Solubility of Silybin in Aqueous Dextran Solutions

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In present work, the solubility of silybin in aqueous dextran solution at the temperature range from (293.15 to 313.15) K was measured by a solid liquid equilibrium method. Experimental results reveal that the solubility of silybin is increased with the increase both in dextran's concentration and temperature. With the increase in dextran's concentration, the transport enthalpy and entropy for silybin from water to aqueous dextran solution are decreased within a negative region. The transport enthalpy is more negative than the entropy term. A modified UNIQUAC model was used to correlate solubility data.

Introduction

The solubility of biologically active compounds is often a limiting factor for their applicability. Drugs are mainly hydrophobic organic compounds. Therefore, the solubility enhancement of drugs is an important task in pharmaceutical technology, because it leads to a better bioavailability. A broad variety of solubilization methods have been developed, ranging from changes of the physicochemical parameters of the solution, including pH adjustment and temperature variation, up to the application of cosolvents and excipients, like complexing agents or surfactants.[1−4]

Silymarin is an antihepatotoxic polyphenolic substance isolated from the milk thistle plant, *Silybum marianum*. Derivatives of milk thistle have been used as herbal remedies for almost 200 years. Silymarin was considered as a pure compound with the structure of 7-chromanol-3-methyl-taxifolin, but after the introduction of more accurate methods of analysis and separation, it was shown that silybmarin consists of a large number of flavonolignans including silybin, isosilybin, silydianin and silychristin. Among them, silybin is the main component and has been separated commercially as a pure substance. The molecular structures of silybin, isosilybin, silydianin, and silychristin are shown in Figure 1. Currently the most important medicinal application of milk thistle is its use as a hepatoprotectant and as supportive treatment of chronic inflammatory liver disorders such as cirrhosis, hepatitis, and fatty infiltration due to alcohol and toxic chemicals.[5] Their use has been widespread since preparations became officially available for clinical use. A major problem in the development of an oral solid dosage form of this drug is the extremely poor aqueous solubility, possibly resulting in dissolution-limited oral absorption.[6]

The solubility enhancement of poorly soluble compounds can be induced by changes of temperature and solvation properties using different cosolvent compositions.[2] Among the techniques to increase aqueous solubility/dissolution rate, the formulation of solid dispersions is one of the most popular ones, although few marketed products rely on this concept. Polymers, such as poly(ethylene glycol) (PEG) and poly(vinyl pyrrolidone) (PVP), have frequently been used as a carrier in solid dispersion formulations.[7] Numerous attempts to understand the physicochemical principle behind the improvement of the dissolution of drugs by solid dispersion formulation with polymers have been reported.[3] Equilibrium solubilities of the drug in aqueous polymer solutions of different polymer concentrations reveal the solubilization capacity of a polymer for the drug. Several approaches have been used to explain the solubility of organic compounds as well as its temperature dependence.[8] Enthalpy of solution values can be measured directly from the temperature dependence of the saturation concentration.[2,3,9]

Dextran is a water-soluble polysaccharide that consists mainly of α-1,6 linked D-glucopyranose residues with a low percentage of α-1,2, α-1,3, and α-1,4 linked side chains. Dextran is essentially nontoxic and is therefore used as a blood plasma substitute. Furthermore, dextran is widely under investigation as a polymeric carrier in novel drug delivery systems.[10−12] Another important application of dextran is as a successful phase-forming polymer in aqueous two-phase systems.[13,14] The aqueous two-phase system has been established to be a powerful tool for biomolecule purification. Thermodynamic properties of aqueous two-phase systems and aqueous dextran solution have been studied extensively.[15,16] In this work, we focus our attention on the solubilization capacity of dextran in a dilute concentration region.

The prediction of the solubility of drugs in aqueous mixed solvents or even a reliable correlation of the available experimental data is of interest to pharmaceutical science and industry. Many methods, mainly empirical and semiempirical, were suggested for the correlation and prediction of the solubility of a solid drug in a mixed solvent.[8,17,18] The main difficulty in predicting the solid solubility in a mixed solvent consists of calculating the activity coefficient of a solute in a ternary mixture.

In the present work, solubilities of silybin (CAS Registry No.: 22888-70-6) in aqueous dextran 40000 solution at temperature (293.15, 298.15, 303.15, 308.15, and 313.15) K were measured by a solid−liquid equilibrium method. The aim of this study was to investigate the possible effect of dextran concentration and temperature on the solubility of the drug. The modified UNIQUAC model was used to correlate the results.

Experimental Section

Materials. Silybin was purchased from Panjin Green Biological Development Co., Ltd., Liaoning, China. Its

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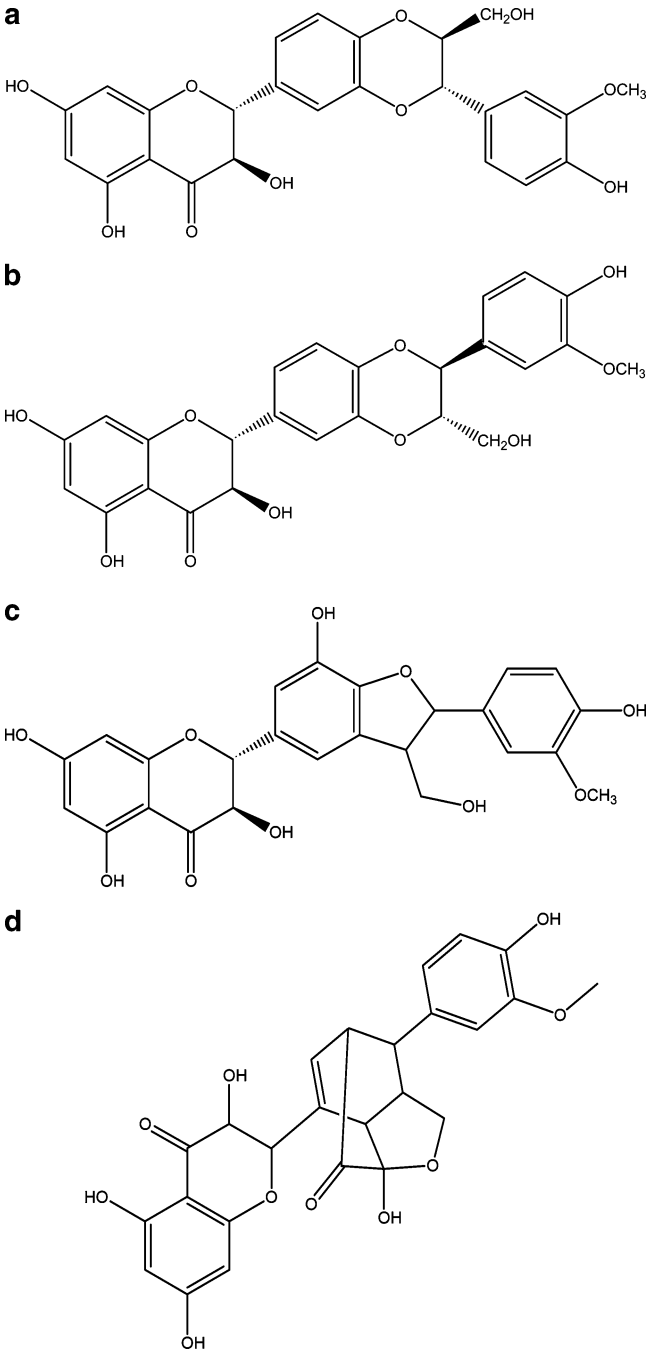

Figure 1. Molecular structures of (a) 3,5,7-trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-2,3-dihydrobenzo-[1,4]dioxin-6-yl]-chroman-4-one, silybin; (b) 3,5,7-trihydroxy-2-[2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzo[1,4]dioxin-6-yl]-chroman-4-one, isosilybin; (c) 3,5,7-trihydroxy-2-[7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzofuran-5-yl]-chroman-4-one, silychristin; and (d) 3-hydroxy-10-(4-hydroxy-3-methoxyphenyl)-8-(3,5,7-trihydroxy-4-oxochroman-2-yl)-4-oxatricyclo[4.3.1.$0^{3,7}$]dec-8-en-2-one, silydianin.

purity was claimed to be 97 % detected by a UV spectrometer at the wavelength (252 to 288) nm by the company. After recrystallization in methanol and being dried under vacuum at 353 K over 24 h, the drug was analyzed by HPLC. Our HPLC measurement reveals that the mass percent of silybin is 96.8 %, isosilybin is 1.1 %, silycristin is 0.1 %, silydianin is 0.8 %, and other impurities are 1.2 %. Their chemical structures are shown in Figure 1. Silycristin and silydianin are hydrophobic drug effective components. They have similar medicine effects as silybin.

Table 1. Physical Properties of Silybin

properties	silybin
M_w/g.mol^{-1}	482.436
T_m/K	424
$\Delta_{fus}H$/J·g^{-1}	93

In a drug sample, the content of these hydrophobic impurities is too small, and they hardly dissolve in water. The impact on the solubility of silybin was difficult to consider. Furthermore, in view of the fact that it is still difficult to separate more pure silybin from natural substances, in solubility measurement the drug was used without further treatment.

Dextran 40000 was received from Shanghai Chem-Reagent Co. Its purity was of analytical grade. Both reagents were stored over P_2O_5 in a desiccator before use.

Differential Scanning Calorimeter Measurement. Some physical properties of silybin are shown in Table 1. The melting temperature (T_m) and enthalpy of fusion ($\Delta_{fus}H$) of silybin are necessary in solubility correlation and were measured by DSC technique. (Instrument: Perkin-Elmer Dsc-7 differential scanning calorimeter, Norwalk, CT). Certified indium wire encapsulated in an aluminum crucible (supplied by instrument manufacturer) was used for temperature and heat flow calibration. An aluminum pan and lid without pinhole were used to contain the sample. An empty container of the same type was employed as a reference. Nitrogen gas of 99 % purity was used as the purge gas for all the experiments performed at a rate of 20 mL/min. Samples (3 to 8) mg were weighed to ± 0.1 mg. Balance model: FA 1004, Shanghai Balance Instrument Factory. A mass losing profile of pure silybin solid was measured by TG instrument. Instrument model, PE-DELTA series 7, with N_2 protection, flowing rate: 20 mL/min. The TG curve shows that silybin is decomposed above 473 K. In DSC measurement, samples were heated at a scanning rate of 5 K·min^{-1}, over a temperature range from (303 to 473) K. Onset temperature and enthalpy of fusion were determined (using the software attached to DSC apparatus). The uncertainty of T_m and $\Delta_{fus}H$ was less than 1 K and 2 J·g^{-1}, respectively.

UV Spectrometer Measurement. The UV spectrometry was used as an experimental analytical method. Model: TU-1800, Beijing Analysis Instrument Co., China. It was suggested by drug quality criterion that silybin should be detected in the wavelength range from (252 to 288) nm.

Silybin standard solutions were prepared in ethanol solvent. The maximum absorption wavelength was shift from (288 to 270) nm with the increase in silybin's concentration. To choose a proper calibration curve range, the optimum detection wavelength should be determined. By considering the relationship between UV maximum absorbance and silybin's concentration, a linear response range was found, where the maximum wavelength is from (288 to 285) nm. For (silybin + dextran + water) solution, the maximum absorption wavelength can be limited within this range by diluting it with known masses of (dextran + water) solution. Therefore, the calibration curve/equation was prepared within the range of (288 to 285) nm. By measuring the absorbance (A) at the maximum wavelength, the correlation equation of A and the mass fraction of silybin (S) was

$$A = 0.00314 + 24410S \quad (1)$$

where the standard deviation is 0.002.

In this work, the solubility data of silybin was measured in dextran aqueous solution. But the calibration equation

Table 2. UV Absorbance of Silybin (1) + Dextran (2) +Water (3) with Two Sets of Reference Solution, Water (A_w) and Dextran (2) + Water (3) (A_{dex}), Respectively, and the Absorbance of Dextran (2) + Water (3) Solution with Water as the Reference Solvent ($A_{dex,w}$), at λ_{max} = 285 nm

$100w_2$	A_w sample: (1) + (2) + (3) reference: (3)	A_{dex} sample: (1) + (2) + (3) reference: (2) + (3)	$A_{dex,w}$ sample: (2) + (3) reference: (3)
1.009	0.113	0.094	0.019
0.8005	0.116	0.099	0.017
0.5952	0.116	0.102	0.014
0.4025	0.112	0.104	0.009
0.2029	0.113	0.104	0.008
0.1022	0.111	0.105	0.006

of silybin was prepared in ethanol. Therefore, the solvent effect on the maximum absorption of UV spectra should be considered. On performing this test, a silybin aqueous solution was prepared. The maximum absorptions of this solution with three different reference solvents were tested. The experimental result shows that when ethanol, aqueous dextran solution (1.249 %) and pure water weres set as reference solvent, respectively, the maximum absorptions of silybin aqueous solution were observed at same wavelength. Here it is 285 nm, and the maximum absorbance was 0.137, 0.105, and 0.140, respectively. A further test was measuring the absorbance of ethanol and dextran aqueous solution (1.249 %) with water as the reference solvent, respectively. The result shows that the absorbance is 0.002 and 0.035 at 285 nm, respectively. By comparing these two sets of experimental data (0.137 + 0.002 and 0.105 + 0.035 are close to 0.140), it reveals that the difference of absorbance between ethanol and water is too small (within the experimental error), but the solvent effect of dextran aqueous solution is obvious.

The second test was to consider the effect of dextran's concentration on the absorbance. The mass fractions of dextran (w_2), the absorbance of silybin (1) + dextran (2) + water (3) solution with water as blank (A_w) and with dextran (2) + water (3) as blank (A_{dex}) at the maximum wavelength 285 nm are listed in Table 2. It is difficult to get a conclusion simply from A_w and A_{dex}. Furthermore, the UV absorbance ($A_{dex,w}$) for dextran + water solution with water as blank was measured for comparison. The absorbances at λ = 285 nm are listed in Table 2. It can be found that A_{dex} is close to $A_w - A_{dex,w}$. This result reveals that using a proper reference solvent can diminishes the solvent effect of aqueous dextran solution on UV absorbance. This result further indicates that the effect of silybin−dextran interaction on UV absorption and the effect of complex formation were not observed.

The third test was to consider whether eq 1 could be used in aqueous dextran solution. An ideal method was to dilute the sample of silybin + dextran + water with ethanol. But there is a problem in doing this since dextran is easily deposited from ethanol in certain concentration region. Therefore, we prepared the silybin solution with dextran + ethanol + water solvent within the soluble concentration range and controlled the concentrations of silybin and dextran to be fixed within the experimental uncertainty. Here, the concentration of silybin is at $(2.85 \pm 0.01) \times 10^{-5}$ g·cm^{-3} for samples (1 to 4), and the concentration of dextran is at $(2.74 \pm 0.01) \times 10^{-4}$ g·cm^{-3} for samples (2, 3, and 4) in Table 3. Then the effect of ethanol concentration on the absorption of the solution was considered. In the process of solution preparation, sample masses were recorded for calculating the mass fraction of each component. The UV absorption determination was performed with the corresponding dilution solvents as the blanks. Experimental results are listed in Table 3. In this test, the concentrations of silybin solution are the same if they are expressed in g·cm^{-3}, but they are different if it is expressed in mass fraction. It can be found from Table 3 that the maximum wavelength is shifted from (288 to 286) nm with the changes of ethanol mass fraction in dilution solvent from (1 to 0.1736). The measured absorbance at maximum wavelength, A(exp), is not a constant, but changes following eq 1 within experimental uncertainty, where the concentration of silybin was expressed in mass fraction instead of in g·cm^{-3}. This result reveals that eq 1 is still suitable for aqueous solution determination.

Table 3. Solvent Effect on the UV Absorption of Silybin Solution[a]

sample no.	$w_{ethanol}$	$10^5 w_{sil}$	λ_{max}/nm	A(exp)	A(cal)
1	1	3.64	288	0.889	0.892
2	0.3497	3.04	287	0.739	0.745
3	0.2700	2.99	287	0.728	0.733
4	0.1736	2.96	286	0.720	0.726

[a] $w_{ethanol}$ is the mass fraction of ethanol in the corresponding dilution−solvent, w_{sil} is the mass fraction of silybin in sample, λ_{max} is the maximum wavelength, A(exp) is the absorbance at λ_{max} by experimental, and A(cal) is the absorbance calculated by eq 1.

In solubility analysis, silybin samples were taken from equilibrium bottles. Known masses of the aqueous dextran solution, with the same concentration as the equilibrium solvents, were added to dilute the sample to prevent solid deposition and to adjust the concentration of silybin to be within the linear response range of the UV absorption. For silybin + dextran + water solution, the wavelength used in the determination is at their maximum absorption, mostly at λ = 285 nm. To eliminate the solvent effect on absorbance, the reference cell was loaded with the identical solvent with the sample cell.

Solubility Measurements. Binary solutions of dextran + water were prepared. Known masses of dextran were added into 250 cm^3 volumetric flask. Water was added into the flask and then heated to ensure that the dextran dissolves. The flasks were put into a thermostatic bath at a temperature of 298.15 K, and water was added into the flask until the flask mark was reached. The polymer concentrations were determined as g·cm^{-3}. Because the temperature had an effect on solvent volume, it was better to convert the polymer concentration from mass per unit volume into the mass fraction for equilibrium calculations. The densities of aqueous dextran solution were measured by a densimeter for the use of converting the polymer concentration. Polymer concentration was controlled within a mass fraction of <2.0 %.

Solubility measurement of silybin was carried out by adding an excess amount to 100 mL of demineralized water or to an aqueous dextran solution [mass fraction is from (0.1 to 1.5) %] in sealed glass containers. The stoppered tubes were rotated for 60 h in water baths at (293.15, 298.15, 303.15, 308.15, and 313.15) K, respectively. Preliminary experiments had shown that this time period was sufficient to ensure saturation. After 60 h, the rotation was stopped, and the saturated solutions were kept still for 2 days at the equilibrium temperature to ensure that the solid was deposited. The solution was filtered through a 0.20 μm membrane filter (Anpel Science Instrument Com., Shanghai, China), which was performed in the water bath at the equilibrium temperature, and then diluted with water or aqueous dextran solution to prevent crystallization. The known masses of saturated solution and dilution solvent were used to ensure that the drug concentration

Table 4. Mass Fraction Solubility (S) of Silybin (1) in Dextran 40000 (2) + Water (3)

	$10^4\,S$				
$100w_2$	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0	0.424	0.540	0.691	0.833	0.997
0.1004	0.610	0.775	0.910	1.10	1.26
0.2005	0.716	0.907	1.02	1.23	1.43
0.4014	0.821	0.966	1.15	1.30	1.53
0.5996	0.878	0.990	1.17	1.37	1.56
0.8010	0.931	0.998	1.14	1.41	1.62
1.001	0.981	1.08	1.24	1.47	1.66
1.201	1.06	1.21	1.35	1.51	1.71
1.498	1.11	1.24	1.40	1.60	1.75

was calculable. Three tubes containing identical aqueous dextran solution were used for comparing tests. Silybin concentration in each tube was detected in triplicate. An experimental uncertainty study for silybin in pure water at temperatures from (293.15 to 313.15) K showed that the mean value of the relative standard deviation is 0.023. The concentration of silybin in the diluted solution was analyzed by a UV−vis spectrometer.

Results and Discussions

Thermodynamic Equations. For ternary solution in this work, component indexes are assigned for (1) silybin, (2) dextran, and (3) water. The solubility (mole fraction) x_1 of a solid solute (1) in solution is given by[19,20]

$$\ln \gamma_1 x_1 = -\frac{\Delta_{\mathrm{fus}}\mathrm{H_m}}{RT}\left(1 - \frac{T}{T_\mathrm{m}}\right) \tag{2}$$

where γ_1 is the acitivity coefficient at temperature T, and T_m is the melting temperature of pure solid solute 1.

In general, solubility of drug is expressed in mass fraction (S). The enthalpy of solution ($\Delta_{\mathrm{sol}}H_\mathrm{m}$) can be evaluated from the slopes of the van't Hoff plots by using

$$\ln S = -\Delta_{\mathrm{sol}}H_\mathrm{m}/(RT) + K \tag{3}$$

where K is independent of temperature, and $-\Delta_{\mathrm{sol}}H_\mathrm{m}$ is related to $-\Delta_{\mathrm{fus}}H_\mathrm{m}$ and $[\partial \ln \gamma_1/\partial(1/T)]$.

On considering the transport Gibbs free energy ($\Delta_{\mathrm{tr}}G$), enthalpy ($\Delta_{\mathrm{tr}}H$), and entropy ($\Delta_{\mathrm{tr}}S$) for silybin from pure water (3) to dextran (2) + water (3), we have

$$\Delta_{\mathrm{tr}}G = -RT \ln[S(2+3)/S(3)] \tag{4}$$

$$\Delta_{\mathrm{tr}}H = \Delta_{\mathrm{sol}}H_\mathrm{m}(2+3) - \Delta_{\mathrm{sol}}H_\mathrm{m}(3) \tag{5}$$

$$\Delta_{\mathrm{tr}}S = (\Delta_{\mathrm{tr}}H - \Delta_{\mathrm{tr}}G)/T \tag{6}$$

where $S(2+3)$ and $S(3)$ is the solubility of drug in aqueous dextran solution and water, respectively. $\Delta_{\mathrm{sol}}H_\mathrm{m}(2+3)$ and $\Delta_{\mathrm{sol}}H_\mathrm{m}(3)$ is the molar enthalpy of solution of silybin in aqueous dextran solution and water, respectively.

Solubility. The solubility of silybin in aqueous dextran 40000 solutions is determined at temperatures of (293.15, 298.15, 303.15 308.15 and 313.15) K, respectively. The data of solubility is provided in Table 4. The dextran concentrations are converted from mass per unit volume at 298.15 K to the mass percent. It can be found from Table 4 that the solubility of silybin is increased with the increase in dextran's concentration and temperature.

Thermodynamic Properties. At fixed dextran concentration, the plots of $\ln S$ versus $1/T$ are approximately linear. The enthalpy of solution ($\Delta_{\mathrm{sol}}H_\mathrm{m}$) can be calculated from the slopes of eq 3. The values of $\Delta_{\mathrm{sol}}H_\mathrm{m}$ are presented in Table 5. In Table 6, the standard deviations (σ) of the linear fitting are listed. From these data, the uncertainty of $\Delta_{\mathrm{sol}}H_\mathrm{m}$ is predicated to be 0.8 kJ·mol^{-1}. The endothermic enthalpy of solution further explains the increase in solubility with temperature. With the increase in dextran concentration, $\Delta_{\mathrm{sol}}H_\mathrm{m}$ decreases, which leads to the solubility increase.

Table 5. Enthalpy of Solution of Silybin ($\Delta_{\mathrm{sol}}H_\mathrm{m}$) and Transport Entropy ($\Delta_{\mathrm{tr}}S$) for Silybin (1) from Water (3) to Dextran (2) + Water (3)

	$\Delta_{\mathrm{sol}}H_\mathrm{m}$	$\Delta_{\mathrm{tr}}S$/J·K^{-1}·mol^{-1} at T/K				
$100w_2$	kJ·mol^{-1}	293.15	298.15	303.15	308.15	313.15
0	32.7					
0.1004	27.6	−15	−14	−15	−14	−14
0.2005	25.8	−19	−19	−19	−19	−19
0.4014	23.5	−26	−26	−26	−26	−26
0.5996	22.6	−29	−29	−29	−29	−29
0.8010	22.0	−30	−31	−31	−30	−30
1.001	20.6	−34	−35	−35	−35	−35
1.201	17.9	−43	−43	−43	−43	−43
1.498	17.6	−43	−44	−44	−43	−43

Table 6. Standard Deviations (σ) and Correlation Coefficient (R) for Linear Fittings of $\ln(10^4\,S) = A + 1000B/(T/\mathrm{K})$, and the Predicted Uncertainty of $\delta\Delta_{\mathrm{sol}}H_\mathrm{m}$, $\delta\Delta_{\mathrm{tr}}G$, and $\delta\Delta_{\mathrm{tr}}S$

$100w_2$	R	σ
0	0.9983	0.022
0.1004	0.9970	0.025
0.2005	0.9961	0.027
0.4014	0.9990	0.012
0.5996	0.9983	0.015
0.8010	0.9841	0.047
1.001	0.9950	0.024
1.201	0.9995	0.006
1.498	0.9987	0.010
average		0.021

$\delta\Delta_{\mathrm{tr}}G$/kJ·mol^{-1}	$\delta\Delta_{\mathrm{sol}}H_\mathrm{m}$/kJ·mol^{-1}	$\delta\Delta_{\mathrm{tr}}S$/J·K^{-1}·mol^{-1}
0.05	0.8	3.1

The transport entropy of silybin from water to aqueous dextran solution ($\Delta_{\mathrm{tr}}S$) can be calculated from eq 6. The values of $\Delta_{\mathrm{tr}}G$ and $\Delta_{\mathrm{tr}}H$ are calculated by eqs 4 and 5, respectively. The values of $\Delta_{\mathrm{tr}}S$ are presented in Table 5. The predicted uncertainty of $\Delta_{\mathrm{tr}}G$ and $\Delta_{\mathrm{tr}}S$ are provided in Table 6. The comparison of enthalpy and entropy effect is shown in Figure 2. Two characteristics can be found in Figure 2. First, for $T\Delta_{\mathrm{tr}}S$, the temperature effect is small. Second, with the increase in dextran's concentration, $\Delta_{\mathrm{tr}}H$ and $T\Delta_{\mathrm{tr}}S$ become more negative, in which $\Delta_{\mathrm{tr}}H$ drops more rapidly. This phenomenon is an indication that, with the increase in dextran concentration, enthalpy effect causes drug dissolution more favorable, but the entropy effect causes the dissolution to be difficult since $\Delta_{\mathrm{tr}}H$ is more negative than $\mathrm{T}\Delta_{\mathrm{tr}}S$.

Activity Coefficient by UNIQUAC. To correlate drug solubility, an important procedure is to calculate the activity coefficient of the drug in aqueous solution. By the UNIQUAC model, the activity coefficient is composed of two parts, the combinatorial and residual part:[19]

$$\ln \gamma_1 = \ln \gamma_1^{\mathrm{com}} + \ln \gamma_1^{\mathrm{res}} \tag{7}$$

In calculating γ_1^{com}, group parameters R_k and Q_k are obtained from literature.[19] Parameters r_i and q_i for silybin and dextran are listed in Table 7. The van der Waals volume (V_w) is calculated by group-contribution method as described by Bondi.[21]

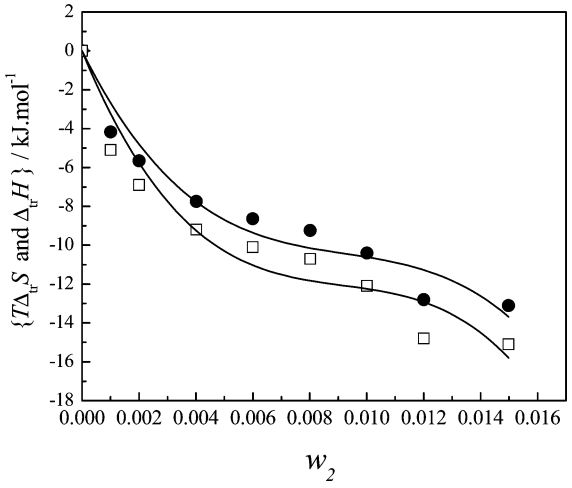

Figure 2. Transport enthalpy ($\Delta_{tr}H$) and entropy ($T\Delta_{tr}S$) for silybin (1) from water (3) to dextran (2) + water (3) as a function of mass fraction of dextran (w_2) at $T = 298.15$ K: □, $\Delta_{tr}H$; ●, $T\Delta_{tr}S$.

Table 7. UNIQUAC Parameters and van der Waals Volume

component	r_i	q_i	V_w/cm^3·mol^{-1}
silybin (1)	16.603	12.384	233.51
dextran monomer unit (2)	6.397	5.760	72.3
water (3)	0.920	1.400	11.49

The term of $\ln \gamma_i^{res}$ is calculated by

$$\ln \gamma_i^{res} = q_i\left[1 - \ln\left(\sum_j \theta_j \tau_{ji}\right) - \sum_j \left(\theta_j \tau_{ij} \Big/ \sum_k \theta_k \tau_{kj}\right)\right] \quad (8)$$

where

$$\tau_{ji} = \exp[-(u_{ji} - u_{ii})/T] \quad (9)$$

Parameters u_{ji} *and* u_{ii} can be obtained by fitting experimental solubility data via eq 2.

For binary system of silybin dissolves in water, solubility data were located within the infinite dilution region; the role of parameter τ_{13} plays in curve fitting is to adjust the intercept of the curve $\ln \gamma_1^{res}$ as a function of $1/T$ curve. To obtain parameters u_{13}, u_{11}, and u_{33}, the solubility data of water in silybin solvent are needed, but this is difficult. Therefore, for the convenience of data fitting, τ_{13} is assumed to be evaluated by $\tau_{13} = \exp[-(u_{13} - u_{33})/T_0]$. Where T_0 is a reference temperature, here it is 293.15 K. By using a nonlinear least-squares fitting technique based on the Levenberg−Marquardt algorithm, which is performed by software of Origin 6.1 (OriginLab Corporation), the fitting results were obtained and presented in Table 8.

For a ternary system, other parameters such as u_{12}, u_{22}, u_{23}, and u_{22} should be regressed from ternary solubility data by eq 8. But the fitting result is not satisfying. The standard deviation and the correlation coefficient are 0.14 and 0.8991, respectively.

To improving the fitting result, modification on UNIQUAC was introduced. It was supposed that the interaction parameter (u_{ij}) is concentration and temperature dependent. For the system studied here, the saturation concentration of silybin was within a much dilute region (so that it was supposed to be at infinite dilution), and the concentration of dextran was within the dilute region too. Parameters u_{13} and u_{12} are connected with the solubility of silybin in pure water and dextran, respectively. Therefore, it was supposed that the change in dextran's concentration is responsible for the changes in parameter u_{23}. That is only u_{23} is dextran concentration dependent, and the composition effect on other parameters, for example, u_{12} and u_{13}, can be neglected. The correctness of this assumption is confirmed by our data fit test. On considering temperature effect, Larsen et al.[22] proposed that interaction parameter is temperature dependent. If we suppose that the temperature and composition effect on u_{23} is described by a linear dependence equation, then we have

$$u_{23} = u_{230} + u_{231}(T - T_0)/T_0 + u_{232}(\theta_3 - \theta_2) \quad (10)$$

where T_0 is an arbitrary reference temperature, here it is 293.15 K. The u_{230}, u_{231}, and u_{232} are linear parameters. In view of concentration limit, temperature dependence for parameters u_{12} and u_{13} are neglected. Applying these modifications to correlate the solubility data, the fitting result was improved greatly. The results are listed in Table 8 and graphically shown in Figure 3. If the temperature and composition dependence modification were applied to parameter u_{12}, the agreement between experimental and theory was not improved further; moreover, the number of adjusting parameter was increased. Therefore, the favorable project is to consider the modification on u_{23} alone.

Table 8. Interaction Parameters (u_{ij} and u_{ijk}) of Modified UNIQUAC Model, Standard Deviation (σ) and Correlation Coefficient (R)[a]

parameter	binary system silybin (1) + water (3)	ternary system silybin (1) + dextran (2) + water (3)
σ	0.027	0.062
R	0.9985	0.9827
u_{13}/K	1.268	1.268
u_{11}/K	120.2	120.2
u_{33}/K	−221.1	−221.1
u_{12}/K		−120.0
u_{22}/K		−923.6
u_{230}/K		−36320
u_{231}/K		−6479
u_{232}/K		37760

[a] $\sigma = \{\sum_j [10^4 S_j^{exp} - 10^4 S_j^{the}]^2/(n - p)\}^{1/2}$, where n is the total number of experimental points and p is the total number of adjustable parameters used in the fitting.

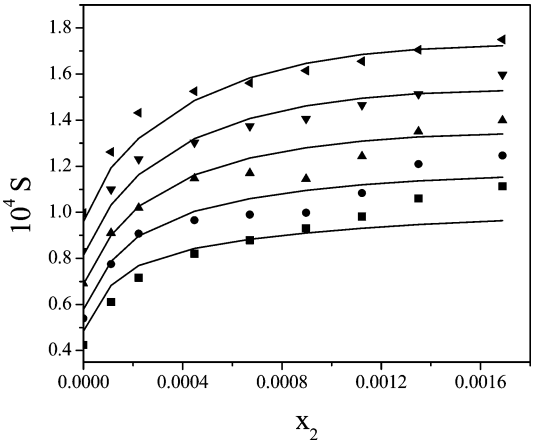

Figure 3. Mass fraction solubility (S) of silybin (1) in dextran (2) + water (3). x_2 mole fraction. Experimental: T = (■, 293.15; ●, 298.15; ▲, 303.15; ▼, 308.15; and sideways solid triangle, 313.15) K. Lines −, modified UNIQUAC correlation.

Conclusion

The solubility of silybin is increased with the increase in both dextran's concentration and temperature. At fixed dextran concentration, the enthalpy of solution ($\Delta_{sol}H_m$) can be calculated from the slopes of the van't Hoff plots.

The characteristic of transport enthalpy and entropy for silybin from water to aqueous dextran solution reveals that, with the increase in dextran's concentration, the enthalpy effect causes drug dissolution to be more favorable, but the entropy effect causes the dissolution to be difficult.

A modified UNIQUAC model was used to correlate drug solubility. By introducing linear adjustable parameters, the model gives good quality correlations.

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