Extended Hildebrand Solubility Approach: Prediction and correlation of solubility of itraconazole in triacetin: water mixtures at 298.15K

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Short title

Solubility study of itraconazole using EHSA

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ABSTRACT

Aims:

To explore the suitability of empirical approach of Extended Hildebrand Solubility Approach (EHSA) to predict and correlate the solubility of crystalline drug itraconazole (ITRA) in triacetin: water mixtures.

Methods and Material:

The physicochemical properties of ITRA like fusion enthalpy, solubility parameter, and ideal mole fraction solubility were estimated. The solubilities of ITRA in mixed solvent blends comprised of triacetin: water were determined at 298.15K. Theoretical solubilities were back calculated using polynomial regression equation of interaction energy parameter $'W'$as a function of solubility parameter (δ_1) of solvent mixture. Similarly, the solubilities were predicted with direct method based on use of logarithmic experimental solubilities ($logX_2$) against solubility parameter (δ_1) solvent mixture. The predictive capabilities of both EHSA and direct method were compared using mean percent deviations.

Results:

The solubility of ITRA was increased in all the triacetin: water blends and was highest in the blend where solubility parameter of ITRA equaled with that of solvent mixture. The prediction capacities of direct method (mean % deviation was -1.89%) were better than EHSA (mean % deviation was 9.76%) in the fifth order polynomial.

Conclusions:

The results indicated that solubility of any crystalline solute can be adequately predicted and correlated with the mere knowledge of physicochemical properties and EHSA. The information obtained would be of help in process and formulation development.

Key-words: Itraconazole, Extended Hildebrand Solubility Approach, Interaction energy, solubility parameter, Prediction and correlation of solubilities

INTRODUCTION

Many pharmaceutically important processes like synthesis, extraction, recrystallization, purification, dosage form development requires the solubilization of active pharmaceutical ingredient (API) in neat and /or solvent blends. Many times these APIs are complex organic substances and are ideal theoretical candidates for understanding their solubility behavior with the use of predictive methods. Itraconazole (Figure 1) is one such triazole compound widely used because of its antifungal activity. But, its use limited due to its poor solubility.[1,2] The knowledge about its solubility behavior and solubility improvement is much needed for the development of better formulations with increased effectiveness. So, ITRA becomes an ideal candidate for estimating its solubility and understanding its solubility behavior in solvent mixtures with the help of empirical predictive models.

The Hildebrand-Scatchard is an empirical approach preferred to predict the solubility of poorly soluble compounds in variety of solvents ranging from non-polar to polar according to regular solution theory.[3] However, in pharmaceuticals many irregular solutions are observed due to self-association of solute or solvent molecules, complexation.

The EHSA is an adaptation of the Hildebrand-Scatchard equation which allows the estimation of solubilities of polar as well as non-polar moieties in variety of solvents with different polarities like water, alcohols, sulphoxides, glycols and acetates.[4] The EHSA has been considered as adventitious empirical model for prediction of solubility due to numerous reasons. It includes - ability of solubility prediction of wide variety of solutes in irregular solutions; ability of predicting the solubility of any solute in pure or mixed solvents using fundamental physicochemical properties; it is not only applicable for crystalline solids in liquid solutions but also applicable for liquid – liquid and gas-liquid systems; it gives more accurate prediction of mole fraction solubilities as compared to other empirical methods. The solubility parameter, an intrinsic physicochemical property of solute and solvent is the square root of cohesive energy density and could be preferred to understand the solution behavior of regular and irregular solutions. Till date, some work has been explored to study the solubility

behavior of pharmaceutically important substances with the use of EHSA by Martin A[5], Bustamante P[6], Rathi P[7], Martínez F[8] and Delgado D.[9]

The solubility of crystalline solids in variety of solutions can be described with EHSA expression as[5]

$$-\log_{10}X_2 = -\log_{10}X_2^i + A\,(\delta_1 - \delta_2)^2 \qquad (1)$$

The solubility of crystalline solid solute in irregular solutions may be estimated using following equation[10]

$$-\log_{10}X_2 = -\log_{10}X_2^i + A\,(\delta_1^2 + \delta_{2-}^2 - 2W) \qquad (2)$$

Where, x_2^i and x_2 are the ideal mole fraction and experimental mole fraction solubility of the solute respectively. The terms δ_1 and δ_2 are the solubility parameters of the respective solvent mixtures and the solute respectively. Furthermore, w represents the interaction energy parameter for the solute solvent blend interaction in irregular solutions.

The term A appeared in Equation 1 and 2 can be expressed as

$$A = \frac{V_2\varphi_1^2}{2.303RT} \qquad (3)$$

Where, V_2 represents the molar volume of the solute i.e. itraconazole, R represents universal gas constant. $\emptyset_1$ expresses the volume fraction of the solvent mixture.

The volume fraction $\emptyset_1$ can be calculated as

$$\varphi_1 = \frac{V_1(1-X_2)}{V_1(1-X_2)+V_2X_2} \qquad (4)$$

Where, V_1 reflected molar volume of the triacetin: water solvent mixture. X_1 and X_2 represents moles of the solute and solvent respectively.

The ideal mole fraction solubility can be expressed as negative logarithm and can be given by following equation 5

$$-\log X_2^i = \frac{\Delta H_f\,(T_m - T)}{2.303RT_mT} \qquad (5)$$

Here, ΔH_f gives fusion enthalpy of solid crystalline itraconazole. T_m reflects melting temperature and T represents the absolute temperature $(298.15K)$.

The logarithmic value of activity coefficient could be expressed by equation

$$\log\gamma_2 = A\,(\delta_1^2 + \delta_{2-}^2 - 2W) = \frac{V_2\varphi_1^2}{2.303RT}(\delta_1^2 + \delta_2^2 - 2w) \qquad (6)$$

As we could not confine the interaction term $'W'$, the other approach will be experimental estimation of interaction energy by determining itraconazole solubility in solvents mixtures equation 2. The realistic equation for determination of $'W'$ is not reported till date. Hence, it is evaluated using equation 6 by back calculations. Then, these values of $'W'$ can be used further for the prediction of solubility of solute in any other solvent system as a function of solubility parameter of respective solvent mixture.

$$w = C_0 + C_1\delta_1 + C_2\delta_1^2 + C_3\delta_1^3 + C_4\delta_1^4 + \ldots\ldots + C_n\delta_1^n \qquad (7)$$

Triacetin - glycerin acetate, is a pharmaceutically important chemical substance used as a solvent[11] for solubilization of various drugs and polymers because of its biocompatibility in topical and injectable preparations.[12,13] It is also capable of affecting the film forming properties[14] as well as adhesive properties in topical preparations and capable of forming stable depots in case of injectable preparations.[15]

Thus, the present work has been carried out to establish the suitability of EHSA to study the solute – solvent interaction, solution behavior and to predict the solubility of ITRA in triacetin: water mixtures as a function of solubility parameter.

MATERIALS AND METHODS:

Materials

The gift sample of Itraconazole was obtained from USV, Mumbai, India. The solvents like triacetin were received from Loba Chemie, India. Double distilled water used in study was prepared in laboratory. Other chemicals and reagents used in study were of analytical grades.

Determination of itraconazole solubility

The saturation solubility study method was employed for the determination of itraconazole solubility.[16] Double distilled water was preferred for the preparation of to prepare solvent mixtures. The binary compositions of triacetin: water was used as 0 to 100% by mass fraction of triacetin. The 10gm of binary solvents blends were taken in screw cap vials and were saturated by the addition of excess of drug. These vials were mounted in orbital shaker (Remi, India) at 298.15 K with 100 rpm for 72 hours (hrs). The saturation time of 72hrs was established through the preliminary studies. After 72 hrs, these vials were removed and solutions were filtered carefully with the help of micro filters of 0.45µm. The filtrate was collected, diluted suitably and was subjected to spectrophotometric analysis by using double beam UV spectrophotometer (Shimadzu, Japan) at 255nm. All the experiments were performed in triplicate. The densities of pure solvent blends and filtered saturated blends were determined and used for the estimation of saturated solubilities in terms of mole fraction.

Differential Scanning Calorimetric (DSC) Study

The melting temperature and melting fusion enthalpy of itraconazole was determined by performing differential scanning calorimetric analysis. The DSC thermogram was produced by using a differential scanning calorimeter (DSC-1, Mettler Toledo, Switzerland). Itraconazole sample weighing 5.0 mg was kept in an aluminium pan and then it was sealed with lid. These pans were subjected to heating from 313.15K to 573.154K at a rate of 10 $K.min^{-1}$ under nitrogen purging.

RESULTS AND DISCUSSION

The melting temperature (T_m) of itraconazole was obtained as 443.5K and the melting fusion enthalpy (ΔH_f) was determined as 65.32 KJ.mol^{-1} at 298.15K. From these values; ideal mole fraction solubility of drug was estimated to be 9.08×10^{-4} and value of $-\log_{10} x_2^i$ was found to be 3.04 expressed in mole fraction by using Eqn. 5. The investigated mole fraction solubilities of ITRA in triacetin: water mixtures with wide range of polarity described in terms of solubility parameter of solvent mixture from 10.77 to 23.40H were given in Table 1.

The uncertainties in solubility investigation were < 2% in all the cases. Table 1, also expresses the mass fractions, volume fractions and solubility parameter of solvent blend with respect to its composition. These volume fractions and solubility parameter were determined by using the additive property phenomenon. The solubilities of ITRA on terms of molarity and mole fractions were also presented in Table 1.

The ideal, experimental and calculated solubilities of ITRA with respect to solubility parameter of solvent blend for regular solutions at 298.15K are presented Figure 2. These calculated solubilities were estimated using molar volume and solubility parameters. The values were fetched from literature for solvents. For itraconazole; these values were calculated by using Fedor's group contribution method.[17] According to regular solutions theory; the peak in solubility would be attained where the solubility parameter of the solvents mixture matches with that of the solute (Figure 2). In this study, it was observed that the peak in solubility of ITRA was achieved in solvent blend of 0.9 mass fractions of triacetin where solubility parameter of ITRA nearly corresponded with solvent mixture (δ_1=12.03 H).This was attributed to the matching of polarities of ITRA and 0.9 mass fraction of solvent mixture of triacetin: water. From the results it could be inferred that the ITRA has the same polarity as that of the 0.9 mass fraction of solvent mixture of triacetin: water. The molar volume and solubility parameter of itraconazole was derived using Fedor's contribution method and were found to be 457.5 cm3.mol^{-1} and 24.3987 (J/cm^3)$^{1/2}$ or 11.93 H respectively.

Volume fractions φ_1 of the solvent mixtures were estimated using Equation 4. It's values were nearly equal to unity due to smaller values of solubility of ITRA in all the solvent mixtures. The values of activity coefficients were also described in Table 1.

These values were greater than one in solvent mixtures where proportion of water was higher. Table 2 summarizes experimental parameters like volume fractions of solvent mixture ($\emptyset_1$), A, K, W_{obs}, $W_{cal}$and for ITRA in triacetin: water mixtures at 298.15 K. It was observed that values of walker parameter K were greater than one indicating the rise in solubilities due to increased solute solvent interactions. The variation of interaction energy parameter W with respect to solubility parameter of solvent blend was shown in Figure 3. The graph showed the deviation from linearity as the value of $'W'$ was estimated by the using squares of two terms (δ_1 and δ_2) and a variable term consisting of (-log10γ_2/A) as reflected in following Equation 8.

$$W = 0.5 \times (\delta_1^2 + \delta_2^2 - \frac{log\gamma_2}{A}) \quad (8)$$

The values of $'W'$ were estimated using regular polynomial equation as a function of solubility parameter of solvent blend in order 5 (Equation 7). The following polynomial regression equation in the order 5 was produced as a function of solubility parameter to back calculate the values of $'W'$.

$$w_{cal} = (-265.2679) + (104.3851)\,\delta_1 + (-12.1646)\delta_1^2 + (0.7556)\delta_1^3 + (-0.0222)\delta_1^4 + (0.0002)\,\delta_1^5 \quad (9)$$

These back calculated values of $'W_{cal}'$ were used to calculate the solubilities of ITRA (Table 3). Such theoretically estimated solubilities were then compared with experimental ones and mean percent deviation was obtained. It was found to be 9.76% for EHSA method. The worth of EHSA method for the correlation and estimation of solubilities with the use of EHSA equation could be established by performing the calculations by using the equation consisting of other variable. Therefore, the theoretical solubility values were calculated using the direct method based upon polynomial equation of log10X_2 as a function of the solubility parameter of solvent blend δ1 in order 5 (Equation 10).

$$log_{10}X_2 = B_0 + B_1\,\delta_1 + B_2\delta_1^2 + B_3\delta_1^3 + B_4\,\delta_1^4 + B_n\delta_1^n \quad \ldots\ldots\ldots\ldots\ldots\ldots (10)$$

Here, calculated solubilities were again compared with experimental ones and mean percent deviation was evaluated. It was obtained as -1.89% (Table 3). The

solubility prediction capabilities of both methods were compared using these mean percent deviation values. Similar, solubility prediction behavior was obtained with the use of polynomial regression equations in order 5 for EHSA and direct method for the drugs like phenacetin[18], meloxicam[19], pirocxicam.[8] In this study, solubility correlation and prediction was observed comparably better by direct method as compared to that of EHSA with polynomial in order 5. Nonetheless, it must be remembered that these methods were based upon the some of the physico-chemical properties. But, there is need of a method for the exact determination of walker parameter K for the estimation of interaction energy parameter W. Already, it has been proved that the EHSA method would be used to calculate drug solubilities as it depended upon some simpler physicochemical properties like solubility parameter, molar volume and experimental solubilities. So, EHSA would have the potential applications in various pharmaceutical science processes

ITRA showed both positive and negative deviations in solubility as reported by Roseman (Figure 4).[20,21] The reason for such deviation from ideal solubilization would be the predominance of Interactions between cosolvent and water over the solute solvent interactions[22]. Similar type of observations were reported by Martínez F[23], Kharwade M[24], Thimmasetty J[25], Rathi P[26], and Delgado D[27]. The major force behind the solubilization in water rich mixtures would be entropy. It might have resulted in loss in structure of water surrounding the non – polar ITRA by triacetin molecules. At the higher proportions of triacetin, the solubilization would be enthalpy driven. At this higher proportions of triacetin water molecules might have lost its three dimensional structure completely and water molecules might have become available for interaction with ITRA molecules[19]. The other reason for the positive deviation from log linear model could be the drug - drug molecules interactions in the saturated solution. This could be further confirmed with spectral studies.

CONCLUSION

The present study showed the application of EHSA to the ITRA solubility data in triacetin: water mixtures at 298.15K with the help of physicochemical properties like fusion enthalpy, molar volume and Hildebrand solubility parameter obtained by Fedor's group contribution method. The peak in experimental solubility was observed at a point where solubility parameter of ITRA matched with that of solvent mixture. Better prediction of solubilities was obtained with the help of polynomial regression equation as a function of solubility parameter in the order 5 for both EHSA and direct method. Direct method exhibited better prediction capacities (mean percent deviations -1.89%) as compared to EHSA (mean percent deviations 9.76%). Furthermore, it would be asserted from the study that EHSA should be preferred to understand the solubility behavior of solutes of different polarities in variety of solvents and their mixtures. The obtained information could be useful for process and formulation development of such drugs.

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CONFLICT OF INTEREST

There is no any conflict of interest.

FIGURE CAPTIONS

Fig. 1 Structure of ITRA.

Fig. 2 Experimental solubilities (dotted line joined by filled circles) and solubilities calculated by fifth order polynomial regression equation (continuous line joined by filled diamonds) for irregular solution of ITRA developed using empirical model of Hildebrand as a function of solubility parameter of the solvent mixtures at 298.15 K. The discontinuous line (long dash joined by crosses) represents ideal solubility of calculated by using Equation 1.

Fig. 3 Variation of interaction energy $'W'$ of ITRA in triacetin:water mixtures as a function of the solubility parameter of the binary solvent mixture at 298.15K.

Fig. 4 log of mole fraction solubility ($\log X_2$) as a function of solubility parameter of ITRA in triacetin:water mixtures at 298.15K.

TABLE HEADINGS

Table 1. Triacetin: water solvent mixture composition, Hildebrand solubility parameter, solubilities of ITRA expressed as molarity and mole fractions. Activity coefficients for ITRA in triacetin: water mixtures are expressed as logarithmic values at 298.15K.

Table 2. Experimental parameters like volume fractions of solvent mixture (φ_1), A, K, Wobs and W_{cal} for ITRA in triacetin: water mixtures at 298.15 K.

Table 3. Calculated solubilities of ITRA in triacetin water mixtures by using calculated $'W'$ values estimated by polynomial regression equations of the order 5 (by EHSA method) and by using $\log X_2$ values determined as a function of solubility parameter with the use of polynomial regression equation of order 5 (by direct method). Percentage differences with respect to experimental solubilities are also indicated at 298.15K.

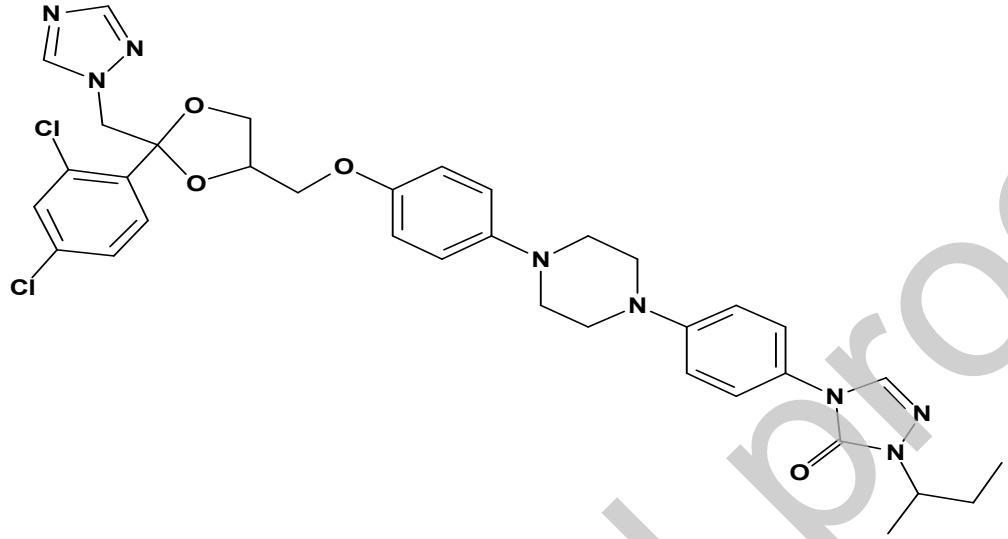

Figure 1. Structure of ITRA

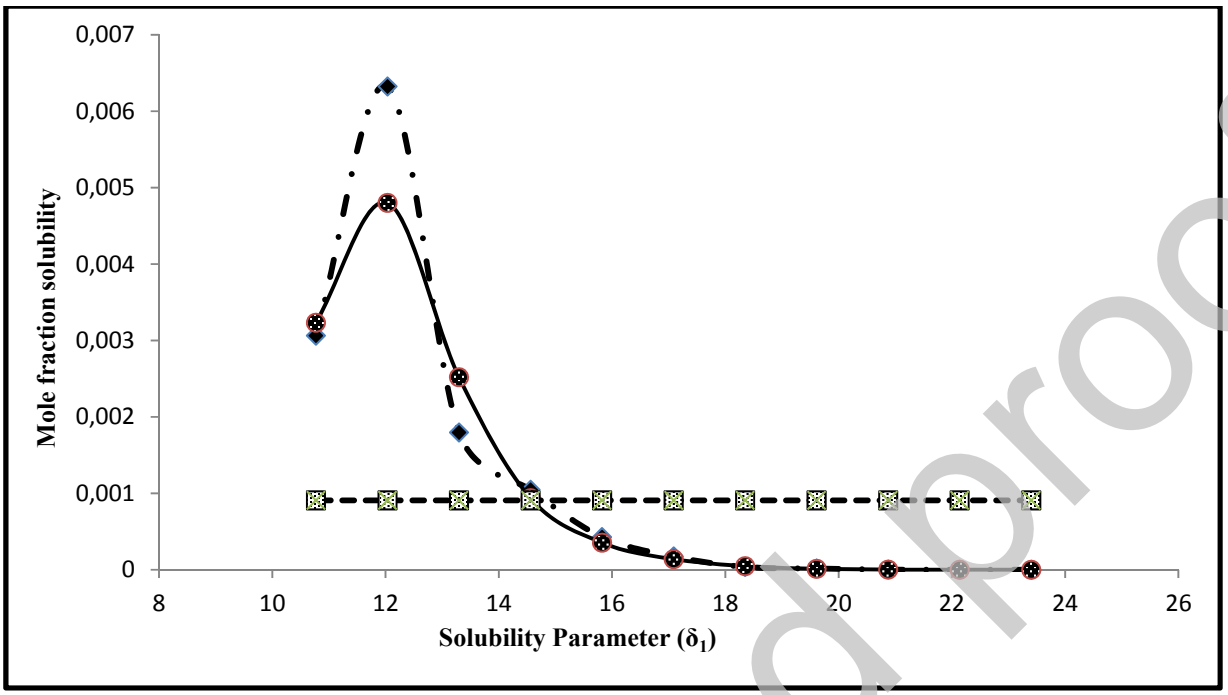

Figure 2. Experimental solubilities (discontinuous line joined by filled diamonds) and calculated solubilities (continuous line joined by filled circles) according to the fifth order polynomial regression equation for irregular solution of ITRA using empirical model of Hildebrand in reference to the respective solubility parameter of the solvent mixtures at 298.15 K. The discontinuous line (long dash) joined by filled squares reveals the ideal solubility of ITRA calculated by using Eqn.5.

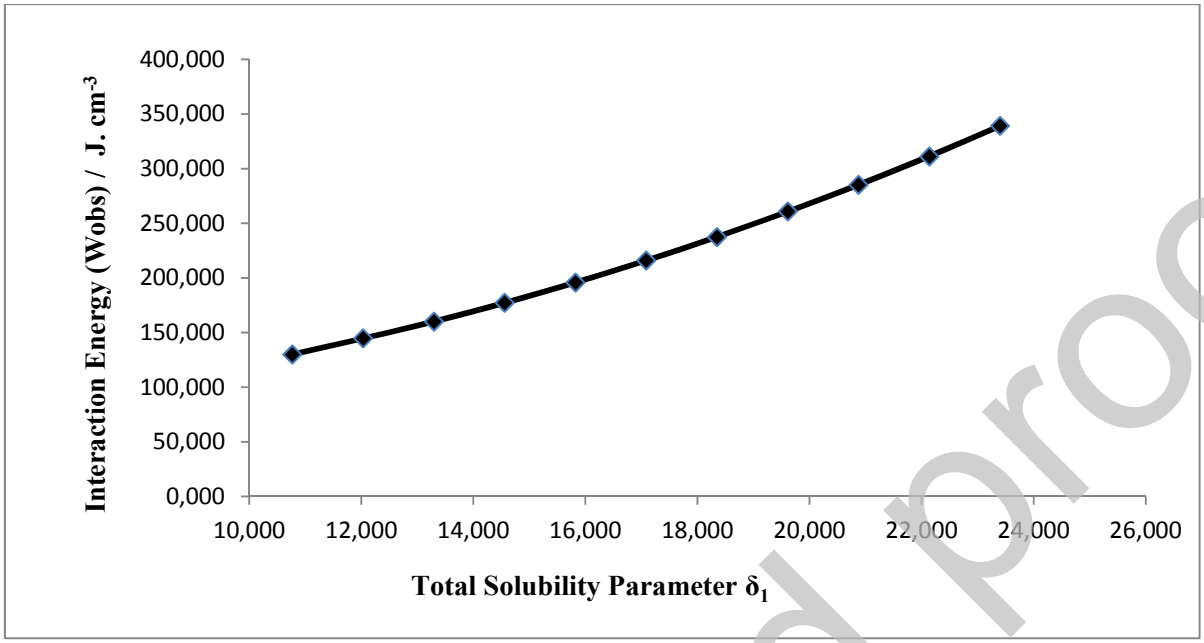

Figure 3. Interaction energy $'W'$ of ITRA in triacetin: water mixtures in reference with solubility parameter of the binary solvent mixture at 298.15 K.

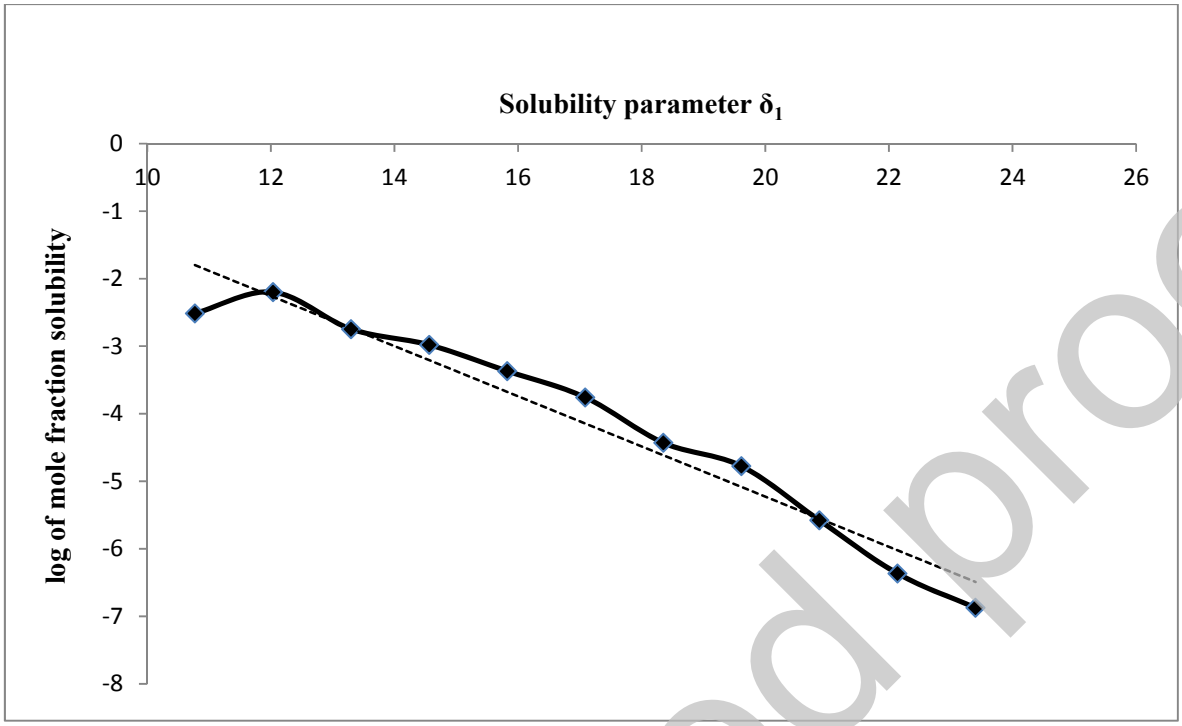

Figure 4. log mole fraction solubility ($\log X_2$) of ITRA in triacetin: water mixtures at 298.15K as a function of solubility parameter of solvent blend.

Table 1. Triacetin (TA): water solvent mixture composition, Hildebrand solubility parameter, solubilities of ITRA expressed as molarity and mole fractions. Activity coefficients for ITRA in TA: water mixtures are expressed as logarithmic values at 298.15K.

TA mass fraction	φ_{TA}	δ_1	Itraconazole Solubility			
			Mol . L^{-1}	X_2obs	Standard deviation	$\log_{10}\gamma_{2obs}$
0.0000	0.0000	23.40	7.41E-06	1.34E-07	1.95E-03	3.8320
0.1000	0.0986	22.14	1.15E-05	4.31E-07	2.08E-03	3.3233
0.2000	0.1943	20.87	4.69E-05	2.65E-06	2.56E-04	2.5355
0.3000	0.2971	19.61	2.24E-04	1.68E-05	2.21E-03	1.7338
0.4000	0.3871	18.35	4.02E-04	3.72E-05	2.37E-04	1.3879
0.5000	0.4845	17.09	1.59E-03	1.75E-04	2.25E-03	0.7161
0.6000	0.5893	15.82	3.39E-03	4.28E-04	2.40E-04	0.3264
0.7000	0.6818	14.56	7.34E-03	1.05E-03	3.25E-03	-0.06165
0.8000	0.7820	13.30	1.13E-02	1.80E-03	3.14E-03	-0.2961
0.9000	0.8975	12.03	3.66E-02	6.32E-03	2.45E-03	-0.8429
1.0000	0.1000	10.77	1.63E-02	3.06E-03	2.15E-04	-0.5279

φ_{TA} – volume fractions of solvent triacetin

Table 2. Experimental parameters like volume fractions of solvent mixture (φ_1), A, K, W_{obs} and W_{cal} for ITRA in triacetin: water mixtures at 298.15 K.

δ_1 (H)	φ_1	10A (cm3. J^{-1})	K ($J.cm^{-3}$)[a]	W_{obs} ($J.cm^{-3}$)	W_{cal} ($J.cm^{-3}$)
23.40	0.99999	3.3532	1.2152	339.2284	338.9677
22.14	0.99998	3.3532	1.1785	311.2304	311.0476
20.87	0.99993	3.3531	1.1454	285.2436	285.0894
19.61	0.99989	3.3528	1.1150	260.8722	260.6502
18.35	0.99980	3.3499	1.0846	237.4166	237.5737
17.09	0.99923	3.3491	1.0599	216.0417	215.8906
15.82	0.99838	3.3486	1.0375	195.8421	195.7189
14.56	0.99653	3.3448	1.0204	177.2373	177.1646
13.30	0.99471	3.3330	1.0087	160.0004	160.2219
12.03	0.98333	3.2825	1.0091	144.8587	144.6741
10.77	0.99261	3.3118	1.0115	129.9579	129.9934

[a] 1 $J.cm^{-3}$ = 1 MPa

Table 3. Calculated solubilities of ITRA in triacetin water mixtures by using calculated *'w'* values estimated by polynomial regression equations of the order 5 (by EHSA method) and by using logX_2 values determined as a function of solubility parameter with the use of polynomial regression equation of order 5 (by direct method). Percentage differences with respect to experimental solubilities are also indicated at 298.15K.

δ_1 (H)	X_{2cal}		% deviation[a]	
	EHSA method	Direct method	EHSA method	Direct method
23.40	8.94E-08	1.33E-07	3.31E+01	4.42E-01
22.14	3.25E-07	4.44E-07	2.46E+01	-2.93E+00
20.87	2.09E-06	2.61E-06	2.12E+01	1.26E+00
19.61	1.19E-05	1.40E-05	2.90E+01	1.67E+01
18.35	4.74E-05	5.33E-05	-2.74E+01	-4.35E+01
17.09	1.38E-04	1.51E-04	2.08E+01	1.34E+01
15.82	3.54E-04	3.78E-04	1.73E+01	1.17E+01
14.56	9.36E-04	9.71E-04	1.05E+01	7.25E+00
13.30	2.52E-03	2.54E-03	-4.03E+01	-4.14E+01
12.03	4.80E-03	4.92E-03	2.41E+01	2.22E+01
10.77	3.23E-03	3.25E-03	-5.56E+00	-6.03E+00
	Mean Value[b]		9.76	-1.89

[a] $\%\ Deviation = 100\ X\ (X_{2expt} - X_{2cal})/X_{2expt}$

Mean Value[b] were calculated using values obtained in neat solvents - triacetin, water and nine binary solvent mixtures

REFERENCES

[1] Pardeike J, Weber S, Haber T, Wagner J, Zarfl HP, Plank H, Zimmer A. Development of an Itraconazole-loaded nanostructured lipid carrier (NLC) formulation for pulmonary application. Int J Pharm. 2011;419:329−338.

[2] Peeters J, Neeskens P, Tollenaere JP, Van Remoortere P, Brewster ME. Characterization of the interaction of 2-hydroxypropyl- β-cyclodextrin with itraconazole at pH 2, 4, and 7. J Pharm Sci. 2002;91:1414−1422.

[3] Wu PL, Martin A. Extended Hildebrand solubility approach: Hydroxybenzoic Acid in mixtures of dioxane and water. J Pharm Sci. 1983 72:587-92.

[4] Subramanyam CVS, Sreenivasa RM, Venkata Rao J, Gundu Rao P. Irregular solution behaviour of paracetamol in binary solvents. Int J Pharm 1992;78:17-24.

[5] Martin A, Newburger J, Adjei A. Extended Hildebrand solubility approach: solubility of theophylline in polar binary solvents. J Pharm Sci.1980;69:487-91.

[6] Bustamante P, Escalera B, Martin A, Selles E. A modification of the extended Hildebrand approach to predict the solubility of structurally related drugs in solvent mixtures. J Pharm Pharmacol. 1993;45:253-7.

[7] Rathi PB, Mourya VK. Extended Hildebrand solubility approach: satranidazole in mixtures of dioxane and water. Indian J Pharm Sci. 2011;73:315-9.

[8] Sotomayor RG, Holguín AR, Cristancho DM, Delgado DR, Martínez F. Extended Hildebrand solubility approach applied to piroxicam in ethanol + water mixtures. J Mol Liq. 2013;180:34-38.

[9] Delgado DR, Peña MA, Martínez F. Extended Hildebrand solubility approach applied to some sulphapyrimidines in some {methanol (1) + water (2)} mixtures. Phy Chem Liq. 2017;256:176-88.

[10] Martin A, Miralles MJ. Extended Hildebrand solubility approach: Solubility of tolbutamide, acetohexamide and sulfisomidine in binary solvent mixtures. J Pharm Sci. 2006;71:439-42.

[11] Fukui E, Miyamura N, Yoneyama T, Kobayashi M. Drug release from and mechanical properties of press-coated tablets with hydroxypropylmethylcellulose acetate succinate and plasticizers in the outer shell. Int J of Pharm. 2001;217;33–43.

[12] Chang DP, Garripelli VK, Rea J, Kelley R, Rajagopal K. Investigation of fragment antibody stability and its release mechanism from poly(lactide-co-glycolide)-triacetin depots for sustained-release applications. J Pharm Sci. 2015;104:3404-3417.

[13] Fiume MZ, Panel CIRRE. Final report on the safety assessment of triacetin. Int J Toxicol. 2003;22:1–10.

[14] Yuksel N, Baykara M, Shirinzade H, Suzen, S. Investigation of triacetin effect on indomethacin release from poly(methyl methacrylate) microspheres: Evaluation of interactions using FT-IR and NMR spectroscopies. Int J of Pharm. 2011;404:102-109.

[15] Liu H, Venkatraman SS. Cosolvent effects on the drug release and depot swelling in injectable *in situ* depot-forming systems. J Pharm Sci. 2012;101:1783–1793.

[16] Higuchi T, Connors KA, Phase-solubility techniques. Adv Anal Chem Instr. 1965;4:117- 122.

[17] Fedors RF. A Method for estimating both the solubility parameters and molar volumes of liquids. Polym Eng Sci. 1974;14:147–154.

[18] Cárdenas ZJ, Almanza OA, Jouyban A, Martínez F, Acree Jr WE, Solubility and preferential solvation of phenacetin in methanol + water mixtures at 298.15 K. Phy Chem Liq. 2018;56:16-32 .

[19] Cristancho DM, Delgado DR, Martínez F. Meloxicam solubility in ethanol + water mixtures according to the extended Hildebrand solubility approach. J Solution Chem. 2013; 42:1706–1716.

[20] Yalkowsky SH, Roseman TJ. Solubilization of drugs by cosolvents. In: Yalkowsky SH (ed.) Techniques of Solubilization of Drugs. New York (NY): Marcel Dekker, Inc; 1981. p. 91–134.

[21] Rubino JT, Obeng EK. Influence of solute structure on deviations from the log-linear solubility equation in propylene glyco1: water mixtures. J Pharm Sci. 1991;80: 479-483.

[22] Li A, Yalkowsky SH, Solubility of organic solutes in ethanol/water mixtures. J Pharm Sci. 1994;83:1735-1740.

[23] Gómez JL, Rodríguez GA, Cristancho DM, Delgado DR, Mora CP, Yurquina A, Martínez F. Extended Hildebrand Solubility Approach applied to Nimodipine in PEG 400 + ethanol mixtures. Rev Colomb Cienc Quím Farm. 2013; 42: 103-121.

[24] Kharwade M, Achyuta G, Subrahmanyam CVS, Sathesh Babu PR. Solubility behavior of lornoxicam in binary solvents of pharmaceutical interest. J Solution Chem. 2012; 41:1364–1374.

[25] Thimmasetty J, Subrahmanyam CVS, Sathesh Babu PR, Maulik MA. Viswanath BA. Solubility behavior of pimozide in polar and nonpolar solvents: partial solubility parameters approach. J Solution Chem.2008; 37: 1365–1378.

[26] Rathi PB, Deshpande KV. Extended Hildebrand approach: an empirical model for solubility prediction of etodolac in 1, 4-dioxane and water mixtures. J Solution Chem. 2014; 43:1886–1903.

[27] Cárdenas ZJ, Jiménez DM, Delgado DR, Peña MA, Martínez F. Extended Hildebrand solubility approach applied to some sulphonamides in propylene glycol + water mixtures. Phy Chem Liq. 2015; 53:763-775.