Solubility of Captopril in 2-Propanol, Acetone, Acetonitrile, Methyl Acetate, Ethyl Acetate, and Butyl Acetate

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The solubility of captopril in 2-propanol, acetone, acetonitrile, methyl acetate, ethyl acetate, and butyl acetate was measured by a synthetic method over the temperature range of (278.15 to 313.15) K at atmosphere pressure. The results show that the solubility of captopril increases with increasing temperature. The experimental data were correlated with the van't Hoff equation, and the agreement was very good.

Introduction

Captopril (CAS No. 62571-86-2, Figure 1), with a molecular formula of $C_9H_{15}NO_3S$, is an orally active angiotensin-I converting enzyme inhibitor and is used in the treatment of hypertension and congestive heart failure. Captopril is considered a drug of choice in antihypertensive therapy because of its effectiveness and low toxicity. Captopril, which is water-soluble, is usually prescribed to patients who are chronically ill and require long-term use for its therapeutic benefits.[1]

The crystallization step plays an important role in the purifying process of captopril, and the determination of its solubility in different solvents is crucial for the solvent selection and process optimization.[2] However, no experimental solubility data of captopril were found in the literature.

In this work, the solubility data of captopril in 2-propanol, acetone, acetonitrile, methyl acetate, ethyl acetate, and butyl acetate over the temperature range of (278.15 to 313.15) K at atmospheric pressure were determined using a synthetic method. At the same time, the enthalpy of dissolution for the captopril/organic solvent system was calculated by the parameter *B*. The results can be used in the purification process of captopril.

Experimental Section

Materials. A white crystalline powder of captopril, with a mass fraction purity of 0.99, was supplied by Huahai Pharmaceutical of China. All of the organic solvents were of analytical reagent grade, purchased from Tianjin Kewei Chemical Reagent Co. Ltd. of China.

Apparatus and Procedure. The solubility of captopril in different pure solvents was measured with a synthetic method.[3,4] The apparatus and the procedure for the measurement are similar to those described in the literature.[5]

The saturated mole fraction of the captopril *x* in different organic solvents can be calculated by the following eq 1:

$$x = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m_1 and m_2 represent the mass of the solute and solvent. M_1 and M_2 are the molecular weight of the solute and solvent, respectively. All experiments were repeated three times at each temperature to check the repeatability in this work, and the estimated uncertainties of the experimental values were about 2 %. The uncertainty in the solubility values can be due to uncertainties in the temperature measurements and weighing procedure and instabilities of the water bath.

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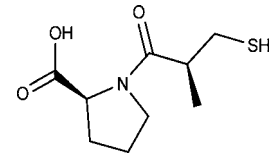

Figure 1. Chemical structure of captopril.

Results and Discussion

The solubility data of captopril in different solvents at different temperatures are listed in Table 1. The temperature dependence of captopril solubility was correlated by the following van't Hoff equation:[6]

$$\ln(x) = A + \frac{B}{T/\mathrm{K}} \tag{2}$$

where *x* is the average mole fraction solubility of captopril for three times, *T* is the temperature in K, and *A* and *B* are the parameters of the equation.

The parameters *A* and *B* were listed in Table 2 together with the root-mean-square deviation. So the enthalpy of dissolution for captopril in organic solvents can be calculated by the relation of $\Delta H_{diss} = -(B \cdot 8.3143)/1000$. The root-mean-square deviation (rmsd) is defined as:

$$\mathrm{rmsd} = \sqrt{\frac{\sum_{i=1}^{N} (x_i - x_i^{calcd})^2}{N}} \tag{3}$$

where *N* is the number of experimental points and x_i and x_i^{calcd} represent the average experimental and calculated values of the solubility, respectively.

From data listed in Table 1, it can be seen that within the temperature range of the measurements, the solubility of captopril increased with the increasing temperature in all six organic solvents .The calculated solubilities show good agreement with the experimental values. The principle "like dissolves like" could, to a certain extent, explain the solvency difference of acetic acid ester solvents.

10.1021/je900401z CCC: $40.75
Published on Web 10/27/2009

Table 1. Experimental Solubility (x) of Captopril in Different Solvents from (278.15 to 313.15) K

2-Propanol			Acetone			Acetonitrile		
T/K	$10^2\ x$	$100(x - x^{cal})/x$	T/K	$10^2\ x$	$100(x - x^{cal})/x$	T/K	$10^2\ x$	$100(x - x^{cal})/x$
278.15	3.146	–0.853	278.15	2.724	6.307	278.15	0.912	6.810
283.15	4.014	–1.923	283.15	3.370	4.148	283.15	1.294	5.994
288.15	5.157	–1.395	288.15	4.090	0.878	288.15	1.814	5.172
293.15	6.564	–0.968	293.15	4.980	–1.387	293.15	2.454	2.098
298.15	8.445	1.323	298.15	6.079	–2.673	298.15	3.223	–2.981
303.15	10.56	1.477	303.15	7.539	–1.638	303.15	4.379	–3.599
308.15	12.91	0.179	308.15	9.277	–0.726	308.15	6.059	–1.309
313.15	15.75	–0.666	313.15	11.49	1.459	313.15	8.349	1.476
Methyl Acetate			Ethyl Acetate			Butyl Acetate		
T/K	$10^2\ x$	$100(x - x^{cal})/x$	T/K	$10^2\ x$	$100(x - x^{cal})/x$	T/K	$10^2\ x$	$100(x - x^{cal})/x$
278.15	1.484	5.875	278.15	0.615	5.194	278.15	0.462	5.162
283.15	1.843	4.208	283.15	0.777	3.234	283.15	0.580	3.954
288.15	2.238	1.111	288.15	0.958	–0.279	288.15	0.710	1.221
293.15	2.716	–1.353	293.15	1.213	–0.456	293.15	0.868	–0.930
298.15	3.324	–2.252	298.15	1.513	–1.273	298.15	1.066	–1.893
303.15	4.084	–2.053	303.15	1.885	–1.454	303.15	1.311	–2.040
308.15	5.037	–0.805	308.15	2.356	–0.600	308.15	1.619	–1.022
313.15	6.243	1.553	313.15	2.946	0.981	313.15	2.019	1.557

Table 2. Parameters of van't Hoff Equation for Captopril in Different Solvents

solvents	A	$10^3\ B$	10^4 rmsd
2-propanol	10.95	−4.004	9.0
acetone	9.662	−3.708	12
acetonitrile	15.54	−5.649	11
methyl acetate	8.983	−3.687	7.0
ethyl acetate	9.263	−4.008	2.2
butyl acetate	8.091	−3.761	2.1

It is known that the solvent used in the crystallization process determines the crystal form and quality of the product. To obtain the required captopril quality, different solvents would be used. According to the dissolution characteristics of captopril in different solvents, different crystallization methods will be established. From Table 1, it can be seen that the solubility of captopril obviously varied with the temperature change in 2-propanol, acetone, acetonitrile, methyl acetate, ethyl acetate, and butyl acetate, so the cooling crystallization is a good choice. However, the solubility of captopril in 2-propanol and acetone is too large, while acetonitrile is toxic and expensive. Then, acetic acid ester is selected as a purifying solvent.

Acknowledgment

The authors are very grateful to Huahai Pharmaceutical Co. Ltd. of China for supplying the experimental material of captopril.

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Received for review May 6, 2009. Accepted October 12, 2009.

JE900401Z