Solubility of Difloxacin in Acetone, Methanol, and Ethanol from (293.15 to 313.15) K

Shipra Baluja,* Rahul Bhalodia, Ravi Gajera, Nayan Vekariya, and Mehul Bhatt

Physical Chemical Laboratory, Department of Chemistry, Saurashtra University, Rajkot (360 005), India

The solubility of difloxacin in methanol, acetone, and ethanol was measured by a gravimetrical method from (293.15 to 313.15) K under atmospheric pressure, and the solubility data were correlated against temperature.

Introduction

Difloxacin is a new member of the fluoroquinolone drug family. Fluoroquinolones are a group of antimicrobials that have become widely used in veterinary medicine because of their broad spectrum of properties.[1,2] The principal advantages of fluoroquinolones include good oral bioavailability, bactericidal activity at low tissue concentrations, and good penetration into phagocytic cells.[3,4] Difloxacin is a fluoroquinolone antibacterial drug that was specifically developed for use in veterinary medicine. It has been shown to be effective in the treatment of experimentally induced pneumonic pasteurellosis in calves.[5] Difloxacin was also found to be as effective as clindamycin−gentamicin in the treatment of experimentally induced intra-abdominal abscess associated with *Bacteroides fragilis*.[6] The pharmacokinetics of difloxacin have been evaluated in dogs, rabbits,[7] sheep,[8] goats, and lambs,[9] and its bactericidal and inhibitory activity against small animal pathogens has been determined.[10−12]

These biological properties prompted us to study the solubility of difloxacin in different solvents at different temperatures.

In the present study, the solubilities of difloxacin in methanol, acetone, and ethanol have been measured from (293.15 to 313.15) K at atmospheric pressure.

Experimental Section

Materials. Difloxacin, with a mole fraction purity of 99.6 %, was purchased from Hiran Orgochem (Ankleshwar, India). It was dried to constant mass in an air oven at 383 K before use. The choice of solvent depends on the solubility and relative permeability. All of the solvents, methanol, acetone, and ethanol were analytical grade reagents. These solvents were purified by fractional distillation. 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 temperature was determined by an open capillary method. The observed value was found to be (551.15 ± 0.1) K. However, the reported value[13] is < 548.15 K. The structure of the drug is shown in Figure 1.

Solubility Measurement. The solubilities were measured by a gravimetric method.[14] For each measurement, an excess mass of difloxacin 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). The vial was quickly and tightly closed and weighed (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. After the solvent in the vial had completely evaporated at room temperature, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid ($m_2 - m_0$). All of the masses were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. Thus, the concentration of the solid sample in the solution, mole fraction, x, could be determined 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 drug and M_2 is the molar mass of the solvent.

At each temperature, the measurement was repeated three times, and an average value is given in Table 1 along with uncertainty.

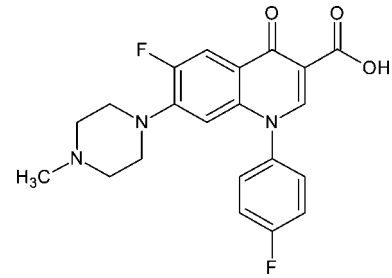

Figure 1. Structure of difloxacin (IUPAC name: 6-fluoro-1-(4-fluorophenyl)-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid).

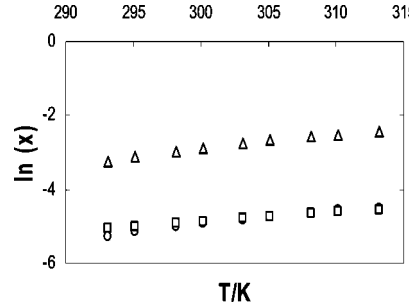

Figure 2. Solubility, x, of difloxacin as a function of temperature in: ○, acetone; □, methanol; △, ethanol.

* Corresponding author. E-mail: shipra_baluja@rediffmail.com.

10.1021/je800742d CCC: $40.75
Published on Web 01/23/2009

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

T/K	10^2x	10^2x_{ci}	100 RD
	Acetone		
293.15	0.52 ± 0.017	0.54 ± 0.020	0.83
295.15	0.58 ± 0.023	0.58 ± 0.014	0.19
298.15	0.67 ± 0.021	0.67 ± 0.024	−0.42
300.15	0.73 ± 0.030	0.71 ± 0.034	−0.64
303.15	0.81 ± 0.052	0.79 ± 0.021	−0.46
305.15	0.87 ± 0.024	0.85 ± 0.037	−0.39
308.15	0.96 ± 0.036	0.96 ± 0.038	−0.08
310.15	1.04 ± 0.020	1.03 ± 0.026	−0.18
313.15	1.10 ± 0.020	1.15 ± 0.049	0.96
	Methanol		
293.15	0.64 ± 0.040	0.64 ± 0.026	−0.05
295.15	0.68 ± 0.041	0.67 ± 0.047	−0.27
298.15	0.73 ± 0.052	0.72 ± 0.052	−0.20
300.15	0.77 ± 0.038	0.76 ± 0.040	−0.28
303.15	0.84 ± 0.026	0.82 ± 0.037	−0.55
305.15	0.88 ± 0.032	0.86 ± 0.051	−0.49
308.15	0.95 ± 0.035	0.93 ± 0.042	−0.54
310.15	0.99 ± 0.028	0.97 ± 0.041	−0.37
313.15	1.04 ± 0.013	1.05 ± 0.020	0.18
	Ethanol		
293.15	3.87 ± 0.047	4.08 ± 0.039	1.67
295.15	4.35 ± 0.023	4.42 ± 0.031	0.54
298.15	5.07 ± 0.043	4.98 ± 0.043	−0.56
300.15	5.59 ± 0.029	5.40 ± 0.061	−1.21
303.15	6.36 ± 0.027	6.08 ± 0.0 67	−1.61
305.15	6.83 ± 0.038	6.59 ± 0.053	−1.35
308.15	7.54 ± 0.032	7.42 ± 0.032	−0.61
310.15	7.95 ± 0.029	8.04 ± 0.065	0.43
313.15	8.56 ± 0.058	9.06 ± 0.055	2.29

Results and Discussion

The mole fraction solubilities, x, of difloxacin in methanol, acetone, and ethanol at different temperatures (293.15 to 313.15) K are summarized in Table 1. The variation of solubility with temperature is also shown in Figure 3. It is observed that solubility linearly increases with the increase in temperature. Furthermore, solubility is higher in ethanol than in methanol and acetone.

As shown in Figure 3, the mole fraction solubility, x, of difloxacin was correlated as a function of temperature. The temperature dependence of difloxacin solubility in solvents is described by the modified Apelblat equation[15,16]

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

where x is the mole fraction solubility of difloxacin, T is the absolute temperature, and A and B are the parameters. The values of these parameters are given in Table 2. The calculated solubilities, x_{ci}, are also reported in Table 1. The experimental solubility of drug in the studied solvents was compared with the calculated solubility (x_{ci}). The difference between experimental and theoretical solubilities ($\Delta x = x - x_{ci}$) is plotted against temperature in Figure 4. Similar behavior has been also reported in literature.[17,18]

Table 2. Constants A and B of Equation 2, Relative Average Deviations (ARD), and Root-Mean-Square Deviation (rmsd) of Difloxacin in Different Solvents

solvents	A	B	10^{-5} rmsd	100 ARD
acetone	−16.27	0.037	0.04	−0.02
methanol	−12.34	0.024	0.02	−0.28
ethanol	−14.85	0.039	4.45	−0.04

Furthermore, relative average deviations (ARD) and root-mean-square deviations (rmsd), calculated by eqs 3 and 4, are listed in Table 2

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

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

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 Tables 1.

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

Furthermore, the enthalpies of solution, ΔH, were calculated using the van't Hoff equation,[19] that is, from the slope of the plot of ln x versus 1/T.

The standard Gibbs energies of the dissolution process, ΔG, were also calculated using the following equation[20,21]

$$\Delta G = -RT\ln x \tag{6}$$

where x is the mole fraction of the investigated substance in the saturated solution.

Using these ΔH and ΔG values, the standard entropies of solution, ΔS, were obtained from the well-known equation[22]

$$\Delta G = \Delta H - T\Delta S \tag{7}$$

where ΔH is the molar enthalpy of solution.

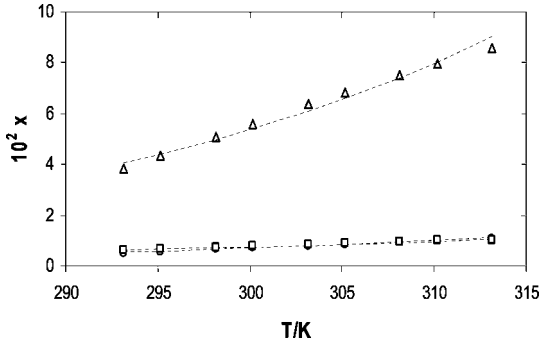

Figure 3. Variation of mole fraction solubilities (x) and calculated mole fraction solubilities (x_{ci}) with temperature for drug in different solvents. Calculated mole fraction solubility, x_{ci}, is shown as a dotted line for all solvents: ○, acetone; □, methanol; △, ethanol.

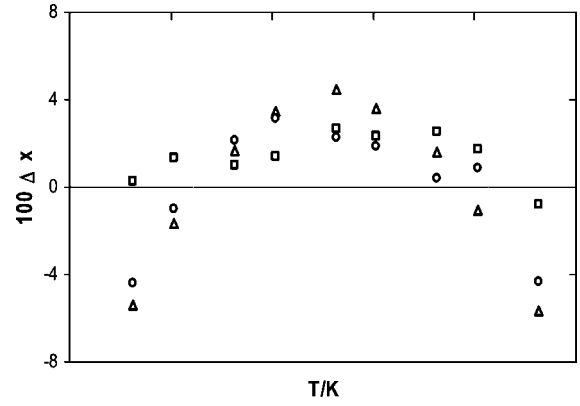

Figure 4. Fractional deviations, $\Delta x = x - x_{ci}$, of difloxacin solubility at various temperatures in: ○, acetone; □, methanol; △, ethanol.

Table 3. Thermodynamic Function of Dissolution of Difloxacin in Various Solvents

solvents	ΔG / kJ·mol^{-1}	$-\Delta H$ / kJ·mol^{-1}	$-T\Delta S$ / kJ·mol^{-1}	ς_H	ς_{TS}
acetone	12.191	51.97	64.16	44.75	55.25
methanol	12.074	36.04	48.12	42.82	57.18
ethanol	7.056	18.53	25.58	42.00	57.99

The Gibbs energy of dissolution process of the drug can also be separated into a relative fraction of both the enthalpy and entropy terms by the following equations[23]

$$\varsigma_H = \frac{\Delta H}{\Delta H + T\Delta S} \cdot 100 \quad (8)$$

$$\varsigma_{TS} = \frac{T\Delta S}{\Delta H + T\Delta S} \cdot 100 \quad (9)$$

These thermodynamic values for different solvents are reported in Table 3. As evident from Table 3, the main driving force of the solution for process for all of the used solvents is the entropy. For acetone, methanol, and ethanol, solution is entropy driven with a fraction of (55.25, 57.18, and 57.99) %.

Acknowledgment

We thank the Head of Chemistry Department, Saurashtra University, Rajkot, India for providing necessary facilities.

Literature Cited

(1) Fluoroquinolones. In *Antimicrobial Therapy in Veterinary Medicine*, 2nd ed.; Prescott, J. F., Baggot, J. D., Eds.; Iowa State University Press: Ames, IA, 1993; pp 252−262.
(2) Gollapudi, S.; Thadepalli, F.; Kim, C. H.; Gupta, S. Difloxacin reverses multidrug resistance in HL-60/AR cells that overexpress the multidrug resistance-related protein (MRP) gene. *Oncol. Res.* **1995**, *7*, 213–225.
(3) Giguere, S.; Sweeney, R. W.; Belanger, M. Pharmacokinetics of enrofloxacin in adult horses and concentration of the drug in serum, body fluids, and endometrial tissues after repeated intragastrically administered doses. *Am. J. Vet. Res.* **1996**, *57*, 1025–1030.
(4) Orsini, J. A.; Perkons, S. The fluoroquinolones: clinical applications in veterinary medicine. *Compend. Contin. Educ. Pract. Vet.* **1992**, *14*, 1491–1496.
(5) Olchowy, T. W. J.; TerHune, T. N.; Herrick, R. L. Efficacy of difloxacin in calves experimentally infected with *Mannheimia haemolytica*. *Am. J. Vet. Res.* **2000**, *61*, 710–713.
(6) Thadepalli, H.; Gollapudi, S. V.; Chuah, S. K. Therapeutic evaluation of difloxacin (A-56619 and A-56620) for experimentally induced *Bacteroides fragilis*-associated intra-abdominal abscess. *Antimicrob. Agents Chemother.* **1986**, *30*, 574–576.
(7) Fernández-varón, E.; Cárceles, C. M.; Marń, P.; Vancraeynest, D.; Montes, A.; Sotillo, J.; García-Martínez, J. D. Disposition kinetics and pharmacokinetics−pharmacodynamic integration of difloxacin against *Staphylococcus aureus* isolates from rabbits. *Res. Vet. Sci.* **2008**, *84*, 90–94.
(8) Marín, P.; Fernández-varón, E.; Escudero, E.; Cárceles, C. Pharmacokinetics and milk penetration of difloxacin after intravenous, subcutaneous and intramuscular administration to lactating goats. *J. Vet. Pharmacol. Ther.* **2007**, *30*, 74–79.
(9) Goudah, A.; Mounei, S. Comparative pharmacokinetics of difloxacin in goat kids and lambs. *Small Ruminant Res.* **2008**, *78*, 186–192.
(10) Heinen, E. Comparative serum pharmacokinetics of the fluoroquinolones enrofloxacin, difloxacin, marbofloxacin, and orbifloxacin in dogs after single oral administration. *J. Vet Pharmacol Ther.* **2002**, *25*, 1–5.
(11) Frazier, D. L.; Thompson, L.; Trettien, A.; Evans, E. I. Comparison of fluoroquinolone pharmacokinetic parameters after treatment with marbofloxacin, enrofloxacin, and difloxacin in dogs. *J. Vet Pharmacol. Ther.* **2000**, *23*, 293–302.
(12) Pirro, F.; Edingloh, M.; Schmeer, N. Bactericidal and inhibitory activity of enrofloxacin and other fluoroquinolones in small animal pathogens. *Compend. Contin. Educ. Pract. Vet.* **1999**, *21*, 19–25.
(13) Dorofeev, V. L.; Arzamastsev, A. P.; Veselova, O. M. Melting point determination for the analysis of drugs of the fluoroquinolone group. *Pharm. Chem. J.* **2004**, *38*, 333–335.
(14) Zhu, M. Solubility and density of the disodium salt hemiheptahydrate of ceftriaxone in water + ethanol mixtures. *J. Chem. Eng. Data* **2001**, *46*, 175–176.
(15) Apelblat, A.; Manzurola, E. Solubilities of *o*-acetylsalicylic, 4-aminosalic, 3,5-di nitrosalicylic, *p*-toluic acid, and magnesium-DL-aspartate in water from T = (278 to 348) K. *J. Chem. Thermodyn.* **1999**, *31*, 85–91.
(16) Gao, J.; Wang, Z. W.; Xu, D. M.; Zhang, R. K. Solubilities of triphenylphosphine in ethanol, 2-propanol, acetone, benzene, and toluene. *J. Chem. Eng. Data* **2007**, *52*, 189–191.
(17) Shalmashi, A.; Eliassi, A. Solubility of salicylic acid in water, ethanol, carbon tetrachloride, ethyl acetate, and xylene. *J. Chem. Eng. Data* **2008**, *53*, 199–200.
(18) Kong, M. Z.; Shi, X. H.; Cao, Y. C.; Zhou, C. R. Solubility of imidacloprid in different solvents. *J. Chem. Eng. Data* **2008**, *53*, 199–200.
(19) Nordstrom, F. L.; Rasmuson, A. C. Solubility and melting properties of salicylic acid. *J. Chem. Eng. Data* **2006**, *51*, 1668–1671.
(20) Perlovich, G. L.; Kurkov, A. N.; Bauer-Brandle, A. The difference between partitioning and distribution from a thermodynamic point of view: NSAIDs as an example. *Eur. J. Pharm. Biopharm.* **2006**, *27*, 150–157.
(21) Glasstone, S. *Thermodynamics for Chemists*, 3rd ed.; R. E. Krieger Pub. Co.: Huntington, NY, 1972; p 206.
(22) Szterner, P. Solubility in water of uracil and its halogenated derivatives. *J. Chem. Eng. Data* **2008**, *53*, 1738–1744.
(23) Perlovich, G. L.; Kurkov, S. V.; Kinchin, A. N.; Bauer-Brandle, A. Solvation and hydration characteristics of ibuprofen and acetylsalicylic. *AAPS PharmSci* **2004**, *6*, 1–9.

Received for review October 11, 2008. Accepted December 22, 2008.

JE800742D