

SOLUBILITIES OF NORFLOXACIN IN ETHANOL, 1-PROPANOL, ACETONE, AND CHLOROFORM FROM 294.15 TO 318.15 K

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The solubilities of norfloxacin in ethanol, 1-propanol, acetone, and chloroform have been determined from 294.15 to 318.15 K by a static equilibrium method. The experimental results showed that the solubilities of norfloxacin in ethanol, 1-propanol, acetone, and chloroform were all small, and increased slightly with the increase of the temperature, respectively. Under the same temperature, the decrease order of solubility of norfloxacin in the different solvents is 1-propanol, chloroform, ethanol, and acetone. The experimental data were correlated with the modified Apelblat equation.

Les solubilités de norfloxacine dans l'éthanol, le 1-propanol, l'acétone et le chloroforme ont été déterminées depuis la méthode de l'équilibre statique 294.15 à 318.15 K. Les résultats expérimentaux montrent que les solubilités de norfloxacine dans l'éthanol, le 1-propanol, l'acétone et le chloroforme étaient toutes faibles et augmentaient légèrement avec hausse de la température, respectivement. En présence d'une même température, la diminution de la solubilité de norfloxacine dans les différents solvants est dans cet ordre: 1-propanol, chloroforme, éthanol et acétone. Les données expérimentales sont en corrélation avec l'équation modifiée d'Apelblat.

Keywords: solubilities, norfloxacin, physicochemical properties, temperature

INTRODUCTION

Norfloxacin is member of quinolones that are widely used in agriculture to prevent diseases in livestock and treat illness; therefore, soil and groundwater body have been badly contaminated. The solubility plays a prominent role in the prediction of the environmental fate of chemicals and can characterize transportation through membranes and the topical activity of drugs (Picó and Andreu, 2007). In determining the transport of norfloxacin in the environment and assessing its risk to terrestrial and aquatic ecosystems, it is necessary to know its solubilities in various solvents. However, only a limited amount of solubility data for norfloxacin has been reported from 293.15 to 323.15 K (Ross and Riley, 1990; Yu et al., 1994; Faller and Ertl, 2007). In this study, solubilities of norfloxacin in ethanol, 1-propanol, acetone and chloroform have been measured from 294.15 to 318.15 K. The experimental data were correlated with the modified Apelblat equation (Apelblat and Manzurola, 1987; Jia et al., 2008).

After filtration and drying, their purity was determined by UV spectrometry (type UV-2401PC, Shimadzu), to be 0.996 in mass fraction. All the solvents selected for the present study were analytical grade reagents, which were obtained from Tianjin Kermel Chemical Reagent (Tianjin, China) and used without any further purification.

The solubility was measured by a static equilibrium method (Martinez et al., 2003). Nearly 100 mg of norfloxacin was added separately to 50 mL of each solvent in glass flasks. The mixtures were then stirred in a mechanical shaker for 1 h. Samples were then allowed to stand in water baths (type 501, Shanghai Laboratory Instrument Works) kept at the appropriate temperature (± 0.02 K). The equilibration of other quinolones has been reported to be achieved after 30 h. Therefore, in this work, the initial equilibration time of the saturated solution was 72 h; then, it was analysed once every 5 h until the analysing results were replicated three consecutive times. After this time, the supernatant

EXPERIMENTAL

Norfloxacin obtained from Daming Biotech, Zhengzhou, China, were further purified by recrystallization from aqueous solutions.

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Table 1. Mole fraction solubility (x) of norfloxacin in water compared with literature data at 298.15 K

System	$10^5 x_{\text{exptl}}$	$10^5 x_{\text{ref}}$	100RD
Norfloxacin + water	2.270 (Zhang and Wang, 2008)	2.258 (Ross and Riley, 1990)	0.53

solutions were filtered to ensure that they were free of particulate matter before sampling. We determined concentrations by measuring UV absorbances after appropriate dilution and interpolation from previously constructed calibration curves for each system. To permit conversion between molarity and mole-fraction concentration scales, the density of the saturated solutions was determined with a digital density meter. All of the solubility experiments were repeated at least three times, and the mean values were considered to be the measured results. The uncertainty of temperature measurements was ± 0.05 K. The reproducibility of temperature measurements was 0.1 K, which corresponds to a relative deviation in composition smaller than 2%. The results showed that the deviation of the measured solubility from the literature values (Ross and Riley, 1990) was less than 1%. Therefore, the reliability of the experimental apparatus was verified.

RESULTS AND DISCUSSION

The solubility of norfloxacin in water at 298.15 K listed in Table 1 is measured to complete the data reported in literature (Ross and Riley, 1990).

The temperature dependence of norfloxacin solubility in ethanol, 1-propanol, acetone, and chloroform has been described by the modified Apelblat equation (Apelblat and Manzurola, 1987; Jia et al., 2008):

$$\ln x = A + \frac{B}{T(\text{K})} + C \ln(T(\text{K})) \quad (1)$$

where x is the mole fraction of norfloxacin, T is the absolute temperature, and A , B , and C are constants determined by least square analysis. The values of these parameters are listed in Table 3. The relative deviations (RD values) between the experimental and calculated values of solubilities are also calculated by Equation (2) and are listed in Table 2

$$\text{RD} = \left(\frac{x - x_c}{x} \right) \quad (2)$$

The average relative deviations (ARD values) for each system in this study are also calculated by Equation (3) and are given in Table 3

$$\text{ARD} = \frac{1}{N} \sum_{i=1}^N \left| \frac{x_i - x_{ci}}{x_i} \right| \quad (3)$$

The data in Tables 2 and 3 indicate that the calculated solubilities show good agreement with the experimental data, which demonstrates that the modified Apelblat equation can be used to correlate the solubility data of norfloxacin in different solvents. The relative deviations among 24 data points for the studied systems do not exceed 1.3%, and the total average relative deviation is 0.46%.

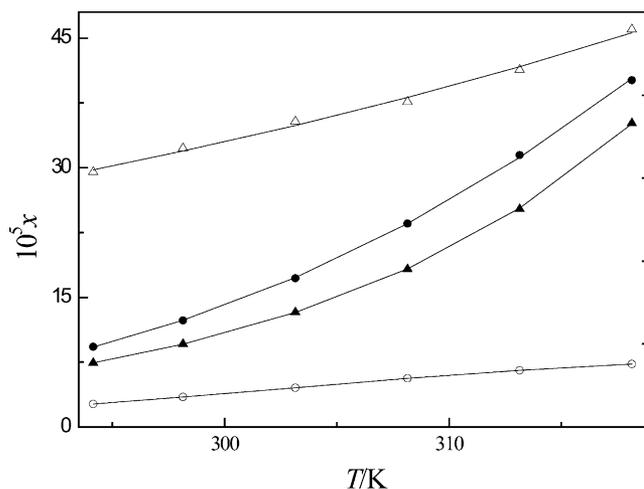
By using the data shown in Table 2, we plotted the solubility curves for the studied systems in Figure 1. It is evident that the solubility of each system is low. The solubility data of norfloxacin in ethanol, 1-propanol, acetone, and chloroform showed a flat up-trend when the temperature increased. Moreover, the structure

Table 2. Solubility data of norfloxacin in different solvents and the regression results obtained using the modified Apelblat equation

$T(\text{K})$	$10^5 x$	100RD	$T(\text{K})$	$10^5 x$	100RD
Norfloxacin + ethanol					
294.15	7.415	-0.14	308.15	18.28	-0.10
298.15	9.602	0.08	313.15	25.23	-0.37
303.15	13.28	0.30	318.15	35.16	0.22
Norfloxacin + 1-propanol					
294.15	29.50	-0.91	308.15	37.64	-1.3
298.15	32.24	0.96	313.15	41.32	-0.91
303.15	35.35	1.3	318.15	46.00	0.81
Norfloxacin + acetone					
294.15	2.671	-0.10	308.15	5.635	0.22
298.15	3.479	0.16	313.15	6.546	-0.35
303.15	4.548	-0.09	318.15	7.296	0.15
Norfloxacin + chloroform					
294.15	9.280	0.35	308.15	23.55	0.10
298.15	12.32	-0.30	313.15	31.46	0.88
303.15	17.20	-0.51	318.15	40.12	-0.51

Table 3. Parameters in the modified Apelblat equation for different systems

System	A	B	C	100ARD
Norfloxacin + ethanol	-290.72	7672.3	44.884	0.20
Norfloxacin + 1-propanol	-91.164	2369.7	13.193	1.04
Norfloxacin + acetone	1270.7	-61 580	-188.57	0.18
Norfloxacin + chloroform	435.08	-25 067	-63.186	0.44

**Figure 1.** Solubilities of norfloxacin in studied solvents: \blacktriangle , norfloxacin + ethanol; \triangle , norfloxacin + 1-propanol; \circ , norfloxacin + acetone; \bullet , norfloxacin + chloroform; $-$, calculated from Equation (1).

of norfloxacin indicates that the molecule is highly aromatic and the functional groups may not contribute much to the aqueous solubility. So, the solubility is minimum in acetone and maximum in 1-propanol.

Table 4. $\Delta_{\text{sol}}H$ and $\Delta_{\text{sol}}S$ for different systems at different temperatures

	T (K)					
	294.15	298.15	303.15	308.15	313.15	318.15
Norfloxacin + ethanol						
$\Delta_{\text{sol}}H$ (kJ mol ⁻¹)	45.98	47.47	49.34	51.20	53.07	54.94
$\Delta_{\text{sol}}S$ (J mol ⁻¹ K ⁻¹)	156.3	159.2	162.7	166.2	169.5	172.7
Norfloxacin + 1-propanol						
$\Delta_{\text{sol}}H$ (kJ mol ⁻¹)	12.56	13.00	13.55	14.10	14.65	15.20
$\Delta_{\text{sol}}S$ (J mol ⁻¹ K ⁻¹)	42.71	43.61	44.70	45.75	46.77	47.76
Norfloxacin + acetone						
$\Delta_{\text{sol}}H$ (kJ mol ⁻¹)	50.82	44.55	36.71	28.87	21.03	13.19
$\Delta_{\text{sol}}S$ (J mol ⁻¹ K ⁻¹)	172.8	149.4	121.1	93.68	67.15	41.46
Norfloxacin + chloroform						
$\Delta_{\text{sol}}H$ (kJ mol ⁻¹)	53.88	51.78	49.15	46.53	43.90	41.27
$\Delta_{\text{sol}}S$ (J mol ⁻¹ K ⁻¹)	183.2	173.7	162.1	151.0	140.2	129.7

According to a pseudochemical reaction process (Wang, 2001), the dissolution process of solid, S, in liquid, W, can be expressed as $S + W = SW$; the relationship of its dissolution equilibrium constants and activities can be expressed as:

$$K_i = \frac{a_i}{a_s a_w} \quad (4)$$

where a_i is the activity of norfloxacin in solution, a_s and a_w are the activities of pure solid, S, and pure liquid, W, respectively.

Because of the relatively small solubility of norfloxacin in each solvent, it is believed that a_s and a_w almost remain constant in the experimental range, and each is considered to be a constant.

$$J' = a_s a_w \quad (5)$$

Therefore, Equation (4) can be written as:

$$K_i = \frac{\gamma_i x_i}{J'} \quad (6)$$

where γ_i is the activity coefficient of norfloxacin, i , in the solution and x_i is the mole fraction of norfloxacin, i , in the solution.

On the basis of the assumption used in the inferential process for the modified Apelblat equation that the activity coefficient is invariable during a certain temperature range (Wang et al., 2004), γ_i in Equation (6) can be merged into J' . Equation (7) can be obtained from Equation (6) by logarithmic treatment:

$$\ln K_i = \ln x_i + J \quad (7)$$

where $J = \ln \gamma_i - \ln J'$ is a temperature-independent constant.

On the basis of the Gibbs equation and the modified Van't Hoff method (Bourgois et al., 2006), the equation for calculating the molar enthalpies of dissolution $\Delta_{\text{sol}}H$ can be obtained:

$$\Delta_{\text{sol}}H = -R \frac{d \ln K_i}{dT^{-1}} \quad (8)$$

Substituting the differential of Equation (7) into Equation (8) yields:

$$\Delta_{\text{sol}}H = -R \frac{d \ln x_i}{dT^{-1}} \quad (9)$$

Using Equation (1) to obtain the derivative and substituting it into Equation (9) gives:

$$\Delta_{\text{sol}}H = RT \left(C - \frac{B}{T(\text{K})} \right) \quad (10)$$

According to the fundamental thermodynamic relation (Prausnitz et al., 1999), the equation for calculating the molar entropies of dissolution $\Delta_{\text{sol}}S$ can be obtained accordingly:

$$\Delta_{\text{sol}}S = R \left(C - \frac{B}{T(\text{K})} \right) \quad (11)$$

According to parameters of the modified Apelblat equation listed in Table 3, $\Delta_{\text{sol}}H$ and $\Delta_{\text{sol}}S$ listed in Table 4 can be calculated from Equations (10) and (11), respectively.

From Table 4, it is found that the course of norfloxacin dissolving in each solvent in the experimental temperature range was endothermic, $\Delta_{\text{sol}}H > 0$, and $\Delta_{\text{sol}}S$ for norfloxacin dissolving in each solvent was relatively large. The positive $\Delta_{\text{sol}}H$ and $\Delta_{\text{sol}}S$ for norfloxacin revealed that norfloxacin being dissolved in each solvent was an entropy-driving process. This phenomenon likely resulted from the different molecular structure and space conformation between solute and solvent. Solvent molecules selected for the present study are strong association complexes with small molecular dimension (Nagata et al., 1996). Owing to the solute norfloxacin molecules containing basic groups such as $>NH$, $>N-$, acidic groups such as $-COOH$, and complicated groups with different characteristics such as $-CH_3$, $-F$, norfloxacin perhaps involve various forces such as electrostatic force, hydrogen bond, hydrophobic interaction, and stereoscopic effect in the dissolving process (Prausnitz et al., 1999). The reason for the entropy increase during the dissolution process is that norfloxacin disrupted the alignment of solvent molecules and therefore reduced the degree of order of the system while they were dissolved in various solvent. The endothermic effect in the dissolving process ($\Delta_{\text{sol}}H > 0$) is perhaps because the interactions between norfloxacin molecules and solvent molecules are more powerful than those between the solvent molecules; the newly formed bond energy between norfloxacin molecule and solvent molecule is not powerful enough to compensate the energy needed for breaking the original association bond in various solvent.

CONCLUSIONS

Using a static equilibrium method, we experimentally determined the solubilities of norfloxacin in ethanol, 1-propanol, acetone, and chloroform from 294.15 to 318.15 K. The experimental data were correlated with the modified Apelblat equation. The calculated results show good agreement with the experimental data.

NOMENCLATURE

a_i	activity of norfloxacin in solution
a_s	activity of pure solid
a_w	activity of pure liquid
A, B, C	parameters in the modified Apelblat equation
ARD	average relative deviation
$\Delta_{sol}H$	molar enthalpy change of dissolution
J	$a_s a_w$
J	$\ln \gamma_i - \ln J$
K_i	$\gamma_i x_i / J$
R	gas constant
RD	relative deviation
γ_i	activity coefficient of norfloxacin
$\Delta_{sol}S$	molar entropy change of dissolution
T	absolute temperature
x	mole fraction of norfloxacin

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