Solubility of Isoniazid in Various Organic Solvents from (301 to 313) K

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The solubility of pyridine-4-carbohydrazide (isoniazid) in ethanol, methanol, ethyl acetate, and acetone has been measured gravimetrically at various temperatures ranging from (301 to 313) K at atmospheric pressure. Isoniazid is most soluble in methanol, followed by acetone, ethanol, and ethyl acetate at a temperature up to 308 K. At higher than 308 K, isoniazid is most soluble in acetone. The experimental data were correlated using the modified Apelblat equation.

Introduction

Isoniazid (INH, pyridine-4-carbohydrazide, CAS Registry No. 54-85-3, Figure 1) is one of the primary drugs used in the treatment of tuberculosis (TB) and is well-known for its definite value in preventive therapy.[1] The most common way for its administration is orally. As an alternative, some researchers tried to formulate a dosage form of TB drugs for administering drugs via the respiratory route.[2] Several techniques have been used for developing drug formulation for pulmonary delivery. One of them is supercritical fluid technology which utilizes carbon dioxide as an antisolvent.[3] In deploying this process, isoniazid should be able to be dissolved in certain organic solvents.[4] It means that knowledge of the solubility of isoniazid is necessary. Furthermore, this information is also necessary in the selection of the most appropriate supercritical antisolvent methods that could be applied.[5] However, from a review on isoniazid literature, it was found that the solubility data of isoniazid in organic solvents are scarce.

This work investigated the solubility of isoniazid in various organic solvents and at temperatures near the critical point of carbon dioxide. Solubility was measured by the gravimetric method.

Experimental Section

Materials. Isoniazid was purchased from Sigma (purity > 99 %) and used as received without any further treatments. Absolute ethanol (Scharlau, > 99.8 %), anhydrous methanol (Mallinckrodt, > 99.8 %), ethyl acetate (Mallinckrodt, 100 %), and acetone (Merck, 99.8 %) were used as solvents without further purification.

Apparatus and Procedure. The solubility of isoniazid was measured using the same apparatus that was described in the literature[6] and explained briefly here (see Figure 2). The experiment was conducted in a glass tube placed into a constant temperature water bath. The actual temperature in the glass tube was monitored by a mercury thermometer with an uncertainty of 0.1 K. A predetermined excess amount of isoniazid was added into the glass tube containing 25 mL of organic solvent. The mixture was then agitated using a magnetic stirrer. Stirring was stopped after 1.5 h. The solution was then left for 1 h, allowing undissolved solids to settle. Then, an approximately 4 g clear aliquot was transferred to a sample weighing bottle. The weighing bottle was closed tightly and weighed to determine the mass of aliquot. The solvent was then evaporated from the aliquot, and the weight of the remaining solid was then determined. Different agitation and settling times were tested to determine a suitable equilibrium time. It was found that 1.5 h agitation and 1 h settling time were enough for isoniazid in all solvents to reach equilibrium. The solubility is determined based on the mass of the aliquot and the remaining solid. The balance (BP221S Sartorius GMBH, Germany) used during the experi-

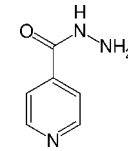

Figure 1. Structure of the isoniazid molecule.

Table 1. Mole Fraction Solubility (x_1) of Isoniazid in Pure Solvents in the Temperature Range (301 to 313) K

T/K	10^3 (x_1 ± sd)	$(x_1 - x_1^{calcd})/x_1$
	Ethanol	
301	5.45 ± 0.09	0.009
303	5.79 ± 0.03	−0.010
308	7.17 ± 0.04	−0.001
311	8.16 ± 0.01	0.002
313	8.87 ± 0.09	0.000
	Methanol	
301	10.70 ± 0.22	0.006
303	11.39 ± 0.02	−0.006
308	13.71 ± 0.03	−0.003
311	15.41 ± 0.16	0.008
313	16.34 ± 0.09	−0.004
	Ethyl Acetate	
301	1.59 ± 0.06	0.000
303	1.72 ± 0.03	0.006
308	2.06 ± 0.04	0.005
311	2.25 ± 0.05	−0.022
313	2.51 ± 0.04	0.012
	Acetone	
301	9.46 ± 0.25	0.010
303	10.42 ± 0.50	0.002
308	13.62 ± 0.34	−0.007
311	16.03 ± 0.35	−0.021
313	18.73 ± 0.48	0.012

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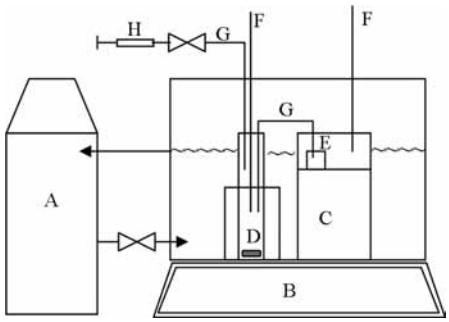

Figure 2. Schematic diagram of isothermal solubility measurement apparatus. A, thermoregulator and refrigerated bath; B, magnetic stirrer; C, sampling compartment; D, test tube (dissolution system); E, weighing bottle; F, thermometer; G, sampling line tubing; and H, syringe.

mental work had an uncertainty of 0.1 mg. The isoniazid solubility measurements were carried out at temperatures of (301, 303, 308, 311, and 313) K. Triplicates of each measurement were made to obtain reliable solubility values. The estimated uncertainty of the solubility values based on error analysis and repeated observations was within 5 %.

Results and Discussion

The solubilities of isoniazid with associated standard deviation (SD) in ethanol, methanol, ethyl acetate, and acetone are listed in Table 1 and presented in Figure 3. It was found that the solubility values are dependent on the system temperature. Increasing the system temperatures increased the isoniazid solubilities in all solvents. To some degree, the solubility of isoniazid in three solvents (methanol, ethanol, and ethyl acetate) follows the empirical rule that "like dissolves like", whereas, based on Reichardt's normalized molar electronic transition energy (E_T^N),[7] the polarity of solvents decreases from methanol, ethanol, acetone to ethyl acetate. Therefore, isoniazid as a polar compound will be more soluble in methanol and less soluble in ethyl acetate.

Concerning the solubility behavior of isoniazid in acetone, it might be attributed to the possibility of forming a molecular complex in solution such as a solvate. An acetone solvate system has shown to be more soluble in an increased temperature environment than a nonsolvate.[8] However, it should be remembered that the aforementioned explanation is only one estimation of many factors influencing the dissolution characteristics. Further discussion of dissolution phenomena is complicated and beyond the scope of this article.

Table 2. Optimized Adjustable Parameters of the Modified Apelblat Equation (Equation 1) for Isoniazid Solubility in Various Organic Solvents

solvent	*a*	*b*	*c*	rmsd
ethanol	−340.44	12300.71	52.79	0.035
methanol	−2.99	−2637.10	2.47	0.074
ethyl acetate	−318.83	11620.97	49.18	0.025
acetone	−810.92	32570.62	123.52	0.190

The dependence of isoniazid solubility in pure solvent on the temperature can be described by many thermodynamics approximation methods. A model commonly used in solubility correlation based on the nonideal solution is the modified Apelblat equation (eq 1).[9]

$$\ln x_1 = a + \frac{b}{T/\mathrm{K}} + c \ln T/\mathrm{K} \quad (1)$$

where x_1 and T are the mole fraction of the solute and absolute temperature, respectively, and a, b, and c are the empirical constants. The c value represents the effect of temperature on the fusion enthalpy, as a deviation of heat capacity (ΔC_p). The values of constants a and b reflect the variation in the solution activity coefficient and provide an indication of the effect of solution nonidealities on the solubility of solute.[9]

The correlated solubility value of isoniazid is shown in Table 1, whereas the parameter values of a, b, and c and the root-mean-square deviation (rmsd) are given in Table 2. The rmsd is defined as

$$\mathrm{rmsd} = \left[\frac{\sum_{i=1}^{N} (x_{1,i} - x_{1,i}^{\mathrm{calcd}})^2}{N}\right]^{1/2} \quad (2)$$

where N is the number of experimental points; $x_{1,i}^{\mathrm{calcd}}$ is the solubility calculated from the modified Apelblat model; and $x_{1,i}$ is the experimental value of solubility. From Tables 1 and 2, it can be observed that the correlated solubility agreed with the experimental values. This indicated that the modified Apelblat

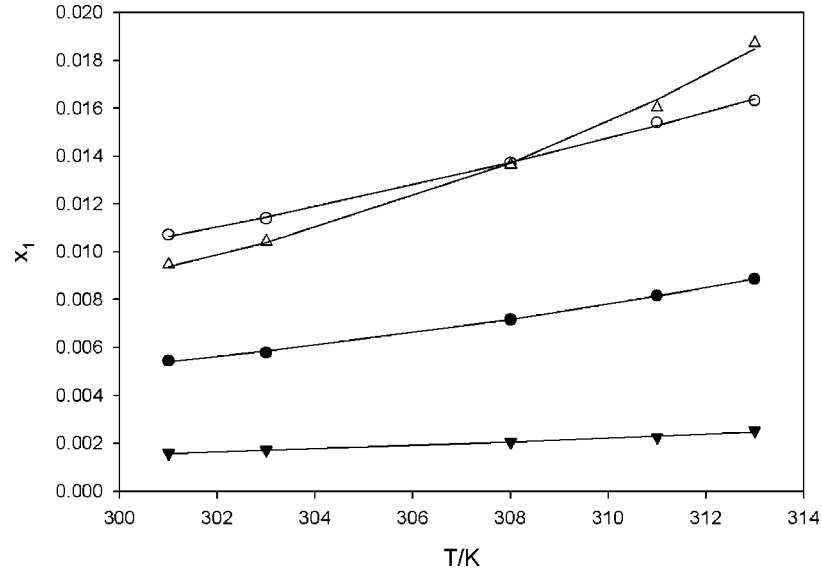

Figure 3. Mole fraction solubility (x_1) of isoniazid in various solvents: ▼, ethyl acetate; ●, ethanol; Δ, acetone; ○, methanol. The line is the best fit of the experimental data calculated with the modified Apelblat equation.

equation is suitable to correlate the measured value of isoniazid solubility in the four solvents and in the tested temperature range.

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