Solubility Prediction of Satranidazole in Aqueous N,N-dimethylformamide Mixtures Using Extended Hildebrand Solubility Approach

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The solubility of satranidazole in several water–N,N-dimethylformamide mixtures was analysed in terms of solute–solvent interactions and data were treated on the basis of extended Hildebrand solubility approach. The solubility profile of satranidazole in water–N,N-dimethylformamide mixtures shows a curve with a solubility maxima well above the ideal solubility of drug. This is attributed to solvation of the drug with the water–N,N-dimethylformamide mixture, and indicates that the solute–solvent interaction energy (W) is larger than the geometric mean ($\delta_1\delta_2$) of regular solution theory. 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. A quartic expression of W in terms of solvent solubility parameter was found for predicting the mole fraction solubility of satranidazole in the studied mixtures. 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, N, N-dimethylformamide, satranidazole, solubility

Extended Hildebrand solubility approach is applied to predict the solubility of satranidazole in mixtures of water and N,N-dimethylformamide (DMF). DMF is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is aprotic and completely miscible with water [1]. Water-DMF mixtures are strongly non ideal and can act in the solute-solvation process via hydrophobic interactions and preferential solvation [2,3]. In terms of polarity, water–DMF mixtures cover a wide range of Hildebrand solubility parameters from 12.1 (pure DMF) to 23.4 (pure water)[4,5].

The extended Hildebrand solubility approach enables 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 key relationship may be written as[6,7],

$$-\log X_2 = -\log X_2^{\,i} + \frac{\varphi_1^2 V_2(\delta_1^{\,2} + \delta_2^{\,2} - 2W)}{2.303RT} \qquad (1)$$

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. 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 nonpolar media in water. Although W cannot be theoretically evaluated, it is assumed that when a range of similar solvents are used for dissolving a fixed solute, $W = \mathrm{K}\ \delta_1\delta_2$, where K is a proportionality constant [8].

Interaction energy (W) values were evaluated as a power series in δ_1 utilizing mixed solvents by polynomial regression[9-11]. By using these polynomial fits, the mole fraction solubility of solutes may be predicted that is in good agreement with the experimental values. This procedure may be applied for calculating solubilities of missing data by interpolation. When the solvent studied is a mixed one, there are a series of parameters to be calculated such as: the solubility parameter, the volume fraction and the mean molar volume of mixed solvents.

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The solubility parameter (δ_1) for the mixture of two solvents DMF and water, *W*, is averaged in terms of volume fractions using the expression[12],

$$\delta_1 = \frac{\delta_{DMF}\varphi_{DMF} + \delta_W\varphi_W}{\varphi_{DMF} + \varphi_W} \quad (2)$$

where $\Phi_1=\Phi_{DMF}+\Phi_W$ is the total volume fraction of two solvents which can be calculated from[13],

$$\varphi_1 = \frac{(1-X_2)V_1}{(1-X_2)V_1 + X_2V_2} \quad (3)$$

where X_2 is the mole fraction solubility of the solute in the mixed solvent and V_1 is the molar volume of the binary solvent. For each mixed solvent composed of water and DMF in various proportions[14]:

$$V_1 = \frac{X_{DMF}M_{DMF} + (1-X_{DMF})M_W}{d_1} \quad (4)$$

Here, X_i and M_i are the mole fraction and the molecular weight of the particular solvent in the mixture, respectively and d_1 is the density of the solvent mixture at the experimental temperature.

Satranidazole, 1–methylsulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone, is one of the large series of nitroimidazoles with a potent antiprotozoal activity against *E. hystolytica, T. vaginalis* and *Giardia*. Satranidazole is not official in IP, USP and BP till date. Though the molecule is found to be effective against these microorganisms, its therapeutic efficacy is hindered due to its poor aqueous solubility (0.01 mg/ml). The poor aqueous solubility and wettability of satranidazole give rise to difficulties in pharmaceutical formulations meant for oral or parenteral use, which may lead to variation in bioavailability[15-18].

As such, no solubility reports are found for its estimation and prediction by any of the method till date. Hence, the aim of this communication is to report the solubility behaviour of satranidazole in individual solvents (water and DMF) and different concentrations of water-DMF mixtures, predict it theoretically by applying the Extended Hildebrand Solubility Approach.

Satranidazole, obtained as gift sample from Erika Pharmaceuticals, Mumbai, India, was purified by recrystallization process. The solvent used for recrystallization of satranidazole was acetone. DMF and acetone both were obtained as gift samples from Qualigens Fine Chemicals, Mumbai, India. Throughout the study, 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, Shimadzu model 1601 with spectral bandwidth of 2 nm, wavelength accuracy ±0.5 nm and a pair of 10 mm matched quartz cells were used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing of satranidazole. Differential scanning calorimeter, Shimadzu TA-60 WS, was used for the determination of melting point and heat of fusion of satranidazole.

Solubilities of satranidazole (δ_2=11.34) were determined in mixed solvent consisting of DMF (δ_{DMF}=12.1) and water (δ_W=23.4). Solvent blends were made covering 0-100% DMF (v/v). About 25 ml of DMF, water, or mixed solvents were placed into screw-capped vials (Thermostated at 25° and under continuous magnetic stirring) containing an excess amount of satranidazole 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°[19].

After equilibration, the solution was 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 satranidazole (λ_{max}-319.80 nm). Calibration graphs of satranidazole in each solvent blend were previously established with correlation coefficients greater than 0.9978. The working concentration range was from 10 to 50 μg/ml satranidazole. The densities of the blends as well as the filtrates of saturated solutions were determined by using 25-ml specific gravity bottle at 25°. Once the densities of solutions are known, the solubilities can be expressed in mole fraction scale.

The molar volume (V_2) and the solubility parameter of satranidazole were previously estimated by using the Fedor's group contribution method [20,21] giving 235.6 cm^3/mol and 11.3928 $(cal/cm^3)^{0.5}$. The ideal solubility of satranidazole was calculated by using the equation [22],

$$-\log X_2^{\,i} = \frac{\Delta S_f}{R}\log\frac{T_0}{T} \quad (5)$$

where, ΔS_f is the entropy of fusion of the crystalline

drug molecule at its melting point T_0 and T is the temperature in Kelvin at which the solubility was determined. The value of ΔS_f was evaluated by [23],

$$\Delta S_f = \Delta H_f / T_0 \quad (6)$$

(ΔH_f=7763.838 cal/mol, T_0=461.83°K) giving 16.811 cal/mol/°K. Thus, the ideal mole fraction solubility of satranidazole (X_2^i) is 0.024561.

The mole fraction solubility of satranidazole in water-DMF mixtures and other parameters of interest (δ_1, Φ_1, V_1) are collected in Table 1. The plot of these experimental solubilities versus the solubility parameter of mixtures, δ_1 is shown in fig. 1. The solubility of satranidazole was far from its ideal value in both pure solvents (DMF, water) as well as in the mixtures. The maximum solubility, although higher than ideal occurred at a δ_1=12.10, very close to the calculated δ_2 for satranidazole.

Observed solubility data were then subjected to the evaluation of interaction energy. The interaction term W can be calculated from Eq.1 at each experimental point (X_2, δ_1). The results are also presented in Table 1. Experimental values of interaction energy (W_{obs}) were regressed against solubility parameter to obtain W_{cal} (fig. 2), which was then used to back-calculate the mole fraction solubility (X_{2cal}). A mathematical model is proposed for individual system as fourth power polynomial. The W values may also be expanded in a power series of δ_1 from fourth degree polynomial regression.

In our case, the following fit was obtained:

$$W_{cal} = -77.483176 + 36.435577\ \delta_1 - 2.810929\ \delta_1^2 + 0.127277\ \delta_1^3 - 0.001788\ \delta_1^4. \quad (n = 11, R^2 = 0.999994) \quad (7)$$

If we insert this equality in Eqn. 1, we can predict the solubility of satranidazole. The back-calculated logarithmic solubilities, log X_{2cal} are recorded in Table 2, together with the experimental values of log X_2 and their differences. The plot of log X_{2cal} against log X_{2obs} gives a straight line passing through the origin with very high degree of correlation coefficient (R^2) 0.9912 and negligible intercept (0.00009) equal to zero as shown in fig. 3.

A careful scrutiny of the behaviour of the solutions of satranidazole in water-DMF mixtures may be

TABLE 1: MOLE FRACTION SOLUBILITY OF SATRANIDAZOLE

ΦDMF	$X_{2(obs)}$	δ_1	Φ_1	V_1	$\delta_1\delta_2$	$W_{(obs)}$
0	3.8119E-05	23.40	0.99950	18.00	265.36	330.51
0.1	7.5836E-05	22.27	0.99925	23.90	252.54	305.57
0.2	1.3239E-04	21.14	0.99895	29.80	239.73	281.74
0.3	2.1919E-04	20.01	0.99856	35.70	226.91	259.12
0.4	4.2637E-04	18.88	0.99759	41.60	214.10	237.97
0.5	5.9677E-04	17.75	0.99705	47.50	201.29	217.70
0.6	1.4499E-03	16.62	0.99363	53.40	188.47	199.38
0.7	3.7972E-03	15.49	0.98508	59.30	175.66	182.42
0.8	1.4453E-02	14.36	0.94967	65.20	162.84	167.23
0.9	2.3516E-02	13.23	0.92610	71.10	150.03	152.32
1.0	4.3502E-02	12.10	0.87784	77.00	137.22	139.00

δ_1=Solubility parameter of solvent blend, δ_2=Solubility parameter of drug, V_1=Molar volume of solvent blend, and Φ_1=Total volume fraction of solvent blend. The values for δ_1, Φ_1 and V_1 are calculated from Eqs. 2-4, respectively and W is calculated from Eq. 1

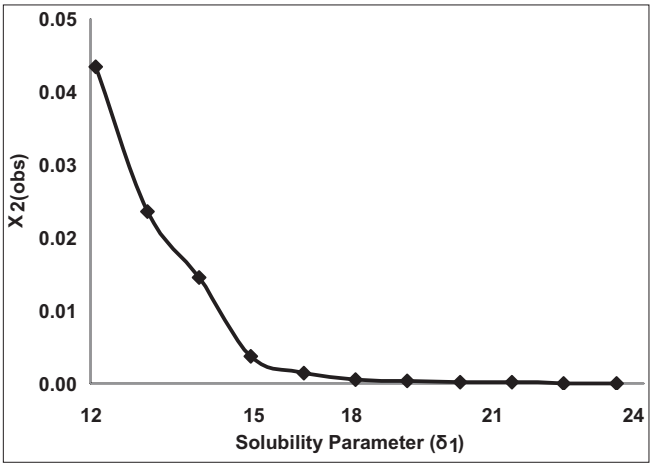

Fig. 1: Solubility parameter versus mole fraction solubility profile. -◆- represents experimental solubilities, and highest mole fraction solubility obtained is $X_2 = 4.3502 * 10^{-2}$ when $\delta_1 = 12.10$ (cal/cm^3)$^{0.5}$ in water-DMF mixtures

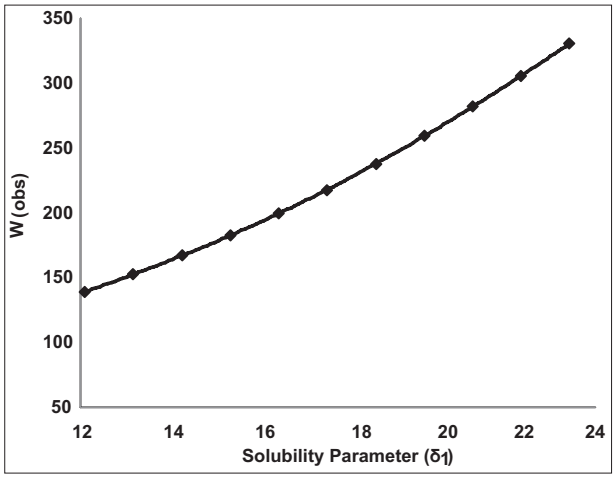

Fig. 2: Solubility parameter versus interaction energy profile. $W_{(cal)}$ obtained from quartic regression Eq. 7, for satranidazole in water-DMF mixtures at 25° and correlation coefficient, r^2, is 0.99999 for n = 11.

TABLE 2: EXPERIMENTAL AND CALCULATED MOLE FRACTION SOLUBILITIES

$-\log X_{(2\ obs)}$	$-\log X_{(2\ cal)}$	Residual (Δ)	Percent difference
4.418857	4.434688	+0.035796	3.58E+00
4.120125	4.091550	–0.068009	–6.80E+00
3.878144	3.865188	–0.030281	–3.03E+00
3.659178	3.671673	+0.028360	2.84E+00
3.370217	3.449925	+0.167680	1.68E+01
3.224190	3.168771	–0.136110	–1.36E+01
2.838657	2.808556	–0.071768	–7.18E+00
2.420537	2.385907	–0.083003	–8.30E+00
1.840041	1.936473	+0.199120	1.99E+01
1.628638	1.577837	–0.124090	–1.24E+01
1.361490	1.368473	+0.015951	1.60E+00

Residuals obtained from quartic regression Eq. 7, for satranidazole in water-DMF mixtures at 25°. Residuals can also be obtained from $(X_{2\ obs}-X_{2\ cal})/X_{2\ obs}$

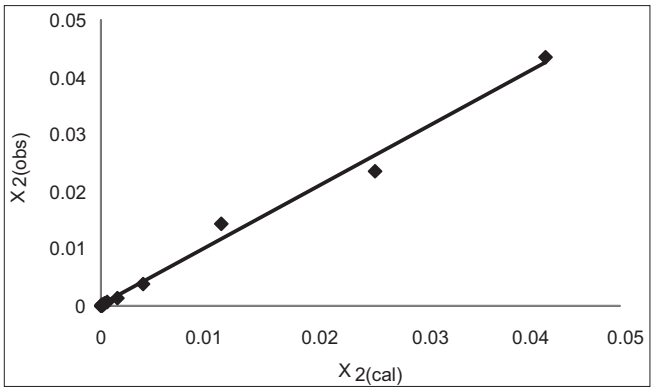

Fig. 3: Comparison of observed and calculated mole fraction solubility.
Comparison of 11 observed satranidazole solubilities in water-DMF mixtures at 25° with solubilities predicted by the extended Hildebrand approach. The intercept of the line is 0.00009, and the slope is 0.9912. The correlation coefficient, r^2, is 0.9912 for n = 11.

performed, comparing the value of the interaction term W at each experimental point with the regular value $W=\delta_1\delta_2$. This comparison is presented also in Table 1. As can be observed, for volume fractions of DMF from 0 to 1, $W>\delta_1\ \delta_2$. But, for volume fractions of DMF from 0 to 0.5, W is far greater than $\delta_1\delta_2$ and for volume fractions of DMF from 0.6 to 0.9, W is nearby closer to $\delta_1\delta_2$. It may be assumed that satranidazole solutions can behave as regular solutions at some point ($W=\delta_1\delta_2$) with 1.0 DMF volume fraction.

Thus, in water-rich mixtures (0-0.5) there seems to be some kind of association between satranidazole 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 neighbourhood of nonpolar groups in water. When adding DMF, HH breaks down. The endothermic shift of the enthalpies of solution upon small additions of aprotic cosolvent to water is known to appear for hydrophobic solutes like satranidazole.

Conversely, in water poor mixtures (0.6-1.0) self-association of solvent, solute or both is not obtained because W is still far greater than $\delta_1\delta_2$. This behaviour may remain as such in rich DMF blends, and therefore, the corresponding satranidazole solubilities are still higher than regular one.

The extended Hildebrand approach applied to the solubility data of satranidazole in water-DMF mixtures leads to an expansion of the W interaction term as a fourth degree power series in δ_1 which reproduces the satranidazole solubility within the accuracy ordinarily achieved in such measurements. The procedure can be used to predict the solubility of satranidazole in pure water or DMF and in any water-DMF mixtures.

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