Solubilities of Salicylic Acid in Pure Solvents and Binary Mixtures Containing Cosolvent†

Hiroyuki Matsuda,*,‡ Kenta Kaburagi,‡ Sho Matsumoto,‡ Kiyofumi Kurihara,‡ Katsumi Tochigi,‡ and Kazuo Tomono§

Department of Materials and Applied Chemistry, Nihon University, 1-8-14 Kanda Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan, and College of Pharmacy, Nihon University, 7-7-7 Narashinodai, Funabashi-shi, Chiba, 274-8555, Japan

The solubility of salicylic acid in water, methanol, ethanol, ethyl acetate, polyethylene glycol (PEG) 300, and 1,4-dioxane and in various binary solvent mixtures, methanol + water, ethanol + water, ethanol + ethyl acetate, PEG 300 + water, and 1,4-dioxane + water, were determined using high-performance liquid chromatography (HPLC). The experimental solubility data were correlated by two local composition models: modified Wilson and nonrandom two-liquid (NRTL) 1.

Introduction

In the oral administration of medicine, the major route of drug administration, the medicine must pass through the mesentery after the disintegration and the dissolution of the medicine.[1] Thus, solubility of drugs highly influences their medical effect.[1,2] The water-solubility of pharmaceutical compounds is an essential property in the pharmaceutical industry.[1−3] However, physical properties of pharmaceutical compounds needed for the development of the new drugs are still well-known since combinatorial chemistry (CC) and high-throughput screening (HTS) have been introduced to basic research for development of new drugs.[4] As a result of these screening methods, poorly water-soluble drugs have increased in number due to the drugs' increased molecular weight and complicated chemical structures, even though the pharmacological activities of the drugs have been enhanced. In using drugs with high medical activity, knowledge of the enhancement of solubility by adding a cosolvent is essential from a practical point of view. Cosolvents, such as ethanol, propylene glycol, and polyethylene glycol (PEG), are commonly used in pharmaceutical formulations to increase the solubility of hydrophobic drugs. Surfactants can also be used to enhance the solubility of them by increasing the wettability of the solute. Therefore, the solubilities in water of pharmaceutical compounds and the enhancement of the solubilities by adding the cosolvent are important parameters in the pharmaceutical process.

This study aims to measure the solubilities of poorly water-soluble drugs and determine the enhancement of these solubilities by adding cosolvents. The solubility was measured using high-performance liquid chromatography (HPLC). We have selected salicylic acid as the pharmaceutical compound. Solubility data containing salicylic acid have been reported.[5−8] To confirm the validity of the designed apparatus and the experimental procedure, we have measured the solubilities of salicylic acid at 298.15 K in six solvents, water, methanol, ethanol, ethyl acetate, PEG 300, and 1,4-dioxane, and five mixed solvents, methanol + water, ethanol + water, ethanol + ethyl acetate, PEG 300 + water, and 1,4-dioxane + water. Experimentally determined solubilities were compared with the values reported in the literature. In addition, the experimental results were correlated by two local composition models (modified Wilson[9] and NRTL 1[10]).

* To whom correspondence should be addressed. Phone: +81-3-3259-0793. Fax: +81-3-3293-7572. E-mail address: matsuda@chem.cst.nihon-u.ac.jp.
† Part of the special issue "Robin H. Stokes Festschrift".
‡ Department of Materials and Applied Chemistry.
§ College of Pharmacy.

Experimental Section

Materials. Salicylic acid (99.5 % purity), methanol (99.8 % purity), ethanol (99.5 % purity), ethyl acetate (99.5 % purity), 1,4-dioxane (99 % purity), benzene (99.5 % purity), and phosphoric acid (85 % purity) were used. These were special-grade chemicals obtained from Wako Pure Chemical Industries Ltd., Japan. First grade PEG 300 (average molecular weight 300) was used. HPLC grade methanol was used for the mobile phase. Water was passed through an ion exchanger and distilled.

Apparatus. In this study, the experimental apparatus for the determination of the solubilities was based on the use of HPLC. This measurement system consisted of an UV−vis detector, a constant flow pump, a column, an injector, and a chromatocoder. Senshu Pak PEGASIL ODS (Senshu Scientific Co., Ltd.) was applied to the column. SSC-5410 (Senshu Scientific Co., Ltd.) was used in the UV−vis detector. A mixture of methanol and 0.1 mass % phosphate aqueous solution (volume ratio of 6:4) was used for the mobile phase.

Establishment of a Calibration Curve. Prior to the solubility measurements, the calibration curve of salicylic acid was established by using the internal standard method. First, aqueous salicylic acid of known composition, where saturation was not achieved, was prepared. This solution was dissolved by shaking in a thermosetting water bath (NTT-2100 and NTS-1300, TOKYO RIKAKIKAI Co. Ltd.). The thermo settee water bath was set at 298.15 K, and the speed of the stirrer was 100 rpm. The mass fraction was determined with a Mettler digital balance (model H315; having a sensitivity of 0.1 mg), and the temperature control of the thermosetting water bath was a maximum of 0.05 K. After the dissolution, benzene, used as an internal standard material, was prepared to 0.01 mass fraction and added to the solution. Finally, the peak area of the salicylic acid and the internal standard material at 254 nm were measured by HPLC. The above procedure was performed by unit difference

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Table 1. Experimental Mole Fraction Solubilities x of Salicylic Acid at 298.15 K with Several Literature Values

	x					
solvent	this work	δx_1[a]	Nordström and Rasmuson[5]	Pẽna et al.[6]	Wang et al.[7]	Shalmashi and Eliassi[8]
water	0.0003	± 0.0000	0.00016	0.0002	0.0003	0.0003
methanol	0.1223	± 0.0003	0.1280		0.0874	
ethanol	0.1450	± 0.0004		0.1397		0.1386
ethyl acetate	0.1383	± 0.0081	0.1357	0.1186		0.1381
PEG 300	0.4931	± 0.0011			0.3921	
1,4-dioxane	0.2610	± 0.0114		0.3117		

[a] δx_1 is the standard deviation.

Table 2. Experimental Mole Solubilities of Salicylic Acid in the Binary Mixture Methanol (2) + Water (3) at 298.15 K

x_2	x_1	δx_1[a]	x_2	x_1	δx_1
0.0000	0.0003	± 0.0000	0.4575	0.0252	± 0.0001
0.0903	0.0006	± 0.0000	0.6922	0.0650	± 0.0001
0.1942	0.0021	± 0.0000	1.0000	0.1223	± 0.0003
0.3599	0.0113	± 0.0000			

[a] δx_1 is the standard deviation.

of the compositions of salicylic acid, and the calibration curve of the mass fraction ratio versus the peak area ratio between the salicylic acid and the internal standard was made. The reproducibility of this calibration curve was within $w = 0.0001$: w is the symbol for mass fraction.

Solubility Measurements. An excess amount of salicylic acid was added to each mixture of known composition. The uncertainty of the calculated mole fraction is ± 0.0001. The dissolution of the salicylic acid was performed by using the thermosetted water bath at (298.15 ± 0.05) K for 24 h. As well as the establishment of the calibration curve, a specific amount of benzene as on the internal standard component was added to the solution, and the insoluble solid phase was separated by a 0.45 μm pore size membrane filter (Millipore, USA). Finally, the peak area for the absorbance for salicylic acid was determined by HPLC (flow rate: 0.3 mL·min^{-1}, wavelength: 254 nm). The solubility of salicylic acid was determined on the basis of the measured peak area, the calibration curve, and the added mass to benzene. Each experimental data point is an average of three experiments with the measured solubilities of mole fraction. The uncertainty of the solubilities due to the experimental procedure is estimated to be ± 6.2 %.

Results and Discussion

Solubilities of Salicylic Acid in Pure Components. The experimental solubilities of salicylic acid in six components (water, methanol, ethanol, ethyl acetate, PEG 300, and 1,4-dioxane) at 298.15 K are listed in Table 1 and are compared with values reported in the literature. The experimental values in this study indicate the same tendency toward the data by Nordström and Rasmuson[5] in water, methanol, and ethyl acetate and by Shalmashi and Eliassi[8] in water and ethyl acetate. Comparisons between the experimental results and reported values showed considerable differences, especially the data reported by Pẽna et al.[6] (except water) and the data for methanol by Wang et al.[7] According to the report of Nordström and Rasmuson,[5] the solubility of salicylic acid is very sensitive to trace amounts of water in organic solvents. Therefore, a slight amount of water in solvents used in each literature seems to influence the differences between our experimental results and literature values.

Solubilities of Salicylic Acid in Binary Mixtures. As shown in Table 1, the mass fraction of salicylic acid in water is 10^{-3}. Pẽna et al.[6] and Wang et al.[7] discuss an improvement of the solubility by measuring in aqueous mixtures by the addition of a cosolvent. Therefore, in this study, the same measurements of the solubilities were performed, and the experimental results were compared with literature values.

Table 3. Experimental Mole Solubilities of Salicylic Acid in the Binary Mixture Ethanol (2) + Water (3) at 298.15 K

x_2	x_1	δx_1[a]	x_2	x_1	δx_1
0.0000	0.0003	± 0.0000	0.3665	0.0449	± 0.0009
0.0329	0.0004	± 0.0000	0.4159	0.0541	± 0.0019
0.0731	0.0007	± 0.0001	0.4774	0.0666	± 0.0015
0.1179	0.0020	± 0.0003	0.5487	0.0781	± 0.0012
0.1707	0.0063	± 0.0006	0.6314	0.0981	± 0.0021
0.2348	0.0161	± 0.0004	0.7407	0.1178	± 0.0085
0.2734	0.0260	± 0.0008	0.8457	0.1295	± 0.0143
0.2899	0.0294	± 0.0010	1.0000	0.1450	± 0.0004
0.3183	0.0342	± 0.0010			

[a] δx_1 is the standard deviation.

Table 4. Experimental Mole Solubilities of Salicylic Acid in the Binary Mixture Ethanol (2) + Ethyl Acetate (3) at 298.15 K

x_2	x_1	δx_1[a]	x_2	x_1	δx_1
0.0000	0.1383	± 0.0081	0.7134	0.1738	± 0.0069
0.1613	0.1653	± 0.0026	0.7947	0.1754	± 0.0019
0.2991	0.1767	± 0.0080	0.8701	0.1616	± 0.0175
0.4201	0.1810	± 0.0011	0.9389	0.1446	± 0.0049
0.5262	0.1808	± 0.0056	1.0000	0.1450	± 0.0004
0.6277	0.1839	± 0.0031			

[a] δx_1 is the standard deviation.

Table 5. Experimental Mole Solubilities of Salicylic Acid in the Binary Mixture PEG 300 (2) + Water (3) at 298.15 K

x_2	x_1	δx_1[a]	x_2	x_1	δx_1
0.0000	0.0003	± 0.0000	0.0826	0.0350	± 0.0001
0.0148	0.0007	± 0.0000	0.1229	0.0729	± 0.0001
0.0251	0.0015	± 0.0000	0.1937	0.1712	± 0.0003
0.0385	0.0041	± 0.0000	0.3508	0.2670	± 0.0008
0.0566	0.0149	± 0.0001	1.0000	0.4931	± 0.0011

[a] δx_1 is the standard deviation.

Table 6. Experimental Mole Solubilities of Salicylic Acid in the Binary Mixture 1,4-Dioxane (2) + Water (3) at 298.15 K

x_2	x_1	δx_1[a]	x_2	x_1	δx_1
0.0000	0.0003	± 0.0000	0.2394	0.0784	± 0.0013
0.0238	0.0008	± 0.0000	0.3294	0.1212	± 0.0053
0.0506	0.0018	± 0.0000	0.4572	0.1616	± 0.0160
0.0832	0.0066	± 0.0001	0.6573	0.2173	± 0.0083
0.1246	0.0221	± 0.0011	1.0000	0.2610	± 0.0114
0.1730	0.0436	± 0.0033			

[a] δx_1 is the standard deviation.

Tables 2 to 6 summarize the values of the experimental solubilities of salicylic acid (1) in the five binary mixtures: methanol (2) + water (3), ethanol (2) + water (3), ethanol (2) + ethyl acetate (3), PEG 300 (2) + water (3), and 1,4-dioxane (2) + water (3). The standard deviations of the experimentally determined solubilities are also listed. These solubility data are graphically shown in Figures 1 to 5 along with the literature

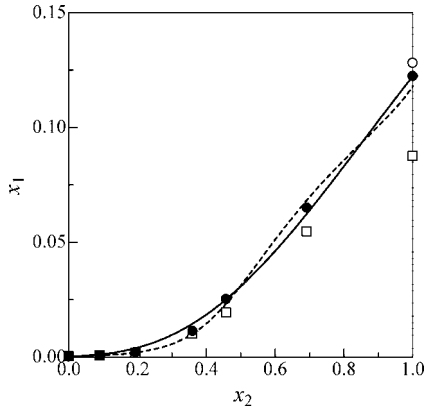

Figure 1. Experimental solubilities of salicylic acid (1) in the binary mixture methanol (2) + water (3) at 298.15 K. ●, this study; ○, Nordström and Rasmuson;[5] □, Wang et al.;[7] —, modified Wilson; - - -, NRTL 1.

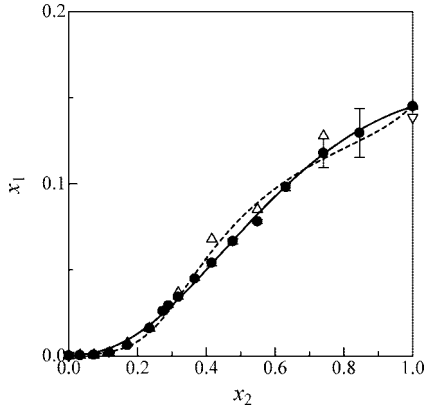

Figure 2. Experimental solubilities of salicylic acid (1) in the binary mixture ethanol (2) + water (3) at 298.15 K. ●, this study; Δ, Pẽna et al.;[6] ▽, Shalmashi and Eliassi;[8] —, modified Wilson; - - -, NRTL 1.

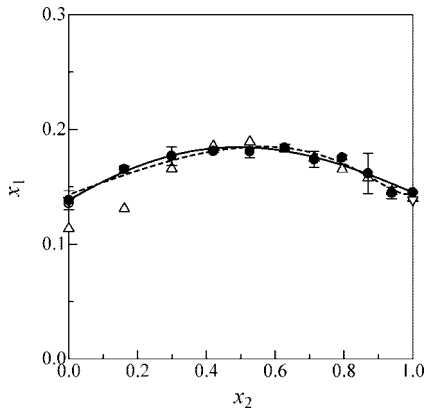

Figure 3. Experimental solubilities of salicylic acid (1) in the binary mixture ethanol (2) + ethyl acetate (3) at 298.15 K. ●, this study; ○, Nordström and Rasmuson;[5] Δ, Pẽna et al.;[6] ▽, Shalmashi and Eliassi;[8] —, modified Wilson; - - -, NRTL 1.

values. Experimental values in four aqueous mixtures, that is, water + methanol, + ethanol, + PEG 300, and + 1,4-dioxane, increase with an increase of the composition of the cosolvent. On the other hand, experimental solubilities in ethanol + ethyl acetate showed a maximum value. The results showed the same tendency as reported in the literature in the two binary mixtures ethanol + water and ethanol + ethyl acetate. In contrast, relatively large differences are noted between the experimental and literature solubilities for the mixtures of methanol, PEG 300, and 1,4-dioxane + water, in the high concentration range of the cosolvent. The literature values of solubilities in the

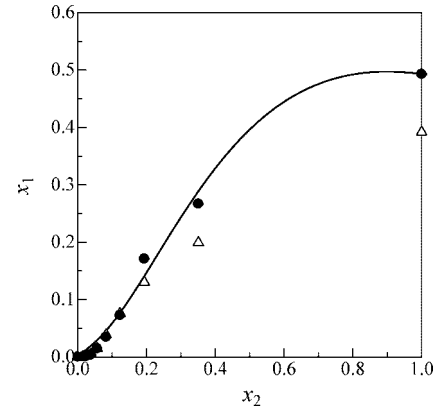

Figure 4. Experimental solubilities of salicylic acid (1) in the binary mixture PEG 300 (2) + water (3) at 298.15 K. ●, this study; Δ, Pẽna et al.;[6] —, modified Wilson.

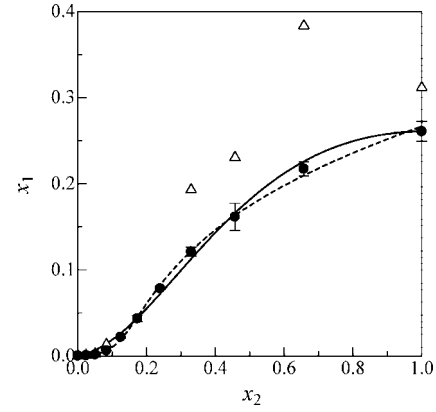

Figure 5. Experimental solubilities of salicylic acid (1) in the binary mixture 1,4-dioxane (2) + water (3) at 298.15 K. ●, this study; Δ, Pẽna et al.;[6] —, modified Wilson; - - -, NRTL 1.

Table 7. Molar Volume of Pure Component at 298 K and Molecular Size Parameter r_i and Molecular Area Parameter q_i of the NRTL 1 Model

component	V_m/cm^3·mol^{-1}	r_i	q_i
salicylic acid	89.2 [a]	2.6119	2.0895
water	18.07 [b]	0.5291	0.4233
methanol	40.73 [b]	1.1926	0.9541
ethanol	58.68 [b]	1.7182	1.3747
ethyl acetate	98.55 [b]	2.8856	2.3085
1,4-dioxane	85.29 [b]	2.4974	1.9979

[a] Ref 21. [b] Ref 22.

mixture 1,4-dioxane + water[6] showed a maximum. However, experimental results in this study did not indicate this behavior. According to the discussion by Desai et al., the solubility in the mixture is affected by many interactions (e.g., hydrogen bonds, solute−solvent, water−cosolvent molecule, dipole−dipole, etc.) and shows externally comprehensive behavior.[11] In the mixture methanol, PEG 300, and 1,4-dioxane + water, it is considered that the hydrogen bonding acts in the cosolvent-rich region. Therefore, these differences in maximum solubilites seem to be the discordant between the experimental and literature solubilities.

Data Reduction

In this study, the experimental solubility data in five binary mixtures were correlated by two local composition models (modified Wilson[9] and NRTL 1[10]). First, the modified Wilson model proposed by Acree and Zvaigzne is a possible representa-

Table 8. Determined Parameters and Deviations between Experimental and Calculated Solubilities of Salicylic Acid in Five Binary Mixtures at 298.15 K Using the Modified Wilson Equation

	Λ_{23}^{adj}	Λ_{32}^{adj}	$\lvert\Delta x_1\rvert_{avg.}$[a]	$\lvert\Delta x_1\rvert_{max.}$
methanol + water	$3.2774 \cdot 10^{-1}$	2.6640	0.0012	0.0033
ethanol + water	$2.1039 \cdot 10^{-1}$	5.2261	0.0013	0.0032
ethanol + ethyl acetate	$7.0691 \cdot 10^{-1}$	$8.5788 \cdot 10^{-1}$	0.0027	0.0083
PEG 300 + water	$3.3000 \cdot 10^{-3}$	5.8142	0.0030	0.0116
1,4-dioxane + water	$1.7910 \cdot 10^{-2}$	4.9496	0.0043	0.0087

[a] $\lvert\Delta x_1\rvert_{avg.} = \sum_{k=1}^{NDP} \lvert x_{1,exptl} - x_{1,calcd}\rvert_k$/NDP, where NDP is the number of data points.

tion model for isothermal solubilities in binary solvents based on the modification of the Wilson equation.[12] Acree and co-workers have applied this model for the representation of their experimental solubilities in binary solvents. Thus, in this study, this model was used for the representation of the experimental solubility data.[10,13,14] This model is given in eq 1

$$\ln\left[\frac{\alpha_1(s)}{x_1^{sat}}\right] = 1 - x_2^0\frac{1 - \ln[\alpha_1(s)/(x_1^{sat})_2]}{x_2^0 + x_3^0\Lambda_{23}^{adj}} - x_3^0\frac{1 - \ln[\alpha_1(s)/(x_1^{sat})_3]}{x_2^0\Lambda_{32}^{adj} + x_3^0} \quad (1)$$

where x_1^{sat} is the saturation solubility of solute 1; x_2^0 and x_3^0 are the initial mole fractions of binary solvent as if solute 1 is not present; $(x_1^{sat})_i$ is the saturated mole fraction solubility of the solute in pure solvent i; NP is the number of adjustable parameters used; and $\alpha_1(s)$ is the activity of the solid solute. Λ_{ij}^{adj} is the adjustable parameter. The activity of solute 1, $\alpha_1(s)$, is calculated by using the following equation

$$\ln \alpha_1(s) = -\frac{\Delta_{fus}H}{RT}\left(1 - \frac{T}{T_{fus}}\right) \quad (2)$$

where $\Delta_{fus}H$ and T_{fus} are the molar enthalpy of fusion and melting temperature of salicylicacid, respectively; T is the temperature; and R is the gas constant. The values of $\Delta_{fus}H$ and T_{fus} were taken from Shalmashi and Eliassi[8] and are 27.09 kJ·mol^{-1} and 432.15 K, respectively. Fitting parameters, Λ_{ij}^{adj} in eq 2 were estimated so that the following objective function (F_{obj}) was minimized for each system by means of the Marquardt algorithm[15]

$$F_{obj} = \sum_{k=1}^{NDP}(x_{1,exptl}^{sat} - x_{1,calcd}^{sat})_k^2 \quad (3)$$

where NDP is the number of data points per system.

Second, with respect to the NRTL 1 model proposed by Nagata and Nakajima,[10] this model has been applied for the correlation of their experimental binary solid−liquid equilibrium data containing especially imidazole and its derivatives, by Domańska and co-workers.[16−18] Therefore, in this study, the correlation by this model was attempted. This model is shown in eqs 4 to 9

$$\ln \gamma_i = \ln\frac{\Phi_i}{x_i} + \frac{Z}{2}q_i + \ln\frac{\theta_i}{\Phi_i} + l_i - \frac{\Phi_i}{x_i}\sum_{j=1}^{n}x_j l_j + \sum_{j=1}^{n}\theta_{ji}\tau_{ji} + \sum_{j=1}^{n}\frac{x_j\theta_{ij}}{x_i}(\tau_{ij} - \sum_{k=1}^{n}\theta_{kj}\tau_{kj}) \quad (4)$$

$$\theta_{ij} = \frac{\theta_i \exp(-\tau_{ij}\alpha_{ij})}{\sum_{k=1}^{n}\theta_k \exp(-\tau_{kj}\alpha_{kj})} \quad (5)$$

$$\Phi_i = \frac{r_i x_i}{\sum_{j=1}^{n} r_j x_j} \quad (6)$$

$$\theta_i = \frac{q_i x_i}{\sum_{j=1}^{n} q_j x_j} \quad (7)$$

$$l_i = \frac{Z}{2}(r_i - q_i) - (r_i - 1) \quad (8)$$

$$\tau_{ij} = \frac{a_{ij}}{T} \quad (9)$$

where r_i and q_i are the volume parameter and surface parameter of pure component i, respectively, and these values were calculated on the basis of the procedure of Vera et al.[19,20]

$$r_i = 0.029281 V_m \quad (10)$$

$$q_i = \frac{(Z-2)r_i}{Z} + \frac{2(1-b_i)}{Z} \quad (11)$$

where V_m is the molar volume of pure component i at 298 K and Z is the coordination number. V_m of salicylic acid was calculated by the group contribution method.[21] On the other hand, V_m of other components were taken from Poling et al.[22] b_i is the bulk factor of component i and was taken as 1. The values of V_m and the calculated values of r_i and q_i used in this study are listed in Table 7. In the solvent PEG 300 + water, these r_i and q_i values of PEG 300 could not be determined. Therefore, in this study, the data reduction for the solubilities in the mixture PEG + 300 was not performed. The values of Z and α_{12} were set to 10 and 0.2, respectively. a_{ij} is the fitting parameters of the NRTL 1 equation. The following equation was applied for the equation of the solid−liquid equilibria needed for the calculation using the NRTL 1 equation

Table 9. Determined Parameters and Deviations between Experimental and Calculated Solubilities of Salicylic Acid in Five Binary Mixtures at 298.15 K Using the NRTL 1 Equation

	methanol + water	ethanol + water	ethanol + ethyl acetate	1,4-dioxane + water
a_{12}/K	$3.3661 \cdot 10^2$	$1.9643 \cdot 10^2$	$1.7164 \cdot 10^3$	$-5.6709 \cdot 10^2$
a_{13}/K	$7.2773 \cdot 10^2$	$6.0762 \cdot 10^2$	$6.8328 \cdot 10^2$	$3.6821 \cdot 10^2$
a_{21}/K	$-9.3036 \cdot 10^2$	$-7.9901 \cdot 10^2$	$-1.4134 \cdot 10^3$	$-4.2720 \cdot 10^2$
a_{23}/K	$2.2291 \cdot 10^3$	$2.3361 \cdot 10^3$	$1.0138 \cdot 10^2$	$2.1981 \cdot 10^3$
a_{31}/K	$-1.1477 \cdot 10^2$	$1.2834 \cdot 10^2$	$-9.1869 \cdot 10^2$	$7.1301 \cdot 10^2$
a_{32}/K	$-1.9641 \cdot 10^3$	$-2.3438 \cdot 10^3$	$1.5302 \cdot 10^3$	$-2.0947 \cdot 10^3$
$\lvert\Delta x_1\rvert_{avg.}$[a]	0.0016	0.0026	0.0032	0.0023
$\lvert\Delta x_1\rvert_{max.}$	0.0043	0.0088	0.0055	0.0076

[a] $\lvert\Delta x_1\rvert_{avg.} = \sum_{k=1}^{NDP} \lvert x_{1,exptl} - x_{1,calcd}\rvert_k$/NDP, where NDP is the number of data points.

$$\ln(\gamma_i x_i) = -\frac{\Delta_{\mathrm{fus},i}H}{RT}\left(1 - \frac{T}{T_{\mathrm{fus},i}}\right) \tag{12}$$

In the NRTL 1 equation, the following objective function was used

$$F_{\mathrm{obj}} = \sum_{k=1}^{\mathrm{NDP}} \left(\frac{\gamma_{1,\mathrm{exptl}} - \gamma_{1,\mathrm{calcd}}}{\gamma_{1,\mathrm{exptl}}}\right)_k^2 \tag{13}$$

The estimated parameters and absolute deviations of solubilities of four models are summarized in Tables 8 and 9. Correlated results of two models are graphically shown in Figures 1 to 5. Deviations listed in Tables 8 and 9 indicate that both models give reasonable correlated results and that the results from the modified Wilson model are better than those from the NRTL 1 model except for the solvent 1,4-dioxane.

Conclusions

An experimental technique is described to measure the solubilities using HPLC. The solubilities of salicylic acid in six solvents and five mixtures containing cosolvent were determined. The experimental results showed that the solubilities of salicylic acid in the pure component agree with the results of Nordström et al.[5] in water, methanol, and ethyl acetate, and with Shalmashi and Eliassi[8] in water and ethyl acetate. On the other hand, with respect to the results in the mixed solvents, experimental solubilities in two mixtures ethanol + water and ethanol + ethyl acetate agreed with the literature data. However, for methanol + water, PEG 300 + water, and 1,4-dioxane + water, relatively large differences were recognized between the experimental and literature solubilities, particularly in the high concentration range of the cosolvent. The experimental solubilities of salicylic acid in the five mixtures were represented by means of two local composition models (modified Wilson and NRTL 1). A reasonable correlation was obtained well by both models, while the modified Wilson model gave better results.

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