Bull. Chem. Soc. Ethiop. **2025**, 39(7), 1425-1435.
© 2025 Chemical Society of Ethiopia and The Authors
DOI: https://dx.doi.org/10.4314/bcse.v39i7.14

ISSN 1011-3924
Printed in Ethiopia
Online ISSN 1726-801X

PREFERENTIAL SOLVATION OF DIFENOCONAZOLE IN BINARY SOLVENT MIXTURES OF METHANOL AND ETHANOL IN WATER AT SEVERAL TEMPERATURES

Adel Noubigh[1*] and Manef Abderrabba[2]

[1]Center for Scientific Research and Entrepreneurship, Northern Border University, 73213, Arar, Saudi Arabia
[2]Université de Carthage, Institut Préparatoire aux Etudes Scientifiques et Techniques 99/UR/1201 Unité de Recherches de Physico – Chimie Moléculaire, 2070, La Marsa, Tunisie

(Received October 9, 2024; Revised February 3, 2025; Accepted March 13, 2025)

ABSTRACT. The present investigation used the inverse Kirkwood-Buff integrals technique to determine the best solvation parameters $\delta x_{1,\mathrm{DIF}}$ for DIF in two distinct alcoholic aqueous solutions, spanning a temperature range from 293.15 K to 323.15 K. The analysis demonstrated that the values of $\delta x_{1,\mathrm{DIF}}$ displayed a nonlinear trend concerning the composition of the co-solvent. The solvation parameters ($\delta x_{1,\mathrm{DIF}}$) for DIF in various aqueous solutions revealed nonlinear variations that were contingent upon the concentration of the co-solvent. Notably, positive values were recorded in mixtures with all compositions for methanol and $0.00 < x_1 < 0.33$-0.35 and $0.50 < x_1 < 1.00$ for ethanol. Conversely, DIF demonstrates a preference for alcohol as the solvent in aqueous mixtures. At 323.15 K, the methanol (1) + water (2) mixtures show the highest preferential solvation of DIF by alcohol, while the ethanol (1) + water (2) mixtures exhibit the lowest.

KEY WORDS: Difenoconazole, Binary solvents, Inverse Kirkwood–Buff integrals, Preferential solvation

INTRODUCTION

The concept of preferential solvation, which occurs when a drug molecule is more effectively surrounded by a particular solvent type within a mixed solvent system, provides essential understanding of these properties and can aid in the formulation design of pharmaceuticals [1-3]. The application of solvent mixtures has been a common practice in the cosmetic and pharmaceutical fields for many years; however, the organized application of physicochemical principles that shed light on the mechanisms of solubility fluctuations is still in its initial phases [4-6]. The inverse Kirkwood-Buff integrals (IKBI) approach is an effective theoretical tool for studying and measuring preferred solvation in systems with mixed solvents. Optimizing medication formulation techniques relies on a thorough knowledge of the interactions between solute and solvent molecules, which this methodology provides [6-9].

The focus of this article is on DIF, which is chemically designated as cis, trans-3-chloro-4-[4-methyl-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxo-lan-2-yl] phenyl 4-chlorophenyl ether according to its IUPAC nomenclature. Its chemical formula is $C_{19}H_{17}Cl_2N_3O_3$, with a molar mass of 406.26 g·mol^{-1}, and it is cataloged under the CAS number 119446-68-3. Their molecular structure is seen in Figure 1.

---

*Corresponding authors. E-mail: adel.noubigh@nbu.edu.sa; anoubigh@yahoo.fr

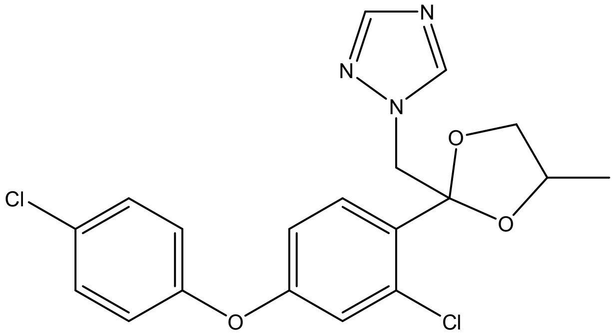


Figure 1. Molecular structure of difenoconazole.

The agricultural sector relies heavily on the broad-spectrum fungicide dienoconazole to stave off a wide range of fungal infections. As a fungicide, it is effective against fungus since it belongs to the triazole family and blocks the production of ergosterol, a component of fungal cell membranes. By doing so, plant fungal infections cannot thrive and spread [10, 11]. Various fungal infections, including rusts, blights, and powdery mildew, may be effectively treated with diflucanazole [12, 13]. Plants used for decoration, as well as grains, fruits, and vegetables, are typical recipients. The systemic nature of difenoconazole allows it to be taken up by the plant and then transported to other areas, where it is protected for a long time. Difenoconazole is recognized as an additive that proficiently improves the wettability of hydrophobic powders [14]. In wastewater treatment applications, it is utilized as a catalytic agent to expedite the decomposition of trace organic compounds and mitigate the toxicity of microorganisms [15, 16].

We still do not fully grasp the physicochemical factors that affect this drug's solubility in both water and alcohol-water solvents. Nevertheless, recent research has investigated its behavior in certain binary aqueous co-solvent combinations and established a correlation using the NRTL, λh, and Jouyban-Acree models [17].

On the other hand, this chemical has not undergone any research into its preferred solvation, which is the selective organization of solvent molecules around the drug molecules. One excellent technique for studying the preferred solvation of non-electrolytes in solvent mixtures is the IKBI approach [18]. This method exposes the local compositions of various components in the mix interacting with the solute.

Evaluation of DIF's preferred solvation in co-solvent solutions, including methanol (1) and water (2) and ethanol (1) and water (2), is the primary goal of this work. This investigation into the physicochemical behavior of DIF within binary solvent systems is informed by thermodynamic principles, which have been previously applied to a range of pharmaceuticals in aqueous co-solvent environments. The findings are articulated through the preferential solvation parameter ($\delta x_{1,\mathrm{DIF}}$), this measures the strength of the bond between the solute and the particular co-solvent in the mixture.

THEORETICAL ASPECTS

The IKBI method shines in finding the preferred solubilization of non-electrolyte pharmaceuticals in binary aqueous co-solvent combinations. It provides a relevant comparison with the mixes' global compositions by characterizing the local solvent composition that envelops the solute. This is the general form of the IKBI equations, as stated in [19, 20]:

$$G_{i,DIF} = \int_0^{r_{cor}} \left(g_{i,DIF} - 1\right) 4\pi r^2 \, dr \tag{1}$$

In this analysis, $g_{i,DIF}$ is identified as the pair correlation function for solvent molecules i in the co-solvent (1) and water (2) mixes around the solute DIF is identified as. The gap between the centers of the DIF molecules and the co-solvent (1) or water (2) molecules is described by the distance r. r_{cor} indicates a correlation distance at which $g_{i,DIF}$ ($r > r_{cor}$) is roughly 1. As a result, for all distances r that exceed r_{cor} and approach infinity, the integral's value is essentially zero.

The following mathematical equation may be used to compute the preferred solvation parameter for the solute DIF in binary solvent systems comprising cosolvents, such as methanol (1) + water (2) and ethanol (1) + water (2) [7, 9, 19, 21-23]:

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

Within the framework of the solute-to-alcohol local mole fraction (DIF), it is shown as $x_{1,\mathrm{DIF}}^{L}$, while the mole fraction of alcohol in the original binary solvent, without the solute, is denoted as x_1. A positive change in the mole fraction, $\delta x_{1,\mathrm{DIF}} > 0$ indicates that alcohol is more favorable for the solvation of the solute. Conversely, a negative change, $\delta x_{1,\mathrm{DIF}} < 0$ suggests that the solute prefers to be solvated by water.

The values of $\delta x_{1,\mathrm{DIF}}$ can be directly calculated from $G_{1,\mathrm{DIF}}$ and $G_{2,\mathrm{DIF}}$, which are obtained from the thermodynamic data of the solvents containing the dissolved drug (DIF). According to Newman's methodology, as shown in the appropriate Equations (3) and (4), the IKBI for each solvent component may be practically determined by using algebraic transformations.

$$G_{1,\mathrm{DIF}} = RTk_T - V_{\mathrm{DIF}} - x_2 V_2 D/Q \tag{3}$$

$$G_{2,\mathrm{DIF}} = RTk_T - V_{\mathrm{DIF}} + x_1 V_1 D/Q \tag{4}$$

where k_T represents the supplied values for the pure solvents and the mixture's composition, the isothermal compressibility of the co-solvent (1) + water (2) mixes is computed as an additive property. In these mixes, V_1 and V_2 represent the solvents' partial molar volumes, while V_{DIF} represents the solute's partial molar volume, 288.07 $\mathrm{cm^3/mol}$. Since the values of k_T depend on the mixture composition. This term is not known for all the systems studied. Additionally, given the minimal impact of RTk_T on the IKBI, the composition dependence of k_T will be approximated using Equation (5), where $k_{T,i}^{o}$ denotes the isothermal compressibility of the pure component *i* [7, 9, 19, 21-23].

$$k_T = x_1 k_{T,1}^{o} + x_2 k_{T,2}^{o} \tag{5}$$

The mathematical expression in Equation (6) defines the parameter D as the outcome of Gibbs free energy changes related to the transfer of the solute into various mixtures of water (1) and the co-solvent (2), as well as water alone. At the same time, Equation (7) represents the second derivative of the excess molar Gibbs free energy (G_{1+2}^{Exc}) concerning the water content in the solvent mixture [19, 24, 25].

$$D = \left(\frac{\partial \Delta_{tr} G_{\mathrm{DIF},2\to 1+2}^{o}}{\partial x_1}\right)_{T,P} \tag{6}$$

$$Q = RT + x_1 x_2 \left[\frac{\partial^2 G_{1+2}^{Exc}}{\partial x_2^2}\right]_{T,P} \tag{7}$$

A definition of the preferred solvation parameter based on the IKBI equation is as follows [7, 19, 26, 27]:

$$\delta x_{1,\mathrm{DIF}} = \frac{x_1 x_2 \left(G_{1,\mathrm{DIF}} - G_{2,\mathrm{DIF}}\right)}{x_1 G_{1,\mathrm{DIF}} + x_2 G_{2,\mathrm{DIF}} + V_{cor}} \tag{8}$$

The equation introduced by Marcus serves as the basis for calculating the correlation volume. V_{cor}[24, 28, 29].

$$V_{cor} = 2522.5\left[r_{DIF} + 0.1363\left(x^{L}_{1,DIF}\overleftarrow{V_1} + x^{L}_{2,DIF}\overleftarrow{V_2}\right)^{1/3} - 0.085\right]^{3} \quad (9)$$

$$r_{\mathrm{DIF}} = \sqrt[3]{\frac{3\times10^{21}V_{\mathrm{DIF}}}{4pN_{AV}}} \quad (10)$$

Precisely determining the correlation volume necessitates an iterative method, which demands that the mole fractions closely match the solutes. This process involves updating $\delta x_{1,\mathrm{DIF}}$ and V_{cor} according to Equations (2), (8), and (9), followed by iteratively calculating $x^{L}_{1,\mathrm{DIF}}$ until a stable value for V_{cor} is achieved.

RESULTS AND DISCUSSION

Using solubility data retrieved from the literature [17], the standard molar Gibbs energy of transfer for DIF was computed using Equation (11), moving from pure water (1) to different cosolvent (1) + water (2) combinations. The $\Delta_{tr}G^{o}_{\mathrm{DIF},2\to1+2}$ values were then fitted to fourth-degree polynomials, as shown in Eq. (12).

$$\Delta_{tr}G^{o}_{\mathrm{DIF},2\to1+2} = RTln\left(\frac{x_{\mathrm{DIF},2}}{x_{\mathrm{DIF},1+2}}\right) \quad (11)$$

$$\Delta_{tr}G^{o}_{\mathrm{DIF},2\to1+2} = A_0 + A_1x_1 + A_2x_1^2 + A_3x_1^3 + A_4x_1^4 \quad (12)$$

where A_0, A_1, A_2, A_3, and A_4 corresponds to the equation parameters. The D values were obtained by taking the first derivatives of polynomial models created using the binary solvent mixture compositions. In this computation, the organic cosolvent's mole fraction was varied methodically in increments of 0.05.

$$D = A_1 + 2A_2x_1 + 3A_3x_1^2 + 4A_4x_1^3 \quad (13)$$

Table 1. $\Delta_{tr}G^{o}_{\mathrm{DIF},2\to1+2}$ (kJ·mol^{-1}) of difenoconazole from pure water (2) to each cosolvents (1) + water (2) mixtures at various temperatures.

Methanol (1) + Water (2)				
$^{a}x_1$	293.15 K	303.15 K	313.15 K	323.15 K
0.000	0.000	0.000	0.000	0.000
0.059	-4.890	-4.943	-4.915	-5.051
0.123	-7.969	-8.076	-8.049	-8.291
0.194	-9.811	-9.974	-9.966	-10.295
0.273	-10.888	-11.103	-11.130	-11.528
0.360	-11.539	-11.818	-11.885	-12.353
0.458	-12.080	-12.407	-12.532	-13.058
0.567	-12.658	-13.040	-13.191	-13.811
0.692	-13.313	-13.751	-13.944	-14.605
0.835	-14.025	-14.517	-14.758	-15.480
1.000	-14.698	-15.236	-15.502	-16.309
Ethanol (1) + Water (2)				
0.000	0.000	0.000	0.000	0.000
0.042	-2.792	-2.830	-2.800	-2.792
0.089	-5.198	-5.263	-5.206	-5.198
0.144	-7.319	-7.473	-7.344	-7.319
0.207	-8.901	-8.980	-8.891	-8.901
0.281	-10.206	-10.252	-10.138	-10.206

0.370	-11.303	-11.354	-11.257	-11.303
0.477	-12.215	-12.361	-12.219	-12.215
0.610	-12.766	-12.758	-12.667	-12.766
0.779	-13.342	-13.500	-13.329	-13.342
1.000	-13.812	-13.731	-13.654	-13.812

[a]x_1 is the mole fraction of alcohol (1) in alcohol (1) + water (2) co-solvent mixtures free of DIF.

Quantification of molar Gibbs energies of mixing (Q values) G^{Exc}_{1+2} are required. Equations (14) and (15) may be used for the methanol + water and ethanol + water mixes, respectively, at 298.15 K. G^{Exc}_{1+2} values at 298.15 K for methanol + water and ethanol + water solutions, as reported by Marcus [19]. At temperatures other than 298.15 K, G^{Exc}_{1+2} values are calculated using Eq. (16), where H^{Exc}_{1+2} represents the excess molar enthalpy [19].

$$G^{Exc}_{1+2} = x_1(1-x_1)[1200 - 87(1-2x_1) + 330(1-2x_1)^2] \tag{14}$$

$$G^{Exc}_{1+2} = x_1(1-x_1)[2907 - 777(1-2x_1) + 494(1-2x_1)^2] \tag{15}$$

$$G^{Exc}_{1+2}(T_2) = G^{Exc}_{1+2}(T_1) - T\int_{T_1}^{T_2} H^{Exc}_{1+2}\, d\left(\frac{1}{T}\right) \approx \frac{T_2}{T_1} G^{Exc}_{1+2}(T_1) + H^{Exc}_{1+2}\left(1-\frac{T_2}{T_1}\right) \tag{16}$$

As also mentioned by Marcus [19], Equations (17) and (18) provide the formulation for H^{Exc}_{1+2} as well as ethanol and water combinations, respectively.

$$H^{Exc}_{1+2} = x_1(1-x_1)[-3102 + 2040(1-2x_1) - 2213(1-2x_1)^2] \tag{17}$$

$$H^{Exc}_{1+2} = x_1(1-x_1)[-1300 + 3567(1-2x_1) - 4971(1-2x_1)^2] \tag{18}$$

Based on the density data for methanol + water and ethanol + water mixtures at various temperatures, Mikhail [30] and Khattab [31] calculated the partial molar volumes of alcohol (1) + water (2) in these solvent mixtures.

The molar volume of the mixture is represented by V in Equation (21), whereas M_1 (g/mol) for MeOH is 32.04, M_1 (g/mol) for EtOH is 46.07, and M_2 (g/mol) for water is 18.02.

$$\bar{V}_1 = V + x_2\frac{dV}{dx_1} \tag{19}$$

$$\bar{V}_2 = V - x_1\frac{dV}{dx_1} \tag{20}$$

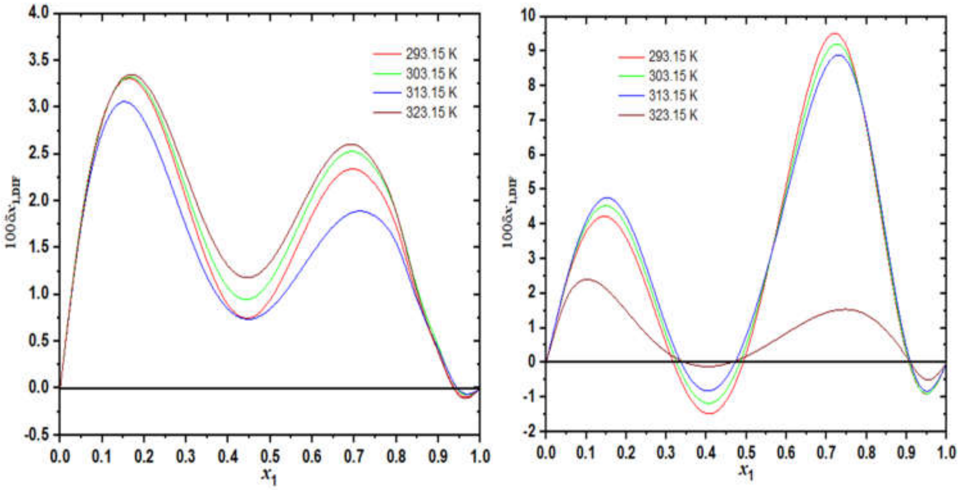
$$V = \frac{x_1M_1 + x_2M_2}{\rho} \tag{21}$$

For DIF, its molar volume can be calculated from its molar mass (406.26 g·mol^{-1}) and density (1.4101 g·cm^{-3}) as 288.107 cm^3.mol^{-1} [17]. The mixtures are considered similar to the pure substance when the partial molar volume of DIF is excluded [32]. Using Equation (10) and this volume value, the solute radius value (r_{DIF}) is computed as 0.4852 nm.

Except for ethanol + water mixes at compositions of $0.95 \le x_1 \le 0.10$, the $G_{1,\mathrm{DIF}}$ and $G_{2,\mathrm{DIF}}$ values for DIF are negative throughout all solvent compositions and cosolvent systems. This drug molecule seems to have an affinity for water and all of the investigated cosolvents when its $G_{2,\mathrm{DIF}}$ and DIF values are positive within this range.

The computed, V_{cor} and, $\delta x_{1,\mathrm{DIF}}$ values for the two solvent mixtures at 293.15 K, 303.15 K, 313.15 K, and 323.15 K are shown in Tables 2 and 3, respectively. Additionally, Figure 2 shows the relationship between $\delta x_{1,\mathrm{DIF}}$ and solvent composition, highlighting the nonlinear variation of $\delta x_{1,\mathrm{DIF}}$ with changes in the co-solvent content in each water-based mixture.

Compared to pure water, $\delta x_{1,\mathrm{DIF}}$ increases as the fraction of methanol (1) or ethanol (1) in water (2) is increased, with the increase continuing at molar fractions of 0.10 and 0.10–0.15, respectively, the first maxima are accrued. The second maxima of $\delta x_{1,\mathrm{DIF}}$ is accrued at the composition of methanol x_1 = 0.70 and ethanol x_1 = 0.75. Figure 2 illustrates this trend, while Tables 2 and 3 provide detailed information.



Methanol (1) + Water (2) Ethanol (1) + Water (2)

Figure 2. $\delta x_{1,\mathrm{DIF}}$ values of difenoconazole (DIF) from water to alcohol (1) + water (2) mixtures at four temperatures.

Table 2. V_{cor} and $\delta x_{1,\mathrm{DIF}}$ values for difenoconazole in methanol (1) + water (2) co-solvent mixtures at several temperatures.

$^ax_1$	V_{cor} (cm^3.mol^{-1})				100 $\delta x_{1,\mathrm{DIF}}$			
	293.15 K	303.15 K	313.15 K	323.15 K	293.15 K	303.15 K	313.15 K	323.15 K
0	1098	1100	1101	1103	0.000	0.000	0.000	0.000
0.05	1134	1136	1138	1141	1.793	1.780	1.737	1.757
0.1	1167	1168	1171	1175	2.864	2.857	2.737	2.846
0.15	1196	1198	1200	1205	3.290	3.298	3.059	3.315
0.2	1222	1225	1227	1233	3.185	3.216	2.857	3.271
0.25	1247	1250	1252	1259	2.698	2.761	2.339	2.863
0.3	1270	1274	1276	1285	2.016	2.120	1.723	2.277
0.35	1294	1298	1302	1310	1.349	1.496	1.185	1.702
0.4	1318	1323	1328	1336	0.887	1.068	0.843	1.303
0.45	1345	1351	1356	1365	0.751	0.950	0.738	1.182
0.5	1374	1380	1385	1395	0.948	1.150	0.851	1.349
0.55	1404	1410	1415	1426	1.374	1.570	1.116	1.725
0.6	1434	1441	1446	1458	1.855	2.047	1.443	2.165
0.65	1464	1472	1477	1489	2.219	2.409	1.730	2.503
0.7	1493	1501	1507	1520	2.341	2.527	1.884	2.602
0.75	1520	1529	1536	1548	2.170	2.341	1.834	2.388
0.8	1546	1556	1564	1575	1.724	1.866	1.546	1.871
0.85	1571	1581	1590	1601	0.964	1.055	0.930	1.023
0.9	1596	1606	1616	1626	0.384	0.442	0.415	0.380
0.95	1622	1632	1643	1653	-0.066	-0.035	-0.025	-0.083
1	1651	1662	1673	1684	0.000	0.000	0.000	0.000

$^a x_1$ is the mole fraction of methanol (1) in methanol (1) + water (2) co-solvent mixtures free of difenoconazole.

Table 3. V_{cor} and $\delta x_{1,\mathrm{DIF}}$ values for difenoconazole in ethanol (1) + water (2) co-solvent mixtures at several temperatures.

$^a x_1$	V_{cor} (cm^3.mol^{-1})				100 $\delta x_{1,\mathrm{DIF}}$			
	293.15 K	303.15 K	313.15 K	323.15 K	293.15 K	303.15 K	313.15 K	323.15 K
0	1098	1099	1102	1105	0.000	0.000	0.000	0.000
0.05	1169	1172	1176	1174	2.294	2.349	2.365	1.831
0.1	1232	1237	1242	1230	3.790	3.981	4.101	2.399
0.15	1284	1291	1298	1277	4.226	4.538	4.768	2.125
0.2	1326	1334	1341	1320	3.598	3.945	4.216	1.489
0.25	1360	1368	1376	1363	2.197	2.500	2.756	0.826
0.3	1392	1400	1408	1407	0.525	0.779	1.032	0.305
0.35	1427	1434	1444	1453	-0.853	-0.594	-0.296	-0.009
0.4	1469	1476	1487	1500	-1.475	-1.175	-0.819	-0.114
0.45	1519	1526	1538	1548	-1.098	-0.785	-0.427	-0.037
0.5	1579	1585	1596	1597	0.293	0.526	0.787	0.182
0.55	1645	1649	1659	1646	2.513	2.559	2.628	0.497
0.6	1714	1716	1724	1695	5.195	4.999	4.830	0.853
0.65	1782	1782	1789	1744	7.755	7.372	7.011	1.192
0.7	1840	1840	1847	1792	9.359	8.976	8.582	1.445
0.75	1882	1884	1892	1838	9.130	8.955	8.737	1.535
0.8	1905	1910	1920	1882	6.781	6.838	6.873	1.376
0.85	1918	1924	1935	1924	3.242	3.349	3.498	0.903
0.9	1935	1942	1953	1965	0.245	0.285	0.406	0.155
0.95	1969	1978	1989	2008	-0.918	-0.908	-0.834	-0.501
1	2022	2034	2048	2065	0.000	0.000	0.000	0.000

$^a x_1$ is the mole fraction of ethanol (1) in ethanol (1) + water (2) co-solvent mixtures free of difenoconazole.

Figure 2 and Tables 2 and 3 show that the $\delta x_{1,\mathrm{DIF}}$ values increase when alcohols are added to water and then decrease twice, relative to their values in pure water. The maximum increase occurs at molar fractions of 0.10 and 0.70 for MeOH (1) + water (2) and at 0.10–0.15 and 0.75 for EtOH (1) + water (2) across all temperatures. Based on the preferential solvation results, it can be inferred that DIF behaves as a Lewis acid in all compositions of aqueous alcohol mixtures, interacting with alcohol molecules due to their higher basicity compared to water. This is supported by the Kamlet-Taft hydrogen bond acceptor parameters (β): 0.66 for MeOH (1), 0.75 for EtOH (1), and 0.47 for water (2) [33]. As a result, DIF shows a stronger preference for alcohol (1) over water. In the EtOH (1) + water (2) mixtures with compositions $0.00 < x_1 < 0.33$-0.35 and $0.50 < x_1 < 1.00$ across the studied temperatures, the local mole fraction of ethanol exceeds its bulk mole fraction and decreases as the temperature increases. This proves that a co-solvent mechanism may increase DIF solubility by causing water to lose its structured hydrogen-bond network around the drug's nonpolar areas. Although the co-solvent mixture did not reach the theoretical maximum solubility, mixtures with a polarity similar to that of DIF exhibited the most significant solvation, indicating that this factor may have contributed to the observed effects. The co-solvents solubility in dissolving the solute may be correlated with its capability to disturb the ordered arrangement of water molecules around the nonpolar regions of DIF. This improved solubility is most noticeable in methanol and water mixtures at $x_1 = 0.10$ and 0.70 and ethanol and water mixtures at, $x_1 = 0.10$-015 and 0.75 for methanol. Bear in mind that uncertainty propagation, not selective solvation, might lead to absolute values lower than 1×10^{-2} [18, 34].

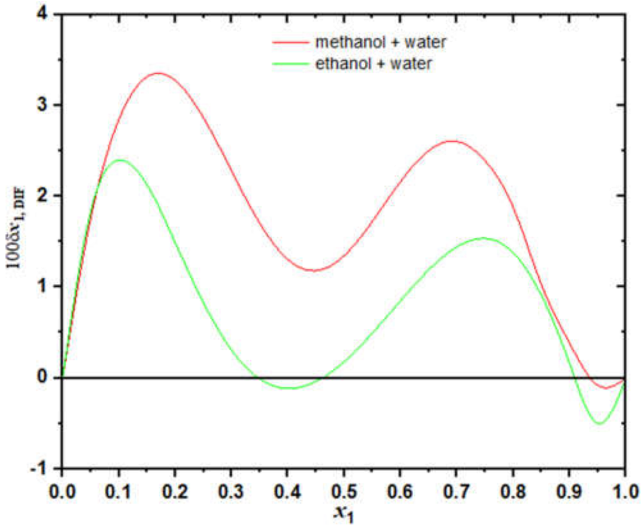


Figure 3**.** $\delta x_{1,\mathrm{BIF}}$ values of DIF in alcohol (1) + water (2) mixtures at 323.15 K.

Figure 3 shows a comparison of two solvent mixes, ethanol (1) + water (2) and methanol (1) + water (2), to show the selective solvation behavior of DIF at 323.15 K. Both mixes exhibit comparable levels of alcohol-mediated preferential solvation of DIF, according to the data; however, the methanol combination exhibits the highest solvation level, followed by ethanol. The solvation maxima occur at different cosolvent ratios: in the methanol + water mixture, x_1 is 0.15, and x_1 is 0.70 resulting in a $\delta x_{1,\mathrm{DIF}}$ of 3.315×10^{-2} and $\delta x_{1,\mathrm{DIF}}$ of 2.602×10^{-2}, respectively , while in the ethanol + water mixture, x_1 also presents two maxima at 0.10 and = 0.75 resulting in a $\delta x_{1,\mathrm{DIF}}$ of 2.399×10^{-2} and $\delta x_{1,\mathrm{DIF}}$ of 1.535×10^{-2}, respectively.

Preferred solvation can be effectively analyzed using the most straightforward model proposed by Yalkowsky and Roseman [35]. Additionally, another approach involves algebraic mixing to determine a drug's solubility in co-solvent mixtures. These methods provide different perspectives for examining semi-polar molecules in binary solvent systems.

$$ln\, x_{\mathrm{DIF}-(1+2)} = x_1 ln x_{DIF-1} + x_2 ln x_{\mathrm{DIF}-2} \qquad (22)$$

In Equation (22), $x_{\mathrm{DIF-2}}$ represents the solubility of DIF in pure water (2), while x_1 and x_2 denote the solubility of the drug in the absence of DIF. Additionally, $x_{\mathrm{DIF-(1+2)}}$ indicates how well DIF dissolves in the specific co-solvent combination that comprises components 1 and 2. Figure 4 depicts the experimental solubilities of DIF at 323.15 K, which deviates positively from the predictions from Equation (22) for both co-solvent systems. The solubility pattern reported with the analgesic chrysin is comparable to this behavior in methanol (1) + water (2) and ethanol (1) + water (2) combinations [6].

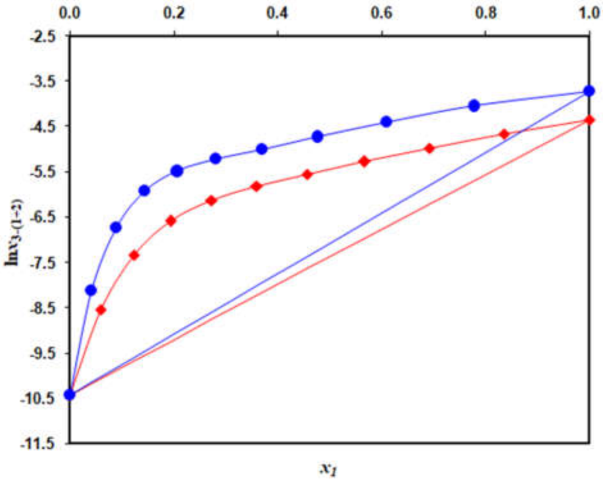


Figure 4. $ln\ x_{\mathrm{DIF-(1+2)}}$ in methanol + water (●) and ethanol + water (◆) mixtures as a function of mole fraction of co-solvents at 323.15 K.

CONCLUSION

We used the IKBI technique to determine the equilibrium solubility of difenoconazole (DIF) in two distinct combinations at various temperatures: (1) methanol + (2) water and (2) ethanol + (2) water. The results provide numerical information on the methanol or ethanol mole fractions and water around DIF. Results showed that difenoconazole dissolved more effectively at all temperatures in combinations containing moderate to high alcohol compositions (1) whether the alcohol was methanol or ethanol. On the other hand, DIF prefers alcohol as a solvent in aqueous mixtures. Moreover, at 323.15 K, the methanol (1) + water (2) combinations exhibit the most preferred solvation of DIF by alcohol, while at 323.15 K, the ethanol (1) + water (2) mixtures exhibit the smallest.

ACKNOWLEDGMENT

The authors extend their appreciation to Northern Border University, Saudi Arabia, for supporting this work through project number (NBU-CRP-2025-1497).

REFERENCES

1. Mantri, R.; Sanghvi, R. *Solubility of Pharmaceutical Solids* in *Developing Solid Oral Dosage Forms*, Elsevier: Amsterdam; **2017**; pp. 3-22.
2. Marcus, Y. Preferential solvation of drugs in binary solvent mixtures. *J. Pharm. Anal. Acta* **2017**, 8, 4172.
3. Padervand, M.; Naseri, S.; Boroujeni, H.C. Preferential solvation of pomalidomide, an anticancer compound, in some binary mixed solvents at 298.15 K. *Chin. J. Chem. Eng.* **2020**, 28, 2626-2633.

4. Yu, Z.; Wang, Y.; Zhu, M.; Zhou, L. Measurement and correlation of solubility and thermodynamic properties of vinpocetine in nine pure solvents and (ethanol + water) binary solvent. *J. Chem. Eng. Data* **2019**, 64, 150-160.
5. Li, X.; Cheng, C.; Cong, Y.; Du, C.; Zhao, H. Preferential solvation of pioglitazone hydrochloride in some binary co-solvent mixtures according to the inverse Kirkwood–Buff integrals method. *J. Chem. Thermodyn.* **2017**, 110, 218-226.
6. Noubigh, A.; Abderrabba, M. Preferential solvation of 5,7-dihydroxyflavone (chrysin) in aqueous co-solvent mixtures of methanol and ethanol. *Phys. Chem. Liq.* **2022**, 60, 931-942.
7. Li, X.; Wang, M.; Du, C.; Cong, Y.; Zhao, H. Preferential solvation of rosmarinic acid in binary solvent mixtures of ethanol + water and methanol + water according to the inverse Kirkwood–Buff integrals method. *J. Mol. Liq.* **2017**, 240, 56-64.
8. Chen, G.; Chen, J.; Cheng, C.; Cong, Y.; Du, C.; Zhao, H. Solubility and preferential solvation of econazole nitrate in binary solvent mixtures of methanol, ethanol and 1,4-dioxane in water. *J. Chem. Thermodyn.* **2017**, 111, 228-237.
9. Chen, J.; Chen, G.; Cong, Y.; Du, C.; Zhao, H. Solubility modelling and preferential solvation of paclobutrazol in co-solvent mixtures of (ethanol, n-propanol and 1,4-dioxane)+water. *J. Chem. Thermodyn.* **2017**, 112, 249-258.
10. Zhang, Z.; Jiang, W.; Jian, Q.; Song, W.; Zheng, Z.; Wang, D.; Liu, X. Residues and dissipation kinetics of triazole fungicides difenoconazole and propiconazole in wheat and soil in Chinese fields. *Food Chem.* **2015**, 168, 396-403.
11. Guo, C.; Li, J.-z.; Guo, B.-y.; Wang, H.-l. Determination and safety evaluation of difenoconazole residues in apples and soils. *Bull. Environ. Contam. Toxicol.* **2010**, 85, 427-431.
12. Dong, F.; Li, J.; Chankvetadze, B.; Cheng, Y.; Xu, J.; Liu, X.; Li, Y.; Chen, X.; Bertucci, C.; Tedesco, D.; Zanasi, R.; Zheng, Y. Chiral triazole fungicide difenoconazole: Absolute stereochemistry, stereoselective bioactivity, aquatic toxicity, and environmental behavior in vegetables and soil. *Environ. Sci. Technol.* **2013**, 47, 3386-3394.
13. Souza, L.P.; Faroni, L.R.D.A.; Heleno, F.F.; Pinto, F.G.; Queiroz, M.E.L.R.; Prates, L.H.F. Difenoconazole and linuron dissipation kinetics in carrots under open-field conditions. *Ecotoxicol. Environ. Saf.* **2019**, 168, 479-485.
14. Ge, Y.; Li, D.; Li, Z.J.B. Effects of lignosulfonate structure on the surface activity and wettability to a hydrophobic powder. *BioRes.* **2014**, 9, 7119-7127.
15. Ma, X.Y.; Wang, Y.; Dong, K.; Wang, X.C.; Zheng, K.; Hao, L.; Ngo, H.H. The treatability of trace organic pollutants in WWTP effluent and associated biotoxicity reduction by advanced treatment processes for effluent quality improvement. *Water Res.* **2019**, 159, 423-433.
16. Verro, R.; Finizio, A.; Otto, S.; Vighi, M. Predicting pesticide environmental risk in intensive agricultural areas. II: Screening level risk assessment of complex mixtures in surface waters. *Environ. Sci. Technol.* **2009**, 43, 530-537.
17. Li, Z.; Huang, C. Solubility measurement and calculation of difenoconazole in several solvents at 278.15 to 323.15 K. *J. Chem. Eng. Data* **2023**, 68, 2471-2482.
18. Marcus, Y. Solubility and solvation in mixed solvent systems. *Pure Appl. Chem.* **1990**, 62, 2069-2076.
19. Marcus, Y. *Solvent Mixtures: Properties and Selective Solvation*; Marcel Dekker: New York, **2002**.
20. Marcus, Y. *Preferential Solvation in Mixed Solvents* in *Fluctuation Theory of Solutions: Applications in Chemistry, Chemical Engineering, and Biophysics*, Smith, P.E.; Matteoli, E.; O'Connell, J.P. (Eds.), CRC Press: Boca Raton; **2013**.

21 Li, X.; Liu, Y.; Cao, Y.; Cong, Y.; Farajtabar, A.; Zhao, H. Solubility modeling, solvent effect, and preferential solvation of thiamphenicol in cosolvent mixtures of methanol, ethanol, N,N-dimethylformamide, and 1,4-dioxane with water. *J. Chem. Eng. Data* **2018**, 63, 2219-2227.

22. Delgado, D.R.; Martínez, F. Solubility and preferential solvation of sulfadiazine in methanol+water mixtures at several temperatures. *Fluid Phase Equilib.* **2014**, 379, 128-138.
23. Noubigh, A.; Abderrabba, M. Thermodynamic modeling of the solubility and preferential solvation of the natural product vanillic acid in some aqueous mixtures of alcohols at different temperatures. *J. Chem. Eng. Data* **2022**, 67, 2675-2686.
24. Marcus, Y. On the preferential solvation of drugs and PAHs in binary solvent mixtures. *J. Mol. Liq.* **2008**, 140, 61-67.
25. Cristancho, D. M.; Jouyban, A.; Martínez, F. Solubility, solution thermodynamics, and preferential solvation of piroxicam in ethyl acetate+ethanol mixtures. *J. Mol. Liq.* **2016**, 221, 72-81.
26. Li, W.; Xing, R.; Zhu, Y.; Farajtabar, A.; Zhao, H. Solvent effect, transfer property and preferential solvation of artesunate in aqueous co-solvent mixtures of some alcohols. *Phys. Chem. Liq.* **2021**, 59, 454-466.
27. Li, X.; Feng, S.; Farajtabar, A.; Zhang, N.; Chen, G.; Zhao, H. Solubility modelling, solvent effect and preferential solvation of 6-chloropurine in several aqueous co-solvent mixtures between 283.15 K and 328.15 K. *J. Chem. Thermodyn.* **2018**, 127, 106-116.
28. Marcus, Y. *The Properties of Solvents*, John Wiley & Sons: Chichester; **1998**.
29. Marcus, Y. The properties of organic liquids that are relevant to their use as solvating solvents. *Chem. Soc. Rev.* **1993**, 22, 409-416.
30. Mikhail, S.Z.; Kimel, W.R. Densities and viscosities of methanol-water mixtures. *J. Chem. Eng. Data* **1961**, 6, 533-537.
31. Khattab, I.S.; Bandarkar, F.; Fakhree, M.A.A.; Jouyban, A. Density, viscosity, and surface tension of water+ethanol mixtures from 293 to 323K. *Korean J. Chem. Eng.* **2012**, 29, 812-817.
32. Jouyban, A.; Acree, W.E.; Martínez, F. Modeling the solubility and preferential solvation of gallic acid in cosolvent plus water mixtures. *J. Mol. Liq.* **2016**, 224, 502-506.
33.Kamlet, M.J.; Taft, R.W. The solvatochromic comparison method. I. The beta-scale of solvent hydrogen-bond acceptor (HBA) basicities. *J. Am. Chem. Soc.* **1976**, 98, 377-383.
34. Martínez, F.; Jouyban, A.; Acree Jr, W.E. Solubility of phenobarbital in aqueous cosolvent mixtures revisited: IKBI preferential solvation analysis. *J. Phys. Chem.* **2017**, 55, 432-443.
35. Yalkowsky, S.H.J. *Techniques of Solubilization of Drugs*, Marcel Dekker: New York; **1981**.