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Articles

Solubility of Sesquihydrous Irbesartan Hydrobromide in Ethanol + Water Binary Solvent Mixtures at pH 1.20 between (283 and 313) K

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The solubilities of sesquihydrous irbesartan hydrobromide in ethanol−water mixtures at pH 1.20 between (288 and 333) K are measured by the light extinction method. A laser technique that determines the mass of suspended solute particles is used, and dissolved mass of solute is calculated. Results are correlated by the λh equation and the (CNIBS)/Redlich−Kister equation. The calculated results of both equations were found to show fine representation of the experimental data.

Introduction

Sesquihydrous irbesartan hydrobromide (Figure 1) is one kind of derivative salt of irbesartan. The solid product is a white powder and may be obtained as flakes. The crystal of the salt belongs to the monoclinic system $P2_1/c$ space group.[1] The hydrobromide is an important intermediate in the production of high purity irbesartan. It is obtained by reacting irbesartan and hydrobromic acid.[2] Solubility data is of interest for the manufacturing process. We obtained the solubility of sesquihydrous irbesartan hydrobromide in ethanol + water binary solvent mixtures at pH 1.20 between (283 and 313) K.

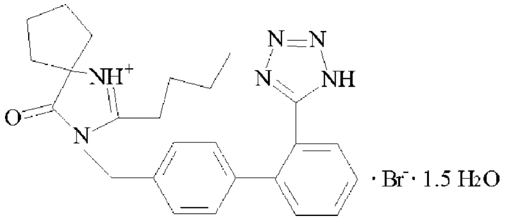

Figure 1. Structure of sesquihydrous irbesartan hydrobromide.

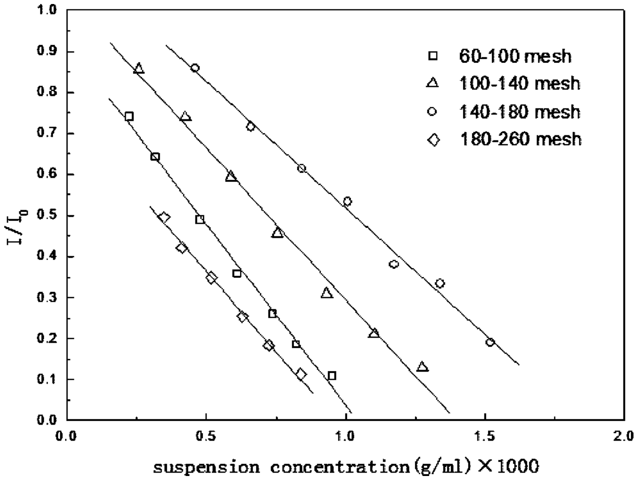

Figure 2. Correlation between suspension concentration and light extinction ratio (I/I_0).

Experimental Section

Materials and Apparatus. Sesquihydrous irbesartan hydrobromide was recrystallized twice to a purity of 99.4 % (mass fraction), as determined by HPLC. The content of crystalline water confirmed by the Karl Fischer method was about 5 % by weight. Reagents 40 % HBr and ethanol, supplied by the Tianjin Chemical Reagent, were of analytical grade. Deionized water was distilled twice before use.

The whole equipment was described in our previous work.[3] A jacketed glass vessel was connected to a super thermostatic water bath (501A China) to ensure that the temperature fluctuation was no more than ± 0.05 K. The laser monitoring system consisted of a laser generator, photoelectric transformer, and an electrical laser intensity recorder. Temperature was measured by a mercury-in-glass thermometer with an uncertainty of ± 0.05 K. Masses of solute and solvents were weighed by an analytical balance (Mettler Toledo AB204-N, Switzerland) with a precision of 0.1 mg, and pH values of the solution were detected by a digital-display pH meter (type PHS-3C, Shanghai Precision Scientific Instrument). To eliminate loss of solvent by evaporation, a condenser connected to a refrigerating source was used.

Method for Measurement. In our work, the light extinction method was applied for the solubility determination. This novel measuring technique was first devised by Wang et al.[4] and successfully applied in the solubility determination of 7-aminocephalosporanic acid in aqueous acetone solvent mixtures. Wang also proved its reliability by applying the method in measuring an aqueous solution of highly soluble potassium chloride and sparingly soluble silver sulfate.[5] Its applicability for measurement over a wide range of values makes it suitable for solubility determination of sesquihydrous irbesartan hydrobromide.

The light extinction method is based on the Lambert−Beer Law, which correlates light intensity and concentration of particles in suspension. To test the relationship between them, we recorded the light intensity change received by a photoelectric transformer as different masses of solute particles were suspended in water. Here a quantitative index light extinction

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Table 1. Linear Correlation between Intensity Extinction Ratio (I/I_0) and Concentration of Suspended Particles (w/g·mL^{-1}) in Different Size Ranges

particle size range (mesh)	linear correlation	R^a	validity range (I/I_0)
60 to 100	$I/I_0 = 1.1327 - 0.6148w$	0.9966	0.19 to 0.85
100 to 140	$I/I_0 = 1.0344 - 0.7404w$	0.9959	0.13 to 0.85
140 to 180	$I/I_0 = 0.9193 - 0.8823w$	0.9972	0.10 to 0.73
180 to 260	$I/I_0 = 0.7499 - 0.7748w$	0.9976	0.11 to 0.49

[a] R is correlation coefficient.

Table 2. Solubility (x_A) of Sesquihydrous Irbesartan Hydrobromide in Ethanol + Water Binary Solvent at pH 1.20 from (283.15 to 313.15) K

	T/K						
x_B[a]	283.15	288.15	293.15	298.15	303.15	308.15	313.15
				10^5x_A			
0.1	2.51	5.91	13.25	21.74	38.29	64.64	100.9
0.2	19.81	41.80	65.99	109.9	197.2	320.3	571.2
0.3	66.81	90.60	150.39	250.5	425.0	652.4	922.3
0.4	111.8	175.4	254.6	365.3	574.0	804.4	1118
0.5	161.5	231.1	325.5	474.5	696.0	967.2	1273
0.6	184.3	283.7	419.1	613.2	831.7	1100	1513

[a] x_B is mole fraction of ethanol in binary solvent.

Table 3. Fitting Parameters of CNIBS/Redlich−Kister Equation

	CNIBS/Redlich−Kister parameters					
T/K	B_0	B_1	B_2	B_3	B_4	10^5 RSDM
283.15	−9.238	22.99	−64.95	82.53	−44.72	0.3996
288.15	−17.55	87.43	−237.9	282.2	−128.2	0.5501
293.15	−16.61	85.81	−238.5	285.8	−129.6	0.4555
298.15	−6.304	16.55	−63.21	93.99	−52.34	0.2729
303.15	−14.57	82.13	−248.7	324.5	−157.6	0.8907
308.15	−14.76	86.57	−263.0	343.0	−165.0	2.1772
313.15	−14.16	84.75	−258.1	335.6	−160.0	2.6928

ratio, I/I_0, was used, where I stands for transmission intensity and I_0 denotes incident intensity, and particle concentration is symbolized as w in g·mL^{-1}. Tested particles were sieved into four size ranges. Figure 2 shows that for particles of all size ranges a linear correlation was found to be true, which means that the mass of undissolved solute could be calculated according to the literature mentioned above by eq 1

$$m_s = m_l \frac{I_1}{I_2} \tag{1}$$

where m_l is the mass of the last dose of solute before the solution gets into the equilibrium state and m_s is the mass of undissolved particles in the last dose. I_1 and I_2 stand for light intensity at the moment of the last dose being just added and after the solution gets into equilibrium, respectively. The total mass of the added solute minus the undissolved mass is the mass of dissolved solute.

It should be noted that the linear correlation is valid only over a moderate laser intensity ratio (I/I_0), and particles in a smaller size range show more accuracy. (See Table 1.) Therefore, it is advised to screen out particles in a suitable size range in advance and confine the mass of the last solute dose.

Procedure. First, the solvent mixture was prepared by mixing a certain amount of ethanol, water, and 40 % HBr reagent. In the mixing solvent, the ethanol content varied from 10 % to 60 % mole percentage, whereas the water content of each mixture included water from 40 % HBr reagent. All solvent mixtures had a pH value of 1.20.

Before determination, solvent mixtures of certain composition were weighed and transferred to the thermostatic vessel. Then, the magnetic stirrer was started, as was the circulating system of the super thermostatic water bath. After the temperature of the solvent mixture fluctuated within 0.05 K, a predetermined mass of solute was added. The mass of each dose of solute was recorded. Once the solution under determination was close to its equilibrium state, the mass of a single solute addition was no more than 0.001 g·mL^{-1}. The light intensity when the solute dose was just added and after solution equilibrium was attained was recorded. During the measuring process, the position of the laser generator, vessel, and photoelectric transformer (laser receiver) and the agitating rate were fixed so that correlation between light intensity and mass of solute did not change. Measurement at each point was repeated at least three times, and the uncertainty was estimated to be 0.5 %. Deviation may originate from the weighing procedure, the fluctuation of the laser light intensity, or the temperature fluctuation of the water bath.

Data Processing and Regression

The saturated mole fraction of the solute in solution at pH 1.20 and mole fraction of water in binary solvents mixtures can be obtained as follows

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \tag{2}$$

$$x_C = \frac{m_C/M_C}{m_B/M_B + m_C/M_C} \tag{3}$$

where x_A is the mole fraction of the solute and x_C is the mole fraction of water in the binary solvent. m_A, m_B, and m_C represent the mass of irbesartan hydrobromide sesquihydrate, ethanol, and water, respectively. M_A, M_B, and M_C represent the mole weight of the solute, ethanol, and water respectively.

Experimental solubility data of sesquihydrous irbesartan hydrobromide in ethanol + water binary solvents at pH 1.20 from (283.15 to 313.15) K are listed in Table 2. Two models are used to correlate the solubility data. Coefficients in both models are obtained by nonlinear least-squares method. Root-mean-square deviation (RMSD) defined by eq 4 is also listed as an evaluation reference for the fitting effect

$$\mathrm{RMSD} = \left[\frac{1}{n}\sum_{i=1}^{n}\left(x_i^{\mathrm{calcd}} - x_i^{\mathrm{exptl}}\right)^2\right]^{1/2} \tag{4}$$

where n represents the number of experimental points. x_i^{calcd} and x_i^{exptl} are the solubility in the form of mole fraction; the former represents data from the experiment and the latter is calculated by the regression equation.

(CNIBS)/Redlich−Kister Equation. The model suggested by Acree et al. is expressed as eq 5[6−8]

$$\ln x_A = x_B^0 \ln(x_A)_B + x_C^0 \ln(x_A)_C + x_B^0 x_C^0 \sum_{i=1}^{N} S_i (x_B^0 - x_C^0)^i \tag{5}$$

where S_i is the model coefficient and $(x_A)_B$ and $(x_A)_C$ denote the mole fraction solubility of solute A in pure solvents B (ethanol) and C (water), respectively. x_B^0 and x_C^0 are the initial mole fractions of ethanol and water, respectively, in the binary solvent and are equal to the value of x_B and x_C, respectively. N could be equal to 0, 1, 2, 3, and so on. For $x_B^0 + x_C^0 = 1$, eq 5 could be transformed as follows

$$\begin{aligned}\ln x_A = {} & \ln(x_A)_B + [\ln(x_A)_C - \ln(x_A)_B + S_0 + S_1 + S_2]x_C^0 \\ & + [-S_0 + 3S_1 + 5S_2]x_C^{02} + [-2S_1 - 8S_2]x_C^{03} + [-4S_2]x_C^{04}\end{aligned} \tag{6}$$

Further simplification gives

$$\ln x_A = B_0 + B_1 x_C^{0} + B_2 {x_C^{0}}^{2} + B_3 {x_C^{0}}^{3} + B_4 {x_C^{0}}^{4} \tag{7}$$

The parameters obtained by fitting the CNIBS/Redlich−Kister equation are listed in Table 3. Experimental points and calculated data (line) are plotted in Figure 3.

λh Equation. This model is derived from the general SLE model by Buchowski et al. and is expressed as the following equation[9,10]

$$\ln\left[1 + \frac{\lambda(1 - x_A)}{x_A}\right] = \lambda h\left(\frac{1}{T} - \frac{1}{T_{mA}}\right) \tag{8}$$

where λ and h are model coefficients, T is the temperature of the solution, and T_{mA} is the transformation temperature of the solute, which according to DSC analysis performed on NETZSCH TG209, is 472.05 K. (See Figure 4.)

Solubility data were correlated by recasting the form of eq 8

$$x_A = \frac{1}{\frac{1}{\lambda}\left[e^{\lambda h\left(\frac{1}{T} - \frac{1}{T_m}\right)} - 1\right] + 1} \tag{9}$$

The fitting parameters of the λh equation are listed in Table 4. Experimental points and calculated data (line) are plotted in Figure 5.

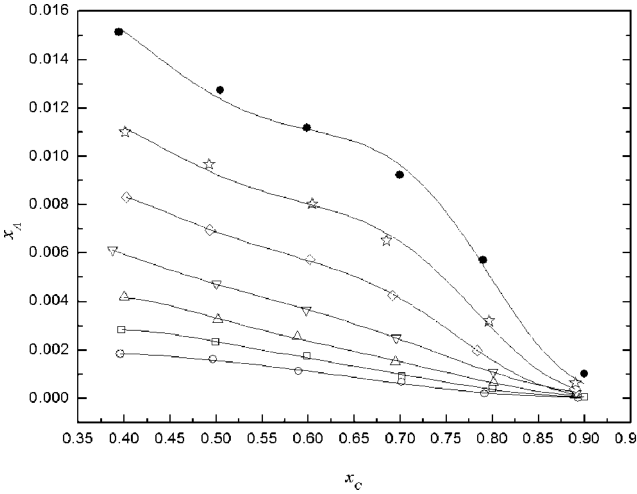

Figure 3. Experimental points of sesquihydrous irbesartan hydrobromide and regressive lines by CNIBS/Redlich−Kister model, where the experiments are performed at ○, 283 K; □, 288 K; △, 293 K; ▽, 298 K; ◇, 303 K; ☆, 308 K; ●, 313 K. x_A, mole fraction of solute in solution; x_C, mole fraction of water in binary solvent (water + ethanol).

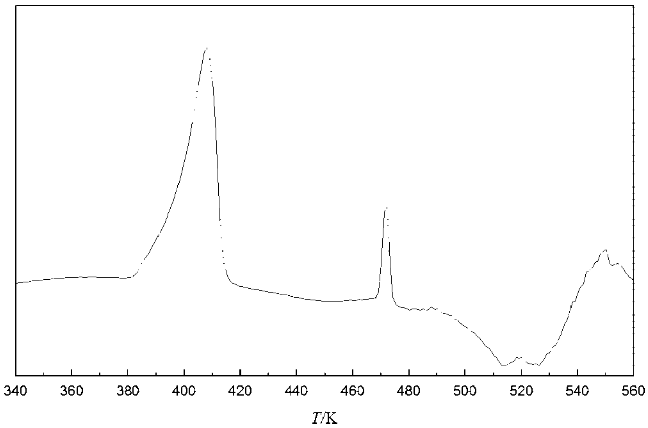

Figure 4. DSC analysis results of sesquihydrous irbesartan hydrobromide: the first peak is the water-releasing peak, which appears around 400 K, and the second peak is the melting peak, which appears at 472 K.

Table 4. Fitting Parameters of λh Equation

x_B[a]	λh equation parameters		
	λ	h	100 rmsd
0.1	27.21	348.1	0.0833
0.2	342.8	29.84	0.4472
0.3	48.35	164.1	0.7931
0.4	16.62	407.4	0.9953
0.5	9.490	407.4	1.1723
0.6	8.933	662.7	1.3839

[a] x_B is mole fraction of ethanol in binary solvents.

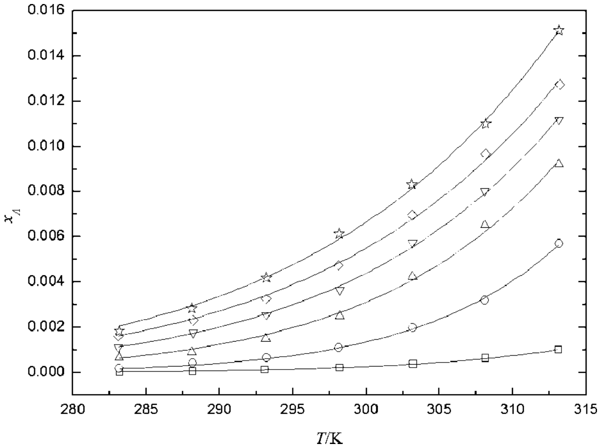

Figure 5. Experimental points of sesquihydrous irbesartan hydrobromide and regression lines by the λh model. Ethanol mole fraction in solvent mixtures are □, 0.1; ○, 0.2; △, 0.3; ▽, 0.4; ◇, 0.5; ☆, 0.6. x_A, mole fraction of solute in solution.

Conclusions and Discussion

New data for the solubility of sesquihydrous irbesartan hydrobromide in binary ethanol + water solvent systems at pH 1.20 from (283.15 to 313.15) K are presented. The solubility of the solute increases with a rise in either temperature or mole ratio of ethanol in the solvents, but the latter factor has greater influence, which in reverse infers that an antisolvating operation is optimal for a crystallization process.

Two models were chosen to fit the experiment data. Although the solubilities were correlated with different factors (x_C as variable in CNIBS/Redlich−Kister model and T as variable in λh model), both showed a good fitting effect. The CNIBS/Redlich−Kister model is better, as the RMSD results indicate, but the quantity of its model parameters (as many as five) may be a disadvantage in its application.

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