Solubility and Density of the Disodium Salt Hemiheptahydrate of Ceftriaxone in Water + Methanol Mixtures

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The solubilities of the disodium salt hemiheptahydrate of ceftriaxone in different concentrations of methanol in water at (25, 35, and 45) °C are measured by using a gravimetrical method. The densities of the saturated solution are also determined with a digital densimeter (Anton Paar, model DMA 45) at corresponding temperatures. The solubility of the disodium salt hemiheptahydrate of ceftriaxone increases with increasing temperature but decreases with increasing concentration of methanol in the solution.

Introduction

For the synthesis and design of industrial separation processes, reliable knowledge of the phase equilibrium for the system to be separated is essential. In the extractive crystallization of salts,[1] the addition of organic solvents such as methanol to an aqueous solution normally decreases the solubility of a salt because of "salting out". This process has certain advantages over other methods of crystallization by cooling and evaporation because ambient temperature may be employed, producing crystals of high purity.

The disodium salt hemiheptahydrate of ceftriaxone is (6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,5-dioxo-*as*-triazin-3-yl)thio]-methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-caboxylic acid, 7^2-(*Z*)-(*O*-methyloxime), disodium salt, sesquaterhydrate. It is a third generation cephalosporin antibiotic. The disodium salt hemiheptahydrate of ceftriaxone is crystallized from mixed solvents in the purification step. To reduce the loss of salt in the mother liquor, the studies of phase equilibrium behavior including solubility data are important. Unfortunately, literature data of the solubility of the disodium salt hemiheptahydrate of ceftriaxone in aqueous + organic solvents are limited.

In continuation of our studies on the effect of organic solvents on the solubility of the disodium salt hemiheptahydrate of ceftriaxone in water,[2] the solubilities of the disodium salt hemiheptahydrate of ceftriaxone in different concentrations of methanol in water at (25, 35, and 45) °C were determined using a gravimetrical method. In addition, the densities of saturated solutions of the disodium salt hemiheptahydrate of ceftriaxone in the mixed solvents were measured at (25, 35, and 45) °C.

Experimental Section

Materials. In all experiments, distilled−deionized water was used. A white crystalline powder of the disodium salt hemiheptahydrate of ceftriaxone, with a melting/decomposition point of (235.6 ± 0.5) °C, was supplied by the Pharmaceutical Co. Ltd. of Hangzhou with a mass purity higher than 99.0 mass %, determined by Agilent 1100 HPLC according to the US Pharmacopoeia 24 (1999). It was dried in a vacuum oven at 40 °C for 24 h and stored in a desiccator to avoid adsorbing water. Methanol (HPLC grade, TEDIA) was dried with molecular sieves. The purity, checked by gas chromatography, was greater than 99.9 mass %. Methanol and water were used to prepare solvent mixtures in the range of methanol mass percents from 20% to 90% on a solute free basis.

Solubility Measurements. Glass-stoppered conical flasks with a Teflon-coated magnetic stirrer were used to prepare saturated solutions (about 50 cm^3) of the disodium salt hemiheptahydrate of ceftriaxone with excess solid solute (about 1 g) in water + methanol. The flasks were stoppered, sealed up with parafilms to prevent evaporation of solvents, and packed with aluminum foil to avoid sunlight. The flasks were then brought to a constant temperature (25, 35, and 45) °C in a thermostatic bath with an accuracy of ±0.05 °C. The experimental temperature was measured using a glass thermometer with ±0.02 °C accuracy. Undissolved solid was allowed to settle for about 24 h to ensure solid−liquid phase equilibrium before sampling. For each data point, three samples of approximately (3 to 7) cm^3 were withdrawn from the clear saturated solution using preheated glass syringes through a 0.2 μm membrane filter and put into sample vials (about 10 cm^3 capacity), which were previously weighed using a Sartorius type 1712 analytical balance with an accuracy of ±0.01 mg. Then the sample vials were closed with rubber plugs to prevent evaporation of the solvents during the weighing procedure, and the samples were allowed to come to room temperature. The masses of the sample vials with the saturated solution were measured. The plugs were removed, and the vials and plugs were placed in oven at 40 °C until the solvents were completely evaporated. The solid residues were then dried in a vacuum oven for 14 h at 40 °C, and the mass of the residues was determined.

The solubility *m* expressed in moles of solute per kilogram of solvent was calculated with the formula

$$m = \frac{1000(W_2 - W_1)}{(W_3 - W_2)M} \tag{1}$$

in which W_1 is the mass of the empty vial, W_2 is the mass

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Table 1. Solubility of the Disodium Salt Hemiheptahydrate of Ceftriaxone *m* in Water + Methanol at (25, 35, and 45) °C

$100w^a$	m /mol·kg^{-1}		
(methanol)	25 °C	35 °C	45 °C
90.0	0.0589 ± 0.0007	0.0626 ± 0.0015	0.0714 ± 0.0016
80.0	0.0757 ± 0.0005	0.0828 ± 0.0015	0.0991 ± 0.0008
70.0	0.1220 ± 0.0006	0.1295 ± 0.0013	0.1691 ± 0.0021
60.0	0.1937 ± 0.0018	0.2167 ± 0.0016	0.2819 ± 0.0031
50.0	0.2543 ± 0.0027	0.3139 ± 0.0044	0.3960 ± 0.0027
40.0	0.3274 ± 0.0017	0.3963 ± 0.0020	0.4924 ± 0.0024
30.0	0.4322 ± 0.0023	0.4807 ± 0.0029	0.5642 ± 0.0028
20.0	0.5223 ± 0.0037	0.5695 ± 0.0030	0.6278 ± 0.0035

[a] Mass fraction on a salt free basis.

Table 2. Densities ρ of the Saturated Solutions of the Disodium Salt Hemiheptahydrate of Ceftriaxone at (25, 35, and 45) °C in Water + Methanol

$100w^a$	ρ/g·cm^{-3}		
(methanol)	25 °C	35 °C	45 °C
90.0	0.8370 ± 0.0008	0.8390 ± 0.0067	0.8436 ± 0.0111
80.0	0.8681 ± 0.0007	0.8699 ± 0.0013	0.8813 ± 0.0124
70.0	0.9087 ± 0.0014	0.9113 ± 0.0031	0.9267 ± 0.0148
60.0	0.9545 ± 0.0016	0.9604 ± 0.0095	0.9845 ± 0.0256
50.0	0.9957 ± 0.0015	1.0087 ± 0.0015	1.0286 ± 0.0072
40.0	1.0424 ± 0.0025	1.0518 ± 0.0098	1.0793 ± 0.0082
30.0	1.0928 ± 0.0038	1.1066 ± 0.0045	1.1210 ± 0.0123
20.0	1.1417 ± 0.0015	1.1447 ± 0.0037	1.1518 ± 0.0004

[a] Mass fraction on a salt free basis.

of the vial plus the dry residue, and W_3 is the mass of the vial plus the saturated solution, respectively. M is the molecular weight of the solute (g·mol^{-1}).

Density Measurements. The oscillation period τ of the saturated solutions was determined by using a digital densimeter (Anton Paar, model DMA 45) at the corresponding temperatures controlled by circulation of the thermostatic bath. The temperature of thermostatic bath was measured using a glass thermometer with ±0.1 °C accuracy. For each solution, the oscillation period was determined three times.

The oscillation periods of the samples were converted into density by using following formula

$$\rho = \frac{\tau^2 - B}{A} \tag{2}$$

in which A and B are apparatus constants, which were calibrated with literature values of the densities of pure water and dry air at the corresponding temperatures. The estimated uncertainty of the measured density is ±0.0002 g·cm^{-3}.

Results and Discussion

It is important to select the drying temperature of the ceftriaxone sodium salt because it is hydrated. The dehydration temperature for the ceftriaxone sodium salt was determined using a thermal analyzer (DT-30, Shimadzu, Japan) in a nitrogen atmosphere from (30 to 350) °C at the rate 5 °C /min. The 0.25 mass % absorbed moisture of the total sample mass was driven off from (30 to 60) °C, and 9.4 mass % hydrates of the total sample mass was driven off from (60 to 155) °C. The sample decomposed at 235.6 °C. From this analysis, 40 °C was chosen as the drying temperature.

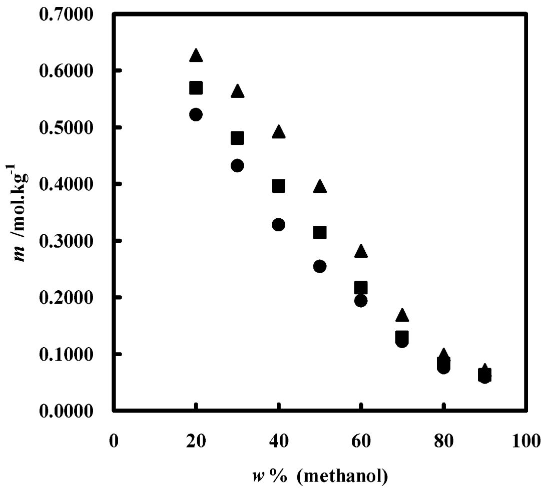

Figure 1. Solubility of the disodium salt hemiheptahydrate of ceftriaxone plotted against the mass fraction of methanol in water at different temperatures: ●, 25 °C; ■, 35 °C; ▲, 45 °C.

To check the reliability of the experimental method, known masses of the disodium salt hemiheptahydrate of ceftriaxone were completely dissolved in (30 and 80) mass % of ethanol at 20 °C, respectively. The solutions were dried in an oven until the solvents were completely evaporated. The solid residue was dried in vacuo at 40 °C for 12 h. The average relative deviations were 1.20% and 3.40%, respectively, which were obtained by comparing the known mass added with the remaining mass.

The solubility data of the disodium salt hemiheptahydrate of ceftriaxone in water + methanol at (25, 35, and 45) °C are given in Table 1. The solubility values in Table 1 are the average values taken from three flasks at the same composition of mixed solvent. The standard deviation for each point is given in Table 1. The relative uncertainty is higher in the ethanol-rich range because of lower solubility.

The densities ρ of the saturated solutions of the disodium salt hemiheptahydrate of ceftriaxone in water + methanol at (25, 35, and 45) °C are given in Table 2. The density values of the saturated solutions are the average values taken from three flasks at the same composition of mixed solvent.

From Figure 1, it can be seen that the solubility of the disodium salt hemiheptahydrate of ceftriaxone increases with increasing temperature but decreases with increasing concentration of methanol in the solution; this is similar to the case of literature data.[3]

CAS Registry Number Supplied by the Authors: $C_{18}H_{25}N_8Na_2O_{10.5}S_3$, disodium salt hemiheptahydrate of ceftriaxone, 104376-79-6.

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