ABSTRACT

The interactions of drug amoxicillin with maltose or galactose solutions with a variation of temperature have been discussed by taking in the volumetric and viscometric procedures. Physical properties [densities ($\rho$) and viscosities ($\eta$)] of amoxicillin (AMOX) aqueous solutions and aqueous solutions of two type saccharides (maltose and galactose 0.05m) have been measured at $T = (298.15, 303.15$ and $308.15)$ K under atmospheric pressure. The apparent molar volume ($\phi$, cm$^3$ mole$^{-1}$) has been evaluated from density data and fitted to a Redlich-Mayer equation. The empirical parameters of the Mayer-Redlich equation and apparent molar volume at infinite dilution $\phi^0$ were explicated in terms of interactions from type solute-solvent and solute–solute interactions. Transfer molar volume $\Delta\phi^0$ for AMOX from water to aqueous maltose and galactose solutions were calculated to comprehend different interactions in the ternary solutions. Limiting apparent molar expansibility ($\Theta^0_\phi$) and Hepler’s coefficient was also calculated to indicate the structure making ability of AMOX in the ternary solutions. Jones–Dole coefficient B and A have been calculated from viscosity data by employing the Jones–Dole equation. The free energy of activation of viscous flow per mole of the solute ($\Delta\mu^0_2$) and solvent ($\Delta\mu^0_1$) have been explained on the basis of the Eyring and Feakins equation.


INTRODUCTION

Amoxicillin or p hydroxyl Ampicillin as visible in Figure 1, is one of the beta-lactam antibiotics and due to its pharmacokinetics, and pharmacodynamics properties it used to treat infectious diseases. Physical or chemical interaction of drugs may be occurring during drug transport, mixing ingredient formulation, and storage. This interaction, drug–macromolecular aggregation in binary or ternary solutions and medicinal chemistry can be understood through thermodynamics and physicochemical studies.

Up to now, the physical properties of antibiotics was investigated by different research groups. Harsh Kumar and Kirtanjot Kaur studied The volumetric and acoustic properties of Ampicillin with glycine and its dipeptides, glycyglycine, and glycylycine at different temperature and the same research group studied the ion-ion and ion–solvent interaction of AMOX and AMP with amino acid L-serine based on viscometric measurement. Also, Harsh Kumar et al. investigated the Solvation behavior of dipeptides of alanine in aqueous solutions of antibacterial drug ampicillin at different temperatures. To the best of our knowledge, no data on thermodynamic studies of Amoxicillin with saccharides have been reported.

Aqueous media and different temperatures play a vital role in the biochemical process, so the various interactions occurring in the ternary systems, structure making and breaking ability of drug Amoxicillin with monosaccharide (galactose) and disaccharides (maltose) aqueous solution have been investigated.

EXPERIMENTAL PART

D-maltose (Merck, ≥ 99.0%, M.wt : 360.31 g/mol, $C_{12}H_{24}O_{12}$), D-galactose (BDH, ≥ 70%, M.wt: 180.16 g/mol, $C_6H_{12}O_6$)
and Amoxicillin (Samarra drugs factory, 97-99%, M.wt: 365.4 g/mol, $C_{16}H_{19}N_{3}O_{5}S$) were used without further purification. All the solutions at different concentrations were prepared freshly in triply distilled water (conductivity $\approx$ 10-6 S.cm$^{-1}$) were weighed by electronic digital balance (Sartorius, Germany) ($\pm$ 0.0001 g). The density was measured with the pycnometer (5 mL) by the relative measurement method with an accuracy of $\pm$ 0.0001 g.cm$^{-3}$, viscosity was determined with the help of An Ostwald’s viscometer (10 mL). Efflux time was determined using a digital chronometer within $\pm$0.01 s. All measurements were made in an electronically digital operated constant temperature visible bathwater (JULABO ME-18V Visco Bath, Germany) containing the experimental solution at desired temperature (25, 30, and 35)$^\circ$C, whose accuracy is maintained at $\pm$ 0.1 $^\circ$C.

RESULT AND DISCUSSION

The experimental densities of three systems AMOX in water (AMOX + water), aqueous maltose (AMOX+maltose) and aqueous galactose (AMOX + galactose) (0.05m) as a function of molality of AMOX at $T = (298.15, 303.15$ and $308.15)$ K are represented in Figure 2.

It is observed that the density of AMOX in water, maltose, and galactose aqueous follow the following trend and vary linearly with a molality of the solution:

$$m_{\text{maltose}} < m_{\text{galactose}} < m_{\text{water}}$$

As usual, as the temperature, an increase in the density of the solution decreases.

$$\phi_v = \frac{M}{\rho} - \frac{1000(\rho - \rho^\circ)}{m\rho^\circ}$$

$(\phi_v, \text{cm}^3\text{mole}^{-1})$ of AMOX aqueous, aqueous galactose and aqueous maltose were calculated from measured densities solution using the following equations.$^9,10$

Where $M, \rho$ and $\rho^\circ$ are referred to the molar mass of AMOX, the densities of solution, and solvent, respectively. The molality of AMOX solution is $m$.

The apparent molar volume values are fitted to the Redlich-Meyer polynomial Equation 1.$^{11,12}$

$$\phi_v = \phi_v^\circ + s_v \sqrt{m} + B_v m$$

Where $\phi_v^\circ$ is apparent molar volume at infinite dilution, refers to solute-solvent interaction, $s_v$, $B_v$, is regression parameters, evaluated by the least square analysis of Equation 2 The parameter provides information about the interactions between the pairs of solute molecules and the parameter represent the interaction between two or more solute molecules and is molality of solution. Figure 3 shows that this simple model accurately fit with our data. Table 1 shows the parameters of Equation 2.

From Table 1 note that the values of $\phi_v^\circ$, are positive in all investigated solutions and increase with increasing temperature indicated presence strong solute-solvent interaction. At each temperature, the values of $s_v$ are positive and higher than $\phi_v^\circ$ values indicate the dominance of solute – solute interaction over solute-solvent interaction. The $s_v$ values decrease with rise in temperature for (AMOX+water) and (AMOX+maltose) except for (AMOX+galactose), where no regular trend is observed. The order of the strength of the solute to solute interactions of each system ordered as below:

(AMOX+maltose) < (AMOX+water) < (AMOX+galactose)

The negative values of $B_v$ are probably due to the presence of weak triplet solute - solute molecules interaction.

<table>
<thead>
<tr>
<th>System</th>
<th>$\phi_v^\circ$ (cm$^3$ mole$^{-1}$)</th>
<th>$s_v$ (cm$^3$ Kg$^{1/2}$ mole$^{-3/2}$)</th>
<th>$B_v$ (cm$^3$ Kg mole$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMOX + water</td>
<td>298.15K, 303.15K, 308.15K</td>
<td>3617, 2718, 1547</td>
<td>-15759, -8708, -5436</td>
</tr>
<tr>
<td>AMOX + maltose</td>
<td>298.15K, 303.15K, 308.15K</td>
<td>3766, 3624, 2349</td>
<td>-15705, -15462, -9032</td>
</tr>
<tr>
<td>AMOX + galactose</td>
<td>298.15K, 303.15K, 308.15K</td>
<td>2366, 2592, 3305</td>
<td>-7511, -9655, -1488</td>
</tr>
</tbody>
</table>
Study of Molecular Interaction for Antibiotic Drug with Sugar Solutions at Different Temperature

Figure 3: The apparent molal volume (\(\phi_v\)) of AMOX in (A) aqueous solution (B) aqueous maltose solution (C) aqueous galactose solution at different temperatures.

Transfer molar volume \(\Delta v\text{tra}O^\circ\) as define in equation 3 was used to analyze the interaction of solute understudy AMOX with mixed solvent (H\(_2\)O+maltose) and (H\(_2\)O+galactose). Table 3 present the calculated values for the partial molar volumes of the transfer of AMOX from water to the mixed solvent (H\(_2\)O+maltose) and (H\(_2\)O+galactose).

\[\Delta v\text{tra}O^\circ = \phi_v(\text{Aqueous}) - \phi_v(\text{water})\]  

(3)

Based on the Friedman and Krishnan’s cosphere overlap model,\(^{15}\) the nature of solute species affected the properties of water molecules in the hydration cosphere when the solute molecules approach each other some of cosphere material overlapping and displacing and that is accompanied by the change in volume of the solution and change in thermodynamic parameters.

The negative volumes of transfer values of AMOX in the presence of maltose as shown in Table 2 indicate that Hydrophilic–hydrophilic group interactions between the OH-NH-COOH groups of AMOX and CH groups of the maltose and Hydrophobic–hydrophobic group interactions between the aromatic ring of AMOX and CH groups of the maltose through CH-\(\pi\) interaction\(^ {14,15}\) predominate over hydrophilic–hydrophilic group interactions and this overlap brings about a decrease in volume because of increase the electrostriction of water by AMOX.

The volume of transfer of AMOX in the presence of galactose has positive values and decreases with increasing temperature due to the predominating the interactions of Hydrophilic–Hydrophilic groups, which make positive contributions to the transfer volume.\(^ {16}\)

The values of \(\Delta v\text{tra}O^\circ\) may be further explained by the model developed by Frank et al.\(^ {17}\) And further modified by shahidi et al.\(^ {18}\) as shown by the following relation:

\[\Delta v\text{tra}O^\circ = V_{\text{sh}} + V_{\text{sol}} - V_a\]  

(4)

Where \(V_{\text{vw}}\) is the van der Waals volume, \(V_{\text{void}}\) is the volume associated with empty space, and is the shrinkage volume. The \(V_{\text{vw}}\) and \(V_{\text{void}}\) assuming to have same magnitudes in water and in maltose solutions for the same solute. According to this model, the negative values of \(\Delta v\text{tra}O^\circ\) from water to aqueous maltose can be attributed to an increase in the volume of shrinkage due to hydrophobic interaction. These interactions will increase the structure breaking effect of maltose on water. In other words, in the presence of AMOX, more water molecules (dense) is expelled from the hydration shells. Since dense (structure broken water) has lower volume contribution than bulk water therefore this factor will also contribute to negative values of \(\Delta v\text{tra}O^\circ\). The positive values of transfer for AMOX indicate decrease in the shrinkage volume due to galactose.

The apparent molar volumes (\(\phi_v\)) at infinite dilution were fitted to a second-order polynomials equation in terms of absolute temperature (\(T\)) as equation below:

\[\Delta v\text{tra}O^\circ = V_{\text{sh}} + V_{\text{sol}} - V_a\]  

(5)

Where \(a\), \(b\) and \(c\) are empirical constants depending on solute and solvent and estimated by fitting line to \(\phi_v\) data. By differentiating relation (5) with respect to temperature \(\partial \phi_v/\partial T\) we obtained limiting apparent molar Expansibility (\(\phi'_v\))

\[\phi'_v = b + 2cT\]  

(6)

The calculated values \(\phi'_v\) of at different temperatures are presented in Table 3. From Table 3 we note that the values of \(\phi'_v\) are negative for AMOX+ water and AMOX+ maltose, indicated weak solute- solvent interaction for these systems at 298.15K.

### Table 2: Values of transfer molar volume \(\Delta v\text{tra}O^\circ\) of AMOX in maltose and galactose aqueous solution at different temperature

<table>
<thead>
<tr>
<th></th>
<th>(\text{298.15 k})</th>
<th>(\text{303.15 k})</th>
<th>(\text{308.15 k})</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMox + maltose</td>
<td>-13.23</td>
<td>-10.74</td>
<td>-37.9</td>
</tr>
<tr>
<td>AMox + galactose</td>
<td>34.78</td>
<td>28.17</td>
<td>-49.4</td>
</tr>
</tbody>
</table>

### Table 3: The partial molal volume expansibilities \(\phi'_v(\text{cm}^3\cdot\text{mole}^{-1}\cdot\text{K}^{-1})\) and \(\partial^2\phi'_v/\partial T^2(\text{cm}^3\cdot\text{mole}^{-1}\cdot\text{K}^{-2})\) for AMOX in aqueous and aqueous maltose and galactose

<table>
<thead>
<tr>
<th></th>
<th>(\text{298.15K})</th>
<th>(\text{303.15K})</th>
<th>(\text{298.15K})</th>
<th>(\text{303.15K})</th>
<th>(\text{298.15K})</th>
<th>(\text{303.15K})</th>
<th>(\text{308.15K})</th>
<th>(\text{308.15K})</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMox + H(_2)O</td>
<td>-4.85</td>
<td>10.05</td>
<td>24.96</td>
<td>-1.57</td>
<td>7.40</td>
<td>16.38</td>
<td>0.53</td>
<td>1.13</td>
</tr>
<tr>
<td>AMox + maltose</td>
<td>888.9</td>
<td>903.8</td>
<td>918.7</td>
<td>535.3</td>
<td>544.3</td>
<td>553.3</td>
<td>35.53</td>
<td>36.13</td>
</tr>
<tr>
<td>AMox + galactose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study of Molecular Interaction for Antibiotic Drug with Sugar Solutions at Different Temperature

Table 4: Parameters of Jones–Dole equation $A$(cm$^3$.mole$^{-1/2}$), $B$(cm$^3$.mole$^{-1}$) and, $\Delta \mu^o_i$, $\Delta \mu^o_i$(KJ.mole$^{-1}$) for AMOX in aqueous solution and maltose, galactose aqueous solution at 298.15,303.15 and 308.15K.

<table>
<thead>
<tr>
<th></th>
<th>298.15K</th>
<th>303.15K</th>
<th>308.15K</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMOX+H2O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.1228</td>
<td>-0.1581</td>
<td>0.0667</td>
</tr>
<tr>
<td>B</td>
<td>5.6184</td>
<td>5.5324</td>
<td>4.5812</td>
</tr>
<tr>
<td>$\Delta \mu^o_i$</td>
<td>20.40</td>
<td>20.74</td>
<td>21.05</td>
</tr>
<tr>
<td>$\Delta \mu^o_i$</td>
<td>69.19</td>
<td>69.58</td>
<td>62.58</td>
</tr>
<tr>
<td>AMOX+0.05m maltose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.7758</td>
<td>0.5371</td>
<td>0.1029</td>
</tr>
<tr>
<td>B</td>
<td>1.5566</td>
<td>1.6802</td>
<td>3.0799</td>
</tr>
<tr>
<td>$\Delta \mu^o_i$</td>
<td>20.58</td>
<td>20.82</td>
<td>21.12</td>
</tr>
<tr>
<td>$\Delta \mu^o_i$</td>
<td>34.36</td>
<td>35.81</td>
<td>48.18</td>
</tr>
<tr>
<td>AMOX+0.05m galactose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.217</td>
<td>0.2643</td>
<td>0.2371</td>
</tr>
<tr>
<td>B</td>
<td>3.7708</td>
<td>2.5796</td>
<td>2.1231</td>
</tr>
<tr>
<td>$\Delta \mu^o_i$</td>
<td>20.50</td>
<td>20.82</td>
<td>21.09</td>
</tr>
<tr>
<td>$\Delta \mu^o_i$</td>
<td>52.56</td>
<td>43.29</td>
<td>39.92</td>
</tr>
</tbody>
</table>

and positive for AMOX+ galactose. The $\theta^*_e$ increases with increase in temperature for all investigated systems.

The structure making and breaking capacity of solute in aqueous solutions can be inferred by differentiating the thermodynamic equation of state eq.7 with respect to moles of solute ($n_2$) at constant P, T and moles of solvent ($n_1$) and then with respect to T at constant $n_2$, $m_1$, and P to obtain Equation 8.

$$\frac{\partial H}{\partial P} = V - T \left( \frac{\partial V}{\partial T} \right)_P$$

(7)

$$\frac{\partial C_p}{\partial P} = - T \left( \frac{\partial V}{\partial T} \right)_P$$

(8)

Since Equation 8 is limited to solute-solvent interactions so we can apply this equation to limiting apparent molal volumes ($\theta^*_e$) at infinite dilution thus Equation 8 can write as the following.\(^{19}\)

$$\frac{\partial C_p}{\partial P} = - T \left( \frac{\partial \theta^*_e}{\partial T} \right)_P$$

(9)

Where $C_p$ is the partial molal heat capacity at infinite dilution, and commonly has a negative value for electrolyte due to the breaking the bulky structure of the water by these solutes.\(^{20}\) Based on this reasoning and the above thermodynamic equation, the structure making solute possess a positive value of $[\partial \theta^*_e/\partial T]^P$. Therefore the left-hand side of the Equation 8 should be negative for all structure making solutes. The positive values of Hepler’s constants as shown in Table 3 suggest that AMOX act as structure maker in water(kosmotropic behavior) or other word AMOX causes an increase in the structure of water.

The viscosities data of AMOX, $\eta$, in (0.05m) aqueous solutions of maltose and galactose at different temperatures are increasing with an increase in the concentration of drug solutions. This may be attributed to increasing frictional resistance of the solution flow. The viscosity values decrease with an increase in temperature. This may be attributed to decrease in the solute-solvent interaction.

The viscosities of (AMOX + water),(AMOX+ maltose aqueous), and (AMOX + galactose aqueous) were interpreted using the Jones–Dole relation.\(^{21,22}\)

$$\left( \frac{\eta}{\eta^*} - 1 \right) / \sqrt{C} = \eta_{rel} = 1 - \sqrt{C} = A + B\sqrt{C}$$

(10)

Where $\eta_{rel}$ is relative viscosity which equal to the ratio of viscosity of solution ($\eta$) to viscosity of solvent ($\eta^*$) (maltose+water)-(galactose + water) C is the molar concentration (calculated from molality) A and B are the solute–solute and solute-solvent interactions on the solution viscosity respectively. these parameters were obtained using the method of the least-squares and tabled in Table 4.

Table 4 exhibit that the values of A-coefficients are positive for AMOX in all systems solution at all temperatures except for AMOX +water at 303.15K. This observation referred to presence of solute – solute interactions. This result supports the results obtained from an apparent molar volume. The values of viscosity B-coefficients of AMOX in all investigated systems are positive at all temperatures, suggesting the presence of solute-solvent interactions. These solute-solvent interactions decrease when the temperatures increase.

The viscosity B-coefficient is related to the free energy of activation of viscous flow per mole of the solute $\Delta \mu^o_i$ according to transition state theory suggested by Feakins et al. by the following relationship.

$$\Delta \mu^o_i = \Delta \mu^o_i + RT(1000B + (\phi^o_i - \phi_{ei}))/\phi^o_i$$

(11)

Where $\Delta \mu^o_i$ is the partial molar volume of the solute at infinite dilution or limiting apparent molar volume, $\phi^o_i$ is the partial molar volume of the solvent and $\Delta \mu^o_i$ is the free energy of activation of viscous flow per mole of solvent were calculated using the following relationship as proposed by Eyring and co-worker.\(^{23}\)

$$\Delta \mu^o_i = RT \ln \eta \phi^o_i / hN_A$$

(12)

Where NA is Avogadro's number, h plank constant the other symbols have their usual meaning. The $\Delta \mu^o_i$ and $\Delta \mu^o_i$ of Amox in aqueous, Amox in 0.05 m aqueous maltose and Amox in 0.05 m aqueous galactose are calculated and provided in Table 4.

It is clear from Table 4 that the values of $\Delta \mu^o_i$ were found to be positive and much larger than $\Delta \mu^o_i$ values at all the
experimental temperatures. These result and positive viscosity B-coefficients according to Feakins et al.26 indicates strong solute-solvent interactions in the ground state or in other word structure-making ability of the solute, thereby suggesting that the solute-solvent interactions in the transition state is less favored in the presence of AMOX and accompanied by rupture and distortion of the intermolecular bonds in solvent structure.

CONCLUSIONS

A volumetric and viscometric study of AMOX in aqueous maltose and galactose solution has been done in this study. The apparent molar volume of AMOX fitted to Mayer equation indicates the presence of solute-solvent interactions as well as solute – solute interaction. From the investigation of \( \Delta \mu^\circ \), it is deduced that the hydrophilic- hydrophobic and the hydrophobic - hydrophobic interactions are predominant for the AMOX from water to aqueous maltose over the hydrophilic-hydrophilic interactions in the case AMOX from water to aqueous galactose. The tendency of \( \partial^2 V/\partial T^2 \) and \( \Delta \mu^\circ_2 \) for AMOX in the aqueous solutions of maltose and galactose indicates AMOX act as structure making.

REFERENCES