Solubility of Artemisinin in Different Single and Binary Solvent Mixtures Between (284.15 and 323.15) K and NRTL Interaction Parameters

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The solubility of artemisnin in 12 different organic solvents, methanol, ethanol, butanol, acetone, ethyl acetate, isopropyl acetate, acetonitrile, hexane, heptane, 2-butanone (MEK), methyl *tert*-butyl ether (MTBE), and toluene, as well as in three binary solvent mixtures of ethyl acetate + ethanol, ethyl acetate + acetone, and ethanol + acetone, within the temperature range of (284.10 and 323.15) K, is obtained. The solubility data were fitted to the Two-Liquid-Non-Random (NRTL) activity coefficient equation to obtain the model binary interaction parameters, which were used to predict the solubility of artemisinin in ethyl acetate and acetone or ethanol binary solvent mixtures. The predicted values compared favorably with the experimental data.

Introduction

The production of pharmaceuticals and oligo-sized biochemicals involves liquid solvent selection as a function of solubility, for purification, chemical reaction, and formulation. Selecting the optimum solvent for a particular application is of critical importance to developing an efficient process; choosing solvents for pharmaceutical processes has been based on experience and empirical description of experimental results. Therefore, a rapid and reliable method for measuring solubility of drug compounds is needed for design and optimization of cost-effective manufacturing processes. For this reason, solubilities for a wide range of pharmaceutical and drug compounds have been measured in different solvents and reported in the literature.[1−8]

Artemisinin, known in Chinese as Qinghaosu, is an important bioactive component in *Artemisia annua* leaves and flowers, which has been used as a traditional Chinese medicine in the treatment of fever for a long time.[9] The compound is a sesquiterpene lactone endoperoxide (shown in Figure 1), and a number of its precursors, metabolites, and semisynthetic derivatives have recently been shown to possess antimalarial properties.[10] Artemisinin itself has physical properties such as poor bioavailability that limit its effectiveness, and therefore, its semisynthetic derivatives, including artemether and artesunate, have been developed.[11] Their activity is not long lasting in the serum, with significant decreases in effectiveness after one to two hours. Therefore, it is typically given with lumefantrine (also known as benflumetol) to treat uncomplicated *falciparum* malaria.[11] The treatments are called "ACT" (artemisinin-based combination therapy); other examples are artemether-lumefantrine, artesunate-mefloquine, artesunate-amodiaquine, and artesunate-sulfadoxine/pyrimethamine.[11] Recent trials have shown that these therapies are more than 90 % effective, with a recovery from symptoms after three days, especially for the chloroquine-resistant *Plasmodium falciparum*.[12]

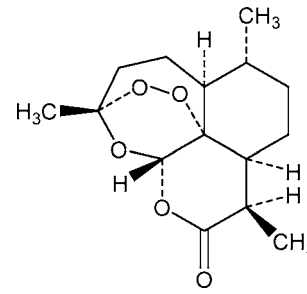

Figure 1. Structure of artemisinin (MW = 282.33).

Malaria is a vector-borne infectious disease caused by protozoan parasites. It is widespread in tropical and subtropical regions, including parts of the Americas, Asia, and Africa.[11] According to the World Health Organization (WHO), each year there are approximately 350 to 500 million cases of malaria, killing between one and three million people, the majority of whom are young children in Sub-Saharan Africa.[11] Malaria is commonly associated with poverty but is also a cause of poverty and a major hindrance to economic development.[12,13] Therefore, industrial production of artemisinin is becoming particularly important.

Most of the *Artemisia annua* grown worldwide is currently processed via solvent extraction, using warm hexane and/or petroleum ether.[11] In as much as both hexane and petroleum ether are cheap solvents, they present considerable safety and environmental hazards. To choose alternative solvents, solubility data will be needed. There is limited solubility data in the literature for artemisinin. Liu and co-workers recently reported the solubility of artemisinin in seven pure organic solvents.[14] Expanded solubility data in other solvents, and a thermodynamic

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Table 1. Polarity Indexes of the Solvents Used in this Study[15]

solvent	polarity index
acetonitrile	5.8
ethanol	5.2
methanol, or acetone	5.1
MEK	4.5
ethyl acetate	4.4
isopropyl acetate	4.2
butanol	4.0
MTBE	2.5
toluene	2.4

model for estimating solubility of artemisinin in binary solvent mixtures using data from single solvent measurements, will be essential for the development of optimum extraction and crystallization processes for this compound.

In this work, we leverage a previously designed automated material-conserving solubility measuring technique[2] to rapidly determine the equilibrium solubility of artemisinin in 12 single organic solvents, methanol, ethanol, butanol, acetone, ethyl acetate, isopropyl acetate, acetonitrile, hexane, heptane, 2-butanone (MEK), methyl *tert*-butyl ether (MTBE), and toluene, within a temperature range of (284.10 and 323.15) K. Additionally, we measure the solubility of artemisinin in three binary solvent mixtures of ethyl acetate + ethanol, ethyl acetate + acetone, and ethanol + acetone, at 273.15 K, 283.15 K, and 303.15 K. The solvents were chosen to represent commonly used pharmaceutical process solvents as well as to cover a wide range of solvent polarity (as reflected in Table 1).

Five solvents studied in this work were considered by Liu et al.,[14] namely, methanol, acetone, ethyl acetate, acetonitrile, and toluene. We compare our solubility with those obtained in that study at (298.15 and 323.15) K. Additionally, we measure the melting point temperature and the enthalpy of fusion of artemisinin by using differential scanning calorimetry (DSC). The solubility data were fitted to a thermodynamic model to obtain the value of the difference in heat capacity of the solid and liquid form of artemisinin, which in turn was combined with the heat of fusion and melting point data to calculate the ideal solubility at different temperatures. The activity coefficients of artemisinin in different solvents were determined from the measured solubility and the estimated ideal solubility. The Non-Random Two-Liquid (NRTL) activity coefficient equation was applied to the data to obtain the binary interaction parameters, which were then used to predict solubility of artemisinin in binary solvent mixtures of ethyl acetate + ethanol, ethyl acetate + acetone, and ethanol + acetone.

Experimental Methods

Material. Crystalline solids of artemisinin ($C_{15}H_{22}O_5$; MW 282.33) were donated by BioResources International Inc. (Somerset, NJ) with mass purity determined by HPLC of 99.8 % wt. HPLC analytical grade reagent solvents (each > 99.5 % purity), methanol, ethanol, butanol, acetone, ethyl acetate, isopropyl acetate, acetonitrile, hexane, heptane, 2-butanone (MEK), methyl *tert*-butyl ether (MTBE), and toluene, were obtained from Fisher Scientific (Suwanee, GA). Each solvent was dried with molecular sieves before use, and purity was confirmed by gas chromatography to be > 99.5 %; water content was determined by Karl Fisher titration to be < 0.005 % wt.

Equipment. A Wrist Action, Burrel, model 75 mechanical shaker; Mettler AE 160 digital analytical balances, sensitivity 0.01 mg; a 2910 Modulated DSC, TA Instruments differential scanning calorimeter; and DSC822e, Mettler-Toledo differential scanning calorimeter were used. Analytical scale solubility experiments were performed using an Agilent HP-1100 HPLC system composed of a quaternary pump, column, and auto sampler thermostat and variable-wavelength detector. A set of five standard stock solutions of the pertinent solute were prepared by appropriate dilution of a stock solution. These were then used to generate a calibration curve (with regression coefficient better than 0.999). The calibration curve was used to determine the equilibrium concentrations of artemisinin upon sampling and analysis.

Reversed-Phase Analytical HPLC Methods. All samples were analyzed by reversed-phase analytical HPLC with UV detection. The column used for the reversed-phase analysis (Symmetry, 4.6 mm I.D. × 50 mm, packed with silica-C-8, 3.5 μm particle diameter) was obtained from Waters Corporation and maintained at 333.15 K. All elutions were carried out at 4.5 mL·min^{-1}, and mobile phase conditions were: started isocratically with 70 % 0.01 M H_3PO_4 (in water) and 30 % acetonitrile for 1 min, followed by a linear gradient to 70 % acetonitrile in 3 min, after which the column was flushed with 100 % acetonitrile for 1 min, then re-equilibrated with 70 % 0.01 M H_3PO_4 (in water) and 30 % acetonitrile for 2 min prior to the next injection (i.e., total run time was 7 min). For each run, the mobile was directed through the sampling needle sample loop into the column to ensure complete loading of the sample to the column. Concentration of the solute was calculated based on a calibration curve, and the value was used to compute the mole fraction solubility, x_1.

Solubility Measurements. Solubility of artemisinin was measured in each of the following 12 organic solvents: methanol, ethanol, butanol, acetone, ethyl acetate, isopropyl acetate, acetonitrile, hexane, heptane, 2-butanone (MEK), methyl *tert*-butyl ether (MTBE), and toluene.

In each pure solvent, or solvent mixture, about 150 mg of the crystalline artemisinin solids (an excess amount of solute) was added to several 2 mL HPLC vials, containing 1.5 mL of the pertinent solvent. The mixtures were stirred in a mechanical shaker, maintained at (325 ± 0.1) K, for 24 h. Visual inspection was carefully made to ensure that there were excess crystalline solids, indicating saturation had been reached. The vials were then loaded into the theromostat-temperature-controlled autosampler of the HPLC, and the temperature was lowered to the desired temperature (at a cooling rate of 0.25 K·h^{-1}). Upon reaching the desired temperature, the mixture was allowed to equilibrate for (24 to 48) h (although our experimental results indicated that 12 h was sufficient for complete equilibration and settling of undissolved solute). Thereafter, the solution was sampled and analyzed by the reversed-phase method to determine the equilibrium concentration of artemisinin in the pertinent solvent.

To avoid any potential differential temperature driven precipitation upon sampling, the HPLC sampling needle was stored in the thermostat-temperature-controlled HPLC autosampler compartment with the samples. Additionally, the needle was positioned to allow careful sampling of 2 μL solution from the top middle portion of the vial; this ensured that the settled solids were not disturbed. Each vial was sampled and analyzed in triplicate to ensure that the system had reached equilibrium at the point of sampling. The solvent mixtures were prepared by weight to within $5 \cdot 10^{-5}$ g.

Differential Scanning Calorimetric (DSC) Measurements. Determination of melting point and enthalpy of fusion were performed by differential scanning calorimetry (DSC). The measurements were carried out at a heating rate of 10 K·min^{-1} in a dynamic nitrogen atmosphere (50 mL·min^{-1}), as follows.

Table 2. Mole Fraction Solubility of Artemisinin, $10^3 \cdot x_1$, in Different Organic Solvents Between (284.15 and 323.15) K

T/K	ethanol	butanol	isopropyl acetate	toluene	methanol	acetone	ethyl acetate	acetonitrile	hexane	heptane	MTBE	MEK
284.15	2.36 ± 0.05	0.85 ± 0.02	6.83 ± 0.14	17.05 ± 0.34	0.56 ± 0.01	4.05 ± 0.05	5.57 ± 0.11	0.84 ± 0.01	(0.50 ± 0.01)·10^{-1}	(0.51 ± 0.01)·10^{-1}	1.09 ± 0.02	16.33 ± 0.33
289.15	3.05 ± 0.3	1.27 ± 0.05	8.38 ± 0.16	22.61 ± 0.28	0.78 ± 0.02	5.30 ± 0.08	7.84 ± 0.09	1.12 ± 0.02	(0.70 ± 0.01)·10^{-1}	(0.72 ± 0.01)·10^{-1}	1.54 ± 0.03	21.21 ± 0.41
295.15	4.12 ± 0.08	2.03 ± 0.03	10.68 ± 0.21	31.61 ± 0.62	1.17 ± 0.02	7.30 ± 0.12	11.76 ± 0.23	1.57 ± 0.04	(1.11 ± 0.02)·10^{-1}	(1.13 ± 0.02)·10^{-1}	2.34 ± 0.05	29.23 ± 0.52
298.15	4.75 ± 0.09	2.53 ± 0.11	11.96 ± 0.23	36.95 ± 0.52	1.42 ± 0.03	8.48 ± 0.09	14.20 ± 0.17	1.84 ± 0.05	(1.32 ± 0.03)·10^{-1}	(1.30 ± 0.01)·10^{-1}	2.85 ± 0.04	33.71 ± 0.65
304.15	6.31 ± 0.12	3.94 ± 0.35	15.05 ± 0.19	50.70 ± 0.89	2.07 ± 0.04	11.47 ± 0.17	20.78 ± 0.32	2.54 ± 0.06	(2.01 ± 0.04)·10^{-1}	(2.02 ± 0.02)·10^{-1}	4.21 ± 0.08	45.99 ± 0.82
309.15	7.96 ± 0.06	5.63 ± 0.07	18.16 ± 0.25	65.57 ± 0.82	2.81 ± 0.04	14.67 ± 0.22	28.30 ± 0.36	3.29 ± 0.04	(2.80 ± 0.11)·10^{-1}	(2.82 ± 0.12)·10^{-1}	5.79 ± 0.02	58.48 ± 1.12
314.15	10.00 ± 0.10	7.99 ± 0.15	21.82 ± 0.39	84.33 ± 0.72	3.80 ± 0.06	18.66 ± 0.11	38.26 ± 0.57	4.24 ± 0.08	(3.81 ± 0.13)·10^{-1}	(3.83 ± 0.11)·10^{-1}	7.90 ± 0.12	76.16 ± 1.02
319.15	12.49 ± 0.22	11.23 ± 0.21	26.13 ± 0.22	107.87 ± 0.98	5.08 ± 0.03	23.62 ± 0.32	51.37 ± 0.21	5.44 ± 0.11	(5.34 ± 0.18)·10^{-1}	(5.31 ± 0.16)·10^{-1}	10.69 ± 0.09	91.90 ± 1.17
323.15	14.87 ± 0.28	14.67 ± 0.29	30.11 ± 0.29	130.85 ± 1.32	6.39 ± 0.08	28.42 ± 0.43	64.70 ± 1.23	6.61 ± 0.12	(6.81 ± 0.21)·10^{-1}	(6.84 ± 0.22)·10^{-1}	13.56 ± 0.22	117.16 ± 2.12

Figure 2. Measured solubility of artemisinin at different temperatures in the following solvents: ●, ethanol; △, toluene; ◆, ethyl acetate; ○, butanol; ■, methanol; ◇, acetonitrile; ▼, isopropyl acetate; □, acetone; ▲, hexane; ⬢, MTBE; ▽, heptane; ⬡, MEK.

The heat capacity measurement procedure involved placing an empty crucible and lid in the sample compartment to serve as reference. The sample was initially equilibrated isothermally, then heated at 0.5 K·min^{-1} for 10 K, afterwhich it was equilibrated isothermally at the higher temperature for 60 min. For each ten minute heating period, the thermogram showed a trapezoidal peak, which represents the differential flow of heat (d*H*/d*t*) to the sample that was necessary to keep the sample and the reference side at essentially the same temperature at every point during the run. Integration of this peak area with respect to time, as obtained by the software, gave the total heat provided to the empty sample pan and its lid (ΔH_{P+l}). Once the temperature range of interest was covered, about 5 mg of the artemisinin powder was carefully weighed into the sample pan, and the lid was then crimped on. The unit was then placed into the sample compartment of the calorimeter, and the run was carried out. Thus, the heat introduced into the unit consisting of the sample pan, lid, and the sample (ΔH_{P+l+s}) was determined along with the corresponding (ΔH_{P+l}).

Results and Discussion

Solubility of Artemisinin in Pure Solvents. Experimentally measured temperature-dependent equilibrium mole fractions of artemisinin in methanol, acetone, ethyl acetate, acetonitrile, hexane, heptane, 2-butanone (MEK), methyl *tert*-butyl ether (MTBE), ethanol, butanol, isopropyl acetate, and toluene are presented in Table 2 and graphically displayed in Figure 2. The values represent the average values taken from triplicate measurements, and the expanded uncertainty (±) associated with each data is given in Table 2. For each solvent studied herein, the equilibrium solubility mole fraction of artemisinin increased with temperature. Generally, solubility decreased according to the following order: toluene > MEK > propyl acetate > ethyl acetate > acetone > ethanol > MTBE > butanol > acetonitrile > methanol > hexane > heptane.

In Table 3, results obtained by Liu and co-workers[14] in methanol, acetone, ethyl acetate, acetonitrile, and toluene, at (298.15 and 323.15) K, are compared to our results. As reflected in the relative percent difference (RPD), at 298.15 K, there is good agreement between results from the two studies for acetone (RPD < 5). However, for ethyl acetate, methanol, toluene, and

Table 3. Relative Percent Difference (RPD) of Mole Fraction Solubility of Artemisinin in Methanol, Acetone, Ethyl Acetate, Acetonitrile, and Toluene at 298.15 K, from this Study When Compared to the Results Obtained By Liu et al.[14]

	(100)·RPD	
	T/K = 298.15	T/K = 323.15
methanol	37.6	2.7
acetone	1.8	2.1
ethyl acetate	7.6	1.5
acetonitrile	71.9	59.2
toluene	63.2	6.4

acetonitrile, the results differ significantly as reflected in RPD values of 7.6, 37.6, 71.9, and 63.2 for ethyl acetate, methanol, acetonitrile, and toluene, respectively.

RPD is defined as

$$\mathrm{RPD} = \left|\frac{x_1 - x_1^{\mathrm{Liu}}}{x_1}\right|$$

where x_1 and x_1^{Liu} are the mole fraction solubility of artemisinin obtained from this study and those obtained by Liu et al.,[14] respectively.

That artemisinin is sparingly soluble in acetonitrile reported in the previous studies is perplexing, considering that acetonitrile is the solvent of choice for most reversed-phase HPLC assays for artemisinin.[15,16] The solubility difference between the two studies is likely due to the variation in the solubility measurement techniques. Specifically, Liu et al. measured solubility by the synthetic-optical method,[14,17] whereas the present study employed the static-analytical method.[17] For the former method, a weighed amount of the solute (or a finite amount of the solvent) is placed in a suitable vessel, and while stirring the solution at a fixed temperature, known amounts of solvent (or the solute) are gradually added until the solution becomes turbid. Care must therefore be taken to ensure that the system has reached equilibrium at the solution temperature. The static-analytical method is similar to the synthetic-optical method, except that the saturated solution is allowed time to reach equilibrium, after which the liquid phase is separated from the solid phase and then analyzed for the concentration of the solute. Here, precaution must be taken to avoid losses of the dissolved solute by adsorption to the filter media and/or onto vessels, pipettes, and syringes.

The observed solubility data can be applied to design improved processes for isolation and separation of artemisinin. As previously reviewed, some of the current manufacturers use hexane to extract the compound.[9] This is surprising considering that solubility of artemisinin is very low in this solvent. This may explain the need to use warm hexane for the extraction. Additionally, the waxes in the plant would have very high solubility in hydrocarbons (e.g., hexane and heptane), and perhaps, this is partially the reason why waxes are coextracted with the product during the bulk initial extraction and hence the penalty on yield during recrystallization.

On the basis of the present data, one proposed approach that minimizes the wax problem and optimizes the yield might be to selectively extract the waxes with hexane or heptane (at low temperature); then extract the artemisinin with a small volume of one of the solvents in which the compound has been identified to have high solubility (e.g., MEK, toluene, or ethyl acetate); and finally, use hexane or heptane, as an antisolvent, to crystallize out the product.

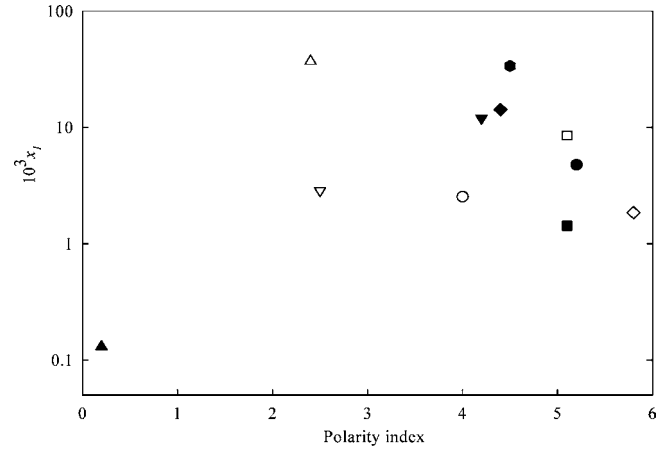

Figure 3. Polarity index versus solubility of artemisinin at 298.15 K in the following solvents: ●, ethanol (ref 15); △, toluene (ref 15); ◆, ethyl acetate (ref 15); ○, butanol (ref 15); ■, methanol (ref 15); ◇, acetonitrile (ref 15); ▼, isopropyl acetate (ref 15); □, acetone (ref 15); ▲, heptane (ref 15); ⬢, MEK (ref 15); ▽, MTBE (ref 15).

Influence of Solvent Polarity. Polarity index is a measure of the relative polarity of a solvent (i.e., the more polar the solvent is, the higher its index). It has been used in some cases to identify a suitable solvent for extraction of drug compounds. The polarity index for the solvent used in this study (Table 1) is plotted against the equilibrium solubility of artemisinin at 298.15 K. Solvents are normally characterized as polar or nonpolar. The general rule of thumb is "Like Dissolves Like." This means that polar solvents will dissolve ionic compounds and covalent compounds which ionize, while nonpolar solvents will dissolve nonpolar covalent compounds. This indicates that a solute will dissolve best in a solvent that has a similar polarity to itself. This is a rather simplistic view since it ignores many solvent−solute interactions, but it is a useful rule-of-thumb. The structure of artemisinin (shown in Figure 1), a sesquiterpene lactone endoperoxide compound, suggests that it is weakly polar and therefore should have relatively high solubility in the medium polarity solvent. As shown in Figure 3, the solubility data are scattered for the medium polarity solvents. This would suggest that the dissolution of artemisinin in some of the solvents is influenced by other factors such as solvent−solute interactions.

Activity Coefficients of Artemisinin in Pure Solvents. The temperature dependence of mole fraction equilibrium solubility of crystalline nonelectrolyte solute in solvent is described by the following thermodynamic relationship[18]

$$\frac{\Delta_{\mathrm{fus}}H}{RT}\left[\frac{T - T_{\mathrm{m}}}{T_{\mathrm{m}}}\right] - \frac{1}{RT}\int_{T_{\mathrm{m}}}^{T}(C_P^{\mathrm{L}} - C_P^{\mathrm{S}})\mathrm{d}T + \frac{1}{R}\int_{T_{\mathrm{m}}}^{T}\frac{C_P^{\mathrm{L}} - C_P^{\mathrm{S}}}{T}\mathrm{d}T = \ln\gamma_1 + \ln x_1 \quad (1)$$

Here, x_1, γ_1, T_{m}, $\Delta_{\mathrm{fus}}H$ [$= H_{\mathrm{L}}(T_{\mathrm{m}}) - H_{\mathrm{S}}(T_{\mathrm{m}})$], R, and T represent the mole fraction solubility of the solute (denoted as component 1) in solution, activity coefficient of the solute in solution, melting temperature of the solute, enthalpy change of melting of the pure solute at its melting temperature, difference in the molar heat capacity (at constant pressure) of the solid and the subcooled liquid form of the solute at the solution temperature, the gas constant, and absolute temperature of the solution, respectively. In the above, C_P^{L}, and C_P^{S}, represent the molar heat capacities of the liquid and solid of artemisinin, respectively.

Table 4. Parameters Obtained from Regression of the Solubility Data for Artemisinin in Hexane, Heptane, Methanol, or Acetonitrile to Equation 4

solvent	ΔC_P / J·mol^{-1}·K^{-1}	A	B	(10^6)·rmsd
hexane	75	4585	−11	0.8440
heptane	79	4448	−11	0.9880
methanol	76	3985	−11	9.4406
acetonitrile	78	3125	−9	1.5100

Table 5. NRTL Model Binary Interaction Parameters and the Average Relative Deviation (ARD) from the Measured Equilibrium Mole Fraction of Artemisnin in Different Solvents

	b_{12}	b_{21}	100·(ARD)
methanol	−2585	15287	0.92
acetone	−1950	9812	2.16
ethyl acetate	−2114	8973	0.87
acetonitrile	−2084	13387	4.28
hexane	−3813	24785	5.21
heptane	−3886	25142	2.56
MTBE	−2302	12876	0.68
MEK	−2337	8212	3.5
ethanol	−2046	11438	1.85
butanol	−2304	12876	0.45
isopropyl acetate	−1607	8309	1.02
toluene	−2074	8566	0.87

In the case of an ideal liquid solution, that is, the activity coefficient $\gamma_1 = 1$, the left-hand side of eq 1 can be identified as the ideal solubility $\ln x_1^{id}$ and can be represented as

$$\ln x_1^{id} = \frac{\Delta_{fus}H}{RT}\left[\frac{T - T_m}{T_m}\right] - \frac{1}{RT}\int_{T_m}^{T}(C_P^L - C_P^S)dT + \frac{1}{R}\int_{T_m}^{T}\frac{C_P^L - C_P^S}{T}dT \quad (2)$$

In eq 2, the ideal mole fraction solubility $\ln x_1^{id}$ can be estimated with knowledge of T_m, $\Delta_{fus}H$, and $\Delta C_P = C_P^L - C_P^S$, and if the actual solute solubility data are available, the activity coefficient $\ln \gamma_1$ can be obtained by subtracting the measured solubility from calculated ideal solubility using eq 1. The melting temperature and heat of fusion of the artemisinin crystalline powders were measured by differential scanning calorimetry (DSC) to be (429.6 ± 0.5) K and (24 300 ± 400) J·mol^{-1}, respectively. The heat capacity term, ΔC_P, for artemisinin is not available but can be estimated from solubility data as described below. For very dilute solution, it is reasonable to assume that the last term in eq 2 denotes the infinite dilution activity coefficient

$$\ln \gamma_1^{\infty} \equiv \frac{\bar{G}_1^{E,\infty}}{RT} = \frac{\bar{H}_1^{E,\infty}}{RT} - \frac{\bar{S}_1^{E,\infty}}{R} = \frac{A}{T} + B \quad (3)$$

where $\bar{H}_1^{E,\infty}$ and $\bar{S}_1^{E,\infty}$, the limiting partial molar excess enthalpy and partial molar excess entropy of artemisinin, respectively, are assumed to be temperature independent represented as empirical constants, A and B.

If we assume ΔC_P to be constant, independent of temperature, and combine eq 2 with eq 3, the mole fraction solubility, x_1, can be written as

$$x_1 = \exp\left\{-\left\{\frac{\Delta_{fus}H}{RT}\left[1 - \frac{T}{T_m}\right] + \frac{\Delta C_P}{R}\left[1 - \frac{T_m}{T} + \ln\left(\frac{T_m}{T}\right)\right]\right\} - \frac{A}{T} - B\right\} \quad (4)$$

The above equation holds for very dilute solutions and can be employed to determine the difference in heat capacity ΔC_P by fitting eq 4 to the solubility of artemisinin in hexane, heptane, methanol, and acetonitrile, which form very dilute or infinitely dilute solutions ($x_1 \leq 10^{-3}$ in the temperature range studied here). Shown in Table 4, the regression gave excellent fit, as reflected by the root-mean-square deviations (rmsd); the rmsd is < 10^{-5}. The value of ΔC_P ranged between (75.2 and 79.1) J·mol^{-1}·K^{-1} for the four solvents, yielding an average value of 77.2 J·mol^{-1}·K^{-1}.

Table 6. Mole Fraction Solubility of Artemisnin, x_1, in Different Ratios of Acetone, x_2, and Ethyl Acetate, x_3, at 273.15 K, 283.15 K, and 303.15 K

T/K = 273.15			T/K = 283.15			T/K = 303.15		
acetone	ethyl acetate	artemisinin	acetone	ethyl acetate	artemisinin	acetone	ethyl acetate	artemisinin
$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$	$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$	$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$
15.73	82.06	22.11 ± 0.21	10.91	86.38	27.07 ± 0.15	10.80	85.46	37.45 ± 0.41
41.73	56.46	18.02 ± 0.33	31.96	65.60	24.30 ± 0.06	31.65	64.96	33.83 ± 0.28
62.40	36.18	14.09 ± 0.09	52.10	45.82	20.76 ± 0.29	51.67	45.44	28.99 ± 0.35
79.29	19.70	10.05 ± 0.03	71.45	26.94	16.11 ± 0.32	70.98	26.76	22.69 ± 0.19
93.39	6.01	5.96 ± 0.11	90.14	8.810	10.41 ± 0.16	89.75	8.77	14.77 ± 0.13

Table 7. Mole Fraction Solubility of Artemisnin, x_1, in Different Ratios of Ethanol, x_2, and Ethyl Acetate, x_3, at 273.15 K, 283.15 K, and 303.15 K

T/K = 273.15			T/K = 283.15			T/K = 303.15		
ethanol	ethyl acetate	artemisinin	ethanol	ethyl acetate	artemisinin	ethanol	ethyl acetate	artemisinin
$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$	$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$	$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$
15.76	81.83	24.11 ± 0.48	10.95	86.24	28.14 ± 0.75	10.84	85.35	38.19 ± 0.26
41.81	56.28	19.08 ± 0.57	32.06	65.47	24.67 ± 0.49	31.77	64.87	33.62 ± 0.15
62.49	36.05	14.53 ± 0.37	52.23	45.71	20.65 ± 0.51	51.82	45.35	28.28 ± 0.42
79.33	19.61	10.52 ± 0.32	71.54	26.83	16.31 ± 0.16	71.09	26.66	22.45 ± 0.48
93.31	5.98	7.10 ± 0.14	90.05	8.76	11.97 ± 0.23	89.63	8.71.53	16.55 ± 0.10

Table 8. Mole Fraction Solubility of Artemisnin, x_1, in Different Ratios of Ethanol, x_2, and Acetone, x_3, at 273.15 K, 283.15 K, and 303.15 K

T/K = 273.15			T/K = 283.15			T/K = 303.15		
ethanol	acetone	artemisinin	ethanol	acetone	artemisinin	ethanol	acetone	artemisinin
$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$	$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$	$10^2 \cdot x_2$	$10^2 \cdot x_3$	$10^3 \cdot x_1$
14.42	85.15	4.24 ± 0.03	9.98	89.37	6.52 ± 0.06	9.95	89.07	9.83 ± 0.02
39.37	60.25	3.80 ± 0.02	29.91	69.44	6.41 ± 0.02	29.82	69.22	9.69 ± 0.03
60.20	39.48	3.21 ± 0.05	49.83	49.58	5.95 ± 0.01	49.68	49.42	9.01 ± 0.01
77.85	21.88	2.64 ± 0.01	69.73	29.73	5.33 ± 0.05	69.54	29.65	8.08 ± 0.02
93.01	6.78	2.13 ± 0.02	89.63	9.91	4.66 ± 0.03	89.41	9.88	7.07 ± 0.01

Table 9. Experimental Mole Fraction Solubility of Artemisnin, x_1^{exptl}, in Different Volumetric Ratios of Acetone and Ethyl Acetate at 273.15 K, 283.15 K, and 303.15 K, When Compared to the NRTL Calculated Mole Fraction Solubility, x_1^{calcd}, with the rmsd Values

% volume of solvent		T/K = 273.15			T/K = 283.15			T/K = 303.15		
acetone	ethylacetate	x_1^{exptl}	x_1^{calcd}	100·RPD	x_1^{exptl}	x_1^{calcd}	100·RPD	x_1^{exptl}	x_1^{calcd}	100·RPD
10	90	22.11	21.81	1.36	27.07	27.85	2.88	37.45	39.12	4.46
30	70	18.02	17.15	4.83	24.3	25.01	2.92	33.83	33.18	1.92
50	50	14.09	14.71	4.40	20.76	21.66	4.34	28.99	29.35	1.24
70	30	10.05	10.41	3.58	16.11	16.48	2.30	22.69	22.15	2.38
90	10	5.96	6.18	3.69	10.41	10.75	3.27	14.97	14.63	2.27

The root-mean-square deviation (rmsd) is defined as

$$\text{rmsd} = \sqrt{\frac{\sum_{i=1}^{N} |(x_1^{\text{exptl}} - x_1^{\text{calcd}})|^2}{N}} \quad (5)$$

where N is the number of experimental data points, and x_1^{exptl} and x_1^{calcd} represent the experimental and calculated values of the mole fraction solubility values, respectively.

Non-Random Two-Liquid (NRTL) Activity Coefficient. The Non-Random Two Liquid (NRTL) activity coefficient can be expressed as[18,19]

$$\ln \gamma_1 = x_2^2 \left[\frac{\tau_{12} G_{12}}{(x_2 + x_1 G_{12})^2} + \tau_{21} \left(\frac{G_{21}}{x_1 + x_2 G_{21}} \right)^2 \right] \quad (6)$$

where

$$G_{12} = \exp(-\alpha \tau_{12}), \text{ and } G_{21} = \exp(-\alpha \tau_{21}) \quad (7)$$

and

$$\tau_{12} = \frac{b_{12}}{RT} \quad \text{and} \quad \tau_{21} = \frac{b_{21}}{RT} \quad (8)$$

where b_{12} and b_{21} are interaction parameters specific to a particular pair of species, independent of temperature and composition, and the parameter α is a measure of the nonrandomness of the mixture; when α is zero, the mixture is said to be completely random.

Combining eq 2 with eq 6 yields

$$x_1 = \exp\left(-\left\{ \frac{\Delta_{\text{fus}} H}{RT} \left[1 - \frac{T}{T_{\text{m}}} \right] + \frac{\Delta C_P}{R} \left[1 - \frac{T_{\text{m}}}{T} + \ln\left(\frac{T_{\text{m}}}{T} \right) \right] \right\} - \left\{ x_2^2 \left[\frac{\tau_{12} G_{12}}{(x_2 + x_1 G_{12})^2} + \tau_{21} \left(\frac{G_{21}}{x_1 + x_2 G_{21}} \right)^2 \right] \right\} \right) \quad (9)$$

Calculation of the ideal solubility of a crystalline solute in a liquid solvent requires knowledge of the difference in the molar

Table 10. Experimental Mole Fraction Solubility of Artemisnin, x_1^{exptl}, in Different Volumetric Ratios of Ethanol and Ethyl Acetate at 273.15 K, 283.15 K, and 303.15 K, When Compared to the NRTL Calculated Mole Fraction Solubility, x_1^{calcd}, with the rmsd Values

% volume of solvent		T/K = 273.15			T/K = 283.15			T/K = 303.15		
ethanol	ethyl acetate	x_1^{exptl}	x_1^{calcd}	100·RPD	x_1^{exptl}	x_1^{calcd}	100·RPD	x_1^{exptl}	x_1^{calcd}	100·RPD
10	90	24.11	24.87	3.15	28.14	29.17	3.66	38.19	39.87	4.40
30	70	19.08	18.34	3.88	24.67	25.34	2.72	33.62	34.04	1.25
50	50	14.53	14.15	2.62	20.65	20.25	1.94	28.28	28.65	1.31
70	30	10.52	10.21	2.95	16.31	16.88	3.49	22.45	22.71	1.16
90	10	7.10	7.32	2.82	11.97	11.39	4.85	16.55	16.89	2.05

Table 11. Experimental Mole Fraction Solubility of Artemisnin, x_1^{exptl}, in Different Volumetric Ratios of Ethanol and Acetone at 273.15 K, 283.15 K, and 303.15 K, When Compared to the NRTL Calculated Mole Fraction Solubility, x_1^{calcd}, with the rmsd Values

% volume of solvent		T/K = 273.15			T/K = 283.15			T/K = 303.15		
ethanol	acetone	x_1^{exptl}	x_1^{calcd}	100·RPD	x_1^{exptl}	x_1^{calcd}	100·RPD	x_1^{exptl}	x_1^{calcd}	100·RPD
10	90	4.24	4.17	1.65	6.52	6.52	6.37	9.83	9.66	1.73
30	70	3.8	3.7	2.63	6.41	6.41	6.16	9.69	9.86	1.75
50	50	3.21	3.18	0.93	5.95	5.95	5.78	9.01	9.18	1.89
70	30	2.64	2.57	2.65	5.33	5.33	5.57	8.08	8.27	2.35
90	10	2.13	2.19	2.82	4.66	4.66	4.49	7.07	7.19	1.70

heat capacity at constant pressure of the solid and the subcooled liquid forms of the solute, ΔC_P, as a function of temperature. Since this is a hypothetical parameter, it is assumed to be a constant and further simplified by three commonly used assumptions:[2,3] (i) ΔC_P can be considered equal to zero; (ii) ΔC_P is an estimate of molar entropy of fusion, ΔS_f; (iii) ΔC_P can be extrapolated from the melting point. Here, we propose a fourth assumption by using the average ΔC_P that was previously obtained in Table 4.

The average ΔC_P was used in eq 9 to regress the solubility data to obtain the NRTL binary interaction parameters, b_{12} and b_{21}; the parameter α was treated as constant with a value of 0.4. The best fit values of the interaction parameters are displayed in Table 5. The values agreed well with the experimental values, as reflected by the average relative deviation (ARD) defined as

$$\mathrm{ARD} = \frac{1}{N}\sum\left[\left|\frac{x_1 - x_{1(\mathrm{calcd})}}{x_1}\right|\right] \tag{10}$$

where N is the number of data points obtained in each set which equal the number of temperatures used, and $x_{1(\mathrm{calcd})}$ is the calculated value based on the NRTL equation.

Artemisinin in Binary Solvent Mixtures. In addition to single solvents, the solubilities of artemisinin in binary solvent mixtures consisting of ethyl acetate/acetone, acetone/ethanol, and ethyl acetate/ethanol were measured and are displayed in Tables 6, 7, and 8.

We apply the multicomponent NRTL activity coefficient equation to model these three-component systems (artemisinin (1) + solvent (2) + solvent (3)). The activity coefficient γ_i, for any given component i, based on the NRTL equation is[20]

$$\ln \gamma_i = \frac{\sum_{j=1}^{m} \tau_{ji} G_{ji} x_j}{\sum_{l=1}^{m} G_{li} x_l} + \sum_{j=1}^{m} \frac{x_j G_{ij}}{\sum_{l=1}^{m} G_{lj} x_l}\left[\tau_{ij} - \frac{\sum_{r=1}^{m} x_r \tau_{rj} G_{rj}}{\sum_{l=1}^{m} G_{lj} x_l}\right] \tag{11}$$

where $G_{ji} = \exp(-\alpha_{ji}\tau_{ji})$, $\tau_{ji} = b_{ji}/RT$, $\alpha_{ji} = \alpha_{ij}$, and $\alpha_{jj} = \alpha_{ii} = 0$.

The solubility of artemisinin in binary solvent mixtures can be predicted using eq 2 and eq 11. As before, the ideal solubility $\ln x_1^{\mathrm{id}}$ can be estimated from values of heat of fusion at the melting point, melting temperature, and ΔC_P. To calculate the activity coefficient of artemisinin from eq 11, the values of the artemisinin−solvent parameters b_{ij} (ij = 12, 21, 13, and 31) obtained for different solvents and an α value of 0.40 were used. For the two solvents (components 2 and 3), the liquid−liquid solvent−solvent interaction parameters, τ_{ij}, were taken from the literature,[21] and α was set to 0.30 for all the solvents. The calculated NRTL activity coefficient was combined with calculated ideal solubility to estimate solubility of artemisinin. The estimated values excellently agreed with the experimentally measured solubility, with < 5 % relative percent deviation for each solvent ratio and temperature studied herein (Tables 9, 10, and 11). This clearly demonstrates that NRTL interaction parameters from the binary system can be used to predict solubility in the ternary solute−binary solvent system.

Conclusion

The solubility of artemisinin in pure methanol, ethanol, butanol, acetone, ethyl acetate, isopropyl acetate, acetonitrile, hexane, heptane, 2-butanone (MEK), methyl *tert*-butyl ether (MTBE), and toluene and binary solvent mixtures of binary solvent mixtures of ethyl acetate/ethanol, or ethyl acetate/acetone, or ethanol acetone was determined by an analytical method over the temperature range from (284.15 to 323.15) K at atmospheric pressure. The results show that the solubility of artemisinin increases with increasing temperature in all 12 solvents investigated.

The experimental data were correlated using the Non-Random Two-Liquid (NRTL) activity coefficient model, and the agreement with the experimental data was very good. The NRTL activity coefficient interaction parameters have been obtained for binary systems of artemisinin and each solvent. The NRTL activity coefficient interaction parameters from the binary system were used to predict the equilibrium mole fraction solubility of artemisinin in binary solvent mixtures of ethyl acetate/ethanol, or ethyl acetate/acetone, or ethanol acetone. The predicted results compared very favorably with the experimental data. In view of the importance of artemisinin for malaria treatment, we hope this study will contribute to the physicochemical database needed to make informed choices of process solvents for manufacture of the drug substance.

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