Investigation of Volumetric and Optical Properties of Anti-Emetic Metoclopramide Hydrochloride Drug in Aqueous-Dimethylsulfoxide (DMSO) Solutions At 303.15 K

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ABSTRACT

In view of pharmaceutical applications, the density (ρ) and refractive index (nD) of antiemetic metoclopramide hydrochloride monohydrate (MHM) drug in aqueous, aqueous-DMSO and DMSO solutions were measured at 303.15 K in the wide range of concentration of drug. Apparent molar volumes (φρ) were calculated from density data and fitted to the Masson relation to determine partial molar volume (φ ρ) of drug. Overall, strong drug-solvent interactions with significant structural changes in pure and mixed solvents have been confirmed.

INTRODUCTION

Nowadays, major efforts are devoted to study physicochemical properties of biomolecules in mixed solvent because of their binding trends with the medium. Volumetric properties such as density, apparent and partial molar volumes of drug solutions are of fundamental importance. These properties are greatly affected by the medium and nature of solvent(s) due to the existence of various molecular interactions in solution. Molecular interactions in different systems such as nicotine in aqueous and aqueous ethanol at different temperatures were studied (Singh et al., 2007); antidepressant drugs in aqueous medium at different temperatures (Iqbal and Chaudhary, 2009), pharmacologically significant drugs in methanol at 298.15 K (Jahagirdar et al., 1998), substituted heterocyclic drugs in 1, 4-dioxane at 303 K (Sonar and Pawar, 2010), isoniazid in water and dimethylsulfoxide were investigated (Markarian et al., 2012), aqueous 70% DMF solutions of some drugs at 300.15K (Chapke et al., 2013) and some drugs in aqueous solutions at different temperatures were studied (Dhondge et al., 2012) have been studied. Apparent molar volume and adiabatic compressibility of aqueous solutions of some drugs and partial molar volumes of some drugs in water and ethanol were studied (Iqbal and Verrall, 1989; Iqbal et al., 1994). Physicochemical properties of some drugs in solution (Baluja et al., 2007) have been studied. Thermodynamic properties of multicomponent liquid mixtures are very interesting subject for teaching and research as well as for design and set up of industrial processes study (Conti et al., 1995). Thermodynamic and transport properties of mixtures are significant from the fundamental viewpoint to understand mixing behaviour (Kumar et al., 2009; Parveen et al., 2010; Singh et al., 2004; Gonzalez et al., 2007; Bhatia et al., 2011). Systems containing hydrogen bonding plays an important role in chemical, physical, and biological processes (Zorebski et al., 2009).

Effect of drug on structure of pure solvents and solvent mixtures are of great importance in view of pharmaceutical research and industrial development. Metoclopramide hydrochloride monohydrate (4-amino-5-chloro-N-(2-diethyl amino)ethyl)-2 methoxybenzamide hydrochloride hydrate, MHM) is a centrally acting anti-emetic drug and it has both hydrophilic and hydrophobic domains. Solution properties of metoclopramide hydrochloride in pure solvents such as water and DMSO and in mixed DMSO-water are lacking despite their physiological importance.

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The drug-solvent interactions have been studied (Deosarkar et al., 2014; Deosarkar et al., 2014; Deosarkar and Kalyankar, 2013; Deosarkar et al., 2012). An effort has been made here to study the physicochemical properties such as density, refractive index and apparent and partial molar volumes of metoclopramide hydrochloride in water, DMSO and 30, 50 and 70% v/v DMSO-water mixtures.

EXPERIMENTAL

Water (HPLC grade, deionized distilled water obtained from Millipore prefiltration kit (Direct-Q™ system series), Metoclopramide hydrochloride monohydrate (MHM) drug was received as a gift sample from Cipla R. & D. Centre, Mumbai (MS) India and it was used as received. The 30%, 50% and 70% v/v DMSO-water mixtures were prepared in calibrated volumetric flasks by mixing appropriate volumes of respective solvents and making the volume by distilled water. MHM solutions were prepared in pure solvents and in mixed solvents by dissolving accurately weighed quantity of drug using calibrated volumetric flasks.

The solutions were kept in airtight flasks. Weighing was done on single pan electronic balance (±0.001 g) and density was measured using single capillary pycnometer. Pycnometer was calibrated with benzene and distilled water at experimental temperature and its volume was corrected for experimental temperature. Average of three readings is reported in each case of density measurements.

RESULTS AND DISCUSSION

Experimental density (ρ) and refractive index data of binary DMSO-water mixtures is reported in Table 1 and 2. It is seen from Table 1 that the density of pure DMSO is in good agreement with the literature values (Chauhan et al., 2013; Kapadi et al., 1997; Oswal and Patel, 1995; Dash et al., 2006; Roy et al., 2005; Hawrylak et al., 2006).

Density increased with percentage of DMSO in binary DMSO-water mixture. A variation in the density of binary DMSO-water mixtures indicates presence of molecular interactions which are mainly due to variations in the intramolecular and intermolecular hydrogen bonding (Figure 1).

Experimental density (ρ) and refractive index (nρ) data of MHM in pure water, pure DMSO and DMSO-water mixtures at 303.15 K is reported in Table 1 and 2. It is seen that the density increased with an increase in concentration of drug in each case which may be attributed to shrinkage in volume due to drug-solvent interactions and enhanced structure of solvent mixture due to added drug (Dash et al., 2006) It has been also found that, the density increased with increase in volume% of DMSO for given concentration of drug.

DMSO is an aprotic solvent and it is highly associated. It is seen from Table 1 that the density of pure DMSO is in good agreement with the literature values (Chauhan et al., 2013; Kapadi et al., 1997; Oswal and Patel, 1995; Dash et al., 2006; Roy et al., 2005; Hawrylak et al., 2006).

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Where, $\rho_0$ is density of pure solvent/solvent mixture in which experimental solutions were prepared, $\rho$ is density of experimental solution, $M_2$ is molar mass of MHM, $m$ is molar concentration of drug. Difference in the volume of solution and volume of pure solvent per mole of solute is apparent molar volume ($\phi_v$). For calculations of $\phi_v$, the molar concentrations were converted into temperature independent molar concentration using standard relation. Calculated $\phi_v$ values with drug concentration are presented in Table 3.

The $\phi_v$ values of drug for all the systems are large and positive which indicate strong drug-solvent interactions in solution. Overall, $\phi_v$ values decreased with increase in the concentration of drug in pure water and in pure DMSO due to relative weakening of drug-solvent interactions. Whereas, these values increased slowly in 30, 50 and 70% v/v DMSO-water mixtures due to strengthening of drug-solvent interactions. The $\phi_v$ values of drug are highest in pure DMSO and lowest in 30% v/v DMSO-water mixture. Relatively strong MHM-DMSO interactions between polar parts of the drug and solvent dipoles exist in solution. It is also seen that the $\phi_v$ are almost linearly depend on drug concentration after 0.03 mol·dm$^{-3}$. For dilute solution of drug (0.01 mol·dm$^{-3}$) the value of $\phi_v$ are large in water and DMSO.

The dependence of $\phi_v$ over concentration of drug was fitted to Massons relation (Equation 2), (Masson, 1929; Ali et al., 2010). From the plots of $\phi_v$ and $\sqrt{c}$ (Figure 2), $S_v$ and $\phi_v^0$ was determined as slope and intercept respectively.

$$\phi_v = \phi_v^0 + S_v \sqrt{c} \tag{2}$$

Where, $\phi_v^0$ is limiting infinite dilution apparent molar volume (partial molar volume) which represents solute-solute interactions (Nikam et al., 2005) and $S_v$ is experimental slope which represents solute-solute interactions. The graphical values are reported in Table 4. The $\phi_v^0$, is partial molar volume at infinite dilution and it represents solute-solute interactions whereas, $S_v$ represents solute-solute interactions. The $\phi_v^0$ is intrinsic volume plus volumetric effects due to solute-solute interactions such as ion-solvent interactions, H-bonding etc. The partial molar volume of drug-HCl is due to individual ionic contributions of $\phi_v^0$ Drug and $\phi_v^0$ HCl (Marcus, 2006; Iqbal et al., 1994; Delgado et al., 2010) significant change in the $\phi_v^0$ of drug is observed from pure water to aqueous-DMSO mixtures and pure DMSO. The $\phi_v^0$ value of drug in all the systems is positive due to existence of strong drug-solvent interactions.

The significant interactions are among the protonated tertiary amine group of MHM with DMSO and water molecule as shown in Figure 3, apart from other interactions between polar groups of drug and solvent/solvent mixture. Comparison of $\phi_v^0$ values of drug indicates that $\phi_v^0$ value of drug in pure DMSO is highest.

### Table 3: Calculated apparent molar volume ($\phi_v$) data of binary and ternary (MHM + water/DMSO-water/DMSO) solutions at 303.15 K

<table>
<thead>
<tr>
<th>$c$ (mol·dm$^{-3}$)</th>
<th>(\phi_v) (x10$^{-3}$ m$^3$·mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>0.01</td>
<td>324.85</td>
</tr>
<tr>
<td>0.03</td>
<td>283.29</td>
</tr>
<tr>
<td>0.05</td>
<td>284.97</td>
</tr>
<tr>
<td>0.07</td>
<td>282.50</td>
</tr>
<tr>
<td>0.09</td>
<td>284.42</td>
</tr>
<tr>
<td>0.11</td>
<td>281.70</td>
</tr>
<tr>
<td>0.13</td>
<td>281.30</td>
</tr>
</tbody>
</table>

Foot Note for Tables 1, 2 and 3: I=MHM + Water; II=MHM + 30% DMSO-Water; III=MHM + 50% DMSO-Water; IV=MHM + 70% DMSO-Water; V=MHM + DMSO.

### Table 4: Graphical values of partial molar volume, $\phi_v^0$, and experimental slope, $S_v$, obtained from the Massons relation of for binary and ternary (MHM + water/DMSO-water/DMSO) solutions at 303.15 K

<table>
<thead>
<tr>
<th>System</th>
<th>$\phi_v^0$ (x10$^{-3}$ m$^3$·mol$^{-1}$)</th>
<th>$S_v$ (cm$^3$·kg$^{-1}$·mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$A$</td>
<td>$B$</td>
</tr>
<tr>
<td>MHM + Water</td>
<td>321.60</td>
<td>286.54</td>
</tr>
<tr>
<td>MHM + 30% DMSO-Water</td>
<td>185.34</td>
<td>185.86</td>
</tr>
<tr>
<td>MHM + 50% DMSO-Water</td>
<td>261.34</td>
<td>255.47</td>
</tr>
<tr>
<td>MHM + 70% DMSO-Water</td>
<td>208.39</td>
<td>219.28</td>
</tr>
<tr>
<td>MHM + DMSO</td>
<td>466.91</td>
<td>337.2</td>
</tr>
</tbody>
</table>

Foot Note: $A$=0.01 mol·dm$^{-3}$−0.13 mol·dm$^{-3}$; $B$=0.03 mol·dm$^{-3}$−0.13 mol·dm$^{-3}$.

Values of $S_v$ parameter are negative for drug in pure solvents and positive for 30, 50 and 70% v/v DMSO-water mixtures. This indicates electrolyte drug shows structure promotion effects on water and DMSO structure and structure non-promotion effect (Torres et al., 2007) in all the ternary MHM + DMSO-water systems. Therefore, drug-drug interactions are weak in MHM + water and MHM + DMSO mixtures and are relatively strong in 30, 50 and 70% v/v DMSO-water systems. Positive value of $S_v$ in 30, 50 and 70% v/v DMSO-water mixtures
indicates that solvent molecules are more structured in bulk phase than in solvation sphere (Yadav et al., 2013).

Fig. 3: Possible interactions of protonated tertiary amine group of MHM with DMSO and water molecule

CONCLUSION

Large and positive values of $\phi_1$ and $\phi_2$, of drug for all systems indicate presence of strong drug-solvent interactions. These interactions are attractive interactions between polar parts of the drug molecule and solvent dipoles. The electrolyte drug interacts strongly through its polar parts and polar functional groups with the solvent and modifies the structure of solvent/solvent mixture. Significant changes in structure and three dimensional orientations of solvent/solvent mixtures have been conformed from the study.

ACKNOWLEDGEMENT

Authors are thankful to the Cipla R. & D. Centre, Mumbai (MS) India for gift sample of the drug. We are also thankful to the Director, School of Chemical Sciences, S.R.T.M. University, Nanded (MS) India for providing necessary facilities to carry out present work.

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How to cite this article: