



## Nabumetone Solubility Prediction in Dioxane-Water Mixtures Using Extended Hildebrand Solubility Approach

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### ABSTRACT

The extended Hildebrand solubility parameter approach is used to estimate the solubility of nabumetone in binary solvent systems. The solubility of nabumetone in various dioxane-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, dioxane-water shows a bell-shaped profile with a solubility maximum well below the ideal solubility of the drug. This is attributed to solvation of the drug with the dioxane-water mixture, and indicates that the solute-solvent interaction energy 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  $\delta_1$  of the binary mixture. Quadratic, cubic, and quartic expressions of ' $W$ ' in terms of solvent solubility parameter were utilized for predicting the solubility of nabumetone in various dioxane-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 solubility and yields an error in mole fraction solubility of ~7.346%, a value approximating that of the experimentally determined solubility. Thus the method has potential usefulness in preformulation and formulation studies during which solubility prediction is important for drug design.

**Keywords:** Dioxane, extended Hildebrand solubility approach, ideal solubility, interaction energy, nabumetone, regular solution theory, solubility parameter.

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### 1. INTRODUCTION

Solubility data on drugs and pharmaceutical adjuncts in Hildebrand solubility approach (EHSA), a modification of mixed solvents have wide applications in the drug sciences. the Hildebrand-Scatchard equation, permits calculation of Knowledge of interaction forces between solutes and the solubility of polar and non polar solutes in solvents solvents are of considerable theoretical and practical ranging from non polar hydrocarbons to highly polar interest throughout the physical and biological sciences solvents such as water, ethanol, and glycols [4]. The [1]. The theory of solution is one of the most challenging solubility parameters of solute and solvent were branch of physical chemistry. The Hildebrand-Scatchard introduced to explain the behaviour of regular and theory of regular solution is the pioneer approach in this irregular solutions [5].The extended Hildebrand solubility field, used to estimate solubility only for relatively non- parameter approach has been developed to reproduce the polar drugs in non-polar solvents [2]. An irregular solution solubility of drugs and other solids in the binary solvent is one in which self-association of solute or solvent, systems [6]. solvation of the solute by the solvent molecules, or The Hildebrand-Scatchard equation for solubility of solids complexation of two or more solute species are involved in a regular solution may be written as [7]: [3]. Polar systems exhibit irregular solution behaviour and are commonly encountered in pharmacy. The extended

$$-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2\delta_1\delta_2) \text{----- (1a) and}$$

$$-\log X_2 = -\log X_2^i + A(\delta_1 - \delta_2)^2 \text{----- (1b)}$$

The extended Hildebrand equation for the solubility of solids in an irregular solution may be written as [8]:

$$-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2W) \text{-----(2)}$$

From the geometric mean:

$$\delta_1\delta_2 = \sqrt{\delta_1^2\delta_2^2} \text{-----(3a),}$$

Where, in pharmaceutical solutions, the square root of geometric mean of  $\delta_1^2$  and  $\delta_2^2$ , that is  $\delta_1\delta_2 = (\delta_1^2\delta_2^2)^{1/2}$ , 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 1a) 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 solubility's,  $X_2$  as [9],

$$W = K\delta_1\delta_2 \text{-----(3b),}$$

Where, K is the proportionality factor relating interaction energy (W) to the geometric mean of solubility parameter ( $\delta$ ).

In Eqns 1 and 2,  $X_2$  and  $X_2^i$  are the mole fraction solubility and ideal mole fraction solubility of the solute respectively. The terms  $\delta_1$  and  $\delta_2$  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 nonpolar) mixtures, whereas W or  $K\delta_1\delta_2$  is required to express solubility's in nonregular systems (irregular solutions) of drugs in associating mixed solvents.

The term A in Eqns 1 and 2 is defined as [10]:

$$A = \frac{V_2\Phi_1^2}{2.303RT} \text{-----(4),}$$

Where,  $V_2$  is the molar volume of the solute taken as a supercooled liquid at solution temperature, R is the universal gas constant, T is the absolute temperature, 298.2 K, of the experiment and  $\Phi_1$ , the volume fraction of the solvent, is [11]:

$$\Phi_1 = \frac{V_1(1-X_2)}{V_1(1-X_2) + V_2X_2} \text{-----(5),}$$

Where,  $V_1$  is the molar volume of the solvent at 25°C.

Nabumetone, [4-(6-methoxy-2-naphthyl)-2-butanone], one of the large series of non-steroidal anti-inflammatory, BCS class II drug [12-14]. It is official only in USP till date [15-18].

A perusal to the structure of nabumetone (fig. 1) indicates that the molecule is aromatic and the functional groups may not contribute much to the aqueous solubility.

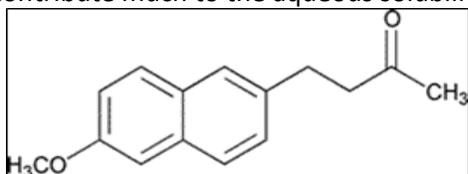


Figure 1: Structure of Nabumetone

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 [19, 20]. Therefore, it is necessary to explore the solubility of nabumetone in dioxane-water binary mixture.

Dioxane is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is completely non-aqueous water miscible solvent [21]. Dioxane-water binary mixtures are strongly non ideal and can act in the solute-solvation process via hydrophobic interactions and preferential solvation because, dioxane-water mixtures cover a wide range of Hildebrand solubility parameters from 10.01 (Cal/cm<sup>3</sup>)<sup>0.5</sup> (pure dioxane) to 23.45 (Cal/cm<sup>3</sup>)<sup>0.5</sup> (pure water). Thus, nabumetone is an ideal candidate for the study of solubility behaviour in mixtures of dioxane and water. The present investigation pertains to the utility of EHSA in relation to the nabumetone solubility in the solvent pair dioxane-water binary solvents.

## 2. MATERIALS AND METHODS:

### Materials:

Nabumetone, obtained as gift sample from GlaxoSmithKline Pharmaceuticals Ltd. Nasik, India. 1, 4-Dioxane was purchased from Research Lab Fine Chemical Industry, Islampur, 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, SICAN 2301, with spectral bandwidth of 2 nm, wavelength accuracy  $\pm 0.5$  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.

### Methods:

The solubility of nabumetone was determined in binary solvent mixtures of dioxane and water. Double distilled water was used to prepare mixtures with dioxane in concentrations of 0-100% by volume of dioxane. About 10 ml of dioxane, water, or binary solvent was introduced into screw-capped vials containing an excess amount of nabumetone. After being sealed with several turns of electrical tape, the vials were submerged in water at 25° and were shaken 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° [22, 23].

After equilibrium was attained, vials were removed for analysis. Firstly, solutions were filtered through Whatman filter paper (No. 41). After appropriate dilutions with double distilled water, the solutions were analyzed by using a spectrophotometer set at the wavelength of

maximum absorption of the nabumetone ( $\lambda_{max}$ -262 nm). Calibration graph of nabumetone in solvent blend was previously established with very high degree of correlation coefficient ( $R^2$ ) 0.9968, slope 0.0294 and negligible intercept (0.0113) as shown in fig 2.

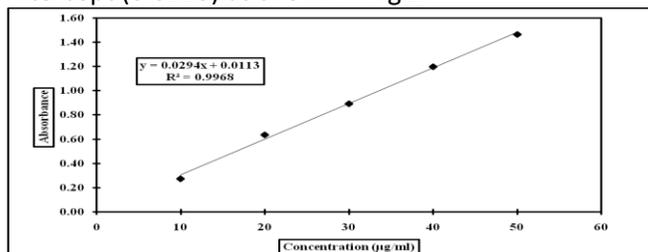


Fig. 2: Lambert-Beer plot of nabumetone

The working concentration range was from 10 to 50  $\mu\text{g/ml}$ . The solubility of the nabumetone was determined at least three times for each solvent, and the average value was taken. The densities of the solvent mixtures and the filtrates of the saturated solutions of nabumetone were determined in triplicate at 25<sup>o</sup> using 10-ml specific gravity bottle.

The solubility parameters of the solvents were obtained from the literature [24]. The solubility parameter of nabumetone was calculated by the method of Fedor [25, 26], which was confirmed by solubility analysis in dioxane-water blend.

**3. RESULTS AND DISCUSSION:**

Experimental data of mole fraction solubility of nabumetone in dioxane-water are plotted against solubility parameters of solvent blend (fig.3)

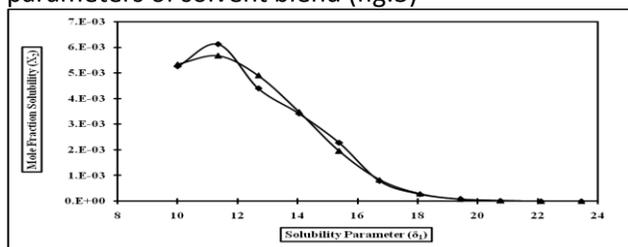


Fig. 3: Solubility parameter versus mole fraction solubility profile

Solubility of nabumetone in dioxane, water, and dioxane-water mixtures at 25<sup>o</sup>. Key: (---◆---) Experimental solubility's and (---Δ---) back-calculated solubility's from Eqn. 2. Highest mole fraction solubility obtained is,  $X_{2obs}=6.118 \times 10^{-3}$  when  $\delta_1=11.35$  (Cal/cm<sup>3</sup>)<sup>0.5</sup> in Dioxane-water mixtures

exhibit a maxima at  $\delta_1 = 11.35$  ( $X_{2obs} = 0.006118$  mol/lit and  $X_{2cal} = 0.005669$  mol/lit). The observed solubility is comparatively lower than the ideal solubility ( $X_2^i = 0.145386$  mol/lit). According to the regular solution theory, solubility cannot depart from ideal solubility. However, in non regular solutions peak solubility may depart from ideal solubility due to solute solvent interactions. This abnormal behavior has been dealt with the theoretical replacement of mean geometric solubility parameters ( $\delta_1\delta_2$ ) term with the interaction energy term (W). To relate these two variables, a fourth power polynomial (quartic expression) has been developed to back calculate the value of  $W_{cal}$ . For Dioxane-water system, the polynomial has following values:  $W_{obs} = 53.967431 - 2.750091 \delta_1 + 0.8828226 \delta_1^2 -$

$0.0206541 \delta_1^3 + 0.0003439 \delta_1^4$ , ( $n=11, R^2 = 0.9999984$ ) ----- (6) This polynomial is further used successfully for the calculation of W, at any value of solubility parameter ( $\delta_1$ ), which was subsequently employed to calculate mole fraction solubility of solute in a solvent blend using backward regression. Representative data along with validation parameters are summarized in Table 1.

Water: Dioxane (%v/v)	Solubility y (g/ml)	$\delta_1$ (Cal/cm <sup>3</sup> ) <sup>0.5</sup>	$V_1$	Density of blend	Mol. Wt of blend	$X_{2(obs)}$	$W_{(obs)}$
100:0	1.9138E-05	23.45	18.0	0.9980	18.0	1.512E-06	312.6
90:10	5.0069E-05	22.11	24.7	1.0016	25.0	5.477E-06	283.5
80:20	1.6759E-04	20.76	31.4	1.0052	32.0	2.339E-05	256.5
70:30	5.0938E-04	19.42	38.1	1.0088	39.0	8.637E-05	231.1
60:40	1.3739E-03	18.07	44.8	1.0124	46.0	2.740E-04	207.3
50:50	3.4179E-03	16.73	51.6	1.0160	53.0	7.838E-04	185.2
40:60	8.7612E-03	15.39	58.3	1.0196	60.0	2.275E-03	164.8
30:70	1.1802E-02	14.04	65.0	1.0232	67.0	3.417E-03	145.5
20:80	1.3784E-02	12.70	71.7	1.0268	74.0	4.397E-03	127.9
10:90	1.7552E-02	11.35	78.4	1.0304	81.1	6.118E-03	112.1
0:100	1.3966E-02	10.01	85.2	1.0340	88.1	5.256E-03	97.61

Table 1: Molar observed solubility and calculation parameters of nabumetone in dioxane-water mixtures.  $\delta_1$ = Solubility parameter of solvent blend,  $V_1$ = molar volume of the solvent blend, and W is calculated from Eqn. 2

$W_{cal}$  values are indicating significant interaction of nabumetone and solvent molecules at the peak of solubility profile.

Observed solubility data was subjected to the evaluation of interaction energy. Experimental values of interaction energy ( $W_{obs}$ ) were regressed against solubility parameter ( $\delta_1$ ), to obtain fourth order polynomial coefficients (fig. 4), which was then used to back calculate interaction energy ( $W_{cal}$ ) and the mole fraction solubility ( $X_{2cal}$ ).

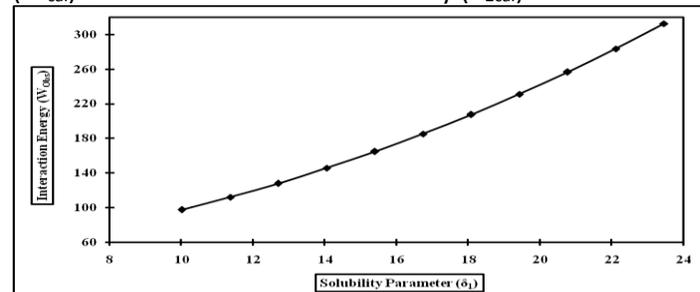


Fig. 4: Solubility parameter versus interaction energy profile  $W_{cal}$  obtained from quartic regression Eqn. 6, for nabumetone in dioxane-water mixtures at 25<sup>o</sup> and correlation coefficient,  $r^2$ , is 0.9999984 for n = 11

The nabumetone solubility within the accuracy ordinarily more precisely using EHSA. The procedure can be explored achieved in such measurements. The predictive capability further to predict the solubility of nabumetone in pure of the model for nabumetone is represented in fig.5, which water or dioxane and in any dioxane-water 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.

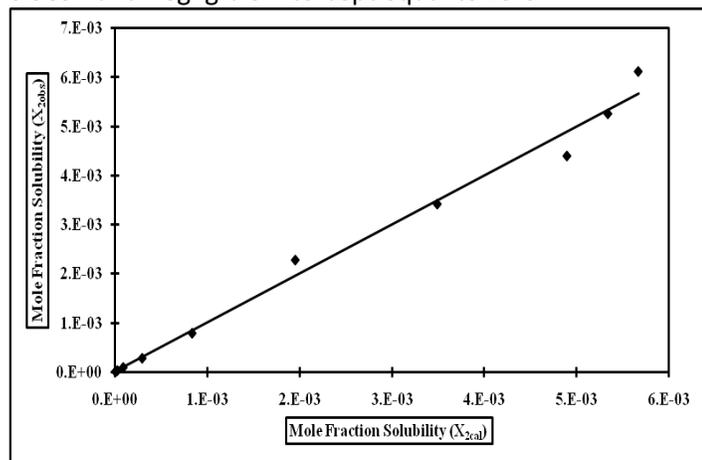


Fig. 5: Comparison of observed and calculated mole fraction solubility Comparison of 11 observed nabumetone solubility's in dioxane-water mixtures at 25° with solubility's predicted by the extended Hildebrand approach. The intercept of the line is zero, and the slope is 0.9978. The correlation coefficient,  $r^2$ , is 0.9897 for  $n = 11$

Another aspect for assessment of extended Hildebrand solubility approach is to plot residuals of solubility versus solubility parameter for dioxane-water binary mixtures (fig.6), which shows values of residuals are closer to zero and scattered around a line with zero slope.

On the basis of validation parameters, it can be expressed that the behavior of non regular solution can be quantified

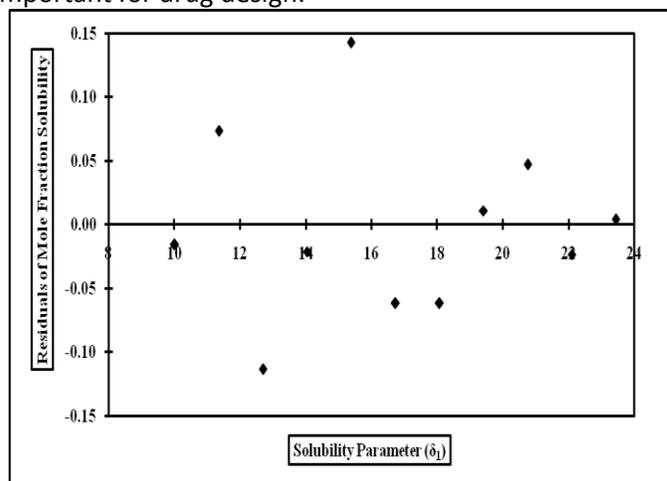


Fig. 6: Scatterplot of residuals of solubility versus solubility parameter

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W <sub>(obs)</sub>	W <sub>(cal)</sub>	X <sub>2(obs)</sub>	X <sub>2(cal)</sub>	[log <sub>2</sub> /A] <sub>(obs)</sub>	[log <sub>2</sub> /A] <sub>(cal)</sub>	Residuals	Percent Difference
312.6029	312.5980	1.512E-06	1.506E-06	28.103	28.113	3.972E-03	3.972E-01
283.5647	283.5929	5.477E-06	5.604E-06	24.952	24.896	-2.327E-02	-2.327E+00
256.5327	256.4737	2.339E-05	2.229E-05	21.402	21.520	4.702E-02	4.702E+00
231.1255	231.1119	8.637E-05	8.542E-05	18.214	18.242	1.104E-02	1.104E+00
207.3319	207.4056	2.740E-04	2.909E-04	15.412	15.265	-6.183E-02	-6.183E+00
185.2064	185.2803	7.838E-04	8.322E-04	12.887	12.739	-6.168E-02	-6.168E+00
164.8799	164.6879	2.275E-03	1.951E-03	10.376	10.760	1.426E-01	1.426E+01
145.5811	145.6077	3.417E-03	3.490E-03	9.422	9.369	-2.139E-02	-2.139E+00
127.9100	128.0456	4.397E-03	4.896E-03	8.826	8.555	-1.135E-01	-1.135E+01
112.1316	112.0346	6.118E-03	5.669E-03	8.057	8.251	7.346E-02	7.346E+00
97.6148	97.6346	5.256E-03	5.340E-03	8.377	8.337	-1.583E-02	-1.583E+00

Table 2: Comparisons of observed and calculated mole fraction solubilities of nabumetone in dioxane-water mixtures at 25° W<sub>cal</sub> obtained from quartic regression Eqn. 6, for Nabumetone in dioxane-water mixtures at 25°. Residuals can also be obtained from, [(X<sub>2obs</sub>-X<sub>2cal</sub>)/X<sub>2obs</sub>]

## 5. REFERENCES:

- Martin A, Newburger J, Adjei A. Extended Hildebrand solubility approach: solubility of theophylline in polar binary solvents. *J Pharm Sci* 1980; 69: 487-491.
- Wu PL, Martin A. Extended Hildebrand solubility approach: hydroxybenzoic acid in mixtures of dioxane and water. *J Pharm Sci* 1983; 72: 587-592.
- Thimmasetty J, Subramanyam CVS, Vishwanath BA, Satish Sabu PR. Solubility parameter estimation of celecoxib by current methods. *Asian J Research Chem* 2009; 2: 188-195.
- Subramanyam CV, Sreenivasa RM, Venkata RJ, Gundu RP. Irregular solution behaviour of paracetamol in binary solvents. *Int J Pharm* 1992; 78: 17-24.
- Babu PR, Subrahmanyam CV, Thimmasetty J, Manavalan R, Valliappan K. Extended Hansen's solubility approach: meloxicam in individual solvents. *Pak J Pharm Sci* 2007; 20: 311-316.
- Martin A, Carstensen J. Extended solubility approach: solubility parameters for crystalline compounds. *J Pharm Sci* 1981; 70: 170-172.
- Martin A, Wu PL, Velasquez T. Extended Hildebrand solubility approach: sulfonamides in binary and ternary solvents. *J Pharm Sci* 1985; 74: 277-282.
- Martin A, Miralles MJ. Extended Hildebrand solubility approach: solubility of tolbutamide, acetohexamide and sulfisomidine in binary solvent mixtures. *J Pharm Sci* 2006; 71: 439-442.
- Mourya VK, Yadav SK, Saini TR. Solubility studies of metronidazole in binary solvent blends. *Indian J Pharm Sci* 1997; 59: 200-202.
- Martin A, Wu PL, Beerbower A. Expanded solubility parameter approach I: naphthalene and benzoic acid in individual solvents. *J Pharm Sci* 1984; 73: 179-188.
- Herrador MA, Gonzalez AG. Solubility prediction of caffeine in aqueous N, N-dimethyl formamide mixtures using the extended Hildebrand solubility approach. *Int J Pharm* 1997; 156: 239-244.
- Chelakara LV, Kulkarni SK, Kolwankar DR. Spherical agglomeration of mefenamic acid and nabumetone to improve micromeritics and solubility: A technical note. *AAPS Pharm Sci Tech* 2006; 7: Article 48 E1-E4.
- Friedel HA, Todd PA. Nabumetone: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in rheumatic diseases. *Drugs* 1988; 35: 504-524.
- Margarita V, Javier T, Licesio J. Encapsulation of nabumetone by means of -drug:( $\beta$ -cyclodextrin):polyvinylpyrrolidone ternary complex formation. *J Lum* 2007; 126: 297-302.
- United States Pharmacopoeia, USP 31/NF, Volume 326, US Pharmacopoeial Convention, Inc., Rockville, 2008; 2743-2744.
- Mohite AH. Development of UV-spectroscopic method for nabumetone in tablet formulation. *J Pharm Res* 2009; 2: 1221-1223.
- Rote R. Development and statistical validation of spectrophotometric methods for the estimation of nabumetone in tablet dosage form. *E J Chem* 2010; 7: 1463-1467.
- Lakshmi PB. Development and validation of nabumetone by isocratic RP-HPLC method. *Int Res J Pharm App Sci* 2012; 2: 92-98.
- Rao KP, Kamamia EK. Characterisation of nabumetone microcrystals prepared by solvent evaporation method. *Int J Res Pharm Biomed Sci* 2011; 2: 1346-1349.
- Shingade G. Development of nabumetone topical gels: effect of formulation variables on the release of nabumetone. *World J Pharm Research* 2012; 1: 776-785.
- Spiegel AJ, Noseworthy MM. Use of non-aqueous solvents in parenteral products. *J Pharm Sci* 1963; 52: 917-927.
- Rathi PB, Mourya VK. Extended Hildebrand solubility approach: satranidazole in mixtures of dioxane and water. *Indian J Pharm Sci* 2011; 73: 315-319.
- Rathi PB. Solubility prediction of satranidazole in propylene glycol-water mixtures using extended Hildebrand solubility approach. *Indian J Pharm Sci* 2011; 73: 670-674.
- Patrick JS. *Martin's Physical Pharmacy and Pharmaceutical Sciences*, 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 245-246, and p. 595-596.
- Barton AF. *CRC Handbook of Solubility Parameters and other Cohesion Parameters*, 2nd ed. New York: CRC Press; 1983. p. 7-59, and p. 157-185.
- Greenhalgh DJ, Williams AC, Timmins P, York P. Solubility parameters as predictors of miscibility in solid dispersions. *J Pharm Sci* 1999; 88: 1182-1190

**Conflict of Interest: None Declared**

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