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Research Article

NABUMETONE IN BINARY SOLVENTS: SOLUBILITY ANALYSIS

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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 '$(\log_{10} \gamma_2)/A$'. These parameters were regressed against a polynomial of δ_1, solubility parameter of solvent blend. Solubility parameter of the nabumetone δ_2 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 solubility[1], chemical kinetics[2], drug action, drug transport kinetics[3,4], structure activity relationship[5], in situ release of theophylline[6], gas-solid chromatography[7], selection of excipients for formulations[8], dosage form technology and design[9], fast prediction of basic properties of materials[10], solvent selection for organic reactions[11], prediction of adhesion of film coating to tablets[12], selection of co-formers for co-crystal formation[13]. 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 Fedors[14], Hoy's and Van Krevelan method[15] 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, regular[2], and irregular solutions[14]. 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 approach[16] . 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)[1,17]. 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 Whattman 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 $mol \cdot L^{-1}$ hydrochloric acid solution and assayed spectrophotometrically (UV- 1700, Shimadzu, Japan) at maximum wavelength of absorption i.e. 330 nm[18]. Nabumetone in 0.01 $mol \cdot L^{-1}$ hydrochloric acid obeys Beer's law in the range of 20 to 100

$\mu g \cdot ml^{-1}$ at 330 nm. The experimental solubility results were recorded as an average of three trials.

Solubility parameter and molar volume of nabumetone

The floatation technique was used to obtain the molar volume of nabumetone experimentally[22] and theoretically by Fedors substituent constants method[16]. The total solubility parameter (δ_2) of nabumetone was calculated by the group contribution methods like Fedors[14], Hoy's and van Krevelan[15]. The solubility parameters of the solvents were taken from the literature[19,20].

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 $ml \cdot min^{-1}$). 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 (X_2^i) of crystalline solid in solvent mixtures was calculated from:

$$-\log_{10} X_2^i = \frac{\Delta S_f}{R} \log \frac{T_0}{T} \quad (1)$$

Where, X_2^i is the ideal mole fraction solubility of solute; ΔS_f, is the entropy of fusion ($kJ \cdot mol^{-1}$), is determined using the relationship $\Delta H_f = T_0 . \Delta S_f$. T_0 is the melting point of the solid solute; T is the temperature of the solution, (25 °C)[19,20].

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 T_0 determined by open capillaries (80-85 ˚C) and DSC fusion temperature (83.6 ˚C) were closer to the literature value of nabumetone (80 ˚C)[18]. The ideal mole fraction solubility of nabumetone was obtained as 0.131467, based on entropy of fusion (eqa.1)[19]. 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.

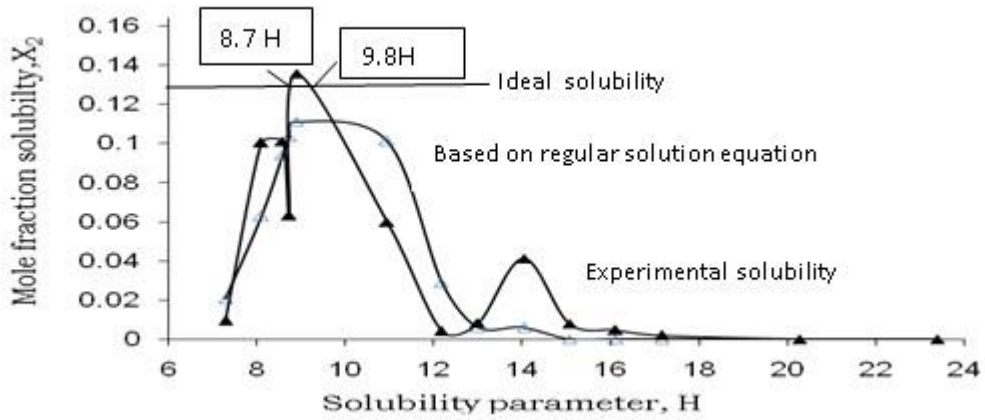

Figure 1: Solubility profiles of nabumetone against solubility parameter of different solvents system.

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[14], Hoy's fragmental constants method and Van Krevelene method[15] and recorded along with experimental results in Table 1. The molar volume estimated from Fedors group contribution method and experimentally was 241.8 $cm^3 \cdot mol^{-1}$ and 224.465 $cm^3 \cdot mol^{-1}$, respectively[16]. 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 $MPa^{1/2}$ (8.9 H) (where $\delta_1 = \delta_2$) (Figure 1).

$$-\log_{10} X_2 = -\log_{10} X_2^i + \frac{V_2 \Phi_1^2}{2.303\ RT} (\delta_1 - \delta_2)^2 \quad (2)$$

where, volume fraction $\Phi_1 = \frac{V_1 (1 - X_2)}{V_1 (1 - X_2) + V_2 X_2}$ (3)

Where, δ_1 and δ_2 are solubility parameters of solvent and solute, respectively, H; V_2 is the molar volume of solute, $cm^3 \cdot mol^{-1}$; Φ_1 is the volume fraction of solvent, 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^i). Consequently, the solubility parameter of solvent (δ_1), can be taken from the graph at the point of peak solubility, which is believed to be equivalent to δ_2, the drug solubility parameter. The δ_2 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)[19,20]. Further, the anthrancene 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[16]. 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 δ value of drug [21], but validity of $X_2 = X_2^i$ is still good in irregular solution[22]. As shown in Figure 1, the ideal solubility curve crosses the graph at two δ values, i.e., 8.7 H (17.79 $MPa^{1/2}$) and 9.8 H (20.04 $MPa^{1/2}$). The δ 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.

Method	Solubility parameter	
	Hildebrand, H	SI units, $MPa^{½}$
Fedor's[a]	10.17	20.80
Hoy's[b]	9.13	18.67
Van Krevelene method[c]	11.67	23.87
From the graph, at condition $X_2 = X_2^i$	9.8 (and 8.7)	17.79 and 20.04
From first derivative plot	9.8	20.04
Experimental peak solubility in different solvent series	8.9	18.20

[a]Estimated from Fedors molar attraction constant [14]
[b]Estimated from Hoys substituent method [15]
[c]Estimated from Van Krevelan method [15]

Further, accurate results were obtained by plotting a first derivative curve (mean δ Vs $\Delta X_1 / \Delta\delta_1$) 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).

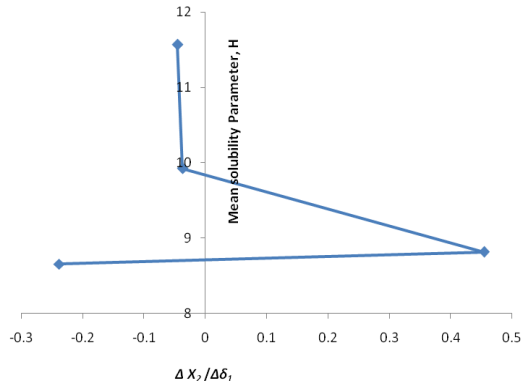

Figure 2: Solubility parameter of nabumetone in different solvents system, first derivative plot

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 Hildebran-Schatchard 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 irrregular behavior of solutions. This approach is partly involve polynomial regression analysis of experimental values, for back ca1culating 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).

$$-\log_{10} X_2 = -\log_{10} X_2^i + A(\delta_1^2 + \delta_2^2 - 2W) \quad (4)$$

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

The 'W' values of nabumetone solubility in different solvent system was regressed against polynomials (quadratic, cubic and quartic) in δ_1 of the solvents. Based on the 'R^2' value and 's' value, the present investigation had chosen quadratic equation (equation 6).

Quadratic equation

$$W = 43.29694 + 0.87437\delta_1 + 0.44014\delta_1^2 \quad (6)$$

n = 14, s = 1.7828, $R^2 = 0.99942$

The equation (6) is not in the standared format, i.e., alternate signs. The distribution of errors is random[23]. 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, $X_{2(calc)}$. 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 $X_{2(calc)}$ and $X_{2(exp)}$ 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

Ratio	δ_1, H	A	W(exp)[c]	W(calc)[a]	X_2(exp) [c]	X_2(calc)[b]	Percent error [d]
Hexane:Ethyl acetate							
100:0	7.3	0.1328132	70.35	73.1347	0.009421	0.051534	-447.035
50:50	8.1	0.0978795	80.2284	79.2567	0.100457	0.064801	35.4913
20:80	8.58	0.0948487	84.2308	83.2003	0.101245	0.064533	36.25771
10:90	8.74	0.1081572	84.7414	84.5599	0.063129	0.057653	8.670852
Ethyl acetate:Ethanol							
100:0	8.9	0.0811128	87.7141	85.9421	0.135912	0.070078	48.43711
50:50	10.95	0.1029870	106.3136	105.6448	0.059883	0.043588	27.20815
20:80	12.18	0.1333208	116.5491	119.2421	0.004100	0.02142	-422.41
Ethanol:Water							
100:0	13	0.1294593	127.8792	129.0469	0.00826	0.016567	-100.564
90:10	14.04	0.1037445	144.1504	142.3336	0.041156	0.017268	58.04183
80:20	15.08	0.1287724	156.9726	156.5724	0.007854	0.006192	21.15174
70:30	16.12	0.1314518	172.4214	171.7633	0.004632	0.003109	32.87698
60:40	17.16	0.1340144	188.4865	187.9063	0.002018	0.00141	30.13956
30:70	20.28	0.1363810	239.3684	242.048	1.66×10^{-5}	8.93×10^{-5}	-439.73
0:100	23.4	0.1363908	306.0054	304.7586	6.45×10^{-6}	2.95×10^{-6}	54.33757

ΔH_f = 8402.6290 cal/mole, melting point = 80°C (353 K), X^i_2 = 0.131467,
Molar volume (V_2) = 182.9278 cm^3/mol, δ_2 = 9.8 H
[a] → As per equation (6)
[b] → As per equation (4)
[c] → Average of three determinations
[d] → Percent error is determined as $[(X_2 \text{ exp} - X_2 \text{ cal})/ (X_2 \text{ exp})] \times 100$

Table 3: Solubility of nabumetone in different solvent system based on (log γ_2)/A, at 25°C*

Ratio	δ_1, H	A	(Log γ_2)/A [c](exp)	(log γ_2)/A (calc)[a]	X_2(exp) [c]	X_2(calc)[b]	Percent error [d]
Hexane:ethyl acetate							
100:0	7.3	0.132813	8.617336	4.66644	0.009421	0.03155	-234.847
50:50	8.1	0.097879	1.193281	3.57422	0.100457	0.05874	41.53031
20:80	8.58	0.094849	1.195640	3.15324	0.101245	0.06602	34.79077
10:90	8.74	0.108157	2.944905	3.05020	0.063129	0.0615	2.585019
Ethyl acetate:Ethanol							
100:0	8.9	0.081113	87.71411	85.94208	0.135912	0.07555	44.41081
50:50	10.95	0.102987	106.3136	105.64482	0.059883	0.05934	0.899992
20:80	12.18	0.133321	116.5491	119.24215	0.0041	0.03073	-649.547
Ethanol:Water							
100:0	13	0.129459	9.2817	6.04812	0.00826	0.02166	-162.24
90:10	14.04	0.103745	4.86074	8.09749	0.041156	0.01899	53.85139
80:20	15.08	0.128772	9.50116	10.49839	0.007854	0.00584	25.59491
70:30	16.12	0.131452	11.05172	13.16934	0.004632	0.00244	47.32043
60:40	17.16	0.134014	13.53251	16.02888	0.002018	0.00093	53.72768
30:70	20.28	0.136381	28.58161	24.92443	1.66×10^{-5}	5.2×10^{-5}	-216.35
0:100	23.4	0.136391	31.58911	32.58464	6.45×10^{-5}	4.7×10^{-5}	26.87167

ΔH_f = 8402.6290 cal/mole, melting point = 80°C (353 K),
X^i_2 = 0.131467, Molar volume (V_2) = 182.9278 cm^3/mol, δ_2 = 9.8 H
[a] →As per equation (7)
[b] →As per equation (8)
[c] →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 ($\log_{10}$ γ_2)/A values obtained from experimental solubilities may be regressed directly against δ_1 bypassing 'W' and obviating the need for δ_2 in the calculations. ($\log_{10}$ γ_2)/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 δ_1 of the solvent blend. Thus ($\log_{10} \gamma_2$)/A values were calculated for each binary mixture (Table 3)

$\log_{10} (X_2^i / X_2) = \log_{10} \gamma_2 = A (\delta_1^2 + \delta_2^2 - 2W)$ (7)

The cubic regressed expression was chosen considering the low solubility.

$(\log_{10} \gamma_2) / A = 43.31162 - 9.54812\delta_1 + 0.67089\delta_1^2 - 0.01207\delta_1^3$ (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 ($\log_{10} \gamma_2$)/A values were calculated and recorded in Table 3. The calculated '($\log_{10} \gamma_2$)/A' values were nearer to '($\log_{10} \gamma_2$)/A' experimental values. The ($\log_{10} \gamma_2$)/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 $MPa^{½}$ (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 $X_2 = X_2^i$ 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 γ_2)/A. Thus solubility of nabumetone in different solvent system gives irregular solution behavior, which is in tune with the nonpolar chemical structure.

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