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ORIGINAL ARTICLE

Experimental analysis and thermodynamic modelling of Nitroxynil solubility in pure solvent and binary solvent

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Abstract Nitroxynil(NIT) is a commonly used anti-liver fluke drug for cattle and sheep, Its solubility is closely related to its preparation. In this work, the molar solubility of NIT in nine pure solvents (methanol, ethanol, 1,2-propanediolethyl, isopropanol, ethyl acetate, acetonitrile, *n*-butanol, phemethylol) and two kinds of binary mixtures with different ratio(ethanol + phemethylol; ethanol + acetonitrile) was determined by shake flask method over the temperature from 278.15 ~ 323.15 K at atmosphere pressure. Results show that the solubility of NIT in all tested solvents was increased with raised temperature. In mono-solvents, the mole fraction solubility of NIT was highest in phemethylol and the solubility order is: phemethylol > acetonitrile > ethyl acetate > methanol > *n*-butanol > ethanol > 1,2-propanediolethyl > isopropanol > water. In binary solvents, the mole fraction solubility increased with increasing ratio of phemethylol/acetonitrile. In mono-solvents, the modified Apelblat equation, λh equation, Van't Hoff model were applied to correlate the solubility data. In binary solvents, the modified Apelblat equation, λh equation, GSM model and Jouyban-Acree model were to correlate the solubility data. Solubility order of NIT in nine pure solvent and two binary solvent systems were analysed by using the Hansen solubility parameter (HSP). Activity coefficient was to access the solute–solvent molecular interactions. In addition, the dissolution of NIT is an endothermic and entropy-friendly process, since thermodynamic parameters such as enthalpy, entropy, and apparent standard Gibbs free energy

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are all greater than zero. The results will supply some essential data on recrystallization process, purification and formulation development of NIT in pharmaceutical applications.

1. Introduction

Solubility is a physical property that shows the thermodynamic balance of active pharmaceutical ingredients in solid–liquid mixtures. Among all the parameters during crystallization process, solid–liquid equilibrium data is of great importance to contribute to the design and optimization of purification processes(Akay et al., 2021). It should be noted that according to FDA, solubility and permeability are the sole critical factors in determining generic bioequivalence(Rezaei et al., 2021). Thus, the determination of solubility of drugs in different cosolvent media is significant, which can supply some reference for future developments.

Nitroxynil (NIT) is an anthelmintic veterinary drug; Its chemical name is 4-hydroxy-3-iodo-5-nitrobenzonitrile(molecular formula: $C_7H_3IN_2O_3$; molar mass: 290.01 g•mol^{-1} and CASRN:1689–89-0; Figure. S1), which has been found as a yellow crystalline powder, almost odorless, slightly soluble in water, soluble in ethanol, ether and other organic solvents(Soliman et al., 2021). Corbett et al. (Corbett and Goose, 1971) studied the effect of NIT on mitochondrial function of mice liver cells, and proved that it is a kind of uncoupling agent for oxidative phosphorylation, it leads to death by blocking oxidative phosphorylation, reducing ATP concentration and reducing the energy required for cell division. A drug can only perform its pharmacological effects if it binds to a specific receptor, so it must exist in dissolved form before it can cross the gut barrier. This means that only soluble drugs can be used in the absorption process(Azarmi et al., 2007). Therefore, the solubility of drugs is closely related to the absorption of drugs in living organisms. To some extent, only understanding the solubility of a drug in a solvent can make it more effective. So far, the experimental solubility data of NIT in various kinds of solvent have not been systematically researched. Therefore, it is necessary to systematically measure the solubility of NIT in different solvent systems and predict solubility behavior using thermodynamic models. Besides, The single solvent we selected is a common solvent in pharmaceutical process, and the choice of binary solvent also provides a theoretical basis for the recrystalization and purification of NIT.

The main objectives of the study are to determine the solubility of NIT in nine pure solvents (methanol, ethanol, 1,2-propanediolethyl, isopropanol, ethyl acetate, acetonitrile, *n*-butanol, phemethylol) and two kinds of binary mixtures with different ratio (ethanol + phemethylol; ethanol + acetonitrile) at temperatures ranging from 278.15 K to 323.15 K under atmospheric pressure (p = 0.1 MPa). Afterwards, experimetal solubility results were correlated by different solubility models, the modified Apelblat model, the λh model, Van't Hoff model, GSM equation and Jouyban-Acree model(Li et al., 2017). Based on the concept of linear solvation energy relationship, Hansen solubility parameters (HSPs) were calculated to investigate the effect of solvents on the solid–liquid equilibrium process of NIT. Furthermore, the thermodynamic properties in dissolution, that is, the change of enthalpy (ΔH^0_{sol}), entropy (ΔS^0_{sol}) and Gibbs free energy (ΔG^0_{sol}), were calculated(Shekaari et al., 2018). The solubility data, solubility parameters and other physicochemical parameters of NIT obtained in this research could be useful in purification, recrystallization, drug discovery, pre-formulation studies and formulation on development of NIT, especially in liquid dosage forms.(Alshehri and Shakeel, 2020).

2. Materials and methods

2.1. Materials

Nitroxinil was purchased from Huana Chemicals Co., ltd. The more information of the solvents used in this study was presented in Table S1.

2.2. Experimental procedure for solubility determination

The solubility measurement method was similar to our previous literature(Chen et al., 2020). In this paper, the solubility of NIT was determined by gravimetric analysis in mono solvents and binary solvent mixtures. NIT concentrations were determined after appropriate gravimetric dilution with pure acetonitrile by measuring the UV light absorbance at the wavelength of second largest absorbance, 400 nm UV/visible spectrophotometry, followed by interpolation from a previously constructed UV spectrophotometric gravimetriccalibration curve(Osorio et al., 2020). In order to obtain an accurate solubility, the reported solubility data is the averages of at least three measurements. The mole fraction solubility (x) of NIT can be obtained by the Eq. (1).

$$x = \frac{m_1/M_1}{m_1/M_1 + \sum (m_i/M_i)} \quad (1)$$

where m_1 and m_i stand for the mass of solute and the solvents, respectively. M_1 and M_i represent the molar mass of solute and the solvents, respectively.

2.3. Characterization methods

Differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD) were used to characterize NIT in solid phases. DSC measurement was carried out by DSC-200F Instrument (NETZSCH Scientific Instruments Trading (Shanghai) ltd., Germany). Sapphire was selected as the reference. 6.05 mg NIT was put into a alumina pan and measured in the range of 293.15 K to 473.15 K at heating rate of 10 K•min^{-1} under a N_2 atmosphere (100 mL•min^{-1}). PXRD analysis of raw and equilibrated NIT was performed using DX-2800 Diffractometer (Haoyuan Instrument Co., ltd., China). The 2θ range for recording these spectra was set at 2-70° with a scan speed of 3.0° min^{-1}(Wei et al., 2021).

2.4. Hansen solubility parameters (HSPs)

Hansen dissolvability coefficient was employed in this study to clarify the dissolution characteristics of solid in the solvents. The overall HSP (δ_t) is determined as Eq (2):(Yang et al., 2019)(Brett, 2007)

$$\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \quad (2)$$

Where δ_d, δ_p and δ_h separately denote dispersion, polar and hydrogen bonded coefficients for Hansen dissolvability. The total and partial Hansen solubility parameters for NIT are estimated by way of group contribution method proposed by Hoftyzer and van Krevelen as Eq (3)-(5) (Shen et al., 2021) (Liu et al., 2021) (Mohammad et al., 2011)

$$\delta d = \frac{\sum Fdi}{V} \quad (3)$$

$$\delta p = \frac{\sqrt{\sum Fpi^2}}{V} \quad (4)$$

$$\delta h = \sqrt{\frac{\sum Ehi}{V}} \quad (5)$$

where the F_{di} and F_{pi} represent dispersion force and polarity force of each structure groups i, respectively. The E_{hi} represents hydrogen bond interaction energy.V is the group contribution to the molar volume of solute. For NIT, the values of $F_{di,}$ F_{pi} and E_{hi} for group contribution method calculation of NIT are given in Table S2.

The HSPs of commonly used solvents can be found in many published literatures, while the HSPs for selected binary solvents mixture (δ_M^{mix}) can be calculated by Eq.(6)(Li et al., 2021)

$$\delta_M^{mix} = \alpha\delta_M^1 + (1-\alpha)\delta_M^2 \text{ for M} = \text{d, p and h} \quad (6)$$

Herein, the superscript of 1 and 2 represent the solvent ethanol and (phemethylol, acetonitrile) respectively, and α represents the volume fraction of positive solvent 1 in the binary solvents mixture.The HSPs ($\delta_{t,}$ δ_d, δ_p and δ_h) of the selected two binary solvents as listed in Tables S3.

The Bagley diagram with a two-dimensional plot of the volume-dependent solubility parameter δ_v against δ_H has been used in the miscibility investigations and predictions the duration of intestinal absorption for various drugs, δ_v can be described as Eq.(7)

$$\delta v = \sqrt{\delta_d^2 + \delta_p^2} \quad (7)$$

and subsequently the $R_{a(v)}$ factor was used to determine the miscibility as Eq.(8)

$$Ra(v) = \sqrt{4(\delta v2 - \delta v1)^2 + (\delta h2 - \delta h1)^2} \quad (8)$$

R_a can be employed to show the miscibility/solubility between solvent and solute. If the solute has better solubility, the R_a magnitude should be < 5.6 $MPa^{1/2}$. So one may estimate the solvent property for solute solubility in terms of the R_a value. The higher the R_a value is, the poor solute solubility will be. The case is vice versa. As a result, the magnitude of $R_a < 5.6$ $MPa^{1/2}$ is suggested for better solubility of a solute (Huang et al., 2021)(Mohammad et al., 2011).

Recently, the difference of total solubility parameters ($\Delta\delta_t$ and $\Delta\delta$) between the solute and solvent has been used as a tool to predict miscibility as Eq.(9)-(10)(Li et al., 2021):

$$\Delta\delta t = |\delta t2 - \delta t1| \quad (9)$$

$$\Delta\delta = \sqrt{(\delta h2 - \delta h1)^2 + (\delta p2 - \delta p1)^2 + (\delta d2 - \delta d1)^2} \quad (10)$$

where the subscript of 1 and 2 represents the solute and the solvent, respectively, and the variables ($\delta_{t,}$ δ_d, δ_p and δ_h) have the same definition as that in the previous equations, and suggested a general trend indicating that materials with $\Delta\delta_t < 7$-$MPa^{0.5}$ are miscible, while with $\Delta\delta_t$ greater than 7 $MPa^{0.5}$ are immiscible. (Greenhalgh et al., 1999).

The HSPs ($\delta_{t,}$ δ_d, δ_p and δ_h) of the selected nine pure solvents can be obtained directly from the literatures (Huang et al., 2021) (Zhang et al., 2021) (Sha et al., 2021a) (Cao et al., 2020), which was listed in Tables S3.

3. Solid-liquid equilibrium models

The solubility data of NIT in different pure solvents and mixture solvents were correlated by various thermodynamic models, such as the modified Apelblat equation, λh equation, Jouyban-Acree equation, GSM equation were employed to correlate the NIT solubility in different solvents.

3.1. Modified Apelblat model

The modified Apelblat model has already been one of the most commonly and widely used models in solubility correlation and prediction, especially in engineering applications.This model can give the variation trend of solubility with temperature in the same proportion of solvent, and the correlation with the three parameters is relatively accurate (Shen et al., 2021) (Liu et al., 2021):

$$\ln x = \frac{a}{T(K)} + b + c\ln(T(K)) \quad (11)$$

Where a, b and c are the empirical parameters, a and b have the same meaning as in the modified Apelblat model, the value of c represents the effect of temperature on the fusion enthalpy.

3.2. λh model

The λh equation is a semi-empirical model and can be used to correlate the experimental solubility data for the solid–liquid equilibrium systems (Jia et al., 2021),

$$\ln\left[1 + \frac{\lambda(1-x)}{x}\right] = \lambda h\left[\frac{1}{T(K)} - \frac{1}{T_m(K)}\right] \quad (12)$$

Where × is the mole fraction of NIT in different solutions, T stands for the absolute temperature and Tm is the standard melting point of Kelvin temperature. λ and h are determined by correlation of solubility data.

3.3. GSM model

GSM equation was used to calculate the solubility in binary solvents which is one of the theoretical models (Chen et al., 2020), The model is presented as Eq. (13)

$$\ln x = a + bx_j^0 + c\left(x_j^0\right)^2 + d\left(x_j^0\right)^3 + e\left(x_j^0\right)^4 \quad (13)$$

Where a, b, c, d and e were the model's five parameters, x_j^0 refers to theinitial mole fraction of ethanol under the assumption of solute is not present.

3.4. Jouyban-Acree model

The Jouyban-Acree model is suggested to describe the solubility of a solute with the variation of both temperature and initial composition of binary solvent mixtures(Yang et al., 2021). The model was presented as Eq. (14)

$$\ln x_T = x_j^0 \ln(x_j)_T + x_i^0 \ln(x_i)_T + x_j^0 x_i^0 \times \sum_{i=0}^{n} J_i \left(x_j^0 - x_i^0\right)^i / T(K) \quad (14)$$

where x_T, $(x_j)_T$ and $(x_i)_T$ are the mole fraction solubility of solute in solvent mixture or pure solvent (j or i) of mixture composition at the same experimental temperature (T) respectively, and J_i is the model constant.

In GSM Eq. (13), $(x_j)_T$ and $(x_i)_T$ can be obtained based on Van't Hoff in the above. When n = 2, a new equation (15) which called Van'*t*-JA model can be obtained.

$$\ln x_T = x_j^0(a_j + b_j/T(K)) + x_i^0(a_i + b_i/T(K)) + \frac{x_j^0 x_i^0 \left[J_0 + J_1\left(x_j^0 - x_i^0\right) + J\left(x_j^0 - x_i^0\right)^2\right]}{T(K)} \quad (15)$$

Introducing constant parameters (V_0 to V_6) to Eq. (15), it can be further simplified as Eq. (16).

$$\ln x = V_0 + \frac{V_1}{T(K)} + V_2 x_j^0 + \frac{\left[V_3 x_j^0 + V_4\left(x_j^0\right)^2 + V_5\left(x_j^0\right)^3 + V_6\left(x_j^0\right)^4\right]}{T(K)} \quad (16)$$

3.5. Evaluation of thermodynamic models

In order to evaluate the applicability of the tested models, the root-mean-square deviations (RMSD) were calculated as follows equation (17)(R. Sun et al., 2021).

$$RMSD = \sqrt{\frac{\sum_{i=1}^{N}\left(x^{exp} - x^{cal}\right)^2}{N}} \quad (17)$$

Where N refers the number of experimental data points, x^{exp} and x^{cal} denote the experimental data and model predicted data, respectively.

4. Results and discussion

4.1. Characterization of NIT in solid phases

The solid phases of pure and equilibrated NIT were characterized using DSC and PXRD techniques. The representative DSC spectra of pure NIT is presented in Figure S2. It can be seen that there is a sharp exothermic peak at 402.62 K, which indicates the melting temperature of NIT is 402.62 K and the fusionenthalpy ($\Delta_{fus}H$) is calculated to be 42.75 kJ/-mol(Alanazi et al., 2020). At present, no literatureshave reported the T_m value and $\Delta_{fus}H$ of NIT. The differences of sample sources, measurement methods and environments(such as heating rates), purity and purification method may be the factor resulting in slightdeviations of melting point and fusion enthalpy between experiment value and literature data(Huang et al., 2021).

The crystalline state for raw material and samples gained from the solution of NIT after dissolution equilibrium were tested by the XRPD and were depicted in Figure S3. From Figure S3, it can be found that no new characteristic peaks were observed, which suggested that no crystal form transition occurred during the dissolution process of NIT in all pure solvents studied. Note that the minor differences among PXRD patterns in peak intensity is likely due to the preferred orientation of samples(Asadi et al., 2020)(Jouyban et al., 2020).

4.1.1. In pure solvents

The studied organic solvents consist of a ester solvent, a nitrile compound and six alcohol solvents. It is obvious that the maximum solubility is in phemethylol and the solubility order in pure solvents is: phemethylol > acetonitrile > ethyl acetate > methanol > *n*-butanol > ethanol > 1,2-propanediolethyl > isopropanol > water, whose sequence was not completely consistent with the polar sequence of solvents (water > methanol > ethanol > phemethylol > *n*-butanol > isopropanol > acetonitrile > ethyl acetate). The experimental data indicates that the "like dissolves like" rule is not the only factor to determine the solubility of NIT. It is known to all that the solubility of solute was not only influenced by polarity of the solvent, but decided by the size of molecular, spatial conformation, solvent–solute interaction and other factors. The solubility is the result of the comprehensive influence of all factors(W. Sun et al., 2021).

The solubility values of NIT in the chosen mono-solvents of at temperature from 278.15 K to 323.15 K are listed in Table 1 and presented graphically in Figure 3. It can be seen clearly from the trend graph that the solubility of the compound increased with increasing temperature in nine pure solvents, The solubility of NIT in phemethylol, acetonitrile and ethyl acetate increased significantly with the increase of temperature, even a saturation trend was not reached at the test temperature; On the contrary, in methanol, *n*-butanol, ethanol, 1,2-propanediolethyl, isopropanol and water, the value did not increase significantly with the increase of temperature, but showed a gentle trend. Experimental data indicate that those with similar structures may be mutually soluble, phemethylol and NIT contain benzene rings, therefore, NIT has the highest solubility in phemethylol. Moreover, NIT and acetonitrile are nitrile compounds. The effect of structural similarity on the solubility of NIT was greater than that of polar similarity.

4.1.2. In binary solvent mixtures

According to the experimental results of 4.2.1, the solubility of NIT in phemethylol and acetonitrile are greater than that of other organic solvents. As we all known, the solubility is a function of temperature and components of solvent, therefore the solubility of NIT at various binary solvent mixtures (ethanol + phemethylol; ethanol + acetonitrile) increases not only with the rising temperature and also the rise of the ratio phemethylol/acetonitrile content at constant temperature, just as displayed in Tables. 2 and 3 and graphically shown in Figures 5 and 6. According to Figures 5 and 6, it can be seen that the solubility of NIT increased along with temperature in both investigated binary solvent mixtures, and the solubility was increased as the mole fraction of phemethylol/acetonitrile

Table 1 Experimental and calculated mole fraction solubility of NIT in nine mono-solvent systems from 278.15 K to 323.15 K (p = 101.3 kpa).[a,b].

T/K	10^3x^{exp}	10^3x^{Apel}	$10^3x^{\lambda h}$	10^3x^{exp}	10^3x^{Apel}	$10^3x^{\lambda h}$
	water			methanol		
278.15	0.66	0.65	0.66	9.50	8.87	8.99
283.15	0.74	0.71	0.72	10.94	10.13	10.22
288.15	0.77	0.79	0.79	11.16	11.55	11.59
293.15	0.88	0.86	0.86	12.02	13.13	13.13
298.15	0.96	0.95	0.94	14.47	14.91	14.86
303.15	1.02	1.04	1.03	16.61	16.88	16.79
308.15	1.13	1.14	1.13	20.39	19.08	18.97
313.15	1.20	1.25	1.24	20.50	21.52	21.43
318.15	1.39	1.36	1.36	25.07	24.22	24.21
323.15	1.51	1.49	1.50	26.95	27.22	27.37
	ethanol			1,2-propanediolethyl		
278.15	7.48	7.22	7.38	6.86	6.14	6.64
283.15	8.12	8.1	8.2	7.45	6.96	7.40
288.15	9.46	9.07	9.1	8.60	7.87	8.24
293.15	10.11	10.13	10.1	8.83	8.89	9.17
298.15	10.97	11.29	11.21	10.21	10.01	10.21
303.15	12.19	12.56	12.44	10.96	11.25	11.36
308.15	14.10	13.94	13.82	12.35	12.62	12.64
313.15	14.85	15.44	15.35	14.47	14.13	14.09
318.15	17.22	17.08	17.08	15.55	15.79	15.71
323.15	19.24	18.86	19.04	17.75	17.62	17.54
	isopropanol			ethyl acetate		
278.15	5.17	5.14	5.24	79.35	79.69	77.55
283.15	6.09	5.78	5.85	85.91	91.48	90.15
288.15	6.83	6.49	6.52	99.12	104.74	104.24
293.15	7.52	7.27	7.26	118.80	119.64	119.90
298.15	7.86	8.13	8.08	142.41	136.35	137.24
303.15	8.48	9.07	9.00	162.33	155.04	156.34
308.15	9.65	10.10	10.02	179.60	175.92	177.31
313.15	11.06	11.23	11.17	196.90	199.19	200.23
318.15	12.93	12.47	12.46	224.39	225.09	225.17
323.15	13.97	13.81	13.93	250.88	253.85	252.23
	acetonitrile			*n*-butanol		
278.15	54.72	57.09	52.95	8.02	7.64	7.53
283.15	72.77	69.05	66.15	9.38	8.76	8.66
288.15	85.91	83.23	81.82	9.90	10.04	9.93
293.15	108.17	100.00	100.23	11.37	11.49	11.36
298.15	119.70	119.79	121.59	12.45	13.13	12.98
303.15	136.32	143.06	146.09	14.26	14.98	14.81
308.15	161.89	170.36	173.89	16.46	17.08	16.88
313.15	200.96	202.29	205.04	18.85	19.44	19.23
318.15	244.40	239.57	239.53	22.42	22.11	21.90
323.15	284.23	282.96	277.25	25.29	25.11	24.95
	phemethylol					
278.15	78.16	75.71	67.12			
283.15	84.33	91.77	85.40			
288.15	110.90	110.85	107.30			
293.15	125.32	133.46	133.12			
298.15	160.99	160.16	163.08			
303.15	199.27	191.60	197.24			
308.15	226.26	228.53	235.52			
313.15	285.49	271.79	277.66			
318.15	317.43	322.34	323.19			
323.15	376.96	381.24	371.52			

x^{Apel}, $x^{\lambda h}$ indicate the calculated mole fraction solubility of NIT obtained by the modified Apelblat model, λh model respectively.

[a] x^{exp} refers to the experimental mole fraction solubility of NIT.

[b] The relative standard deviation of the solubility measurement u(x) = 0.001, u(T) = 0.05 K, u(P) = 2 KPa.

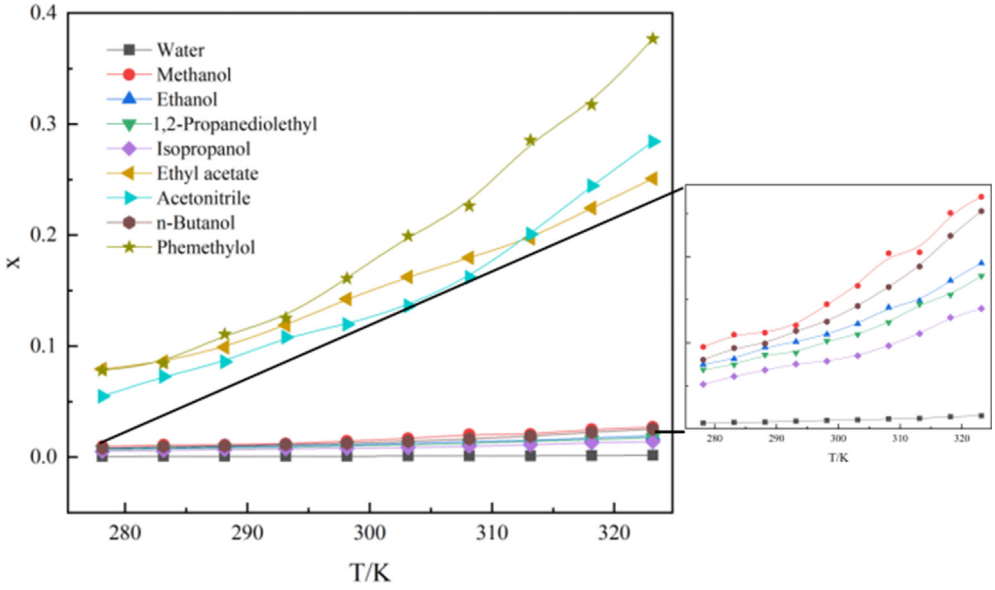

Fig. 1 Mole fraction solubility (x) of NIT in nine pure solvents.

increases. As long as phemethylol or acetonitrile was added into the binary solvent, the solubility of NIT showed an obvious increasing trend, indicating that phemethylol and acetonitrile can significantly increase the dissolution of NIT, and the greater the proportion of phemethylol and acetonitrile, the more obvious the dissolution ability.

There are many factors that affect the solubility and its changed trends. In addition to the interaction between the solvents, the interaction between the solute and the solvent, the properties of solvent and solute (such as dielectric constant, polarity, dipole moment, cohesive energy, ionization constant, the surface tension etc.) and so on will also affect the solubility. The influencing factors are numerous and complex, and the specific reasons that affecting the solubility of NIT need to be further studied (Xue et al., 2021).

4.2. Solubility parameters for NIT and various organic solvents

Values of δ_d, δ_p, δ_h, $\Delta\delta_t$ and δ_v for NIT and selected monosolvents are listed in Table S4, and values of F_{di}, F_{pi} and E_{hi} for group contribution method calculation of NIT are presented in Table S2. Total HSP (δ) for NIT was obtained as

Table 2 Experimental and calculated mole fraction solubility of NIT in binary mixed solvents of ethanol + phemethylol with different ratio within a temperature range from 278.15 K to 323.15 K (p = 101.3 kpa).[a,b,c].

T/K	10^3x^{exp}	10^3x^{Apel}	$10^3x^{\lambda h}$	10^3x^{GSM}	$10^3x^{Van't\text{-}JA}$
x_j^0 = 0.00					
278.15	78.16	75.71	67.12	77.51	70.51
283.15	84.33	91.77	85.40	83.12	87.32
288.15	110.90	110.85	107.30	110.62	107.33
293.15	125.32	133.46	133.12	124.94	131.01
298.15	160.99	160.16	163.08	161.12	158.85
303.15	199.27	191.60	197.24	198.22	191.38
308.15	226.26	228.53	235.52	226.65	229.18
313.15	285.49	271.79	277.66	285.06	272.88
318.15	317.43	322.34	323.19	317.44	323.13
323.15	376.96	381.24	371.52	374.62	380.64
x_j^0 = 0.10					
278.15	64.22	67.27	61.50	64.22	64.72
283.15	77.06	80.90	76.72	80.74	79.31
288.15	105.87	96.97	94.71	106.91	96.49
293.15	110.99	115.86	115.71	112.22	116.62
298.15	132.72	138.01	139.94	131.91	140.05
303.15	161.87	163.91	167.54	165.82	167.18
308.15	197.56	194.12	198.56	195.76	198.41
313.15	229.06	229.27	232.99	231.29	234.20
318.15	289.44	270.05	270.69	290.07	275.01

Table 2 (*continued*)

T/K	10^3x^{exp}	10^3x^{Apel}	$10^3x^{\lambda h}$	10^3x^{GSM}	$10^3x^{Van't\text{-}JA}$
323.15	302.88	317.27	311.43	313.52	321.33
$x_j^0 = 0.20$					
278.15	56.69	56.79	52.76	56.58	57.64
283.15	76.05	68.67	65.87	73.23	69.92
288.15	93.36	82.76	81.43	91.54	84.25
293.15	99.00	99.43	99.69	97.32	100.87
298.15	109.27	119.09	120.88	110.71	120.04
303.15	141.83	142.21	145.20	137.47	142.03
308.15	161.14	169.33	172.78	162.92	167.14
313.15	195.20	201.06	203.69	189.30	195.67
318.15	247.20	238.10	237.93	243.19	227.94
323.15	282.20	281.23	275.39	264.33	264.28
$x_j^0 = 0.30$					
278.15	52.37	50.64	49.05	49.12	50.09
283.15	64.84	59.75	58.78	63.75	60.17
288.15	71.99	70.28	69.99	74.30	71.83
293.15	80.21	82.45	82.80	82.63	85.23
298.15	94.87	96.47	97.37	93.94	100.55
303.15	112.45	112.59	113.84	113.06	117.97
308.15	128.64	131.07	132.36	132.47	137.71
313.15	143.32	152.22	153.08	154.33	159.95
318.15	183.59	176.37	176.13	193.35	184.91
323.15	205.05	203.89	201.66	219.84	212.81
$x_j^0 = 0.40$					
278.15	41.34	41.06	39.81	43.20	42.59
283.15	49.37	53.86	48.37	54.24	50.69
288.15	58.77	62.21	58.37	59.81	59.97
293.15	69.75	72.15	69.95	69.23	70.55
298.15	82.55	76.83	83.28	79.52	82.53
303.15	97.43	91.05	98.53	92.12	96.06
308.15	114.68	114.25	115.88	106.10	111.25
313.15	134.62	136.50	135.50	124.04	128.25
318.15	157.64	159.20	157.56	149.29	147.18
323.15	184.14	184.47	182.23	177.68	168.19
$x_j^0 = 0.50$					
278.15	38.70	36.59	36.29	38.16	35.44
283.15	44.12	42.63	42.57	45.48	41.81
288.15	47.98	49.55	49.71	48.89	49.04
293.15	57.95	57.43	57.79	57.30	57.22
298.15	74.10	66.40	66.92	66.29	66.40
303.15	76.94	76.60	77.22	74.10	76.69
308.15	82.78	88.15	88.80	83.94	88.16
313.15	93.89	101.22	101.80	97.50	100.89
318.15	113.20	115.98	116.40	113.20	114.97
323.15	141.75	132.62	132.75	138.29	130.49
$x_j^0 = 0.60$					
278.15	32.34	33.58	30.49	33.30	28.80
283.15	36.70	36.05	34.48	37.54	33.69
288.15	40.36	39.14	38.89	40.62	39.19
293.15	43.60	42.96	43.79	46.60	45.36
298.15	46.91	47.61	49.24	53.72	52.24
303.15	52.88	53.25	55.28	58.50	59.89
308.15	59.60	60.07	62.02	65.42	68.36
313.15	68.32	68.31	69.52	74.52	77.69
318.15	78.46	78.24	77.91	85.55	87.95
323.15	90.30	90.23	87.31	103.33	99.17
$x_j^0 = 0.70$					
278.15	26.82	24.22	24.34	28.00	22.72
283.15	30.23	27.86	28.00	30.16	26.37
288.15	32.72	31.98	32.11	33.61	30.44
293.15	35.30	36.63	36.73	36.82	34.98
298.15	41.05	41.86	41.92	41.80	40.00
303.15	46.44	47.75	47.74	44.94	45.54

(*continued on next page*)

Table 2 (*continued*)

T/K	10^3x^{exp}	10^3x^{Apel}	$10^3x^{\lambda h}$	10^3x^{GSM}	$10^3x^{Van't\text{-}JA}$
308.15	52.07	54.35	54.28	49.81	51.63
313.15	59.78	61.75	61.63	55.21	58.30
318.15	69.61	70.03	69.91	63.55	65.58
323.15	82.64	79.28	79.26	74.34	73.50
x_j^0 = 0.80					
278.15	23.79	23.27	23.77	21.95	17.28
283.15	25.11	25.28	25.55	23.10	19.90
288.15	27.34	27.43	27.48	26.51	22.82
293.15	30.71	29.72	29.57	27.74	26.04
298.15	32.41	32.16	31.87	30.86	29.58
303.15	34.22	34.75	34.38	33.24	33.46
308.15	36.73	37.51	37.15	36.56	37.70
313.15	39.34	40.44	40.21	39.59	42.32
318.15	42.58	43.55	43.62	45.93	47.33
323.15	48.81	46.85	47.43	51.95	52.75
x_j^0 = 0.90					
278.15	16.48	15.65	15.91	15.38	12.52
283.15	18.25	17.56	17.73	16.37	14.33
288.15	19.56	19.67	19.74	18.70	16.33
293.15	20.94	21.98	21.95	19.46	18.52
298.15	24.58	24.53	24.40	21.35	20.92
303.15	27.34	27.31	27.13	23.37	23.53
308.15	29.88	30.37	30.16	25.36	26.37
313.15	33.07	33.70	33.54	27.52	29.45
318.15	37.39	37.34	37.34	31.57	32.76
323.15	42.08	41.31	41.61	35.79	36.34
x_j^0 = 1.00					
278.15	7.48	7.22	7.38	9.18	8.53
283.15	8.12	8.10	8.20	10.31	9.72
288.15	9.46	9.07	9.10	10.80	11.01
293.15	10.11	10.13	10.10	12.31	12.43
298.15	10.97	11.29	11.21	13.69	13.97
303.15	12.19	12.56	12.44	15.38	15.64
308.15	14.10	13.94	13.82	16.23	17.45
313.15	14.85	15.44	15.35	18.61	19.40
318.15	17.22	17.08	17.08	19.98	21.50
323.15	19.24	18.86	19.04	24.82	23.74

[a] x^{exp} is the experimental mole fraction solubility of NIT. × ^{Apel}, $x^{\lambda h}$, $x^{Van't\text{-}JA}$ and x^{GSM} indicate the calculated mole fraction solubility of NIT obtained by the modified Apelblat model, λh model, Van'*t*-JA model, GSM model respectively.

[b] x_j^0 represents the initial mole fraction of ethanol in (ethanol + phemethylol) binary solvent system.

[c] The relative standard deviation of the solubility measurement u(x) = 0.001, u(T) = 0.05 K, u(P) = 2 KPa.

24.94 $MPa^{1/2}$, indicating that NIT had lower polarity. It has been reported that the solvents having $R_{a(v)} < 5.6$ $MPa^{0.5}$ are the most suitable for miscibility/solubility of solutes (Alanazi et al., 2020). From Table S3, values of $R_{a(v)}$ between NIT and all solvents are greater than 5.6 $MPa^{0.5}$, which means that NIT may be not soluble in all solvents. It has been reported that the solvents having $\Delta\delta_t < 7.0$ $MPa^{0.5}$ are the most suitable for miscibility/solubility of solutes.(Alanazi et al., 2020) Except water and ethyl acetate all the investigated organic solvents had $\Delta\delta_t < 7.0$ $MPa^{0.5}$.

In order to have a deeper illustration of the relationship between solubility sequence of NIT and the investigated binary solvents, HSPs of measured solvents and NIT including (δ_d, δ_p, δ_h, $\Delta\delta_t$, δ_t and δ_v) were summarized in Table S2. As can be seen in Table S2, the δ_h of selected binary solvent was very close to that of NIT, indicating that hydrogen bond might be the main interaction energy in NIT and selected binary-solvents. With the increment of mass fraction (x_j^0) of ethanol, the $\Delta\delta_d$, $\Delta\delta_p$ and $\Delta\delta_h$ of NIT in ethanol + phemethylol increased, the $\Delta\delta_d$ and $\Delta\delta_p$ of NIT in ethanol + acetonitrile decreased, however, the $\Delta\delta_h$ of NIT in ethanol + acetonitrile system decreased sharply with the rising mass fraction (x_j^0) of ethanol, achieved the minimum at a mass fraction of ethanol being 0.6000, and then followed by a sharp increase. Furthermore, all values of $\Delta\delta_t$ in ethanol + phemethylol was lower than 5.0 $MPa^{0.5}$. the $\Delta\delta_t$ of NIT in all two selected binary solvents decreased.

4.3. Activity coefficient

The activity coefficient calculation aimed to evaluate the solute–solvent molecular interactions to determine the optimal solvent for the solubilization of NIT. The ideal solubility of NIT is calculated by equation(18)(Liu and Guo, 2021)

Table 3 Experimental and calculated mole fraction solubility of NIT in binary mixed solvents of ethanol + acetonitrile with different ratio within a temperature range from 278.15 K to 323.15 K (p = 101.3 kpa).[a,b,c].

T/K	10^3x^{exp}	10^3x^{Apel}	$10^3x^{\lambda h}$	10^3x^{GSM}	$10^3x^{Van't\text{-}JA}$
x_j^0 = 0.00					
278.15	78.16	75.71	67.12	77.51	70.51
283.15	84.33	91.77	85.4	83.12	87.32
288.15	110.9	110.85	107.3	110.62	107.33
293.15	125.32	133.46	133.12	124.94	131.01
298.15	160.99	160.16	163.08	161.12	158.85
303.15	199.27	191.6	197.24	198.22	191.38
308.15	226.26	228.53	235.52	226.65	229.18
313.15	285.49	271.79	277.66	285.06	272.88
318.15	317.43	322.34	323.19	317.44	323.13
323.15	376.96	381.24	371.52	374.62	380.64
x_j^0 = 0.10					
278.15	64.22	67.27	61.5	64.22	64.72
283.15	77.06	80.9	76.72	80.74	79.31
288.15	105.87	96.97	94.71	106.91	96.49
293.15	110.99	115.86	115.71	112.22	116.62
298.15	132.72	138.01	139.94	131.91	140.05
303.15	161.87	163.91	167.54	165.82	167.18
308.15	197.56	194.12	198.56	195.76	198.41
313.15	229.06	229.27	232.99	231.29	234.2
318.15	289.44	270.05	270.69	290.07	275.01
323.15	302.88	317.27	311.43	313.52	321.33
x_j^0 = 0.20					
278.15	56.69	56.79	52.76	56.58	57.64
283.15	76.05	68.67	65.87	73.23	69.92
288.15	93.36	82.76	81.43	91.54	84.25
293.15	99	99.43	99.69	97.32	100.87
298.15	109.27	119.09	120.88	110.71	120.04
303.15	141.83	142.21	145.2	137.47	142.03
308.15	161.14	169.33	172.78	162.92	167.14
313.15	195.2	201.06	203.69	189.3	195.67
318.15	247.2	238.1	237.93	243.19	227.94
323.15	282.2	281.23	275.39	264.33	264.28
x_j^0 = 0.30					
278.15	52.37	50.64	49.05	49.12	50.09
283.15	64.84	59.75	58.78	63.75	60.17
288.15	71.99	70.28	69.99	74.3	71.83
293.15	80.21	82.45	82.8	82.63	85.23
298.15	94.87	96.47	97.37	93.94	100.55
303.15	112.45	112.59	113.84	113.06	117.97
308.15	128.64	131.07	132.36	132.47	137.71
313.15	143.32	152.22	153.08	154.33	159.95
318.15	183.59	176.37	176.13	193.35	184.91
323.15	205.05	203.89	201.66	219.84	212.81
x_j^0 = 0.40					
278.15	41.34	41.06	39.81	43.2	42.59
283.15	49.37	53.86	48.37	54.24	50.69
288.15	58.77	62.21	58.37	59.81	59.97
293.15	69.75	72.15	69.95	69.23	70.55
298.15	82.55	76.83	83.28	79.52	82.53
303.15	97.43	91.05	98.53	92.12	96.06
308.15	114.68	114.25	115.88	106.1	111.25
313.15	134.62	136.5	135.5	124.04	128.25
318.15	157.64	159.2	157.56	149.29	147.18
323.15	184.14	184.47	182.23	177.68	168.19
x_j^0 = 0.50					
278.15	38.7	36.59	36.29	38.16	35.44
283.15	44.12	42.63	42.57	45.48	41.81
288.15	47.98	49.55	49.71	48.89	49.04
293.15	57.95	57.43	57.79	57.3	57.22
298.15	74.1	66.4	66.92	66.29	66.4
303.15	76.94	76.6	77.22	74.1	76.69

(*continued on next page*)

Table 3 (*continued*)

T/K	10^3x^{exp}	10^3x^{Apel}	$10^3x^{\lambda h}$	10^3x^{GSM}	$10^3x^{Van't\text{-}JA}$
308.15	82.78	88.15	88.8	83.94	88.16
313.15	93.89	101.22	101.8	97.5	100.89
318.15	113.2	115.98	116.4	113.2	114.97
323.15	141.75	132.62	132.75	138.29	130.49
$x_j^0 = 0.60$					
278.15	32.34	33.58	30.49	33.3	28.8
283.15	36.7	36.05	34.48	37.54	33.69
288.15	40.36	39.14	38.89	40.62	39.19
293.15	43.6	42.96	43.79	46.6	45.36
298.15	46.91	47.61	49.24	53.72	52.24
303.15	52.88	53.25	55.28	58.5	59.89
308.15	59.6	60.07	62.02	65.42	68.36
313.15	68.32	68.31	69.52	74.52	77.69
318.15	78.46	78.24	77.91	85.55	87.95
323.15	90.3	90.23	87.31	103.33	99.17
$x_j^0 = 0.70$					
278.15	26.82	24.22	24.34	28	22.72
283.15	30.23	27.86	28	30.16	26.37
288.15	32.72	31.98	32.11	33.61	30.44
293.15	35.3	36.63	36.73	36.82	34.98
298.15	41.05	41.86	41.92	41.8	40
303.15	46.44	47.75	47.74	44.94	45.54
308.15	52.07	54.35	54.28	49.81	51.63
313.15	59.78	61.75	61.63	55.21	58.3
318.15	69.61	70.03	69.91	63.55	65.58
323.15	82.64	79.28	79.26	74.34	73.5
$x_j^0 = 0.80$					
278.15	23.79	23.27	23.77	21.95	17.28
283.15	25.11	25.28	25.55	23.1	19.9
288.15	27.34	27.43	27.48	26.51	22.82
293.15	30.71	29.72	29.57	27.74	26.04
298.15	32.41	32.16	31.87	30.86	29.58
303.15	34.22	34.75	34.38	33.24	33.46
308.15	36.73	37.51	37.15	36.56	37.7
313.15	39.34	40.44	40.21	39.59	42.32
318.15	42.58	43.55	43.62	45.93	47.33
323.15	48.81	46.85	47.43	51.95	52.75
$x_j^0 = 0.90$					
278.15	16.48	15.65	15.91	15.38	12.52
283.15	18.25	17.56	17.73	16.37	14.33
288.15	19.56	19.67	19.74	18.7	16.33
293.15	20.94	21.98	21.95	19.46	18.52
298.15	24.58	24.53	24.4	21.35	20.92
303.15	27.34	27.31	27.13	23.37	23.53
308.15	29.88	30.37	30.16	25.36	26.37
313.15	33.07	33.7	33.54	27.52	29.45
318.15	37.39	37.34	37.34	31.57	32.76
323.15	42.08	41.31	41.61	35.79	36.34
$x_j^0 = 1.00$					
278.15	7.48	7.22	7.38	9.18	8.53
283.15	8.12	8.1	8.2	10.31	9.72
288.15	9.46	9.07	9.1	10.8	11.01
293.15	10.11	10.13	10.1	12.31	12.43
298.15	10.97	11.29	11.21	13.69	13.97
303.15	12.19	12.56	12.44	15.38	15.64
308.15	14.1	13.94	13.82	16.23	17.45
313.15	14.85	15.44	15.35	18.61	19.4
318.15	17.22	17.08	17.08	19.98	21.5
323.15	19.24	18.86	19.04	24.82	23.74

[a] x^{exp} is the experimental mole fraction solubility of NIT. × ^{Apel}, $x^{\lambda h}$, $x^{Van't\text{-}JA}$ and x^{GSM} indicate the calculated mole fraction solubility of NIT obtained by the modified Apelblat model, λh model, Van'*t*-JA model, GSM model respectively.

[b] x_j^0 represents the initial mole fraction of ethanol in (ethanol + acetonitrile) binary solvent system.

[c] The relative standard deviation of the solubility measurement u(x) = 0.001, u(T) = 0.05 K, u(P) = 2 KPa.

Table 4 Thermodynamic parameters of NIT dissolution in nine pure solvents.[a].

Solvent	ΔH^0_{sol}	ΔS^0_{sol}	ΔG^0_{sol}	ξ_H	ξ_S
	($KJ{\cdot}mol^{-1}$)	($J{\cdot}mol^{-1}{\cdot}K^{-1}$)	($KJ{\cdot}mol^{-1}$)		
Water	13.56	−12.32	17.25	0.7858	0.2142
Methanol	18.03	25.61	10.35	0.7012	0.2988
Ethanol	15.49	14.75	11.06	0.7778	0.2222
1,2-Propanediolethyl	15.71	14.73	11.29	0.7806	0.2194
Isopropanol	15.78	13.00	11.88	0.8017	0.1983
Ethyl acetate	19.87	50.09	4.84	0.5694	0.4306
Acetonitrile	26.20	70.36	5.09	0.5538	0.4462
n-Butanol	18.87	27.35	10.67	0.6970	0.3030
Phemethylol	27.33	76.49	4.39	0.5436	0.4564

[a] ΔH^0_{sol}, ΔS^0_{sol} and ΔG^0_{sol} are the enthalpy, entropy and Gibbs energy of the solute, respectively. ξ_H and ξ_S are the contribution of enthalpy and entropy to the standard Gibbs energy, respectively.

Table 5 Thermodynamic parameters of NIT dissolution in binary solvent mixture of ethanol + phemethylol with different ratio.[a,b].

x_j^0	ΔH^0_{sol}	ΔS^0_{sol}	ΔG^0_{sol}	ξ_H	ξ_S
	($KJ{\cdot}mol^{-1}$)	($J{\cdot}mol^{-1}{\cdot}K^{-1}$)	($KJ{\cdot}mol^{-1}$)		
0.00	27.33	76.49	4.39	0.5436	0.4564
0.10	26.31	71.82	4.77	0.5498	0.4502
0.20	25.44	67.82	5.09	0.5556	0.4444
0.30	22.25	55.36	5.65	0.5727	0.4273
0.40	24.07	60.14	6.03	0.5716	0.4284
0.50	20.58	46.66	6.59	0.5953	0.4047
0.60	16.47	30.34	7.36	0.6440	0.3560
0.70	18.28	35.12	7.75	0.6344	0.3656
0.80	11.38	9.64	8.49	0.7973	0.2027
0.90	15.60	21.58	9.12	0.7067	0.2933

[a] x_j^0 refers to the initial mole fraction of ethanol in the binary solvent.
[b] ΔH^0_{sol}, ΔS^0_{sol} and ΔG^0_{sol} are the enthalpy, entropy and Gibbs energy of the solute, respectively. ξ_H and ξ_S are the contribution of enthalpy and entropy to the standard Gibbs energy, respectively.

Table 6 Thermodynamic parameters of NIT dissolution in binary solvent mixture of ethanol + acetonitrile with different ratio.[a,b].

x_j^0	ΔH^0_{sol}	ΔS^0_{sol}	ΔG^0_{sol}	ξ_H	ξ_S
	($KJ{\cdot}mol^{-1}$)	($J{\cdot}mol^{-1}{\cdot}K^{-1}$)	($KJ{\cdot}mol^{-1}$)		
0.00	25.65	68.59	5.07	0.5549	0.4451
0.10	25.34	66.40	5.42	0.5599	0.4401
0.20	25.02	64.09	5.80	0.5655	0.4345
0.30	24.86	62.31	6.16	0.5708	0.4292
0.40	24.43	59.55	6.56	0.5776	0.4224
0.50	24.61	58.69	7.00	0.5830	0.4170
0.60	22.42	49.64	7.53	0.6009	0.3991
0.70	20.57	40.33	8.48	0.6297	0.3703
0.80	21.56	40.85	9.31	0.6377	0.3623
0.90	17.29	23.14	10.35	0.7136	0.2864

[a] x_j^0 refers to the initial mole fraction of ethanol in the binary solvent.
[b] ΔH^0_{sol}, ΔS^0_{sol} and $\Delta G^0_{sol}$are the enthalpy, entropy and Gibbs energy of the solute, respectively. ξ_H and ξ_S are the contribution of enthalpy and entropy to the standard Gibbs energy, respectively.

$$\ln x^{idl} = \frac{-\Delta fus\mathrm{H}(Tfus - T)}{\mathrm{R}\,Tfus\,T} + \left(\frac{\Delta Cp}{R}\right)\left[\frac{Tfus - T}{T} + \ln\left(\frac{T}{Tfus}\right)\right] \quad (18)$$

Where R denotes the gas constant (8.314 $J/K^{-1}{\cdot}mol^{-1}$);T_{fus} and $\Delta_{fus}H$ express fusion/melting temperature and fusion enthalpy of NIT, respectively, as achieved from DSC analysis; ΔC_p represents the difference in the molar heat capacity of the solid state from that of the liquid state. The ΔC_p was calculatedby equation(19)

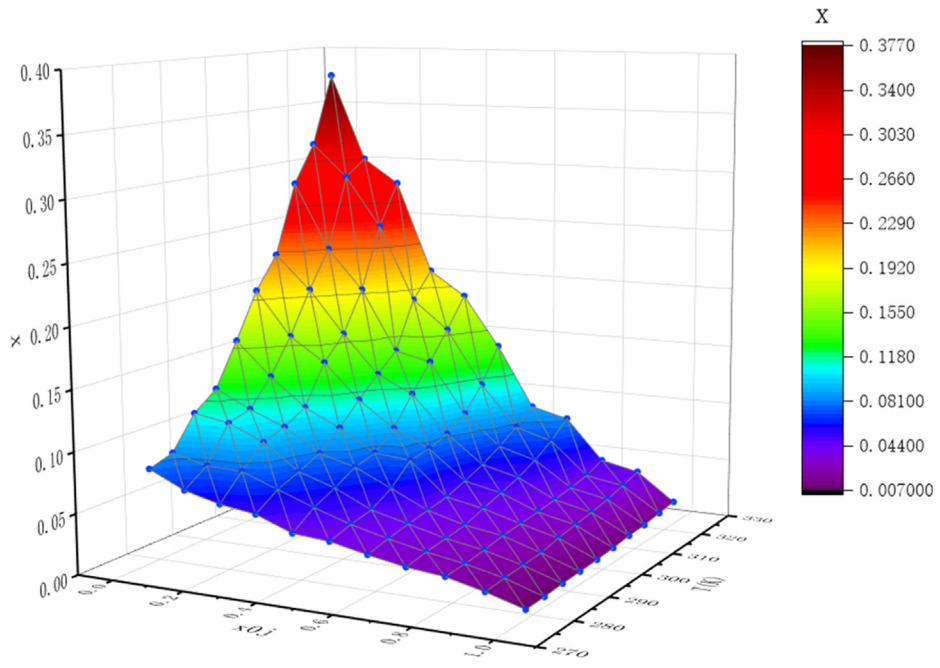

Fig. 2 Experimental solubility data of NIT at various temperatures T(K) and different mole fraction compositions of acetone x_j^0 in the binary solvent mixtures of ethanol + phemethylol.

$$\Delta Cp = \frac{\Delta fusH}{T_{fus}} \tag{19}$$

The activity coefficient (γ_i) for NIT in different organic solvents was obtained by equation(20)

$$\gamma_i = \frac{x^{idl}}{x^{exp}} \tag{20}$$

where x^{idl} and x^{exp} are ideal solubility and experimental values.

Table S5-S7 summarizes the calculated values of γ_i for NIT in nine pure solvent and two binary solvent systems from T (278.15–323.15 K). γ_i in nine pure solvents satisfied the sequence of Phemethylol < Acetonitrile < Ethyl acetate < Methanol < *n*-Butanol < Ethanol < 1,2-Propanediolethyl < Isopropanol < Water, which is opposed to the order of decreasing

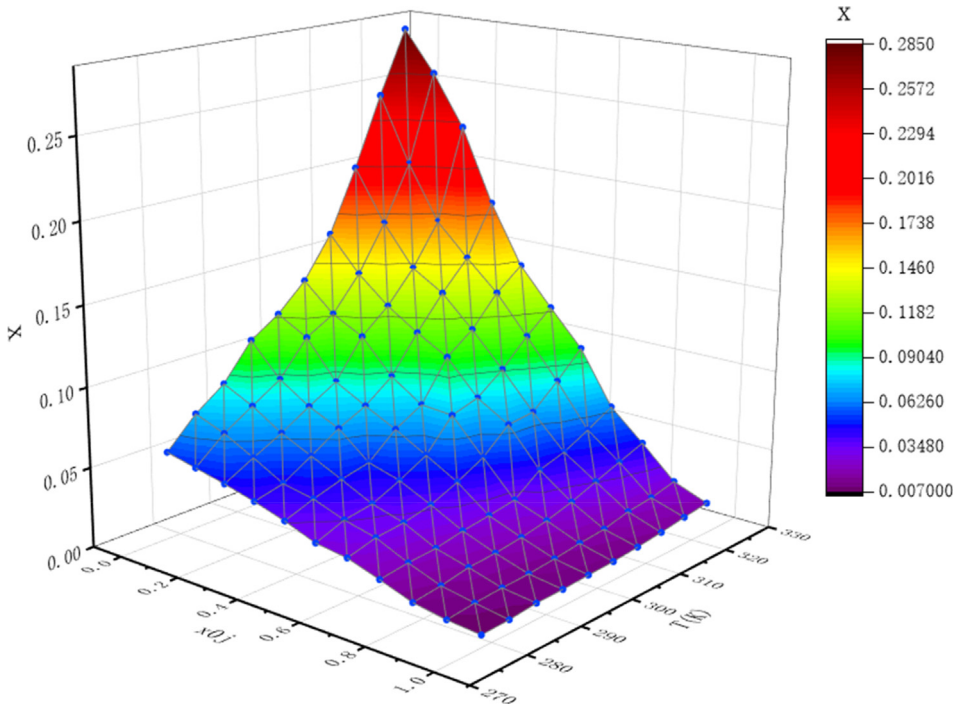

Fig. 3 Experimental solubility data of NIT at various temperatures T(K) and different mole fraction compositions of acetone x_j^0in the binary solvent mixtures of ethanol + acetonitrile.

solubility. The values of γ_i were recorded < 1.0 in organic solvents i.e., phemethylol, acetonitrile and ethyl acetate. Besides, the γ_i was decreased with the mole fraction of phemethylol/acetonitrile increases in two binary solvent mixtures.

4.4. Comparison of model results

In this paper, the modified Apelblat model, λh model, GSM model and the Van'*t*-JA model were used to fit the solubility of NIT in nine pure solvents and two binary mixed solvents.

As we can see from Tables 7-8, In pure solvent, both the modified Apelblat model and the λh model show a good fitting trend, the correlation coefficients (R^2) are above 0.98, the RMSD values are < 0.001, the RMSD values of phemethylol, acetonitrile and ethyl acetate with good solubility were significantly higher than those of other solvents with poor solubility. it is worth noting that the modified Apelblat model(ORMSD = 1.9958×10^3) can give better correlation results though other models can also give satisfactory correlation results by used the 10^3RMSD and 10^3ORMSD values as appraisal standard in mono-solvents. From the theoretical values by the modified Apelblat model illustrated in Table 1, it can be found that the differences between the experimental and calculated values are very small.

As Tables 9-12 shown, the 10^3RMSD and 10^3ORMSD values of modified Apelblat model, λh model, Van'*t*-JA model and GSM equation were calculated respectively, The correlation coefficients (R^2) were all greater than 0.7, and the fitting linearity was good. In modified Apelblat model, λh model and Van'*t*-JA model, the higher the ratio of phemethylol and acetonitrile, the higher the RMSD value, in GSM equation, RMSD value increased with the increase of temperature, which is similar to the result of the single solvent, It can be inferred that the stronger the solubility, the faster the solubility value increases, which will have an impact on the linear fitting. And the value of GSM model(ORMSD = 3.9109×10^3) is lowest in ethanol + phemethylol and Van'*t*-JA model(RMSD = 4.41×10^3) is lowest in ethanol + acetonitrile.The results show that the GSM equation fits ethanol better, and ethanol + acetonitrile can be better fitted by Van't JA equation.

4.5. Apparent thermodynamics functions of dissolution

Thermodynamic properties are essential to the research of solid–liquid equilibrium systems, which can help us better understand the dissolution behavior of a drug. For the purpose of understand the dissolution process of NIT in the temperature range of 278.15 K–323.15 K, enthalpies of solution (ΔH^0_{sol}), Gibb's energy of dissolution (ΔG^0_{sol}) and entropy of solutions (ΔS^0_{sol}) have also been calculated by Van't Hoff plot from the intercept and slope.(Jia et al., 2021)(Yang et al., 2021).

$$\Delta H^0_{sol} = -R\left[\frac{\partial \ln x}{\partial\left(\frac{1}{T}-\frac{1}{T_{mean}}\right)}\right] = -R \cdot slope \tag{21}$$

$$\Delta G^0_{sol} = -RT\text{mean} \cdot \text{intercept} \tag{22}$$

Table 7 Parameters of the Modified Apelblat equation for NIT in nine mono-solvents.[a].

solvent	modified Apelblat model					
	a	b	c	R^2	10^3RMSD	10^3ORMSD
water	53.03	−39.85	5.74	0.9918	0.0243	1.9958
methanol	46.73	−47.85	7.63	0.9819	0.8233	
ethanol	−280.91	−34.70	5.47	0.9926	0.3172	
1,2-propanediolethyl	−261.20	−36.14	5.70	0.9908	0.3316	
isopropanol	−93.46	−40.30	6.28	0.9846	0.3428	
ethyl acetate	−62.64	−44.61	7.52	0.9943	4.2577	
acetonitrile	7.91	−63.12	10.70	0.9954	4.8693	
n-butanol	87.64	−52.14	8.34	0.9918	0.4982	
phemethylol	−75.71	−61.56	10.53	0.9956	6.4976	

[a] a, b and c refer to the parameters of the modified Apelblat model.

Table 8 Parameters of the Van't Hoff model for NIT in nine mono-solvents.[a].

solvent	λh model				
	λ	h	R^2	10^3RMSD	10^3ORMSD
water	0.01	840250.60	0.9944	0.0200	2.1026
methanol	0.05	32855.55	0.9821	0.7901	
ethanol	0.02	56588.44	0.9937	0.2569	
1,2-propanediolethyl	0.02	60099.83	0.9937	0.2749	
isopropanol	0.02	75751.85	0.9880	0.3029	
ethyl acetate	1.12	2141.11	0.9880	3.6055	
acetonitrile	3.19	1144.96	0.9911	6.7735	
n-butanol	0.06	33297.20	0.9933	0.4531	
phemethylol	6.44	629.54	0.9957	6.4464	

[a] λ and h refer to the parameters of the λh model.

Table 9 Parameters of the modified Apelblat model for NIT in different ratio binary-solvents.[a].

x_j^0	modified Apelblat model					
	a	b	c	R^2	10^3RMSD	10^3ORMSD
ethanol + phemethylol						
0.00	−280.91	−34.70	5.47	0.9956	6.4976	3.3570
0.10	−42.43	−59.96	10.20	0.9884	8.6838	
0.20	33.57	−63.66	10.78	0.9912	6.6963	
0.30	49.31	−56.36	9.45	0.9925	4.2191	
0.40	11.90	−59.52	10.00	0.9943	3.4297	
0.50	33.62	−52.39	8.70	0.9906	2.9556	
0.60	11614.42	−300.49	45.37	0.9985	0.6908	
0.70	207.11	−52.86	8.60	0.9876	1.9374	
0.80	62.07	−31.41	4.87	0.9855	0.9086	
0.90	16.02	−40.95	6.53	0.9948	0.5908	
1.00	−280.91	−34.70	5.47	0.9926	0.3172	
ethanol + acetonitrile						
0.00	7.91	−63.12	10.70	0.9954	4.8693	2.9990
0.10	58.03	−64.71	10.93	0.9896	6.3577	
0.20	71.50	−65.54	11.04	0.9843	6.7618	
0.30	17.62	−61.49	10.33	0.9970	2.4260	
0.40	−3875.64	26.40	−2.83	0.9895	3.7742	
0.50	23.39	−58.21	9.70	0.9912	2.8446	
0.60	150.83	−59.79	9.86	0.9890	2.4416	
0.70	226.65	−59.92	9.77	0.9805	2.1067	
0.80	9.45	−55.86	9.13	0.9929	0.5275	
0.90	77.79	−47.20	7.50	0.9900	0.5621	
1.00	−280.91	−34.70	5.47	0.9926	0.3172	

[a] a, b and c refer to the parameters of the modified Apelblat model.

Table 10 Parameters of the λh model for NIT in different ratio binary-solvents.[a].

x_j^0	λh model				
	λ	h	R^2	10^3RMSD	10^3ORMSD
ethanol + phemethylol					
0.00	6.44	629.54	0.9957	6.4464	3.8761
0.10	3.80	965.82	0.9895	8.2454	
0.20	3.14	11161.42	0.9852	8.6500	
0.30	1.21	2732.88	0.9898	4.9260	
0.40	1.26	2467.75	0.9922	4.0026	
0.50	0.52	4660.43	0.9736	5.0275	
0.60	0.17	9853.52	0.9883	1.9564	
0.70	0.21	9684.66	0.9882	1.8951	
0.80	0.02	28673.64	0.9899	0.7588	
0.90	0.05	24591.54	0.9966	0.4727	
1.00	0.02	56588.44	0.9952	0.2569	
ethanol + acetonitrile					
0.00	3.19	1144.96	0.9911	6.7735	3.5425
0.10	2.46	1439.67	0.9825	8.2570	
0.20	1.94	1790.47	0.9777	8.0578	
0.30	1.31	2455.99	0.9953	3.0505	
0.40	0.90	3316.02	0.9894	3.7884	
0.50	0.64	4384.81	0.9920	2.7070	
0.60	0.43	6155.71	0.9883	2.5154	
0.70	0.23	10433.87	0.9798	2.1414	
0.80	0.16	14744.23	0.9930	0.9137	
0.90	0.05	34743.54	0.9919	0.5063	
1.00	0.02	56588.44	0.9952	0.2569	

[a] λ and h refer to the parameters of the λh model.

Table 11 Parameters of the GSM model for NIT in different ratio binary-solvents.[a].

T/K	GSM model							
	a	b	c	d	e	R^2	10^3RMSD	10^3ORMSD
ethanol + phemethylol								
278.15	−4.69	6.16	−10.92	10.32	−3.42	0.9937	1.6240	3.9109
283.15	−4.57	5.37	−8.34	9.09	−4.03	0.9911	1.8154	
288.15	−4.53	6.83	−15.34	20.03	−9.20	0.9984	1.3355	
293.15	−4.40	5.21	−6.99	6.79	−2.69	0.9968	2.0535	
298.15	−4.29	0.86	−4.37	1.84	0.13	0.9939	3.5572	
303.15	−4.17	4.57	−4.18	3.14	−0.98	0.9970	3.1666	
308.15	−4.12	4.97	−5.53	5.50	−2.29	0.9969	3.8060	
313.15	−3.98	4.03	−1.10	−1.16	0.96	0.9944	6.3159	
318.15	−3.91	5.12	−6.16	7.69	−3.88	0.9967	5.7776	
323.15	−3.70	3.54	1.64	−4.96	2.49	0.9928	9.6574	
ethanol + acetonitrile								
278.15	−5.00	3.99	−1.81	−0.72	0.63	0.9970	0.8790	4.2904
283.15	−4.99	5.71	−7.36	5.85	−1.82	0.9958	1.3602	
288.15	−4.73	4.06	−2.86	1.49	−0.41	0.9991	24.1827	
293.15	−4.65	3.47	0.93	−4.84	2.86	0.9979	1.4197	
298.15	−4.71	5.38	−4.75	2.25	−0.28	0.9952	2.4877	
303.15	−4.59	4.85	−1.03	−3.76	2.54	0.9911	3.8989	
308.15	−4.41	4.62	1.02	−7.53	4.49	0.9984	1.9284	
313.15	−4.20	3.64	3.71	−10.36	5.61	0.9995	1.3448	
318.15	−4.17	4.98	−0.47	−5.48	3.73	0.9992	1.9917	
323.15	−4.18	7.67	−12.20	12.64	−5.18	0.9985	3.4107	

[a] a,b,c,d and e refer to the parameters of the GSM model.

Table 12 Parameters of the Van'*t*-JA model for NIT in different ratio binary-solvents.[a].

x_j^0	Van'*t*-JA model								
	V_0	V_1	V_2	V_3	V_4	V_5	V_6	R^2	10^3RMSD
ethanol + phemethylol									
	2.58	−2043.70	6.87	−746.10	−1073.05	810.37	−315.37	0.9920	6.85
ethanol + acetonitrile									
	4.85	−2855.87	4.25	325.69	−991.31	−138.40	313.98	0.9944	4.41

[a] V_0, V_1, V_2, V_3, V_4, V_5 and V_6 refer to the parameters of the Van'*t*-JA model.

$$\Delta S^0_{sol} = \frac{\Delta H^0_{sol} - \Delta G^0_{sol}}{T_{mean}} \tag{23}$$

where R is the universal gas constant, T_{mean} represents the mean temperature and "intercept" is the intercept of $\ln x_1$ and $(1/T - 1/T_{mean})$ curve.

Where T_{mean} represents the mean harmonic temperature of the temperature range which is given as Eq.(24).

$$T_{mean} = \frac{n}{\sum_{i=1}^{n} \frac{1}{Ti}} \tag{24}$$

Where n is the number of experimental temperatures points. In this work, the value of T_{mean} is 299.96 K.

The resulting data of ΔH^0_{sol},ΔG^0_{sol} and ΔS^0_{sol} for NIT dissolution are furnished in Table. 4-6. Besides, the contribution of enthalpy and entropy to the standard Gibbs energy also be calculated as Eq.(25), and shown in Table 4-6, too.

$$\xi_H = \frac{|\Delta H^0_{sol}|}{|\Delta H^0_{sol}| + |Tmean \cdot \Delta S^0_{sol}|}$$
$$\xi_S = \frac{|Tmean \cdot \Delta S^0_{sol}|}{|\Delta H^0_{sol}| + |Tmean \cdot \Delta S^0_{sol}|} \tag{25}$$

From Table. 4-6, In single solvent except water, the values of ΔS^0_{sol} were positive, which indicated the entropically driven dissolution process of NIT in the solvent. When NIT was dissolved in water, the degree of the system chaos is decreased, that is, the entropy of the system is decreased, so the ΔS^0_{sol} showed negative values. The conclusion can be drawn that ΔH^0_{sol} and ΔG^0_{sol} for NIT dissolution are positive in the studied mono and binary solvent mixtures, which explains the increasing solubility of NIT as the temperature increases. $\Delta G^0_{sol} > 0$ indicating that the dissolution process of NIT is apparently not spontaneous. In addition, the higher the mole fraction solubility of NIT shows, the smaller the values of ΔG^0_{sol} are. It indicated that forming the force between solute and solvent needed less energy in the solvent system corresponding to the better dissolving performance, $\Delta H^0_{sol} > 0$, which suggests that the dissolution process is endothermic(Wei et al., 2021). All of the ΔH^0_{sol} values are positive and the reason may be that the solute–solvent interaction force is less than other interactions (solute–solute and solvent–solvent interaction) in the dissolution process of NIT. Furthermore, $\xi_H > \xi_S$ in both pure

and mixed solvent, which suggests ΔH^0_{sol} is the main contributor to the standard molar Gibbs energy of solution during the dissolution and the values of ξ_H are $\geq$ 54.36 %.

5. Conclusions

In this work, the solubility of NIT in nine pure solvents and two kinds of binary mixtures at tested temperature range (278.15 K $\sim$ 323.15 K) under atmospheric pressure (p = 0.1 MPa). In all the tested solvent systems, the solubility of NIT increases with the increasing temperature and the ratio of phemethylol/acetonitrile in binary solvents. The overall root mean square deviations(ORMSD) of the Van't Hoff model is lowest in both mono-solvents. The value of GSM model is lowest in ethanol + phemethylol and Van'*t*-JA model is lowest in ethanol + acetonitrile. The results prove that the solubility of NIT in the tested solvent is the result of the combined effect of volume-dependent, solvent polarity and other factors.

Based on the apparent thermodynamic analysis, the thermodynamic properties for the solution process including enthalpy, entropy and Gibbs energy were calculated. According to the results, indicating that the dissolution process of NIT in all solvents is endothermic and not spontaneous. Through the above research will offer an assistance for design and optimization of crystallization and dosage form of NIT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2022.104531.

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