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Solubility of Lobenzarit Disodium Salt in Ethanol−Water Mixtures

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The solubility of lobenzarit disodium salt in water + ethanol at (15, 30, and 50) °C is reported. At each temperature, the solubility of lobenzarit disodium decreases with increasing ethanol concentration, and all three curves exhibit an inflection point in the region of 25−45 mass % of ethanol.

Introduction

Solubility data of bioactive compounds have a broad application and importance in the pharmaceutical industry. A variety of pure solvents, including water, and solvent mixtures (e.g., binary, ternary mixtures) can usually be employed in a particular crystallization process during manufacturing of pharmaceuticals (Grant and Higuchi, 1990).

A powerful antiarthritic agent (Budavari, 1989), the lobenzarit disodium salt, $C_{14}H_8ClNNa_2O_4$, disodium *N*-(2-carboxyphenyl)-4-chloroanthranilate (CCA), is produced by neutralization of lobenzarit acid ($C_{14}H_{10}ClNO_4$) with aqueous NaOH solution and precipitated with ethanol (Pellón, 1992; Pellón et al., 1993). A few solubility data of CCA and its intermediate lobenzarit acid in pure solvents at 20 °C have been reported previously (Suzuki et al., 1984). Jáuregui-Haza et al. (1995) measured CCA solubility in water in the temperature range 5−80 °C using UV spectrometry. In the present work, solubility data for CCA in water + ethanol are reported for the temperature range 15−50 °C.

Experimental Section

The solubility of CCA in ethanol−water mixtures at (15, 30, and 50) °C has been determined gravimetrically. A white light-yellow CCA, with a melting/decomposition point of 388 °C, produced and purified at the Center of Pharmaceutical Chemistry in Havana (Pellón, 1992; Pellón et al., 1993), was used. The CCA fine powder had a minimum purity of 99.64 mass %, determined by HPLC and acid−base nonaqueous titration using tetrahydrofuran + diethylether as solvents and bromophenol blue as indicator (Suzuki et al., 1984). Ethanol (Solveco Chemicals AB, Sweden; 96 mass % of ethanol) and distilled water were used to prepare 17 binary solvent mixtures in the range of ethanol mass fractions from 0 to 0.96.

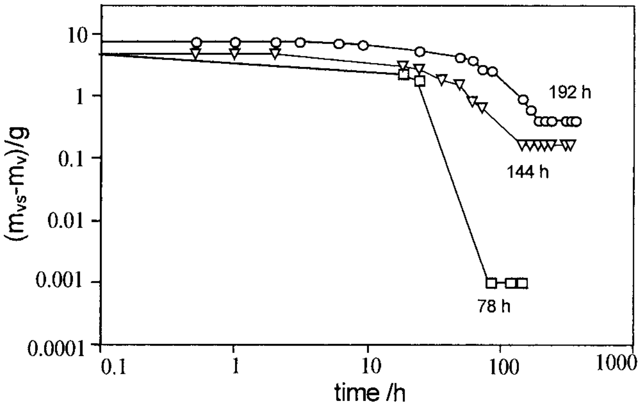

Figure 1. Drying curves (log−log scale) at 40 °C of solution samples saturated at 50 °C in (○) 0; (▽) 24; (□) 96 mass % of ethanol.

Table 1. Solubility C_S (g/kg solvent) of Lobenzarit Disodium in Water (1) + Ethanol (2)

	t/°C		
$100w_2$	15	30	50
0.0	39.25 ± 0.76	45.61 ± 0.72	53.27 ± 0.42
4.8	35.02 ± 1.13	37.95 ± 1.50	46.38 ± 1.52
9.6	29.25 ± 1.05	32.92 ± 1.52	43.08 ± 0.83
12.0	26.63 ± 1.08	30.93 ± 1.32	40.15 ± 1.53
14.4	24.93 ± 1.00	28.55 ± 1.25	
16.8	22.95 ± 1.06	26.83 ± 1.82	37.83 ± 0.52
19.2	21.88 ± 0.94	25.04 ± 1.76	36.71 ± 0.57
24.0	20.43 ± 1.04	23.78 ± 1.87	34.81 ± 1.25
28.8	19.97 ± 1.00	23.42 ± 1.91	34.21 ± 0.85
33.6	19.88 ± 1.01	22.24 ± 2.50	32.87 ± 0.48
38.4	18.82 ± 1.01	20.85 ± 2.57	32.56 ± 0.19
48.0	16.27 ± 0.97	18.00 ± 2.14	26.11 ± 0.66
57.6	10.63 ± 0.91	13.16 ± 0.33	17.09 ± 0.01
67.2	5.62 ± 0.29	7.37 ± 0.09	10.70 ± 0.13
76.8	1.91 ± 0.16	2.96 ± 0.37	3.69 ± 0.15
86.4	0.79 ± 0.05	0.93 ± 0.13	0.99 ± 0.09
96.0	0.25 ± 0.05	0.24 ± 0.05	0.23 ± 0.14

The experimental setup consists of a thermostated water bath standing on a serial magnetic stirrer. Round-bottomed glass tubes with a Teflon-coated magnetic stirrer, filled with excess solute (about 3 g), and the respective solvent mixture (about 45 cm^3) are used to prepare saturated solutions. The tubes are put under plastic cover and sealed up with parafilm to prevent evaporation losses. Each tube is immersed in the water bath, and the suspension is continuously stirred at the selected constant bath temperature (15, 30, or 50 ± 0.05 °C). At least 96 h is allowed to ensure that equilibrium is reached. Then, undissolved residue is allowed to settle for at least 12 h at constant temperature without stirring. A sample of the clear saturated solution (approximately 5 cm^3) is transferred with a preheated syringe through a 0.45 μm membrane filter into a previously weighed sample vial with mass m_v. The vials had teflon septums to ensure nonevaporation of the solvent during the weighing procedure. The mass of the sample vial with the saturated solution,

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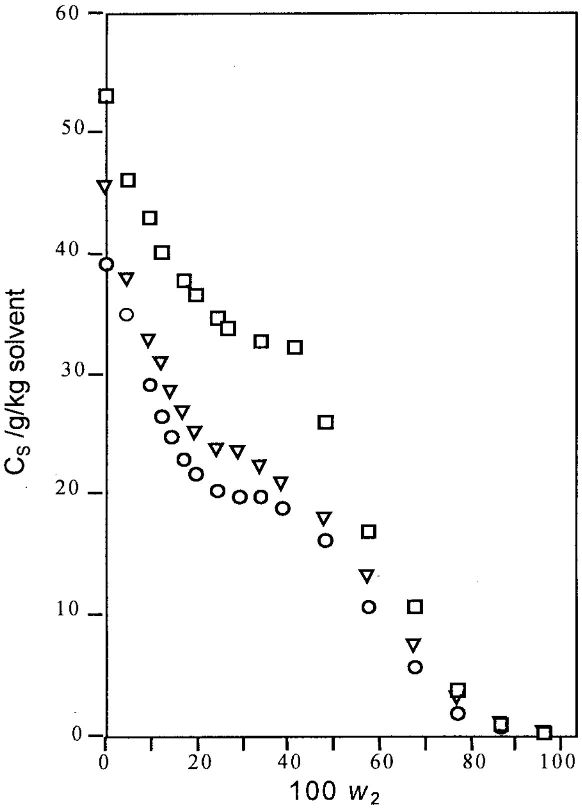

Figure 2. Solubility C_S of lobenzarit disodium salt in ethanol–water mixtures as a function of mass fractions w_2 of ethanol in the solvent mixture at (○) 15, (▽) 30, and (□) 50 °C.

m_{vs}, is measured. Then, the septums are removed, and the solvent is allowed to evaporate in an air oven at 40 °C for approximately 8 days. After that the solid residue is placed in a vacuum desiccator, and the constant "dry residue" mass, m_{vdr}, is determined.

The solubility concentration, expressed in g solute/kg solvent, is then calculated by the following equation:

$$C_S = 10^3\,(m_{vdr} - m_v)/(m_{vs} - m_{vdr}) \tag{1}$$

Results and Discussion

Figure 1 presents the drying curves of three different samples. The time needed to achieve the constant mass increases with increasing water concentration. This concentration leads to decreasing vapor pressure and an increasing amount of solid residue, from which the solvent evaporation may be slower. In the case of 96% ethanol, constant mass is reached after about 78 h. In the case of pure water, at least 192 h is needed. In this study, all samples are dried for at least 192 hours and until the remaining mass of the sample does not change with time. The experimental procedure has been proved as follows. Weighed precise amounts of CCA, with the known purity (above), are completely dissolved at 50 °C in pure water and in ethanol (96 mass % of ethanol), respectively. The solutions are then dried in the air oven at 40 °C for 8 days. The remaining mass differs from the original mass of CCA by 0.06 and 1.43%, respectively. In addition, no further mass loss is found if the drying is continued at 100 °C for 72 h, and lobenzarit disodium is not known to exhibit hygroscopic properties (Suzuki et al., 1984).

Table 1 lists experimental CCA solubilities in the 17 ethanol–water mixtures studied. The solvent mixture composition, w_2, is given as the fraction of ethanol in the ethanol–water mixture on a solute-free basis. Solubility values, C_S, represent the average value of samples taken from three different tubes. One to three samples from each tube have been analyzed, and the average solubility value of all samples from all tubes having the same solvent mixture composition is reported. The corresponding range of confidence on the 95% level is reported for each mean value. The relative uncertainty is higher in some cases because of the lower mass that is dissolved in the sample. The solubilities in pure water at 15, 30, and 50 °C deviate about 3% or less from the values obtained by the correlation given by Jáuregui-Haza et al. (1995). Solubility of CCA increases with temperature but decreases with increasing concentration of ethanol in the solution. The solubility curves (Figure 2) exhibit inflection points in the region of 25–45 mass % of ethanol.

Registry Number Supplied by Author. $C_{14}H_8ClNNa_2O_4$, 64808-48-6.

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