Solubility of Racemic Paroxetine Intermediate in Supercritical Carbon Dioxide

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The solubility of racemic paroxetine intermediate in supercritical carbon dioxide was measured in the pressure range from (9 to 24) MPa and at temperatures of (308.2, 318.2, and 328.2) K using a continuous flow-type apparatus equipped with a high-pressure UV−Vis detector. Results showed that under the present operation conditions, the experimentally determined solubility of the racemic compound was in the range of (7.3×10^{-5} to 1.2×10^{-3}) in mole fraction. The solubility increased with rising pressure at constant temperature, and the crossover pressure was found to locate at around 12 MPa for the three solubility isotherms. An empirical density-based Chrastil's equation was used to fit the experimental solubility data, giving a good correlation with an AARD of 7.56 %.

Introduction

trans-(−)-Paroxetine (Figure 1), a potent and selective 5-hydroxytryptamine reuptake inhibitor, is currently used in the treatment of a variety of human diseases such as depression, obsessive compulsive disorder, and panic disorder.[1,2] Most of the synthetic routes developed toward the preparation of this compound involve the key intermediate racemic *trans*-4-(4′-fluorophenyl)-3-hydroxymethyl-1-methyl-piperidine. As the active pharmaceutical ingredient *trans*-(−)-paroxetine is an optically pure compound, the racemic key intermediate needs to be resolved. The enantiomeric separation can be achieved by enantioselective chromatography or enzymatic resolution.[3,4] Recently, supercritical carbon dioxide (SC-CO_2) has been used as a solvent of enantiomeric separations using supercritical fluid chromatography and supercritical fluid simulated moving bed chromatography with chiral stationary phases.[5,6] Knowledge of the solubility of enantiomers in SC-CO_2 is therefore essential for the design and development of chemical and pharmaceutical processes for optical resolutions and for establishing optimum conditions of operation.

In the present work, the solubility of the racemic paroxetine intermediate in supercritical carbon dioxide was measured from (9 to 24) MPa and at temperatures of (308.2, 318.2, and 328.2) K using a continuous flow-type apparatus equipped with a high-pressure UV−Vis detector. Modeling of the experimental solubility data was carried out using an empirical density-based Chrastil's equation.

Experimental Section

Materials. Carbon dioxide of 99.9 % purity was used for all experiments. HPLC grade methanol (99.9 % purity) was obtained from Burdick & Jackson (Honeywell, USA). Racemic *trans*-4-(4′-fluorophenyl)-3-hydroxymethyl-1-methyl-piperidine (more than 99 % purity) was purchased from Zhejiang Haisen Pharmaceutical Co., Ltd (China).

Apparatus and Procedure. The apparatus used to determine the solubility of paroxetine intermediate in SC-CO_2 is shown schematically in Figure 2. The determination of the solubility in this study was performed in a manner similar to that described by Xing et al.,[7] which is described again for convenience: From a gas cylinder (1), CO_2 was supplied and was liquefied through a cooling unit (4). A syringe pump (5) equipped with a circulating water jacket was used to pump CO_2 at the desired pressure to a saturation cell (12) containing the solute. Pressurized CO_2 was then introduced into the column via a 2-m stainless steel coil (8) immersed in a thermostated water bath (14) to ensure that CO_2 was at the correct temperature prior to entering the cell. A commercially available empty HPLC column (150 mm × 4.6 mm) was used as the saturation cell connected to a Rheodyne six-port valve, which enables the cell to be switched in or out of the flow path. Approximately 0.5 g of the solute was mixed well with clean sand and packed into the saturation cell. A sintered stainless steel frit of 2 μm at each end of the cell was used to prevent any entrainment of the solute. A liquid chromatographic multiwavelength UV−Vis detector (ALLTECH model 200) equipped with a high-pressure flow cell was used to detect the solute concentration in SC-CO_2, with its signals captured and processed by a computer (19) using N2000 version 3.3 software (Zhejiang University Zhida Information Engineering Co., Ltd, China). The pressure at the inlet of the saturation cell was measured with a pressure transducer (9) (KYB18, Kangyu Control System Co., Ltd. China) with an accuracy of ± 0.05 MPa. The system temperature was controlled within ± 0.1 K, and measured by a thermocouple. The saturated SC-CO_2 was depressurized through a pressure regulator (16) connected to the outlet of detector. To minimize the risk of plugging the tubing, the regulator was placed in a heating block (15) at a temperature above the melting point of the detected solute. The actual flow rate of CO_2 expanded to an ambient

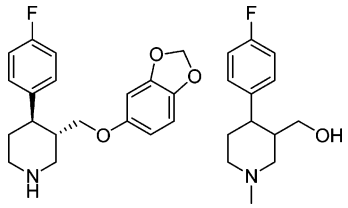

Figure 1. Structures of paroxetine and its intermediate.

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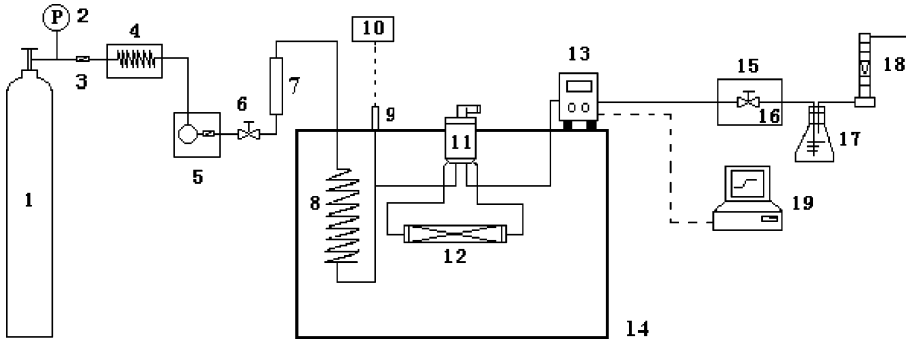

Figure 2. Schematic diagram of experimental apparatus: 1, gas cylinder; 2, pressure gauge; 3, filter; 4, cooling unit; 5, syringe pump; 6, check valve; 7, surge tank; 8, preheating coil; 9, pressure transducer; 10, pressure display; 11, Rheodyne six-port valve; 12, saturation cell; 13, UV−Vis detector; 14, thermostated water bath; 15, heating block; 16, pressure regulator; 17, water saturator; 18, flowmeter; 19, chromatographic workstation.

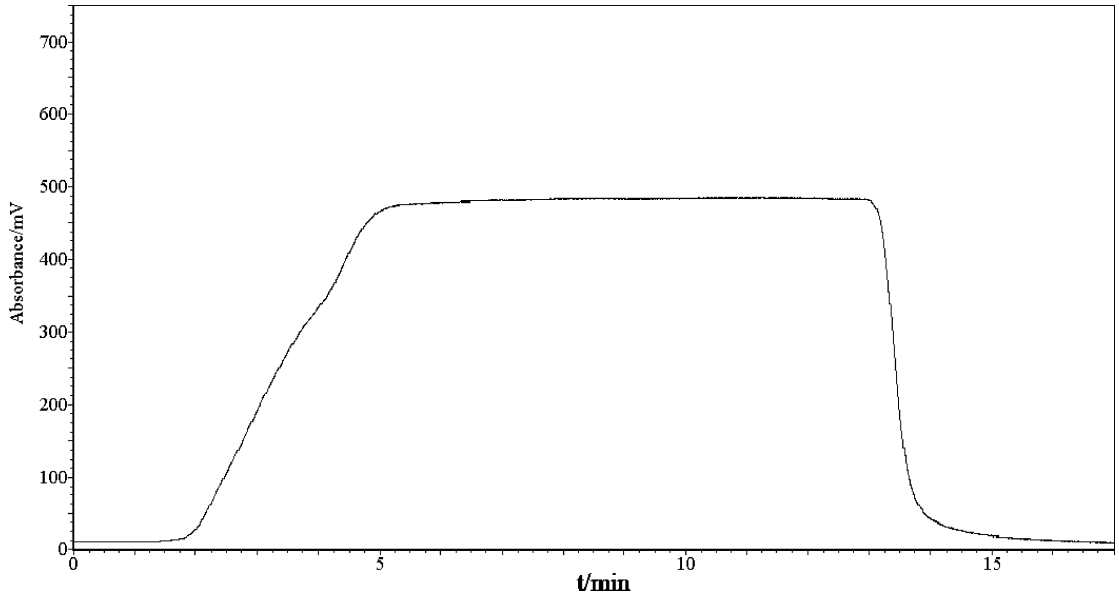

Figure 3. Typical solute solubility profile in SC-CO_2 with UV detection at 254 nm.

pressure, after passing through a water saturator (17), was adjusted to about 30 mL·min^{-1} and measured by a flowmeter (18).

A typical solute solubility profile is shown in Figure 3. The detector wavelength is set to 254 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 and flush the tubing and flow cell. Once a UV response baseline was established in the detector, the saturation cell was brought on-line, allowing the SC-CO_2 to saturate with solute. Equilibration typically occurred within several minutes and kept for about 10 min. The net solute UV response at 254 nm for each solubility run was determined by subtracting the average baseline signal of solute-free CO_2 from the average UV response plateau of CO_2 that was saturated with the solute after the equilibration was established.

Referring to Figure 2, 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 racemic paroxetine intermediate in methanol. 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 on-line, and a typical response for each calibration was recorded until the signal returned to the baseline. Response factor K was calculated at each temperature and pressure by eq 1, and the mole fraction solubility at the employed experimental pressures and temperatures was calculated by eq 2:

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

$$y_2 = \frac{H_i}{K\rho M_s} \tag{2}$$

where K is the response factor of UV detector, H_i (mV) is the average UV response plateau, m_0 (g) is the amount of the solute injected from sample loop, F_0 (L·s^{-1}) is the SC-CO_2 flow rate, A_0 (mV·s) is the elution area of an amount of m_0 solute, ρ (mol·L^{-1}) is the density of SC-CO_2, and M_s (g·mol^{-1}) is the molecular weight of the test solute. All the solubility measurements and calibrations processes were performed more than three times at the same condition, and each solubility was expressed by an arithmetic average.

Results and Discussion

Solubility measurements were performed under several flow rates of CO_2 (15 to 70 mL·min^{-1}) at given temperature and pressure. The solubility obtained was found to be independent of the flow rate, thereby confirming that the equilibrium saturation was achieved. The experimental solubility of the solute in SC-CO_2 is listed in Table 1. The experimental solubility

Table 1. Experimental Solubility of Racemic Paroxetine Intermediate in Supercritical Carbon Dioxide

T / K	*p* / MPa	*ρ* / kg·m^{-3}	$y \times 10^4$	*S* / g·L^{-1}
308.2	8.83	648.7	2.22	0.73
	10.05	714.7	2.72	0.99
	12.15	770.1	3.59	1.40
	14.01	801.6	3.87	1.57
	15.96	826.7	4.70	1.97
	18.01	848.1	5.20	2.24
	20.05	866.1	5.36	2.35
	22.03	881.4	6.41	2.86
	24.05	895.2	6.76	3.07
318.2	10.01	499.8	1.43	0.36
	12.02	658.6	3.13	1.04
	14.05	721.6	4.45	1.63
	15.91	758.5	5.64	2.17
	18.05	789.9	6.92	2.77
	20.02	812.9	7.44	3.07
	21.98	832.2	8.58	3.62
	24.20	851.0	9.28	4.00
328.2	10.00	325.1	0.727	0.12
	11.95	500.5	2.36	0.60
	14.00	618.4	4.26	1.34
	16.04	682.1	6.77	2.34
	18.02	723.4	8.36	3.07
	20.06	755.4	10.04	3.84
	22.07	780.7	11.84	4.69

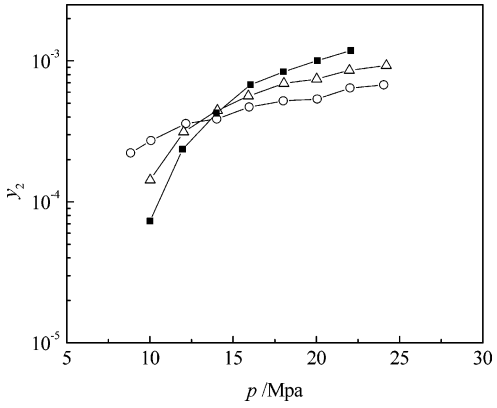

Figure 4. Experimental solubility of racemic paroxetine intermediate in supercritical carbon dioxide: □, 308.2 K; ○, 318.2 K; △, 328.2 K.

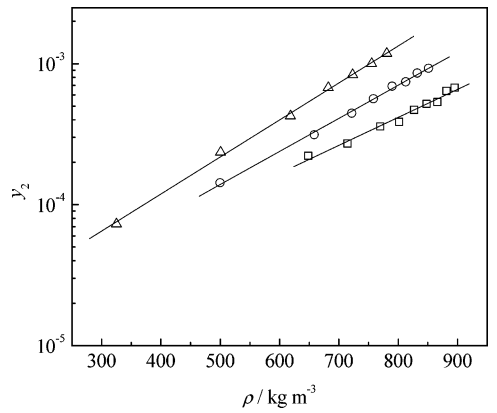

Figure 5. Logarithmic relationship between solubility of racemic paroxetine intermediate and pure SC-CO_2 density at different temparutres: □, 308.2 K; ○, 318.2 K; △, 328.2 K. Solid lines represent regression fit of the data.

of the solute at temperatures of (308.2, 318.2, and 328.2) K in SC-CO_2 is also plotted in Figure 4 as a function of pressure. As shown in Figure 4, it is noted that the solubility increases with rising pressure in all cases, which can be easily explained in terms of the specific interaction between the solute and the solvent molecules. Density and solvent power rise with increasing pressure, which mean that the intermolecular mean distance decreases. Consequently, the specific interaction between the solute and the solvent molecules increases, thereby leading to higher solubility. However, the effect of temperature on solubility is more complex, and the crossover behavior can also be observed as reported previously.[8] It can be seen from Figure 4 that the crossover pressure point is located at around 12 MPa among three solubility isotherms. Below this crossover pressure, the solubility increases with decreasing temperature. Above the value, the effect of the temperature on the solute vapor pressure overlays the effect on the solvent density, resulting in an increase of the solubility with the temperature increases.

Table 2. Regression Parameters of Chrastil's Model for Paroxetine Intermediate Solubility in SC-CO_2

k	*A*	*b*	% AARD[a]	ΔH/kJ·mol^{-1}
5.15 ± 0.10	-2171 ± 118	-26.5 ± 0.4	7.56	−18.0

[a] % AARD $= 1/N\Sigma^N|(S_{exp} - S_{calc})/S_{exp}| \times 100$ %.

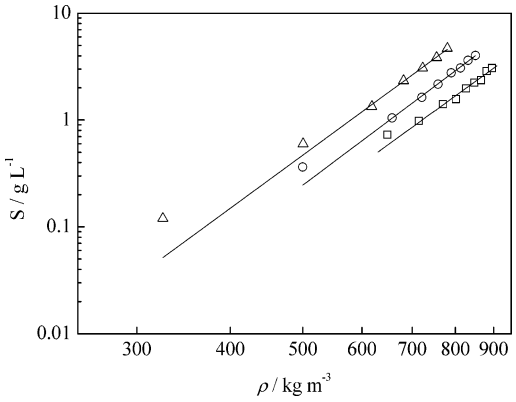

Figure 6. Linear relationship between ln *S* and ln *ρ* at different temparutres: □, 308.2 K; ○, 318.2 K; △, 328.2 K. Solid lines represent Chrastil's regression fit.

To confirm the reliability of the experimental data, we also examined the internal consistency of solubility data using the following equation proposed by Kumar and Johnston:[9]

$$\ln y_2 = C_0 - \left(\frac{\bar{V}_2}{RT\beta_T}\right)_{\rho_r=1} \rho_r \qquad (3)$$

where C_0 is a constant, $\bar{V}_2$ is the partial molar volume of solute in the supercritical fluid, ρ_r is the reduced density of the supercritical fluid phase, and β_T is the isothermal compressibility of the supercritical fluid phase.

As indicated by Figure 5, the logarithm of the experimental solubility data gave a good linear relationship with pure SC-CO_2 density. This was also observed by other workers.[10−12]

Data Correlation

Models based on equations of state, together with different mixing rules, are the most widely used to correlate and predict the solubility of solid in SC-CO_2. However, these models normally require the solute properties, such as critical parameters, acentric factor, solid molar volume, and vapor pressure that are often unavailable, especially for pharmaceutical compounds. To avoid the disadvantages above as well as complicated computational procedures, we adopt an empirical density-based model proposed by Chrastil.[13]

Chrastil's model is the most commonly used model, which correlates the solubility of a solute in a supercritical fluid to

the density and temperature. The equation between solubility and density can be expressed as

$$S = \rho^k \exp(a/T + b) \quad (4)$$

where S is the solubility (g/L) of the solute in SC-CO_2 and ρ is the density (g/L) of the pure CO_2 at the experimental temperature and pressure. The constant k is the number of CO_2 molecules associated with the solute. The parameter a is defined as $\Delta H/R$, where ΔH is the sum of the enthalpies of vaporization and solvation. The parameter b is dependent on the molecular weights of supercritical fluid and solute. By performing a multiple linear regression on ln S as a function of ln ρ and $1/T$, the results are presented in Table 2 along with ΔH calculated from a. The representative plots of ln S versus ln ρ are illustrated in Figure 6. As seen from Figure 6, there is a good correlation between calculation value and the experimental data, with an overall average absolute relative deviation of 7.56 %. It can be also noted that there exists relatively significant error at the lower pressures, especially near critical point, which might be contributed to the remarkable variation of the solvent properties under such operation condition.

Conclusions

The solubility of the racemic key intermediate of paroxetine in supercritical carbon dioxide was measured by a continuous flow-type apparatus equipped with a high-pressure UV−Vis detector from (9 to 24) MPa and at (308.2, 318.2, and 328.2) K. The experimentally determined solubility of the racemic compound at the present conditions was in the range of (7.3×10^{-5} to 1.2×10^{-3}) in mole fraction. 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. Below this crossover pressure, the solubility increases with decreasing temperature, and above this value, the reverse is the case. The experimental solubility data was correlated by an empirical density-based Chrastil's equation with an AARD of 7.56 %. The results are useful for the design and development of chemical and pharmaceutical processes for optical resolutions.

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