

Article

Measurement and Correlation of the Solubility of Florfenicol in Four Binary Solvent Mixtures from $T = (278.15 \text{ to } 318.15) \text{ K}$

Xinyuan Zhang ¹, Pingping Cui ¹, Qiuxiang Yin ^{1,2} and Ling Zhou ^{1,*}
¹ State Key Laboratory of Chemical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China

² Collaborative Innovation Center of Chemical Science and Engineering of Tianjin, Tianjin 300072, China

* Correspondence: zhouling@tju.edu.cn

Abstract: Florfenicol is an excellent antibiotic and is widely used in animal bacterial diseases. However, its poor water solubility leads to various problems, such as poor absorption and bioavailability. The development of nanocrystals is one of the most useful methods for solubilizing florfenicol, which often requires solubility data of florfenicol in different mixed solvents. In this work, the solubility of florfenicol was determined by the gravimetric method in methanol + water, ethanol + water, 1-propanol + water, and isopropanol + water binary solvents at temperatures from 278.15 to 318.15 K. In these four mixed solvents, the solubility of florfenicol increased with the increase in temperature. The solubility of florfenicol in methanol + water mixed solvent increases with the decrease in water ratio, while the solubility of florfenicol in ethanol + water, 1-propanol + water, or isopropanol + water mixed solvents increased first and then decreased with the decrease in water ratio, indicating a cosolvency phenomenon. The modified Apelblat model, CNIBS/R-K model, Jouyban–Acree model, and NRTL model were used to correlate the solubility data of florfenicol in four binary solvents. RMSD values indicated that the calculated values are in good agreement with the experimental solubility data for all four models, among which the CNIBS/R-K model provides the best correlation.

Keywords: florfenicol; solubility; binary solvent system; cosolvency; correlation model



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1. Introduction

Florfenicol ($\text{C}_{12}\text{H}_{14}\text{Cl}_2\text{FNO}_4\text{S}$, Figure 1) is broad-spectrum chloramphenicol antibiotic for bacterial diseases in animals [1]. Florfenicol has the advantages of good antibacterial effect, high safety, low toxicity and side effects, and low possibility for the development of drug resistance [2]. However, the solubility of florfenicol in water is only 0.9 mg/mL at 25 °C under atmospheric pressure. Its poor water solubility leads to problems such as poor absorption in animals and poor drug bioavailability [3], which limit the clinical application of florfenicol and the diversity of pharmaceutical preparations to a certain extent [4]. Therefore, it is of great importance to improve its bioavailability by solubilization.

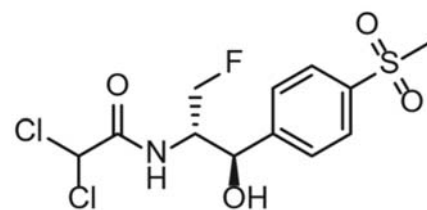


Figure 1. Chemical structure of florfenicol.

Many studies have focused on the solubilization of drugs, and various solubilization methods have been developed such as chemical modification [5], cyclodextrin inclusion [6],

and application of nanocrystals [7]. Among these methods, the development of nanocrystals is preferable for the solubilization of florfenicol due to the advantages of avoiding the involvement of unexpected chemicals or impurities, which can produce florfenicol products with higher drug purity, and less toxicity and side effects [8]. Antisolvent crystallization is an effective method to prepare nanocrystals. Meanwhile, florfenicol exhibited good solubility in alcohol solvents such as methanol, ethanol, 1-propanol, and isopropanol, which makes them potential solvents for the antisolvent crystallization of florfenicol. The determination of the solubility of florfenicol in the binary solvent mixtures is essential for the design of the antisolvent crystallization process and the production of nanocrystals. However, the fundamental data in these mixed solvents are rarely reported in the literature [9–13].

Many thermodynamic models have been commonly used to correlate solubility data and check the accuracy of the determined data. These models can describe the solid–liquid phase equilibrium relationship in the solution such as the dependence of solubility data on temperature and cosolvent composition, which allow the models to have practical application value in the field of engineering calculation and engineering design. In this work, the solubility of florfenicol in methanol + water, ethanol + water, 1-propanol + water, and isopropanol + water binary solvents was determined using the gravimetric method at temperatures ranging from 278.15 to 318.15 K under atmospheric pressure. To extend the applicability of the experimental solubility, the solubility data were then correlated by the modified Apelblat model, the CNIBS/R-K model, the Jouyban–Acree model, and the NRTL model, respectively.

2. Materials and Methods

2.1. Materials

Florfenicol was offered by Ruipu Bio-Pharmacy Co., Ltd. (Tianjin, China) with a mass fraction purity higher than 99.5%. The organic solvents including methanol, ethanol, 1-propanol, and isopropanol used in this work were offered by Jiangtian Chemical Co., Ltd. (Tianjin, China) and the mass fraction purities of all selected solvents are higher than 99.5%. Deionized water was supplied by Yuanli Chemical Co., Ltd. (Tianjin, China).

2.2. Characterization of Florfenicol

The crystal form of florfenicol samples was identified by Powder X-ray diffraction (PXRD, Rigaku, Japan, D/MAX 2500). The region of scanning angle was from 2 to 45° with a scanning rate of 5°/min. All the X-ray diffraction measurements were carried out at room temperature and atmospheric pressure. The melting properties of florfenicol were measured using a differential scanning calorimeter (DSC, Mettler Toledo, Zurich, Switzerland). The measurement was under the protection of nitrogen at a heating rate of 2 K/min.

2.3. Solubility Measurement

The solubility of florfenicol in methanol + water, ethanol + water, 1-propanol + water, and isopropanol + water was determined using a gravimetric method [14] in this work. The mass fraction of alcohol in four kinds of binary solvents varies from $\omega_A = 0$ to 1, with an interval of 0.1. The experimental procedures are described as follows: firstly, 10 mL of binary solvents was added into a 20 mL glass vial and placed into a big jacket vessel in which the temperature was controlled by a high-precision constant temperature water bath (XOYS-2009, accuracy: ± 0.1 K). After the temperature of the mixture solvents remained stable, an excess amount of florfenicol solid was added to the glass vial. The mixture in the sealed vial was continuously stirred using magnetic stirring for 12 h to achieve solid–liquid equilibrium. The duration of 12 h is determined by a preliminary experiment. Then, the stirring was stopped and the suspension was left for another 1 h to assure the undissolved solids settle down completely. The supernatant was then drawn out using a syringe fitted with a Millipore filter (0.45 μm), which was precooled/preheated to the measurement

temperature. After that, the supernatant was transferred into a pre-weighed glass beaker rapidly. Then the beaker with supernatant inside was weighed again using an analytical balance (AL204-C, Mettler Toledo, Zurich, Switzerland) with an accuracy of ± 0.0001 g. Finally, the beaker was dried in a vacuum oven (type DZF-2BC, Tianjin Taisite Instrument Co., Ltd., Tianjin, China) at 313.15K and weighed periodically until the weight did not change. All the experiments were repeated at least three times to reduce accidental errors and the average value of three measurements was used to calculate the mole ratio fraction solubility of florfenicol (x_F) according to Equation (1).

$$x_F = \frac{m_F/M_F}{m_F/M_F + m_w/M_w + m_A/M_A} \quad (1)$$

where m_F , m_w , and m_A represent the mass of florfenicol, water, and alcohol solvents (methanol, ethanol, 1-propanol, or isopropanol), respectively. M_F , M_w , and M_A represent the molar mass of florfenicol, water, and alcohol solvents (methanol, ethanol, 1-propanol, or isopropanol), respectively.

After the solubility measurement experiments, the undissolved florfenicol solid in the equilibrium saturated solution was filtered and tested by PXRD.

3. Theoretical Basis

A variety of thermodynamic models have been proposed to correlate solubility data. These models can be used to check the accuracy of the determined data and describe the solid–liquid phase equilibrium relationship in the solution. In this work, the experimental solubility data were correlated by the modified Apelblat model, CNIBS/R-K model, the Jouyban–Acree model, and the NRTL model.

3.1. Modified Apelblat Model

The modified Apelblat model was proposed by Apelblat et al. [15,16] and can be used to correlate the solid–liquid equilibrium solubility of the solute in pure solvents and binary solvents. This semi-empirical model is applied to describe the relationship between mole fraction solubility and temperature. The equation is expressed as follows:

$$\ln x_F = A + \frac{B}{T} + C \ln T \quad (2)$$

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

3.2. CNIBS/R-K Model

The CNIBS/R-K model was proposed by Acree et al. [17,18] and is used to study the solid–liquid equilibrium solubility of the solutes in binary solvents. This equation describes the relationship between mole fraction solubility of solute and solvent composition. The equation is defined as Equation (3):

$$\ln x_F = x_a \ln X_a + x_b \ln X_b + x_a x_b \sum_{i=0}^N S_i (x_a - x_b)^i \quad (3)$$

where X_a and X_b refer to the saturated mole solubility of the solute in a pure solvent a and b at the same temperature, respectively. x_a and x_b are the initial mole fraction composition of solvent a and b in binary solvent mixtures in the absence of solute. The S_i is the model parameter and N refers to the amount of solvent. For the binary solvent system, the value of N is 2 and $x_a = 1 - x_b$. Therefore, Equation (3) can be simplified to Equation (4):

$$\ln x_F = B_0 + B_1 x_a + B_2 x_a^2 + B_3 x_a^3 + B_4 x_a^4 \quad (4)$$

where B_0 , B_1 , B_2 , B_3 , and B_4 are model parameters.

3.3. The Jouyban–Acree Model

The Jouyban–Acree model is a more general model that can be used to describe the effects of both solvent composition and temperature on the solid–liquid equilibrium solubility of solute [19]. Based on the CNIBS/R-K model, the temperature parameter T is introduced as the second variable. The equation is shown in Equation (5):

$$\ln x_F = x_a \ln X_a + x_b \ln X_b + x_a x_b \sum_{i=0}^N \frac{J_i (x_a - x_b)^i}{T} \quad (5)$$

where J_i is a model parameter. Other symbols have the same meanings as those in the CNIBS/R-K model. By applying the Apelblat equation [20], the Jouyban–Acree model can be transformed into Equation (6):

$$\begin{aligned} \ln x_F = & A_0 + \frac{A_1}{T} + A_2 \ln T + A_3 x_a + \frac{A_4 x_a}{T} + \frac{A_5 x_a^2}{T} \\ & + \frac{A_6 x_a^3}{T} + \frac{A_7 x_a^4}{T} + A_8 x_a \ln T \end{aligned} \quad (6)$$

where $A_0 \sim A_8$ are model parameters.

3.4. NRTL Model

The NRTL model was proposed by Renon et al. and can be used to calculate the activity coefficients γ_i of non-polar or polar miscible systems [21]. The model is expressed as follows:

$$\begin{aligned} \ln \gamma_i = & \frac{(x_j G_{ji} + x_k G_{kj})(x_j G_{ji} \tau_{ji} + x_k G_{ki} \tau_{ki})}{(x_i + x_j G_{ji} + x_k G_{ki})^2} + \\ & \frac{[\tau_{ij} G_{ij} x_j^2 + G_{ij} G_{kj} x_j x_k (\tau_{ij} - \tau_{kj})]}{(x_j + x_i G_{ij} + x_k G_{kj})^2} + \\ & \frac{[\tau_{jk} G_{jk} x_k^2 + G_{jk} G_{ik} x_j x_k (\tau_{ik} - \tau_{jk})]}{(x_k + x_i G_{ik} + x_j G_{jk})^2} \end{aligned} \quad (7)$$

with

$$G_{ij} = \exp(-\alpha_{ij} \tau_{ij}) \quad (8)$$

$$\tau_{ij} = \frac{\Delta g_{ij}}{RT} \quad (9)$$

where $i \neq j$, Δg_{ij} is the interaction parameter that is related to the Gibbs energy that is listed in Table 8, G_{ij} and τ_{ij} are model parameters. α_{ij} is a random parameter.

The calculated solubility corrected by the activity coefficient is shown as Equation (10):

$$\ln x_i = \frac{\Delta_{\text{fus}} H}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) - \ln \gamma_i \quad (10)$$

where $\Delta_{\text{fus}} H$ and T_m are the melting enthalpy and melting point of florfenicol.

4. Results and Discussion

4.1. Solid-State Characterization

The PXRD patterns of florfenicol (Figure 2) in different solvents show that the characteristic peaks of florfenicol in the equilibrium saturated solution remained consistent with that of the raw material. This indicates that florfenicol did not undergo a phase transition during the solubility experiment. The PXRD pattern of the florfenicol in this work was consistent with the form I data in the literature [9]. The melting temperature (T_m) and the enthalpy of fusion ($\Delta_{\text{fus}} H$) of florfenicol were calculated from the DSC result (Figure 3). The melting temperature (T_m) of florfenicol is 426.21 K and the enthalpy of fusion ($\Delta_{\text{fus}} H$) of florfenicol is 34.13 kJ mol^{−1}. These two results are consistent with the values from other literature [12].

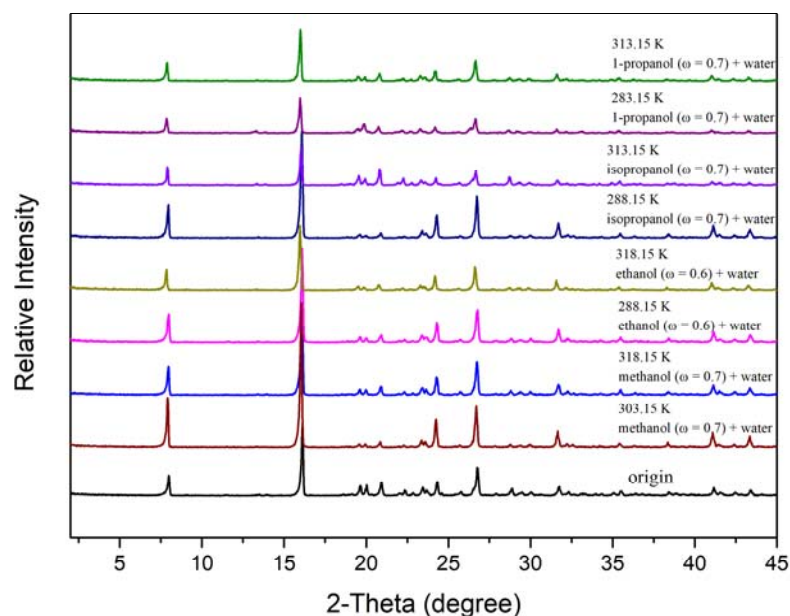


Figure 2. PXRD patterns of florfenicol.

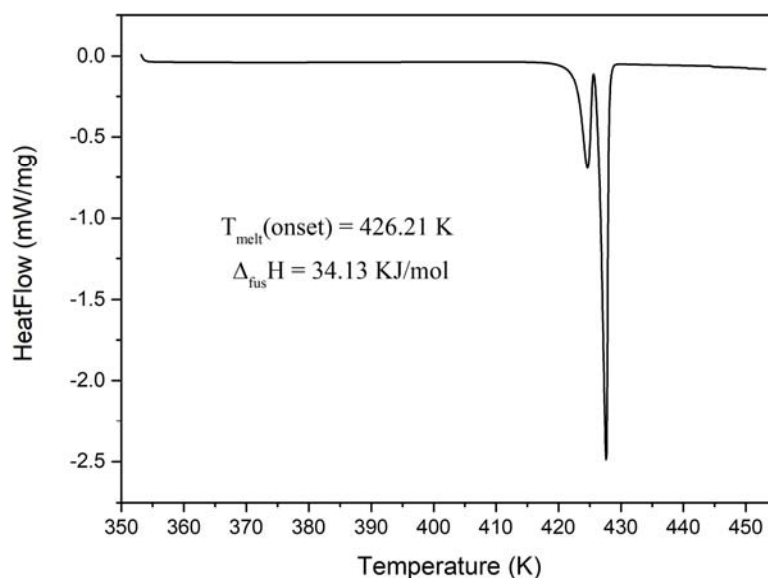


Figure 3. Thermal analysis spectrum (DSC) of florfenicol.

4.2. Solubility Data

The experimental and calculated molar ratio solubility of florfenicol in binary solvents of methanol + water, ethanol + water, 1-propanol + water, and isopropanol + water is listed in Tables 1–4, and are plotted in Figures 4–7.

The experimental results show that at constant solvent composition, the solubility of florfenicol in all four binary solvent mixtures increases with increasing temperature. Moreover, at the same temperature, the proportion of water in the binary solvent has a great influence on the solubility of florfenicol. The solubility of florfenicol increases first and then decreases with the decrease in the ratio of water in ethanol + water, 1-propanol + water, and isopropanol + water binary solvent, indicating a cosolvency phenomenon occurs in these three binary solvents. The peak position of the maximum solubility of florfenicol slightly shifted from 0.9 to 0.7 with the increase in the experimental temperature. While the solubility of florfenicol in methanol + water mixed solvent increases with the decrease in water ratio and there was no obvious cosolvency phenomenon. Furthermore, at the same

temperature and mass fraction of water, the solubility of florfenicol in the tested solvent systems follows the order: (ethanol + water) > (1-propanol + water) > (isopropanol + water), which is the same as the order of the polarity of alcohol. Considering that florfenicol is a polar molecule, the effect of binary solvent mixtures on the solubility can be explained by the ‘Similar Dissolution Rule’.

Table 1. Experimental and calculated molar ratio solubility of florfenicol in binary solvent mixtures of methanol + water from $T = 278.15$ to 318.15 K.

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 278.15$ K					
0.0	0.0019	0.0019	0.0020	0.0011	0.0012
0.1	0.0033	0.0038	0.0034	0.0038	0.0023
0.2	0.0059	0.0069	0.0060	0.0066	0.0048
0.3	0.0114	0.0132	0.0112	0.0118	0.0102
0.4	0.0211	0.0248	0.0211	0.0220	0.0207
0.5	0.0399	0.0445	0.0400	0.0410	0.0403
0.6	0.0738	0.0764	0.0738	0.0751	0.0742
0.7	0.1294	0.1253	0.1294	0.1309	0.1281
0.8	0.2096	0.1968	0.2096	0.2120	0.2056
0.9	0.3151	0.3010	0.3151	0.3213	0.3049
1.0	0.4815	0.4654	0.4815	0.5052	0.4176
$T = 283.15$ K					
0.0	0.0022	0.0023	0.0021	0.0018	0.0018
0.1	0.0041	0.0041	0.0040	0.0032	0.0032
0.2	0.0075	0.0074	0.0077	0.0060	0.0066
0.3	0.0147	0.0140	0.0148	0.0115	0.0135
0.4	0.0282	0.0271	0.0282	0.0228	0.0269
0.5	0.0530	0.0509	0.0526	0.0448	0.0517
0.6	0.0940	0.0920	0.0943	0.0842	0.0939
0.7	0.1597	0.1570	0.1597	0.1450	0.1604
0.8	0.2523	0.2490	0.2522	0.2202	0.2553
0.9	0.3724	0.3697	0.3724	0.2961	0.3756
1.0	0.5408	0.5464	0.5408	0.4018	0.5098
$T = 288.15$ K					
0.0	0.0028	0.0027	0.0027	0.0028	0.0025
0.1	0.0051	0.0047	0.0049	0.0049	0.0044
0.2	0.0090	0.0084	0.0090	0.0091	0.0088
0.3	0.0166	0.0159	0.0170	0.0174	0.0177
0.4	0.0325	0.0312	0.0324	0.0340	0.0347
0.5	0.0614	0.0606	0.0614	0.0662	0.0657
0.6	0.1122	0.1131	0.1123	0.1232	0.1180
0.7	0.1935	0.1978	0.1933	0.2105	0.2001
0.8	0.3044	0.3143	0.3046	0.3181	0.3161
0.9	0.4400	0.4540	0.4400	0.4267	0.4616
1.0	0.6309	0.6453	0.6309	0.5777	0.6229
$T = 293.15$ K					
0.0	0.0035	0.0034	0.0032	0.0041	0.0034
0.1	0.0060	0.0057	0.0058	0.0071	0.0060
0.2	0.0110	0.0101	0.0108	0.0129	0.0117
0.3	0.0200	0.0191	0.0207	0.0246	0.0230
0.4	0.0403	0.0380	0.0400	0.0477	0.0446
0.5	0.0763	0.0748	0.0766	0.0920	0.0832
0.6	0.1416	0.1420	0.1412	0.1698	0.1482
0.7	0.2431	0.2508	0.2433	0.2884	0.2494
0.8	0.3809	0.3959	0.3809	0.4343	0.3917
0.9	0.5418	0.5573	0.5418	0.5818	0.5685
1.0	0.7594	0.7663	0.7594	0.7871	0.7621

Table 1. Cont.

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 298.15 \text{ K}$					
0.0	0.0043	0.0043	0.0038	0.0056	0.0047
0.1	0.0074	0.0072	0.0069	0.0096	0.0081
0.2	0.0130	0.0129	0.0131	0.0174	0.0154
0.3	0.0251	0.0244	0.0255	0.0328	0.0298
0.4	0.0503	0.0484	0.0505	0.0631	0.0569
0.5	0.0993	0.0956	0.0991	0.1208	0.1051
0.6	0.1866	0.1817	0.1865	0.2215	0.1860
0.7	0.3246	0.3194	0.3245	0.3743	0.3120
0.8	0.5036	0.4975	0.5037	0.5621	0.4882
0.9	0.6936	0.6838	0.6935	0.7531	0.7030
1.0	0.9242	0.9145	0.9242	1.0196	0.9328
$T = 303.15 \text{ K}$					
0.0	0.0056	0.0056	0.0055	0.0072	0.0063
0.1	0.0096	0.0095	0.0096	0.0123	0.0107
0.2	0.0179	0.0173	0.0177	0.0222	0.0201
0.3	0.0337	0.0327	0.0337	0.0415	0.0384
0.4	0.0655	0.0644	0.0656	0.0792	0.0722
0.5	0.1273	0.1262	0.1272	0.1504	0.1321
0.6	0.2366	0.2366	0.2369	0.2742	0.2323
0.7	0.4078	0.4087	0.4073	0.4615	0.3882
0.8	0.6215	0.6239	0.6218	0.6921	0.6041
0.9	0.8370	0.8387	0.8369	0.9286	0.8632
1.0	1.0917	1.0963	1.0917	1.2598	1.1367
$T = 308.15 \text{ K}$					
0.0	0.0072	0.0075	0.0073	0.0088	0.0085
0.1	0.0128	0.0131	0.0128	0.0150	0.0142
0.2	0.0237	0.0243	0.0237	0.0268	0.0261
0.3	0.0451	0.0461	0.0452	0.0498	0.0491
0.4	0.0877	0.0895	0.0877	0.0943	0.0914
0.5	0.1689	0.1716	0.1685	0.1781	0.1660
0.6	0.3091	0.3131	0.3095	0.3232	0.2907
0.7	0.5225	0.5252	0.5224	0.5424	0.4841
0.8	0.7803	0.7806	0.7803	0.8133	0.7498
0.9	1.0273	1.0280	1.0273	1.0938	1.0627
1.0	1.3203	1.3197	1.3203	1.4890	1.3893
$T = 313.15 \text{ K}$					
0.0	0.0104	0.0102	0.0102	0.0102	0.0113
0.1	0.0185	0.0188	0.0185	0.0173	0.0186
0.2	0.0347	0.0356	0.0346	0.0308	0.0337
0.3	0.0663	0.0679	0.0661	0.0569	0.0628
0.4	0.1260	0.1292	0.1264	0.1072	0.1158
0.5	0.2366	0.2400	0.2367	0.2013	0.2094
0.6	0.4209	0.4206	0.4205	0.3639	0.3659
0.7	0.6845	0.6773	0.6847	0.6096	0.6073
0.8	0.9904	0.9747	0.9904	0.9147	0.9346
0.9	1.2745	1.2593	1.2745	1.2344	1.3127
1.0	1.6084	1.5947	1.6084	1.6881	1.7014

Table 1. *Cont.*

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 318.15 \text{ K}$					
0.0	0.0142	0.0142	0.0142	0.0113	0.0149
0.1	0.0281	0.0279	0.0280	0.0191	0.0242
0.2	0.0549	0.0544	0.0547	0.0338	0.0435
0.3	0.1053	0.1044	0.1052	0.0621	0.0803
0.4	0.1953	0.1935	0.1956	0.1165	0.1477
0.5	0.3465	0.3444	0.3465	0.2178	0.2664
0.6	0.5738	0.5731	0.5738	0.3925	0.4630
0.7	0.8731	0.8765	0.8728	0.6568	0.7612
0.8	1.2054	1.2144	1.2057	0.9871	1.1579
0.9	1.5324	1.5415	1.5323	1.3382	1.6139
1.0	1.9252	1.9337	1.9252	1.8405	2.0787

^a ω_A represents the mass fraction of alcohols (methanol, ethanol, 1-propanol, or isopropanol) in binary solvent mixtures; x_F^{exp} is the experimental mole fraction solubility of florfenicol in the binary solvents; $x_F^{\text{cal,Apel}}$, $x_F^{\text{cal,RK}}$, $x_F^{\text{cal,JA}}$, and $x_F^{\text{cal,NRTL}}$ are the mole fraction solubility calculated by Equations (2), (4), (6), and (10), respectively.

^b The standard uncertainty of temperature is $u_c(T) = 0.1 \text{ K}$. The relative standard uncertainty of pressure is $u_r(P) = 0.05$. The relative standard uncertainty of binary solvent composition and solubility measurement is $u_r(\omega_A) = 0.002$ and $u_r(x_F) = 0.05$.

Table 2. Experimental and calculated molar ratio solubility of florfenicol in binary solvent mixtures of ethanol + water from $T = 278.15$ to 318.15 K .

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 278.15 \text{ K}$					
0.0	0.0019	0.0019	0.0019	0.0009	0.0013
0.1	0.0037	0.0036	0.0036	0.0042	0.0032
0.2	0.0072	0.0070	0.0071	0.0080	0.0072
0.3	0.0139	0.0133	0.0139	0.0152	0.0151
0.4	0.0271	0.0255	0.0271	0.0286	0.0300
0.5	0.0517	0.0493	0.0518	0.0528	0.0563
0.6	0.0942	0.0916	0.0942	0.0929	0.0987
0.7	0.1572	0.1566	0.1570	0.1514	0.1575
0.8	0.2294	0.2321	0.2295	0.2205	0.2190
0.9	0.2828	0.2863	0.2828	0.2822	0.2536
1.0	0.2991	0.2986	0.2991	0.3410	0.2396
$T = 283.15 \text{ K}$					
0.0	0.0022	0.0023	0.0021	0.0016	0.0018
0.1	0.0043	0.0044	0.0043	0.0034	0.0043
0.2	0.0088	0.0088	0.0088	0.0073	0.0094
0.3	0.0178	0.0173	0.0178	0.0155	0.0195
0.4	0.0356	0.0339	0.0357	0.0324	0.0382
0.5	0.0688	0.0656	0.0689	0.0645	0.0713
0.6	0.1250	0.1201	0.1247	0.1177	0.1249
0.7	0.2036	0.1990	0.2038	0.1876	0.1989
0.8	0.2878	0.2839	0.2877	0.2462	0.2747
0.9	0.3383	0.3353	0.3383	0.2554	0.3142
1.0	0.3351	0.3343	0.3351	0.2241	0.2931

Table 2. Cont.

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 288.15 \text{ K}$					
0.0	0.0028	0.0027	0.0027	0.0026	0.0025
0.1	0.0055	0.0055	0.0054	0.0055	0.0057
0.2	0.0113	0.0113	0.0109	0.0116	0.0123
0.3	0.0223	0.0228	0.0222	0.0244	0.0249
0.4	0.0441	0.0455	0.0444	0.0503	0.0483
0.5	0.0854	0.0879	0.0853	0.0988	0.0896
0.6	0.1531	0.1585	0.1534	0.1781	0.1564
0.7	0.2488	0.2555	0.2483	0.2809	0.2490
0.8	0.3462	0.3521	0.3465	0.3660	0.3423
0.9	0.4005	0.3999	0.4004	0.3781	0.3887
1.0	0.3804	0.3827	0.3804	0.3310	0.3589
$T = 293.15 \text{ K}$					
0.0	0.0035	0.0034	0.0035	0.0040	0.0034
0.1	0.0072	0.0071	0.0070	0.0082	0.0076
0.2	0.0144	0.0148	0.0143	0.0172	0.0160
0.3	0.0291	0.0305	0.0290	0.0358	0.0319
0.4	0.0582	0.0615	0.0581	0.0729	0.0615
0.5	0.1113	0.1186	0.1118	0.1415	0.1137
0.6	0.2009	0.2106	0.2005	0.2525	0.1998
0.7	0.3206	0.3311	0.3207	0.3947	0.3183
0.8	0.4345	0.4420	0.4346	0.5114	0.4339
0.9	0.4780	0.4851	0.4780	0.5274	0.4827
1.0	0.4395	0.4473	0.4395	0.4619	0.4403
$T = 298.15 \text{ K}$					
0.0	0.0043	0.0043	0.0044	0.0057	0.0046
0.1	0.0091	0.0092	0.0092	0.0116	0.0101
0.2	0.0191	0.0197	0.0191	0.0240	0.0208
0.3	0.0396	0.0412	0.0396	0.0493	0.0411
0.4	0.0802	0.0838	0.0803	0.0992	0.0791
0.5	0.1557	0.1609	0.1554	0.1903	0.1478
0.6	0.2773	0.2816	0.2773	0.3365	0.2623
0.7	0.4356	0.4326	0.4358	0.5224	0.4199
0.8	0.5724	0.5612	0.5722	0.6745	0.5651
0.9	0.6041	0.5976	0.6042	0.6958	0.6120
1.0	0.5410	0.5330	0.5410	0.6116	0.5476
$T = 303.15 \text{ K}$					
0.0	0.0056	0.0056	0.0056	0.0076	0.0062
0.1	0.0125	0.0122	0.0125	0.0154	0.0133
0.2	0.0277	0.0266	0.0277	0.0314	0.0271
0.3	0.0598	0.0563	0.0596	0.0637	0.0538
0.4	0.1221	0.1149	0.1225	0.1269	0.1049
0.5	0.2338	0.2193	0.2334	0.2414	0.2001
0.6	0.3994	0.3787	0.3995	0.4233	0.3585
0.7	0.5917	0.5696	0.5917	0.6539	0.5662
0.8	0.7342	0.7201	0.7341	0.8426	0.7382
0.9	0.7548	0.7470	0.7548	0.8714	0.7785
1.0	0.6579	0.6465	0.6579	0.7706	0.6807

Table 2. Cont.

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 308.15 \text{ K}$					
0.0	0.0072	0.0075	0.0073	0.0095	0.0083
0.1	0.0163	0.0166	0.0163	0.0191	0.0174
0.2	0.0359	0.0363	0.0360	0.0387	0.0350
0.3	0.0770	0.0776	0.0772	0.0778	0.0692
0.4	0.1579	0.1583	0.1578	0.1536	0.1358
0.5	0.2987	0.3003	0.2987	0.2896	0.2614
0.6	0.5078	0.5118	0.5075	0.5047	0.4737
0.7	0.7470	0.7551	0.7475	0.7765	0.7492
0.8	0.9252	0.9329	0.9249	1.0004	0.9681
0.9	0.9465	0.9463	0.9466	1.0392	0.9999
1.0	0.7872	0.7974	0.7872	0.9268	0.8442
$T = 313.15 \text{ K}$					
0.0	0.0104	0.0102	0.0104	0.0114	0.0110
0.1	0.0230	0.0229	0.0229	0.0225	0.0228
0.2	0.0503	0.0503	0.0503	0.0452	0.0457
0.3	0.1070	0.1079	0.1070	0.0900	0.0908
0.4	0.2173	0.2194	0.2172	0.1762	0.1813
0.5	0.4078	0.4128	0.4081	0.3300	0.3575
0.6	0.6875	0.6950	0.6872	0.5720	0.6612
0.7	0.9975	1.0077	0.9977	0.8778	1.0460
0.8	1.2073	1.2196	1.2072	1.1325	1.3160
0.9	1.2005	1.2139	1.2005	1.1837	1.3043
1.0	0.9957	0.9989	0.9957	1.0672	1.0691
$T = 318.15 \text{ K}$					
0.0	0.0142	0.0142	0.0143	0.0128	0.0147
0.1	0.0321	0.0321	0.0320	0.0252	0.0299
0.2	0.0705	0.0705	0.0707	0.0501	0.0601
0.3	0.1517	0.1514	0.1511	0.0990	0.1215
0.4	0.3061	0.3055	0.3063	0.1924	0.2499
0.5	0.5713	0.5697	0.5717	0.3581	0.5117
0.6	0.9506	0.9477	0.9505	0.6182	0.9689
0.7	1.3575	1.3526	1.3573	0.9475	1.5270
0.8	1.6141	1.6075	1.6144	1.2258	1.8612
0.9	1.5814	1.5753	1.5813	1.2914	1.7629
1.0	1.2723	1.2695	1.2723	1.1795	1.3705

^a ω_A represents the mass fraction of alcohols (methanol, ethanol, 1-propanol, or isopropanol) in binary solvent mixtures; x_F^{exp} is the experimental mole fraction solubility of florfenicol in the binary solvents; $x_F^{\text{cal,Apel}}$, $x_F^{\text{cal,RK}}$, $x_F^{\text{cal,JA}}$, and $x_F^{\text{cal,NRTL}}$ are the mole fraction solubility calculated by Equations (2), (4), (6) and (10), respectively.

^b The standard uncertainty of temperature is $u_c(T) = 0.1 \text{ K}$. The relative standard uncertainty of pressure is $u_r(P) = 0.05$. The relative standard uncertainty of binary solvent composition and solubility measurement is $u_r(\omega_A) = 0.002$ and $u_r(x_F) = 0.05$.

Table 3. Experimental and calculated molar ratio solubility of florfenicol in binary solvent mixtures of 1-propanol + water from $T = 278.15$ to 318.15 K.

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 278.15$ K					
0.0	0.0019	0.0019	0.0019	0.0008	0.0010
0.1	0.0034	0.0035	0.0034	0.0040	0.0027
0.2	0.0062	0.0064	0.0062	0.0072	0.0057
0.3	0.0113	0.0115	0.0113	0.0127	0.0115
0.4	0.0202	0.0203	0.0202	0.0218	0.0217
0.5	0.0347	0.0343	0.0347	0.0356	0.0379
0.6	0.0553	0.0553	0.0553	0.0535	0.0601
0.7	0.0783	0.0784	0.0783	0.0720	0.0831
0.8	0.0946	0.0947	0.0946	0.0865	0.0967
0.9	0.0960	0.0957	0.0960	0.0969	0.0922
1.0	0.0770	0.0762	0.0770	0.0888	0.0712
$T = 283.15$ K					
0.0	0.0022	0.0023	0.0022	0.0015	0.0015
0.1	0.0041	0.0043	0.0041	0.0032	0.0037
0.2	0.0079	0.0081	0.0079	0.0067	0.0078
0.3	0.0149	0.0151	0.0149	0.0137	0.0154
0.4	0.0274	0.0276	0.0274	0.0266	0.0288
0.5	0.0475	0.0473	0.0475	0.0475	0.0499
0.6	0.0751	0.0757	0.0751	0.0747	0.0788
0.7	0.1042	0.1054	0.1042	0.0991	0.1086
0.8	0.1239	0.1252	0.1239	0.1087	0.1258
0.9	0.1275	0.1272	0.1275	0.1026	0.1201
1.0	0.0961	0.0960	0.0961	0.0671	0.0926
$T = 288.15$ K					
0.0	0.0028	0.0027	0.0028	0.0025	0.0022
0.1	0.0054	0.0054	0.0054	0.0053	0.0052
0.2	0.0105	0.0105	0.0105	0.0109	0.0107
0.3	0.0202	0.0203	0.0202	0.0220	0.0207
0.4	0.0376	0.0377	0.0376	0.0423	0.0383
0.5	0.0655	0.0654	0.0655	0.0748	0.0661
0.6	0.1033	0.1036	0.1033	0.1170	0.1041
0.7	0.1417	0.1416	0.1417	0.1545	0.1425
0.8	0.1652	0.1649	0.1652	0.1696	0.1642
0.9	0.1666	0.1676	0.1666	0.1606	0.1561
1.0	0.1209	0.1211	0.1209	0.1063	0.1198
$T = 293.15$ K					
0.0	0.0035	0.0034	0.0035	0.0039	0.0031
0.1	0.0070	0.0068	0.0070	0.0081	0.0072
0.2	0.0140	0.0139	0.0140	0.0164	0.0145
0.3	0.0274	0.0275	0.0274	0.0328	0.0278
0.4	0.0518	0.0520	0.0518	0.0625	0.0510
0.5	0.0906	0.0907	0.0906	0.1097	0.0880
0.6	0.1422	0.1420	0.1422	0.1704	0.1384
0.7	0.1920	0.1899	0.1920	0.2245	0.1883
0.8	0.2195	0.2163	0.2195	0.2466	0.2149
0.9	0.2191	0.2192	0.2191	0.2346	0.2030
1.0	0.1519	0.1529	0.1519	0.1572	0.1544

Table 3. Cont.

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 298.15 \text{ K}$					
0.0	0.0043	0.0043	0.0044	0.0057	0.0044
0.1	0.0091	0.0089	0.0091	0.0115	0.0098
0.2	0.0190	0.0186	0.0190	0.0232	0.0196
0.3	0.0382	0.0377	0.0382	0.0457	0.0373
0.4	0.0729	0.0722	0.0729	0.0863	0.0688
0.5	0.1272	0.1260	0.1272	0.1502	0.1189
0.6	0.1952	0.1946	0.1952	0.2321	0.1859
0.7	0.2545	0.2543	0.2545	0.3052	0.2496
0.8	0.2826	0.2828	0.2826	0.3359	0.2805
0.9	0.2846	0.2846	0.2846	0.3212	0.2638
1.0	0.1930	0.1932	0.1930	0.2181	0.1985
$T = 303.15 \text{ K}$					
0.0	0.0056	0.0056	0.0055	0.0076	0.0062
0.1	0.0119	0.0119	0.0119	0.0153	0.0134
0.2	0.0255	0.0254	0.0255	0.0306	0.0264
0.3	0.0523	0.0522	0.0523	0.0598	0.0505
0.4	0.1009	0.1007	0.1009	0.1118	0.0932
0.5	0.1755	0.1755	0.1755	0.1932	0.1620
0.6	0.2653	0.2668	0.2653	0.2970	0.2528
0.7	0.3370	0.3402	0.3370	0.3899	0.3338
0.8	0.3649	0.3684	0.3649	0.4301	0.3680
0.9	0.3678	0.3670	0.3678	0.4138	0.3433
1.0	0.2444	0.2443	0.2444	0.2849	0.2544
$T = 308.15 \text{ K}$					
0.0	0.0072	0.0075	0.0072	0.0097	0.0086
0.1	0.0159	0.0163	0.0159	0.0192	0.0183
0.2	0.0345	0.0352	0.0345	0.0380	0.0359
0.3	0.0720	0.0731	0.0720	0.0735	0.0685
0.4	0.1402	0.1412	0.1402	0.1364	0.1282
0.5	0.2446	0.2448	0.2446	0.2341	0.2262
0.6	0.3670	0.3657	0.3670	0.3583	0.3525
0.7	0.4574	0.4544	0.4574	0.4699	0.4573
0.8	0.4808	0.4784	0.4808	0.5198	0.4894
0.9	0.4701	0.4703	0.4701	0.5035	0.4469
1.0	0.3095	0.3092	0.3095	0.3520	0.3254
$T = 313.15 \text{ K}$					
0.0	0.0104	0.0102	0.0104	0.0116	0.0120
0.1	0.0230	0.0226	0.0230	0.0227	0.0252
0.2	0.0499	0.0494	0.0499	0.0445	0.0494
0.3	0.1035	0.1032	0.1035	0.0854	0.0957
0.4	0.1995	0.1990	0.1995	0.1573	0.1821
0.5	0.3419	0.3419	0.3419	0.2682	0.3239
0.6	0.5001	0.5013	0.5001	0.4091	0.5001
0.7	0.6047	0.6060	0.6047	0.5361	0.6294
0.8	0.6181	0.6190	0.6181	0.5951	0.6514
0.9	0.5984	0.5987	0.5984	0.5808	0.5835
1.0	0.3922	0.3915	0.3922	0.4125	0.4159

Table 3. *Cont.*

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 318.15 \text{ K}$					
0.0	0.0142	0.0142	0.0143	0.0131	0.0167
0.1	0.0320	0.0320	0.0320	0.0255	0.0347
0.2	0.0701	0.0702	0.0701	0.0495	0.0686
0.3	0.1464	0.1469	0.1464	0.0942	0.1359
0.4	0.2818	0.2817	0.2818	0.1720	0.2653
0.5	0.4785	0.4780	0.4785	0.2917	0.4793
0.6	0.6868	0.6868	0.6868	0.4434	0.7325
0.7	0.8071	0.8068	0.8071	0.5811	0.8876
0.8	0.7988	0.7985	0.7988	0.6475	0.8778
0.9	0.7579	0.7578	0.7579	0.6370	0.7647
1.0	0.4953	0.4958	0.4953	0.4600	0.5314

^a ω_A represents the mass fraction of alcohols (methanol, ethanol, 1-propanol, or isopropanol) in binary solvent mixtures; x_F^{exp} is the experimental mole fraction solubility of florfenicol in the binary solvents; $x_F^{\text{cal,Apel}}$, $x_F^{\text{cal,RK}}$, $x_F^{\text{cal,JA}}$, and $x_F^{\text{cal,NRTL}}$ are the mole fraction solubility calculated by Equations (2), (4), (6), and (10), respectively.

^b The standard uncertainty of temperature is $u_c(T) = 0.1 \text{ K}$. The relative standard uncertainty of pressure is $u_r(P) = 0.05$. The relative standard uncertainty of binary solvent composition and solubility measurement is $u_r(\omega_A) = 0.002$ and $u_r(x_F) = 0.05$.

Table 4. Experimental and calculated molar ratio solubility of florfenicol in binary solvent mixtures of isopropanol + water from $T = 278.15$ to 318.15 K .

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 278.15 \text{ K}$					
0.0	0.0019	0.0019	0.0020	0.0009	0.0011
0.1	0.0033	0.0033	0.0033	0.0037	0.0025
0.2	0.0057	0.0057	0.0057	0.0063	0.0051
0.3	0.0098	0.0099	0.0098	0.0108	0.0098
0.4	0.0166	0.0166	0.0166	0.0179	0.0177
0.5	0.0275	0.0274	0.0273	0.0284	0.0297
0.6	0.0421	0.0423	0.0425	0.0421	0.0456
0.7	0.0599	0.0597	0.0596	0.0565	0.0624
0.8	0.0724	0.0726	0.0725	0.0681	0.0742
0.9	0.0750	0.0751	0.0750	0.0765	0.0748
1.0	0.0707	0.0700	0.0707	0.0785	0.0629
$T = 283.15 \text{ K}$					
0.0	0.0022	0.0023	0.0022	0.0015	0.0016
0.1	0.0039	0.0040	0.0039	0.0030	0.0035
0.2	0.0071	0.0072	0.0071	0.0059	0.0071
0.3	0.0127	0.0129	0.0126	0.0115	0.0133
0.4	0.0222	0.0223	0.0222	0.0213	0.0237
0.5	0.0370	0.0375	0.0372	0.0369	0.0395
0.6	0.0581	0.0579	0.0579	0.0572	0.0604
0.7	0.0801	0.0805	0.0802	0.0760	0.0823
0.8	0.0963	0.0964	0.0963	0.0842	0.0975
0.9	0.1006	0.1000	0.1006	0.0805	0.0982
1.0	0.0882	0.0882	0.0882	0.0620	0.0821

Table 4. Cont.

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 288.15 \text{ K}$					
0.0	0.0028	0.0027	0.0028	0.0026	0.0023
0.1	0.0051	0.0050	0.0051	0.0050	0.0049
0.2	0.0094	0.0093	0.0094	0.0096	0.0096
0.3	0.0173	0.0171	0.0171	0.0184	0.0179
0.4	0.0301	0.0304	0.0304	0.0339	0.0316
0.5	0.0514	0.0514	0.0513	0.0582	0.0525
0.6	0.0794	0.0794	0.0794	0.0897	0.0801
0.7	0.1086	0.1085	0.1085	0.1187	0.1088
0.8	0.1275	0.1276	0.1276	0.1316	0.1281
0.9	0.1314	0.1321	0.1314	0.1262	0.1284
1.0	0.1110	0.1112	0.1110	0.0982	0.1066
$T = 293.15 \text{ K}$					
0.0	0.0035	0.0034	0.0036	0.0039	0.0032
0.1	0.0066	0.0065	0.0067	0.0076	0.0067
0.2	0.0126	0.0123	0.0126	0.0145	0.0130
0.3	0.0235	0.0230	0.0235	0.0275	0.0240
0.4	0.0421	0.0418	0.0422	0.0501	0.0423
0.5	0.0715	0.0709	0.0712	0.0853	0.0701
0.6	0.1089	0.1089	0.1091	0.1307	0.1066
0.7	0.1461	0.1461	0.1462	0.1726	0.1441
0.8	0.1687	0.1682	0.1686	0.1916	0.1683
0.9	0.1728	0.1729	0.1728	0.1847	0.1676
1.0	0.1395	0.1404	0.1395	0.1451	0.1378
$T = 298.15 \text{ K}$					
0.0	0.0043	0.0043	0.0043	0.0057	0.0045
0.1	0.0084	0.0085	0.0084	0.0107	0.0090
0.2	0.0165	0.0164	0.0165	0.0204	0.0176
0.3	0.0316	0.0314	0.0316	0.0383	0.0322
0.4	0.0582	0.0577	0.0580	0.0692	0.0566
0.5	0.0981	0.0981	0.0986	0.1170	0.0939
0.6	0.1500	0.1494	0.1497	0.1783	0.1430
0.7	0.1962	0.1963	0.1962	0.2349	0.1916
0.8	0.2203	0.2208	0.2204	0.2613	0.2210
0.9	0.2248	0.2247	0.2248	0.2532	0.2184
1.0	0.1772	0.1774	0.1772	0.2012	0.1775
$T = 303.15 \text{ K}$					
0.0	0.0056	0.0056	0.0057	0.0076	0.0063
0.1	0.0112	0.0113	0.0113	0.0143	0.0121
0.2	0.0223	0.0224	0.0224	0.0269	0.0236
0.3	0.0432	0.0433	0.0434	0.0500	0.0432
0.4	0.0801	0.0803	0.0801	0.0897	0.0762
0.5	0.1365	0.1363	0.1359	0.1505	0.1273
0.6	0.2041	0.2051	0.2046	0.2284	0.1932
0.7	0.2638	0.2634	0.2637	0.3005	0.2569
0.8	0.2898	0.2887	0.2897	0.3350	0.2917
0.9	0.2899	0.2898	0.2899	0.3266	0.2843
1.0	0.2244	0.2244	0.2244	0.2626	0.2280

Table 4. Cont.

ω_A	$10^2 \cdot x_F^{\text{exp}}$	$10^2 \cdot x_F^{\text{cal,Apel}}$	$10^2 \cdot x_F^{\text{cal,RK}}$	$10^2 \cdot x_F^{\text{cal,JA}}$	$10^2 \cdot x_F^{\text{cal,NRTL}}$
$T = 308.15 \text{ K}$					
0.0	0.0072	0.0075	0.0071	0.0096	0.0086
0.1	0.0151	0.0153	0.0146	0.0179	0.0162
0.2	0.0302	0.0309	0.0300	0.0334	0.0317
0.3	0.0592	0.0604	0.0596	0.0615	0.0582
0.4	0.1119	0.1125	0.1116	0.1094	0.1039
0.5	0.1895	0.1899	0.1898	0.1825	0.1748
0.6	0.2818	0.2816	0.2818	0.2758	0.2659
0.7	0.3533	0.3529	0.3530	0.3625	0.3477
0.8	0.3753	0.3760	0.3756	0.4053	0.3855
0.9	0.3715	0.3710	0.3714	0.3978	0.3703
1.0	0.2842	0.2839	0.2842	0.3239	0.2920
$T = 313.15 \text{ K}$					
0.0	0.0104	0.0102	0.0104	0.0115	0.0120
0.1	0.0215	0.0212	0.0215	0.0212	0.0218
0.2	0.0439	0.0432	0.0438	0.0391	0.0432
0.3	0.0864	0.0853	0.0861	0.0714	0.0803
0.4	0.1588	0.1583	0.1591	0.1263	0.1447
0.5	0.2655	0.2654	0.2658	0.2094	0.2457
0.6	0.3869	0.3865	0.3864	0.3153	0.3725
0.7	0.4713	0.4721	0.4716	0.4142	0.4763
0.8	0.4877	0.4880	0.4876	0.4645	0.5134
0.9	0.4711	0.4717	0.4711	0.4592	0.4821
1.0	0.3601	0.3595	0.3601	0.3790	0.3737
$T = 318.15 \text{ K}$					
0.0	0.0142	0.0142	0.0142	0.0129	0.0164
0.1	0.0296	0.0297	0.0297	0.0237	0.0292
0.2	0.0611	0.0613	0.0612	0.0435	0.0589
0.3	0.1212	0.1215	0.1211	0.0787	0.1115
0.4	0.2239	0.2240	0.2239	0.1382	0.2055
0.5	0.3717	0.3717	0.3714	0.2280	0.3545
0.6	0.5303	0.5305	0.5307	0.3422	0.5336
0.7	0.6308	0.6305	0.6305	0.4495	0.6646
0.8	0.6312	0.6310	0.6313	0.5059	0.6889
0.9	0.5961	0.5959	0.5961	0.5039	0.6295
1.0	0.4548	0.4552	0.4548	0.4218	0.4777

^a ω_A represents the mass fraction of alcohols (methanol, ethanol, 1-propanol, or isopropanol) in binary solvent mixtures; x_F^{exp} is the experimental mole fraction solubility of florfenicol in the binary solvents; $x_F^{\text{cal,Apel}}$, $x_F^{\text{cal,RK}}$, $x_F^{\text{cal,JA}}$, and $x_F^{\text{cal,NRTL}}$ are the mole fraction solubility calculated by Equations (2), (4), (6), and (10), respectively.

^b The standard uncertainty of temperature is $u_c(T) = 0.1 \text{ K}$. The relative standard uncertainty of pressure is $u_r(P) = 0.05$. The relative standard uncertainty of binary solvent composition and solubility measurement is $u_r(\omega_A) = 0.002$ and $u_r(x_F) = 0.05$.

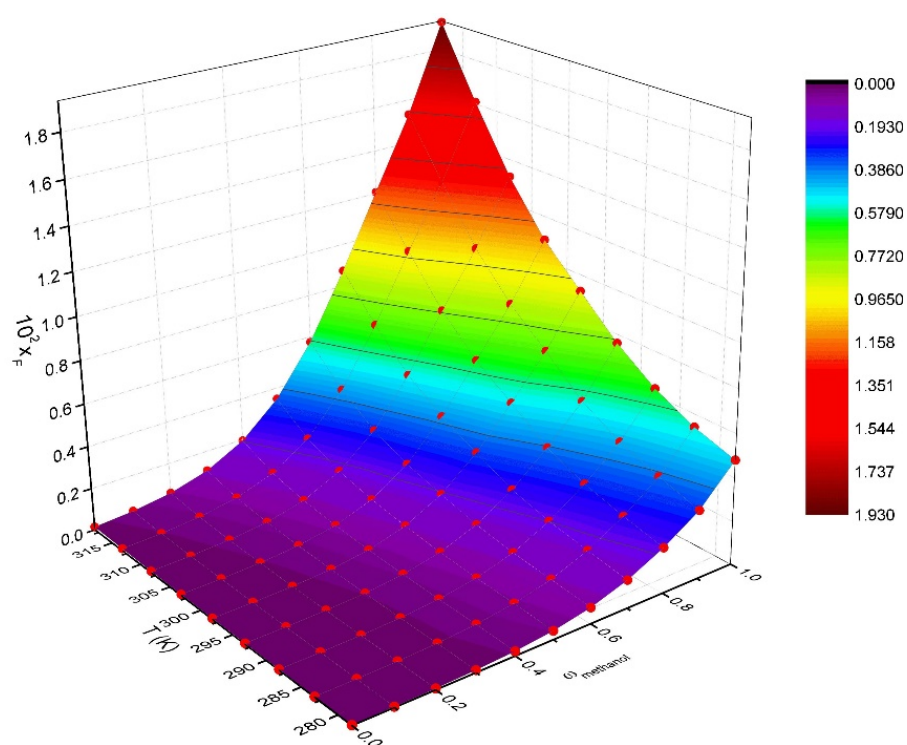


Figure 4. Molar ratio solubility data of florfenicol in methanol + water binary solvents at $T = 278.15$ K to 318.15 K.

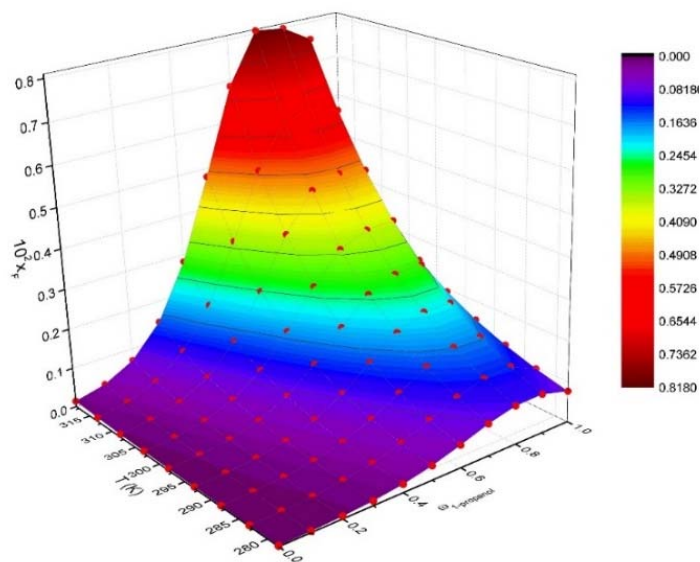


Figure 5. Molar ratio solubility data of florfenicol in ethanol + water binary solvents at $T = 278.15$ K to 318.15 K.

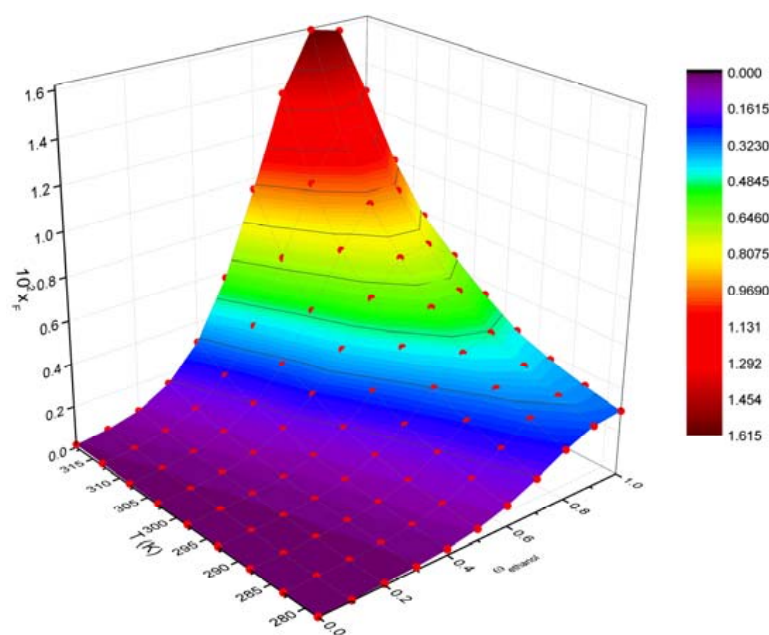


Figure 6. Molar ratio solubility data of florfenicol in 1-propanol + water binary solvents at $T = 278.15$ K to 318.15 K.

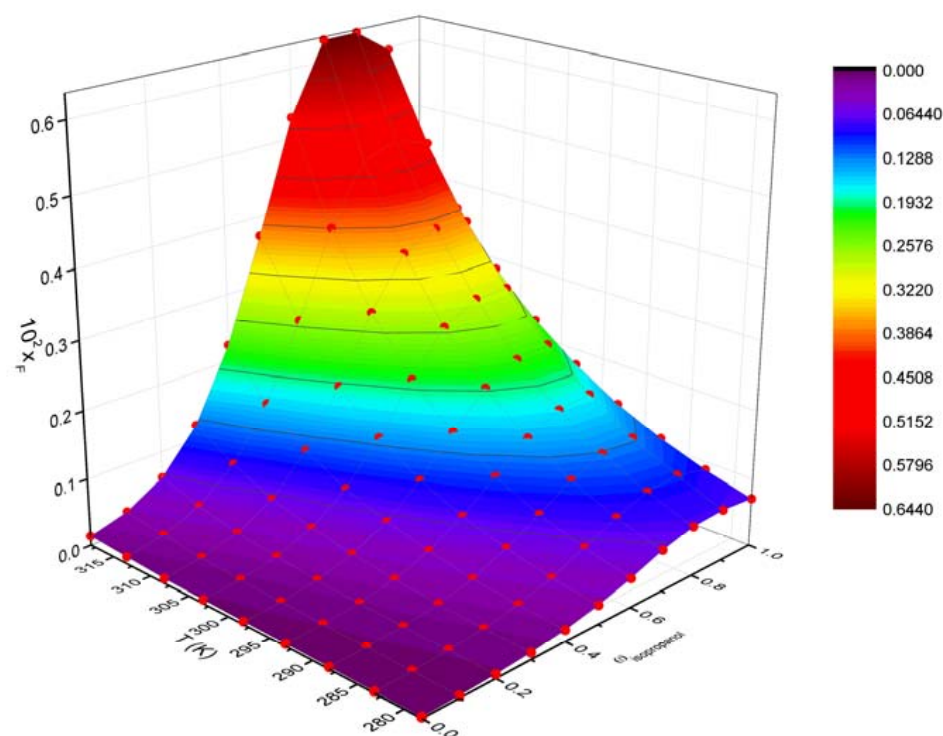


Figure 7. Molar ratio solubility data of florfenicol in isopropanol + water binary solvents at $T = 278.15$ K to 318.15 K.

4.3. Data Correlation

The experimental solubility data in this work were correlated by the modified Apelblat model, the CNIBS/R-K model, the Jouyban–Acree model, and the NRTL model. Root-mean-square deviations (RMSD) were used to evaluate the accuracy and applicability of these models. It is defined as follows:

$$\text{RMSD} = \sqrt{\frac{1}{N} \sum_{j=1}^N (x_j^{\text{cal}} - x_j^{\text{exp}})^2} \quad (11)$$

where N stands for the total number of experiments, x_j^{exp} refers to the experimental mole fraction solubility, and x_j^{cal} refers to the calculated mole fraction solubility of florfenicol.

The model parameters and RMSD values are listed in Tables 5–8. The RMSD values obtained by the modified Apelblat model, the Jouyban–Acree model, and the NRTL model are less than 0.001. The RMSD values obtained by the CNIBS/R-K model are less than 0.00001, indicating that the calculated solubility data of the CNIBS/R-K model is in best agreement with the experimental data.

Table 5. Model parameters of modified Apelblat model for molar ratio solubility of florfenicol in binary solvents.

ω_A	A	$10^{-3} B$	C	10^5 RMSD
Methanol + water				
0.0	−808.13	31,693.03	121.41	0.13
0.1	−1247.43	51,196.87	187.13	0.29
0.2	−1405.06	58,101.88	210.83	0.66
0.3	−1448.94	60,069.52	217.49	1.09
0.4	−1265.91	52,002.49	190.23	2.21
0.5	−964.28	38,656.35	145.27	2.72
0.6	−612.52	23,123.44	92.78	2.42
0.7	−294.48	9157.60	45.29	4.71
0.8	−121.01	1711.19	19.30	9.82
0.9	−144.46	3117.79	22.64	10.82
1.0	−245.25	7999.35	37.51	10.12
Ethanol + water				
0.0	−808.13	31,693.03	121.41	0.13
0.1	−692.87	26,257.05	104.52	0.16
0.2	−574.18	20,756.06	87.06	0.48
0.3	−484.37	16,577.92	73.89	1.46
0.4	−389.78	12,315.84	59.92	3.15
0.5	−352.72	10,766.72	54.44	6.18
0.6	−356.69	11,178.37	54.99	8.71
0.7	−388.18	12,934.37	59.56	9.84
0.8	−435.46	15,461.08	66.42	8.77
0.9	−509.61	19,190.21	77.25	6.60
1.0	−568.06	22,266.08	85.68	6.53

Table 5. *Cont.*

ω_A	A	$10^{-3} B$	C	10^5 RMSD
1-Propanol + water				
0.0	−808.13	31,693.03	121.41	0.13
0.1	−730.72	27,893.79	110.19	0.18
0.2	−611.35	22,249.17	92.70	0.26
0.3	−495.99	16,869.26	75.74	0.46
0.4	−391.10	12,093.60	60.25	0.53
0.5	−297.79	7967.05	46.40	0.45
0.6	−243.35	5785.18	38.21	0.71
0.7	−187.66	3677.54	29.72	1.77
0.8	−119.49	1030.92	19.34	1.85
0.9	−33.04	−2688.41	6.35	0.47
1.0	−198.02	4989.83	30.72	0.52
Isopropanol + water				
0.0	−803.53	31,693.18	121.42	12.57
0.1	−670.31	25,192.77	101.17	0.16
0.2	−614.35	22,428.78	93.09	0.35
0.3	−540.78	18,938.95	82.35	0.60
0.4	−406.90	12,831.21	62.55	0.35
0.5	−332.50	9549.48	51.52	0.30
0.6	−246.67	5901.59	38.68	0.43
0.7	−188.89	3672.04	29.90	0.38
0.8	−112.41	647.18	18.27	0.52
0.9	−17.13	−3411.03	3.94	0.41
1.0	−197.97	4983.43	30.70	0.47

Table 6. Model parameters of CNIBS/R-K model for molar ratio solubility of florfenicol in binary solvents.

T/K	B_0	B_1	B_2	B_3	B_4	10^6 RMSD
Methanol + water						
278.15	−10.84	9.21	0.29	−9.07	5.07	0.86
283.15	−10.77	11.31	−6.39	−1.24	1.87	1.68
288.15	−10.51	9.99	−1.61	−7.34	4.41	1.66
293.15	−10.35	10.18	−1.55	−7.81	4.65	3.05
298.15	−10.17	10.15	−0.12	−10.22	5.69	2.64
303.15	−9.81	9.45	1.51	−12.11	6.44	2.18
308.15	−9.53	9.61	0.95	−11.79	6.43	1.84
313.15	−9.19	10.24	−1.73	−8.76	5.30	1.94
318.15	−8.86	12.11	−9.35	0.48	1.68	1.67

Table 6. Cont.

T/K	B_0	B_1	B_2	B_3	B_4	10^6 RMSD
Ethanol + water						
278.15	−10.88	16.50	−19.06	8.80	−1.17	0.97
283.15	−10.76	17.76	−22.37	11.93	−2.26	1.13
288.15	−10.54	17.82	−22.82	12.56	−2.59	2.44
293.15	−10.27	17.72	−21.99	10.62	−1.51	2.18
298.15	−10.02	18.38	−23.54	11.58	−1.62	1.29
303.15	−9.79	20.56	−31.51	21.25	−5.53	1.79
308.15	−9.52	20.61	−32.18	22.54	−6.28	2.07
313.15	−9.17	20.36	−31.48	21.24	−5.55	1.58
318.15	−8.86	20.74	−33.10	23.29	−6.44	2.69
1-Propanol + water						
278.15	−10.88	19.40	−35.74	29.69	−9.64	0.84
283.15	−10.74	21.34	−42.71	39.17	−14.00	1.90
288.15	−10.49	22.05	−45.03	41.86	−15.10	0.90
293.15	−10.27	23.11	−48.76	46.64	−17.22	1.96
298.15	−10.04	24.62	−55.04	55.41	−21.20	0.73
303.15	−9.80	25.78	−59.73	61.81	−24.07	2.45
308.15	−9.54	26.50	−62.14	64.34	−24.94	0.99
313.15	−9.17	26.66	−64.04	67.32	−26.31	0.95
318.15	−8.86	27.17	−66.55	70.57	−27.65	2.29
Isopropanol + water						
278.15	−10.82	17.01	−29.32	22.14	−6.26	1.49
283.15	−10.72	19.06	−36.19	31.21	−10.39	1.07
288.15	−10.49	20.04	−39.52	35.31	−12.14	1.26
293.15	−10.24	20.98	−43.21	40.36	−14.46	1.24
298.15	−10.06	22.56	−48.77	47.46	−17.52	1.75
303.15	−9.78	23.06	−50.73	49.82	−18.47	2.60
308.15	−9.56	24.39	−55.68	56.13	−21.15	2.56
313.15	−9.17	24.23	−56.16	56.91	−21.43	2.43
318.15	−8.86	24.74	−58.55	59.89	−22.61	1.84

Table 7. Model parameters of Jouyban–Acree model for molar ratio solubility of florfenicol in binary solvents.

Parameters	Methanol + Water	Ethanol + Water	1-Propanol + Water	Isopropanol + Water
A_0	1150.09	1283.14	1319.05	1311.57
A_1	−55,906.60	−62,424.52	−64,161.55	−63,771.45
A_2	−170.66	−190.18	−195.46	−194.37
A_3	−202.15	−297.98	−117.67	−102.52
A_4	11,130.77	18,497.31	11,834.44	10,480.10

Table 7. Cont.

Parameters	Methanol + Water	Ethanol + Water	1-Propanol + Water	Isopropanol + Water
A_5	633.01	−6878.54	−15,035.27	−13,079.80
A_6	−3937.48	3236.22	14,406.50	11,955.51
A_7	2128.14	−374.34	−5287.30	−4158.02
A_8	30.53	44.60	17.81	15.56
10^4 RMSD	6.05	8.94	5.06	3.99

Table 8. Model parameters of NRTL model for molar ratio solubility of florfenicol in binary solvents.

Parameters	Methanol + Water	Ethanol + Water	1-Propanol + Water	Isopropanol + Water
Δg_{ij}	−11,849.11	−8212.77	−4953.91	−4872.17
Δg_{ik}	16,346.95	−3890.03	−614.55	4267.26
Δg_{ji}	20,776.62	19,191.90	14,438.84	14,463.19
Δg_{jk}	−24,560.44	−1492.57	−11,331.24	−54,803.48
Δg_{ki}	13,303.06	21,868.77	15,568.84	13,816.73
Δg_{kj}	6591.86	5907.92	15,793.93	7239.98
10^4 RMSD	3.33	4.50	1.55	1.01

5. Conclusions

In this work, the solubility of florfenicol was determined by a gravimetric method in four binary solvents (methanol + water, ethanol + water, 1-propanol + water, and isopropanol + water) with temperatures from 278.15 to 318.15 K under atmospheric pressure. In these four mixed solvents, the solubility of florfenicol increased with the increase in temperature. At the same temperature, the solubility of florfenicol increases with the decrease in the water ratio in the methanol + water mixture solvent. While the solubility of florfenicol increases first and then decreases with the decrease in the ratio of water in ethanol + water, 1-propanol + water, and isopropanol + water mixture solvent, indicating a cosolvency phenomenon occurs in these three binary solvents. In this study, the modified Apelblat model, the CNIBS/R-K model, the Jouyban–Acree model, and the NRTL model were used to correlate the solubility data of florfenicol in four binary solvents. The RMSD values of each model show that the calculated solubility data are in good agreement with the experimental data for all four models, among which the CNIBS/R-K model provides the best fitting result. Most of the previous solubility articles only determined the solubility of florfenicol in pure solvents, and rarely determined the solubility of florfenicol in binary solvents. However, considering the solubilization requirements of florfenicol, especially in the research of preparing nanocrystals by antisolvent crystallization, the solubility data of florfenicol in binary solvents are highly desirable. The four alcohols involved in this study are the most commonly used organic solvents in experimental research and industry, in which Florfenicol has good solubility, so alcohol solvent can be used as an effective proper solvent. Needless to say, water is the most suitable antisolvent for florfenicol. Therefore, the solubility data obtained by this study can be used as fundamental data for research on the florfenicol nanocrystal preparation to achieve florfenicol solubilization.

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