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Prediction of solubility of vitamins in the mixed solvents using equation of state

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ABSTRACT

In this work, the perturbed hard-sphere chain (PHSC) equation of state (EOS) has been utilized to predict the solubility of vitamins in mixed solvents. The solubilities of vitamins C, E, D3, K3, and B6H have been studied at various solvents and temperatures. The model parameters have been obtained using binary solubility experimental data at arbitrary temperatures. Using obtained temperature-independent model parameters, the solubility of the aforementioned vitamins in the binary systems has been predicted. The model has been used for twelve binary vitamin C-solvent and D3-solvent systems between 243 K to 323 K. The solubilities of vitamins in the ternary systems have been predicted without using any adjustable parameters. The performance of the PHSC EOS has been evaluated by comparing the results with the PC-SAFT model. The average AADs of the PHSC and the PC-SAFT EOSs for four studied vitamins in the ternary systems have been obtained 0.28 and 0.76, respectively. The results show that, the PHSC EOS can predict the vitamin solubility in the mixed solvent satisfactory.

1. Introduction

Vitamins are one of the main types of nutrients that our body needs to survive and stay healthy. There are thirteen essential vitamins contain vitamins A, C, D, E, K, and B. Most vitamins need to come from food because the human body does not produce them. For example, dogs can produce all the vitamin C that they need, but humans need to get it from food. Vitamins are either soluble, or dissolvable, in fat or water; vitamins A, D, E, and K are fat-soluble and vitamin C and all the B vitamins are water-soluble. Generally, the solubility data in the pure and mixed solvents at various temperatures are important during the process design of vitamin extraction from their sources. Considering the complexity of vitamin molecules, and the variety of solvents, thermodynamic modeling of such systems (especially in the case of mixed solvents) is a challenge. The solubility study of vitamins in different aqueous and organic solvents is essential in crystallization, purification, and discovery processes. The new technology for the purification of vitamins needs to study solid-liquid equilibrium (SLE) and liquid-liquid equilibrium (LLE) calculations of each process [1]. Therefore, the prediction of SLE and LLE of such systems in various solvents using a robust and efficient thermodynamic model is important. Among all thermodynamic models, the regular solution theory is widely used in pharmaceutical industries [2]. In the case of regular solution theory, the minimum activity coefficient is one; therefore, solubilities higher than the ideal solubility cannot be described [3]; it is an important disadvantage of the model. On the other hand, the activity coefficient models such as NRTL, UNIFAC, and UNIQUAC models are widely utilized to correlate and predict the phase equilibria and thermodynamic properties of pure components and their mixtures [4–8]. One of the main disadvantages of the Gibbs free energy model is its correlative nature of them. Their model parameters are limited to the available experimental data; hence, the applicability of these models is limited. The conductor-like screening model for real solvent (COSMO-RS) was widely used for pharmaceutical solubility [9–11]. The COSMO-based models are considered predictive

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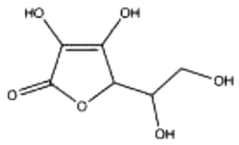
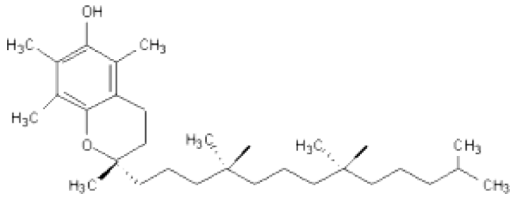
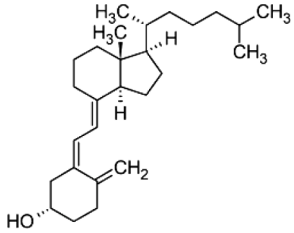
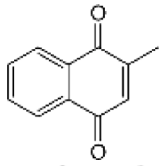
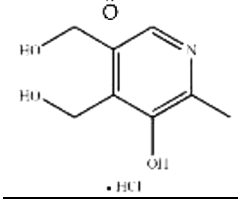
Table 1
Melting temperature (T_m), and enthalpy of fusion (ΔH_f) for the vitamins compounds

Vitamins	T_m (K)	ΔH_f (kj/mol)	Ref.
C	465.0	29.20	Joback method
D3	511.6	38.79	
E	624.7	56.28	
K3	376.0	12.71	
B6H	489.9	29.90	

Table 2
molecular structure of vitamins

Structure	Vitamin
	C
	E
	D3
	K3
	B6H

models. These models predict the thermodynamic properties of fluids and solutions based on quantum mechanical data. The COSMO-based models have an important disadvantage. These models give the pressure-independent activity coefficient [12].

The successful models are EOSs, which had been used to predict the phase equilibrium of complex mixtures, especially at high pressures [3,9,10,13-18]. Zarei Mahmoudabadi and Pazuki proposed a predictive SAFT-based EoS to predict the solubility of pharmaceuticals in pure and mixed solvents [9,10]. Ruether and Sadowski used the PC-SAFT EOS to predict the solubility of five drugs in pure and mixed solvents [17]. They predicted the solubility in mixed solvents without any additional fitting parameters. F.L. Mota et al. utilized the CPA EOS to model the organic phase solubilities of drugs in a wide range of temperatures [3]. They correlated the vitamin C (ascorbic acid) solubility in seven solvents at 293 K to 323 K. In this regard, one binary interaction coefficient (BIC) between vitamin C and solvents was considered [3]. Using the fitted BIC, good results were obtained in the binary systems. Recently, Faraz et al. used the PHSC EOS to estimate the solubility of the pharmaceutical in pure, mixed, and supercritical solvents [12]. In this regard, twenty-one ternary systems were considered to predict the solubility of pharmaceuticals in mixed solvents. K. Wysoczanska et al. utilized the PC-SAFT EOS to estimate the solubility of the vitamins ascorbic acid, riboflavin, nicotinic acid, folic acid, and cyanocobalamin in the pure solvents [19]. They used the experimental liquid density data and osmotic coefficient data of aqueous vitamin solutions to optimize the model parameters. In addition to model parameters, they used the BIC between vitamins and solvents. The PC-SAFT EOS showed an accurate prediction of VB3 solubility within the range of 283.59-332.09 K. The highest error was observed for VB9 (ARD%=4.13%). As a result, vitamin solubility at different temperatures was predicted satisfactory.

In this research, the PHSC EOS has been used to predict vitamin solubility in mixed solvents. Song et al. developed the PHSC EOS based on the modified Chiew EOS for hard-sphere chains as the reference term [20]. Then, Song et al. utilized the PHSC EOS to predict liquid-liquid equilibria (LLE) for polymer solutions and blends [21]. Lee and Kim proposed the PHSC-AS (PHSC plus association) EOS to describe phase equilibria for the fluid system containing self-associating compounds such as alcohol, amine and carboxylic acid, etc. [22]. Khoshsima and Dehghani utilized the PHSC EOS to study the vapor–liquid and liquid–liquid equilibrium in mixtures containing glycol ether surfactant, non-polar and polar compounds [23]. Their results show that, the PHSC EOS can correlate the phase behavior of binary polar - surfactant and non-polar - surfactant systems [23]. Khoshsima and Shahriari studied the phase behavior of fatty acid ester mixtures [24]. As well, they predicted the melting and eutectic points of binary fatty acid ester systems. Recently, Faraz et al. utilized the PHSC EOS to predict the solubility of the pharmaceuticals in pure, mixed, and supercritical solvents [12]. They considered twenty-one ternary systems to study the solubility of pharmaceuticals in mixed solvents. In recent years, the PHSC EOS has been widely used to study the phase behavior and thermodynamic properties of various systems. In this regard, the main goal of this work is to study the capability of the PHSC EOS for the prediction of vitamin solubility in mixed solvents.

The model parameters have been obtained using experimental solubility data at a specific temperature. Therefore, one experimental solubility data in binary SLE has been used to optimize the vitamin model parameters. The BICs between components have been ignored (k_{ij} has been set to zero). Using obtained model parameters, the solubility of vitamins in binary mixtures at various temperatures has been predicted. In the case of mixed solvents, the model parameters have been used without using any additional adjustable parameters. The solubility of vitamins in some ternary systems (mixed solvent) shows a maximum value. Prediction of the maximum solubility in the ternary system plays an important role in separation processes and vitamin formulations. The thermodynamic model must be able to predict the maximum solubility values accurately. In this work, the capability of PHSC EOS has been evaluated to predict the maximum solubility region.

2. Theory

The PHSC model based on the compressibility factor is written as follows [25,26]:

$$Z = Z^{ref} + Z^{pert} + Z^{assoc} \tag{1}$$

where the superscripts ref, pert, and assoc refer to the reference, perturbation, and association contribution.

The reference and perturbation terms have been given as follows:

$$Z^{pert} = -\frac{\rho}{k_b T}\sum_{i,j} x_i x_j r_i r_j a_{ij}(T) \tag{2}$$

Table 3
The PHSC and PC-SAFT models pure parameters

Model	Vitamins	Parameters					*Associating sites*		*Selected solvents*	T(K)	Ref.
		r(-)	σ(Å)	ε/k_B(K)	ε^{ab}/k_B(K)	k^{AB}	Donor	Acceptor			
PHSC	C	4.9272	2.3115	166.85	1310.48	0.00789	4	6	Water/Methanol/Acetone	298.15	[31]
PC-SAFT		2.3278	3.9456	444.43	1144.55	0.0018					
PHSC	D3	13.957	2.3547	101.75	3187.61	0.04433	1	1	Water/Methanol/Acetonenitrile	273.15	[32,33]
PC-SAFT		2.8806	3.5046	230.27	1043.60	0.0041					
PHSC	K3	5.4135	2.5141	76.49	2635.48	0.000703	2	2	Water	306.15	[34]
PC-SAFT		3.1808	3.4788	169.10	939.72	0.0021					
PHSC	E	10.1566	2.5532	138.73	3759.84	0.00186	1	2	Water	306.15	[34]
PC-SAFT		3.6226	2.8543	283.64	1274.01	0.0045					
PHSC	B6H	3.6321	2.3010	199.04	1533.86	0.008207	3	3	Water/Methanol/Acetone	298.15	[35]
PC-SAFT		1.4271	3.8205	451.16	1325.31	0.00241					

Table 4
The PHSC and PC-SAFT EOSs parameters of solvents

Model	Solvent	*Parameters* *r(-) or m(-)*	σ(Å)	ε/k_B(K)	ε^{ab}/k_B(K)	k^{AB}	Ref.
PHSC	Water	1.405	3.043	460.52	1633.282	0.03804	[13,36]
PC-SAFT		1.0656	3.001	366.51	2500.67	0.0349	
PHSC	Methanol	1.4426	3.8492	257.23	2628.79	0.02187	[22,36]
PC-SAFT		1.5255	3.23	188.9	2899.5	0.03517	
PHSC	Ethanol	1.8213	4.0448	265.38	2644.31	0.01049	
PC-SAFT		2.3827	3.1771	198.24	2653.4	0.032384	
PHSC	1-Propanol	2.3632	4.0178	259.35	2645.12	0.00873	
PC-SAFT		2.9997	3.2522	233.4	2276.8	0.01527	
PHSC	2-Propanol	1.9821	4.313	262.26	2736.79	0.00582	
PC-SAFT		3.0929	3.2085	208.42	2253.9	0.024675	
PHSC	1-Buthanol	2.7462	4.0738	254.05	2678.67	0.01051	
PC-SAFT		2.7515	3.6139	259.59	2544.6	0.006692	
PHSC	Acetone	3.578	3.182	232.7	-	-	[20]
PC-SAFT		5.063	3.9441	249.47	-	-	[37]
PHSC	Ethyl Acetate	5.17	3.022	196.5	-	-	[20]
PC-SAFT		3.9278	3.3310	215.47	-	-	This work
PHSC	Acetonitrile	2.3505	4.0921	325.28	-	-	This work
PC-SAFT		3.0864	3.6513	247.8900	-	-	

$$Z^{ref} = 1 + \rho \sum_{i,j} x_i x_j r_i r_j b_{ij}(T) g_{ij}^{hs}(d_{ij}) - \sum_i x_i (r_i - 1)\left[g_{ij}^{hs}(d_{ij}) - 1\right] \quad (3)$$

where r and k_b are the number of effective hard spheres per molecule and Boltzmann constant, respectively. The $a(T)$ and $b(T)$ were given by Song et al. [20]:

$$a_{ij}(T) = \frac{2\pi}{3}\sigma_{ij}^3 \varepsilon_{ij} F_a\left(\frac{k_B T}{\varepsilon_{ij}}\right) \quad (4)$$

$$b_{ij}(T) = \frac{2\pi}{3}\sigma_{ij}^3 F_b\left(\frac{k_B T}{\varepsilon_{ij}}\right) \quad (5)$$

where $F_a\left(\frac{k_B T}{\varepsilon}\right)$ and $F_b\left(\frac{k_B T}{\varepsilon}\right)$ are universal functions and are determined by fitting the vapor pressure and the densities of the saturated liquid and vapor of argon and methane; for more details refer to [20].

For a mixture, classical combining rules are used for calculation of σ_{ij} and ε_{ij} as follows:

$$\sigma_{ij} = \frac{(\sigma_{ii} + \sigma_{jj})}{2} \quad (6)$$

$$\varepsilon_{ij} = \sqrt{\varepsilon_{ii}\varepsilon_{jj}}(1 - k_{ij}) \quad (7)$$

where k_{ij} is the adjustable binary interaction parameter. The radial distribution function of hard sphere mixtures is given by [27]:

$$g_{ij}^{hs}(d_{ij}^{+}) = \frac{1}{1-\eta} + \frac{3}{2}\frac{\zeta_{ij}}{(1-\eta)^2} + \frac{1}{2}\frac{\zeta_{ij}}{(1-\eta)^3} \quad (8)$$

In Eq. (1) Z^{assoc} is defined based on the SAFT model introduced by Chapman et al [28]:

$$Z^{assoc} = \rho \sum^{x_i} \sum_{A_i} \left[\frac{1}{X^{A_i}} - \frac{1}{2}\right]\left(\frac{\partial X^{A_i}}{\partial \rho_i}\right) \quad (9)$$

where X^{A_i} is the mole fraction of the molecules not-bonded at the associating site A and x_i is the mole fraction of component i.

$$X^{A_i} = \left[1 + \rho \sum^{x_i} \sum_{B_j} X^{B_j} \Delta^{A_i B_j}\right]^{-1} \quad (10)$$

$$\Delta^{A_i B_j} = g_{ij}^{hs}\left(d_{ij}^{+}\right)\left[exp\left(\frac{\varepsilon^{A_i B_j}}{k_b T}\right) - 1\right]\left(\sigma_{ij}^3 \kappa^{A_i B_j}\right) \quad (11)$$

The cross association energy and volume are calculated according to the combining rules proposed by Wolbach and Sandler [29]:

$$\varepsilon^{A_i B_j} = \frac{1}{2}\left(\varepsilon^{A_i B_i} + \varepsilon^{A_j B_j}\right) \quad (12)$$

Table 5
The RMSD and AAD of PHSC and PC-SAFT models for vitamin-solvent system

Vitamins	Solvent	T(K)	PHSC RMSD[1]	AAD[2]	PC-SAFT RMSD	AAD
C	Acetone	293.15-323.15	0.00077	0.053	0.00045	0.032
	Methanol	293.15-323.15	0.0095	0.70	0.0045	0.36
	Ethanol	293.15-323.15	0.022	1.91	0.019	1.82
	2-Propanol	293.15-323.15	0.021	1.82	0.022	1.95
	Ethyl acetate	293.15-323.15	0.00089	0.07	0.0013	0.012
	Water	293.15-323.15	0.0006	0.051	0.00128	0.092
Average error			**0.0091**	**0.767**	**0.0080**	**0.711**
D3	Water	248.15-298.15	1e-7	1e-5	1e-7	5e-6
	Methanol	248.15-298.15	0.0021	0.19	0.0054	0.47
	Ethanol	248.15-298.15	0.092	8.7	0.096	9.14
	1-propanol	248.15-298.15	0.13	12.2	0.14	12.9
	2-propanol	248.15-298.15	0.012	1.1	0.016	0.96
	Buthanol	248.15-298.15	0.015	12.7	0.016	13.2
Average error			**0.041**	**5.81**	**0.045**	**6.11**

[1] $\mathrm{RMSD}=\left(1/n\sum_{i=1}^{n}(x_i^{exp}-x_i^{calc})^2\right)^{0.5}$

[2] $\mathrm{AAD}(\%)=\frac{100}{n}\sum_{i=1}^{n}\left|x_i^{exp}-x_i^{calc}\right|$

$$\kappa^{A_iB_j}=\sqrt{\kappa^{A_iB_i}\kappa^{A_jB_j}}\left(\frac{\sqrt{\sigma_i\sigma_j}}{0.5(\sigma_i+\sigma_j)}\right)^3 \tag{13}$$

Through the SLE framework, the mole fraction of vitamin i in a solvent is obtained by:

$$\ln\left(\frac{1}{x_i}\right)=\ln\gamma_i+\frac{\Delta H_f}{RT_m}\left(\frac{T_m}{T}-1\right) \tag{14}$$

where x_i is solute mole fraction solubility, T is the absolute temperature, γ_i is solute activity coefficient, ΔH_f and T_m are enthalpy of fusion and melting temperature, respectively. The fusion enthalpy and melting temperature of vitamins are listed in Table 1.

As shown in Table 1, the fusion enthalpy and temperature have been estimated using the Joback method [30]. The molecular structure of vitamins has been depicted in Table 2.

3. Results and discussion

3.1. Model parameters

Similar to SAFT-based models, the PHSC EOS has five parameters for associating components and three parameters for non-associating components. In this study, two association sites have been considered for solvents (water and alcohols). In the case of vitamins, the number of associating sites has been considered based on the donor and acceptor sites on vitamin molecules. The number associating sites on vitamin E and C have been set to three and ten, respectively. In the case of vitamin D3 and K3, two and four associating sites on molecules have been considered. As well, the number of associating sites on vitamin B6H is set to six. The binary interaction coefficient (BIC) between solute and solvent has been set to zero for all systems (k_{ij}=*0.0*). In this work, the model parameters have been optimized using binary SLE experimental data at arbitrary temperatures. Similar to Faraz et al. work [12], three suitable candidates have been selected to obtain reliable model parameters. Three selected candidates are as follows: water/-alcohols/acetone or acetonitrile. The following objective function (OF) is utilized to optimize the model parameters:

$$OF=\sum_{i=1}^{1\ or\ 3}\left|\frac{x_i^{exp}-x_i^{calc}}{x_i^{exp}}\right| \tag{15}$$

where i is data points, x_i^{exp} and x_i^{calc} are experimental and calculated solubility based on mole fraction. Similar to the PHSC EOS, five model parameters of the PC-SAFT EOS have been optimized using the proposed methodology and eq. 15. The PHSC and PC-SAFT model parameters have been reported in Table 3.

In the case of the PHSC model, the segment number of vitamins D3 and E are higher than others. It is consistent with the molecular structures of vitamins that are depicted in Table 2. In the case of the PC-SAFT EOS, the segment numbers of five vitamins have been obtained between 1.4 to 3.7, while the segment diameters of the PHSC model are higher than the PC-SAFT EOS. The segment diameters and the segment energies have been obtained between 2 to 4 and 70 to 500, respectively. As reported in Table 3, for two vitamins C, D3 and B6H, three solvents have been considered to optimize the model parameters. On the other hand, the parameters of vitamins E and K3 have been optimized using a binary vitamin-water system. Using this method, the temperature-independent

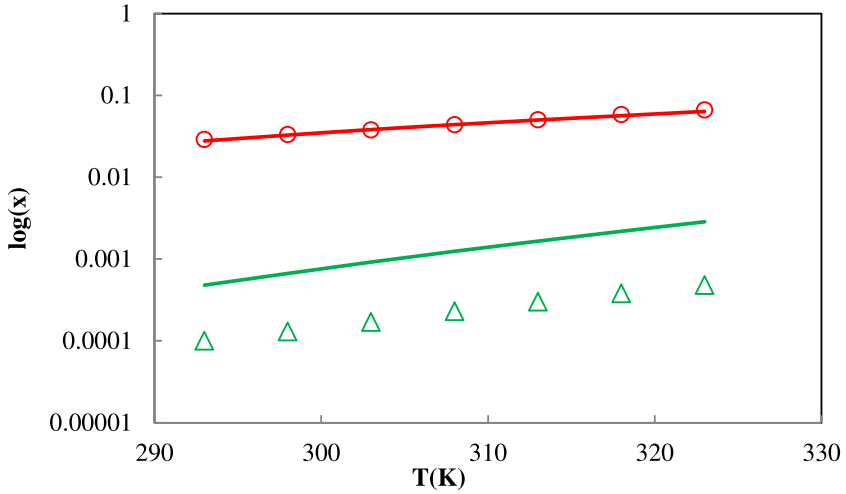


Fig. 1. Solubility of vitamin C in water (○) and ethyl acetate (Δ). Lines are PHSC EOS predictions and points are experimental data.

Table 6
The RMSD and AAD of PHSC and PC-SAFT models for vitamin-mixed solvent system

Vitamins	Solvent (1)	Solvent (2)	T(K)	PHSC RMSD	PHSC AAD	PC-SAFT RMSD	PC-SAFT AAD	Ref.
C	Ethanol	Water	293.15-323.15	0.025	0.74	0.031	2.01	[38]
	iso-propanol	Water	293.15-323.15	0.0095	0.82	0.028	2.2	
	Ethanol	iso-propanol	293.15-323.15	0.0097	1.2	0.036	1.04	
	Methanol	iso-propanol	293.15-323.15	0.0195	0.91	0.067	0.91	
	Methanol	Ethanol	293.15-323.15	0.0025	0.21	0.002	0.15	
Average error				**0.0132**	**0.776**	**0.0328**	**1.262**	
B6H	Acetone	Water	278.15-313.15	0.0032	0.23	0.0045	0.38	[35]
	Methanol	Water	278.15-313.15	0.0021	0.25	0.0029	0.26	
	Propanol	Water	278.15-313.15	0.0020	0.27	0.0017	0.12	
	Aceonitrile	Water	278.15-313.15	0.0035	0.25	0.0055	0.40	
Average error				**0.0027**	**0.25**	**0.00365**	**0.29**	
E	Ethanol	Water	303.15	**0.0012**	**0.009**	**0.00024**	**0.012**	[34]
K3	Ethanol	Water	303.15	**0.0010**	**0.05**	**0.026**	**1.5**	[34]

model parameters have been obtained. The association between vitamin molecules and associative solvents (water and alcohols) has been considered to model the cross-association. It must be noted that, in this study the BIC between solute and solvent has been ignored (k_{ij}=*0*). F. L. Mota et al. used the BIC between vitamin C and solvents in addition to model parameters to correlate the solubility data using CPA EOS [3]. The average ARD% before and after BIC fitting is about 90 and 12, respectively. However, when the BIC and model parameters have been optimized simultaneously, the adjusted BIC effect on model parameters. If the magnitude of adjusted BIC is a high value, the unphysical model parameters may be obtained. Therefore, in this study the model parameters have been optimized using experimental binary solubility data without using any BIC.

All solvent parameters have been reported in the previous articles except for acetonitrile and Ethyl Acetate (in the case of PC-SAFT EOS). The model parameters of acetonitrile and Ethyl Acetate have been optimized using experimental vapor pressure data and reported in Table 4. In Table 4, the solvents model parameters have been reported.

In the next section, the PHSC and PC-SAFT EOSs have been used to predict the solubility of vitamins in the mixed solvents.

3.2. Solubility of vitamins in mixed solvents

As mentioned in the previous section, the model parameters have been obtained in binary vitamin-solvent systems at arbitrary temperatures. To check the model performance, the solubilities of vitamins C and D3 in the binary vitamin-solvent mixtures at various temperatures have been predicted. The average root mean square deviation (RMSD) and average absolute deviation (ARD) of the aforementioned systems have been reported in Table 5.

In the case of the PHSC EOS, the average RMSDs of vitamins C and D3 are 0.0091 and 0.041, respectively. On the other hand, the average RMSDs of mentioned vitamins are obtained 0.008 and 0.045 using the PC-SAFT EOS. The results show that, the temperature-independent parameters of models can predict vitamin solubility at various temperatures satisfactory. In Fig. 1, the solubility of vitamin C in water and ethyl acetate at various temperatures has been predicted and compared to experimental data.

As shown in Table 5 and Fig. 1, the prediction results are in good agreement with experimental data. The effect of temperature on the solubility of vitamin C in water and ethyl acetate is obvious and the model has been able to accurately predict this effect. In the case of vitamin C solubility in six solvents (using PHSC EOS) good prediction results were obtained and the maximum RMSD is about 0.022 (ethanol solvent). In the case of vitamin D3, the maximum RMSD is about 0.13 for the vitamin D3-1-propanol system. On the other hand, the maximum deviations of the PC-SAFT EOS refer to vitamin C-2-propanol and vitamin D3-1-propanol; 0.022 and 0.14 respectively. As shown in Table 5, the equilibrium temperature of vitamin D3-solvent is between 248 to 298 K. It is indicated that the model predictions show good results at low temperatures (248.15 K).

The main goal of this study is the prediction of vitamin solubility in mixed solvents. In this regard, using obtained model parameters and without using any adjustable parameters, the solubility of vitamins in the mixed solvents has been studied to evaluate the model performance. In Table 6, the calculated RMSD and AAD of vitamin solubility in the mixed solvents have been reported.

As shown in Table 6, the PHSC EOS predicts the vitamin solubility in the mixed solvent, accurately. Generally, vitamin C is produced from D-glucose by a Reichstein procedure [31]. The mass fraction purity of vitamin C is in the range of 96 to 98%, which is obtained by recrystallization from water [31]. This process needs solubility data as a function of temperature and solvent types. In the case of the PHSC EOS, the average RMSD of vitamin C solubility in mixed solvents is 0.0132. The aforementioned RMSD using the PC-SAFT EOS is obtained 0.0328. The solubility of vitamin C in the mixed solvents has been predicted at 293.15 K to 323.15 K satisfactory, while the model parameters of vitamin C have been optimized at 298.15 K. As described in section 3.1, the vitamin C model parameters were obtained in binary mixtures containing water, methanol, and acetone. The results show that, obtained parameters can use for the binary and ternary systems that contain candidate solvents or other solvents. In Fig. 2, the vitamin C solubility in ethanol-methanol and isopropanol-water ternary systems at three temperatures has been depicted.

As shown in Fig. 2, the PHSC EOS predicts the vitamin C solubility in the mixed solvents satisfactory. The maximum solubility is observed in Fig. 2 for the solubility of vitamin C in the isopropanol-water solvent. This behavior is predicted accurately using PHSC EOS. The predicted maximum solubility of the aforementioned system is about 0.1 which is consistence with the reported experimental data. The predicted maximum solubility of vitamin C is utilized to optimize and design the separation process.

In Figs. 3 and 4 the solubility of vitamins E and K3 has been predicted at 303.15 K.

The results show that, the PHSC EOS predicts the solubility of vitamins E and K3 in ethanol-water ternary systems, satisfactory. It must be mentioned the solubilities of vitamins E and K3 are of interest because of the extremely low aqueous solubilities of these vitamins [28]. Understanding the thermodynamic properties of the mentioned vitamins will help us to improve formulations and separation processes. Alcohols such as ethanol are fully miscible with water it providing a hydrophobic environment to solubilize the aforementioned vitamins [34]. Vitamins E and K3 are fat-soluble and are mostly hydrophobic with some polarity due to hydrogen bonding. In this study, two acceptor and one donor sites have been considered to model the self-association between vitamin E molecules and the cross-association between vitamin and solvent molecules. In the case of vitamin K3, two donor and two acceptor sites have been considered. Similar to vitamin E, the self and cross-association

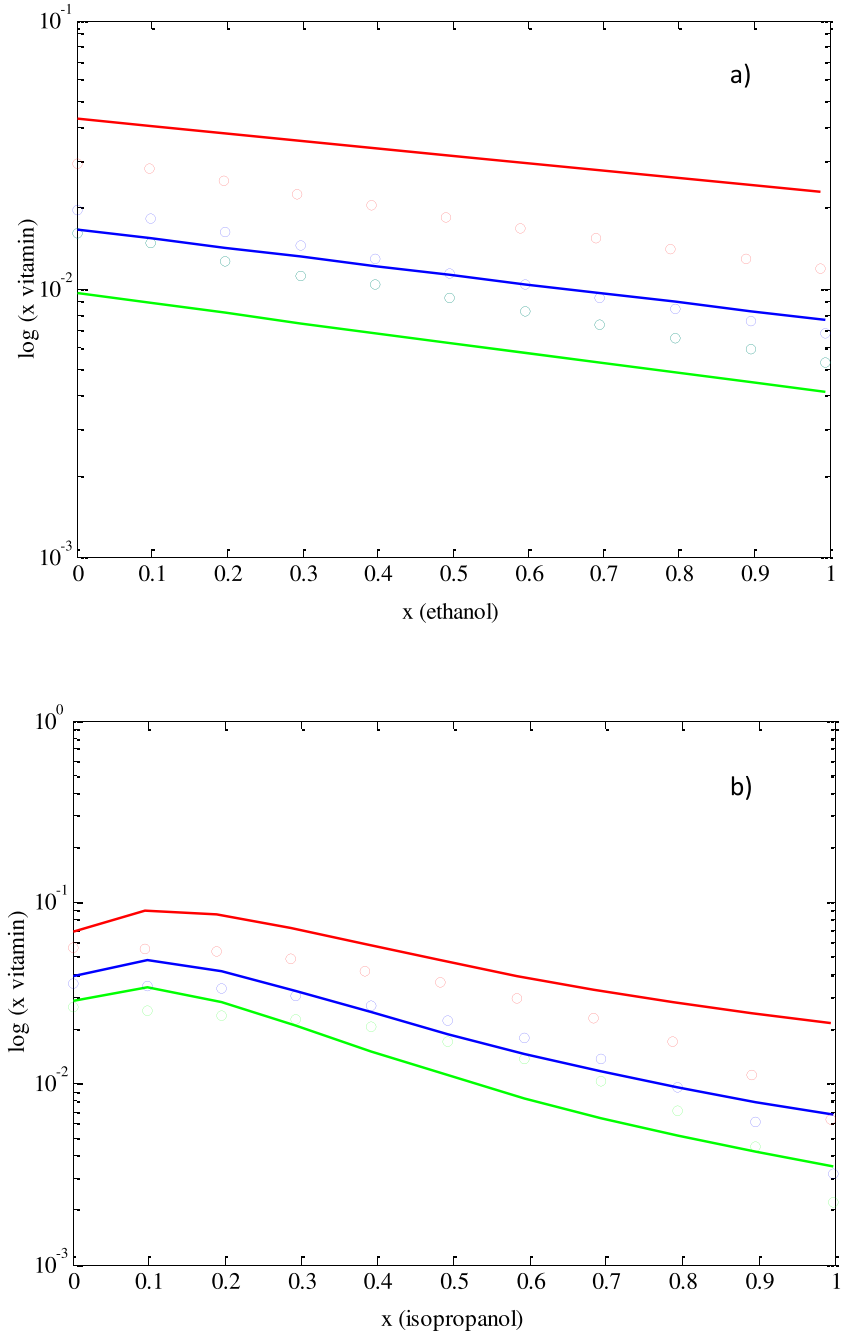


Fig. 2. Solubility of vitamin C in the binary mixture of a) ethanol-methanol, b) isopropanol-water at (green) 293.15 K, (blue) 303.15 K and (red) 323.15 K. Comparison between experimental data (points) and PHSC predictions (lines).

between vitamin molecules and solvents have been considered. These vitamins have low solubility in water due to hydrophobic repulsion between water and vitamin molecules. Their solubilities increase with the addition of ethanol in water. As shown in Figs. 3 and 4, the solubility of vitamin K3 is higher than vitamin E but the enhancement is higher for vitamin E; vitamin E is more hydrophobic than vitamin K3 [34].

The solubility of vitamin B6H in the binary mixture of acetone-water, propanol-water, and acetonitrile-water at three temperatures has been depicted in Fig. 5.

As shown in Fig. 5, at a constant temperature, there is a maximum solubility of vitamin B6H in propanol-water and acetonitrile-water. The PHSC EOS predicts this behavior satisfactory. This behavior of the solubility of vitamin B6H in the binary mixed solvents might result from hydrogen bonding and ionic interactions [35]. Before reaching the maximum solubility, the solute-solvent interactions are stronger. Then with increasing the mole fraction of acetonitrile or propanol, the solute-solvent interactions decrease due to strong hydrogen-bonding interactions between the solvents. P. Shi et al. studied the solutes-solvent and solvent-solvent interactions using molecular simulations [35]. They calculated the solvation free energy of the vitamin B6H-water- acetonitrile system. Their results show that, there is maximum solvation free energy at a specific acetonitrile concentration ($x \approx 0.1$); the strongest solute-solvent interaction [35]. They show that the solute-solvent and solvent-solvent interactions play an important role in vitamin B6H solubility in the mixed solvent.

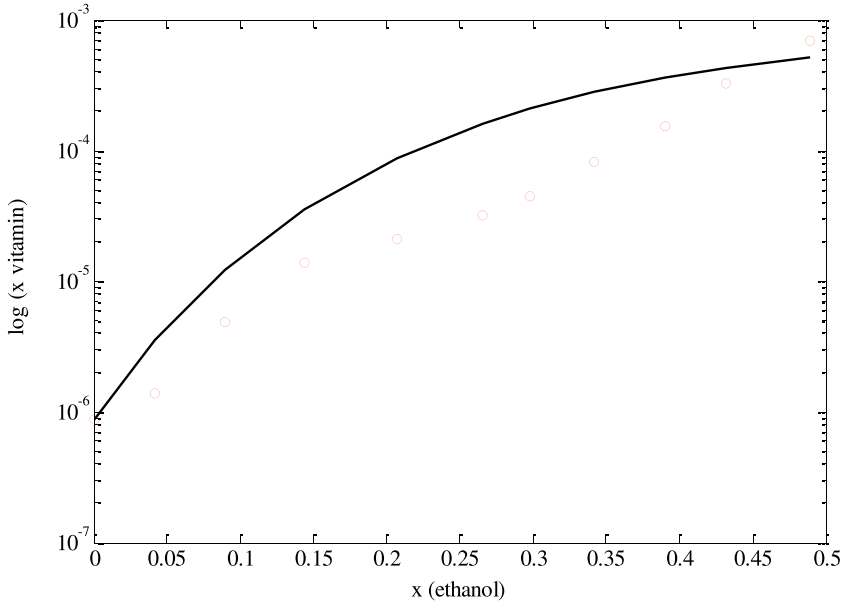


Fig. 3. Solubility of vitamin E in the binary mixture of ethanol-water at 303.15 K. Comparison between experimental data (points) and PHSC predictions (lines).

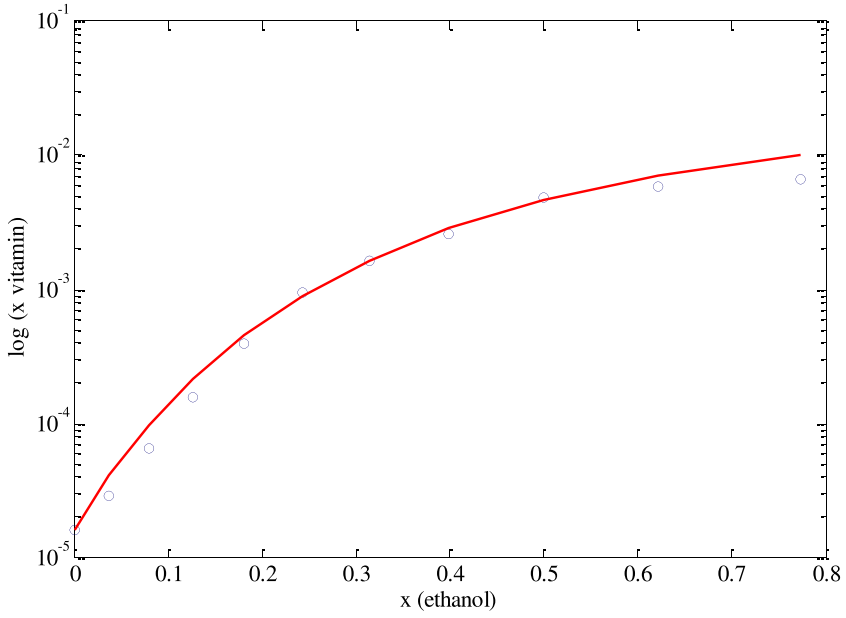


Fig. 4. Solubility of vitamin K3 in the binary mixture of ethanol-water at 303.15 K. Comparison between experimental data (points) and PHSC predictions (lines).

4. Conclusion

In this research, the solubility of vitamins C, E, D3, K3, and B6H in the mixed solvent has been predicted using the PHSC and PC-SAFT EOSs. The solubility of vitamins in the pure solvents at various temperatures has been predicted satisfactory. On the other hand, the PHSC and PC-SAFT EOSs have been used to predict the solubility of vitamins in the mixed solvent at different temperatures. The average RMSD of vitamin solubility in the mixed solvents is acceptable by considering prediction without any adjustable parameters. The maximum solubility prediction of vitamin-solvent play a crucial role in the design of the purification processes of vitamins. The PHSC EOS predicts the maximum solubility of vitamins B6H and C in the mixed solvent, satisfactory. The results show that the obtained model parameters are global and can be used to predict the solubility of vitamins in different mixed solvents. This model capability is very efficient for pre-designing and formulating vitamins.

CRediT authorship contribution statement

Abduladheem Turki Jalil: Writing – original draft, Validation, Investigation, Methodology. **Hayder Imad jabar:** Software, Formal analysis. **Muataz Mohammed Al-Taee:** Writing – review & editing. **Muhjaha Ahmed:** Data curation, Investigation, Writing – review & editing, Validation. **Zahraa Khazal Hamdoon:** Writing – review & editing. **Rahman S. Zabibah:** Data curation, Investigation, Writing – review & editing, Validation. **Reza Shariyati:** Supervision, Project administration, Software, Methodology, Conceptualization.

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.

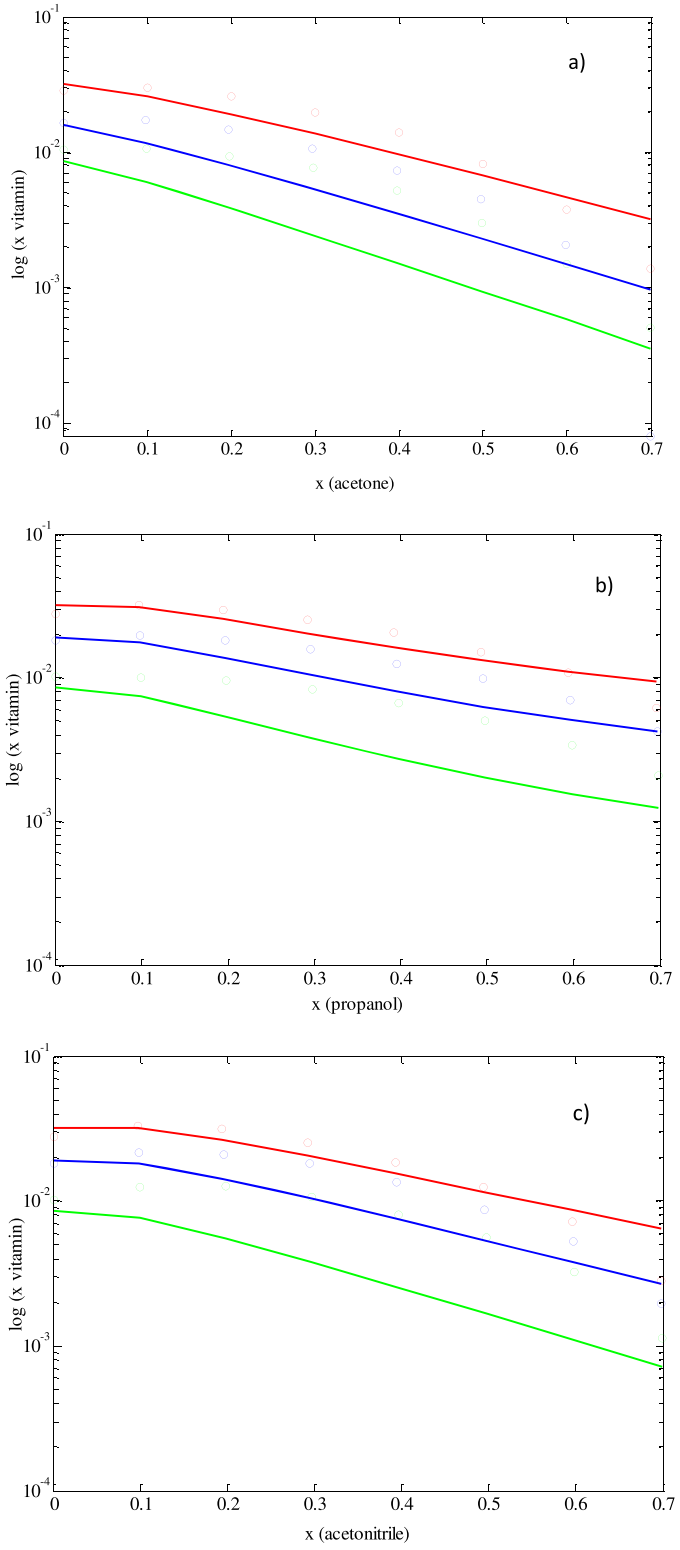


Fig. 5. Solubility of vitamin B6H in the binary mixture of (a) acetone-water, (b) propanol-water and (c) acetonitrile-water at (green) 278.15 K, (blue) 298.15 K and (red) 313.15 K. Comparison between experimental data (points) and PHSC predictions (lines).

Data availability

Data will be made available on request.

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