Extended Hildebrand Solubility Approach: Prophecy of Satranidazole Solubility in Water-1, 2-Butanediol Mixtures
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ABSTRACT
Extended Hildebrand Solubility Approach (EHSA) is used to estimate the solubility of satranidazole in binary solvent systems. The solubility of satranidazole in various water-1, 2-Butanediol 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 $\delta_1$ and $\delta_2$ 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 $\delta_i$ of the binary mixture. Quadratic, cubic, and quartic expressions of ‘W’ in terms of solvent solubility parameter were found for predicting the solubility of satranidazole in water-1, 2-Butanediol mixtures. But from these expressions, quartic expression yields an error in mole fraction solubility of ~1.27%, 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.

Keywords: Extended Hildebrand approach; Satranidazole; Solubility parameter; Regular solution theory

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INTRODUCTION

Solubility data on drugs and adjuncts in binary solvent system have wide applications in the pharmaceutical sciences. Knowledge of interaction forces between solutes and solvents are of considerable theoretical and practical importance 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 physical 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]. EHSA has been developed to reproduce the solubility of drugs and other solids in the binary solvent systems [6].

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

\[-\log_{10} X_i = -\log_{10} X_i^i + (\delta_i^2 + \delta_s^2 - 2\delta_i \delta_s) \]  \hspace{1cm} (Eq. 1a)

\[-\log_{10} X_i = -\log_{10} X_i^i + A(\delta_i^2 - \delta_s^2) \]  \hspace{1cm} (Eq. 1b)

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

\[-\log_{10} X_i = -\log_{10} X_i^i + A(\delta_i^2 + \delta_s^2 - 2W) \]  \hspace{1cm} (Eq. 2)

From the geometric mean [9]:

\[\delta_1\delta_2 = \sqrt{\delta_1^2 \delta_2^2} \]  \hspace{1cm} (Eq. 3a)

In pharmaceutical solutions, the geometric mean of \(\delta_1\) and \(\delta_2\), 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 \(X_i\) as [10],

\[W = K\delta_1\delta_2 \]  \hspace{1cm} (Eq. 3b)

\(K\) is the proportionality factor relating ‘\(W\)’ to the geometric mean of solubility parameter.

In equation 1 and 2, \(X_i\) and \(X_i^i\) are the mole fraction solubility and ideal mole fraction solubility of the solute respectively. The terms \(\delta_i\) and \(\delta_s\) 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 (\(-\log_{10} X_i\)) can be taken as [11]:

\[\begin{align*}
-\log_{10} X_i &= \frac{\Delta H_{\text{ fus}}}{2.303 R T} \left( \frac{I_i - T}{T} \right) \quad \text{-- (Eq. 4)}
\end{align*}\]

Where, \(\Delta H_{\text{ fus}}\) is enthalpy 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 [12]:

\[A = \frac{V_2 \Phi_1^2}{2.303 R T} \]  \hspace{1cm} (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 \(\Phi_1\), the volume fraction of the solvent, is [13]:

\[\phi_1 = \frac{V_1(1 - X_i)}{V_1(1 - X_i) + V_2X_2} \]  \hspace{1cm} (Eq. 6)

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

The term logarithmic solute activity coefficient (\(\log_{10} \gamma_i\)) from Eq. 2 and Eq. 5 can be written as [14],

\[\log_{10} \gamma_i = A(\delta_i^2 + \delta_s^2 - 2W) = \frac{\Phi_1}{2.303RT} (\delta_i^2 + \delta_s^2 - 2W) \]  \hspace{1cm} (Eq. 7)

A best 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 other solvent mixture. Therefore, the present investigation pertains to the usefulness of EHSA in relation to the satranidazole solubility in water-1, 2-butenediol binary solvent mixtures.
MATERIALS AND METHODS

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. 1, 2-Butanediol and Acetone were purchased from Chemical International; 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.

Methods
Solubility measurement
The solubility of satranidazole was determined in binary solvent mixtures of water and 1, 2-Butanediol. Double distilled water was used to prepare mixtures with 1, 2-Butanediol in concentrations of 0-100% by volume of 1, 2-Butanediol. About 10 ml of 1, 2-Butanediol, 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 °C and were shaken at 150 rpm for 72 h in a constant-temperature bath. Preliminary studies showed that this time period was sufficient to ensure saturation at 25 °C [15].

After equilibration, the solutions were micro filtered (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 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 [16,17]. The solubility parameter of satranidazole was calculated previously by the method of Fedor’s [18,19] which was confirmed by solubility analysis in dioxane-water blend [20].

Differential scanning calorimetry
The thermogram of satranidazole was obtained with a differential scanning calorimeter [21]. 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.

RESULTS
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_{10}X_{2}′ =1.60974602). The mole fraction solubilities of satranidazole at 25±0.4 °C in water-1, 2-Butanediol binary mixtures which cover a large range of the solubility parameter scale, from 11.20 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-1, 2-Butanediol mixtures is plotted in Figure 1 versus the solubility parameter, δ_{i}, of the various mixed solvent systems. The mole fraction solubility of satranidazole (δ_{i}=13.64), in pure 1, 2-Butanediol (δ_{i}=13.64), pure water (δ_{i}=23.4), and in the mixture of the two solvents is represented by the solid circles in Figure 1.

Figure 1: Mole fraction solubility of satranidazole in water, 1, 2-Butanediol, and water-1, 2-Butanediol mixtures at 25±0.4 °C.

The maximum solubility of satranidazole in the mixture is X_{2}′=0.00025619 mol/ lit and occurs at δ_{i} = 13.64. This value is well below the ideal solubility, X_{2}′=0.0245614 mol/lit, as predicted from regular solution theory. The discrepancy
between the results using the original experimental points demonstrates that Eq. 1a and 1b cannot be used to predict drug solubility in water-1, 2-Butanediol 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 ($W$).

**Solubility prediction using regression of $W$ versus $\delta_1$**

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 physicochemical properties of the solute and solvent, ‘$W$’ may be regressed against a polynomial in $\delta_1$ of the water-1, 2-Butanediol binary solvent mixtures (Figure 2).

![Figure 2: Plot of observed interaction energy versus solubility parameter of water-1, 2-Butanediol binary mixtures](image)

The following equations were obtained using the experimental solubility data for satranidazole in water-1, 2-Butanediol mixtures:

$$W_{\text{cal}} = 0.471961732\delta_1^2 + 0.775811609\delta_1 + 53.60733583$$

(n=11, $R^2 = 0.99997012$)

**Quadratic (Eq.8)**

$$W_{\text{cal}} = 0.002376243\delta_1^3 + 0.348645437\delta_1^2 + 2.846012538\delta_1 + 42.39658776$$

$n=11$, $R^2 = 0.999997012$)

**Cubic (Eq.9)**

$$W_{\text{cal}} = -0.000318867\delta_1^4 + 0.024439926\delta_1^3 - 0.211986641\delta_1^2 + 9.037610699\delta_1 + 17.34544632$$

(n=11, $R^2 = 0.999999821$)

**Quartic (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-1, 2-Butanediol mixtures at most points within an error of ~1.27%, 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 ($\delta_1$), which was subsequently employed to calculate mole fraction solubility of solute ($X_{2\text{cal}}$) in a solvent blend using backward regression. Representative data along with validation parameters are summarized in Table 1. $W_{\text{cal}}$ values are indicating significant interaction of satranidazole and solvent molecules at the peak of solubility profile.

![Figure 3: Relationship of observed and calculated mole fraction solubility of satranidazole](image)

<table>
<thead>
<tr>
<th>1,2-Butanediol (% v/v)</th>
<th>Solubility (g/ml)</th>
<th>$d_1$ (Cal/cm)$^{0.5}$</th>
<th>$d_2$ $(d_1-d_2)$</th>
<th>$d_0$</th>
<th>Density of blend</th>
<th>Mol. Wt of blend</th>
<th>$X_{2\text{cal}}$</th>
<th>$W_{\text{cal}}$</th>
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</table>

Table 1: Molar observed solubility and validation parameters of satranidazole in water-1, 2-Butanediol mixtures $\delta_1$ = Solubility parameter of solvent blend, $\delta_2$ = Solubility parameter of drug in solvent blend, $V_1$ = molar volume of the solvent blend. The binary solvent blends, $\delta_1$ and $\delta_1$, and the corresponding values of equilibrium experimental solubility and mole fraction solubility.
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 ($R^2$) 0.997 and negligible intercept equal to zero.

| $W_{(obs)}$ | $W_{(cal)}$ | $X_{(obs)}$ | $X_{(cal)}$ | $|\log r/(A_{(obs)}$ | $|\log r/(A_{(cal)}$ | Residual | Percent Difference |
|------------|-------------|-------------|-------------|-----------------|-----------------|---------|------------------|
| 302.988427 | 303.010166  | 4.7994E-05  | 4.8830E-05  | 15.694338       | 15.650860       | 1.743E-02 | 1.74E+00         |
| 229.732279 | 229.724899  | 1.2892E-04  | 1.2818E-04  | 13.213495       | 13.228076       | 5.776E-03 | 5.78E-01         |
| 208.207934 | 208.205486  | 1.6766E-04  | 1.6733E-04  | 12.554334       | 12.559230       | 1.942E-03 | 1.94E+01         |
| 188.120275 | 188.125535  | 2.0910E-04  | 2.0997E-04  | 12.000066       | 11.989545       | 4.187E-03 | 4.19E+01         |
| 169.420105 | 169.450744  | 2.4045E-04  | 2.4635E-04  | 11.648782       | 11.587804       | 2.455E-02 | 2.46E+00         |
| 152.113856 | 152.129752  | 2.5619E-04  | 2.5944E-04  | 11.488521       | 11.456703       | 1.270E-02 | 1.27E+00         |
| 136.152130 | 136.094225  | 2.4319E-04  | 2.3232E-04  | 11.617180       | 11.732988       | 4.496E-02 | 4.50E+00         |
| 121.234946 | 121.258863  | 1.6187E-04  | 1.6497E-04  | 12.635018       | 12.587183       | 1.919E-02 | 1.92E+00         |

Table 2: Comparison of observed and calculated mole fraction solubility’s of satranidazole in water-1, 2-butanediol mixtures at 25 ±0.4°C. Calculation of interaction energy and mole fraction solubilities were obtained with the help of Eq. 2 and 10 as described in the text.

CONCLUSION

Extended Hildebrand Approach to solubility employs a power series (quartic) equation in $\delta_1$ to back-calculate ‘$W$’, which reproduces the solubility of satranidazole in water-1, 2-Butanediol 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 1, 2-Butanediol and in any water-1, 2-Butanediol 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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REFERENCES


Conflict of Interest: None declared