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Solubility of naringin in ethanol and water mixtures from 283.15 to 318.15 K

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ABSTRACT

The solubility of naringin in the binary system of ethanol and water was measured by using UV spectrophotometric method at the maximum absorption wavelength (UV = 283 nm) from 283.15 K to 318.15 K under atmospheric pressure. The solubility increases with the increasing temperature and in the solvent system it exhibits a synergistic effect. The modified Apelblat model was applied to correlate the experimental solubility data, and the calculated solubilities were in good agreement with the experimental results. The process of the dissolution of naringin was always endothermic, and was influenced by two mechanisms which are enthalpy-driven and entropy-driven. Non-linear enthalpy–entropy compensation was found for naringin in the binary system of ethanol and water.

1. Introduction

Naringin ($C_{27}H_{32}O_{14}$, CAS 10236-47-2) is a double-hydrogen flavonoids compound, its chemical name is naringenine-7-rhamnosidoglucoside (structure is shown in Fig. 1). There are studies that have found that the solubility of naringin is poor, which leads to low bioavailability and hinders further studies on its pharmacological actions [1]. At present, many investigations have sought to find some ways to increase the solubility of naringin to improve its bioavailability, which include the synthesis of naringin inclusion complexes, for instance, beta-cyclodextrin (β-CD) complexation could significantly increase the solubility of naringin [2], adding the flavonoids as a compatibilizer [3], and the preparation of an appropriate dosage form such as solid dispersion [4].

Naringin has been widely researched. Naringin shows the ability of an antioxidant [5,6], as well as its anti-inflammatory [5,7], anti-cancer (breast cancer) [8], anti-allergic [9], and anti-diabetic activities [10,11]. Recently, naringin has been demonstrated that it is able to enhance anti-angiogenesis activity [12,13]. More recently, a study found that naringin could effectively inhibit osteoclastogenesis and mature osteoclasts in vitro and in vivo [14]. In addition, the study also suggested that naringin which strongly inhibits polymethyl methacrylate (PMMA) particles induced osteolysis in vivo [14,15].

The drug solubility affects the drug efficacy directly. Having a detailed understanding for the drug solubility in common solvents can contribute to correct design and application of drug dosage forms to enhance absorption and bioavailability. Consequently, the solubility evaluation of naringin is very important for its further study. In the pharmaceutical industry solvent mixing is a simple, efficient, most frequent and feasible solubilization method. Water and ethanol are commonly used solvents for extracting active ingredients from plants for their safety. However, there is no investigation about the solubility of naringin in the binary system of ethanol and water at different temperatures so far. In our study, the solubility of naringin and its dissolution process thermodynamic transformation in water, absolute ethanol, and the binary mixtures of ethanol and water at a temperature range from 283.15 K to 318.15 K were evaluated. The solubility of naringin was measured by an ultraviolet spectrophotometric (UV) method and the data of the solubility of naringin were analyzed by thermodynamic principles.

2. Experimental

2.1. Materials and apparatus

The naringin sample ($C_{27}H_{32}O_{14}$, CAS 10236-47-2) was supplied by Shaanxi Jiahe Phytochem Co., Ltd. (Shaanxi, China) with minimum purities of 98.0% (mass fraction). Other reagents used were of analytical

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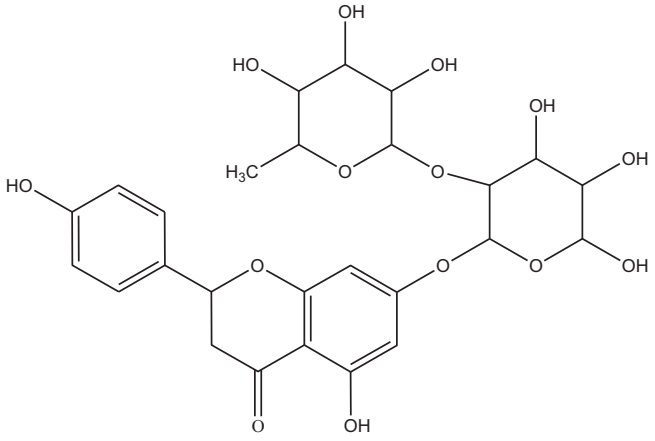

Fig. 1. Molecular structure of naringin.

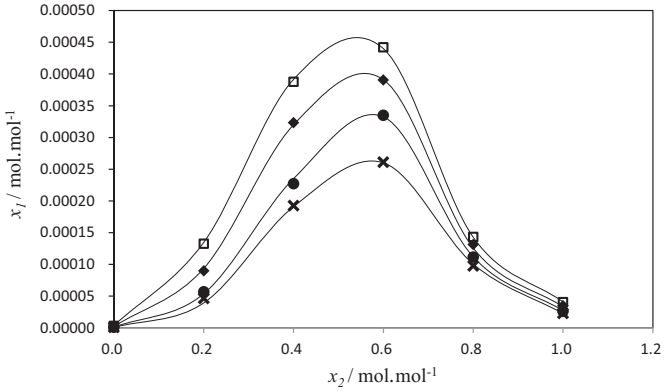

Fig. 2. Solubility of naringin versus the composition of solvent mixtures at T = 283.15 K (×), T = 288.15 K (●), T = 293.15 K (⬥), and T = 298.15 K (□).

purity grade; the ethanol used in the experiment has a minimum purity of 98.0% (mass fraction) and redistilled deionized water was used throughout. The absorbance measurements were carried out on a SP-752 UV–vis spectrophotometer (Shanghai Spectrum Instrument Co., Ltd., Shanghai, China).

2.2. Sample preparation

The solubility in pure solvent according to United States Pharmacopeia (USP) is: only where a special, quantitative solvent solubility test is given in the individual monograph, and is designated by a test heading, is it a test for purity. On the basis of that, we design this experiment. Specially designed sealed 10 mL dual-wall glass flasks were utilized in our study. In order to maintain the constant temperature of the internal environment of the flask, between the outer and the inner walls of the flask, circulated water was filled and the temperature of the water was controlled by a thermostat (uncertainty of ±0.1 K). 5 mL of water, absolute ethanol, and ethanol + water mixtures was added into the flasks respectively; excess amount of naringin was subsequently added into the solvents, and then magnetic stirrers were used to stir the suspensions for 4 h to make it reach solid–liquid equilibrium. After equilibration, the stirrers were stopped, the suspensions were taken out about 1 mL from the upper parts and were filtered through 0.45 μm membranes. The filtered solutions were poured into volumetric flasks and diluted to appropriate concentrations for UV analysis.

Table 1
Mole fraction solubility (x_1) of naringin in the binary solvent system of ethanol and water from 283.15 K to 318.15 K at pressure $p = 0.1$ MPa.[a]

T/K	$10^5\,x_1^{exp}$	$10^5\,x_1^{cal\text{-}MA}$	$10^5\,x_1^{cal\text{-}JA}$	$10^4\,x_1^{exp}$	$10^4\,x_1^{cal\text{-}MA}$	$10^4\,x_1^{cal\text{-}JA}$
	$x_2 = 0.0$	$x_2 = 0.0$	$x_2 = 0.0$	$x_2 = 0.2$	$x_2 = 0.2$	$x_2 = 0.2$
283.15	0.0621	0.0494	0.0468	0.4632	0.2918	0.3620
288.15	0.0714	0.1007	0.0844	0.5682	0.5371	0.5610
293.15	0.0976	0.1934	0.1491	0.8958	0.9353	0.8566
298.15	0.2869	0.3515	0.2585	1.3243	1.5463	1.2893
303.15	0.6149	0.6062	0.4402	2.5902	2.4344	1.9147
308.15	1.0975	0.9954	0.7367	3.5229	3.6605	2.8072
313.15	1.5520	1.5608	1.2127	5.4588	5.2711	4.0657
318.15	2.3221	2.3431	1.9652	7.2116	7.2875	5.8202
T/K	$10^3\,x_1^{exp}$	$10^3\,x_1^{cal\text{-}MA}$	$10^3\,x_1^{cal\text{-}JA}$	$10^4\,x_1^{exp}$	$10^4\,x_1^{cal\text{-}MA}$	$10^4\,x_1^{cal\text{-}JA}$
	$x_2 = 0.4$	$x_2 = 0.4$	$x_2 = 0.4$	$x_2 = 0.6$	$x_2 = 0.6$	$x_2 = 0.6$
283.15	0.1926	0.1810	0.1646	2.6119	2.8505	1.6912
288.15	0.2271	0.2399	0.2304	3.3481	3.2351	2.1919
293.15	0.3233	0.3154	0.3186	3.9045	3.7112	2.8158
298.15	0.3878	0.4116	0.4359	4.4199	4.2998	3.5870
303.15	0.5667	0.5332	0.5902	5.0220	5.0278	4.5331
308.15	0.6585	0.6859	0.7914	5.7897	5.9294	5.6854
313.15	0.8930	0.8764	1.0512	6.8571	7.0481	7.0793
318.15	1.1079	1.1127	1.3840	8.5915	8.4394	8.7543
T/K	$10^4\,x_1^{exp}$	$10^4\,x_1^{cal\text{-}MA}$	$10^4\,x_1^{cal\text{-}JA}$	$10^4\,x_1^{exp}$	$10^4\,x_1^{cal\text{-}MA}$	$10^4\,x_1^{cal\text{-}JA}$
	$x_2 = 0.8$	$x_2 = 0.8$	$x_2 = 0.8$	$x_2 = 1.0$	$x_2 = 1.0$	$x_2 = 1.0$
283.15	0.9756	1.0033	0.8802	0.2262	0.2248	0.3042
288.15	1.1150	1.1179	1.0694	0.2571	0.2712	0.3489
293.15	1.3122	1.2574	1.2906	0.3452	0.3307	0.3983
298.15	1.4299	1.4266	1.5478	0.4047	0.4072	0.4527
303.15	1.6428	1.6317	1.8451	0.5166	0.5059	0.5123
308.15	1.8222	1.8803	2.1870	0.6245	0.6338	0.5775
313.15	2.1901	2.1820	2.5783	0.7959	0.8002	0.6484
318.15	2.5610	2.5483	3.0239	1.0212	1.0175	0.7255

[a] The relative standard uncertainty u_r for the mole fraction solubility $u_r(x_1)$ is 0.05, for solvent composition $u_r(x_2)$ is 0.02.

2.3. Sample analysis

The mole fraction solubility of the solute (x_1) in the binary system of ethanol and water solvents could be calculated by the following Eq. (1). The composition of solvent mixtures x_2 is defined in Eq. (2).

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

$$x_2 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \quad (2)$$

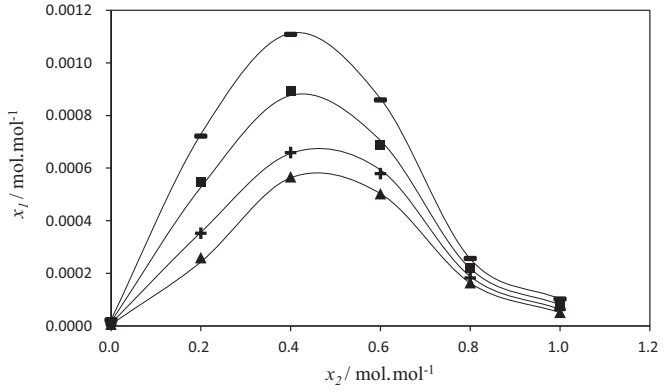

Fig. 3. Solubility of naringin versus the composition of solvent mixtures at T = 303.15 K (▲), T = 308.15 K (+), T = 313.15 K (■), and T = 318.15 K (−).