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Research Article

PREDICTION OF SOLUBILITY PARAMETERS OF CHOLESTEROL IN SOME ORGANIC SOLVENTS

ShipraBaluja*and KalpenV. Chavda

Physical Chemical Laboratory, Department of Chemistry, Saurashtra University, Rajkot - 360 005, Gujarat, India.

ABSTRACT

Solubility of cholesterol is determined in different solvents at 298.15 K. From the experimental solubility data, solubility parameters are evaluated using Hansen's three dimensional concepts. Further, solubility parameters of cholesterol are also estimated using different models such as Hoy, Bowden, Van Krevelen, Fedorsetc for which only the chemical structure of cholesterol and a convenient list of increments are used. It is observed that there is good agreement between solubility parameter values for some models.

Keywords: alcohol,cholesterol,solubility parameter, mole fraction.

INTRODUCTION

The solubility parameter is basically a physicochemical property of a substance which is defined as the square root of the cohesive energy density. The concept of the solubility parameter was first developed by Scatchard[1]. Later on, Hildebrand[2] developed an expression to determine it from energy of vaporization.

Solubility parameter is one of the key parameters for selecting solvents in industry, predicting solubility and for numerous other applications[3-9]. This concept plays an important role to interpret structure activity relationship[10], compatibility[11], miscibility[12, 13], adsorptions[14] etc., of materials with solvents. So, nowadays there is much interest in utilizing solubility parameters for designing new processes especially the drug delivery processes[15, 16]. It also influences structure activity[17, 18] and transport kinetics of a drug substance[19]. The solubility parameter concept has been applied to theoretically predict the solubility of compounds, especially drugs in solvents and cosolvents. The evaluation of solubility parameter in different solvents of various polarities would provide important insight about solubility of a substance. The close value of solubility parameters of solute and solvent indicate their similar ability to intermolecular interactions. This is because the energy of mixing within the components is balanced by the energy released by the interaction between the components.

In the present study, an attempt has been made to estimate solubility parameter (δ_T) of cholesterol by Hansen's three dimensional concept.

Cholesterol is a sterol (a combination steroid and alcohol) and a lipid found in the cell membranes of all body tissues. Lesser amounts of cholesterol are also found in plant membranes. It is also required to build and maintain cell membranes and act as an antioxidant[20]

The pharmacokinetic property of any substance depends on their interaction with biological membrane. The main qualification of a substance for itsability to penetrate through membranes by diffusion is lipophylic-hydrophilic balance. The diffusion process is a function of strengths of various types of interactions.

It has been reported that cholesterol is present in cell membrane[21, 22]. So, it participates in various types of interactions such as hydrogen bonding, Van der Waals, dipole-dipole etc.The hydrogen bonding and Vander Waals interactions are important for the cholesterol biological functions.

As solubility parameter is related to cohesive energy which represents the amount of energy associated with all the molecular interactions in a

specified volume of material, it would be interesting to determine solubility parameter for cholesterol. From solubility parameter (δ_T), one can determine its partial components δ_d, δ_p and δ_h, for dispersion, the polar and the hydrogen bonding contribution respectively. The partial solubility parameters of solvents play a role in solubilization of solute molecules depending upon compound's structure. Thus, the aim of present work is to study the solubility of cholesterol in some solvents. Further, different theoretical methods were used to evaluatesolubility parameters of cholesterol.

EXPERIMENTAL

Materials

Cholesterol, with a mass fraction purity of 99.5 %, was purchased from HiMediaPvt. Ltd. (Mumbai, India).All the solvents selected for the present study were analytical grade reagents which were purified by fractional distillation. Their purities were checked by SHIMADZU GC-MS (Model No QP-2010) and were found to be greater than 99.60%.

The drug was recrystallized and its melting temperature and enthalpy of fusion were determined by differential scanning calorimeter. The observed value of melting point and enthalpy of fusion were found to be 422 K and 140.9KJ/mole, which are in good agreement with the reported value 422.3Kas reported[23] and 141.4KJ/mole[24]. Fig. 1 shows the structure of Cholesterol.

Method

The solubility of Cholesterol was measured by a gravimetric method reported earlier[25]. For each measurement, an excess mass of cholesterol was added to a known mass of solvent. Then, the equilibrium cell was heated to a constant temperature with continuous stirring. After, at least 3 h (the temperature of the water bath approached constant value, then the actual value of the temperature was recorded), the stirring was stopped and the solution was kept still for 2 h. A portion of this solution was filtered and by a preheated injector, 2 ml of this clear solution was taken in another weighted measuring vial (m_0). The vial was quickly and tightly closed and weighted (m_1) to determine the mass of the sample (m_1- m_0). Then, the vial was covered with a piece of filter paper to prevent dust contamination and placed at room temperature to evaporate the solvent. After the solvent in the vial had completely evaporated, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid (m_2- m_0). All the masses were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. Thus, the solid concentration of the sample solution of mole fraction, x, could be determined from eq 1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

Where M_1 is the molar mole of drug and M_2 is the molar mass of the solvent.

At each temperature, the measurement was repeated three times and an average value is given in Table 1 along with uncertainty.

The molar volumes and partial solubility parameters of the solvents were taken from the literature[26] and are given in Table 1.

RESULTS AND DISCUSSION

The extended Hansen method[27], the three parameter regression models relates the partial solubility parameters of solvents and the activity coefficients of cholesterol in thestudied solvents to the partial solubility parameters of cholesterol.

$$\ln\gamma_2/A = C_0 + C_1\delta_{1d} + C_2\delta_{1d}^2 + C_3\delta_{1p} + C_4\delta_{1p}^2 + C_5\delta_{1h} + C_6\delta_{1h}^2 \quad (2)$$

where subscripts 1 and 2 refer to the solvent and solute respectively. The values of coefficients, C_0 to C_6 are evaluated by multiple regression analysis. γ_2 is the activity coefficient of cholesterol in a solvent and is determined by the equation:

$$\ln\gamma_2 = \ln\frac{x_2^i}{x_2} \quad (3)$$

where x_2^i and x_2 are the ideal mole fraction solubility and experimental molefraction solubility of cholesterol in a solvent.

The ideal mole fraction solubility is calculated by using enthalpy of fusion and melting temperature of cholesterol.

$$\ln x_2^i = \left(\frac{\Delta H_f}{RT}\right)\left(\frac{T - T_m}{TT_m}\right) \quad (4)$$

where ΔH_f is the molar heat of fusion of cholesterol, T_m and T are the melting temperature and experimental temperatures respectively.

The parameter A in equation (2) is evaluated by the following equation:

$$A = \frac{V_2\varphi_1^2}{RT} \quad (5)$$

where V_2 is the molar volume of cholesterol, φ_1 is the volume fraction of solvent and R is the gas constant.

The value of φ_1 is calculated by the following equation:

$$\emptyset_1 = \frac{V_1(1-x_2)}{V_1(1-x_2)+V_2x_2} \quad (6)$$

When the extended Hansen approach is applied to experimental solubilities of cholesterol, the following regression equation is obtained.

$$\ln\gamma_2/A = -901.85 - 13.57\delta_{1d}^2 + 222.83\delta_{1d} + 0.60\delta_{1p}^2 - 3.91\delta_{1p} + 0.54\delta_{1h}^2 - 7.54\delta_{1h} \quad (7)$$

where n =13 , s =2.37 and R^2 =0.72.

The parameters represent the standard error of the γ estimate.

By determining the values of different coefficients C_0 to C_6, the partial solubility parameters of cholesterol can be calculated by the following equations:

$$\delta_{1d} = -\left(\frac{c_1}{2c_2}\right) ; \delta_{1p} = -\left(\frac{c_3}{2c_4}\right) ; \delta_{1h} = -\left(\frac{c_5}{2c_6}\right) \quad (8)$$

The partial solubility parameters of cholesterol calculated by above relations are given in Table 2.

Bustamante et al[28]suggested that partial solubility parameters can also be evaluated by regression of only $\ln x_2$ againstthe partial solubility parameters of the solvents used.

$$\ln x_2 = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1h}^2 + C_6\delta_{1h} \quad (9)$$

When multiple regression is applied to this equation, we get:

$$\ln x_2 = 197.35 + 3.14\delta_{1d}^2 - 51.86\delta_{1d} - 0.21\delta_{1p}^2 + 1.36\delta_{1p} - 0.19\delta_{1h}^2 + 2.63\delta_{1h} \quad (10)$$

where n =13, s =0.80 and R^2 =0.83

So, the correlation coefficient is improved using equation (10) by 11%. Using relation (10), the partial solubility parameters of cholesterol were calculated and are given in Table 2.

The three parameter approach was modified using Flory-Huggins size correction term[29]"B". This B can be written as:

$$B = \frac{RT[\log\gamma_2 - \log(V_2 - V_1) - 1 + (V_2/V_1)]}{V_2\emptyset_1^2} \quad (11)$$

B can be used in regression model as:

$$B = D_0 + D_1\delta_{1d} + D_2\delta_{1d}^2 + D_3\delta_{1p} + D_4\delta_{1p}^2 + D_5\delta_{1h} + D_6\delta_{1h}^2 \quad (12)$$

The Flory-Huggins size correction approach for cholesterol in individual solvents was attempted and following equation was obtained.

$$B = -431.19 + 105.68\delta_{1d} - 6.25\delta_{1d}^2 - 1.83\delta_{1p} + 0.36\delta_{1p}^2 - 9.17\delta_{1h} + 0.69\delta_{1h}^2 \quad (13)$$

Where n=13, s=2.37, and R^2=0.89.

The correlation coefficient (R^2) is improved in equation (13) by 6%. Thus, this equation (13) gives better results as compared to equations (7) and (10). From these values of coefficients, the partial solubility parameters of cholesterol were calculated and are reported in Table3.

Further, using values of coefficients from equations (7), (10) and (13), mole fraction solubilities were also evaluated in different solvents. These values are reported in Table 2.

It is observed that in some solvents, there is much difference between estimated solubility and experimental solubility values. This variation may be due to the fact that there may exist proton-donor-acceptor type interactions. For this, four parameter approach should be adopted where δ_h should be replaced by δ_a and δ_b. These two parameters are proton-donor and proton-acceptor parameters. However, for some of the studied solvents, these parameters are not known. So, our study is limited to only three parameter approach.

Table 2 shows that there are some differences between the experimental and calculated values for some solvents.

Further, solubility parameters of cholesterol were estimated using different models. For this, only the chemical structure of cholesterol and a convenient list of increments (Hoy[30], Bowden[31], Van Krevelen[32], Fedors[33]) are needed.

Table 3 shows the predicted solubility parameters evaluated by different methods are in good agreement. However, there is wide variation in values of solubility parameters evaluated by Hoy, Bowden, Van Krevelen and Fedors models. It is observed that Bowden and Fedor models gave values closeto extended Hansen method.

CONCLUSION

Using extended Hansen three parameter approach, term "B" improved the correlation coefficient. The predicted solubility parameters evaluated by different methods are in good agreement. Further, values ofsolubility parameter are close to those calculated from Bowden and Fedor models. Although there is difference between experimental and calculated solubilities, the best solvent can be selected on the basis of total solubility parameter between 9 and 12.

Table 1:Molar volume and partial solubility parameters of some solvents

Solvent	Molar volume	δ_d	δ_p	δ_h	δ_T
Methanol	40.7	7.4	6.0	11.2	14.7
Ethanol	58.7	7.7	4.3	9.7	13.1
1-Propanol	75.1	7.8	3.3	8.5	12.0
1-Butanol	92.0	7.8	2.8	7.7	11.3
Pentanol	108.6	7.8	2.8	6.8	10.7
Hexanol	125.2	8.0	2.1	6.3	10.4
Heptanol	141.9	8.1	2.0	6.2	10.4
Octanol	158.4	8.3	1.6	5.8	10.2
Acetone	73.43	7.6	5.1	3.5	9.8
Acetonitrile	52.23	9.0	8.0	5.1	13.1
Methoxy ethanol	78.85	7.9	4.6	8.2	12.3
Ethoxy ethanol	96.80	7.92	4.5	7.0	11.5
Butoxy ethanol	131.3	7.82	2.5	6.0	10.2

Table 2: Experimental and Calculated mole fraction solubility of Cholesterol in different solvents at 298.15 K

Solvent	x_2 (exp)*10^3	$(\log \gamma_2)/A$ (exp)	x_2 (calc) *10^3 from eq.(7)	lnx_2 (exp)	x_2 (calc) *$10^3$from eq.(10)	B (exp)	x_2 (calc) *10^3 from eq.(13)
Methanol	0.6760	-15.4668	0.5823	-7.2993	0.6096	-5.9519	0.5621
Ethanol	3.1000	-18.4321	4.3545	-5.7764	3.7731	-12.6879	4.0795
1-Propanol	10.9000	-21.9510	6.8488	-4.5190	8.5942	-17.8183	8.4380
1-Butanol	15.2000	-22.8783	8.9512	-4.1865	11.1049	-19.9493	9.9237
Pentanol	3.3000	-18.2375	35.0091	-5.7138	11.7089	-16.3138	29.0564
Hexanol	3.0000	-17.9957	7.6191	-5.8091	5.4164	-16.5838	9.3030
Heptanol	4.0600	-18.5555	4.9245	-5.5066	4.4215	-17.5012	5.0432
Octanol	3.3700	-18.1509	2.4362	-5.6928	2.7115	-17.3641	2.1372
Acetone	0.9889	-16.0507	1.2431	-6.9189	1.1376	-12.1494	1.3174
acetonitrile	0.1710	-13.0950	0.1766	-8.6738	0.1755	-6.4911	0.1801
Methoxy ethanol	4.1990	-18.9474	5.7946	-5.4729	5.2624	-15.3879	5.7289
Ethoxy ethanol	11.0000	-21.4822	5.4133	-4.5099	6.7223	-18.9173	4.9856
Butoxy ethanol	26.8900	-24.6270	4.2242	-3.6160	8.3796	-23.1822	3.7907

Properties of Cholesterol: mp. 422.4 K, V_2 = 367.54 cm^3/ mol, x_2^i = 5.1742*10^{-8}, log x_2^i = -2.5044.

Table 3: Solubility parameters for cholesterol by different methods

S. No.	Method used	Solubility parameter
1	Fedors	10.50
2	Hoy	9.76
3	Bowden	11.48
4	VanKrevelen	14.37
		δ_{2T} (δ_{2d}, δ_{2p},δ_{2h})
5	Flory-Huggins size correction term B	11.03 (8.45,2.51,6.63)
6	Three parameter approach with log $(\gamma_2)/A$	11.28 (8.21, 3.27, 7.01)
7	Three parameter approach with log x_2	11.35 (8.25, 3.26, 7.08)

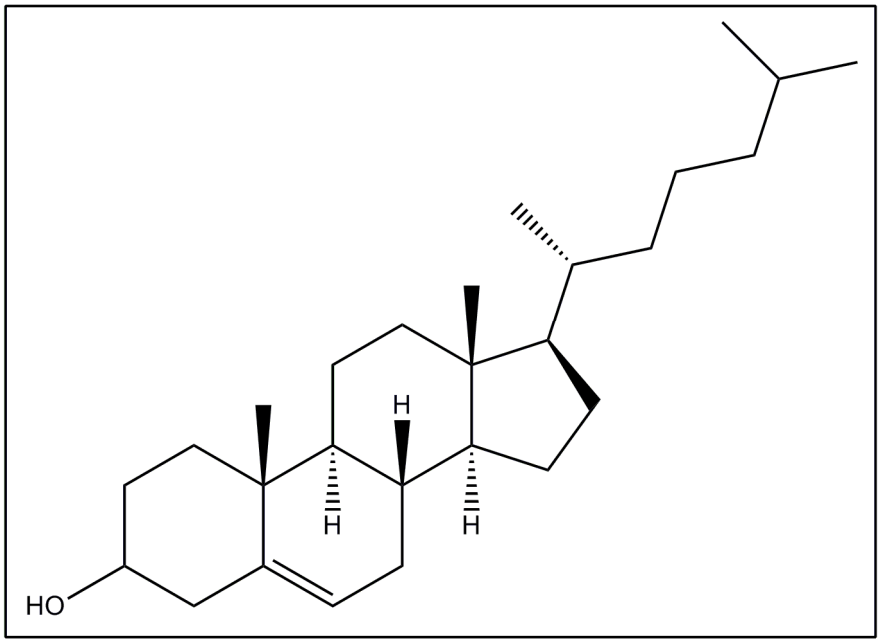

Fig. 1: Structure of Cholesterol

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