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SHORT ARTICLE

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Solubilities of Pioglitazone Hydrochloride in Different Solvents

Mengying Tao, Jing-kang Wang, and Yongli Wang*

School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China

ABSTRACT: The solubility of pioglitazone hydrochloride (form I) in methanol, ethanol, 1-propanol, acetic acid, and *N*,*N*-dimethylacetamide has been measured between 278.15 and 323.15 K at atmospheric pressure. The solubility of pioglitazone hydrochloride (form I) increases with increasing temperature and the order is *N*,*N*-dimethylacetamide > methanol > acetic acid > ethanol >1-propanol. The experimental data were correlated well by the Apelblat equation.

INTRODUCTION

Pioglitazone hydrochloride (CAS Registry No. 112529-15-4 (supplied by author); (±)5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione monohydrochloride, shown in Figure 1) is an oral antidiabetic agent used in the treatment of type II diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies suggest that pioglitazone hydrochloride can improve sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. It effectively improves glycemic control while reducing circulating insulin levels.[1,2]

Two different polymorphs of pioglitazone hydrochloride have been reported, form I and form II.[3] Crystalline polymorphs are defined as substances which have the same chemical composition but different crystal packing arrangements and/or different molecular conformations and, therefore, different physicochemical properties (e.g., solubility).[4,5] By using different solvents, different polymorphs can be obtained in the crystallization process. The X-ray powder diffraction patterns are shown in Figure 2, with characteristic peaks (2θ) at 8.6, 17.4, 20.8 for form I, while at 9.2, 10.4, 15.2, 16.4, 18.6, and 21.4 for form II.[3]

To obtain the required polymorph and to optimize the crystallization process, it is necessary to know the solubility of pioglitazone hydrochloride in various solvents at different temperatures. However, from a thorough study of the pioglitazone hydrochloride literature, it was found that no experimental solubility data of pioglitazone hydrochloride in organic solvents have been reported. In this work, the solubility of pioglitazone hydrochloride (form I) was measured in methanol, ethanol, 1-propanol, acetic acid, and *N*,*N*-dimethylacetamide over the temperature range (278.15 to 323.15) K at atmospheric pressure.

EXPERIMENTAL SECTION

Materials. Pioglitazone hydrochloride (characterized to be form I by X-ray powder diffraction) was supplied by the Zhejiang Huahai Pharmaceutical Co., Ltd., China, and its melting temperature was (471.15 ± 0.5) K (determined by Netzsch DSC 204 differential scanning calorimeter), which is approximately the same as that reported in the literature.[3] The mass fraction purity of pioglitazone hydrochloride was greater than 0.99 (determined by high-performance liquid chromatography, HPLC). It was dried under vacuum at 318.15 K for 24 h and then stored in a desiccator. Methanol (CAS Registry No. 67-56-1), ethanol (CAS Registry No. 64-17-5), 1-propanol (CAS Registry No. 71-23-8), acetic acid (CAS Registry No. 64-19-7), and *N*,*N*-dimethylacetamide (CAS Registry No. 127-19-5),[6] obtained from the Tianjin Kewei Chemical Reagent Co., China, were of analytical reagent grade with a mass fraction purity >0.995. (CAS Registry Nos. supplied by the author.)

Apparatus and Procedure. The solubilities of pioglitazone hydrochloride (form I) were measured by a synthetic method. As shown in Figure 3, a 150 mL jacketed glass vessel was used to maintain the solution at a constant temperature (fluctuations within ±0.05 K) by circulating water from a water bath (Wanda/sida instrument HC2010, China) with a thermoelectric controller (type 501, China). Continuous stirring was achieved with a magnetic stir bar. A laser monitoring system, including a laser generator, a photoelectric transformer, and a light intensity display, was employed to determine the dissolution of the solute in the solvent at a fixed temperature. A mercury-in-glass thermometer with an uncertainty of ±0.05 K was inserted into the vessel for the measurement of the solution temperature. The masses of both the solute and the solvents were weighed by an analytical balance (Mettler Toledo AB204-N) with an uncertainty of ±0.00005 g. The condenser was connected to the vessel to prevent the solvent from evaporating.

In the experiments, the solubility was determined by the method of gradually adding known masses of a solid to a stirred solution kept at a fixed temperature, monitored by a laser beam.[7] At the beginning, predetermined excess amounts of solvent and solute of known mass were put into the jacketed vessel. The mixture of solid and liquid was stirred at a fixed temperature until the solute dissolved completely. At this moment, the solution was clear (since the solvent is in excess), and the laser intensity penetrating the vessel reached the maximum value. Then an additional solute of certain mass [(2 to 5) mg] was placed into the vessel and stirred continuously. This procedure was repeated until the last addition of solute could not dissolve completely (with continuous stirring for at least 1 h, and the laser intensity did not increase any more, so the equilibrium was considered to be attained). In other words, when the laser intensity did not

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exceed 90% of the maximum, the solute was believed not to be completely dissolved. By tests, the amount of solute that decreased the laser intensity 10% from the maximum is less than 1.0 mg. The whole process lasted more than 6 h. Then the total amount of solute consumed was recorded. Compared to the total amount of the solute we used (including the lowest solubility), the uncertainty of the experimental solubility values is estimated to be 1.0%. The same experiment was repeated two more times, and the mean values were used to calculate the mole fraction solubility as follows.

$$x = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

where x is the mole fraction solubility of pioglitazone hydrochloride, m_1 and m_2 are the masses of the solute and solvent, and M_1 and M_2 are the molecular weights of the solute and the solvent, respectively.

According to the method above, the solubilities of pioglitazone hydrochloride were measured in five pure solvents (methanol, ethanol, 1-propanol, acetic acid, and *N*,*N*-dimethylacetamide) at temperatures ranging from (278.15 to 323.15) K. The undissolved solute was kept suspended for 26 h and then characterized by X-ray diffraction. The results suggest that, under all the experimental conditions, the solute maintained form I.

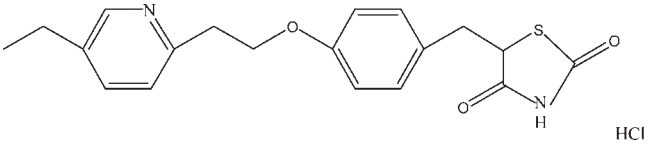

Figure 1. Chemical structure of pioglitazone hydrochloride.

RESULTS AND DISCUSSION

The solubilities of pioglitazone hydrochloride (form I) in methanol, ethanol, 1-propanol, acetic acid, and *N*,*N*-dimethyla-

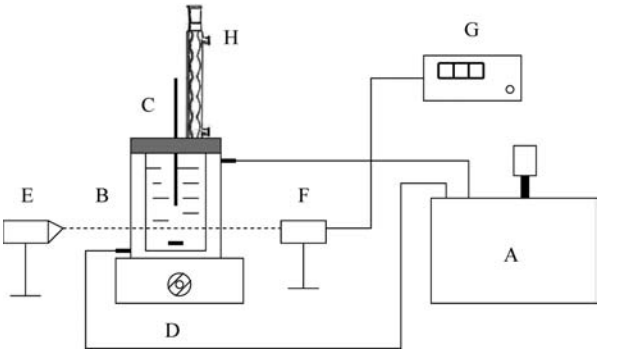

Figure 3. Experimental apparatus for the solubility measurement: A, water bath; B, jacketed glass vessel; C, mercury-in-glass thermometer; D, magnetic stirrer; E, laser generator; F, photoelectric transformer; G, light intensity display; H, condenser.

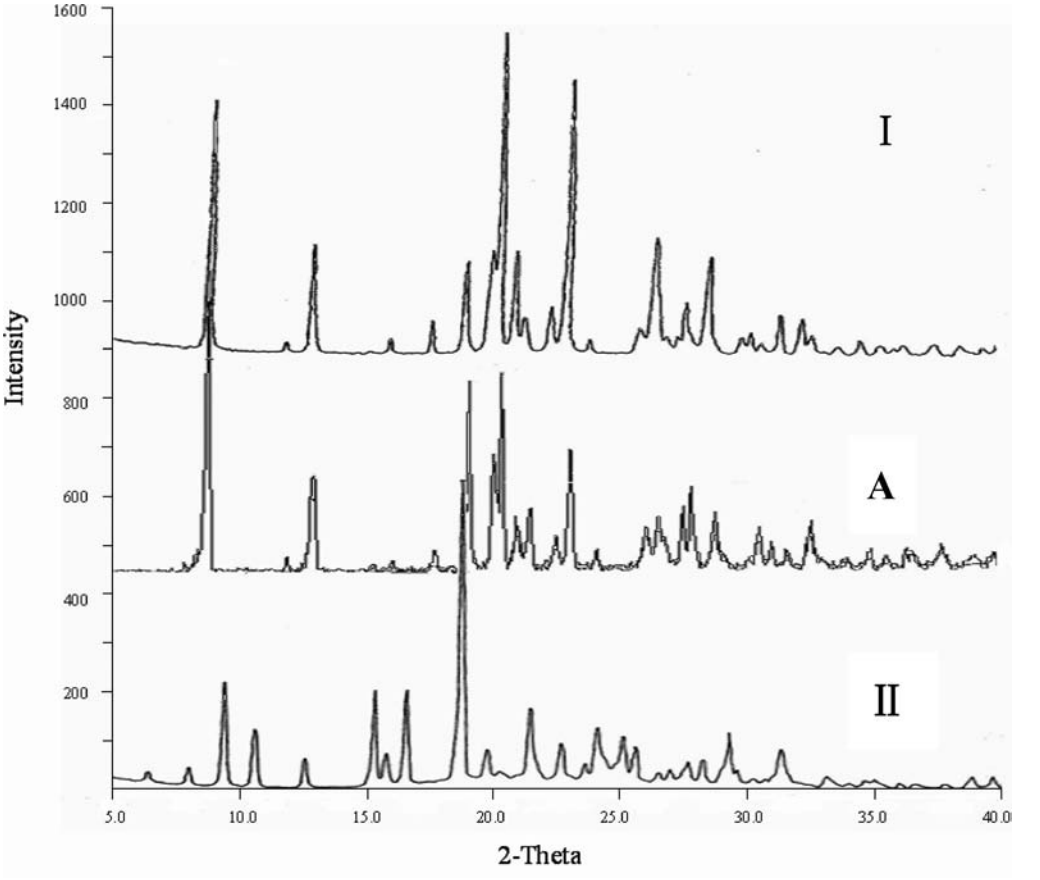

Figure 2. X-ray power diffraction patterns of pioglitazone hydrochloride: I, II, standard XRD patterns of forms I and II, respectively;[3] A, recrystallized product.

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Table 1. Solubility of Pioglitazone Hydrochloride (Form I) in Methanol, Ethanol, 1-Propanol, Acetic Acid, and *N*,*N*-Dimethylacetamide

T/K	$10^3 x^{exptl}$	$10^3 x^{caled}$
	Methanol	
278.15	3.9978	4.1419
283.15	4.9350	4.9633
288.15	6.1475	5.9465
293.15	7.3788	7.1225
298.15	8.5977	8.5280
303.15	10.1101	10.2062
308.15	12.0906	12.2084
313.15	14.3983	14.5951
318.15	17.3031	17.4375
323.15	21.0504	20.8194
	Ethanol	
278.15	0.5345	0.5302
284.15	0.6261	0.6373
288.15	0.7231	0.7253
293.15	0.8790	0.8582
298.15	1.0256	1.0225
303.15	1.2085	1.2260
308.15	1.4691	1.4788
313.15	1.7850	1.7933
318.15	2.2173	2.1855
323.15	2.6610	2.6757
	1-Propanol	
278.15	0.3255	0.3348
283.15	0.3949	0.3906
288.15	0.4560	0.4575
293.15	0.5220	0.5378
298.15	0.6296	0.6343
303.15	0.7501	0.7504
308.15	0.8801	0.8901
313.15	1.0407	1.0584
318.15	1.2721	1.2613
323.15	1.4899	1.5062
	Acetic Acid	
288.15	1.0830	0.8630
293.15	1.5039	1.2798
298.15	2.0301	1.8831
303.15	2.7585	2.7498
308.15	3.7977	3.9861
313.15	5.5831	5.7378
318.15	8.0358	8.2033
323.15	11.8434	11.6518
	N,*N*-Dimethylacetamide	
278.15	16.1247	16.1321
283.15	17.0270	17.0913
288.15	18.2974	18.2107
293.15	19.4495	19.5058
298.15	20.9768	20.9951
303.15	22.6955	22.7002
308.15	24.6933	24.6467
313.15	26.8853	26.8639
318.15	29.2039	29.3858
323.15	32.3228	32.2514

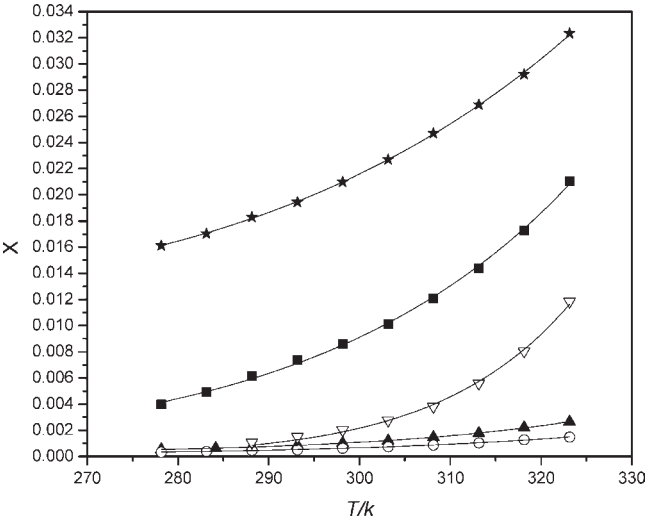

Figure 4. Mole fraction solubilities (x) of pioglitazone hydrochloride (form I) in various solvents: ■, methanol; ▲, ethanol; ○, 1-propanol; ▽, acetic acid; ★, N,N-dimethylacetamide.

Table 2. Parameters of eq 1 for Solubility of Pioglitazone Hydrochloride (Form I) in Different Solvents

solvent	A	B	C	10^3 rmsd
methanol	−127.139	2727.1263	19.8729	0.1630
ethanol	−290.5402	9928.0508	43.9406	0.0151
1-propanol	−201.8233	6137.2751	30.5174	0.0111
acetic acid	−107.9302	−1257.5811	18.5821	0.1748
N,*N*-dimethylacetamide	−167.3622	6130.5559	25.0872	0.0748

cetamide at different temperatures are listed in Table 1 and presented in Figure 4.

The temperature dependence of pioglitazone hydrochloride solubility in pure solvents is described by the modified Apelblat equation[8,9]

$$\ln(x) = A + \frac{B}{T/K} + C\ln(T/K) \qquad (2)$$

where x is the mole fraction solubility of pioglitazone hydrochloride, T is the absolute temperature, and A, B, and C are the parameters of the equation. The calculated solubility values of pioglitazone hydrochloride (x^{caled}) are also given in Table 1. The values of parameters A, B, and C and the root-mean-square deviations (rmsd) are listed in Table 2. The rmsd is defined as

$$\text{rmsd} = \left[\frac{1}{2}\sum_{i=1}^{n}(x_i^{calcd} - x_i^{exptl})^2\right]^{1/2} \qquad (3)$$

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where n is the number of experimental points, x_i^{caled} is the solubilities calculated from eq 1, and x_i^{exptl} is the experimental values of solubility.

From Tables 1 and 2 and Figure 4, the following conclusions can be drawn: (1) The solubilities of pioglitazone hydrochloride (form I) in methanol, ethanol, 1-propanol, acetic acid, and *N*,*N*-dimethylacetamide increase with increasing temperature. (2) The solubilities of pioglitazone hydrochloride (form I) in different solvents is in the following order: *N*,*N*-dimethylacetamide > methanol > acetic acid > ethanol >1-propanol. For alcohols, we found that the solubilities of pioglitazone hydrochloride (form I) increased with increasing polarity. However, this explanation cannot be applied for acetic acid and *N*,*N*-dimethylacetamide, for the different functional groups in the solvent molecules. [polarity: methanol (76.2) > ethanol (65.4) > acetic acid (64.8) > 1-propanol (61.7) > *N*,*N*-dimethylacetamide (40.1)].[6] (3) The modified Apelblat equation is appropriate to describe the temperature dependence of pioglitazone hydrochloride (form I) in pure solvents. Therefore, the experimental solubility data and the correlated equation in this work can be used as fundamental data and models in the crystallization process of pioglitazone hydrochloride.

AUTHOR INFORMATION

Corresponding Author

*E-mail: wylcry@163.com. Fax: +86-22-27374971.

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