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Solubility Behavior of Pimozide in Polar and Nonpolar Solvents: Partial Solubility Parameters Approach

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Abstract The solubility behavior of pimozide in individual solvents ranging from nonpolar to highly polar was studied. For understanding the solute-solvent interactions, the partial solubility parameters concept was utilized. Solutions containing excess drug were shaken in a water bath for 72 hours at 25 °C. After the solutions attained equilibrium, they were filtered and analyzed for drug content. A multiple regression method, using extended Hansen's partial solubility parameters, was applied to verify the solubilities of pimozide in pure polar and nonpolar solvents and to predict its solubility in untested solvents. The three-parameter approach and the Flory-Huggins size correction term 'B' give predictions of solubilities with correlations up to 97%. The four-parameter approach involving proton-donor and proton-acceptor parameters was also used in fitting the solubility data. The correlations are appreciable (94%). Further, the 'B' term coupled with four-parameter approach was examined in order to improve the data representation, and resulted in a 1% improvement (98%) in the correlation when compared to the Flory-Huggins size-correction method. The solubility parameter obtained by this method is 10.43 H which is closer to the values obtained by theoretical methods, such as Fedors' and Hoy's. The resulting partial solubility parameters are $\delta_{2d} = 8.85$ H, $\delta_{2p} = 2.17$ H, $\delta_{2a} = 3.15$ H, and $\delta_{2b} = 4.08$ H, which give insights into the interaction capability of pimozide and are consistent with its chemical structure. Pimozide is a Lewis base as its $\delta_{2b} > \delta_{2a}$. The total solubility parameter of pimozide is assigned at 10.43 H. This work demonstrates for the first time the validity of the four-parameter ap-

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proach coupled with the Flory-Huggins size-correction term and therefore the result is interesting.

Keywords Pimozide · Solubility parameter · Partial solubility parameters · Solubility behavior · Extended Hansen's approach · Flory-Huggins size correction

1 Introduction

The nature of liquid mixtures may be interpreted in terms of molecular interactions broadly classified as either "reactive" (involving relatively strong "chemical" forces such as complex formation, etc.) or "non reactive" (involving relatively weak "physical" or van der Waals forces). Solution nonideality can of course be best explained if both "chemical" and "physical" forces are considered; the true situation is generally intermediate between these two extremes [1].

The solubility parameter approach is basically "physical", but the introduction of specific interaction components has taken it towards a reasonably balanced position. The solubility parameter, δ_T, is an intrinsic physicochemical property of a substance, which is identified with the square root of the cohesive energy density of the substance and is expressed as the Hildebrand solubility parameter or Hildebrand parameter [1]. The cohesive energy density itself is defined as the ratio of the energy of vaporization to the molar volume at the same temperature [2]. This one-dimensional solubility-parameter approach was applied primarily to nonpolar liquid. This has been used to explain drug action [3], structure activity relationship [4, 5], drug absorption [6, 7], in situ release of a drug [8], gas-solid chromatography [9], swelling of polymers [10], HPLC [11], fast prediction of the basic properties of materials [12], interaction between materials including drug-excipient and drug-plasma protein [13], solvent selection for organic reactions [14], selection of polymer-surfactant combinations [15], predicting cohesive and adhesive properties of materials [1], prediction of the adhesion of film coatings to tablets [16, 17], and dosage form technology and design [18–20]. It has been suggested that the solubility parameter is a possible substitute for the partition coefficient in the study of the passage of drugs across living membranes [4, 5]. In addition, the solubility parameter has been shown to be connected to other physical properties such as surface tension, wettability, the ratio of the coefficient of thermal expansion to compressibility, the boiling points in the case of nonpolar liquids, the ultimate strength of materials, and the glass transition temperature of polymers, to cite a few examples [2].

The solubility parameter concept has since been extended to various systems such as polar, polymer-solvent, and polymer-polymer systems. The solubility parameter, δ_T, has been applied to theoretically predicting the solubility of drugs in solvents and cosolvents. Compounds with similar values for their solubility parameters are likely to be miscible. This is because the energy of mixing within the components is balanced by the energy released by interaction between the components. Substances are classified based on difference between the solubility parameters of substances and drugs, $\Delta\delta$. Greenhalgh et al. [21] demonstrated that compounds with $\Delta\delta < 7.0$ MPa$^{1/2}$ are likely to be miscible whereas compounds with a $\Delta\delta > 10$ MPa$^{1/2}$ are likely to be immiscible [22]. In this context, it is proposed that the closer are the δ_T values of drug and solvent, the higher will be its solubility. Solubility parameters have been experimentally determined for many liquids and polymers [1]. The methods used for liquids is based upon the enthalpy of vaporization, but cannot usually be applied to drugs because many of them are crystalline solids that decompose at temperatures before they can evaporate.

Hansen extended the original Hildebrand parameter to three-dimensional solubility parameters (Hansen solubility parameters) for polar and hydrogen bonding systems. According to this concept, the total solubility parameter is separated into three different types of partial solubility parameters, δ_d representing the London dispersion forces, δ_p representing the Keesom dipolar interactions, and δ_h representing generalized electron transfer bonding including hydrogen bonding and acid-base interaction [23]. These quantities are related by the expression:

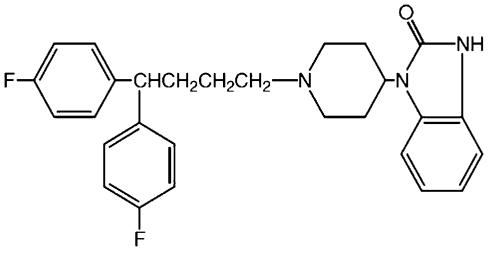
$$\delta_{\mathrm{T}}^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \tag{1}$$

where δ_{T} is the total solubility parameter and is quite similar to the δ as defined by Scatchard and Hildebrand [24]. Hansen's total solubility parameter corresponds to the Hildebrand parameter. Nevertheless, these two quantities are probably different when they are obtained by different methods.

The partial solubility parameters of solvents are found to play a role in the solubilization of drug molecules, which in turn depends on the drug's chemical structure. However, the partial solubility parameters have not been widely employed in pharmacokinetics and structure activity studies. Only a few values for the partial solubility parameters of drugs have been determined experimentally [1, 25, 26]. The extended Hansen's approach, the Flory-Huggins size-correction term (B), and the four-parameter approach are 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 [27, 28]. The partial solubility parameters can also be predicted from various methods including group contribution calculations [29]. The bifurcation of the total solubility parameter, δ_{T}, of the drug into partial solubility parameters may provide greater insights on interactions, though such correlations have not been explored.

This work tests the applicability of the extended Hansen method (three- and four-parameter approaches) and Flory-Huggins size-correction term approach to determine the partial solubility parameters. Thereafter the four-parameter approach is coupled with the Flory-Huggins size-correction-term approach to verify its suitability. The method uses a regression analysis of the logarithm of the experimental mole fraction solubility of pimozide against the partial solubility parameters of the solvents.

Pimozide is a diphenylbutylpiperidine derivative with neuroleptic properties that has been found to be useful in the management of chronic schizophrenia. It is relatively non-sedating and can be administered as a single daily dose. The chemical formula of pimozide ($C_{28}H_{29}F_2N_3O$) is 1-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one. The solubility of pimozide in water is less than 0.01 mg·mL^{-1}, and it is slightly soluble in most organic solvents [30]. For this drug, the in vitro dissolution testing is more stringent. The structure of pimozide is given below.



Pimozide was chosen for this study because of its chemical structure. A perusal of the structure of pimozide indicates that the molecule is highly aromatic with a hydrophobic

group such as fluorine. The oxygen atom of the C=O group may participate in hydrogen bonding. The molecule as a whole behaves as a nonpolar solute as reflected by its low solubility in polar solvents. It is necessary to evaluate the relative contributions of nonpolar, polar, and hydrogen bonding, rather than just evaluating the gross behavior of its total solubility parameter. Thus pimozide is a suitable candidate for the study of solubility behavior.

The present work is an attempt to determine the solubility behavior of pimozide (which may serve as a model drug molecule) in individual solvents ranging from nonpolar (e.g., hexane), semipolar (e.g., benzene), to polar (e.g., water). The substituted aromatic groups and flexible chains of drug molecules, exhibiting dipolar forces, hydrogen bonding, steric interferences, and ionic charges, make the prediction of solubility in drug research and development a formidable task. Various approaches are used to analyze the experimental solubility and obtain regression equations, so that the drug solubility can be predicted in untested solvents. The results obtained for benzoic acid by the UNIFAC (Universal Functional Activity Coefficient) procedure and for *p*-hydroxy benzoic acid by the four-parameter equation are satisfactory [31]. Using solubility data, an equation is developed based on the four-parameter method coupled with the '*B*' term. Using this equation, the partial solubility parameters and thereafter solubility parameter values are calculated. The values so obtained are compared with theoretically obtained ones [2, 32, 33] using fragmental constants. The correlation developed may serve as a benchmark—a goal to be achieved in predicting the solubility of drugs in general. The methods used here and the conclusions drawn are not generally applicable to the binary solvent systems.

2 Materials and Methods

The pimozide was a gift sample (Vasudha Pharmaceuticals Ltd., Hyderabad, India). The set of solvents used covers a wide range on the Hildebrand solubility parameter scale, from hexane (7.3 H) to water (23.4 H). Other chemicals used are of analytical grade. The molar enthalpy of fusion (ΔH_f) was determined calorimetrically as 46.903 kJ·mol^{-1} using a differential scanning calorimeter (DSC 7, Perkin-Elmer, USA) at the temperature of fusion $T_o = 493.5$ K. These data are used here to calculate the ideal mole fraction solubility [27] at 298 K as 0.00313, or $\log_{10} X_2^i = -2.5045$. The solubility of pimozide was determined in a number of solvents representative of several chemical classes ranging from nonpolar to highly polar (Table 1). Among the solvents used, isopropyl alcohol is used in cosmetics and dermatological preparations [34]; whereas ethanol, propylene glycol, and glycerin are used in injectable preparations [35] and liquid orals. Excess amounts of drug were added directly to the solvents. The flasks were shaken in a cryostat, constant temperature, reciprocating shaker bath (Research and Test equipments, Bangalore, India) at room temperature (25 ±1 °C) for at least 72 hours in order to achieve equilibrium, which was confirmed by comparing the concentrations in various samples equilibrated at 72 and 96 hours. After 72 hours of equilibration, aliquots were withdrawn, filtered (0.22 μm pore size), and diluted suitably. These samples were then analyzed at 279 nm on a Shimadzu UV/Vis spectrophotometer (UV-1601 PC, Shimadzu, Japan). After dilution of the samples, the solvents did not interfere with the spectrophotometric readings. All solubility experiments were conducted in triplicate. The molar volumes and partial solubility parameters of the solvents collected from the literature [36] are shown in Table 1. The total solubility parameter of pimozide is calculated by the methods of Fedors and of Hoy [2, 32]. Partial solubility parameter values of pimozide are calculated using a group contribution method (Table 2) [33]. The properties of pimozide are included in the footnotes of Table 1.

Table 1 Experimental and calculated solubilities of pimozide—partial solubility parameters of individual solvents[a]

Solvent	Molar volume (V_1) $cm^3 \cdot mol^{-1}$	Partial solubility parameters					δ_T	$(\log_{10}\gamma_2)/A$ (expt.)	X_2 (expt.)	X_2 (calc.) Eq. 13	Percent error (%)
		δ_d	δ_p	δ_h	δ_a	δ_b					
Hexane	131.6	7.3	0	0	0	0	7.3	9.3511	7.40×10^{-6}	0.0005	−6642.41
Ethyl acetate	98.6	7.4	2.6	4.5	5.3	1.9	8.9	0.5988	0.0021	0.0050	−135.00
Benzene	89.4	9	0.5	1	0.7	0.7	9.1	2.2032	7.60×10^{-4}	0.0022	−185.13
Dioxane	85.7	9.3	0.9	3.6	1	6.5	10	−2.1869	1.13×10^{-2}	−0.0019	117.16
n-Octanol	158.7	8.3	1.6	5.8	5.2	3.2	10.23	−0.4296	4.11×10^{-3}	0.0109	−164.97
n-Heptanol	141.9	8.1	2	6	5.3	3.4	10.28	−0.4334	4.12×10^{-3}	0.0077	−88.13
n-Hexanol	125.2	8	2.1	6.3	5.7	3.5	10.41	−0.0898	3.31×10^{-3}	0.0095	−187.98
n-Pentanol	108.6	7.8	2.2	6.8	5.4	4.3	10.59	−0.0547	3.24×10^{-3}	0.0035	−7.46
n-Butanol	91.5	7.8	2.8	7.7	6.4	4.6	11.3	1.1413	2.49×10^{-3}	0.0039	−55.98
Isopropyl alcohol	76.9	7.7	3	8	7.1	4.5	11.5	1.635	1.10×10^{-3}	0.0053	−382.57
n-Propanol	75.2	7.8	3.3	8.5	7.5	4.8	12	1.1413	1.51×10^{-3}	0.0042	−179.91
Ethanol	58.5	7.7	4.3	9.5	8.3	5.5	13	1.5279	0.0012	0.0019	−57.79
Methanol	40.7	7.4	6	10.9	8.4	7.1	14.5	2.1023	8.21×10^{-4}	0.0007	19.47
Propylene glycol	73.6	8.2	4.6	11.4	14.1	4.6	14.8	3.9084	2.52×10^{-4}	0.0024	−838.33

Table 1 (*Continued*)

Solvent	Molar volume (V_1) $cm^3 \cdot mol^{-1}$	Partial solubility parameters					δ_T	$(\log_{10}\gamma_2)/A$ (expt.)	X_2 (expt.)	X_2 (calc.) Eq. 13	Percent error (%)
		δ_d	δ_p	δ_h	δ_a	δ_b					
Glycerin	73.3	8.5	5.9	14.3	20	5.1	17.7	5.4062	9.52×10^{-5}	0.0006	−552.49
Water	18	7.6	7.8	20.7	6.7	32	23.4	13.3153	5.70×10^{-7}	0.0002	−28626.62
Cyclo-hexane	108.7	8.2	0	0	0	0	8.2	8.7382	1.10×10^{-5}	0.0008	−7565.77
Toluene	106.8	8.8	0.7	1	0.8	0.6	8.9	0.4847	2.30×10^{-3}	0.0018	22.73

[a]Molar enthalpy of fusion $\Delta H_f = 46.903$ kJ·mol^{-1}, melting point $T_o = 493.5$ K, solubility parameter $\delta_2 = 9.7$ H (where H refers to the Hildebrand solubility scale), molar volume $V_2 = 383.06$ cm^3·mol^{-1}, ideal solubility $(X_2^i) = 0.0031307$, $\log_{10} X_2^i = -2.5044$, X_2(expt.) = experimental mole fraction solubility, and X_2 (calc.) = calculated mole fraction solubility

Table 2 Solubility parameter values for pimozide by different methods

Sl No	Method/system	Solubility parameter	
		H, Hildebrand (CGS units)	$MPa^{1/2}$ (SI units)
1.	Fedors[a]	11.08	22.60
2.	Hoy's[b]	11.10	22.64
		$\delta_{2T}(\delta_{2d}, \delta_{2p}, \delta_{2h})$	$\delta_{2T}(\delta_{2d}, \delta_{2p}, \delta_{2h})$
3.	Group contribution method[c]	9.28 (8.62, 1.58, 3.07)	18.93 (17.62, 3.23, 6.28)
4.	Three-parameter approach with $(\log_{10}\gamma_2)/A$[d]	12.63 (8.08, 5.40, 8.07)	25.77 (16.53, 11.05, 16.51)
5.	Flory-Huggins size correction term B[e]	11.32 (9.43, 2.64, 5.68)	23.09 (19.29, 5.40, 11.62)
6.	Four-parameter approach with $(\log_{10}\gamma_2)/A$[f]	13.16 (11.60, 5.60, 2.69)	26.85 (23.73, 11.46, 5.50)
7.	Four-parameter approach with B[g]	10.43 (8.85, 2.17, 5.07)	21.28 (18.10, 4.44, 10.37)

[a]Estimated from Fedors' molar attraction constants [2]

[b]Estimated from the Hoy's substituent method [32]

[c]Estimated from the fragmental constants for partial solubility parameters [33]

[d]Three-parameter approach using $(\log_{10}\gamma_2)/A$, Eq. 7

[e]Three-parameter approach using B replacing $(\log_{10}\gamma_2)/A$, Eq. 10

[f]Four-parameter approach using $(\log_{10}\gamma_2)/A$, Eq. 12

[g]Four-parameter approach using B replacing $(\log_{10}\gamma_2)/A$, Eq. 13

The absorption spectrum of pimozide in 0.1 $mol{\cdot}L^{-1}$ hydrochloric acid solution was obtained ($\lambda_{max} = 279$ nm). The calibration curve was constructed and Beer's law was obeyed in the concentration range of 5 to 60 $\mu g{\cdot}mL^{-1}$. The densities of the saturated solutions were determined in a 25 mL specific gravity bottle. The molar volume was determined experimentally by the floatation technique [37]. For solubility calculations, the necessary in-house developed software GW BASIC was used. The quantities 's' represent the standard error of the 'y' estimate at the 99% confidence level. A P4 Wipro computer was used.

3 Results and Discussion

The extended Hansen method, the three-parameter approach, has been proposed to obtain partial solubility parameters of crystalline drug compounds [28]. The extended Hansen's model can be written as:

$$\frac{1}{A}\log_{10}\left(\frac{X_2^i}{X_2}\right) = \frac{\log_{10}\gamma_2}{A} = C_o + C_1(\delta_{1d} - \delta_{2d})^2 + C_2(\delta_{1p} - \delta_{2p})^2 + C_3(\delta_{1h} - \delta_{2h})^2 \quad (2)$$

where δ_d, δ_p, and δ_h have been described earlier. X_2^i is the ideal mole fraction solubility and X_2 is the experimental mole fraction solubility. C_1, C_2, and C_3 are coefficients obtained by multiple regression analysis. C_0 is a constant that represents the solute dissolved in a series of solvents. Throughout this paper, subscript 1 refers to the solvent and subscript 2 refers to the solute. Here $\log_{10}\gamma_2$ is the logarithm of the solute activity coefficient, where

$$\gamma_2 = X_2^i/X_2 \quad (3)$$

and

$$A = \frac{V_2 \phi_1^2}{2.303RT} \tag{4}$$

where V_2 is the molar volume of the solute, considered as a hypothetical super-cooled liquid at the temperature of the solution. The molar volume of pimozide, as determined by the floatation technique [37], is 383.06 $cm^3 \cdot mol^{-1}$. This value is also supported by the molar volume calculated by the group contribution method of Fedors. R and T have their usual meanings. The solvent volume fraction, ϕ_1, is as follows:

$$\phi_1 = \frac{V_1(1 - X_2)}{V_1(1 - X_2) + V_2 X_2} \tag{5}$$

This method was successfully adopted for drugs such as sulfamethoxypyridazine [38], haloperidol [39], and trimethoprim [40].

The total solubility parameter and partial solubility parameters of pimozide, calculated by theoretical methods, are shown in Table 2. The experimental solubilities of pimozide in individual solvents and other associated parameters are recorded in Table 1. When the extended Hansen approach is applied to the experimental solubilities of pimozide, the following regression equation is obtained:

$$\frac{(\log_{10} \gamma_2)}{A} = -149.20 + 40.43\delta_{1d} - 2.60\delta_{1d}^2 - 1.99\delta_{1p} + 0.34\delta_{1p}^2 - 0.90\delta_{1h} + 0.05\delta_{1h}^2 \tag{6}$$

where $n = 18$, $s = 1.86$, and $R^2 = 0.86$.

The signs of the coefficients agree with the standard format of Eq. 2. Equation 6 is written according to the model expression given by Eq. 2, and the partial solubility parameters obtained are $\delta_{2d} = 7.76$ H, $\delta_{2p} = 2.97$ H, and $\delta_{2h} = 9.33$ H. The total solubility parameter, δ_{2T}, was calculated using Eq. 1 and found to be 12.49 H. The differences between the experimental and the calculated solubility values are found to be high, with errors ranging from −475 to +78%. Such large errors are possible as pimozide is poorly soluble. Therefore, the analysis was repeated by excluding four solvents (hexane, cyclohexane, glycerin, and propylene glycol), which were the least well fitted by the model and showed high percent errors in the calculated solubility using Eq. 6. This is similar to the observation made by Bustamante et al. [41]. For the rest of the solvents, the regression equation is obtained as:

$$\frac{(\log_{10} \gamma_2)}{A} = -62.34 + 15.88\delta_{1d} - 0.98\delta_{1d}^2 + 1.97\delta_{1p} - 0.18\delta_{1p}^2 - 1.29\delta_{1h} + 0.08\delta_{1h}^2 \tag{7}$$

where $n = 14$, $s = 0.86$, and $R^2 = 0.97$.

The signs of the coefficients agree with the standard format of Eq. 2. The regression coefficient is improved by 11% and the standard error of the y-estimate is decreased in comparison with Eq. 6. Equation 7 is written according to the model expression represented by Eq. 2 and the partial solubility parameters obtained are $\delta_{2d} = 8.08$ H, $\delta_{2p} = 5.40$ H, and $\delta_{2h} = 8.07$ H. The δ_{2d} value is almost the same as that of the value obtained from the group contribution method. The total solubility parameter, δ_{2T}, was calculated using Eq. 1 and found to be 12.63 H. The differences between the experimental and the calculated solubility values are found to be in the range of −166 to 42%. Obviously, there is a need to improve the correlations by different methods.

The three-parameter approach was modified using the Flory-Huggins size-correction term 'B' [40]. This term accounts for the deviation of a drug solution from regular solution behavior because of specific solute-solvent interactions, if any, and size differences between the solute and solvent [22]. This 'B' can be written as follows:

$$B = \frac{RT[\log_{10}\gamma_2 - \log_{10}(V_2/V_1) - 1 + (V_2/V_1)]}{V_2\phi_1^2} \tag{8}$$

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

$$B = D_1\delta_{1d} + D_2\delta_{1d}^2 + D_3\delta_{1p} + D_4\delta_{1p}^2 + D_5\delta_{1h} + D_6\delta_{1h}^2 + D_o \tag{9}$$

Equation 9 can also be transformed into an expression analogous to Eq. 2. This method has been successfully applied for drugs such as haloperidol. The Flory-Huggins size-correction approach for pimozide in individual solvents was investigated in order to improve the correlation coefficients and get a better fit to the experimental values. The following equation is obtained:

$$B = 135.49 - 27.29\delta_{1d} + 1.45\delta_{1d}^2 - 2.12\delta_{1p} + 0.40\delta_{1p}^2 - 1.52\delta_{1h} + 0.13\delta_{1h}^2 \tag{10}$$

where $n = 18$, $s = 2.26$, and $R^2 = 0.97$.

Equation 10 is found to give a better correlation by 11% when compared to Eq. 6. The signs of the coefficients agree with the standard format of Eq. 2. Equation 10 is written according to the model represented by Eq. 2 and the partial solubility parameters obtained are $\delta_{2d} = 9.43$ H, $\delta_{2p} = 2.64$ H, and $\delta_{2h} = 5.68$ H. The total solubility parameter, δ_{2T}, was calculated using Eq. 1 and found to be 11.32 H. When the 'B' value obtained from Eq. 10 is used in calculating the mole fraction solubility of pimozide in different solvents, the calculated solubilities are higher than the experimental ones. The error between the experimental and calculated values is high and the data are shown in Fig. 1. Because the size correction for differences in molar volumes of pimozide and solvents are adjusted, there is a need to verify the presence of a proton donor-acceptor type of interaction.

In order to improve the correlation, the four-parameter approach [36] is adopted. This approach is based on the principle that the parameter δ_{2h} does not reliably reflect the proton donor-acceptor characteristics of complex organic molecules. Therefore, δ_a proton donor and δ_b proton acceptor parameters are used to replace δ_h in the regression analysis and the following equation is proposed:

$$\frac{(\log_{10}\gamma_2)}{A} = (\delta_{1d} - \delta_{2d})^2 + (\delta_{1p} - \delta_{2p})^2 + 2(\delta_{1a} - \delta_{2a})(\delta_{1b} - \delta_{2b}) \tag{11}$$

where δ_{1a}, δ_{1b} and δ_{2a}, δ_{2b} are the acid and base partial solubility parameters of solvent and solute, respectively. The expanded Eq. 11 can be used to predict the solubility of a compound in various individual solvents, similar to Eq. 9. This type of regression equation was obtained by processing the solubility data for benzoic acid against the partial solubility parameters of the solvents [36]. In the case of naphthalene, there is an improvement in the regression coefficient [28].

The four-parameter approach is used to improve the correlation. The following regression equation is obtained by use of a multiple regression program for pimozide in 18 solvents at 25 °C:

$$\frac{(\log_{10}\gamma_2)}{A} = 59.04 - 9.89\delta_{1d} + 0.43\delta_{1d}^2 - 3.92\delta_{1p} + 0.35\delta_{1p}^2 - 0.16\delta_{1a} - 0.73\delta_{1b} + 0.18\delta_{1a}\delta_{1b} \tag{12}$$

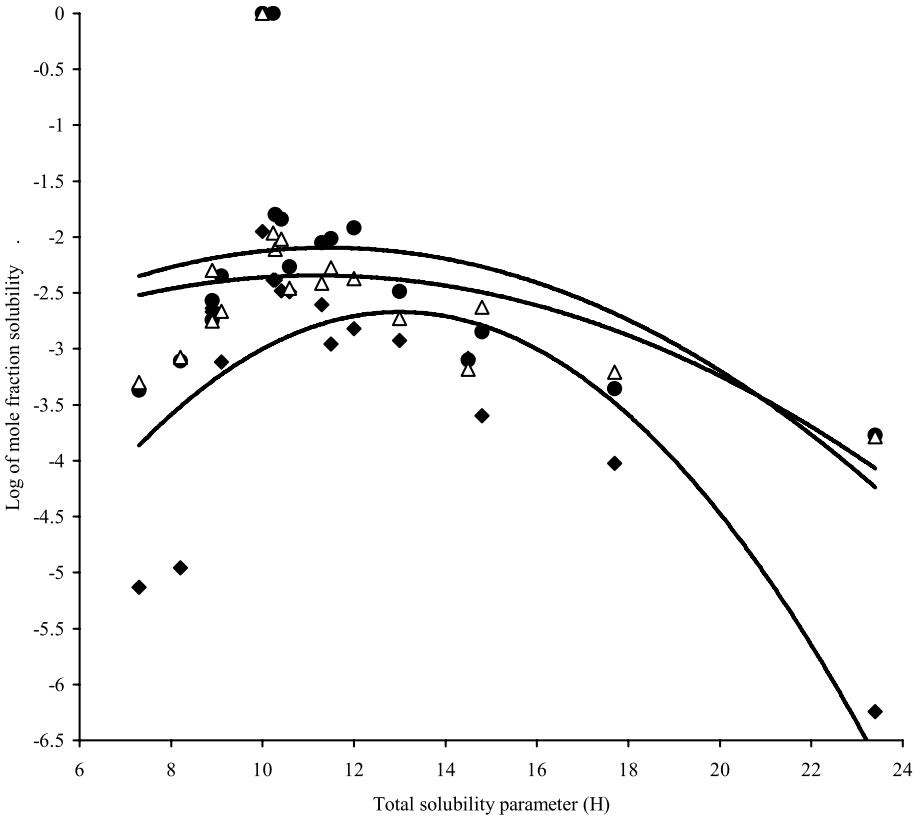


Fig. 1 Decadic logarithm (base 10) of the mole fraction solubility of pimozide versus the corresponding solubility parameter for individual solvents at 25 °C. Key: logarithm of the experimental mole fraction solubility (♦); logarithm of the calculated mole fraction solubility by Flory-Huggins' method using Eq. 10 (•); logarithm of the calculated mole fraction solubility by Flory-Huggins' method coupled with the four-parameter method using Eq. 13 (Δ)

where $n = 18$, $s = 1.35$, and $R^2 = 0.94$.

Equation 12 was found to have a better R^2 value (0.94) and the standard error of the 'y' estimate is smaller compared to Eq. 6. The signs of the coefficients agree with the standard format of Eq. 11. From Eq. 12, the partial solubility parameter values obtained are $\delta_{2d} = 11.60$ H, $\delta_{2p} = 5.60$ H, δ_{2a} (acidic partial parameter) = 4.06 H, and δ_{2b} (basic partial parameter) = 0.89 H. The δ_{2h} value is calculated from δ_{2a} and δ_{2b} and is found to be 2.69 H and $\delta_{2T} = 13.16$ H.

In the above methods, the Flory-Huggins size-correction approach and the four-parameter approach are considered separately for drawing a correlation. In order to improve the correlation coefficient and to get a regression equation with a better fit to the experimental values, an effort was made here to combine these two approaches empirically, as both involve simple statistical analysis. In other words, Eq. 12 was modified by replacing $(\log_{10} \gamma_2)/A$ with the 'B' term (from in Eq. 11). The following regression equation is obtained:

$$B = 135.05 - 28.74\delta_{1d} + 1.62\delta_{1d}^2 - 1.21\delta_{1p} + 0.28\delta_{1p}^2 - 1.35\delta_{1a} - 1.04\delta_{1b} + 0.33\delta_{1ab} \quad (13)$$

where $n = 18$, $s = 1.88$, and $R^2 = 0.98$.

A perusal of Eq. 13 indicated that the regression coefficient R^2 is improved by 12% in comparison with Eq. 6. Further, the signs of the coefficients agree with the standard format. For regression Eq. 13, the partial solubility parameters obtained are $\delta_{2d} = 8.85$ H, $\delta_{2p} = 2.17$ H, $\delta_{2a} = 3.15$ H, and $\delta_{2b} = 4.08$ H. The δ_{2h} value is calculated from the δ_{2a} and δ_{2b} values and is found to be 5.07 H and $\delta_{2T} = 10.43$ H. This value is nearer to the values obtained from the theoretical methods. Thus, combination of the four-parameter approach with the Flory-Huggins size-correction '*B*' proved to be successful for improving the analysis. This observation is encouraging. From Eq. 13, the '*B*' values are back-calculated and mole fraction solubility values in different solvents are obtained. Some differences between the experimental and calculated solubility values are found as shown in Fig. 1, but the different methods indicate the same range for optimal solubilities of pimozide. The maximum solubility region is located at intermediate solubility parameter values (9 to 12 H) leaving a few solvents in the right and left parts of the plot. Thus, the best solvents can be selected with a total solubility parameter ranging between 9 and 12 H.

Among the methods adopted to analyze solubility behavior and to calculate partial solubility parameters, the Flory-Huggins size correction term '*B*' coupled with four-parameter approach is the most successful. This approach improved the correlation coefficient by up to 98% (from 86% obtained in the case of the three-parameter approach) and also the solubility data analysis is marginally improved. The δ_{2T} value obtained with the Flory-Huggins term coupled with four-parameter approach was compared with the values obtained from Fedors' and Hoy's methods. The agreement between the total solubility parameters obtained using theoretical methods, Fedors' and Hoy's [2, 32], is excellent and is also nearer to the values obtained from Eq. 13. This observation suggests that a theoretical method of obtaining total solubility parameters is of great help to support experimental results [12].

The values of the partial parameters obtained were found to vary with the method used in analyzing the solubility data. They may also vary with the nature and number of solvents used for the correlations. This may be a result of interaction between the solute and solvent [32]. The basic partial solubility parameter δ_{2b} of pimozide is larger than its acidic partial parameter δ_{2a}. This could be anticipated because the number of proton-accepting (Lewis base) groups is larger than the number of proton-donating (Lewis acid) groups. This drug possesses a carbonyl group having proton acceptor capability, whereas the –NH group may act either as proton donor or proton acceptor toward the solvents. This behavior is similar to that found for piroxicam [12], a drug with –C=O and –NH groups. On the other hand, the experimental total solubility parameter of pimozide is lower than the total solubility parameter of piroxicam. This agrees with the fact that pimozide is less polar than piroxicam (piroxicam has two carbonyl groups versus a single carbonyl group on pimozide). This result is very interesting as it demonstrates for the first time the validity of the four-parameter approach coupled with the Flory-Huggins size correction '*B*' for a mainly proton-acceptor compound. The solubility of pimozide in normal alcohols could be due to their strong hydrogen bonding property. Thus, the nature of the solvents and the chemical structure of pimozide affect the solubility.

Pimozide is expected to be of lower polarity as its lipophilic moiety is larger. Accordingly, the highest solubility of pimozide is obtained in solvents with lower solubility parameter values, such as toluene and ethylacetate, and lipophilic alcohols (*n*-butanol to *n*-octanol). The solubility decreases in the most polar alcohols (methanol and glycerin) and propyleneglycol (large δ value).

The dispersion partial solubility parameter represents London forces, a kind of interaction that is common to all molecules, polar and nonpolar [12]. The dispersion partial solubility parameter (δ_{2d}) obtained from Eq. 13 is almost equal to the value obtained from the

group contribution method, and it is also close to the values for most common solvents. However, the dipole (δ_{2p}) and hydrogen bonding parameters (δ_{2h}, δ_{2a}, and δ_{2b}) are not so close, being lower in all cases, as was also found for citric acid, paracetamol, niflumic acid, and piroxicam [12, 26] and, therefore contribute most to the observed differences among the total solubility parameters. On the other hand, the polar and hydrogen bonding parameters seem to be more important to differentiate the behavior of pimozide in solution rather than the dispersion parameter.

The R^2 values indicate that more significant partial solubility parameter values are obtained from the four-parameter approach coupled with the Flory-Huggins size correction term ('*B*'). This model is superior to either the four-parameter model alone or the Flory-Huggins size-correction-term approach.

As pimozide possesses different functional groups, the separation of the hydrogen bonding parameter into acidic and basic parameters provides a better description of the system. This confirms previous findings for citric acid, paracetamol, niflumic acid, and piroxicam [12, 26]. Pimozide is a weak base ($pK_a = 7.32$), probably due to the low value of the ratio of the partial acidic parameter to the partial basic parameter [30]. The values of the partial solubility parameters give insight into the interaction capability of the drug and are consistent with its chemical structure. Hence pimozide is a proton acceptor and thus is a Lewis base.

4 Conclusions

The solubility behavior of pimozide was evaluated and the results where analyzed in the light of existing systems of data analysis with reference to partial solubility parameters. As expected, pimozide exhibited irregular behavior in the analysis with Hansen's extended three-parameter approach. However, the Flory-Huggins size-correction term improved the correlations to the extent of 97%. In the four-parameter approach, the hydrogen bonding parameter is replaced by acid and base partial solubility parameters, which gave encouraging results. Empirically, the Flory-Huggins size-correction and four-parameter approaches where combined and statistical analysis was attempted. The results improved the correlation up to 98%. The δ_{2T} values, as well as partial solubility parameter values obtained from the above analysis, wheree closer to the values obtained theoretically from fragmental analysis. In the case of pimozide, the hydrogen bonding partial solubility parameter might be responsible for deviations from the predictions.

As the R^2 value is high for the Flory-Huggins method coupled with the four-parameter approach, and the total solubility parameter obtained by this method closely matched the values obtained from Fedors' and Hoy's methods, the δ_{2T} value of pimozide was assigned the value 10.43 H. Although some differences between the experimental and calculated solubilities where observed, the different methods indicated the same range for an optimal solubility of pimozide; the best solvent can be selected based on possessing a total solubility parameter somewhere between 9 and 12 H. The results indicated that the four-parameter model coupled with Flory-Huggins size correction term can be applied to determine the partial solubility parameters of drugs.

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