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Molar Refraction and Polarizability of Metoclopramide in {Aqueous-NaCl/LiCl} Solutions at 30°C

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Abstract-Metoclopramide exhibits antiemetic and parasympathomimetic activity. Density (ρ) and refractive index (n_D) measurements were carried out as a function of metoclopramide 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.

Keywords: Density, Refractive index, Molecular interactions, Polarizability

Introduction

Refractive index has many applications and it is directly related to interactions in the solution [1]. 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 [2-6].

Refractive index along with density of solution is useful for calculation of important properties such as molar refraction and polarizability. Valuable information on electronic polarizability of individual ions in solution can be collected from refractive index and molar refractivity data [7].

Refractive index studies are being increasingly used as a tool for understanding molecular interactions in solution [8-11]. Metoclopramide hydrochloride monohydrate (MCP·HCl·H_2O) is a centrally acting anti-emetic, stimulating the motility of the upper gastrointestinal tract and possessing parasympathomimetic activity [12]. It is weakly basic and contains many interacting groups. Therefore, in continuation with our efforts to understand interactions in drug solution [13-15], here, we report physicochemical behavior of metoclopramide in aqueous-NaCl/LiCl solutions in terms of density, refractive index and molar refractions at 30°C.

Experimental

MCP·HCl·H_2O was received from Cipla R. & D. Centre, Mumbai. Water (HPLC grade) was used. Weighing was carried out on single pan electronic balance (±0.001g). Densities were measured by pycnometric method using single capillary calibrated pycnometer. Pycnometer was kept in transparent walled constant temperature water bath to attain thermal equilibrium. Refractive index was measured on thermostatically controlled Cyber LAB-Cyber Abbe Refractometer (*Amkette Analytics*, 1.3000 to 1.7000). Accuracy of refractive index was up to ±0.0002. Temperature was maintained constant by water circulation system water bath. Averages of three readings of density and refractive index are reported.

Results and discussion

Density (g·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 of solution increased with concentration of drug as well as salts.

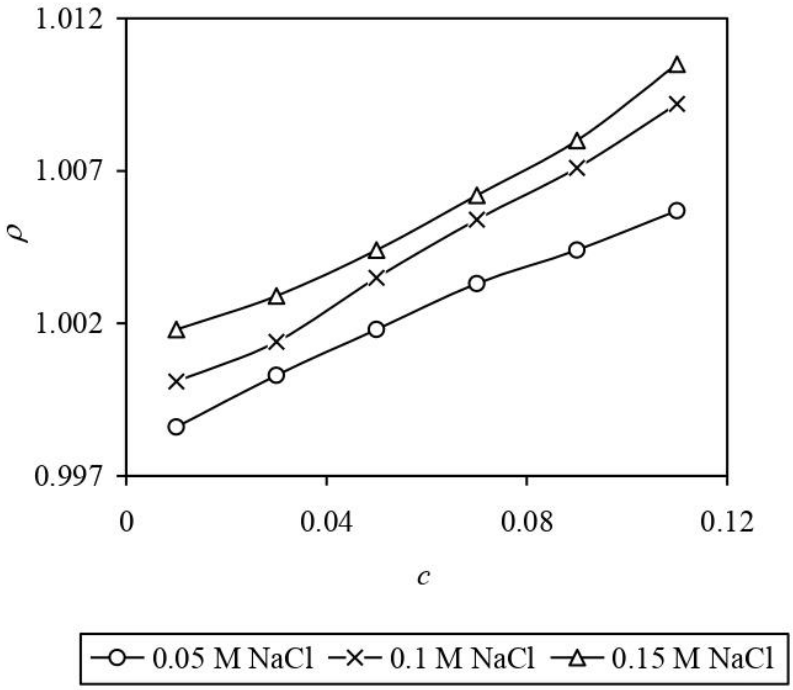


Fig. 1: Density as a function of drug concentration in aqueous-NaCl solutions at 30°C

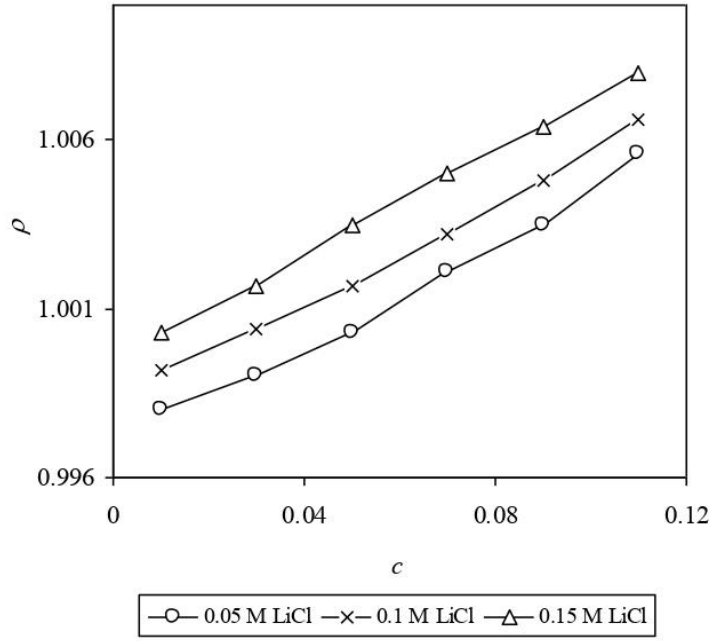


Fig. 2: Density as a function of drug concentration in aqueous-LiCl solutions at 30°C

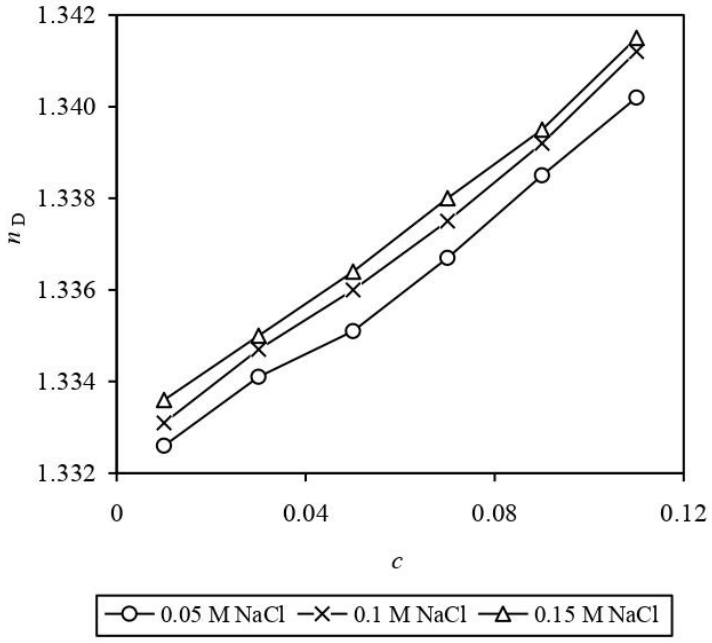


Fig. 3: Refractive indices vs. molar concentration of drug in aqueous-NaCl solutions at 30°C

Refractive index is an important optical parameter which relates with molecular interactions in solution [16-17]. Refractive indices data show increasing tendency with increasing molarity of drug. Densities versus refractive index plots are linear up to $r^2 > 0.978$.

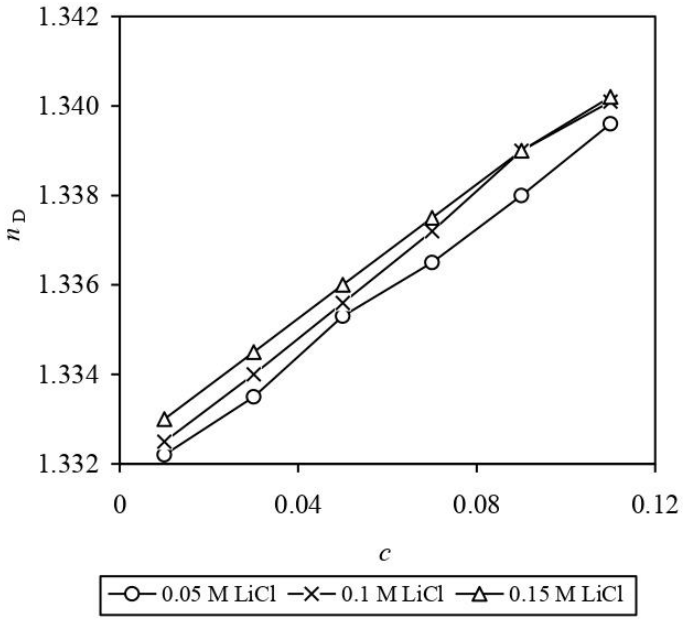


Fig. 4: Refractive indices vs. molar concentration of drug in aqueous-LiCl solutions at 30ºC

Concentration dependence of refractive index was studied using following Equation [18]:

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

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, 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 and n^0_D are reported in Table 1 with R^2 values. Values of K are slightly greater in aqueous-NaCl solutions than in aqueous-LiCl solutions. The n^0_D increased with increase in amount of salt in both salt systems. Refractive index obeyed following 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.

Table 1. The n^0_D and K for MCP·HCl·H_2O in aqueous-salt solutions at 30ºC

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 30ºC

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.

Molar refractivity (R_M) is calculate using Lorentz–Lorenz Equation [17, 19-20]:

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

Where, n_D= refractive index; x_i= mole fractions, M_i= molecular mass of drug, water and salts and ρ= density of ternary solution.

The α which is a result of displacement of individual electrons, is proportional to R_M as [21-22]:

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

Where, N=Avogadro's constant (6.023 × 10^{23} mol^{-1}). R_M and α values are reported in Table 2.

The R_M (T, P, x) of mixture is an electronic polarizability per mole of different components and it includes contributions from each component of mixture [23]. Use of R_M and α has become increasingly important in the study of drug interaction. Variation in R_M and α is presented in Figure 5.

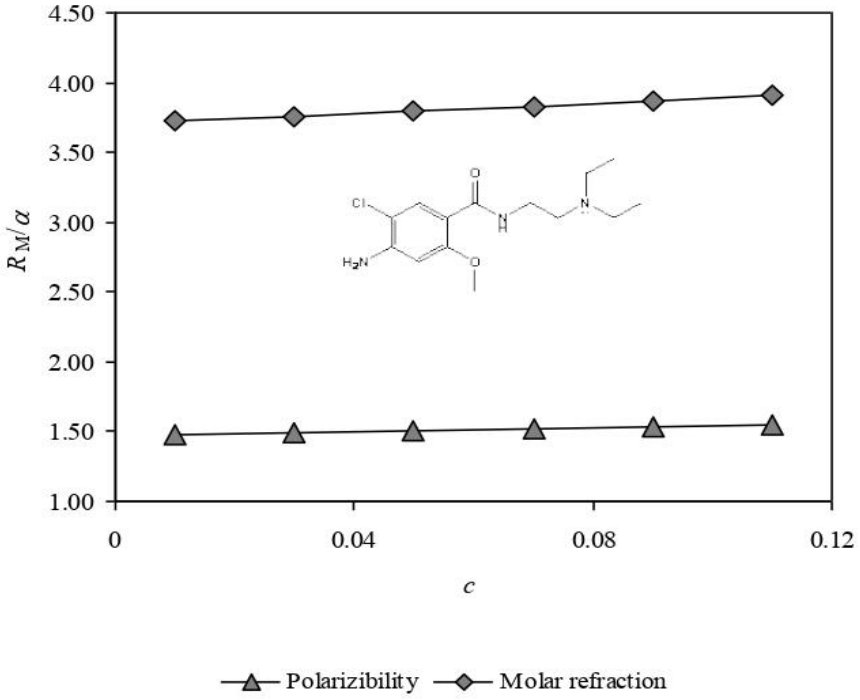


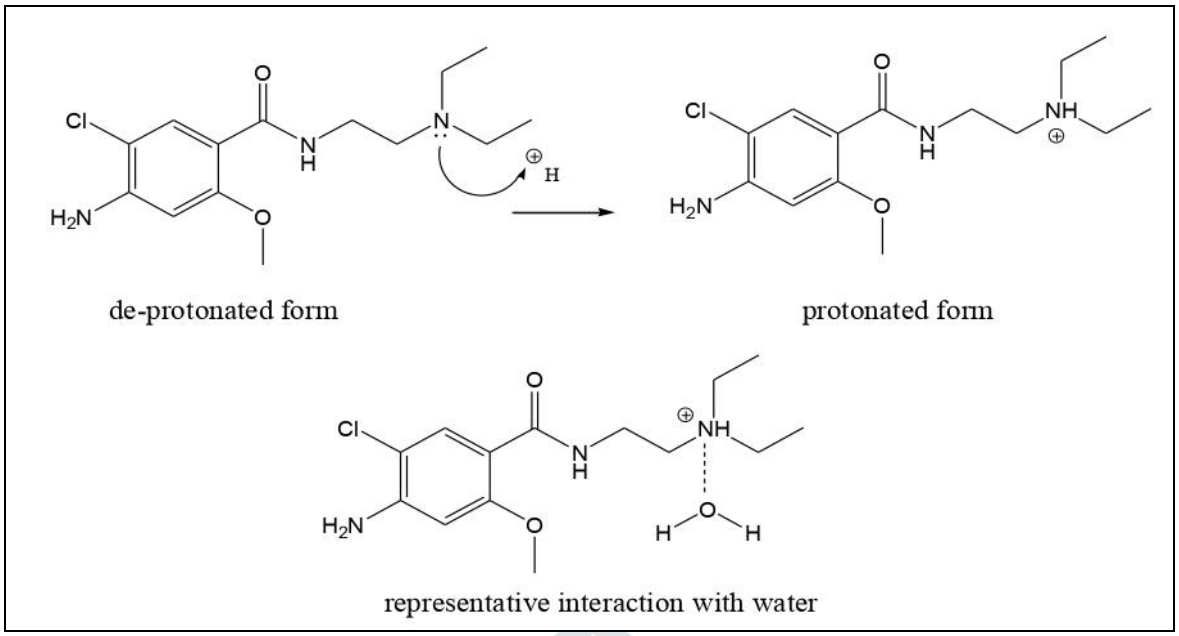
Fig. 5: R_M and α of MCP·HCl·H_2O in aqueous solutions at 30°C

R_M and α is response to combined effects of a number of intermolecular forces between solute and its surroundings [24]. Deviation in R_M is an indication of interactions between components [7]. R_M of drug in aqueous-NaCl solutions is larger than in aqueous-LiCl solutions. R_M is highly used in QSAR studies for drug design [25]. R_M increases with increase in metoclopramide concentration. R_M increased slightly with increase in salt concentration. Plots of R_M with drug concentration are found to increase linearly with increase in amount of drug in aqueous salt solutions (r^2>0.998).

R_M is directly proportional to polarizability [7, 26-27]; therefore, overall polarizability of ternary systems solutions increases [28] and becomes stronger with increase in amount of drug which elucidates structural cause of change in density of solution. Overall behavior of R_M indicates existence and modification of molecular interactions.

The extrapolated values of R_M to c=0 are smaller than R_M values for respective systems for $c\neq0$ which indicates smaller polarization in aqueous-drug solutions compared to drug + aqueous-salt solution. Packing of drug molecules become tighter as drug concentration increases which is due to strengthening of drug interactions with solvent or co-solute. Packing of the drug molecules become tighter up on addition of salt.

Polarizability (α) is applicable in drug design, QSPR and QSAR studies and it plays an important role in modeling molecular properties and biological activities [21]. α is related with drug-receptor interactions [29]. Polarizability of drug in aqueous solution is higher than in aqueous-salt solution indicates that capability of electronic system of drug molecule to be distorted is more in water environment as compared to in aqueous NaCl/LiCl environment. The α of binary aqueous-salt mixtures increased with metoclopramide concentration due to presence of polar groups in drug. The α increased slightly with concentration of salt. Polarizability follows order: α(aqueous-NaCl) > α(aqueous-LiCl) for same molarity of drug. Addition of drug introduced stronger polarizability to solution due to interactions between polar parts of drug and water dipoles.



Scheme 1: De-protonated and protonated MCP·HCl·H_2O showing interaction with water

Ions salts get hydrated in aqueous media and up on addition of drug, drug-water interactions occurs as a result of which molar volume, refractions and overall polarizability of system changes. MCP contains interacting groups such as amide (-CONH), primary amine (-NH_2), and tertiary amine (R_3-N). R_3-N group get protonated and form cationic species through which interaction with water molecule occurs as represented in Scheme 1.

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 solution becomes stronger with increase in relative amount of drug. Present work gives significant information for prediction of the absorption and permeability of the metoclopramide drug through membranes which finds applications in the field of medicinal and pharmaceutical chemistry.

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