**Solubility and preferential solvation of some n-alkyl-parabens in methanol + water mixtures
at 298.15 K**

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ABSTRACT

Methyl, ethyl and propyl parabens equilibrium solubility was determined in (methanol + water) binary mixtures at 298.15 K. The mole fraction solubility of these compounds increased in 503 (from 2.40×10^{-4} to 0.121), 1377 (from 9.86×10^{-5} to 0.136) and 4597 (from 3.73×10^{-5} to 0.171) times when passing from neat water to neat methanol, for methyl, ethyl and propyl parabens, respectively. All these solubility values were correlated with the Jouyban-Acree model. Preferential solvation parameters by methanol ($\delta x_{1,3}$) of these parabens were derived from their thermodynamic solution properties using the inverse Kirkwood-Buff integrals (IKBI) method. For all compounds $\delta x_{1,3}$ values are negative in water-rich mixtures but positive in mixtures with methanol mole fraction greater than 0.32. It is conjecturable that in the former case the hydrophobic hydration around non-polar groups of parabens plays a relevant role in the solvation. Besides, the preferential solvation of these solutes by methanol in mixtures of similar co-solvent compositions and in methanol-rich mixtures could be explained in terms of the higher basic behaviour of methanol.

KEYWORDS: parabens, solubility, methanol + water mixtures, Jouyban-Acree model, inverse Kirkwood-Buff integrals, preferential solvation.

1. Introduction

Alkyl-parabens are esters of 4-hydroxybenzoic acid (Figure 1), only differing in the ester group length, which may be a methyl, ethyl, propyl or butyl group. These compounds are widely used alone or in combination as antimicrobial preservatives in cosmetics, food products, and pharmaceutical formulations. The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity [1, 2]. Aqueous solubility of these compounds is really low but it is high in alcohols [3, 4-7]. Although the equilibrium solubility of some parabens in different solvent mixtures has been reported in the literature [8-10], the solubility data in aqueous and organic media is still far to be complete [11].

Figure 1

As described earlier, the experimental drug behaviour in solvent mixtures is normally required for purification, pre-formulation studies, and pharmaceutical dosage design purposes [11, 12]. Thus, the determination of drug solubility in all possible mixtures is still required to obtain complete physicochemical data about pharmaceutical and chemical liquid systems [13].

Although co-solvency has widely been employed in pharmaceutical practice as a powerful drug solubilizing technique, it was recently that the main mechanisms involved in the increasing or decreasing drug solubility started to be analysed from a deep thermodynamic viewpoint, which includes the preferential solvation of the solutes by all the components of the mixtures [14, 15].

In this way, the main purposes of this paper are to determine the equilibrium solubility of methyl, ethyl, and propyl parabens (3) in several {methanol (1) + water (2)} mixtures at 298.15 K, to correlate the parabens solubility with the Jouyban-Acree model [16], and to evaluate the preferential solvation of these pharmaceutical adjuvants, based on well-established thermodynamic definitions [14, 15]. Thus, this research is similar to those presented in the literature by our research groups dealing with the solubility and preferential solvation of several drugs in {methanol (1) + water (2)} mixtures as has recently been shown in our previous research [13].

As it is well known, methanol is not used in liquid pharmaceutical dosage forms' development owing its acute toxicity, but in some instances it is used in drug purification procedures by crystallization. Otherwise, methanol is used as polymer dissolvent in some

microencapsulation techniques, as well as one of the most common solvents in preparing mobile phases for high performance liquid chromatography analysis [17, 18].

Regarding parabens, these compounds exhibit classical behaviour as non-dissociate weak organic electrolytes in aqueous co-solvent mixtures [8-10]. Therefore, the use of the inverse Kirkwood-Buff integrals (IKBI) allows the preferential solvation analysis of these compounds by describing the local solvent proportions around the solute molecules compared with the composition of the bulk co-solvent mixtures [14, 15]. This thermodynamic treatment depends on the values of the standard molar Gibbs energies of transfer of the solutes (component 3) from neat water (component 2) to the {methanol (component 1) + water (2)} mixtures and on the values of excess molar Gibbs energy of mixing for the binary mixtures free of solute. Although IKBI method is mainly useful when applied to organic compounds exhibiting low solubility in the mixtures, it is also used even when drug solubility is significant in co-solvent-rich mixtures [19].

2. Experimental

2.1. Reagents

In this research, methyl, ethyl and propyl parabens (Sigma-Aldrich, USA; compound 3; with purities of at least 0.990 in mass fraction), methanol (Merck A.R., Germany; the solvent component 1, purity at least 0.998 in mass fraction) and distilled water with conductivity $< 2 \mu\text{S}\cdot\text{cm}^{-1}$ (the solvent component 2) were used. Table 1 summarizes the sources and purities of the compounds studied.

Table 1

2.2. Preparation of solvent mixtures

All {methanol (1) + water (2)} solvent mixtures were prepared by mass in quantities of 5.00 g, using an analytical balance with sensitivity $\pm 0.1 \text{ mg}$ (Ohaus Pioneer TM PA214, USA). The mass fractions of methanol (1), w_1 , of the nine mixtures prepared varied by 0.10 from 0.10 to 0.90.

2.3. Solubility determinations

Procedures were similar to those followed in the study of other compounds in similar mixtures [13, 20, 21] and the analgesic drug naproxen in {ethyl acetate (1) + ethanol (2)} mixtures [22]. Briefly described, an excess of each paraben was added to 5.00 g of the respective co-solvent mixture or neat solvent (methanol or water), in stoppered dark glass flasks. Solid-liquid mixtures were placed in ultrasonic bath (Elma[®] E60H Elmasonic, USA) during 15 minutes. After this treatment the

1 mixtures were stirred in a thermostatic mechanical shaker (Julabo SW23, Germany) kept at 298.15
2 K for at least four days to reach the saturation equilibrium. After this time the supernatant solutions
3 were filtered at isothermal conditions (Millipore Corp. Swinnex®-13, USA) to ensure that they
4 were free of particulate matter before sampling. In the mixtures with $0.00 \leq w_1 \leq 0.40$ the parabens
5 concentrations were determined by using UV spectrophotometric analytic techniques ($\lambda_{\text{max}} = 291$
6 nm for methyl paraben or 293 nm for ethyl and propyl parabens, in NaOH $0.10 \text{ mol} \cdot \text{dm}^{-3}$) (UV/VIS
7 BioMate 3 Thermo Electron Company spectrophotometer, USA) after appropriate gravimetric
8 dilutions with NaOH $0.10 \text{ mol} \cdot \text{dm}^{-3}$. The obtained calibration curves were as follows: Abs. =
9 $0.1439 \cdot \text{Conc.} + 0.0037$ for methyl paraben, Abs. = $0.1367 \cdot \text{Conc.} + 0.0020$ for ethyl paraben, and
10 Abs. = $0.1269 \cdot \text{Conc.} + 0.0043$ for propyl paraben, where Abs. is absorbance and Conc. is the
11 paraben concentration expressed as $\mu\text{g} \cdot \text{g}^{-1}$. In the mixtures with $0.50 \leq w_1 \leq 1.00$ the parabens
12 concentrations were determined by mass balance by weighing a specified quantity of the respective
13 saturated solution and allowing the solvent evaporation up to constant mass. The density of the
14 saturated solutions was determined by using a digital density meter (DMA 45 Anton Paar, Austria)
15 connected to a re-circulating thermostatic bath (Neslab RTE 10 Digital One Thermo Electron
16 Company, USA) at 298.15 K to allow the conversion of mole fractions to molar concentrations
17 ($\text{mol} \cdot \text{dm}^{-3}$). All the solubility experiments were run at least in triplicates and the results were
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31 2.4. Calorimetric study

32 Melting point and enthalpy of fusion of the parabens as original samples were determined by DSC
33 studies (TA Instruments DSC 2920, USA). Thermal analyses were performed at a heating rate of 10
34 K min^{-1} in a dynamic nitrogen atmosphere ($10 \text{ cm}^3 \cdot \text{min}^{-1}$). Nearly 7.0 mg of each paraben were
35 analysed. The equipment was calibrated using Indium as standard.
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41 2.5. X-ray diffraction analysis

42 In order to identify possible polymorphs of the parabens samples studied here, the respective X-ray
43 diffraction spectra for original samples were recorded. These were obtained by using a PANalytical
44 X'Pert PRO diffractometer with Cu K α I radiation line ($\lambda = 0.1540598 \text{ nm}$) and Bragg-Brentano
45 geometry. Equipment was operated in continuous mode between $2\theta = 5^\circ$ and $2\theta = 90^\circ$ and angle
46 variation of 0.02° with detector data acquisition time of 60 s.
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56 3. Results and discussion

57 3.1. Equilibrium solubility of parabens

Table 2 reports the experimental solubility of the three parabens expressed in mole fraction and molarity at 298.15 K. The mole fraction solubility of these compounds increased in 503, 1377 and 4597 times when passing from neat water to neat methanol, for methyl, ethyl and propyl parabens, respectively. Whereas, when molarity scale is considered the increasing values are 181, 471 and 1366 times for the same compounds respectively. These differences in increasing values is a consequence of the scales definitions, being the mole fraction a gravimetric scale considering solute and solvent moles, whereas, the molarity is a volumetric scale considering only the solute moles [12]. Table 2 via footnotes c and d shows that our parabens solubility values in neat solvents are in good agreement with those reported in the literature [5, 24-29]. Nevertheless, it is noteworthy that the different reported aqueous solubility values for parabens vary in some extent [23-26]. This could be due to differences in analysed polymorphic crystals, equilibration times, or the analytical techniques employed [11].

Table 2

Figures 2 and 3 depict DSC thermograms and X-ray diffraction spectra of the original parabens samples. Our calorimetric values are in good agreement with those reported in the literature [30-36]. Onset fusion temperatures including standard uncertainties are: (398.9 ± 0.5) K, (388.8 ± 0.5) K and (369.4 ± 0.5) K for methyl, ethyl and propyl parabens, respectively; while, the enthalpies of fusion including standard uncertainties were: (25.7 ± 0.5) kJ·mol⁻¹, (27.3 ± 0.5) kJ·mol⁻¹ and (28.4 ± 0.6) kJ·mol⁻¹ for methyl, ethyl and propyl parabens, respectively. Values reported by Perlovich *et al.* are as follows: fusion temperatures: (399.2 ± 0.4) K, (389.0 ± 0.7) K and (369.3 ± 0.5) K for methyl, ethyl and propyl parabens, respectively [30]; whereas, the enthalpies of fusion: (25.3 ± 0.7) kJ·mol⁻¹, (26.4 ± 0.8) kJ·mol⁻¹ and (27.2 ± 0.8) kJ·mol⁻¹ for methyl, ethyl and propyl parabens, respectively [30]. Values reported by Prankerd are as follows: fusion temperatures: 404.15 K, 389.15 K and 369.65 K for methyl, ethyl and propyl parabens, respectively [30], and the enthalpies of fusion are as follows: 25.7 kJ·mol⁻¹, 26.5 kJ·mol⁻¹ and 28.0 kJ·mol⁻¹ for methyl, ethyl and propyl parabens, respectively [32]. Other values reported for methyl paraben are as follows: (399.0 ± 0.1) K and (26.4 ± 0.1) kJ·mol⁻¹ [33], 398.6 K and (26.3 ± 0.1) kJ·mol⁻¹ [34], $(398.5 \text{ and } 24.31)$ kJ·mol⁻¹ [35] and 399.2 K and 25.3 kJ·mol⁻¹ [36]. Moreover, other values reported for ethyl paraben are: 388.7 K and 25.76 kJ·mol⁻¹, and for propyl paraben are: 369.6 K and 26.51 kJ·mol⁻¹ [6]. Otherwise, regarding density of paraben solutions, Jahagirdar *et al.* reported the density of methyl paraben in methanol at several concentrations up to 0.200 mol·dm⁻³ at 298.15 K observing a linear trend. The obtained equation is: $\rho/\text{kg}\cdot\text{m}^{-3} = 61.697 \cdot \text{Conc}/\text{mol}\cdot\text{dm}^{-3} + 786.51$ [37]. Accordingly, an extrapolated density value of 0.9352 g·cm⁻³ is obtained when the experimental molar solubility of this paraben is considered ($C^* = 2.41$ mol·dm⁻³). The difference observed regarding our experimental value (0.9257 g·cm⁻³) could be due to the solute-solute

intermolecular interactions present at high concentrations and/or to the simple fact of considering as linear the variation of the solution density with the solute concentration up to saturation.

Figs. 2 and 3

On the other hand, in order to evaluate the effect of other co-solvents on the molar and/or mole fraction solubility of these parabens in aqueous mixtures, Figure 4 compares the molar solubility profiles at 298.15 K in {methanol (1) + water (2)} and {ethanol (1) + water (2)} [9], as a function of the composition of the mixtures expressed in volume fraction of co-solvent, f_1 . It is noteworthy that the solubility of all the parabens is higher in ethanolic mixtures compared with methanolic mixtures although the solubility in both alcohols is very similar. Furthermore, Figure 5 compares the mole fraction solubility profiles at 298.15 K in {methanol (1) + water (2)} and {propylene glycol (1) + water (2)} [9], as a function of f_1 . In this case, the solubility of all the parabens is higher in methanolic mixtures compared with aqueous propylene glycol mixtures even though the solubility is slightly higher in neat propylene glycol.

Figs. 4 and 5

3.2. The co-solvency models

Several methods to estimate the solubility in co-solvent mixtures have been reported in the pharmaceutical and chemical literature [11, 16]. The simplest model to predict drug solubility in co-solvent mixtures is based on the algebraic rule of mixing [38]. For semi-polar compounds in binary mixtures when molarity scale is used this model takes the form:

$$\ln C'_{3(1+2)} = f_1 \ln C'_{3(1)} + f_2 \ln C'_{3(2)} \quad (1)$$

where $C'_{3(1+2)}$ is the molar drug solubility calculated in the respective co-solvent mixture, $C'_{3(1)}$ is the molar drug solubility in neat methanol (component 1), $C'_{3(2)}$ is the molar drug solubility in neat water (component 2), and f_1 and f_2 are the volume fractions of methanol (1) and water (2) in the solvent mixtures in the absence of drug (3). Equation (1) is sometimes used to correlate mole fraction (x_3) solubility with compositions of co-solvent mixtures expressed in mass or mole fraction (w_1 or x_1) [11, 16]. Figure 6 shows the logarithmic molar solubility of these parabens in {methanol (1) + water (2)} mixtures. Negative deviations are observed in water-rich mixtures but positive deviations are observed in methanol-rich mixtures regarding the additive behaviour as described by Eqn. (1). For this reason, the differences between experimental and ideal-additive solubility are shown in Figure 7. Negative deviation regions and magnitudes are lower for methyl paraben ($0 \leq f_1 \leq 0.34$ and -0.25 natural log units as maximum) and higher with propyl paraben ($0 \leq f_1 \leq 0.42$ and $-$

0.36 natural log units as maximum). Conversely, positive deviation regions and magnitudes are lower in region interval but higher in deviation for propyl paraben ($0.42 \leq f_1 \leq 1.00$ and 1.17 natural log units as maximum) compared with methyl paraben that exhibits higher region interval but lower deviation ($0.34 \leq f_1 \leq 1.00$ and 0.70 natural log units as maximum). Ethyl paraben is almost in the middle with respect to region ranges and deviation magnitudes regarding methyl and propyl parabens as explained before. These differences could be attributed mainly to polarity differences being methyl paraben the most polar compound and propyl paraben the less polar as represented by their respective Hildebrand solubility parameters, *i.e.* $\delta_h = 27.2, 26.2$ and $25.4 \text{ MPa}^{1/2}$ for methyl ethyl and propyl parabens, respectively, as calculated based on the Fedors' method [39]. Octanol-water molar partition coefficients also confirm this polarity order as follows: $K_{ow}^c = 105$ for methyl paraben and 689 for propyl paraben at 298.5 K [2]. Similar behaviours have been observed with other drugs in {methanol (1) + water (2)} [14, 22-28] and also in {propylene glycol (1) + water (2)} mixtures [10, 40, 41]. It is noteworthy that methanol and propylene glycol have similar polarities as described by their Hildebrand solubility parameters, *i.e.* 29.6 MPa and $30.2 \text{ MPa}^{1/2}$, respectively [42].

Figs. 6 and 7

A non-linear model is presented for providing more accurate correlations as:

$$\ln x_{3(1+2)} = \frac{\ln x_{3(2)} + \alpha \cdot w_1}{1 + \beta \cdot w_1 + \gamma \cdot w_1^2} \quad (2)$$

where α , β and γ are the model constants [43]. The constants obtained for solubility of parabens in (methanol + water) mixtures and the computed mean percentage deviations (*MPDs*) are listed in Table 3. The *MPD* is computed using:

$$MPD = \frac{100}{N} \sum \frac{|x_{3-(1+2)}^{cal} - x_{3-(1+2)}|}{x_{3-(1+2)}} \quad (3)$$

where N equals the number of experimental data points. The overall *MPD* of 8.5 % was obtained for Eqn. (2).

*** Table 3 ***

In addition to above mentioned models, the solubility of drugs in mixed solvents could be correlated using a number of co-solvency models reported in the literature [44]. These models include the non-linear model of the modified Wilson [45] and the multiple linear regression model of the Jouyban-Acree [46]. The modified Wilson model is expressed as:

$$-\ln x_{3(1+2)} = 1 - \frac{w_1(1 + \ln x_{3(1)})}{w_1 + w_2 \lambda_{12}^{adj}} - \frac{w_2(1 + \ln x_{3(2)})}{w_1 \lambda_{21}^{adj} + w_2} \quad (4)$$

where λ_{12}^{adj} and λ_{21}^{adj} are adjustable parameters of the model which could be evaluated via a non-linear least squares analysis or using a simple computer program which calculates the solute solubility at each composition of the co-solvent and employs pre-selected values for the adjustable parameters [45]. The obtained λ_{12}^{adj} and λ_{21}^{adj} values for solubility of parabens in (methanol + water) mixtures and the *MPD* values obtained are reported in Table 3 where the overall *MPD* of 25.1 % was obtained. Equation (4) represents the solubility of a drug in binary solvent mixtures at isothermal conditions. However, in many practical applications solvent mixing and temperature alteration are used simultaneously. The Jouyban-Acree model describes the solubility of a drug in binary solvent mixtures at various temperatures and expressed as:

$$\ln x_{3(1+2)} = w_1 \ln x_{3(1)} + w_2 \ln x_{3(2)} + \left(\frac{w_1 w_2}{T} \right) \sum_{i=0}^2 J_i (w_1 - w_2)^i \quad (5)$$

where J_i terms are the model constants computed using a no intercept least square analysis [45]. Among various co-solvency models, the Jouyban-Acree model [46] is the most accurate model to represent the solubility of drugs in mixed solvents at various temperatures. The generated solubility values for parabens (3) in {methanol (1) + water (2)} were fitted to the Jouyban-Acree model and the model constants and the *MPD* values obtained are listed in Table 3. The overall *MPD* of 5.4 % was obtained for Eqn. (5).

Although the Jouyban-Acree model provides very accurate correlation for solubility of solutes in (co-solvent + water) mixtures, it requires a minimum number of experimental solubility data points to compute its model constants. When the solubility of parabens in $w_1 = 0.00, 0.30, 0.50, 0.70$ and 1.00 were used to train three models and the rest of the data points were predicted, the prediction overall *MPDs* of (24.0, 76.6 and 10.6)% were obtained, respectively for Eqns. (2), (4) and (5). This finding was also confirmed in earlier works employing other drugs and co-solvent mixtures [47-50]. To reduce the number of required experimental solubility values needed in the prediction process, a general trained version of the Jouyban-Acree model employing Abraham parameters was developed to predict the solubility of drugs in binary solvent mixtures [50] as:

$$\begin{aligned}
\ln x_{3(1+2)} = & w_1 \ln x_{3(1)} + w_2 \ln x_{3(2)} \\
& + 2.303 \left(\frac{w_1 w_2}{T} \right) \left\{ 1843.99 - 730.65[(c_1 - c_2)^2] - 1585.60[E(e_1 - e_2)^2] - 16.31[S(s_1 - s_2)^2] \right\} \\
& + 0.89[A(a_1 - a_2)^2] + 1.40[B(b_1 - b_2)^2] + 1.98[V(v_1 - v_2)^2] \\
& + 2.303 \left(\frac{w_1 w_2 (w_1 - w_2)}{T} \right) \left\{ -833.40 + 860.17[(c_1 - c_2)^2] + 135.24[E(e_1 - e_2)^2] + 0.92[S(s_1 - s_2)^2] \right\} \\
& + 34.99[A(a_1 - a_2)^2] - 2.03[B(b_1 - b_2)^2] - 2.94[V(v_1 - v_2)^2] \\
& + 2.303 \left(\frac{w_1 w_2 (w_1 - w_2)^2}{T} \right) \left\{ 2281.87 - 1386.20[(c_1 - c_2)^2] - 166.92[E(e_1 - e_2)^2] - 16.60[S(s_1 - s_2)^2] \right\} \\
& + 7.98[A(a_1 - a_2)^2] + 7.72[B(b_1 - b_2)^2] - 16.07[V(v_1 - v_2)^2] \quad (6)
\end{aligned}$$

where E is the excess molar refraction, S is dipolarity/polarizability of solute, A denotes the solute's hydrogen-bond acidity, B stands for the solute's hydrogen-bond basicity and V is the McGowan volume of the solute. In Eq. (6) the coefficients c , e , s , a , b and v are the model constants (*i.e.* solvent's coefficients). The Abraham solvent coefficients (c , e , s , a , b and v) for methanol are 0.329, 0.299, -0.671, 0.080, -3.389 and 3.512, respectively. The corresponding values for water are -0.994, 0.577, 2.549, 3.813, 4.841 and -0.869. It should be noted that subscript 1 and 2 in this work mean methanol and water. The Abraham solute parameters (E , S , A , B and V) and the obtained MPD values for the predicted solubility of parabens in (methanol + water) mixtures are listed in Table 4. The overall MPD for the predicted solubility is 17.0%. When these data points were predicted using a similar generally trained model of Yalkowsky [51]:

$$\ln x_{3-(1+2)} = \ln x_{3(2)} + 2.303 f_1 (0.89 \log K_{ow}^C + 0.36) \quad (7)$$

in which $\log K_{ow}^C$ is the logarithm of partition coefficient of the solute. The $\log K_{ow}^C$ values and the obtained prediction $MPDs$ are listed in Table 4 in which the overall MPD is 43.6%. It should be noted that Eqns. (6) and (7) require two and one solubility data points as input values, respectively.

Table 4

3.3. Thermodynamic quantities of dissolution, mixing and solvation of parabens

The ideal solubility of crystalline drugs is calculated as follows:

$$\ln x_3^{id} = -\frac{\Delta H_{fus}(T_{fus} - T)}{RT_{fus}T} + \left(\frac{\Delta C_p}{R} \right) \left[\frac{(T_{fus} - T)}{T} + \ln \left(\frac{T}{T_{fus}} \right) \right] \quad (8)$$

where, ΔH_{fus} is the molar enthalpy of fusion of the solid at the melting point, T_{fus} is the absolute melting point, T is the absolute solution temperature, R is the gas constant ($8.314 \text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$), and ΔC_p^* is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical super-cooled liquid form of the solute, at the solution temperature [52]. Since ΔC_p^* is not frequently reported in the literature, it may be approximated to the entropy of fusion, ΔS_{fus} , calculated as: $\Delta H_{fus}/T_{fus}$. Ideal solubilities of these parabens at 298.15 K calculated based on the calorimetric values reported in Section 3.1 are as follows: $x_3^{id} = 0.1050, 0.1062$ and 0.1383 for methyl, ethyl and propyl parabens, respectively (Table 2).

The experimental solubility expressed in mole fraction allows the calculation of the apparent standard Gibbs energy of the dissolution process according to [53]:

$$\Delta_{soln} G^o = -RT \ln x_3 \quad (9)$$

Table 5 shows that $\Delta_{soln} G^o$ values diminish with the methanol (1) proportion in the mixtures indicating higher affinity of the parabens by the methanol-rich media in comparison with neat water. As described in the literature [14, 20], another physicochemical property used to analyse solute-solvent affinity is the activity coefficient of the drug in the saturated solutions (γ_3) [54]. The γ_3 values are defined on an asymmetric basis and are calculated as follows:

$$\gamma_3 = \frac{x_3^{id}}{x_3} \quad (10)$$

Table 5

Table 5 shows that the activity coefficients of these parabens are higher in neat water (2) (437, 1076 and 3711, for methyl, ethyl and propyl parabens) and diminish as the proportion of methanol (1) increases. It is remarkable that in neat methanol the γ_3 values are lower than unity because experimental solubility values are higher than the ideal solubility. As has been made previously with other organic compounds in this binary solvent system [13, 20, 21], a rough estimate of solute-solvent intermolecular interactions can be made from γ_3 values by considering the following expression [55]:

$$\ln \gamma_3 = (e_{11} + e_{33} - 2e_{13}) \frac{V_3 \phi_1^2}{RT} \quad (11)$$

Here subscript 1 stands for the complete solvent system (methanol + water co-solvent mixtures). Thus, e_{11} , e_{33} and e_{13} represent the solvent-solvent, solute-solute and solvent-solute interaction energies, respectively; V_3 is the molar volume of the super-cooled liquid solute; and φ_1 is the volume fraction of the solvent system in the saturated solution. For compounds with low x_3 solubility, the term $V_3\varphi_1^2/RT$ may be considered almost constant in these mixtures and therefore, γ_3 would depend mainly on e_{11} , e_{33} and e_{13} [55]. As described earlier [54], the e_{11} and e_{33} terms are unfavourable for the dissolution process, but the e_{13} term is favourable.

In a qualitative way, the following analysis could be made based on the energetic quantities described in Eqn. (11): the e_{11} values are highest in neat water (with Hildebrand solubility parameter $\delta_2 = 47.8 \text{ MPa}^{1/2}$) and lower in methanol (with $\delta_1 = 29.6 \text{ MPa}^{1/2}$) [42]. Water and water-rich mixtures exhibiting higher γ_3 values would imply high e_{11} and low e_{13} values. In methanol-rich mixtures or neat methanol, exhibiting γ_3 values near the unity, the e_{11} values are low and the e_{13} values would relatively be high.

Moreover, the overall dissolution process may be represented by the following hypothetical stages [56]:

where the hypothetical dissolution stages are the heating and fusion of the drug, the cooling of the liquid drug to the considered temperature ($T = 298.15 \text{ K}$), and the subsequent mixing of the hypothetical super-cooled liquid drug with the co-solvent mixture at this temperature [56]. Because the ideal solubility values of the drugs are related to the thermodynamic properties of fusion of the same solid forms, the apparent standard Gibbs energy of mixing ($\Delta_{\text{mix}} G^0$, that could also be identified as the excess Gibbs energy, $\Delta_{\text{soln}} G^{\text{nl}}$) could be calculated by means of Eqn. (12), instead of considering only the fusion properties of the drug as has been made sometimes in the literature [53]. Main reasons to use treatments based on ideal dissolution processes instead of those based solely on fusion properties have been well exposed previously [57]. Table 5 shows that the $\Delta_{\text{mix}} G^0$ values in almost all the co-solvent mixtures and neat water are positive because real solubilities are lower than ideal solubility. As would be expected $\Delta_{\text{mix}} G^0$ values in neat methanol are negative because the experimental solubility values are higher than the ideal solubility.

$$\Delta_{\text{mix}} G^0 = \Delta_{\text{soln}} G^0 - \Delta_{\text{soln}} G^{\text{co-id}} \quad (12)$$

Additionally to the previous fusion-mixing process, the dissolution process may also be represented by the other following hypothetical stages [58]:

where the respective partial processes toward the dissolution process are in this case the sublimation and solvation of the drug, which allows to calculate the apparent Gibbs energy of solvation by means of Eqn. (13):

$$\Delta_{\text{solv}} G^{\circ} = \Delta_{\text{solv}} G^{\circ} - \Delta_{\text{subl}} G^{\circ} \quad (13)$$

where the sublimation enthalpies, $\Delta_{\text{subl}} G^{\circ} = (42.2, 43.4 \text{ and } 46.7) \text{ kJ}\cdot\text{mol}^{-1}$ for methyl, ethyl and propyl parabens, respectively, were taken from the literature [30]. Table 5 shows that all the Gibbs energies of solvation are negative demonstrating the preference of these parabens by the dissolution states rather than their respective vapour phases.

3.4. Preferential solvation of parabens

As described earlier [13, 59], in these {methanol (1) + water (2)} mixtures, the preferential solvation parameter of the parabens (3) by methanol (1) is defined as:

$$\delta x_{1,3} = x'_{1,3} - x_1 = -\delta x_{2,3} \quad (14)$$

where $x'_{1,3}$ is the local mole fraction of methanol (1) in the environment near to the paraben molecule (component 3). If $\delta x_{1,3} > 0$ then the paraben (3) is preferentially solvated by methanol (1). On the contrary, if this parameter is < 0 the drug (3) is preferentially solvated by water (2) [60-62]. The values of $\delta x_{1,3}$ are obtainable from the inverse Kirkwood-Buff integrals for the individual solvent components analysed in terms of some classical thermodynamic quantities as shown in equations (15) and (16) [14, 15, 63]:

$$G_{1,3} = RT\kappa_1 - V_3 + x_2 V_2 D/Q \quad (15)$$

$$G_{2,3} = RT\kappa_1 - V_3 + x_1 V_1 D/Q \quad (16)$$

In these equations, κ_1 is the isothermal compressibility of the methanol (1) + water (2) mixtures, V_1 and V_2 are the partial molar volumes of the solvents in the mixtures, and V_3 is the partial molar volume of the parabens in these mixtures. D is the derivative of the standard molar Gibbs energies of transfer of the parabens [from neat water (1) to {methanol (1) + water (2)} mixtures] with respect

to the methanol proportion in the mixtures and Q involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents ($G_{1,2}^E$) with respect to the water proportion in the mixtures:

$$D = \left(\frac{\partial \Delta_u G_{1,2}^o}{\partial x_1} \right)_{T,P} \quad (17)$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1,2}^E}{\partial x_2^2} \right)_{T,P} \quad (18)$$

In this way, the preferential solvation parameter by methanol can be calculated from the Kirkwood-Buff integrals as follows:

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{\text{cor}}} \quad (19)$$

Here, the correlation volume (V_{cor}) is obtained by means of the following expression [64]:

$$V_{\text{cor}} = 2522.5 \left(r_3^3 + 0.1363 (x_1' V_1 + x_2' V_2)^{1/3} - 0.085 \right)^3 \quad (20)$$

where r_3 is the molecular radius of the solute (in nm) that could be calculated as:

$$r_3 = \left(\frac{3 \cdot 10^{-24} V_3}{4\pi N_{\text{Av}}} \right)^{1/3} \quad (21)$$

in which V_3 is the molar volume of the solute and N_{Av} is the Avogadro number. However, the definitive correlation volume requires iteration, because it depends on the local mole fractions around the paraben molecules.

Table 5 and Figure 8 show the Gibbs energy of transfer behaviour of the three parabens (3) from neat water (2) to {methanol (1) + water (2)} mixtures at 298.15 K. These values were calculated from the respective mole fraction solubility (Table 2) by using the following expression:

$$\Delta_u G_{1,2}^o = RT \ln \left(\frac{x_{1,2}}{x_{1,2}^0} \right) \quad (22)$$

The $\Delta_{tr}G_{3,2}^{o, s+2}$ values were correlated according to regular polynomials in fourth degree presented as Eqn. (23). The obtained coefficients ($\text{kJ}\cdot\text{mol}^{-1}$) are shown in Table 6.

$$\Delta_{tr}G_{3,2}^{o, s+2} = L_1 + L_2x_1 + L_3x_1^2 + L_4x_1^3 + L_5x_1^4 \quad (23)$$

Figure 8, Table 6

Thus, D values were calculated from the first derivative of the polynomial models solved according to the methanol proportion in the mixtures (Table 7). Otherwise, Q and $RT\cdot\kappa_I$ values for the {methanol (1) + water (2)} mixtures, as well as the partial molar volumes of methanol and water at 298.15 K, were taken from the literature [65, 66].

The molar volume of the parabens is considered here as independent of the co-solvent composition as we did earlier in previous research [67]. These values were calculated according to the Fedors' method as (113.9, 130.0 and 146.1) $\text{cm}^3\cdot\text{mol}^{-1}$ for methyl, ethyl and propyl parabens, respectively [38, 68].

Table 7 shows that D values for the parabens are negative in all the mixtures compositions. The $G_{1,3}$ and $G_{2,3}$ values are also negative in all the co-solvent compositions indicating that these compounds exhibits affinity for both methanol (1) and water (2) in all the mixtures considered.

Table 7

Solute radius (r_3) values, required to calculate the correlation volumes, were taken from the literature as 0.356, 0.372 and 0.387 nm for methyl, ethyl and propyl parabens, respectively [68]. Thus, the respective correlation volumes were iterated three times by using equations (14), (19) and (20) to obtain the values reported in Table 8. As typical, V_{cor} values increase as the molar volume of the co-solvent mixtures also increase because of the higher molar volume of methanol (1) compared with water (2).

Table 8

Figure 9 and Table 8 show that the $\delta x_{1,3}$ values for all the parabens vary non-linearly with the methanol (1) proportion in all the aqueous mixtures studied. It is very important to note that the absolute values of $\delta_{1,3}$ are higher than 1.0×10^{-2} and thus the results are a consequence of the preferential solvation of the parabens rather than the effect of uncertainties propagation [60-62]. Addition of methanol (1) to water (2) makes negative the $\delta x_{1,3}$ values of the parabens from the neat

water to the mixture with $x_1 = 0.32$, reaching minimum $\delta x_{1,3}$ values of -3.13×10^{-2} , -3.35×10^{-2} and -3.70×10^{-2} , in the mixture $x_1 = 0.15$, for methyl, ethyl and propyl parabens, respectively. Probably, the structuring of water molecules around the non-polar groups of the parabens (phenyl ring and alkyl chains) contributes to make negative the net $\delta x_{1,3}$ values in these water-rich mixtures.

Figure 9

In the mixtures with compositions $0.32 < x_1 < 1.00$, the parabens are preferentially solvated by methanol (1) because of the positive $\delta x_{1,3}$ values. The co-solvent action may be related to the breaking of the ordered structure of water around the non-polar moieties of these compounds. The preferential solvation by methanol (1) reach maximum values in the mixture $x_1 = 0.50$ with $\delta x_{1,3} = 3.97 \times 10^{-2}$, 5.34×10^{-2} and 6.27×10^{-2} for methyl, ethyl and propyl parabens, respectively.

Based on the molecular structure of the parabens (Figure 1), these compounds could act in solution as Lewis acids and/or bases to establish hydrogen bonds with proton-acceptor or proton-donor functional groups of methanol (1) and water (2) molecules. Regarding the preferential solvation by methanol molecules, it is conjecturable that in mixtures of similar compositions and in methanol-rich mixtures, the parabens are acting as Lewis acid with methanol molecules because this co-solvent is more basic than water owing its higher non-shared electron density of the pairs present in the hydroxyl oxygen atom. This is described by the respective Kamlet-Taft hydrogen bond acceptor parameters, *i.e.* $\beta = 0.66$ for methanol and 0.47 for water [69, 70].

Furthermore, Figure 10 compares the preferential solvation of these parabens in {methanol (1) + water (2)} and {propylene glycol (1) + water (2)} mixtures at 298.15 K [68]. The preferential solvation magnitudes of the parabens by both water and methanol are higher in {methanol (1) + water (2)} mixtures compared to {propylene glycol (1) + water (2)} mixtures. Furthermore, the composition regions of preferential solvation are different with both co-solvents. Thus, preferential solvation by water is observed in mixtures with $0.00 < x_1 < 0.32$ in {methanol (1) + water (2)} mixtures but it is observed in mixtures with $0.00 < x_1 < 0.20$ in {propylene glycol (1) + water (2)} mixtures. Moreover, the mixtures of maximum preferential solvation by water and co-solvent are also different in both cases, *i.e.* $x_1 = 0.15$ and 0.50 in {methanol (1) + water (2)} mixtures and $x_1 = 0.10$ and 0.40 in {propylene glycol (1) + water (2)} mixtures, respectively [68]. These differences could be attributed to the slight higher polarity of propylene glycol compared with methanol.

Figure 10

Figures 11 and 12 show the effect of the alkyl chain length (number of methylene groups) on the preferential solvation magnitude of the parabens by water (Figure 11) and co-solvent (Figure 12) in {methanol (1) + water (2)} and {propylene glycol (1) + water (2)} mixtures at 298.15 K [68].

As described previously, the preferential solvation by both water and co-solvent increase as the number of methylene groups' increase for both binary solvent systems. Moreover, the preferential solvation by both water and co-solvent are higher in {methanol (1) + water (2)} mixtures compared with {propylene glycol (1) + water (2)} mixtures, as was already mentioned.

Figs. 11 and 12

4 Conclusions

Equilibrium solubility of three parabens, namely, methyl, ethyl and propyl parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K has been determined and reported. These values of the solubility were adequately correlated with the Jouyban-Acree model. Expressions for the local mole fraction of methanol (1) and water (2) around these compounds were derived on the basis of the IKB1 method applied to the solubility values obtained. Thus, these parabens are preferentially solvated by water in water-rich mixtures, probably due to hydrophobic hydration around alkyl and phenyl groups, but preferentially solvated by methanol in mixtures with intermediate compositions and also in methanol-rich mixtures, probably due to their behaviours as Lewis acids with this co-solvent. Finally, the solubility results presented in this report contribute to expand the physicochemical information about pharmaceutical organic compounds in binary aqueous-co-solvent mixtures [11].

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Table 1. Source and purities of the reagents used in this research.

Reagent	CAS ^a	Formula	Molar mass / g·mol ⁻¹	Source	Purity in mass fraction ^b	Analytic technique ^c
Methyl Paraben	99-76-3	C ₈ H ₈ O ₃	152.15	Sigma-Aldrich, USA	0.990	HPLC
Ethyl Paraben	120-47-8	C ₉ H ₁₀ O ₃	166.18	Sigma-Aldrich, USA	0.990	HPLC
Propyl Paraben	94-13-3	C ₁₀ H ₁₂ O ₃	180.20	Sigma-Aldrich, USA	0.990	HPLC
Methanol	67-56-1	CH ₄ O	32.04	Merck, Germany	0.998	GC
Water	7732-18-5	H ₂ O	18.02	Obtained by distillation	>0.999	-

^a Chemical Abstracts Service Registry Number.

^b All parabens and methanol were used without further purification.

^c As reported by the suppliers. HPLC is high liquid performance chromatography; GC is gas chromatography.

Table 2. Solubility and density of saturated solutions of parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K and local pressure $p = 73.9$ kPa.

Mixtures composition ^a				Solubility ^b						$\rho / \text{g} \cdot \text{cm}^{-3} \text{ } ^b$	
				Methyl Paraben		Ethyl Paraben		Propyl Paraben			
$w_1 \text{ } ^{b,c}$	f_1	x_1	x_3	$\text{mol} \cdot \text{dm}^{-3}$	x_3	$\text{mol} \cdot \text{dm}^{-3}$	x_3	$\text{mol} \cdot \text{dm}^{-3}$	Methyl Paraben	Ethyl Paraben	Propyl Paraben
0.000 ^d	0.0000	0.0000	2.40×10^{-4}	1.33×10^{-2}	9.86×10^{-3}	5.45×10^{-3}	3.73×10^{-3}	2.06×10^{-3}	0.9973	0.9971	0.9971
0.100	0.1234	0.0588	3.95×10^{-4}	2.05×10^{-2}	1.81×10^{-2}	9.40×10^{-3}	7.45×10^{-3}	3.85×10^{-3}	0.9805	0.9810	0.9770
0.200	0.2406	0.1232	7.41×10^{-4}	3.61×10^{-2}	3.50×10^{-2}	1.71×10^{-2}	1.67×10^{-2}	8.15×10^{-3}	0.9678	0.9663	0.9661
0.300	0.3519	0.1942	1.90×10^{-3}	8.60×10^{-2}	8.21×10^{-2}	3.75×10^{-2}	4.61×10^{-2}	2.11×10^{-2}	0.9517	0.9512	0.9520
0.400	0.4579	0.2726	5.00×10^{-3}	0.209	2.60×10^{-3}	0.110	1.63×10^{-3}	6.90×10^{-2}	0.9405	0.9385	0.9341
0.500	0.5589	0.3599	1.19×10^{-2}	0.450	8.43×10^{-3}	0.322	5.80×10^{-3}	0.223	0.9318	0.9262	0.9222
0.600	0.6552	0.4575	2.39×10^{-2}	0.808	2.36×10^{-2}	0.781	2.02×10^{-2}	0.672	0.9309	0.9207	0.9171
0.700	0.7472	0.5675	3.98×10^{-2}	1.20	4.96×10^{-2}	1.39	5.41×10^{-2}	1.46	0.9327	0.9245	0.9255
0.800	0.8352	0.6922	6.00×10^{-2}	1.59	7.68×10^{-2}	1.86	9.41×10^{-2}	2.10	0.9344	0.9294	0.9392
0.900	0.9194	0.8350	8.69×10^{-2}	2.01	0.107	2.24	0.134	2.51	0.9311	0.9306	0.9439
1.000 ^e	1.0000	1.0000	0.121	2.41	0.136	2.57	0.171	2.82	0.9257 ^f	0.9280	0.9436
Ideal process				0.1050	0.1062		0.1383				

^a w_1, f_1 and x_1 are the mass, volume, and mole fractions of methanol (1) in the methanol (1) + water (2) mixtures free of paraben (3), respectively.

^b Standard uncertainties are $u(T) = 0.05$ K, $u(p) = 2.2$ kPa, $u(w_1) = 0.0003$. Average relative standard uncertainty in solubility, $u(x_3)$ and $u(\rho)$ (mol dm⁻³), are 0.030 (or 3.0%). Average standard uncertainty in densities is $u(\rho) = 0.0007$ g·cm⁻³. Standard uncertainty in temperature for density values is $u(T) = 0.12$ K.

^c UV analysis was used for paraben quantification in the mixtures with $0.00 \leq w_1 < 0.40$ but gravimetric analysis was used for paraben quantification in the mixtures with $0.50 \leq w_1 \leq 1.00$.

^d Other reported molar solubility values in neat water (2) at 298.15 K vary as follows: from 1.141×10^{-2} to 3.162×10^{-2} mol·dm⁻³ for methyl paraben [23-25], from (4.090×10^{-3}) to 9.628×10^{-3} mol·dm⁻³ for ethyl paraben [23, 24, 26], and from (1.778×10^{-3}) to 2.863×10^{-3} mol·dm⁻³ for propyl paraben [23, 25, 27].

^e Other reported mole fraction solubility values in neat methanol (1) at 298.15 K are as follows: $x_3 = 0.121$, $x_3 = 0.125$ and $x_3 = 0.1254$ for methyl paraben [5, 28, 29], $x_3 = 0.135$ and $x_3 = 0.137$ for ethyl paraben [5, 28], and $x_3 = 0.172$ and $x_3 = 0.173$ for propyl paraben [5, 28].

^f The density value $\rho = 0.9352$ g·cm⁻³ is obtained by extrapolation from the data reported by Jahagirdar *et al.* for methyl paraben in neat methanol [37].

Table 3. The model constants and mean percentage deviations (*MPD*) for the investigated models trained by whole data points and the minimum number of data points

Compound	Yalkowsky model (Eqn. (2))			
	α	β	γ	<i>MPD</i>
Whole data points				
Methyl Paraben	-2.287	0.426	3.616	3.8
Ethyl Paraben	2.161	-0.112	3.036	8.3
Propyl Paraben	5.111	-0.297	2.636	13.5
			Overall	8.5
Minimum <i>N</i> of data points				
Methyl Paraben	-5.286	0.457	4.967	7.0
Ethyl Paraben	-4.276	0.323	6.349	46.0
Propyl Paraben	2.234	-0.518	4.317	18.9
			Overall	24.0
Modified Wilson model (Eqn. (4))				
	λ_{12}^{adj}	λ_{21}^{adj}	-	<i>MPD</i>
Whole data points				
Methyl Paraben	8.124	1.073		16.7
Ethyl Paraben	-0.005	1.863		27.3
Propyl Paraben	81745499.1	1.144		31.4
			Overall	25.1
Minimum <i>N</i> of data points				
Methyl Paraben	132.148	1.030		38.2
Ethyl Paraben	-0.237	2.591		152.4
Propyl Paraben	127223256.1	1.175		39.3
			Overall	76.6
Jouyban-Acree model (Eqn. (5))				
	J_0	J_1	J_2	<i>MPD</i>
Whole data points				
Methyl Paraben	912.422	973.219	-1243.002	2.5
Ethyl Paraben	957.663	1771.501	-748.816	7.0
Propyl Paraben	1024.571	2092.285	-454.649	6.6
			Overall	5.4
Minimum <i>N</i> of data points				
Methyl Paraben	944.938	981.309	-1658.966	4.7
Ethyl Paraben	994.570	2146.840	-1286.943	12.7
Propyl Paraben	991.702	2472.613	-147.274	14.3
			Overall	10.6

Table 4. The model constants and mean percentage deviations (*MPD*) for the investigated models trained by whole data points and the minimum number of data points

Compound	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	$\log K_{o,w}^c$	<i>MPD</i> (Eqn. (6))	<i>MPD</i> (Eqn. (7))
Methyl Paraben	0.87	1.24	0.66	0.72	1.1313	1.86	22.8	44.3
Ethyl Paraben	0.87	1.25	0.66	0.72	1.2722	2.40	11.8	41.9
Propyl Paraben	0.87	1.25	0.66	0.73	1.4131	2.93	16.3	44.7
Overall							17.0	43.6

Table 5. Some apparent thermodynamic properties of parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K and local pressure $p = 73.9$ kPa.

$w_1^{a,b}$	γ_3^b	$\Delta_{\text{soln}}G^\circ /$ kJ mol ^{-1b}	$\Delta_{\text{mix}}G^\circ /$ kJ mol ^{-1b}	$\Delta_{\text{soln}}G^\circ /$ kJ mol ^{-1b}	$\Delta_u G^\circ /$ kJ mol ^{-1b}
Methyl Paraben					
0.000	437	20.66	15.07	-21.54	0.00
0.100	266	19.42	13.84	-22.78	-1.24
0.200	142	17.87	12.28	-24.33	-2.79
0.300	55.4	15.54	9.95	-26.66	-5.12
0.400	21.0	13.13	7.55	-29.07	-7.53
0.500	8.84	10.99	5.40	-31.21	-9.67
0.600	4.40	9.26	3.67	-32.94	-11.40
0.700	2.64	7.99	2.41	-34.21	-12.67
0.800	1.75	6.98	1.39	-35.22	-13.68
0.900	1.21	6.06	0.47	-36.14	-14.60
1.000	0.870	5.24	-0.35	-36.96	-15.42
Ethyl Paraben					
0.000	1076	22.87	17.31	-20.53	0.00
0.100	587	21.36	15.81	-22.04	-1.50
0.200	303	19.72	14.16	-23.68	-3.14
0.300	129	17.61	12.05	-25.79	-5.25
0.400	40.8	14.75	9.20	-28.65	-8.11
0.500	12.6	11.84	6.28	-31.56	-11.03
0.600	4.51	9.29	3.73	-34.11	-13.58
0.700	2.14	7.45	1.89	-35.95	-15.42
0.800	1.38	6.36	0.80	-37.04	-16.50
0.900	0.993	5.54	-0.02	-37.86	-17.32
1.000	0.782	4.95	-0.61	-38.45	-17.92
Propyl Paraben					
0.000	3711	25.28	20.37	-21.42	0.00
0.100	1857	23.56	18.66	-23.14	-1.72
0.200	829	21.56	16.66	-25.14	-3.72
0.300	300	19.05	14.14	-27.65	-6.23
0.400	84.7	15.91	11.01	-30.79	-9.37
0.500	23.8	12.77	7.86	-33.93	-12.51
0.600	6.85	9.67	4.77	-37.03	-15.61
0.700	2.56	7.23	2.33	-39.47	-18.05
0.800	1.47	5.86	0.96	-40.84	-19.42
0.900	1.03	4.98	0.08	-41.72	-20.30
1.000	0.807	4.37	-0.53	-42.33	-20.91

^a w_1 is the mass of methanol (1) in {methanol (1) + water (2)} mixtures free of paraben (3).

^b Standard uncertainties are $u(T) = 0.05$ K, $u(p) = 2.2$ kPa, $u(w_1) = 0.0003$. Average relative standard uncertainty in activity coefficients are $u_r(\gamma_3) = 0.036$ (or 3.6%). Average relative standard uncertainty in the apparent thermodynamic quantities of real solution processes are $u_r(\Delta_{\text{soln}}G^\circ) = 0.031$ (or 3.1%), $u_r(\Delta_{\text{mix}}G^\circ) = 0.036$ (or 3.6%), $u_r(\Delta_{\text{soln}}G^\circ) = 0.040$ (or 4.0%), $u_r(\Delta_u G^\circ) = 0.042$ (or 4.2%).

Table 6. Equation (23) parameters of parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K.

Paraben	L_1	L_2	L_3	L_4	L_5	r^2
Methyl Paraben	0.16	-23.25	-37.19	94.36	-49.58	0.9988
Ethyl Paraben	-0.06	-17.51	-80.52	153.31	-73.18	0.9995
Propyl Paraben	-0.06	-21.57	-83.43	157.52	-73.37	0.9999

Table 7. Some solvation properties of parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K.

x_1^a	$D / \text{kJ} \cdot \text{mol}^{-1}$			$G_{1,1} / \text{cm}^3 \cdot \text{mol}^{-1}$			$G_{2,1} / \text{cm}^3 \cdot \text{mol}^{-1}$		
	Methyl Paraben	Ethyl Paraben	Propyl Paraben	Methyl Paraben	Ethyl Paraben	Propyl Paraben	Methyl Paraben	Ethyl Paraben	Propyl Paraben
0.00	-23.25	-17.51	-21.57	-282.5	-256.7	-302.5	-112.8	-128.9	-145.0
0.05	-26.29	-24.45	-28.77	-292.7	-296.3	-342.0	-132.1	-146.8	-166.1
0.10	-28.05	-29.31	-33.83	-297.2	-321.6	-367.4	-155.1	-173.1	-196.1
0.15	-28.71	-32.31	-36.96	-296.8	-336.1	-382.1	-180.8	-205.5	-232.6
0.20	-28.39	-33.67	-38.39	-292.0	-341.5	-387.5	-207.9	-241.7	-273.7
0.25	-27.25	-33.60	-38.34	-282.7	-338.5	-384.2	-234.7	-279.4	-316.8
0.30	-25.44	-32.33	-37.03	-269.0	-327.6	-372.6	-259.1	-315.0	-358.2
0.35	-23.11	-30.09	-34.67	-251.2	-309.3	-353.0	-278.3	-344.6	-393.6
0.40	-20.40	-27.07	-31.49	-230.1	-284.8	-326.5	-289.3	-363.4	-418.0
0.45	-17.46	-23.52	-27.71	-207.0	-256.1	-295.0	-290.0	-367.8	-426.6
0.50	-14.45	-19.64	-23.55	-183.8	-225.7	-261.3	-279.3	-355.5	-417.0
0.55	-11.52	-15.66	-19.23	-162.5	-196.9	-228.8	-258.9	-327.9	-389.6
0.60	-8.80	-11.79	-14.96	-144.9	-172.3	-200.4	-232.1	-289.1	-348.6
0.65	-6.45	-8.25	-10.97	-131.7	-153.5	-178.1	-203.8	-245.7	-300.8
0.70	-4.62	-5.27	-7.49	-123.0	-140.7	-162.4	-179.2	-204.9	-253.5
0.75	-3.46	-3.07	-4.72	-118.0	-133.3	-152.6	-162.7	-173.0	-213.7
0.80	-3.11	-1.86	-2.89	-115.6	-130.0	-147.5	-157.8	-155.1	-186.7
0.85	-3.73	-1.86	-2.22	-114.8	-129.0	-145.5	-167.4	-155.2	-176.8
0.90	-5.46	-3.29	-2.92	-114.4	-129.1	-145.0	-194.5	-177.4	-188.0
0.95	-8.45	-6.37	-5.23	-113.4	-128.9	-144.6	-243.6	-227.1	-225.3
1.00	-12.85	-11.33	-9.36	-110.8	-126.9	-143.0	-322.0	-313.2	-296.9

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

Table 8. Correlation volume and preferential solvation parameter properties of parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K.

x_1^a	$V_{\text{cor}} / \text{cm}^3 \cdot \text{mol}^{-1}$			$100 \Delta \epsilon_{1,3}$		
	Methyl Paraben	Ethyl Paraben	Propyl Paraben	Methyl Paraben	Ethyl Paraben	Propyl Paraben
0.00	628	677	724	0.00	0.00	0.00
0.05	640	691	739	-1.53	-1.32	-1.48
0.10	655	705	753	-2.63	-2.58	-2.86
0.15	671	722	770	-3.13	-3.35	-3.70
0.20	691	742	791	-2.89	-3.32	-3.68
0.25	714	765	816	-1.93	-2.35	-2.62
0.30	738	793	845	-0.44	-0.56	-0.63
0.35	764	822	877	1.24	1.64	1.86
0.40	789	850	908	2.72	3.64	4.17
0.45	812	876	936	3.67	4.95	5.73
0.50	833	898	960	3.97	5.34	6.27
0.55	852	917	980	3.69	4.90	5.87
0.60	870	934	997	3.03	3.92	4.82
0.65	887	951	1014	2.25	2.74	3.52
0.70	904	967	1030	1.55	1.67	2.28
0.75	923	985	1048	1.06	0.88	1.30
0.80	942	1005	1068	0.82	0.46	0.69
0.85	963	1026	1089	0.80	0.37	0.42
0.90	984	1049	1112	0.84	0.48	0.40
0.95	1005	1071	1135	0.70	0.50	0.39
1.00	1023	1091	1156	0.00	0.00	0.00

^a x_1 is the mole fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of paraben (3).

Figure 1. Molecular structure of parabens. n = 1: Methyl Paraben, n = 2: Ethyl Paraben, and n = 3: propyl paraben.

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Figure 2. DSC thermograms of parabens as original samples.

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Figure 3. X-ray diffraction spectra of parabens as original samples.

Figure 4. Logarithmic molar solubility of parabens (3) in some {co-solvent (1) + water (2)} mixtures at 298.15 K. $\circ$: methanol (1) + water (2); $\square$: ethanol (1) + water (2) [9].

Figure 5. Logarithmic mole fraction solubility of parabens (3) in some {co-solvent (1) + water (2)} mixtures at 298.15 K. $\circ$: methanol (1) + water (2); $\square$: propylene glycol (1) + water (2) [10].

Figure 6. Logarithmic molar solubility of parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K. $\circ$: methyl paraben; $\square$: ethyl paraben; Δ : propyl paraben. Dotted lines represent calculated solubilities by using Eqn. (1).

Figure 7. Excess logarithmic molar solubility of parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K. $\circ$: methyl paraben; $\square$: ethyl paraben; Δ : propyl paraben.

Figure 8. Gibbs energy of transfer of parabens (3) from neat water (2) to {methanol (1) + water (2)} mixtures at 298.15 K. ○: methyl paraben; ◻: ethyl paraben; Δ: propyl paraben.

Figure 9. $\Delta x_{1,3}$ values parabens (3) in {methanol (1) + water (2)} mixtures at 298.15 K. ○: methyl paraben; ◻: ethyl paraben; Δ: propyl paraben.

Figure 10. $\delta x_{1,3}$ values of parabens (3) in some {co-solvent (1) + water (2)} mixtures at 298.15 K.
 ○: methanol (1) + water (2); □: propylene glycol (1) + water (2) [68].

Figure 11. Effect of the alkyl-chain length on the maximum preferential solvation by water of parabens (3) in some {co-solvent (1) + water (2)} mixtures at 298.15 K. $\circ$: methanol (1) + water (2) (obtained in $x_1 = 0.15$); $\square$: propylene glycol (1) + water (2) (obtained in $x_1 = 0.10$) [68].

Figure 12. Effect of the alkyl-chain length on the maximum preferential solvation by co-solvent of parabens (3) in some {co-solvent (1) + water (2)} mixtures at 298.15 K. $\circ$: methanol (1) + water (2) (obtained in $x_1 = 0.50$); $\square$: propylene glycol (1) + water (2) (obtained in $x_1 = 0.40$) [68].