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Solubility and Solution Thermodynamics of Tylosin in Pure Solvents and Mixed Solvents at Various Temperatures

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Thermodynamic data of drug is important to industrial design and industrial application. In this paper, solubility data of tylosin in pure solvents and acetone +water mixture solvents were experimentally determined from 279.75 K to 323.15 K. The experiment results indicated that solubility of tylosin in pure solvents gradually decreased and followed this order: chloroform > buty lacetate > acetonitrile > tetrahydrofuran > acetone > benzene > n-butanol > ethy lacetate > n-propanol > ethanol > methanol > water, and solubility gradually decreased with water increasing in water+acetone mixture solvents. Moreover, experimental solubility increased with temperature increasing except for water（$x_c \geqslant$ 0.9281）+acetone mixture solvents. Thermodynamic models correlating solubility data showed that modified Apelblat model was litter better agreement than Van't Hoff model, Wilson model, NRTL model in pure solvents and C/R-K model, Jouyban Acree model in acetone+water solvents by ARD, RMSD and R^2. Furthermore, thermodynamic properties for dissolution process of tylosin were calculated and discussed by modified Apelblat model paramaters.

Keywords: Tylosin； Solubility; Thermodynamics models; Dissolution process

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1. Introduction

Tylosin (CAS:1401-69-0, Fig. 1) is a kind of antibiotic drugs that are greatly applied livestock not only to treat disease, but also to improve the feed utilization as feed additive.[1-3] Because tylosin is a medium spectrum antibiotic to treat infections caused by most Gram-positive bacteria, mycoplasmas, some Gram-negative bacteria, Chlamydia, and to increase the rates of weight gain and improve the feed efficiency of companion animals, such as cattle, chicken, turkey, and swine[1-3]. Therfore,investigations and research thermodynamic properties of drugs are vital to understand nature of molecular interactions and explore new fields. The solid–liquid equilibrium solubility data of drugs plays an important role separation and purification for process choosing in industry application. In this research, the solubility of tylosin were experimentally determined in chloroform, butyl acetate, acetonitrile, tetrahydrofuran, acetone, benzene, n-butanol, ethyl acetate, n-propanol, ethanol, methanol, water and acetone+water mixture solvents, and were correlated with modified Apelblat model, Van't Hoff model, Wilson model, NRTL model, C/R-K model and Jouyban–Acree model from 279.75 K to 323.15 K. Furthermore, $\Delta_{sol}H^o$, $\Delta_{sol}S^o$ and $\Delta_{sol}G^o$ for the dissolution processes of tylosin were calculated by modified Apelblat model parameters.

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2. Experimental

2.1 Materials

In the paper, tylosin was supplied from Ningxia Tairui Pharmaceutical Co.Ltd., China and purified before use by dilution crystallization method. Purity of tylosin was determined by HPLC (type Agilent 1200, Agilent Technologies).All solvents are analytical grade without further detection. Resources information were presented in Table 1.

2.2 Thermal analysis

The DSC measurements were operated for tylosin in a nitrogen atmosphere with a differential scanning calorimeter (NETZSCH, STA409PC). Tylosin sample was scanned from 270.6K to 772.9K at heating rate of 5K·min^{-1}.

2.3 Characterization

The powder X-ray diffraction equipment (Bruker D8 Advance) was

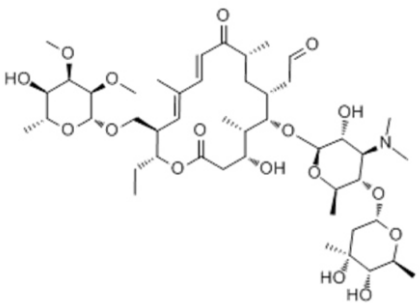

Fig. 1 Molecular structure of tylosin.

used to collect samples data and to ensure crystal form of samples. Diffraction angle was range from 2° to 50° (2θ) and a scanning speed of 5 ° min^{-1} with a current of 40 mA and a voltage of 40 kV.

2.4. Solubility determination

In this work, the gravimetric method was adopted to determine solubility of tylosin from 279.75 K to 323.15 K at the pressure of 0.1 MPa.[4-5] Firstly, the excess drug of tylosin sample and a certain amount of selected solvents was set into the cylindrical double-jacketed glass container with a designed temperature (±0.05K). The glass container was kept a designed temperature with water circulating. The prepared mixed solution was stirred more than 12 h to reach dissolution equilibrium.[4-5] Then, solid–liquid solution was set to stop stirring, precipitate and stratify 12 h. Next, 5 mL sampling was extracted from upper liquid and placed in double dish, weighed and set into a vacuum oven to dry for 12 h at 323.15 K. Lastly, Experimental solubility were measured at least three times to reduce mistakes. The solubility x of tylosin could be calculated by following equation:

$$x = \frac{m_1 / M_1}{m_1 / M_1 + m_2 / M_2} \quad (1)$$

$$x = \frac{m_1 / M_1}{m_1 / M_1 + m_B / M_B + m_C / M_C} \quad (2)$$

$$x_c = \frac{m_{B0} / M_B}{m_{B0} / M_B + m_{C0} / M_C} \quad (3)$$

where m_1 and m_2 (or m_B and m_C) stand for the mass of tylosin and the mass of solvents, respectively. M_1 and M_2 (or M_B and M_C) are the molar masses of tylosin and solvent, respectively. x_c is initial composition of water in acetone+water mixture solvent under condition of without tylosin.

3. Results and discussion

3.1 DSC and XRD analysis

From DSC curve, It was shown that there was a bigger and wider peak at 547.41 K, this revealed that the drug of tylosin had not fixed melting point and decomposed before melting temperature, Because tylosin had larger molecular weight and complex structure from Fig. 1. So, the thermal decomposition temperature was 547.41K and enthalpy of fusion H_{fus} was 88.9 kJ·mol^{-1} from Fig. 2.

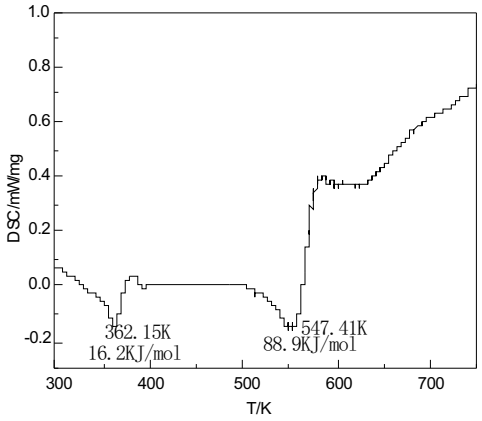

Fig. 2 DSC curve.

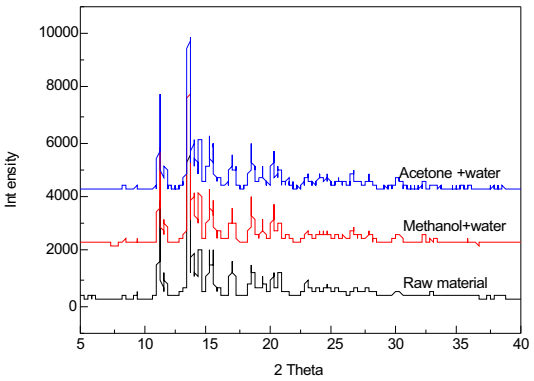

Fig. 3 XRD pattern of before and after recrystallization of tylosin.

Table 1 Description of materials used in this paper.

Chemical name	Formula	Source	Mass fraction purity
Tylosin	$C_{46}H_{77}NO_{17}$	Ningxia Tairui Pharmaceutical	≥0.99
Methanol (AR)	CH_3OH	Tianjin Wind Ship Chemical	≥0.995
Ethanol (AR)	C_2H_5OH	Tianjin Wind Ship Chemical	≥0.997
n-Propanol (AR)	C_3H_7OH	Tianjin Wind Ship Chemical	≥0.998
n-Butanol (AR)	C_4H_9OH	Tianjin Wind Ship Chemical	≥0.995
Acetone (AR)	C_4H_6O	Tianjin Wind Ship Chemical	≥0.99
Chloroform (AR)	$CHCl_3$	Tianjin Wind Ship Chemical	≥0.99
Acetonitrile (AR)	C_2H_3N	Tianjin Kermel Chemical	≥0.995
Butyl acetate (AR)	$C_6H_{12}O_2$	Tianjin Kermel Chemical	≥0.99
Ethyl acetate (AR)	$C_4H_8O_2$	Tianjin Kermel Chemical	≥0.995
Benzene (AR)	C_6H_6	Tianjin Wind Ship Chemical	≥0.995
Tetrahydrofuran (AR)	C_4H_8O	Tianjin Wind Ship Chemical	≥0.995

[a] AR means analytical reagent.

Fig. 3 presented the XRD pattern of the crystal. It could be seen that the morphologies of tylosin was not changed after recrystallization according with comparing with the powder diffraction spectrum of before and after recrystallization of tylosin.

3.2 Solubility data

The determination solubility data of tylosin were shown in Tables 2-3 and correlated Figs. 4-6 in pure solvents and acetone+water binary solvents systems with the temperature range from 279.75-323.15K. From Table 2 and Fig. 4, the solubility values of tylosin increased with increasing temperature except for water in pure solvents, the solubility gradually decreased and followed this order: chloroform > butyl acetate > acetonitrile > tetrahydrofuran > acetone > benzene > n-butanol > Ethyl acetate > n-propanol > ethanol > methanol > water. According to

Table 2 The measured and calculated mole fraction solubility of tylosin in different solvents from 279.75 to 323.15 K.

T/K	10^2x_{exp}	10^2x_{cal}				T/K	10^2x_{exp}	10^2x_{cal}			
		Apel	Van′t	Wilson	NRNL			Apel	Van′t	Wilson	NRNL
		Methanol						*Ethanol*			
280.25	0.4486	0.4536	0.4195	0.3101	0.4637	281.75	0.6949	0.7228	0.6687	0.5073	0.6444
287.05	0.6448	0.5987	0.576	0.5146	0.6901	287.95	0.8668	0.9405	0.8991	0.8768	0.8936
292.85	0.7529	0.7576	0.7462	0.8656	0.718	293.45	1.1856	1.185	1.1569	1.2076	1.1321
297.85	0.9183	0.9271	0.9252	1.1682	0.8844	298.05	1.3738	1.4348	1.4183	1.6681	1.4277
302.55	1.0885	1.1199	1.1251	1.4968	1.0527	303.05	1.7245	1.7631	1.7574	2.0835	1.7667
307.15	1.3308	1.3462	1.3546	1.6775	1.3409	307.85	2.1497	2.1448	2.145	2.4057	2.1363
312.35	1.6099	1.6557	1.66	1.9058	1.632	312.55	2.581	2.5938	2.5918	2.7484	2.589
317.35	2.0405	2.018	2.0057	1.7289	2.085	317.45	3.1633	3.1566	3.1381	2.9079	3.102
321.65	2.3784	2.3902	2.3491	1.7092	2.3397	322.55	3.764	3.8649	3.8059	3.1401	3.7946
		n-Propanol						*n-Butanol*			
279.75	2.0177	2.0553	1.9293	1.7018	2.0176	279.75	1.3455	1.285	1.3618	1.1597	1.2947
287.65	2.328	2.3672	2.3075	2.3258	2.3139	287.75	1.7681	1.7683	1.8329	1.8858	1.8113
293.05	2.5884	2.6178	2.5934	2.7118	2.5418	293.05	2.1935	2.1544	2.2118	2.3448	2.2088
297.35	2.7577	2.8421	2.8375	3.2361	2.8526	297.35	2.5941	2.5095	2.5634	2.7083	2.5694
302.55	3.1517	3.1464	3.1529	3.2107	3.0045	302.65	3.1376	3.0016	3.0569	3.1612	3.067
307.45	3.366	3.4701	3.4708	3.8773	3.4998	307.15	3.5062	3.4688	3.5329	3.8061	3.5953
312.65	3.8096	3.8579	3.8306	3.8055	3.7753	312.05	4.1351	4.0311	4.1163	4.1614	4.1488
317.15	4.154	4.2348	4.1611	3.9793	4.1805	316.35	4.7012	4.5718	4.6887	4.5181	4.6882
321.65	4.5785	4.6545	4.5096	3.938	4.5512	321.15	5.3616	5.2288	5.4	4.9444	5.3461
		Chloroform						*Acetonitrile*			
280.25	3.2637	3.3176	3.2157	2.8894	3.3192	281.85	5.7934	5.8306	5.6223	5.2853	5.6922
287.05	4.1595	4.0205	4.029	3.8975	3.9472	289.35	6.1877	6.2474	6.1703	6.5079	6.2455
292.85	4.8502	4.7406	4.843	5.1344	4.8227	292.85	6.4903	6.4659	6.4335	6.3232	6.3867
297.85	5.4514	5.4667	5.6431	6.4615	5.8135	298.65	6.8681	6.8637	6.8799	7.0578	6.8583
302.55	6.4828	6.2523	6.4853	6.9455	6.3689	303.45	7.182	7.2289	7.2585	7.8071	7.3157
307.15	7.453	7.1318	7.4006	7.6318	7.1949	307.95	7.618	7.6028	7.6207	7.6391	7.5888
312.35	8.4904	8.2772	8.5517	8.7068	8.5211	313.25	7.9915	8.085	8.0562	8.5663	8.1968
317.35	9.6805	9.5525	9.7832	9.5157	9.9105	318.25	8.4851	8.5845	8.4754	8.6603	8.6239
321.65	11.064	10.805	10.947	9.6175	10.949	322.65	9.0895	9.0624	8.8508	7.9343	8.7809
		Butyl acetate						*Ethyl acetate*			
281.95	6.5687	6.4234	6.4199	6.0072	6.4454	282.05	3.7167	3.7369	3.6229	2.8413	3.7545
289.35	6.9708	6.7715	6.9524	6.8768	6.9065	289.45	3.8761	3.8556	3.8441	3.428	3.8369
292.75	7.1825	6.957	7.2019	7.17	7.1248	292.65	3.9461	3.9205	3.9402	3.7296	3.8987
298.75	7.5316	7.3259	7.6493	8.072	7.6306	298.85	4.0908	4.0698	4.1271	4.332	4.0557

Table 2 continued

T/K	10^2x_{exp}	10^2x_{cal}				T/K	10^2x_{exp}	10^2x_{cal}			
		Apel	Van't	Wilson	NRNL			Apel	Van't	Wilson	NRNL
303.45	7.8937	7.6535	8.0058	8.2336	7.9503	303.35	4.1638	4.198	4.2633	5.2817	4.2384
307.95	8.1842	8.001	8.3517	8.9865	8.4158	307.95	4.3304	4.3469	4.4027	5.1867	4.3714
313.15	8.6832	8.4461	8.7569	8.8047	8.7427	313.15	4.5469	4.5378	4.5607	4.9144	4.5368
318.15	9.0999	8.9212	9.1516	9.3123	9.2487	317.95	4.7386	4.7363	4.7068	4.9013	4.7376
322.55	9.7004	9.3802	9.5029	8.4664	9.3327	322.45	4.9519	4.943	4.8438	4.6916	4.9297
		Benzene						*Tetrahydrofuran*			
281.75	1.7597	1.7321	1.8745	1.5464	1.6363	281.85	4.3457	4.2923	4.4041	4.199	4.1908
288.45	2.2856	2.364	2.4408	2.396	2.3394	288.45	4.9004	5.0832	5.0478	5.258	4.818
293.25	2.8574	2.9042	2.9273	3.0145	2.9194	293.25	5.482	5.6828	5.5529	5.5999	5.567
298.05	3.403	3.5207	3.4902	3.8098	3.6129	298.05	5.9855	6.296	6.0898	6.3274	6.1291
303.45	4.3595	4.3072	4.2257	4.4143	4.3729	303.45	6.9123	6.9939	6.7326	6.1407	7.0223
308.15	5.2081	5.0712	4.9637	5.0256	5.1011	308.05	7.4199	7.5881	7.313	6.9977	7.4941
313.05	6.0844	5.9444	5.8405	5.7978	5.9377	312.75	8.1896	8.1885	7.9379	7.2401	8.0053
318.15	7.0391	6.9319	6.8814	6.6836	6.8553	317.75	8.6256	8.8129	8.6383	8.8668	8.5522
323.15	7.7743	7.9717	8.0411	8.0956	7.9944	323.15	9.1533	9.463	9.4365	10.78	9.2041

[a] x_{exp} *and* x_{cal} are experimental and calculated mole fraction of tylosin in solvents;
Standard uncertainties *of temperature* is u(T) = 0.05 K, standard uncertainty of pressure is u(P) = 0.3 kPa; relative standard uncertainty of solubility measurement is $u_r(x)$ = 2%.

Table 3 The measured and calculated mole fraction solubility of tylosin acetone(1- x_c)+water (x_c) solvents.

T/K	100 x_{exp}	100 x_{cal}^{Apel}	T/K	100 x_{exp}	100 x_{cal}^{Apel}	T/K	100 x_{exp}	100 x_{cal}^{Apel}
	x_c=0.0000			x_c=0.1955			x_c=0.3629	
281.75	2.866	2.8253	281.85	2.696	2.7794	281.85	2.521	2.6199
287.95	3.256	3.337	288.65	3.187	3.2617	288.65	2.979	3.0768
293.45	4.014	3.8525	293.35	3.826	3.6354	293.35	3.423	3.4064
298.05	4.273	4.3322	298.15	4.175	4.0541	298.15	3.857	3.7516
302.85	4.771	4.884	302.95	4.51	4.5134	302.95	4.173	4.1027
307.75	5.297	5.5054	307.95	4.873	5.0382	307.85	4.535	4.4644
312.65	5.997	6.1901	312.65	5.544	5.5783	312.55	4.839	4.8115
316.75	6.883	6.8152	317.65	6.186	6.2063	317.55	5.117	5.1780
323.25	7.898	7.9114	322.05	6.873	6.8080	321.85	5.421	5.4885
	x_c=0.4466			x_c=0.5182			x_c=0.6827	
279.95	2.287	2.2910	281.85	1.977	1.9773	281.45	0.906	0.8989
287.85	2.654	2.6740	288.65	2.296	2.2747	288.05	0.995	1.0291
293.25	3.001	2.9477	293.35	2.482	2.4910	293.75	1.149	1.1460
297.95	3.169	3.1925	298.15	2.703	2.7201	298.55	1.26	1.2470
302.85	3.452	3.4529	302.85	2.931	2.9518	302.95	1.359	1.3411
307.65	3.686	3.7122	307.75	3.207	3.2003	307.85	1.478	1.4471

Table 3 continued

T/K	100 x_{exp}	100 x_{cal}^{Apel}	T/K	100 x_{exp}	100 x_{cal}^{Apel}	T/K	100 x_{exp}	100 x_{cal}^{Apel}
312.65	3.975	3.9854	312.45	3.487	3.4444	313.15	1.581	1.5624
316.75	4.247	4.2109	317.45	3.706	3.7094	318.05	1.637	1.6690
322.85	4.534	4.5473	321.65	3.922	3.9355	322.95	1.779	1.7750
	x_c=0.7634			x_c=0.8288			x_c=0.8827	
281.45	0.627	0.6391	281.55	0.488	0.4930	281.15	0.201	0.1980
288.05	0.736	0.7409	288.05	0.584	0.5755	288.05	0.235	0.2365
293.75	0.846	0.8318	293.75	0.646	0.6531	293.75	0.266	0.2712
298.55	0.935	0.9095	298.55	0.72	0.7222	297.35	0.289	0.2943
302.95	0.981	0.9810	302.95	0.786	0.7882	302.95	0.337	0.3322
307.85	1.05	1.0604	307.65	0.858	0.8614	307.45	0.371	0.3641
312.95	1.166	1.1420	312.85	0.966	0.9453	312.75	0.413	0.4032
317.95	1.222	1.2202	317.75	1.043	1.0268	317.55	0.437	0.4400
322.85	1.291	1.2945	322.55	1.089	1.1086	322.35	0.473	0.4779
	x_c=0.9281			x_c=0.9667			x_c=1	
281.95	0.12	0.1195	281.95	0.0492	0.0502	281.95	0.0192	0.0194
288.45	0.0992	0.1010	288.45	0.0431	0.0421	288.45	0.0147	0.0147
293.25	0.0922	0.0906	293.25	0.0381	0.0372	293.25	0.0123	0.0121
298.05	0.0842	0.0824	298.05	0.034	0.0330	298.05	0.0102	0.0101
303.25	0.0744	0.0754	303.15	0.0299	0.0292	303.15	0.0087	0.0084
307.95	0.068	0.0703	307.85	0.0257	0.0261	307.75	0.0074	0.0071
312.65	0.067	0.0663	312.55	0.0238	0.0235	312.45	0.0057	0.0061
317.75	0.0635	0.0628	317.75	0.0202	0.0210	317.75	0.0049	0.0052
322.65	0.0602	0.0603	322.35	0.0186	0.0190	322.15	0.0043	0.0045

[a] x_{exp} *and* x_{cal} are experimental and calculated mole fraction of tylosin in solvents;
x_c is initial composition of water in acetone+water mixture solvent under condition of without tylosin;
Standard uncertainties *of temperature* is u(T) = 0.05 K, standard uncertainty of pressure is u(P) = 0.3 kPa; relative standard uncertainty of solubility measurement is $u_r(x)$ = 2%.

the thermodynamics of solutions, solubility of tylosin in solvent are affected many factors that are solvent polarity, the same molecules self-association and the different molecules cross-association.[6-7] The polarity of tylosin was weaker by Fig. 1. According with the principle of "like dissolves like," tylosin dissolved highly in poorer polarity solvents like chloroform, butyl acetate and acetone than in stronger polarity solvents like water, methanol and ethanol. Especially, solubility of tylosin was confirmed to decrease with increasing temperature and was consistent with reference in water.[8]

From Table 3 and Fig. 5, in acetone+water mixture solvents, solubility values of tylosin increased with the increasing temperature when x_c was less than 0.9281, and decreased with the increasing mole fraction of water in mixture solvents. Because solubility was affected obviously and sensitive with water content. All factors influencing separation ways of tylosin could be considered as temperature, toxicity, cost, source of solvent and operability of purification process. Dilution crystallization process will be selected to separate and purify for tylosin with acetone+water solvents system in industry according with solubility data measured.

3.3 Solubility modeling

3.3.1 Modified Apelblat model

The modified Apelblat model is widely applied and well-correlated the relation between solubility data and different temperatures, which is described as following equation:[9,10]

$$\ln x = A + \frac{B}{T/K} + C\ln(T/K) \tag{4}$$

where x is experimental determination mole fraction solubility, T is thermodynamic absolute temperature. A, B and C are three model parameters in Eq. (4) and are listed in the Table 4 and Table 6. *ARD* is named corresponding average absolute deviation, and *RMSD* is named root mean square deviations, *ARD* and *RMSD* are calculated with Eq. (5) and Eq. (6) :

$$ARD = \frac{\left(\sum_{i=1}^{n} \frac{\left|x_{i,cal} - x_i\right|}{x_i}\right)}{n} \tag{5}$$

The root-mean-square deviations (*RM*) is defined as follows:

$$RMSD=\left[\sum_{i=1}^{n}\frac{(x_{i,cal}-x_i)^2}{n}\right]^{1/2} \quad (6)$$

where $x_{i,cal}$ and x_i represent the calculated and determination values, n is total times of experimental points. *ARD* and *RMSD* are presented in Tables 4-8.

3.3.2 Vant Hoff model

Based on thermodynamic principles of the solid-liquid equilibrium[13,14], the Van't Hoff model is considered as the simplest equation describing relationship of solubility and temperature.

$$\ln x = a + \frac{b}{T/K} \quad (7)$$

In Eq. (7), the two model parameters of a and b are gained from fitting results by solubility data and are shown in Table 4.

3.3.3 Wilson model

According to the theory of phase equilibrium, the fugacity of solid phase and liquid phase equals when solid sample in solvent reaches at the state of dissolving equilibrium. The Wilson model is organized and simplified into binary form.[15,16]

$$\ln\gamma_1 = -\ln(x_1+\Lambda_{12}x_2)+x_2\left[\frac{\Lambda_{12}}{x_1+\Lambda_{12}x_2}-\frac{\Lambda_{21}}{x_2+\Lambda_{21}x_1}\right] \quad (8)$$

$$\ln\gamma_2 = -\ln(x_2+\Lambda_{21}x_1)+x_1\left[\frac{\Lambda_{21}}{x_2+\Lambda_{21}x_1}-\frac{\Lambda_{12}}{x_1+\Lambda_{12}x_2}\right] \quad (9)$$

$$\Lambda_{12}=\frac{V_2}{V_1}\exp(-\frac{\lambda_{12}-\lambda_{11}}{RT})=\frac{V_2}{V_1}\exp(-\frac{\Delta\lambda_{12}}{RT}) \quad (10)$$

$$\Lambda_{21}=\frac{V_1}{V_2}\exp(-\frac{\lambda_{21}-\lambda_{22}}{RT})=\frac{V_1}{V_2}\exp(-\frac{\Delta\lambda_{21}}{RT}) \quad (11)$$

where V_1 and V_2 represent mole volumes of solute and pure solvent, $m^3\cdot mol^{-1}$, the two parameters of $\Delta\lambda_{12}$ and $\Delta\lambda_{21}$ stand for energy of cross interaction between different molecule, $J\cdot mol^{-1}$ and are shown in Table 5.

3.3.4 NRTL model

Another about activity coefficient equal is expressed as NRTL model, where three parameters exist in binary interaction, NRTL model can be organized and simplified into the following equations.[16,17,18]

$$\ln\gamma_1 = x_2^2\left[\frac{\tau_{21}G_{21}^2}{(x_1+x_2G_{21})^2}+\frac{\tau_{12}G_{12}}{(x_2+x_1G_{12})^2}\right] \quad (12)$$

$$\tau_{12}=\frac{(g_{12}-g_{11})}{RT}=\frac{\Delta g_{12}}{RT} \quad (13)$$

$$\tau_{21}=\frac{(g_{21}-g_{22})}{RT}=\frac{\Delta g_{21}}{RT} \quad (14)$$

$$G_{12}=\exp(-\alpha\tau_{12}),\ G_{21}=\exp(-\alpha\tau_{21}) \quad (15)$$

where Δg_{12} and Δg_{21} are considered as model constants and stand for energy of cross interaction between different molecules, $Jmol^{-1}$; α is a parameter related to non-randomness of a solution; all of parameters are presented in Table 5.

3.3.5 C/R-K model

At a constant temperature, C/R-K model is applied as the most appropriate and direct model to build the inherently complex relationship between composition and solubility in binary mixture solvents. The model can be simplify and deduced to Eq.(16) in ref[19]:

$$\ln x = B_0 + B_1x_c + B_2x_c^2 + B_3x_c^3 + B_4x_c^4 \quad (16)$$

where there are five model parameters from B_0 to B_4 in Eq.(16); x_c represents initial composition of water in mixture solvent; B_0,B_1,B_2,B_3 and B_4 are presented in Table 7.

3.3.6 Jouyban Acree model

Jouyban Acree model[19] is frequently applied another semi-empirical equation to correlate solubility data and temperature in mixtures solvent, which is described to Eq.(17) as follows:

$$\ln(x_A) = x_B\ln(x_A)_B + x_C\ln(x_A)_C + x_Bx_C\sum_{i=0}^{2}\frac{J_i(x_B-x_C)^i}{T} \quad (17)$$

$\ln(x_A)_B$ and $\ln(x_A)_C$ can be expressed with modified Apelblat model as Eq. (18) and Eq. (19) Eq.(17) can be simplified to Eq. (20) by the combination of Eq. (17), Eq. (18) and Eq. (19) .[20-23]

$$\ln(x_A)_B = a_1+\frac{b_1}{T}+c_1\ln T \quad (18)$$

$$\ln(x_A)_C = a_2+\frac{b_2}{T}+c_2\ln T \quad (19)$$

$$\ln(x) = A_1+\frac{A_2}{T}+A_3\ln T+A_4x_c+A_5\frac{x_c}{T}+A_6(\frac{x_c}{T})^2+A_7(\frac{x_c}{T})^3 + A_8(\frac{x_c}{T})^4+A_9x_c\ln T \quad (20)$$

where x represents solubility data of tylosin in acetone+water solvents, x_c represents initial composition of water in mixture solvent; there are nine model parameters from A_1 to A_9 , All of parameters are presented in Table 8, together with R^2.

The solubility values of tylosin in pure solvents were fitted by modified Apelblat model, Vant Hoff model, Wilson model and NRTL model, respectively. The computed solubility values with the modified Apelblat model are plotted in Fig. 4. Comparing of the total *ARD, RMSD* and R^2 from Tables 4-5. Tables 4-5 showed that R^2 values varied more than 0.993, *ARD* and *RMSD* values were less than 2.69% and 2.2×10^{-3} by modified Apelblat model. It could be said that the modified Apelblat model was little better than other three models. At the same time, the solubility values of tylosin in acetone+water solvents were fitted by modified Apelblat model, C/R-K model and Apelblat-Jouyban Acree model, respectively. The computed solubility values are plotted with the modified Apelblat model in Fig. 5 and with the C/R-K model in Fig. 6. Comparing of the total *ARD, RMSD* and R^2 from Tables 6-8. It indicated that R^2 values varied between 0.991 and 0.999 from modified Apelblat model, *ARD* and *RMSD* values from modified Apelblat model were less than 3.11% and 1.12×10^{-3} and less than from C/R-K model and Apelblat-Jouyban Acree model. These data in Tables 4-8 indicated that modified Apelblat model can litter better agree with solubility data of tylosin and provides reliable results for data prediction in pure solvents and in acetone+water solvents at varying temperature between 279.75 K and 323.15 K under the pressure of 0.1 MPa.

Table 4 Parameters of the modified Apelblat model and Van′t Hoff model for tylosin in pure solvent.

Solvents	Modified Apelblat model						Van′t Hoff model				
	A	*B*	*C*	R^2	10^2ARD	10^3RMSD	*a*	*b*	R^2	10^2ARD	10^3RMSD
Methanol	-129.96	2531.45	20.5	0.998	2.03	0.26	7.91	-3750.8	0.996	3.33	0.36
Ethanol	-109.64	1561.19	17.58	0.998	2.54	0.49	8.74	-3873.4	0.999	1.95	0.3
n-Propanol	-129.57	4143.14	19.68	0.998	1.76	0.63	2.57	-1823.4	0.994	1.52	0.58
n-Butanol	77.6	-6220.28	-10.6	0.999	252	0.92	6.39	-2989.5	0.999	1.29	0.4
Chloroform	-116.15	2883.04	18.18	0.998	2.39	1.88	6.08	-2667.2	0.998	1.31	0.98
Acetonitrile	-98.2	3455.62	14.73	0.997	0.61	0.55	0.71	-1011.4	0.99	0.99	1.05
Butyl acetate	-113.48	4259.55	16.96	0.998	2.69	2.2	0.37	-878.49	0.984	1.25	1.17
Ethyl acetate	-123.32	4860.94	18.22	0.997	0.43	0.19	-1	-653.76	0.968	1.28	0.66
Benzene	177.45	-10976.2	-25.27	0.996	2.25	1.12	7.39	-3202.6	0.991	3.97	1.77
Tetrahydrofuran	141.76	-7976.67	-20.68	0.993	2.53	1.94	2.84	-1680.6	0.989	1.97	1.59

[a] *A, B* and *C* are parameters of Apelblat model; *a* and *b* are parameters of Van′t Hoff model;

Table 5 Parameters of Wilson model and NRTL model for tylosin in pure solvent.

Solvents	Wilson model					NRTL model					
	$\Delta\lambda_{12}$	$\Delta\lambda_{21}$	R^2	10^2ARD	10^3RMSD	Δg_{12}	Δg_{21}	α	R^2	10^2ARD	10^3RMSD
Methanol	-6156.2	332.82	0.931	24.28	3.38	-11760	30168	0.3	0.998	3.1	0.33
Ethanol	-17079	508.36	0.969	12.81	2.98	-2273	-20953	1.63	0.999	2.77	0.42
n-Propanol	-13416	-1162.47	0.992	8.13	3.41	-4356	-15589	0.89	0.996	1.84	0.77
n-Butanol	-20944	-373.76	0.995	5.93	2.06	63319	-58013	0.04	0.999	2.71	0.46
Chloroform	-28851	504.12	0.993	7.66	6.43	-3154	-25430	1.05	0.997	2.55	1.91
Acetonitrile	-19996	-1821.32	0.997	5.58	5.28	128530	-118240	0.01	0.989	1.58	1.49
Butyl acetate	-17893	-4824.58	0.997	5.31	5.73	144729	-134897	0.01	0.985	1.61	1.67
Ethyl acetate	$1.3*10^{12}$	-4882.22	0.988	12.21	6.04	183825	-158117	0.01	0.995	0.83	0.4
Benzene	-26376	422.85	0.995	5.89	2.57	110424	-37889	0.07	0.998	3.1	1.42
Tetrahydrofuran	-24809	-684.71	0.995	7.5	7.2	-32038	413596	0.03	0.997	1.71	1.15

$\Delta\lambda_{12}$ and $\Delta\lambda_{21}$ are parameters of Wilson model; Δg_{12}, Δg_{21} and are parameters of NRTL model.

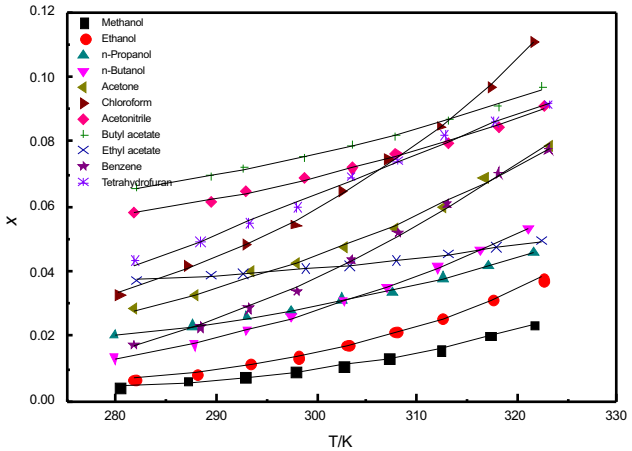

Fig. 4 The measured and calculated mole fraction solubility of tylosin from the modified Apelblat model in pure solvents from at various temperatures.

Table 6 Parameters of the Apelblat model for tylosin in acetone(1- x_c)+water (x_c) solvents.

Solvents	A	B	C	R^2	$10^2 ARD$	$10^3 RMSD$
x_c=0	-28.24	-791.25	4.87	0.9931	2.05	1.12
x_c=0.1955	-42.25	34.37	6.83	0.9914	2.07	1.03
x_c=0.3629	107.22	-6383.22	-15.64	0.9915	1.85	0.74
x_c=0.4466	55.21	-3854.6	-8.02	0.9982	0.62	0.25
x_c=0.5182	48.12	-3652.47	-6.93	0.9987	0.50	0.19
x_c=0.6827	70.05	-4608.74	-10.35	0.9924	1.36	0.21
x_c=0.7634	109.34	-6437.15	-16.23	0.9941	1.16	0.30
x_c=0.8288	56.65	-4289.54	-8.28	0.9951	1.11	0.11
x_c=0.8827	62.29	-4701.23	-9.19	0.9947	1.48	0.05
x_c=0.928 1	-250.46	12231.75	35.51	0.9931	1.46	0.01
x_c=0.9667	-16.94	2254.3	0.24	0.9922	2.33	0.00
x_c=1	-95.81	6680.6	11.27	0.9965	3.11	0.00

[a] *A, B* and *C* are parameters of Apelblat model;
x_c is initial composition of water in acetone+water mixture solvent.

Table 7 Parameters of the C/ R-K model for tylosin in acetone(1- x_c)+water (x_c) solvents.

T/K	B_0	B_1	B_2	B_3	B_4	R^2	$10^2 ARD$	$10^3 RMSD$
281.15	-3.5924	-0.5511	4.7253	-11.3427	3.4646	0.996	15.39	0.54
288.15	-3.4048	-0.6102	4.4083	-10.5526	2.9689	0.996	25.19	0.68
293. 15	-3.2744	-0.6178	3.9287	-9.5583	2.4072	0.995	33.96	0.8
298.15	-3.1468	-0.5982	3.2466	-8.2068	1.6612	0.995	44.15	0.94
303.15	-3.022	-0.5454	2.3251	-6.4188	0.6782	0.995	55.58	1.08
308.15	-2.8999	-0.4615	1.181	-4.2244	-0.5275	0.995	68.33	1.22
313.15	-2.7803	-0.3376	-0.2537	-1.4757	-2.0516	0.994	81.79	1.36
318.15	-2.6633	-0.1848	-1.89	1.6387	-3.7771	0.995	95.57	1.5
323.15	-2.55	0.0003	-3.75	5.1692	-5.7357	0.995	110.19	1.65

[a] *B_0, B_1, B_2, B_3 and B_4 are parameters of C/ R-K model*

Table 8 Parameters of the Jouyban-Acree model for tylosin in acetone(1- x_c)+water (x_c) solvents.

System	A_0	A_1	A_2	A_3	A_4	A_5
	267.6	-14032.2	-38.45	-279.91	14273.35	162.25
Aectone+water	A_6	A_7	A_8	R^2	*ARD*	*RMSD*
	-929	-368.21	40.69	0.994	56.46	2.54

[a] *A_0, A_1, A_2, A_3, A_4, A_5, A_6, A_7 and A_8* are parameters of Jouyban-Acree model.

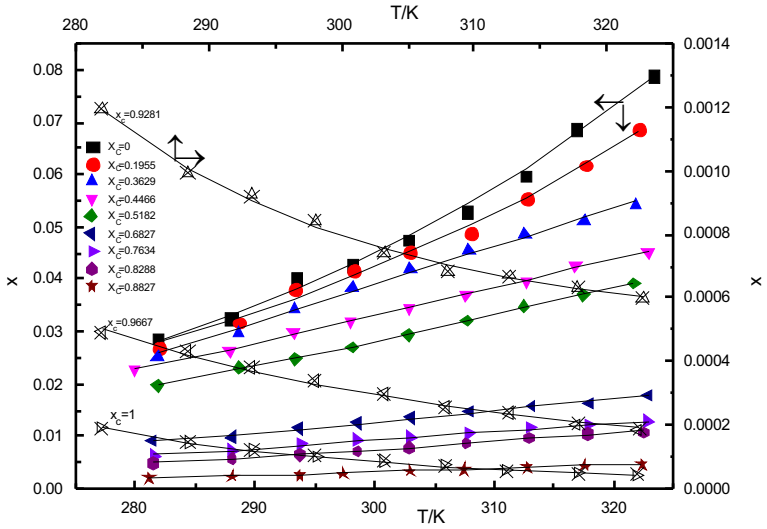

Fig. 5 The measured and calculated mole fraction solubility of tylosin from the modified Apelblat model in acetone (1- x_c) + water (x_c) solvents from at various temperatures.

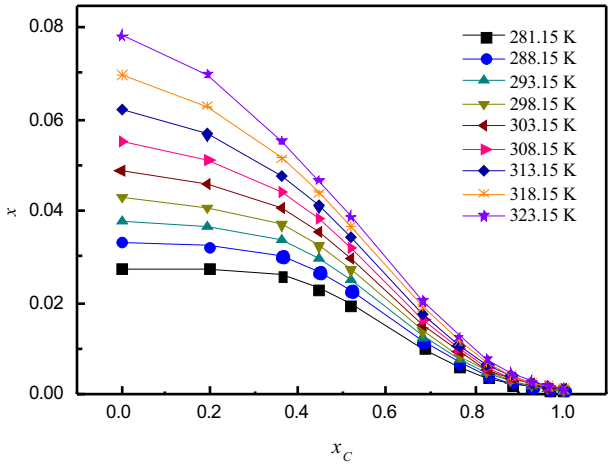

Fig. 6 The measured and calculated mole fraction solubility of tylosin from the C/R-K model in acetone (1- x_c) + water (x_c) solvents from at various temperatures.

3.3 Thermodynamic properties for the solution

The research of thermodynamic properties for dissolution process is necessary to analyzing and optimization design for industry application. $\Delta_{sol}H^o$ is defined as standard dissolution enthalpy, $\Delta_{sol}S^o$ is defined as standard dissolution entropy, and $\Delta_{sol}G^o$ is defined as standard dissolution Gibbs energy change. $\Delta_{sol}H^o$, $\Delta_{sol}S^o$ and $\Delta_{sol}G^o$ of solution of tylosin dissolution process in different solvents can be calculated with Eq. (21), Eq. (22) and Eq. (23)[24,25] by Gibbs-Duhem equation, Van't Hoff equation and modified Apelblat model. ζ_H and ζ_{TS} are defined as the comparison of the relative contribution of $\Delta_{sol}H^o$ and $\Delta_{sol}S^o$ to $\Delta_{sol}G^o$ in dissolution process process.[26-30]

$$\Delta_{sol}H^o = RT\left(C - \frac{B}{T}\right) \tag{21}$$

$$\Delta_{sol}S^o = R\left(A + C + C\ln T\right) \tag{22}$$

$$\Delta_{sol}G^o = -RT\left(A + B/T + C\ln T\right) \tag{23}$$

$$\varsigma_H = \frac{\left|\Delta_{sol}H^0\right|}{\left|\Delta_{sol}H^0\right| + \left|T\Delta_{sol}S^0\right|} \times 100 \tag{24}$$

$$\varsigma_{TS} = \frac{\left|T\Delta_{sol}S^0\right|}{\left|\Delta_{sol}H^0\right| + \left|T\Delta_{sol}S^0\right|} \times 100 \tag{25}$$

where R is the universal gas constant (8.314 J·mol^{-1}·K^{-1}), three parameters of A, B and C are from modified Apelblat. T is 298.15 K.

The values of $\Delta_{sol}H^o$, $\Delta_{sol}S^o$ and $\Delta_{sol}G^o$ were listed in Tables 9 and 10 together with ζ_H and ζ_{TS}. It indicated that $\Delta_{sol}H^o$, $\Delta_{sol}S^o$ and $\Delta_{sol}G^o$ values of tylosin dissolution process were all positive in solvents except for x_c>0.8827 mixture solvents. $\Delta_{sol}H^o > 0$ proved that the dissolving process of tylosin in solvents was expressed as endothermic process. $\Delta_{sol}S^o > 0$ showed it was an entropy-drives in dissolving process of tylosin. Further, $\zeta_H > 0.55$ showed that $\Delta_{sol}H^o$ was the main contributor to $\Delta_{sol}G^o$ during the dissolution. Otherwise, $\zeta_{TS} > 0.55$ showed that $\Delta_{sol}S^o$ was the main contributor to $\Delta_{sol}G^o$.

4. Conclusions

Table 9 Thermodynamic functions relative to dissolution process of tylosin in pure solvents.

Systems	$\triangle_{sol}H^o$	$\triangle_{sol}S^o$	$\triangle_{sol}G^o$	ζ_H	ζ_{TS}
	kJ·mol^{-1}	J·mol^{-1}·K^{-1}	kJ·mol^{-1}	%	%
Methanol+tylosin	29.77	61.03	11.57	62.06	37.94
Ethanol+tylosin	30.60	67.37	10.51	60.37	39.63
n-Propanol+tylosin	14.34	18.61	8.79	72.09	27.91
n-Butanol+tylosin	25.44	54.92	9.07	60.84	39.16
Chloroform+tyl osin	21.10	46.66	7.18	60.26	39.74
Acetonitrile+tylosin	7.78	3.79	6.65	87.33	12.67
Butyl acetate+tylosin	6.63	0.92	6.35	96.01	3.99
Ethyl acetate +tylosin	4.75	10.72	7.95	59.78	40.22
Benzene+tylosin	28.62	68.19	8.29	58.46	41.54
Tetrahydrofuran+tylosin	15.06	27.05	6.99	65.12	34.88

[a]$\Delta_{sol}H^o$, $\Delta_{sol}S^o$ and $\Delta_{sol}G^o$ are the standard molar enthalpy, standard molar entropy and standard molar Gibbs energy change of solution of tylosin in different solvents;
The ζ_H and ζ_{TS} represent the comparison of the relative contribution to the standard Gibbs energy by enthalpy and entropy in the solution process, respectively.

Table 10 Thermodynamic functions relative to dissolution process of tylosin in acetone(1- x_c)+water (x_c) solvents.

Systems	$\triangle_{sol}H^o$	$\triangle_{sol}S^o$	$\triangle_{sol}G^o$	ζ_H	ζ_{TS}
	kJ·mol^{-1}	J·mol^{-1}·K^{-1}	kJ·mol^{-1}	%	%
x_c=0	18.65	36.40	7.80	63.22	36.78
xc=0.1955	16.64	29.05	7.98	65.77	34.23
x_c=0.3629	14.30	20.53	8.18	70.03	29.97
x_c=0.4466	12.17	12.43	8.46	76.65	23.35
x_c=0.5182	13.19	14.18	8.96	75.72	24.28
x_c=0.6827	12.66	6.07	10.85	87.5	12.5
x_c=0.7634	13.29	5.30	11.71	89.36	10.64
x_c=0.8288	15.14	9.93	12.18	83.65	16.35
x_c=0.8827	16.31	6.14	14.47	89.9	10.1
x_c=0.9281	-13.67	-104.99	17.63	30.4	69.6
x_c=0.9667	-18.15	-127.4 8	19.86	32.32	67.68
x_c=1	-27.61	-169.16	22.82	35.38	64.62

New experimental results for solubility of tylosin in different solvents were investigated at temperature from 279.75 to 323.15 K. It could be seen that the solubility of tylosin in chloroform was the highest and followed by butyl acetate, acetonitrile, tetrahydrofuran, acetone, benzene, n-butanol, ethyl acetate, n-propanol, ethanol, methanol and water. Solubility of tylosin gradually decreased with water increasing in water+acetone mixture solvents. Data fitting results showed the modified Apelblat model agreed litter better with experimental data than Van′t Hoff model, Wilson model NRTL model in pure solvents, and C/R-K model, Jouyban Acree model in acetone+water solvents according with *ARD, RMSD* and R^2 .The calculated data of $\Delta_{sol}H^o$, $\Delta_{sol}S^o$, $\Delta_{sol}G^o$, ζ_H and ζ_{TS} indicated that solution process of tylosin in solvents was expressed as endothermic process and an entropy-drives process. Dilution crystallization process will be selected to separate and purify for tylosin according with experimental results.

Conflict of interest

There are no conflicts to declare.

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