Preferential Solvation of the Antioxidant Agent Daidzein in some Aqueous Co-Solvent Mixtures according to IKBI and QLQC Methods

Daniel M. Jiménez[1], Zaira J. Cárdenas[1], Daniel R. Delgado[2], María Á. Peña[3] and Fleming Martínez[1,*]

[1]Grupo de Investigaciones Farmacéutico Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Cra. 30 No. 45-03, Bogotá D.C., Colombia

[2]Programa de Ingeniería Industrial, Facultad de Ingeniería, Universidad Cooperativa de Colombia, Neiva, Colombia

[3]Departamento de Ciencias Biomédicas, Facultad de Farmacia, Universidad de Alcalá, Alcalá de Henares, Madrid, Spain

Abstract: The preferential solvation parameters by ethanol (EtOH) or propylene glycol (PG) of daidzein were derived from their solution thermodynamic properties by means of the inverse Kirkwood-Buff integrals and the quasi-lattice-quasi-chemical (QLQC) methods. According to IKBI method, the preferential solvation parameter by the co-solvent, $\delta x_{1,3}$, is negative in water-rich mixtures but positive in co-solvent-rich mixtures in both kinds of systems. This could demonstrate the relevant role of hydrophobic hydration around the aromatic rings in the drug solvation in water-rich mixtures. Furthermore, the more solvation by co-solvent in co-solvent-rich mixtures could be due mainly to polarity effects and acidic behavior of the hydroxyl groups of the compound in front to the more basic solvents present in the mixtures, i.e. EtOH or PG. Otherwise, according to QLQC method, this drug is preferentially solvated by the co-solvents in all the mixtures in both kind of systems.

Keywords: Daidzein, ethanol, propylene glycol, preferential solvation, inverse Kirkwood-Buff integrals, quasi-lattice-quasi-chemical.

INTRODUCTION

As has been widely described, phytoestrogens are a diverse group of naturally derived compounds that resemble 17-beta-estradiol (E_2) and they may protect against a wide range of bad conditions including several forms of cancer, cardiovascular disease, osteoporosis and menopausal symptoms [1]. In particular, some studies have indicated the possible effect in prevention of breast cancer [2]. Daidzein (Figure **1**, IUPAC name: 7-Hydroxy-3-(4-hydroxyphenyl) chromen-4-one, molar mass: 254.23 g mol^{-1}, CAS 486-66-8) could be considered as a phyto-estrogen compound and it corresponds to an isoflavone, which is abundant in soybean [3]. It has been demonstrated to be a potent antioxidant and has gained relevance in relation to the human health [4].

Solubility determination of drugs and of similar organic compounds, in all possible co-solvent mixtures, is very important for scientists involved in several development stages such as substances purification and design of homogeneous liquid medicines [5]. Co-solvency has been employed in pharmacy as a solubilizing method in order to design homogeneous pharmaceutical liquid dosage forms during a long time [5-7]. In this way, two researches have been carried out to evaluate the thermodynamic effect of mixtures composition and temperature on the solubility of daidzein in ethanol + water and propylene glycol + water mixtures [8, 9]. It is important to note that ethanol and propylene glycol are the most widely used co-solvents to design and develop liquid pharmaceutical products [10]; besides, they are also used as additives in several kinds of industrial foods [11]. Furthermore, they are considered as environmentally benign solvents, useful for the purification procedures of several food components [12, 13]. Nevertheless, the preferential solvation of daidzein by the solvents in the respective mixtures i.e. the co-solvent specific composition around the daidzein molecules, has not been studied. This knowledge would lead to a better understanding of the molecular phenomena occurring during the solution processes.

In this way, the inverse Kirkwood-Buff integrals (IKBI) are an efficient technique for analyzing the preferential solvation of non-electrolyte compounds in co-solvent mixtures, describing the local compositions around the solute, by the components present in the

---

*Address correspondence to this author at the Grupo de Investigaciones Farmacéutico Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Cra. 30 No. 45-03, Bogotá D.C., Colombia; Tel: 571-3165000-14608; Fax: 571-3165050;
E-mail: fmartinezr@unal.edu.co

E-ISSN: 1929-5030/15

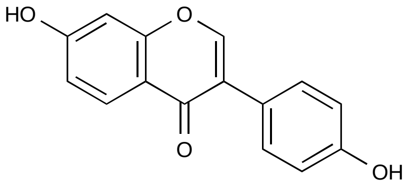

Figure 1: Molecular structure of daidzein.

same mixtures [14-16]. Applied to the present research, this treatment depends on the values of the standard molar Gibbs energies of transfer of daidzein from neat water to the co-solvent + water mixtures and also on the excess molar Gibbs energy of mixing of the binary mixtures without dissolved solute on them. In similar way, the quasi-lattice quasi-chemical (QLQC) approach is also useful to evaluate preferential solvation, although it is not too much rigorous as the IKBI approach is. Thus, this method assumes that the number of nearest neighbors of a molecule (i.e. the lattice parameter *Z*) is the weighted mean of the lattice parameter of the neat components. It also presumes that the interaction energy of the molecules of any component with the other molecules is independent of the nature of these neighbors. This model also assumes that ideal volumes and ideal entropies of mixing take place. The main advantage of this method is that non-derivative quantities are required as they are in the case of the IKBI method [14-16].

In this research the IKBI and QLQC approaches were applied to evaluate the preferential solvation of antioxidant agent daidzein in the binary mixtures conformed by ethanol (EtOH) or propylene glycol (PG) and water (W) in order to contribute to the understanding the respective molecular behaviors. QLQC method is applicable in both co-solvent systems because the maximum solubility of daidzein is obtained in the neat co-solvents [8, 9]. The results are expressed in terms of the preferential solvation parameter ($\delta x_{1,3}$) of the solute by the co-solvent, i.e. ethanol or propylene glycol, according to the mixtures composition. Thus, this study is similar to that developed by analyzing the behavior of the analgesic drug ketoprofen in either EtOH (or PG) + water mixtures [17]. In this way, this research expands the use of IKBI and QLQC methods to studying the preferential solvation of organic compounds with interest in food chemistry.

THEORETICAL BACKGROUND

According to IKBI method, the solute solvation results in binary mixtures are expressed in terms of the preferential solvation parameter ($\delta x_{1,3}$) of the solute by the co-solvent (compound 1) according to the following expression:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \tag{1}$$

where x_1 is the mole fraction of co-solvent in the bulk solvent mixture and $x_{1,3}^{L}$ is the local mole fraction of co-solvent in the environment near to the solute molecule. If $\delta x_{1,3} > 0$ daidzein is preferentially solvated by co-solvent; on the contrary, if it is < 0 this compound is preferentially solvated by water. $\delta x_{1,3}$ values are obtainable from those of $G_{1,3}$ and $G_{1,3}$, and these in turn, are calculable from some thermodynamic data of the co-solvent mixtures with the solute dissolved on them, as it is shown in equations 2 and 3 [15, 18]:

$$G_{1,3} = RT\kappa_T - \bar{V}_3 + x_2\bar{V}_2 D / Q \tag{2}$$

$$G_{2,3} = RT!_T \quad \bar{V}_3 + x_1\bar{V}_1 D / Q \tag{3}$$

Here κ_T is the isothermal compressibility of the co-solvent + water solvent mixtures (expressed in GPa^{-1}), $\bar{V}_1$ and $\bar{V}_2$ are the partial molar volumes of the solvents in the mixtures (expressed in cm^3 mol^{-1}); similarly, $\bar{V}_3$ is the partial molar volume of the solute in these mixtures (expressed in cm^3 mol^{-1}). The function *D* is the derivative of the standard molar Gibbs energies of transfer of the drug (from neat water to co-solvent + water mixtures) with respect to the co-solvent proportion in the mixtures (expressed in kJ mol^{-1}, as also is *RT*). Finally, the function *Q* involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents (G_{1+2}^{Exc}) with respect to the water proportion in the mixtures (also expressed in kJ mol^{-1}) [15, 18]. These two quantities are calculated according to equations (4) and (5), respectively.

$$D = \left(\frac{\partial \Delta_{\mathrm{tr}} G_{3,2\to1+2}^{\circ}}{\partial x_1} \right)_{T,p} \tag{4}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1,2}^{Exc}}{\partial x_2^2} \right)_{T,p} \tag{5}$$

The preferential solvation parameter of the solute by the component 1 (i.e. co-solvent) can be calculated from the Kirkwood-Buff integrals as follows [15, 18]:

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3}\right)}{x_1 G_{1,2} + x_2 G_{2,3} + V_{\mathrm{cor}}} \tag{6}$$

Here V_{cor} is the correlation volume of daidzein and it could be obtained by using the following relationship [15, 18]:

$$V_{\mathrm{cor}} = 2522.5\left(r_3 + 0.1363\left(x_{1,3}^L V_1 + x_{2,3}^L V_2\right)^{1/3} - 0.085\right)^3 \qquad (7)$$

where r_3 is the radius of daidzein (expressed in nm). However, the definitive correlation volume requires several iterations, because it depends on the local mole fractions around daidzein. These iterations are done by replacing the $\delta x_{1,3}$ value in the equation (1) to calculate $x_{1,3}^L$ until a non-variant value of V_{cor} is obtained.

For the QLQC method [18], the local mole fraction of co-solvent around the daidzein molecules is defined as:

$$x_{\mathrm{A}}^L = 1/\left[1 + \left(N_{11}/N_{22}\right)^{0.5}\exp\left(\Delta E_{12,3}/2RT\right)\right] \qquad (8)$$

$$N_{11}/N_{22} = \left[x_1 - N_{12}/Z\left(N_1 + N_2\right)\right]/\left[x_2 - N_{12}/Z\left(N_1 + N_2\right)\right] \qquad (9)$$

$$\frac{N_{12}}{Z\left(N_1 + N_2\right)} = \frac{1 - \left[1 - 4x_1x_2\left(1 - \exp\left\{-\Delta E_{12}/RT\right\}\right)\right]^{0.5}}{2\left[1 - \exp\left(-\Delta E_{12}/RT\right)\right]} \qquad (10)$$

$$\Delta E_{12,3} = \Delta_{\mathrm{tr}}G_{3,2\to 1}^{\mathrm{o}}/Z \qquad (11)$$

$$\exp\left(\Delta E_{12}/RT\right) = \left[\left(2\exp\left\{-G_{12(x=0.5)}^{\mathrm{Exc}}/ZRT\right\}\right) - 1\right]^2 \qquad (12)$$

In these equations, the lattice parameter (Z) is usually assumed as 10. In turn, N_1 and N_2 are the number of molecules of both components in the bulk, whereas, N_{11}, N_{22}, and N_{12} are the number of neighboring pairs of these molecules present in the quasi lattice. Equation (11) expresses the difference in the molar neighbor interaction energies of daidzein with the co-solvent and water ($\Delta E_{12,3}$) by the molar Gibbs energy of transfer of daidzein from water to co-solvent per neighboring lattice. ΔE_{12} denotes the molar energy of interaction of solvent on the neighboring quasi-lattice sites. It is important to keep in mind that only the Gibbs energy of transfer of daidzein between the neat solvents and the excess Gibbs energy of mixing, at equimolar composition of both solvents, are required for this method [18].

RESULTS AND DISCUSSION

Standard molar Gibbs energy of transfer of daidzein from neat water to all the co-solvent + water mixtures (Table **1**) was calculated and correlated to non-regular polynomials by using the equation (13) from the solubility data already reported [8, 9]. Thus, the coefficients of the obtained polynomials are shown in Table **2**.

$$\Delta_{\mathrm{tr}}G_{3,2\to 1+2}^{\mathrm{o}} = RT\ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) = a + bx_1 + cx_1^{1.5} + dx_1^2 + ex_1^{0.5} \qquad (13)$$

D values (Table **3**) were calculated from the first derivative of the polynomial models solved according to the proportion of co-solvent in the mixtures. As has been made previously with other similar compounds,

Table 1: Gibbs Energy of Transfer (kJ mol^{-1}) of Daidzein from Neat Water to Co-Solvent + Water Mixtures at Both Temperatures

Ethanol + Water Mixtures [a]			Propylene Glycol + Water Mixtures [b]		
x_1 [c]	298.2 K	313.2 K	x_1 [c]	298.2 K	313.2 K
0.0000	0.00	0.00	0.0000	0.00	0.00
0.0716	–2.59	–3.60	0.0256	–1.13	–1.18
0.1707	–9.55	–9.47	0.0559	–2.16	–2.56
0.3166	–15.68	–14.85	0.0921	–4.27	–4.54
0.5527	–18.46	–17.96	0.1364	–6.52	–6.75
1.0000	–19.85	–19.37	0.1915	–8.77	–8.91
			0.2621	–10.80	–10.73
			0.3559	–12.67	–12.54
			0.4865	–14.03	–13.75
			0.6807	–15.14	–14.88
			1.0000	–16.03	–15.58

[a] Values calculated from the solubility values reported by Yang *et al.* [8].
[b] Values calculated from the solubility values reported by Zeng *et al.* [9].
[c] x_1 are the mole fractions of co-solvent in the co-solvent + water mixtures free of daidzein.

Table 2: Coefficients (kJ mol^{-1}) of the Equation (13) Applied to Gibbs Energy of Transfer of Daidzein from Neat Water to Co-Solvent + Water Mixtures at both Temperatures

Coefficient	Ethanol + Water Mixtures		Propylene Glycol + Water Mixtures	
	298.2 K	313.2 K	298.2 K	313.2 K
a	–0.01	0.00	–0.08	–0.04
b	–355.14	–242.69	–160.37	–151.09
c	487.96	326.48	214.48	206.51
d	–207.28	–133.99	–86.86	–84.74
e	54.62	30.83	16.81	13.78

Table 3: *D* Values (kJ mol^{-1}) of Daidzein in Co-Solvent + Water Mixtures at both Temperatures

x_1 [a]	Ethanol + Water Mixtures		Propylene Glycol + Water Mixtures	
	298.2 K	313.2 K	298.2 K	313.2 K
0.00	–100.42	–90.64	–72.11	–73.32
0.05	–90.06	–77.64	–59.52	–59.50
0.10	–78.77	–65.87	–49.42	–48.30
0.15	–63.33	–53.41	–40.12	–38.76
0.20	–49.65	–42.80	–32.44	–31.06
0.25	–38.19	–33.99	–26.13	–24.81
0.30	–28.75	–26.70	–20.92	–19.70
0.35	–21.05	–20.70	–16.63	–15.51
0.40	–14.87	–15.77	–13.09	–12.09
0.45	–9.98	–11.78	–10.20	–9.30
0.50	–6.24	–8.59	–7.85	–7.06
0.55	–3.51	–6.10	–5.99	–5.30
0.60	–1.67	–4.23	–4.55	–3.95
0.65	–0.63	–2.92	–3.49	–2.98
0.70	–0.31	–2.11	–2.76	–2.33
0.75	–0.65	–1.76	–2.34	–1.99
0.80	–1.60	–1.81	–2.20	–1.92
0.85	–3.09	–2.24	–2.31	–2.10
0.90	–5.09	–3.02	–2.65	–2.50
0.95	–7.55	–4.12	–3.21	–3.12
1.00	–10.46	–5.52	–3.97	–3.93

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of daidzein.

this procedure was done varying in 0.05 mole fraction of co-solvent [17, 19].

Q and $RT \cdot \kappa_T$ values, as well as the partial molar volumes of co-solvents and water, in these binary mixtures, were taken from the literature [19-21]. Otherwise, the partial molar volumes of non-electrolyte drugs in mixtures are not frequently reported in the literature. For this reason, as was made previously with other drugs in similar studies [22], the molar volume of daidzein was considered here as independent of co-solvent composition and temperature. Thus, the V_3 value presented in Table **4** was calculated according to the method proposed by Fedors [23]. Furthermore, the molecular radius of daidzein was also calculated as 0.383 nm from the respective molar volume by using the equation (14), where N_{Av} is the Avogadro number.

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{\mathrm{Av}}} \right)^{1/3} \qquad (14)$$

Table **5** shows that the $G_{1,3}$ and $G_{2,3}$ are negative in all compositions, at both temperatures considered, indicating that daidzein exhibits good affinity for both components in the mixtures i.e. co-solvent and water.

To use the IKBI method, the correlation volume was iterated three times by using the equations (1), (6) and (7) to obtain the values reported in Table **6**. V_{cor} is almost independent on temperature in water-rich mixtures but it increases slightly in co-solvent-rich mixtures. This behavior is proportional to the increasing

Table 4: Internal Energy, Molar Volume, and Hildebrand Solubility Parameter of Daidzein (Compound 3), according to the Fedors Method [23]

Group	Number	$\Delta U°$ / kJ mol^{-1}	$V°$ / cm^3 mol^{-1}
–OH	2	2 x 29.8 = 59.6	2 x 10.0 = 20.0
–CO–	1	17.4	10.8
–O–		3.35	3.8
–C=	1	4.31	13.5
>C=	1	4.31	–5.50
Disubstituted phenyl ring	1	31.9	52.4
Trisubstituted phenyl ring	1	31.9	33.4
Ring closure	1	1.05	16.0
Conjugated bond	1	1.67	–2.20
	Σ	155.49	142.20
	δ_3 = (155,490/142.20)$^{1/2}$ = 33.07 MPa$^{1/2}$		

Table 5: $G_{1,3}$ and $G_{2,3}$ Values (cm^3 mol^{-1}) of Daidzein in Co-Solvent + Water Mixtures at both Temperatures

x_1 [a]	Ethanol + Water Mixtures				Propylene Glycol + Water Mixtures			
	$G_{1,3}$		$G_{2,3}$		$G_{1,3}$		$G_{2,3}$	
	298.2 K	313.2 K	298.2 K	313.2 K	298.2 K	313.2 K	298.2 K	313.2 K
0.00	–873.2	–772.6	–141.1	–141.0	–667.2	–652.8	–141.1	–141.0
0.05	–836.5	–751.8	–249.7	–238.5	–554.9	–559.5	–225.7	–227.5
0.10	–766.5	–697.7	–351.0	–331.4	–466.3	–473.7	–283.0	–287.7
0.15	–645.3	–602.4	–414.7	–395.6	–389.3	–395.8	–315.2	–321.4
0.20	–530.0	–503.5	–445.6	–428.9	–328.4	–331.6	–329.5	–334.3
0.25	–431.7	–414.9	–450.2	–435.8	–280.9	–280.7	–331.0	–331.9
0.30	–352.2	–342.4	–435.3	–424.4	–244.2	–241.4	–323.3	–319.5
0.35	–290.0	–286.2	–406.9	–402.2	–216.0	–211.9	–309.4	–301.1
0.40	–242.5	–244.0	–369.8	–374.8	–194.6	–190.2	–291.7	–279.9
0.45	–207.0	–213.1	–327.4	–345.8	–178.6	–174.5	–272.1	–258.3
0.50	–180.9	–190.6	–282.3	–317.0	–166.9	–163.4	–252.4	–237.8
0.55	–162.5	–174.4	–237.2	–289.8	–158.5	–155.7	–233.7	–219.5
0.60	–150.4	–163.0	–196.1	–264.9	–152.6	–150.6	–217.3	–204.1
0.65	–143.7	–155.1	–165.2	–243.8	–148.7	–147.2	–204.0	–192.1
0.70	–141.5	–150.0	–154.5	–228.9	–146.2	–145.1	–194.5	–184.1
0.75	–142.7	–147.1	–173.2	–223.8	–144.7	–143.9	–189.5	–180.5
0.80	–145.1	–145.5	–221.2	–230.1	–143.8	–143.3	–189.8	–182.1
0.85	–146.2	–144.2	–282.4	–244.1	–143.2	–142.9	–195.8	–189.3
0.90	–145.2	–142.7	–335.8	–257.5	–142.7	–142.5	–208.6	–203.1
0.95	–142.6	–141.0	–370.4	–264.8	–142.1	–141.9	–229.1	–224.2
1.00	–139.3	–139.2	–386.8	–265.8	–141.0	–140.9	–259.0	–253.3

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water free of daidzein.

Table 6: Correlation Volume ($cm^3\ mol^{-1}$) of Daidzein in Co-Solvent + Water Mixtures at both Temperatures

x_1 [a]	Ethanol + Water Mixtures		Propylene Glycol + Water Mixtures	
	298.2 K	313.2 K	298.2 K	313.2 K
0.00	713	714	713	715
0.05	700	710	733	735
0.10	698	720	784	787
0.15	753	771	854	858
0.20	834	844	924	930
0.25	903	911	988	994
0.30	957	965	1045	1052
0.35	1001	1009	1098	1104
0.40	1038	1048	1146	1152
0.45	1071	1083	1191	1197
0.50	1101	1117	1235	1241
0.55	1130	1149	1278	1285
0.60	1160	1181	1321	1328
0.65	1191	1213	1364	1372
0.70	1225	1246	1407	1416
0.75	1262	1280	1450	1459
0.80	1301	1315	1493	1503
0.85	1339	1350	1536	1547
0.90	1373	1384	1579	1590
0.95	1404	1416	1620	1632
1.00	1432	1448	1660	1672

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of daidzein.

in the molar volume of the co-solvent mixtures with the temperature [24, 25].

Based on the molecular structure of daidzein, this compound could act in solution as a Lewis acid because of the hydrogen atoms in its –OH groups (Figure **1**) to establish hydrogen bonding with the proton-acceptor functional groups of the solvents (oxygen atoms in –OH groups). Additionally, daidzein could act as a Lewis base thorough its free electron pairs in oxygen atoms of –O–, >C=O, and –OH groups (Figure **1**) to interact with acidic hydrogen atoms of water and EtOH or PG.

Regarding to IKBI method, the values of $\delta x_{1,3}$ vary non-linearly with the co-solvent proportion in the aqueous mixtures (Table **7**, Figures **2** and **3**). Addition of co-solvent to water makes negative the $\delta x_{1,3}$ values of daidzein from the pure water up to the mixture with $x_1 = 0.24$ (or 0.20) in both systems reaching maximum negative values near to $x_1 = 0.10$. Probably the association of water molecules around the non-polar groups of daidzein (Figure **1**) contributes to lowering the net $\delta x_{1,3}$ values in these water-rich mixtures. IKBI $\delta x_{1,3}$ values are higher in EtOH + water mixtures compared with PG + water mixtures.

In the mixtures with composition 0.24 (or 0.20) < x_1 < 1.00, the local mole fractions of co-solvents are greater than those for water. In this way, the co-solvent action may be related to the breaking of the ordered structure of associated water (present as aggregates stabilized by hydrogen bonding) around the non-polar moieties of daidzein. This fact could increase the drug solvation, exhibiting maximum values near to $x_1 = 0.40$ in both systems. It is conjecturable that in intermediate compositions and in co-solvent-rich mixtures, daidzein is acting as Lewis acid with both co-solvents, EtOH or PG, because these co-solvents are more basic than water, as described by the respective Kamlet-Taft hydrogen bond acceptor parameters, i.e. $\beta = 0.75$ for EtOH, 0.78 for PG and 0.47 for water [26, 27].

Otherwise, to use the QLQC method, the excess Gibbs energy of mixing values of the equimolar mixture of EtOH + water mixtures were calculated according to

Table 7: IKBI and QLQC $\delta x_{1,3}$ Values (x 100) of Daidzein in Co-Solvent + Water Mixtures at both Temperatures

x_1 [a]	Ethanol + Water Mixtures				Propylene Glycol + Water Mixtures			
	IKBI		QLQC		IKBI		QLQC	
	298.2 K	313.2 K	298.2 K	313.2 K	298.2 K	313.2 K	298.2 K	313.2 K
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.05	–6.62	–5.47	2.65	2.46	–3.19	–3.21	1.75	1.62
0.10	–12.24	–9.37	4.81	4.46	–3.42	–3.48	3.26	3.02
0.15	–9.67	–7.66	6.53	6.07	–1.79	–1.80	4.55	4.21
0.20	–3.64	–2.98	7.87	7.32	0.03	0.07	5.62	5.20
0.25	0.76	0.82	8.87	8.25	1.40	1.42	6.48	6.00
0.30	3.19	3.05	9.56	8.90	2.23	2.17	7.15	6.62
0.35	4.19	4.08	9.99	9.29	2.59	2.43	7.62	7.06
0.40	4.25	4.33	10.16	9.46	2.61	2.37	7.92	7.34
0.45	3.74	4.12	10.12	9.42	2.41	2.12	8.05	7.46
0.50	2.92	3.66	9.88	9.19	2.08	1.79	8.01	7.42
0.55	1.98	3.09	9.46	8.80	1.72	1.43	7.82	7.24
0.60	1.11	2.50	8.88	8.26	1.36	1.11	7.48	6.93
0.65	0.47	1.96	8.15	7.58	1.05	0.84	6.99	6.47
0.70	0.25	1.55	7.29	6.77	0.81	0.65	6.36	5.89
0.75	0.51	1.29	6.31	5.86	0.65	0.53	5.60	5.19
0.80	1.07	1.17	5.22	4.84	0.55	0.46	4.72	4.37
0.85	1.48	1.07	4.03	3.74	0.48	0.42	3.71	3.44
0.90	1.42	0.84	2.76	2.56	0.41	0.38	2.58	2.39
0.95	0.87	0.46	1.41	1.31	0.28	0.26	1.35	1.25
1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of daidzein.

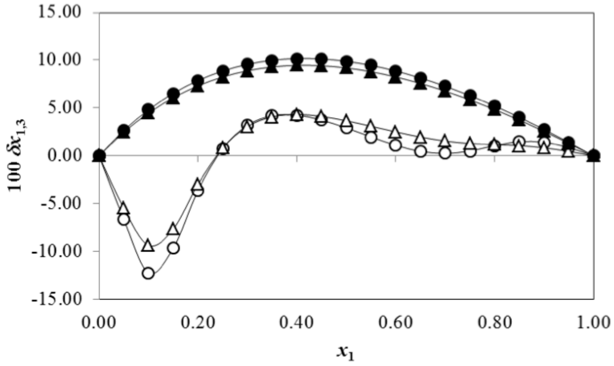

Figure 2: IKBI (white symbols) and QLQC (black symbols) $\delta x_{1,3}$ values of daidzein in ethanol + water mixtures at both temperatures. Circles: 298.2 K; triangles: 313.2 K.

some equations already presented in the literature [19, 27], whereas for PG + water mixtures they were taken directly from the literature as: –6.06 x 10^{-2} at 298.15 K and –1.35 x 10^{-2} kJ mol^{-1} at 313.15 K [28]. In accordance with the QLQC method (Table **7** and Figures **2** and **3**), daidzein is preferentially solvated by the co-solvent in all the mixtures. Clearly the QLQC $\delta x_{1,3}$ values are higher than those obtained by using the IKBI method in all the mixtures. Maximum values are found in the mixtures with x_1 = 0.40 and 0.45 for

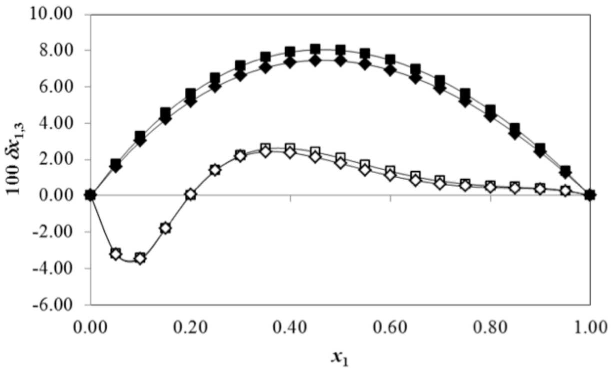

Figure 3: IKBI (white symbols) and QLQC (black symbols) $\delta x_{1,3}$ values of daidzein in propylene glycol + water mixtures at both temperatures. Squares: 298.2 K; Rhombic: 313.2 K.

EtOH + water and PG + water mixtures, respectively. As has already been indicated in the literature, the IKBI method is more adequate than QLQC method to discriminate the effect of the co-solvent composition on the local mole fraction of the solvents around the drug molecules, in particular in the water-rich mixtures [19, 21]. Nevertheless, it is important to keep in mind that QLQC method only requires the Gibbs energy of transfer of daidzein from neat water to neat co-solvents and the excess Gibbs energy of mixing of the co-solvent mixtures with composition $x_1 = 0.50$, and thus, it is more easy to use.

Finally, just as a comparison, Figure **4** shows the preferential solvation behavior of daidzein in both co-solvent + water systems at 313.2 K. It is noteworthy that in all cases, the magnitudes of IKBI and QLQC preferential solvation parameters by water or co-solvent, are higher in EtOH + water mixtures compared with PG + water mixtures. On the other hand, the composition region where daidzein is preferentially solvated by water is also higher for EtOH + water mixtures. These behaviors are similar to those reported for ketoprofen in the same mixtures [17]. In a first approximation, apparently these differences could be attributed to the polarity of every co-solvent (compound 1). Thus, the Hildebrand solubility parameters (δ_1) are 26.5 and 30.2 MPa$^{1/2}$ for EtOH and PG, respectively [29]. Thus, both co-solvents are less polar than daidzein is (compound 3, δ_3 = 33.1 MPa$^{1/2}$, Table **4**), but the difference in polarity between daidzein and co-solvent is higher with EtOH. Nevertheless, an opposite behavior in the mixtures composition has been reported for some sulfonamides in EtOH + water mixtures *vs*. 1-propanol + water mixtures [30]. In this way, it is clear that besides polarity, some other properties of the mixtures would be involved in the preferential solvation of these compounds.

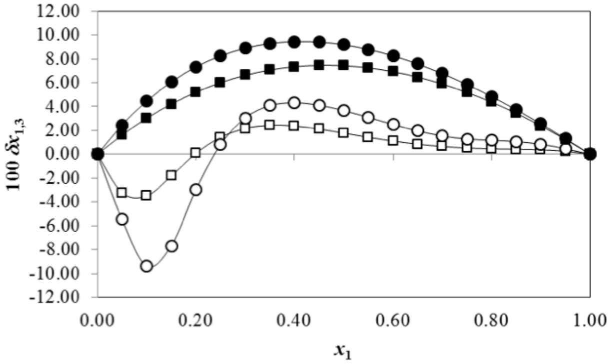

Figure 4: IKBI (white symbols) and QLQC (black symbols) $\delta x_{1,3}$ values of daidzein in both co-solvent + water systems at 313.2 K. Circles: ethanol + water mixtures. Squares: propylene glycol + water mixtures.

CONCLUSIONS

Regarding to IKBI method daidzein is preferentially solvated by water in water-rich mixtures but preferentially solvated by co-solvents in mixtures with compositions from $x_1 = 0.24$ (or 0.20) to neat co-solvent in EtOH + water or PG + water mixtures at both temperatures considered. It is possible that the hydrophobic hydration around both aromatic rings of daidzein plays a relevant role in the drug solvation in water-rich mixtures. The more drug solvation by co-solvents in mixtures of similar composition and in co-solvent-rich mixtures could be due to the acidic behavior of daidzein towards co-solvents, which are the more basic solvents. On the other hand, according to the QLQC method, this compound would be preferentially solvated by the co-solvents in all the possible mixtures. Nevertheless, it is important to consider that IKBI is more rigorous than QLQC and more reliable results are thus obtained with the former method. Finally, although the specific interactions between daidzein and the components in the mixtures is still unclear, it is noteworthy that the treatments developed here contribute to the understanding of the physicochemical behavior of pharmaceutical and food components in complex aqueous solutions.

CONFLICT OF INTEREST

The authors report no conflict of interest related with this manuscript.

REFERENCES

[1] Liggins J, Bluck LJ, Runswick S, Atkinson C, Coward WA, Bingham SA. Daidzein and genistein contents of vegetables. Br J Nutr 2000; 84: 717-25.

[2] Coward L, Barnes NC, Setchell KDR, Barnes S. Genistein, daidzein, and their β-glycoside conjugates: Antitumor isoflavones in soybean foods from American and Asian diets. J Agric Food Chem 1993; 41: 1961-7. http://dx.doi.org/10.1021/jf00035a027

[3] Budavari S, O'Neil MJ, Smith A, Heckelman PE, Obenchain, Jr. JR, Gallipeau JAR, D'Arecea MA, Eds. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 13th ed. Whitehouse Station, NJ: Merck & Co., Inc.; 2001.

[4] Liang J, Tian YX, Fu LM, Wang TH, Li HJ, Wang P, Han RM, Zhang JP, Skibsted LH. Daidzein as an antioxidant of lipid: effects of the microenvironment in relation to chemical structure. J Agric Food Chem 2008; 56: 10376-83. http://dx.doi.org/10.1021/jf801907m

[5] Jouyban A. Handbook of solubility data for pharmaceuticals. Boca Raton, FL: CRC Press; 2010.

[6] Rubino JT. Cosolvents and cosolvency. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology. Vol 3. New York, NY: Marcel Dekker, Inc. 1988; p. 375-98.

[7] Yalkowsky SH. Solubility and solubilization in aqueous media. New York, NY: American Chemical Society and Oxford University Press; 1999.

[8] Yang G-D, Huang Y-R, Nan G-J, Chen H-J, Zeng A-G, Bian X-L. Solubility of daidzein in the binary system of ethanol and water. J Mol Liq 2013; 180: 160-3. http://dx.doi.org/10.1016/j.molliq.2012.12.035

[9] Zeng A-G, Pang X-L, Wu N, Wang D, Nan G-J, Yang G-D, Bian X-L. Solubility of daidzein in propylene glycol plus water cosolvent mixtures. Fluid Phase Equilib 2014; 366: 127-33. http://dx.doi.org/10.1016/j.fluid.2013.12.024

[10] Aulton ME. Pharmaceutics: The science of dosage forms design. 2nd ed. London: Churchill Livingstone; 2002.

[11] Smolinske SC. Handbook of drug, food and cosmetic excipients. Boca Raton, FL: CRC Press LLC; 1992.

[12] Anwer MK, Al-Shdefat R, Jamil Sh, Alam P, Abdel-Kader MS, Shakeel F. Solubility of bioactive compound hesperidin in six pure solvents at (298.15 to 333.15) K. J Chem Eng Data 2014; 59: 2065-9. http://dx.doi.org/10.1021/je500206w

[13] Shakeel F, Haq N, Siddiqui NA. Solubility and thermodynamic function of vanillin in ten different environmentally benign solvents. Food Chem 2015; 180: 244-8. http://dx.doi.org/10.1016/j.foodchem.2015.01.102

[14] Marcus Y. Solvent mixtures: Properties and selective solvation. New York, NY: Marcel Dekker, Inc.; 2002.

[15] Marcus Y. Preferential solvation of ibuprofen and naproxen in aqueous 1,2-propanediol. Acta Chim Sloven 2009; 56: 40-4.

[16] Marcus Y. Preferential solvation in mixed solvents. In: Smith PE, Matteoli E, O'Connell JP, editors. Fluctuation theory of solutions: Applications in chemistry, chemical engineering, and biophysics. Boca Raton, FL: CRC Press, Taylor & Francis Group 2013; p. 65-92. http://dx.doi.org/10.1201/b14014-4

[17] Cárdenas ZJ, Jiménez DM, Martínez F. Preferential solvation of ketoprofen in some co-solvent binary mixtures. J Solution Chem 2014; 43: 1904-15. http://dx.doi.org/10.1007/s10953-014-0255-3

[18] Marcus Y. On the preferential solvation of drugs and PAHs in binary solvent mixtures. J Mol Liq 2008; 140: 61-7. http://dx.doi.org/10.1016/j.molliq.2008.01.005

[19] Delgado DR, Martínez F. Preferential solvation of sulfadiazine, sulfamerazine and sulfamethazine in ethanol + water solvent mixtures according to the IKBI method. J Mol Liq 2014; 193: 152-9. http://dx.doi.org/10.1016/j.molliq.2013.12.021

[20] Jiménez DM, Cárdenas ZJ, Delgado DR, Martínez F, Jouyban A. Preferential solvation of methocarbamol in aqueous binary cosolvent mixtures at 298.15 K. Phys Chem Liq 2014; 52: 726-37. http://dx.doi.org/10.1080/00319104.2014.915755

[21] Peña MÁ, Delgado DR, Martínez F. Preferential solvation of acetaminophen in propylene glycol + water co-solvent mixtures. J Appl Sol Chem Model 2014; 3: 65-73.

[22] Delgado DR, Peña MÁ, Martínez F. Preferential solvation of some sulfonamides in propylene glycol + water solvent mixtures according to the IKBI and QLQC methods. J Solution Chem 2014; 43: 360-74. http://dx.doi.org/10.1007/s10953-014-0130-2

[23] Fedors RF. A method for estimating both the solubility parameters and molar volumes of liquids. Polym Eng Sci 1974; 14: 147-54. http://dx.doi.org/10.1002/pen.760140211

[24] Jiménez J, Manrique J, Martínez F. Effect of temperature on some volumetric properties for ethanol + water mixtures. Rev Colomb Cienc Quím Farm 2004; 33: 145-55.

[25] Jiménez J, Martínez F. Study of some volumetric properties of 1,2-propanediol + water mixtures at several temperatures. Rev Colomb Cienc Quím Farm 2005; 34: 46-57.

[26] Kamlet MJ, Taft RW. The solvatochromic comparison method. I. The beta-scale of solvent hydrogen-bond acceptor (HBA) basicities. J Am Chem Soc 1976; 98: 377-83. http://dx.doi.org/10.1021/ja00418a009

[27] Marcus Y. The properties of solvents. Chichester, UK: John Wiley & Sons; 1998.

[28] Holguín AR, Delgado DR, Martínez F, Marcus Y. Solution thermodynamics and preferential solvation of meloxicam in propylene glycol + water mixtures. J Solution Chem 2011; 40: 1987-99. http://dx.doi.org/10.1007/s10953-011-9769-0

[29] Barton AFM. Handbook of solubility parameters and other cohesion parameters. 2nd ed. BocaRaton, FL: CRC Press LLC; 1991.

[30] Delgado DR, Martínez F. Preferential solvation of some structurally related sulfonamides in 1-propanol + water co-solvent mixtures. Phys Chem Liq 2015; 53: 293-306. http://dx.doi.org/10.1080/00319104.2014.961191

Received on 30-04-2015 Accepted on 18-05-2015 Published on 16-06-2015

DOI: http://dx.doi.org/10.6000/1929-5030.2015.04.02.3