PREDICTION OF SOLUBILITY OF ETODOLAC IN BINARY SOLVENTS USING EXTENDED HILDEBRAND SOLUBILITY APPROACH

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The solubility of etodolac in binary solvent system i.e. methanol-water system was analyzed in term of solute-solvent interaction using extended Hildebrand solubility approach (EHSA). The solubility equation employs the term interaction energy (W) to replace the geometric mean (δ₁δ₂), where δ₁ and δ₂ 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 δ₁ of the binary mixture. TisconSonicator A-72 & UV-Visible spectrophotometer shimadzu UV-1700 were used in prediction & evaluation of solubility of Etodolac. Ideal Solubility of Etodolac was calculated by heat of fusion and absolute melting point obtained from DSC data reported in literature. Molar volume and solubility parameter of Etodolac were calculated from Fedor fragmental constant using flotation & experimentally solubility method. Results showed the solubility of Etodolac in the binary solvent, methanol-water shows a bell-shaped profile with a solubility maximum well below the ideal solubility of the drug. This is an attribute to solvation of the drug with the methanol-water mixture, and indicates that the solute-solvent interaction energy is larger than the geometric mean (δ₁δ₂) of regular solution. It was observed that in binary Methanol-water system maximum solubility occurs at 17.17δ i.e. (30:70) & 21.6 δ (80:20) system.

Keywords: Extended Hildebrand solubility approach, ideal solubility, interaction energy, Etodolac, solubility parameter, methanol water system

INTRODUCTION
Solubility defines as the phenomenon of dissolution of solute in solvent to give a homogenous system [1]. Aqueous solubility for organic compounds is most important physiochemical properties and has wide applications in the modern drug discovery and drug sciences. The interaction forces between solutes and solvents are of considerable importance in physical and biological sciences [2]. Numbers of approaches have been developed for the estimation of solubility of drugs.
Amongst various approaches the extended Hildebrand solubility approach (EHSA), a modification of the Hildebrand-Scatchard equation used for estimation of solubility for relatively non-polar drugs in non-polar solvents, permits calculation of the solubility of polar and non-polar species [3-5]. In extended Hildebrand solubility approach the solubility parameter has been developed to reproduce the solubility of drugs and other solids in the binary solvent systems [6]. In EHSA approach the solubility equation employs term interaction energy (W) to replace the geometric mean (δ₁δ₂), where δ₁ and δ₂ 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 [8-10].

In the present work the solubility of etodolac in various methanol-water mixtures was analyzed in terms of solute-solvent interactions using a modified version of Hildebrand-Scatchard approach for regular solutions [7]. The energy term is regressed against a polynomial in δ₁ of the binary mixture. A quartic expression of W in terms of solvent solubility parameter was found for predicting the solubility of etodolac in methanol-water mixtures.

**Material and Methods [11-13]**

All the chemicals of AR grade were used; Etodolac was obtained as gift samples from Ranbaxy Laboratories Distt. Sirmour, H.P., India. Shimadzu UV-1700 spectrophotometer and Tiscon Sonicator A-72 was used for determining solubility of the drug. From solubility studies it was observed that Etodolac is poorly water soluble drug while it is soluble in methanol. Different combination of Methanol with water was selected to predict the suitable solvent combination for maximum solubility of drug.

The standard curve of etodolac was prepared by dissolving accurately weighed 10mg of in volumetric flask using methanol as solvent. The volume was made up to prepare concentration of 1000 µg/ml. From the stock solution concentration of 20-50µg/ml was prepared and absorbances were recorded at λ max 273.5nm shown in figure 1.

**Figure 1.** UV-Spectra of Etodolac
Distilled water and methanol was used to prepare binary solvent blends by adding different ratio’s of Methanol: water volume by volume in the range 0-100. The supersaturated solution of drug was prepared by dissolving excess amount (50mg) of drug in 2ml of binary solvent blends into screw capped vials. The Vials were sealed with tap and were submerged in water at 35±0.4 °C and sonicated in sonicator for 30 minutes. The Vials were shaken for 24 to 36 hr. Solutions was filtered through whatman filter paper & 0.1ml of solution was diluted to prepare concentration in the range 20-50 µg/ml. The absorbance were recorded at λmax 273.5nm showed in Table 1 and calibration curve were prepared shown in figure 3.

| Conc. (μg/ml) | Absorbance | Replicate 1 | Replicate 2 | Replicate 3 | Mean | S.D. | S.E. |
|---------------|------------|-------------|-------------|-------------|------|------|------|
| 10            | 0.272      | 0.279       | 0.268       | 0.273       |      | 0.005568 | 0.003215 |
| 20            | 0.51       | 0.501       | 0.514       | 0.508333    |      | 0.006658 | 0.003844 |
| 30            | 0.776      | 0.78        | 0.778       | 0.778       |      | 0.002 | 0.001155 |
| 40            | 1.094      | 1.078       | 1.074       | 1.082       |      | 0.010583 | 0.00611 |
| 50            | 1.37       | 1.364       | 1.362       | 1.365333    |      | 0.004163 | 0.002404 |

SD= Standard deviation, SE= Standard Mean Error

The density, solubility parameter, molecular volume and molecular weight of binary solvent were determined by the formula showed in figure 2

| S.No | Parameter                  | Formula                                                                 |
|------|----------------------------|------------------------------------------------------------------------|
| 1    | Density                    | = % of Water/100 x Density of water + % of Co-solvent/100 x Density of Co-solvent |
| 2    | Solubility                 | = % of water/100 x solubility parameter of water + % of Co-solvent/100 x solubility parameter of Co-solvent |
| 3    | Molar Volume               | = % of water/100 x Molar Volume of water + % of Co-solvent/100 x Molar Volume of Co-solvent |
| 4    | Molecular Weight           | = % of water/100 x Molecular Weight of water + % of Co-solvent/100 x Molecular Weight of Co-solvent |
| 5    | Molar volume               | Molecular weight / Density                                             |
| 6    | Solubility by Fedor’s method | $\delta_1 = \sqrt{\frac{\Sigma U_1}{\Sigma U}}$                      |
| 7    | Ideal mole fraction        | $-\log X_2 = \frac{\Delta H_r}{2.303R} \left( \frac{T_0 - T}{T_0} \right)$ |
| 8    | Interaction Energy $W_{(obs)}$ | $2W_{(obs)} = (\delta_1)^2 + (\delta_2)^2 - \log f_2 (obs.) / A$        |
| 9    | Activity Coefficient       | $\log f_2 (obs.) - \log 10 (X2i/X2_{(obs)})$                         |
| 10   | Mole Fraction Solubility X2 (Obs) | $n_i = \frac{\text{Density of solvent blend} - \text{solubility (gm/ml)}}{\text{Molecular weight of solvent blend}}$ |
|      |                            | $n_i = \frac{\text{Solubility in gm/ml}}{\text{Molecular weight of drug}}$ |

**Figure 2.** Formula’s for calculation of parameters

The molar volume & solubility parameters were also determine by Fedor’s Substitution Constants method shown in Table 3. From the solubility data the ideal mole fraction (-log X2), mole fraction (X2) and interaction Energy (W) was calculated. The interaction energy
(W) values were regressed against the fourth polynomial of solubility parameter $\delta_1$ of the solvent blend. The quadratic equation was obtained for the solvent blend from which again précised value of interaction energy was calculated.

Table 2. Interaction energy and molar volume by Fedors’ substituent constants

| Fragments groups         | Number of groups | $\Delta U*$ for each cal. mol$^{-1}$ | Total $\Delta U*$ cal. | $\Delta V*$ for each cm$^3$mol$^{-1}$ | Total $\Delta V$ cm$^3$mol$^{-1}$ |
|--------------------------|------------------|--------------------------------------|------------------------|----------------------------------------|----------------------------------|
| CH$_3$                   | 02               | 1125                                 | 2250                   | 33.5                                   | 67.0                             |
| CH$_2$                   | 05               | 1180                                 | 5900                   | 16.1                                   | 80.5                             |
| =CH-                     | 03               | 1030                                 | 3090                   | 13.5                                   | 40.5                             |
| C=                       | 05               | 1030                                 | 5150                   | -5.5                                   | -27.5                            |
| C-O                      | 01               | 4150                                 | 4150                   | 10.8                                   | 10.8                             |
| -COOH                    | 01               | 6600                                 | 6600                   | 28.5                                   | 28.5                             |
| NH                       | 01               | 2000                                 | 2000                   | 4.5                                    | 04.5                             |
| Ring Closure 5 & More    | 03               | 250                                  | 750                    | 16                                     | 48.0                             |
| Conjugated bond          | 03               | 400                                  | 1200                   | -2.2                                   | -06.6                            |

$\Sigma \Delta U$ = Interaction energy, $\Sigma \Delta V$ = molar volume

Result & Discussion
The solubility of Etodolac was predicted by Extended Hildebrand Solubility Approach (EHSA) where solubility was expressed in terms of mole fraction.

The linear curve was established at concentration 10-50µg/ml at $\lambda_{max}$ 273.5nm. The significant value of the absorbance at the linear range were observed, the calibration curves were plotted from the mean value with $r^2$ value 0.998 and equation $y=0.027x-0.026$.

![Chart Title](image)

Figure 3. Calibration curve of Etodolac

The Concentration of the drug was calculated in different solvent blends. The dilutions were back calculated to determine the concentration of drug in vials in g/ml, shown in Table 3.

Density($d_1$), Solubility parameters ($\delta_1$), Molar Volume ($V_1$), Molecular Weight ($M_1$) were calculated in different concentration range i.e. 0-100, the result is shown in Table 4.
Table 3. Absorbance & Concentration of drug in vials of different solvent blends

| S.no. | % of water | % of Methanol | Absorbance | Concentration Obtained in |
|-------|------------|---------------|------------|--------------------------|
|       |            |               |            | Diluents | Vials               |
| 1.    | 100        | 0             | 0.004      | 1.111111 | 0.0013889          |
| 2.    | 90         | 10            | 0.009      | 1.2962963 | 0.0016204         |
| 3.    | 80         | 20            | 0.013      | 1.4444444 | 0.0018056         |
| 4.    | 70         | 30            | 0.018      | 1.6296296 | 0.002037          |
| 5.    | 60         | 40            | 0.024      | 1.8518519 | 0.0023148         |
| 6.    | 50         | 50            | 0.039      | 2.4074074 | 0.0030093         |
| 7.    | 40         | 60            | 0.058      | 3.1111111 | 0.0038889         |
| 8.    | 30         | 70            | 0.073      | 3.6666667 | 0.0045833         |
| 9.    | 20         | 80            | 0.089      | 4.2592593 | 0.0053241         |
| 10.   | 10         | 90            | 0.096      | 4.5185185 | 0.0056481         |
| 11.   | 0          | 100           | 0.088      | 4.2222222 | 0.0052778         |

Table 4. Density (D₁), Solubility Parameter (δ₂), Molar Volume (V₁) and Molecular Weight (M₁) of different solvent blends

| % of water | % of Methanol | Density (D₁) | Solubility Parameter (δ₂) | Molar Volume (V₁) | Molecular Weight (M₁) |
|------------|---------------|--------------|---------------------------|-------------------|------------------------|
| 100        | 0             | 0.9980       | 23.40                     | 18.00             | 18.00                  |
| 90         | 10            | 0.9772       | 22.51                     | 20.27             | 19.40                  |
| 80         | 20            | 0.9564       | 21.62                     | 22.54             | 20.81                  |
| 70         | 30            | 0.9356       | 20.73                     | 24.81             | 22.21                  |
| 60         | 40            | 0.9148       | 19.84                     | 27.08             | 23.62                  |
| 50         | 50            | 0.8940       | 18.95                     | 29.35             | 25.02                  |
| 40         | 60            | 0.8732       | 18.06                     | 31.62             | 26.42                  |
| 30         | 70            | 0.8524       | 17.17                     | 33.89             | 27.83                  |
| 20         | 80            | 0.8316       | 16.28                     | 36.16             | 29.23                  |
| 10         | 90            | 0.8108       | 15.39                     | 38.43             | 30.64                  |
| 0          | 100           | 0.7900       | 14.50                     | 40.70             | 32.04                  |

From experimental calculation the density & molar volume of etodolac was observed to be 1.1190g/cc and 241.371ml respectively. By Fedor substitution method the molar volume, interaction energy and solubility parameter were observed to be $\sum \Delta V=245.7$, $\sum \Delta \Delta U=31090$ & $\delta_2 = 11.248841096$ respectively shown in Table 2.

Table 5. Observed & calculated Mole fraction solubility and Interaction Energy

| Water % | Methanol % | \( n_1 \) | \( n_2 \) | X₂(obs) | X₂(calc) | W(obs) | W(calc) |
|---------|------------|-----------|-----------|---------|----------|--------|---------|
| 100     | 0          | 0.05537   | 4.8351E-06 | 8.7321E-05 | 8.8525E-05 | 330.604476 | 330.621041 |
| 90      | 10         | 0.05028   | 5.6410E-06 | 1.1218E-04 | 1.0982E-04 | 310.475365 | 310.449610 |
| 80      | 20         | 0.04588   | 6.2857E-06 | 1.3699E-04 | 1.3541E-04 | 291.077547 | 291.063477 |
| 70      | 30         | 0.04203   | 7.0915E-06 | 1.6870E-04 | 1.6992E-04 | 272.481598 | 272.490326 |
| 60      | 40         | 0.03864   | 8.0585E-06 | 2.0852E-04 | 2.1935E-04 | 254.681996 | 254.743281 |
| 50      | 50         | 0.03561   | 1.0476E-05 | 2.9409E-05 | 2.9164E-05 | 237.831047 | 237.820906 |
| 40      | 60         | 0.03290   | 1.3538E-05 | 4.1135E-04 | 3.9334E-04 | 221.761538 | 221.707202 |
| 30      | 70         | 0.03047   | 1.5956E-05 | 5.2345E-04 | 5.2347E-04 | 206.371559 | 206.371608 |
| 20      | 80         | 0.02827   | 1.8535E-05 | 6.5529E-04 | 6.6342E-04 | 191.753997 | 191.769006 |
| 10      | 90         | 0.02628   | 1.9663E-05 | 7.4761E-04 | 7.6063E-04 | 177.818696 | 177.839713 |
| 0       | 100        | 0.02449   | 1.8373E-05 | 7.4962E-04 | 7.4142E-04 | 164.522878 | 164.509486 |

X₂= mole fraction Solubility, W= interaction Energy
The Heat of Fusion of Etodolac $\Delta H_f$ is 8139.897 cal/mol. The Ideal mole fraction and mole fraction $X_2i$ was founds to be 1.7439 and 0.01803, the mole fraction solubility of different concentration were shown in Table 5.

The mole fraction solubility of Etodolac is very less as compare to ideal mole fraction solubility, showed in Figure 4.

![Figure 4. Mole Fraction Solubility vs Solubility parameter of Etodolac in Methanol: Water](image)

The interaction energy ($W$) observed were calculated & were regressed against the fourth polynomial of solubility parameter $\delta_1$ of the solvent blend, shown in figure 5.

![Figure 5. Polynomial Curve between W (obs) and Solubility Parameter in Water: Methanol System](image)

The fourth Polynomial quadratic equation of water: Methanol system was observed as $y = -0.00096699x^4 + 0.07880137x^3 - 1.88514076x^2 + 31.43020226x - 92.36757498$
From the above equation the value of \(x\) were obtained from which after back calculations \(W_{\text{cal.}}\) , \(X_2(\text{cal.})\) and \(\log y(\text{cal.})\) were calculated which described the actual interaction energy, mole fraction and rational active coefficient of the drug in different blends. The back calculations of interaction energy were showed in Table 6. The equation observed to be highly significant showing the \(r^2\) value 0.99999971

**Table 6.** Back calculation & Residual error in Water Methanol system

| Water  | Cosolvent | \(W(\text{calc})\) | \(-\log X_2(\text{calc})\) | \(X_2(\text{calc})\) | \(\log y(\text{calc})\) | Residual | % Error |
|--------|-----------|---------------------|-----------------------------|----------------------|------------------------|----------|---------|
| 100    | 0         | 330.621041          | 4.052933                    | 8.8525E-05           | 2.30898                | -1.3797E-02 | -1.38E+00 |
| 90     | 10        | 310.449610          | 3.959316                    | 1.0982E-04           | 2.21537                | 2.1073E-02  | 2.11E+00  |
| 80     | 20        | 291.063477          | 3.868349                    | 1.3541E-04           | 2.12440                | 1.1565E-02  | 1.16E+00  |
| 70     | 30        | 272.490326          | 3.769758                    | 1.6992E-04           | 2.02581                | -7.2383E-03 | -7.24E-01 |
| 60     | 40        | 254.743281          | 3.658868                    | 2.1935E-04           | 1.91492                | -5.1928E-02 | -5.19E+00 |
| 50     | 50        | 237.820906          | 3.535148                    | 2.9164E-04           | 1.79120                | 8.3333E-03  | 8.33E-01  |
| 40     | 60        | 221.707202          | 3.405232                    | 3.9334E-04           | 1.66128                | 4.3781E-02  | 4.38E+00  |
| 30     | 70        | 206.371608          | 3.281109                    | 5.2347E-04           | 1.53716                | -4.0117E-05 | -4.01E-03 |
| 20     | 80        | 191.769006          | 3.178210                    | 6.6342E-04           | 1.43426                | -1.2411E-02 | -1.24E+00 |
| 10     | 90        | 177.839713          | 3.118828                    | 7.6063E-04           | 1.37488                | -1.7411E-02 | -1.74E+00 |
| 0      | 100       | 164.509486          | 3.129938                    | 7.4142E-04           | 1.38599                | 1.0945E-02  | 1.09E+00  |

\(W=\) interaction Energy, \(\log X_2=\) ideal mole fraction, \(\log y=\) Activity coefficient, \(X_2=\) mole fraction

The observed mole fraction solubility and calculated mole fraction solubility were compared. The mole fraction and observed mole fractionsolubilities (shown in Table 5) were extra plotted against solubility parameter \(\delta_1\) shown in Figure 6. The calculated mole fraction solubility lies with observed mole fraction solubility indicating the similarities in theoretical & experimental solubility’s of the etodolac in water methanol system. The interaction Energy \(W(\text{obs})\) were calculate as per the formula mentioned in Table 2 and shown in Table 6. From the result it is clear that observed and calculated interaction energies are coinciding on each other.

**Figure 6.** Curve of Observed & Calculated Mole Fraction Solubility against Solubility parameter in Water Methanol system

The Residual solubility of etodolac in binary solvent were calculated by dividing \(X_2(\text{obs})-X_2(\text{cal})/X_2(\text{obs})\) reported in table 6, which was plotted against solubility parameter which
indicated the scatter graph for the etodolac at different solubility parameter in both calculated and observed scale, showed in figure 7.

![Residual solubility of etodolac in water methanol system](image)

**Figure 7.** Residual solubility of etodolac in water methanol system

The result indicates that in methanol water system maximum solubility occurs at 17.17 δ i.e (30:70 water methanol) and 21.6 δ (80:20 water methanol system). Solubility was also observed at 23.4 δ & 22.4 δ. The maximum solubility of etodolac in water methanol system is predicted at 30:70 & 80: 20 water methanol system.

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