

**EXTENDED HANSEN'S SOLUBILITY APPROACH:
MELOXICAM IN INDIVIDUAL SOLVENTS**

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ABSTRACT

The solubility behaviour of meloxicam in individual solvents ranging from non-polar to highly polar was studied. For understanding the solute-solvent interactions, partial solubility parameters concept was utilized. The extended Hansen's method was used for analyzing the solubility data and for obtaining partial solubility parameters of meloxicam. The analysis was not successful though correlations were 81%. The Flory-Huggins size correction term 'B' was found to improve the prediction of solubility. The correlations were high (92%) and total solubility parameter was 11.6 H. The four-parameter approach involving proton-donor and proton-acceptor parameters was also used in fitting the solubility data. The correlations were appreciable (87%) and total solubility parameter was 11.2 H. The term 'B' combined with four-parameter approach was also used in order to improve the data, and was found to be improved the correlations ($R^2 = 0.94$). This new approach may thus be used in fitting the experimental solubility data and to predict solubility behaviour of meloxicam in untested solvents. The total solubility parameter of meloxicam was assigned at 11.2 H.

Keywords: Meloxicam; solubility behaviour; Extended Hansen,s approach; Flory-Huggins size correction; partial solubility parameters.

INTRODUCTION

The solubility parameter, δ_r is an intrinsic physicochemical property of a substance, which has been used to explain drug action (Mullins, 1954), structure activity relationship (Khalil *et al.*, 1976a; Khalil *et al.*, 1976b), drug transport kinetics (Khalil and Martin, 1967), *in situ* release of drug (Adjei *et al.*, 1984), gas solid chromatography (Phuoc *et al.*, 1986), swelling of polymer (Javier *et al.*, 2005), and HPLC (Wells, 1988). It has been suggested that the solubility parameter is a possible substitute for partition coefficient in the study of the passage of drugs across living membranes (Khalil *et al.*, 1976a; Khalil *et al.*, 1976b).

Hansen defined three partial parameters, δ_d representing the London dispersion forces, δ_p representing the Keesom dipolar interactions, and δ_h representing the generalized electron transfer bonding including hydrogen bonding and acid base interaction (Hansen, 1967). These are related by the expression:

$$\delta_r^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

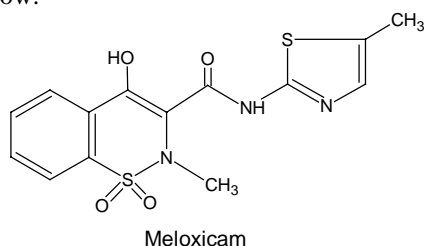
where δ_r is the total solubility parameter and is quite similar to the δ as defined by Scatchard and Hildebrand (Adjei *et al.*, 1980). The partial solubility parameters of solvents are found to play a role in the solubilization of the drug molecules, which in turn depends on the drug's chemical structure and its solubility parameter. However, the partial solubility parameters have not been more widely employed in pharmacokinetics and structure activity studies. The extended Hansen's approach, the Flory-Huggins size correction term, and the four-parameter approach were the methods proposed to obtain partial solubility parameters of crystalline drug substances, thereby predicting their solubilities in solvents normally encountered in pharmacy, either in formulation or in pharmaceutical analysis (Martin *et al.*, 1981; Beerbower *et al.*, 1984).

The solubility parameter, δ_r has been applied for predicting the solubility of drugs in solvents and cosolvents, theoretically. In this context, it is proposed that the closer the δ_r values of drug and that of solvent, the higher would be its solubility (Martin and Mauger, 1988). The bifurcation of total solubility parameter (δ_r) of drug into partial solubility parameters may provide greater insights on interactions, though such correlations

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are not explored, because there are a few methods for the determination, which can be applied to the drug molecules.

Meloxicam, [4-hydroxy-2 methyl-N-(5-methyl-2-thiaoly)-2H-1,2 benzothiazine-3-carboxamide 1,1-dioxide], is a highly effective non-steroidal anti-inflammatory drug (NSAID) used to treat rheumatoid arthritis, osteoarthritis, and other joint pains. It is a preferential cyclooxygenase (COX)-II inhibitor and has a superior gastro intestinal tolerability (Sameer *et al.*, 2005). Meloxicam has a poor aqueous solubility and wettability, and has a very poor dissolution in aqueous fluids especially in acidic medium, which pose difficulties in the design of pharmaceutical formulations thereby leads to variability. Many studies have been performed on improving dissolution and bioavailability of meloxicam such as preparation of complexes with β -cyclodextrins (Ghorab *et al.*, 2004). The structure of meloxicam is given below.



A perusal to the structure of meloxicam indicates that the molecule is highly aromatic and the functional groups may not contribute much to the aqueous solubility. It is necessary to evaluate relative contribution of nonpolar, polar, and hydrogen bonding, rather than evaluating the gross behaviour of its total solubility parameter. Thus, meloxicam is an ideal candidate for the study of solubility behaviour.

The aim of this communication is to report the solubility behaviour of meloxicam in individual solvents ranging from nonpolar (eg. hexane), semipolar (eg. benzene), through amphiprotic (e.g., alcohol, propylene glycol, and water) to dipolar aprotic (eg. N, N-dimethylformamide and dimethylsulfoxide). Different approaches were used to analyse the experimental solubility, so that the meloxicam solubility was calculated in untested solvents using regressed equations. The additional support was obtained from the theoretical methods, namely fragmental constants (Fedors, 1974; Hoy, 1970) for total solubility parameter and partial solubility parameters (Barton, 1983) of meloxicam.

MATERIALS AND METHODS

Meloxicam was as a gift sample (Dr. Reddy labs, Hyderabad). Solvents and other chemicals were of analytical grade. The heat of fusion was determined calorimetrically by differential scanning calorimeter

(Perkin Elmer DSC 7). The melting point was determined in open capillaries. From the above data, ideal mole fraction solubility (X_2^i) is calculated using entropy of fusion expression and found to be 0.000084978 or $\log X_2^i$ is -4.0707 . The solubility of meloxicam was determined in a number of solvents (table 1). The solutions containing excess drug were shaken in a constant temperature shaker water bath held at $25 \pm 0.5^\circ\text{C}$ (Research and Test equipment, Bangalore). The solutions are filtered after attaining equilibrium (72 h) using filters of pore size 0.2μ (millipore) and meloxicam content was estimated using double beam UV- visible spectrophotometer (Shimadzu, Japan). The physico-chemical properties of solvents were taken from literature (Hansen and Beerbower, 1971). The solubility parameter value of meloxicam was calculated using Fedors, Hoy's, and partial solubility parameter values of meloxicam were also calculated.

The absorption spectrum of meloxicam in 0.1 N hydrochloric acid solution was obtained ($\lambda_{\text{max}} - 345 \text{ nm}$). The calibration curve was constructed and Beer's law obeyed in the concentration range of $2 - 14 \mu\text{g/mL}$. The densities of the saturated solutions were determined in a 25 mL specific gravity bottle. Analyses were done in triplicate. The molar volume was determined experimentally by the floatation technique (Beckett and Stenlake, 1986). For solubility calculations, the necessary in-house software was developed using BASIC. The multiple regression analysis was performed on Lotus 1-2-3. The parameter 's' represents the standard error of the 'y' estimate and the confidence level of 99%.

RESULTS AND DISCUSSION

The extended Hansen's method, the three-parameter approach, has been proposed to obtain partial solubility parameters of crystalline drug compounds (Beerbower *et al.*, 1984). The extended Hansen's model is written as:

$$\frac{1}{A} \log \frac{X_2^i}{X_2} = \frac{\log \gamma_2}{A} = C_0 + C_1(\delta_{1d} - \delta_{2d})^2 + C_2(\delta_{1p} - \delta_{2p})^2 + C_3(\delta_{1h} - \delta_{2h})^2 \quad (2)$$

$$A = \frac{V_2 \phi_1^2}{2.303RT} \quad (3)$$

$$\phi_1 = \frac{V_1(1 - X_2)}{V_1(1 - X_2) + V_2 X_2} \quad (4)$$

where X_2^i is the solute ideal mole fraction solubility, X_2 is the experimental observed mole fraction solubility, γ_2 is the activity coefficient of the solute, and C_i (where $i = 1, 2, 3$) values are regression coefficients obtained from regression analysis. C_0 is a constant. Throughout this paper, 1 is referred to the solvent and 2 is referred to the solute. This method was successfully adopted for drugs

such as sulfamethoxy pyridazine (Bustamante *et al.*, 1989), haloperidol (Subrahmanyam and Sarasija, 1999), and trimethoprim (Subrahmanyam *et al.*, 1996).

Group contribution method was used for calculation of partial solubility parameters values of meloxicam were obtained (Barton, 1983). The data were reported in Table 1. The experimental solubilities of meloxicam in individual solvents and other associated parameters are recorded in the Table 2. When the extended Hansen's approach was applied to the experimental solubilities of meloxicam the following regression equation was obtained:

$$\frac{(\log \gamma_2)}{A} = 63.27 - 12.0\delta_{1d} + 0.54\delta_{1d}^2 - 2.02\delta_{1p} + 0.09\delta_{1p}^2 + 0.11\delta_{1h} + 0.03\delta_{1h}^2 \quad (5)$$

$$n = 27; s = 3.05; R^2 = 0.66$$

The signs of coefficients were not agreeing with the standard format of equation (2). Hence it is not possible to calculate the partial solubility parameters. Further, the regression coefficient was low ($R^2 = 0.66$). Therefore, the analysis was repeated by excluding four solvents, (cyclohexane, ethylacetate, acetophenone, and glycerin), which showed a high percent error in the calculated solubility using the equation (5). For the rest of solvents, the regression was obtained as given below:

$$\frac{(\log \gamma_2)}{A} = 92.68 - 18.02\delta_{1d} + 0.83\delta_{1d}^2 - 3.42\delta_{1p} + 0.25\delta_{1p}^2 + 0.68\delta_{1h} - 0.001\delta_{1h}^2 \quad (6)$$

$$n = 23; s = 2.09; R^2 = 0.81$$

The signs of coefficients were agreeing with the standard format of equation (2). The regression coefficient was improved by 15% ($R^2 = 0.81$) in comparison with the equation (5). The equation (6) was written according to the model expression represented by the equation (2) and partial solubility parameters obtained were; $\delta_{2d} = 10.92$ H, $\delta_{2p} = 6.76$ H, and $\delta_{2h} = 241.1$ H. Since hydrogen bonding partial solubility parameter is high ($\delta_{2h} = 241.1$ H), it is not appropriate to calculate total solubility parameter, δ_{2T} , though correlation coefficient is appreciable ($R^2 = 0.81$). This gives the *prima facie* evidence of anomalous behaviour of meloxicam. Empirically the coefficients of δ_{1h} and δ_{1h}^2 must be differed by one decimal place, the later being lower. The differences between the experimental and the calculated solubility values were found to be high, the error ranging from - 238 to 77%. Such a large error is possible as the meloxicam is poorly soluble. There was a need to improve the correlations by different methods.

The three-parameter approach was modified using the Flory-Huggins size correction 'B' (Subrahmanyam and Sarasija, 1999). This term accounts for the deviation of a

drug solution from the regular solution behaviour, because of the specific solute-solvent interactions, if any, and size difference between solute and solvent (Martin and Mauger, 1988), 'B' can be written as follows:

$$B = \frac{RT[\ln \gamma_2 - \ln(V_2/V_1) - 1 + (V_2/V_1)]}{V_2\phi_1^2}$$

'B' can be incorporated into the regression model as follows.

$$B = D_1\delta_{1d} + D_2\delta_{1d}^2 + D_3\delta_{1p} + D_4\delta_{1p}^2 + D_5\delta_{1h} + D_6\delta_{1h}^2 + D_o \quad (8)$$

The equation (8) can also be transformed into an expression analogous to the equation (2). This method was successfully applied for the drugs such as haloperidol and trimethoprim. The Flory-Huggins size correction approach for the meloxicam in individual solvents was attempted. In order to improve the correlation coefficients and for a better fit of experimental values. The following equation was obtained:

$$B = 159.84 - 33.99\delta_{1d} + 1.81\delta_{1d}^2 - 2.27\delta_{1p} + 0.18\delta_{1p}^2 - 0.48\delta_{1h} + 0.1\delta_{1h}^2 \quad (9)$$

$$n = 27; s = 2.33; R^2 = 0.92$$

The equation (9) was found to have better correlation by 11% when compared to the equation (6). The signs of coefficients were agreeing with the standard format of the equation (2). The equation (9) was written according to the model expression represented by the equation (2) and partial solubility parameters obtained were; $\delta_{2d} = 9.39$ H, $\delta_{2p} = 6.48$ H, and $\delta_{2h} = 2.44$ H. The total solubility parameter, δ_{2T} , was calculated using the equation (1) and found to be 11.67 H. This δ_{2T} value was agreeing with the values obtained from other methods (table 1). When the 'B' value, obtained from the equation (9) was used in calculating mole fraction of meloxicam solubility in different solvents. The estimated solubility was higher than the experimental solubility. The error between experimental and calculated values was higher. It was coincidence to note the error is same in most of the solvents. Since the size correction for differences in molar volumes of meloxicam and solvents were adjusted, there was a need to verify the proton donor-acceptor type of interaction.

In order to improve the correlation, the four-parameter approach (Sameer *et al.*, 2005) was adopted. This approach was based on the principle that the parameter δ_{2h} does not reflect the proton donor-acceptor characteristics of complex organic molecules. Therefore, δ_a proton donor and δ_b proton acceptor parameters were used to replace δ_h in the regression analysis and the following equation was proposed:

$$\frac{(\log \gamma_2)}{A} = (\delta_{1d} - \delta_{2d})^2 + (\delta_{1p} - \delta_{2p})^2 + 2(\delta_{1a} - \delta_{2a})(\delta_{1b} - \delta_{2b}) \quad (10)$$

Table 1: Solubility parameter values for meloxicam by different methods.

S. No.	Method/system	Solubility parameter	
		H, Hildebrand (CGS units)	MPa ^{1/2} , Mega Pascal (SI units)
1	Fedors ^a	12.42	25.34
2	Hoy's ^b	11.05	22.54
		$\delta_{2T}(\delta_d^2, \delta_p^2, \delta_h^2)$	$\delta_{2T}(\delta_d^2, \delta_p^2, \delta_h^2)$
3	Group contribution method ^c	10.33 (7.68, 3.54, 5.93)	21.07 (15.67, 7.22, 12.1)
4	Flory-Huggins size correction term B^d	11.67 (9.39, 6.48, 2.44)	23.81 (19.16, 13.22, 5.0)
5	Four-parameter approach with $\log(\gamma_2/A)^e$	11.20 (9.01, 6.25, 2.3)	22.85 (18.38, 12.75, 4.69)
6	Four-parameter approach with B^{e*}	11.22 (9.07, 5.75, 3.25)	22.89 (18.5, 11.73, 6.63)

^aEstimated from the Fedors molar attraction constants.

^bEstimated from the Hoy's substituent method.

^cEstimated from the fragmental constants for partial parameters.

^d $\log(\gamma_2/A)$ replaced by B , in three parameter approach, Equation (9).

^{e&e*}Extended Hansen's approach, Equations (11&12).

where δ_{1a} , δ_{1b} and δ_{2a} , δ_{2b} are acid and base partial solubility parameters of solvent and solute, respectively. The expansion of the equation (10) gives an equation, which can be used to predict solubility of a compound in various individual solvents, similar to the equation (8). This type of regression equation was obtained by processing the solubility parameters of the solvents (Martin *et al.*, 1981). In the case of naphthalene, there was an improvement in the regression coefficient (Sameer *et al.*, 2005).

The four-parameter approach was used to improve the correlation. Since the relevant parameters for methyl acetate was not available in the literature, the remaining 26 solvents were considered for regression analysis. The following equation was obtained:

$$\frac{(\log \gamma_2)}{A} = 190.03 - 42.04\delta_{1a} + 2.33\delta_{1a}^2 - 3.02\delta_{1p} + 0.24\delta_{1p}^2 + 0.08\delta_{1a} - 0.91\delta_{1b} + 0.17\delta_{1a}\delta_{1b} \quad (11)$$

$$n = 26; s = 1.94, R^2 = 0.87$$

The equation (11) was found to have better R^2 value (0.87) and the standard error of 'y' estimate was less compared to the equation (6). The signs of coefficients were agreeing with the standard format of the equation (10). From the equation (11), the partial solubility parameter values obtained were; $\delta_{2d} = 9.01$ H, $\delta_{2p} = 6.25$ H, $\delta_{2a} = 5.31$ H, and $\delta_{2b} = 0.5$ H. The δ_{2h} value was calculated from δ_{2a} and δ_{2b} values and was found to be 2.30 H and δ_{2T} was 11.2 H. This value was closer to the δ_{2T} value obtained by other methods (table 1).

Till today, the Flory-Huggins size correction approach and the four-parameter approach were considered separately for drawing correlation. In this article, an attempt was made to combine these two approaches empirically, as both involved statistical analysis only. In other words, the equation (11) was modified by replacing $(\log \gamma_2)/A$ with 'B' term (as observed in the equation 10). The following regression equation was obtained:

$$B = 201.95 - 44.13\delta_{1a} + 2.43\delta_{1a}^2 - 2.55\delta_{1p} + 0.22\delta_{1p}^2 - 0.48\delta_{1a} - 0.9\delta_{1b} + 0.29\delta_{1ab} \quad (12)$$

$$n = 26; s = 2.09; R^2 = 0.94$$

A perusal to the equation (12) indicated that the regression coefficient (R^2) was found to higher by 3%. Further, the signs of coefficients were agreeing with the standard format. From the regression equation (12), the partial solubility parameters obtained were; $\delta_{2d} = 9.07$ H, $\delta_{2p} = 5.75$ H, $\delta_{2a} = 3.14$ H, and $\delta_{2b} = 1.68$ H. The δ_{2h} value was calculated from δ_{2a} and δ_{2b} values and was found to be 3.25 H and δ_{2T} was 11.22 H. This value was almost similar to the value obtained from four-parameter approach alone. Thus, the combination of four-parameter approach with Flory-Huggins size correction 'B' was proved to be successful in improving analysis. This observation is encouraging.

CONCLUSIONS

The solubility behaviour of meloxicam was evaluated and the results were analysed in the light of existing systems of data analysis with reference to the partial solubility parameters. As expected, meloxicam exhibited irregular

Table 2: Mole fraction solubility of meloxicam in the individual solvents at 25°C: Partial solubility parameters – Four-parameter approach with Flory-Huggins size correction term.

Solvent	Molar volume (V_1)	Total solubility parameter (δ_T)	$\log \gamma_2/A$ (exp)	B (exp)	X_2 (exp)	X_2 (calc) equation 12	Percent error
Hexane	131.6	7.3	4.9768	5.79761	7.701E-06	1.1E-05	-43.2502
Cyclohexane	108.7	8.2	6.1023	7.47501	4.474E-06	3.8E-05	-749.738
Butyl acetate	132.5	8.5	-3.1959	-2.3902	0.0003961	0.000625	-57.7952
Carbontetrachloride	97.1	8.7	0.6651	2.45544	6.166E-05	-0.00259	4303.863
Toluene	106.8	8.9	-1.4361	-0.0017	0.0001698	-5.7E-05	133.5757
Ethyl acetate	98.5	8.9	1.8531	3.58212	3.476E-05	0.000127	-265.787
Benzene	89.4	9.1	-1.3284	0.81762	0.0001612	-5.4E-05	133.7318
Chloroform	80.7	9.3	-6.4262	-3.7462	0.001814	-2.1E-05	101.1722
Acetone	74.0	9.8	-4.0891	-0.9438	0.0006055	-2.5E-05	104.1213
Dioxane	85.7	10.0	-6.3997	-4.0293	0.001796	-1.5E-05	100.8379
<i>n</i> -Octanol	158.7	10.23	-2.6787	-2.2378	0.000309	-6.5E-05	121.0348
<i>n</i> -Heptanol	141.9	10.28	-2.0292	-1.3783	0.000226	-7.3E-05	132.1305
<i>n</i> -Hexanol	125.2	10.41	-1.0056	-0.0575	0.000138	-0.00011	176.8303
<i>n</i> -Pentanol	108.6	10.59	-0.5163	0.86026	0.000109	0.000457	-319.174
Acetophenone	117.4	10.63	-6.9081	-5.7670	0.0022946	-1.4E-05	100.6086
<i>n</i> -Butanol	91.5	11.3	0.07313	2.11413	8.803E-05	0.001963	-2129.61
Isopropyl alcohol	76.9	11.5	1.5987	4.50805	3.93E-05	0.000176	-348.481
Benzyl alcohol	103.9	11.64	-6.437	-4.8907	0.0018386	-1.9E-05	101.0168
<i>n</i> -Propanol	75.2	12.0	0.8788	3.91637	5.562E-05	0.00049	-781.53
Dimethylformamide	77.0	12.1	-12.172	-8.9133	0.0158522	-1.1E-05	100.0711
Ethanol	58.5	13.0	1.281	6.04726	4.582E-05	8.86E-05	-93.4725
Dimethylsulfoxide	71.3	13.0	-9.0287	-5.5217	0.0054956	-1E-05	100.1851
Methanol	40.7	14.5	0.8509	9.29756	5.638E-05	2.29E-05	59.46281
Propylene glycol	73.6	14.8	0.0866	3.25153	8.15E-05	4.15E-05	49.13656
Glycerin	73.3	17.7	6.6764	9.86388	3.392E-06	1.15E-05	-237.694
Water	18.0	23.4	4.3903	29.4996	1.023E-05	4.4E-06	56.96599

Molar heat of fusion (ΔH_f) = 17143.47 cal/mole, Melting point (T_m) = 530 K, Solubility parameter (δ_2) = 12.30 H, Molar volume (V_2) = 285.7496 cm³/mol, Ideal solubility (X_2^i) = 0.000084978, $\log X_2^i = -4.0707$

behaviour in the analysis of Hansen's extended three parameters approach. However, the Flory-Huggins size correction term showed the correlations to the tune of 92%. In the four parameter approach, hydrogen bonding parameter is replaced by acid and base partial solubility parameters. This analysis also gave encouraging results. Empirically the Flory-Huggins size correction and four parameter approach was combined and statistical analysis was attempted. The results improved the correlations up to 94%. The δ_{2T} values as well as partial solubility parameter values obtained from the above analysis were

closer to the δ values obtained theoretically from fragmental analysis. The δ_{2T} value of meloxicam is 11.20 H. In meloxicam, the hydrogen bonding partial solubility parameter might be responsible for deviations from the predictions.

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