



Thermodynamic models for determination of the solubility of omeprazole in pure and mixture organic solvents from $T = (278.15 \text{ to } 333.15) \text{ K}$



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ABSTRACT

Data on corresponding (solid + liquid) equilibrium of omeprazole in different solvents are essential for a preliminary study of industrial applications. In this paper, the (solid + liquid) equilibrium of omeprazole in water, methanol, ethanol, 1-butanol, acetonitrile, acetone, ethyl acetate, tetrahydrofuran pure solvents and (tetrahydrofuran + ethyl acetate) mixture solvents were explored within the temperatures from 278.15 K to 333.15 K under atmosphere pressure. For the temperature range investigated, the solubility of omeprazole in the solvents increased with increasing temperature. From (278.15 to 333.15) K, the solubility of omeprazole in tetrahydrofuran is superior to other selected pure solvents. The modified Apelblat model, the Buchowski–Ksiazczak λh model, and the ideal model were adopted to describe and predict the change tendency of solubility. Computational results showed that the modified Apelblat model has advantages than the other two models. Numerical values of the solubility were fitted using a modified Apelblat equation, a variant of the combined nearly ideal binary solvent/Redlich–Kister (CNIBS/R–K) model and Jouyban–Acree model in (tetrahydrofuran + ethyl acetate) binary solvent mixture. Computational results showed that the CNIBS/R–K model is superior to the other equations. In addition, the calculated thermodynamic parameters indicate that in each solvent studied the dissolution of omeprazole is endothermic, non-spontaneous and is an entropy-driven process.

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1. Introduction

Omeprazole is a kind of medicine which is used to curing stomach ailments. Omeprazole (figure 1, $C_{17}H_{19}N_3O_3S$, FW345.42, CASRN: 73590-58-6), a white powder, is composed of a substituted pyridine ring linked to a benzimidazole by a sulfoxide chain. As a potent reversible inhibitor of the gastric proton pump H^+/K^+ -ATPase, omeprazole can be used in the treatment of gastroesophageal reflux disease (GERD), peptic ulcers, erosive esophagitis, and Zollinger–Ellison syndrome [1–3]. Omeprazole is one of the most widely prescribed drugs internationally and is available over the counter in some countries.

The solubility of the different organic solvents plays an important role in understanding the phase equilibria or (solid + liquid) equilibria in the research of crystallization or the (liquid + liquid) equilibria in extraction processes. The purity is an important part of a medicinal substance. This work aims to provide some useful

data for the industrial production of omeprazole. And then, we plan to research the thermodynamic properties of omeprazole. This knowledge would permit exploration of separation processes such as the safety of operating and extractive crystallization.

In this study, the solubility of omeprazole in pure and mixture organic solvents was measured over the temperature from 278.15 K to 333.15 K under atmospheric pressure by the gravimetric method. Values of the solubility were correlated to the modified Apelblat model, the Buchowski–Ksiazczak λh model, the ideal model or the combined nearly ideal binary solvent/Redlich–Kister (CNIBS/R–K) model and Jouyban–Acree model. We can calculate thermodynamic parameters (including enthalpy, entropy and Gibbs energy) by the van't Hoff analysis and Gibbs equation. We expect to determine the best pure solvent in the crystallization process of omeprazole from the selected solvents according to experimental data. Besides, the analysis of thermodynamic properties would also help to determine the best temperature interval and provide information regarding the temperature dependence of the solubility.

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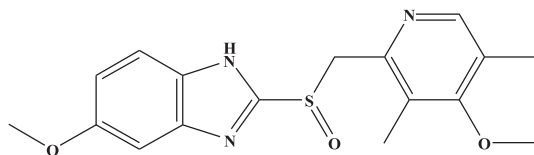


FIGURE 1. Chemical structure of omeprazole.

2. Experimental

2.1. Materials and apparatus

Omeprazole with a mass fraction purity ≥ 0.980 was obtained from Shang Hai DEMO Medical Tech. Co., Ltd. Its purity was measured by high performance liquid chromatography (HPLC type DIONEX P680 DIONEX Technologies). We measured the melting point by the melting point apparatus (HCRD-2C), which is from Chengdu Huacheng Instruments Co., Ltd. The double distilled water was produced by an ultrapure water system, which is from Shandong Flom Co., Ltd. in our laboratory. Other chemical reagents were used without further purification. The purities of the solvents were determined in our laboratory by gas chromatography (GC type Agilent 7820A Agilent Technologies). The detailed information of the materials used in the experiment is listed in table 1. The analytical balance (model: BSA224S) was bought from Sartorius Scientific Instruments (Beijing) Co., Ltd. with the accuracy of ± 0.1 mg. The Smart water-circulator thermostatic bath (model: DC-2006) was bought by Ningbo Scientz Biotechnology Co., Ltd. with the accuracy of $T = \pm 0.05$ K.

2.2. Methods

The solid (omeprazole) was put into the melting point apparatus, and the temperature increased. The temperature was recorded when the solid melted. The melting points were measured by five times. The melting points were $T = 427.15$ K, $T = 431.15$ K, $T = 430.65$ K, $T = 428.15$ K and $T = 428.65$ K respectively. So our can calculate the melting point temperature is 429.15 K ($u(T) = 0.85$ K). Our result and the result of literature are consistent, which the melting point is in the range of temperature from 429.15 K to 435.15 K [4].

The solubility of omeprazole was measured, in various solvents, by the analytical stirred-flask method, and we used the gravimetric method to measure the compositions of the saturated solutions. Saturated solutions of omeprazole, which were produced by 8 mL solvent mixtures and some excess omeprazole, were prepared in a spherical, 10 mL Pyrex glass flask with a bottle stopper (avoid evaporation of solvent during experimental steps). The flask was maintained in a jacket glass vessel full of water at the desired temperature through circulating water, whose temperature was

controlled by a thermostat bath. For each measurement, some excess omeprazole were added to a known volume of solvent mixtures. Continuous stirring was achieved for fully mixing the suspension using a magnetic stirrer at the required temperature. The stirring continued for about 24 h to ensure the (solid + liquid) equilibrium and the solution was allowed to settle for 12 h or more before sampling for achieving a static state [5,6]. The supernatant was taken, filtered, and poured into a warmed flask pre-weighed by using an analytical balance. At last, 1 mL solution supernatant was transferred into 5 mL warmed breaker with a cover and weighted immediately in order to prevent the cooling crystallization. This breaker had been weighted before. All breakers were put into a dryer at room temperature and weighted weekly until reaching constant weight. All determinations were repeated three times to check reproducibility, and then an average value was given. The saturated mole fraction solubility of omeprazole (x) in different solvents is calculated by Eq. (1). The mole fraction of tetrahydrofuran (x_A) in the binary solvent mixtures is calculated by Eq. (2).

$$x = \frac{m_1/M_1}{m_1/M_1 + \sum m_i/M_i} \quad (1)$$

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

where m_1 , m_2 , m_3 represent the mass of omeprazole, tetrahydrofuran and according solvent, respectively; and M_1 , M_2 , M_3 represent the molar mass of omeprazole, tetrahydrofuran and according solvent, respectively.

3. Results and discussion

3.1. In pure solvents

3.1.1. Solubility and correlation models

The saturated mole fraction solubility (x) of omeprazole in water, methanol, ethanol, 1-butanol, acetonitrile, acetone, ethyl acetate and tetrahydrofuran over the temperature range of (278.15 to 333.15) K is recorded in table 2 and plotted in figure 2.

The relative deviations (RD) between the experimental values and the calculated values are also presented in table 2. The RD is defined as follows:

$$RD = \frac{x_i - x_{ci}}{x_i} \quad (3)$$

where x_i stand for the experimental solubility values, and x_{ci} represent the calculated solubility values.

The average absolute deviations (RAD) are listed in tables 3–5.

The relative average deviations (RAD) are expressed as:

$$RAD = \frac{1}{N} \sum_{i=1}^N \left| \frac{x_i - x_{ci}}{x_i} \right| \quad (4)$$

TABLE 1
Provenance and mass fraction purity of the compounds studied.

Material	Properties			
	Molar mass ($\text{g} \cdot \text{mol}^{-1}$)	Mass fraction purity	Analysis method	Source
Omeprazole	345.42	0.980	HPLC	Shang Hai DEMO Medical Tech. Co., Ltd.
Water	18.02	Double distilled	GC	Our Laboratory
Methanol	32.04	0.995	GC	Shenbo Chemical Industry
Ethanol	46.07	0.997	GC	Shenbo Chemical Industry
1-Butanol	74.12	0.990	GC	Shenbo Chemical Industry
Acetonitrile	41.05	0.999	GC	Shenbo Chemical Industry
Acetone	58.08	0.995	GC	Shenbo Chemical Industry
Ethyl acetate	88.11	0.997	GC	Shenbo Chemical Industry
Tetrahydrofuran	72.11	0.990	GC	Shenbo Chemical Industry

TABLE 2
Mole fraction solubility (x) of omeprazole in pure organic solvents over the temperature range from (278.15 to 333.15) K under 0.1 MPa.^{a,b}

T/K	1000x	100RD		
		Eq. (5)	Eq. (6)	Eq. (9)
<i>Water</i>				
278.15	0.0407	6.14	-9.15	-5.35
283.15	0.0500	2.03	-8.45	-5.81
288.15	0.0615	-0.69	-7.00	-5.39
293.15	0.0764	-1.02	-3.89	-3.14
298.15	0.0936	-1.46	-1.75	-1.69
303.15	0.1145	-0.97	0.52	0.09
308.15	0.1377	-0.95	1.58	0.84
313.15	0.1652	-0.13	2.75	1.87
318.15	0.1959	0.58	3.13	2.33
323.15	0.2297	1.09	2.68	2.15
328.15	0.2631	0.16	0.14	0.11
333.15	0.2994	-0.53	-2.89	-2.11
<i>Methanol</i>				
278.15	2.058	3.33	-9.66	-7.27
283.15	2.639	0.41	-8.70	-6.98
288.15	3.480	1.65	-3.95	-2.87
293.15	4.350	-1.10	-4.10	-3.50
298.15	5.691	1.97	1.08	1.26
303.15	6.863	-1.90	-1.33	-1.46
308.15	8.573	-1.10	0.39	0.05
313.15	10.55	-0.69	1.21	0.75
318.15	12.89	-0.06	1.73	1.29
323.15	15.62	0.81	2.01	1.69
328.15	18.61	0.81	0.95	0.90
333.15	21.65	-0.62	-2.06	-1.67
<i>Ethanol</i>				
278.15	1.574	7.74	0.37	3.55
283.15	1.875	2.51	-2.76	-0.43
288.15	2.243	-1.56	-4.89	-3.37
293.15	2.612	-7.61	-9.30	-8.50
298.15	3.465	0.81	0.56	0.70
303.15	4.130	-0.90	-0.20	-0.50
308.15	5.085	1.45	2.70	2.12
313.15	6.047	1.12	2.60	1.87
318.15	7.019	-0.91	0.47	-0.23
323.15	8.316	-0.19	0.70	0.22
328.15	9.818	0.84	0.87	0.83
333.15	11.26	-0.44	-1.66	-1.02
<i>1-Butanol</i>				
278.15	1.282	6.99	-5.84	-2.64
283.15	1.532	-0.36	-9.60	-7.25
288.15	1.962	0.30	-5.21	-3.78
293.15	2.404	-2.17	-4.88	-4.15
298.15	3.026	-0.71	-1.20	-1.06
303.15	3.702	-0.96	0.08	-0.21
308.15	4.550	0.31	2.25	1.68
313.15	5.401	-0.89	1.43	0.72
318.15	6.504	0.33	2.42	1.75
323.15	7.788	1.86	3.19	2.74
328.15	8.842	-1.03	-0.98	-1.02
333.15	10.35	-0.02	-1.85	-1.23
<i>Acetonitrile</i>				
278.15	1.177	5.78	-6.29	-3.07
283.15	1.425	-0.26	-8.87	-6.52
288.15	1.821	0.20	-4.97	-3.52
293.15	2.221	-2.80	-5.39	-4.64
298.15	2.732	-3.77	-4.28	-4.12
303.15	3.538	1.57	2.49	2.22
308.15	4.286	1.27	3.04	2.49
313.15	5.126	0.65	2.77	2.09
318.15	6.075	0.05	2.01	1.35
323.15	7.113	-0.88	0.40	-0.06
328.15	8.431	0.27	0.32	0.28
333.15	9.775	0.00	-1.69	-1.09
<i>Acetone</i>				
278.15	1.463	4.30	-4.47	-0.95
283.15	1.731	-0.89	-7.03	-4.52
288.15	2.155	-0.09	-3.67	-2.17
293.15	2.648	0.35	-1.23	-0.54

(continued on next page)

TABLE 2 (continued)

T/K	1000x	100RD		
		Eq. (5)	Eq. (6)	Eq. (9)
298.15	3.126	-2.25	-2.33	-2.27
303.15	3.773	-1.76	-0.75	-1.18
308.15	4.638	1.41	3.01	2.30
313.15	5.415	0.22	2.05	1.21
318.15	6.372	0.56	2.19	1.41
323.15	7.388	0.13	1.15	0.64
328.15	8.496	-0.45	-0.48	-0.49
333.15	9.815	0.07	-1.47	-0.71
<i>Ethyl acetate</i>				
278.15	0.9807	3.66	2.86	6.65
283.15	1.124	-0.27	-0.98	1.76
288.15	1.338	0.02	-0.52	1.15
293.15	1.565	-1.03	-1.38	-0.60
298.15	1.854	-0.45	-0.59	-0.54
303.15	2.199	0.66	0.72	0.22
308.15	2.535	-0.74	-0.52	-1.37
313.15	2.927	-1.62	-1.29	-2.29
318.15	3.426	-0.75	-0.41	-1.31
323.15	4.049	1.36	1.62	1.05
328.15	4.696	1.92	1.96	1.97
333.15	5.226	-1.37	-1.71	-0.83
<i>Tetrahydrofuran</i>				
278.15	4.577	12.68	-6.92	-10.04
283.15	6.437	10.74	-2.96	-5.29
288.15	8.434	4.13	-5.27	-7.03
293.15	11.31	1.43	-4.07	-5.26
298.15	14.62	-3.18	-5.70	-6.42
303.15	19.63	-2.13	-2.37	-2.68
308.15	25.88	-1.20	-0.04	-0.03
313.15	32.73	-2.88	-0.99	-0.77
318.15	42.45	-0.46	1.42	1.74
323.15	54.51	2.34	3.65	3.93
328.15	66.34	1.19	1.46	1.60
333.15	78.86	-1.06	-2.35	-2.53

^a The relative standard uncertainty is $u_r(x) = 2.00\%$. The standard uncertainty u are $u(T) = \pm 0.05$ K, $u(p) = \pm 2$ kPa.

^b x denotes the mole fraction solubility of omeprazole.

3.1.2. The modified Apelblat model

The change of temperatures on the solubility of omeprazole has been fitted in with the following modified Apelblat model [7–9]:

$$\ln x = A + \frac{B}{(T/K)} + C \ln(T/K) \quad (5)$$

where T represents absolute Kelvin temperature, A , B , C represent the model parameters, while x represents the mole fraction solubility of omeprazole in aqueous solutions. The factors A and B represent the variation in the solution activity coefficient and provide an indication of the effect of the non-ideal solution of solute solubility, and the factors C represent the temperature effect upon the fusion enthalpy, which is a deviation of heat capacity (ΔC_p) [10,11]. The regression curve parameters of modified Apelblat model are listed in table 3.

3.1.3. Buchowski–Ksiazaczak λh model

The Buchowski–Ksiazaczak λh model was requested to describe the solution behavior by Buchowski firstly. The λh equation would fit experimental values using two parameters λ and h . The λh equation is defined as follows:

$$\ln \left[1 + \frac{\lambda(1-x)}{x} \right] = \lambda h \left[\frac{1}{(T/K)} - \frac{1}{(T_m/K)} \right] \quad (6)$$

where x is the mole fraction solubility of omeprazole, T is the experimental Kelvin temperature and T_m is the standard melting Kelvin temperature [12–14]. The parameters of λ and h are presented in table 4.

3.1.4. Ideal model

The ideal model is a universal equation for (solvent + solute) equilibrium which based on thermodynamic principles [15]. The equation is defined as:

$$\ln x\gamma = \frac{\Delta_{\text{disso}}H}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) \quad (7)$$

While the solution is an ideal solution ($\gamma = 1$), and then we have some transformation as follows:

$$A \stackrel{\text{def}}{=} \frac{\Delta_{\text{disso}}H}{R} \times \frac{1}{T_m}, \quad B \stackrel{\text{def}}{=} -\frac{\Delta_{\text{disso}}H}{R} \quad (8)$$

We can get the Eq. (9):

$$\ln x = A + \frac{B}{T} \quad (9)$$

where x is the mole fraction solubility of omeprazole, T is the Kelvin temperature in corresponding. The parameters of A and B are recorded in table 5.

3.1.5. Thermodynamic parameters

The van't Hoff analysis is a common method in the thermodynamic field. The standard molar dissolution enthalpy ($\Delta_{\text{sol}}H_m^0$) is expressed as:

$$\Delta_{\text{sol}}H_m^0 = -R \times \left(\frac{\partial \ln x}{\partial (1/T)} \right) \quad (10)$$

where the parameter of R represents universal gas constant ($8.314 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$) and T represent the corresponding absolute Kelvin temperature. Rearranging Eq. (5), we obtain Eq. (11) [16]:

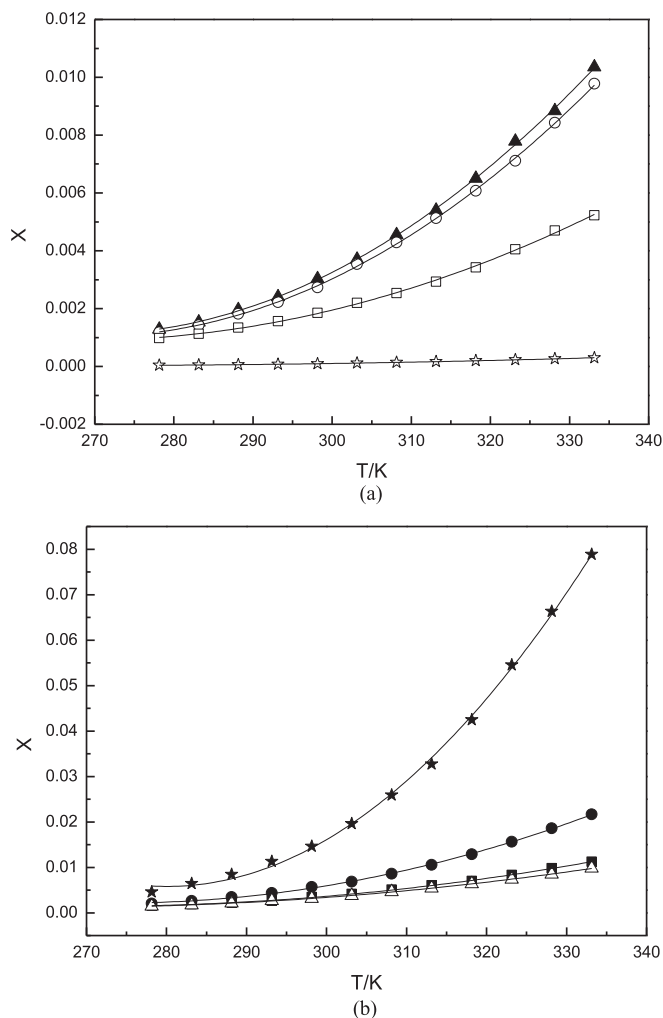


FIGURE 2. Mole fraction solubility (x) of omeprazole versus temperature (T) in the selected organic solvents: (a) ☆, Water; □, Ethyl acetate; ○, Acetonitrile; ▲, 1-Butanol; (b) △, Acetone; ■, Ethanol; ●, Methanol; ★, Tetrahydrofuran.

$$\Delta_{\text{sol}}H_m^0 = -(b - cT)R \quad (11)$$

Because the values of activity coefficients of the systems considered at the saturation concentration are immeasurable, it is only possible to determine the apparent Gibbs energy of solution by neglecting the activity coefficient.

The equation of mole Gibbs energy becomes ($\Delta_{\text{sol}}G_m^0$) is:

$$\Delta_{\text{sol}}G_m^0 = -RT \ln x \quad (12)$$

TABLE 3

Parameters of the modified Apelblat model for omeprazole in pure organic solvents over the temperature range from (278.15 to 333.15) K.

Solvent	A	B	C	10^2RAD
Water	128.17	-9170.28	-18.72	1.31
MethanSol	110.16	-8641.07	-15.16	1.20
Ethanol	53.88	-5627.47	-7.14	2.17
1-Butanol	110.12	-8334.80	-15.44	1.33
Acetonitrile	100.63	-7929.87	-14.02	1.46
Acetone	65.40	-6002.12	-8.95	1.04
Ethyl acetate	-34.21	-1199.77	5.61	1.15
Tetrahydrofuran	207.2	-13842.9	-28.9	3.62
			$\sum(10^2\text{RAD}) = 13.29$	

TABLE 4

Parameters of the λh model for omeprazole in pure organic solvents.

Solvent	100λ	h	10^2RAD
Water	0.21	1453065	3.66
Methanol	25.80	14540.97	3.10
Ethanol	8.66	36768.28	2.26
1-Butanol	8.72	37881.21	3.24
Acetonitrile	8.47	39469.21	3.54
Acetone	6.36	46625.85	2.49
Ethyl acetate	2.64	100547.6	1.21
Tetrahydrofuran	210.30	2278.137	3.10
		$\sum(10^2\text{RAD}) = 22.60$	

TABLE 5

Parameters of ideal model for omeprazole in pure organic solvents over the temperature range from (278.15 to 333.15) K.

Solvents	A	B	10^2RAD
Water	1.84	-3310.50	2.57
Methanol	7.82	-3875.08	2.47
Ethanol	5.71	-3392.12	1.95
1-Butanol	5.93	-3495.80	2.35
Acetonitrile	5.99	-3533.63	2.62
Acetone	5.00	-3203.27	1.53
Ethyl acetate	3.61	-2948.77	1.15
Tetrahydrofuran	11.52	-4676.96	3.94
		$\sum(10^2\text{RAD}) = 18.60$	

According to the Gibbs equation, we can find the equation of mole entropy of solution ($\Delta_{\text{sol}}S_m^0$) and the equations of contribution of enthalpy and entropy to the standard Gibbs energy [17]. The research for the $\% \xi_H$ and $\% \xi_S$ is aimed at comparing the relative contribution to the $\Delta_{\text{sol}}G_m^0$ by entropy and enthalpy in the solution process.

$$\Delta_{\text{sol}}S_m^0 = \frac{\Delta_{\text{sol}}H_m^0 - \Delta_{\text{sol}}G_m^0}{T} \quad (13)$$

$$\% \xi_H = \frac{|\Delta_{\text{sol}}H_m^0|}{|\Delta_{\text{sol}}H_m^0| + |T \cdot \Delta_{\text{sol}}S_m^0|} \times 100\% \quad (14)$$

$$\% \xi_S = \frac{|T \cdot \Delta_{\text{sol}}S_m^0|}{|\Delta_{\text{sol}}H_m^0| + |T \cdot \Delta_{\text{sol}}S_m^0|} \times 100\% \quad (15)$$

The average values of $\Delta_{\text{sol}}H_m^0$, $\Delta_{\text{sol}}S_m^0$, $\Delta_{\text{sol}}G_m^0$, $\% \xi_H$ and $\% \xi_S$ from 278.15 K to 333.15 K are listed in table 6.

3.2. Binary solvent mixtures

3.2.1. Solubility and correlation models

The saturated mole fraction solubility (x) of omeprazole in (tetrahydrofuran + ethyl acetate) binary solvent mixtures over

TABLE 6

Thermodynamic parameters of dissolution of omeprazole in pure organic solvents of average value from 278.15 K to 333.15 K.

Solvents	$\Delta_{\text{sol}}H_m^0 / \text{kJ} \cdot \text{mol}^{-1}$	$\Delta_{\text{sol}}S_m^0 / \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$	$\Delta_{\text{sol}}G_m^0 / \text{kJ} \cdot \text{mol}^{-1}$	$\% \xi_H (\%)$	$\% \xi_S (\%)$
Water	28.67	19.49	22.87	83.84	16.16
Methanol	33.32	68.88	12.39	61.40	38.60
Ethanol	28.64	49.04	13.71	65.72	34.28
1-Butanol	30.06	52.93	14.01	65.21	34.79
Acetonitrile	30.30	53.10	14.18	65.28	34.72
Acetone	27.16	43.47	13.94	67.26	32.74
Ethyl acetate	24.23	28.93	15.34	73.30	26.70
Tetrahydrofuran	41.65	105.44	9.66	56.51	43.49

TABLE 7
Mole fraction solubility (x) of omeprazole in (tetrahydrofuran + ethyl acetate) binary solution mixtures from 278.15 K to 333.15 K under 0.1 MPa.^{a,b}

x_A	100x	$100 x - x^{cal} /x(\text{Eq. (5)})$	$100 x - x^{cal} /x(\text{Eq. (17)})$	$100 x - x^{cal} /x(\text{Eq. (20)})$
<i>T = 278.15 K</i>				
0.0000	0.0981	3.6649	0.0000	5.5665
0.1748	0.1348	5.9638	5.5327	1.8428
0.3397	0.1652	1.2125	4.1823	1.5203
0.4955	0.2227	5.2449	0.1319	1.9871
0.6429	0.2767	6.7786	1.2538	2.1144
0.7826	0.3242	5.5088	0.0160	2.2598
0.9153	0.3882	8.9930	0.5848	1.7342
1.0000	0.4577	12.6848	0.0000	0.7236
<i>T = 283.15 K</i>				
0.0000	0.1124	0.2684	0.0000	4.8445
0.1748	0.1714	2.3923	3.5859	1.5088
0.3397	0.2358	4.2893	0.5303	0.6774
0.4955	0.3108	4.0902	1.5784	1.3937
0.6429	0.3905	5.7810	0.1742	1.4349
0.7826	0.4756	7.3272	2.1831	1.1860
0.9153	0.5453	6.3833	1.9287	1.2373
1.0000	0.6437	10.7355	0.0000	0.2921
<i>T = 288.15 K</i>				
0.0000	0.1338	0.0192	0.0000	8.5736
0.1748	0.2260	3.4979	0.9541	3.1181
0.3397	0.3254	5.7285	0.7396	0.2739
0.4955	0.4389	5.9433	0.3892	1.1966
0.6429	0.5454	5.7368	0.3353	1.5966
0.7826	0.6589	5.8666	0.3530	1.3970
0.9153	0.7654	5.7591	0.2405	1.3186
1.0000	0.8434	4.1327	0.0000	0.9861
<i>T = 293.15 K</i>				
0.0000	0.1565	1.0316	0.0000	9.0428
0.1748	0.2832	0.7754	1.2106	3.1296
0.3397	0.4197	2.3069	0.8292	0.5059
0.4955	0.5756	2.5284	0.3702	1.2927
0.6429	0.7218	2.4412	0.3262	1.6508
0.7826	0.8778	2.5783	0.3813	1.3477
0.9153	1.024	2.5414	0.2698	1.2624
1.0000	1.131	1.4290	0.0000	0.8699
<i>T = 298.15 K</i>				
0.0000	0.1854	0.4524	0.0000	7.5555
0.1748	0.3514	1.9198	1.4146	2.3090
0.3397	0.5301	1.7739	0.8929	0.9857
0.4955	0.7344	2.0184	0.3503	1.5828
0.6429	0.9259	2.2710	0.3160	1.9021
0.7826	1.130	2.3162	0.4016	1.6145
0.9153	1.322	2.4211	0.2918	1.5817
1.0000	1.462	3.1847	0.0000	1.2283
<i>T = 303.15 K</i>				
0.0000	0.2199	0.6572	0.0000	12.2283
0.1748	0.4465	1.1276	1.7652	4.4016
0.3397	0.6905	1.2900	0.9918	0.9167
0.4955	0.9694	1.4826	0.3114	1.5215
0.6429	1.231	1.6392	0.2955	1.9652
0.7826	1.510	1.6802	0.4334	1.3696
0.9153	1.771	1.7388	0.3275	1.3651
1.0000	1.963	2.1316	0.0000	0.7413
<i>T = 308.15 K</i>				
0.0000	0.2535	0.7413	0.0000	8.2666
0.1748	0.5570	1.2135	2.2370	3.7023
0.3397	0.8838	1.1731	1.1098	0.3657
0.4955	1.257	1.1371	0.2545	0.4095
0.6429	1.607	1.1322	0.2656	0.6697
0.7826	1.981	1.1100	0.4722	0.0570
0.9153	2.331	1.0983	0.3720	0.1113
1.0000	2.588	1.2049	0.0000	0.4408
<i>T = 313.15 K</i>				
0.0000	0.2927	1.6211	0.0000	8.6342
0.1748	0.6801	2.5013	2.6160	4.6684
0.3397	1.097	2.7898	1.1954	1.9404
0.4955	1.574	2.8591	0.2072	1.4026
0.6429	2.021	2.8849	0.2411	1.8411
0.7826	2.498	2.9148	0.5011	0.7072
0.9153	2.945	2.9194	0.4055	1.0413
1.0000	3.273	2.8761	0.0000	0.1045

TABLE 7 (continued)

x_A	100x	$100 x - x^{cal} /x(\text{Eq. (5)})$	$100 x - x^{cal} /x(\text{Eq. (17)})$	$100 x - x^{cal} /x(\text{Eq. (20)})$
$T = 318.15 \text{ K}$				
0.0000	0.3426	0.7523	0.0000	2.0653
0.1748	0.8499	0.5386	3.1017	4.7896
0.3397	1.396	0.6556	1.2962	0.0444
0.4955	2.021	0.6305	0.1458	1.2213
0.6429	2.606	0.5997	0.2098	0.9049
0.7826	3.230	0.6067	0.5358	1.9213
0.9153	3.816	0.5905	0.4461	1.3964
1.0000	4.245	0.4593	0.0000	2.1521
$T = 323.15 \text{ K}$				
0.0000	0.4049	1.3603	0.0000	3.2393
0.1748	1.061	2.1093	3.5451	5.4543
0.3397	1.767	2.0965	1.3810	2.1463
0.4955	2.575	2.1482	0.0896	3.7452
0.6429	3.332	2.1898	0.1816	3.4442
0.7826	4.139	2.1907	0.5659	4.2983
0.9153	4.896	2.2087	0.4813	3.5521
1.0000	5.451	2.3398	0.0000	4.1167
$T = 328.15 \text{ K}$				
0.0000	0.4696	1.9167	0.0000	10.1601
0.1748	1.271	1.5017	3.8228	2.8242
0.3397	2.134	1.2996	1.4312	0.2445
0.4955	3.120	1.2209	0.0545	2.0362
0.6429	4.045	1.1883	0.1641	1.6015
0.7826	5.032	1.1547	0.5841	2.2424
0.9153	5.956	1.1398	0.5026	1.1901
1.0000	6.634	1.1873	0.0000	1.5623
$T = 333.15 \text{ K}$				
0.0000	0.5226	1.3652	0.0000	10.8603
0.1748	1.480	1.2143	4.2287	1.0755
0.3397	2.511	1.0496	1.5010	1.8659
0.4955	3.689	1.0167	0.0034	0.7902
0.6429	4.793	1.0105	0.1390	1.0476
0.7826	5.972	0.9886	0.6099	0.8115
0.9153	7.076	0.9870	0.5328	1.4920
1.0000	7.886	1.0636	0.0000	1.3953

^a The relative standard uncertainty is $u_r(x) = 2.0000\%$, $u_r(x_A) = 2.00\%$. The standard uncertainties u are $u(T) = \pm 0.05 \text{ K}$, $u(p) = \pm 2 \text{ kPa}$.

^b x_A denotes the mole of fraction of tetrahydrofuran in the binary solvent mixtures. x denotes the mole fraction solubility of omeprazole; x^{cal} denotes the calculated solubility.

the temperature in the range of 278.15 K to 333.15 K is recorded in table 7. There are vividly shown in figure 3.

3.2.2. Modified Apelblat model

The regression curve parameters of the modified Apelblat model are calculated as previously described in Section 3.1 and listed in table 8.

3.2.3. CNIBS/R-K Model

The changing trends of solubility against different ratio of isopropanol under isothermal condition are described by the Combined Nearly Ideal Binary Solvent/Redlich-Kister (CNIBS/R-K) model [18–22], which is one of the theoretical models for calculating the solute solubility in binary solvents and represented in Eq. (4):

$$\ln x = x_A \ln X_A + x_B \ln X_B + x_A x_B \sum_{i=0}^N S_i (x_A - x_B)^i \quad (16)$$

where x represents the mole fraction solubility of omeprazole, x_A and x_B represent the initial mole fraction composition of the binary solvent when the solute was not added, X_A and X_B respectively represent the saturated mole solubility of omeprazole in pure tetrahydrofuran and ethyl acetate. S_i is the model constant and N can be equal to 0, 1, 2 and 3. When $N = 2$ and substituting $(1 - x_A)$ for x_B , Eq. (16) can be rearranged as:

$$\ln x - (1 - x_A) \ln X_B - x_A \ln X_A = (1 - x_A) x_A [S_0 + S_1 (2x_A - 1) + S_2 (2x_A - 1)^2] \quad (17)$$

This is a variant of CNIBS/R-K model. The parameters S_i could be obtained by regressing

$$\{\ln x - (1 - x_A) \ln X_B - x_A \ln X_A\} \text{ versus } \{(1 - x_A) x_A [S_0 + S_1 (2x_A - 1) + S_2 (2x_A - 1)^2]\}$$

The values of parameters are listed in table 9. However, the CNIBS/R-K model only can be used to describe the solubility and to predict solubility for different concentrations of a mixed solvent at a fixed temperature. To describe the effect of both solvent compositions and temperature on the solubility of omeprazole, we adopt another equation.

3.2.4. Jouyban-Acree model

This is a relatively more versatile model to describe the solubility of a solute with the variation of both temperature and initial composition of binary solvent mixtures [23]:

$$\ln x = x_A \ln X_A + x_B \ln X_B + x_A x_B \sum_{i=0}^N \frac{J_i (x_A - x_B)^i}{T} \quad (18)$$

where J_i is the parameter and T is the absolute temperature. Other symbols mean the same as Eq. (16). When $N = 2$ and substituting $(1 - x_A)$ for x_B , Eq. (18) can be rewritten as:

TABLE 8

Parameters of the modified Apelblat equation for omeprazole in the binary solution mixtures.

x_A	A	B/100	C	MD
0.0000	-34.21	-12.00	5.61	1.1542
0.1748	69.05	-69.08	-9.04	2.0630
0.3397	150.4	-109.65	-20.9	2.1388
0.4955	185.1	-127.02	-25.9	2.5267
0.6429	200.8	-134.88	-28.1	2.8044
0.7826	215.8	-142.27	-30.3	2.8536
0.9153	223.1	-145.89	-31.3	3.0650
1.0000	207.2	-138.43	-28.9	3.6191
				$\sum(\text{MD}) = 20.2248$

TABLE 9

Parameters of the CNIBS/R-K model for omeprazole in the binary solution mixtures.

T/K	S_0	S_1	S_2	MD
278.15	0.23	-0.07	-0.79	1.4627
283.15	0.67	-0.25	-0.65	1.2476
288.15	1.08	-0.37	0.02	0.3765
293.15	1.27	-0.50	0.08	0.4234
298.15	1.39	-0.59	0.13	0.4584
303.15	1.58	-0.73	0.20	0.5156
308.15	1.78	-0.89	0.29	0.5889
313.15	1.93	-1.01	0.35	0.6458
318.15	2.09	-1.16	0.43	0.7169
323.15	2.23	-1.28	0.50	0.7806
328.15	2.31	-1.35	0.55	0.8199
333.15	2.43	-1.45	0.61	0.8768
				$\sum(\text{MD}) = 8.9131$

$$\ln x = \ln X_B + (\ln X_A - \ln X_B)x_A + \frac{(J_0 - J_1 + J_2)x_A}{T} + \frac{(-J_0 + 3J_1 - 5J_2)x_A^2}{T} + \frac{(-2J_1 + 8J_2)x_A^3}{T} + \frac{(-4J_2)x_A^4}{T} \quad (19)$$

This can be simplified as:

$$T \ln x = A_0 + A_1 T + A_2 T x_A + A_3 x_A + A_4 x_A^2 + A_5 x_A^3 + A_6 x_A^4 \quad (20)$$

where $A_0, A_1, A_2, A_3, A_4, A_5$ and A_6 are parameters of this model and can be calculated by regressing $T \ln x$ against $T, T x_A, x_A, x_A^2, x_A^3, x_A^4$ by least-square analysis, which are listed in table 10.

3.2.5. Mean deviation

The mean deviation (MD) [24] is adopted to describe the deviation between experimental and calculated values.

$$\text{MD} = 100 \frac{\sum \frac{|x - x^{\text{cal}}|}{x}}{N} \quad (21)$$

where N represents the number of experimental points, x and x^{cal} respectively represent experimental and calculated values. The values of MD are listed in tables 3–5, together with the parameters.

3.2.6. Thermodynamic parameters

The average values of the van't Hoff analysis are also calculated as previously described in Section 3.1 and listed in table 11.

3.3. Chart analysis

3.3.1. Pure solvents

According to table 2 and figure 2, we see that the solubility of omeprazole in different solvents is a function of temperature, while the solubility increases with the temperature rising.

According to tables 3–5, we see that the sum of RAD values of the modified Apelblat equation, the λh model and the van't Hoff model are 13.29, 22.60 and 18.60, respectively. This result shows

TABLE 10

Parameters of the Jouyban–Acree model for omeprazole in the binary solution mixtures.

T/K	MD	Parameters	
278.15	2.2186	A_0	-4520.05
283.15	1.5718	A_1	8.51
288.15	2.3076	A_2	3.16
293.15	2.3877	A_3	970.35
298.15	2.3449	A_4	-2430.06
303.15	3.0637	A_5	1783.14
308.15	1.7529	A_6	-528.15
313.15	2.5425		
318.15	1.8119		
323.15	3.7496		
328.15	2.7327		
333.15	2.4173		
$\sum(\text{MD}) = 28.9011$			

TABLE 11Thermodynamic functions relative to the solution process of omeprazole in the binary solution mixtures for average values from $T = (278.15 \text{ to } 333.15) \text{ K}$.

x_A	$\Delta_{\text{sol}} H_m^0 / \text{kJ} \cdot \text{mol}^{-1}$	$\Delta_{\text{sol}} S_m^0 / \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$	$\Delta_{\text{sol}} G_m^0 / \text{kJ} \cdot \text{mol}^{-1}$	% $\xi_H(\%)$	% $\xi_S(\%)$
0.0000	24.23	28.93	15.34	73.30	26.70
0.1748	34.46	68.97	13.46	62.11	37.89
0.3397	38.05	84.62	12.36	59.67	40.33
0.4955	39.79	93.26	11.49	58.40	41.60
0.6429	40.73	98.42	10.88	57.67	42.33
0.7826	41.29	101.99	10.36	57.13	42.87
0.9153	41.76	104.90	9.95	56.71	43.29
1.0000	41.65	105.44	9.66	56.51	43.49

that the modified Apelblat equation is the best that compared with the λh model and the van't Hoff model.

According to table 6, the thermodynamic parameters of $\Delta_{\text{sol}} H_m^0$ and $\Delta_{\text{sol}} G_m^0$ are both positive value. Moreover, the main contributor to the standard molar Gibbs energy of solution is the enthalpy during the dissolution, because all values of $\% \xi_H$ are $\geq 56.51\%$. These indicate that the dissolution of omeprazole is endothermic, non-spontaneous and entropy-driven. According to table 6, the value of $\Delta_{\text{sol}} G_m^0$ for omeprazole in the tetrahydrofuran is the minimum value among those in the table. This is consistent with our experimental results. We speculate that the polarity of omeprazole should lie between methanol and ethanol. Following a similar principle, methanol and ethanol have a higher solubility for omeprazole. However, due to its cyclic structure, the oxygen atom in the ring is more exposed, which makes tetrahydrofuran easier to form intermolecular hydrogen bonds with omeprazole. The hydrogen bonding is much greater than the polar forces. Therefore, the solubility of omeprazole in tetrahydrofuran is greater than others.

3.3.2. Binary solvent mixtures

According to table 7 and figure 3, the solubility of omeprazole in (tetrahydrofuran + ethyl acetate) binary solvent mixtures is a function of temperature, while the solubility increases with temperature rising. And it also increases with the rise of the ratio isopropanol content at constant temperature. Hydrogen bonding is considered. We suspect that the intermolecular hydrogen bonds are formed between omeprazole and tetrahydrofuran.

As we can see from tables 8–10, the sum of MD values of the modified Apelblat equation, CNIBS/R-K model and Jouyban–Acree model are 20.2248, 8.9131 and 28.9011, respectively. This result shows that the CNIBS/R-K model is the best compared to the modified Apelblat equation and Jouyban–Acree model. Actually, the modified Apelblat equation leads to a higher deviation at lower temperature and the Jouyban–Acree model leads to a higher

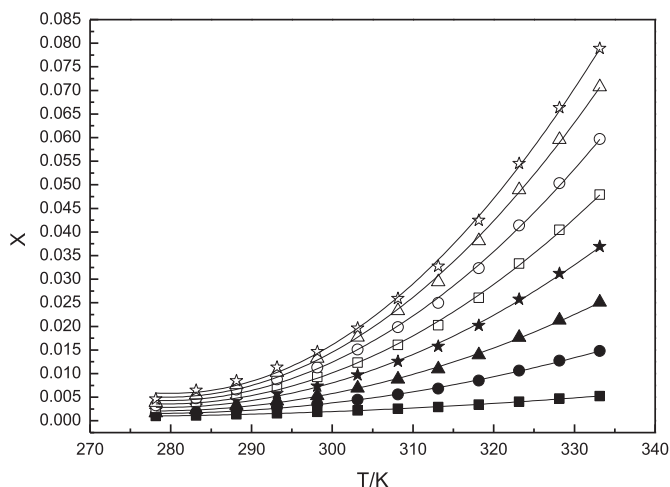


FIGURE 3. Mole fraction solubility (x) of omeprazole versus temperature (T) in the binary solvent mixtures: ■, $x_A = 0.0000$; ●, $x_A = 0.1748$; ▲, $x_A = 0.3397$; ★, $x_A = 0.4955$; □, $x_A = 0.6429$; ○, $x_A = 0.7826$; △, $x_A = 0.9153$; ☆, $x_A = 1.0000$.

deviation in the lower ratio of tetrahydrofuran. So, the modified Apelblat equation and the Jouyban–Acree model can be adopted and assisted by the CNIBS/R–K model.

According to the table 11, the thermodynamic parameters of $\Delta_{\text{sol}}H_m^0$ and $\Delta_{\text{sol}}G_m^0$ are both positive. That means the dissolution process of omeprazole in the studied binary solvent mixtures is endothermic and non-spontaneous. Moreover, the main contributor to the standard molar Gibbs energy of solution is the enthalpy during the dissolution, because all values of $\% \zeta_H$ are $\geq 56.51\%$.

4. Conclusions

We can conclude from tables 2–11 and figure 2 and 3: (1) in the temperature range from 278.15 K to 333.15 K, the solubility of omeprazole in pure and mixture solvents is increasing with the temperature rising, but the increment is different in different solvents. In binary solvent mixtures, the solubility increases with the rise of the ratio of tetrahydrofuran. So tetrahydrofuran could be considered as an effective solvent in the crystallization process and ethyl acetate could be used as an effective anti-solvent; (2) the solubility can be successfully correlated using three equations (van't Hoff, modified Apelblat, and the λh) in pure solvents, and the modified Apelblat fits the data best, and the data can be successfully correlated using three equations (the modified Apelblat equation, CNIBS/R–K model and Jouyban–Acree model) in binary

solvent mixtures, and the CNIBS/R–K model is correlated best because of the lowest MD values, while the modified Apelblat equation and the Jouyban–Acree model can be adopted and assisted by the CNIBS/R–K model; (3) according to the thermodynamic parameters of the van't Hoff analysis and Gibbs equation, the dissolution process of omeprazole is endothermic and non-spontaneous.

In general, the experimental values and the parameters can be used for optimizing the purification process of omeprazole in industry.

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