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Preferential solvation of naproxen and piroxicam in ethanol + water mixtures

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The preferential solvation parameters of naproxen (NAP) and piroxicam (PIR) in ethanol (EtOH) + water binary mixtures were obtained from their thermodynamic properties by means of the inverse Kirkwood-Buff integrals method. NAP and PIR are very sensitive to specific solvation effects, so the preferential solvation parameter by EtOH, $\delta x_{1,3}$, is negative in the water-rich mixtures but positive in all the other compositions for both drugs at temperatures of 293.15, 303.15 and 313.15 K. It is conjecturable that in water-rich mixtures the hydrophobic hydration around the aromatic and methyl groups of the drugs plays a relevant role in the solvation. The higher drugs solvation by EtOH in mixtures of similar solvent proportions and in EtOH-rich mixtures could be due mainly to polarity effects. In these mixtures both drugs would be acting as Lewis acids with the EtOH molecules because this co-solvent is more basic than water.

Key words: naproxen, piroxicam, ethanol, preferential solvation, IKBI.

INTRODUCTION

Naproxen (NAP, Fig. 1, 230.26 g mol^{-1}, (+)-(S)-2-(6-methoxynaphthalen-2-yl)-propanoic acid, CAS number: 22204-53-1) and piroxicam (PIR, Fig. 2, 331.35 g mol^{-1}, 4-Hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, CAS number: 36322-90-4) are non-steroidal anti-inflammatory drugs used as analgesics and antipyretics [1, 2]. Although NAP and PIR are widely used in current therapeutics, the physicochemical information about their solubilities in aqueous-rich and organic-rich media is not abundant [3]. Nevertheless, some physicochemical studies about their solution thermodynamics in pharmaceutical co-solvent mixtures conformed by water and ethanol (EtOH) have been reported [4, 5]. Moreover, some semiempirical methods have also been challenged to correlate their solubilities as a function of temperature. In particular the extended Hildebrand solubility approach [6] has been analyzed at 298.15 K for both drugs [7, 8]; the log-linear model of Yalkowsky and Roseman [9] and the Jouyban-Acree model [10] have also been studied for NAP al temperatures from 293.15 to 313.15 K [11, 12]. Nevertheless, none of these studies has been specifically carried out to study the preferential solvation of these drugs by the solvent components according to the mixtures composition.

In this way, the inverse Kirkwood-Buff integrals (IKBI) method is a powerful tool for evaluating the preferential solvation of non-electrolyte compounds in binary co-solvent mixtures, describing the local composition of both solvents around the solute molecules [13-18]. Specifically, in the case of aqueous ethanolic solutions this treatment depends on the values of the standard molar Gibbs energies of transfer of the drug from neat water to EtOH + water mixtures, as well as on the excess molar Gibbs energy of mixing of the co-solvent mixtures.

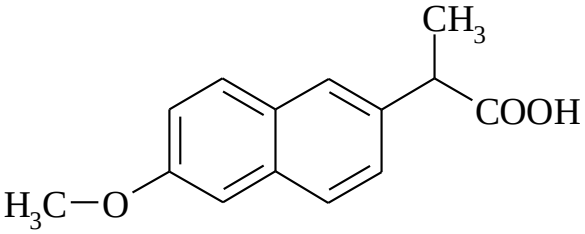

Fig. 1. Molecular structure of naproxen.

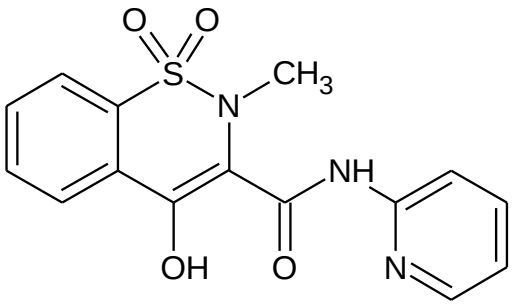

Fig. 2. Molecular structure of piroxicam.

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Thus, the main goal of this paper was to evaluate the preferential solvation of NAP and PIR in EtOH + water co-solvent mixtures, based on thermodynamic definitions, as has been made for several drugs in the same aqueous co-solvent mixtures [19-21]. These drugs were chosen for the present research because they have very different molecular structures, NAP being composed of C, H and O atoms; whereas PIR additionally contains N and S atoms. It is important to keep in mind that ethanol is the co-solvent more widely used in the development of homogeneous liquid pharmaceutical dosage forms [22, 23]. Thus, the results are expressed in terms of the preferential solvation parameter ($\delta x_{1,3}$) of the drugs by EtOH in the mixtures.

COMPUTATIONAL BACKGROUND

In binary EtOH + water mixtures the preferential solvation parameter by EtOH (component 1) is defined as:

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

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 EtOH in the environment near to NAP or PIR (component 3). If $\delta x_{1,3} > 0$ then the drug is preferentially solvated by EtOH; on the contrary, if this parameter is < 0 the drug is preferentially solvated by water. Values of $\delta x_{1,3}$ are obtainable from the inverse Kirkwood-Buff integrals for the individual solvent components analyzed in terms of some thermodynamic quantities as shown in equations (2) and (3) [17-21]:

$$G_{1,3} = RT\kappa_T - V_3 + x_2 V_2 D/Q \qquad (2)$$

$$G_{2,3} = RT\kappa_T - V_3 + x_1 V_1 D/Q \qquad (3)$$

where κ_T is the isothermal compressibility of the co-solvent + water solvent mixtures (expressed in GPa^{-1}), V_1 and V_2 are the partial molar volumes of the solvents 1 and 2 in the mixtures (expressed in $cm^3\ mol^{-1}$), similarly, V_3 is the partial molar volume of the drug in these mixtures (also 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 the EtOH + water mixtures, with respect to the solvent composition (expressed in kJ mol^{-1}, as also is RT). Otherwise, 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}), as defined in equations (4) and (5) [17-21]:

$$D = \left(\frac{\partial \Delta_{tr} G^{o}_{(3,2\rightarrow 1+2)}}{\partial x_1} \right)_{T,p} \qquad (4)$$

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

Because the dependence of κ_T on composition is unknown for a lot of the systems investigated and because of the small contribution of $RT\ \kappa_T$ to the IKBI, the dependence of κ_T on composition could be approximated. This is made by considering additive behavior, according to: $\kappa_{T,\mathrm{mix}} = \sum_{i=1}^{n} x_i \kappa_{T,i}^{o}$, where x_i is the mole fraction of component i in the mixture and $\kappa_{T,i}^{o}$ is the isothermal compressibility of the pure component i [24, 25]. Thus, the preferential solvation parameter by the co-solvent is calculated from the inverse Kirkwood-Buff integrals as follows:

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

Here, the correlation volume (V_{cor}) is estimated by means of the following expression [17-21]:

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

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

RESULTS AND DISCUSSION

The experimental solubility of NAP and PIR in EtOH + water systems was taken from the literature [4, 5]. As was mentioned earlier, the solubility of these drugs continuously increases from neat water to EtOH indicating higher affinity of NAP and PIR for semipolar organic media. Standard molar Gibbs energy of transfer of NAP and PIR from neat water to EtOH + water mixtures is calculated and correlated to regular third order polynomials from the drugs solubility data by using Eq. (8). Figure 3 shows the Gibbs energy of transfer behaviors at 293.15 K, whereas Table 1 also shows the behaviors at all the temperatures studied. The coefficients of the polynomials obtained are shown in Table 2.

Table 1. Gibbs energy of transfer (kJ mol^{-1}) of naproxen and piroxicam in ethanol + water co-solvent mixtures at several temperatures.

x_1 [a]	Naproxen [b]			Piroxicam [c]		
	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.0000	0.00	0.00	0.00	0.00	0.00	0.00
0.0417	–0.47	–1.12	–1.64	–1.41	–1.82	–2.21
0.0891	–2.70	–3.57	–4.51	–2.16	–4.02	–4.58
0.1436	–6.27	–7.66	–8.61	–4.43	–6.81	–7.38
0.2068	–9.91	–10.87	–11.61	–7.02	–8.70	–9.24
0.2812	–12.53	–13.42	–14.29	–9.36	–10.11	–10.79
0.3698	–14.65	–15.56	–16.60	–10.84	–11.54	–12.07
0.4772	–16.28	–17.12	–18.00	–12.20	–12.89	–13.37
0.6101	–17.54	–18.48	–19.41	–13.40	–14.03	–14.49
0.7788	–18.62	–19.51	–20.46	–14.50	–15.09	–15.40
1.0000	–19.42	–20.45	–21.39	–15.79	–15.63	–15.83

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of drug.
[b] Calculated from solubility values reported in Ref. [4].
[c] Calculated from solubility values reported in Ref. [5].

Table 2. Coefficients of the equation (8) applied to the Gibbs energy of transfer of naproxen and piroxicam from neat water to ethanol + water mixtures at several temperatures.

Coefficient	Naproxen			Piroxicam		
kJ mol^{-1}	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
a	1.34	1.00	0.73	0.55	–0.03	–0.20
b	–65.67	–71.21	–75.94	–44.79	–52.30	–55.76
c	73.51	85.89	95.04	46.33	65.71	73.23
d	–28.51	–36.12	–41.26	–17.80	–29.15	–33.27

Table 3. *D* values (kJ mol^{-1}) for naproxen and piroxicam in ethanol + water mixtures at several temperatures.

x_1 [a]	Naproxen			Piroxicam		
	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	–65.67	–71.21	–75.94	–44.79	–52.30	–55.76
0.10	–51.83	–55.11	–58.17	–36.06	–40.04	–42.11
0.20	–39.69	–41.19	–42.87	–28.39	–29.52	–30.46
0.30	–29.27	–29.43	–30.05	–21.80	–20.75	–20.80
0.40	–20.56	–19.84	–19.71	–16.27	–13.72	–13.14
0.50	–13.55	–12.41	–11.84	–11.81	–8.45	–7.48
0.60	–8.26	–7.16	–6.45	–8.41	–4.93	–3.81
0.70	–4.68	–4.07	–3.53	–6.09	–3.15	–2.14
0.80	–2.81	–3.14	–3.09	–4.83	–3.12	–2.47
0.90	–2.65	–4.39	–5.12	–4.64	–4.84	–4.79
1.00	–4.20	–7.80	–9.63	–5.52	–8.31	–9.11

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of drug.

Table 4. $G_{1,3}$ values (cm^3 mol^{-1}) for naproxen and piroxicam in ethanol + water mixtures at several temperatures.

x_1 [a]	Naproxen			Piroxicam		
	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	–663.6	–688.2	–706.3	–518.0	–561.6	–574.8
0.10	–580.6	–623.6	–668.6	–466.9	–510.5	–542.0
0.20	–480.7	–508.1	–540.2	–403.3	–423.3	–444.1
0.30	–390.7	–395.3	–403.8	–345.2	–339.9	–343.0
0.40	–320.4	–310.9	–306.0	–299.4	–278.5	–271.9
0.50	–268.5	–254.5	–245.8	–265.7	–238.6	–229.3
0.60	–230.3	–218.6	–211.1	–240.4	–214.5	–205.9
0.70	–202.4	–197.1	–193.0	–219.4	–201.5	–195.3
0.80	–185.4	–186.2	–185.7	–201.3	–195.3	–192.8
0.90	–178.6	–180.5	–181.2	–189.9	–190.1	–189.9
1.00	–175.5	–175.4	–175.3	–184.6	–184.5	–184.4

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of drug.

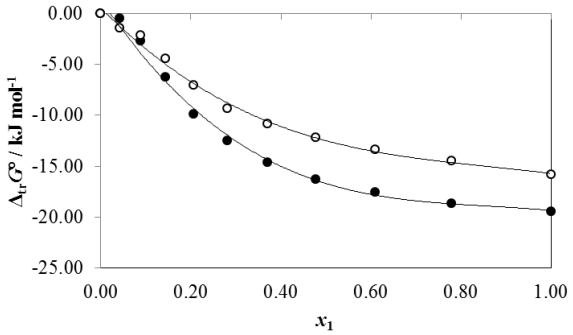

Fig. 3. Gibbs energy of transfer of naproxen (●) and piroxicam (○) from neat water to ethanol + water mixtures at 293.15 K.

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = RT\ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) = a + bx_1 + cx_1^2 + dx_1^3 \quad (8)$$

Thus D values are calculated from the first derivative of polynomial models, Eq. (9), solved according to the solvent mixtures composition. This procedure was done varying by 0.05 in mole fraction of EtOH but in the following tables, the respective values varying only by 0.10 are reported. D values are shown in Table 3.

$$D = b + 2cx_1 + 3dx_1^2 \qquad (9)$$

Q and $RT\ \kappa_T$ values for EtOH + water binary mixtures, as well as the partial molar volumes of EtOH and water, at the three temperatures considered here, were taken from the literature [20, 21].

Otherwise, partial molar volumes of non-electrolyte drugs are not frequently reported in the literature. This is because of the large uncertainty obtained in its determination due to their low solubilities, in particular in aqueous media. For this reason, in the first approach, the molar volumes of NAP and PIR were considered as independent of co-solvent composition and temperature, as they are calculated according to the groups contribution method proposed by Fedors [26]. Thus, these values were taken from the literature as V_3 = 178.3 cm^3 mol^{-1} for NAP [27] and 187.4 cm^3 mol^{-1} for PIR [8]. On the other hand, from these values the radii of the drug molecules were calculated by using: $r_3 = \left(3\cdot 10^{21}\cdot V_3 / 4\cdot\pi\cdot N_{Av}\right)^{1/3}$, where N_{Av} is the Avogadro number, as r_3 = 0.413 nm and 0.420 nm for NAP and PIR, respectively.

Tables 4 and 5 show that the $G_{1,3}$ and $G_{2,3}$ values are negative for both co-solvent systems at all temperatures under study. Nevertheless, depending on co-solvent compositions in some cases $G_{1,3}$ values are larger in magnitude in comparison with $G_{2,3}$ values, but in other cases the behavior is opposite. As has been described in the literature, these differences are associated with the affinity of both drugs to each of the components of the mixtures, EtOH or water [15, 16].

In order to apply the IKBI method, the correlation volume was iterated three times by using the equations (1), (6) and (7) to obtain the final values reported in Table 6. This property is almost independent on temperature in water-rich mixtures but increases to some extent in EtOH-rich mixtures. This would be expectable according to the variation of the respective molar expansibilities with the mixtures composition [28].

According to Fig. 4 the values of $\delta x_{1,3}$ vary non-linearly with the EtOH proportion in the aqueous mixtures at 293.15 K. In this way, the addition of EtOH to water tends to make negative the $\delta x_{1,3}$ values of NAP and PIR from pure water up to the mixtures of 0.23 in mole fraction of EtOH.

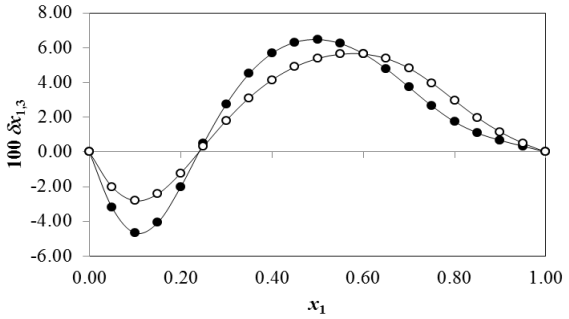

Fig. 4. $\delta x_{1,3}$ values for naproxen (●) and piroxicam (○) in ethanol + water mixtures at 293.15 K.

In these water-rich mixtures the maximum negative values are found in x_1 = 0.10 ($\delta x_{1,3}$ = -4.665×10^{-2} for NAP and -2.806×10^{-2} for PIR, at 293.15 K). These magnitudes are similar to those found for some other drugs in the same mixtures [20, 21]. As was previously indicated, possibly the structuring of water molecules around the non-polar groups of this drug leading to hydrophobic hydration of the aromatic and methyl groups (Figs. 1 and 2), contributes to lowering of the net $\delta x_{1,3}$ to negative values in these water-rich mixtures. Similar behaviors are observed at the other temperatures as can be seen in Table 7. On the other hand, the maximum negative values increase with the temperature increase. The possibility of hydrophobic hydration of NAP and PIR in water-rich mixtures has been exposed previously from enthalpy-entropy compensation plots and some thermodynamic quantities of transfer [4, 5]. Additionally, the negative deviations to the log-linear model proposed by Yalkowsky and Roseman [9], exhibited by NAP in water-rich mixtures, have also been attributed to an increase of water-structuring in these compositions [11, 12].

Table 5. $G_{2,3}$ values ($cm^3\ mol^{-1}$) for naproxen and piroxicam in ethanol + water mixtures at several temperatures.

x_1 [a]	Naproxen			Piroxicam		
	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	–177.2	–177.1	–177.1	–186.3	–186.2	–186.2
0.10	–311.9	–328.1	–345.2	–280.0	–295.9	–307.9
0.20	–413.6	–437.6	–465.4	–355.3	–372.8	–390.9
0.30	–473.0	–482.0	–496.1	–406.5	–401.0	–406.9
0.40	–497.7	–478.6	–469.4	–439.8	–394.6	–380.9
0.50	–496.0	–449.1	–420.1	–463.9	–371.1	–339.4
0.60	–467.6	–405.8	–366.3	–482.1	–343.3	–297.7
0.70	–403.4	–359.5	–324.8	–481.1	–327.2	–275.4
0.80	–320.3	–335.1	–330.0	–433.6	–343.1	–308.1
0.90	–277.4	–345.6	–375.6	–363.3	–372.3	–371.7
1.00	–275.9	–357.9	–396.0	–316.8	–379.0	–393.1

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of drug.

Table 6. Correlation volume ($cm^3\ mol^{-1}$) of naproxen and piroxicam in ethanol + water mixtures at several temperatures.

x_1 [a]	Naproxen			Piroxicam		
	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	814	815	817	839	840	841
0.10	857	853	849	898	896	895
0.20	959	961	963	993	996	1000
0.30	1076	1082	1090	1098	1103	1110
0.40	1177	1180	1185	1197	1196	1201
0.50	1260	1260	1262	1285	1277	1280
0.60	1331	1329	1331	1366	1352	1354
0.70	1393	1396	1400	1437	1426	1428
0.80	1453	1464	1473	1499	1500	1507
0.90	1520	1533	1545	1561	1572	1582
1.00	1588	1599	1610	1627	1638	1649

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of drug.

Table 7. $\delta x_{1,3}$ values (× 100) of naproxen and piroxicam in ethanol + water mixtures at several temperatures.

x_1 [a]	Naproxen			Piroxicam		
	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	0.000	0.000	0.000	0.000	0.000	0.000
0.10	–4.665	–5.364	–6.176	–2.806	–3.337	–3.736
0.20	–2.021	–2.214	–2.479	–1.224	–1.318	–1.421
0.30	2.755	2.906	3.119	1.812	1.781	1.858
0.40	5.677	5.239	5.019	4.145	3.284	3.027
0.50	6.479	5.359	4.690	5.385	3.405	2.765
0.60	5.660	4.337	3.520	5.640	2.847	1.983
0.70	3.736	2.964	2.371	4.825	2.225	1.390
0.80	1.740	1.909	1.834	2.970	1.855	1.429
0.90	0.668	1.112	1.301	1.153	1.203	1.190
1.00	0.000	0.000	0.000	0.000	0.000	0.000

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of drug.

The bigger preferential solvation parameters by water obtained for NAP compared with those obtained for PIR could be attributed to the differences in the drug polarities in comparison with the polarity of EtOH and water. Thereby, if the Hildebrand solubility parameters (δ) are considered, i.e. 23.4, 30.4, 26.5, and 47.8 $MPa^{1/2}$ for NAP, PIR, EtOH, and water, respectively [8, 27, 29], it follows that EtOH exhibits an intermediate polarity between both drugs, and NAP is the drug more distant in polarity with respect to water. Accordingly, the hydrophobic hydration of NAP would be higher than the one for PIR.

In the EtOH + water mixtures with composition $0.23 < x_1 < 1.00$ the local mole fractions of EtOH are greater than the ones for water for both drugs.

In this way, the co-solvent action could be related to the breaking of the ordered structure of water (by hydrogen bonding) around the non-polar moieties of the drugs. This fact would increase the

drug solvation reaching maximum values in compositions near to x_1 = 0.50 and 0.60 for NAP and PIR, with $\delta x_{1,3} = 6.479 \times 10^{-2}$ and 5.640×10^{-2} at 293.15 K, respectively. These magnitudes are also similar to those found for other drugs in the same mixtures [19-21]. In opposite way to the water-rich mixtures behavior, the maximum positive values decrease with the temperature increase.

As has been indicated earlier, NAP and PIR could act in solution as Lewis acids due to the hydrogen atom in their –OH groups (and also by the –CO–NH– group for PIR, Figs. 1 and 2), in order to establish hydrogen bonds with proton-acceptor functional groups in EtOH and water (oxygen atom in –OH). In addition, these drugs could act as Lewis bases due to free electron pairs in oxygen atoms of hydroxyl and carbonyl groups (and also by the $–SO_2–$ group for PIR, Figs. 1 and 2) to interact with hydrogen atoms present in both solvents. In this context, NAP has one hydrogen-bonding donor and three hydrogen-bonding acceptor groups, whereas PIR has two hydrogen-bonding donor and four hydrogen-bonding acceptor groups, excluding the aromatic nitrogen [4, 5].

According to the preferential solvation results, it is conjecturable that in intermediate composition mixtures and EtOH-rich mixtures, NAP and PIR are acting as Lewis acids with the EtOH molecules because this co-solvent is more basic than water as indicated by the Kamlet-Taft hydrogen bond acceptor parameters (β), i.e. 0.75 for EtOH and 0.47 for water [24, 30]. In this way, these drugs would prefer EtOH instead of water.

CONCLUSIONS

According to the performed analyses, NAP and PIR are preferentially solvated by water in water-rich mixtures but preferentially solvated by EtOH in mixtures with intermediate composition and those rich in EtOH at all temperatures considered. It is important to note that these results are in good agreement with those described previously, based on classical thermodynamic and extra-thermodynamic treatments [4-8]. Nevertheless, the specific solvent-drug interactions remain unclear.

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ПРЕФЕРЕНЦИАЛНА СОЛВАТАЦИЯ НА НАПРОКСЕН И ПИРОКСИКАМ В СМЕСИ ОТ ЕТАНОЛ/ ВОДА

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(Резюме)

Предпочитаните параметри на солватация за напроксен (NAP) и пироксин (PIR) в бинарни смеси на етанол (EtOH) и вода са получени от техните термодинамични свойства с помощта на метода на обратните интеграли на Kirkwood-Buff. NAP и PIR са много чувствителни спрямо специфичните ефекти на солватация, като преференциалният параметър на солватация с EtOH, $\delta x_{1,3}$, е отрицателен в смеси, богати на вода, но са положителни за всички други смеси за двете лекарства при температури 293.15, 303.15 и 313.15 K. Оказва се, че в богатите на вода смеси хидрофобната хидратация около ароматните и метиловите групи играе основна роля при солватацията. По-високата солватация с етанол в подобни смеси и в смеси, богати на етанол може би се дължи на полярни ефекти. В тези смеси двете лекарства се отнася като киселини на Lewis спрямо молекулите на етанола, тъй като този разтворител е по-базичен от водата.