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Solubility enhancement of hydrophobic compounds by cosolvents: Role of solute hydrophobicity on the solubilization effect

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ABSTRACT

Drug solubilization is an important aspect of drug development. We investigate the relationship between solute hydrophobicity on the solubilization properties of water–cosolvent mixtures. The solubilization in water–cosolvent mixtures of seven chemically unrelated drugs was determined. The set of solutes included hydrocortisone, sulfanilamide, acetophenetidine, benzocaine, indomethacin, thymol and ibuprofen. Two sets of water–cosolvent mixtures were used in the study. A group of polar cosolvents consisting of three aliphatic alcohols, and a group of the less polar cosolvents NMP, tetraglycol and labrasol. The hydrophobicity of the drug has a direct impact on the solubilization obtained in the water–cosolvent mixtures. However, the role of hydrophobicity is different in the case of the polar cosolvents compared with the less polar ones. In polar cosolvents, the solubilization behavior is typical of polarity match, where the collective trend of solubility enhancement decreases as the activity coefficient of the solute in the solvent mixture increases. The result is a linear profile comprising the combined data of all solutes and all solvents. On the other hand, while the less polar cosolvents exhibit greater positive deviations from the log-linear cosolvency model, the collective solubility enhancement in these systems exhibits no readily discernible pattern. However, by taking into account the hydrophobicity of the solutes, a systematic effect becomes clearly apparent. In this case, the hydrophobicity of the solute demarcates its region in the solubilization profile.

1. Introduction

The use of organic cosolvents for solubilizing drugs with low aqueous solubility is a widespread formulation approach (Yalkowsky, 1999; Jouyban, 2008; Yeh et al., 2009), particularly so during the screening of new molecular entities as potential drug candidates (Miyako et al., 2008), where large numbers of molecules need to be brought into solution for to be tested for biological activity. There are two scenarios where solubility screening in mixed solvents is extensively used. One is during the late stages of drug discovery, where a number of lead compounds share a common (pharmacophore) moiety but differ in the various substituents linked to the common substructure. Another situation is during the early stages of drug discovery, where large numbers of chemically diverse compounds are subjected to solubility screening, often in a high throughput mode. The former situation can be roughly approximated by studying a homologous series of solutes. In a homologous series, the underlying chemistry of solution remains somewhat invariant, so that differences in solubility properties among solutes are attributable to a roughly monotonic change in hydrophobicity.

One key aspect of drug solubilization with the aid of cosolvents rests on creating a solvent mixture that closely matches the polarity of the hydrophobic solute (Rubino, 2002). While polarity match between solute and solvent is conceptually straightforward, a quantitative assessment is less so (Reichardt, 2003). Strictly speaking, polarity is a term that underscores the ability of a molecular structure to delocalize its electronic charges. Such a property favors solvation of the compound by solvents with strong dipoles, such as water. For this reason, the term a practical connotation of the term "polarity" is commonly associated with hydrophilicity of the compound, and low or less polarity in a molecule is commonly associated with hydrophobicity. In the context of solubility, a number of different parameters can be used to quantify the polarity of a compound (Rubino and Yalkowsky, 1987a). Even though each polarity parameter reflects a different aspect of the behavior of the compound in solution, the different parameters are strongly correlated (Yalkowsky, 1999). However, even in the case of homologous series, the clearly observable relationships between polarity and solubil-

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ity are not necessarily monotonic but show some distinguishing features (Miyako et al., 2008). Such observations suggest that in searching for polarity match between solvent medium and solute, solute-solvent interactions could manifest themselves as seemingly erratic variability without necessarily being so. Published cosolvency studies have mainly focused on the (important) effect that water–cosolvent interactions have on the observed solubilization profiles (Williams and Amidon, 1984; Rubino and Yalkowsky, 1987b; Pinal et al., 1991; Powell et al., 1995; Fan and Jafvert, 1997; Li, 2001; Ruckenstein and Shulgin, 2003; Machatha et al., 2004; Jouyban et al., 2005; Miyako et al., 2009). Consequently, there have been more progress toward the understanding of the general solubilization profiles obtained with different combinations of water with organic cosolvents. However, there is comparatively little published information on the equally important effect of the solute hydrophobicity in cosolvent systems (Rubino and Yalkowsky, 1985; Bustamante et al., 2002; Millard et al., 2002). The purpose of this study is to investigate the relationship between the hydrophobicity of the drug and its solubilization behavior in water–cosolvent mixtures, without restriction to a homologous series, but by including diverse chemical structures. To this effect, we use a group of structurally diverse drugs as model for a set of compounds subjected to solubilization screening by means of cosolvents. We investigate the role of solute hydrophobicity on the ability of cosolvents of different polarity to increase the solubility of the drugs. The cosolvents included in this study belong, in turn, to two groups. One is the alcohol series of polar alcohols methanol, ethanol and propanol. The other set includes the less polar solvents N-methyl pyrrolidone (NMP), tetraglycol and labrasol.

1.1. Solubility

The aqueous solubility of organic weak and non-electrolytes is given by:

$$\ln X = \ln X_{id} - \ln \gamma \tag{1}$$

where X denotes mole fraction solubility, X_{id} is the ideal solubility and γ is the activity coefficient. The ideal solubility in turn is given by:

$$\ln X_{id} = -\frac{\Delta S_f(T_m - T)}{RT} \tag{2}$$

where T is the absolute temperature, R is the gas constant, and ΔS_f and T_m are the entropy and temperature of melting of the solute, respectively. While the ideal solubility is a property exclusively of the solute, the activity coefficient is a property of the (solute–solvent) mixture. The ideal solubility is the theoretical value that would be obtained in a perfect solvent. This term depends exclusively on the (melting) parameters of the solid and is the same for every solvent. A high melting point is a reasonable indicator of the lattice energy (stability) of the crystal (Brittain, 1999). The higher the melting point of the crystalline solute, the lower the solubility of the compound (Yalkowsky, 1981; Yalkowsky and Valvani, 1980). The contribution of Eq. (2) toward the observed solubility is the same for every solvent. However, the actual solubility varies a great deal from one solvent to another. Such a variation is accounted for by the second term in Eq. (1), which represents the non-ideality of the solute–solvent mixture. The activity coefficient is a measure of the excess free energy required to solvate the solute molecules once loose from the crystal lattice. A hydrophobic solute dissolved in water results in a very large activity coefficient, such that the observed solubility is much lower (by orders of magnitude) than the ideal solubility. Conversely, the same hydrophobic solute, dissolved in an equally hydrophobic solvent, results in a small activity coefficient ($\gamma \approx 1, \log \gamma \approx 0$), such that the measured solubility is closer to the ideal value. Solubility measurements are often obtained on a mass/volume basis. For dilute solutions, such as saturated solutions of poorly soluble drugs, the solubility expression can be approximated as follows (Yalkowsky and Valvani, 1979, 1980):

$$\log S \approx -\frac{\Delta S_f(T_m - T)}{2.303RT} - \log \gamma - \log \bar{V} \tag{3}$$

where S is molar solubility of the drug and $\bar{V}$ is the molar volume of the solvent. The above expression can be used to express the solubility of the drug in pure water and in the pure cosolvent:

$$\log S_w \approx -\frac{\Delta S_f(T_m - T)}{2.303RT} - \log \gamma_w - \log \bar{V}_w \tag{3a}$$

$$\log S_c \approx -\frac{\Delta S_f(T_m - T)}{2.303RT} - \log \gamma_c - \log \bar{V}_c \tag{3b}$$

where the subscripts w and c denote pure water and the neat cosolvent as the solvent, respectively. The same general expression can be applied to the solubility in the water–cosolvent mixture (S_m):

$$\log S_m \approx -\frac{\Delta S_f(T_m - T)}{2.303RT} - \log \gamma_m - \log \bar{V}_m \tag{4}$$

where the subscript m denotes the water–cosolvent mixture. According to the log-linear cosolvency model, Eq. (4) can be represented by the linear combination of Eqs. (3a) and (3b). In other words, drug solubility in a mixed solvent can be estimated from a linear combination of the solubilities in the pure components of the solvent mixture, as discussed below.

1.2. Cosolvency

The solubility of organic compounds in solvent mixtures composed of water and an organic cosolvent, can be estimated by the log-linear cosolvency model (Yalkowsky and Roseman, 1981). According to this model, the solubility in the water–cosolvent mixture (S_m), corresponds to the weighted average of the solubilities in pure water (S_w) and in the pure cosolvent (S_c):

$$\log S_m = f_c \log S_c + f_w \log S_w \tag{5}$$

where f_c and f_w are the volume-fraction concentrations of the organic cosolvent and water, respectively, in the solvent mixture. The log-linear model is based on the assumption that the free energy of solution of the mixture corresponds to the (volume-fraction) weighted average of the free energy of solution in the pure solvent components (Yalkowsky, 1999). The linear combination can be seen explicitly by substituting Eqs. (3a) and (3b) into Eq. (5). Accordingly, Eq. (5) predicts an exponential change in solubility as a function of f_c in the solvent mixture. In the logarithmic scale, the model predicts a straight solubilization line with a slope $\sigma = \log(S_c/S_w)$, so that Eq. (5) is often presented in the alternative form:

$$\log S_m = \log S_w + \sigma f_c \tag{6}$$

The σ term above is often referred to as the cosolvency power, since it provides a measure of the inherent ability of the particular cosolvent to solubilize the solute in relation to its solubility in water. The σ parameter has the properties of a hypothetical partition coefficient (Yalkowsky and Roseman, 1981), i.e.,

$$\sigma = \log\left(\frac{\gamma_w}{\gamma_c}\right) \tag{7}$$

where γ_w and γ_c are the activity coefficients in water and the cosolvent, as defined above (Eq. (3a) and (3b)). This attribute of the solubilization power translates into some additional predictive capabilities of the log-linear model. For example, for a given organic solvent, the σ parameter of different solutes is linearly related to their octanol–water partition coefficient, such that σ estimates can

be made from the σ values of other solutes in the same cosolvent (Millard et al., 2002).

The log-linear model assumes that the solute–water and solute–cosolvent interactions are present in the water–cosolvent mixture in direct proportion to the respective concentration of water in cosolvent in the solvent blend. The model also assumes that no additional interactions exist in the solvent mixture besides the binary solute–water and solute–cosolvent interactions mentioned above. Accordingly, Eq. (5) or Eq. (6) provide reference solubility estimates from which the observed values deviate to a degree that varies from very small to significant, depending on the particular cosolvent. There are two main sources of deviations from the log-linear model. One is the effect of water–cosolvent interactions, another is the presence of interactions of the solute with the mixed solvent, other than the binary interactions present when the solute is dissolved in the pure solvents (Rubino and Yalkowsky, 1987b; Miyako et al., 2009). Deviations from log-linearity due to water–cosolvent interactions reflect the non-ideality of the solvent mixture. More often than not, these deviations are positive, leading to somewhat greater solubility values than those predicted by Eq. (5) (Machatha et al., 2004). Deviations from linear behavior arising from interactions between the solute and the mixed solvent vary with the particular solute. Such deviations can be positive or negative, and there is no reliable method or empirical rule of thumb to tell *a priori* their magnitude. In practical terms, the log-linear model provides easily obtainable solubility estimates from which observed solubilities deviate to different degree, depending on the solute of interest. In this report, we use a set of drugs to explore the relationship between cosolvency power and deviations from the log-linear behavior in relation to the hydrophobicity of the drug.

2. Materials and methods

Seven structurally different drugs covering a wide range of hydrophobicity were used as model solutes for this study. The solutes selected are hydrocortisone (Hyd), sulfanilamide (Sul), acetophenetidine (Ace), benzocaine (Ben), indomethacin (Ind), thymol (Thy) and ibuprofen (Ibu). Ace, Ben and Ind were purchased from Sigma Chemical, St. Louis, MO. Hyd, USP was purchased from Amend Drug Chemical, Irvington, NJ. Sul was purchased from Merck, Rahway, NJ. Ibu, USP was purchased from BHC, Bishop TX, and Thy, NF was purchased from Mallinckrodt, Hazelwood MO. Water used for experiment was house deionized, distilled water. The chemical structures of the solutes used in this study are shown in Fig. 1.

The cosolvents used include ethyl alcohol, USP Grade was purchased from AAPER Alcohol and Chemical Co., Shelbyville, KY. Methanol and n-propyl alcohol were purchased from Mallinckrodt, Hazelwood MO. Tetraglycol and 1-methyl-2-pyrrolidone (NMP) were purchased from Sigma-Aldrich, St. Louis, MO, and Labrasol was purchased from Gattefossé, St. Priest, France.

Solubility determinations. A sufficient amount of drug necessary to create a saturated solution in water, cosolvent or mixture were placed into glass vials and sealed. The sealed vials were then incubated for 24 h at 25 °C by using shaker of rotor type (099A RD4512, Glascol). After incubation, filtration was performed for any samples using Cameo 3N Syringe filter 0.22 micron, 3 mm (Osmonics Inc.) and a 1 mL syringe (Becton Dickinson). Filtered samples were diluted to suitable concentration for UV analysis. The UV/vis spectra (200 nm to 600 nm) of each compound were measured previously by using spectrophotometer (UV–Visible Recording Shimadzu UV160U), and peak wavelength of the spectrum (maximum absorbance) was obtained for each drug. Concentration of the drug in the solution was assessed by UV spectrophotometry. Solutions for the standard curve were prepared in 50% (w/w) ethanol–water (methanol–water for sulfapyridine) mixtures. The same solvent mixtures were used for diluting the saturated solutions in order to bring the concentration to a range suitable for UV analysis.

Thermal analysis. DSC measurements for all compounds were carried out on a DSC analyzer (Model 2920, TA Instruments). Each accurately weighted sample (3–7 mg) was placed in an aluminum pan and the pan was sealed. Measurement of the sealed aluminum pan was performed under nitrogen purge (50 ml/min), with a heating rate of 10 °C/min. The DSC was previously calibrated against NIST traceable indium and zinc. The entropy of melting was obtained from the enthalpy (ΔH_f) and the absolute temperature of

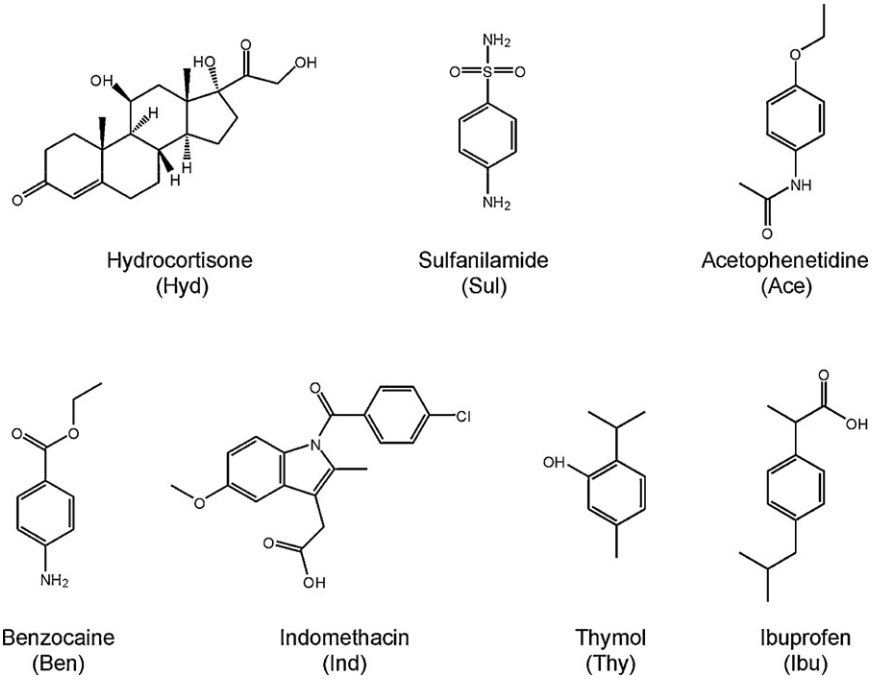

Fig. 1. Chemical structures of the solutes included in this study.

melting:

$$\Delta S_f = \frac{\Delta H_f}{T_m} \quad (8)$$

3. Results and discussion

The aqueous solubility data of the different solutes are presented in Fig. 2. The dark and white portions of the bars correspond to the contributions from the ideal solubility ($\log X_{id}$) and the aqueous activity coefficient ($\log \gamma_w$), respectively, according to Eq. (1). The melting data used to obtain the ideal solubility values are presented in Table 1. Our data of thermal analysis are in good agreement with data in the literature (Yalkowsky and Roseman, 1981), except for the value of indomethacin, for which a melting point of 134 °C is reported. The difference can be traced to the use of different crystal forms of the drug. The reported melting point of the form IV of indomethacin is 134 °C (Borka, 2004). We used the γ form of the crystal was in our experiments, which has the melting point listed in Table 1. It is important that the melting parameters (Eq. (8)) used to calculate the ideal solubility (Eq. (2)) correspond to the crystal form of the experiment. There are two situations where the melting point and enthalpy of melting cannot be directly determined. One corresponds to the case where the drug undergoes a polymorphic transformations during the DSC run, such that the melting observed corresponds to that of a different crystal form. In such cases, the ideal solubility can be determined by using the combined information from the solid-solid and solid-liquid transitions (Mao et al., 2005), such that the approach presented here is readily applicable. The other situation corresponds to the case where the drug undergoes thermal degradation before or during melting. In such cases, the ideal solubility cannot be readily obtained, and the approach for obtaining the activity coefficient is not directly applicable.

Since the activity coefficient is a measure of the energetic hindrance for the solvation of the solute by water, the magnitude of $\log \gamma_w$ represents a direct measure of the hydrophobicity of the solute. Accordingly, the solutes in Fig. 1 are arranged in increasing order of hydrophobicity (white portion of the solubility bar). This type of presentation useful in the sense that it provides a visual assessment of the solubilization challenge when designing solubilization studies. For example, Fig. 2 shows that the crystal lattice energy of hydrocortisone, more than its hydrophobicity, is the main factor responsible for its low solubility. The figure also shows that, despite being measurably less hydrophobic than ibuprofen, indomethacin has lower solubility by the effect of its stronger crystalline structure.

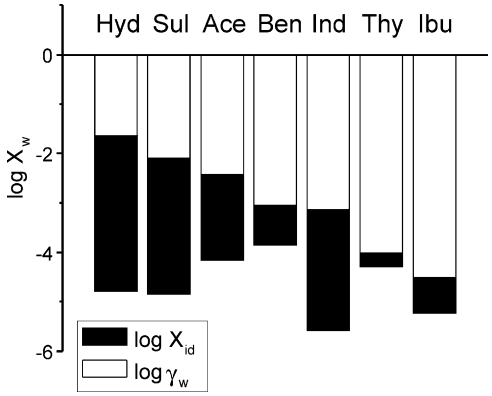

Fig. 2. Aqueous solubility of different solutes. The bars break down to the two independent factors that determine solubility, the ideal solubility (dark) and the activity coefficient (white). The solutes are arranged in increasing order of hydrophobicity represented by the activity coefficient.

Table 1
Melting data used to obtain the crystallinity (ideal solubility) of the solutes.

Compound	MP (°C)	ΔH_f (kJ mol^{-1})	ΔS_f (J mol^{-1} K^{-1})
Acetophenetidine	134.4	36.93	90.61
Benzocaine	89.4	25.65	70.75
Hydrocortisone	219.2	45.50	92.41
Ibuprofen	74.2	28.92	83.26
Indomethacin	159.1	45.02	104.1
Sulfapyridine	190.8	44.06	94.97
Thymol	49.3	20.99	65.10

The solubilizing effect obtained by mixing an organic cosolvent with water is realized through a change in the activity coefficient of the solute in the resulting solution. Adding an organic cosolvent to water makes the solvating environment less polar, resulting in a more favorable mixing (solvation) of a hydrophobic solute in the liquid phase. In general, the more hydrophobic the solute, the greater the solubilizing effect produced by an organic cosolvent that is less polar than water (Millard et al., 2002). Fig. 3 shows the relationship between solute hydrophobicity and the solubilization power (σ) of the different cosolvents. The plots use a single letter labeling system to identify each individual solute. Graphs on the top row present the data for aliphatic alcohols. This set of cosolvents is useful for investigating the effect of a systematic change in solvent polarity. The alcohols exhibit fairly linear relationships between solute hydrophobicity and cosolvency power. Measures of polarity tend to be linearly related, and the effects of such a phenomenon are often observed in cosolvency (Rubino and Yalkowsky, 1987a, Miyako et al., 2008). The octanol–water partition coefficient ($\log P$) for example, is commonly used as a measure of hydrophobicity. This is so because $\log \gamma_w$ and $\log P$ are linearly related (Valvani et al., 1981). In similar fashion, since σ represents a hypothetical cosolvent–water partition coefficient, it also exhibits a linear relationship with $\log \gamma_w$. The data on the bottom row of Fig. 3 are somewhat different, however. These graphs show the solubilization power the less polar, solvents NMP, tetraglycol and labrasol. These solvents are known to be stronger solubilizers of drugs than the aliphatic alcohols of the top row in Fig. 3. Data of the less polar solvents show noticeably greater scatter compared with data for the alcohols. In addition to the absence of a clear linear relationship between σ and $\log \gamma_w$, a best fit line would not pass near the origin in any of the plots on the bottom row. The less polar vehicles of the bottom row of Fig. 3 show a comparatively better ability to solubilize the less hydrophobic solutes (higher cosolvency power in the lower $\log \gamma_w$ region). This suggests in turn that powerful solvents have a greater ability to engage in specific interactions with the solutes. The graphs on the top row of Fig. 3 correspond to three solvent systems with a common underlying solution chemistry; they all involve the same type of functional groups, hence the same possible specific interactions. Consequently, differences in cosolvency power among the three alcohols primarily reflect their differences in polarity as bulk liquids. If we compare methanol and NMP for example, the two solvents have similar $\log P$ values (−0.14 and −0.11, respectively), so the two can be considered as having similar polarity. Nonetheless, NMP exhibits somewhat greater cosolvency power for the same set of solutes, a result most likely due to the different ability of each of the two solvents to engage in specific interactions with the different drugs. It is therefore reasonable to expect greater deviations from log-linear cosolvency behavior for those pharmaceutical vehicles that are particularly strong solubilizers.

Another important source of deviations from the log-linear cosolvency behavior is the effect of water–cosolvent interactions. These interactions are quantitatively described by the non-ideality of the water–cosolvent mixture and their effect on cosolvency to date has proven to be somewhat more tractable, from a modeling standpoint, than the effect of specific solute–solvent interactions

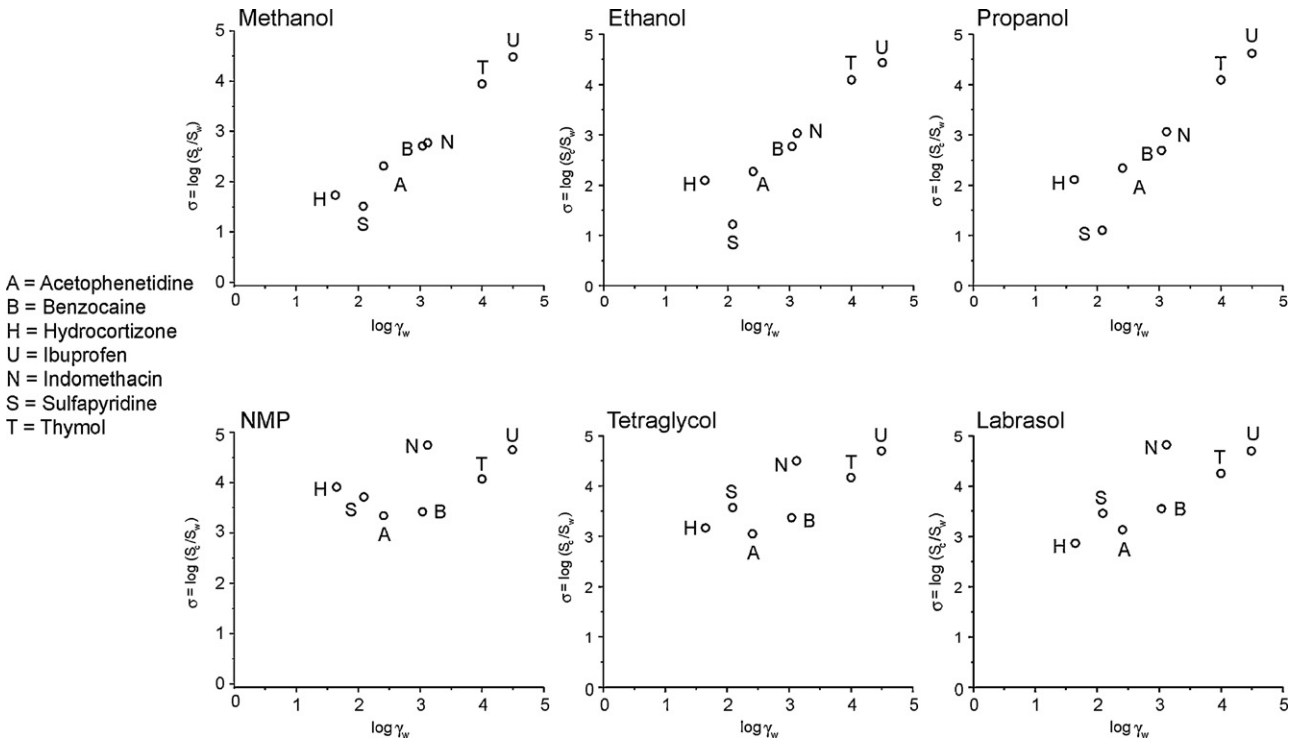

Fig. 3. Relationship between solute hydrophobicity and the solubilization power (s) produced by different cosolvents. Top row: aliphatic alcohols. These cosolvents show linear relationships between solute hydrophobicity and cosolvency power. Bottom row: stronger solubilizers, tetraglycol, labrasol and NMP.

(Williams and Amidon, 1984; Rubino and Yalkowsky, 1987b; Pinal et al., 1991; Powell et al., 1995; Fan and Jafvert, 1997; Li, 2001; Ruckenstein and Shulgin, 2003; Machatha et al., 2004; Jouyban et al., 2005; Miyako et al., 2009). Using the breakdown of solubility in Fig. 2 (Eq. (1)) as starting point, the effect of cosolvent addition is visually represented in Fig. 4. Since the ideal solubility is the same for every solvent, the length of the black portion of the bar is constant for each solute in Figs. 2 and 4. By changing the solvent from pure water (Fig. 2) to a water–cosolvent mixture (Fig. 4), the activity coefficient contribution changes from $\log \gamma_w$ to $\log \gamma_m$, each represented by the white portion of the bars in the corresponding graph. The additional gray bars above the horizontal axis in Fig. 4 represent the difference between $\log \gamma_w$ and $\log \gamma_m$, i.e., the change in activity coefficient in going from water to the mixed solvent. Accordingly, the extent of the upward shift, represented by the gray bar above the horizontal axis in Fig. 4, corresponds to the factor by which the solubility increased by effect of the added cosolvent. The predicted solubility increase, based on the log-linear model (Eq. (6)), is also represented in Fig. 4 by the shadowed bars above the horizontal axis. Therefore, the difference between the gray and shadowed bars corresponds to the deviations from the log-linear model, or excess solubility. The solubilization results in Fig. 4 reflect the influence of polarity match between solute and solvent that is so important in cosolvency. Methanol is the most polar of the three alcohols. Deviations from the log-linear behavior in 50:50 methanol water mixtures go from negative to positive as the hydrophobicity of the solute increases. In contrast, the cosolvency of propanol, the least polar of the three alcohols, results almost exclusively in positive deviations from log-linearity for the same set of hydrophobic solutes. Hydrocortisone is a hydrophobic compound whose poor solubility is nevertheless dominated by the strength of its crystalline structure, rather than by its hydrophobicity. Note that ethanol or propanol present at 50% provide a compatible enough solvation medium as to remove the solubility barrier presented by the activity coefficient of hydrocortisone.

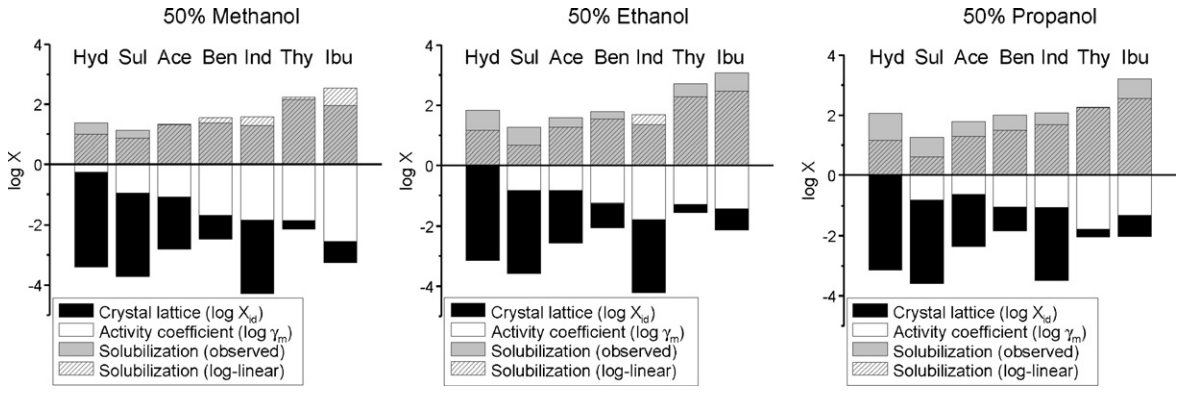

Fig. 4. Graphical representation of the effect of cosolvent addition (50:50 proportion) on solubility. The difference between the gray portion (factor by which the solubility increases relative to the aqueous solubility) and the shadowed part (log-linear prediction) represents the extent of deviation from the log-linear model.

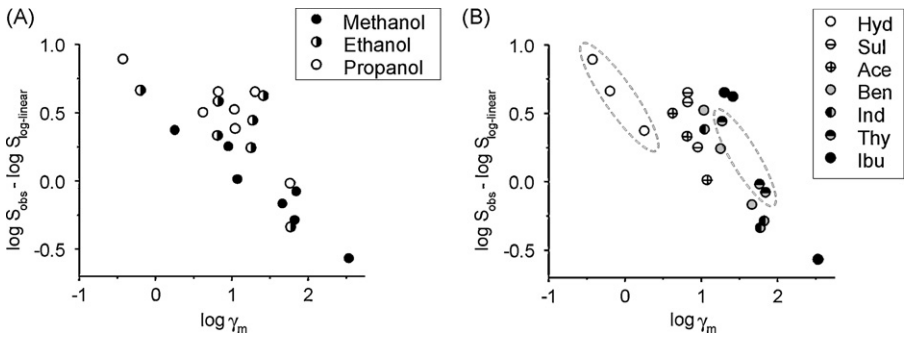

Fig. 5. Relationship between polarity match ($\log \gamma_m$) and the deviations from log-linear solubilization model (excess solubility) for 50% (v/v) water–alcohol mixtures. (A) Data grouped by solvent. (B) Same data grouped by solute.

Hydrophobicity, i.e., the magnitude of $\log \gamma_w$, can also be viewed as a practical measure of the "mismatch" in polarity, or incompatibility, between the solute and water. In exactly the same way, $\log \gamma_m$ is a measure of the degree of lyophobicity or "solvophobicity" between the solute and a mixed solvent. The deviations from log-linear solubilization for the three alcohols and the different solutes are plotted as a function of $\log \gamma_m$ in Fig. 5. The plot shows a roughly linear profile comprising the entire set of data. The greater the value of $\log \gamma_m$, the greater the incompatibility between the solute and the solvating medium. This effect is clearly observable in Fig. 5, where a decrease in relative solubility as a function of $\log \gamma_m$ is observed. However, positive deviations from the log-linear model are observed up to $\log \gamma_m \approx 1$, at which point the deviations from the log-linear model become negative. Fig. 5B presents the same data as Fig. 5A with the difference that the points are grouped by solute. It is noteworthy from Fig. 5B that in going from positive to negative values of the excess solubility on the horizontal axis, the breakdown of the data, by solute, changes in increasing order of hydrophobicity. These results are an illustration of polarity match; the three aliphatic alcohols are polar solvents whose performance as cosolvents is best when the solute is not highly hydrophobic (e.g., hydrocortisone). However, the same polar alcohols are less effective cosolvents for highly hydrophobic drugs.

The relationship between $\log \gamma_m$ and the deviation from the log-linear model was also investigated for NMP, tetraglycol and labrasol. For this set of stronger solubilizers, the solvent mixtures contained 25% cosolvent and the results are shown in Fig. 6. The solubilization data appear scattered with no discernible pattern like the linear profile of Fig. 5. At this point, a comparison between the systems represented in Figs. 5 and 6 is pertinent. Figs. 5B and 6B show that in both cases, the solutes are spread from left to right in increasing order of hydrophobicity. However, the alcohol series in Fig. 5 provides a system where any given solute maintains the same type of specific interactions with all three alcohols. Therefore, the data for the different solutes are also vertically "stacked", so to speak, as a function of their hydrophobicity. As a visual aid, two solutes in Fig. 5A are encircled to illustrate the trend, where the solutes' data shifts from top to bottom and left to right as a function of their hydrophobicty. In contrast, Fig. 6 reflects a situation where each solute–cosolvent pair represents different intermolecular interactions. As a result, Fig. 6A does not show a discernible pattern from the combined contributions of all solutes. Grouping the data by solute, as shown in Fig. 6B, reveals the horizontal spread as a function of solute hydrophobicity. Two solutes bands are encircled on the graph. In terms of the shape of the profile, the difference between the solubilization data in Figs. 5 and 6 is the vertical stacking of the former and its absence in the latter. However, it is noteworthy that in the case of the more powerful cosolvents (Fig. 6), virtually all data are on the positive side of the vertical axis, whereas in the case of the more polar solvents of Fig. 5, the relative solubility goes from positive to negative. As a general rule, the more hydrophobic the solute, the more it will be solubilized by cosolvent addition (Millard et al., 2002). The results in Fig. 4 are in agreement with this notion. However, the same results also show that the greater degree of solubilization has two sources, greater log-linear solubilization (σ effect) but also greater positive deviations from linearity (excess solubility). The data in Fig. 5 exemplify the polarity match profile described by Rubino, 2002. In contrast, the data from the stronger, less polarity cosolvents in Fig. 6, do not conform to the typical polarity match profile. The less polar solvents of Fig. 6 are stronger solvents presumably by virtue of their specific interactions with the drugs, such that those interactions dominate and occlude, to some degree, the background solvent polarity effect. Nonetheless, although differently, the hydrophobicity of the solute is systematically manifested in the cosolvency of both the alcohols and of the less polar cosolvents. In the case of polar solvents, the polarity match produces a linear profile. In the case of the less polar, more powerful cosolvents, what may seem an arbitrary scatter of solubilization data, also bears a systematic and distinctly clear effect of solute hydrophobicity. One aspect, common to every indi-

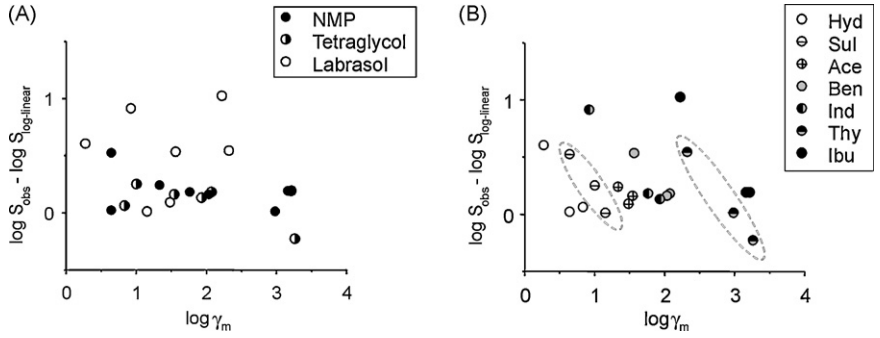

Fig. 6. Relationship between $\log \gamma_m$ and the deviations from log-linear solubilization model (excess solubility) for 25% (v/v) water cosolvent mixtures containing NMP, tetraglycol and labrasol. (A) Data grouped by solvent. (B) Same data grouped by solute.

vidual solute, whether presented in Fig. 5B or in Fig. 6B, is that the corresponding data appear as clusters spread in nearly parallel fashion, where a decrease in solubility with increasing log γ_m is clearly observed (see encircled clusters in Figs. 5B and 6B).

4. Conclusion

The use of cosolvents is an effective means of solubilizing hydrophobic drugs. As such, cosolvency is an essential part of drug screening studies. The log-linear cosolvency model presents a simple means of estimating solubility in water–cosolvent mixtures. A number of different cosolvency models dealing with deviations from log-linear behavior have been proposed in the literature. Such studies focus for the most part on modeling the shape of the solubilization profile in different water–cosolvent blends. In this report, we focus on the relationship between drug hydrophobicity and solvent polarity. The drugs selected for the study cover a representative range of hydrophobicity used to investigate how an increasing hydrophobicity manifests itself when solubilizing drugs with cosolvents of high and low polarity. The hydrophobicity of the solute is clearly manifested in each case but in distinctly different way. Deviations from the log-linear behavior follow the more traditionally expected profile in the case of the polar solvents. Namely, grouped solubility of the different solutes exhibits a decreasing trend as log γ_m increases. On the other hand, for the less polar solvents, which are also more powerful solubilizers of hydrophobic drugs, the excess solubility is comparatively greater. Most significantly, solubilization of hydrophobic drugs with the strong, low polarity cosolvents does not result in a general solubilization profile encompassing the data of the different solutes. Instead, the pattern consists of each solute separated from the others by its hydrophobicity. Deviations from the log-linear cosolvency model are of great practical relevance since they constitute quite a significant portion of the solubility enhancement levels achievable with cosolvency. Solvent polarity and solute hydrophobicity are both measurable properties whose interplay determines the solubilization profile obtainable for a particular drug. A proper account of the nature and magnitude of the deviations from the log-linear cosolvency model will make it possible to fully exploit the effect as part of drug solubilization strategies.

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