Measurement and correlation of cholesterol solubility in some glycol ethers at (298.15 to 318.15)K

Abstract

The solubility of cholesterol in methoxyethanol, ethoxyethanol and butoxy ethanol was measured by a gravimetric method from (298.15 to 318.15)K at atmospheric pressure. It is observed that solubility increases with increase in temperature. The mole fraction solubility was found to be higher in butoxyethanol and minimum in methoxyethanol. The correlation coefficient in methoxyethanol, ethoxyethanol and butoxyethanol were observed in the range 0.994-0.997. The experimental solubility data were correlated with temperature by modified Apelblat and Buchowski-Ksiazczak $\lambda h$ equations. It is observed that the theoretical values evaluated by these equations are in good agreement with the experimental solubility values. Further, some thermodynamic parameters such as Gibb’s free energy, enthalpy and entropy of dissolution were evaluated from solubility data. It is observed that the evaluated thermodynamic parameters are negative. The negative enthalpy and Gibb’s free energy suggest exothermic and spontaneous dissolution of cholesterol in all the three glycol ethers whereas negative entropy indicates that dissolution causes more ordered structure in these solvents.

Keywords: cholesterol, solubility, glycol ethers, apelblat equation, buchowski-ksiazczak $\lambda h$ equation, thermodynamic parameters

Introduction

Cholesterol (Chemical Name: Cholest-5-en-3β-ol) is a sterol and a lipid found in the cell membranes of all body tissues, and transported in the blood plasma of all animals. Small amount of cholesterol is also found in plant membranes. It is also required to build and maintain cell membranes and act as an antioxidant. It has been reported that due to its presence in cell membrane, 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. Further, cholesterol is the major component of most gallstones and it is sparingly soluble in water.

In the present work, the solubilities of cholesterol in some glycol ethers, such as methoxyethanol ethoxyethanol and butoxyethanol have been measured from (298.15 to 318.15)K at atmospheric pressure. The Apelblat and Buchowski-Ksiazczak $\lambda h$ equations were used for correlation of experimental solubility data with temperature. Using these solubility data, some thermodynamic parameters have also been evaluated.

Experimental section

Materials

Cholesterol, with a mass fraction purity of 99.5%, was purchased from HiMedia Pvt. Ltd. (Mumbai, India). All the solvents, i.e., methoxyethanol, ethoxyethanol and butoxyethanol 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 99.80% (Figure 1).

Figure 1 Structure of Cholesterol

Cholesterol was recrystallized and its melting temperature was determined using Differential Scanning Calorimeter (DSC) (Model-Shimadzu-DSC-60). The observed value was found to be 149°C which is in good agreement with the reported value of 149.8°C. The purity of solvents was checked by GC-MS (SHIMADZU Model No.-QP-2010) and found to be greater than 99.0%.

Apparatus and procedure

The solubility was measured by gravimetric method in methoxyethanol, ethoxyethanol and butoxyethanol from (298.15 to 318.15)K at atmospheric pressure of 0.1MPa. For each measurement, an excess amount of cholesterol was added to a known amount of solvent in an equilibrium cell, which 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 2h. A portion of this solution was filtered and by a preheated injector, 2ml of this clear solution was taken in another weighted measuring vial. The vial was quickly and tightly closed and weighted to determine the mass of the sample. 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 to determine the mass of the constant residue solid. All the masses were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ±0.0001g. Thus, the solid concentration of the sample solution of mole fraction, x, could be determined from eq 1.

\[ x = \frac{m_1 / M_2}{m_1 / M_1 + m_2 / M_2} \]  
where \( m_1 \) and \( m_2 \) represent the masses of pure solvent and cholesterol respectively. \( M_1 \) and \( M_2 \) are the molecular weights of pure solvent and cholesterol respectively. At each temperature, the measurement was repeated three times and an average value is given in Table 1 along with uncertainty.

Results and discussion

The experimental mole fraction solubilities \( x \) of cholesterol in methoxyethanol, ethoxyethanol and butoxyethanol at different temperatures (298.15 to 318.15K) are summarized in Table 1. The variation of solubility with temperature is also shown in Figure 2. It is observed that solubility increases linearly with increase in temperature. Further, solubility is higher in butoxyethanol and minimum in methoxyethanol. Thus, solubility increases as number of carbon increases. The solubility in these three glycol ethers can also be related to their dielectric constants and dipole moments which are given in Table 2. It is observed that dielectric constant is maximum for methoxyethanol in which solubility is minimum. Whereas for butoxyethanol, dielectric constant is minimum and solubility is maximum. Thus in the present study, solubility is reverse to dielectric constant. The dipole moment of all the three solvents is not much different and no concrete relation between solubility and dipole moment can be decided. Further, the increase of chain length causes a decrease in acidity and polarity of molecules and an increase in basicity of hydroxyl oxygen. Cholesterol has ability for self-association and acts as proton donor in the association process with proton acceptors as reported by Garalski. So, it readily associates with the selected solvents and association increases with increase in chain length. This association takes place mainly by hydrogen bonding. Also, the growing number of carbon atoms causes a decrease in self association i.e., solvent-solvent interactions, which can be attributed to the presence of intermolecular hydrogen bonds. This may results in an increase in solubility of cholesterol in butoxyethanol.

The temperature dependence of cholesterol solubility in solvents is described by modified Apelblat equation:

\[ \ln x^\infty = A + B / T + C \ln(T) \]  
where \( x^\infty \) is the mole fraction solubility calculated by equation 2 and \( T \) is the absolute temperature. \( A, B \) and \( C \) are the empirical model parameters determined by least square method and the values are given in Table 3. The values of \( A \) and \( B \) represent the variation in the solution activity and the solution behavior resulting from the non idealities on the solubility of solute, and the value of \( C \) represents the association between the temperatures and the enthalpy of fusion.

![Figure 2 Variation of mole fraction solubilities (\( x \)) with temperature for cholesterol in glycol ethers. \( \bullet \): methoxyethanol; \( \square \): ethoxyethanol; ▲: butoxyethanol. Corresponding dotted (-----) lines are for calculated solubility by Apelblat equation](image)

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compound in K. \( \lambda \) and \( h \) are the parameters of Buchowski-Ksiažczak \( \lambda h \) model which are given in Table 4.

### Table 2: Dielectric constants and dipole moments of some glycol ethers

| Solvents       | Dielectric constant | Dipole moment |
|----------------|---------------------|---------------|
| Methoxy ethanol| 17.20               | 2.36          |
| Ethoxy ethanol | 13.38               | 2.10          |
| Butoxy ethanol | 9.30                | 2.10          |

### Table 3: Constants A, B and C of equation 2, Absolute Average Deviation (AAD) and Root Mean Square Deviation (RMSD) of Cholesterol in some glycol ethers

| Solvents       | A       | B       | C       | RMSD    | AAD     |
|----------------|---------|---------|---------|---------|---------|
| Methoxy ethanol| -2.2071 | 92.60917| 0.3336  | 1.9657E-05 | 1.3154E-05 |
| Ethoxy ethanol  | -2.1471 | 44.9123 | 0.3523  | 4.5545E-05 | 6.2918E-04 |
| Butoxy ethanol  | -2.1538 | 58.7932 | 0.3481  | 9.6675E-05 | 8.8491E-07 |

### Table 4: Constants \( \lambda \) and \( h \) of equation 3, Absolute Average Deviation (AAD) and Root Mean Square Deviation (RMSD) of Cholesterol in some glycol ethers

| Solvents       | \( \lambda \) | \( h \)    | RMSD    | AAD     |
|----------------|--------------|------------|---------|---------|
| Methoxy ethanol| 0.0352       | 55381.8363| 3.3572E-05 | -0.0024 |
| Ethoxy ethanol  | 0.6839       | 5493.4271 | 2.7568E-04 | -0.0016 |
| Butoxy ethanol  | 0.1429       | 10686.2133| 1.3240E-04 | -0.0019 |

The solubility of compounds calculated by Apelblat equation \( (x_a) \) and Buchowski-Ksiažczak \( \lambda h \) equation \( (x_b) \) are also given in Table 1 and Figure 2, Figure 3. It is observed from the Table 1 that the values obtained by modified Apelblat equation and Buchowski-Ksiažczak \( \lambda h \) equation shows good agreement with each other and also with experimental solubility data.

### Table 5: The relative deviation (RD) evaluated by Apelblat and Buchowski equations of Cholesterol in some glycol ethers

| T/K     | 100RD (Apelblat) | 100RD (Buch) |
|---------|------------------|--------------|
| Methoxy ethanol |                    |              |
| 298.15  | -0.1342          | 0.3753       |
| 302.15  | 0.2983           | -0.2192      |
| 306.15  | 0.3098           | -1.1624      |
| 310.15  | -0.0433          | -0.7608      |
| 314.15  | 0.5417           | 0.2809       |
| 318.15  | -0.3446          | 0.0491       |
| Ethoxy ethanol |                    |              |
| 298.15  | 0.3267           | -2.6548      |
| 302.15  | 0.2560           | 1.5038       |
| 306.15  | 0.2684           | 1.9108       |
| 310.15  | -0.1998          | 0.0000       |
| 314.15  | 0.0085           | 0.0000       |
| 318.15  | -0.2823          | -1.6064      |
| Butoxy ethanol |                    |              |
| 298.15  | 0.3167           | -0.3003      |
| 302.15  | 0.2560           | 1.5038       |
| 306.15  | 0.2684           | 1.9108       |
| 310.15  | -0.1998          | 0.0000       |
| 314.15  | 0.0085           | 0.0000       |
| 318.15  | -0.2823          | -1.6064      |

The dissolution of compound in a solvent is associated with changes in thermodynamic functions such as enthalpy \( (\Delta H_{\text{sol}}) \), Gibb’s energy \( (\Delta G_{\text{sol}}) \) and entropy of solution \( (\Delta S_{\text{sol}}) \).

The enthalpy of solution \( (\Delta H_{\text{sol}}) \) was calculated by the following modified Van’t Hoff equation:

\[
\left( \frac{\partial \ln x_i}{\partial (\frac{1}{T}-\frac{1}{T_m})} \right)_p = -\frac{\Delta H_{\text{sol}}}{R}
\]

where \( T \) is the experimental temperature, \( R \) is universal gas constant.
constant (8.314 J/mol K) and $T_H$ is mean harmonic temperature\textsuperscript{12} which is calculated by equation:

$$T_H = \frac{n}{\sum_{i=1}^{n} \left( \frac{1}{T_i} \right) \left( \frac{1}{T_i} \right)}$$ \hfill (8)

where $n$ is the number of experimental temperatures studied. In the present study, value of $T_H$ calculated by this equation is found to be 307.998K.

The slope of the plot of $lnx$ versus $(1/T - 1/T_H)$ gives the enthalpy of solution ($\Delta H_{sol}$) whereas Gibb’s free energy is calculated by intercept using the following relation:

$$\Delta G_{sol} = - R \times T_H \times \text{Intercept}$$ \hfill (9)

Finally, the entropy of solution ($\Delta S_{sol}$) was obtained from these evaluated $\Delta H_{sol}$ and $\Delta G_{sol}$ values at $T_H$:\textsuperscript{13,14}

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_H}$$ \hfill (10)

These evaluated thermodynamic parameters are given in Table 6.

It is observed from Table 6 that all the three thermodynamic parameters i.e., $\Delta H_{sol}$, $\Delta G_{sol}$ and $\Delta S_{sol}$ are negative for all the three solvents.

**Table 6** Thermodynamic parameters of dissolution of cholesterol in some glycol ethers

| Solvents      | $\Delta G$/kJ.mol$^{-1}$ | $\Delta H$/kJ.mol$^{-1}$ | $\Delta S$/J.mol$^{-1}$ |
|---------------|--------------------------|--------------------------|--------------------------|
| Methoxy ethanol | -13.4923                 | -16.2289                 | -8.8851                  |
| Ethoxy ethanol | -10.4528                 | -31.2357                 | -67.4773                 |
| Butoxy ethanol | -8.8369                  | -12.6955                 | -12.5277                 |

Comparison of solubility data with Gibb’s energy values shows that these two are inversely related. The $\Delta G_{sol}$ is more negative in butoxyethanol which further suggests more spontaneous dissolution than in methoxyethanol and ethoxyethanol. The negative enthalpy of dissolution ($\Delta H_{sol}$) indicates exothermic dissolution process whereas negative entropy is due to more order in solutions.\textsuperscript{15}

**Conclusion**

Solubility of cholesterol increases linearly with increase in temperature and solubility is higher in butoxyethanol. The solubility data calculated by modified Apelblat and $\lambda h$ equations are in good agreement with experimental values. Thermodynamic parameters suggest that dissolution of cholesterol in studied glycol ethers is spontaneous and exothermic. Further, solutions of cholesterol in these solvents are more ordered.

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**Conflict of interest**

Author declares that there is no conflict of interest.

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