Solubility of Irbesartan (Form A) in Different Solvents between 278 K and 323 K

Lin Wang, Jingkang Wang,* Ying Bao, and Tonghe Li

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

The solubilities of irbesartan (form A) in ethanol, acetone, chloroform, dioxane, and tetrahydrofuran between 278 K and 323 K are measured by a synthetic method. A laser technique is used to determine the disappearance of undissolved solute particles. Results are correlated by a semiempirical equation, the calculated results of which are proved to show fine representation of experimental data.

Introduction

Irbesartan is a kind of N-substituted heterocyclic derivative. Its crystal form A is chemically described as 2-butyl-3-[[4-[2-(2*H*-tetrazol-5-yl)phenyl]phenyl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (CAS No. 138402-11-6, Figure 1). It is a white powder and clinically an angiotensin II receptor antagonist used mainly for the treatment of hypertension.[1,2] Crystallization is a critical step in forming different polymorphs of irbesartan. As one common form among other published polymorphs, irbesartan (form A) could be crystallized from pure solvents and usually exists in the form of stable and nonhygroscopic needles.[3] So, solubility of irbesartan (form A) in pure solvents is of great importance in manufacturing and purifying processes, and few data are available among published work except for irbesartan (form A) in isopropanol.[4] In this paper, we carry out the systematic studies on solubilities of irbesartan (form A) in a series of solvents: ethanol, acetone, chloroform, dioxane, and tetrahydrofuran. Solubility is measured by a synthetic method between 278 K and 323 K at atmospheric pressure.

Experimental Section

Materials. Irbesartan (form A) was obtained and purified as described in the literature.[3] The crude irbesartan (form A + form B) from Zhejiang Huahai Pharmaceutical was dissolved in pure ethanol, filtered to eliminate undissolved solids, and recrystallized. The consequent product's mass fraction is above 99.5 % determined by HPLC and has a single crystalline morph of form A according to the results of X-ray powder diffraction. Ethanol, acetone, chloroform, dioxane, and tetrahydrofuran are analytical research grade reagents from Tianjin Chemical Reagent Co. Ltd. (China).

Apparatus and Procedures. Solubility was measured by the synthetic method.[5−7] The apparatus set was similar to that described in the previous literature.[8] We have used the laser monitoring technique to measure solubilities of irbesartan (form A) in different solvents at a constant temperature. The laser system consists of a laser generator, a photoelectric transformer, and a digital light-intensity display. Solutions under measurement are in a jacketed glass vessel, where a constant temperature of the measured solution within stability of ± 0.05 K was maintained by circulating water from a water bath with a digital thermoelectric controller (type XMT-420, BCHY.COM, China). Temperature was measured by a mercury-in-glass thermometer with an uncertainty of ± 0.05 K. A magnetic stirrer was used to keep continuous stirring, and a condenser was used to prevent evaporation of the solvents in experiment. Masses of solute and solvents are weighed using an analytical balance (type TG332A, China) with an accuracy of ± 0.1 mg.

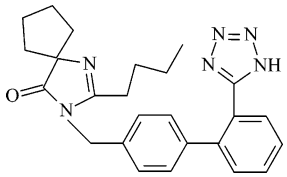

Figure 1. Structure of irbesartan (form A).

First, predetermined known masses of irbesartan (form A) and solvents are transferred in the jacketed vessel. Then the contents of the vessel are stirred. Until the temperature fluctuation varies within 0.05 K, a suitable dose of solute was added so that it does not exceed the solubility too much. Then the solvent was added by injector. Each additional amount of either solute or solvent was recorded. When the last portion of solids disappears, the light penetrating the vessel reaches its maximum and the total amounts of solute and solvent are obtained. The saturated mole fraction solubility of solute x_1 can be obtained as follows

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m and M represent mass and mole weight and subscripts 1 and 2 represent solute irbesartan (form A) and solvents, respectively. All the experiments are repeated three times at each temperature, and estimated uncertainties of the experimental values are about 0.5 %.

Results and Discussion

The results of irbesartan (form A) solubility in different solvents are listed in Table 1. Figure 2 gives the plot of the solubility of irbesartan (form A) in these solvents at a temperature range of about 278 K to 323 K.

The temperature-dependent solubility can be correlated by a semiempirical equation[9]

$$\ln x_1 = a + \frac{b}{T/\mathrm{K}} + c \ln T/\mathrm{K} \tag{2}$$

where T is absolute temperature and a, b, and c are all empirical constants. Correlated values of a, b, and c of different solvents are listed in Table 2.

* To whom correspondence should be addressed. Email: wanglin19811012@yahoo.com.cn. Fax: 86-22-2737497.

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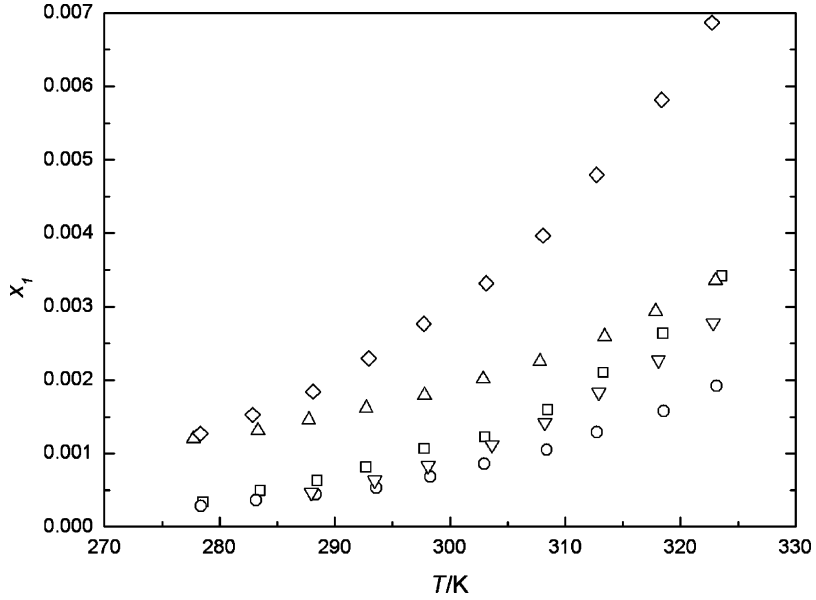

Figure 2. Mole fraction solubility x_1 of irbesartan (form A) in: □, ethanol; ○, acetone; □, chloroform; □, dioxane; and □, tetrahydrofuran.

Table 1. Solubilities of Irbesartan (Form A) in Ethanol, Acetone, Chloroform, Dioxane, and Tetrahydrofuran

T/K	10^5x_1	$10^5(x_1 - x_{calcd})$	T/K	10^5x_1	$10^5(x_1 - x_{calcd})$
		Ethanol			
278.60	33.28	−3.16	303.05	122.0	−5.41
283.55	48.9	1.56	308.50	159.3	−6.66
288.50	62.7	1.42	313.30	209.8	0.914
292.70	80.9	4.76	318.50	263.0	−3.30
297.80	105.9	7.65	323.60	341.1	4.19
		Acetone			
278.35	28.37	0.32	302.95	86.1	2.25
283.15	36.40	1.40	308.40	104.7	−0.65
288.35	44.4	0.19	312.75	129.1	3.07
293.60	53.0	−2.90	318.55	157.9	−1.61
298.25	67.8	−0.78	323.10	192.1	0.68
		Chloroform			
277.70	119.5	4.73	302.85	201.2	−3.22
283.30	130.9	0.82	307.80	225.2	−4.43
287.70	145.7	1.94	313.40	259.2	−3.41
292.70	161.5	0.28	317.80	293.5	1.60
297.75	179.4	−2.01	323.00	335.1	4.34
		Dioxane			
287.90	46.6	−2.10	308.20	142.1	0.82
293.45	63.4	−2.53	312.90	183.0	5.57
298.00	83.2	−1.17	318.05	226.9	0.58
303.65	111.5	−0.98	322.85	277.8	−3.52
		Tetrahydrofuran			
278.30	126.9	3.94	303.15	331.6	−4.62
282.85	152.4	3.05	308.05	396.5	−7.73
288.10	184.2	−1.66	312.70	479.2	0.38
292.95	229.4	3.39	318.35	581.5	−3.65
297.70	276.5	3.62	322.75	686.7	5.95

Root-mean-square deviation, σ_y, is defined as follows

$$\sigma_y = \{[\sum_{i=1}^{N}(x^{exptl} - x^{calcd})^2]/N\}^{1/2} \quad (3)$$

where N is the number of experimental points and x^{exptl} and x^{calcd} are the experimental and calculated solubility according to eq 2. The σ_y of each solvent is also listed in Table 2.

Conclusion

The solubility of irbesartan (form A) in ethanol, acetone, chloroform, dioxane, and tetrahydrofuran is determined using laser monitoring techniques. The results show that solubility in the five selected solvents increases as temperature rises, but the increment with temperature varies according to different solvents. Results show that irbesartan dissolved much more in tetrahydrofuran than in the other four solvents, especially at higher temperature. The calculated solubility data are proved to be in fine agreement with experimental values, inferring that the correlated equation in our work could provide essential data for manufacturing and purifying processes in industry.

Table 2. Parameters of Equation 2 for Irbesartan (Form A) in Different Solvents

solvents	a	b	c	$10^5\sigma_y$
ethanol	−84.01	−335.0	13.73	4.5
acetone	−68.01	−566.5	10.99	1.7
chloroform	−118.8	3240	17.83	3.1
dioxane	−1.826	−4196	1.549	2.7
tetrahydrofuran	−24.72	−2100	4.541	4.3

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