Solubility of Ceftriaxone Disodium in Acetone, Methanol, Ethanol, *N*,*N*-Dimethylformamide, and Formamide between 278 and 318 K

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Experimental results are reported for the solubility of ceftriaxone disodium in acetone, methanol, ethanol, formamide, and *N*,*N*-dimethylformamide between 278 and 318 K. The isothermal method and the laser monitoring observation technique were used for the determination of the mole fraction concentration. The solubility of ceftriaxone disodium in pure solvents increases with increasing temperature and in the following order: acetone < ethanol < *N*,*N*-dimethylformamide < methanol < formamide. The experimental solubility data were correlated with a semiempirical equation.

Introduction

Solubility data of bioactive compounds have a broad application and great importance in the pharmaceutical industry, such as the solvent selection for the reaction and separation process. A variety of pure solvents and solvent mixtures (e.g., binary, ternary mixtures) have usually been employed in a particular crystallization process during manufacturing of pharmaceuticals.[1] Ceftriaxone disodium (CAS Registry No. 74578-69-1), $C_{18}H_{16}N_8Na_2O_7S_3{\cdot}3.5H_2O$, is a third generation, semisynthetic, broad-spectrum cephalosporin antibiotic. Its structural formula is given in Figure 1. Since it first came into the market in 1982, ceftriaxone disodium has become great salable all around the world and one of the most important parenterally applied antibiotics. In the pharmaceutical industry, ceftriaxone disodium is customarily synthesized from 7-AminoCephalosporanic Acid (7-ACA) and finally crystallized from solution for further purification step. To select the proper solvent and to design an optimized separation process, the studies of phase equilibrium behavior, especially solubility data, are essential.[2,3] However, a survey of the literature indicates that studies on ceftriaxone disodium have been focused on preparations or clinical treatments, while little work has been carried out on the solubility data except that in three mixed solvents (methanol−water, ethanol−water, and acetone−water) through gravimetrical method and the metastable zone in acetone−water system.[4−7] Gravimetrical method seems more reliable but more tedious and more time-consuming. Furthermore, longtime residence in solution may cause the active ingredient of the pharmaceuticals to hydrolyze. Recently, more and more solubility data, determined by the laser monitoring observation technique, have been published, and the results agree with the known results.[8−11] In the present work, the above method, where the solubility data can be obtained more rapidly, has been used to measure the solubility of ceftriaxone disodium in five pure solvents, (acetone, methanol, ethanol, *N*,*N*-dimethylformamide, and formamide).

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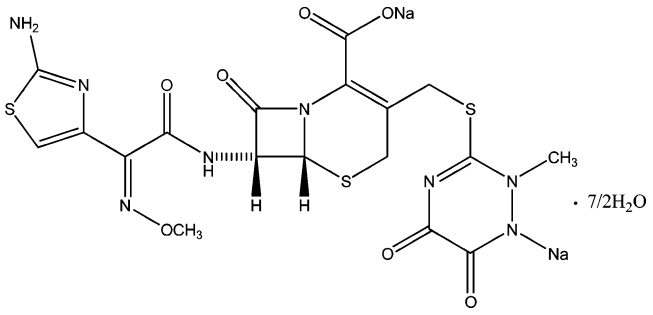

Figure 1. Molecular structure of ceftriaxone disodium (CAS Registry No. 74578-69-1).

Experimental Sections

Materials. A white crystalline powder of ceftriaxone disodium was supplied by a pharmaceutical company (Shandong Province, China) and purified by recrystallization in the State Research Center of Industrial Crystallization and Technology with a purity (>99.5 %) determined by HPLC according to BP2000. The product crystals were vacuum-dried at ambient temperature for 24 h. Later, the crystals were ground in an agate mortar, then fractionated into the particle size range of (57 to 65) μm with USP standard sieves, and finally stored in a desiccator. No polymorphic transition was found in the treatment of the material. The acetone, methanol, ethanol, *N*,*N*-dimethylformamide, and formamide (purchased from Tianjin Chemical Reagent Comp., China) used for experiments were of analytical reagent grade and were dehydrated with 4 Å molecular sieves before use. Their mass fraction purities were better than 99.5 %. Distilled-deionized water was used in all our experiments.

Apparatus and Procedure. An isothermal method[2] was used to measure the solubility of ceftriaxone disodium. As the amount of the suspending solid particles in the solution decreases, the intensity of the laser penetrating through the solution increases. The moment the last solid particle disappears, the intensity reaches a maximum. The apparatus for solubility measurement is somewhat modified from that described in the literature[8] and shown in Figure 2. The laser monitoring system consists of a laser generator, a photoelectric transformer, and a laser intensity

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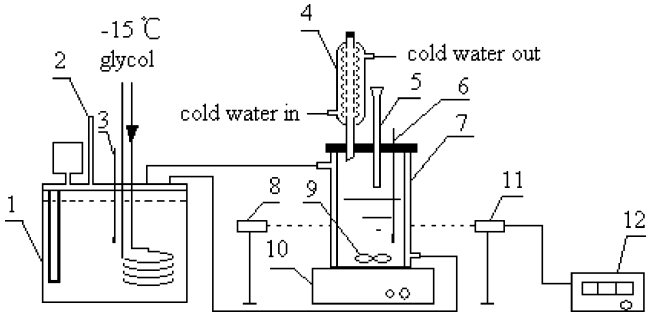

Figure 2. Schematic setup for the solubility determination: (1) superthermostatic bath; (2) thermocouple thermometer; (3, 6) thermometer; (4) condenser; (5) sample injector; (7) dissolution vessel; (8) laser generator; (9) stir bar; (10) magnetic stirrer; (11) photoelectric switch; (12) signal display.

display. The experiment was performed in a jacketed glass vessel with a Teflon-coated magnetic stirrer, maintained at a desired temperature by water circulating from a thermostatic bath with a thermoelectric controller (Wanda/Sida Instrument HC2010, China). The temperature of the solution inside the jacket can be maintained within ± 0.05 K. To prevent the evaporation of the solvent, a condenser vessel was introduced. A glass thermometer (Kewei Chemical Reagent & Instrument Comp., China) with the uncertainty of ± 0.05 K was used to determine the solution temperature and an analytical balance (Metler Toledo AB204-N, Switzerland) with an accuracy of ± 0.0001 g was employed to measure the masses of the solvent and solute.

In our experiments, predetermined amounts of solute and solvent were transferred into the jacketed vessel, and the amount of solvent was a small excess. The solution was stirred at a fixed temperature for about 2 h, and an unsaturated solution was obtained. The intensity of the laser penetrated through the solution was regarded as the maximum. Then additional solute of known mass (about 3 mg) was introduced into the vessel, and the intensity would decrease. If the intensity reaches the previous value, another addition was made. The above procedure was repeated until the intensity was below the maximum and constant for more than 30 min. Finally, the total amount of the solute added was used to compute the solubility. All the determinations were repeated three times at each temperature. The uncertainty in the solubility values is estimated to be less than 0.5 %.

Results and Discussion

The solubility data of ceftriaxone disodium measured in acetone, methanol, ethanol, *N*,*N*-dimethylformamide, and formamide from 278 to 318 K are listed in Table 1 and presented in Figure 3. The mole fraction solubility x was calculated as the following relationship:

$$x = \frac{m_2/M_2}{m_2/M_2 + m_1/M_1} \tag{1}$$

where m_1, M_1, m_2, and M_2 are the mass and the molecular weight of the solvent and solute, respectively.

Many equations have been proposed for the correlation and prediction of solubility data. Nevertheless, there is frequently a need for a simple mathematical expression of solubility to assist the recording and correlation of data.[3] According to the result of differential scanning calorimetry (DSC),[12] ceftriaxone disodium has no melting temperature because of thermal decomposition, which results in that almost no theoretical modes based on thermodynamic relationships relating to phase equilibrium could be used for the correlation and prediction solubility of ceftriaxone disodium. Hence, the temperature dependence of solubility of ceftriaxone disodium in pure solvents was correlated by the following semiempirical equation:[13]

$$\ln(x) = a + \frac{b}{T/\mathrm{K}} + c\,\ln(T/\mathrm{K}) \tag{2}$$

where x is the mole fraction solubility; T is the absolute temperature; and a, b, and c are constants for a particular solvent. The experimental data were fit to eq 2 using a nonlinear least-squares regression. The values of a, b, c, and the root-mean-square deviations (RMSDs) are listed in Table 2. The RMSD of the mole fraction is defined as follows:

$$\sigma_x = \left\{\frac{1}{N-2}\sum_{i=1}^{N}(x_i - x_i^{\mathrm{cal}})^2\right\}^{1/2} \tag{3}$$

where N is the number of experimental points, x_i^{cal} is the solubilities calculated from eq 2, and x_i is the experimental values of solubility. Figure 3 shows that the calculated values are in good agreement with the experimental ones.

The experimental results state that the ceftriaxone disodium solubility in each solvent increases with increasing temperature. Furthermore, ceftriaxone disodium is very slightly soluble in ethanol and acetone, sparingly soluble in methanol and *N*,*N*-dimethylformamide, and very soluble in formamide. Hence, acetone, ethanol, methanol, and *N*,*N*-dimethylformamide can be used as an antisolvent while formamide can be used as a solvent for ceftriaxone disodium.

Relative permittivity is commonly regarded as a degree of molecular polarity, while dipole moment as a degree of polarization.[14] Relative permittivity and dipole moment of solvents studied[14] are listed in Table 3. The polarity of the solvents are in the order acetone < ethanol < methanol < formamide (Table 3), so are the solubility determined by experiments (seen Table 1 and Figure 3). Polar molecule dissolves easily in polar solvent, which is the so-called empirical rule that "like dissolves like". During dissolution, the cohesive energy of the bonds holding solute together and the energy cost of disrupting the solvent−solvent bonds must be overcome by the cohesive energy released by the formation of the solute−solvent bonds. If these energies are approximately equal, which occurs when the solute and the solvent meleculars are structurally similar, then the solute will dissolve in the solvent. The molecular structure of the title compound (seen Figure 1) shows that ceftriaxone disodium has a strong polarity; hence, the more polar the solvent is, the higher the solubility is. However, *N*,*N*-dimethylformamide seems to be an exception. The polarity of *N*,*N*-dimethylformamide is higher than methanol, while the solubility in *N*,*N*-dimethylformamide is lower than that in methanol.

The process of dissolution is comparatively complex and mainly influenced by the characteristics of the solute and solvent besides temperature.[2,3] Ceftriaxone disodium is a polar molecule, of which the carbonyl and amidocyanogen group may result in forming intermolecular hydrogen bonding. To have a reasonable solubility, therefore, ceftriaxone disodium must need some polar solvents with the capability of forming hydrogen bonds to replace the intermolecular hydrogen bonding between the solute molecules

Table 1. Mole Fraction Solubility (x) of Ceftriaxone Disodium in Pure Solvents between 278 and 318 K

T/K	10^4x	T/K	10^4x	T/K	10^4x	T/K	10^4x
			Acetone				
277.95	0.01799 ± 0.00044	289.50	0.02520 ± 0.00013	305.25	0.03985 ± 0.00040	313.15	0.05058 ± 0.00092
282.50	0.02079 ± 0.00014	294.30	0.03047 ± 0.00038	309.35	0.04613 ± 0.00022	318.45	0.05553 ± 0.00055
285.70	0.02360 ± 0.00027	298.75	0.03532 ± 0.00023				
			Methanol				
278.30	4.184 ± 0.008	293.25	8.052 ± 0.007	305.60	13.45 ± 0.00	313.80	18.55 ± 0.01
283.20	5.129 ± 0.003	297.90	9.813 ± 0.006	309.65	15.40 ± 0.01	317.90	21.66 ± 0.01
288.00	6.491 ± 0.009	303.10	12.16 ± 0.00				
			Ethanol				
277.85	0.1302 ± 0.0027	291.70	0.2120 ± 0.0028	304.15	0.2505 ± 0.0042	314.85	0.3871 ± 0.0028
282.05	0.1651 ± 0.0032	297.10	0.2242 ± 0.0030	309.40	0.3312 ± 0.0046	316.35	0.4368 ± 0.0036
286.40	0.1903 ± 0.0031	299.25	0.2307 ± 0.0018				
			N,*N*-Dimethylformamide				
278.20	0.5677 ± 0.0056	294.45	1.190 ± 0.006	305.65	1.898 ± 0.006	313.80	2.675 ± 0.005
282.65	0.6704 ± 0.0063	300.35	1.510 ± 0.007	310.65	2.229 ± 0.004	317.60	2.863 ± 0.010
289.55	0.9076 ± 0.0033	303.20	1.764 ± 0.002				
			Formamide				
278.40	66.41 ± 0.04	294.05	148.8 ± 0.0	305.10	247.4 ± 0.0	311.80	333.0 ± 0.1
282.25	81.93 ± 0.02	299.65	194.5 ± 0.1	307.70	278.7 ± 0.1	315.25	385.2 ± 0.1
287.75	108.3 ± 0.1						

Table 2. Parameters of Equation 2 for Ceftriaxone Disodium in Pure Solvents between 278 and 318 K

solvent	a	b	c	$10^5\sigma_x$
acetone	74.30	−5992	−11.72	0.0125
methanol	−24.36	−2344	4.442	1.41
ethanol	−173.6	5259	25.50	0.257
N,*N*-dimethylformamide	−52.94	−1313	8.504	0.896
formamide	26.60	−4917	−2.478	10.2

Table 3. Physicochemical Properties of the Solvents Studied[a]

solvent	M/g·mol^{-1}	R	D/10^{-30} C·m
acetone	58.08	20.70 (298.15 K)	8.97
methanol	32.04	31.20	5.55
ethanol	46.07	25.70	5.60
N,*N*-dimethyl-formamide	73.10	36.71 (298.15 K)	12.88 (298.15 K)
formamide	45.04	111.0	11.24 (276.15 K)

[a] M = molecular mass, R = relative permittivity at 293.15 K, D = dipole moment at 293.15 K.

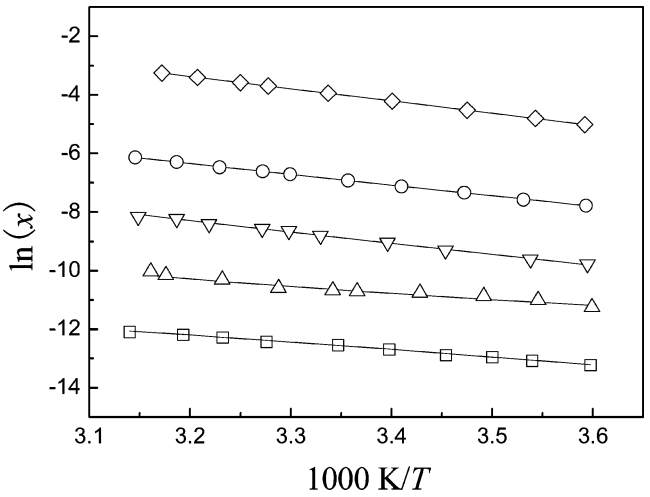

Figure 3. Mole fraction solubility of ceftriaxone disodium in five different pure solvents between 278 and 318 K: ◇, formamide; ○, methanol; ▽, *N*,*N*-dimethylformamide; △, ethanol; □, acetone. Full lines were calculated using Equation 2 with the parameters listed in Table 2.

in the solid state.[3] The hydroxyl group of methanol and ethanol can act as both hydrogen bond donor and acceptor, while the carbonyl group of acetone can act only as a hydrogen bond acceptor. It is then attractive to suggest that solvent molecules able to form hydrogen bonding to the functional groups exposed at ceftriaxone disodium crystal surface may accelerate the process of dissolution. Accordingly, the solubility in acetone is lower than that in methanol and ethanol. While the less alkyl of alcohol, the stronger polarity it has. So the solvency of methanol is higher than ethanol. Formamide can also act as both hydrogen bond donor and acceptor, while *N*,*N*-dimethylformamide can act only as a hydrogen bond acceptor. What is more, the polarity of formamide is higher than that of *N*,*N*-dimethylformamide. Thereby, ceftriaxone disodium is more soluble in formamide than *N*,*N*-dimethylformamide. The polarity of methanol is lower than that of *N*,*N*-dimethylformamide; however, methanol can act as both hydrogen bond donor and acceptor while *N*,*N*-dimethylformamide can act only as a hydrogen bond acceptor. This may be the reason that the solubility in methanol is higher than that in *N*,*N*-dimethylformamide. The above conclusions can be supported by the experimental results to some extent. Owing to the intermolecular hydrogen bonding and association phenomena, however, solubility of drugs in organic solvent is of much interest but more complicated, so further study is needed.

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