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Molar Refraction and Polarizability of Antiemetic drug 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2 methoxybenzamide hydrochloride monohydrate in {Aqueous-Sodium or Lithium Chloride} Solutions at 30°C

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ABSTRACT

The 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2 methoxybenzamide hydrochloride monohydrate exhibits antiemetic and parasympathomimetic activity. Density (ρ) and refractive index (n_D) measurements were carried out as a function of drug concentration (c=0.01-0.11 mol·L^{-1}) in aqueous NaCl/LiCl (c=0.05, 0.10 and 0.15 mol·L^{-1}) solutions at 30°C. Linear relation of concentration dependence of density and refractive index were studied. Molar refractivity (R_M) of solution was calculated from density and refractive index data and polarizability (α) was calculated from molar refractivity data. Stronger polarizability effects have been observed with increase in drug concentration.

INTRODUCTION

Refractive index has many applications and it is directly related to interactions in the solution (Li *et al.,* 2010). It is applied to identify a substance, confirm the purity, or measure its concentration. Thermodynamic methods based on density and the refractive index is used for investigated intermolecular interactions in solution (Roy *et al.,* 2007; Baragi *et al.,* 2005; Oswal *et al.,* 2006 Iqbal *et al.,* 2009). Theoretical and empirical equations relating refractive index of solutions with other thermochemical or electronic properties are available. Refractive index along with density of solution is useful for calculation of important properties such as molar refraction and polarizability. Study of density and refractive index of drug solutions is of great significance in chemical and pharmaceutical sciences. Valuable information on electronic polarizability of individual ions in solution can be collected from refractive index and molar refractivity data (Pacak *et al.,* 1988). Refractive index studies are being increasingly used as a tool for understanding molecular interactions in solution (Banik *et al.,* 2012; Herraez *et al.,* 2006; Belda *et al.,* 2005). Pharmacokinetics and pharmacodynamics of drug is governed by different interactions in solution such as drug-solvent, drug-drug and drug-co-solute interactions. Most of the biochemical process occurs in aqueous media, therefore molar refractions and polarizability of aqueous drug solutions gives significant information which is useful in pharmaceutical and medicinal chemistry. The 4-amino-5-chloro-N- (2-(diethylamino)ethyl)-2 methoxybenzamide hydrochloride monohydrate (Metoclopramide hydrochloride monohydrate) is a centrally acting anti-emetic, stimulating the motility of the upper gastrointestinal (GI) tract and possessing parasympathomimetic activity (Abraham., 2003). It is weakly basic and contains many interacting groups which make its structure active and easily ionizable (hydrophilic). Therefore, physico-chemical properties of this drug are extensively studied.

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In view of pharmaceutical applications of drug, it is significant to formulate and model refractive index and molar refraction data of its aqueous solutions. Therefore, in continuation with our efforts to understand interactions in drug solution (Deosarkar *et al.*, 2015; Deosarkar *et al.*, 2014; Deosarkar *et al.*, 2013). Here, we report physicochemical behavior of this dug in aqueous-NaCl/LiCl solutions in terms of density, refractive index and molar refractions at 30°C.

Experimental

The 4-amino-5-chloro-N- (2-(diethylamino)ethyl)-2 methoxybenzamide hydrochloride monohydrate drug was received as a gift sample from Cipla R. & D. Centre, Mumbai (MS) India and it was used as received. Water (HPLC grade, deionized distilled water obtained from Millipore prefiltration kit) was used. Weighing was carried out on single pan electronic balance (±0.001g). Densities were measured by pycnometric method using single capillary pycnometer of 10 cm^3. Pycnometer was calibrated with benzene and distilled water at 30°C and its volume was corrected. Pycnometer was kept in transparent walled constant temperature water bath to attain thermal equilibrium for 15 min. Refractive index was measured on thermostatically controlled Cyber LAB-Cyber Abbe Refractometer (*Amkette Analytics*, 1.3000 to 1.7000). Accuracy of refractive index measurement was up to ±0.0002. Temperature of solution was maintained constant by water circulation system surrounding the prism box available with refractometer using specially designed water bath. Refractometer was calibrated with deionized water at 30°C. Averages of three readings of density and refractive index are reported.

RESULTS AND DISCUSSION

Density ($g \cdot cm^{-3}$) data of {MCP·HCl·H_2O + aqueous-salt} solutions at 30°C are presented in Figure 1 and 2. It is seen that density increased with concentration of drug as well as salts.

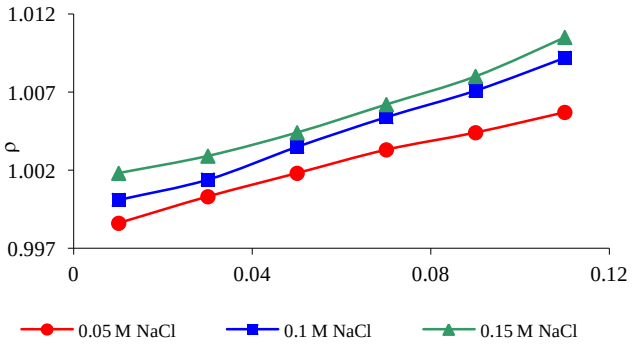

Fig. 1: Density as a function of drug concentration in aqueous-NaCl solutions at 30°C

Refractive index is an important optical parameter which directly related with the molecular interactions in solution (Iqbal *et al.*, 2009; Ali *et al.*, 2006). Refractive indices data show an increasing tendency with increasing molarity of drug. The density versus refractive index plots for different systems are linear up to $r^2 > 0.978$. Concentration dependence of refractive index was studied using following Equation (Koohyar *et al.*, 2011):

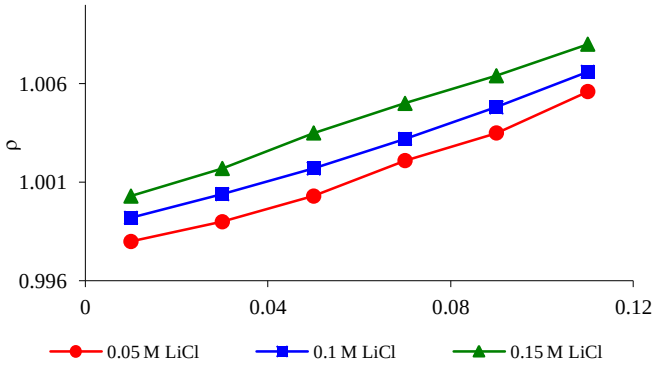

Fig. 2: Density as a function of drug concentration in aqueous-LiCl solutions at 30°C

$$n_D = K \times c + n_D^{\ 0} \quad (1)$$

Where; n_D= refractive index of solution, K=constant which depends on chemical and physical properties of drug (slope of plot: n_D vs. c; dn_D/dc), c=molar concentration of drug solution, and n^0_D is refractive index at infinite dilution. Plots of n_D vs. c are presented in Figure 3 and 4. Values of K (slope of the plot: n_D vs. c; dn_D/dc, $L \cdot mol^{-1}$) and n^0_D are reported in Table 1 along with R^2 values for each plot. Values of K are slightly greater in aqueous-NaCl solutions than in aqueous-LiCl solutions. Linear fit for n_D vs. c plot is better for aqueous-LiCl solutions compared to aqueous-NaCl solutions. Refractive index at infinite dilution (n^0_D) increased with increase in the relative amount of salt in solution in both the salt systems. The refractive index for aqueous-drug solution obeyed following general Equation (r^2=0.994):

$$n_D = 0.0796 \times c + 1.3315 \quad (2)$$

The n^0_D is larger for {drug + aqueous-salt} solutions compared to aqueous-drug solution.

Density and refractive index data were used to calculate molar refractivity (R_M) using Lorentz–Lorenz Equation (Ali *et al.*, 2006; Lorentz *et al.*, 1952; Fucaloro *et al.*, 2002):

$$R_M = \frac{(n_D^{\ 2} - 1)}{(n_D^{\ 2} + 2)} \times \sum_{i=1}^{3} \frac{x_i M_i}{\rho_i} \quad (3)$$

Where, n_D= refractive index; x_i= mole fractions of i-th component of mixture (i.e. drug, water and salts), M_i= molecular mass of drug, water and salts and ρ= density of ternary solution.

The electronic polarizability, α which is a result of displacement of individual electrons, is proportional to R_M as (Wang *et al.*, 2007; Yadav *et al.*, 2013):

$$\alpha = \frac{3}{4\pi N} \frac{R_M}{} \quad (4)$$

Where, N=Avogadro's constant (6.023×10^{23} mol^{-1}). Molar refractivity and polarizability values of drug solutions are reported in Table 2.

Table 1: Refractive index at infinite dilution (n^0_D) and constant K for MCP·HCl·H_2O in aqueous-salt solutions at 30°C.

c, mol·L^{-1}	MCP·HCl·H_2O + aq. NaCl			MCP·HCl·H_2O + aq. LiCl		
	n^0_D	K	r^2	n^0_D	K	r^2
0.05	1.3317	0.075	0.9927	1.3314	0.074	0.9981
0.10	1.3322	0.079	0.9952	1.3317	0.078	0.9974
0.15	1.3327	0.078	0.9961	1.3323	0.073	0.9988

Foote Note: K=dm^3·mol^{-1}.

Table 2: Molar refraction and polarizability of MCP·HCl·H_2O in aqueous-salt solutions at 30°C.

c, mol·L^{-3}	R_M	α	R_M	α	R_M	α
	0.05 mol·L^{-1} aq. NaCl		0.10 mol·L^{-1} aq. NaCl		0.15 mol·L^{-1} aq. NaCl	
0.00	3.707	1.470	3.713	1.472	3.720	1.475
0.01	3.724	1.477	3.731	1.480	3.736	1.482
0.03	3.757	1.490	3.766	1.493	3.771	1.495
0.05	3.787	1.502	3.798	1.506	3.805	1.509
0.07	3.823	1.516	3.83	1.519	3.84	1.523
0.09	3.862	1.532	3.867	1.534	3.873	1.536
0.11	3.899	1.546	3.904	1.548		1.550
	0.05 mol·L^{-1} aq. LiCl		0.10 mol·L^{-1} aq. LiCl		0.15 mol·L^{-1}aq. LiCl	
0.00	3.707	1.470	3.715	1.473	3.722	1.476
0.01	3.718	1.474	3.722	1.476	3.727	1.478
0.03	3.754	1.489	3.758	1.490	3.762	1.492
0.05	3.792	1.504	3.795	1.505	3.796	1.505
0.07	3.823	1.516	3.829	1.518	3.83	1.519
0.09	3.857	1.530	3.868	1.534	3.866	1.533
0.11	3.891	1.543	3.897	1.545	3.896	1.545

Foote Note: R_M= cm^3·mol^{-1}, α=× 10^{-24} cm^3.

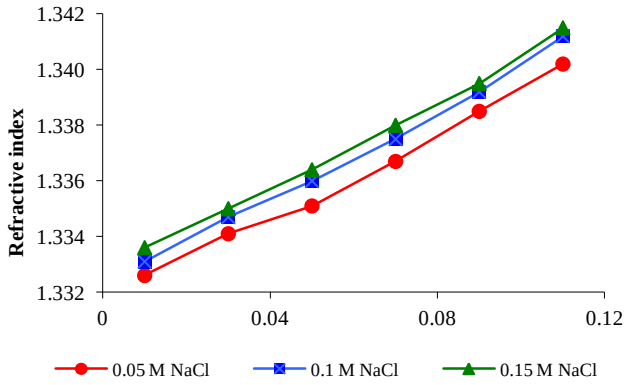

Fig. 3: Linearity between refractive indices and molar concentration of drug in aqueous-NaCl solutions at 30°C

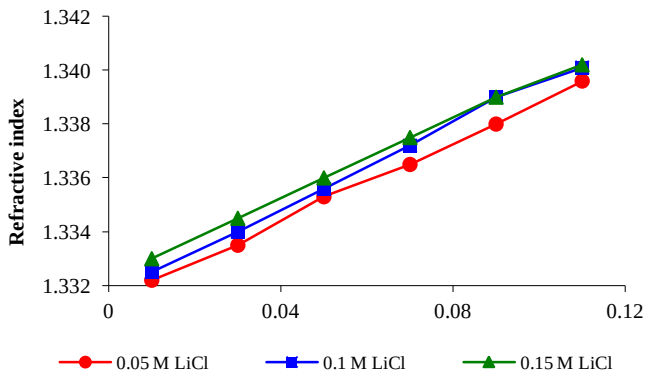

Fig. 4: Linearity between refractive indices and molar concentration of drug in aqueous-LiCl solutions at 30°C

Molar refraction, R_M (T, P, x) of mixture has a unit of molar volume and is an electronic polarizability per mole of different components and it includes contributions from each component of mixture (Fucaloro *et al.*, 2011). Use of R_M and α has become increasingly important in the study of drug interaction. Variation in the R_M and α of MCP·HCl·H_2O in aqueous solution is presented in Figure 5. Molar refraction, molar volume, and polarizability appear as a response to the combined effects of a number of intermolecular forces between the solute and its surroundings (Castillo *et al.*, 2010). Molar refractivity, R_M=f (T, P, n_D) is calculated in additive manner from refractivity of individual components of solution, and any deviation in refractivity is an indication of interactions between components (Pacak *et al.*, 1988). It is a measure of total polarizability of a mole of substance. Molar refractive indices of drug in aqueous-NaCl solutions are larger than those in aqueous-LiCl solutions with the same molarity. The conclusion is consistent with that drawn from density study. R_M is highly used in QSAR studies for drug design (Tiwari *et al.*, 2006). Here, R_M i.e. true molar volume is found to be strongly dependent over concentration of drug and increase with increase in drug concentration in given aqueous salt solution. R_M increased slightly with increase in salt concentration. Plots of R_M with concentration of drug are found to increase linearly with increase in relative amount of drug in aqueous salt solutions (r^2>0.998). The R_M is directly proportional to polarizability (Pacak *et al.*, 1988; Ali *et al.*, 2005; Anwar *et al.*, 2007); therefore, overall polarizability of ternary systems containing {drug + aqueous-salt} solutions increases (Chen *et al.*, 2013) and becomes stronger with increase in relative amount of drug which also elucidates structural cause of change in density of solution. Overall behavior of R_M with concentration of drug in each aqueous-salt system indicates existence and modification of molecular interactions. It is seen

that, the extrapolated values of R_M to c=0 are smaller than R_M values for respective systems for $c \neq 0$ which is indicative of smaller polarization in aqueous-drug solutions compared to drug + aqueous-salt solution. Refractive index and molar refraction increased with drug concentration which indicates that packing of drug molecules become tighter as drug concentration increases which is due to strengthening of drug interactions with solvent or co-solute, sodium or lithium chloride. Further, the packing of drug molecule become tighter up on increase in salt concentration.

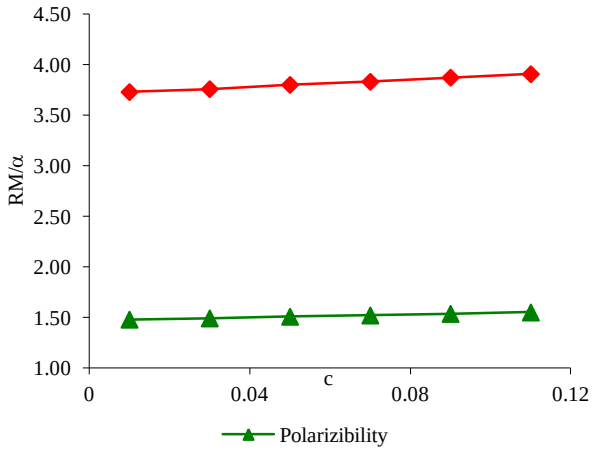

Fig. 5: Molar refractions ($cm^3 \cdot mol^{-1}$) and polarizability ($\times 10^{-24}$ cm^3) of MCP·HCl·H_2O in aqueous solution at 30°C

Polarizability is applicable in the drug design, QSPR and QSAR studies and it plays an important role in modeling many molecular properties and biological activities (Wang *et al.*, 2007). Polarizability is a fundamental molecular property which is related with the intermolecular forces in the given system, such as drug-receptor interactions (Franklin *et al.*, 1975). Polarizability of drug in aqueous solution is higher than in aqueous-salt solution for given drug concentration this indicates that the capability of electronic system of drug molecule to be distorted is more in water environment as compared to in aqueous sodium or lithium chloride environment. Polarizability (α) of binary aqueous-salt mixtures increased with addition of drug and it further increased with drug concentration in given aqueous-salt system which is due to presence of many polar groups (hydrophilic) in the structure of drug. The α increased slightly with concentration of salt for the same molarity of drug. Overall polarizability of drug in aqueous-salt solutions follows the order: α(aqueous-NaCl) > α(aqueous-LiCl) for same molarity of drug. Addition of drug in binary aqueous-salt solution introduced the stronger polarizability to solution due to interactions between polar parts of the drug and water dipoles.

Ions from salts get hydrated in aqueous media (Figure 6) and up on addition of drug in aqueous-salt solutions, drug-water interactions occurs as a result of which molar volume, refractions and overall polarizability of the system changes. Resultant structure and orientation of drug molecule in aqueous-salt solution is consistent with the cause of change in molar refractions and polarizability of solution.

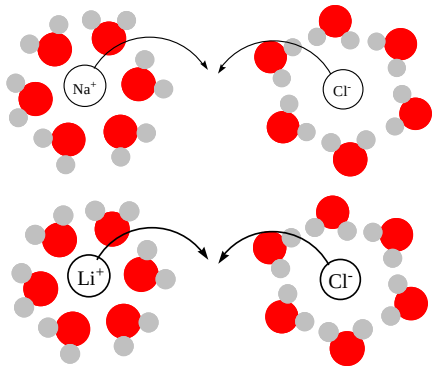

Fig. 6: Hydration of ions in aqueous medium.

Drug contains different interacting groups such as amide (-CONH), primary amine (-NH_2), and tertiary amine (R_3-N). Up on protonation, R_3-N group get protonated and form cationic species through which the interaction with water molecule occurs as represented in Figure 7. Also, the ion-dipole interactions between ions and polar parts of drug occur, Figure 8.

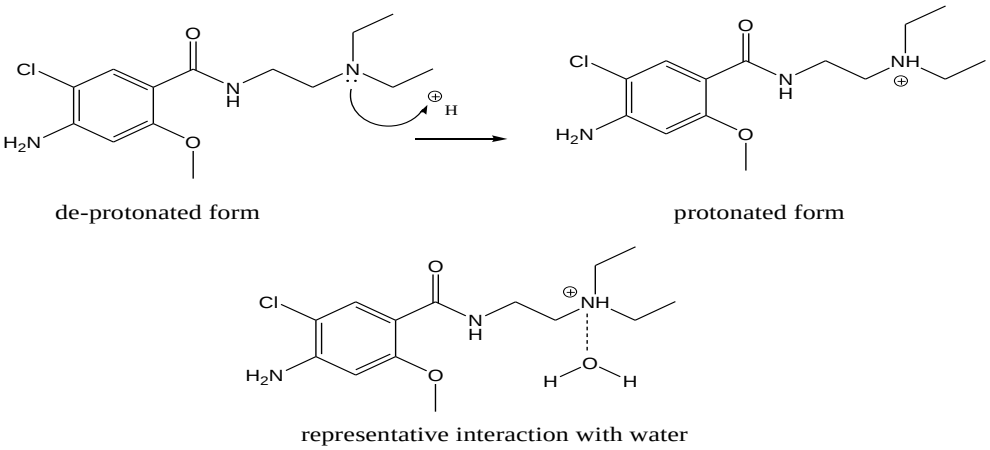

Fig. 7: De-protonated and protonated (amine group) forms of drug with protonated amine group interaction with water.

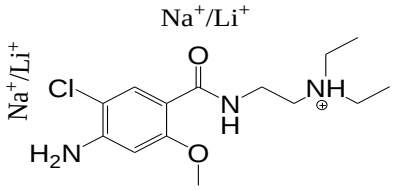

Fig. 8: Ion-dipole interactions between ions and polar parts of drug.

CONCLUSION

Density and refractive index are found to be strongly dependent over concentration of both MCP·HCl·H_2O and salts. Modification in solvation pattern of aqueous ionic solutions of salts upon addition of drug is observed. Molar refractions showed linear dependence over concentration of drug in all the studied systems. Overall polarizability of drug in aqueous-NaCl solutions is larger than those in aqueous-LiCl solutions with same molarity of drug. Polarizability of ternary systems containing {drug + aqueous-salt} solution becomes stronger with increase in relative amount of drug. Present work gives significant information for prediction of the absorption and permeability of the drug through membranes which finds applications in the field of medicinal and pharmaceutical chemistry.

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