Iranian Journal of Pharmaceutical Sciences
Winter 2011: 7(1): 17-24
ijps.sums.ac.ir

Original Article

Prediction of Satranidazole Solubility in Water-Polyethylene Glycol 400 Mixtures Using Extended Hildebrand Solubility Approach

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Abstract

The Extended Hildebrand Solubility Parameter Approach (EHSA) is used to estimate the solubility of satranidazole in binary solvent systems. The solubility of satranidazole in various water-PEG 400 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 water-PEG 400 mixtures. The expression yields an error in mole fraction solubility of ~2.17%, a value approximating that of the experimentally determined solubility. The method has potential usefulness in pre-formulation and formulation studies during which solubility prediction is important for drug design.

Keywords: Extended hildebrand approach; Satranidazole; Solubility parameter; Regular solution theory.
Received: September 10, 2010; *Accepted:* November 29, 2010

1. Introduction

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

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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 behavior of regular and irregular solutions [5]. 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]:

$$-\log X_2 = -\log X_2^{\,i} + A(\delta_1^{\,2} + \delta_2^{\,2} - 2\delta_1\delta_2) \quad \text{(Eq.1a)}$$

$$-\log X_2 = -\log X_2^{\,i} + A(\delta_1 - \delta_2)^2 \quad \text{(Eq.1b)}$$

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

$$-\log X_2 = -\log X_2^{\,i} + A(\delta_1^{\,2} + \delta_2^{\,2} - 2W) \quad \text{(Eq.2)}$$

From the geometric mean:

$$\delta_1\delta_2 = \sqrt{\delta_1^2\delta_2^2} \quad \text{(Eq.3a)}$$

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

$$W = K\delta_1\delta_2 \quad \text{(Eq.3b)}$$

K is the proportionality factor relating 'W' to the geometric mean of solubility parameter. In equation 1 and 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 nonpolar) mixtures, whereas W or $K\delta_1\delta_2$ is required to express solubility's in nonregular 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]

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

Where, ΔH_f is heat of fusion of the crystalline drug molecule, T0 is the melting point of solute in absolute degrees.

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

$$A = \frac{V_2\Phi_1^{\,2}}{2.303\,RT} \quad \text{(Eq.5)}$$

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]:

$$\phi_1 = \frac{V_1(1 - X_2)}{V_1(1 - X_2) + V_2X_2} \quad \text{(Eq.6)}$$

Where, V_1 is the molar volume of the solvent at 25 °C.

The term logarithmic solute activity coefficient ($\log \gamma_2$) from Eq. 2 and Eq. 5 can be written as [13],

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

A better approach is not to restrict the interaction term 'W' to a geometric mean but rather to evaluate it experimentally from the solubility of the solute in various solvent concentrations in a binary mixture employing Eq. 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 Eq. 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 water-PEG 400 binary solvent mixtures.

2. Materials and methods

2.1. Materials

Satranidazole was obtained as a gift sample from Alkem Laboratories Ltd., Baddi, India, and was purified by recrystallization process. The solvent used for recrystallization of Satranidazole was acetone. Polyethylene Glycol 400 and acetone were purchased from Research Laboratory; Mumbai, India and Qualigens Fine Chemicals, Mumbai, India, respectively. Freshly prepared double distilled water was used for experimental purpose throughout the study. 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.

2.2. Methods

2.2.1. Solubility measurements

The solubility of satranidazole was determined in binary solvent mixtures of water and PEG 400. Double distilled water was used to prepare mixtures with PEG 400 in concentrations of 0-100% by volume of PEG 400. About 10 ml of PEG 400, water, or binary solvent blends were introduced into screw-capped vials containing an excess

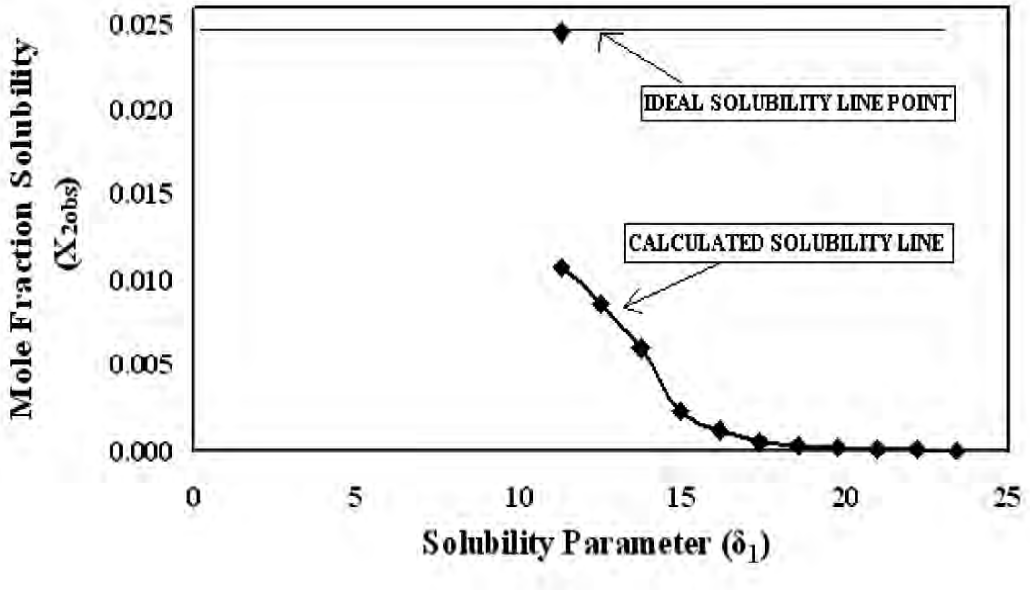

Figure 1. Mole fraction solubility of satranidazole in water, PEG 400, and water-PEG 400 mixtures at 25±0.4 °C. Key: (♦) represents experimental solubilities in water-PEG 400 binary solvent system and (------) back-calculated solubilities from Extended Hildebrand Eq. 2.

Table 1. Molar observed solubility and validation parameters of satranidazole in water-PEG 400 mixtures.

Water: PEG 400 (%v/v)	Solubility (g/ml)	δ_1 $(Cal/cm^3)^{0.5}$	V_1	Density of blend	Mol. Wt of blend	$X_{2(obs)}$	$W_{(obs)}$
100:0	0.0004700	23.40	18.00	0.9980	18.00	2.9322E-05	330.18
90:10	0.0004484	22.19	68.70	1.0110	56.20	8.6193E-05	303.96
80:20	0.0005207	20.98	119.40	1.0240	94.40	1.6599E-04	278.66
70:30	0.0005930	19.77	170.10	1.0370	132.60	2.6221E-04	254.58
60:40	0.0006725	18.56	220.80	1.0500	170.80	3.7830E-04	231.85
50:50	0.0008895	17.35	271.50	1.0630	209.00	6.0473E-04	210.72
40:60	0.0015186	16.14	322.20	1.0760	247.20	1.2064E-03	191.32
30:70	0.0026395	14.93	372.90	1.0890	285.40	2.3915E-03	173.38
20:80	0.0059660	13.72	423.60	1.1020	323.60	6.0526E-03	157.21
10:90	0.0076654	12.51	474.30	1.1150	361.80	8.5840E-03	141.78
0:100	0.0088224	11.30	525.00	1.1280	400.00	1.0783E-02	127.67

δ_1=Solubility parameter of solvent blend, V_1=molar volume of the solvent blend

amount of satranidazole. After being sealed with several turns of electrical tape, the vials were submerged in water at 25±0.4 °C 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 °C [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 the saturated solutions of satranidazole were determined in triplicate at 25±0.4 °C using 10 ml specific gravity bottles. 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

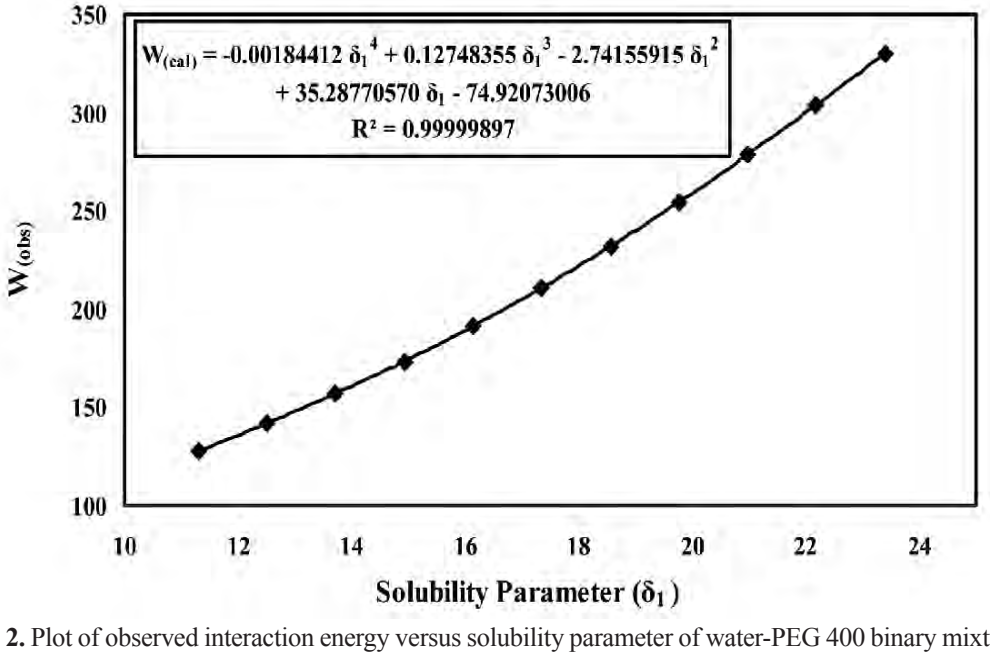

Figure 2. Plot of observed interaction energy versus solubility parameter of water-PEG 400 binary mixtures. Quartic expression provides relation between two variables (W_{obs} and δ_1), which has been used to back calculate W_{cal}.

Table 2. Comparison of observed and calculated mole fraction solubility's of satranidazole in water-PEG 400 mixtures at 25 ±0.4 0C.

$W_{(obs)}$	$W_{(cal)}$	$X_{2(obs)}$	$X_{2(cal)}$	$\log\gamma_2/A_{(obs)}$	$\log\gamma_2/A_{(cal)}$	Residual	Percent Difference
330.180117	330.170282	2.9322E-05	2.9093E-05	16.931866	16.951536	7.7888E-03	7.79E-01
303.955691	303.985923	8.6193E-05	8.8290E-05	14.216819	14.156353	-2.4331E-02	-2.43E+00
278.661628	278.662736	1.6599E-04	1.6614E-04	12.569244	12.567028	-8.8160E-04	-8.82E-02
254.582485	254.538073	2.6221E-04	2.5312E-04	11.420030	11.508854	3.4694E-02	3.47E+00
231.853422	231.854413	3.7830E-04	3.7860E-04	10.498855	10.496874	-7.8763E-04	-7.88E-02
210.716801	210.759363	6.0473E-04	6.2553E-04	9.320999	9.235875	-3.4407E-02	-3.44E+00
191.321541	191.305657	1.2064E-03	1.1913E-03	7.588618	7.620387	1.2537E-02	1.25E+00
173.382081	173.451155	2.3915E-03	2.5262E-03	5.872838	5.734689	-5.6320E-02	-5.63E+00
157.212832	157.058847	6.0526E-03	5.3591E-03	3.544835	3.852806	1.1458E-01	1.15E+01
141.783405	141.896847	8.5840E-03	9.3876E-03	2.665390	2.438505	-9.3613E-02	-9.36E+00
127.666283	127.638398	1.0783E-02	1.0549E-02	2.089535	2.145303	2.1731E-02	2.17E+00

Calculation of interaction energy and mole fraction solubilities were obtained with the help of Eq. 2 and 10 as described in the text.

calculated previously by the method of Fedor [17, 18] which was confirmed by solubility analysis in dioxane-water blend.

2.2.2. Differential scanning calorimetry

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 °C/min. under nitrogen purge. The temperature range studied was 25-225 degrees.

3. Results and discussion

3.1. Mole fraction solubility and solubility parameter

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 ($-\log X_2^i$=1.60974602). The mole fraction solubilities of satranidazole at 25±0.4 °C in water-PEG 400 binary mixtures which cover a large range of the solubility parameter scale, from 11.30 to 23.40 (Cal/cm^3)0.5, are listed in Table 1. The experimental mole fraction solubility of satranidazole at 25±0.4 °C in water-PEG 400 mixtures is plotted in Figure 1 versus the solubility parameter, δ_1, of the

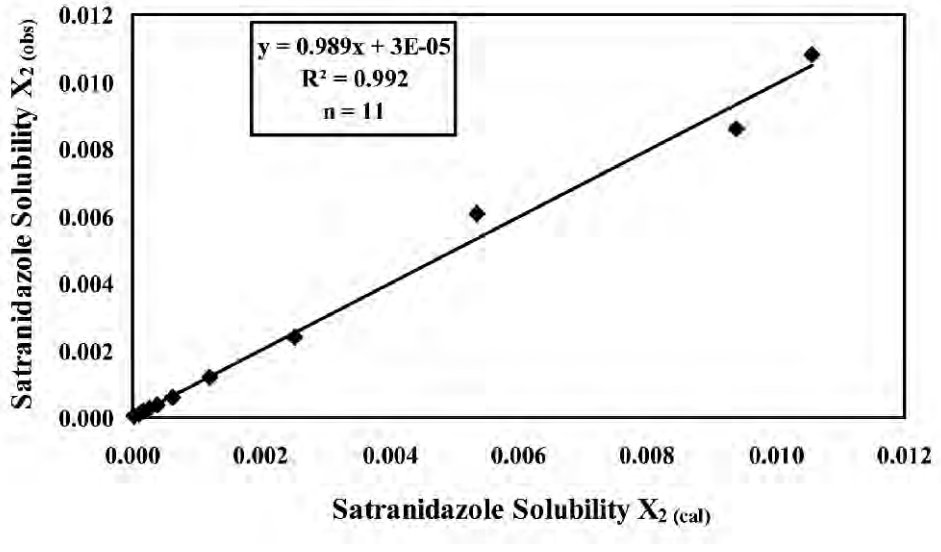

Figure 3. Relationship of observed and calculated mole fraction solubility of satranidazole. Comparison of 11 observed satranidazole solubilities in water-PEG 400 systems at 25±0.4 °C with solubilities predicted by extended Hildebrand approach.

various mixed solvent systems. The mole fraction solubility of satranidazole (δ_2=11.30) in pure PEG 400 (δ_2=11.30), pure water (δ_1=23.4), and in the mixture of the two solvents is represented by the solid circles in Figure 1. The maximum solubility of satranidazole in the mixture is X_2=0.010783 mol/ lit and occurs at δ_1=11.30. This value is well below the ideal solubility, X_2^i=0.0245614 mol/lit, as predicted from regular solution theory. The discrepancy between the results using the original Hildebrand-Scatchard equation and experimental points demonstrates that Eq 1a and 1b cannot be used to predict drug solubility in water-PEG 400 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).

3.2. Solubility prediction using regression of W versus δ_1

Equation 2, differing from Equation 1 in that the geometric mean is not used provides an accurate prediction of solubility once 'W' is obtained. Although 'W' presently cannot be estimated based on fundamental physico-chemical properties of the solute and solvent, 'W' may be regressed against a polynomial in δ1 of the water-PEG 400 binary solvent mixtures (Figure 2). The following quadratic, cubic, and quartic equations were obtained using the experimental solubility data for satranidazole in water-PEG 400 mixtures:

W_{cal}= 69.77056 – 0.45826 δ_1 + 0.49572 δ_1^2
(n=11, R^2= 0.9999847) (Eq.8)

W_{cal}=72.14947-0.89558 δ_1+0.52168 δ_1^2 - 0.00050 δ_1^3
(n=11, R^2= 0.9999848) (Eq.9)

W_{cal}=-74.92073+35.28771 δ_1-2.74156 δ_1^2+0.12749 δ13-0.00185 δ14
(n=11, R^2= 0.9999989) (Eq.10)

The 'W' values calculated using these expressions compared favorably with the original 'W' values computed using Eq. 2. The solid line plotted in Figure 1 was obtained employing the quartic expression (Eq.10). This calculated solubility curve fits the experimental data points quite well (Figures 1 and 3), predicting the solubility of satranidazole in water-PEG 400 mixtures at most points within an error of ~2.17%, a value 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 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. Wcal values are indicating significant interaction of satranidazole and solvent molecules at the peak of solubility profile.

Validation of Eq. 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 Figure 3, which indicates a very high degree of correlation coefficient (R^2) 0.992 and negligible intercept (0.00003) equal to zero.

4. Conclusion

The Extended Hildebrand Approach to solubility employs a power series(quartic) equation in δ_1 to back-calculate 'W', which reproduces the solubility of satranidazole in water-PEG 400 mixtures within the accuracy ordinarily achieved in experimental solubility results.

On the basis of validation parameters, it can be expressed that the behavior of non regular solution can be quantified more precisely using EHSA. The procedure can be explored further to predict the solubility of

satranidazole in pure water or PEG 400 and in any water-PEG 400 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.

Acknowledgement

The author wishes to express his gratitude to M/S Alkem Laboratories Limited, Baddi for providing gift sample of Satranidazole.

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