Solubility studies of Metronidazole in Binary solvent blends

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The Extended Hildebrand Solubility Parameter Approach (EHSA) is suggested to predict the solubility of drug in binary and ternary solvent blends. The solubility profile of metronidazole in Dioxane-water blends shows a bell shaped curve with a solubility maxima different from the calculated ideal solubility. The approach was found better for the prediction of solubility.

SOLUBILITY data of drugs in mixed solvent blends have wide applications in pharmaceutical and allied fields[1]. Information about the interaction forces in solution systems are of considerable importance in pharmaceutical and biological sciences[2]. The present investigation pertains to the utility of Extended Hildebrand Solubility Approach in relation to the metronidazole solubility in binary solvents.

Dioxane, Dimethyl formamide, Dimethyl acetamide, Propylene glycol and tetrahydrofuran have been used after suitable distillation procedure. Throughout the work distilled deionized water was used. Solubilities were determined by adding excess of solute in 15 ml solvent (blends), kept in screw capped vial. The systems were allowed to equilibrated in thermostatic water bath at 35 ± 0.2°. The saturated solutions were carefully filtered and were analyzed spectrophotometrically at 273 nm using Shimadzu 160A UV Vis Spectrophotometer. The solubility parameters of solvents were obtained from literature. Metronidazole solubility parameter was calculated by the method of Fedor[3], which was confirmed by solubility analysis in dioxane water blend.

Modification to the original Hildebrand solubility approach (eq. 1) yields a more general solubility expression (eq. 3), referred to as Extended Hildebrand Solubility Equation[4,5].

$$-\log X_2 = -\log X_2^1 + A(\delta_1^2 + \delta^2_2 - 2\delta_1.\delta_2) \quad \ldots\ldots (1)$$

$$-\log X_2 = -\log X^1_2 + A(\delta_1 - \delta_2)^2 \quad \ldots\ldots (2)$$

$$-\log X_2 = -\log X^1_2 + A(\delta^1 - \delta_2 - 2.W)^2 \quad \ldots\ldots (3)$$

The assumption that the geometric mean of two solubility parameters can be replaced by a more general term W, interaction energy parameter as[4]:

$$W = K.\delta_1.\delta_2 \quad \ldots\ldots (4)$$

K is the proportionality constant relating W to the geometric mean of solubility parameter; X_{12} is the ideal mole fraction solubility parameter, δ_1 and δ_2 are the solubility parameter of solvent and solute. The geometric mean of these two provides a good estimate of solute solvent interaction in regular solutions of non polar substances.

$$A = V_2\varnothing_1^2/(2.303.R.T) \quad \ldots\ldots (5)$$

$$\text{and } \varnothing 1 = V_1(1-X_2)(V_1(1-X_2) + V_2 X_2) \quad \ldots\ldots (6)$$

Experimental data of solubility of metronidazole in dioxane-water (unbuffered) are plotted against solubility parameters of solvent blend (Fig. 1) exhibit a maxima at $\delta = 11.3$ (Peak solubility = 0.0158). The observed solubility is comparatively higher then the ideal solubility (0.002281 moles per. l) According to

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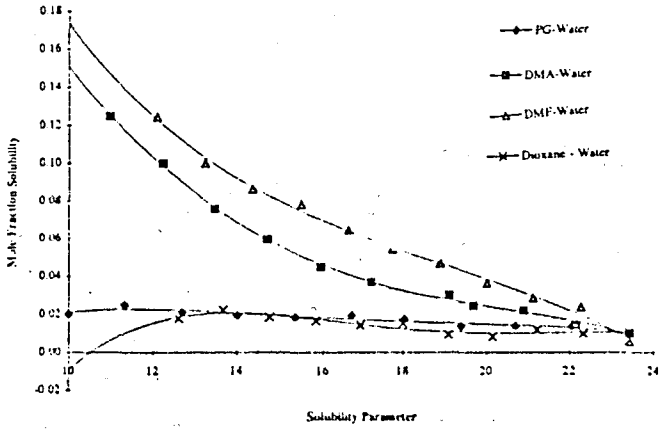
Fig. 1 Observed Solubility of Metronidazole in different solvents



the regular solution theory, solubility can not exceed ideal solubility. However, in non regular solutions peak solubility may depart from ideal solubility due to solute solvent interactions. This abnormal behaviour has been dealt with the theoretical replacement of mean geometric solubility parameters term with the interaction energy term. To relate the two variables, a fourth power polynomial has been developed to back calculate the values of W_{cal}. For Dioxane - water system the polynomial has following values:

$$W_{cal} = 74.5994 + 13.9691.\delta_1 - 0.8414.\ \delta_{12} + 0.95552.\delta_{13} - 0.0084.\delta_{14}$$

(MSE = 0.6073, n = 21, R^2 = 0.988)

These polynomials are used successfully for the calculation of W, for any value of solubility parameters, which subsequently were employed to calculate solubility of solute in a solvent blend using backward regression. Representative data alongwith validation parameters are summarised in table 1. W_{cal} values are indicating significant interaction of metronidazole and solvent molecules at the peak of solubility profile. It is confirmed by findings higher values of W and solubility in powerful solvents.

DMA (δ=11.0), DMF (δ=12.1), PG(δ12.6), THF(δ=9.3) and water (δ=22.06) were selected solvent. The Maximum solubility was encountered in DMA, which has a close value of solubility parameter with the drug. Analysis of W, were found in decreasing order as PG (205), DMF (197)

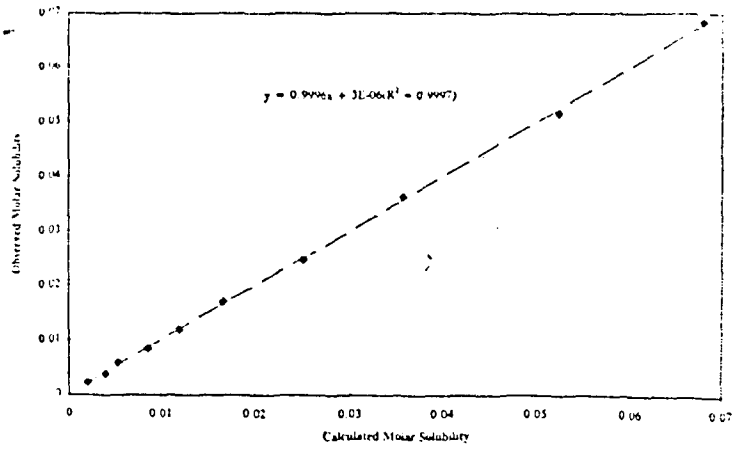
Table 1 : Molar observed solubility and calculation parameters of metronidazole in dioxane unbuffered water system

Dioxane	Solubility	Solubility Parameter	Φ Blend	D Blend	M.W. Blend	OBS. Solu.	W_{OBS}
100	0.01894	10	85.70	1.0209	96.16	0.01054	176.4464
90	0.02701	11.34	78.93	1.0186	88.344	0.013882	191.7290
80	0.02112	12.68	72.16	1.01632	80.528	0.009855	206.5973
70	0.01894	14.02	65.39	1.01483	72.712	0.008064	223.7612
60	0.01843	15.36	58.62	1.01174	64.896	0.007007	242.9514
50	0.01745	16.70	51.85	1.00945	57.080	0.005835	263.7778
40	0.01562	18.04	45.08	1.00716	49.264	0.004501	286.1248
30	0.01394	19.38	38.31	1.00487	41.448	0.003377	310.1689
20	0.01394	20.72	31.54	1.00258	33.362	0.002748	336.2989
10	0.01305	22.06	24.77	1.00029	25.816	0.001983	363.8949
0	0.01	23.4	18.00	0.99800	18.0000	0.001056	392.0000

Table 2
Performance of model in solubility prediction along with the intermediate calculation terms

δ_1 Blend	W_{OBS}	W_{CAL}	LOG α/A[Obs]	LOG α/A[Cal]	MOL. SOL[OBS]	MOL. SOL. [CAL]	Residual	% Difference
11.000000	193.613173	193.634230	-7.981446	-8.023560	.067997	.068399	-0.00040	-0.591203
12.240000	207.097968	207.039370	-6.133436	-6.016240	0.052515	0.051661	0.000854	1.626202
13.480000	221.663218	221.714430	-3.371136	-3.473560	0.035691	0.036206	-0.000515	-1.442941
14.720000	237.878060	237.837410	-0.832820	-0.751520	-0.025028	0.024746	0.000282	1.126738
15.960000	255.451585	255.518810	2.063330	1.928880	0.016695	0.017012	-0.000317	-1.898772
17.200000	274.825549	274.801630	4.433802	4.481640	0.011985	0.011905	0.000080	0.667501
18.440000	295.749201	295.661330	6.780098	6.955840	0.008633	0.008424	0.000209	2.420943
19.680000	317.808190	318.005860	9.930920	9.535580	0.005557	0.005873	-0.000316	-5.686522
20.920000	341.928305	341.675650	12.034690	12.540000	0.004141	0.003859	0.000282	6.809949
22.160000	366.271699	366.443610	16.767102	16.423280	0.002137	0.002242	-0.000105	-4.913430

Fig. 2: Relationship of Observed and Calculated Solubility of Metronidazole



DMA(194), Dioxane(196), Water (363.8). These values do not bear direct correlation with the observed solubility. It reflects the need of incorporation of molar volume term in the ultimate solubility prediction scheme.

Observed solubility data were subjected to the evaluation of interaction energy. Experimental values of W, were regressed against solubility parameter to obtain W_{calc} which are used to back calculate the mole fraction solubility(X_{2cal}). A mathematical model is proposed for individual system as fourth power polynomial. Validation of these equation has been done by comparing experimentally obtained and calculated values of solubility by estimating residuals and percent difference (Table 2). The predictive capability of the model for metronidazole is represented in Fig. 2, which indicates a very high degree of correlation 0.997.

On the basis of validation parameters, it can be expressed that the behaviour of non regular solution can be quantified more precisely using EHSA. Simultaneously, this tool may become useful in optimization problems of clear solution formulations.

REFERENCES

1. Sunwoo, C. and Eisen, H.; **J. Pharm. Sci.**, 1971, 60, 238.
2. Chow, S.L. and Sim, E.B.; **J. Pharm. Sci.**, 1981, 70, 924.
3. Martin. A. and Wu, P.L., **J. Pharm. Sci.**, 1985, 74, 277.
4. James K.C.; Solubility and related properties, Ist Ed., Marcel Deker Inc, 1981, 234.
5. Fedor, R.F., **Poly. Eng. Sci.**, 1974, 14, 147.