Research Article

EXTENDED HILDEBRAND SOLUBILITY APPROACH: SATRANIDAZOLE IN MIXTURES OF ETHANOL AND WATER

Pavan B. Rathi*

*Department of Pharmaceutics, Shri Bhagwan College of Pharmacy, N-6, CIDCO, Auranagabad, Maharashtra-431003.

***Corresponding author's E-mail:** pavanbrathi@gmail.com

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ABSTRACT

The solubilities of satranidazole in several ethanol-water mixtures have been determined. The data were treated on the basis of the Extended Hildebrand Solubility Approach and the results were discussed according to association phenomena between solute and solvent blend. An equation has been obtained for predicting the mole fraction solubility of satranidazole in the studied mixtures.

Keywords: Satranidazole, Solubility, Solubility Parameter, Extended Hildebrand Approach.

INTRODUCTION

Extended Hildebrand Approach is applied to predict the solubility of satranidazole in mixtures of ethanol and water. ETH is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is completely miscible with water [1]. ETH-Water mixtures are strongly non ideal and can act in the solute-solvation process via hydrophobic interactions and preferential salvation [2, 3]. In terms of polarity, ETH -water mixtures cover a wide range of Hildebrand solubility parameters from 13.00 $(cal/cm^3)^{0.5}$ (pure ETH) to 23.40 $(cal/cm^3)^{0.5}$ (pure water) [4, 5].

The Extended Hildebrand Approach enables us to predict the solubility of semipolar crystalline drugs in irregular solutions involving self-association and hydrogen bonding, like occurs in pure solvents or in solvent blends. The key relationship may be written as: [6, 7]

$$-\log X_2 = -\log X_2^{\,i} + \frac{\phi_1^2 V_2(\delta_1^{\,2} + \delta_2^{\,2} - 2W)}{2.303RT} \text{ ----------(1)}$$

Where W is an interaction term for estimating energy between solute and solvent for an irregular solution. This interaction parameter W accurately quantifies the cohesive energy density between solute and solvent. When $W = \delta_1\,\delta_2$ the solution is said to be regular. $W > \delta_1\,\delta_2$ appears when the blended solvents are able to hydrogen bond with each other but not with their own kind. The case of $W < \delta_1\,\delta_2$ occurs when like molecules associate and unlike molecules do not, such as for non polar media in water. Although W cannot be theoretically evaluated, it assumed that when a range of similar solvents are used for dissolving a fixed solute, $W = K\,\delta_1\,\delta_2$, where K is a proportionality constant [8].

Interaction energy (W) values were evaluated as a power series in δ_1 utilizing mixed solvents by polynomial regression [9, 10, 11]. By using these polynomial fits, the mole fraction solubility of solutes may be predicted in good agreement with the experimental values. This procedure may be applied for calculating solubilities of missing data by interpolation.

When the solvent studied is a mixed one, there are a series of parameters to be calculated: the solubility parameter, the volume fraction and the mean molar volume of mixed solvents.

The solubility parameter δ_1 for the mixture of two solvents ETH and water, is averaged in terms of volume fractions using the expression [12]

$$\delta_1 = \frac{\delta_{ETH}\phi_{ETH} + \delta_W\phi_W}{\phi_{ETH} + \phi_W} \text{ ----------(2)}$$

Where $\Phi_1 = \Phi_{ETH} + \Phi_W$ is the total volume fraction of the two solvents which can be calculated from [13]

$$\phi_1 = \frac{(1 - X_2)V_1}{(1 - X_2)V_1 + X_2V_2} \text{ ----------(3)}$$

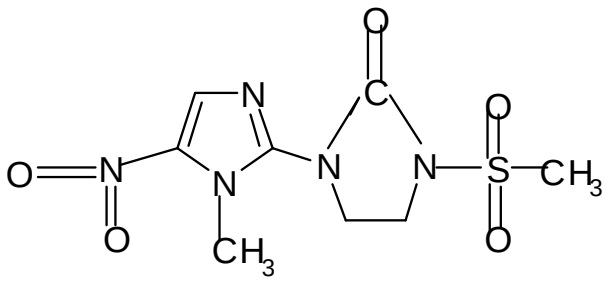
Where X_2 is the mole fraction solubility of the solute in the mixed solvent and V_1 is the molar volume of the binary solvent. For each mixed solvent composed of ETH and water in various proportions [14]:

$$V_1 = \frac{X_{ETH}M_{ETH} + (1 - X_{ETH})M_W}{d_1} \text{ ----------(4)}$$

Here, X_i and M_i are the mole fraction and the molecular weight of the particular solvent in the mixture, respectively and d_1 is the density of the solvent mixture at the experimental temperature.

Satranidazole,1-methylsulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone, is a sparingly water soluble drug (0.01 mg/ml) with a potent antiprotozoal activity, against *E. hystolytica, T.vaginalis* and *giardia* widely used in pharmaceutical formulations mainly in tablet and

suspension form for the treatment of amoebiasis [15, 16, 17]. The structure of satranidazole is given below-



A perusal to the structure of satranidazole indicates that the molecule is highly aromatic and the functional groups may not contribute much to the aqueous solubility. Literature survey revealed that solubility of satranidazole in ethanol is not reported till date and it is not official in any pharmacopoeia [18].

So the aim of this communication is to report the solubility behavior of satranidazole in individual solvents (Ethanol and Water) and different concentrations of ETH-water mixtures, predict it theoretically by applying the Extended Hildebrand Approach. Therefore, the present investigation pertains to the utility of Extended Hildebrand Solubility Approach in relation to the satranidazole solubility in mixtures of Ethanol-water binary system.

Table 1: Absorbance data of Satranidazole in ethanol-water mixtures

Concentration (µg/ml)	Absorbance	Concentration (µg/ml)	Absorbance
5	0.162	30	0.968
10	0.325	35	1.126
15	0.498	40	1.296
20	0.642	45	1.432
25	0.805	50	1.594

Table 2: Mole fraction solubility of satranidazole (x_2) and other related parameters against the volume fraction of ETH (Φ_{ETH})

Φ_{ETH}	$X_{2(obs)}$	δ_1	Φ_1	V_1	$\delta_1\delta_2$	$W_{(obs)}$
0	3.2929E-05	23.40	0.99957	18.00	265.36	330.33
0.1	4.4024E-05	22.36	0.99953	22.05	253.56	306.89
0.2	5.5985E-05	21.32	0.99949	26.10	241.77	284.48
0.3	7.5811E-05	20.28	0.99941	30.15	229.98	263.23
0.4	1.1606E-04	19.24	0.99920	34.20	218.18	243.21
0.5	1.5754E-04	18.20	0.99903	38.25	206.39	224.13
0.6	2.3797E-04	17.16	0.99868	42.30	194.60	206.26
0.7	2.9995E-04	16.12	0.99848	46.35	182.80	189.24
0.8	3.6639E-04	15.08	0.99829	50.40	171.01	173.27
0.9	3.3186E-04	14.04	0.99857	54.45	159.21	158.00
1.0	1.8195E-04	13.00	0.99927	58.50	147.42	143.19

The values for δ_1, Φ_1, and V_1 are calculated from Eqs. (2)- (4), respectively. W is calculated from Eq. (1).

Table 3: Logarithmic values of experimental and calculated mole fraction solubilities and their residuals

$-\log X_{(2obs)}$	$-\log X_{(2cal)}$	Residual (Δ)	Percent Difference
-4.482424	-4.482634	4.8350E-04	4.84E-02
-4.356309	-4.360900	1.0515E-02	1.05E+00
-4.251930	-4.242718	-2.1439E-02	-2.14E+00
-4.120267	-4.110968	-2.1642E-02	-2.16E+00
-3.935313	-3.959639	5.4474E-02	5.45E+00
-3.802605	-3.794887	-1.7929E-02	-1.79E+00
-3.623477	-3.632217	1.9923E-02	1.99E+00
-3.522947	-3.500541	-5.2945E-02	-5.29E+00
-3.436052	-3.437706	3.8012E-03	3.80E-01
-3.479051	-3.494913	3.5864E-02	3.59E+00
-3.740039	-3.733129	-1.6038E-02	-1.60E+00

Figure 1: Lambert-Beer plot of satranidazole

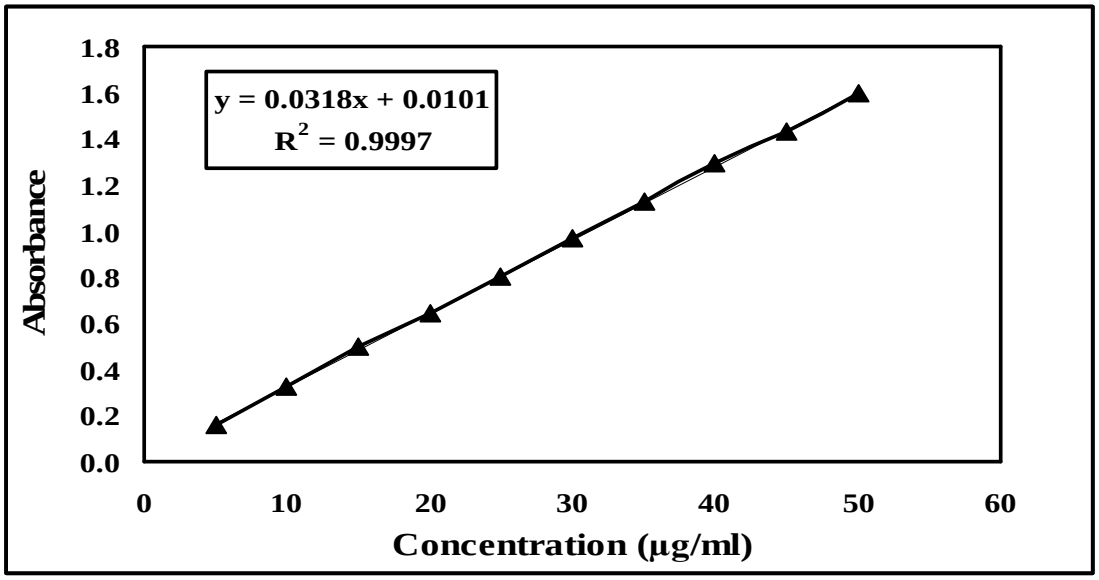


Figure 2: Plot of mole fraction solubility of satranidazole against the solubility parameter of the ETH-water blend

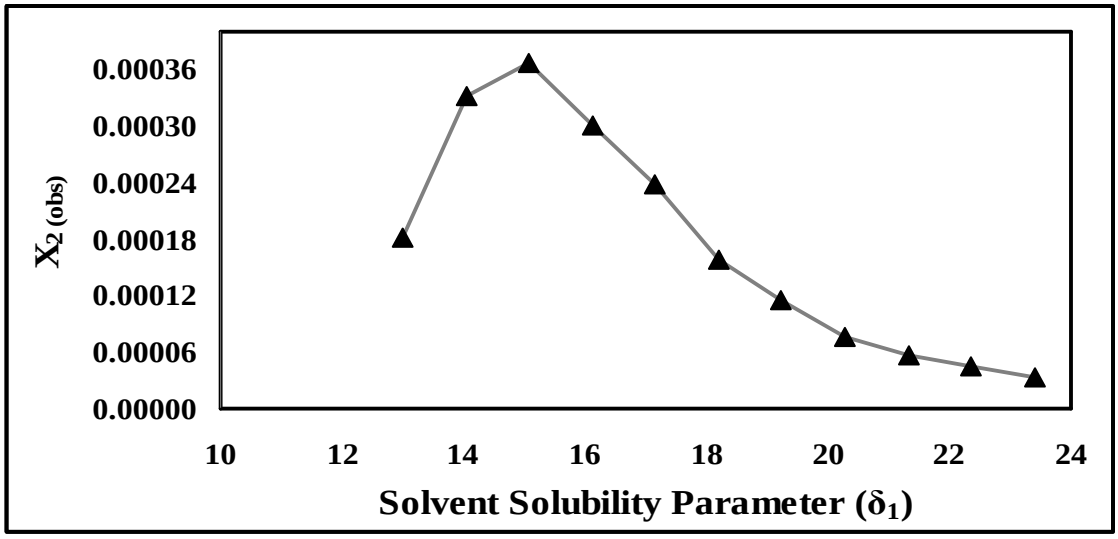


Figure 3: Plot of observed interaction energy versus solubility parameter of ETH-water binary mixtures

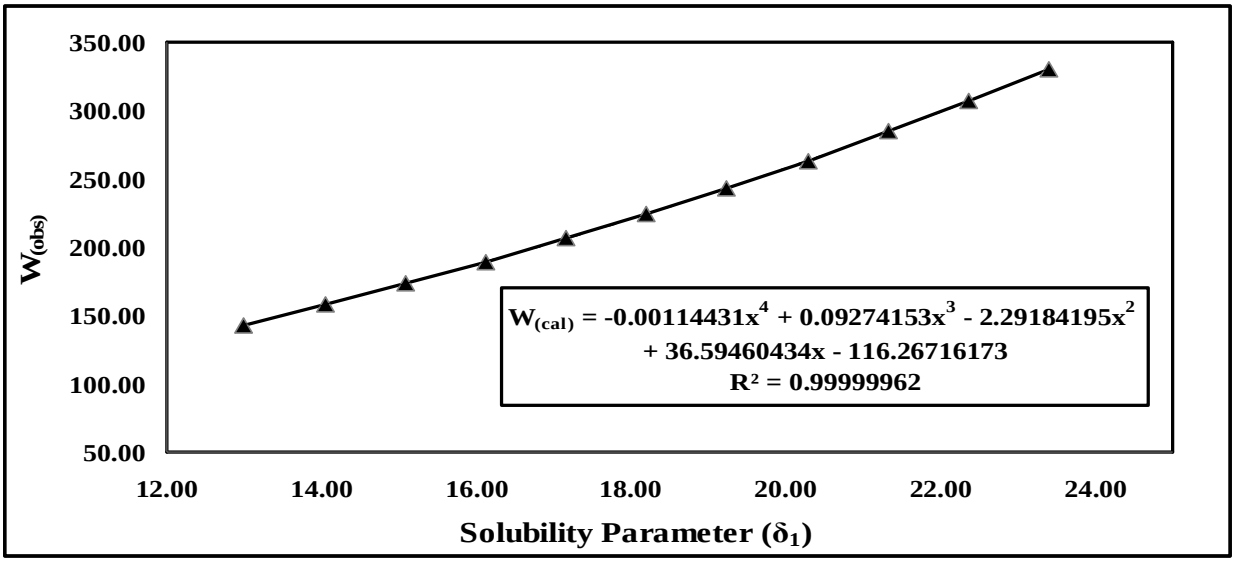
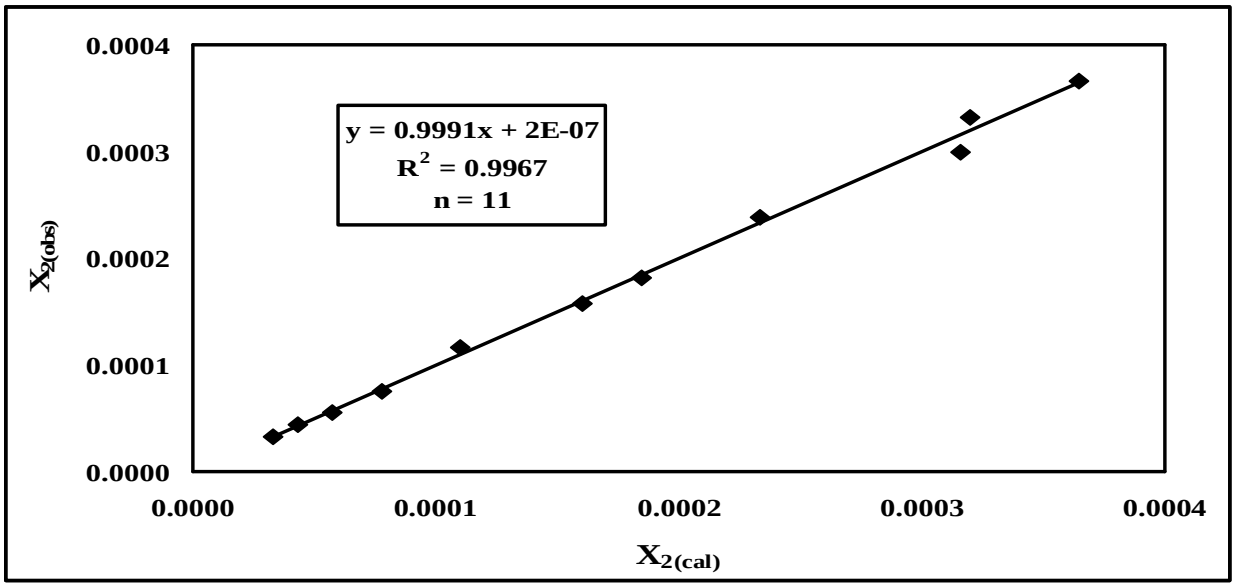


Figure 4: Relationship of observed and calculated mole fraction solubility of satranidazole



MATERIALS AND METHODS

Satranidazole, obtained as gift sample from Alkem Laboratories Ltd., Baddi, India, was purified by recrystallization process. The solvent used for recrystallization of Satranidazole was Acetone. Ethanol and Acetone were purchased from Dipa Chemical Industries, Pvt., Ltd., Aurangabad and Qualigens Fine Chemicals, Mumbai, respectively. 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 1 cm matched quartz cells was used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing purpose. Differential Scanning Calorimeter, Shimadzu TA-60 WS, was used for determination of melting point and heat of fusion of satranidazole.

Solubility measurements:

Solubilities of satranidazole (δ_2 = 11.34) were determined in mixed solvent consisting of ETH (δ_{ETH} = 13.00) and Water (δ_W = 23.40). Solvent blends were made covering 0-100% ETH (v/v). About 10 ml of ETH, water, or mixed solvent blends were placed into screw-capped vials (Thermostated at 25^0 and under continuous stirring) containing an excess amount of satranidazole and agitation was maintained at 100 rpm for 72 h in a constant-temperature bath. Preliminary studies showed that this time period was sufficient to ensure saturation at 25^0 [19].

After equilibration, the solution was microfiltered (0.22 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). Calibration graph of satranidazole in each solvent blend was previously established with very high degree of correlation coefficient (R^2) 0.9997, slope 0.0318 and negligible intercept (0.0101) as shown in fig. 1. The working concentration range was from 5 to 50 µg/ml satranidazole (Table 1). The densities of the blends as well as the filtrates of saturated solutions were determined by using 10-ml specific gravity bottle at 25^0. Once the densities of solutions are known, the solubilities can be expressed in mole fraction scale.

RESULTS AND DISCUSSION

Molar volume (V_2) and Solubility parameter (δ_2) of satranidazole were previously estimated by using the Fedor's group contribution method [20, 21] giving 235.6 cm^3/mol and 11.3928 $(cal/cm^3)^{0.5}$. The ideal solubility of satranidazole was calculated by using the equation [22]

$$-\log X_2^{\,i} = \frac{\Delta S_f}{R}\log\frac{T_o}{T} \quad -----(5)$$

Where ΔS_f is the entropy of fusion of the crystalline drug molecule at its melting point T_0. T is the temperature in Kelvin at which the solubility was determined. The value of ΔS_f was evaluated by [23]

$$\Delta S_f = \Delta H_f / T_o \quad -----(6)$$

(ΔH_f = 7763.838 cal/mol, T_0 = 461.83 ^{0}K) giving 16.811cal/mol/^{0}K. Thus, the ideal mole fraction solubility of satranidazole (X_2^i) is 0.024561.

The mole fraction solubility of satranidazole in ETH -water mixtures and other parameters of interest (δ_1, Φ_1, V_1) are collected in Table 2. The plot of these experimental solubilities versus the solubility parameter of mixtures, δ_1 is shown in fig.2. The solubility of satranidazole was far from its ideal value in both pure solvents (ETH, water) as

well as in the mixtures. The maximum mole fraction solubility occurred at a δ_1 =15.08 is lesser than ideal mole fraction solubility.

Observed solubility data was then subjected to the evaluation of interaction energy. The interaction term W can be calculated from Eq. (1) at each experimental point (X_2, δ_1). The results are also presented in Table 2. Experimental values of interaction energy (W_{obs}) were regressed against solubility parameter to obtain W_{cal} (fig. 3), which was then used to back calculate the mole fraction solubility (X_{2cal}). A mathematical model is proposed for individual system as fourth power polynomial. The W values may also be expanded in a power series of δ_1 from fourth degree polynomial regression.

In our case, the following fit was obtained:

$W_{cal} = -116.267162 + 36.594605\ \delta_1 - 2.291842\ \delta_1^2 + 0.092742\ \delta_1^3 - 0.001144\ \delta_1^4$

($n = 11$, R^2=0.99999962)

If we insert this equality in Eq. (1), we can predict the solubility of satranidazole. The back-calculated logarithmic solubilities, $\log X_{2cal}$ are recorded in Table 3, together with the experimental values of $\log X_2$ and their differences. The plot of $\log X_{2cal}$ against $\log X_{2obs}$ gives a straight line with very high degree of correlation coefficient (R^2) 0.9967, slope 0.9991 and negligible intercept ($2*10^{-7}$) equal to zero as shown in fig. 4.

A careful scrutiny of the behavior of the solutions of satranidazole in ETH-water mixtures may be performed, comparing the value of the interaction term W at each experimental point with the regular value $W = \delta_1\delta_2$. This comparison is presented also in Table 2. As can be observed, for volume fractions of ETH from 0 to 0.8, $W > \delta_1\delta_2$. However, for volume fractions of ETH from 0.9 to 1.0, $W < \delta_1\delta_2$. It may be assumed that satranidazole solutions can behave as regular solutions at some point ($W= \delta_1\delta_2$) within 0.8-0.9 ETH volume fraction.

Thus, in water-rich mixtures it seems to be some kind of association between satranidazole and the solvent mixture according to $W > \delta_1\delta_2$. This could be explained considering the hydrophobic hydration (HH). HH is featured by an enhanced hydrogen bonding between water molecules in the neighbourhood of nonpolar groups in water. When adding ETH, HH breaks down. The endothermic shift of the enthalpies of solution upon small additions of cosolvents ($\Phi_w > 0.9$) to water is known to appear for hydrophobic solutes like satranidazole.

Conversely, in water poor mixtures self association of solvent, solute or both is expected because $W < \delta_1\delta_2$. It is well known that, ETH exhibit self association leading to low values of permittivity by cancellation of dipole moments according to the geometrical arrangement. This behavior may remain as such in rich ETH blends, and, therefore, the corresponding satranidazole solubilities are less than regular one (i. e. $\delta_1\delta_2$).

CONCLUSION

The Extended Hildebrand Approach applied to the solubility data of satranidazole in ETH-water mixtures leads to an expansion of the W interaction term as a fourth degree power series in δ_1 which reproduces the satranidazole solubility within the accuracy ordinarily achieved in such measurements. Thus this procedure can be used to predict the solubility of satranidazole in pure water or ETH and in any ETH-water mixtures.

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