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

Ming Zhu

Zhejiang Provincial Institute for Drug Control, Hangzhou, 310004, P. R. China

The solubilities of the disodium salt hemiheptahydrate of ceftriaxone in water + ethanol at (10, 20, and 30) °C are presented by using the gravimetrical method. The densities of the saturated solutions are also determined with a digital densimeter (Anton Paar, model DMA 45) at 30 °C. The solubility of the disodium salt hemiheptahydrate of ceftriaxone increases with temperature but decreases with increasing concentration of ethanol in the solution.

Introduction

Ceftriaxone is a third-generation cephalosporin of great therapeutical interest and is one of the most important parenterally applied antibiotics. The disodium salt hemiheptahydrate of ceftriaxone is crystallized from an aqueous solution of organic solvent, for example, ethanol (Xu et al., 1994) or acetone (Dankmaier et al., 1996), in the final purification step. To reduce loss of the ceftriaxone sodium in the mother liquor, it is worthwhile to investigate the phase equilibrium behaviors, for example, the solubility data, that were required in the synthesis and design of the crystallization process. Unfortunately, the solubility data of the disodium salt hemiheptahydrate of ceftriaxone in aqueous organic solvents are missing in the literature.

The aim of this work is to study the effect of ethanol on the solubility of the disodium salt hemiheptahydrate of ceftriaxone in water at (10, 20, and 30) °C by using the gravimetrical method. Meanwhile, the densities of the saturated solutions are determined at 30 °C.

Experimental Section

Materials. A white crystalline powder disodium salt hemiheptahydrate of ceftriaxone, with a melting/decomposition point of 235.6 ± 0.5 °C, was supplied by the pharmaceutical company in Hangzhou with a purity greater than 99.0 mass %, determined by HPLC according to the US Pharmacopoeia 24 (1999). It was dried in vacuo at 40 °C for 24 h and stored in a desiccator. Ethanol was dehydrated with the help of molecular sieves. The purity was greater than 99.8 mass %, checked by gas chromatography. Deionized water was distilled. Ethanol and water were used to prepare solvent mixtures in the range of ethanol mass percents from 30% to 90% on a solute-free basis.

Solubility Measurements. Glass-stoppered 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 + ethanol. The flasks were stoppered and sealed up with Parafilm to prevent evaporation of solvents, and then the flasks were brought to a constant temperature (10, 20, and 30 °C) in a thermostatic bath that is capable of maintaining the temperature within ±0.05 °C. The experimental temperature was measured using a glass thermometer with 0.02 °C accuracy. The solutions in the flasks were continuously stirred at least for 24 h to ensure solid−liquid phase equilibrium. Then, undissolved solid was allowed to settle at least for 8 h without stirring. According to the solubilities of the disodium salt hemihydrate of ceftriaxone in water + ethanol, approximately 3−7 cm^3 of the clear saturated solutions was sampled with a preheated syringe through a 0.2 μm membrane filter and put into a previously weighed sample vial (about 10 cm^3) using a Sartorius Type 1712 analytical balance with an accuracy of ±0.01 mg. After the sample vials were tightly closed by means of rubber plugs to ensure nonevaporation of the solvent during the weighing procedure and 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 were placed in an oven at 40 °C until the solvents in the vials were completely evaporated. Then, the solid residue was dried in vacuo at 40 °C for 12 h, and the mass of constant residue was weighed.

Table 1. Solubility C_S (g/kg solvent) of the Disodium Salt Hemihydrate of Ceftriaxone in Water + Ethanol

ethanol wt %	C_S/(g/kg solvent) 10 °C	20 °C	30 °C
28.72	124.193 ± 0.392	159.466 ± 0.837	201.844 ± 0.879
39.84	68.376 ± 0.273	91.917 ± 0.384	121.828 ± 0.490
50.35	35.141 ± 0.243	51.892 ± 0.273	71.833 ± 0.425
59.86	19.814 ± 0.272	28.402 ± 0.268	38.296 ± 0.213
68.44	10.381 ± 0.126	14.835 ± 0.257	21.184 ± 0.212
80.20	2.510 ± 0.083	4.418 ± 0.157	5.785 ± 0.146
84.48	1.808 ± 0.064	2.891 ± 0.095	3.252 ± 0.088
88.95	0.962 ± 0.037	1.199 ± 0.049	1.517 ± 0.060

The solubility C_S expressed in grams of solute/kilogram of solvent was calculated by the formula

$$C_S = 1000(W_2 - W_1)/(W_3 - W_2) \quad (1)$$

in which W_2 is the weight of the vial plus dry residue, W_1 is the weight of the empty vial, and W_3 is the weight of the vial plus the saturated solution.

Density Measurements. The densities of the mixed solvents without salts and the solutions saturated with salts were determined by using a digital densimeter (Anton Paar, model DMA 45) at 30 °C. The temperature of the measuring cell was controlled by a circulating thermostatic water bath. The temperature was measured using a glass thermometer with ±0.1 K accuracy.

10.1021/je000101c CCC: $20.00
Published on Web 01/06/2001

Table 2. Densities ρ (g/cm^3) of the Saturated Solutions of the Disodium Salt Hemihydrate of Ceftriaxone in Water + Ethanol at 30 °C

	ρ/(g/cm^3)			
ethanol wt %	pure solvents	10 °C	20 °C	30 °C
28.72	0.9528 ± 0.0003	0.9769 ± 0.0031	0.9995 ± 0.0052	1.0218 ± 0.0044
39.84	0.9324 ± 0.0002	0.9493 ± 0.0038	0.9684 ± 0.0040	0.9864 ± 0.0040
50.35	0.9101 ± 0.0003	0.9222 ± 0.0064	0.9344 ± 0.0049	0.9490 ± 0.0056
59.86	0.8883 ± 0.0003	0.8960 ± 0.0123	0.9039 ± 0.0085	0.9157 ± 0.0051
68.44	0.8683 ± 0.0002	0.8731 ± 0.0106	0.8774 ± 0.0152	0.8854 ± 0.0089
80.20	0.8399 ± 0.0003	0.8408 ± 0.0276	0.8422 ± 0.0300	0.8453 ± 0.0214
84.48	0.8292 ± 0.0002	0.8297 ± 0.0292	0.8306 ± 0.0274	0.8315 ± 0.0225
88.95	0.8177 ± 0.0002	0.8181 ± 0.0315	0.8190 ± 0.0333	0.8197 ± 0.0324

The oscillation period, τ, of the sample in the vibrating U-tube was converted into density by using the formula

$$\rho = (\tau^2 - B)/A \qquad (2)$$

in which A and B are apparatus constants, which were calibrated with the literature values of the densities of the pure water and dry air at 30 °C. The estimated uncertainty of the measured density is ±0.0002 g·cm^{-3}.

3. Results and Discussion

It is very important to select dried temperature because the ceftriaxone sodium salt is hydrated. The dehydrates of temperature and the melting/decomposition point for the ceftriaxone sodium salt were determined by using a thermal analyzer DT-30 (Shimadzu, Japan) in a nitrogen atmosphere from 30 to 350 °C at a rate of 5 °C/min. The 0.25% (wt) absorbed moisture of the total sample weight was driven off from 30 to 60 °C. The 9.40% (wt) hydrates of the total sample weight were driven off from 60 to 155 °C. The sample was decomposed at 235.6 °C.

According to the results above, 40 °C as dried temperature was chosen in this work. To prove the reliability of the experimental method, the known amounts 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 at 40 °C 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.

Table 1 lists the experimental values of solubility of the disodium salt hemiheptahydrate of ceftriaxone in the water + ethanol mixtures at (10, 20, and 30) °C. The composition of mixed solvents is given as the mass fraction of ethanol in water + ethanol on a solute-free basis. 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. Solubility of the disodium salt hemiheptahydrate of ceftriaxone increases with temperature but decreases with increasing concentration of ethanol in the solution; it is similar to literature data (Pino-García and Rasmuson, 1998).

The densities of mixed solvents without salts and solutions saturated with salts are given in Table 2. Density values of pure solvents represent the average value of four samples at the same composition. But density values of solutions saturated with salts are the average value taken from three flasks at the same composition of mixed solvent.

CAS Registry Number Supplied by Author: $C_{18}H_{18}N_8Na_2O_7S_3 \cdot 3^1/_2H_2O$, disodium salt hemiheptahydrate of ceftriaxone, 74573-69-1.

Literature Cited

Danklmaier, J.; Macher, I.; Prager, B. Process for the synthesis of the disodium salt hemiheptahydrate of ceftriaxone. United States Patent No. 5574155, 1996.

Pino-García, O.; Rasmuson, Å. C. Solubility of Lobenzarit Disodium Salt in Ethanol−Water Mixtures. *J. Chem. Eng. Data* **1998**, *43* (4), 681−682.

Xu, S.; Lu, L.; Jiang, Y.; Li, J.; Zhu, B.; Yu, N. Synthesis of disodium salt of ceftriaxone. *Zhongguo Kangshengsu Zazhi* **1994**, *19* (2), 124−127.

Received for review April 5, 2000. Accepted September 7, 2000. This work was sponsored by the Scientific Research Foundation for the Returned Overseas Chinese Schlars.

JE000101C