

Preferential Solvation of Fenofibrate in (Ethanol or Acetone) + Water Mixtures at 298.15 K

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ABSTRACT: The aim of this communication was to expand the results of numerical analyses performed by Sun et al. on their experimental solubility of fenofibrate in aqueous mixtures of ethanol and acetone at 298.15 K, in terms of the evaluation of the preferential solvation of this compound by the organic solvents and water in the saturated mixtures based on the inverse Kirkwood-Buff integrals (IKBI). According to the results, this drug is preferentially solvated by water in water-rich mixtures but preferentially solvated by the cosolvents in mixtures with intermediate composition and also in cosolvent-rich mixtures. Preferential solvation by water in water-rich mixtures may be due to hydrophobic hydration around non-polar moieties of this drug. Moreover, it is conjecturable that in regions with preferential solvation by the cosolvents the drug is acting as Lewis acid with the cosolvent molecules because they are more basic than water.

KEYWORDS: Fenofibrate; Cosolvent + water mixtures; Jouyban-Acree model; Preferential solvation; IKBI.

INTRODUCTION

Fenofibrate (CAS Number: 49562-28-9, IUPAC name: propan-2-yl 2-[4-[(4-chlorophenyl)carbonyl]phenoxy]-2-methylpropanoate, molecular formula: $C_{20}H_{21}ClO_4$, molar mass: 360.83 g/mol, molecular structure is shown in Fig. 1) is a drug commonly used to reduce the cholesterol levels in patients with risk of cardiovascular disease [1]. According to the

US Pharmacopeia, fenofibrate is normally prescribed as tablets and capsules [2]. Reported aqueous solubility of this drug is 0.087 mg/ml [3], being thus considered as practically insoluble in water [4]. Recently, the solubility of fenofibrate was reported in some ethanol (1) + water (2) and some acetone (1) + water (2) binary mixtures at several temperatures [5]. It is well known that cosolvency

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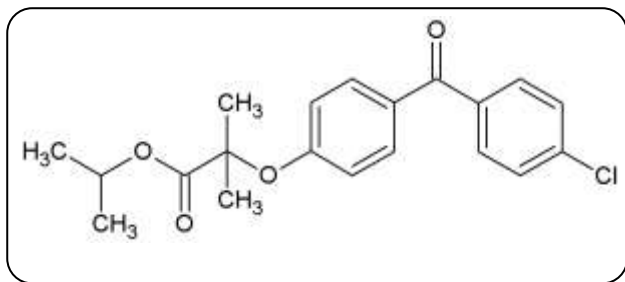


Fig. S1: Molecular structure of fenofibrate.

is the most powerful technique to increase the solubility of drugs [6-8]. Molecular mechanisms involved in the solubility increasing effect by addition of cosolvents have been approached by means of enthalpy-entropy compensation analysis [9, 10], as well as, by means of preferential solvation analysis [11, 12].

In this way, it is possible to obtain valuable information regarding the interactions of fenofibrate with both solvent components in every binary system through preferential solvation computations based on solubility values [1], as illustrated below.

RESULTS AND DISCUSSION

The preferential solvation parameter of fenofibrate (compound 3) by cosolvent (compound 1) in cosolvent (1) + water (2) mixtures is defined as [11, 12]:

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

Where, $x_{1,3}^L$ is the local mole fraction of cosolvent (1) in the environment near to the fenofibrate (solute). The solute is preferentially solvated by cosolvent (1) whenever the numerical value of $\delta x_{1,3}$ is greater than zero. If this parameter is negative fenofibrate is preferentially solvated by water (2). Numerical values of $\delta x_{1,3}$ are determined from the Inverse Kirkwood-Buff Integrals (IKBI) for the individual solvent components as shown in Equations (2) and (3):

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

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

Where κ_T is the isothermal compressibility of the solvent mixtures (expressed in units of GPa^{-1}), V_1 and V_2 are the partial molar volumes of the cosolvent (1) and water (2), respectively, and V_3 is the partial molar volume

of fenofibrate. The function D is the derivative of the standard molar Gibbs energies of transfer of fenofibrate (3) from neat water (2) to the cosolvent (1) + water (2) mixtures, with respect to the mole fraction of cosolvent (1) in the mixtures. The second terms in the function Q contains the second derivative of the excess molar Gibbs energy of mixing of the two solvents with respect to the mole fraction of water (2) in the mixtures:

$$D = \left(\frac{\partial \Delta_{\text{tr}} G_{3,2 \rightarrow 1+2}^0}{\partial x_1} \right)_{T,p} \quad (4)$$

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

The numerical values of the preferential solvation parameter of fenofibrate by cosolvent (1) were calculated at each solvent composition from the Inverse Kirkwood-Buff Integrals (IKBI) as follows:

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

The correlation volume (V_{cor}) used in Eq. (6) was obtained by means of the following expression:

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

Where r_3 denotes the molecular radius of the solute (in nm) calculated by using Eq. (8) and N_{Av} refers to Avogadro's number.

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{\text{Av}}} \right)^{1/3} \quad (8)$$

Several interactions were required to obtain the final numerical value of the definitive correlation volume. The iterations were accomplished by replacing $\delta x_{1,3}$ in the Eq. (1) to calculate $x_{1,3}^L$ until a non-variant value of V_{cor} was obtained.

Fig. 2 depicts the Gibbs energy of transfer behavior of fenofibrate (3) from neat water (2) to the various cosolvent (1) + water (2) mixtures at 298.15 K. These values were calculated from the mole fraction solubilit

Table 1: Some properties associated to preferential solvation of fenofibrate (3) in ethanol (1) + water (2) mixtures at 298.15 K.

x_1^a	D (kJ/mol)	$G_{1,3}$ (cm ³ /mol)	$G_{2,3}$ (cm ³ /mol)	V_{cor} (cm ³ /mol)	$100 \delta x_{1,3}$
0.00	-38.48	-554.6	-274.1	1066	0.00
0.05	-36.06	-552.4	-317.5	1101	-1.45
0.10	-33.72	-541.7	-363.8	1143	-2.10
0.15	-31.45	-524.3	-409.8	1193	-1.91
0.20	-29.26	-503.1	-453.4	1249	-1.01
0.25	-27.14	-480.5	-493.6	1309	0.30
0.30	-25.10	-458.4	-530.9	1370	1.77
0.35	-23.14	-437.9	-566.4	1430	3.22
0.40	-21.26	-419.5	-601.5	1488	4.55
0.45	-19.45	-403.2	-637.8	1545	5.73
0.50	-17.71	-388.8	-676.5	1600	6.74
0.55	-16.06	-375.7	-717.9	1652	7.55
0.60	-14.48	-363.1	-759.9	1702	8.07
0.65	-12.98	-350.0	-796.2	1747	8.18
0.70	-11.55	-335.4	-813.6	1787	7.68
0.75	-10.20	-319.1	-794.2	1820	6.44
0.80	-8.92	-302.8	-728.6	1848	4.67
0.85	-7.73	-289.1	-630.1	1876	2.83
0.90	-6.60	-279.9	-527.5	1906	1.39
0.95	-5.56	-274.7	-442.4	1941	0.48
1.00	-4.59	-272.3	-381.0	1980	0.00

^a x_1 is the mole fraction of ethanol (1) in the ethanol (1) + water (2) mixtures free of fenofibrate (3).

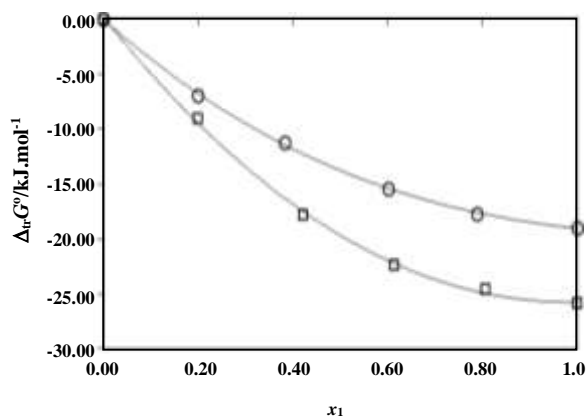


Fig. 1: Gibbs energy of transfer of fenofibrate (3) from neat water (2) to cosolvent (1) + water (2) mixtures at 298.15 K. ○: ethanol (1) + water (2); □: acetone (1) + water (2).

data reported by Sun *et al.* [5], through the following expression:

$$\Delta_{tr} G_{3,2 \rightarrow 1+2}^{\circ} = RT \ln \left(\frac{x_{3,2}}{x_{3,1+2}} \right) \quad (9)$$

$\Delta_{tr} G_{3,2 \rightarrow 1+2}^{\circ}$ values were correlated according to the following third-order polynomials:

$$\Delta_{tr} G_{3,2 \rightarrow 1+2}^{\circ} = -0.05 - 38.48x_1 + 24.59x_1^2 - 5.096x_1^3 \quad (10)$$

$$\Delta_{tr} G_{3,2 \rightarrow 1+2}^{\circ} = 0.13 - 54.06x_1 + 29.59x_1^2 - 1.386x_1^3 \quad (11)$$

The coefficient of determinations (r^2) were 0.9999 (Eq. (13)) and 0.9996 (Eq. (14)), for ethanol (1) + water (2) and acetone (1) + water (2) mixtures, respectively. The D values reported in Tables 1 and 2 were calculated from the first derivative of the polynomial models, solved according to the cosolvent proportions. The values of Q , $RT \kappa_T$, V_1 and V_2 of the ethanol (1) + water (2) mixtures were taken from the literature [13]. On the other hand, for all the acetone (1) + water (2) mixtures, the values of Q at 298.15 K were calculated from the published values

Table 2: Some properties associated to preferential solvation of fenofibrate (3) in acetone (1) + water (2) mixtures at 298.15 K.

x_1^a	D (kJ/mol)	Q (kJ/mol)	$RT \kappa_T$ (cm ³ /mol)	V_1 (cm ³ /mol)	V_2 (cm ³ /mol)	$G_{1,3}$ (cm ³ /mol)	$G_{2,3}$ (cm ³ /mol)	V_{cor} (cm ³ /mol)	100 $\delta x_{1,3}$
0.00	-54.06	2.479	1.133	65.91	18.06	-668.0	-274.1	1066	0.00
0.05	-51.11	1.670	1.240	67.11	18.03	-798.4	-376.7	1094	-2.88
0.10	-48.19	1.146	1.348	68.19	17.94	-953.0	-560.6	1108	-6.96
0.15	-45.28	0.839	1.455	69.15	17.81	-1090.1	-833.2	1106	-13.97
0.20	-42.39	0.690	1.563	70.00	17.63	-1139.4	-1133.2	1320	-0.54
0.25	-39.53	0.647	1.670	70.74	17.41	-1071.4	-1354.1	1487	26.01
0.30	-36.68	0.665	1.778	71.39	17.17	-936.2	-1454.6	1594	36.94
0.35	-33.86	0.710	1.885	71.94	16.90	-797.5	-1474.9	1718	32.09
0.40	-31.05	0.753	1.993	72.42	16.62	-684.4	-1467.8	1814	28.51
0.45	-28.27	0.776	2.100	72.81	16.33	-600.1	-1466.1	1887	26.44
0.50	-25.51	0.769	2.208	73.13	16.04	-539.0	-1485.9	1950	25.24
0.55	-22.77	0.728	2.315	73.39	15.75	-494.6	-1535.2	2011	24.58
0.60	-20.05	0.659	2.422	73.59	15.48	-461.1	-1615.8	2069	24.18
0.65	-17.35	0.576	2.530	73.75	15.22	-433.1	-1716.2	2123	23.52
0.70	-14.67	0.501	2.637	73.86	15.00	-404.3	-1786.9	2164	21.59
0.75	-12.01	0.464	2.745	73.93	14.80	-368.3	-1709.1	2176	17.07
0.80	-9.37	0.503	2.852	73.98	14.65	-327.0	-1375.7	2161	10.33
0.85	-6.76	0.665	2.960	74.00	14.54	-294.4	-911.4	2152	4.46
0.90	-4.16	1.005	3.067	74.01	14.49	-278.1	-547.9	2172	1.30
0.95	-1.59	1.586	3.175	74.01	14.49	-272.7	-342.3	2215	0.17
1.00	0.97	2.479	3.282	74.00	14.57	-271.9	-243.0	2267	0.00

^a x_1 is the mole fraction of acetone (1) in the acetone (1) + water (2) mixtures free of fenofibrate (3).

as described in the monograph by Marcus [11]. $RT \kappa_T$ values were calculated by assuming mole fraction additive mixing with the reported κ_T values for these solvents at 298.15 K [14]. In similar way, the partial molar volumes of both solvents were calculated by classical methods from reported density values of these mixtures at 298.15 K [15]. The molar volume of fenofibrate (3) was calculated as 275.2 cm³/mol by means of the Fedors' method as shown in Table 3 [16]. The numerical values of $G_{1,3}$ and $G_{2,3}$ listed in Tables 1 and 2 are negative in all cases indicating that fenofibrate (3) exhibits affinity for all solvents in the mixtures, i.e. ethanol or acetone (1) and water (2). Solute radius value (r_3) was calculated to be 0.478 nm. The correlation volume was iterated

three times by using Equations (4), (9) and (10) to obtain the values reported in Tables 1 and 2. The last columns of these tables list the preferential solvation parameters of fenofibrate by cosolvents (1), $\delta x_{1,3}$.

Careful examination of Fig. 3 reveals that the values of $\delta x_{1,3}$ vary non-linearly with the mole fraction composition of cosolvent in all of the mixtures studied. For ethanol (1) + water (2) mixtures, the numerical $\delta x_{1,3}$ values of fenofibrate are negative from neat water (2) to the mixture of $x_1 = 0.23$ and reaches a minimum value in $x_1 = 0.10$ ($\delta x_{1,3} = -2.10 \times 10^{-2}$). For acetone (1) + water (2) mixtures, the numerical $\delta x_{1,3}$ values are negative from pure water (2) to the mixture $x_1 = 0.21$ and reaches a minimum value in $x_1 = 0.15$ ($\delta x_{1,3} = -0.1397$).

Table 3: Fedors' method applied to the estimation of internal energy, molar volume, and Hildebrand solubility parameter of fenofibrate.

Group or atom	Group number	ΔU° (kJ/mol)	V (cm ³ /mol)
-CH ₃	4	4 x 4.71 = 18.84	4 x 33.5 = 134.0
>CH-	1	3.43	-1.0
>C<	1	1.47	-19.2
m-Phenylene	2	2 x 31.9 = 63.8	2 x 52.4 = 104.8
-O-	1	3.35	3.8
-CO-	1	17.4	10.8
-COO-	1	18.0	18.0
-Cl aromatic	1	11.55 x 0.8 = 9.24	24.0
		$\Sigma \Delta U^\circ = 135.53$	$\Sigma V = 275.2$
		$\delta_3 = (135,530/275.2)^{1/2} = 22.2 \text{ MPa}^{1/2}$	

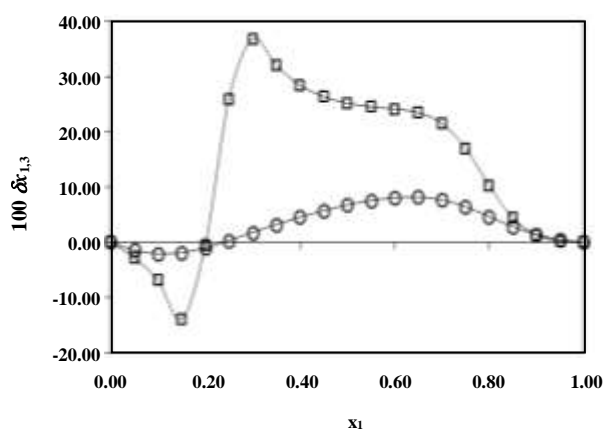


Fig. 2: $\delta x_{1,3}$ values of fenofibrate (3) in cosolvent (1) + water (2) mixtures at 298.15 K. \circ : ethanol (1) + water (2); \square : acetone (1) + water (2).

Fig. 3: $\delta x_{1,3}$ values of fenofibrate (3) in cosolvent (1) + water (2) mixtures at 298.15 K. \circ : ethanol (1) + water (2); \square : acetone (1) + water (2).

This indicates that fenofibrate is preferentially solvated by water (2) in all these water-rich mixtures. Preferential solvation by water (2) in water-rich mixtures may be due to hydrophobic hydration around non-polar moieties of fenofibrate as has been indicated previously in the literature for other compounds [17-21].

Otherwise, in all the other mixtures ($0.23 < x_1 < 1.00$) for ethanol (1) + water (2) and ($0.21 < x_1 < 1.00$) for acetone (1) + water (2), the $\delta x_{1,3}$ values are positive, obtaining maximum values in the mixtures with $x_1 = 0.65$ ($\delta x_{1,3} = 8.18 \times 10^{-2}$) for ethanol (1) + water (2) and

$x_1 = 0.30$ ($\delta x_{1,3} = 0.3694$) for acetone (1) + water (2) mixtures. Thus, in these concentration regions the solute is preferentially solvated by cosolvent (1). In this way, the cosolvent action to increase fenofibrate solubility may be related to the breaking of the ordered structure of water (hydrogen bonds) around the non-polar moieties of the solute which increases the drug solvation. It is conjecturable that in these regions the drug is acting as Lewis acid with the cosolvent molecules because they are more basic than water as described by the respective Kamlet-Taft hydrogen bond acceptor parameters, i.e. $\beta = 0.86$ for ethanol, 0.48 for acetone and 0.47 for water [14, 22]. Nevertheless, in the case of acetone + water mixtures some polarizability effects could be present because β parameters are almost the same for acetone and water.

CONCLUSIONS

Quantitative values for the local mole fraction of ethanol or acetone and water around fenofibrate were calculated based on the IKBI method applied to the reported solubility values [5]. Thus, this drug is preferentially solvated by water in water-rich mixtures but preferentially solvated by the cosolvents in mixtures with intermediate composition and also in cosolvent-rich mixtures.

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