Solubility of Andrographolide in Various Solvents from (288.2 to 323.2) K

Meili Chen,[†,‡] Chunying Xie,[†] and Longxiao Liu*[,†]

Zhejiang University, Institute of Pharmaceutics, Hangzhou 310058, P. R. China, and Shaoxing People's Hospital of Zhejiang Province, Shaoxing 312000, P. R. China

The solubilities of andrographolide in methanol, ethanol, butan-1-ol, propanone, and water over the temperature range of (288.2 to 323.2) K were measured. The solubilities of andrographolide in selected solvents increased with an increase of temperature. The experimental results were fitted with the modified Apelblat equation.

Introduction

Andrographolide ([1*R*-[1α[*E*(*S**)],4a*β*,5α,6α,8aα]]-3-[2-[decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylene-1- naphthalenyl]ethylidene]dihydro-4-hydroxy-2(3*H*)-furanone; CAS Registry No. 5508-58-7; molecular mass 350.45 g·mol^{-1}; Figure 1) is the major active component of the medicinal plant of *Andrographis paniculata,* known as the "King of Bitters" in the *Acanthaceae* family.[1,2] It has been widely used in China, India, and other southeast Asian countries for centuries in the treatment of respiratory infection, fever, bacterial dysentery, and diarrhea.[3,4] In the past decade, new functions of hepatoprotectivity,[5] antitumor,[6] and antihyperglycaemia have been found.[7]

Andrographolide is usually obtained from *A. paniculata*.[8−10] Organic solvents and water must be applied in the process of separation and purification of andrographolide. To select suitable solvents and to design an optimal production process, it is important to know the solubility of andrographolide in various solvents. Unfortunately, no systematic solubilities of andrographolide in water and commonly used organic solvents such as methanol and ethanol as a function of temperature are available in the literature.

In this study, the solubility of andrographolide in methanol, ethanol, butan-1-ol, propanone, and water over the temperature range of (288.2 to 323.2) K was measured. The results were fitted by the modified Apelblat equation.

Experimental Section

Reagents and Apparatus. Andrographolide (mass fraction purity 0.991 by high-performance liquid chromatography, HPLC) was obtained from Chengdu Okay Plant & Chemical Co., Ltd. (Chengdu, China). Methanol (AR grade, mass fraction purity 0.995) was purchased from Shanghai Chemical Reagent Co., Ltd. (Shanghai, China). Ethanol (AR grade, mass fraction purity 0.997) was supplied by Hangzhou Dafang Chemical Reagent Co., Ltd. (Zhejiang, China). Butan-1-ol (AR grade, mass fraction purity 0.990) was supplied by Gaojing Fine Chemical Co., Ltd. (Zhejiang, China). Propanone (AR grade, mass fraction purity 0.995) was supplied by Hangzhou Chemical Reagent Co., Ltd. (Zhejiang, China).

* Corresponding author. Tel.: +86 571 8820 6791. Fax: +86 571 8796 4475. E-mail address: liulx@zju.edu.cn.
† Zhejiang University.
‡ Shaoxing People's Hospital of Zhejiang Province.

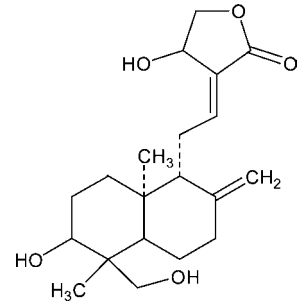

Figure 1. Chemical structure of andrographolide.

Deionized water was used throughout. A THZ-C shaker was supplied by Taicang Laboratorial Equipment Co., Ltd. (Jiangsu, China). A Spectrumlab 52 spectrophotometer was supplied by Lengguang Technology Co., Ltd. (Shanghai, China).

Sample Preparation. Twenty-five cm^3 volumetric flasks were used to prepare saturated solutions. Excess amounts of andrographolide were added into 5 cm^3 of various solvents (methanol, ethanol, butan-1-ol, propanone, and water) at various temperatures from (288.2 to 323.2) K. Then the suspensions were shaken in a shaker for 22 h. After equilibrium was attained, the shaker was turned off to let the suspensions settle for 2 h.[11,12] The temperature of the sample was automatically controlled by the shaker with a precision of ± 0.2 K in the incubation period. The supernatant was withdrawn, filtered with a 0.45 μm membrane filter, appropriately diluted, and analyzed for andrographolide content using a UV spectrophotometer. Each experiment was conducted in triplicate.

Sample Analysis. To determine the andrographolide concentration in solutions, the standards and samples were analyzed by the UV spectrophotometer at 223 nm, which is the maximum absorption wavelength of andrographolide as determined by us. The calibration equation established by using the standard solution was as $Y = 8.0\cdot10^{-5}X - 8.0\cdot10^{-7}$ ($R^2 = 0.9998$) in the concentration range of ($7.17\cdot10^{-6}$ to $6.27\cdot10^{-5}$) mol·dm^{-3}, where Y was concentration of standard solutions and X was UV absorbance.

Results and Discussion

The solubility values of andrographolide in methanol, ethanol, butan-1-ol, propanone, and water were summarized in Table 1.

10.1021/je100344z
Published on Web 06/04/2010

Table 1. Solubility of Andrographolide in Methanol (1), Ethanol (2), Butan-1-ol (3), Propanone (4), and Water (5)

T	c_1	c_2	c_3	c_4	c_5
K	10^{-2} mol·dm^{-3}	10^{-2} mol·dm^{-3}	10^{-2} mol·dm^{-3}	10^{-2} mol·dm^{-3}	10^{-4} mol·dm^{-3}
288.2	2.69 ± 0.00	1.65 ± 0.05	0.98 ± 0.00	1.00 ± 0.01	0.96 ± 0.03
293.2	3.14 ± 0.02	1.90 ± 0.06	1.12 ± 0.03	1.19 ± 0.02	1.13 ± 0.03
298.2	3.85 ± 0.04	2.10 ± 0.05	1.29 ± 0.03	1.30 ± 0.04	1.32 ± 0.04
303.2	4.67 ± 0.02	2.44 ± 0.03	1.57 ± 0.01	1.50 ± 0.03	1.58 ± 0.04
308.2	5.41 ± 0.04	3.00 ± 0.06	1.74 ± 0.03	1.78 ± 0.05	1.86 ± 0.05
313.2	6.27 ± 0.07	3.49 ± 0.00	2.06 ± 0.01	2.02 ± 0.03	2.07 ± 0.01
318.2	7.80 ± 0.04	4.01 ± 0.00	2.51 ± 0.00	2.26 ± 0.00	2.53 ± 0.02
323.2	9.36 ± 0.03	5.07 ± 0.02	3.05 ± 0.03	2.71 ± 0.04	3.01 ± 0.04

Table 2. Parameters of Equation 1 for Andrographolide in Selected Solvents

solvent	A	B	C	rmsd
methanol	−221.2	7104.8	34.06	$2.4 \cdot 10^{-3}$
ethanol	−432.4	16957.5	65.24	$1.3 \cdot 10^{-3}$
butan-1-ol	−401.9	15520.3	60.63	$9.7 \cdot 10^{-4}$
propanone	−183.7	5953.5	27.98	$4.1 \cdot 10^{-4}$
water	−207.4	6472.3	31.02	$4.9 \cdot 10^{-6}$

The solubilities in methanol were the highest, whereas those in water were the lowest. The solubility results in all selected solvents increased with an increase of temperature in the range of (288.2 to 323.2) K.

The solubility of andrographolide as a function of temperature was fitted by the modified Apelblat equation[13,14]

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

where c is the solubility of andrographolide; T is the absolute temperature; A, B, and C are parameters. The parameters of A, B, and C were obtained using a nonlinear regression and were listed in Table 2 together with the root-mean-square deviations (rmsd's) which is defined as

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

where N is the number of experimental points, c_i^c represents the solubility calculated, and c_i represents the experimental solubility. It could be seen that the calculated solubilities showed good agreement with the experimental values from the small rmsd, which indicated that the modified Apelblat equation could be employed to fit the measured solubility of andrographolide in the selected five solvents in the specified temperature range. The experimental solubilities and the parameters might be used as fundamental data for the study of andrographolide.

Acknowledgment

Special thanks are given to Mr. Jun Chen for his technical help.

Literature Cited

(1) Samy, R. P.; Thwin, M. M.; Gopalakrishnakone, P. Phytochemistry, pharmacology and clinical use of *Andrographis paniculata*. *Nat. Prod. Commun.* **2007**, *2*, 607–618.
(2) Singha, P. K.; Roy, S.; Dey, S. Protective activity of andrographolide and arabinogalactan proteins from *Andrographis paniculata* Nees. against ethanol-induced toxicity in mice. *J. Ethnopharmacol.* **2007**, *111*, 13–21.
(3) Poolsup, N.; Suthisisang, C.; Prathanturarug, S.; Asawamekin, A.; Chanchareon, U. *Andrographis paniculata* in the symptomatic treatment of uncomplicated upper respiratory tract infection: systematic review of randomized controlled trials. *J. Clin. Pharm. Ther.* **2004**, *29*, 37–45.
(4) Jarukamjorn, K.; Nemoto, N. Pharmacological aspects of *Andrographis paniculata* on health and its major diterpenoid constituent andrographolide. *J. Health Sci.* **2008**, *4*, 370–381.
(5) Trivedi, N. P.; Rawal, U. M.; Patel, B. P. Hepatoprotective effect of andrographolide against hexachlorocyclohexane-induced oxidative injury. *Integr. Cancer Ther.* **2007**, *6*, 271–280.
(6) Zhao, F.; He, E. Q.; Wang, L.; Liu, K. Anti-tumor activities of andrographolide, a diterpene from *Andrographis paniculata*, by inducing apoptosis and inhibiting VEGF level. *J. Asian Nat. Prod. Res.* **2008**, *10*, 473–479.
(7) Yu, B. C.; Hung, C. R.; Chen, W. C.; Cheng, J. T. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. *Planta Med.* **2003**, *69*, 1075–1079.
(8) Wongkittipong, R.; Part, L.; Damronglerd, S.; Gourdon, C. Solid-liquid extraction of andrographolide from plants-experimental study, kinetic reaction and model. *Sep. Purif. Technol.* **2004**, *40*, 147–154.
(9) Chen, L. G.; Jin, H. Y.; Ding, L.; Zhang, H. R.; Wang, X. P.; Wang, Z. M.; Li, J.; Qu, C. L.; Wang, Y. T.; Zhang, H. Q. On-line coupling of dynamic microwave-assisted extraction with high-performance liquid chromatography for determination of andrograpgolide and dehydroandrographolide in *Andrographis panciculata* Nees. *J. Chromatogr., A* **2007**, *1140*, 71–77.
(10) Du, Q. Z.; Jerz, G.; Winterhalter, P. Separation of andrographolide and neoandrographolide from the leaves of *Andrographis paniculata* using high-speed counter-current chromatography. *J. Chromatogr., A* **2003**, *984*, 147–151.
(11) Mohsen-Nia, M.; Modarress, H.; Razzaghi, D. Solubility of 1,3,5-trioxane in methanol, ethanol, and 2-propanol. *J. Chem. Eng. Data* **2004**, *49*, 1613–1614.
(12) Wang, L. H.; Cheng, Y. Y. Solubility of puerarin in water, ethanol, and acetone from (288.2 to 328.2) K. *J. Chem. Eng. Data* **2005**, *50*, 1375–1376.
(13) Shi, L. X.; Zhang, B. H.; Song, S. Q.; Zhu, Y. Y. Solubility of 1-*H*-tetrazole-1-acetic acid in different solvents between 283 K. *J. Chem. Eng. Data* **2007**, *52*, 1856–1857.
(14) Liu, L. X.; Chen, J. Solubility of hesperetin in various solvents from (288.2 to 323.2) K. *J. Chem. Eng. Data* **2008**, *53*, 1649–1650.

Received for review April 9, 2010. Accepted May 28, 2010. This work was supported by Key Project of Chinese National Programs for Fundamental Research and Development (973 Program) (No. 2009CB930300) and Zhejiang Provincial Science and Technology Fund of China (No. 2007C23010).

JE100344Z