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Solubility of Imperatorin in Ethyl Acetate, Ethanol, Methanol, *n*-Hexane, and Petroleum Ether from (278.2 to 318.2) K

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ABSTRACT: The solubility of imperatorin in ethyl acetate, ethanol, methanol, *n*-hexane, and petroleum ether was measured at temperatures ranging from (278.2 to 318.2) K at atmospheric pressure. The solubility of imperatorin in the above solvents decreased in the order ethyl acetate > methanol > ethanol > *n*-hexane and petroleum ether. The solubility data were well correlated with a modified Apelblat equation.

INTRODUCTION

Imperatorin, also called as ammidin or 8-iaoamylenoxypsoralen, of chemical name 9-(3-methylbut-2-enoxy)-7-furo[3,2-*g*] chromenone ($C_{16}H_{14}O_4$, CASRN 482-44-0, Figure 1) is a furocoumarin and a phytochemical isolated from traditional Chinese herbs such as *Cnidium monnieri Cuss*, *Aralia cordata Thumb*, or Angelica *dahurica*. Imperatorin has many medical effects such as anticonvulsant, antiinflammatory, antitumor, antibacterial, and anticoagulant activities.[1,2] Furthermore, imperatorin induces vasodilatation via inhibiting voltage-dependent calcium channels and receptor-mediated Ca^{2+} influx and release.[3]

For pharmaceutical use, imperatorin is usually extracted from plant matrices using solvents such as alcohol, followed by further purification.[4,5] Chen and his co-workers reported supercritical fluid extraction of imperatorin and isoimperatorin from *Angelica dahurica* and developed a new HPLC method of simultaneously detecting them.[6] Recently, preparative HPLC has also been reported to be an effective technology for the separation of imperatorin and other coumarins.[7] But crystallization from solution is still widely used to obtain high purity products. Therefore it is important to determine solubility data for imperatorin in different solvents.

In this work, the solubility of imperatorin in ethyl acetate, ethanol, methanol, *n*-hexane, and petroleum ether at temperatures ranging from (278.2 to 318.2) K at atmospheric pressure was measured. The solubility data were fitted by the modified Apelblat equation.

EXPERIMENTAL SECTION

Reagents and Apparatus. Imperatorin of pharmaceutical purity grade (more than 99.0%) was a kind gift from the Kunming Longjing Pharmaceutical Co., Ltd. (Yunnan, China). It was dried in a vacuum at 45 °C for 12 h before use. Other reagents were analytical grade reagents from the Hangzhou Chemical Reagent Factory (Hangzhou, China). The methanol used as the solvent of the mobile phase was purchased from Merck for HPLC analysis. Redistilled deionized water was used throughout.

A THZ-C shaker was supplied by the Taicang Laboratorial Equipment Factory (Hangzhou, China), and an HPLC Instrument (Agilent 1200) coupled with a UV detector was used for analysis of the samples.

Sample Preparation. In this experiment, the solubility measurements were carried out by adding an excess amount of imperatorin to a stirred solution kept at a fixed temperature. At the beginning, predetermined amounts of solvent (about 50.0 mL) were loaded into a specially designed sealed dual-wall flask, and then an excess amount of imperatorin was transferred into the solvent. The solution was constantly stirred using a magnetic stirrer for 12 h. The temperature of the circulating water was controlled by a thermostat within ±0.1 K. After attaining equilibrium, the stirrer was turned off to let the solution settle for 2 h. Then the upper portion was taken, filtered, and diluted to an appropriate concentration for HPLC analysis.[8] The uncertainty of the solubility values was estimated to be less than % 1. An average value was taken from three measurements for each temperature.

Sample Analysis. The HPLC system was equipped with a quaternary pump, online degasser, column heater, autosampler and a UV detector. Data collection and analysis were treated by ChemStation software (Agilent Technologies, Wilmington, DE). The chromatographic column was a Lichrospher C_{18} column (250 mm × 4.6 mm i.d., 5.0 μm particle size) from Hanbang Science & Technology (Jiangsu, China) coupled with an Agilent C_{18} precolumn (4 mm × 5 mm). The column temperature was maintained at 25 °C, and the injection volume of sample was 10 μL. The mobile phase consisted of methanol and water with gradient. The gradient elution of the mobile phase was 80% (methanol) in (0 to 5) min, (80 to 68)% in (5 to 7) min, and 68% in (7 to 10) min. The calibration curve for imperatorin was established by using the standard solutions in an appropriate concentration range of (5.07 to 101.4) $mg \cdot L^{-1}$.

RESULTS AND DISCUSSION

The solubility values of imperatorin in ethyl acetate, ethanol, methanol, *n*-hexane, and petroleum ether at different temperatures are presented in Table 1. The solubility of imperatorin in ethyl acetate is the highest, whereas those in petroleum ether and *n*-hexane are the lowest.

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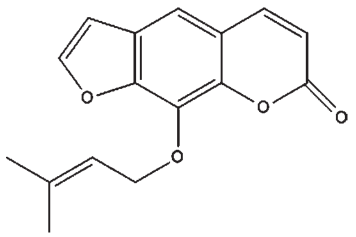

Figure 1. Molecular structure of imperatorin.

Table 1. Solubility (c) of Imperatorin in Ethyl Acetate, Ethanol, Methanol, n-Hexane, and Petroleum Ether from (278.2 to 318.2) K

T/K	10^3c / mol·L^{-1}	$10^2(c - c^{calc})/c$	T/K	10^3c / mol·L^{-1}	$10^2(c - c^{calc})/c$
	Ethyl Acetate			Ethanol	
278.2	61.38	1.63	278.2	4.442	0.79
283.2	62.31	−0.71	283.2	4.930	−3.46
288.2	69.86	5.27	288.2	5.691	−6.67
293.2	69.53	−1.73	293.2	7.454	0.48
298.2	76.54	−0.34	298.2	8.815	−5.33
308.2	96.29	3.58	308.2	16.28	4.58
318.2	117.8	0.40	318.2	26.67	−5.36
	Methanol			n-Hexane	
278.2	11.70	0.27	278.2	1.462	−1.26
283.2	12.60	−0.38	283.2	1.748	6.23
288.2	13.39	−4.22	288.2	1.903	3.43
293.2	15.18	−3.15	293.2	2.104	0.98
298.2	18.15	1.74	298.2	2.426	1.62
308.2	24.43	1.11	308.2	3.222	0.01
318.2	33.58	−2.40	318.2	4.660	3.49
	Petroleum Ether				
278.2	1.317	0.88			
283.2	1.557	−1.93			
288.2	1.962	2.18			
293.2	2.300	−0.54			
298.2	2.712	−2.32			
308.2	4.069	2.86			
318.2	5.491	−1.06			

Table 2. Parameters of eq 1 for Imperatorin in Different Solvents

solvent	A	B	C	10^3 rmsd
ethyl acetate	−344.9	13952	51.87	2.0105
ethanol	−714.3	28024	108.05	0.2383
methanol	−447.7	17667	67.47	0.3046
n-hexane	−341.1	12785	51.28	0.0011
petroleum ether	−48.52	−831.84	51.28	0.0585

The experimental data show that the solubility of imperatorin in five solvents increases with increasing temperature. Thus the temperature dependence of imperatorin solubility in pure solvents can be correlated by the modified Apelblat equation.[9,10]

$$\ln(c/\text{mol}\cdot\text{L}^{-1})) = A + B/(T/\text{K}) + C\ln(T/\text{K}) \quad (1)$$

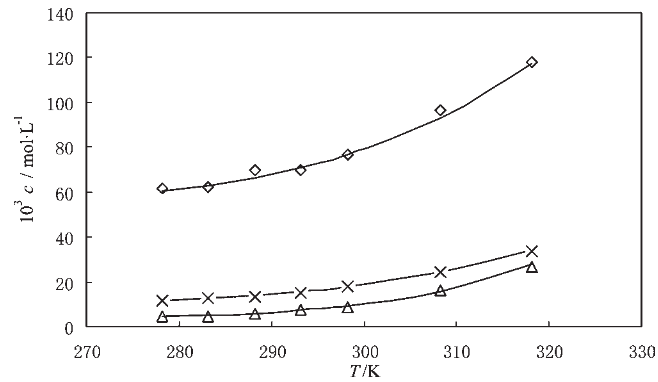

Figure 2. Solubility of imperatorin in three solvents: □, ethyl acetate; ×, methanol; △, ethanol; —, calculated by eq 1.

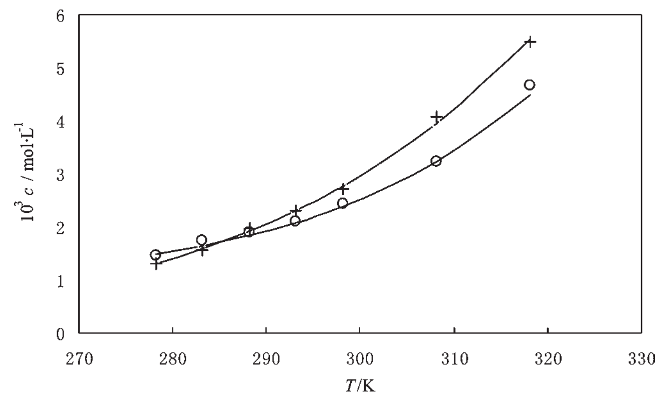

Figure 3. Solubility of imperatorin in two solvents: +, petroleum ether; ○, n-hexane; —, calculated by eq 1.

where c is the molar solubility of imperatorin, T is the absolute temperature, and A, B, and C are the parameters of the equation. The values of parameters A, B, and C and the root-mean-square deviations (rmsd) are listed in Table 2. The rmsd is defined as

$$\text{rmsd} = \sqrt{\frac{\sum_{i=1}^{N}(c_i^{calc} - c_i)^2}{N}} \quad (2)$$

where N is the number of experimental points and c_i^{calc} and c_i represent the solubility calculated and the experimental solubility values, respectively. Figures 2 and 3 show the calculated solubility of imperatorin at different temperatures together with the experimental values.

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