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Solubility study of ketoconazole in propylene glycol and ethanol mixtures at different temperatures: A laser monitoring method

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ABSTRACT

The solubility of ketoconazole in the mixtures of propylene glycol and ethanol is measured by a laser monitoring technique in the temperature range of 293.2–313.2 K. The generated solubility data are fitted to some linear and non-linear cosolvency models and the accuracy of each model is investigated by calculating the mean relative deviations (*MRD%*) for the back-calculated data. The apparent thermodynamic parameters of ketoconazole dissolution are also computed according to the van't Hoff and Gibbs equations.

1. Introduction

Ketoconazole (*cis*-1-acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-(1H-imidazole-1-ylmethyl)-1,3-dioxolon-4-yl] methoxy] piperazin, Fig. 1) is a highly effective broad spectrum antifungal agent used in the treatment of a wide variety of superficial and systematic mycoses [1]. It prevents the synthesis of ergosterol and the fungal equivalent of cholesterol and finally increases the membrane fluidity and prevents the growth of the fungus [2–4]. According to the biopharmaceutics classification system, ketoconazole is classified as a class II drug meaning that it has low solubility and high permeability [5]. Solubility and related properties of a drug in various aqueous and non-aqueous mono-solvents or solvent mixtures are the important physicochemical features in different steps of the drug discovery or development procedure, such as preformulation studies, design of liquid pharmaceutical dosage forms purification, and/or extract ingredients from a synthetic or natural source [6,7]. Different techniques were reported for the solubility improvement of ketoconazole including nanoparticle formulation [8], solid dispersion [9], micro-emulsion formation [10], crystal engineering [11], and cosolvency. Cosolvency is a simple, popular and efficient method to increase the aqueous solubility of the drug molecule with low solubility. Some previously reported cosolvency mixtures for increasing the ketoconazole solubility are the binary systems of (propylene glycol (PG) + 2-propanol) [12], (carbitol + water) [13], (2-propanol + water) [14], (1,4-dioxane + water) [15], (PG + water) [16], (*N*-methyl-2-pyrrolidone (NMP) + water) [17], (ethanol + water) [18], (PEG 200 + water) [19], (PEG 200, or 400, or 600 + ethanol) [20], (1-propanol + water) [21], (acetonitrile + water) [22], and (NMP + ethanol) [23] which details of studied solubility data in above mixtures and the constants for Jouyban-Acree-van't Hoff model are summarized in Table 1. As far as we know, there is no report for ketoconazole solubility study in the mixtures of PG and ethanol. Both PG and ethanol are commonly used solvents in the pharmaceutical industries.

In continues of our previous works, for providing solubility database for drugs in the cosolvency systems, the aims of this study are (1) solubility data measurement for ketoconazole in the PG and ethanol mixtures at different temperatures; (2) correlation of the obtained data with some mathematical cosolvency models; and (3) calculation of the apparent thermodynamic parameters for the ketoconazole dissolution process in the investigated mixtures.

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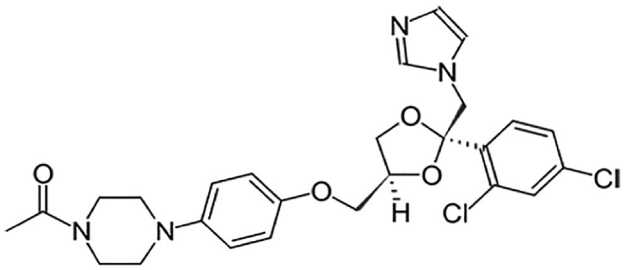

Fig. 1. Molecular structure of ketoconazole.

2. Materials and method

2.1. Materials

Ketoconazole with mass fraction purity of 0.998 from Arastoo pharmaceutical company (Tehran, Iran), PG with a purity of 0.995 (The Central Drug House, India), and ethanol (Scharlau Chemie, Spain) are the used solvent in the current work.

2.2. Determination of ketoconazole solubility

A lab-made setup is used for the determination of the ketoconazole solubility in the PG and ethanol mixtures. For this purpose, after setting temperature at 293.2, 298.2, 303.2, 308.2 and 313.2 K, the ketoconazole is dispersed by a robotic arm into the dissolution vessel containing 120 g of mono-solvents (ethanol or PG) and the mixtures of the different ratios of PG and ethanol. A magnet into the dissolution vessel is employed for stirring the solution during the laser monitoring. The ketoconazole powder injecting by a robot continues until the under-saturated solution is converted to a saturated solution which is identified by turning on the green light on the instrument. Based on the prescribed program, the saturation point is checked several times, and the solubility value is obtained by weighting the dispensed powder into the dissolution vessel.

2.3. Computational section

The measured ketoconazole solubility data (in the mole fraction unit) are correlated with some linear and non-linear models reported for cosolvency systems. These models are the van't Hoff, the mixture response surface (MRS), the Jouyban-Acree, the Jouyban-Acree-van't Hoff and the modified Wilson models. The details of each model are mentioned in the following sections.

The measured data are fitted to the cosolvency models and the obtained equations are employed to back-calculate the solubility data of ketoconazole. The mean relative deviation (*MRD*%) of the predicted solubility data is computed by Eq. (1) and reported as a measure of the model's accuracy.

$$MRD\% = \frac{100}{N}\sum\left(\frac{|Calculated\ Value - Observed\ Value|}{Observed\ Value}\right) \quad (1)$$

N is the number of data points.

2.3.1. van't Hoff equation

The van't Hoff equation with a theoretical basis relates natural logarithm of solubility data to the temperature is written as [24]:

$$\ln x = A + \frac{B}{T} \quad (2)$$

Herein, A and B are the model constants.

2.3.2. The mixture response surface (MRS) method

MRS model as a linear model correlates the solubility data at isothermal condition and is shown as:

$$\ln x_m = \beta_1 w\prime_1 + \beta_2 w\prime_2 + \beta_3\left(\frac{1}{w\prime_1}\right) + \beta_4\left(\frac{1}{w\prime_2}\right) + \beta_5 w\prime_1.w\prime_2 \quad (3)$$

where x_m is the mole fraction solubility of the solute in the solvent mixtures, $\beta_1 - \beta_5$ are equation parameters and $w_1^{'}$ and $w_2^{'}$ are obtained by using $w_1^{'} = 0.96w_1 + 0.02$ and $w_2^{'} = 0.96w_2 + 0.02$ [25]. W_1 and W_2 are the mass fractions of mono-solvents 1 and 2 in the absence of solute.

2.3.3. Jouyban-Acree model

The Jouyban-Acree model as another cosolvency model relates the solubility data to temperature and solvent composition simultaneously, and its general form is as [26]:

$$\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \frac{w_1.w_2}{T}\sum_{i=0}^{2} J_i.(w_1 - w_2)^i \quad (4)$$

J_i terms are the model parameters obtained by linear regression of $(\ln x_{m,T} - w_1 \ln x_{1,T} - w_2 \ln x_{2,T})$ against $\frac{w_1.w_2}{T}$, $\frac{w_1.w_2(w_1-w_2)}{T}$, and $\frac{w_1.w_2(w_1-w_2)^2}{T}$.

2.3.4. Jouyban-Acree-van't Hoff model

The Jouyban-Acree-van't Hoff model as a combination of the Jouyban-Acree model with the van't Hoff equation can be written as the following equation:

$$\ln x_{m,T} = w_1(A_1 + \frac{B_1}{T}) + w_2(A_2 + \frac{B_2}{T}) + \frac{w_1.w_2}{T}\sum_{i=0}^{2} J_i.(w_1 - w_2)^i \quad (5)$$

A_1, B_1, A_2, B_2 and J_i are the model's parameters obtained by a simple regression.

Table 1
Details of studied solubility of ketoconazole in solvent mixtures and the constants for Jouyban-Acree-van't Hoff model.

Solvent 1	Solvent 2	Solvent composition	Solubility unit	A_1	B_1	A_2	B_2	J_0	J_1	J_2	N	Ref.
PG	2-Propanol	Mass fraction	Mole fraction	11.816	−5361.089	13.810	−6168.115	681.428	126.246	336.815	40	[12]
Carbitol	Water	Mass fraction	Mole fraction	9.887	−4271.109	−5.502	−2741.594	1596.697	−641.558	2907.219	55	[13]
2-Propanol	Water	Mass fraction	Mole fraction	10.819	−5290.760	−10.280	−1313.480	5170.380	0[a]	0[a]	55	[14]
1,4-Dioxane	Water	Mass fraction	Mole fraction	9.265	−4203.015	−5.372	−2801.374	4058.263	2534.735	2534.735	55	[15]
PG	Water	Mass fraction	Mole fraction	10.840	−5062.628	−10.28	−1315.980	876.160	0[a]	0[a]	55	[16]
NMP	Water	Mass fraction	Mole fraction	11.881	−4700.982	−2.689	−3598.241	1498.292	−1410.488	2529.695	55	[17]
Ethanol	Water	Mass fraction	Molarity	3.454	−1431.877	4.044	2619.746	1524.794	322.958	0[a]	55	[18]
PEG 200	Water	Mass fraction	Mole fraction	3.868	−1818.100	−1.181	−1560.004	358.261	290.886	0[a]	55	[19]
1-Propanol	Water	Mass fraction	Mole fraction	12.796	−5284.178	−10.288	−1313.478	2261.716	−681.401	2446.864	55	[21]
Acetonitrile	Water	Mass fraction	Mole fraction	5946.538	306.805	1240.013	6.672	−4031.573	−6.067	−2576.922	55	[22]
NMP	Ethanol	Mass fraction	Mole fraction	3.146	−2049.460	6.435	−3656.918	144.542	−113.464	−51.302	55	[23]

[a] Not statistically significant (p-value > 0.05).

Table 2
Experimental mole fraction solubility ($x_{m,T}$) data measured for ketoconazole in the mixtures of PG and ethanol at different temperatures.

w_1[a]	T (K)				
	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	2.75 × (±0.03) 10^{-3}	3.58 × (±0.32) 10^{-3}	4.34 × (±0.39) 10^{-3}	5.61 × (±0.52) 10^{-3}	6.49 × (±0.05) 10^{-3}
0.10	3.03 × (±0.04) 10^{-3}	4.18 × (±0.22) 10^{-3}	4.53 × (±0.20) 10^{-3}	5.79 × (±0.30) 10^{-3}	6.97 × (±0.29) 10^{-3}
0.30	3.82 × (±0.23) 10^{-3}	4.42 × (±0.08) 10^{-3}	4.93 × (±0.44) 10^{-3}	6.36 × (±0.06) 10^{-3}	7.37 × (±0.19) 10^{-3}
0.50	3.50 × (±0.38) 10^{-3}	4.07 × (±0.02) 10^{-3}	4.64 × (±0.40) 10^{-3}	6.17 × (±0.03) 10^{-3}	7.14 × (±0.24) 10^{-3}
0.70	3.13 × (±0.03) 10^{-3}	3.46 × (±0.03) 10^{-3}	4.48 × (±0.45) 10^{-3}	5.88 × (±0.18) 10^{-3}	6.98 × (±0.11) 10^{-3}
0.80	2.97 × (±0.18) 10^{-3}	3.25 × (±0.06) 10^{-3}	4.17 × (±0.40) 10^{-3}	5.64 × (±0.52) 10^{-3}	6.53 × (±0.49) 10^{-3}
0.90	2.01 × (±0.48) 10^{-3}	2.32 × (±0.02) 10^{-3}	3.21 × (±0.28) 10^{-3}	4.95 × (±0.66) 10^{-3}	6.13 × (±0.25) 10^{-3}
1.00	1.48 × (±0.37) 10^{-3}	1.98 × (±0.03) 10^{-3}	2.64 × (±0.18) 10^{-3}	3.90 × (±0.09) 10^{-3}	5.62 × (±0.16) 10^{-3}

[a] w_1 is mass fraction of PG in the PG and ethanol mixtures in the absence of ketoconazole.

2.3.5. The modified Wilson model

A non-linear model of the modified Wilson is also used to obtain the drug solubility in the binary mixed solvents at isothermal condition. The model is as [27]:

$$-\ln x_m = 1 - \frac{w_1[1+\ln(x_1)]}{w_1 + w_2\lambda_{12}} - \frac{w_2[1+\ln(x_2)]}{w_1\lambda_{21} + w_2} \tag{6}$$

in which, λ_{12} and λ_{21} are the model parameters and obtained by a non-linear analysis.

2.4. Apparent thermodynamic parameters

The enthalpy, entropy and Gibbs free energy change which are defined as the apparent thermodynamic parameters can be obtained according to the van't Hoff and Gibbs equations. The modified form of the van't Hoff equation is as:

$$\frac{\partial \ln x}{\partial\left(\frac{1}{T} - \frac{1}{T_{hm}}\right)_p} = -\frac{\Delta H^\circ}{R} \tag{7}$$

x is solubility in the mole fraction unit of solute, T is the absolute temperature and R is the ideal gas constant, respectively [28]. T_{hm} is the mean harmonic temperature and obtained from the equation of $T_{hm} = n\sum_{i=1}^{n}(1/T)$, where n is the number of set temperatures. The intercept and the slope of the plot of ln × against $(1/T - 1/T_{hm})$ are employed for computing ΔG° and ΔH° of the dissolution process, and Gibbs equation is used to calculating ΔS°.

The relative contributions of entropy (ζ_{TS}) and enthalpy (ζ_H) to ΔG° are obtained using the following equations [29].

$$\zeta_H = \frac{|\Delta H^\circ|}{(|\Delta H^\circ| + |T\Delta S^\circ|)} \tag{8}$$

$$\zeta_{TS} = \frac{|T\Delta S^\circ|}{(|\Delta H^\circ| + |T\Delta S^\circ|)} \tag{9}$$

3. Results and discussions

3.1. Solubility data for ketoconazole and mathematical modeling

The experimental solubility data (in mole fraction unit) for ketoconazole in the PG and ethanol mixtures at different temperatures along with the standard deviation are summarized in Table 2. Moreover, as a visual help for comparison, Fig. 2 (top) depicts the solubility at all temperatures. As the solubility of ketoconazole in neat ethanol is higher than neat PG, so it shows an increase in solubility with increasing ethanol mass fraction and presents a maximum value in PG mass fraction of 0.3. Furthermore, the solubility of ketoconazole increases with the increase of temperature so that the lowest solubility is observed for neat PG at 293.2 K, and the highest one is observed for w_1 = 0.3 at 313.2 K.

Because both the solute and solvent polarities are crucial for drugs solubility and dissolution, Fig. 2 (bottom) shows the ketoconazole solubility profiles as a function of the polarity of the mixtures free of drug, as expressed by their Hildebrand solubility parameters (δ_{1+2}) [30]. δ_{1+2} values were calculated from the respective δ values of the pure solvents (δ_1 = 30.2 MPa$^{1/2}$ for PG and δ_2 = 26.5 MPa$^{1/2}$ for ethanol) and the volume fraction (f_i), by assuming additive volume fractions, as follows [31–33]:

$$\delta_{1+2} = \sum_{i=1}^{2} f_1\delta_1 \tag{10}$$

By considering the entire polarity range the solubility curves at all temperatures show maximum in the mixture of δ_{1+2} = 27.4 MPa$^{1/2}$ (w_1 = 0.3). According to the literature, solutes reach their maximum solubilities in solvent systems with the same

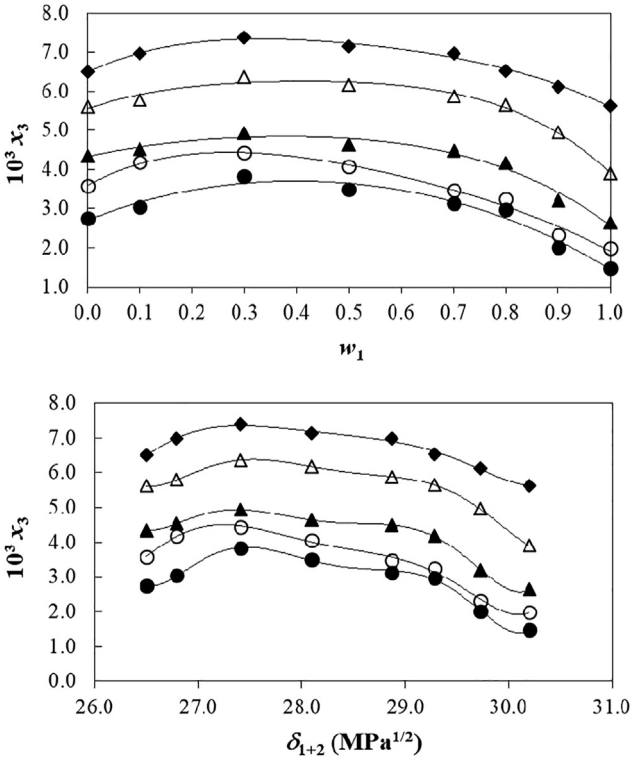

Fig. 2. Mole fraction solubility of ketoconazole (x_3) as function of the mass fraction of PG (top) and Hildebrand solubility parameter (bottom) of the PG and ethanol mixtures at different temperatures. ●: 293.2 K, ○: 298.2 K, ▲: 303.2 K, Δ: 308.2 K, ◆: 313.2 K.

polarity [30], and thus, δ_3 value of ketoconazol would be 27.4 $MPa^{1/2}$ at 298.2 K. However, this value is higher regarding the one calculated by using the Fedors' method (*i.e.* 24.4 $MPa^{1/2}$) [34]. This discrepancy could be attributed to specific solvation processes of ketoconazole by PG or ethanol, which are not considered in Fedors' calculations [35].

The experimental solubility data for ketoconazole in PG + ethanol mixtures are fitted to some mathematical models such as the van't Hoff, MRS, Jouyban-Acree, Jouyban-Acree–van't Hoff and the modified Wilson models. The models' constant and *MRD%* values for back-calculated solubility data are given in Tables 3-6. The overall *MRD%* values for ketoconazole in the investigated mixtures are 3.7% for the van't Hoff equation as a linear model that correlates the solubility data at the different temperature at the same solvent mixture, 2.9% for MRS model as a linear model that correlates the solubility data at isothermal conditions, 7.0% and 6.3% for Jouyban–Acree and Jouyban-Acree-van't Hoff models as two models that correlate solubility data at different temperatures as well as different solvent mixtures. Furthermore, the modified Wilson model is a non-linear model that correlates solubility data at isothermal condition. Low *MRD%* values (<8.0%) for all used models indicate the high accuracy and reliability of investigated models for the solubility prediction which can be helpful in the pharmaceutical industries. In another effort, the prediction capability of Jouyban-Acree-van't Hoff model is also checked using training the model with the minimum number of solubility data, *i.e.,* solubility data in neat solvents 1 and 2 at low and high temperature and mixed solutions with w_1 of 0.7, 0.5 and 0.3 at 298.2 K. The *MRDs%* of predicted data are 10.1%, 4.7%, 8.3%, 6.6% and 11.6% for 293.2, 298.2, 303.2, 308.2 and 313.2 K, respectively (overall *MRD* is 8.3%).

Table 3
The van't Hoff model parameters and the corresponding *MRD%* for ketoconazole in the mixtures of PG and ethanol.

w_1	*A*	*B*	*MRD%*
0.00	7.707	−3983.343	2.1
0.10	6.723	−3660.952	3.2
0.30	4.900	−3077.023	2.7
0.50	5.734	−3377.770	3.1
0.70	7.528	−3914.166	3.8
0.80	7.423	−3900.256	4.6
0.90	12.395	−5478.685	6.3
1.00	14.371	−6137.166	3.5
Overall			3.7

Table 4
The MRS model parameters at the investigated temperatures and the *MRD%* for back-calculated ketoconazole in the mixtures of PG and ethanol.

T (K)	β_1	β_2	β_3	β_4	β_5	*MRD%*
293.2	−6.525	−5.979	0[a]	0[a]	2.708	4.8
298.2	−6.282	−5.640	0[a]	0[a]	1.979	3.1
303.2	−5.934	−5.946	0[a]	0[a]	1.614	4.3
308.2	−5.363	−5.203	0[a]	−0.004	0.879	1.3
313.2	−5.197	−5.041	0[a]	0[a]	0.800	0.9
Overall *MRD%*						2.9

[a] Not statistically significant (*p*-value > 0.05)

Table 5
Parameters of the Jouyban-Acree and Jouyban-Acree-van't Hoff models for ketoconazole in the mixtures of PG and ethanol.

	Jouyban-Acree		Jouyban-Acree-van't Hoff	
PG + ethanol	J_0	490.161	A_1	11.123
	J_1	0[a]	B_1	−5143.578
	J_2	0[a]	A_2	5.150
			B_2	−3213.612
			J_0	473.650
			J_1	0[a]
			J_2	0[a]
MRD%	7.0		6.3	

[a] Not statistically significant (*p*-value > 0.05)

Table 6
The modified Wilson model parameters at the investigated temperatures and the *MRD%* for back-calculated ketoconazole in the mixtures of PG and ethanol.

T (K)	λ_{12}	λ_{21}	*MRD%*
293.2	1.755	0.889	3.7
298.2	1.175	1.245	3.0
303.2	1.925	0.680	2.2
308.2	2.257	0.565	1.3
313.2	1.057	1.142	0.8
Overall			2.2

3.2. Calculation of the thermodynamic parameters

Fig. 3 depicts the van't Hoff plots for ketoconazole solubility behavior in all the mixtures of PG and ethanol. Table 7 lists the apparent thermodynamic parameters of ketoconazole dissolution in PG and ethanol mixtures. The van't Hoff and Gibbs equations are used to compute these parameters. $\Delta H°$ values are positive in all studied mixtures with the highest (51.07 kJ·mol^{-1}) and lowest (25.57 kJ·mol^{-1}) values in w_1 = 1.0 and w_1 = 0.3, respectively. The $\Delta S°$ values are also positive in all mixtures and the lowest

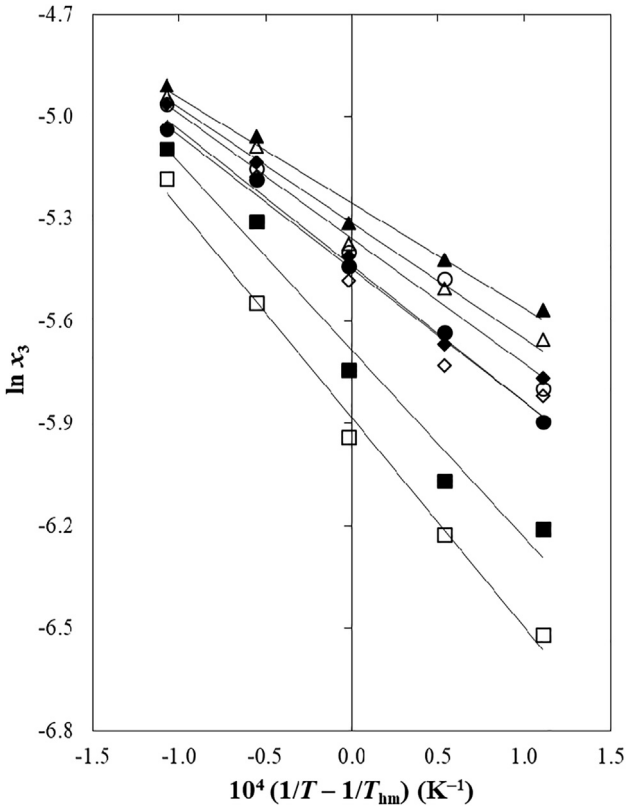

Fig. 3. van't Hoff plot of the solubility of ketoconazole in PG and ethanol solvent systems. ●: w_1 = 0.0 (neat PG), ○: w_1 = 0.1, ▲: w_1 = 0.3, Δ: w_1 = 0.5, ◆: w_1 = 0.7, ◇: w_1 = 0.8, ■; w_1 = 0.9, □: w_1 = 1.0 (neat ethanol).

Table 7
Apparent thermodynamic parameters for dissolution behavior of ketoconazole in the mixtures of PG and ethanol at T_{hm} = 303.0 K.

w_1	$\Delta G°$(kJ·mol^{-1})	$\Delta H°$(kJ·mol^{-1})	$\Delta S°$(J·mol^{-1}·K^{-1})	$T\Delta S°$(kJ·mol^{-1})	ζ_H	ζ_{TS}
0.00	13.70	33.08	63.95	19.38	0.631	0.369
0.10	13.50	30.38	55.72	16.88	0.643	0.357
0.30	13.24	25.57	40.71	12.34	0.675	0.325
0.50	13.39	28.09	48.52	14.70	0.656	0.344
0.70	13.58	32.51	62.48	18.93	0.632	0.368
0.80	13.73	32.38	61.58	18.66	0.634	0.366
0.90	14.33	45.55	103.05	31.22	0.593	0.407
1.00	14.82	51.07	119.63	36.25	0.585	0.415

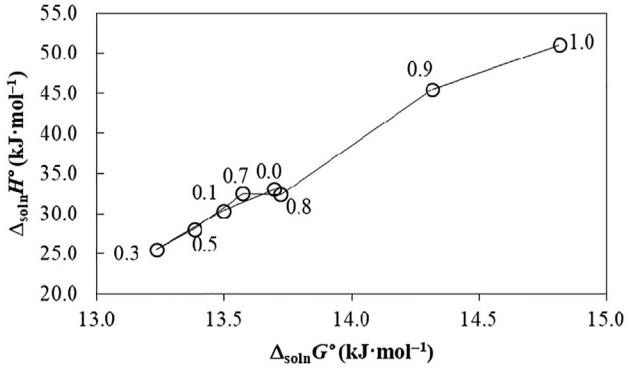

Fig. 4. Enthalpy-entropy compensation plot for the solubility of ketoconazole in PG and ethanol mixtures at T_{hm} = 303.0 K. The points represent the mass fraction of PG in the PG and ethanol mixtures in the absence of ketoconazole.

and highest values are 40.71 and 119.63 J·mol^{-1}·K^{-1}, in w_1 = 0.3 and w_1 = 1.0, respectively. Moreover, $\Delta G°$ values decrease with increasing ethanol mass fraction and show a minimum value in the mixture with the highest solubility of ketoconazole (*i.e.*, w_1 = 0.3). According to these results, it can be concluded that ketoconazole dissolution process in PG and ethanol is an endothermic and entropy-driven process. ζ_H and ζ_{TS} are also given in Table 7. In all mixtures $\zeta_H > \zeta_{TS}$ demonstrating that the enthalpy is the main contributor of $\Delta G°$ in this procedure. (SEE Fig. 4.)

Enthalpy-entropy compensation plot is employed to investigate the main mechanism involved in the cosolvent action. This plot for ketoconazole dissolution in PG and ethanol mixtures is shown in Fig. 2. As can be seen, ketoconazole exhibits a trend with a positive slope in the investigated mixtures indicating enthalpy-driven mechanism for drug transfer processes.

4. Conclusions

In the current work, the solubilization of ketoconazole is studied by cosolvency method in the PG and ethanol mixtures at 293.2 – 313.2 K. The results demonstrate that the solubility increases in ethanol-rich mixtures and show a maximum at w_1 = 0.3 and it shows an increase with temperature increasing. The measured data are fitted to some cosolvency models and the calculated results of all investigated models only have low differences with determined solubility data (*MRD*% <8.0%) showing the reliability of these models for solubility prediction. Moreover, thermodynamic parameters for the ketoconazole dissolution process are calculated using Gibbs and van't Hoff equations. The results show that the dissolution process of ketoconazole is endothermic and entropy-driven, and the main contributor to $\Delta G°$ is the enthalpy. Finally, the reported solubility values expand the database about the drugs behavior in mixtures of PG and ethanol [36,37].

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.

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Declaration of competitive interest.

The authors declare no conflict of interest.

References

[1] J.H. Van Tyle, Ketoconazole; mechanism of action, spectrum of activity, pharmacokinetics, drug interactions, adverse reactions and therapeutic use, Pharmacotherapy, J. Human Pharmacol. Drug Ther. 4 (1984) 343–373.
[2] T.K. Daneshmend, D.W. Warnock, Clinical pharmacokinetics of ketoconazole, Clin. Pharmacokinet. 14 (1988) 13–34.
[3] A.K. Gupta, D.C. Lyons, The rise and fall of oral ketoconazole, J. Cutaneous Med. Surg. 19 (2015) 352–357.
[4] T.H. Kim, B.H. Kim, Y.W. Kim, D.M. Yang, Y.S. Han, S.H. Dong, H.J. Kim, Y.W. CHANG, J.I. Lee, R. Chang, Liver cirrhosis developed after ketoconazole-induced acute hepatic injury, J. Gastroenterol. Hepatol. 18 (2003) 1426-1429.
[5] A.K. Aggarwal, S. Jain, Physicochemical characterization and dissolution study of solid dispersions of ketoconazole with nicotinamide, Chem. Pharm. Bull. 59 (2011) 629–638.
[6] A.D. Khan, L. Singh, Various techniques of bioavailability enhancement: a review, J. Drug Delivery Ther. 6 (2016) 34–41.
[7] V. Shukla, R. Scholar, Techniques for solubility enhancement of poorly soluble drugs: an overview, J. Med. Pharm. App. Sci. 1 (2012) 18–38.
[8] S. Basa, T. Muniyappan, P. Karatgi, R. Prabhu, R. Pillai, Production and in vitro characterization of solid dosage form incorporating drug nanoparticles, Drug Develop. Ind. Pharm. 34 (2008) 1209–1218.
[9] G. Van den Mooter, M. Wuyts, N. Blaton, R. Busson, P. Grobet, P. Augustijns, R. Kinget, Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25, Eur. J. Pharm. Sci. 12 (2001) 261–269.
[10] M.R. Patel, R.B. Patel, J.R. Parikh, A.B. Solanki, B.G. Patel, Investigating effect of microemulsion components: in vitro permeation of ketoconazole, Pharm. Develop. Technol. 16 (2011) 250–258.
[11] S. Hiendrawan, A.W. Hartanti, B. Veriansyah, E. Widjojokusumo, R.R. Tjandrawinata, Solubility enhancement of ketoconazole via salt and cocrystal formation, Int. J. Pharm. Pharm. Sci. 7 (2015) 160–164.
[12] V. Jouyban-Gharamaleki, A. Jouyban, F. Martinez, H.K. Zhao, E. Rahimpour, A laser monitoring technique for solubility study of ketoconazole in propylene glycol and 2-propanol mixtures at various temperatures, J. Mol. Liq. 320 (2020) 114444.
[13] M. Barzegar-Jalali, E.M.H. Agha, K. Adibkia, F. Martinez, A. Jouyban, The solubility of ketoconazole in binary carbitol + water mixtures at T=(293.2–313.2) K, J. Mol. Liq. 297 (2020) 111756.
[14] S. Zadaliasghar, A. Jouyban, F. Martinez, M. Barzegar-Jalali, E. Rahimpour, Solubility of ketoconazole in the binary mixtures of 2-propanol and water at different temperatures, J. Mol. Liq. 300 (2020) 112259.
[15] M. Barzegar-Jalali, E.M.H. Agha, K. Adibkia, F. Martinez, M. Kuentz, A. Jouyban, Solubility of ketoconazole in 1, 4-dioxane + water mixtures at T=(293.2 to 313.2) K, J. Mol. Liq. 306 (2020) 112830.
[16] S. Zadaliasghar, E. Rahimpour, T. Ghafourian, F. Martinez, M. Barzegar-Jalali, A. Jouyban, Measurement and mathematical modeling of ketoconazole solubility in propylene glycol + water mixtures at various temperatures, J. Mol. Liq. 291 (2019) 111246.
[17] A. Hatefi, E. Rahimpour, T. Ghafourian, F. Martinez, M. Barzegar-Jalali, A. Jouyban, Solubility of ketoconazole in *N*-methyl-2-pyrrolidone+ water mixtures at T=(293.2 to 313.2) K, J. Mol. Liq. 281 (2019) 150–155.

[18] N. Hashemzadeh, A. Jouyban, Solubility of ketoconazole in ethanol + water mixtures at various temperatures, Chem. Eng. Commun. 202 (2015) 1211–1215.
[19] A. Jouyban, J. Soleymani, S. Soltanpour, Solubility of ketoconazole in polyethylene glycol 200 + water mixtures at 298.2–318.2 K, J. Solution Chem. 43 (2014) 950–958.
[20] S. Soltanpour, V. Nazemi, Solubility of ketoconazole in binary and ternary solvents of polyethylene glycols 200, 400 or 600 with ethanol and water at 298.2 K. Data report and analysis, J. Solution Chem. 47 (2018) 65–79.
[21] A. Hatefi, E. Rahimpour, F. Martinez, M. Barzegar-Jalali, A. Jouyban, Ketoconazole solubility in aqueous binary mixtures of 1-propanol at various temperatures, J. Mol. Liq. 292 (2019) 111382.
[22] M. Barzegar-Jalali, E. Mazaher Haji Agha, S.N. Mirheydari, K. Adibkia, F. Martinez, A. Jouyban, Measurement and modelling of the solubility for ketoconazole in {acetonitrile+ water} mixtures at T=(293.2 to 313.2) K, Phys. Chem. Liq. (2019) 1-14. doi: 10.1080/00319104.2019.1706178.
[23] M. Moradi, E. Rahimpour, H. Zhao, F. Martinez, A. Jouyban, Solubility study of ketoconazole in the mixtures of N-methyl-2-pyrrolidone and ethanol at different temperatures, J. Mol. Liq. 326 (2021) 115287.
[24] C. Zhou, X. Shi, H. Wang, N. An, Measurement and correlation of solubilities of trans-ferulic acid in solvents, J. Chem. Ind. Eng. 58 (2007) 2705–2709.
[25] A.B. Ochsner, R.J. Belloto Jr, T.D. Sokoloski, Prediction of xanthine solubilities using statistical techniques, J. Pharm. Sci. 74 (1985) 132–135.
[26] A. Jouyban, W.E. Acree Jr, Mathematical derivation of the Jouyban-Acree model to represent solute solubility data in mixed solvents at various temperatures, J. Mol. Liq. 256 (2018) 541–547.
[27] A. Jouyban-Gharamaleki, The modified Wilson model and predicting drug solubility in water-cosolvent mixtures, Chem. Pharm. Bull. 46 (1998) 1058–1061.
[28] S. Vahdati, A. Shayanfar, J. Hanaee, F. Martínez, W.E. Acree Jr, A. Jouyban, Solubility of carvedilol in ethanol+ propylene glycol mixtures at various temperatures, Ind. Eng. Chem. Res. 52 (2013) 16630–16636.
[29] G.L. Perlovich, S.V. Kurkov, A. Bauer-Brandl, Thermodynamics of solutions: II. Flurbiprofen and diflunisal as models for studying solvation of drug substances, Eur. J. Pharm. Sci. 19 (2003) 423–432.
[30] A. Martin, P. Bustamante, A.H.C. Chun, Physical Chemical Principles in the Pharmaceutical Sciences, 4th ed., Lea & Febiger, Philadelphia, 1993.
[31] A.F.M. Barton, Handbook of Solubility Parameters and Other Cohesion Parameters, 2nd ed., CRC Press, New York, 1991.
[32] Y. Marcus, The Properties of Solvents, John Wiley & Sons, Chichester, 1998.
[33] K.A. Connors, Thermodynamics of Pharmaceutical Systems: An Introduction for Students of Pharmacy, Wiley-Interscience, Hoboken, NJ, 2002.
[34] A. Jouyban, W.E. Acree Jr., F. Martínez, Preferential solvation of apremilast in some (Transcutol® + water) mixtures, J. Mol. Liq. 316 (2020) 113905.
[35] R.F. Fedors, A method for estimating both the solubility parameters and molar volumes of liquids, Polym. Eng. Sci. 14 (1974) 147–154.
[36] V. Jouyban-Gharamaleki, A. Jouyban, M. Kuentz, S. Hemmati, F. Martinez, E. Rahimpour, A laser monitoring technique for determination of mesalazine solubility in propylene glycol and ethanol mixtures at various temperatures, J. Mol. Liq. 304 (2020) 112714.
[37] A. Jouyban, M. Khoubnasabjafari, F. Martínez, A model to predict the solubility of drugs in ethanol + propylene glycol mixtures at various temperatures, Bulg. Chem. Commun. 47 (3) (2015) 800–803.