Solubility of Irbesartan Form B in an Aqueous Ethanol Mixture

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The solubilities of irbesartan form B in ethonal−water mixtures between 283.15 K and 333.15 K are measured by the 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 (CAS No. 138402-11-6) is a kind of N-substituted heterocyclic derivative. It is found to exist in two distinct crystal forms: form A and form B, the latter form chemically described as 2-butyl-3-[[2′-(2*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (Figure 1). It is a white powder and clinically an angiotensin II receptor antagonist used mainly for the treatment of hypertension.[1,2] Irbesartan form B usually has a morphology of a rectangular column or block under microscopy, which forms a remarkable visual distinction from the needle-like irbesartan form A. Lower electrostatics and better flowability of the form B irbesartan than form A make it more easily subjected to any treatment under the usual conditions of pharmaceutical techniques.

Crystallization is a critical step in forming different crystal polymorphs of irbesartan. To optimize the crystallization process, the solubility of irbesartan form B in a mixture of water and ethanol is of great importance. It was reported that the form B irbesartan could be crystallized from a mixture of water with one other organic solvent. For the binary system of ethanol–water solvent, the irbesartan form B is stable, and no phase transition occurred when the amount of water was 10 % or more by volume. However, few data are available among published work except irbesartan form A in pure solvents.[3,4]

In this paper, we carry out a systematic study on solubilities of irbesartan form B in mixtures of ethanol–water solvents. Laser monitoring equipment set as illustrated by Figure 2 is used. The amount of water ranges from 10 % to 50 % of volume percentage. The solubility is measured by a synthetic method from 283.15 K to 333.15 K at atmospheric pressure, which covers the conventional operating temperature range in a crystallization process. The XRD results of undissolved crystals indicated that no phase transition occurred during the experiment.

Experimental Section

Materials. Irbesartan form B ($C_{25}H_{28}N_6O$) was obtained and purified as described in the literature.[5] The crude irbesartan (form A + form B) from Zhejiang Huahai Pharmaceutical was dissolved in 80 % ethanol–water solvent, then active carbon was added and filtered. Filtrate was reheated to eliminate undissolved solids and recrystallized by cooling. The consequent product's mass fraction is above 99.6 %, determined by HPLC,

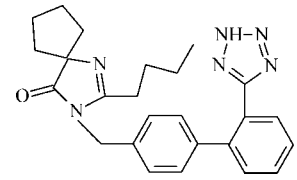

Figure 1. Molecular structure of irbesartan form B.

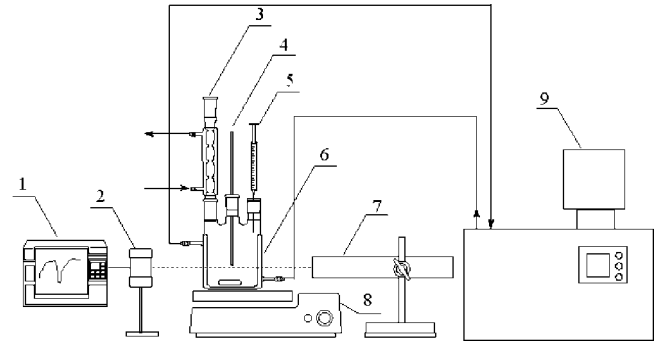

Figure 2. Schematic setup for the solubility determination: 1, digital light intensity display; 2, photoelectric transformer; 3, condenser; 4, thermometer; 5, injector; 6, jacketed glass vessel; 7, laser generator; 8, magnetic stirrer; 9, water bath equipped with a thermoelectric controller.

and has a single crystalline morph of form B according to the results of X-ray powder diffraction. The 80 % ethanol–water solvent is obtained by mixing ethanol and deionized water. Ethanol is an analytical research grade reagent from Tianjin Chemical Reagent Co., Ltd. (China). Distilled–deionized water of HPLC grade was used.

Apparatus and Procedures. Solubility was measured by the synthetic method.[6,7] The apparatus set was similar to that described in previous literature.[8] We have used the laser monitoring technique to measure solubilities of irbesartan form B 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 measurements are in a jacketed glass vessel, where a constant temperature of the measured solution within a 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 uncertainty of ± 0.05 K. The magnetic stirrer was used to keep continuous stirring, and a condenser was used to prevent evaporation of the solvents in experiment. Masses

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Table 1. Mole Fraction Solubility x_1 of Irbesartan Form B in Ethanol (2) + Water (3) Solvent Mixtures in the Temperature Range from 283.15 K to 333.15 K[a]

T/K	$10^5 x_1$	$10^5(x^{calcd} - x^{exptl})$	T/K	$10^5 x_1$	$10^5(x^{calcd} - x^{exptl})$
		$x_2 = 0.7357$			
283.15	3.845	0.0543	313.15	20.03	−0.2246
288.15	4.771	0.3996	318.15	25.99	−0.4159
293.15	6.270	0.5550	323.15	33.20	−0.3043
298.15	8.555	0.4112	328.15	42.01	0.1493
303.15	11.63	0.0987	333.15	53.57	0.2578
308.15	15.59	−0.3188			
		$x_2 = 0.5531$			
283.15	2.460	0.0013	313.15	14.52	−0.0118
288.15	2.771	0.5825	318.15	19.22	−0.0618
293.15	3.964	0.5783	323.15	25.59	−0.4081
298.15	5.743	0.3761	328.15	33.40	−0.4490
303.15	8.345	−0.1449	333.15	42.50	0.4282
308.15	11.05	−0.1136			
		$x_2 = 0.4192$			
283.15	2.002	0.0783	313.15	9.572	0.7398
288.15	2.295	0.4538	318.15	11.97	1.2883
293.15	3.293	0.3227	323.15	15.98	0.9895
298.15	4.255	0.4763	328.15	19.77	1.8626
303.15	5.653	0.5092	333.15	25.63	1.8403
308.15	7.354	0.6347			
		$x_2 = 0.3170$			
283.15	1.028	−0.0417	313.15	5.740	−0.1528
288.15	1.239	0.0943	318.15	7.185	0.1539
293.15	1.645	0.1480	323.15	9.804	−0.2049
298.15	2.133	0.2667	328.15	12.65	−0.1500
303.15	2.999	0.1962	333.15	16.18	0.0478
308.15	4.050	0.1846			
		$x_2 = 0.2363$			
293.15	0.7498	0.0230	318.15	2.958	−0.0641
298.15	0.9994	0.0233	323.15	3.936	−0.2510
303.15	1.118	0.2242	328.15	4.581	0.0799
308.15	1.672	0.0747	333.15	5.778	0.0871
313.15	2.346	−0.0889			

[a] Note: x_1 and x_2 are defined according to eqs 1 and 2.

of solute and solvents are weighed using an analytical balance (type TG332A, China) with an accuracy of ± 0.1 mg.

First, predetermined known masses of irbesartan form B and solvent are transferred in the jacketed vessel. Then, the contents of the vessel are stirred. Until the temperature fluctuation varied within 0.05 K, a suitable dose of solute was added so that it did not exceed the solubility too much. Then solvent was added by an 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

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

$$x_2 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \quad (2)$$

where m and M represent mass and mole weight; and subscripts 1, 2, and 3 represent solute irbesartan form B, ethanol, and water, respectively. The same experiment was conducted three times under the same condition, and the uncertainty of the experiment values is about 0.5 %.

Results and Discussion

The results of irbesartan form B solubility in ethanol–water binary solvent mixtures are listed in Table 1. Figure 3 gives the plot of solubility of irbesartan form B in these solvents at a temperature range of about 283.15 K to 333.15 K. Values of x_1 correspond to a volume fraction of water of about 10 %, 20 %, 30 %, 40 %, and 50 %.

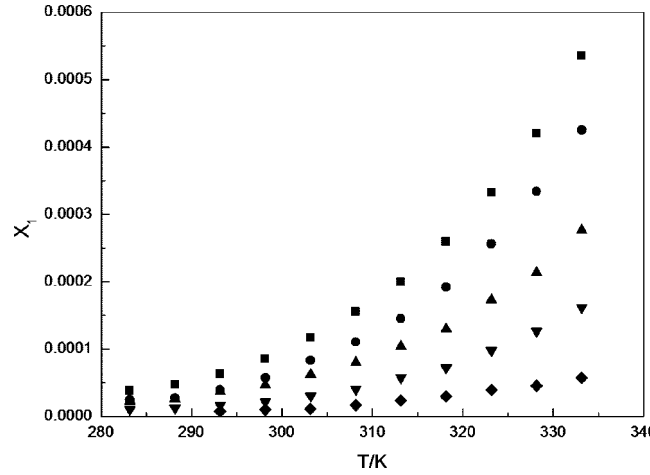

Figure 3. Mole fraction solubility x_1 of irbesartan form B in the water/ethanol binary solvent system. Different values of mole fractions of ethanol x_2 are represented by symbols as follows: ■, 0.7357; ●, 0.5531; ▲, 0.4192; ▼, 0.3170; □, 0.2363.

Table 2. Parameters of Equation 3 for Irbesartan Form B in Ethanol–Water Binary Solvent Systems in the Temperature Range from 283.15 K to 333.15 K

x_2	a	b	c	10^6 rmsd
0.7357	−102.76	66.851	16.3608	3.3999
0.5531	−102.43	−339.30	16.4742	3.7476
0.4192	−94.364	−274.29	14.9755	10.6052
0.3170	−108.97	10.862	17.2528	1.7030
0.2363	−14.7325	−4027.6	2.9399	1.2078

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

$$\ln x_1 = a + \frac{b}{T/\mathrm{K}} + c \ln T/\mathrm{K} \quad (3)$$

where T is the 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.

The root mean square deviation (rmsd) is defined as follows

$$\mathrm{rmsd} = \left\{ \left[\sum_{i=1}^{N} (x^{exptl} - x^{calcd})^2 \right] / N \right\}^{\frac{1}{2}} \quad (4)$$

where N is the number of experimental points and x^{exptl} and x^{calcd} are the experimental and calculated solubility according to eq 3. The rmsd of each solvent mixture is also listed in Table 2.

Conclusion

The solubilities of irbesartan (form B) in ethanol–water mixture solvents all increased with a temperature increase but decreased as the fraction of water in the mixture rose. When the mole fraction of water reached 0.2363 (about 50 % volume fraction), the mole fraction solubility x_1 of irbesartan form B was too small to determine by the experiment introduced here at low temperatures. The experimental data in this work can be regressed by eq 3 for each solvent mixture. They can also be used as essential data and models in the crystallization process of irbesartan form B.

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