



Chemical Engineering Thermodynamics

Measurement and correlation of solubility of meropenem trihydrate in binary (water + acetone/tetrahydrofuran) solvent mixtures☆

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ABSTRACT

The solubility of meropenem trihydrate in water + acetone mixtures and water + tetrahydrofuran mixtures were determined from $T = (278.15 \text{ to } 303.15) \text{ K}$ by static method under atmospheric pressure. Effects of solvent composition and temperature on solubility of meropenem trihydrate were discussed. To extend the applicability of the solubility data, experimental solubility data in two kinds of binary solvent mixtures were correlated by the Apelblat equation and NIBS/Redlich–Kister model. It was found that the two models could satisfactorily correlate the experimental data and the Apelblat equation could give better correlation results.

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1. Introduction

Crystallization as a unit operation serves the dual purpose separation and purification of the active pharmaceutical ingredients in the pharmaceuticals industry [1]. The behavior of crystalline solids in various co-solvent mixtures is mainly evaluated for the purposes of substance purification and understanding of the mechanisms involved in the physical and chemical stability of dissolutions [2]. Moreover, the design of this significant crystallization process partly relies on the solid–liquid equilibrium solubility of the product, which is deeply influenced by the temperature and the solvent components [3–5]. Therefore, solubility, a basic data of crystallization, is very important when it comes to the control and optimization of the drug producing process.

Meropenem trihydrate as an important solvate form of meropenem ($\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_5\text{S} \cdot 3\text{H}_2\text{O}$, CAS No.: 119478-56-7 Fig. 1) is widely used which belonging to a very broad antibacterial and can be used for injection to cure various infections, including meningitis and pneumonia [6]. It is reported that meropenem is unstable at high temperature [7–9]. So anti-solvent crystallization is more applied to the purification of meropenem in manufacture.

Although, the solubility of meropenem in methanol–water solution has been reported by Wei *et al.*, and methanol solvate of meropenem

was found in this binary solvent system [10]. This work aims to explore the solubility of meropenem trihydrate in numerous water + acetone and water + tetrahydrofuran binary solvent mixtures in the temperatures ranging from 278.15 to 303.15 K. And then the solubility data were correlated with Apelblat equation and CNIBS/Redlich–Kister equation. The preliminary investigations would be useful for industries in purification of meropenem trihydrate.

2. Experimental

2.1. Materials

The supplied meropenem trihydrate purified by recrystallization from the raw material was provided by Northern Pharmaceutical Co., Ltd. Its purity was measured by high performance liquid chromatograph (HPLC, Agilent 1200) with a mass fraction $\geq 99.5\%$. Acetone and tetrahydrofuran (99.5% in mass fraction) were purchased from Tianjin Kewei Chemical reagent Co. (Tianjin, China) and were of analytical purity grade ($\geq 99.5\%$). Ultrapure water was obtained from deionized water filtered through the Milli-Q-UF-Plus equipment (Millipore). The triethylamine and acetonitrile (99.9% in mass fraction) were supplied by Kewei Chemical Reagent Co. (Tianjin, China) at chromatographic grade.

2.2. XRPD measurement

To ensure that the crystal form of meropenem trihydrate remains the same during the experiments, X-ray powder diffraction (abbreviation XRPD) was used to measure the crystal form of solids.

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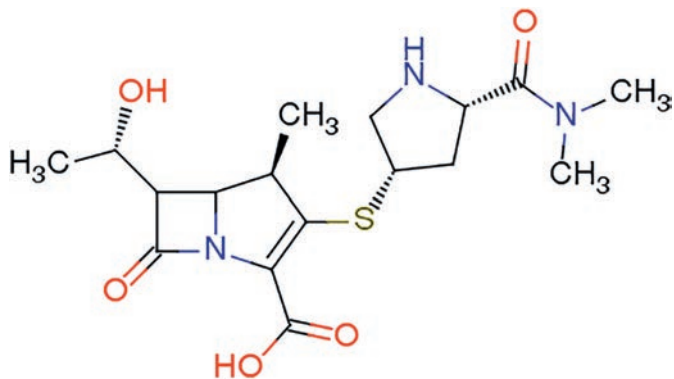


Fig. 1. The molecular structure of meropenem.

The XRPD spectrum is collected by Rigaku D / MAX 2500 (Japan, 2008) using Cu α (0.154 nm) radiation. The sample was scanned continuously from 5° to 40° at 40 kV 100 mA with the rate of 8(°)·min⁻¹ and 0.02° per step.

2.3. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was used to verify the stoichiometry of the water in meropenem trihydrate, and it was performed on the Mettler-Toledo TGA 1/SF equipment which was calibrated before experiment. Approximately 5 to 10 mg sample was put in an open aluminum oxide pan, and was heated at 10 °C·min⁻¹ rates under 50 ml·min⁻¹ nitrogen purge.

2.4. Solubility measurement

The solubility of meropenem trihydrate in binary mixtures solvents (water + acetone) and (water + tetrahydrofuran) was measured from 278.15 K to 303.15 K using static method [11]. Slightly excess meropenem trihydrate was dissolved in mixed solvent over the whole range of water mole fraction in a 50 ml cylindrical double-jacketed crystallizer. The jacketed temperature was controlled within ± 0.1 K by a thermostat (XOYS-2006, Nanjing Xianou Instrument Manufacturing Co., Ltd., China). The solid-liquid mixtures should be under stirring for 6 h, which was experimentally proved to be long enough to reach equilibrium. Then the agitation was stopped and the solution was kept still for about 2 h to make sure that the undissolved particles settled down. The upper clear saturated solution was filtered with 0.45 μ m membranes and analyzed by HPLC and UV. Each experiment w^{-1} as repeated three times and the average value was used to calculate the mole fraction solubility.

2.5. HPLC analysis

An Agilent HPLC equipment with VWD spectroscopy and C18 reverse-phase column (Agilent Eclipse plus, 5 μ m 250 mm $\times$ 4.6 mm) was used to measure the concentration of meropenem trihydrate. The mobile phase was a buffer solution of triethylamine (0.3%) and acetonitrile (93:7, V/V), and the pH value of the mobile phase solution was adjusted to 5.00 $\pm$ 0.01 using by 0.1% phosphoric acid. The analysis was conducted at 30 °C and 220 nm UV light, and the velocity of mobile phase was set to be 0.5 ml·min⁻¹. The absorption standard curve has been determined through measuring absorption areas of a series of known concentration of meropenem trihydrate, and is shown in Fig. S1 in the supplementary material. The solubility was calculated as follows:

$$m_s = \frac{S_i}{k} \times n \quad (1)$$

$$x_s = \frac{m_s/M_s}{m_s/M_s + m_1/M_1 + m_2/M_2} \quad (2)$$

where S_i represents the area of absorption peak by HPLC; k is the slope of standard curve; n is the diluted times; m_s and m_i represent the mass of meropenem trihydrate and solvents; M_s and M_i are molar mass of meropenem trihydrate and solvents, respectively.

2.6. UV analysis

UV spectrophotometer (HITACHI-3010, Japan) is also applied to analyze the concentration of meropenem trihydrate. The UV was calibrated by measuring molar absorption coefficient, using potassium dichromate as standard material (wavelength 235 nm, $E_{cm} = 124.5 \text{ L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$; wavelength 257 nm, $E_{cm} = 144.0 \text{ L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$; wavelength 313 nm, $E_{cm} = 48.60 \text{ L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$; wavelength 350 nm, $E_{cm} = 106.6 \text{ L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$) [11]. The standard curve was measured and shown in Fig. S2 in the supplementary material, and the concentration of meropenem trihydrate was calculated by Eq. (3), and solubility was expressed as Eq. (2).

$$m = \frac{(A_i - A_0)}{k} \times n \quad (3)$$

where A_i and A_0 represent the absorbance value of saturated solution diluted and blank sample, respectively; k is the slope of standard curve; n is the diluted times.

To verify the reliability of the method used in this paper, the experimental solubility data in water obtained in this work were compared with the published results in literature [10], but the experimental results are very different. In addition, we used UV analysis to determine several sets of data to compare with the results of HPLC analysis. As seen from Table 1, all of RAD values were less than 1%. The results show that the repeatability is very good.

Table 1

Solubility of meropenem trihydrate (x_s) measured by HPLC and UV analysis in water + acetone at different temperatures ($p = 0.1 \text{ MPa}$)

x_{ace}	T/K	$10^4 x_s$ (HPLC)	$10^4 x_s$ (UV)	10^2 RAD
0.000	278.15	4.0816	4.0813	0.01
	283.15	4.4536	4.4972	0.97
	288.15	5.0982	5.1020	0.07
	293.15	5.5573	5.5327	0.44
	298.15	6.6009	6.6308	0.45
	303.15	7.8236	7.8200	0.05
0.109	278.15	1.4293	1.4394	0.70
	283.15	1.7687	1.7604	0.47
	288.15	2.2445	2.2310	0.60
	293.15	2.7460	2.7627	0.61
	298.15	3.2464	3.2735	0.83
	303.15	4.3158	4.3418	0.60

Note: x_{ace} represent the mole fraction of acetone, x_s represent the mole fraction of meropenem trihydrate.

The standard uncertainty of u is $u(T) = 0.05 \text{ K}$.

The standard uncertainty of the pressure u is $u(p) = 6 \text{ kPa}$.

The relative standard uncertainty of the solubility measurement u is $u_r(x_1) = 0.02$.

The relative standard uncertainty of the mole fraction of solvent $u_r(x_2) = 0.005$.

3. Results and Discussion

3.1. XRPD results

The XRPD patterns of meropenem powder have been measured in the process of solubility experiment, and the results are shown in Fig. 2. It can be concluded that the crystal forms of all solid used is in agreement with meropenem trihydrate reported [10].

3.2. TGA results

As can be seen from the TGA analysis (Fig. 3), there are two stages in the thermal decomposition process. The first one corresponds to crystal water loss which is about 12.15% when the temperature reaches

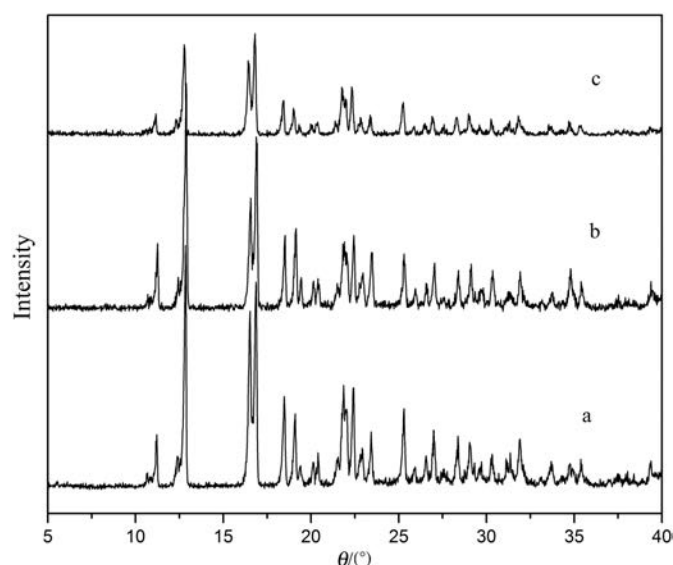


Fig. 2. XRPD diffraction pattern of (a) meropenem trihydrate, (b) crystalline powder, (c) excess solids.

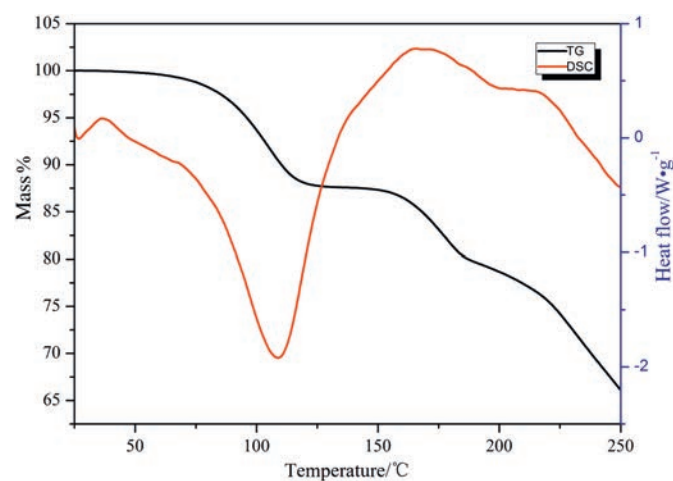


Fig. 3. DSC/TGA plots of crystalline powder.

to 130 °C what is nearly consistent with the calculated weight loss according to stoichiometry of water in meropenem trihydrate (12.35%) and the second step from 150 °C with a weight loss because of decomposition. For DSC curve, the first endothermic peak is regarded as dehydration process combining with TGA results, and when the temperature is up to 150 °C, the endothermic peak appears because of the decomposition of meropenem.

3.3. Solubility data

The solubility of meropenem trihydrate in two binary mixed solvent systems containing good solvent and poor solvent was measured to meet the demand of controlling and optimizing the drug producing process. As a result, the experimental solubility data of meropenem

Table 2

Experimental solubility (x_s) and calculated mole fraction solubility (x_{cal}) of meropenem trihydrate at different mole fractions of acetone (x_{ace}) and different temperatures ($p = 0.1$ MPa)

T/K	Acetone + water			Tetrahydrofuran + water		
	$10^4 x_s$	$10^4 x_{cal}^{Apel}$	$10^4 x_{cal}^{CNIBS}$	$10^4 x_s$	$10^4 x_{cal}^{Apel}$	$10^4 x_{cal}^{CNIBS}$
	0.000			0.000		
278.15	4.082	4.103	4.082	4.082	4.103	4.078
283.15	4.454	4.465	4.445	4.454	4.465	4.439
288.15	5.098	4.976	5.089	5.098	4.976	5.082
293.15	5.557	5.668	5.548	5.557	5.668	5.565
298.15	6.601	6.591	6.611	6.601	6.591	6.639
303.15	7.824	7.812	7.827	7.824	7.812	7.861
	0.058			0.044		
278.15	2.152	2.132	2.130	3.099	3.036	3.111
283.15	2.444	2.479	2.517	3.378	3.440	3.430
288.15	3.003	2.972	3.052	3.917	3.955	3.969
293.15	3.612	3.666	3.664	4.562	4.612	4.533
298.15	4.699	4.644	4.653	5.599	5.447	5.468
303.15	6.013	6.030	5.977	6.447	6.511	6.313
	0.084			0.101		
278.15	1.676	1.709	1.715	1.912	1.948	1.895
283.15	2.121	2.057	2.063	2.303	2.275	2.223
288.15	2.506	2.522	2.532	2.718	2.667	2.665
293.15	3.114	3.148	3.113	3.118	3.137	3.174
298.15	4.013	3.992	3.962	3.648	3.700	3.834
303.15	5.137	5.139	5.149	4.403	4.376	4.606
	0.109			0.152		
278.15	1.429	1.464	1.437	1.143	1.152	1.138
283.15	1.769	1.774	1.743	1.400	1.415	1.410
288.15	2.245	2.175	2.151	1.784	1.748	1.738
293.15	2.746	2.696	2.681	2.193	2.168	2.136
298.15	3.246	3.376	3.392	2.643	2.701	2.592
303.15	4.316	4.267	4.406	3.400	3.379	3.287
	0.155			0.199		
278.15	1.140	1.135	1.072	0.691	0.665	0.706
283.15	1.320	1.336	1.298	0.824	0.840	0.896
288.15	1.626	1.613	1.599	1.037	1.068	1.112
293.15	2.000	1.995	2.010	1.366	1.364	1.406
298.15	2.512	2.522	2.495	1.786	1.750	1.733
303.15	3.258	3.255	3.173	2.237	2.253	2.272
	0.197			0.248		
278.15	0.784	0.764	0.822	0.422	0.425	0.443
283.15	0.956	0.966	0.981	0.571	0.538	0.553
288.15	1.176	1.215	1.197	0.634	0.690	0.673
293.15	1.555	1.523	1.497	0.920	0.898	0.876
298.15	1.906	1.900	1.835	1.191	1.182	1.111
303.15	2.355	2.362	2.256	1.567	1.573	1.458
	0.235			0.307		
278.15	0.615	0.583	0.634	0.288	0.256	0.274
283.15	0.697	0.706	0.743	0.311	0.312	0.315
288.15	0.813	0.855	0.893	0.370	0.384	0.361
293.15	0.989	1.034	1.107	0.454	0.477	0.486
298.15	1.357	1.249	1.357	0.595	0.599	0.648
303.15	1.464	1.506	1.610	0.771	0.756	0.802
	0.329			0.355		
278.15	0.316	0.315	0.292	0.215	0.203	0.201
283.15	0.355	0.365	0.328	0.228	0.234	0.209
288.15	0.429	0.422	0.379	0.256	0.270	0.222
293.15	0.498	0.489	0.456	0.304	0.310	0.305
298.15	0.559	0.566	0.597	0.380	0.356	0.425
303.15	0.655	0.655	0.655	0.398	0.408	0.482
	0.424			0.404		
278.15	0.115	0.118	0.124	0.151	0.144	0.160
283.15	0.144	0.145	0.138	0.161	0.163	0.147
288.15	0.176	0.177	0.151	0.180	0.186	0.143
293.15	0.216	0.216	0.177	0.198	0.211	0.199
298.15	0.256	0.262	0.261	0.250	0.239	0.286
303.15	0.326	0.318	0.278	0.273	0.271	0.291
	0.595			0.605		
278.15	0.090	0.089	0.102	0.101	0.112	0.121
283.15	0.092	0.093	0.133	0.112	0.113	0.129
288.15	0.096	0.097	0.118	0.114	0.114	0.132
293.15	0.101	0.101	0.123	0.117	0.114	0.131
298.15	0.105	0.105	0.139	0.118	0.115	0.123
303.15	0.111	0.110	0.161	0.123	0.116	0.145

Notes to Table 2:

x_s represents the mole fraction of meropenem trihydrate obtained from HPLC analysis.

x_{cal}^{Apel} represents the calculated solubility data by Apelblat model.

x_{cal}^{CNIBS} represents the calculated solubility data by the NIBS/R-K model.

The standard uncertainty of u is $u(T) = 0.05$ K.

The standard uncertainty of the pressure u is $u(p) = 6$ kPa.

The relative standard uncertainty of the solubility measurement u is $u_r(x_1) = 0.02$.

The relative standard uncertainty of the mole fraction of solvent $u_r(x_2) = 0.005$.

trihydrate in the binary mixed solvent systems including (acetone + water) and (tetrahydrofuran + water) from 278.15 K to 303.15 K by HPLC analysis are showed in Table 2 and plotted against temperature in Figs. 4 and 5. From the solubility data, we can easily find that the solubility trends conform to the famous rule “dissolve like dissolve”. What's more, the solubility of meropenem trihydrate increases with the rise of the water composition in binary mixed solvent systems at a constant temperature. Additionally, although the solvent composition kept unchanged, the solubility of meropenem trihydrate increases with the rise of the temperature.

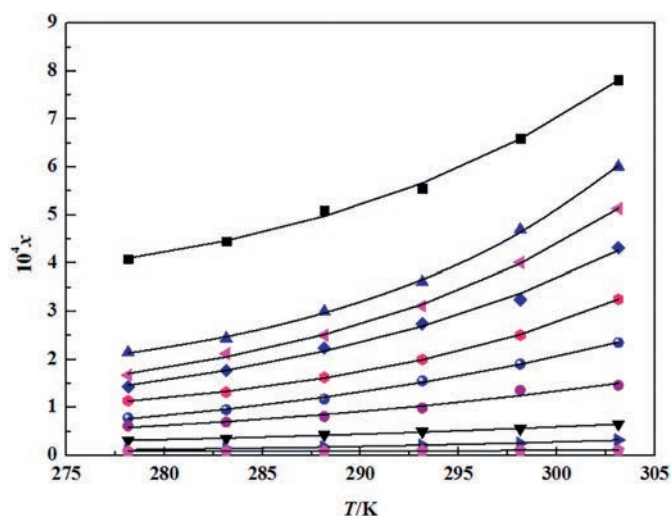


Fig. 4. Experimental solubility data of meropenem trihydrate in acetone + water binary solvents: ■, $x_{\text{ace}} = 0$; ▲, $x_{\text{ace}} = 0.058$; ◆, $x_{\text{ace}} = 0.084$; ♦, $x_{\text{ace}} = 0.109$; ●, $x_{\text{ace}} = 0.155$; ●, $x_{\text{ace}} = 0.197$; ●, $x_{\text{ace}} = 0.235$; ▼, $x_{\text{ace}} = 0.329$; ▲, $x_{\text{ace}} = 0.424$; ●, $x_{\text{ace}} = 0.595$. The solid lines represent the correlated solubility by Apelblat equation.

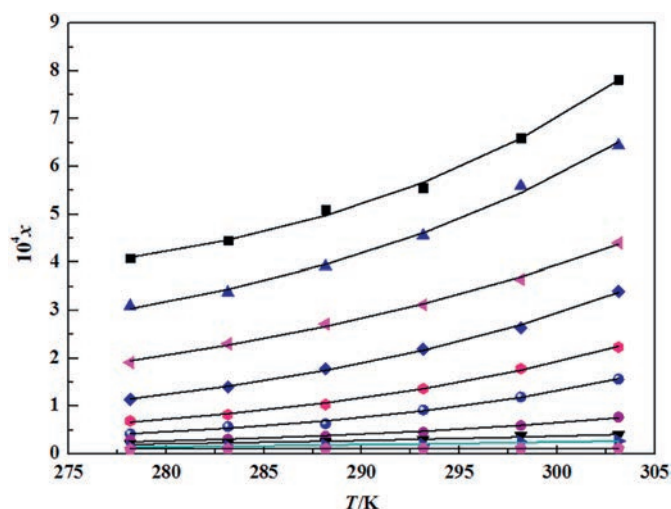


Fig. 5. Experimental solubility data of meropenem trihydrate in tetrahydrofuran + water binary solvents: ■, $x_{\text{ace}} = 0$; ▲, $x_{\text{ace}} = 0.044$; ◆, $x_{\text{ace}} = 0.101$; ♦, $x_{\text{ace}} = 0.152$; ●, $x_{\text{ace}} = 0.199$; ●, $x_{\text{ace}} = 0.248$; ●, $x_{\text{ace}} = 0.307$; ▼, $x_{\text{ace}} = 0.355$; ▲, $x_{\text{ace}} = 0.404$; ●, $x_{\text{ace}} = 0.605$. The solid lines represent the correlated solubility by Apelblat equation.

3.4. Data correlation

3.4.1. The modified Apelblat equation

The Apelblat equation is a semi-empirical thermodynamic equation, which is suitable to describe the relationship between temperature and mole fraction. The equation is expressed as follows [12]:

$$x = A + \frac{B}{T/K} + C \ln T/K \quad (4)$$

where A , B , and C represent the association constant of the model, T represents the absolute temperature.

3.4.2. CNIBS/Redlich-Kister model

Generationally speaking, the CNIBS/Redlich-Kister model is popular to calculate the solubility of mixed solvents, and is simplified in binary solvents as Eq. (5) [13].

$$\ln x = B_0 + B_1 x_1 + B_2 x_1^2 + B_3 x_1^3 + B_4 x_1^4 \quad (5)$$

where B_0 , B_1 , B_2 , B_3 , B_4 represented the parameters of CNIBS/Redlich-Kister model, x_1 represented the molar fraction of one component in the binary solvent.

3.4.3. Equation fitting

To extend the application range of experimental solubility data, the modified Apelblat equation and NIBS/Redlich-Kister model were used to correlate the solubility data. The relative average deviation (RAD)

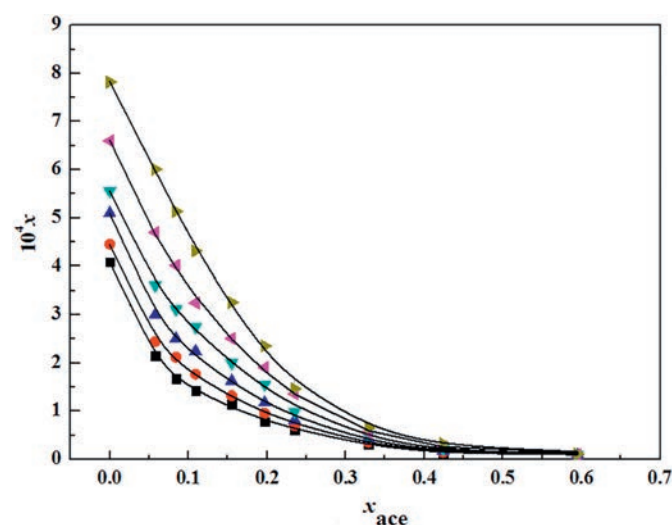


Fig. 6. Experimental solubility data of meropenem trihydrate in acetone + water binary solvents: ■, 278.15 K; ●, 283.15 K; ▲, 288.15 K; ▼, 293.15 K; ◆, 298.15 K; ♦, 303.15 K. The solid lines represent the correlated solubility by CNIBS/Redlich-Kister model.

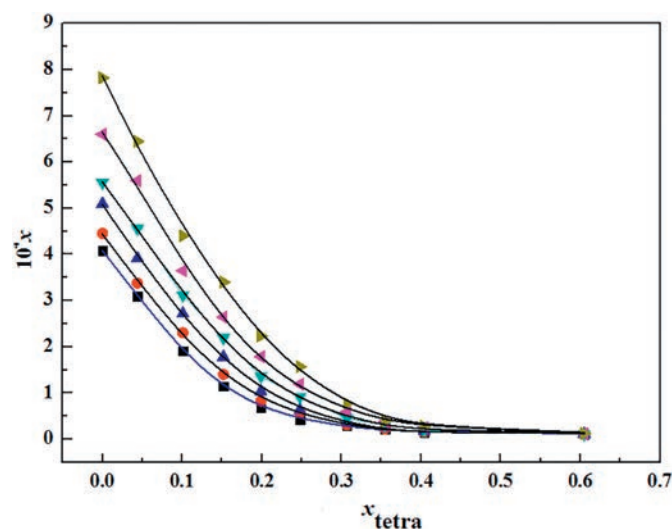


Fig. 7. Experimental solubility data of meropenem trihydrate in tetrahydrofuran + water binary solvents: ■, 278.15 K; ●, 283.15 K; ▲, 288.15 K; ▼, 293.15 K; ◆, 298.15 K; ♦, 303.15 K. The solid lines represent the correlated solubility by CNIBS/Redlich-Kister model.

which is calculated Eq. (6), was adopted to estimate the accuracy of the solubility models.

$$\text{RAD} = \frac{\sum_{i=1}^n \frac{|x_i^{\text{exp}} - x_i^{\text{cal}}|}{x_i^{\text{cal}}}}{n} \times 100\% \quad (6)$$

where x_i^{cal} and x_i^{exp} represent the calculated solubility and the experimental solubility of meropenem trihydrate respectively. n is the total number of the experimental points.

Table 3

Parameters of the modified Apelblat equation for meropenem trihydrate in acetone + water mixed solvents ($P = 0.1$ MPa)

x_{ace}	A	B	C	10^2RAD
0	−580.00	23,051.00	87.00	0.91
0.058	−778.00	30,525.00	117.00	1.06
0.084	−544.00	20,175.00	82.00	1.22
0.109	−400.00	13,984.00	61.00	2.13
0.155	−78.00	−228.90	12.32	0.53
0.197	−679.00	26,137.00	102.00	1.61
0.235	−122.10	2190.00	18.60	4.53
0.329	−117.00	2558.80	17.30	1.30
0.424	−105.60	1281.20	159.00	1.55
0.595	−32.85	319.84	3.57	0.87
Overall				$10^2\text{RAD} = 1.57$

Table 4

Parameters of the modified Apelblat equation for meropenem trihydrate in tetrahydrofuran + water mixed solvents ($P = 0.1$ MPa)

x_{tetra}	A	B	C	10^2RAD
0.000	−580.00	23,050.00	87.00	0.91
0.044	−419.00	1570.10	63.00	1.60
0.101	−193.80	5757.00	29.20	1.27
0.152	−264.20	8041.80	40.20	1.30
0.199	−288.60	8667.20	44.00	1.97
0.248	−481.00	16,780.00	73.00	3.18
0.307	−369.00	12,527.00	56.00	3.85
0.355	−85.80	1283.50	12.50	3.95
0.404	−81.90	1280.00	11.80	3.50
0.605	−44.70	1277.60	5.10	3.56
Overall				$10^2\text{RAD} = 2.51$

Table 5

Parameters of the CNIBS/R–K equation for meropenem trihydrate in acetone + water mixed solvents at the temperature from 278.15 K to 303.15 K ($P = 0.1$ MPa)

T/K	B_0	B_1	B_2	B_3	B_4	10^2RAD
278.15	−7.8037	−14.1005	59.1599	−181.0058	174.5787	4.15
283.15	−7.7186	−12.0921	47.7034	−160.5326	164.438	6.78
288.15	−7.5833	−10.6531	39.0119	−142.3284	149.5661	6.36
293.15	−7.497	−8.3372	26.3799	−115.8711	129.394	6.21
298.15	−7.3216	−6.2609	5.736	−47.9007	63.238	4.80
303.15	−7.1528	−4.033	−10.1439	−15.8921	43.5326	7.26
Overall						$10^2\text{RAD} = 5.92$

Table 6

Parameters of the CNIBS/R–K equation for meropenem trihydrate in tetrahydrofuran + water mixed solvents at the temperature range from 278.15 K to 303.15 K ($P = 0.1$ MPa)

T/K	B_0	B_1	B_2	B_3	B_4	$\text{RAD}/\%$
278.15	−7.8047	−4.6554	−38.9152	105.0836	−72.593	4.27
283.15	−7.7199	−4.9847	−21.5272	29.9031	5.4738	4.74
288.15	−7.5846	−5.0832	−12.0212	−14.4431	52.4341	6.58
293.15	−7.4939	−3.9615	−16.166	−0.0888	34.2164	2.97
298.15	−7.3174	−3.5157	−21.8831	28.5445	−1.2935	5.39
303.15	−7.1484	−4.9649	1.6544	−56.7041	81.8329	6.34
Overall						$10^2\text{RAD} = 5.05$

The correlated solubility data of meropenem trihydrate in two binary mixed solvent systems by modified Apelblat equation and NIBS/Redlich–Kister model is represented in Figs. 4 to 7. Calculated solubility data of meropenem trihydrate from the modified Apelblat equation NIBS/Redlich–Kister model are also given in Table 2.

The Correlated model parameters of the modified Apelblat equation and NIBS/Redlich–Kister model in the two binary solvents and the calculated RAD in this correlation are listed in Tables 3 to 6. It can be seen from tables that the RAD is 1.57 and 5.92 for the Apelblat equation and the NIBS/Redlich–Kister model in the acetone + water mixtures and 2.51 and 5.05 for the Apelblat equation and the NIBS/Redlich–Kister model in the tetrahydrofuran + water mixtures. These results indicate that the Apelblat equation can give better correlation result than the NIBS/Redlich–Kister model although both models can give satisfactory correlation results.

4. Conclusions

The solubility of meropenem trihydrate in binary mixed solvents of water and acetone/tetrahydrofuran was measured by static method, and the mole fraction of saturated solution was analysis by HPLC and UV respectively to ensure the accuracy of solubility data. The results indicate that the solubility of meropenem trihydrate in binary mixture solvents of water + acetone and water + tetrahydrofuran gradually decreases with increasing the mole fraction of acetone and tetrahydrofuran, and increases with elevating temperature in mixed solvents of the certain component. It also can be concluded from solubility data that both acetone and tetrahydrofuran can be used as anti-solvents in crystallization operation when water is a good solvent. The modified Apelblat equation and CNIBS/Redlich–Kister equation are applied to correlate the solubility data, and the very small values of RAD show good agreement between the calculated values and experiment data.

Supplementary Material

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.cjche.2017.05.002>.

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