Solubility Prediction of Pioglitazone Hydrochloride in Aqueous N, N-Dimethylsulfoxide Mixtures Using Extended Hildebrand Solubility Approach

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Abstract
Aims: Models for predicting solubility of drugs in solvent mixtures have an important practical application. Solubility behavior of pioglitazone hydrochloride in solvent blends ranging from non-polar to highly polar is essential. So the present investigation deals with study of pioglitazone hydrochloride in binary solvent systems.

Methods: The solubility of pioglitazone hydrochloride in various dimethylsulfoxide-water mixtures was analyzed in terms of solute-solvent interactions using modified Hildebrand-Scatchard treatment. The solubility of pioglitazone hydrochloride in dimethylsulfoxide-water shows a curve with solubility maxima well above the ideal solubility of the drug.

Results: The discrepancy between the results using the original Hildebrand-Scatchard equation and experimental points demonstrates that regular solution theory cannot be used to predict drug solubility in dimethylsulfoxide-water binary 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 ($W$). This is attributed to solvation of drug with the dimethylsulfoxide-water mixture, and indicates that the solute-solvent interaction energy ($W$) is larger than the geometric mean ($\delta_1\delta_2$). The new approach 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 $\delta_1$ of the binary solvent mixture. Quadratic, cubic, and quartic expressions were utilized for predicting the solubility of pioglitazone hydrochloride in dimethylsulfoxide-water mixtures. But a quartic expression of '$W$' in terms of solvent solubility parameter was found appropriate for predicting the mole fraction solubility and yields an error ~27.68%, a value approximating that of the experimentally determined solubility.

Conclusions: Extended Hildebrand Solubility Approach was successfully applied to reproduce the solubility behavior of pioglitazone hydrochloride in dimethylsulfoxide-water binary mixtures within the accuracy. The method has potential usefulness in preformulation and formulation studies during which solubility prediction is important for drug design.

Keywords: Extended Hildebrand solubility approach, N, N-dimethylsulfoxide, pioglitazone hydrochloride, regular solution theory, solubility parameter.

Cite this article as:
1. INTRODUCTION

Extended Hildebrand Solubility Approach is applied to predict the solubility of pioglitazone hydrochloride in mixtures of water and N, N-dimethylsulfoxide (DMSO). DMSO is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is aprotic and completely miscible with water[1]. Water-DMSO mixtures are strongly non ideal and can act in the solute-solution process via hydrophobic interactions and preferential solvation[2,3]. In terms of polarity, water-DMSO mixtures cover a wide range of Hildebrand solubility parameters from 13 (pure DMSO) to 23.4 (pure water)[4].

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

$$\log X_2 = \log X_1 + \frac{\phi_1 V_1 (\delta_1^2 + \delta_2^2 - 2W)}{2.303RT}$$

(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’ can not be theoretically evaluated, it is 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 $\delta_i$ utilizing mixed solvents by polynomial regression[9-11]. By using these polynomial fits, the mole fraction solubility of solutes may be predicted that is 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 such as: the solubility parameter, the volume fraction and the mean molar volume of mixed solvents.

The solubility parameter ($\delta_i$) for the mixture of two solvents, DMSO and water, is averaged in terms of volume fractions using the expression[12],

$$\delta_i = \frac{\delta_{DMSO} \phi_{DMSO} + \delta_W \phi_W}{\phi_{DMSO} + \phi_W}$$

(2)

where, $\phi_i = \phi_{DMSO} + \phi_W$ is the total volume fraction of the solvents which can be calculated from[13],

$$\phi_i = \frac{(1 - X_2) V_1}{X_2 V_1 + X_3 V_3}$$

(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 water and DMSO in various proportions[14],

$$V_i = \frac{X_{DMSO} M_{DMSO} + (1 - X_{DMSO}) M_W}{d_i}$$

(4)

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

Pioglitazone (PGZ) is an oral hypoglycemic agent used in the treatment of type II diabetes which acts by decreasing insulin resistance[15]. PGZ freebase and its hydrochloride salt have very low aqueous solubility’s, and the hydrochloride salt (PGZ-HCl) is used in the pharmaceutical formulations[16]. Pioglitazone hydrochloride is 5-[[4-[2-(ethylpyridine-2-yl) ethoxy] phenyl] methyl]-1, 3-thiazolidine-2, 4-Dione, hydrochloride[17]. It is official in IP 2010 till date[18]. Though the molecule is found to be effective, its therapeutic efficacy is hindered due to its poor aqueous solubility[19]. The drugs with low aqueous solubility i.e., less than 1 mg/ml usually suffer oral bioavailability problems because of limited gastrointestinal transit time of the undissolved drug particles and limited solubility at the absorption site[20]. The poor aqueous solubility and wettability of pioglitazone hydrochloride give rise to difficulties in pharmaceutical formulations meant for oral or parenteral use, which may lead to variation in bioavailability[21, 22].

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As such, no solubility reports are found for its estimation and prediction by any of the method till date. Hence, the aim of this communication is to report the solubility behavior of pioglitazone hydrochloride in individual solvents (water and DMSO) and different concentrations of water-DMSO mixtures, predict it theoretically by applying the Extended Hildebrand Solubility Approach.

2. MATERIALS AND METHODS:

Pioglitazone hydrochloride, obtained as gift sample from Lupin Pharmaceuticals, Ltd., Aurangabad, India. N, N-Dimethylsulfoxide was purchased from Research Lab Fine Chemical Industry, Islampur, India. 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, Jasco model V-503 with spectral bandwidth of 2 nm, wavelength accuracy ±0.5 nm and a pair of 10 mm matched quartz cells were used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing of pioglitazone hydrochloride. Differential Scanning Calorimeter, Shimadzu TA-60 WS, was used for determination of melting point and heat of fusion of pioglitazone hydrochloride.
Table 1: Mole Fraction Solubility of Pioglitazone Hydrochloride.

<table>
<thead>
<tr>
<th>DMSO (g/ml)</th>
<th>Solubility (g/ml)</th>
<th>$\delta_1$ (Cal/cm$^3$)$^{0.5}$</th>
<th>$\phi_1$</th>
<th>$V_1$</th>
<th>Density of blend</th>
<th>Mol. Wt of blend</th>
<th>$X_{2(\text{obs})}$</th>
<th>$W_{(\text{obs})}$</th>
<th>$\delta_1\delta_2$</th>
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</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.000031</td>
<td>23.40</td>
<td>0.99997</td>
<td>18.00</td>
<td>0.9945</td>
<td>18.00</td>
<td>1.4427E-06</td>
<td>325.05</td>
<td>254.10</td>
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<tr>
<td>0.1</td>
<td>0.000199</td>
<td>22.36</td>
<td>0.99981</td>
<td>23.30</td>
<td>1.0088</td>
<td>24.01</td>
<td>1.2073E-05</td>
<td>303.04</td>
<td>242.81</td>
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<td>0.2</td>
<td>0.000333</td>
<td>21.32</td>
<td>0.99969</td>
<td>28.60</td>
<td>1.0230</td>
<td>30.03</td>
<td>2.4917E-05</td>
<td>280.94</td>
<td>231.51</td>
</tr>
<tr>
<td>0.3</td>
<td>0.001054</td>
<td>20.28</td>
<td>0.99902</td>
<td>33.90</td>
<td>1.0373</td>
<td>36.04</td>
<td>9.3271E-05</td>
<td>260.41</td>
<td>220.22</td>
</tr>
<tr>
<td>0.4</td>
<td>0.001316</td>
<td>19.24</td>
<td>0.99878</td>
<td>39.20</td>
<td>1.0516</td>
<td>42.06</td>
<td>1.3410E-04</td>
<td>240.16</td>
<td>208.93</td>
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<tr>
<td>0.5</td>
<td>0.002479</td>
<td>18.20</td>
<td>0.99771</td>
<td>44.51</td>
<td>1.0659</td>
<td>48.07</td>
<td>2.8511E-04</td>
<td>221.32</td>
<td>197.63</td>
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<tr>
<td>0.6</td>
<td>0.005434</td>
<td>17.16</td>
<td>0.99503</td>
<td>49.81</td>
<td>1.0801</td>
<td>54.08</td>
<td>6.9553E-04</td>
<td>203.67</td>
<td>186.34</td>
</tr>
<tr>
<td>0.7</td>
<td>0.023152</td>
<td>16.12</td>
<td>0.97899</td>
<td>55.11</td>
<td>1.0944</td>
<td>60.10</td>
<td>3.2948E-03</td>
<td>187.64</td>
<td>175.05</td>
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<tr>
<td>0.8</td>
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<td>15.08</td>
<td>0.88520</td>
<td>60.41</td>
<td>1.1087</td>
<td>66.11</td>
<td>2.1433E-02</td>
<td>173.06</td>
<td>163.75</td>
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<tr>
<td>0.9</td>
<td>0.243204</td>
<td>14.04</td>
<td>0.80038</td>
<td>65.71</td>
<td>1.1229</td>
<td>72.13</td>
<td>4.3813E-02</td>
<td>158.86</td>
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<tr>
<td>1.0</td>
<td>0.282657</td>
<td>13.00</td>
<td>0.75113</td>
<td>71.01</td>
<td>1.1372</td>
<td>78.14</td>
<td>6.1722E-02</td>
<td>145.44</td>
<td>141.17</td>
</tr>
</tbody>
</table>

$W_{(\text{obs})}$ obtained from quartic Eq. 7, for Pioglitazone hydrochloride in DMSO-water mixtures at 25±0.4°C. Residuals can also be obtained from, [(X$_{2(\text{obs})}$-X$_{2(\text{cal})}$)/X$_{2(\text{obs})}$].

Table 2: Experimental and Calculated Mole Fraction Solubilities.

<table>
<thead>
<tr>
<th>Percent Residual</th>
<th>$W_{(\text{cal})}$</th>
<th>$X_{2(\text{cal})}$</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.517</td>
<td>325.04862</td>
<td>1.4427E-06</td>
<td>4.517</td>
</tr>
<tr>
<td>4.750</td>
<td>303.04034</td>
<td>1.2073E-05</td>
<td>4.0301E-01</td>
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<tr>
<td>27.683</td>
<td>280.93561</td>
<td>3.4960E-05</td>
<td>2.7683E-01</td>
</tr>
<tr>
<td>8.736</td>
<td>260.40951</td>
<td>6.7451E-05</td>
<td>3.6128E-02</td>
</tr>
<tr>
<td>25.567</td>
<td>240.16340</td>
<td>1.2239E-04</td>
<td>2.3567E-01</td>
</tr>
<tr>
<td>13.896</td>
<td>221.32347</td>
<td>8.7355E-04</td>
<td>1.3896E-01</td>
</tr>
<tr>
<td>17.968</td>
<td>203.67494</td>
<td>2.7481E-04</td>
<td>1.7968E-01</td>
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<td>1.463</td>
<td>187.69376</td>
<td>6.5945E-04</td>
<td>1.4635E-02</td>
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<td>1.727</td>
<td>173.06241</td>
<td>3.8813E-02</td>
<td>1.7266E-02</td>
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<tr>
<td>0.00031</td>
<td>158.86170</td>
<td>4.3813E-02</td>
<td>0.00031</td>
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<tr>
<td>0.000199</td>
<td>145.44109</td>
<td>6.1722E-02</td>
<td>0.000199</td>
</tr>
</tbody>
</table>

Solubility measurements:
Solubilities of pioglitazone hydrochloride ($\delta_2 = 11.34$) were determined in mixed solvent consisting of DMSO ($\delta_{\text{DMSO}} = 13$) and water ($\delta_w = 23.4$). Solvent blends were made covering 0-100% DMSO (v/v). About 25 ml of DMSO, water, or mixed solvents were placed into screw-capped vials (Thermostated at 25°C and under continuous magnetic stirring) containing an excess amount of pioglitazone hydrochloride and agitation was maintained 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[23].

After equilibration, the solution was 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 pioglitazone hydrochloride ($\lambda_{\text{max}} = 269$ nm). Calibration graphs of pioglitazone hydrochloride in each solvent blend were previously established with correlation coefficients greater than 0.9969. The working concentration range was from 10 to 60 μg/ml pioglitazone hydrochloride. The densities of the blends as well as the filtrates of saturated solutions were determined by using 25-ml specific gravity bottle at 25°C. Once the densities of solutions are known, the solubilities can be expressed in mole fraction scale.

3. RESULTS AND DISCUSSION:
The molar volume ($V_2$) and the solubility parameter of pioglitazone hydrochloride were previously estimated by using the Fedor’s group contribution method[24,25] giving 357.67 cm$^3$/mol and 10.859 (cal/cm$^3$)$^{0.5}$. The ideal solubility of pioglitazone hydrochloride was calculated by using the equation[26],

$$-\log X_2 = \frac{\Delta S_f}{R} \log \frac{T_o}{T}$$

where, $\Delta S_f$ is the entropy of fusion of the crystalline drug molecule at its melting point $T_o$ and $T$ is the temperature in Kelvin at which the solubility was determined. The value of $\Delta S_f$ was evaluated by[27],

$$\Delta S_f = \Delta H_f / T_o$$

($\Delta H_f = 8213.78$ cal/mol, $T_o = 469.04$ K) giving 17.5118 cal/mol/K. Thus, the ideal mole fraction solubility of pioglitazone hydrochloride ($X_2^i$) is 0.02126.

The mole fraction solubility of pioglitazone hydrochloride in water-DMSO mixtures and other
parameters of interest ($\delta_1$, $\Phi_1$, $V_1$) are collected in Table 1. The plot of these experimental solubilities versus the solubility parameter of mixtures, $\delta_1$ is shown in fig. 1. The solubility of pioglitazone hydrochloride was far from its ideal value in both pure solvents (DMSO, water) as well as in the mixtures. The maximum solubility, although higher than ideal occurred at a $\delta_1 = 13.00$, very close to the calculated $\delta_2$ for pioglitazone hydrochloride.

A mathematical model is proposed for individual system as fourth power polynomial. The $W^*$ values may also be expanded in a power series of $\delta_1$ from fourth degree polynomial regression.

In our case, the following fit was obtained:

$W_{(obs)}= -321.0820130 + 91.9009097 \delta_1 - 7.5646783 \delta_1^2 + 0.3062110 \delta_1^3 - 0.0042883 \delta_1^4$, (n = 11, $R^2= 0.9999928$) ------------ (7)

If we insert this equality in Eq.1, we can predict the solubility of pioglitazone hydrochloride. The back-calculated logarithmic solubilities, log$X_{2cal}$ are recorded in Table 2, 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 passing through the origin with very high degree of correlation coefficient ($R^2$) 0.9965 and negligible intercept (0.00026) equal to zero as shown in fig. 3.

A careful scrutiny of the behavior of the solutions of pioglitazone hydrochloride in water-DMSO 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 1. As can be observed, for volume fractions of DMSO from 0 to 1, $W > \delta_1 \delta_2$. But, for volume fractions of DMSO from 0 to 0.5, $W^*$ is far greater than $\delta_1 \delta_2$ and for volume fractions of DMSO from 0.6 to 0.9, $W^*$ is nearby closer to $\delta_1 \delta_2$. It may be assumed that pioglitazone hydrochloride solutions can behave as regular solutions at some point ($W = \delta_1 \delta_2$) with 1.0 DMSO volume fraction.

Thus, in water-rich mixtures (0-0.5) it seems to be some kind of association between pioglitazone hydrochloride and the solvent mixture according to $W > \delta_1 \delta_2$. This finding 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 DMSO, HH breaks down. The endothermic shift of the enthalpies of solution upon small additions of aprotic cosolvent to water is known to appear for hydrophobic solutes like pioglitazone hydrochloride.

Conversely, in water poor mixtures (0.6-1.0) self association of solvent, solute or both is not obtained because still ‘W’ is far greater than δ₁ δ₂. This behavior may remain as such in rich DMSO blends, and therefore, the corresponding pioglitazone hydrochloride solubilities are still higher than regular one.

The Extended Hildebrand Approach applied to the solubility data of pioglitazone hydrochloride in water-DMSO mixtures leads to an expansion of the W interaction term as a fourth degree power series in δ₁ which reproduces the pioglitazone hydrochloride solubility within the accuracy ordinarily achieved in such measurements. The procedure can be used to predict the solubility of pioglitazone hydrochloride in pure water or DMSO and in any water-DMSO mixtures. Another aspect for assessment of extended Hildebrand solubility approach is to plot residuals of solubility versus solubility parameter for pioglitazone hydrochloride in dimethylsulfoxide-water binary mixtures (fig. 4), which shows values of residuals are closer to zero and scattered around a line with zero slope. Simultaneously, this tool may become useful in optimization problems of clear solution formulations.

5. ACKNOWLEDGEMENTS:
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6. REFERENCES:


