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Investigation of the solubility relationships of polar, semi-polar and non-polar drugs in mixed co-solvent systems

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Summary

The solubility relationships of a non-polar (tioconazole), polar (oxfenicine) and semi-polar (caffeine) drug have been investigated in aqueous ethanol, propylene glycol and polyethylene glycol 400 (PEG 400) binary co-solvent systems. A semi-empirical equation was deduced to describe the relationship between the amount of drug dissolved and the volume fraction of co-solvent employed. The data for tioconazole and oxfenicine followed the expected semi-logarithmic relationship between solubility and fraction co-solvent. However, the semi-polar drug, caffeine followed this relationship only with PEG 400; the other two co-solvents yielded parabolic relationships.

Using the binary solubility data, multiple linear regression was used to deduce an equation for the solubility of tioconazole in ternary ethanol, propylene glycol and PEG 400 co-solvent systems. The derived relationship gave excellent prediction of the drug solubility throughout the complete volume fraction range. This allowed a graphical representation of the drug solubility–co-solvent fraction relationship to be established. This visualization of the drug solubility relationship was then used to demonstrate its utility to optimize drug solubility within the competing constraints of the pharmaceutical system.

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Introduction

One of the frequent problems a formulator faces when developing a parenteral presentation of a drug is that the drug may be only poorly water-soluble. If the drug solubility cannot be improved by manipulation of the pH of the vehicle, the formulator often has to resort to using co-solvents (water-miscible non-aqueous solvents) such as ethanol, propylene glycol or one of the polyethylene glycols to enhance the solubility. However, the use of high levels of these co-solvents may adversely affect the toxicity and viscosity of the final presentation.

There have been several reports dealing with investigations of drug solubility and solvent composition. Many of the observations to date indicate that the solubility of many drugs in binary systems is enhanced exponentially by the addition of co-solvents (Yalkowsky et al., 1972; Chien and Lambert, 1975). However, it appears that this relationship is only true when the solute is less polar than the mixed solvent system (Yalkowsky and Roseman, 1981). Only recently has any systematic account of the solubility characteristics of drugs of varying polarity in binary aqueous (i.e. single co-solvent) systems been attempted (Yalkowsky et al., 1976). In addition, little attention has been paid to the investigation of drug solubility in aqueous systems containing two or more different co-solvents.

This paper sets out to investigate the relationship between solubility and solvent composition for drugs of varying hydrophobicities. We report the dependence of drug solubility on the fraction of co-solvent in the system, and present a theoretical relationship between these two quantities. In addition, we use the method to evaluate the solubility of a drug in a mixed co-solvent system and demonstrate how multiple co-solvent combinations offer improvements over solubilization with a high volume fraction of a single co-solvent.

Theory

In non-ideal solutions (Martin, 1960), the solubility of a drug in a pure water system (S_w), at temperature T is given by:

$$\log S_w = -\frac{\Delta S_f}{2.303RT}(T_m - T) + \log \gamma_w \qquad (1)$$

where ΔS_f is the entropy of fusion of the drug, T_m is the melting point and γ_w is the molar activity coefficient of the drug in water.

Similarly the solubilities of the drug (S_x, S_y) in pure (co)solvents x, y may be defined:

$$\log S_x = -\frac{\Delta S_f}{2.303RT}(T_m - T) + \log \gamma_x \qquad (2)$$

$$\log S_y = -\frac{\Delta S_f}{2.303RT}(T_m - T) + \log \gamma_y \quad (3)$$

where γ_x, γ_y are the corresponding drug activity coefficients in the pure (co)solvent x and y.

Thus in a non-ideal ternary co-solvent system, where the volume fractions of co-solvents x and y are f_x and f_y, respectively, and that for water, f_w, is $[1 - (f_x + f_y)]$, the overall solubility of the drug (S_m) in the system will be given by:

$$\log S_m = f_w \log S_w + f_x \log S_x + f_y \log S_y$$

$$= \log S_w + f_x(\log S_x - \log S_w) + f_y(\log S_y - \log S_w) \quad (4)$$

Since

$$\log S_x - \log S_w = \log \frac{\gamma_x}{\gamma_w} \quad (5)$$

and

$$\log S_y - \log S_w = \log \frac{\gamma_y}{\gamma_w} \quad (6)$$

substituting Eqs. 5, 6 into Eqn. 4 gives:

$$\log S_m = \log S_w + f_x \log \frac{\gamma_x}{\gamma_w} + f_y \log \frac{\gamma_y}{\gamma_w} \quad (7)$$

Eqn. 7 therefore shows that the solubility of the drug (S_m) in a ternary co-solvent system is exponentially related to the volume fractions of co-solvents x and y. Furthermore, the slopes σ_x, σ_y of the semi-logarithmic relationship between drug solubility and composition of the co-solvent system are given by:

$$\sigma_x = \log \frac{\gamma_x}{\gamma_w} \text{ and } \sigma_y = \log \frac{\gamma_y}{\gamma_w}$$

for co-solvents x and y respectively.

In order to investigate these slope terms further, it is useful to consider the octanol/water partition coefficient, $P_{o/w}$, of the drug (Yalkowsky and Roseman, 1981). Since:

$$P_{o/w} = \frac{\gamma_o}{\gamma_w} \quad (8)$$

where γ_o is the activity coefficient of the drug in octanol, and

$$\log P_{o/w} = \log \gamma_o - \log \gamma_w$$

it can be shown that:

$$\sigma_x = \log P_{o/w} - \log P_{o/x} \tag{9}$$

$$\sigma_y = \log P_{o/w} - \log P_{o/y} \tag{10}$$

where $\log P_{o/x}$ and $\log P_{o/y}$ are the logarithms of the octanol–co-solvent x, octanol–co-solvent y partition coefficients, respectively.

Thus, the slopes of the semi-logarithmic relationships between drug solubility and fraction co-solvent are simply a balance between the solute polarity, as measured by the $\log P_{o/w}$ term, and the solvent polarity as measured by the $\log P_{o/\text{co-solvent}}$ term.

If we now consider a single co-solvent system (i.e. $f_y = 0$) Eqn. 7 reduces to:

$$\log S_m = \log S_w + f_x \log \frac{\gamma_x}{\gamma_w}$$

$$= \log S_w + f_x(\log P_{o/w} - \log P_{o/x}) \tag{11}$$

For the above relationship, it is clear that for non-polar drugs $\log P_{o/x} \ll \log P_{o/w}$, indicating that the slope of the $\log S_m$ vs f_x plot should be positive, and proportional to the magnitude of $\log P_{o/w}$. For polar drugs, the converse should apply, with the $\log P_{o/x}$ term dominating and the slope being of negative sign and its magnitude proportional to $\log P_{o/x}$. For semi-polar drugs neither term will dominate and, at best only a small increase in solubilizing power will be observed.

However, the above treatment for polar and semi-polar drug is probably oversimplified since the regular solution theory employed assumes the excess entropy of mixing to be zero, i.e. a random distribution of molecules, where only non-polar and weakly polar forces exist. Polar and semi-polar drugs form irregular solutions in polar and hydrogen-bonding solvents. Under these conditions, Martin and co-workers (1980) have shown that the activity coefficient terms in Eqns. 1–3 have to be corrected by an additional term, which represents the contributions from stronger drug–solvent interactions. The modified activity coefficient term, $\log \gamma'$, in Eqns. 1–3 is then given by:

$$\log \gamma' = \log \gamma + \frac{2\phi^2}{2.303RT} V_D(\delta_D\delta_S - W) \tag{12}$$

where δ_S and δ_D are the solubility parameters of solvent and drug, respectively, W is the energy of interaction of the drug with the solvent in the irregular solution, ϕ is the volume fraction of solvent and V_D is the molar volume of the drug.

Thus Eqn. 7 for a binary co-solvent system has a revised slope term σ', where:

$$\sigma' = \log \gamma'_x - \log \gamma'_w \tag{13}$$

for a co-solvent X and water system.

Substituting Eqn. 12 into 13, and assuming dilute solution where ϕ is approximately unity, the revised slope term becomes

$$\sigma' = \log \gamma_X - \log \gamma_W + 2b[(\delta_D\delta_X - W_X) - (\delta_D\delta_W - W_W)]$$

$$\sigma' = \sigma + 2b[\delta_D(\delta_X - \delta_W) + (W_W - W_X)] \quad (14)$$

where subscripts D, X and W refer to drug, co-solvent X and water, respectively, and $b = V_D/2.303\ RT$.

Thus Eqn. 11 derived previously to account for the solubility relationships in binary systems only holds for non-polar systems where the second term on the right-hand side of Eqn. 14 is negligible (i.e. regular solution). Thus for the extended treatment for polar drugs, Eqn. 15 should then apply:

$$\log S_M = \log S_W + f_X[\sigma + 2b(\delta_D(\delta_X - \delta_W) + (W_W - W_X)] \quad (15)$$

and since σ will be highly negative, and the irregular solution term will also be negative (Martin et al., 1980), a highly negative σ' will result.

For semi-polar drugs the σ term in Eqn. 15 would be expected to be neutral or slightly positive. Taking into account the weakly negative irregular solution term, the overall σ' value would be expected to be either slightly positive, slightly negative or zero.

Thus, the treatment using irregular solution for polar and semi-polar drugs leads to the same conclusions to that previously found using regular solutions.

Experimental

Materials and methods

Tioconazole (UK-20,349), oxfenicine (UK-25,842) were from Pfizer (Sandwich, Kent, U.K.) and caffeine from Aldrich (Dorset U.K.). The propylene glycol (PG), polyethylene glycol 400 (PEG 400) and absolute ethanol (E) were of normal pharmaceutical grade and used as received. Parenteral quality distilled water was used for the preparation of the 0–80% co-solvent–water combinations. Methanol (Analar grade) was employed for the dilution of filtered drug solution to a suitable concentration for spectrophotometric measurement.

Determination of drug solubility

Excess drug solid was equilibrated with 10 ml of a co-solvent–water combination at $22 \pm 2°C$ for 16 h with constant agitation. Following equilibration, the drug solution was filtered (Millipore FGL, 0.2 μm) and then diluted up to 10^4 times with methanol to a suitable drug concentration for spectrophotometric measurement. The magnitude of the absorbance at the λ_{max} was then used to calculate the amount of drug dissolved in the given solvent system. In the case of tioconazole corrections were made at high ethanol (> 50%) combinations for the changes in volume following dissolution.

Results and Discussion

The experimental dependence of the solubility of 3 model drugs of varying polarity (tioconazole, log P = 4.52; caffeine, log P = 0.57; oxfenicine, log P = −2.5) in binary co-solvent systems (propylene glycol, polyethylene glycol 400 and ethanol individually with water) are given in Figs. 1 , 2 and 3 respectively.

As expected, the non-polar example, tioconazole (Fig. 1), produces semi-logarithmic plots with large and positive slopes for each of the co-solvent systems studied; the maximum slope being with ethanol, since it is the least polar of the co-solvents investigated, and leads to the smallest log $P_{o/x}$ term.

Hydrophilic oxfenicine (Fig. 2) shows the expected exponential reduction in

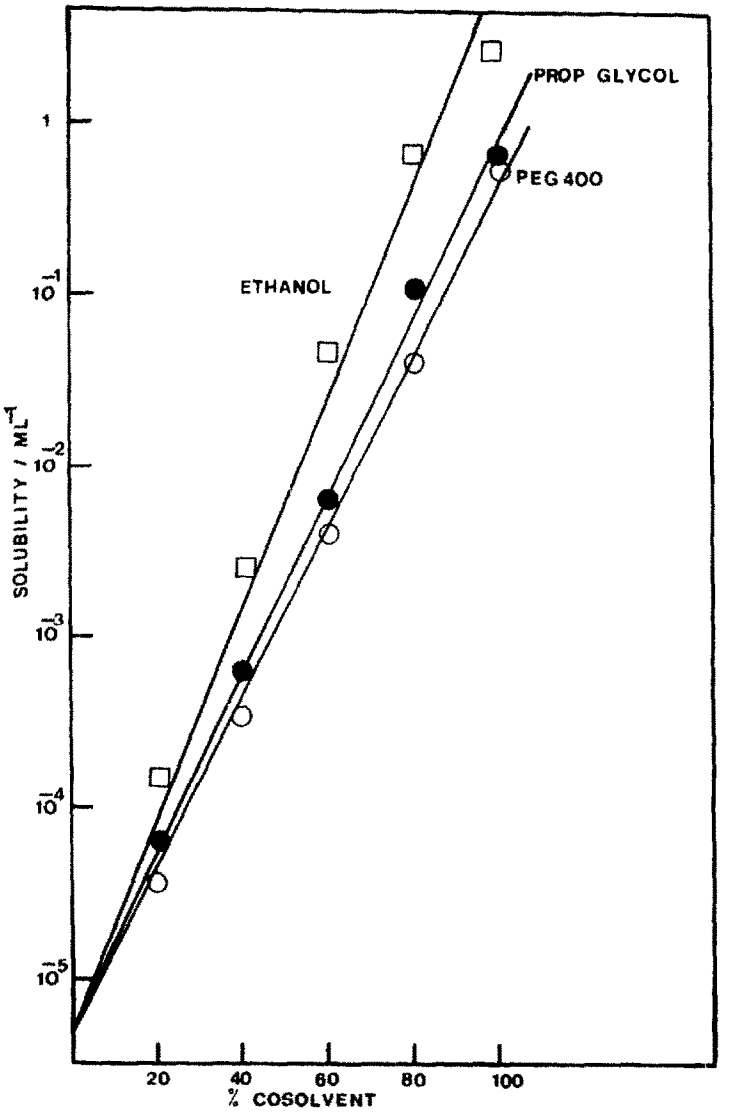

Fig. 1. Solubility vs co-solvent fraction relationship for non-polar case, tioconazole.

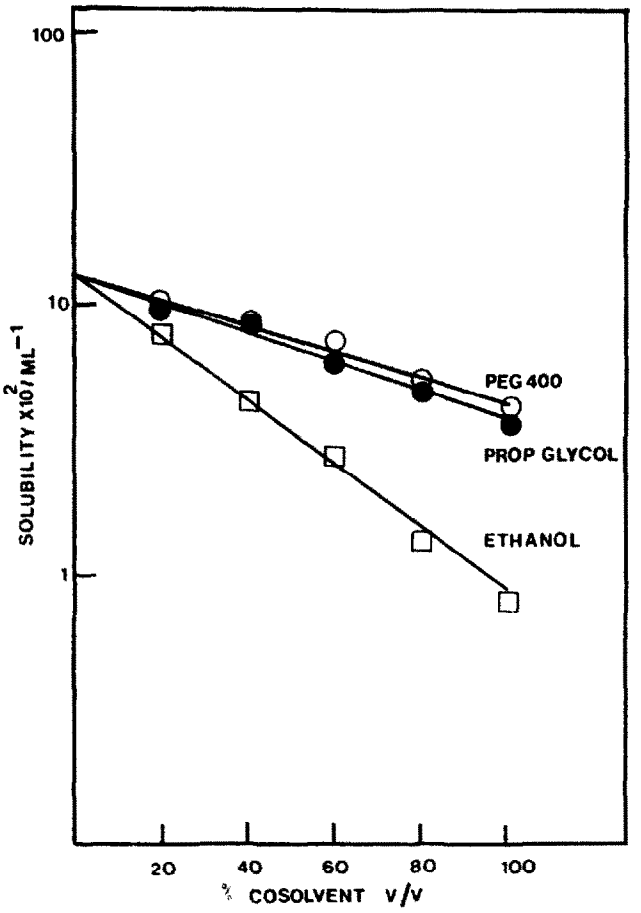

Fig. 2. Solubility vs co-solvent fraction relationship for polar case, oxfenicine.

solubility with increasing volume fraction of co-solvent. The magnitude of the slope of the log S_m vs f plot being once again greatest for ethanol, since it is the least polar co-solvent and thus results in the largest log $P_{o/x}$ term.

Whereas linear relationships between the logarithm of the solubility and the fraction co-solvent were observed for all co-solvents in the previous cases, this is not observed for the semi-polar example, caffeine (Fig. 3). Ethanol and propylene glycol show distinct parabolic relationships, whilst PEG 400 shows the more expected linear relationship of shallow slope. Paruta and co-workers (1965) have shown that the solubility of caffeine in dioxane–water mixtures exhibits a multiplicity of peak solubilities at various values of the dielectric requirements of the drug. These maxima correspond to volume fractions of 83, 55 and 33% ethanol in Fig. 3 and are believed to be the result of self-complexation of the drug in aqueous solution (Higuchi and Guttman, 1957); the state of this complexation changing from monomeric to tetrameric states as the polarity of the solvent system increases. This then causes the drug to have a log $P_{o/w}$ that changes with the volume fraction co-solvent in Eqn. 11, and the δ_D value in Eqn. 14. This could then explain the parabolic relationships found with ethanol and propylene glycol.

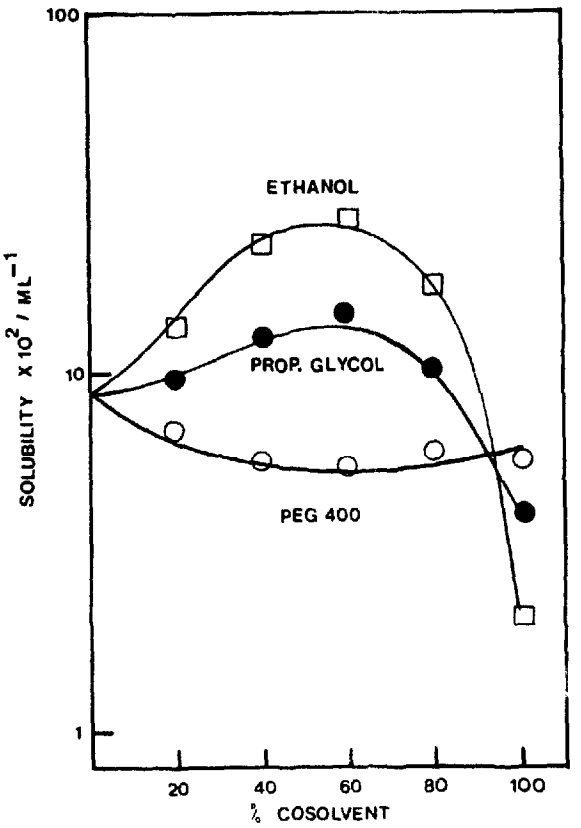

Fig. 3. Solubility vs co-solvent fraction relationship for semi-polar case, caffeine.

Investigation of mixed co-solvent systems

One feature of further interest emerges from Eqn. 7. The slope terms from the individual co-solvent systems can be combined into a function that will allow estimation of the solubility of a drug in a mixed co-solvent system. This was examined by fitting all the binary solvent data for tioconazole by multiple linear regression (BMDP statistical package). This yielded the following ternary solvent equation:

$$\log S_m = [0.059 \pm 0.003]\%E + [0.047 \pm 0.003]\%PG + [0.050 \pm 0.003]\%PEG\ 400 - 5.136$$

$r = 0.990$; $r^2 = 0.981$; n = 15; $P < 0.001$

where all co-solvent coefficients are significant at the 95% confidence level and over 98% of the variation in the solubility data is accounted for by the regression model. Prior to the analysis, all independent variables were shown to be non-correlated at the 10% level of significance, and the number of solubility determinations conducted sufficient to avoid undue risk of chance correlations (Topliss and Costello, 1972).

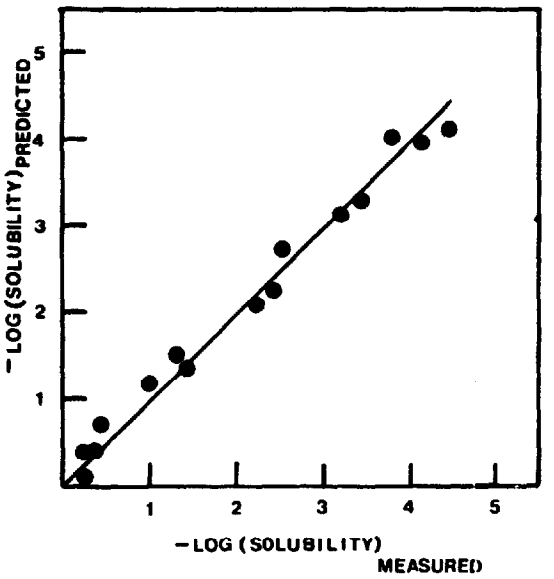

Fig. 4. Solubility of tioconazole calculated (predicted) vs solubility observed. Solid line is for a residual of zero.

Fig. 4 shows a plot of the calculated vs observed solubilities for the 15 observation training set used to derive the model. The agreement over the whole of the solubility range is excellent. The equation can now be used to calculate solubilities, within the defined region ($\log S_M = 0.15–4.88$), for any new mixed co-solvent formulation of interest. This was tested by further determining the solubility of tioconazole in a variety of mixtures of ethanol, propylene glycol and PEG 400. The results (Table 1) for the 'predictor' data set shows, once again, excellent agreement between the predicted and measured solubilities. Thus this method has the potential utility to estimate the solubility of hydrophobic drugs in mixed co-solvent systems.

However, in formulation terms it is also of interest to consider the relationship

TABLE 1

MEASURED AND CALCULATED SOLUBILITY OF TIOCONAZOLE IN MIXED ETHANOL, PROPYLENE GLYCOL AND PEG 400 SOLUTIONS. CALCULATED VALUES WERE OBTAINED FROM EQN. 12

% Ethanol	% Propylene glycol	% PEG 400	$-\log_{10}$Sm calculated	$-\log_{10}$Sm measured	Residual
20	40	0	2.076	2.019	−0.057
40	20	0	1.836	1.645	−0.191
15	0	25	3.001	3.031	+0.030
25	0	15	2.911	2.921	+0.010
0	20	20	3.196	3.210	+0.014
0	30	30	2.226	2.325	+0.099
15	15	15	2.796	2.795	−0.001
30	10	10	2.396	2.285	−0.111
10	30	10	2.636	2.673	+0.037

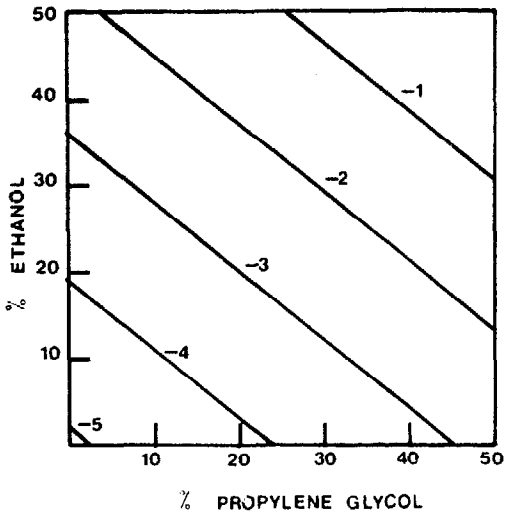

Fig. 5. Solubility of tioconazole in mixed ethanol/propylene glycol/water ternary solvent systems. Contours are log S_M.

between the solubility of the drug and the total levels of co-solvent employed. If we consider the propylene glycol/ethanol data for tioconazole, then a representation of the solubility as a function of co-solvent levels is depicted in Fig. 5. Inspection of Fig. 5 shows that as the level of total co-solvent rises, a correspondingly larger increase in solubilization level is obtained. For example, the solubilization level with 20% propylene glycol could in practice also be achieved with a 10% ethanol/8% propylene glycol combination. Similarly the solubilization level produced with 60% propylene glycol could be achieved with a 30% ethanol/24% propylene glycol combination. In both cases a net reduction in the total level of co-solvent in the system could be achieved. This effect has been even more marked in other systems we have investigated (Gould et al., 1982). This feature, and plots such as Fig. 5, are of great benefit to the formulator, as they allow optimization of the solubility of the drug in a mixed co-solvent combination, which can then be judged against the competing constraints of the pharmaceutical system, e.g. vehicle viscosity, co-solvent toxicity or the drug's hydrolytic stability profile.

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