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Solubility of silybin in aqueous poly(ethylene glycol) solution

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Abstract

Silybin is a main component in silymarin, which is an antihepatotoxic polyphenolic substance isolated from the milk thistle plant, *Silybum marianum*. A major problem in the development of an oral solid dosage form of this drug is the extremely poor aqueous solubility. In present work, the solubility of silybin in aqueous poly(ethylene glycol) 6000 (PEG 6000) solution at the temperature range from 293.15 to 313.15 K was measured by a solid liquid equilibrium method. The aim of this study is to investigate the possible effect of poly(ethylene glycol) concentration and temperature on the solubility of the drug, and to reveal the solubilization capacity of the polymer for the drug. Experimental results reveal that the solubility of silybin increases with the increase both in PEG's concentration and temperature. With the increase in PEG's concentration, the transfer enthalpy and entropy for silybin from water to aqueous PEG solution increases first in a positive region, and then decreases to a negative region. The transfer enthalpy is lower than the entropy term. A modified Universal Quasi Chemical (UNIQUAC) model was used to correlate solubility data.

Keywords: Silybin; Poly(ethylene glycol); Solubility; The Universal Quasi Chemical (UNIQUAC) model

1. 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 has been developed, reaching 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 (Jinno et al., 2000; Kallinteri and Antimisiaris, 2001; Verheyen et al., 2002; Viernstein et al., 2003).

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 structure of silybin, isosilybin, silydianin and silychristin are shown in Fig. 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 (Kvasnicka et al., 2003). Its 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 (Li et al., 2003).

The solubility enhancement of poorly soluble compounds can be induced by changes of temperature and solvation properties using different cosolvent compositions (Viernstein et al., 2003). 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) (Verheyen et al., 2002; Damian et al., 2000) and poly(vinylpyrrolidone) (PVP) (Van den Mooter et al., 2001), have frequently been used as a

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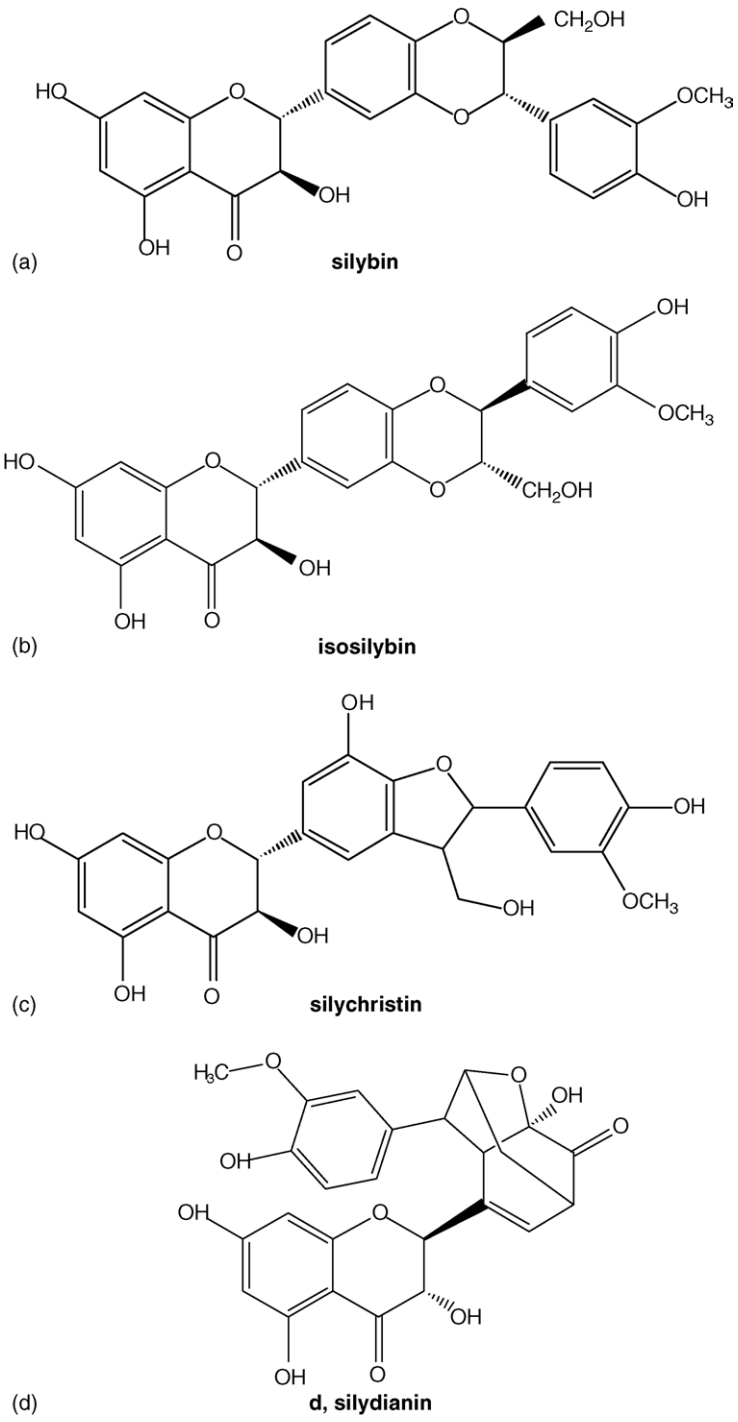

Fig. 1. Molecular structures of (a) 3,5,7-trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-2,3-dihydrobenzo[1,4]dioxin-6-yl]-chroman-4-one, silybin; (b) 3,5,7-trihydroxy-2-[2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzo[l,4]dioxin-6-yl]-chroman-4-one, isosilybin; (c) 3,5,7-trihydroxy-2-[7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzofuran-5-yl]-chroman-4-one, silychristin; (d) 8-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4-(3,5,7-trihydroxy-4-oxo-chroman-2-yl)-9-oxa-tricyclo[4.3.1.$0^{3,8}$]dec-4-en-7-one, silydianin.

carrier in solid dispersion formulations. Numerous attempts to understand the physico-chemical principle behind the improvement of the dissolution of drugs by solid dispersion formulation with polymers have been reported (Verheyen et al., 2002). 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 (Jouyban-Gharamaleki and Acree, 1998). Enthalpy of solution values can be measured directly from the temperature dependence of the saturation concentration (Viernstein et al., 2003; Verheyen et al., 2002; Reinwald and Zimmermann, 1998). In this work, we focus our attention on the solubilization capacity of PEG in 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 the 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 (Jouyban-Gharamaleki and Acree, 1998; Jouyban-Gharamaleki et al., 1999, 2001). 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 present work, solubilities of silybin in aqueous PEG 6000 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 is to investigate the possible effect of PEG concentration and temperature on the solubility of the drug. The modified Universal Quasi Chemical (UNIQUAC) model was used to correlate the solubility data.

2. Experimental

2.1. Materials

Silybin was purchased from Panjin Green Biological Development Co. Ltd., Liaoning, China. Its purity was claimed to be 97% detected by a UV-spectrometer at the wavelength 252–288 nm by the company. The drug was recrystallized in methanol and being dried under vacuum at 353 K over 24 h, and then 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 Fig. 1. Silycristin and silydianin are hydrophobic drug effective components. They have similar medicine effect as silybin. In a drug sample, the content of these hydrophobic impurities is too small, and they hardly dissolve in water. Their impact on the solubility of silybin is difficult to consider. 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.

PEG 6000 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.

2.2. 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 a differential scanning calorimeter (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 3–8 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 thermogravimetry (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.

Table 1
Physical properties of silybin

Properties	Silybin
M_w (g mol^{-1})	482.436
T_m (K)	424 ± 1
$\Delta_{fus}H$ (J g^{-1})	93 ± 2

2.3. 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. Therefore, calibration equation was prepared within the range of 288–285 nm. For silybin + PEG + water solution, the maximum absorption wavelength can be controlled within this maximum wavelength range by diluting it with known masses of PEG + water solution.

In this work, the solubility data of silybin was measured in PEG 6000 aqueous solution. But the calibration equation of silybin was prepared in ethanol. By considering the solvent effect on the maximum absorption of UV spectra, we noticed that, the difference of absorbance between ethanol and water is much small (within the experimental error), but the solvent effect of PEG aqueous solution is obvious. However, by using a proper reference solvent (the blank), the solvent effect of aqueous PEG solution on UV absorbance can be eliminated.

In solubility determination, silybin samples were taken from equilibrium bottles. Known masses of the aqueous PEG 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 + PEG + water solution, the wavelength used in the determination is at their maximum absorption, mostly at $\lambda = 287$ nm. To eliminate the solvent effect on absorbance, the blank was filled with the identical solvent with the sample.

2.4. Solubility measurements

Binary solutions of PEG 6000 + water were prepared. Known masses of PEG were added into 250 cm^3 volumetric flask. Water was added into the flask. 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 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 PEG 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 PEG solution [mass fraction is from 0.1 to 2.0%] 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 the solid was deposited. The solution was filtered through a 0.20 μm membrane filter (Anpel Science Instrument Co., Shanghai), which was performed in the water bath at the equilibrium temperature, and then diluted with water or aqueous PEG solution to prevent crystallization. The known masses saturated solution and dilution solvent were used to ensure that the drug concentration was calculable. Three tubes containing identical aqueous PEG solution were used for comparing test. Silybin concentration in each tube was detected triplicate. 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.

3. Results and discussions

3.1. Thermodynamic equations

For ternary solution in this work, component indexes are assigned for (1) silybin, (2) PEG and (3) water. The solubility (mole fraction) x_1 of a solid solute (1) in solution is given by Reid et al. (1987) and Acree (1984)

$$\ln \gamma_1 x_1 = -\frac{\Delta_{fus} H_m}{RT}\left(1 - \frac{T}{T_m}\right) \quad (1)$$

where γ_1 is the acitivity coefficient at temperature T, and T_m is the melting temperature of pure solid solute (1). $\Delta_{fus}H_m$ is the molar enthalpy of fusion of solute (1).

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

$$\ln S = -\frac{\Delta_{sol} H_m}{RT} + K \quad (2)$$

Table 2
Solubility (mass fraction, $\times 10^4 S$) of silybin in aqueous PEG 6000 solution, w_2 mass fraction of PEG

$100w_2$	T (K)				
	293.15	298.15	303.15	308.15	313.15
0	0.424	0.540	0.691	0.833	0.997
0.1000	0.626	0.780	0.916	1.16	1.52
0.2005	0.725	0.975	1.19	1.50	1.82
0.5001	0.866	1.11	1.40	1.85	2.29
0.7997	1.01	1.27	1.61	2.13	2.67
0.9995	1.12	1.50	1.96	2.36	2.79
1.203	1.23	1.53	1.95	2.36	2.98
1.501	1.42	1.70	2.10	2.51	3.12
2.000	1.74	2.13	2.55	3.02	3.53

The relative standard error is 0.023.

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

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

$$\Delta_{tr}G = -RT \ln\left[\frac{S(2+3)}{S(3)}\right] \quad (3)$$

$$\Delta_{tr}H = \Delta_{sol}H_m(2+3) - \Delta_{sol}H_m(3) \quad (4)$$

$$\Delta_{tr}S = \frac{\Delta_{tr}H - \Delta_{tr}G}{T} \quad (5)$$

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

3.2. Solubility

The solubility of silybin in PEG 6000 aqueous solution is determined at temperatures of 293.15, 298.15, 303.15 308.15 and 313.15 K, respectively. The data of solubility is presented in Table 2. The PEG concentrations are converted from mass per unit volume at 298.15 K to the mass percent. It can be found from Table 2 that, the solubility of silybin increases with the increase in PEG's concentration and temperature.

3.3. Thermodynamic properties

At fixed PEG concentration, the plots of $\ln S$ versus $1/T$ are approximately linear. The enthalpy of solution ($\Delta_{sol}H_m$) can be calculated from the slopes of Eq. (2). The values of $\Delta_{sol}H_m$ are presented in Table 3. From the standard deviations of the linear fitting, the uncertainty of $\Delta_{sol}H_m$ is predicated to be 0.5 kJ mol^{-1}. The endothermic enthalpy of solution further explains the increase in solubility with temperature. With the increase in PEG concentration, $\Delta_{sol}H_m$ increases first, and then decreases.

The transfer entropy ($\Delta_{tr}S$) can be calculated by Eq. (5). The values of $\Delta_{tr}G$ and $\Delta_{tr}H$ are calculated by Eqs. (3) and (4), respectively. The values of $\Delta_{tr}S$ are presented in Table 3. The

Table 3
The enthalpy of solution ($\Delta_{sol}H_m$) of silybin in aqueous PEG solution, the transfer entropy ($\Delta_{tr}S$) for silybin from water to aqueous PEG solution, and the predicted uncertainty on enthalpy of solution ($\delta\Delta_{sol}H_m$), transfer free energy ($\delta\Delta_{tr}G$) and transfer entropy ($\delta\Delta_{tr}S$)

$100w_2$	$\Delta_{sol}H_m$ (kJ mol^{-1})	$\Delta_{tr}S$ (J K^{-1} mol^{-1}) at T (K)				
		293.15	298.15	303.15	308.15	313.15
0	32.7					
0.1000	33.1	4.66	4.46	3.73	4.13	4.85
0.2005	34.7	11.2	11.5	11.1	11.3	11.3
0.5001	37.5	22.3	22.1	21.7	22.2	22.3
0.7997	37.6	23.8	23.5	23.1	23.6	23.8
0.9995	34.9	15.4	15.7	15.8	15.7	15.5
1.203	33.5	11.5	11.3	11.2	11.2	11.6
1.501	29.9	0.47	0.12	−0.03	0.06	0.52
2.000	26.9	−8.15	−8.13	−8.36	−8.21	−8.10
$\delta\Delta_{tr}G$ (kJ mol^{-1})			0.05			
$\delta\Delta_{sol}H_m$ (kJ mol^{-1})			0.5			
$\delta\Delta_{tr}S$ (J K^{-1} mol^{-1})			0.2			

predicted uncertainty of $\Delta_{tr}G$ and $\Delta_{tr}S$ are listed in Table 3. The comparison of enthalpy and entropy effect is shown in Fig. 2. Two characteristics can be observed from Fig. 2. First, for $T\Delta_{tr}S$, the temperature effect is small. Second, the concentration effect: with the increase in PEG's concentration, $\Delta_{tr}H$ and $T\Delta_{tr}S$ increases first within positive region, and then decreases to a negative region. The curve of $\Delta_{tr}H$ always locates in a lower side. This phenomenon is an indication that within the positive region, the process of drug dissolution is entropy favorable and enthalpy unfavorable, and entropy effect is over the enthalpy effect. But within the negative region, the contribution from enthalpy term and entropy term is reversed, the enthalpy effect causes drug dissolution more favorable, but the entropy effect leads to the dissolution to be difficult, since $\Delta_{tr}H$ is more negative than $T\Delta_{tr}S$.

To discuss the meaning of the convex curves of enthalpy, we simply suppose that the transfer enthalpy can be expressed by a polynomial expansion, this is a customary way of dealing with interaction between solutes in a solvent (Jones, 1988; Lilley, 1994).

$$\Delta_{tr}H = h_{12}w_2 + h_{13}w_3 + h_{23}w_2w_3 \quad (6)$$

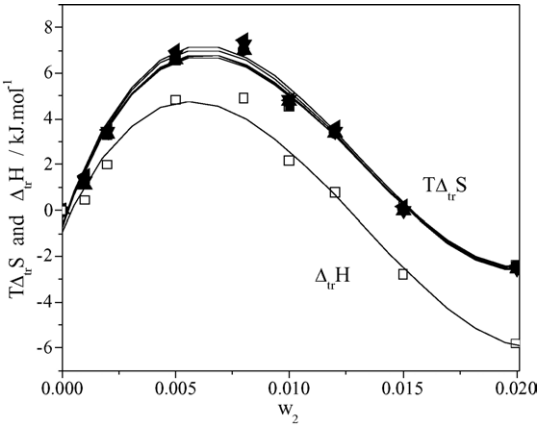

Fig. 2. Transfer enthalpy ($\Delta_{tr}H$, □) and transfer entropy ($T\Delta_{tr}S$) at T = (■) 293.15; (●) 298.15; (▲) 303.15; (▼) 308.15; (◀) 313.15 K, for silybin from water to aqueous PEG solution as a function of mass fraction of PEG (w_2).

where the w_2 and w_3 are the mass fraction of PEG and water, respectively. Qualitatively, the coefficients of h_{12} and h_{13} express the effect from the interaction of silybin (1)–PEG (2), and silybin (1)–water (3) on $\Delta_{tr}H$, respectively. The coefficient of h_{23} expresses the effect from the interaction between PEG (2) and water (3) on the $\Delta_{tr}H$. Using least square method to fit the data of $\Delta_{tr}H$, coefficients h_{12}, h_{13} and h_{23} can be obtained ($h_{12} = -1.06 \times 10^5$, $h_{13} = -0.284$ and $h_{23} = 1.07 \times 10^5$). By comparing their relative magnitude, we can get some information. Because the value of h_{13} is much small, the effect from the interaction between silybin and water is unobservable. Because the value of h_{12} is negative and much lower, the interaction between silybin and PEG is in favor of the silybin dissolution. On the opposite side, the value of h_{23} is positive and much high, the interaction between PEG and water obstruct the dissolution of silybin. In much dilute concentration region of w_2, h_{23} is responsible for the raise of the $\Delta_{tr}H$ curve. This means that the effect of the interaction between PEG and water is in the ascendant. With the increase in PEG's concentration, the effect of h_{12} is rising, and overcomes h_{23} at the maximum point.

3.4. Activity coefficient by UNIQUAC

To evaluate drug solubility, an important procedure is to calculate the activity coefficient of the drug in aqueous solution. By UNIQUAC model, the activity coefficient is composed of two parts, the combinatorial (γ_1^{com}) and residual (γ_1^{res}) part (Acree, 1984; Reid et al., 1987).

$$\ln\gamma_1 = \ln\gamma_1^{com} + \ln\gamma_1^{res} \quad (7)$$

For a multi-component mixture, the combinatorial term is

$$\ln\gamma_i^{com} = \ln\left(\frac{\Phi_i}{x_i}\right) + \left(\frac{z}{2}\right)q_i\ln\left(\frac{\theta_i}{\Phi_i}\right) + l_i - \left(\frac{\Phi_i}{x_i}\right)\sum x_j l_j \quad (8)$$

with

$$l_i = \left(\frac{z}{2}\right)(r_i - q_i) - (r_i - 1), \quad z = 10 \quad (9)$$

Table 4
UNIQUAC parameters

Component	r_i	q_i
Silybin (1)	16.603	12.384
PEG monomer unit (2)	1.5927	1.32
Water (3)	0.920	1.400

$$\theta_i = \frac{q_i x_i}{\sum q_j x_j}, \qquad \Phi_i = \frac{r_i x_i}{\sum r_j x_j} \tag{10}$$

$$r_i = \sum \nu_k^i R_k, \qquad q_i = \sum \nu_k^i Q_k \tag{11}$$

where θ_i is the surface area fraction, Φ_i the volume fraction for component i. ν_k^i is the number of groups of type k in molecular i. Q_k and R_k are the surface area parameter and volume parameter for group k. In this work, R_k and Q_k are obtained from literature (Reid et al., 1987). Parameters r_i and q_i are listed in Table 4.

For ternary solution in this work, component index are assigned for (1) silybin, (2) PEG and (3) water. Under condition of x_1 approaches to infinite dilution, $\ln \gamma_i^{com}$ can be written as

$$\ln\gamma_i^{com} = \ln\left(\frac{r_1}{\sum r_j x_j}\right) + \left(\frac{z}{2}\right) q_1 \ln\left(\frac{q_1 \sum r_j x_j}{r_1 \sum q_j x_j}\right) + l_1 - \left(\frac{r_1}{\sum r_j x_j}\right) \sum x_j l_j \tag{12}$$

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

$$\ln \gamma_i^{res} = q_i \left[1 - \ln\left(\sum_j \theta_j \tau_{ji}\right) - \sum_j \left(\frac{\theta_j \tau_{ij}}{\sum_k \theta_k \tau_{kj}}\right)\right] \tag{13}$$

where

$$\tau_{ji} = \exp\left[-\frac{u_{ji} - u_{ii}}{T}\right] \tag{14}$$

τ_{ji} is the Boltzmann factor in UNIQUAC model. Parameters u_{ji} and u_{ii} are related to the molecular interaction of j–i and i–i, respectively, and usually are obtained by fitting experimental data. In this work, u_{ji} and u_{ii} are obtained by fitting experimental solubility data via Eq. (1). The UNIQUAC model can mathematically represent thermodynamic excess properties with a reasonable degree of accuracy.

For binary system of silybin dissolves in water, solubility data was 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 $1/T$. To obtain parameters u_{13}, u_{11} and u_{33}, the solubility data of water in silybin solvent is 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 5.

Table 5
The interaction parameters (u_{ij} and u_{ijk}) of modified UNIQUAC model, the adjustable parameters in Eq. (15), the standard deviation (σ) and the correlation coefficient (R)

Parameter	Binary system, silybin (1) + water (3)	Ternary system, silybin (1) + PEG (2) + water (3)	
	UNIQUAC	UNIQUAC	Modified UNIQUAC
σ	0.027	0.108	0.078
R	0.9984	0.9907	0.9954
u_{13} (K)	1.268	1.268	1.268
u_{11} (K)	120.2	120.2	120.2
u_{33} (K)	−221.1	−221.1	−221.1
u_{12} (K)		−117.4	−111.5
u_{22} (K)		−887.4	−816.2
u_{230} (K)		1299	1114
u_{231} (K)			−383400
u_{232} (K)			386500

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

For a ternary system, other parameters, such as u_{12}, u_{23} and u_{22} should be regressed from ternary solubility data by Eq. (13). But the fitting result is not satisfying. The standard deviation is 0.108. However, the correlation coefficient is fairly good ($R = 0.9907$).

To improve the fitting accuracy, modification on UNIQUAC was introduced. It was supposed that the interaction parameter (u_{ij}) is concentration and temperature dependent. In this work, the saturation concentration of silybin is within a much dilute region, and the concentration of PEG was within the dilute region too. Therefore, it was supposed that only u_{23} is concentration dependent. On considering the temperature effect, Larsen et al. (1987) proposed that interaction parameter is temperature dependent. Combining the temperature and concentration effect on u_{23}, we proposed an equation

$$u_{23} = u_{230} + [u_{231} + u_{232}(\theta_3 - \theta_2)]\frac{T - T_0}{T_0} \tag{15}$$

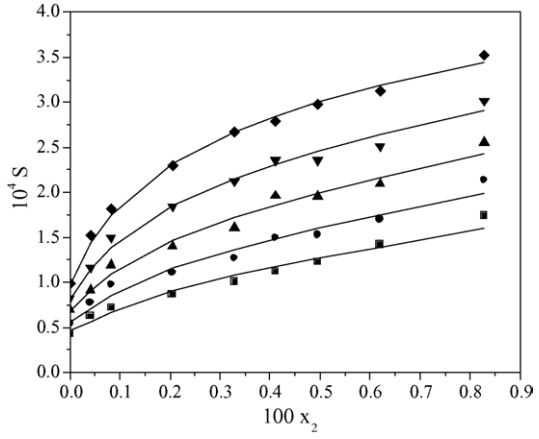

Fig. 3. Mass fraction solubility (S) of silybin (1) in PEG 6000 (2) + water (3), x_2 mole fraction of PEG monomer unit. Experimental: T = (■) 293.15; (●) 298.15; (▲) 303.15; (▼) 308.15; (♦) 313.15 K. Lines (—) modified UNIQUAC correlation.

where T_0 is an arbitrary reference temperature, here it is 293.15 K. The u_{230}, u_{231} and u_{232} are adjustable parameters. The effect of concentration and temperature on u_{12} and u_{13} are neglected. Applying these modifications to correlate the solubility data, the fitting result was improved significantly. The interaction parameters and adjustable parameters are listed in Table 5. Correlation results are graphically shown in Fig. 3.

4. Conclusion

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

The characteristics of transfer enthalpy and entropy for silybin from water to aqueous PEG solution reveal that, with the increase in PEG's concentration, $\Delta_{tr}H$ and $T\,\Delta_{tr}S$ increase first and then decrease from a positive region to a negative region. Within the positive region, the dissolution process is entropy favorable and enthalpy unfavorable, and entropy effect is overcomes the enthalpy effect. However in the negative region, drug dissolution is enthalpy favorable and entropy unfavorable, and enthalpy effect is overcomes the entropy effect.

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

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