ImmunoAnalysis, 2024, 4, 5
doi:10.34172/ia.4088
https://ia.tbzmed.ac.ir/

Original Article

Preferential Solvation of Cyclosporin in Aqueous Mixtures of Some Polymeric Cosolvents

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ARTICLE INFO

Article History:
Received: April 16, 2024
Accepted: June 29, 2024
ePublished: August 1, 2024

Keywords:
Cyclosporin, (Polymeric solvent + water) mixtures, Inverse Kirkwood-Buff integrals, Preferential solvation

Abstract

Background: Cyclosporin is a cyclic peptide-drug used as immunosuppressant for the prophylaxis of transplant rejection whose physicochemical properties in mixed aqueous solvent systems is still not well understood. The preferential solvation parameters of cyclosporin in aqueous binary mixtures of diethylene glycol monoethyl ether (DEGME), polyethylene glycol 200 (PEG 200) and polyethylene glycol 400 (PEG 400) were computed.

Methods: Reported mole fraction solubilities of cyclosporin in DEGME-aqueous mixtures, PEG 200-aqueous mixtures, and PEG 400-aqueous mixtures were processed by following the inverse Kirkwood-Buff integrals (IKBI) method as suggested by Marcus and Ben-Naim using some thermodynamic parameters reported in the literature for these aqueous-polymeric mixtures at 298.15 K.

Results: It is observed that cyclosporin is sensitive to preferential solvation effects in these aqueous-polymeric binary solvent systems. The preferential solvation parameter by DEGME ($\delta x_{1,3}$) is negative in water-rich mixtures but positive in mixtures of $0.12 < x_1 < 1.00$. It is conjecturable that hydrophobic hydration around the non-polar methyl and methylene groups of this drug that could be present in water-rich mixtures can significantly impact the drug solvation. Otherwise, in mixtures of $0.12 < x_1 < 1.00$ in DEGME-aqueous mixtures, as well as in almost all the mixtures with PEGs, the preferential solvation by polymeric cosolvents could be due to the acidic behavior of cyclosporin in front of ether and hydroxyl oxygen atoms of these polymeric cosolvents.

Conclusion: Cyclosporin is preferentially solvated by the polymeric solvents in almost all the studied mixtures of these aqueous-polymeric binary solvent systems.

Introduction

Cyclosporin (condensed formula $C_{62}H_{111}N_{11}O_{12}$, molar mass 1202.64 g·mol^{-1}, CAS Number: 59865-13-3, PubChem CID 5284373, molecular structure shown in Figure 1), is a lipophilic cyclic polypeptide of 11 amino acids produced by the fungus *Beauveria nivea*, also known as *Tolypocladium inflatum*, is an immunosuppressant drug which binds with high affinity to an immunophilin termed cyclophilin. The complex cyclosporin-cyclophilin specifically inhibits calcineurin, a calcium- and calmodulin-dependent phosphatase distributed in all cellular compartments. The blockage of calcineurin prevents signal transduction of the nuclear factor of activated T-cells (NF-AT) which impairs gene transcription of interleukin (IL)-4 and CD40 ligand necessary for B-cell activation and those required for T-cell activation including IL-2 and interferon gamma. In this way, cyclosporin inhibits the first phase of T-cell activation leading to a reduced proliferation of T helper lymphocytes. It is also known that cyclosporin inhibits CD4 + CD25 + regulatory T cells, which may obstruct the ability for host immune tolerance.[1-3]

Cyclosporin is used for the prophylaxis of transplant rejection, or in the treatment of graft rejection in patients previously treated with other immunosuppressants. It is also used in severe forms of immune diseases as uveitis, atopic dermatitis, psoriasis, amyotrophic lateral sclerosis, inflammatory bowel disease or rheumatoid arthritis when conventional therapy is ineffective or inappropriate. It is also useful in nephrotic syndrome and in other autoimmune component diseases like aplastic anemia,

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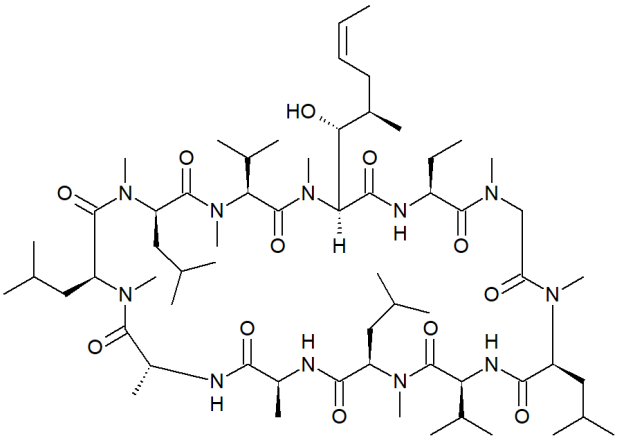

Figure 1. Molecular structure of cyclosporin

asthma, Behçet's syndrome, chronic active hepatitis, multiple sclerosis, myasthenia gravis, polymyositis, and Kawasaki disease.[4-6] Moreover, recently this drug was investigated for the treatment of COVID-19.[7]

From a solid-conglomerate point of view this drug is hydrophobic and the absorption can be affected by first-pass metabolism, mode of administration, formulation, and drug interactions. Its oral bioavailability ranges from 30% to 90% and exhibits a 95% lipoprotein bounding. Cyclosporin acts as a substrate and inhibitor of P-glycoprotein and it is metabolized by the CYP3A enzyme system in the liver, the gastrointestinal tract and kidney. Therefore, when cyclosporin is administered with inhibitors of both CYP3A4 and P-glycoprotein its bioavailability is improved leading to increased cyclosporin concentrations. In patients with normal hepatic function, the average half-life ranges from 16 to 27 hours, but can vary from 10-40 hours.[3,8]

Cyclosporin is available in several formulations: as an oral solution (100 mg/mL) or liquid-filled capsules (strength 25-50 and 100 mg); as an ophthalmic emulsion (strength 0.05%) and ophthalmic solution (strength 0.09% and 0.1%), and as a sterile solution (50 mg/mL) that must be diluted in 0.9% sodium chloride or 5% dextrose for intravenous slow infusion. The commercially available oral formulations of cyclosporin differ in their bioavailability, and patients should not be transferred from one to another without appropriate monitoring.[3]

The dosage and routes of administration depend on the indication. Intravenous route is preferred for kidney transplant reject prophylaxis, for treatment of graft-versus-host disease, acute severe ulcerative colitis, and Kawasaki disease. The oral route is used for other solid organ transplant reject prophylaxis and immune diseases. The ophthalmic route is used only for uveitis and keratoconjunctivitis.[4,5]

Adverse effects of cyclosporin are many and involves multiple vital organs. The most common is nephrotoxicity due to intense renal vasoconstriction, which reduces glomerular filtration rate. Hypertension and arrhythmia are also frequent. Metabolic and endocrinological adverse effects include hypertrichosis, hypomagnesaemia, hyperkalemia, dyslipidemia and gynecomastia. As cyclosporin may cause immunosuppression, patients are at increased risk of developing bacterial, viral, fungal, and protozoal infections. To reduce the most important adverse effects, monitoring serum levels of cyclosporin is mandatory. It is also important to check serum creatinine/BUN, serum bilirubin and serum electrolytes.[4,5]

Owing the low solubility of cyclosporin in neat water, for improving its apparent solubility several procedures have been proposed in the literature, as follows: solubilization with d-alphatocopheryl-polyethylene-glycol-1000 succinate[9]; solubilization by cosolvency with ethanol, propylene glycol, polyethylene glycol (PEG 400), glycofurol and glycerin, micellization with cremophor, tween 80 and tween 20, and complexation with α-cyclodextrin and hydroxypropyl β-cyclodextrin[10]; micellization with sodium cholate/lecithin-mixed micelles;[11] complexation with mixed α-cyclodextrin and hydroxypropyl-β-cyclodextrin,[12] liposomes and other heterogeneous systems[13]; self-microemulsifying systems[14]; polymeric nanospheres[15]; microspheres based on αβ-cyclodextrins polymers[16]; microfiber obtained by electrospinning[17]; liposomes and other colloidal systems[18]; and drug-loaded nanofibers.[19] In particular, dosage forms intended for ophthalmic administration has specially studied.[20-22]

Regarding molecular dispersion-solubility studies of cyclosporin in water the investigations by Ismailos et al[23] and Molpeceres et al[24] demonstrated some non-common behaviors involving drug solubility diminishing with temperature-arising. More recently, Berton et al reported the cyclosporin solubility in six ionic liquids at 25 and 100 °C;[25] whereas, Ha et al reported the solubility of this drug at 25.0 °C in 20 mono-solvents, namely, acetone, acetonitrile, 1-butanol, chloroform, diethylene glycol monoethyl ether (DEGME), dichloromethane, N,N-dimethylformamide, dimethyl sulfoxide, ethanol, glycerol, methanol, N-methyl-2-pyrrolidone, 1-propanol, 2-propanol, propylene glycol, PEG 200, PEG 300, PEG 400, tetrahydrofuran, and water, as well as in some aqueous-polymeric cosolvent mixtures.[26]

As indicated above the physicochemical information about cyclosporin dispersed at molecular level in multi-component solvent systems is not complete as required for optimum liquid pharmaceutical dosage forms design. From practical and theoretical points of view, the drug behavior in binary or ternary cosolvent mixtures is frequently studied for improving substances purification and pharmaceutical preformulation stages.[27-30]

Owing the low solubility of cyclosporin in neat water, some binary aqueous cosolvent mixtures, involving the following polymeric cosolvents: DEGME (also known as carbitol and transcutol), PEG 200, PEG 300 and PEG 400 have been studied to increase its solubility.[26] It is important to note that DEGME, PEG 200 and PEG 400 are common polymeric cosolvents used for several liquid medicines including injectable products.[31,32] For this

reason, the main purposes of this communication were evaluation the effect of mixtures polarity on cyclosporine solubility as well as reporting the preferential solvation of cyclosporin by cosolvents and water in some {polymeric cosolvent + water} mixtures at 298.15 K based on literature solubility values and some thermodynamic properties by means of the inverse Kirkwood-Buff integrals (IKBI).[33-35] The results are expressed in terms of changing the preferential solvation parameter ($\delta x_{1,3}$) of cyclosporin (compound 3) by the respective cosolvent (component 1, i.e. polymeric cosolvent DEGME, PEG 200 or PEG 400) regarding the mixtures composition.

Methods and Computation

Physicochemical properties of cyclosporin dissolutions, involving cosolvency effects and preferential solvation, were calculated as reported earlier in the literature for other organic compounds in similar solvent mixtures as shown below.[36,37] All computations were performed with MS Excel® and TableCurve 2D v.5.01.

Results and Discussion

Effect of polarity on the cyclosporin solubility in aqueous mixtures

Mole fraction solubility of cyclosporin in aqueous binary mixtures of polymeric cosolvents is reported in the research article written by Ha et al.[26] Thus, Figure 2 allows the comparison of mole fraction solubilities of this drug in the aqueous mixtures of polymeric cosolvents DEGME, PEG 200 and PEG 400 as function of the Hildebrand solubility parameter of the mixtures free of drug (δ_{1+2}/ MPa$^{1/2}$) at 298.15 K. It is noteworthy that δ_{1+2} values were calculated assuming additive behavior as shown in Eq. (1).[27-29] Solubility parameters of DEGME, PEG 200, PEG 400 and water are 22.3, 21.6, 24.3 and 47.8 MPa$^{1/2}$, respectively.[38,39]

$$\delta_{1+2} = \sum_{i=1}^{2} f_i \cdot \delta_i \qquad (1)$$

As observed in all cases, the maximum solubility is observed in pure polymeric cosolvents. Moreover, cyclosporin solubility is similar in DEGME and PEG 200 mixtures and lower in aqueous-PEG 400 mixtures.

Table 1 summarizes the apparent Gibbs energies of dissolution at 298.15 K calculated by using Eq. (2).[40] As observed all $\Delta_{soln}G°$ are positive and diminish with the polymeric cosolvent proportion, regardless the cosolvent that demonstrates the cyclosporin preference by semi-polar media.

$$\Delta_{soln}G^{o} = -RT \ln x_3 \qquad (2)$$

Preferential solvation of cyclosporin by mixtures components

The preferential solvation parameters of cyclosporin (identified here as compound 3) by polymeric cosolvent molecules, namely, DEGME, PEG 200 or PEG 400 (identified here as compound 1) molecules in the different {polymeric cosolvent (1) + water (2)} mixtures ($\delta x_{1,3}$), are defined as[33-35]:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \qquad (3)$$

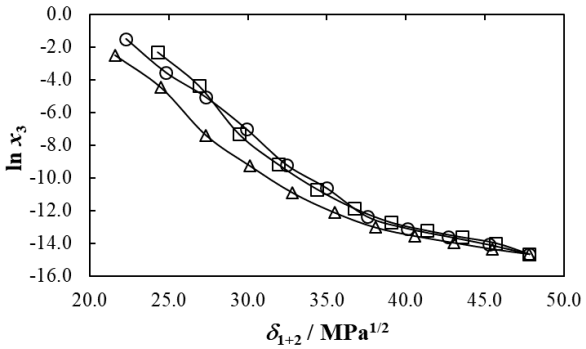

Figure 2. Logarithmic mole fraction solubility of cyclosporin as function of the Hildebrand solubility parameter in some aqueous-polymeric cosolvent mixtures at T = 298.15 K. ○: DEGME (1) + water (2); □: PEG 200 (1) + water (2); Δ: PEG 400 (1) + water (2)

Table 1. Apparent Gibbs energies of dissolution and transfer of cyclosporin in some {polymeric cosolvent (1) + water (2) mixtures at T = 298.15 K

w_1	DEGME + water			PEG 200 + water			PEG 400 + water		
	x_1	$\Delta_{soln}G°$ / kJ·mol^{-1}	$\Delta_{tr}G°$ / kJ·mol^{-1}	x_1	$\Delta_{soln}G°$ / kJ·mol^{-1}	$\Delta_{tr}G°$ / kJ·mol^{-1}	x_1	$\Delta_{soln}G°$ / kJ·mol^{-1}	$\Delta_{tr}G°$ / kJ·mol^{-1}
0.00	0.0000	36.35	0.00	0.0000	36.35	0.00	0.0000	36.35	0.00
0.10	0.0147	34.91	-1.43	0.0099	34.68	-1.67	0.0050	35.58	-0.76
0.20	0.0325	33.70	-2.65	0.0220	33.78	-2.57	0.0111	34.63	-1.72
0.30	0.0544	32.47	-3.88	0.0372	32.78	-3.57	0.0189	33.62	-2.73
0.40	0.0822	30.66	-5.68	0.0566	31.54	-4.80	0.0291	32.30	-4.04
0.50	0.1184	26.36	-9.99	0.0826	29.42	-6.92	0.0431	30.06	-6.29
0.60	0.1676	22.81	-13.54	0.1190	26.51	-9.84	0.0633	27.07	-9.28
0.70	0.2386	17.38	-18.97	0.1737	22.78	-13.56	0.0951	22.98	-13.36
0.80	0.3494	12.59	-23.75	0.2649	18.19	-18.16	0.1527	18.36	-17.99
0.90	0.5472	8.85	-27.50	0.4477	10.86	-25.48	0.2884	11.14	-25.21
1.00	1.0000	3.74	-32.60	1.0000	5.76	-30.58	1.0000	6.23	-30.12

w_1 and x_1 are the mass and mole fractions of polymeric cosolvent (1) in the {polymeric cosolvent (1) + water (2)} mixtures free of cyclosporin (3), respectively.

where $x_{1,3}^{L}$ is the local mole fraction of polymeric cosolvent in the molecular environment of cyclosporin and x_1 is the bulk mole fraction of polymeric cosolvent in the initial {polymeric cosolvent (1) + water (2)} binary solvent mixture free of cyclosporin. Thus, if $\delta x_{1,3}$ value is positive cyclosporin molecules are preferentially solvated by polymeric cosolvent molecules in the respective dissolution. In contrast, cyclosporin molecules are preferentially solvated by water molecules if this $\delta x_{1,3}$ parameter is negative. When $|\delta x_{1,3}| \leq 0.01$ the values are within the error of the determination that implies negligible preferential solvation. Complete selective solvation of cyclosporin (3) by polymeric solvent (1) takes place when $\delta x_{1,3} \approx x_2$, implying that $\delta x_{1,3}$ cannot be larger than x_2.[33-35]

The preferential solvation of cyclosporin (3) in the {polymeric cosolvent (1) + water (2)} mixture depends not only on the interactions of cyclosporin with polymeric solvent (1) and with water (2) but also on the mutual interactions of the two solvents as described by the molar excess Gibbs energy of their mixing in the absence of cyclosporin (3) (G_{1+2}^{Exc}). It is important to note that competitive interactions among all three components can take place in the solutions. The values of $\delta x_{1,3}$ were obtained from the IKBI based on Ben-Naim equations as described earlier[33-35]:

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3}\right)}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \tag{4}$$

with,

$$G_{1,3} = RT \cdot \kappa_T - \overline{V}_3 + x_2 \cdot \overline{V}_2 \cdot \left(\frac{D}{Q}\right) \tag{5}$$

$$G_{2,3} = RT \cdot \kappa_T - \overline{V}_3 + x_1 \cdot \overline{V}_1 \cdot \left(\frac{D}{Q}\right) \tag{6}$$

$$V_{cor} = 2522.5\left(r_3 + 0.1363\left(x_{1,3}^{L} \cdot \overline{V}_1 + x_{2,3}^{L} \cdot \overline{V}_2\right)^{1/3} - 0.085\right)^3 \tag{7}$$

Table 2. Coefficients and statistical parameters of equation (12) applied to Gibbs energies of transfer of cyclosporin from neat water (1) to some {polymeric solvent (1) + water (2)} mixtures at T = 298.15 K

Coefficient or statistical parameter	DEGME + water	PEG 200 + water	PEG 400 + water
a	-0.246	-0.007	-0.019
b	-2.818	1.500×10^3	8.121×10^2
c	-6.070×10^1	-1.317×10^3	-4.724×10^1
d	1.129×10^1	8.495×10^2	3.004×10^3
e	4.496×10^1	-1.151×10^5	-1.248×10^5
f	1.215×10^1	3.768×10^3	1.667×10^4
g	-6.888×10^2	-7.074×10^4	-4.924×10^5
Adjusted r^2	0.998	0.999	0.999
Typical error	0.476	0.298	0.322
F statistic	957	1947	1717

Here, κ_T denotes the isothermal compressibility of the (1 + 2) aqueous-polymeric cosolvent mixtures. $\overline{V}_1$, $\overline{V}_3$ and $\overline{V}_3$ are respectively the partial molar volumes of polymeric cosolvent (DEGME, PEG 200 or PEG 400), water, and cyclosporin in the solutions. The function D as defined in Eq. (8) corresponds to the first derivative of the standard molar Gibbs energies of transfer of cyclosporin from neat water to every (1 + 2) aqueous-polymeric cosolvent mixture regarding the mole fraction of polymeric cosolvent. The function Q as defined in Eq. (9) involves the second derivative of the excess molar Gibbs energy of mixing of polymeric cosolvent (1) and water (2) (G_{1+2}^{Exc}) regarding the mole fraction of water (2).[33-35] V_{cor} and r_3 are respectively the correlation volume and the gyration molecular radius of cyclosporin. Here, r_3 was roughly calculated by using Eq. (10), where N_{Av} is the number of Avogadro, regardless the non-spherical of these drug molecules.[41]

$$D = \left(\frac{\partial \Delta_{tr} G^{o}_{3,2\rightarrow 1+2}}{\partial x_1}\right)_{T,p} \tag{8}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial\ G_{1+2}^{Exc}}{\partial x_2^2}\right)_{T,p} \tag{9}$$

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

To obtain definitive V_{cor} values some iteration processes were performed because they depend on the local mole fractions of polymeric cosolvent (1) and water (2) around the cyclosporin (2) molecules in the respective solutions. Thus, these iteration processes were performed by replacing $\delta x_{1,3}$ and V_{cor} in equations (3), (4) and (7) to recalculate the $x_{1,3}^{L}$ values until obtaining non-variant values of V_{cor}.

Table 2 and Figure 3 shows the apparent Gibbs energies of transfer of cyclosporin (3) from neat water (2) to all aqueous-polymeric cosolvent (1 + 2) mixtures ($\Delta_{tr} G^{o}_{3,2\rightarrow 1+2}$) at 298.15 K. These $\Delta_{tr} G^{o}_{3,2\rightarrow 1+2}$ values were calculated from the experimental mole fraction solubility values reported in the Ha et al research article,[26] by using Eq. (11). $\Delta_{tr} G^{o}_{3,2\rightarrow 1+2}$ values can also be calculated by using the $\Delta_{soln} G°$ values reported in Table 1 of this work.

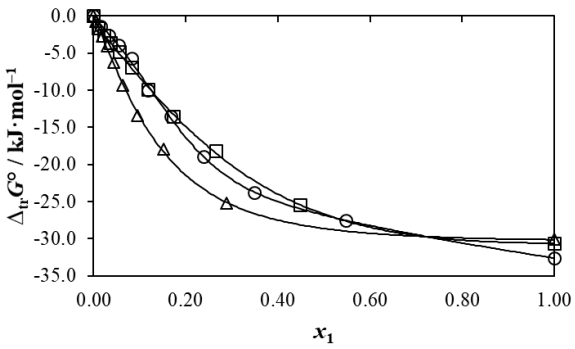

Figure 3. Gibbs energy of transfer of cyclosporin (3) from neat water (2) to some {polymeric solvent (1) + water (2)} mixtures at T = 298.15 K. ○: DEGME (1) + water (2); □: PEG 200 (1) + water (2); Δ: PEG 400 (1) + water (2)

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = RT\cdot \ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) \quad (11)$$

It is important to keep in mind that cyclosporin–cyclosporin interactions may be disregarded and thus the cyclosporin (3) molecules are surrounded by polymeric cosolvent (1) and water (2) molecules only. Otherwise, activity coefficients of cyclosporin at each cosolvent mixture composition need to be employed. Another requirement for the application of Eq. (11) is that no crystal solvates are formed by cyclosporin, which means that the conglomerate identity of the cyclosporin solid form at equilibrium with the saturated solutions is independent of the cosolvent mixtures composition.

Obtained $\Delta_{tr}G^{o}_{3,2\rightarrow 1+2}$ values were correlated by using the quotient-polynomial shown as Eq. (12). Coefficients and statistical parameters obtained with Eq. (12) for all the aqueous-polymeric cosolvent systems are shown in Table 2.

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = \frac{a + c\cdot x_1 + e\cdot x_1^2 + g\cdot x_1^3}{1 + b\cdot x_1 + d\cdot x_1^2 + f\cdot x_1^3} \quad (12)$$

The D values summarized in Table 3 were calculated as the first derivative of Eq. (12) solved in mixtures composition steps of $x_1 = 0.05$. For the studied aqueous-polymeric cosolvent mixtures, the Q, $RT\cdot\kappa_T$, $\overline{V}_2$ and $\overline{V}_2$ values at 298.15 K were taken from the literature as follows, for aqueous-DEGME mixtures,[42] for aqueous-PEG 200 mixtures,[43] and for aqueous-PEG 400 mixtures.[44]

Table 3. Some properties associated to preferential solvation of cyclosporin (3) in some {polymeric cosolvent (1) + water (2)} mixtures at $T = 298.15$ K

x_1	D / kJ·mol^{-1}	$G_{1,3}$ / cm^3·mol^{-1}	$G_{2,3}$ / cm^3·mol^{-1}	V_{cor} / cm^3·mol^{-1}	100 $\delta x_{1,3}$
DEGME + water					
0.00	-61.39	-1381	-935	2455	0.00
0.05	-75.63	-1567	-1174	2647	-1.28
0.10	-87.64	-1715	-1569	2901	-1.00
0.15	-87.98	-1705	-1948	3263	2.29
0.20	-74.94	-1539	-2084	3586	5.41
0.25	-56.43	-1337	-1975	3802	6.02
0.30	-40.27	-1183	-1777	3962	5.28
0.35	-29.05	-1088	-1605	4111	4.37
0.40	-22.08	-1035	-1490	4264	3.69
0.45	-17.92	-1006	-1426	4422	3.27
0.50	-15.45	-989	-1399	4582	3.02
0.55	-13.92	-978	-1397	4743	2.90
0.60	-12.93	-971	-1413	4902	2.83
0.65	-12.22	-966	-1444	5058	2.77
0.70	-11.68	-961	-1486	5210	2.69
0.75	-11.23	-957	-1533	5357	2.53
0.80	-10.83	-953	-1576	5497	2.25
0.85	-10.46	-948	-1601	5630	1.82
0.90	-10.12	-943	-1592	5757	1.23
0.95	-9.79	-938	-1540	5879	0.58
1.00	-9.47	-934	-1455	6001	0.00
PEG 200 + water					
0.00	-1306.70	-10455	-935	2456	0.00
0.05	-75.30	-1175	-1056	2783	-0.33
0.10	-71.54	-1108	-1122	3119	0.06
0.15	-66.10	-1081	-1190	3436	0.62
0.20	-59.54	-1068	-1270	3737	1.29
0.25	-52.47	-1062	-1370	4028	2.12
0.30	-45.37	-1060	-1500	4315	3.13
0.35	-38.60	-1062	-1668	4600	4.39
0.40	-32.36	-1065	-1882	4884	5.89
0.45	-26.77	-1066	-2119	5159	7.42
0.50	-21.86	-1057	-2297	5401	8.33
0.55	-17.63	-1034	-2294	5582	7.84
0.60	-14.02	-1003	-2092	5712	6.12
0.65	-10.96	-977	-1813	5831	4.17
0.70	-8.40	-959	-1565	5963	2.64
0.75	-6.27	-948	-1378	6112	1.59
0.80	-4.49	-942	-1243	6271	0.91
0.85	-3.03	-938	-1143	6435	0.48
0.90	-1.82	-936	-1063	6603	0.20
0.95	-0.83	-935	-995	6771	0.05
1.00	-0.02	-935	-936	6939	0.00
PEG 400 + water					
0.00	-32.12	-1169	-935	2457	0.00
0.05	-139.34	-1709	-1719	3147	0.03
0.10	-107.70	-1422	-2013	3984	2.62
0.15	-77.87	-1232	-2026	4583	3.78
0.20	-55.12	-1117	-1929	5054	3.95
0.25	-39.03	-1049	-1806	5466	3.69
0.30	-27.92	-1008	-1691	5849	3.29
0.35	-20.24	-983	-1594	6216	2.87
0.40	-14.88	-968	-1514	6574	2.48
0.45	-11.10	-958	-1450	6925	2.14
0.50	-8.38	-952	-1399	7269	1.83
0.55	-6.39	-948	-1357	7607	1.56
0.60	-4.93	-945	-1322	7938	1.32
0.65	-3.83	-943	-1291	8262	1.10
0.70	-2.99	-941	-1262	8578	0.89
0.75	-2.35	-940	-1231	8887	0.69
0.80	-1.85	-939	-1197	9189	0.50
0.85	-1.46	-938	-1158	9484	0.33
0.90	-1.16	-936	-1116	9772	0.18
0.95	-0.91	-935	-1075	10054	0.07
1.00	-0.72	-935	-1038	10330	0.00

x_1 is the mole fraction of polymeric cosolvent (1) in the {polymeric cosolvent (1) + water (2)} mixtures free of cyclosporin (3).

In this research, the $\bar{V}_1$ value was considered as one calculated by using the groups contribution method proposed by Fedors, namely 935.8 $cm^3 \cdot mol^{-1}$,[26,45] regardless the aqueous-polymeric cosolvent mixture under consideration. Table 3 shows that both the $G_{1,3}$ and $G_{2,3}$ values are negative in all the aqueous-polymeric cosolvent systems indicating the affinity of cyclosporin (3) for both solvents in the mixtures, polymeric cosolvent (1) and water (2). Cyclosporin r_3 value was calculated as 0.719 nm. As indicated above, V_{cor} values shown in Table 3 were obtained after three iterations. V_{cor} values increase with the polymeric cosolvent-proportion in the mixtures because the $\bar{V}_1$ values are higher than the $\bar{V}_2$ values in all cases.[46-48] Further, Table 3 additionally summarizes the preferential solvation parameters of cyclosporin by polymeric cosolvent molecules ($\delta x_{1,3}$) in all these mixtures at 298.15 K.

Figure 4 shows a non-linear variation of cyclosporin $\delta x_{1,3}$ values regarding the polymeric cosolvent-proportion in the solvent mixtures as expressed by the mole fraction of every polymeric cosolvent before solute adding. Initially, the addition of DEGME to neat water as solvent makes negative the $\delta x_{1,3}$ values of cyclosporin in the composition interval of $0.00 < x_1 < 0.12$. The maximum negative $\delta x_{1,3}$ value is obtained in the mixture of $x_1 = 0.05$ with $\delta x_{1,3} = -1.28 \times 10^{-2}$, being its absolute value slightly higher than 1.0×10^{-2}. As indicated above, $\delta x_{1,3}$ values over 1.0×10^{-2} are considered as consequence of real preferential solvation effects.[49,50] Otherwise, in the case of aqueous-PEG 200 mixtures a negative $\delta x_{1,3}$ value of -3.3×10^{-3} is observed which could be a consequence of uncertainties propagation toward IKBI calculations.[49,50] Regarding preferential hydration in observed in the {DEGME (1) + water (2)} cosolvent system, it is probable that the structuring of water molecules by hydrogen-bonding around the methyl and methylene groups of this compound (Figure 1) conducting hydrophobic hydration contributes to lowering of the net $\delta x_{1,3}$ to negative values in these water-rich mixtures.

In the mixtures composition interval of $0.12 < x_1 < 1.00$ the local mole fractions of DEGME around cyclosporin molecules are higher than those in the bulk aqueous-DEGME cosolvent mixtures in the absence of this drug. The maximum positive $\delta x_{1,3}$ value is obtained in the mixture of $x_1 = 0.25$, with $\delta x_{1,3} = 6.02 \times 10^{-2}$, which is higher than $|1.0 \times 10^{-2}|$. Hence, it could be considered as a consequence of preferential solvation effects of cyclosporin by DEGME molecules. For PEG 200 and PEG 400 aqueous mixtures $\delta x_{1,3}$ values are positive in almost all the mixtures compositions reaching maximum positive $\delta x_{1,3}$ values in the mixtures of $x_1 = 0.50$ with $\delta x_{1,3} = 8.33 \times 10^{-2}$ for PEG 200-aqueous mixtures and $x_1 = 0.20$ with $\delta x_{1,3} = 3.95 \times 10^{-2}$ for PEG 400-aqueous mixtures. In these mixtures composition intervals cyclosporin could be acting as a Lewis acid in front of the cosolvent polymeric molecules by means of its hydroxyl and primary amide groups (Figure 1), whose hydrogen atoms would be interacting with the unshared electron pairs of the oxygen atoms of polymeric cosolvent by hydrogen bonding. It is important to keep in mind that polymeric cosolvent exhibit a higher Lewis base behavior compared with water.[42-44]

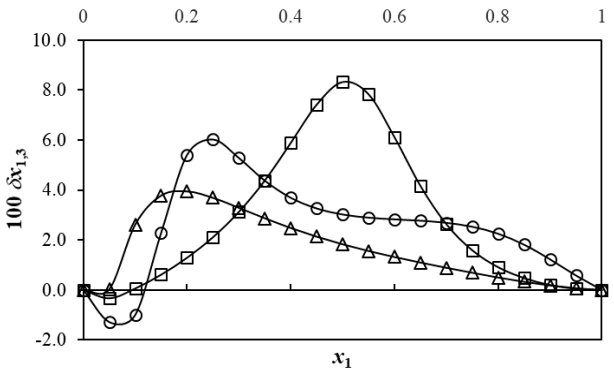

Figure 4. Preferential solvation parameters ($\delta x_{1,3}$) of cyclosporin (3) by polymeric cosolvent in some {polymeric cosolvent (1) + water (2)} mixtures at $T = 298.15$ K. ○: DEGME (1) + water (2); □: PEG 200 (1) + water (2); Δ: PEG 400 (1) + water (2)

Conclusions

Based on solubility values reported earlier,[26] the preferential solvation parameters of cyclosporin in aqueous polymeric cosolvent mixtures were derived by means of the IKBI method at 298.15 K. Thus, this drug in DEGME-aqueous mixtures is preferentially solvated by water in water-rich mixtures but preferentially solvated by DEGME in mixtures of $0.12 < x_1 < 1.00$. In this way, it is possible that the preferential hydration in water-rich mixtures is due to hydrophobic hydration around methyl and methylene moieties (Figure 1). Otherwise, in PEG-aqueous mixtures cyclosporin is preferentially solvated by PEG in almost all the mixtures owing the more basic behavior of all these polymeric cosolvents compared with water. However, the specific cyclosporin-cosolvent or cyclosporin-water interactions are not well understood despite the thermodynamic treatment performed here owing the complexity of these ternary mixtures including the high molecular size of this drug.

Acknowledgements

We thank the Department of Pharmacy of the Universidad Nacional de Colombia for for facilitating computational resources.

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Competing Interests
No potential conflict of interest was reported by the authors.

Data Availability Statement
All data generated or analyzed during this study are included in this published article.

Ethical Approval
Not applicable.

Funding
This research was funded by the Research Directorate of the National University of Colombia with grant number HERMES 56224.

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