Solubility of Enrofloxacin Sodium in Various Solvents at Various Temperatures

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The solubility of enrofloxacin sodium in methanol, acetone, 1,2-dichloromethane, and 1,2-dichloroethane was measured by a gravimetrical method from (293.15 to 310.15) K under atmospheric pressure, and the solubility data were correlated against temperature.

Introduction

Enrofloxacin sodium (Hiran Orgochem Ltd.) is a yellowish powdered crystal, which is an extremely valuable drug as an antibiotic.[1] A considerable number of clinical studies have been conducted with enrofloxacin.[2] It has been reported to be effective in the treatment of a wide variety of bacterial infections in both humans and animals.[3] It has a wide spectrum of antibacterial activity against organisms that are resistant to many other antibacterial substances, such as β-lactam antibiotics, aminoglycosides, cephalosporins, tetracyclines, sulfonamides, and macrolides.[4] Its potency against many bacteria[5−8] and good pharmacokinetic properties[9,10] suggest that it would be an excellent antimicrobial agent for the treatment of bacterial infections in pigs. Further, enrofloxacin is effective in the treatment of porcine respiratory diseases.[2,11,12]

Thus, to use enrofloxacin sodium as a drug, it is necessary to purify it. For this, the solubility of enrofloxacin sodium in various solvents is needed.

In the present study, the solubilities of enrofloxacin sodium in methanol, acetone, 1,2-dichloromethane, and 1,2-dichloroethane have been measered from (293.15 to 310.15) K at atmospheric pressure.

Experimental Section

Materials. All the solvents, methanol, acetone, 1,2-dichloromethane, and 1,2-dichloroethane, were analytical grade reagents. These solvents were purified by fractional distillation by the methods reported in the literature.[13] Their purities were checked by SHIMADZU GC-MS (model No QP-2010) and were found to be greater than 99.65 %.

The drug was recrystallized, and its melting point was determined with the open capillary method. The observed value was found to be 208 °C. However, the reported value[14] is (219 to 221) °C. The structure of the drug is shown in Figure 1.

Solubility Measurement. The solubilities were measured by a gravimetric method.[15] For each measurement, an excess mass of enrofloxacin sodium was added to a known mass of solvent. Then, the equilibrium cell was heated to a constant temperature with continuous stirring. After at least 3 h (the temperature of the water bath approached constant value, then the actual value of the temperature was recorded), the stirring was stopped, and the solution was kept still for 2 h. A portion of this solution was filtered, and by a preheated injector, 2 mL of this clear solution was taken in another weighted measuring vial (m_0).

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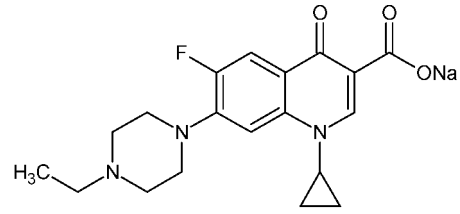

[IUPAC name: sodium 1-cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-4-oxo-1, 4- dihydroquinoline-3-carboxylate].

Figure 1. Structure of enrofloxacin sodium.

The vial was quickly and tightly closed and weighted (m_1) to determine the mass of the sample ($m_1 - m_0$). Then, the vial was covered with a piece of filter paper to prevent dust contamination. Then, the vial was placed in at room temperature to evaporate the solvent. After the solvent in the vial had completely evaporated, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid ($m_2 - m_0$). All the weights were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. Thus, the solid concentration of the sample solution of mole fraction, x, could be determine from eq 1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

where M_1 is the molar mass of the drug and M_2 is the molar mass of the solvent.

Results and Discussion

The mole fraction solubilities x of enrofloxacin sodium in methanol, acetone, 1,2-dichloromethane, and 1,2-dichloroethane at different temperatures (293.15 to 310.15) K are summarized in Table 1. The variation of solubility with temperature is also shown in Figure 2. It is observed that solubility increases linearly with increase in temperature. Further, in 1,2-dichloroethane, solubility is much affected by the change in temperature, and the increase is nonlinear. The solubility in the studied solvents is in the order: 1,2-dichloromethane > 1,2-dichloroethane > acetone > methanol.

The temperature dependence of enrofloxacin solubility in solvents is described by the modified Apelblat equation[16,17]

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

where x is the mole fraction solubility of enrofloxacin; T is the absolute temperature; and A, B, and C are the parameters in eq

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Table 1. Observed Mole Fraction Solubilities (x), Calculated Mole Fraction Solubilities (x_{ci}), and Relative Deviation (RD) of Enrofloxacin in Different Solvents

T/K	10^3x	10^3x_{ci}	100 RD
	Acetone		
293.15	1.33 ± 0.02	1.31	−0.30
295.15	1.47 ± 0.05	1.47	0.02
298.15	1.71 ± 0.03	1.75	0.33
300.15	1.98 ± 0.01	1.97	−0.09
303.15	2.52 ± 0.02	2.34	−1.20
305.15	2.73 ± 0.02	2.63	−0.61
308.15	3.13 ± 0.01	3.13	0.02
310.15	3.47 ± 0.03	3.52	0.25
	Methanol		
293.15	0.96 ± 0.03	0.96	0.48
295.15	1.02 ± 0.01	1.02	0.27
298.15	1.15 ± 0.04	1.15	−0.26
300.15	1.20 ± 0.06	1.20	−0.19
303.15	1.30 ± 0.01	1.30	−0.25
305.15	1.35 ± 0.02	1.35	−0.03
308.15	1.44 ± 0.02	1.44	0.20
310.15	1.49 ± 0.03	1.49	0.49
	1,2-Dichloroethane		
293.15	2.48 ± 0.02	2.39	−0.66
295.15	2.79 ± 0.05	2.88	0.57
298.15	3.58 ± 0.02	3.84	1.23
300.15	4.15 ± 0.03	4.64	2.05
303.15	6.56 ± 0.01	6.18	−1.19
305.15	8.58 ± 0.04	7.47	−2.89
308.15	9.96 ± 0.02	9.95	−0.01
310.15	10.86 ± 0.03	12.03	2.28
	1,2-Dichloromethane		
293.15	8.09 ± 0.02	8.44	−0.06
295.15	8.18 ± 0.06	8.46	−0.11
298.15	8.35 ± 0.02	8.49	−0.25
300.15	8.38 ± 0.03	8.51	−0.15
303.15	8.44 ± 0.04	8.54	−0.01
305.15	8.53 ± 0.05	8.50	−0.07
308.15	8.68 ± 0.03	8.61	−0.18
310.15	8.74 ± 0.01	8.68	−0.12

2. The values of these parameters are given in Table 2. The calculated solubilities x_{ci} are also reported in Table 1. These calculated values are also plotted in Figure 2 along with the experimental data, for comparison.

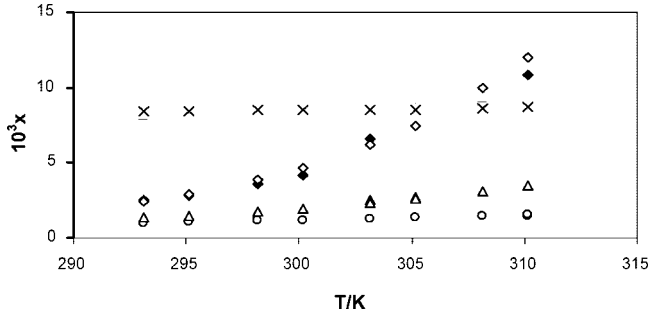

Figure 2. Variation of mole fraction solubilities (x) and calculated mole fraction solubilities (x_{ci}) with temperature for drug in different solvents. Solubilities of enrofloxacin in acetone; ●, methanol; Δ, 1,2-dichloroethane; ♦, 1,2 dichloromethane; ×.

Table 2. Constants A and B of Equation 2, Absolute Average Deviation (AAD), and Root Mean Square Deviation (rmsd) of Enrofloxacin in Different Solvents

solvents	A	B	C	10^{-7} rmsd	100 AAD
acetone	7576	−2692.3	239.21	0.41	1.26
methanol	−1255.5	430.81	−36.903	0.04	−0.46
1,2-dichloromethane	64.898	−30.823	3.6663	2.25	−1.31
1,2-dichloroethane	49926	−17.651	1560.1	26.95	−1.34

Further, absolute average deviations (AAD) and root-mean-square deviations (rmsd), calculated by eqs 3 and 4, are listed in Table 2.

$$\mathrm{AAD} = \frac{1}{N}\sum_{i}^{N}\frac{x_i - x_{ci}}{x_i} \tag{3}$$

$$\mathrm{rmsd} = \left[\sum_{i=1}^{N}\frac{(x_{ci} - x_i)^2}{N-1}\right]^{1/2} \tag{4}$$

where N is the number of experimental points and x_{ci} is the solubility calculated by eq 2.

The relative deviations (RD) between the experimental and calculated values of solubilities are also calculated by eq 5 and are given in Table 1.

$$\text{relative deviation} = \left(\frac{x - x_{ci}}{x}\right) \tag{5}$$

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Supporting Information Available:

Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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