Drug Development and Industrial Pharmacy, 34:499–505, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701744020

informa
healthcare

Solubility Screening on a Series of Structurally Related Compounds: Cosolvent-Induced Changes on the Activity Coefficient of Hydrophobic Solutes

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A homologous series of solutes was chosen as a model for a group of structurally related compounds with different physicochemical properties, as is commonly the case during the screening of potential drug candidates. Thermal properties of the crystalline solutes and solubility determinations were used to quantify the two independent factors that determine the solubility of organic compounds: crystallinity and hydrophobicity. A solubility screening study was conducted on the series. By expressing the obtained solubility enhancement expressed as changes in the activity coefficient, it is possible to visually compare the effect of different cosolvents. The results show the importance of solute-solvent polarity match. Polarity match between water miscible cosolvents and hydrophobic compounds is not truly attainable, but comparison of the screening results points out the closest matches (optimal effect), facilitating the systematic evaluation of solubilization approaches.

Keywords solubility; solubilization; activity coefficient; polarity; cosolvents; screening

INTRODUCTION

Poor aqueous solubility of new chemical entities (NCEs) is a challenge frequently faced in the pharmaceutical industry. Even if highly specific, poor solubility of the NCE can lead to a suboptimal therapeutic effect. For this reason, aqueous solubility is one of the main criteria employed in selecting a lead compound from drug discovery to drug development. A typical situation during the candidate selection phase is that different lead compounds share a common pharmacophore moiety, responsible for the underlying pharmacological effect. The various lead compounds differ by the distinct functional groups present as substituents on the common moiety. When selecting a lead compound, investigators are typically faced with choosing one candidate from among a number of structurally related compounds, each with a slightly different molecular structure. Differences in molecular structure result in differences in solubility related properties, and selection approaches such as the well known Rule of Five find widespread use in drug candidate selection (Lipinski, Lombardo, Dominy, & Feeney, 1997). In this report, we present a scheme suitable for screening structurally related compounds for their solubility properties in relation to variations in chemical structure. The study encompasses two equally important factors affecting solubility: polarity and crystallinity. We use organic solvent-water mixtures in order to quantitatively assess the relationship between the polarity of the solute and the solvent and the ability of the latter to solubilize hydrophobic compounds.

Factors Influencing Solubility

The vast majority of drugs are hydrophobic organic compounds. This property has the effect of limiting their solubility

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in water. However, if hydrophobicity were the only factor limiting the solubility of drugs, from the well known adage, "like dissolves like," solubility issues could be resolved by simply changing the solvent to something more *like* the drug in terms of its hydrophobicity. Solubility issues faced in drug development are typically more challenging than that. Quite frequently, pharmaceutical scientists are faced with the task of solubilizing hydrophobic drugs that besides being poorly soluble in water, are also poorly soluble in oils and other pharmaceutical vehicles. It is the combination of these two factors that determines how challenging drug solubilization can turn out to be.

When a hydrophobic, crystalline organic solid is solubilized in water, two separate processes take place: (a) the solute molecules have to be dislodged from their positions in the crystalline lattice and (b) the dislodged molecules have to be solvated by solvent molecules. Each of these two effects contributes, separately, to the free energy of the solubilization process and, therefore, to the observed solubility value. The first factor, referred to as the crystallinity effect, is quantitatively represented as follows:

$$\log X_{ideal} = -\frac{\Delta S_f (T_m - T)}{2.303RT} \tag{1}$$

where X_{ideal} is the ideal (mole fraction) solubility, T_m and ΔS_f are the melting point and entropy of melting of the solute, respectively, T is the (absolute) temperature of interest, and R is the gas constant. The ideal solubility is a property of the solute alone (it is the same for every solvent) because it depends solely on the strength of the crystal lattice of the solute. For this reason, NCEs with strong crystal structures (roughly characterized by high melting points) are often inherently insoluble, that is, difficult to solubilize in virtually all vehicles. Equation 1 is the baseline, maximum theoretical solubility value, observed when the solute and solvent form an ideal mixture.

The second process described above becomes very important when the solution involves a hydrophobic solute dissolved in water, since in such cases, the solution is highly nonideal. The hydrophobicity of the solute will impose a significant restriction (in addition to the theoretical limit of Equation 1) to the solubility of the drug in water. The actual solubility is then given by:

$$\log X = \log X_{ideal} - \log \gamma \tag{2}$$

where X is the observed solubility and γ is the activity coefficient of the solute in that particular solvent. The activity coefficient in Equation 2 is a measure of the deviations from ideal mixing when water solvates solute molecules and reflects the difficulty of forming a hydration shell around a hydrophobic solute molecule. For dilute solutions, Equation 2 can be expressed in the form (Yalkowsky and Valvani 1980):

$$\log S_m = -\frac{\Delta S_f (T_m - T)}{2.303RT} - \log \gamma + 1.74 \tag{3}$$

where S_m is the solubility expressed in units of mole·L^{-1}. Yalkowsky and coworkers (1983b) showed that the octanol-water partition coefficient ($P_{o/w}$) of organic compounds provides a reasonable estimate for its activity coefficient in water. Namely, for a hydrophobic compound (e.g., log $P_{o/w}$ = 4), the second term in Equation 2 would result in a 10,000-fold decrease in solubility, beyond the theoretical limitation already imposed by Equation 1.

The solubilization of poorly soluble drugs is a common challenge faced in pharmaceutical development. There are a number of commonly used solubilization approaches. These can be divided into three main categories: (a) those based on solvent modification, such as the use of organic vehicles and cosolvents, surfactants, complexing and hydrotropic agents, and emulsification; (b) those based on the physical transformation of the solute, such as the use of amorphous dispersions or metastable crystal forms; and (c) approaches involving a change in chemical structure, such as prodrug synthesis, the use of salt forms, as well as the change to a chemical analogue. This general classification is of practical significance in the context of the equations presented above, since it can help set a solubilization assessment. Equation 2 shows the quantitative effect of the two equally important but independent factors that limit the solubility of drugs in water. Solubilization approaches based on solvent manipulation (category a, above) alter solubility exclusively through their effect on the second term of Equation 2, that is, by decreasing the contribution of log γ while leaving the crystallinity effect unaltered. Conversely, solubilization approaches based on physical modification of the solute (category b, above) lead to solubility increases through their effect on the first term of Equation 2, that is, by reducing (or eliminating altogether) the limitation imposed by the ideal solubility, while leaving the contribution of log γ unchanged. Finally, solubilization methods involving change in chemical composition (category c, above) affect solubility through changes in both the first and second terms of Equation 2. In this paper, we focus on the combined effects of categories a and c. To this effect, we present a study where cosolvency as the solubilization approach (category a) for a group of chemically related but structurally different compounds (category c). The analysis presented here is analogous to a situation involving solubility screening during candidate selection from a series of structurally related compounds. Selection of solutes and solvents was made such that the in both cases a wide range of polarity and hydrophobicity, respectively, were obtained. With this approach, the effect of solute-solvent polarity matching (or lack of it) can be visually observed.

MATERIALS AND METHODS

A homologous series of benzoic acid (BA) derivatives was used in this study as a model series of structurally related compounds with varying characteristics in both their crystalline and hydrophobicity properties. Benzoic acid (ACS reagent), 4-methylbenzoic acid (*p*-toluic acid), 4-ethylbenzoic acid, 4-propylbenzoic acid, and 4-butylbenzoic acid were purchased from Sigma-Aldrich (St. Louis, MD). Water used for the experiment was in-house distilled, deionized water. As cosolvents, ethyl alcohol (United States Pharmacopoeia) was purchased from AAPER Alcohol (Shelbyville, Kentucky) and Chemical and *n*-propyl alcohol was purchased from Mallinkrodt Chemicals (Hazelwood, Missouri). Tetraglycol and 1-methyl-2-pyrrolidone (NMP) were purchased from Sigma-Aldrich (St. Louis, Missouri), and propylene glycol (PG) was purchased from J. T. Baker (Phillipsburg, New Jersey). Labrasol® was purchased from Gattefossé (St. Priest, France) and Solutol® HS 15 was purchased from BASF (Ludwigshafen, Germany).

Solubility Measurements

The solvent of interest (water or water-cosolvent mixture) was placed in a scintillation vial. The solid solute of interest was then added to the vial in sufficient amount to produce a saturated solution. Vials containing the solute-solvent mixture were sealed and placed inside an incubator chamber set at 25°C on a rotor type shaker (099A RD4512, Glascol). The vials were then tumbled while in the incubator for 24 hours. After equilibration, aliquots form the solution were withdrawn with a 1-ml syringe (Beckton Dickinson, Franklin Lakes, New Jersey) and filtered through a 0.22 μm membrane using a Cameo 3N Syringe (Osmonics, Inc., Minnetonka, Minnesota). The filtered samples were then diluted with a 50:50 ethanol-water solution to a concentration suitable for ultraviolet (UV) analysis. The samples were scanned in the UV-VIS spectrum (from 200–600 nm) in a spectrophotometer (UV-Visible Recording Shimadzu UV160U). The peak absorbance wavelength for each compound was obtained from the resulting spectra and used to determine the sample concentration. For each solute, a standard curve was prepared with solutions of known concentration in 50:50 ethanol-water, read at the maximum absorbance wavelength. The solubility of the solutes in the different solvents was determined by comparing the measured absorbance with the standard curve and making the appropriate correction for the dilution factor. Solubility measurements were conducted in triplicate.

Crystallinity

The parameters necessary to obtain the ideal solubility ($\log X_{ideal}$ in Equation 1) were experimentally determined by differential scanning calorimetry (DSC). Measurements were carried out on a model FC100AXOTA DSC analyzer (TA Instruments, New Castle, Delaware). Samples were placed in aluminum pans and sealed. The samples were heated in the DSC under nitrogen purge (50 ml·min^{-1}) at a heating rate of 10°C·min^{-1}. The melting temperature (T_m) was obtained from the onset of the melting event and the enthalpy of fusion (ΔH_f) from the area of the melting endotherm. From these quantities, the entropy of fusion was obtained ($\Delta S_f = \Delta H_f / T_m$).

Hydrophobicity

The activity coefficients of the different solutes in water and the different water-cosolvent mixtures were obtained from Equation 2, namely:

$$\log \gamma = \log X_{ideal} - \log X \tag{4}$$

The mole fraction solubility (X) was obtained from the measured molar solubility (S_m) and the known solvent composition as follows:

$$\log X = \log\left(\frac{S_m}{S_m + S_w + S_c}\right) \tag{5}$$

where S_w and S_c denote the molar concentration of water and cosolvent, respectively, in the solution.

RESULTS AND DISCUSSION

The experimentally determined crystal properties necessary to obtain $\log X_{ideal}$ are listed on Table 1. It should be pointed out that in addition to the melting event, some of the solutes in this series underwent solid-solid phase transitions during the DSC runs. While solid phase transitions are not uncommon when screening drug solubility, their presence affects the ideal solubility and a correction to Equation 1 becomes necessary. Since both entropy and free energy are state functions, Mao and coworkers (2005) showed that when a solid phase transition

TABLE 1
Physicochemical Properties for Characterizing the Solubility Properties (Crystallinity and Hydrophobicity) of the Solutes Used in this Study

Compound	log $P_{o/w}$	T_m (°C)	ΔH_f (kcal·mol^{-1})	T_t (°C)	ΔH_t (kcal·mol^{-1})
Benzoic acid (BA)	1.87	122.78	3.72	–	–
4-methyl-BA	2.42	179.75	4.93	–	–
4-ethyl-BA	2.91	113.55	3.06	30.51	0.76
4-propyl-BA	3.40	142.31	4.36	21.97	0.50
4-butyl-BA	3.89	102.47	2.55	35.63	1.25

takes place, the ideal solubility needs to be corrected by adding the contribution of the entropy of the transition to the ideal solubility, such that:

$$\log X_{ideal} = -\frac{\Delta S_f (T_m - T) + \Delta S_t (T_t - T)}{RT} \quad (6)$$

where ΔS_t and T_t are the entropy and temperature of the solid-solid phase transition, respectively. Analogous to melting, for a solid phase transition $\Delta S_t = \Delta H_t / T_t$.

The ideal solubility represents the hypothetical case where solute and solvent molecules have the same size and shape, and where solute-solute, solvent-solvent, and solute-solvent interactions are all of the same nature and magnitude (such that log $\gamma = 0$ in Equation 2). Therefore, X_{ideal} corresponds to the upper limit solubility value for the particular solute. When solute and solvent form a highly nonideal solution, as in the case of a hydrophobic solute dissolved in water, the solubility is significantly lowered in relation to the ideal limit. This effect is quantified by the activity coefficient. The relative magnitude of the crystallinity and hydrophobicity effect for the solutes in this study are graphically presented in Figure 1. This graphic representation of solubility helps visualize the different factors at play and point toward solubilization strategies. The dark portion of the solubility bar in the figure represents the extent to which the strength of the crystal lattice of the solutes limits their solubility. The extent to which the solutes' hydrophobicity limits their solubility is represented by the white portion in the bars. It should be emphasized that the two effects are completely independent. As expected, the impact of hydrophobicity on solubility closely reflects the hydrocarbon chain length (n) of the solute. Figure 1 also shows that there is no correlation between hydrocarbon chain length and the ideal solubility. The methyl substituted solute, while having intermediate hydrophobicity, is the structure that results in the strongest crystal packing and, consequently, the one with the lowest ideal solubility. Conversely, the butyl (n = 4) substituted compound, while being the most hydrophobic, is also the one with the weakest crystal packing. Figure 1 also shows an aspect of practical significance. For example, the aqueous solubilities of the n = 1 (4-methyl-) and n = 2 (4-ethyl-) substituted compounds are virtually the same. However, the contributions from their crystallinity and hydrophobicity are significantly different.

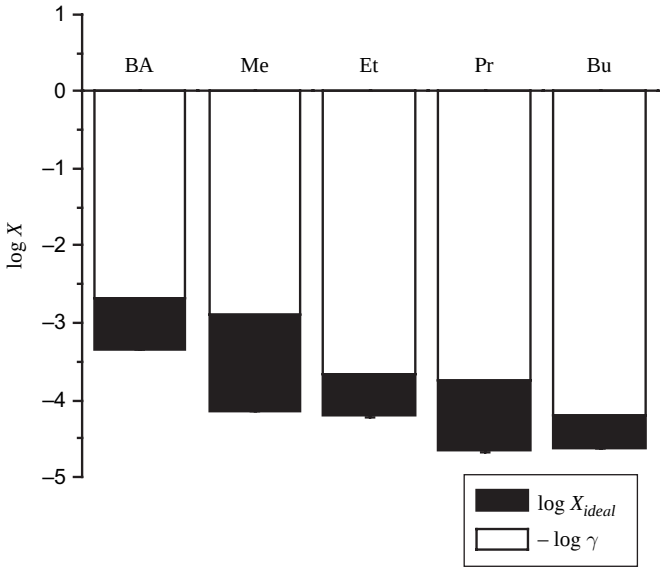

FIGURE 1. Contributions to the observed aqueous (log mole fraction) solubility of a homologous series of benzoic acid derivatives. The black portion of the bars represents the solubility limit imposed by the crystallinity of the solutes (ideal, maximum solubility). The white portion of the bar represents the additional reduction on solubility resulting form the hydrophobicity of the solute (activity coefficient). BA is benzoic acid, Me, Et, Pro and Bu denote the 4-Methyl, 4-Ethyl, 4-Propyl and 4-Butyl derivatives of BA, respectively.

The magnitude of the white portion of the bars in Figure 1 (i.e., log γ) represents, the extent (factor) to which solubility can be (theoretically) enhanced, relative to the value in water, by altering the polarity of the solvent, as would be the case, for example, using an organic cosolvent. However, the actual solubility enhancement obtained will depend on how well the solute and solvent match each other in terms of their polarities (Rubino, 2002). Organic cosolvents are among the most commonly used agents for solubilizing pharmaceutical compounds (Millard, Alvarez-Núñez, & Yalkowsky, 2002), particularly during early development. Organic cosolvents can enhance solubility by orders of magnitude, since a linear increase in cosolvent concentrations translates in an exponential increase in solubility (Yalkowsky, Valvani, & Johnson, 1983a). However, in order to prevent irritation or hemolysis, the concentration of cosolvent in pharmaceutical vehicles need to be maintained at a relatively low level (Millard et al., 2002) such that the solution remains predominantly an aqueous medium, and the risk of drug precipitation following administration or solvent-induced hemolysis are prevented (Yalkowsky, Krzyzaniak, & Ward, 1998). The solubility of the different solutes in water-cosolvent mixtures containing 25% (v/v) cosolvent are presented in Figure 2. In this figure, the black and white portions of the bar represent the same factors (crystallinity and polarity, respectively) as in Figure 1. The black portions of the bars remain unchanged since they are independent of the solvent. The gray part of the solubility bars in Figure 2 represents the change in activity coefficient (-Δlog γ), produced by changing the solvent from pure water to a cosolvent-water mixture. A decrease in activity coefficient corresponds to an increase in solubility, so that the gray portion of the solubility bars represents the factor by which the solubility of the solute increased (relative to water) by the addition of the cosolvent. For each compound, the combined length of the solubility bars in Figures 1 (black and white) and 2 (black, white and gray) are exactly the same, with the difference being that the gray portion in Figure 2 shows the obtained solubility enhancement. This graphical

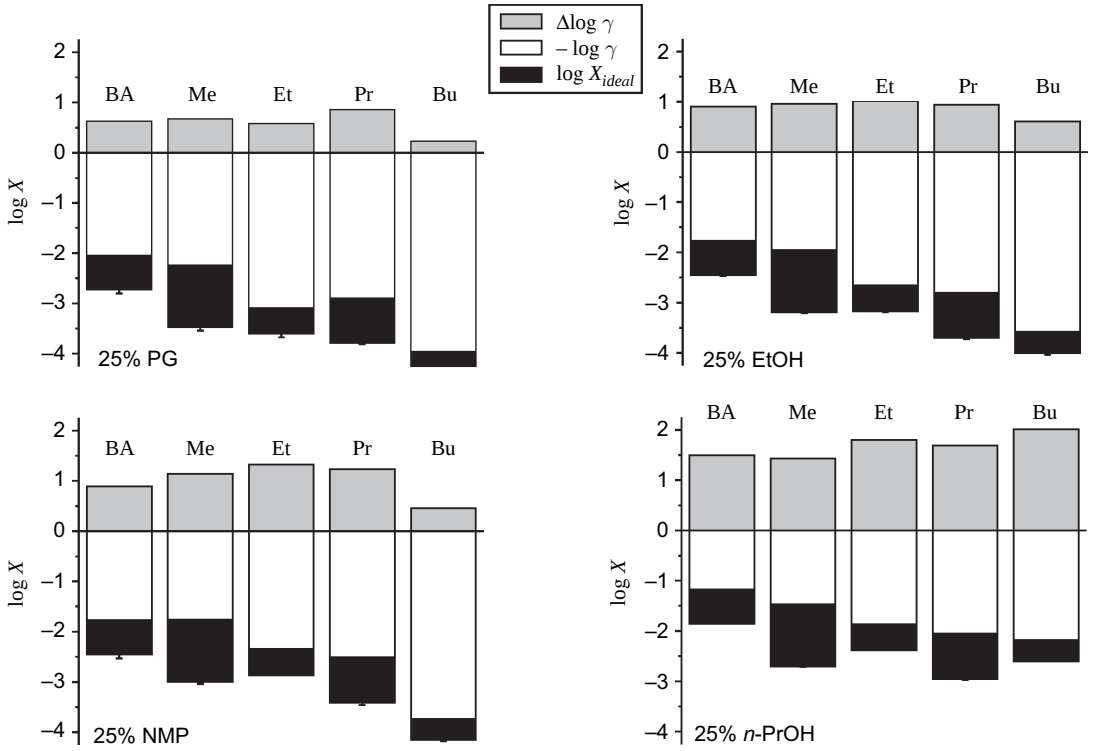

FIGURE 2. Graphical representation of the solubility enhancement produced by the addition of 25% (v/v) of cosolvent (PG, EtOH, NMP, and n-PrOH). The gray portion of the bars represents the factor by which solubility increases relative to the aqueous solubility. This factor is the same as the reduction produced on the activity coefficient (white portion of the bar) relative to the value in water.

representation makes it very easy to visualize, in one graph, the relative contribution for each of the effects under consideration, that is, crystallinity, polarity, and solubility enhancement.

The results shown in Figure 2 illustrate the importance of polarity match between solute and solvent for solubilization. Using the octanol-water partition coefficient of the cosolvent as a measure of solvent polarity, the relationship between solvent and solvent polarity can be assessed. The decreasing order of cosolvent polarity in Figure 2 is PG > EtOH > NMP > *n*-PrOH (with log $P_{o/w}$ values of –0.78, –0.14, –0.11, and 0.35, respectively). Figure 2 shows that PG and EtOH, which are the most polar (hydrophilic) solvents, exert roughly the same solubility enhancement for the solutes from $n = 0$ to $n = 3$, with the exception of the butyl derivative, for which the solubilizing effect is markedly lower. The butyl ($n = 4$) derivative is too hydrophobic for polar solvents such as PG or EtOH to exert a sizable solubilization effect. The significance of the relationship between the hydrophobicity of the solute and solvent polarity is more clearly seen from the NMP data in Figure 2. In this case, as the hydrocarbon chain length increases, the solubility enhancements exhibits somewhat of a bell-shaped trend with a maximum at $n = 2$. In this case, too, the butyl derivative is too hydrophobic for NMP to be as effective a solubilizer as for the ethyl substituted compound. Of the four cosolvents shown in Figure 2, *n*-propanol is the one of lowest polarity. In fact, since *n*-PrOH has a positive log $P_{o/w}$ value, it is the only solvent in the group that preferentially partitions into the hydrophobic (octanol) phase. This attribute of propanol is consistent with its observed solubilizing properties. In contrast to the solubility enhancement seen with the more polar cosolvents, the solubilizing effect of *n*-PrOH is strongest for the butyl derivative, that is, for the most hydrophobic solute of the series.

The relationship between solute hydrophobicity and the observed solubility enhancement is shown in Figure 3. All cosolvents investigated increase the solubility of the solutes, which is an expected result. However, the most polar solvents, PG and EtOH, produce an almost flat initial solubility enhancement factor. When the solutes are highly hydrophobic (log $P_{o/w} > \approx 3.5$), the above trend vanishes and a clear distinction between the two classes of cosolvents becomes clear. Hydrophilic cosolvents (those with negative log $P_{o/w}$ values) become almost ineffective in solubilizing highly hydrophobic solutes. Only *n*-PrOH, which based on its log $P_{o/w}$, can be technically considered hydrophobic, produces greater solubility enhancement as the solute hydrophobicity increases. These considerations are of significance because the need for solubilizing highly hydrophobic drugs (log $P_{o/w} \geq 4$) is actually very common in pharmaceutical development.

We investigated the cosolvency attributes of three solvents: Labrasol (LB), Solutol HS 15 (SL), and Tetraglycol (TG). All three are powerful organic solvents used in pharmaceutical

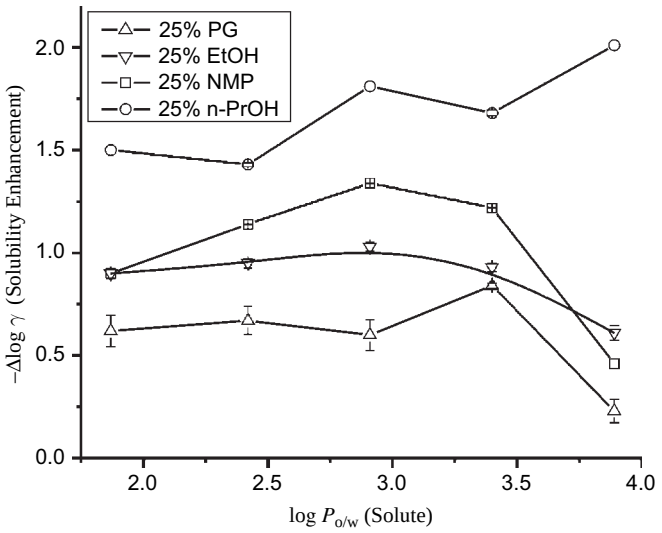

FIGURE 3. Relationship between solute hydrophobicity (log $P_{o/w}$) and the solubility enhancement factor obtained with the addition of 25% (v/v) of cosolvent (PG, EtOH, NMP, and n-PrOH).

formulations. LB is a mixture of glyceride and polyethylene glycol esters. SL is a mixture with ≈70% lipophilic composition consisting of polyglycol mono- and diesters of 12-hydroxystearic acid and ≈30% hydrophilic composition consisting of polyethylene glycol. This solvent is used in commercial pharmaceutical products in various countries. TG or glycofurol (tetrahydrofurfurylethileneglycol) is commonly used as a solubilizing vehicle during drug screening studies (Strickley, 2004).

The cosolvency of TG, LB, and SL, each at 25% (v/v), is shown in Figure 4 as a function of solute hydrophobicity (log $P_{o/w}$). The solubilizing properties of TG are very similar to those of the polar

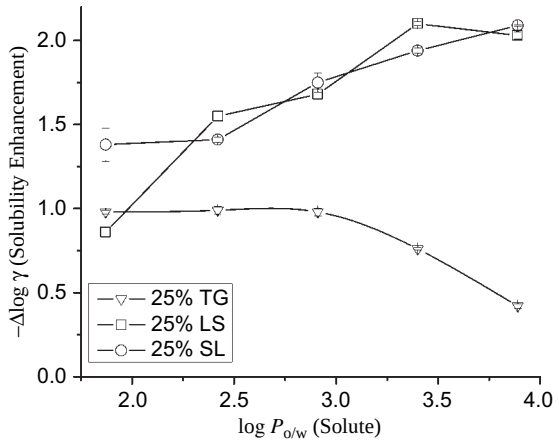

FIGURE 4. Relationship between solute hydrophobicity (log $P_{o/w}$) and the solubility enhancement.The solvent used consists of 75% (V/V) water plus 25% of the following solvents: Water (log $P_{o/w}$= –1.38, reference value), PG (log $P_{o/w}$ = –0.78), TG (log $P_{o/w}$ = –0.66), EtOH (log $P_{o/w}$ = –0.14), NMP (log$P_{o/w}$ = –0.11), and n-PrOH(log $P_{o/w}$ = 0.35).

cosolvents, particularly EtOH (Figure 3). Solubility enhancement by TG is essentially the same for solutes with hydrocarbon chain substitution from n = 0 to n = 2 (about 10-fold) and decreases for the more hydrophobic solutes (with hydrocarbon chain lengths of 3 and 4 carbons). On the other hand, the solubility enhancement obtained with SL is very much like that of *n*-PrOH (Figure 3). LB and SL produce greater solubility enhancement as the hydrocarbon chain length increases. The two cosolvents produce similar solubility enhancement for the substituted solutes. The solutes chosen in this study are all hydrophobic and represent the simplest (monotonic) case of hydrophobicity variation among solutes. There is an optimum solute hydrophobicity for which each solvent exerts the strongest solubilizing effect. These results point toward the importance of polarity matching when solubilizing organic compounds. However, the polarity of a solvent can be quantitatively defined in different ways. Parameters such as the dielectric constant, solubility parameter, interfacial tension, and octanol-water partition coefficients are all measures of polarity (Rubino & Yalkowsky, 1987). Figure 5 shows the relationship between the polarity of the cosolvent (log $P_{o/w}$) and the solubility enhancement produced on the different solutes. The relationship is linear for most solutes with the notable exception of 4-butyl-BA. For all solutes investigated, the less hydrophilic the solvent, the greater the solubility enhancement. However, despite the difference in hydrophobicity between BA and 4-methyl-BA (log $P_{o/w}$ values of 1.87 and 2.47, respectively), there is no difference in solubility enhancement between the two compounds. The solubility enhancement is greatest for 4-ethyl-BA (log $P_{o/w}$ = 2.9) and drops again for 4-propyl-BA (log $P_{o/w}$ = 3.4). For the most hydrophobic compound (4-butyl-BA, log $P_{o/w}$ = 3.9), the solubilization effect is minimal, and it takes a hydrophobic solvent (log $P_{o/w}$ > 0) like *n*-PrOH to produce any appreciable solubility enhancement. Since the solutes in this study are a homologous series, there is no difference among solutes in terms of the underlying chemistry of the solute-solvent interactions. Differences in activity coefficients among solutes can be attributed to the match (or lack of it) between solute hydrophobicity and solvent polarity and not to differences in intermolecular interactions. The impact of polarity match is clearly seen in Figures 1 and 3. While the white portions of the bars in Figure 1 represent the factor of maximum solubilization enhancement (theoretically) achievable through solvent manipulation, the extent of solubility enhancement shown in Figure 3 is significantly smaller in all cases. In order to attain maximum solubility enhancement, (theoratically) the solvent would need to have a log $P_{o/w}$ similar to that of the solute to match its polarity. All the solutes in the study have high log $P_{o/w}$ values, and solvents with similar log $P_{o/w}$ would not be miscible with water. In a predominately aqueous environment, polar cosolvents begin to lose their ability to solubilize highly hydrophobic compounds.

Another important consideration is that the polarity match between solute and solvent, while conceptually straightforward, is quantitatively less so. All solutes in the series are

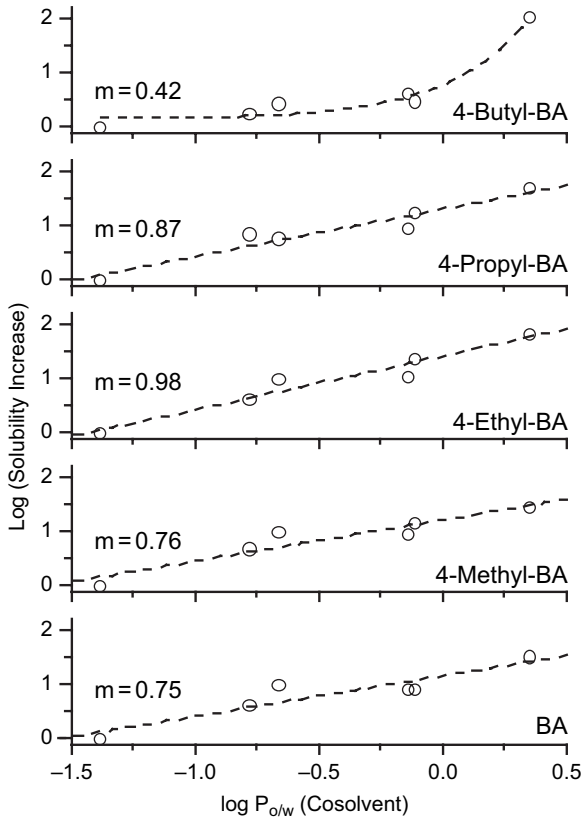

FIGURE 5. Relationship between cosolvent polarity and solubility enhancement for a homologous series of benzoic acid derivatives. The m value corresponds to the slope of the regression line. The m value for 4-butyl-BA corresponds to the first five points of the corresponding plot.

hydrophobic. It would be expected that for all solutes in the series, the higher the log $P_{o/w}$ of the cosolvent, the higher its solubilizing effect (Millard et al., 2002). Since the type of intermolecular interaction is the same for all solutes, simple polarity matching rules would result in monotonically increasing (or decreasing) slopes on the trend lines in Figure 5. The fact that this is not the case (even for a homologous series) indicates that a full theoretical account of polarity-matching is yet to be developed. It has been argued that the solubilization efficiency of an additive depends on the size of the hydrophobic portion in its structure, relative to the hydrophilic part (Bauduin, Renoncourt, Kopf, Touraud, & Kunz, 2005). Furthermore, Machatha and Yalkowsky found that in going from very polar to very nonpolar drugs solubilized with ethanol, the cosolvent concentration of maximum solubility exhibits a sigmoidal relationship with the log $P_{o/w}$ of the solute (Machatha & Yalkowsky, 2004). From a practical point of view, however, through measurements of the thermal properties of the solid and solubility determinations, it is possible to experimentally separate the two factors limiting the solubility of organic compounds. By doing so, solubilization screening can be objectively compared, thus facilitating optimization efforts.

CONCLUSIONS

The aqueous solubility of organic compounds is limited by two separate but additive factors: the crystallinity and hydrophobicity (polarity) of the solute. The contribution from each factor can be experimentally assessed, which provides an objective scale for visually evaluating the effect of solubilization approaches. Polarity matching between solute and solvent, although the goal during solubilization, is neither readily attained (when solubilizing hydrophobic compounds in predominately aqueous media) nor easily predicted from the properties of the solute and solvent. For this reason, the ability to consistently compare the degree of polarity matching becomes very important when testing solubilization approaches. Specifically, the impact of different cosolvents can be evaluated against the activity coefficient of the solute, which is the functional measure of hydrophobicity. The graphical representation used in this report can be used with other cosolvents, with different cosolvent concentrations or with mixtures of solubilizing agents, thus facilitating the systematic evaluation of solubilization approaches.

ACKNOWLEDGMENT

National Science Foundation I/UCRC 000364-EEC, Dane O. Kildsig Center for Pharmaceutical Processing Research.

REFERENCES

Bauduin, P., Renoncourt, A., Kopf, A., Touraud, D., & Kunz, W. (2005). Unified concept of solubilization in water by hydrotropes and cosolvents. *Langmuir, 21*, 6769–6775.

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev., 23*, 3–25.

Machatha, S., & Yalkowsky, S. (2004). Estimation of the ethanol/water solubility profile from the octanol/water partition coefficient. *Int. J. Pharm., 286*, 111–115.

Mao, C., Pinal, R., & Morris, K. R. (2005). A quantitative model to evaluate solubility relationship of polymorphs from their thermal properties. *Pharm. Res., 22*, 1149–1157.

Millard, J. W., Alvarez-Núñez, F. A., & Yalkowsky, S. H. (2002). Solubilization by cosolvents: Establishing useful constants for the log–linear model. *Int. J. Pharm., 245*, 153–166.

Rubino, J. T. (2002). Cosolvents and cosolvency. In J. Swarbrick and J. C. Boylan (Eds.), *Encyclopedia of pharmaceutical technology* (pp. 658–670). New York: Marcel Dekker, Inc.

Rubino, J. T., & Yalkowsky, S. H. (1987). Cosolvency and cosolvent polarity. *Pharm. Res., 4*, 220–230.

Strickley, R. G. (2004). Solubilizing excipients in oral and injectable formulations. *Pharm. Res., 21*, 201–230.

Yalkowsky, S. H., Krzyzaniak, J. F., Ward, G. H. (1998). Formulation-related problems associated with intravenous drug delivery. *J. Pharm. Sci., 87*, 787–796.

Yalkowsky, S. H., & Valvani, S. C. (1980). Solubility and partitioning. 1. Solubility of non-electrolytes in water. *J. Pharm. Sci., 69*, 912–922.

Yalkowsky, S. H., Valvani, S. C., & Johnson, B. W. (1983a). In vitro method for detecting precipitation of parenteral formulations after injection. *J. Pharm. Sci., 72*, 1014–1017.

Yalkowsky, S. H., Valvani, S. C., & Roseman, T. J. (1983b). Solubility and partitioning. 6. Octanol solubility and octanol-water partition-coefficients. *J. Pharm. Sci., 72*, 866–870.