Solubility of Isoniazid in Supercritical Carbon Dioxide

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Solubility data of isoniazid in supercritical carbon dioxide are important in selecting the most appropriate supercritical methods for pharmaceutical material processing, such as the micronization of isoniazid or the production of isoniazid composites. The solubility of isoniazid in supercritical carbon dioxide was measured using a dynamic analytical method at temperatures of (308, 311, and 313) K and pressures ranging from (13.0 to 18.5) MPa. The result showed that isoniazid solubility increased with the increase of pressure at an isothermal condition and it also increased with the increase of temperature. The experimental data were correlated using the Chrastil and Mendez-Santiago and Teja models. The calculated results show good agreement with the experimental data.

Introduction

A stronger medicine is not always required for better medical treatments. Drug efficacy can be increased by finding an optimal drug formulation or using a suitable delivery system.[1] It is agreement with one of the basic tenets of clinical pharmacology to deliver the right drug at the right dose to the right patient so as to have optimum therapeutics. This tenet includes how the drug is delivered, which is choosing the correct route of drug administration, for example, oral, parenteral, transdermal, and inhalation routes.[2] A comparison between two delivery systems for rivastigmine demonstrated that a transdermal patch of rivastigmine provides efficacy similar to the highest dose of an oral capsule with a superior tolerability profile.[3]

Isoniazid (INH, pyridine-4-carbohydrazide, CAS Registry No. 54-85-3) is one of the primary drugs used in the treatment of tuberculosis (TB) and is well-known for its definite value in preventive therapy.[4] The most common way for its administration is oral uptake. As an alternative, some researchers tried to formulate a dosage form of TB drugs via a respiratory route. It showed that this type of delivery can improve drug bioavailability and reduce the dosing frequency for better management of pulmonary tuberculosis.[5] However, its preparation used emulsification and a solvent evaporation technique known to have several drawbacks, such as residual organic solvent in the final product and volatile organic compound emission.[6] Methods based on supercritical carbon dioxide technology for material processing would be an alternative to overcome these shortcomings.

Supercritical carbon dioxide offers several advantages to pharmaceutical processing due to its mild operation conditions, nontoxicity, and relatively contaminant-free products. There are several pieces of research dealing with particle processing for pulmonary delivery using supercritical carbon dioxide.[7−9] These research are performed using different process arrangements and apparatuses. Amidi et al.[10] have been successful in preparing inhalable insulin-loaded particles using supercritical fluid technology, where the particle preserved the original insulin structure. A number of different acronyms are used to indicate the supercritical carbon dioxide particle processing, that is, RESS (rapid expansion of *supercritical* fluid solutions), GAS (gas antisolvent), PCA (precipitation by compressed antisolvent), ASES (aerosol solvent extraction system), SEDS (solution enhanced dispersion by supercritical fluids), and SAS (supercritical antisolvent) processes.[11]

It is important to consider the phase behavior of supercritical fluid systems in selecting the most appropriate supercritical methods for pharmaceutical material processing. It includes the knowledge of equilibrium solubility of the solute in the supercritical fluids. Precipitation from supercritical solution as one of basic mechanisms for material processing is often limited by the solute solubility.[12] A large number of solubility data of pharmaceutical compounds in supercritical carbon dioxide have been measured, reported, and reviewed.[13] However, through our intensive literature survey on isoniazid, we found no works reporting experimental solubility data of isoniazid in supercritical carbon dioxide.

This study is part of a research project for the production of isoniazid composites using supercritical fluid carbon dioxide. In this study, the equilibrium solubility of isoniazid in supercritical carbon dioxide was measured from (13.0 to 18.5) MPa at (308, 311, and 313.0) K.

Experimental Section

Materials. Carbon dioxide (purity 0.997) was supplied by Air Products (M) Berhad. Isoniazid and naphthalene were purchased from Sigma (purity 0.990) and used without any further treatments. Hexane (Merck, purity 0.960), iron(III) chloride hexahydrate (Merck, purity 0.990), and potassium hexacyanidoferrate(III) (Merck, purity 0.990) were used as solvents and reagents without further purification. All of the purities are referred to as a mass fraction.

Apparatus and Procedures. The solubility of isoniazid was experimentally determined by a dynamic analytical method in an apparatus illustrated in Figure 1. The main part of this apparatus is the high-pressure vessel made of stainless steel with an inner diameter of 10 mm and 200 mm long. The vessel was immersed in a constant-temperature water bath controlled by a thermoregulator (Thermo Haake, model DC10) that maintained

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10.1021/je900622h
Published on Web 05/18/2010

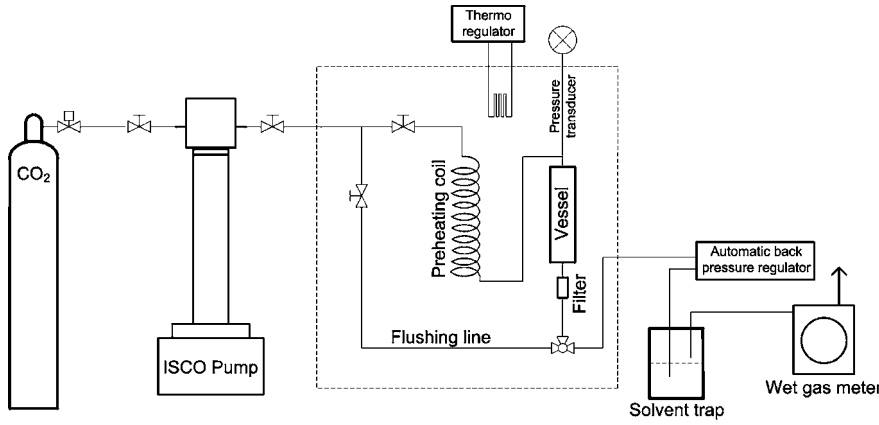

Figure 1. Schematic diagram of the experimental apparatus.

a constant temperature within ± 0.1 K. The system pressure was measured by a pressure transducer (Druck, PDCR 4030) accurate to ± 0.01 MPa. An automatic back-pressure regulator (Thar, model ABPR-200-2) was used to depressurize CO_2 and to maintain the pressure of the system constantly. A syringe pump (ISCO, model 260 DM) was used to compress and to deliver the liquid CO_2. The volume of CO_2 was determined using a wet gas meter.

First, the vessel was filled with an appropriate amount of solute distributed in stainless steel balls and packed at each end with glass wool to avoid channelling and physical entrapment. It is brought to the desired temperature by immersion in a water bath. The syringe pump was filled with liquid CO_2 at 278 K, which then fed into the vessel through a preheating coil until the desired pressure was achieved. The system was left further at the desired temperature and pressure for 30 min to reach equilibrium before starting an experiment. The syringe pump delivered a total of approximately 2 mol of CO_2 into the vessel at a constant flow rate (0.5 mL·min^{-1} at 278 K). The solute-saturated CO_2 stream was then depressurized to ambient conditions through the BPR. The dissolved solutes, after exiting from the ABPR, were trapped in a solvent trap, and CO_2 was released through a wet gas meter. To ensure that there were no residual precipitate solutes in the upstream line of ABPR, a fresh stream of CO_2 (0.5 mL·min^{-1}) drained through the flushing line for at least 20 min. The reliability of the instrument was cross-checked against binary solubility data in literature for naphthalene.

The analysis of the solutes was carried out offline by using spectrophotometric methods. Naphthalene trapped in hexane was diluted to a convenient volume and measured at 265 nm using UV−vis spectrophotometer (Perkin-Elmer, Lambda 35). The concentration of naphthalene was calculated based on a calibration curve from UV analysis of naphthalene standard solution. The amount of isoniazid was determined by spectrophotometric methods utilizing potassium ferricyanide as a spectroscopic probe reagent.[14] An aqueous isoniazid solution was mixed with ferric chloride, and then potassium ferricyanide solution was added into the mixture. This would result in a prussian blue color solution. Afterward, the solution's absorbance was measured at 735 nm against a reagent blank. Then, the concentration of isoniazid was calculated on the basis of a calibration curve from visible spectrophotometric analysis of isoniazid standard solution.

Each piece of solubility data reported in this experiment was taken from the average of triplicate measurements. The coefficient of variation of measurements was generally less than 12 %.

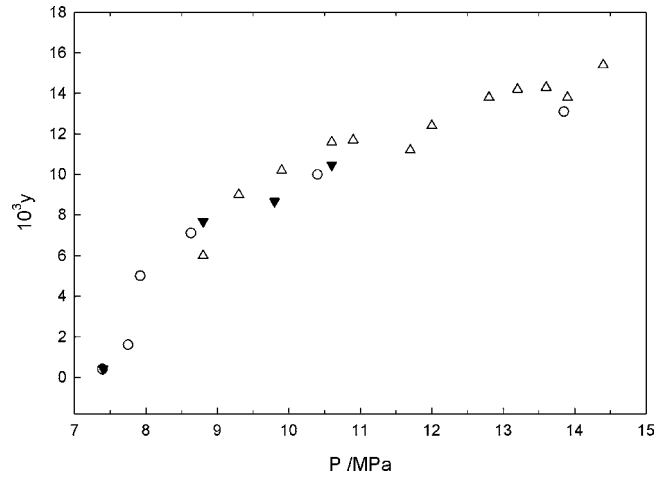

Figure 2. Comparison of naphthalene solubility data in supercritical carbon dioxide at 308 K: △, ref 15; ○, ref 16; ▼, this work.

Results and Discussion

The reliability and validity of the experimental apparatus and procedures were first confirmed by measuring naphthalene solubility in supercritical carbon dioxide at 308 K and then compared with the literature data. The solubility comparisons of naphthalene in terms of the mole fraction, y, of the solutes in supercritical carbon dioxide are shown in Figure 2. We observe that there is good agreement between various measurements.[15,16]

The solubility of isoniazid with associated standard deviation (SD) in supercritical carbon dioxide along with temperature, pressure, and density of CO_2[17] related to each measurement is listed in Table 1 and presented in Figure 3. S and y_2 are the experimental values of the solubility in terms of the concentration and mole fraction. It was found that the solubility of isoniazid is considerably small compared to naphthalene. This was expected since isoniazid is a polar compound and it is more soluble in polar solvents.[18] Carbon dioxide has no dipole moment and has only a small quadrupole moment, a small polarizability volume, and a low relative permittivity. In supercritical conditions, its polarity corresponds to that of hydrocarbons such as cyclohexane.[19]

All isothermal isoniazid solubility data in supercritical carbon dioxide shows the same trend if it is plotted as a function of pressure. The solubility increases with the increase of pressure at a constant temperature. This was predicted because a pressure increase along an isotherm will increase the density of carbon dioxide. Thereby, it will increase the specific interaction between isoniazid and carbon dioxide molecules.[20] Furthermore, the

Table 1. Experimental Solubility Data of Isoniazid in Supercritical Carbon Dioxide

T / K	P / MPa	ρ_{CO_2} / g·L^{-1}	$10^6\ y_2$ / mol·mol^{-1}	$10^2\ S$ / g·L^{-1}
308	13.0	787	0.53 ± 0.03	0.13 ± 0.01
	14.0	802	0.79 ± 0.08	0.20 ± 0.02
	15.0	816	1.00 ± 0.01	0.25 ± 0.00
	16.0	828	1.13 ± 0.04	0.29 ± 0.01
	17.0	839	1.41 ± 0.16	0.37 ± 0.04
	18.5	853	1.61 ± 0.03	0.43 ± 0.01
311	13.0	762	1.17 ± 0.01	0.28 ± 0.00
	14.0	780	1.59 ± 0.07	0.39 ± 0.02
	15.0	795	1.81 ± 0.18	0.45 ± 0.04
	16.0	809	2.17 ± 0.12	0.55 ± 0.03
	17.0	821	2.99 ± 0.15	0.77 ± 0.04
	18.5	837	4.02 ± 0.22	1.05 ± 0.06
313	13.0	744	2.12 ± 0.08	0.49 ± 0.02
	14.0	764	3.28 ± 0.10	0.78 ± 0.02
	15.0	781	4.14 ± 0.32	1.01 ± 0.08
	16.0	796	4.85 ± 0.04	1.20 ± 0.01
	17.0	809	5.45 ± 0.12	1.37 ± 0.03
	18.5	826	6.05 ± 0.11	1.56 ± 0.03

increase of carbon dioxide density will also increase the polarity of its molecules.[21]

In the range of pressure studied here, the solubility of isoniazid increases with the increase of temperature. The effects of temperature on the solubility are rather complex. It can be attributed to the combination effects of temperature toward solute vapor pressure, solvent density, and intermolecular interaction in the fluid phase.[20] The same temperature effects can be found in the solubility of caffeic acid[22] and dichlorobis(triphenylphosphine)nickel(II)[23] in supercritical carbon dioxide.

The experimental solubility data were correlated using two semiempirical models, namely, the Chrastil model[24] and Mendez-Santiago and Teja (MST) model.[25] The Chrastil model was developed from the idea that the molecules of solute associate with the molecules of gas by forming a solvate complex, which is in equilibrium with the gas. This model leads to the following equation:

$$\ln S = k \ln \rho + a/T + b \qquad (1)$$

where S (g·L^{-1}) is the solubility of solute in supercritical fluids, ρ (g·L^{-1}) is the density of supercritical fluids, k is an association number, a is a constant as a function of the heat solvation and heat vaporization, b is a constant as a function of the molecular weights of the solute and supercritical fluids, and T is the temperature.

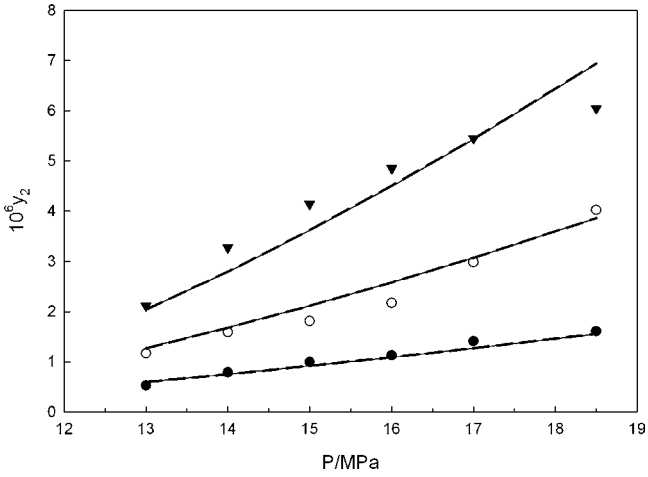

Figure 3. Solubility isotherms of isoniazid in supercritical carbon dioxide as a function of pressure: ●, T = 308 K; ○, T = 311 K; ▼, T = 313 K; —, the Chrastil model;[24] ---, the Mendez-Santiago and Teja model.[25]

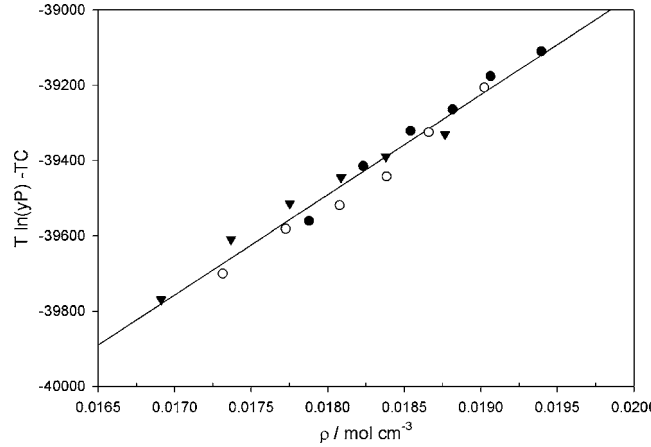

Figure 4. Test of consistency for solubility data of isoniazid using the Mendez-Santiago and Teja model: ●, T = 308 K; ○, T = 311 K; ▼, T = 313 K; —, the Mendez-Santiago and Teja model.

Table 2. Correlated Results of Isoniazid Solubility Data in Supercritical Carbon Dioxide

model	parameters	AARD (%)[a]
Chrastil (eq 1)	$k = 12.7 \pm 0.8$	8.6
	$a = (-3.6 \pm 0.1)\cdot 10^4$	
	$b = 26 \pm 5$	
Mendez-Santiago and Teja (eq 2)	$A = (-4.4 \pm 0.2)\cdot 10^4$	8.5
	$B = (2.6 \pm 0.1)\cdot 10^5$	
	$C = 117 \pm 4$	

[a] AARD(%) = $(100/n)\sum_1^n(|y_2^{cal} - y_2^{exp}|)/(y_2^{exp})$; n is the number of data points.

The MST model originated from the theory of dilute solution. It proposes a linear expression to correlate the solubility of solids in supercritical carbon dioxide (eq 2).

$$T \ln y_2 P = A + B\rho + CT \qquad (2)$$

where A, B, and C are constants and considered as temperature-independent, y_2 (mol·mol^{-1}) is the mole fraction of solute in supercritical fluids, ρ (mol·cm^{-3}) is the density of supercritical fluids, P (MPa) is the pressure of the system, and T is the temperature. In addition to the experimental data correlation, the models (the Chrastil or MST model) can be utilized for a self-consistency data test. Applying the MST for the self-consistency test was done through plotting the value of $T \ln(yP) - CT$ against the density supercritical CO_2. The data at different temperatures can collapse to a single straight line.[25] Figure 4 shows how the solubility data of isoniazid in supercritical carbon dioxide fall into a straight line. Therefore, it confirms that the experimental data are internally self-consistent.

The correlated solubility data of isoniazid in supercritical carbon dioxide are presented in Figure 3, while Table 2 gives the adjustable parameters and the average absolute relative deviation (AARD) of both models. From Figure 3 and Table 2, it can be observed that the correlated solubility fairly agreed with the experimental values. The Chrastil and MST model give similar AARD values, that is, 8.6 % and 8.5 %, respectively.

Conclusion

The solubility of isoniazid in supercritical carbon dioxide was measured over temperatures from (308 to 313) K and pressures between (13.0 and 18.5) MPa. At the range of temperature and pressure studied, the solubility of isoniazid increases with the increase of pressure at an isothermal condition, and it also

increases with the increase of temperature. Two semiempirical models (i.e., the Chrastil and MST models) used to correlate the solubility of isoniazid in supercritical carbondioxide could correlate the data satisfactorily.

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Received for review July 21, 2009. Accepted May 13, 2010. This research was carried out with the aid of a research grant from Kuok Foundation and PPP Project of University of Malaya, No. PS040/2007B.

JE900622H