PERFORMANCE OF THE JOUYBAN-ACREE AND YALKOWSKY-ROSEMAN MODELS FOR ESTIMATING THE SOLUBILITY OF INDOMETHACIN IN ETHANOL + WATER MIXTURES

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Abstract

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Indomethacin (IMC) is an anti-inflammatory drug whose physiochemical properties in aqueous solutions have not been studied thoroughly. For this reason, in this work the validity of the Jouyban-Acree and Yalkowsky-Roseman models is evaluated to predict the solubility of this compound in ethanol + water cosolvent mixtures. The solubility estimation is studied as a function of temperature and cosolvent composition. Both models require only the experimental solubility values in the pure solvents at all the temperatures evaluated. The solubility calculated values by using both models deviate notoriously from experimental values in several cases.

Key words: indomethacin; ethanol + water cosolvent mixtures; Jouyban-Acree and Yalkowsky-Roseman models.

Resumen

"Desempeño de los modelos de Jouyban & Acree y Yalkowsky & Roseman en la estimación de la solubilidad de indometacina en mezclas cosolventes etanol + agua".

La indometacina (IMC) es un fármaco antinflamatorio cuyas propiedades fisicoquímicas en solución acuosa no han sido estudiadas ampliamente. Por esta razón, en este trabajo se evaluó la utilidad de los modelos Jouyban-Acree (J-A) y Yalkowsky-Roseman (Y-R) en la predicción de la

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solubilidad de este fármaco en mezclas cosolventes etanol + agua. La estimación de la solubilidad se estudió en función de la temperatura y la composición cosolvente. Los dos modelos requieren únicamente los valores de solubilidad en los solventes puros a todas las temperaturas de interés. Los valores calculados se desvían significativamente de los experimentales en muchos casos.

Palabras clave: indometacina; mezclas etanol + agua; modelos de Jouyban-Acree y Yalkowsky-Roseman.

Introduction

Indomethacin (IMC, Fig. 1) is an anti-inflammatory drug sometimes used in actual therapeutics (**Budavari, S. *et al.*** 2001; **Raffa, R.B.**, 2005). Unfortunately, physicochemical properties of IMC useful at industrial level have not been thoroughly studied. In this context, it is well known that several physicochemical properties such as, the solubility and occupied volumes by active ingredients and excipients in adequate solutions, are very important for all the pharmaceutical scientists, because they facilitate the processes associated to design and development of new products in the pharmaceutical industries (**Jiménez, F. & Martínez, F.**, 1995). Moreover, the reported techniques intended to predict these values are highly appreciated for practical applications because they diminish the economic and experimental efforts which imply significant reductions in costs and time during the design and development stages (**Jouyban, A.**, 2010).

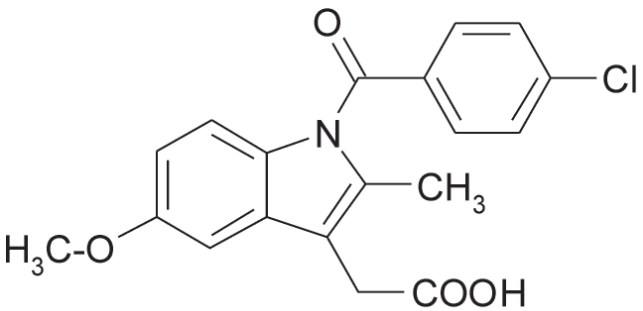

Figure 1. Molecular structure of indomethacin.

For these reasons, the main objective of this study was to evaluate the usefulness of Jouyban-Acree model (**Jouyban, A. & Acree Jr., W.E.**, 2006) to predict the equilibrium solubility of IMC in binary mixtures conformed by ethanol and water as a function of the solvent composition and temperature. In similar way, the log-lineal model proposed by **Yalkowsky, S.H. & Roseman, T.J.** (1981) was also challenged in front to the experimental solubility values at equilibrium of this drug. Thus, this investigation expands the information reported previously for the solubility estimation of naproxen and ketoprofen in the same cosolvent system (**Vargas, E. *et al.*** 2008; **Gantiva, M. *et al.*** 2009).

Theoretical

The different strategies intended to estimate physicochemical properties of drugs are highly valued at industrial level. Several methods to estimate the solubility in solvent mixtures have been reported in the pharmaceutical and chemical literature (**Jouyban-Gharamaleki, A. *et al*.** 1999; **Nokhodchi, A. *et al*.** 2002). Some of them have been challenged recently in the correlation of the equilibrium solubility of several drugs (**Jouyban, A.**, 2008; **Jouyban, A.**, 2010).

As was already exposed (**Vargas, E. *et al.*** 2008; **Gantiva, M. *et al*.** 2009), the simplest model to predict drug solubility in cosolvent mixtures is the one based on the algebraic rule of mixing, which for semipolar compounds in binary mixtures takes the following form:

$$\log X_{2-\text{Mix}} = f \log X_{2-\text{Cosolv}} + (1-f) \log X_{2-\text{Water}} \quad (1)$$

where $X_{2\text{-Mix}}$ is the drug solubility calculated in the cosolvent mixture considered, $X_{2\text{-Cosolv}}$ is the drug solubility in the neat cosolvent, $X_{2\text{-Water}}$ is the drug solubility in neat water, and f is the volume fraction of cosolvent in the mixture free of drug dissolved. This last term is calculated assuming additive volumes according to:

$$f = V_{\text{Cosolv}} / (V_{\text{Cosolv}} + V_{\text{Water}}) \quad (2)$$

where, V_{Cosolv} and V_{Water} are the respective volumes of cosolvent and water (**Connors, K.A.**, 2002). Equation 1 is a practical form of the logarithmic-lineal model developed by **Yalkowsky, S.H. & Roseman, T.J.** (1981), which has the form:

$$\log S_{2-\text{Mix}} = \log S_{2-\text{Water}} + \sigma \cdot f \quad (3)$$

where $S_{2\text{-Mix}}$ and $S_{2\text{-Water}}$ are the solubilities (as molarity or mole fraction) in the cosolvent mixture and water, respectively, and σ is the solubilizing power factor in the same solute-solvent system. The σ term in equation 3 has

been correlated with several polarity indexes such as, octanol-water partition coefficients, Hildebrand solubility parameters, and interfacial tensions, among others (**Rubino, J.T. & Yalkowsky, S.H.**, 1987).

Nevertheless, it was found experimentally that the behavior of several lipophilic solutes deviate notoriously from this simple additive rule of solubility, in particular when the solvents used are amphiprotic. In particular, in the case of propylene glycol + water mixtures, **Rubino, J.T. & Obeng, E.K.** (1991) by studying the solubility of homologous series of some alkyl *p*-hydroxibenzoates and *p*-aminobenzoates, found negative deviations to equation 1 in water-rich mixtures and positive deviations in propylene glycol-rich mixtures. These authors suggested that cosolvent-water interactions were responsible on the observed deviations, and thereby, they exposed that cosolvent interact with water by two mechanisms, namely, (a) hydrophobic hydration by forming water "icebergs" around the non-polar groups in the cosolvent, and (b) interaction between the cosolvent hydroxyl group and water molecules by hydrogen bonding, which could increase the water-structure formation obtained because of the hydrophobic effect. Thus, both interactions lead to diminish the solute-solvent interactions and thereby, the drug solubility. Opposite, in those mixtures with high cosolvent proportion the hydrogen bonding among cosolvent and water is also present but the water-structure formation has diminished or it has disappeared.

As good attempt to consider the deviations non taken into account by equation 1 Jouyban and Acree proposed the equation 4, where T is the absolute temperature and J_i are the respective polynomial coefficients. J_i coefficients have theoretical meaning because each one of them is a function of the interaction energies among two and three bodies, which in turn describe the attractions among the different molecules present in solution. Equation 4 is derivate from the equation originally proposed by **Redlich, O. & Kister, A.T.** (1948), and its development as well as its meaning has been described previously in the literature (**Acree Jr., W.E.**, 1992; **Jouyban, A. *et al.*** 2006).

$$\log X_{2\text{–Mix}} = f \log X_{2\text{–Cosolv}} + (1-f)\log X_{2\text{–Water}} + f(1-f)\sum_{i=0}^{n}\frac{J_i(f-(1-f))^i}{T} \quad (4)$$

Recently, **Jouyban, A. & Acree Jr., W.E.** (2006) processed by regression analysis the reported solubility values (as mole fraction) of several drugs in ethanol + water mixtures in front to equation 4, obtaining the equation 5, whose coefficients were statistically significant with $p < 0.05$ according to the Student's t-test.

$$\log X_{2\text{–Mix}} = f \log X_{2\text{–Cosolv}} + (1-f)\log X_{2\text{–Water}} + \text{J - A factor} \quad (5)$$

where the Jouyban-Acree factor is defined according to:

$$\text{J-A factor} = f(1-f)\left[\frac{724.21}{T} + \frac{485.17(f-(1-f))}{T} + \frac{194.41(f-(1-f))^2}{T}\right] \quad (5b)$$

Experimental

Reagents and Materials

In this investigation the following reagents and materials were used: indomethacin accomplishing the British Pharmacopoeia quality requirements (**BP 1998**, 1998), absolute ethanol A.R. Merck (EtOH), distilled water with conductivity < 2 μS cm^{-1}, molecular sieve Merck (numbers 3 and 4, pore size 0.3 and 0.4 nm, respectively), and Durapore® 0.45 μm filters from Millipore Corp.

Solvent mixtures preparation

The dehydrated EtOH employed was maintained over molecular sieve (Merck Number 3, 0.3 nm in pore diameter) to obtain a dry solvent previously to prepare the cosolvent mixtures. The ethanol dryness was demonstrated by the respective density value obtained (0.7854 g cm^{-3} at 298.15 K), which was thus coincident with those reported in the literature (**Resa, J.M. *et al.*** 2004; **Belda, R. *et al.*** 2004). All EtOH + water cosolvent mixtures were prepared in quantities of 10.00 g by mass using an Ohaus Pioneer TM PA214 analytical balance with sensitivity ± 0.1 mg, in mass fractions from 0.10 to 0.90 varying by 0.10, in order to study nine binary mixtures and both pure solvents.

Solubility determination

An excess of IMC was added to each aqueous cosolvent mixture evaluated in stoppered dark glass flasks. Solid-liquid mixtures were placed on thermostatic baths (Neslab RTE 10 Digital One Thermo Electron Company) kept at temperatures from 293.15 ± 0.05 to 313.15 ± 0.05 K with sporadic stirring for at least three days to reach the solution equilibrium (this equilibrium time was established by quantifying the IMC concentration up to obtain constant values). It is important to note that in water-rich mixtures this time was thus longer. Once at equilibrium, supernatant solutions were filtered (at isothermal conditions) to remove insoluble particles before the respective composition analyses. IMC concentrations in EtOH + water mixtures up to 0.40 in mass fraction of water were determined by mass balance by weighing a specified

quantity of the respective saturated solution and allowing the solvent evaporation up to constant mass. In the other hand, IMC concentrations in all the other systems studied (from 0.50 in mass fraction of water to pure water) were determined by measuring UV-absorbance after appropriate gravimetric dilutions with ethanol and interpolation from a previously constructed UV spectrophotometric calibration curve (UV/VIS BioMate 3 Thermo Electron Company spectrophotometer). All the solubility experiments were run at least in triplicate.

Deviation calculations

As a deviation criterion between single experimental and calculated values by means of the Yalkowsky-Roseman and Jouyban-Acree models (**Jouyban, A. & Acree Jr., W.E.**, 2006), the absolute errors (AE) were calculated for logarithmic solubilities according to:

$$AE = \left| \log X_{2-Calc} - \log X_{2-Expt} \right| \quad (6)$$

On similar way, as a general criterion of the usefulness of both equations the mean absolute errors (MAE) were calculated by means of the equation 7, where *n* is the number of mixtures compositions considered.

$$MAE = \frac{1}{n} \sum_{i=1}^{n} \left| \log X_{2-Calc} - \log X_{2-Expt} \right| \quad (7)$$

Results and discussion

It is well known that the volume expressions of mixtures concentration are dependent on temperature because the volumes of liquids change with temperature according to their thermal volume expansion coefficients (α). For this reason, the variation of *f* with temperature in EtOH + water mixtures has been reported in the literature (**Jiménez, J. *et al.***, 2004). In all cases this variation is lower than 0.60% and the mean values obtained at temperatures from 293.15 to 313.15 K are concordant with those reported at 303.15 K. For this reason the volume fractions obtained at 303.15 K were used in all calculations as has been made in other studies (**Vargas, E. *et al.*** 2008; **Gantiva, M. *et al.*** 2009).

Table 1 shows the experimental values of equilibrium solubility for this pharmaceutical compound expressed as decimal logarithms of mole fraction. The values used as input in equations 1 and 5 were those obtained in the neat solvents at all temperatures.

Table 2 shows the values of logarithmic solubility calculated by means of equations 1 and 5 as a function of mixtures composition and temperature. Individual and group percentage deviations with respect to equilibrium solubilities are also showed in this table.

By comparing the predictive results obtained for this drug by using both models it is clear that Jouban-Acree model (equation 5) is not better than additive behavior

Table 1. Experimental solubility of IMC expressed as decimal logarithm as a function of mixtures composition and temperature. Values in parentheses are logarithmic uncertainties on equilibrium solubility.

μ_{EtOH}	f_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	0.0000	–6.108 (0.021)	–6.031 (0.024)	–5.957 (0.020)	–5.895 (0.016)	–5.818 (0.027)
0.1000	0.1241	–5.915 (0.018)	–5.823 (0.026)	–5.727 (0.023)	–5.631 (0.019)	–5.552 (0.023)
0.2000	0.2417	–5.618 (0.010)	–5.514 (0.026)	–5.415 (0.025)	–5.309 (0.019)	–5.182 (0.024)
0.3000	0.3533	–5.070 (0.026)	–4.941 (0.020)	–4.816 (0.021)	–4.710 (0.023)	–4.563 (0.023)
0.4000	0.4594	–4.466 (0.023)	–4.344 (0.010)	–4.194 (0.010)	–4.076 (0.021)	–3.946 (0.018)
0.5000	0.5604	–3.922 (0.019)	–3.797 (0.024)	–3.676 (0.017)	–3.538 (0.011)	–3.394 (0.005)
0.6000	0.6566	–3.476 (0.004)	–3.335 (0.021)	–3.190 (0.027)	–3.093 (0.027)	–2.974 (0.029)
0.7000	0.7484	–3.099 (0.009)	–2.976 (0.028)	–2.844 (0.024)	–2.746 (0.021)	–2.649 (0.028)
0.8000	0.8360	–2.771 (0.017)	–2.661 (0.020)	–2.556 (0.021)	–2.463 (0.023)	–2.368 (0.006)
0.9000	0.9198	–2.568 (0.024)	–2.469 (0.017)	–2.371 (0.024)	–2.282 (0.029)	–2.207 (0.026)
1.0000	1.0000	–2.479 (0.025)	–2.380 (0.011)	–2.311 (0.005)	–2.210 (0.007)	–2.130 (0.004)

Table 2. Solubility of IMC calculated by means of additive-logarithmic model (equation 1) and Jouyban-Acree model (equation 4) expressed as decimal logarithm as a function of mixtures composition and temperature. Values in parentheses are absolute errors calculated according to equation 6.

Yalkowsky-Roseman model

f_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	MAE [a]
0.1241	–5.66 (0.26)	–5.58 (0.25)	–5.50 (0.22)	–5.44 (0.19)	–5.36 (0.19)	0.22 ± 0.03
0.2417	–5.23 (0.39)	–5.15 (0.37)	–5.08 (0.34)	–5.00 (0.31)	–4.93 (0.26)	0.33 ± 0.05
0.3533	–4.83 (0.24)	–4.74 (0.20)	–4.67 (0.15)	–4.59 (0.12)	–4.51 (0.05)	0.15 ± 0.08
0.4594	–4.44 (0.03)	–4.35 (0.01)	–4.28 (0.09)	–4.20 (0.13)	–4.12 (0.18)	0.09 ± 0.07
0.5604	–4.07 (0.15)	–3.98 (0.19)	–3.91 (0.24)	–3.83 (0.29)	–3.75 (0.36)	0.25 ± 0.08
0.6566	–3.73 (0.25)	–3.63 (0.30)	–3.56 (0.37)	–3.48 (0.38)	–3.40 (0.42)	0.35 ± 0.07
0.7484	–3.39 (0.29)	–3.30 (0.32)	–3.23 (0.38)	–3.14 (0.39)	–3.06 (0.41)	0.36 ± 0.05
0.8360	–3.07 (0.30)	–2.98 (0.32)	–2.91 (0.35)	–2.81 (0.35)	–2.73 (0.37)	0.34 ± 0.03
0.9198	–2.77 (0.20)	–2.67 (0.20)	–2.60 (0.23)	–2.51 (0.22)	–2.43 (0.22)	0.22 ± 0.01
						0.25 ± 0.11 [b]

Jouyban-Acree model

f_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	MAE [a]
0.1241	–5.48 (0.43)	–5.41 (0.42)	–5.34 (0.39)	–5.27 (0.36)	–5.20 (0.35)	0.39 ± 0.03
0.2417	–4.90 (0.72)	–4.83 (0.69)	–4.76 (0.66)	–4.69 (0.62)	–4.62 (0.56)	0.65 ± 0.06
0.3533	–4.36 (0.71)	–4.28 (0.66)	–4.22 (0.60)	–4.15 (0.56)	–4.08 (0.49)	0.60 ± 0.09
0.4594	–3.86 (0.61)	–3.78 (0.56)	–3.72 (0.47)	–3.65 (0.43)	–3.58 (0.37)	0.49 ± 0.10
0.5604	–3.41 (0.51)	–3.34 (0.46)	–3.28 (0.40)	–3.20 (0.34)	–3.13 (0.26)	0.39 ± 0.10
0.6566	–3.04 (0.44)	–2.96 (0.38)	–2.90 (0.29)	–2.82 (0.27)	–2.75 (0.22)	0.32 ± 0.09
0.7484	–2.74 (0.36)	–2.66 (0.32)	–2.60 (0.24)	–2.52 (0.23)	–2.45 (0.20)	0.27 ± 0.07
0.8360	–2.54 (0.23)	–2.46 (0.21)	–2.39 (0.16)	–2.31 (0.15)	–2.24 (0.13)	0.18 ± 0.04
0.9198	–2.45 (0.12)	–2.36 (0.11)	–2.29 (0.08)	–2.20 (0.08)	–2.13 (0.08)	0.09 ± 0.02
						0.38 ± 0.19 [b]

[a] MAE is the mean absolute error at each mixture composition calculated according to equation 7.

[b] This MAE value is the overall mean absolute error by considering all cosolvent compositions.

(equation 1), because of their MAE values, namely, 0.38 ± 0.19 in the first case, in front to 0.25 ± 0.11 in the case of equation 1. Thus, Yalkowsky-Roseman model would be useful at industrial level if equilibrium solubility estimations within 0.25 as decimal logarithm in uncertainty are allowed in the research and development of new homogeneous liquid products in the pharmaceutical industry.

To see more clearly these effects, Figure 2 shows the differences obtained between experimental solubilities for IMC at 298.15 K in front to those calculated by means of equation 1. In similar way, Figure 2 also shows the differences obtained between equations 1 and 5, respectively.

Figure 2 shows that differences obtained in front to Jouyban-Acree model are negative in all cases and dependent on solvent composition being larger in water-rich mixtures. Thus, experimental solubilities for IMC are lower than those predicted by equation 5.

As comparison Figure 2 also shows the behavior reported for naproxen (**Vargas, E. *et al.*** 2008) and ketoprofen (**Gantiva, M. *et al.*** 2009) which also are analgesic drugs. Accordingly, IMC exhibits similar trend as those reported for these drugs, but the results for IMC are almost the same as those reported for ketoprofen. Nevertheless, the main reasons for the last result are unclear because not apparent similitude is found between the physicochemical properties associated to IMC and ketoprofen polarities such as molar volume and Hildebrand solubility parameters (δ values), as can be seen in Table 3 (**Ruidiaz, M.A. & Martínez, F.**, 2009; **Gantiva, M. & Martínez, F.**, 2010). More over, molar volume of ketoprofen is almost on the middle of those for IMC and naproxen, whereas, Hildebrand solubility parameter of ketoprofen is thus close to that for naproxen (**Aragón, D.M. *et al.*** 2008).

Because the equation 5 (Jouyban-Acree model) is an extension of equation 1, Figure 2 shows the excess factor

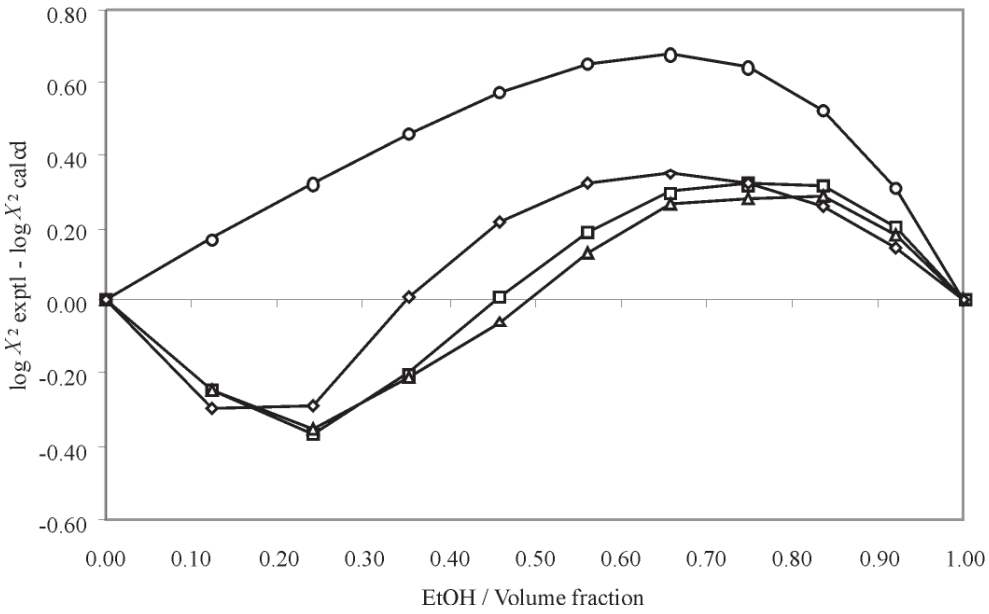

Figure 2. Logarithmic differences of drugs solubilities [experimental value minus calculated value according to Yalkowsky-Roseman model (equation 1)] for IMC (□), naproxen (◊, taken from **Vargas, E. *et al.*** (2008)), and ketoprofen (Δ, taken from **Gantiva, M. *et al.*** (2009)) and logarithmic difference of calculated solubilities [value according to Jouyban-Acree model (equation 5) minus value according to Yalkowsky-Roseman model (equation 1)] (○), as a function of the EtOH proportion in EtOH + water mixtures at 298.15 K.

Table 3. Molar volume and Hildebrand solubility parameter of some analgesic drugs.

Drug	Mol. Vol. / cm^3 mol^{-1}	δ/ $MPa^{1/2}$
IMC[a]	230.0	24.5
Ketoprofen[b]	195.6	22.5
Naproxen[c]	166.7	22.1

[a] Taken from **Ruidiaz, M.A. & Martínez, F.** (2009).

[b] Taken from **Gantiva, M. & Martínez, F.** (2010).

[c] Taken from **Aragón *et al.*** (2008).

of Jouyban-Acree (J - A factor), which is equivalent to the logarithmic difference between calculated solubilities using both equations, and it is a global excess solubility function.

Besides, Fig. 2 shows the logarithmic differences obtained between experimental values of IMC solubility and those calculated by assuming log-linear behavior (logarithmic additivity). This figure also shows the differences obtained in IMC calculated solubilities by using log-linear behavior (equation 1) and by using equation 5 (Jouyban-Acree model) at 298.15 K.

According to Fig. 2, IMC exhibits negative and positive deviations with respect to log-linear model and negative in front to Jouyban-Acree model. It is important to note that IMC does not follow a similar trend to that described by Jouyban-Acree model which assumes positive deviations with respect to logarithmic additivity (log-linear model) in all mixtures. Thus IMC exhibits negative deviations in water-rich mixtures and positive deviations in EtOH-rich mixtures.

The trend exhibited by IMC in Fig. 2 is similar to those reported by **Rubino, J.T. & Obeng, E.K.** (1991) for the solubility of homologue series of some alkyl p-hydroxybenzoates and p-aminobenzoates in propylene glycol + water cosolvent mixtures. These solutes also exhibited negative deviations in water-rich mixtures and positive in PG-rich mixtures with respect to log-linear equation.

A possible explanation for negative deviations observed in the drug solubility at low cosolvent proportions could be found in the research reported by **Kimura, F. *et al.*** (1975), where similar behaviors were found in dissolution enthalpies of 1-methyl-2-pyrrolidinone in EtOH + water mixtures. According to these investigators at low cosolvent proportions the water retains its ability to form ordered structures.

Although alcohols of low molar masses have been considered as polar compounds, **Matsumoto, Y. *et al.***

(1977) based on excess molar enthalpy values have presented some evidence about the influence of the ending methyl group on the water structure formation. The interactions present between alcohols and water could diminish the interactions between water and the drug leading to lower solubility values as expected according to log-linear model.

On the other hand, at high cosolvent concentrations in the mixtures the tridimensional structure of water is lost and therefore the water molecules could be available to interact with the drug molecules. This event would lead to larger solubilities than those expected according to log-linear model (equation 1). According to the literature another plausible explanation to positive deviations to log-linear equation could be due to possible drug association phenomenon in the saturated solution (**Rubino, J.T. & Obeng, E.K.**, 1991). Nevertheless, in order to verify this fact it would be necessary to dispose of any other kind of experimental evidence, such as organic solvent/water drug distribution coefficients at several concentrations and temperatures.

Conclusions

From all topics discussed previously it follows that IMC experimental solubilities present negative deviations in front to those predicted by the Jouyban-Acree model in the EtOH + water binary solvent system at all compositions studied. Opposite, IMC solubility shows negative and positive deviations in front to Yalkowsky-Roseman model. These estimation differences are within 0.38 in decimal logarithm units as mean, whereas, Yalkowsky-Roseman model imply differences around 0.25 in log units as mean. These results make possible the use of the Yalkowsky-Roseman model if these differences are allowed along the different stages involved in the design and development of new products in the pharmaceutical industries.

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