Research Article

NABUMETONE IN BINARY SOLVENTS: SOLUBILITY ANALYSIS
Meena Kharwade *1, C.V.S. Subrahmanyam 2, Pramod Kharwade 3
1Assistant Professor, Anjuman-I-Islam Kalsekar Technical Campus, New Panvel, Navi Mumbai, India
2Professor & Principal, Dept. of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Osmania University, Bachupally, Hyderabad, AP, India
*Corresponding Author Email: meenakharwade@yahoo.com

ABSTRACT

The solubility prediction of nabumetone was studied in different solvent system (hexane- ethyl acetate- ethanol- water). The theories such as ideal, Hildebrand-Scatchard and extended Hildebrand solubility approaches were used for finalizing the solubility behavior of nabumetone. Entropy of fusion expression was used to calculate the ideal solubility. The experimental mole fraction solubility deviated from the ideal mole fraction solubility, indicating the self association of solute or solvent or both in solution. The extended Hildebrand equation was used to reproduce solubilities of nabumetone in selected solvent blend. The solubilities of nabumetone were back calculated with an interaction energy term ‘W’ and rational activity coefficient term ‘(logα/α)/A’. These parameters were regressed against a polynomial of δi, solubility parameter of solvent blend. Solubility parameter of the nabumetone δ; was determined and found to be - 20 MPa^1/2. 

Key words: Nabumetone, interaction energy term, solubility behavior, extended Hildebrand, solubility parameter.

INTRODUCTION

Solubility parameter, δ, is an intrinsic physicochemical property of a substance, and is expressed as square root of the cohesive energy density. It affords a numerical approximation of the degree of interaction between materials. It has been found particular use in predicting solubility, selection of solvents and cosolvents for increased solubility1, chemical kinetics2, drug action, drug transport kinetics3,4, structure activity relationship5, in situ release of theophylline6, gas-solid chromatography7, selection of excipients for formulations8, dosage form technology and design9, fast prediction of basic properties of materials10, solvent selection for organic reactions11, prediction of adhesion of film coating to tablets12, selection of co-formers for co-crystal formation13. Therefore, the specific value of the solubility parameter of a drug is of concern. Various theoretical as well as experimental methods exist to determine the solubility parameter of drug. Current theoretical methods, i.e. group contribution methods Fedors14, Hoy’s and Van Krevelen method15 and experimental method for δ, are detailed in this paper.

The rationale of present investigation is to test current approaches for estimating the solubility behavior and solubility parameter of nabumetone in the context of existing theories, such as ideal, regular16, and irregular solutions17. Solubility of nabumetone was determined in n-hexane – ethyl acetate – ethanol – water systems to emphasize the solution behavior. Selected drug (nabumetone) belongs to BCS class II, i.e., low solubility and high permeability. Nabumetone has naphthalene as a skeleton structure without any ionizable functional groups. The solubility behavior of naphthalene was analyzed in individual solvents using extended Hansen’s approach, three parameter approach18 . It is doable to fortify the concept by evaluating structural analogue of naphthalene, namely nabumetone. The extended Hildebrand solubility approach [EHS] used in this article is empirical involving statistical analysis of the obtained datum to recognize the solubility behavior and allows the inference of solubility parameter.

MATERIALS AND METHODS
Materials

The nabumetone was as a gift sample kindly supplied by Dr. Reddys Laboratories Ltd., Hyderabad and used as received. The selected binary solvent mixtures were prepared on the volume basis covers wide range of Hildebrand solubility parameter scale i.e. hexane, ethyl acetate, ethanol, water [analytical grade].

Methods

Solubility measurement

The solubility of nabumetone was determined in saturated solutions of varying compositions of mixed solvent blends (hexane-ethyl acetate-ethanol-water system)17. An excess of nabumetone was introduced into stoppered flasks containing binary solvent system. Flasks were shaken (number of strokes was 100 ± 2 per minute) in orbital shaking incubator (Kemi Instruments, Kerala, India) at 25 ± 1 °C for 72 hours. Preliminary studies indicated that the time period of 72 hrs is sufficient for saturation at 25 °C. These equilibrated solutions were removed, filtered (using Whatman filter papers of pore size 0.22 μ) to separate the saturated solutions from excess solid drug. The saturated solutions were diluted with 0.01 mol·L⁻¹ hydrochloric acid solution and assayed spectrophotometrically (UV- 1700, Shimadzu, Japan) at maximum wavelength of absorption i.e. 330 nm18. Nabumetone in 0.01 mol·L⁻¹ hydrochloric acid obeys Beer’s law in the range of 20 to 100
µg·ml⁻¹ at 330 nm. The experimental solubility results were recorded as an average of three trials.

Solubility parameter and molar volume of nabumetone

The floation technique was used to obtain the molar volume of nabumetone experimentally and theoretically by Fedors substituent constants method. The total solubility parameter (δt) of nabumetone was calculated by the group contribution methods like Fedors, Hoy’s and van Krevelan. The solubility parameters of the solvents were taken from the literature.

Differential scanning calorimeter

Differential scanning calorimeter (DSC of 6300, Sicko, Japan) of nabumetone was done to determine the heat of fusion and fusion temperature. The thermal behavior of the drug was studied at heating rate of 5 °C per min under nitrogen atmosphere (flow rate 50-60 ml·min⁻¹). The molar heat of fusion was calculated in 35.16 KJ/mol using the molecular weight of nabumetone (228.29 g/mol) at a fusion temperature of 83.6 °C. This value was measured in triplicate and found certainty in the value. The ideal mole fraction solubility (Xf) of crystalline solid in solvent mixtures was calculated from:

\[ -\log_{10} X_f = \frac{\Delta S_f}{R} \log \frac{T_0}{T} \]  

Where, Xf is the ideal mole fraction solubility of solute; ΔSf is the entropy of fusion (kJ·mol⁻¹), is determined using the relationship \( \Delta H_f = T_0 \cdot \Delta S_f \). T0 is the melting point of the solid solute; T is the temperature of the solution, (25 °C). Statistical analysis

In-house software was developed in BASIC and used for calculating the drug solubility. Mean, standard deviation and regression analysis of the experimental data and the graphs were generated using statistical function of the M.S. Excel program. The graphs were generated using M.S. Excel and the entire text was processed in MS Office.

RESULTS AND DISCUSSION

The melting point T0 determined by open capillaries (80-85 °C) and DSC fusion temperature (83.6 °C) were closer to the literature value of nabumetone (80 °C). The ideal mole fraction solubility of nabumetone was obtained as 0.131467, based on entropy of fusion (eqa.1). The mole fraction experimental solubilities of nabumetone in different solvents system (hexane-ethyl acetate- ethanol-water) at 25 °C plotted against the solubility parameter of solvent blends are shown in Figure 1.

As per Figure 1, the experimental solubility curve appears to be an asymmetrical bell-shaped with a peak at 8.9 H. The observed solubilities were lower in most of the solvent blends than the ideal solubilities except in one solvent blend (peak) indicating the self association of drug or solvent (or both) (failure of ideal solution theory).

Solubility Parameter and regular solution

The solubility parameter of nabumetone was computed by Fedors method, Hoy’s fragmental constants method and Van Krevelene method and recorded along with experimental results in Table 1. The molar volume estimated from Fedors group contribution method and experimentally was 241.8 cm³·mol⁻¹ and 224.465 cm³·mol⁻¹, respectively. The nabumetone solubility data were verified from the regular solution theory (Hildebrand-Scatchard equation 2) and the peak solubility was found to be 18.205 MPa⁻¹2 (8.9 H) (where \( \delta_1 = \delta_s \)) (Figure 1).

\[ \log_{10} X_f = -\log_{10} X_2^i + \frac{V_1 \Phi_1^2}{2.303 RT} \left( \delta_1 - \delta_2 \right)^2 \]  

where, \( V_1 \) is the molar volume of solute, \( \Phi_1 = \frac{V_1 (1 - X_2)}{V_1 (1 - X_2) + V_2 X_2} \)

Where, \( \delta_1 \) and \( \delta_2 \) are solubility parameters of solvent and solute, respectively, \( H \); \( V_2 \) is the molar volume of solute, cm³·mol⁻¹; \( \Phi_1 \) is the volume fraction of solute, T is the absolute temperature of the solution (room temperature), °C; R is the Ideal gas constant; \( X_2^i \) is the ideal solubility and \( X_2 \) is the experimental mole fraction solubility of regular solution.
According to Hildebrand-Scatchard equation, regular solubility is utmost and can be equalize to ideal mole fraction solubility \((X^2)\). Consequently, the solubility parameter of solvent \((\delta_i)\) can be taken from the graph at the point of peak solubility, which is believed to be equivalent to \(\delta_i\), the drug solubility parameter. The \(\delta_i\) value of nabumetone i.e. 8.9 H (18.205 MPa\(^{1/2}\)) (from the peak method) did not agree with the values obtained from fragmental constant method (Table 1). Nabumetone has naphthalene as a skeleton structure. The solubility parameter of naphthalene as reported is 9.64 H (19.67 MPa\(^{1/2}\)) (group contribution method) and 9.6 H (19.63 MPa\(^{1/2}\)) (Extended Hansen approach)\(^9\)\(^\text{20}\). Further, the anthracene has solubility parameter of (20.3 MPa\(^{1/2}\)), i.e., 9.92 H. The solubility parameter of nabumetone must be nearer to the values of other congeners. The addition of methoxy group to naphthalene in nabumetone is expected to decrease the solubility parameter, as similar trends were observed in a number of compounds, i.e., n–propanol and 2-propanol\(^10\). In other words, the solubility parameter of nabumetone expected to be around 9.9 H (20.24 MPa\(^{1/2}\)). Considering this, re-verification of solubility analysis is a must. Sometimes the peak solubility fails to provide the \(\delta\) value of drug \(^2\) but validity of \(X^2 = \delta^2\) is still good in irregular solution\(^2\). As shown in Figure 1, the ideal solubility curve crosses the graph at two \(\delta\) values, i.e., 8.7 H (17.79 MPa\(^{1/2}\)) and 9.8 H (20.04 MPa\(^{1/2}\)). The \(\delta\) value of 9.8 H (20.04 MPa\(^{1/2}\)) may be a reasonable estimate of solubility parameter, which is nearer to the values obtained by the other methods (Table 1).

**Table 1: Solubility parameters of nabumetone from different methods.**

<table>
<thead>
<tr>
<th>Method</th>
<th>Solubility parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hildebrand, H SI units, MPa(^{1/2})</td>
</tr>
<tr>
<td>Fedor’s method</td>
<td>10.17</td>
</tr>
<tr>
<td>Hoy’s method</td>
<td>9.13</td>
</tr>
<tr>
<td>Van Krevelene method(^1)</td>
<td>11.67</td>
</tr>
<tr>
<td>From the graph, at condition (X_i = X^2)</td>
<td>9.8 (and 8.7)</td>
</tr>
<tr>
<td>From first derivative plot</td>
<td>9.8</td>
</tr>
<tr>
<td>Experimental peak solubility in different solvent series</td>
<td>8.9</td>
</tr>
</tbody>
</table>

\(^1\)Estimated from Fedor’s molar attraction constant [14]  
\(^2\)Estimated from Hoy’s substituent method [15]  
\(^3\)Estimated from Van Krevelan method [15]

Further, accurate results were obtained by plotting a first derivative curve (mean \(\delta\) vs \(\Delta X^2/\Delta \delta_i\)) and observing the point it crosses the zero value of \(x\)-axis. The experimental mole fraction solubility of nabumetone was processed and the plot is drawn (Figure 2). The line crossed the ordinate at about 9.8 H, conforming the solubility parameter of nabumetone as 9.8 H which is also near to the values obtained by other methods (Table 1).

**Figure 2: Solubility parameter of nabumetone in different solvents system, first derivative plot**

For regular solution behavior, mole fraction solubility was calculated using Hildebrand-Scatchard equation (2) using in-house software. As per Figure 1, solubilities pointed that the experimentally determined mole fraction solubilities were superior to the calculated solubility based on regular solution equation (2) (Figure 1). Therefore, it was assumed that the present data did not satisfy the regular solution theory. The difference in solubilities (poor fit of Hildebrand-Scatchard equation) may be due to selection of polar solvents and difference in molar volumes of solute and solvent.

**Extended Hildebrand Solubility Approach**

The extended Hildebrand solubility approach (EHS) was proposed to understand the irregular behavior of solutions. This approach is partly involve polynomial regression analysis of experimental values, for back calculating the solubility of drugs in polar and nonpolar solvents. Basically, two parameters were evaluated in EHS approach, i.e., ‘\(W\)’ term (interaction energy) or rational activity term \((\log_{10} \gamma_2)/A\) values were regressed against the power series, e.g. quadratic, cubic or quartic of the solvent solubility parameter\(^23\)\(^24\).

**Interaction energy term (w)**

The ‘\(W\)’ expression was an interaction energy term, which in regular solution theory, was taken to be equal to “geometric mean”. Although ‘\(W\)’ presently cannot be estimated based on fundamental physicochemical properties of solute and solvent, ‘\(W\)’ may be obtained from the experimental values using equation (4) for each solvent blend (Table 4). Presently, ‘\(W\)’ was evaluated from the knowledge of other terms obtained experimentally (equations 4 and 5).

\[-\log_{10} X_2 = -\log_{10} X^2 + A (\delta^2_i + \delta^2 - 2W) (4)\]

Where, \(A = \frac{V_2 \Phi_1^2}{2.303 \, RT}\)  
(5)

The ‘\(W\)’ values of nabumetone solubility in different solvent system was regressed against polynomials (quadratic, cubic and quartic) in \(\delta\) of the solvents. Based on the ‘\(R^2\)’ value and ‘\(s\’\) value, the present investigation had chosen quadratic equation (equation 6).

**Quadratic equation**

\[W = 43.29694 + 0.87437 \delta_i + 0.44014 \delta_i^2 \quad (6)\]

\(n = 14, \, s = 1.7828, \, R^2 = 0.99942\)
The equation (6) is not in the standard format, i.e., alternate signs. The distribution of errors is random. The calculated ‘W’ values (using equation 6) were nearer to ‘W’ experimental values (Table 2). The ‘W’ calculated values were substituted in equation (4) to back calculate the solubility of nabumetone, \( X_{(calc)} \). A perusal to Table 2, indicates that the solubility curve does not fit well with experimental values, as a result, the percent error is high (-447 to +58). The percentage error was high at extreme data points, which was considered reason for a drug exhibiting low solubility. The lack of close agreement between \( X_{(calc)} \) and \( X_{(exp)} \) may be due to peak and shoulder observed in the experimental solubility profile. Such a high error was quite common, when nabumetone was intrinsically low soluble.

### Table 2: Mole fraction solubility of nabumetone in different solvent system based on interaction energy term (W), at 25 °C

<table>
<thead>
<tr>
<th>Ratio</th>
<th>( \delta_i )</th>
<th>( H )</th>
<th>( A )</th>
<th>( W_{(exp)} )</th>
<th>( W_{(calc)} )</th>
<th>( X_{(exp)} )</th>
<th>( X_{(calc)} )</th>
<th>Percent error&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane:Ethyl acetate</td>
<td>100:0</td>
<td>7.3</td>
<td>0.1329132</td>
<td>70.35</td>
<td>73.1547</td>
<td>0.009421</td>
<td>0.051534</td>
<td>-447.035</td>
</tr>
<tr>
<td>50:50</td>
<td>8.1</td>
<td>0.0978795</td>
<td>80.2284</td>
<td>79.2567</td>
<td>0.104057</td>
<td>0.064801</td>
<td>35.4913</td>
<td></td>
</tr>
<tr>
<td>20:80</td>
<td>8.58</td>
<td>0.0948487</td>
<td>84.2308</td>
<td>83.2003</td>
<td>0.101245</td>
<td>0.064533</td>
<td>36.25771</td>
<td></td>
</tr>
<tr>
<td>10:90</td>
<td>8.74</td>
<td>0.1081572</td>
<td>84.7414</td>
<td>84.5599</td>
<td>0.063129</td>
<td>0.057653</td>
<td>8.670852</td>
<td></td>
</tr>
<tr>
<td>Ethyl acetate:Ethanol</td>
<td>100:0</td>
<td>8.9</td>
<td>0.0811128</td>
<td>87.7141</td>
<td>85.9421</td>
<td>0.135912</td>
<td>0.070078</td>
<td>48.43711</td>
</tr>
<tr>
<td>50:50</td>
<td>10.95</td>
<td>0.1029870</td>
<td>106.3136</td>
<td>105.6448</td>
<td>0.059883</td>
<td>0.045588</td>
<td>27.20815</td>
<td></td>
</tr>
<tr>
<td>20:80</td>
<td>12.18</td>
<td>0.1333208</td>
<td>116.5497</td>
<td>119.2421</td>
<td>0.004100</td>
<td>0.02142</td>
<td>-422.41</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 3: Solubility of nabumetone in different solvent system based on (log \( \gamma_i \))/A, at 25°C<sup>*</sup>

<table>
<thead>
<tr>
<th>Ratio</th>
<th>( \delta_i )</th>
<th>( H )</th>
<th>( A )</th>
<th>( (\log \gamma_{i}/A)^{(exp)} )</th>
<th>( (\log \gamma_{i}/A)^{(calc)} )</th>
<th>( X_{(exp)} )</th>
<th>( X_{(calc)} )</th>
<th>Percent error&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexanee:Ethyl acetate</td>
<td>100:0</td>
<td>7.3</td>
<td>0.132813</td>
<td>8.617336</td>
<td>4.66644</td>
<td>0.009421</td>
<td>0.03155</td>
<td>-234.847</td>
</tr>
<tr>
<td>50:50</td>
<td>8.1</td>
<td>0.0978795</td>
<td>1.193281</td>
<td>3.57422</td>
<td>0.100457</td>
<td>0.05874</td>
<td>41.5031</td>
<td></td>
</tr>
<tr>
<td>20:80</td>
<td>8.58</td>
<td>0.0948487</td>
<td>1.195640</td>
<td>3.15324</td>
<td>0.101245</td>
<td>0.06062</td>
<td>34.79077</td>
<td></td>
</tr>
<tr>
<td>10:90</td>
<td>8.74</td>
<td>0.1081572</td>
<td>2.944905</td>
<td>3.05020</td>
<td>0.063129</td>
<td>0.0615</td>
<td>2.585019</td>
<td></td>
</tr>
</tbody>
</table>

### Ethanol:Water | 100:0  | 8.9    | 0.0811138 | 87.7141 | 85.9428 | 0.135912       | 0.07555       | 44.41081                  |
| 50:50        | 10.95  | 0.1029870 | 106.3136 | 105.6448     | 0.059883       | 0.05934        | 0.899992      |                         |
| 20:80        | 12.18  | 0.1333208 | 116.5497 | 119.2421     | 0.0041         | 0.03073        | -649.547      |                         |

\[ \Delta H_{f} = 8402.6290 \text{cal/mole, melting point = 80°C (353 K), } X'_{i} = 0.131467, \text{ Molar volume (} V_{j} = 182.9278 \text{cm}^3/\text{mol, } \delta_{i} = 9.8 \text{ H} \]

\[ \rightarrow \text{ As per equation (6)} \]

\[ \rightarrow \text{ As per equation (4)} \]

\[ \rightarrow \text{ Average of three determinations} \]

\[ \rightarrow \text{ Percent error is determined as } |X'_{i} \exp - X_{i} \calc|/(X'_{i} \exp) \times 100 \]

### Table 3: Solubility of nabumetone in different solvent system based on (log \( \gamma_i \))/A, at 25°C<sup>*</sup>

\[ \Delta H_{f} = 8402.6290 \text{cal/mole, melting point = 80°C (353 K), } X'_{i} = 0.131467, \text{ Molar volume (} V_{j} = 182.9278 \text{cm}^3/\text{mol, } \delta_{i} = 9.8 \text{ H} \]

\[ \rightarrow \text{ As per equation (7)} \]

\[ \rightarrow \text{ As per equation (8)} \]

\[ \rightarrow \text{ Average of three determinations} \]

The polynomial expressions are empirical and cannot be expected to reproduce the accurate change in solubility. Variable error is observed for individual solvents namely n-hexane, ethyl acetate, ethanol, and water; these might be due to the differences in the nature of solvents.

### Rational activity coefficient

The (log<sub>10</sub> \( \gamma_i \))/A values obtained from experimental solubilities may be regressed directly against \( \delta_i \) bypassing ‘W’ and obviating the need for \( \delta_i \) in the calculations. (log<sub>10</sub> \( \gamma_i \))/A values were calculated from the experimental solubility of nabumetone in different solvent system using equation (7) for each solvent blend (Table 3). These values can be regressed against a...
polynomial in δi of the solvent blend. Thus (log$_{10}$ γi)/A values were calculated for each binary mixture (Table 3)

\[
\log_{10}(X_1\delta_1 X_2\delta_2) = A (\delta_1^2 + \delta_2^2 - 2W) \quad (7)
\]

The cubic regression expression was chosen considering the low solubility,

\[
\frac{\log_{10} γi}{A} = 43.31162 - 9.54812 \delta_i + 0.670896 \delta_i^2 - 0.01207 \delta_i^3 \quad (8)
\]

n = 14, s = 3.5363, R$^2$ = 0.8965

Alternative signs of coefficients are in tune with the standard format. The scatter gram indicated the random distribution of errors. From the regression equation (8), the (log$_{10}$ γi)/A values were calculated and recorded in Table 3. The calculated (log$_{10}$ γi)/A values were nearer to (log$_{10}$ γi)/A experimental values. The (log$_{10}$ γi)/A calculated values were substituted in equation (7) to back calculate the solubility of lornoxicam $X_2$(calc). A perusal to Table 3, indicates that the solubility curve did not fit well with the experimental solubility (percent error was high ranging from –649 to + 54), particularly near the peak solubility. Keeping in view of the diverse nature of solvents used in this series, the differences in $X_2$ values can be understandable. However, the present regression analysis and the results are useful for predicting the solubility of nabumetone and justifiable.

**CONCLUSION**

Solubility analysis of nabumetone was evaluated in different solvent system to predict solubility behavior and solubility parameter of nabumetone. The solubility parameter of nabumetone from various theoretical methods and experimental method was finalized as -20 MPa$^1/3$ (9.8 H). When the peak solubility is closer to ideal solubility, solubility parameter of a nonpolar drug molecule can be considered at a point that satisfies the condition $X_2 = X_3$ in irregular solutions. The solubility behavior failed to satisfy the ideal solubility and Hildebrand-Scatchard equation (regular solution). Extended Hildebrand approach satisfactorily explains the solubility behavior with the help of polynomial expressions in terms of W and (log γi)/A. Thus solubility of nabumetone in different solvent system gives irregular solution behavior, which is in tune with the nonpolar chemical structure.

**REFERENCES**


Cite this article as: