Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(5):1107-1110

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Solvent effects on molar refraction and polarizability of 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2 methoxybenzamide hydrochloride hydrate solutions at 30^0C

S. D. Deosarkar[1*], M. P. Pawar[1], R. T. Sawale[1], A. R. Hardas[2] and T. M. Kalyankar[3]

[1]*School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded(MS), India*
[2]*Department of Chemistry, Saint Francis De Sales College, Seminary Hills, Nagpur(MS), India*
[3]*School of Pharmacy, Swami Ramanand Teerth Marathwada University, Nanded(MS), India*

ABSTRACT

Molar refraction (R_M) and polarizability (α) of binary 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2 methoxybenzamide hydrochloride hydrate drug in different solvents like water, methanol, ethanol and dimethyl sulfoxide were computed from experimental density (ρ) and refractive index (n_D) data at 30^0C. Enhancement in overall polarizability of drug solution with relative drug concentration in each solvent and strong drug-solvent interaction due to perturbation in structural orientation of drug indifferent solvent has been observed.

Keywords: Density, Refractive index, Drug-solvent molecular interaction

---

INTRODUCTION

Drug-solvent interactions are of great interest in chemical and pharmaceutical sciences. Molar refractivity data provides valuable information on electronic polarizability of individual ions in solution [1]. Studies based on refractive index measurements are used as an important tool for understanding molecular interactions in solution [2-5]. Different interactions in solution govern the pharmacokinetics and pharmacodynamics of drug. 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2 methoxybenzamide hydrochloride hydrate (Metoclopramide hydrochloride monohydrate) drug is a centrally acting anti-emetic, stimulating the motility of upper gastrointestinal tract and having parasympathomimetic activity [6].

In view of pharmaceutical significance of present drug and in continuation with our earlier work [7-11] an effort has been made here to study molar refractivity and polarizability of drug in water (H_2O), methanol (MeOH), ethanol (EtOH) and dimethylsulfoxide (DMSO) at 30^0C.

EXPERIMENTAL SECTION

Metoclopramide hydrochloride monohydrate (Figure 1) was received as a gift sample from Cipla R. & D. Centre, Mumbai (MS) India. Deionized distilled water (Millipore), MeOH (Merck), EtOH (Changshuyangyuan China) and DMSO (Spectrochem) were used for preparation of drug solutions. Density measurements were carried out using single capillary pycnometer of different volumes. Weighing was done on single pan electronic balance (±0.001 g). Refractive index measurements were carried out on thermostatically controlled Cyber LAB-Cyber Abbe Refractometer (*Amkette Analytics*, 1.3000-1.7000; ±0.0002) by direct reading. All measurements were carried out at 30^0 C. Detail of experimental part is given in our earlier publication [12]. Density and refractive index data reported is of triplicate measurements.

THEORETICAL SECTION

Molar refractivity of drug solutions is calculated using Lorentz–Lorenz Equation [13-15]:

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

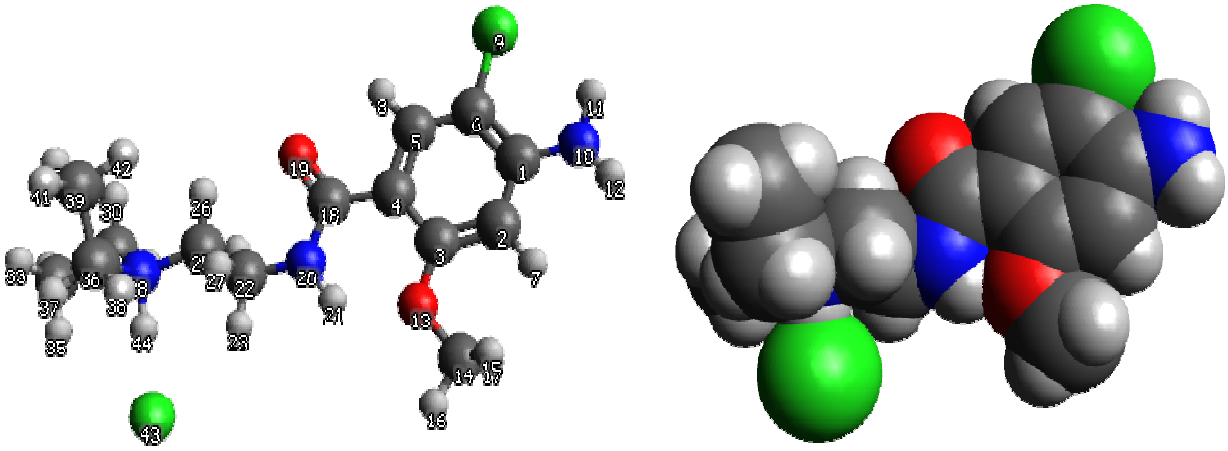
Concentration dependence of molar refractivity of drug solutions in different solvents was fitted to following Equation 2:

$$R_M = a_0 + a_1 \times c \quad (2)$$

Molecular polarizability of drug solution in different solvents was calculated using following Equation 3 [16-17]:

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

Where, c=drug concentration, ρ=density of solution, n_D=refractive index of solution, n^0_D=refractive index at infinite dilution, x_i= mole fraction of i-th component of mixture, M_i= molecular mass i-th component, R_M =molar refraction of solution, N=Avogadro's constant (6.023×10^{23} mol^{-1}), α=electronic polarizability, a_0 and a_1=coefficients of linear fitting.



a **b**

Figure 1: Structure of drug a) Ball and Stick and b) Van der Waals Spheres models

RESULTS AND DISCUSSION

Molar refractivity and molecular polarizability data for binary {4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2 methoxybenzamide hydrochloride hydrate + H_2O/MeOH/EtOH/DMSO} at 30^0 C are reported in Table 1.

Table 1. Molar refractivity and molecular polarizability of drug in different solvents at 30^0C

c	R_M	α	R_M	α	R_M	α	R_M	α
	Drug + H_2O		*Drug + MeOH*		*Drug + EtOH*		*Drug + DMSO*	
0.01	3.728	1.478	4.664	1.850	5.072	2.011	4.706	1.866
0.03	3.757	1.490	4.737	1.878	5.151	2.043	4.843	1.921
0.05	3.799	1.507	4.793	1.901	5.234	2.076	4.978	1.974
0.07	3.830	1.519	4.849	1.923	5.333	2.115	5.112	2.027
0.09	3.871	1.535	4.922	1.952	5.417	2.148	5.252	2.083
0.11	3.905	1.549	4.980	1.975	5.505	2.183	5.390	2.137
0.13	3.932	1.559	5.020	1.991	5.593	2.218	5.529	2.193

*R_M=$cm^3 \cdot mol^{-1}$; α=10^{-24} cm^3.

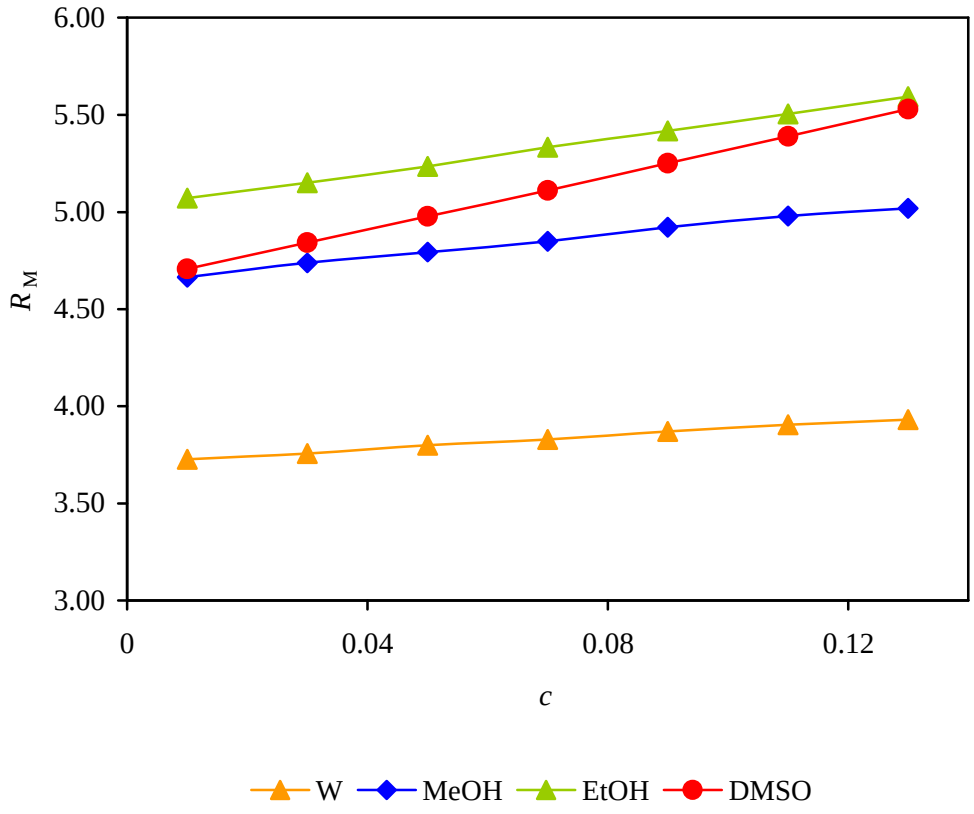


Figure 2: Molar refraction ($cm^3 \cdot mol^{-1}$) with drug concentration in different solvents at 30°C

Coefficients a_0 and $a_1$of linear fitting of R_M with drug concentration (Equation 2; Figure 2) are reported in Table 2 and, linear fit Equations of $R_M=f(c)$ i.e. $R_M=a_0+a_1 \times c$ are presented in following Equations 4-7.

***Drug + H_2O*:** $R_M = 1.75\ c + 3.7092$; $r^2 = 0.9976$. (4)

***Drug + MeOH*:** $R_M = 3.0054\ c + 4.6418$; $r^2 = 0.996$. (5)

***Drug + EtOH*:** $R_M = 4.3821\ c + 5.0225$; $r^2 = 0.9995$. (6)

***Drug + DMSO*:** $R_M = 6.8518\ c + 4.6361$; $r^2 = 1.000$. (7)

Coefficient a_0, which is extrapolated value of R_M on *y*-axis to zero drug concentration (or infinite dilution) increased from water to DMSO. For all the systems, r^2 value of plots is good (>0.995), this indicate linear dependence of R_M over drug concentration. R_M value follows the trend: H_2O < MeOH < DMSO < EtOH for given drug concentration. The R_M increased with drug concentration due to relatively tighter packing of drug molecule, enhancement in the overall polarizability of solutions [18] because of strengthening of drug-solvent interactions like –OH from solvent (H_2O, MeOH and EtOH) or –S=O (DMSO) and R_3HN^+ from drug etc.

R_M and α values are affected by intermolecular forces between solute molecules and its surroundings [19]. R_M is used for drug design in QSAR studies [20] and is directly proportional to polarizability [21-22].

Table 2. Coefficients of linear fit of R_M with drug concentration (Equation 2) at 30°C

Binary system	a_0 coefficient	a_1 coefficient	r^2 value
Drug + H_2O solution	3.7092	1.7500	0.9976
Drug + MeOH solution	4.6418	3.0054	0.9960
Drug + EtOH solution	5.0225	4.3821	0.9995
Drug + DMSO solution	4.6361	6.8518	1.0000

Polarizability (α) is used in modeling of molecular properties, biological activities, drug design, QSPR and QSAR studies [16]. It is related with intermolecular forces in system such as drug-receptor interactions [23]. Here, α is

increased with drug concentration in all the solvents due to increase in the polarizability of solution with concentration of drug. As a result of strong drug-solvent interactions, addition of drug into solvents introduced stronger polarizability to each solution. It follows same trend as R_M that is α values are higher as compared to any other sovent which indicates electronic system of drug is more distorted in ethanol environment compared other solvents. Intermolecular interactions between drug and solvent are reflected in properties as R_M and α. Apart from interactions of -OH group with protonated amine and other polar groups of drug, additional interactions due to hydrophobic $–CH_3$ and $–CH_2CH_3$ groups of MeOH and EtOH with hydrophobic parts of drug molecule occurs in alcoholic-drug solutions. Additional structure of MeOH and EtOH (alkyl groups) and also DMDS ($-CH_3$) compared to H_2O may have been resulted in more distortion of electronic system of drug. It is seen that R_M and α properties for drug in H_2O are much smaller than in MeOH, EtOH and DMSO. Magnitude and trends of R_M and α in are consistent with structure of solvent.

CONCLUSION

Existence of drug-solvent molecular interactions with different structural modification in different solvents has been observed. Observed results are representative of intermolecular interactions of solvent –OH or -S=O group with protonated amine (R_3HN^+) group of drug and other possible interactions of solvents with drug. The electronic system of drug is more distorted in ethanol environment compared other solvents. Addition of drug into solvents resulted in strong drug-solvent interaction and stronger polarizability to each solution. Solvation of the dipolar parts of the drug by different solvents occurs.

Acknowledgement
We are thankful to Cipla R. & D. Centre, Mumbai for valuable gift of drug sample and to Director, School of Chemical Sciences, S. R. T. M. University Nanded for providing necessary facilities.

REFERENCES

[1] P Pacak; Z Kodejs, *Can. J. Chem.*, **1988**, 66, 2244.
[2] MJ Iqbal; MA Chaudhry, *J. Chem. Thermodyn.* **2009**, 41, 221-226.
[3] I Banik, MN Roy, *J. Mol. Liq*., **2012**, 169, 8-14.
[4] JV Herraez; R Belda, *J. Solut. Chem.*, **2006**, 35, 1315-1328.
[5] R Belda; JV Herraez, O Diez, *Phys. Chem. Liq.*, **2005**, 43, 91-101.
[6] DJ Abraham, *Burgers medicinal chemistry and drug discovery*, John-Wiley and Sons, Inc., Publications, 6th Edn. Vol. 1, **2003**.
[7] SD Deosarkar; RT Sawale; PD Tawde; TM Kalyankar, *Russ. J. Phy. Chem. A*, **2015**, 89(2), 232-235.
[8] S.D Deosarkar; SM Deoraye; TM Kalyankar, *Russ. J. Phy. Chem. A*, **2014**, 88(7) 1129-1132.
[9] SD Deosarkar; TM Kalyankar, *Russ. J. Phy. Chem. A*, **2013**, 87(6), 1060-1062.
[10] SD Deosarkar; AR Ban; RT Sawale; SD Padghan; AJ Pawar; TM Kalyankar, *J. Chem. Pharm. Res.,* **2014**, 6(4), 917-923.
[11] SD Deosarkar; UB Shaikh, *Russ. J. Gen. Chem. A*, **2013**, 83(12), 2392–2394.
[12] SD Deosarkar; AR Ban; PD Tawde; RT Sawale, *Int. J. Chem. Sci.*, **2014**, 12(4), 1231-1238.
[13] A Ali; S Hyder; S Sabir; D Chand, AK Nain, *J. Chem. Thermodyn.*, **2006**, 38, 136-143.
[14] HA Lorentz, *The theory of electrons*, Dover, New York (1952).
[15] F. Fucaloro. Anthony, *J. Solut. Chem.*, **2002**, 31, 601-605.
[16] J Wang; X Xie; T Hou; X Xu, *J. Phys. Chem. A*, **2007**, 111(20), 4443-4448.
[17] SS Yadav; D Khare, R Pande, *J. Mol. Liq.*, **2013**, 177, 243-251.
[18] A Chen; M Liu; Y Zheng; D Sun; B Wang; Xu Wang, *J. Solut. Chem.*, **2013**, 42, 2213-2228.
[19] MV Castillo, MA Checa, ME Manzur, FH Ferretti, EF Vargas, MR Fleming, A Yurquina, *Vitae*, **2010**, 17, 299-308.
[20] V Tiwari; R Pande, *Chem. Biol. Drug Des.*, **2006**, 68(4), 225-228.
[21] A Ali; S Khan; S Hyder, *J. Chinese Chem. Soc.*, **2005**, 52, 215-222.
[22] A Anwar, S Sabir, S Shahjahan Hyder, *Acta Phys. Chim. Sin.*, 23(7) **2007** 1007-1012.
[23] FE Norrington; RM Hyde; SG Williams; R Wooten, *J. Med. Chem.*, **1975**, 18, 604-607.