH_4/water/$scCO_2$. The results are shown in Table 1 The solubility of oxymatrine was two magnitudes higher than other systems when PFPE-NH_4 and enough water existed in $scCO_2$; that is, the solubility of oxymatrine in $scCO_2$ was enhanced by the W/C microemulsions.

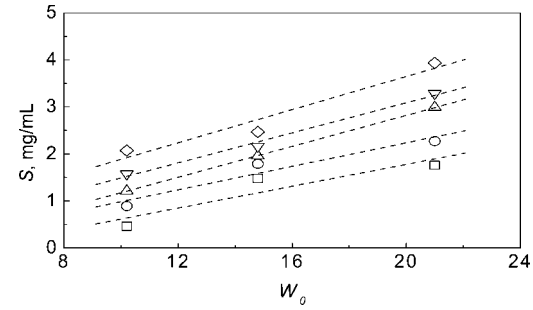

Figure 3. Influence of W_0 and temperature on solubilization of oxymatrine. In all experiments, the mass ratio of PFPE-NH_4/CO_2 is 0.0256 ($\pm$0.0004) and the density of CO_2 is 0.822 ($\pm$ 0.002) mg·mL^{-1}. □, 308.15 K; ○, 313.15 K; △, 318.15 K; ▽, 323.15 K; ◇, 328.15 K; ----, guide for eyes.

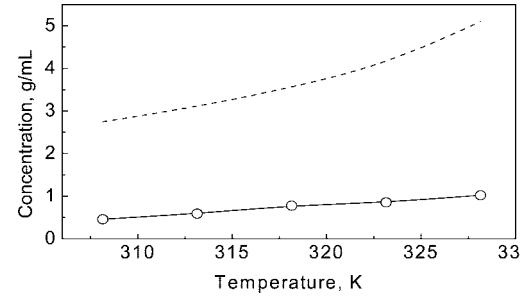

Figure 4. Comparison of oxymatrine concentration in solubilized water and oxymatrine solubility in bulk water. ○, the concentration of oxymatrine in solubilized water at $W_0 = 21.0$; ----, the solubility of oxymatrine in bulk water.

Effects of W_0 and Temperature. The solubilization amount of oxymatrine in W/C microemulsions was determined at a W_0 of (10.2, 14.8, 21.0) and temperatures of (308.15, 313.15, 318.15, 323.15, and 328.15) K. In all experiments, the volume of the autoclave and the density of the W/C microemulsions were maintained constant. Taking the volume of the autoclave as the volume reference, the resulting solubilization amounts in terms of mass concentration, S, of the solute in the W/C microemulsions are shown in Table 2. Each redported data point is the average value obtained from at least three replicated experiments with the reproduciblity within 5 %. The experimental results are also presented in Figure 3 as a function of W_0. It can be observed that the solubilization amount of oxymatrine increases with an increase of W_0 when the temperature remains unchanged. This variation was caused by an increase of solvent capacity when much water was solubilized in the microemulsions. Temperature is also an important factor affecting the solubilization amount. When temperature increases, the solubilization amount increases at the same W_0. However, the effect of temperature is more complex than that of W_0. On one hand, the solubility of oxymatrine in bulk water increases with an increase of temperature. On the other hand, while temperature increases, the water solubilized in the core of microemulsions decreases,[10] because more water transfers to the bulk CO_2.[11] This decreases the radius and polarity of the core water[12] and subsequently decreases the solubilization

amount of oxymatrine. Obviously, the former factor is more important to solubilization.

Comparison to the Solubility of Oxymatrine in Bulk Water. The solubilization amount was transformed into the concentration of oxymatrine in the solubilized water in the W/C microemulsions, and it was compared to the solubility of oxymatrine in bulk water as shown in Figure 4. In bulk water, the solubility of oxymatrine is 5 to 6 times higher than that in solubilized water. This can be explained by the polarity decrease when water solubilized into the core of the W/C microemulsions.

Conclusions

The solubilization amount of oxymatrine in ammonium carboxylate perfluoropolyether (PFPE-NH_4) water-in-supercritical carbon dioxide microemulsions with a water-to-surfactant molar ratio of (10.2, 14.8, and 21.0) was determined at temperatures of (308.15, 313.15, 318.15, 323.15, and 328.15) K and a density of 0.822 $g \cdot mL^{-1}$ using a static apparatus with a sampling part. The determined solubilization amount of oxymatrine was in the range of (0.462 to 3.938) $mg \cdot mL^{-1}$, which was two magnitudes higher than the solubility of oxymatrine in supercritical carbon dioxide and about 1/6 to 1/5 of the solubility of oxymatrine in bulk water. It was indicated that the solubilization amount of oxymatrine increased with an increase of W_0 at the same temperature and increased with an increase of temperature at the same W_0 conditions.

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Received for review December 7, 2007. Accepted May 9, 2008. This work was financially supported by the National Natural Science Foundation of China (No. 20676112), the National Key Project of Scientific and Technical Supporting Programs Funded by the Ministry of Science & Technology of China (No. 2006BAD27B03), and the Zhejiang Provincial Natural Science Foundation of China (No. Y405102).

JE700719R