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SHORT ARTICLE

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Solubility of Dexibuprofen in Different Solvents from (263.15 to 293.15) K

Jinli Zhang,[†] Lijuan Wang,[†] Dan Wang,[‡] Junbo Gong,[§] Wei Li,[*,‡] and Jingkang Wang[§]

[†]Key Laboratory of Systems Bioengineering MOE, Tianjin University, Tianjin 300072, People's Republic of China

[‡]Key Laboratory for Green Chemical Technology MOE, Tianjin University, Tianjin 300072, People's Republic of China

[§]School of Chemical Engineering & Technology, Tianjin University, Tianjin 300072, People's Republic of China

ABSTRACT: The solubility of dexibuprofen in ethanol, *n*-propanol, isopropyl alcohol, ethyl acetate, and *n*-hexane was measured in the temperature range between (263.15 and 293.15) K under atmospheric pressure. The results indicated that the solubility of dexibuprofen in the selected solvents increased with increasing temperature. The experimental data were correlated by the modified Apelblat model.

INTRODUCTION

Chirality is an important factor in pharmacology, attracting increasingly more attentions in the design, development, and marketing of new drugs. Regulatory control of chiral drugs in the US has demanded that the applicants must recognize the occurrence of chirality in new drugs, attempt to separate the stereoisomers, and assess the activity of the various stereoisomers.[1] Ibuprofen, an analgesic and antipyrotic drug having a chiral carbon atom in its molecule (Figure 1), is previously applied as a racemate in clinic. However, recent studies found that only (*S*)-enantiomer (CAS Registry No. 51146-56-6, named as dexibuprofen) is more biologically active,[2−4] while the (*R*)-enantiomer is teratogenic for the first three months of pregnancy.[4,5] To increase efficacy and reduce side effects, some international manufacturers have already put dexibuprofen, the pure (*S*)-enantiomer, into the drug market.[6] Solubility data are fundamental to the manufacturing process of drugs, owing to the significant influence of solvents on the separation efficiency through changing crystallization kinetics, solution thermodynamics, and crystal interface structure.[7] The solubility of the racemate ibuprofen was reported in some solvents;[8] however, so far no experimental solubility data of dexibuprofen has been reported in any solvent. In this article, the solubility of dexibuprofen in ethanol, *n*-propanol, isopropyl alcohol, ethyl acetate, and *n*-hexane was measured by ultraviolet visible spectrophotometry over the temperature range of (263.15 to 293.15) K under atmospheric pressure. The results were fitted with the modified Apelblat equation.

EXPERIMENTAL SECTION

Materials. A white crystalline powder of dexibuprofen with the purity of the mass fraction higher than 99 % was purchased from the Hubei Baike Hengdi Co., China and was purified through twice crystallization in ethanol before utilization. All of the solvents used in our study, including ethanol, *n*-propanol, isopropyl alcohol, ethyl acetate, and *n*-hexane, have a purity higher than 99 % (mass fraction) and were purchased from the Tianjin Chemical Reagent Co., China.

Apparatus and Procedures. The solubility of dexibuprofen was determined via the balance method using a UV−vis spectrophotometer similar to that in previous literature.[9] The samples were weighed using an analytical balance (Sartorious CP224S, Germany) with an uncertainty of ± 0.0001 g. An excess amount of dexibuprofen was dissolved stirringly in certain solvent in a three-necked bottle maintained at the programmed temperature. A thermometer (with the precision of ± 0.05 K) was used to calibrate the inside temperature of the necked bottle. The equilibrium was verified by measuring the concentration of the solute in the supernatant at different time intervals until the concentration value reached the constant. Then the supernatant fluid was diluted appropriately for spectrophotometric analysis on a Cary-300 UV−visible spectrophotometer (Varian Ltd.). All of the measurements were repeated at least three times, and the average of the measurements is considered to be the solubility. The uncertainty of the experimental solubility values is less than 2 %, which results from the uncertainties in temperature measurements, measuring the weight, and the disturbance of the absorbance of the UV−vis spectrophotometer.

RESULTS AND DISCUSSION

The solubility of dexibuprofen in ethanol, *n*-propanol, isopropyl alcohol, ethyl acetate, and *n*-hexane from (263.15 to 293.15) K is listed in Table 1. X-ray diffraction (XRD) patterns show that the dexibuprofen crystals obtained from each solvent have no structural transformation, compared with the raw material. The solubility of dexibuprofen as a function of temperature is fitted by the modified Apelblat equation:[10]

$$\ln(x^{\mathrm{exptl}}) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \qquad (1)$$

where T is the absolute temperature and A, B, C are model parameters. The calculated solubility values of dexibuprofen

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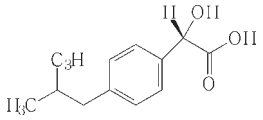

Figure 1. Chemical structure of *S*-(+)-ibuprofen.

Table 1. Solubility of Dexibuprofen in Five Different Solvents from T = (263.15 to 293.15) K

T/K	$x^{exptl,a}$	x^{calcd}	$100(x^{exptl} - x^{calcd})/x^{exptl}$
		Ethanol	
263.15	0.1242	0.1237	0.354
268.15	0.1287	0.1299	−0.955
273.15	0.1391	0.1367	1.743
278.15	0.1404	0.1441	−2.631
283.15	0.1541	0.1521	1.258
288.15	0.1622	0.1608	0.848
293.15	0.1691	0.1703	−0.685
		n-Propanol	
263.15	0.1161	0.1168	−0.560
268.15	0.1288	0.1274	1.057
273.15	0.1380	0.1377	0.231
278.15	0.1452	0.1474	−1.522
283.15	0.1581	0.1565	1.003
288.15	0.1642	0.1648	−0.367
293.15	0.1724	0.1722	0.135
		Isopropyl Alcohol	
263.15	0.1279	0.1279	0.001
268.15	0.1441	0.1433	0.552
273.15	0.1581	0.1584	−0.205
278.15	0.1694	0.173	−2.079
283.15	0.1897	0.1867	1.62
288.15	0.2012	0.1993	0.944
293.15	0.2088	0.2106	−0.879
		Ethyl Acetate	
263.15	0.1507	0.1504	0.153
268.15	0.1687	0.169	−0.184
273.15	0.1883	0.1871	0.638
278.15	0.2014	0.2043	−1.47
283.15	0.2202	0.2204	−0.113
288.15	0.2399	0.235	2.019
293.15	0.2452	0.2479	−1.084
		n-Hexane	
263.15	0.0303	0.0297	2.223
268.15	0.0406	0.0412	−1.399
273.15	0.0547	0.0573	−4.739
278.15	0.0803	0.0797	0.82
283.15	0.1159	0.1109	4.286
288.15	0.1556	0.1544	0.754
293.15	0.2104	0.215	−2.214

[a] The mole fraction solubility (x^{exptl}) based on the following equation: $x^{exptl} = (m_A/M_A)/(m_A/M_A + m_S/M_S)$, where m_A and m_S represent the mass of the solute and the solvent, respectively, and M_A and M_S are the molecular weight of the solute and the solvent, respectively.

Table 2. Parameters of Equation 1 for Dexibuprofen in Five Different Solvents from T = (263.15 to 293.15) K

	solvents				
	ethanol	*n*-propanol	isopropyl alcohol	ethyl acetate	*n*-hexane
A	−70.7086	131.5510	180.4262	199.6839	−237.371
B	2183.865	−6439.2727	−8721.97	−9523.07	5511.749
C	10.8241	−19.6005	−26.7981	−29.6784	38.20531
R^2	0.9831	0.9958	0.9955	0.9960	0.9982
10^3 rmsd	2.1691	1.3036	2.2201	2.6118	3.0458

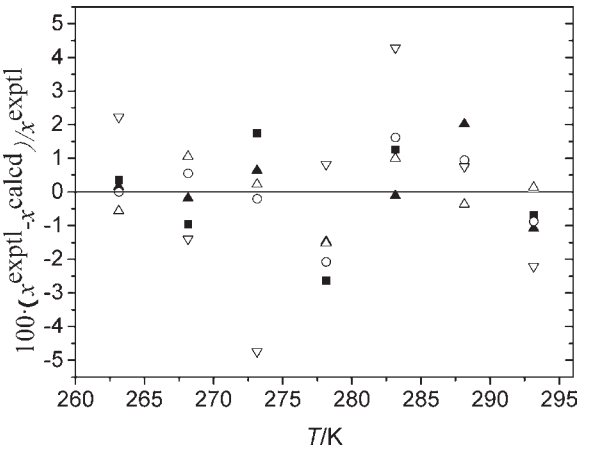

Figure 2. Difference between the experimental data and calculated results of dexibuprofen solubility in different solvents from T = (263.15 to 293.15) K: ■, ethanol; △, *n*-propanol; ○, isopropyl alcohol; ▲, ethyl acetate; ▽, *n*-hexane.

from eq 1 and the relative error between experimental solubility and calculated values are also given in Table 1. The values of the model parameters *A*, *B*, and *C* together with the root-mean-square deviation (rmsd) defined by eq 2 are listed in Table 2:

$$\text{rmsd} = \left\{ \frac{1}{N-1} \sum_{i=1}^{N} (x_i^{calcd} - x_i^{exptl})^2 \right\}^{1/2} \quad (2)$$

where N is the number of experimental points, x_i^{exptl} represents the experimental solubility value, and x_i^{calcd} represents the solubility calculated from eq 1.

Figure 2 compares the deviation range of estimated solubility of dexibuprofen in five different solvents. According to Tables 1 and 2, the following conclusions can be drawn: The solubility increases with the temperature in five different solvents, whereas the increasing rate varies as the solvent changes. The solubility of dexibuprofen in the five different solvents decrease in the order: ethanol > isopropyl alcohol > ethyl acetate > *n*-propanol > *n*-hexane. The calculated solubility shows good agreement with the experimental data, which indicates that the modified Apelblat equation can be employed to fit the measured solubility of dexibuprofen in the selected five solvents over the studied temperature range. In addition, for the solvent *n*-hexane the deviation between the experimental and the calculated solubilities is the relative highest. It is suggested that the polarity of solvent affects greatly the interaction between solvent and solute molecules and then influence the solubility. The experimental

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solubility and correlation equations presented here are essential to develop new techniques to separate dexibuprofen from the racemate through the crystallization process.

AUTHOR INFORMATION

Corresponding Author

*Tel.: +86-22-27890643. Fax: +86-22-27403389. E-mail: liwei@tju.edu.cn.

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