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

Santosh D. Deosarkar[1], Rajendrakumar T. Sawale[1], Tukaram M. Kalyankar[2]

[1]School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431 606 (MS) India.
[2]School of Pharmacy, Swami Ramanand Teerth Marathwada University, Nanded-431 606 (MS) India.

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ABSTRACT

In view of pharmaceutical applications, the density (ρ) and refractive index (n_D) 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 (φ_v) were calculated from density data and fitted to the *Masson relation* to determine partial molar volume ($\varphi\,°_v$) 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.

** Corresponding Author*
Santosh D. Deosarkar, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431 606 (MS) India.
Email: sandeo24@yahoo.co.in

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^{TM} 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.

Table 1: Density (ρ) data of binary and ternary {MHM + water/DMSO-water/DMSO} solutions at 303.15 K.

c (mol·dm^{-3})	**ρ (g·cm^{-3})**				
	I	**II**	**III**	**IV**	**V**
0.00	-	1.0382	1.0832	1.0863	1.0903
0.01	0.9960	1.0397	1.0839	1.0875	1.0885
0.03	0.9978	1.0422	1.0856	1.0896	1.0905
0.05	0.9991	1.0433	1.0868	1.0904	1.0910
0.07	1.0006	1.0443	1.0871	1.0907	1.0923
0.09	1.0019	1.0464	1.0883	1.0913	1.0932
0.11	1.0035	1.0473	1.0910	1.0944	1.0937
0.13	1.0049	1.0482	1.0921	1.0956	1.0940

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).

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 (n_D) 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.

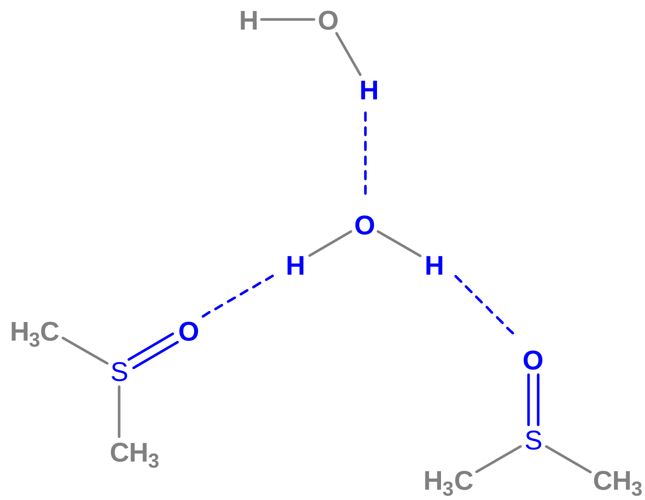

Fig. 1: Hydrogen bonding interactions in binary DMSO-water mixture.

Table 2: Refractive index (n_D) data of binary and ternary {MHM + water/DMSO-water/DMSO} solutions at 303.15 K

c (mol·dm^{-3})	**n_D**				
	I	**II**	**III**	**IV**	**V**
0.00	-	1.3757	1.4230	1.4309	1.4730
0.01	1.3325	1.3790	1.4235	1.4460	1.4725
0.03	1.3336	1.3775	1.4245	1.4425	1.4737
0.05	1.3357	1.3785	1.4254	1.4377	1.4740
0.07	1.3368	1.3797	1.4266	1.4337	1.4747
0.09	1.3388	1.3802	1.4275	1.4370	1.4758
0.11	1.3403	1.3816	1.4285	1.4395	1.4765
0.13	1.3410	1.3835	1.4295	1.4416	1.4773

It is seen that the refractive index increased with an increase in concentration of drug in all systems. Highest values of refractive index are found for MHM + DMSO mixture and lowest values of refractive index are found for MHM + pure water mixture. In case of MHM + 70% DMSO-water mixture, the refractive index first decreased with concentration of drug and then increased. Variations in refractive index indicate existence of solvent-solvent and drug-solvent interactions.

Density data has been used to calculate the apparent molar volume (φ_v) (Roy *et al.*, 2005) of MHM drug in pure water, 30, 50 and 70% v/v DMSO-water mixtures and in pure DMSO using Equation 1, (Hawrylak *et al.*, 2006; Karanth and Bhat 2013; Rajagopal and Edwin, 2011).

$$\varphi_v = \frac{M_2}{\rho} + \frac{10^3(\rho_0 - \rho)}{m\rho\rho_0} \quad (1)$$

Where, ρ_0 is density of pure solvent/solvent mixture in which experimental solutions were prepared, ρ is density of experimental solution, M_2 is molar mass of MHM, m is molal concentration of drug. Difference in the volume of solution and volume of pure solvent per mole of solute is apparent molar volume (φ_v). For calculations of φ_v, the molar concentrations were converted into temperature independent molal concentration using standard relation. Calculated φ_v values with drug concentration are presented in Table 3.

The φ_v values of drug for all the systems are large and positive which indicate strong drug-solvent interactions in solution. Overall, φ_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 φ_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 φ_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 φ_v are large in water and DMSO.

Table 3. Calculated apparent molar volume (φ_v) data of binary and ternary {MHM + water/DMSO-water/DMSO} solutions at 303.15 K

c (mol·dm^{-3})	φ_v (×10^6 m^3·mol^{-1})				
	I	II	III	IV	V
0.01	324.85	208.97	266.52	222.04	471.74
0.03	283.29	217.68	257.19	233.29	319.31
0.05	284.97	245.61	263.77	256.08	312.83
0.07	282.50	258.78	277.77	271.99	299.97
0.09	284.42	255.29	276.62	277.85	296.59
0.11	281.70	262.53	264.45	262.19	297.57
0.13	281.30	267.47	266.16	263.46	299.57

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.

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

$$\varphi_v = \varphi_v^0 + S_v\sqrt{c} \qquad (2)$$

Where, φ^0_v is limiting infinite dilution apparent molal volume (partial molar volume) which represents solute-solvent 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 φ^0_v is partial molar volume at infinite dilution and it represents solute-solvent interactions whereas, S_v represents solute-solute interactions. The φ^0_v is intrinsic volume plus volumetric effects due to solute-solvent interactions such as ion-solvent interactions, H-bonding etc. The partial molar volume of drug-HCl is due to individual ionic contributions of $\varphi^0_{v\,\mathrm{Drug}}$ and $\varphi^0_{v\,\mathrm{HCl}}$ (Marcus, 2006; Iqbal *et al.*, 1994; Delgado *et al.*, 2010) significant change in the φ^0_v of drug is observed from pure water to aqueous-DMSO mixtures and pure DMSO. The φ^0_v 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 φ^o_v values of drug indicates that φ^o_v value of drug in pure DMSO is highest.

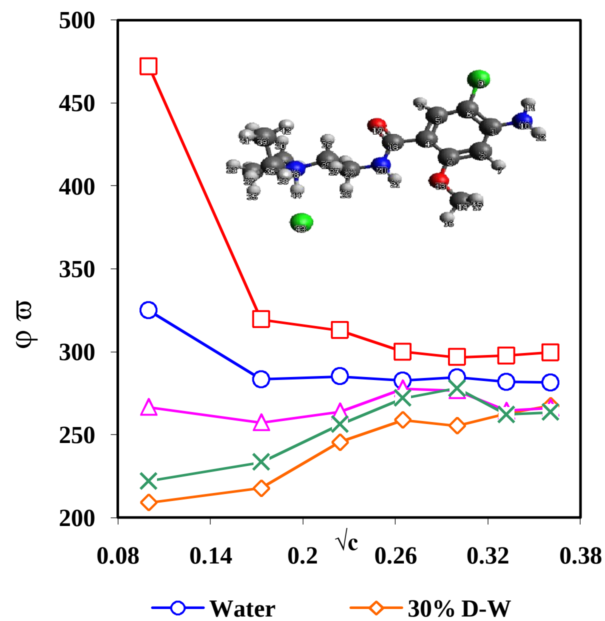

Fig. 2: Plots of apparent molar volume, φ_v versus square root of concentration of drug, $\sqrt{c}$ (*Massons relation*; Equation 2) for determination of graphical values of φ^o_v and S_v of MHM in different media at 303.15 K

Table 4: Graphical values of partial molar volume, φ^0_v and experimental slope, S_v obtained from the Massons relation for of binary and ternary {MHM + water/DMSO-water/DMSO} solutions at 303.15 K.

System	φ^0_v (×10^6 m^3·mol^{-1})		S_v (cm^3·kg$^{3/2}$·mol$^{-3/2}$)	
	A	*B*	*A*	*B*
MHM + Water	321.60	286.54	-129.99	-12.72
MHM + 30% DMSO-Water	185.34	185.86	238.92	236.98
MHM + 50% DMSO-Water	261.34	255.47	24.550	44.203
MHM + 70% DMSO-Water	208.39	219.28	186.99	150.55
MHM + DMSO	466.91	337.2	-553.17	-119.24

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).

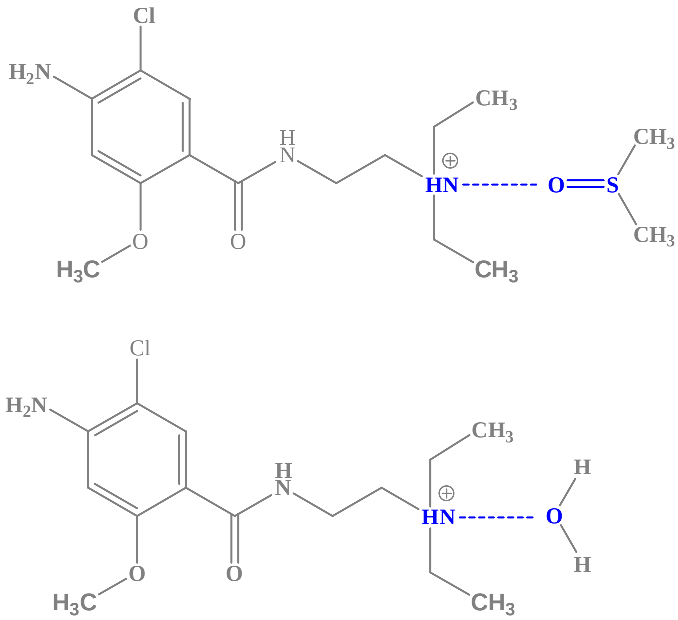

Fig. 3: Possible interactions of protonated tertiary amine group of MHM with DMSO and water molecule

CONCLUSION

Large and positive values of φ_v and φ^o_v of drug for all systems indicates 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.

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