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Research paper

Solubility behaviour of haloperidol in individual solvents determination of partial solubility parameters

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Abstract

The solubility behaviour of haloperidol in individual solvents ranging from non-polar to highly polar solvents was studied. Extended Hansen's method was used to analyze the solubility data and obtain partial solubility parameters of haloperidol. Flory-Huggin's size connection term '*B*' was found to further improve the prediction of solubility. A four parameter extended Hansen's approach involving proton-donor and proton-acceptor parameters was also used in fitting the solubility data to a theoretical model. The term W_h, used as an empirical measure of solute-solvent interaction due to hydrogen bonding was used in calculating *B*. Different approaches were thus used in fitting the experimental solubility data to obtain regression equations which aim to provide a reasonable prediction of solubility of haloperidol in untested solvents. Solubility parameter was calculated from the partial solubility parameter values obtained from the different methods of data analysis, and compared with the theoretically obtained values. Solubility parameter of haloperidol is fixed at 10.58 H.

Keywords: Solubility behaviour; Extended Hansen's approach; Flory-Huggin's size correction; Four-parameter approach; Partial solubility parameter

1. Introduction

Solubility parameter, δ_T, is an intrinsic physicochemical property of a substance which has been used to explain drug action [1], structure activity relationship [2], drug transport kinetics [2] and in situ release of drug [3]. It has been suggested as a possible substitute for partition coefficient in a study of the passage of drugs across living membranes [3].

Hansen [4], defined three partial parameters, δ_d representing London dispersion forces, δ_p the Keesom dipolar interactions and δ_h representing generalized electron transfer bonding, including hydrogen bonding and other acid base interaction.

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They are related by the expression:

$$\delta_T{}^2 = \delta_d{}^2 + \delta_p{}^2 + \delta_h{}^2 \quad (1)$$

where δ_T is the total solubility parameter and is quite similar to the δ as defined by Scatchard and Hildebrand [5]. Partial solubility of solvents are found to play a role in solubilization of drug molecules which in turn depends on the drugs chemical structure and its solubility parameter. However, partial solubility parameters have not been more widely employed in pharmacokinetics and structure activity studies perhaps, because there are few methods for their determination which can be applied to drugs. Extended Hansen's approach [6,7], Flory-Huggin's size correction term [8] and four parameter approach [9] were the methods proposed to obtain partial solubility parameters of crystalline pharmaceutical drug compounds and, thereby, predict their solubility in solvents normally encountered in pharmacy.

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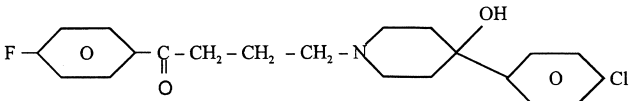
Haloperidol belongs to chemical category of butyrophenones and is used as a tranquilizer [10]. It has chosen for this study because of its structure. It has a straight chain having hydrophobic groups such as fluorine and chlorine. Only the OH group and oxygen atom of the CO group may participate in hydrogen bonding. The molecule in total behaves as a non-polar solute, as reflected by its low polarity in polar solvents. Its structure is:



The aim of this project is to study the solubility behaviour of haloperidol in individual solvents ranging from apolar, such as benzene and toluene through amphiprotic such as alcohol, glycol and water to dipolar aprotic such as N, N-dimethyl formamide and dimethyl sulfoxide. The objective is to use different approaches to analyze the experimental solubility data and obtain regression equations, that can predict the solubility of haloperidol in untested solvents and to calculate solubility parameter values from the partial solubility parameter values obtained from the different methods of solubility data analysis. The solubility parameter values thus obtained are compared with theoretically obtained values such as from Fedors [11] molar attraction constants, Hoy's [12] and group contribution methods [8].

2. Theoretical development

Extended Hansen's method, the three parameter approach [7] has been proposed to obtain partial solubility parameters of crystalline drug compounds. The extended Hansen's model is written as:

$$\log \frac{X_2^i}{X_2} = \log \gamma_2 = C_0 A + C_1 A(\delta_{1d} - \delta_{2d})^2 + C_2 A(\delta_{1p} - \delta_{2p})^2 + C_3 A(\delta_{1h} - \delta_{2h})^2 \quad (2)$$

Where X_2^i is the solute ideal mole fraction solubility, calculated using ideal mole fraction solubility equation [13], X_2 is the observed mole fraction solubility, γ_2 is the activity coefficient of the solute and C_i (where $i = 0, 1, 2, 3$) are regression coefficients obtained from regression analysis. C_o is a constant which represents solute dissolved in a series of solvents. Throughout this paper, 1 is for solvent and 2 is for solute.

The three parameter approach was modified by using Flory-Huggin's size correction term '*B*' This term accounts for the deviation of a drug solution from regular solution behaviour because of specific solute solvent interaction and size difference between solute and solvent [8]. *B* is equal to:

$$B = RT[\ln \gamma_2 - \ln(V_2/V_1) - 1 + (V_2/V_1)]/V_2 \varnothing_1^2 \quad (3)$$

B can be incorporated into the regression model as follows

$$B = D_1\delta_{1d} + D_2\delta_{1d}^2 + D_3\delta_{1p} + D_4\delta_{1p}^2 + D_5\delta_{1h} + D_6\delta_{1h}^2 + D_0 \quad (4)$$

In order to improve the correlation, four parameter approach [9] was adopted. This approach is based on the principle that the parameter δ_{2h} does not 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 obtained:

$$\log(\gamma_2/A) = (\delta_{1d} - \delta_{2d})^2 + (\delta_{1p} - \delta_{2p})^2 + 2(\delta_{1a} - \delta_{2a})(\delta_{1b} - \delta_{2b}) \quad (5)$$

Where δ_{1a}, δ_{1b} and δ_{2a}, δ_{2b} are acid and base solubility parameters, respectively of solvent and solute respectively. Expansion of Eq. (5) gives an equation which can be used to predict solubility of a compound in various single solvents, similar to Eq. (4). This type of regression equation was obtained by processing the solubility data of benzoic acid against the partial solubility parameters of the solvent [6]. Improvement in the value of regression coefficient for napthalene was obtained when four the parameter approach was adopted [9]. Similarly, the result was improved by 0.4% when compared with the three parameter approach in the case of sulfamethoxypyridazine [14].

Eq. (2) is a linear combination of dispersion, polar and hydrogen bonding interactions written as perfect squares in which geometric means are assumed for the three kinds of interaction. However, Keller et al. [15] suggested that the original scheme of Hansen can be improved by dividing the polar term δ_p into orientation δ_o and induction δ_{in} contributions. In the present study, this correction was used to see if the correlation could be further improved over other approaches. Thus applying this idea to solubility, the Hansen polar term $(\delta_{1p} - \delta_{2p})$ may be substituted by [14]:

$$(\delta_{10} - \delta_{20})^2 + 2(\delta_{1d} - \delta_{2d})(\delta_{1\,in} - \delta_{2\,in}) \quad (6)$$

The term involving δ_h in the Hansen model assumes a geometric mean of δ_{1h} and δ_{2h}, that is $\delta_{lh}\ \delta_{2h} = (\delta_{1h}^2\ \delta_{2h}^2)^{1/2}$. In order to correct this assumption, the hydrogen bonding interaction tern is written as $(\delta_{1h}^2\ \delta_{2h} - 2W_h)$. W_h is thus introduced as an empirical adhesive energy density parameter for the interaction in a solution of hydrogen bonded species 1 and 2 and substitutes for the original Hansen's terms $\delta_{1h}\ \delta_{2h}$. Applying these ideas a new model may be written [14]:

$$B = C_0 + C_1\delta_{1d} + C_2\delta_{2d} + C_3\delta_{1d}\delta_{1\,in} + C_4\delta_{1\,in} + C_5\delta_{10}^2 + C_6\delta_{10} + C_7\delta_{1h}^2 + C_8W_h \quad (7)$$

Where C_o to C_8 are constant coefficients obtained by regression analysis. The term C_o as in case of Eq. (2), includes the partial parameters of the solute (which are constants and therefore do not appeal in the regression equation) and their associated regression coefficients. The

Table 1
Solubility parameter values for haloperidol by different methods

Method/system	Solubility parameter	
	Hildebrand (H)	SI units
Fedors[a]	10.38 (9.41)[g]	21.175 (19.196)
Hoys[b]	11.39 (10.84)[h] δ_{2d} δ_{2p} δ_{2h}	23.24 (22.114)
Group contribution method[C]	8.30 (6.94, 1.63, 4.28)	16.93 (14.16,3.33,8.73)
Regression of log (γ_2/A)[d]	10.71 (8.39, 5.22, 4.13)	21.85 (17.12,10.65,8.43)
Flory-Huggins term, B[e]	10.91 (8.45, 4.42, 5.29)	22.26 (17.24,9.02,10.79)
Four parameter approach[f]	10.58 (8.41, 4.56, 4.53)	21.57 (17 16,9.3,9.24) 11

[a]Estimated from Fedors molar attraction constant [11].
[b]Estimated from Hoy's substituent method [12].
[c]Estimated from fragmental constants for partial parameters [16]
[d]δ_{2T} value obtained from $(\delta_d^2 + \delta^{p2} + \delta^{h2})^{1/2}$.
[d]Extended Hansen's approach, Eq. (8).
[e]Log (γ_2/A) replaced by B, in three parameter approach, Eq. (9).
[f]From Eq. (10).
[g,h]The values based on the experimental molar volume = 357.566 cc/mole, calculated using flotation technique [16].

correlation obtained can be compared with the values obtained by other approaches to see if results could be improved to get a better fit of experimental solubilities and, thus, obtain a theoretical model which could provide a reasonable prediction of solubilities of drug molecules in a number of solvents.

3. Materials and methods

The heat of fusion was determined calorimetrically by differential scanning calorimeter (DuPont 9900 Computer Thermal Analyzer System with 910 DSC module). The solubility of haloperidol (Microlabs, Bangalore, India) was determined in a number of solvents (analytical and spectrophotometric grade, Loba Chemie and SD Fine Chem), shown in Table 1 in a constant temperature shaker water bath (Remi Sales, India) held at 25 ± 0.5°C. After equilibrium is attained (72 h) the solutions were filtered using filters of pore size 0.2 μ (millipore) and sample quantified using double beam UV-visible spectrophotometer (Shimadzu).

The densities of the saturated solution were determined in a 25 ml specific gravity bottle. All analysis were done in triplicate. Molar volume was determined experimentally by flotation technique [16]. For calculations, the necessary software was developed using BASIC. Multiple regression analysis was performed on Lotus 1-2-3. F-ratio is calculated using standard statistical procedures [17]. A Neptune Minicomp PC/AT was used.

4. Results and discussion

When extended Hansen approach was applied to the experimental solubilities of haloperidol in individual solvents, the following regression equation was obtained:

$$\log(\gamma_2/\mathrm{A}) = 130.920 - 31.052\,\delta_{1d} + 1.862\,\delta_{1d}^2 - 0.572\,\delta_{1p} + 0.0627\,\delta_{1p}^2 - 0.373\,\delta_{1h} + 0.0393\,\delta_{1h}^2 \quad (8)$$

$n = 17;\ s = 0.9577;\ R^2 = 0.9162$

$F = 18.232;\ F(6, 10, 0.01) = 5.39$

When Eq. (8) was written according to the model represented by Eq. (2), δ_{2d} obtained was 8.39 H, δ_{2p} was 5.22 H and δ_{2h} was 4.13 H. The total solubility parameter δ_{2T} calculated using Eq. (1) was 10.71 H. These values were compared with the theoretically obtained partial and total solubility parameter values. The values obtained by different methods are summarized in Table 2. When group contribution method was used to calculate the solubility parameter, δ_{2d} obtained was 6.94 H, δ_{2p} was 1.63 H, δ_{2h} was 4.28 H and δ_{2T} was 8.31 H. These values do not agree with the value obtained from Eq. (8) using extended Hansen's approach, however δ_{2h} is almost similar. δ_{2T} calculated using Fedor's method is nearer to the δ_{2T} value obtained by three parameter approach. From Eq. (8), log (γ_2/A) values were back calculated and used to calculate mole fraction solubility of haloperidol in the different solvents. The difference between the experimental and calculated solubility values were found to be high, shown in Fig. 1.

In order to improve the correlation coefficient and to get a regression equation with a better fit of experimental values, the Flory-Huggin's size correction term B was used for the analysis of the data. The following equation was obtained:

$$B = 471.174 - 109.818\,\delta_{1d} + 6.499\,\delta_{1d}^2 - 0.178\,\delta_{1p} + 0.020\,\delta_{1p}^2 - 1.557\,\delta_{1h} + 0.147\,\delta_{1h}^2 \quad (9)$$

$n = 17;\ s = 2.0004;\ R^2 = 0.972$

Table 2

Mole fraction solubility of haloperidol in individual solvents at 25°C: partial solubility parameter – Flory-Huggin's size corrections

Solvent	Molar volume (V_1)	Solulibility parameter						Log γ	B_{obs}	B_{calc}	$X^2 \times 10^3$ exp	$X^2 \times 10^3$ calc	Percent error
		Dispersion δ_d	Dipolar δ_p	Hydrogen bonding δ_h	Acidic δ_a	Basic δ_b	Total δ_T						
Butyl acetate	132.6	7.7	1.8	3.1	2.8	1.7	8.49	3.095	6.462	9.799	4.946	2.13	–42.06
Toluene	106.9	8.8	0.7	1.0	0.8	0.6	8.88	2.229	6.031	6.812	11.768	7.608	–63.65
Ethylacetate	98.5	7.4	2.6	4.5	5.3	1.9	9.04	2.384	6.633	7.874	10.07	5.008	–48.72
Benzene	89.4	9.0	0.5	1.0	0.7	0.7	9.07	2.316	7.087	7.852	10.78	7.053	–64.43
Chloroform	80.8	8.7	1.5	2.8	3.0	1.3	9.26	–0.381	8.752	4.801	159.88	322.960	–201.00
Acetone	74.0	7.6	5.1	3.4	2.4	2.4	9.76	3.567	9.933	9.799	3.09	3.342	–107.14
Dioxane	85.7	9.3	0.9	3.6	1.0	6.5	10.01	2.966	8.172	8.475	5.63	4.728	–82.98
Butanol	92.0	7.8	2.8	7.7	6.4	4.6	11.29	2.644	7.367	7.402	7.77	7.489	–95.38
Isopropyl alcohol	76.9	7.7	3.0	8.0	7.1	4.5	11.50	2.243	8.02	8.594	11.6	8.502	–72.30
Propanol	75.1	7.8	3.3	8.5	7.5	4.8	11.99	3.512	9.748	8.213	3.26	7.987	244.74
Dimethyl formamide	77.4	8.5	6.7	5.5	3.4	4.4	12.13	0.993	4.317	5.283	40.47	94.505	–232.5
Ethanol	58.7	7.7	4.3	9.5	8.3	5.5	12.96	2.954	11.064	10.542	5.70	7.65	–133.27
Dimethyl sulfoxide	71.3	9.0	8.0	5.0	2.2	5.7	13.04	2.335	8.709	7.867	10.576	16.727	–157.16
Methanol	40.7	7.4	6.0	10.9	8.4	7.1	14.49	4.269	16.806	16.721	1.53	1.609	–104.15
Propylene glycol	73.7	8.2	4.6	11.4	14.	4.6	14.77	4.799	11.813	10.292	0.9	3.542	–38.36
Glycerine	73.2	8.5	5.9	14.3	20.0	5.1	17.64	5.604	13.138	16.597	4.24×10^{-1}	0.050	–11.49
Water	18.1	7.6	7.8	20.7	6.7	32.0	23.40	12.044	46.236	45.363	6.43×10^{-4}	9.80×10^{-4}	–151.59

Heat of fusion (ΔH_f) = 5359.704 cal/mole; melting point = 148°C (421°K): molar volume of liquid solute (V^2) = 357.566 cc/mole; ideal solubility of solute (X^{2i}) = 0.1092735; $Ø_1$ and X_2(calc) value computed using the iteration procedure.

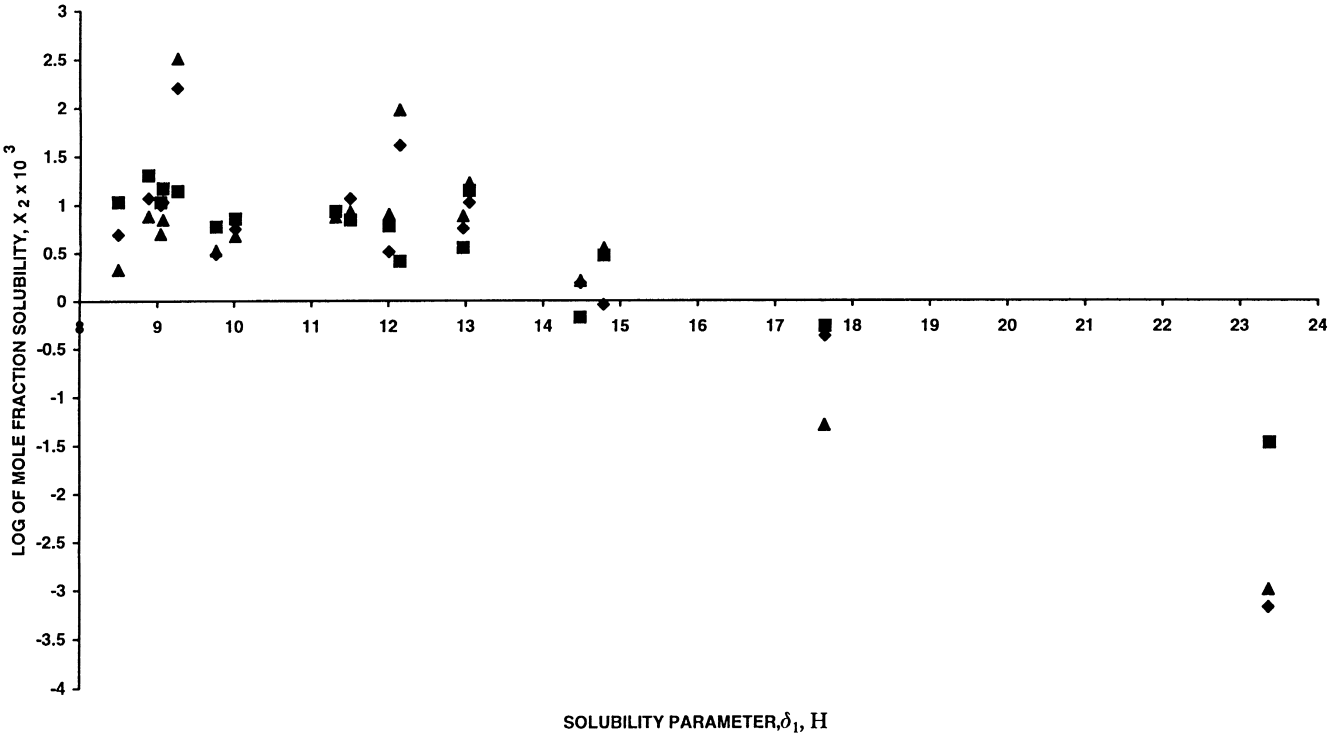


Fig. 1. Mole fraction solubility of haloperidol in individual solvents at 25°C. Key: log of experimental mole fraction solubility (♦); log of calculated mole fraction solubility from Eq. (8) (■); log of calculated mole fraction solubility from Eq. (9) (▲).

$F = 58.393;\ F(6, 10, 0.01) = 5.39$

Eq. (9) was found to have better correlation when compared with Eq. (8). The partial solubility values obtained are, δ_{2d} was 8.45 H, δ_{2p} was 4.4 H, δ_{2h} was 5.294 and δ_{2T} was l 0.91 H. This value is closer to the δ_{2T} value obtained by Hoy's method as shown in Table 1. When B values obtained from Eq. (9) was used in calculating mole fraction of haloperidol solubility in different solvents, the error between experimental and calculated values was lesser than in case of extended Hansen's approach The values are recorded in Table 1 and shown in Fig. 1.

When the four parameter approach involving proton donor, δ_a and proton acceptor, δ_b was used instead of δ_{2h}, to improve the correlation and get a better fit of experimental data, the following equation was obtained:

$$B = 366.765 - 88.098\,\delta_{1d} + 5.367\,\delta_{1d}{}^2 + 2.491\,\delta_{1p} - 0.273\,\delta_{1p}{}^2 - 1.356\,\delta_{1a} - 0.885_{1b} + 0.3421\,\delta_{1a}\,\delta_{1b} \qquad (10)$$

$n = 17;\ s = 1.722;\ R^2 = 0.982$

$F = 68.43;\ F(7, 9, 0.01) = 5.62$

Eq. (10) was found to have better R^2 value and the standard error of y estimate was less. From this equation, the partial solubility parameter values obtained were as follows: δ_{2d} was 8.4 H, δ_{2p} was 4.56 H, δ_{2a} the acidic partial parameter obtained from Eq. (10) was 2.59 H and δ_{2b}, the basic partial parameter was 3 96 H. The δ_{2a} and δ_{2b} values indicate that haloperidol is more of a Lewis base than Lewis acid. The δ_{2h} value was calculated from δ_{2a} and δ_{2b} values and was found to be 4.53 H and δ_{2T} was 10.58 H. This value is closer to the δ_{2T} value obtained by Fedors method [11] which was 10.38 H. Thus the solubility parameter of haloperidol is considered to be 10.58 H. The values obtained by different methods are shown in Table l.

The values of the partial parameters were found to vary with the method used in analyzing the solubility data. It may also vary with the nature and number of solvents. This may be as a result of interaction between the solute and solvent as suggested by Hoy [12]. So the term W_h was used instead of δ_{lh} δ_{2h} as a measure of solute solvent interaction due to hydrogen bonding and other acid base interactions and $\delta_0\delta_{1n}$ was used instead of δ_p to correct the geometric mean assumed by the term. The regression equation thus obtained is:

$$B = 51.296\,\delta_{1d} + 3.121\,\delta_{1d}{}^2 - 1.219_{10} + 0.127\,\delta_{10}{}^2 + 10.622\,\delta_{1\ in} - 1.20\,\delta_{1h}\,\delta_{1d} - 0.02\,\delta_{1h}{}^2 - 0.022\,W_h\ (\text{Calc}) + 218.288 \qquad (11)$$

$n = 17;\ s = 1.193;\ R^2 = 0.979$

$F = 47.494;\ F(8, 8, 0.01) = 6.03$

From the *B* values obtained, solubility of drugs in different solvents can be obtained. This equation is compared with Eq. (9) for *B* obtained by using Flory-Huggin's size correction term. Eq. (11) had better R^2 value, less standard error of estimate, *s* value. Thus the term W_h may be used to account for unsymmetric interaction between solute and solvent seen in irregular solutions.

Among the methods adopted to analyze the solubility behaviour and calculate the partial solubility parameters, Flory-Huggin's size correction term *B* coupled with four parameter approach was the most successful. This approach improved the correlation coefficient up to 97.2% from 91.62% obtained in the case of the three parameter approach and also the solubility data analysis was marginally improved. It was observed that δ_{2T} values obtained by the three methods of data analysis were closer to one another as shown in Table 1. The δ_{2T} obtained by the four parameter approach was closer to the value obtained by Fedors method [11] and δ_{2T} value by Flory-Huggin's term closer to the value by Hov's method. The δ_{2T} value of haloperidol may extrapolated to 10.58 H.

From the above study, haloperidol was found to maximum solubility in chloroform followed by dimethyl formamide, toluene, dimetyl sulfoxide and benzene. Chloroform shows a strong proton donor, δ_a, when compared with the proton acceptor, δ_b characteristics. This could explain the greater solubility of haloperidol in chloroform as it is more of a Lewis base than a Lewis acid, as shown by its δ_a and δ_b values. Similarly δ_a and δ_b values of toluene and benzene could account for moderate solubility of haloperidol in these solvents. Though dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) are stronger Lewis bases than Lewis acids, haloperidol showed high solubility in these solvents. These solvents had large δ_p values which could have contributed to the high solubility of haloperidol. Methanol and ethanol were found to have high δ_p and δ_a values but haloperidol was slightly soluble in these solvents. This behaviour may be explained by the high δ_h, values of these alcohols when compared with DMF and DMSO. Thus the nature of the solvents, the chemical structure of haloperidol affects the solubility of the drug.

References

[1] L. Mullins,, Chem. Rev. 54 (1954) 289.
[2] S.A. Khalil, A.N. Martin,, J. Pharm. Sci. 56 (1967) 1223–1225.
[3] A. Adjei, J. Newburger, S. Stavchansky, A. Martin,, J. Pharm. Sci. 73 (1984) 742.
[4] C.M. Hansen,, J. Paint Technol. 39 (1967) 104.
[5] A. Adjei, J. Newburger, A. Martin,, J. Pharm. Sci. 69 (1980) 659–661.
[6] C.M. Hansen, A. Beerbower, Encyclopedia of Chemical Technology, Suppl. Vol., second ed., Wiley, New York, 1971, p. 889.
[7] A. Martin, P.L. Wu, A. Adjei, A. Beerbower, J.M. Prausnitz, J. Pharm. Sci. 70 (1981) 1260–1270.
[8] A.F.M. Barton, Handbook of Solubility Parameter and Other Cohesion Parameters, CRC, Boca Raton, 1983, pp. 85-86.
[9] A. Beerbower, P.L. Wu, A. Martin,, J. Pharm. Sci. 73 (1984) 179.
[10] E.F. James Reynolds, The Extra Pharmacoepia, twenty ninth ed., Martindale, 1989, p. 745.
[11] R.F. Fedors,, Poly. Eng. Sci. 14 (1974) 147.
[12] K.C. Hoy,, J. Paint Technol. 41 (1970) 76.
[13] A. Martin, J. Swarbrick, A. Cammarata, Physical Pharmacy, Lea and Febiger, Philadelphia, 1983, pp. 281–289.
[14] P. Bustamante, B. Escalera, A. Martin, E. Selles,, J. Pharm. Sci. 78 (1989) 567.
[15] R.A. Keller, B.L. Karger, L.R. Snyder, in: R. Stact (Ed.), Gas Chromatography, Institute of Petroleum, London, 1971, p. 125.
[16] A.H. Beckett, J.B. Stenlake, Practical Pharmaceutical Chemistry, Vol. 2, third ed., CBS, New Delhi, 1986, pp. 1–5.
[17] G.W. Snedecor, W.G. Cochran, Statistical Methods, sixth ed., IBH, New Delhi, 1967, p. 402.