Solubility of Sodium Cefotaxime in Different Solvents

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The dissolution of sodium cefotaxime in 15 solvents were investigated. Only five solvents (formamide, *N*,*N*-dimethylformamide, dimethyl sulfoxide, water, and *N*-methylpyrrolidone) showed good solvency for the solid. The solubilities of sodium cefotaxime in *N*,*N*-dimethylformamide, formamide, and *N*-methylpyrrolidone were determined between the temperature range from (278.15 to 308.15) K, in water they were measured between (278.15 and 303.15) K, and in dimethyl sulfoxide they were determined between (293.15 and 308.15) K. A laser monitoring observation technique was used to determine the dissolution of the solid phase in a solid−liquid mixture. The solubilities of sodium cefotaxime in all solvents measured increase with temperature, and the solubilities of sodium cefotaxime also depend on the polarity of the solvent to some extent. The experimental solubility data were correlated with a semiempirical equation.

Introduction

Solubility is an important physicochemical property and is particularly useful in a wide variety of phenomena relevant to the chemical and pharmaceutical industries, such as the solvent selection for a reaction and for separation processes. Sodium cefotaxime salt is a broad spectrum third-generation cephalosporin antibiotic.[1−3] Until today, only solubility in some pure solvents such as methanol, ethanol, acetone, *n*-hexane, dichloromethane, diethyl ether, and ethyl acetate and binary 2-propanol + water solvent mixtures have been reported in the literature.[4,5] During manufacturing, to select the proper solvent and to design an optimized separation process for the pharmaceutical, it is necessary to know its solubility in more solvents. In this work, the solubilities of the title compound in *N*,*N*-dimethylformamide, formamide, *N*-methylpyrrolidone, water, and dimethyl sulfoxide were measured using a synthetic method.[6−14] A laser monitoring observation technique employing an isothermal method was introduced to determine the dissolution of the solute. In addition, the solubilities of sodium cefotaxime in dimethyl carbonate, toluene, isopropanol, *n*-butanol, isobutanol, benzyl alcohol, chloroform, pyridine, tetrahydrofuran, and 1,4-dioxane were also investigated in this work.

Experimental Section

Materials. A white crystalline powder of sodium cefotaxime ($C_{16}H_{16}N_5O_7S_2Na$, molecular weight 477.44, Figure 1) obtained from Shenzhen Jiuxin Pharmaceutical Co., Ltd., China, with a melting/decomposition point of 273.5 °C, measured using a NETZSCH DSC204 differential scanning calorimeter, was purified by recrystallization from methanol by a drowning out method with ethyl acetate as the anti-solvent. It was dried in vacuo at 40 °C for 24 h and stored in a desiccator. Its mass fraction purity, determined by HPLC, was better than 99.0 %. Agilent 1200 HPLC and Zorbax Eclipse XDB-C18 column (250 × 4.6 mm, 5 μm) were utilized. *p*-Acylaminophenol was employed as the internal standard. The mobile phase with a flow rate of 1.5 mL·min^{-1} was phosphate-buffered saline + methanol (75:25), and the UV detection was at 236 nm.

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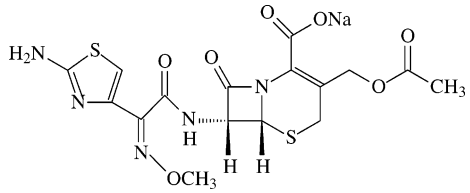

Figure 1. Chemical structure of sodium cefotaxime.

Table 1. Comparison of the Experimental Solubility (ω) of Potassium Chloride (1) in Water (2) with the Literature Data

	T/K					
	283.15	293.15	198.15	303.15	313.15	333.15
100 ω_1	23.82	25.56	26.36	27.12	28.62	31.19
100 ω_1 (ref 17)	23.83	25.55	26.34	27.14	28.57	31.21
relative deviation/%	0.04	−0.04	−0.08	0.078	−0.18	0.06

N,*N*-Dimethylformamide, formamide, *N*-methylpyrrolidone, dimethyl sulfoxide, dimethyl carbonate, toluene, isopropanol, 1-butanol, isobutanol, benzyl alcohol, chloroform, pyridine, tetrahydrofuran, and 1,4-dioxane (purchased from Tianjin Chemical Reagent Co., China) used for the experiments were of analytical reagent grade and were used without any treatment before use. Their mass fraction purities were better than 99.5 %. Distilled deionized water was also used.

Apparatus and Procedure. The solubility of sodium cefotaxime was measured by the isothermal method. The apparatus for solubility measurement is the same as that described in the literature[15,16] and is only briefly described here. A 100 mL jacketed vessel with water circulated from a water bath was used to determine the solubility; the temperature was controlled to be constant (fluctuates within 0.05 K) through the thermostated bath (type 501A, China). The dissolution of the solute was examined by the laser beam penetrating the vessel. The laser monitoring system consisted of a laser generator, a photoelectric transformer, and a light intensity display. Continuous stirring was achieved with a magnetic stir bar. To prevent the evaporation of the solvent, a condenser vessel was introduced. A mercury-in-glass thermometer with an uncertainty of 0.05 K was inserted into the inner chambers of the vessels for the measurement of the temperature. The masses of the samples and

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Table 2. Physical Properties of Solvents Used in This Work[a]

solvent	n_D^{20}	ρ/g·cm^{-3}	ϵ	η/mPa·s	γ/mN·m^{-1}
N,*N*-dimethylformamide	1.431	0.945	36.71	0.802	35.20
formamide	1.448	1.133	111.0	3.764	58.35
N-methylpyrrolidone	1.468	1.028	32.00	1.650	41.00
water	1.333	0.998	80.10	1.002	72.58
dimethyl sulfoxide	1.478	1.096	48.90	1.996	43.00
isopropanol	1.378	0.786	17.90	2.431	21.70
n-butanol	1.399	0.810	17.10 (298.15 K)	2.950	24.60
isobutanol	1.396	0.802	17.95	4.000	23.00
benzyl alcohol	1.540	1.046	13.10	7.760 (288.15 K)	40.41 (298.15 K)
chloroform	1.447	1.489	4.900	0.563	27.14
toluene	1.497	0.867	2.240	0.587	28.53
pyridine	1.510	0.983	12.40	0.952	36.88
1, 4-dioxane	1.422	1.034	2.250	1.300	36.90
tetrahydrofuran	1.407	0.889	7.580	0.550	26.40
dimethyl carbonate	1.370	1.073	2.600	0.625	28.90

[a] All values measured at 293.15 K, except where indicated. n_D^{20}, refractive index; ρ, density; ϵ, dielectric constant; η, viscosity; γ, surface tension.

Table 3. Mole Fraction Solubilities of Sodium Cefotaxime in Pure Solvents

T/K	$10^2 x_A^{exptl}$	$10^2 (x_A^{exptl} - x_A^{calcd})$	T/K	$10^2 x_A^{exptl}$	$10^2 (x_A^{exptl} - x_A^{calcd})$	T/K	$10^2 x_A^{exptl}$	$10^2 (x_A^{exptl} - x_A^{calcd})$
N,*N*-dimethylformamide			formamide			*N*-methylpyrrolidone		
278.15	4.0727	0.2117	278.15	4.8303	−0.2657	278.15	0.0254	−0.0816
280.15	4.1300	0.0570	280.15	5.0265	−0.2000	280.15	0.0935	−0.0565
283.15	4.3607	−0.0513	283.15	5.2955	−0.1335	283.15	0.1523	−0.0947
285.15	4.6185	−0.0340	285.15	5.6184	0.0470	285.15	0.1915	−0.1505
288.15	4.7428	−0.2932	288.15	5.9646	0.1726	288.15	0.2788	−0.2762
290.15	5.3743	0.0650	290.15	6.1517	0.2040	290.15	0.3829	−0.3791
293.15	5.6962	−0.0488	293.15	6.4359	0.2479	293.15	0.5241	−0.6929
295.15	6.0021	−0.0520	295.15	6.5158	0.1590	295.15	0.8686	−0.7884
298.15	6.6202	0.0732	298.15	6.7434	0.1254	298.15	1.1798	−1.4342
300.15	6.9022	0.0040	300.15	6.8772	0.0770	300.15	3.8016	0.2736
303.15	7.5678	0.1118	303.15	7.0191	−0.0669	303.15	7.3655	1.8685
305.15	7.8517	−0.0010	305.15	7.1863	−0.0980	305.15	8.2957	0.9367
308.15	8.4511	−0.0329	308.15	7.3271	−0.2669	308.15	10.297	−1.0344
water			dimethyl sulfoxide					
278.15	1.8026	−0.0074	293.15	7.3768	−0.0300			
280.15	1.8095	−0.0055	295.15	7.4391	−0.0270			
282.15	1.8216	0.0016	297.15	7.5085	−0.0200			
283.15	1.8304	0.0074	298.15	7.5490	−0.0130			
285.15	1.8351	0.0051	300.15	7.6973	0.0660			
287.15	1.8394	0.0010	302.15	7.7655	0.0630			
288.15	1.8415	−0.0005	303.15	7.7911	0.0511			
290.15	1.8539	0.0029	305.15	7.8328	0.0150			
292.15	1.8618	0.0008	307.15	7.8537	−0.0440			
293.15	1.8758	0.0088	308.15	7.8797	−0.0590			
295.15	1.8799	0.0019						
297.15	1.8851	−0.0049						
298.15	1.8884	−0.0086						

solvents were weighed using an analytical balance (Metler Toledo AB204-N, Switzerland) with an uncertainty of 0.0001 g.

During experiments, predetermined excess amounts of sodium cefotaxime and solvent of known mass were placed in the jacketed vessel. The contents of the vessel were stirred continuously at an invariable and required temperature, and the solvent was added to the vessel simultaneously in batches with the interval of addition of 30 min. The additional solvent of known mass was about 50 mg each batch. When the last portion of solute just disappeared, the intensity of the laser beam penetrating the vessel reached the maximum, and the solvent mass consumed in the measurement would be recorded. Together with the mass of the solute, the solubility would be obtained.

The saturated mole fraction solubility of the solute (x_1) in solvent can be obtained as follows:

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

In which m_1 and m_2 represent the mass of solute and solvent; M_1 and M_2 are the molecular weight of solute and solvent, respectively.

To verify the uncertainty of the measurement, one other experiment was done in which the solubility of KCl in water was measured. The solubility of potassium chloride in water in the literature[17] and in this paper are shown in Table 1. Considering other factors, the uncertainty of the experimental solubility values is about 0.5 %.

The results indicated the deviation between the literature values and the experiment values were less than 0.2 %. All determinations were repeated two more times, and the mean values were used to calculate the mole fraction solubility.

Results and Discussion

In this work, 15 solvents (as shown in Table 2) were employed to determine the dissolution behavior of sodium cefotaxime. The results indicate that most of the solvents selected in this paper including dimethyl carbonate, toluene, isopropanol, *n*-butanol, isobutanol, benzyl alcohol, chloroform, pyridine, tetrahydrofuran, and 1,4-dioxane are not good solvents for the title compound. The solubilities of sodium cefotaxime in them are less 0.0001 g of sodium cefotaxime per 100 g of solvent, and the values are too low to be detected by the method

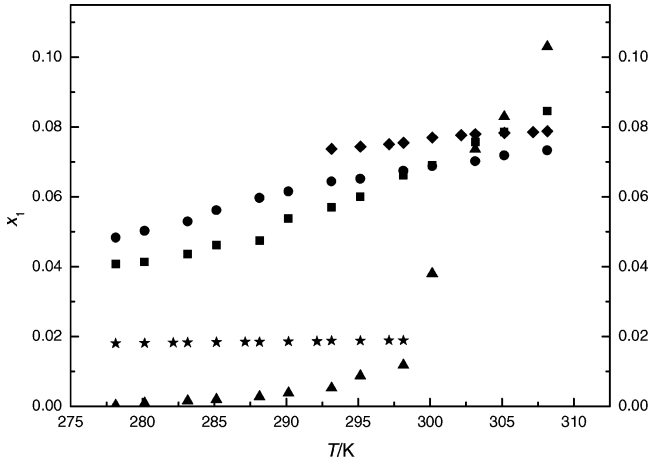

Figure 2. Mole fraction solubilities of sodium cefotaxime (x_1) in different solvents at different temperature ranges: ■, *N*,*N*-dimethylformamide; ●, formamide; ▲, *N*-methylpyrrolidone; ★, water; ◆, dimethyl sulfoxide.

used here. Only five solvents (formamide, *N*,*N*-dimethylformamide, dimethyl sulfoxide, water, and *N*-methylpyrrolidone) show good solvency for the solid. The solubility of sodium cefotaxime in *N*,*N*-dimethylformamide, formamide, *N*-methylpyrrolidone was determined between the temperature range from (278.15 to 308.15 K. However, to avoid decomposition of sodium cefotaxime in water at a higher temperature, the solubility of sodium cefotaxime in water was only measured between (278.15 and 303.15) K. At atmospheric pressure, the melting point of dimethyl sulfoxide is 291.69 K, and so the solubilities of sodium cefotaxime in dimethyl sulfoxide were only determined between (293.15 and 308.15) K.

The measured solubilities of sodium cefotaxime in the five pure solvents at different temperature range are listed in Table 3 and Figure 2. It can be seen that the solubilities of sodium cefotaxime in all five solvents increase with temperature. The solubilities of sodium cefotaxime in water increase slowly with temperature, and the change is almost negligible. In formamide, *N*,*N*-dimethylformamide, and dimethyl sulfoxide, the solubilities of sodium cefotaxime almost linearly increase with temperature. However, it is interesting that the solubilities of sodium cefotaxime in *N*-methylpyrrolidone display an exponential upward trend with the enhancement of temperature. Perhaps it can be attributed to the change of the interaction between the molecule of sodium cefotaxime and the molecule of *N*-methylpyrrolidone with the increase in temperature.

On the basis of the results, the solubility of sodium cefotaxime also depends on the polarity of the solvent to some degree. The solubility increases with the enhancement of the polarity of the solvent. From Table 2, it could be seen that the value[18] of dielectric constants of the five solvents that display good solvency for sodium cefotaxime all exceed 30 at 20 °C. In the other solvents investigated such as ethyl acetate, toluene and 1,4-dioxane, whose polarity is much lower, the solute is almost insoluble. The solid−liquid equilibrium behavior may be explained by discussing the interaction between the homogeneous solute, the solvent, and the heterogeneous molecules in solution.

The process of dissolution is determined by a combination of enthalpy and entropy factors. The chemical structure and the polarity also influence the dissolution of solute. If the interactions in the solute and solvent are similar, then the energy of interaction between homogeneous and heterogeneous molecules is nearly identical, which facilitates the dissolution of the molecules of the solute. If the chemical structures of the solute and solvent molecules differ greatly in polarity, then swelling and dissolution do not easily happen. This is reflected in the empirical rule that "like dissolves like".

Table 4. Curve-Fitting Parameters for Solubilities of Sodium Cefotaxime in Pure Solvents

solvent	*a*	*b*	*c*	$10^3\,\sigma_x$
N,*N*-dimethylformamide	−79.087	1427.3	12.562	1.18
formamide	−78.233	2336.7	11.879	1.82
N-methylpyrrolidone	−62.242	−8789.0	15.458	8.63
water	−77.230	3000.7	11.092	0.05
dimethyl sulfoxide	−76.484	2957.3	11.230	0.46

The molecule of sodium cefotaxime has a 2-amino-4-thiazolyl side chain and α-methoxyimino group, and its molecular possesses many polar groups such as amido, sulfonyl, and carbonyl groups(Figure 1). The interactions in the solute were not only van der Waals forces but also the hydrogen bond force. Therefore, it would require more energy to destroy the interaction between the solute molecules in order to disperse to the solvent. However, the interaction in the nonpolar solvents such as ethyl acetate, toluene, and 1,4-dioxane is mainly the van der Waals force. The interaction between nonpolar solvent molecules and solute molecules cannot offset the energy loss in destroying the normal interactions in solvent and sodium cefotaxime crystals. Therefore, the title compound in nonpolar solvents (ethyl acetate, toluene, and 1,4-dioxane in this study) are almost insoluble. However, in the strong polar solvents (*N*,*N*-dimethylformamide, formamide, *N*-methylpyrrolidone, water, and dimethyl sulfoxide in this paper), the interaction between the solvent molecules is mainly the hydrogen bond force. When sodium cefotaxime added to the solvent, the solute molecules and the solvent molecules could easily form intermolecular hydrogen bonding, and the interaction in the solute molecules would been broken. After the mixing of solute and solvent molecules, the total energy of the whole system does not change too much. So, the dissolubility of sodium cefotaxime in strong polar solvents is better than in nonpolar solvents. Owing to the insufficient polarity of isopropanol and chloroform, the solubility of sodium cefotaxime is very low.

Concerning the exponential upward trend of the solubilities of sodium cefotaxime in *N*-methylpyrrolidone, it is perhaps attributed to the special characteristic of the interaction of the solvent and the title compound. The probability of forming a molecular complex in solution may be another explanation for the sharp increase of the solubility of solute. But it should be pointed out that the above explanations are only one measure of many factors affecting the dissolution behavior. Further discussion of the dissolution of an organic solute in an organic solvent is complicated and beyond the scope of this article.

The temperature dependence solubilities in the five pure solvents were correlated by the semiempirical equation deduced from the solid−liquid phase equilibrium:[12,19]

$$\ln x_1 = a + \frac{b}{T/\mathrm{K}} + c\,\ln(T/\mathrm{K}) \tag{2}$$

in which x_1 is the mole fraction solubility of sodium cefotaxime; T is the absolute temperature; and a, b, and c are the parameters. The values of parameters a, b, and c and the root mean square deviations (rmsd) are listed in Table 4. The rmsd of the mole fraction is defined as follows:[20]

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

where n is the number of experimental points, x_i^{calcd} represents the solubilities calculated from eq 2, and x_i^{exptl} represents the experimental solubility values. It can be seen that the correlated solubilities show good agreement with the experimental values. In the meantime, it is noticeable that the rmsd for *N*-methylpyrrolidone presents a high value as compared to other solvents with the correlated equation used here.

Conclusions

(i) The solubilities of sodium cefotaxime in 15 solvents were investigated, and the results indicate that most of the solvents are not good solvents for the title compound. Only five solvents (formamide, *N*,*N*-dimethylformamide, dimethyl sulfoxide, water, and *N*-methylpyrrolidone) show good solvency for the solid.

(ii) The solubilities of sodium cefotaxime in the five solvents measured increase with temperature. The solubility of sodium cefotaxime also depends on the polarity of the solvent to some degree. The title compound is almost insoluble in nonpolar solvents.

(iii) The experimental solubility data were correlated with a semiempirical equation. The systems show satisfactory agreement between the experimental solubilities and the calculated values.

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