Measurement and Correlation of Griseofulvin Solubility in Different Solvents at Temperatures from (281.95 to 357.60) K

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The solubility of griseofulvin in acetone, 2-butanone, 1,2-dichloroethane, *N*,*N*-dimethylacetamide, dimethyl sulfoxide, and *N*-methyl-2-pyrrolidone have been determined by the dynamic method. The experimental data were well-correlated with the modified Apelblat equation.

Introduction

The study of phase equilibria is very important for many industrial applications. More particularly, knowledge of an accurate solubility is needed for the design of separation processes such as extractive crystallization[1] or for the safe operation of different processing units such as distillation columns, absorption units, and extraction plants.[2] They can also supply basic and theoretical data for industrial production.[3]

Griseofulvin (CAS: 126-07-8) is a pharmaceutical with powerful antifungal action; its chemical structure is shown in Figure 1. It was prepared by fermentation, extraction, concentration, crystallization, and recrystallization.[4,5] At present, we were investigating and improving griseofulvin production technology, such as extraction, crystallization, and recrystallization.[6] We found the solubility of griseofulvin extremely important for the optimal unit operation conditions. But, no literature has been published on the solubility data on griseofulvin in acetone, 2-butanone, 1,2-dichloroethane, *N*,*N*-dimethylacetamide, dimethyl sulfoxide, and *N*-methyl-2-pyrrolidone. Therefore, in this work, we report the solubility of griseofulvin measured respectively in the temperature range (281.95 to 357.60) K. The experimental data were correlated with the modified Apelblat equation, and the solubility correlated using the Apelblat model showed good agreement with the experimental data.

Experimental Section

Chemicals. In all experiments, griseofulvin (purity 99.2 %) was supplied by Shanghai Chinese Pharmaceutical Factory. Acetone, 2-butanone, 1,2-dichloroethane, *N*,*N*-dimethylacetamide, dimethyl sulfoxide, and *N*-methyl-2-pyrrolidone were supplied by Tianjin Kermel Chemical Reagent Co. and were of analytical reagent grade with a purity higher than 99.5 %.

Apparatus and Procedure. The solubility of griseofulvin in different solvents was measured by the dynamic method. The laser monitoring observation technique was used to determine the dissolution temperature of the solid−liquid mixture of known composition. The laser monitoring system consists of a laser generator, a photoelectric transformer, and a light intensity display.[7]

These experiments were carried out in a 50 mL jacketed glass vessel with a magnetic stirrer. A mercury microthermometer

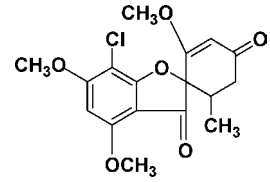

Figure 1. Chemical structure of griseofulvin.

was inserted into the inner chamber of the vessels for measuring the temperature[8,9] of griseofulvin solutions. The temperature of the jacketed vessel was controlled by an external constant circulating water bath that thermostatted the vessel. The temperature of the bath was selected by an external thermoelectric controller and kept constant (± 0.02 K).

For solubility measurements, predetermined mass of griseofulvin and the solvents were weighed by an electronic balance (Mettler Toledo AB204-N) with an accuracy of ± 0.0001 g and then transferred into the vessel. The contents of the vessel were heated very slowly at the heating rate of 1 K per hour until the system reached the equilibrium state. In an early stage, the laser beam was blocked by the suspended particles of griseofulvin in solution. As temperature increases, the intensity of the laser beam is increased due to griseofulvin dissolution. The intensity of the laser beam reached a maximum when the last portion of griseofulvin disappeared. Then, the equilibrium temperature was measured. The solubility of griseofulvin was expressed by mole fraction with the formula as follows:[7]

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

where m_1 represents the mass of solute and m_2 represenst the mass of the solvents, respectively. M_1 is the molecular mass of solute; M_2 is the molecular mass of the solvents, correspondingly.

Each experiment was repeated three times, and the relative deviation (RD) of the uncertainty in the mole fraction solubility is within ± 2.71 % except for two points in acetone beyond 3.00 %.

Table 1. Solubility of Sodium Chloride in Water

	NaCl + H_2O			
T/K	293.15	203.15	213.15	233.15
x	0.0998	0.1002	0.1012	0.1028
x (lit.)[10]	0.0996	0.1001	0.1009	0.1026
RD	0.0020	0.0010	0.0030	0.0019

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Table 2. Solubility of Griseofulvin in Different Solvents

T/K	$x \cdot 10^2$	100 RD
	Acetone	
281.95	0.648	4.1
286.40	0.710	3.1
291.85	0.776	−0.4
296.40	0.853	−1.3
300.80	0.941	−1.6
305.05	1.021	−3.3
310.25	1.170	−1.6
313.65	1.286	0.0
317.05	1.430	2.7
	2-Butanone	
289.65	0.826	0.6
296.95	0.941	−0.2
302.95	1.035	−1.5
308.25	1.167	1.4
315.05	1.281	−0.6
320.40	1.412	0.7
325.45	1.508	−0.4
330.35	1.629	0.0
	1,2-Dichloroethane	
290.05	1.967	0.9
294.30	2.087	1.5
300.25	2.216	−0.2
305.55	2.361	−0.9
310.05	2.514	−0.7
315.65	2.682	−2.0
319.35	2.888	0.2
324.05	3.105	0.8
329.65	3.354	0.5
	N,*N*-Dimethylacetamide	
296.20	2.521	−1.7
301.25	2.756	−1.0
305.75	3.032	1.5
310.75	3.260	1.1
314.95	3.437	0.1
319.25	3.695	1.1
324.75	3.951	0.1
330.05	4.223	−0.5
336.15	4.522	−1.7
340.25	4.878	0.7
345.75	5.176	−0.3
350.55	5.485	−0.3
354.78	5.823	0.6
	Dimethyl Sulfoxide	
296.75	1.673	−0.9
301.15	1.855	0.7
306.15	2.036	0.7
310.85	2.177	−0.9
315.55	2.391	0.5
320.55	2.599	0.8
326.55	2.819	−0.2
331.95	3.019	−1.0
336.75	3.239	−0.5
341.05	3.450	0.3
346.25	3.683	0.4
351.70	3.932	0.6
357.60	4.150	−0.5
	N-Methyl-2-pyrrolidone	
295.55	4.206	−1.1
300.65	4.511	−0.1
305.75	4.798	0.0
310.00	5.114	1.4
315.10	5.407	1.0
320.60	5.695	0.0
325.45	6.011	−0.1
330.45	6.312	−0.8
335.55	6.660	−1.1
340.35	7.040	−0.7
345.55	7.581	1.1
350.35	7.954	0.8
355.65	8.301	−0.5

Test of Apparatus. To ensure the reliability and the uncertainty of the measurement, the solubilities of NaCl in water were measured and compared with the values reported in the literature.[10] The experimental measurements agreed with the reported values with a mean RD of 0.20 %. The measured values are listed in Table 1.

Table 3. Modeling Parameters and Correlation Coefficient of Griseofulvin in Different Solvents by Equation 2

solvent	A	B	C	R^2	10^3 rmsd	10^2 RAD
acetone	−97.27	2383.34	14.84	0.9922	0.24	2.0
2-butanone	8.39	−1958.98	−1.13	0.9988	0.10	0.7
1,2-dichloroethane	−89.44	2829.52	13.36	0.9968	0.27	0.9
N,*N*-dimethylacetamide	−2.65	−1272.49	0.58	0.9988	0.37	0.8
dimethyl sulfoxide	47.00	−3768.51	−6.74	0.9995	0.19	0.6
N-methyl-2-pyrrolidone	−29.45	265.08	4.46	0.9985	0.52	0.7

Results and Discussion

The solubility data of griseofulvin in different solvents at different temperatures were presented in Tables 2 and 3. The temperature dependence of grideofulvin in different solvents is described by the modified Apelblat equation:

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

where x is the mole fraction solubility of griseofulvin. T is the absolute temperature. A, B, and C are the model parameters.

The solubility curves by eq 2 are shown in Figure 2. The values of parameters A, B, and C and the root-mean-square deviations (rmsds) are calculated according to:

$$\mathrm{rmsd} = \left[\frac{1}{N-1}\sum_{i=1}^{N}(x_{ci} - x_i)^2\right]^{1/2} \tag{3}$$

where N is the number of experimental points, x_{ci} represents the solubility calculated from eq 2, and x_i represents the experimental solubility values. The RDs between the experimental value and the calculated value are also listed in Table 2. The RDs are calculated according to:

$$\mathrm{RD} = \frac{x - x_c}{x} \tag{4}$$

The relative average deviations (RAD) and the rmsd by eq 2 are listed in Table 3. The RAD is defined as

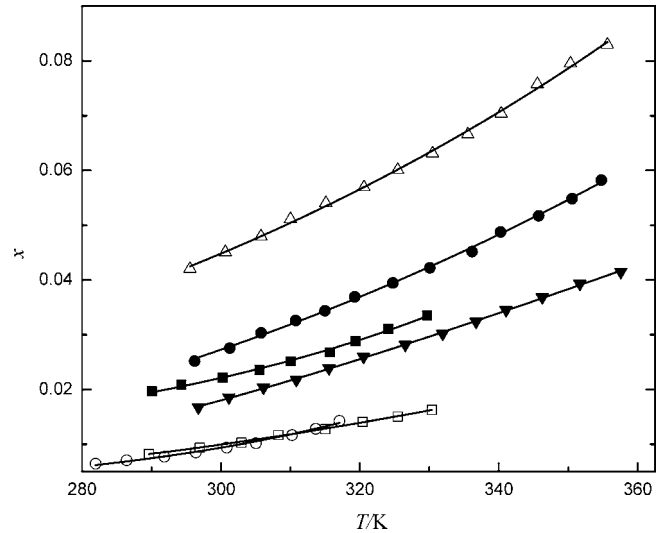

Figure 2. Solubility curves of griseofulvin in different aolvents: ○, acetone; □, 2-butanone; ■, 1,2-dichloroethane; ●, *N*,*N*-dimethylacetamide; ▼, dimethyl sulfoxide; △, *N*-methyl-2-pyrrolidone.

$$\mathrm{RAD} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{x_i - x_{ci}}{x_i}\right| \quad (5)$$

From Table 3, it can be found that the calculated solubility data show good agreement with the experimental data, the overall rmsd of 65 data points for the griseofulvin in different solvents being $0.32 \cdot 10^{-3}$. The RDs by eq 2 among all of these values do not exceed 4.1 %; the RADs are 2.0 %, 0.7 %, 0.9 %, 0.8 %, 0.6 %, and 0.7 %, respectively, which indicates that the modified Apelblat equation is suitable to correlate the solubility data of griseofulvin in the selected solvent systems.

The graph of solubility of griseofulvin in the selected solvent systems is shown in Figure 2. It can be observed from the figure that solubility increases as temperature is increased and follows the order *N*-methyl-2-pyrrolidone > *N*,*N*-dimethylacetamide > 1,2-dichloroethane > dimethyl sulfoxide > 2-butanone > acetone on the whole. This is because griseofulvin has intense polarity, and the higher the polarity of solvents is, the greater the solubility of griseofulvin; meanwhile, the solubility of griseofulvin which has an atom of chlorine in 1,2-dichloroethane is higher. These experimental results agree with the principle that like dissolves like.

Conclusion

The solubility of griseofulvin in the selected solvent systems has been measured from (281.95 to 357.60) K by a dependable experimental method and simple solubility apparatus.

The modified Apelblat equation based on solid−liquid phase equilibrium principles is used to correlate the solubility data of griseofulvin in the selected solvent systems. The RD among all of these values does not exceed ± 4.1 %, and the solubility calculated by the model shows good agreement with the experimental data.

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