Extended Hildebrand Solubility Approach: Satranidazole in Mixtures of Dioxane and Water

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Rathi and Mourya: Solubility Prediction of Satranidazole in Dioxane-Water Mixtures

The extended Hildebrand solubility parameter approach is used to estimate the solubility of satranidazole in binary solvent systems. The solubility of satranidazole in various dioxane-water mixtures was analyzed in terms of solute-solvent interactions using a modified version of Hildebrand-Scatchard treatment for regular solutions. The solubility of satranidazole in the binary solvent, dioxane-water shows a bell-shaped profile with a solubility maximum well above the ideal solubility of the drug. This is attributed to solvation of the drug with the dioxane-water mixture, and indicates that the solute-solvent interaction energy is larger than the geometric mean ($\delta_1\delta_2$) of regular solution theory. The new approach provides an accurate prediction of solubility once the interaction energy 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 dioxane-water mixtures. The method has potential usefulness in preformulation and formulation studies during which solubility prediction is important for drug design.

Key words: Dioxane, extended Hildebrand solubility approach, ideal solubility, interaction energy, 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 branch 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

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and are commonly encountered in pharmacy. The extended Hildebrand solubility approach (EHSA), a 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 extended Hildebrand solubility parameter approach has been developed to reproduce the solubility of drugs and other solids in the binary solvent systems[6].

The Hildebrand-Scatchard Eqn. for solubility of solids in a regular solution may be written as[7], $-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2\delta_1\delta_2)$-- (1a) and $-\log X_2 = -\log X_2^i + A(\delta_1 - \delta_2)^2$--(1b).

The extended Hildebrand Eqn for the solubility of solids in an irregular solution may be written as[8]: $-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2W)$--(2). From the geometric mean: $\delta_1\delta_2 = \sqrt{\delta_1^2\delta_2^2}$---(3a), where, in pharmaceutical solutions, the square root of geometric mean of δ_1^2 and δ_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 $\delta_1\delta_2$ (eqn 1a) 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], $W = K\delta_1\delta_2$---(3b), Where, K is the proportionality factor relating interaction energy (W) to the geometric mean of solubility parameter (δ).

In Eqns 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 A in Eqns 1 and 2 is defined as[10]: $A = \frac{V_2\Phi_1^2}{2.303RT}$---(4),
where, V_2 is the molar volume of the solute taken as a 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[11]: $\varphi_1 = \frac{V_1(1-X_2)}{V_1(1-X_2)+V_2X_2}$--(5),
where, V_1 is the molar volume of the solvent at 25º.

Satranidazole, [1-methylsulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone], a potent broad spectrum antiprotozoal, is very sparingly soluble in water (0.01mg/ml)[12,13]. It is not official in I.P., U.S.P. and B.P till date[14,15].

A perusal to the structure of satranidazole (fig. 1) indicates that the molecule is highly aromatic and the functional groups may not contribute much to the aqueous solubility. The poor aqueous solubility and wettability of satranidazole give rise to difficulties in pharmaceutical formulations meant for oral or parenteral use, which may lead to variation in bioavailability[16]. Therefore, it is necessary to explore the solubility of satranidazole in water-dioxane binary mixture.

Dioxane is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is completely non-aqueous water miscible solvent[17]. Water-dioxane binary mixtures are strongly non ideal and can act in the solute-solvation process via hydrophobic interactions and preferential solvation because, water-dioxane mixtures cover a wide range of Hildebrand solubility parameters from 10.00 $(Cal/cm^3)^{0.5}$ (pure dioxane) to 23.4 $(Cal/cm^3)^{0.5}$ (pure water). Thus, satranidazole is an ideal candidate for the study of solubility behaviour in mixtures of dioxane and water. The present investigation pertains to the utility of EHSA in relation to the satranidazole solubility in the solvent pair dioxane-water binary solvents.

Satranidazole, obtained as gift sample from Alkem Laboratories Ltd., Baddi, India, was purified by

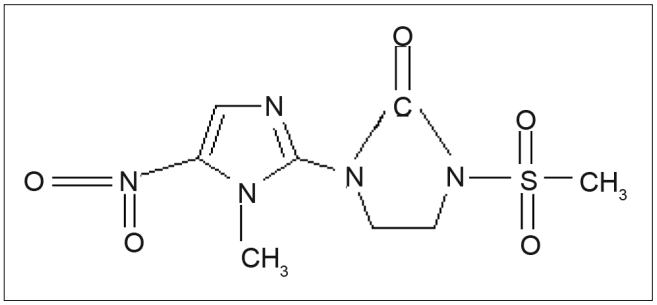

Fig. 1: Structure of satranidazole

recrystallization process. The solvent used for recrystallization of satranidazole was acetone. 1,4-Dioxane and acetone were obtained as gift sample from E. Merck, Ltd.; Mumbai, India and Qualigens Fine Chemicals, Mumbai, India, respectively. Throughout the study 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.

The solubility of satranidazole was determined in binary solvent mixtures of dioxane and water. Double distilled water was used to prepare mixtures with dioxane in concentrations of 0-100% by volume of dioxane. About 10 ml of dioxane, water, or binary solvent was 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°.

After equilibrium was attained, vials were removed for analysis. Firstly, solutions were filtered through Whatman filter paper (No. 41). After appropriate dilutions with double distilled water, the solutions were analyzed by using a spectrophotometer set at the wavelength of maximum absorption of the satranidazole (λ_{max}-319.80 nm). Calibration graph of satranidazole in 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. 2. The working concentration range was from 5 to 50 µg/ml. The solubility of the satranidazole was determined at least three times for each solvent, 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° using 10-ml specific gravity bottle.

The solubility parameters of the solvents were obtained from the literature[18]. The solubility parameter of satranidazole was calculated by the method of Fedor[19,20], which was confirmed by solubility analysis in dioxane-water blend.

Experimental data of mole fraction solubility of satranidazole in dioxane-water are plotted against solubility parameters of solvent blend (fig. 3) exhibit a maxima at δ_1= 11.34 (peak solubility = 0.0096347 mol/l). The observed solubility is comparatively higher than the ideal solubility (X_2^i= 0.00245614 mol/l). According to the regular solution theory, solubility cannot exceed ideal solubility. However, in non regular solutions, peak solubility may depart from ideal solubility due to solute solvent interactions. This abnormal behavior has been dealt with the theoretical replacement of mean geometric solubility parameters ($\delta_1\delta_2$) term with the interaction energy term (W). To relate these two variables, a fourth power polynomial (quartic expression) has been developed to back calculate the value of W_{cal}. For Dioxane-water system, the polynomial has following values: W_{cal}= 21.70104+10.372731 δ_1-0.401841 δ_1^2 +0.032507δ_1^3 -0.000435δ_1^4, (n=11, R^2= 0.9999) -- (6)

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 in a solvent blend using backward regression. Representative data along with validation parameters are summarized in Table 1. W_{cal} values are indicating significant interaction of satranidazole and solvent molecules at the peak of solubility profile.

Observed solubility data was subjected to the evaluation of interaction energy. Experimental values of interaction energy (W_{obs}) were regressed against solubility parameter to obtain W_{cal} (fig. 4), which was then used to back calculate the mole fraction solubility (X_{2cal}). A mathematical

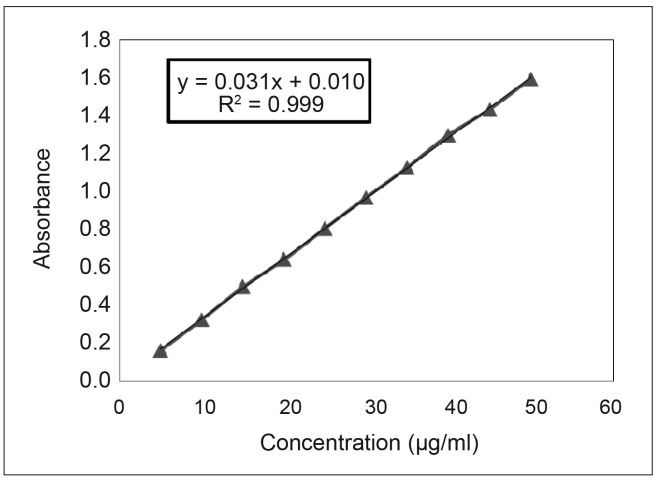

Fig. 2: Lambert-Beer plot of satranidazole

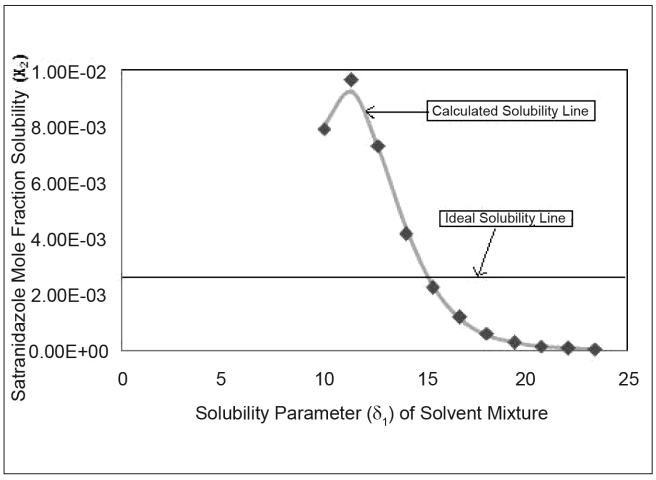

Fig. 3: Solubility of satranidazole in dioxane, water, and dioxane-water mixtures

Solubility of satranidazole in dioxane, water, and dioxane-water mixtures at 25^0. Key: ◆ Experimental solubilities and back-calculated solubilities from Eq. 2.

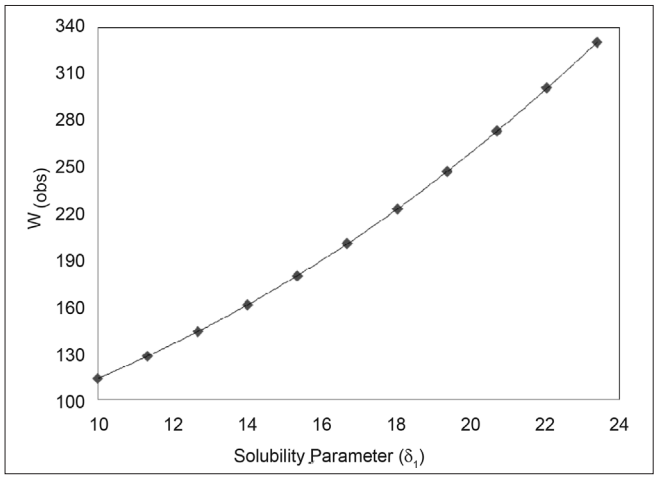

Fig. 4: Solubility parameter versus interaction energy profile $W_{(cal)}$ obtained from quartic regression Eqn. 6, for satranidazole in water-dioxane mixtures at 25^0 and correlation coefficient, r^2, is 0.999999 for n = 11

TABLE 1: MOLAR OBSERVED SOLUBILITY AND CALCULATION PARAMETERS OF SATRANIDAZOLE IN DIOXANE-WATER MIXTURES

Water: Dioxane (%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	0.0005821	23.40	18.00	0.9980	18.00	3.6317E-05	330.45
90:10	0.0009112	22.06	24.77	1.0014	25.01	7.8740E-05	300.96
80:20	0.0012872	20.72	31.54	1.0048	32.02	1.4198E-04	273.03
70:30	0.0020104	19.38	38.31	1.0082	39.03	2.6954E-04	246.97
60:40	0.0039050	18.04	45.08	1.0116	46.04	6.1647E-04	222.93
50:50	0.0064722	16.70	51.85	1.0150	53.06	1.1757E-03	200.45
40:60	0.0109196	15.36	58.62	1.0184	60.07	2.2456E-03	179.77
30:70	0.0180788	14.02	65.39	1.0218	67.08	4.1594E-03	160.85
20:80	0.0286006	12.68	72.16	1.0252	74.09	7.2968E-03	143.66
10:90	0.0344943	11.34	78.93	1.0286	81.10	9.6347E-03	127.92
0:100	0.0262503	10.00	85.70	1.0320	88.11	7.8876E-03	113.38

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

model is proposed for individual system as fourth power polynomial. Validation of this equation has been done by comparing experimentally obtained and calculated values of mole fraction solubility by estimating residuals and percent difference (Table 2). The Extended Hildebrand Approach applied to the solubility data of satranidazole in water-dioxane mixtures, which reproduces the satranidazole solubility within the accuracy ordinarily achieved in such measurements. The predictive capability of the model for satranidazole is represented in fig.5, which indicates a very high degree of correlation coefficient (R^2) 0.9983 and negligible intercept (-0.00003) equal to zero.

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 dioxane and in any water-dioxane 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.

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TABLE 2: COMPARISONS OF OBSERVED AND CALCULATED MOLE FRACTION SOLUBILITIES OF SATRANIDAZOLE IN DIOXANE-WATER MIXTURES AT 25°

$W_{(obs)}$	$W_{(cal)}$	$X_{2(obs)}$	$X_{2(cal)}$	$\log\gamma_2/A_{(obs)}$	$\log\gamma_2/A_{(cal)}$	Residual	Percent difference
330.447760	330.457908	3.6317E-05	3.6612E-05	16.396580	16.376285	-8.0988E-03	-8.10E-01
300.959157	300.911658	7.8740E-05	7.5824E-05	14.457387	14.552385	3.7032E-02	3.70E+00
273.034580	273.083225	1.4198E-04	1.4757E-04	12.981340	12.884050	-3.9377E-02	-3.94E+00
246.968191	247.040724	2.6954E-04	2.8550E-04	11.380118	11.235053	-5.9205E-02	-5.92E+00
222.925499	222.818600	6.1647E-04	5.6651E-04	9.322702	9.536501	8.1035E-02	8.10E+00
200.450067	200.417633	1.1757E-03	1.1460E-03	7.721966	7.786834	2.5208E-02	2.52E+00
179.769542	179.804938	2.2456E-03	2.3086E-03	6.122616	6.051824	-2.8046E-02	-2.80E+00
160.846625	160.913961	4.1594E-03	4.3814E-03	4.599250	4.464578	-5.3374E-02	-5.34E+00
143.657648	143.644482	7.2968E-03	7.2243E-03	3.199204	3.225536	9.9401E-03	9.94E-01
127.918366	127.862615	9.6347E-03	9.2394E-03	2.490968	2.602470	4.1024E-02	4.10E+00
113.375305	113.400807	7.8876E-03	8.0423E-03	2.981490	2.930486	-1.9622E-02	-1.96E+00

Residuals obtained from quartic regression Eqn. 6, for satranidazole in water-dioxane mixtures at 25°. Residuals can also be obtained from, $[(X_{2obs}-X_{2cal})/ X_{2obs}]$

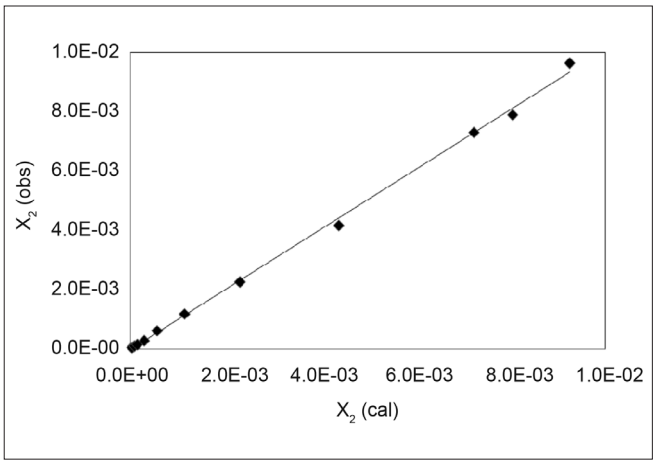

Fig. 5: Comparison of observed and calculated mole fraction solubility

Comparison of 11 observed satranidazole solubilities in water-dioxane mixtures at 25^0 with solubilities predicted by the extended Hildebrand solubility approach. The intercept of the line is 0.00003, and the slope is 1.012. The correlation coefficient, r^2, is 0.9983 for n = 11

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