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Original Article

Prediction of nabumetone solubility in propylene glycol-water mixtures using extended hildebrand solubility approach

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Abstract

Extended Hildebrand solubility approach is used to estimate the solubility of nabumetone in binary solvent systems. The solubility of nabumetone in various propylene glycol-water mixtures was analyzed in terms of solute-solvent interactions using a modified version of Hildebrand-Scatchard treatment for regular solutions. The solubility of nabumetone in the binary solvent, propylene glycol-water, shows a bell-shaped profile with solubility maxima well below the ideal solubility of the drug. 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 propylene glycol-water 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), where δ_1 and δ_2 are the cohesive energy densities for the solvent and solute, respectively. 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 δ_1 of the binary solvent mixture. Quadratic, cubic, and quartic expressions of 'W' in terms of solvent solubility parameter were utilized for predicting the solubility of nabumetone in propylene glycol-water mixtures. But from these three polynomial expressions, a quartic expression of 'W' in terms of solvent solubility parameter was found suitable for predicting the mole fraction solubility and yields an error in mole fraction solubility of ~7.72%, 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.

Key words: Extended Hildebrand solubility approach, propylene glycol, regular solution theory, nabumetone, solubility parameter

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1. Introduction

Solubility data on drugs and pharmaceutical adjuncts in mixed solvents have wide applications in the drug sciences. Knowledge of interaction forces between solutes and solvents are of considerable theoretical and practical interest 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, salvation of the solute by the solvent molecules, or complexation of two or more solute species are involved [3]. Polar systems exhibit irregular solution behavior and are commonly encountered in 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]. The EHSA has been developed to reproduce the solubility of drugs and other solids in the binary solvent systems [6].

Hence, EHSA has been applied to predict the solubility of nabumetone in mixtures of water and propylene glycol (PG). PG is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is completely miscible with water [7]. PG-water mixtures are strongly non ideal and can act in the solute-solvation process via hydrophobic interactions and preferential salvation [8,9].

The Hildebrand-Scatchard equation for the solubility of crystalline solids in a regular solution may be written as [10],

$$[-\log X_2 = -\log X_2^{\,i} + A(\delta_1^{\,2} + \delta_2^{\,2} - 2\delta_1\delta_2)] \quad \ldots\ldots\ldots(1a)$$

$$[-\log X_2 = -\log X_2^{\,i} + A(\delta_1 - \delta_2)^2] \quad \ldots\ldots\ldots(1b)$$

The EHSA enable 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 extended Hildebrand equation for the solubility of solids in an irregular solution may be written as [11,12],

$$[-\log X_2 = -\log X_2^{\,i} + A(\delta_1^{\,2} + \delta_2^{\,2} - 2W)] \quad \ldots\ldots(2)$$

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.

From the geometric mean:

$$\delta_1\delta_2 = \sqrt{\delta_1^2\delta_2^2} \quad \ldots\ldots\ldots(3a)$$

In pharmaceutical solutions, the geometric mean of δ_1 and δ_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 $\delta_1\delta_2$ (Eqn. 1) can be replaced by a less restrictive term '*W*' (Eqn. 2), interaction energy parameter, which is allowed to take on values as required to yield correct mole fraction solubilities, X_2 as [13],

$$W = K\delta_1\delta_2 \quad \ldots\ldots\ldots(3b)$$

Where, K is the proportionality factor relating '*W*' to the geometric mean of solubility parameter.

In Eqn. 1 and Eqn. 2, X_2 and X_2^i are the mole fraction solubility and ideal mole fraction solubility of the solute respectively. The terms δ_1 and δ_2 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 non-polar) mixtures, whereas '*W*' or K δ_1 δ_2 is required to express solubility's in non-regular systems (irregular solutions) of drugs in associating mixed solvents.

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.

The term negative logarithm of the ideal solubility ($-\log X_2^i$) can be taken as [14],

$$[-\log X_2^{\,i}] = \frac{\Delta H_f}{2.303RT}\left(\frac{T_o - T}{T_o}\right) \ldots\ldots\ldots (4)$$

where, ΔH_f is heat 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 [15],

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

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, 298.2^0K, of the experiment and Φ_1, the volume fraction of the solvent, is [16],

$$\phi_1 = \frac{V_1(1 - X_2)}{V_1(1 - X_2) + V_2 X_2} \ldots\ldots\ldots (6)$$

where, V_1 is the molar volume of the solvent at 25^0.

The term logarithmic solute activity coefficient ($\log \gamma_2$) from Eqn. 2 and Eqn. 5 can be written as [17],

$$\log \gamma_2 = A(\delta_1^{\,2} + \delta_2^{\,2} - 2W) = \frac{V_2 \Phi_1^{\,2}}{2.303RT}(\delta_1^{\,2} + \delta_2^{\,2} - 2W) \ldots\ldots\ldots\ldots (7)$$

A better approach is not to restrict the interaction term '*W*' to a geometric mean but evaluate it experimentally from the solubility of the solute in various solvent concentrations in a binary mixture employing Eqn. 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 Eqn. 2 permit the mole fraction solubility of a drug (solute) to be predicted in essentially any solvent mixture. Therefore, the present investigation pertains to the utility of EHSA in relation to the nabumetone solubility in PG-water binary solvent mixtures.

Nabumetone, 4-(6-methoxy-2-naphthyl)-2-butanone, is one of the large series of non-steroidal anti-inflammatory, BCS class II drug [18-20]. It is official in USP [21-24].Nabumetone is a prodrug that undergoes extensive first pass metabolism to 6-methoxy-2-naphthylacetic acid (6-MNA), the major circulating metabolite. 6-MNA is mainly responsible for the therapeutic efficacy of nabumetone. It decreases prostaglandin synthesis via inhibition of cyclooxygenase, an enzyme involved in the arachidonic acid conversion [25]. Though the molecule is found to be effective orally, its therapeutic efficacy is hindered due to poor aqueous solubility [26]. The poor aqueous solubility and wettability of nabumetone give rise to difficulties in pharmaceutical formulations

meant for oral or parenteral use, which may lead to variation in absorption and bioavailability [27, 28].

2. Materials and Methods

Nabumetone, obtained as gift sample from GlaxoSmithKline Pharmaceuticals Ltd. Nasik, India. PG was purchased from Research Lab Fine Chemical Industry, Islampur, India. Throughout the study freshly prepared 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, SICAN 2301 with spectral bandwidth of 2 nm, wavelength accuracy ± 0.5 nm and a pair of 10 mm matched quartz cells was used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing of nabumetone. Differential Scanning Calorimeter, Shimadzu TA-60 WS, was used for determination of melting point and heat of fusion of nabumetone.

2.1 Solubility measurements:

Solubilities of nabumetone (δ_2 =11.35) were determined in binary solvent mixtures of PG (δ_{PG} = 14.80) and water (δ_W = 23.45). Double distilled water was used to prepare mixtures with PG in concentrations of 0-100% by volume of PG. About 10 ml of PG, water, or binary solvent blends were placed into screw-capped vials (Thermostated at 25^0 and under continuous magnetic stirring) containing an excess amount of nabumetone 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 25^0 [29].

After equilibration, the solutions were 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 nabumetone (λ_{max}-262 nm). Calibration graphs of nabumetone in each solvent blend were previously established with correlation coefficients greater than 0.996. The working concentration range was from 10 to 50 µg/ml nabumetone. All experimental results were expressed as the average of at least three determinations. The coefficient of variation (SD/mean*100) was within 2% among replicated samples for the solubility measurements. The densities of the blends and the filtrates of saturated solutions were determined at 25 ± 0.4^0 using 25-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 [30,31]. The molar volume (V_2) and solubility parameter of nabumetone were estimated previously by Fedor's group substitution method [32, 33] giving 241.8 cm^3/mol and 10.1689 $(cal/cm^3)^{0.5}$ which was confirmed by solubility analysis in dioxane-water blend.

2.2 Differential scanning calorimeter:

The thermogram of nabumetone was obtained with a differential scanning calorimeter [34]. The melting point and heat of fusion were measured. Sample was scanned at the heating rate of 20^0/min under nitrogen purge. The temperature range studied was $70\text{-}300^0$.

3. Results and Discussion

3.1 Mole fraction solubility and Solubility parameter:

The molar enthalpy of fusion of nabumetone was 142.44 J/g (7771.713 cal/mol) and the temperature of fusion is 355^0K. Neither decomposition nor polymorphic change was observed at the experimental temperature range. The ideal mole fraction solubility of nabumetone was calculated from these values ($-\log X_2^i$ = 0.8375). The mole fraction solubilities of nabumetone at 25 ± 0.4^0 in PG-water binary mixtures which cover a large range of the solubility parameter scale, from 14.80 to 23.45 $(Cal/cm^3)^{0.5}$, are listed in Table 1. The experimental mole fraction solubility of nabumetone at 25 ± 0.4^0 in PG-water mixtures is

plotted in fig. 1 versus the solubility parameter, δ_1, of the various mixed solvent systems. The mole fraction solubility of nabumetone in PG (δ_1 = 14.80), water (δ_1 = 23.45), and in the mixture of the two solvents is represented by the solid circles in fig. 1. The maximum solubility of nabumetone in the mixture is X_2 = 0.00086434 mol/l and occurs at δ_1 = 15.67. This value is well below the ideal solubility, X_2^i = 0.145386 mol/l, as predicted from regular solution theory. The discrepancy between the results using the original Hildebrand-Scatchard equation and experimental points demonstrates that Eqn. 1a and Eqn. 1b cannot be used to predict drug solubility in PG-water 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*'.

3.2 Solubility prediction using regression of '*W*' versus δ_1:

Eqn. 2, differs from Eqn. 1, in that the geometric mean is not used, hence 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 δ_1 of the PG-water binary solvent mixtures (fig. 2). Following quadratic, cubic, and quartic equations respectively were obtained using the experimental solubility data for nabumetone in PG-water mixtures:

W_{obs} = 46.291252 + 0.528610 δ_1 + 0.461168 δ_1^2 (n = 11, R^2 = 0.999956) ----- (8),

W_{obs} = -71.518715 + 19.47415 δ_1 – 0.541620 δ_1^2 + 0.017478 δ_1^3 (n = 11, R^2 = 0.999985) ----- (9),

W_{obs} = -742.263995 + 163.495560 δ_1 – 12.035029 δ_1^2 + 0.421564 δ_1^3 – 0.005282 δ_1^4 (n = 11, R^2 = 0.999998) ----- (10)

The 'W_{cal}' values calculated using these expressions compared favorably with the original '*W*obs' values computed using Eqn. 2. The solid line plotted in fig. 2 was obtained employing the quartic expression (Eqn. 10). The calculated solubility curve fits the experimental data points quite well (figs. 1 and 3), predicting the solubility of nabumetone in PG-water mixtures at most points within an error of ~7.72%, approximating the error in experimentally determined solubility values. These polynomials are used successfully for the calculation of '*W*cal', at any value of solubility parameter (δ_1), which was then subsequently employed to calculate mole fraction solubility of solute (X_{2cal}) in a solvent blend using backward regression. Representative data along with validation parameters are summarized in Table 1. 'W_{cal}' values are indicating the significant interaction of nabumetone and solvent molecules at the peak of solubility profile.

Validation of Eqn. 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 nabumetone is represented in fig. 3, which indicates a very high degree of correlation coefficient (R^2) 0.9977 and negligible intercept equal to zero.

A careful scrutiny of the behaviour of the solutions of nabumetone in PG-water mixtures may be performed, comparing the value of the interaction term 'W_{obs}' at each experimental point with the regular value ($\delta_1\delta_2$). This comparison is presented also in Table 1. As can be observed, for volume fractions of PG from 0 to 1, $W > \delta_1 \delta_2$. But, for volume fractions of PG from 0 to 0.6, '*W*' is far greater than $\delta_1\delta_2$ and for volume fractions of PG from 0.7 to 0.9, '*W*' is nearby closer to $\delta_1\delta_2$. It may be assumed that nabumetone solutions can behave as regular solutions at some point ($W = \delta_1\delta_2$) with 1.0 PG volume fraction.

Table 1: Mole fraction solubility of nabumetone

Φ_{PG}	Solubility (g/ml)	δ_1 $(Cal/cm^3)^{0.5}$	V_1	Density of blend	Mol. Wt of blend	$X_{2(obs)}$	$W_{(obs)}$	$\delta_1\delta_2$
0.0	0.000017	23.45	18.00	0.9980	18.00	1.3431E-06	312.46	238.46
0.1	0.000031	22.59	23.55	1.0018	23.81	3.2275E-06	293.62	229.66
0.2	0.000051	21.72	29.09	1.0056	29.62	6.5806E-06	275.33	220.87
0.3	0.000068	20.86	34.64	1.0094	35.43	1.0456E-05	257.48	212.07
0.4	0.000126	19.99	40.18	1.0132	41.24	2.2467E-05	240.75	203.28
0.5	0.000285	19.13	45.73	1.0170	47.05	5.7769E-05	224.99	194.48
0.6	0.000559	18.26	51.27	1.0208	52.86	1.2685E-04	209.78	185.68
0.7	0.001142	17.40	56.82	1.0246	58.67	2.8668E-04	195.35	176.89
0.8	0.002038	16.53	62.36	1.0284	64.48	5.6053E-04	181.49	168.09
0.9	0.002892	15.67	67.91	1.0322	70.29	8.6434E-04	168.08	159.30
1.0	0.001904	14.80	73.45	1.0360	76.10	6.1339E-04	154.50	150.50

δ_1= Solubility parameter of solvent blend, δ_2= Solubility parameter of drug, V_1= molar volume of the solvent blend, Φ_1= total volume fraction of solvent blend and W is calculated from Eqn. 2.

Table 2: Experimental and calculated mole fraction solubilities

$W_{(obs)}$	$W_{(cal)}$	$X_{2(obs)}$	$X_{2(cal)}$	$\log\gamma_2/A_{(obs)}$	$\log\gamma_2/A_{(cal)}$	Residual	Percent Residual
312.4579	312.5336	1.3431E-06	1.4288E-06	28.39332	28.24176	-6.383E-02	-6.38E+00
293.6210	293.6422	3.2275E-06	3.2838E-06	26.24672	26.20438	-1.744E-02	-1.74E+00
275.3311	275.2873	6.5806E-06	6.3495E-06	24.50277	24.59030	3.510E-02	3.51E+00
257.4841	257.6495	1.0456E-05	1.1968E-05	23.36941	23.03859	-1.446E-01	-1.45E+01
240.7541	240.8382	2.2467E-05	2.4063E-05	21.49834	21.33025	-7.102E-02	-7.10E+00
224.9905	224.8920	5.7769E-05	5.3307E-05	19.19119	19.38820	7.724E-02	7.72E+00
209.7803	209.7784	1.2685E-04	1.2666E-04	17.27361	17.27732	1.510E-03	1.51E-01
195.3497	195.3941	2.8668E-04	2.9724E-04	15.29319	15.20443	-3.681E-02	-3.68E+00
181.4872	181.5646	5.6053E-04	5.9690E-04	13.67295	13.51829	-6.489E-02	-6.49E+00
168.0842	168.0446	8.6434E-04	8.3701E-04	12.63040	12.70958	3.162E-02	3.16E+00
154.4997	154.5178	6.1339E-04	6.2248E-04	13.44712	13.41094	-1.482E-02	-1.48E+00

W_{cal} obtained from quartic Eqn. 10, for Nabumetone in PG-water mixtures at 25±0.4^0. Residuals can also be obtained from, $[(X_{2(obs)}-X_{2(cal)})/ X_{2(obs)}]$.

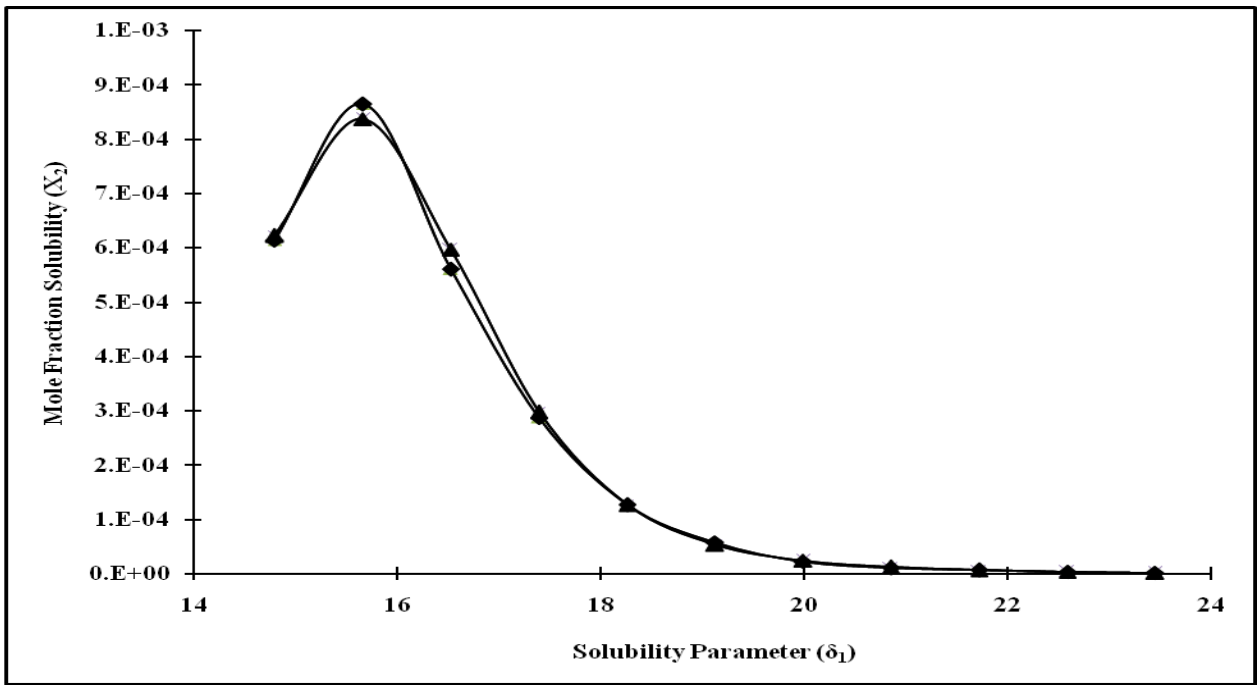

Fig. 1: Solubility parameter versus mole fraction solubility profile.
Key: ◆ Experimental solubilities (X_{2obs}) and Δ back-calculated solubilities (X_{2cal}) from Eqn. 2. Highest mole fraction solubility obtained is, $X_{2obs} = 8.6434*10^{-4}$ and $X_{2cal} = 8.3701*10^{-4}$ when $\delta_1 = 14.80$ $(Cal/cm^3)^{0.5}$ in PG-water mixtures.

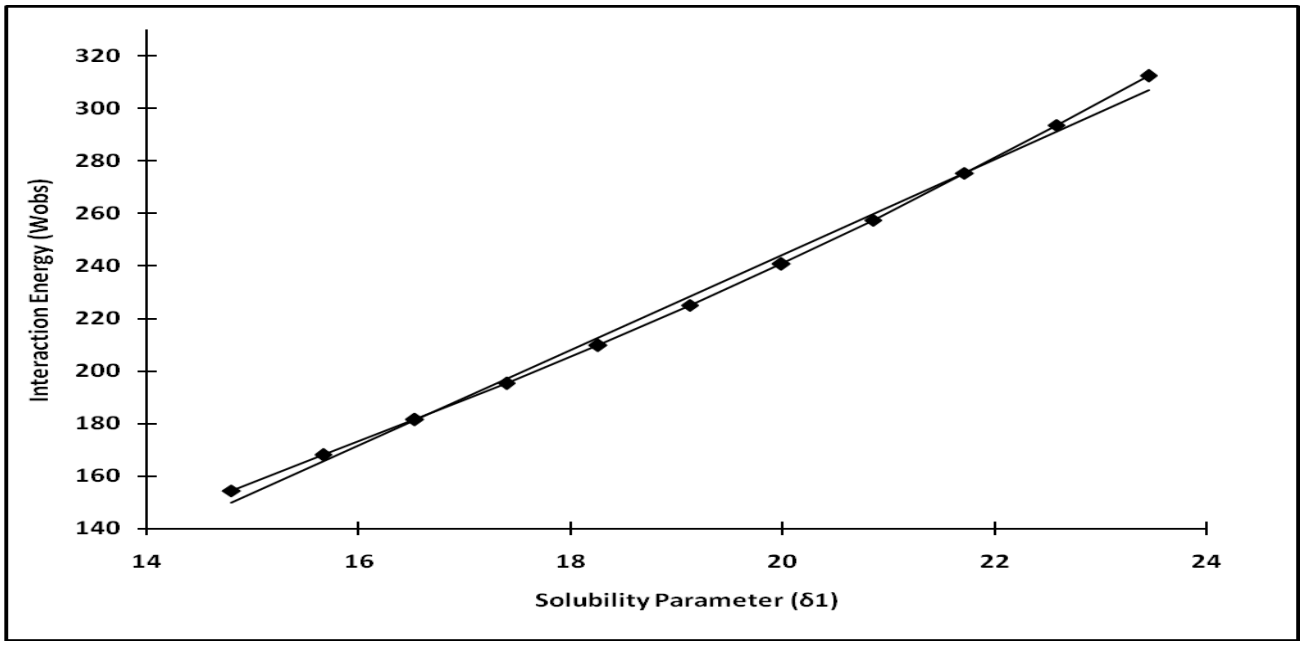

Fig. 2: Solubility parameter versus interaction energy profile.
$W_{(cal)}$ obtained from quartic regression Eqn. 10, for nabumetone in PG-water mixtures at 25 ± 0.4^0 and correlation coefficient, r^2, is 0.999998 for n = 11.

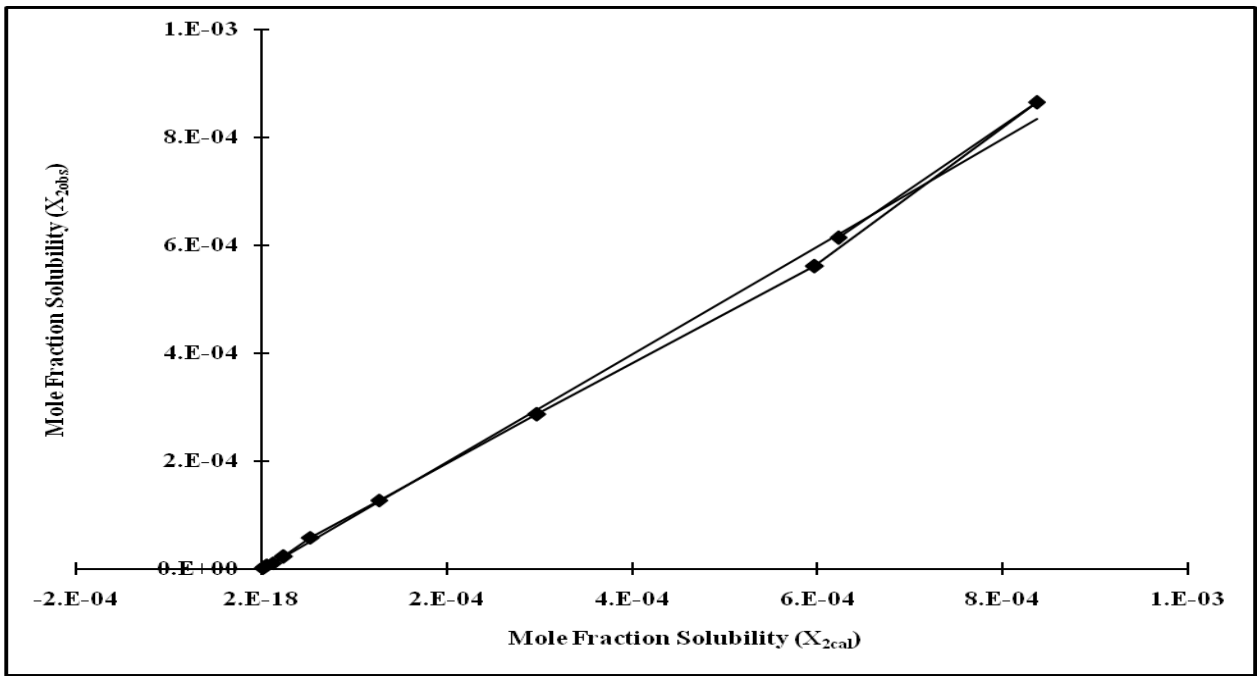

Fig. 3: Comparison of observed and calculated mole fraction solubility.
Comparison of 11 observed nabumetone solubilities in PG-Water systems at 25±0.4^0 with solubilities predicted by extended Hildebrand approach. The intercept of the line is zero, and the slope is 0.9989. The correlation coefficient, r^2, is 0.9977 for n = 11.

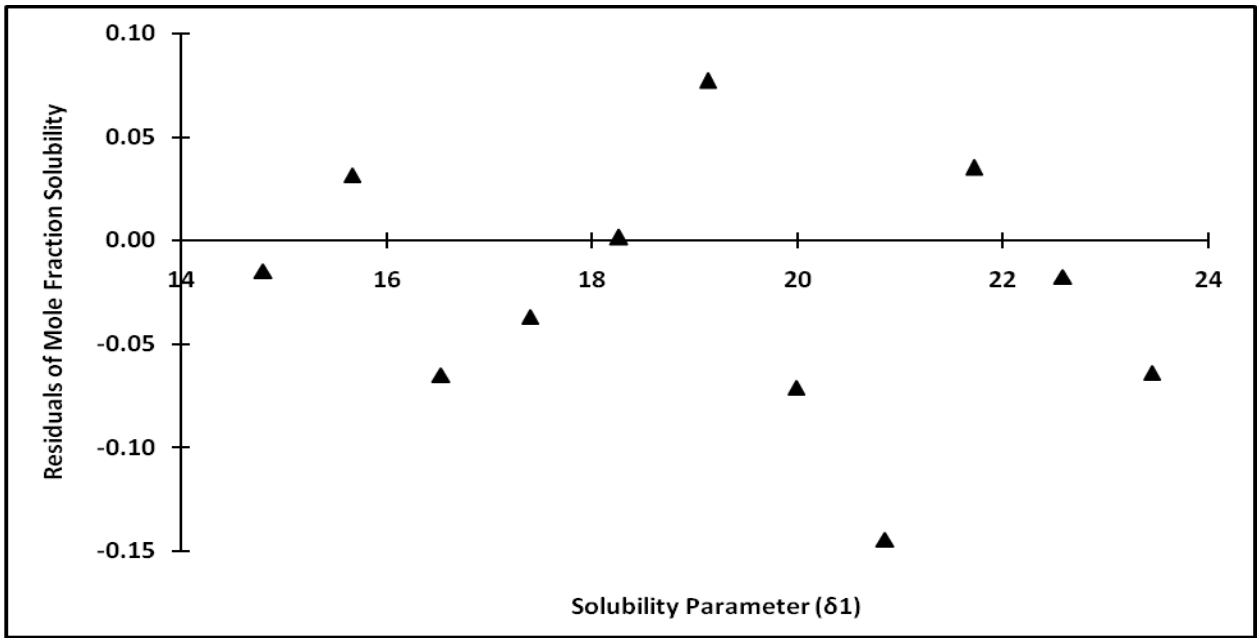

Fig. 4: Scatter plot of residuals of solubility versus solubility parameter.

Thus, in water-rich mixtures (0-0.6) there seems to be some kind of association between nabumetone 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 neighborhood of nonpolar groups in water. When adding PG, HH breaks down. The endothermic shift of the enthalpies of solution upon small additions of cosolvent to water is known to appear for hydrophobic solutes like nabumetone.

Conversely, in water poor mixtures (0.7-1.0) self association of solvent, solute or both is not obtained because still 'W_{obs}' is far greater than $\delta_1\delta_2$. This behavior may remain as such in rich PG blends, and therefore, the corresponding nabumetone solubilities are still higher than regular one.

Another aspect for assessment of extended Hildebrand solubility approach is to plot residuals of solubility versus solubility parameter for PG-water binary mixtures (fig.4), which shows values of residuals are closer to zero and scattered around a line with zero slope.

Conclusion

EHSA employs a power series (quartic) equation in δ_1 to back-calculate interaction energy term 'W_{cal}', which reproduces the solubility of nabumetone in PG-water mixtures within the accuracy ordinarily achieved in such experimental solubility results. On the basis of validation parameters, it can be further expressed that the behaviour of irregular solution can be quantified more precisely using EHSA. The procedure can be explored further to predict the solubility of nabumetone in any other binary solvent 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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