Solubility Prediction of Satranidazole in Propylene Glycol-Water Mixtures Using Extended Hildebrand Solubility Approach

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Rathi: Solubility Prediction of Satranidazole in Propylene Glycol-Water Mixtures

Extended Hildebrand solubility approach is used to estimate the solubility of satranidazole in binary solvent systems. The solubility of satranidazole in various propylene glycol-water mixtures was analyzed in terms of solute-solvent interactions using a modified version of Hildebrand-Scatchard treatment for regular solutions. The solubility equation employs term interaction energy (W) to replace the geometric mean ($\delta_1\delta_2$), where δ_1 and δ_2 are the cohesive energy densities for the solvent and solute, respectively. The new equation provides an accurate prediction of solubility once the interaction energy, W, is obtained. In this case, the energy term is regressed against a polynomial in δ_1 of the binary mixture. A quartic expression of W in terms of solvent solubility parameter was found for predicting the solubility of satranidazole in propylene glycol-water mixtures. The expression yields an error in mole fraction solubility of ~3.74%, a value approximating that of the experimentally determined solubility. The method has potential usefulness in preformulation and formulation studies during which solubility prediction is important for drug design.

Key words: Extended Hildebrand solubility approach, propylene glycol, regular solution theory, satranidazole, solubility parameter

Solubility data on drugs and pharmaceutical adjuncts in mixed solvents have wide applications in the drug sciences. Knowledge of interaction forces between solutes and solvents are of considerable theoretical and practical interest throughout the physical and biological sciences[1]. The theory of solution is one of the most challenging branches of physical chemistry. The Hildebrand-Scatchard theory of regular solution is the pioneer approach in this field, used to estimate solubility only for relatively non-polar drugs in non-polar solvents[2]. An irregular solution is one in which self-association of solute or solvent, solvation of the solute by the solvent molecules, or complexation of two or more solute species are involved[3]. Polar systems exhibit irregular solution behaviour and are commonly encountered in pharmacy. Extended Hildebrand solubility approach (EHSA), modification of the Hildebrand-Scatchard equation, permits calculation of the solubility of polar and non-polar solutes in solvents ranging from non-polar hydrocarbons to highly polar solvents such as water, ethanol, and glycols[4]. The solubility parameters of solute and solvent were introduced to explain the behaviour of regular and irregular solutions[5]. The EHSA has been developed to reproduce the solubility of drugs and other solids in the binary solvent systems[6].

The Hildebrand-Scatchard equation for the solubility of crystalline solids in a regular solution may be written as[7],

$$[-\log X_2 = -\log X_2{}^i + A(\delta_1{}^2 + \delta_2{}^2 - 2\delta_1\delta_2)],\qquad(1a)$$

$$[-\log X_2 = -\log X_2{}^i + A(\delta_1 - \delta_2)^2].\qquad(1b)$$

The Extended Hildebrand equation for the solubility of solids in an irregular solution may be written as[8],

$$[-\log X_2 = -\log X_2{}^i + A(\delta_1{}^2 + \delta_2{}^2 - 2W)].\qquad(2)$$

From the geometric mean:

$$\delta_1\delta_2 = \sqrt{\delta_1^2\delta_2^2} .\qquad(3a)$$

In pharmaceutical solutions, the geometric mean of δ_1 and δ_2 is too restrictive and ordinarily provides a

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poor fit to experimental data in irregular solutions. The assumption that the geometric mean of two geometric parameters $\delta_1\delta_2$ (Eqn. 1) can be replaced by a less restrictive term W (Eqn. 2), interaction energy parameter, which is allowed to take on values as required to yield correct mole fraction solubilities, X_2 as[9],

$$W = K\delta_1\delta_2, \tag{3b}$$

where, K is the proportionality factor relating W to the geometric mean of solubility parameter.

In Eqn. 1 and Eqn. 2, X_2 and X_2^i are the mole fraction solubility and ideal mole fraction solubility of the solute respectively. The terms δ_1 and δ_2 are the solubility parameters for the solvent and solute respectively. The geometric mean, $\delta_1\delta_2$, provides a reasonable estimate of solvent-solute interaction in regular (ordinarily non-polar) mixtures, whereas W or K $\delta_1\delta_2$ is required to express solubility's in non-regular systems (irregular solutions) of drugs in associating mixed solvents.

The term negative logarithm of the ideal solubility ($-\log X_2^i$) can be taken as[10],

$$[-\log X_2^i = \frac{\Delta H_f}{2.303RT}\left(\frac{T_o - T}{T_o}\right), \tag{4}$$

Where, ΔH_f is heat of fusion of the crystalline drug molecule, T_0 is the melting point of solute in absolute degrees.

The term A in equations 1 and 2 is defined as[11],

$$A = \frac{V_2\Phi_1^2}{2.303RT}, \tag{5}$$

Where, V_2 is the molar volume of the solute as a hypothetical supercooled liquid at solution temperature, R is the universal gas constant, T is the absolute temperature, 298.2°K, of the experiment and Φ_1, the volume fraction of the solvent, is[12],

$$\varphi_1 = \frac{V_1(1-X_2)}{V_1(1-X_2) + V_2X_2}, \tag{6}$$

Where, V_1 is the molar volume of the solvent at 25°. The term logarithmic solute activity coefficient ($\log \gamma_2$) from Eqn. 2 and Eqn. 5 can be written as[13],

$$\log\gamma_2 = A(\delta_1^2 + \delta_2^2 - 2W) = \frac{V_2\Phi_1^2}{2.303RT}(\delta_1^2 + \delta_2^2 - 2W) \tag{7}$$

A better approach is not to restrict the interaction term W to a geometric mean but evaluate it experimentally from the solubility of the solute in various solvent concentrations in a binary mixture employing Eqn. 2. An empirical equation for W as a function of solubility parameters of the solvent mixture remains to be discovered. Then, back-calculating W and substituting into Eqn. 2 permit the mole fraction solubility of a drug (solute) to be predicted in essentially any solvent mixture. Therefore, the present investigation pertains to the utility of EHSA in relation to the satranidazole solubility in propylene glycol (PG)-water binary solvent mixtures.

Satranidazole, obtained as gift sample from Alkem Laboratories Ltd., Baddi, India, was purified by recrystallization from acetone. Propylene glycol and acetone were purchased from ICPA Laboratories; Ankleshwar, India and Qualigens Fine Chemicals, Mumbai, India respectively. Throughout the study freshly prepared double distilled water was used for experimental purpose. All chemicals and reagents used in the study were of analytical grade and used as such. Double beam UV/Vis spectrophotometer, Shimadzu model 1601 with spectral bandwidth of 2 nm, wavelength accuracy ±0.5 nm and a pair of 10 mm matched quartz cells was used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing of Satranidazole. Differential Scanning Calorimeter, Shimadzu TA-60 WS, was used for determination of melting point and heat of fusion of satranidazole.

The solubility of satranidazole was determined in binary solvent mixtures of PG and water. Double distilled water was used to prepare mixtures with PG in concentrations of 0-100% by volume of PG. About 10 ml of PG, water, or binary solvent blends were introduced into screw-capped vials containing an excess amount of satranidazole. After being sealed with several turns of electrical tape, the vials were submerged in water at 25±0.4° and were shaken at 150 rpm for 24 h in a constant-temperature bath. Preliminary studies showed that this time period was sufficient to ensure saturation at 25°[14].

After equilibration, the solutions were microfiltered (0.45 µm) and the filtrate was then diluted with double distilled water to carry out the spectrophotometric determination at the maximum wavelength of absorption of the satranidazole (λ_{max}-319.80 nm). The solubility of the satranidazole was determined at least three times for this solvent mixture, and the average value was taken. The densities of the solvent mixtures and the filtrates of saturated solutions of satranidazole were determined in triplicate at 25±0.4° using 10-ml specific gravity bottle. Once the densities of solutions are known, the solubilities can be expressed in mole fraction scale.

The solubility parameters of the solvents were obtained from the literature[15,16]. The solubility parameter of satranidazole was calculated previously by Fedor's group contribution method[17,18], which was confirmed by solubility analysis in dioxane-water blend.

The thermogram of satranidazole was obtained with a differential scanning calorimeter[19]. The melting point and heat of fusion were measured. Sample of 8.8 mg in perforated pan was heated at a rate of 15°/min under nitrogen purge. The temperature range studied was 25-225°. The molar enthalpy of fusion of satranidazole was 112.30 J/g (7763.838 cal/mol) and the temperature of fusion is 461.83°K. Neither decomposition nor polymorphic change was observed at the experimental temperature range. The ideal mole fraction solubility of satranidazole was calculated from these values ($-\log X_2^i = 1.61$). The mole fraction solubilities of satranidazole at

25±0.4° in PG-water binary mixtures which cover a large range of the solubility parameter scale, from 14.80 to 23.40 $(Cal/cm^3)^{0.5}$, are listed in Table 1. The experimental mole fraction solubility of satranidazole at 25±0.4° in PG-water mixtures is plotted in fig. 1 versus the solubility parameter, δ_1, of the various mixed solvent systems. The mole fraction solubility of satranidazole (δ_2=14.80) in PG (δ_2=14.80), water (δ_1=23.4), and in the mixture of the two solvents is represented by the solid circles in fig. 1. The maximum solubility of satranidazole in the mixture is X_2=0.0002545 mol/l and occurs at δ_1=14.80. This value is well below the ideal solubility, X_2^i=0.0245614 mol/l, as predicted from regular solution theory. The discrepancy between the results using the original Hildebrand-Scatchard equation and experimental points demonstrates that Eqn. 1a and Eqn. 1b cannot be used to predict drug solubility in PG-water binary solvent systems. This behavior has been dealt with the theoretical replacement of mean geometric solubility parameters ($\delta_1\delta_2$) term with the interaction energy term (W).
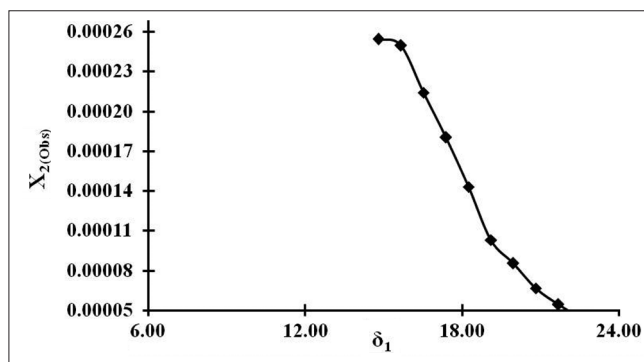

Fig. 1: Solubility parameter versus mole fraction solubility profile. ◆ Experimental solubilities and back-calculated solubilities from Eq. 2. Highest mole fraction solubility obtained is, $X_2 = 2.545*10^{-4}$ when $\delta_1 = 14.80$ $(Cal/cm^3)^{0.5}$ in PG-water mixtures

TABLE 1: MOLE FRACTION SOLUBILITY OF SATRANIDAZOLE

PG-Water (%v/v)	Solubility (g/ml)	δ_1 $(Cal/cm^3)^{0.5}$	V_1	Density of blend	Mol. Wt of blend	$X_{2(obs)}$	$W_{(obs)}$
0:100	0.0005025	23.40	18.00	0.9980	18.00	3.1350E-05	330.26
10:90	0.0005350	22.54	23.56	1.0018	23.81	4.3980E-05	310.93
20:80	0.0005350	21.68	29.12	1.0056	29.62	5.4505E-05	292.19
30:70	0.0005495	20.82	34.68	1.0094	35.43	6.6711E-05	274.17
40:60	0.0006073	19.96	40.24	1.0132	41.24	8.5499E-05	256.95
50:50	0.0006435	19.10	45.80	1.0170	47.05	1.0298E-04	240.38
60:40	0.0007990	18.24	51.36	1.0208	52.86	1.4313E-04	224.74
70:30	0.0009111	17.38	56.92	1.0246	58.67	1.8048E-04	209.71
80:20	0.0009870	16.52	62.48	1.0284	64.48	2.1410E-04	195.35
90:10	0.0010593	15.66	68.04	1.0322	70.29	2.4957E-04	181.71
100:0	0.0010015	14.80	73.60	1.0360	76.10	2.5450E-04	168.63

δ_1= Solubility parameter of solvent blend, V_1= molar volume of the solvent blend, and W is calculated from Eqn. 2

Eqn. 2, differs from Eqn. 1, in that the geometric mean is not used, hence provides an accurate prediction of solubility once W is obtained. Although W presently cannot be estimated based on fundamental physicochemical properties of the solute and solvent, W may be regressed against a polynomial in δ_1 of the PG-water binary solvent mixtures (fig. 2). The following quadratic, cubic, and quartic equations were obtained using the experimental solubility data for satranidazole in PG-water mixtures: $W_{cal} = 59.67364 + 0.15209 \, \delta_1 + 0.48767 \, \delta_1^2$ (n = 11, R^2 = 0.99999816)--- (8), $W_{cal} = 39.74407 + 3.36052 \, \delta_1 + 0.31765 \, \delta_1^2 + 0.00297 \, \delta_1^3$ (n = 11, R^2 = 0.99999892)---(9), $W_{cal} = -132.17742 + 40.31464 \, \delta_1 - 2.63481 \, \delta_1^2 + 0.10690 \, \delta_1^3 - 0.00136 \, \delta_1^4$ (n = 11, R^2 = 0.99999971)---(10).

The W values calculated using these expressions compared favorably with the original W values computed using Eqn. 2. The solid line plotted in fig. 2 was obtained employing the quartic expression (Eqn. 10). The calculated solubility curve fits the experimental data points quite well (figs. 1 and 3), predicting the solubility of satranidazole in PG-water mixtures at most points within an error of ~3.74%, approximating the error in experimentally determined solubility values. These polynomials are used successfully for the calculation of W, at any value of solubility parameter (δ_1), which was then subsequently employed to calculate mole fraction solubility of solute (X_{2cal}) in a solvent blend using backward regression. Representative data along with validation parameters are summarized in Table 1. W_{cal} values are indicating the significant interaction of satranidazole and solvent molecules at the peak of solubility profile.

Validation of Eqn. 10 was done by comparing experimentally obtained and calculated values of mole fraction solubility by estimating residuals and percent difference (Table 2). The predictive capability of the model for satranidazole is represented in fig. 3, which
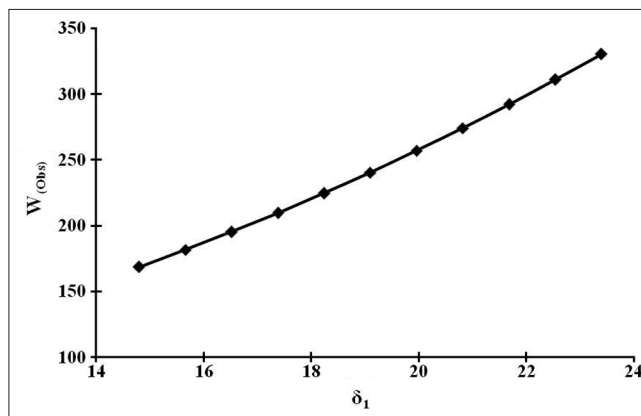

Fig. 2: Solubility parameter versus interaction energy profile. $W_{(cal)}$ obtained from quartic regression Eqn. 10, for satranidazole in PG-water mixtures at 25±0.4° and correlation coefficient, r^2, is 0.9999 for n = 11
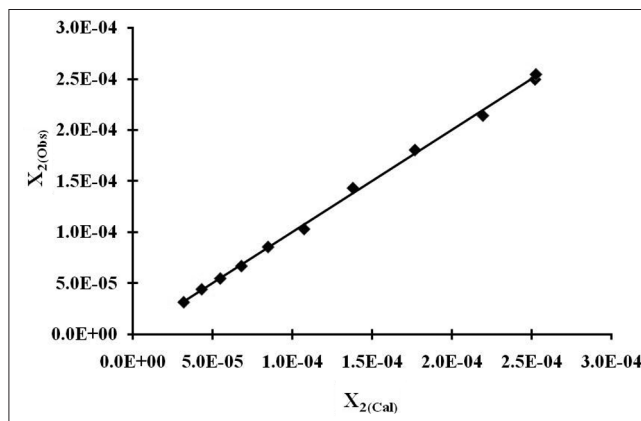

Fig. 3: Comparison of observed and calculated mole fraction solubility. Comparison of 11 observed satranidazole solubilities in PG-Water systems at 25 ± 0.4⁰ with solubilities predicted by extended Hildebrand approach. The intercept of the line is 0.0000009, and the slope is 0.997. The correlation coefficient, r^2, is 0.998 for n = 11

TABLE 2: EXPERIMENTAL AND CALCULATED MOLE FRACTION SOLUBILITIES

$W_{(obs)}$	$W_{(cal)}$	$X_{2(obs)}$	$X_{2(cal)}$	$\log\gamma_2/A_{(obs)}$	$\log\gamma_2/A_{(cal)}$	Residual	Percent difference
330.263794	330.277402	3.1350E-05	3.1691E-05	16.764513	16.737296	-1.0877E-02	-1.1
310.934967	310.905039	4.3980E-05	4.2946E-05	15.913766	15.973622	2.3510E-02	2.4
292.190240	292.192184	5.4505E-05	5.4589E-05	15.374020	15.370132	-1.5463E-03	-0.2
274.169268	274.190019	6.6711E-05	6.7820E-05	14.865963	14.824463	-1.6631E-02	-1.7
256.945357	256.931866	8.5499E-05	8.4587E-05	14.242986	14.269967	1.0666E-02	1.1
240.383226	240.433191	1.0298E-04	1.0715E-04	13.775647	13.675717	-4.0511E-02	-4.1
224.739543	224.691600	1.4313E-04	1.3778E-04	12.950614	13.046501	3.7379E-02	3.7
209.713663	209.686837	1.8048E-04	1.7667E-04	12.369174	12.422825	2.1086E-02	2.1
195.350960	195.380792	2.1410E-04	2.1923E-04	11.940579	11.880916	-2.3980E-02	-2.4
181.705894	181.717492	2.4957E-04	2.5188E-04	11.555913	11.532715	-9.2549E-03	-0.9
168.633292	168.623108	2.5450E-04	2.5245E-04	11.505517	11.525884	8.0566E-03	0.8

W_{cal} obtained from quartic Eqn. 10, for Satranidazole in PG-water mixtures at 25±0.4°. Residuals can also be obtained from, $[(X_{2(obs)}-X_{2(cal)})/ X_{2(obs)}]$

indicates a very high degree of correlation coefficient (R^2) 0.998 and negligible intercept equal to zero.

EHSA employs a power series (quartic) equation in δ_1 to back-calculate W, which reproduces the solubility of satranidazole in PG-water mixtures within the accuracy ordinarily achieved in such experimental solubility results. On the basis of validation parameters, it can be expressed that the behavior of irregular solution can be quantified more precisely using EHSA. The procedure can be explored further to predict the solubility of satranidazole in any other binary solvent mixtures. Simultaneously, this tool may become useful in optimization problems of clear solution formulations. Thus the method has potential usefulness in preformulation and formulation studies during which solubility prediction is important for drug design.

ACKNOWLEDGEMENTS

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