Solubility of Cefotaxime Sodium Salt in Seven Solvents Used in the Pharmaceutical Industry

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The solubility of cefotaxime sodium salt (sodium (7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)-acetamido]cephalosporanate) in methanol, ethanol, acetone, *n*-hexane, dichloromethane, diethyl ether, and ethyl acetate in the temperature range from 5 to 40 °C was determined.

Introduction

Cefotaxime sodium salt (cefotaxime) is a broad spectrum third-generation cephalosporin antibiotic. Since one of the last steps of the cefotaxime process production is its crystallization, the knowledge of cefotaxime solubility in different industrial solvents is important.

The Martindale Pharmacopoeia (Reynolds, 1989) lists cefotaxime as practically insoluble in organic solvents. However, according to a bibliographical search, there are no quantitative values of the cefotaxime solubility in these solvents.

We have measured the solubility of cefotaxime in seven organic solvents commonly used in the pharmaceutical industry. The solubility of cefotaxime in water was not studied since it decomposes in this solvent (Fabre, 1984).

Experimental Section

Methanol (Panreac, p.a.), absolute ethanol (Panreac, p.a.), acetone (Merck, p.a.), diethyl ether (Carlo Erba, for spectroscopy), ethyl acetate (Fluka, for spectroscopy), hexane (Merck, p.a.), and dichloromethane (Fluka, for IR spectroscopy) were used without further purification. Measured physical properties of solvents appear in Table 1.

Cefotaxime was supplied by Roussel, U.K. Cefotaxime was verified by HPLC (Merck-Hitachi L-4200), and the purity after recrystallization (98.54 mass %) was determined by HPLC according to U.S. Pharmacopoeia (1990).

Solubility measurements were made at 5, 10, 15, 20, 30, and 40 °C. Cefotaxime decomposes at temperatures higher than 40 °C (Cartensen, 1990). We verified by HPLC that cefotaxime did not decompose in the seven solvents used.

The cefotaxime concentration was determined by ultraviolet (235 nm) spectrometry with a UV spectrometer Biochrom 4060, Pharmacia LKB.

A mechanically stirred jacketed glass vessel (200 cm^3), protected from light, equipped with a thermometer, a reflux condenser, and a $CaCl_2$ trap, and closed by a glass plug, was used for the solubility studies. The temperature of the vessel was controlled by circulating thermostated water in the jacket, and it was kept constant. Temperature was measured with an accuracy of ±0.1 °C.

The contents of the vessel were stirred at 250 revolutions per minute. The mass of cefotaxime (about 2 g) was chosen to be in excess of the highest estimated solubility in the chosen solvents (150 cm^3). At each temperature, samples of supernatant (1 cm^3) were withdrawn from the stirred vessel after 45 min. Samples were filtered through a 0.45 μm (Sartorius, Switzerland) membrane to exclude solid cefotaxime. Each experiment was conducted in triplicate.

To evaluate the behavior of the cefotaxime dissolution process, two experiments were carried out in the same vessel used for determining the solubility. Samples at 5 and 40 °C were withdrawn from the vessel after elapsed

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Table 1. Physical Properties of Solvents Used in This Work[a]

	n^{20}_D		ρ/g·cm^{-3}		
solvent	lit.	exptl	lit.	exptl	moisture %
methanol	1.3288	1.3300	0.7914	0.7953	0.1
ethanol	1.3611	1.3614	0.7893	0.8102	0.2
acetone	1.3588	1.3589	0.7899	0.7910	0.2
diethyl ether	1.3526	1.3530	0.7138	0.7207	0.02
ethyl acetate	1.3723	1.3720	0.9003	0.9018	0.05
hexane	1.3751	1.3751	0.6603	0.6748	0.03
dichloromethane	1.4246	1.4240	1.3266	1.3188	0.02

[a] Moisture was determined by a Karl-Fischer titration. Literature data were taken from Potekhin (1984). n^{20}_D and ρ are the refractive index and the density at 20 °C.

Table 2. Average Values of the Cefotaxime Sodium Salt Solubility in Seven Organic Solvents Used in the Pharmaceutical Industry. Values of the Standard Deviations (*S*) Are in Parentheses

	solubility (g of cefotaxime per 100 g of solvent)					
t/°C	5	10	15	20	30	40
methanol	1.385 (0.053)	1.409 (0.089)	1.417 (0.047)	1.453 (0.032)	1.531 (0.059)	1.573 (0.062)
acetone	0.881 (0.055)	0.887 (0.051)	0.905 (0.032)	0.934 (0.062)	0.987 (0.063)	1.015 (0.039)
ethanol	0.195 (0.011)	0.216 (0.028)	0.264 (0.032)	0.307 (0.037)	0.379 (0.023)	0.429 (0.020)
ethyl acetate ethyl ether hexane dichloromethane	<10^{-4}					

Table 3. Values for the Van't Hoff Parameters α and β and the Correlation Coefficients (*r*) for eq 1

solvent	α	β	*r*
methanol	1.525 786	−335.843	0.989
acetone	1.254 569	−387.316	0.989
ethanol	5.344 643	−1928.300	0.987

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times of 1, 5, 10, 30, and 60 min, as well as after 2, 4, and 6 h. These experiments were repeated for all solvents. It was determined that after 30 min the concentration of cefotaxime remains constant.

Results and Discussion

Table 2 shows the average values of the solubility of cefotaxime in the solvents studied. Measurable concentrations of cefotaxime were not found in hexane, ethyl acetate, dichloromethane, and diethyl ether, for all temperatures studied. In this sense, if cefotaxime is dissolved by these solvents, its solubility is lower than 10^{-4} g of cefotaxime per 100 g of solvent. The solubility of cefotaxime increased with an increase in temperature.

The solubility of cefotaxime in methanol, acetone, and ethanol was correlated according to the van't Hoff equation

$$\ln C_S(\text{g}/100\text{ g solv}) = \alpha + \beta/T(\text{K}) \qquad (1)$$

where C_S is the solubility of cefotaxime and T is the temperature. Table 3 shows the values for the parameters α and β and the correlation coefficients. The slope β from the van't Hoff equation yields the standard heat of solution.

Registry Number Supplied by Authors. $C_{16}H_{16}N_5NaO_7S_2$: 64485-93-4.

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