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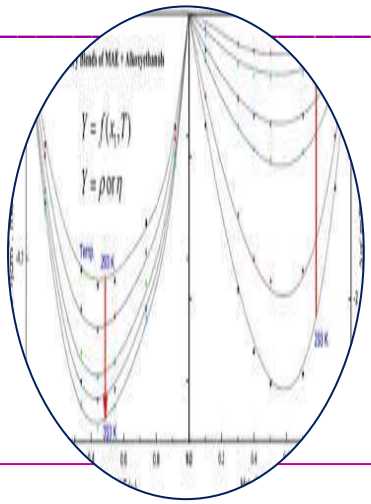
VISCOSITY AND OPTICAL PROPERTIES OF BINARY {AQUEOUS-2-[(DIMETHYLAMINO)METHYL]-1-(3-METHOXYPHENYL) CYCLOHEXANOL HYDROCHLORIDE} SOLUTIONS AT DIFFERENT TEMPERATURES



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ABSTRACT

In view of pharmaceutical value of narcotic like pain reliever, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (DMH), the density (ρ), relative viscosity (η_r) and refractive index (n) of its aqueous solutions were measured at 297.15, 302.15 and 307.15 K as a function of drug concentration. Relative viscosity data has been fitted to *Jones-Dole relation* to get viscosity *A* and *B*-coefficients. Linearity relations of refractive index with density and drug concentration were studied. Refractive index and density data has been used to calculate molar refractions and polarizability of solution. Results have been interpreted in terms of temperature effects on drug-solvent molecular interactions.

***KEYWORDS*:** Drug, Molecular interactions, Jones-Dole equation, Molar refraction, Polarizability

INTRODUCTION:-

Physical chemistry of pharmaceutically significant drug molecules is of great interest to number of researchers which are looking for various physical properties of drug molecules in solution. Drug-water molecular interactions are immensely important in pharmaceutical and industrial processes and in many fundamental sciences. These interactions are characterized by measurement of different thermophysical properties of aqueous drug solutions. Complex association of drug molecules, drug action and pharmaceutical dosage forms can be recognized from thermophysical properties. Thermophysical properties of solutions over a wide range of drug concentrations and temperature give information regarding drug-solvent and drug-drug molecular interactions, solvent structure making/breaking ability of drug and overall structural fittings in solution. Drug action can be understood from drug-water molecular interactions and their temperature dependence [1-2]. Increasing interest in understanding molecular interactions in drug solutions can be seen from recent publications in this area [3-11]. Changing molecular environment with composition and temperature leads to modifications in forces acting between molecules that lead to variations in thermodynamic properties of solutions.

The 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (DMH, Tramadol Hydrochloride) is used as a narcotic like pain reliever. In this context and in continuation with our interest for studying thermophysical behavior in drug solutions [12-14], and in view of pharmaceutical importance, present work reports systematic study of density, relative viscosity and refractive index of aqueous solutions of DMH at different temperatures.

EXPERIMENTAL

DMH was used as received from Supriya Lifescience Ltd., Mumbai (MS) India. Aqueous solutions of DMH were prepared by dissolving accurate quantity of drug in double distilled water in standard volumetric flasks (Borosil). Care was taken while transferring drug to flask and complete transfer was ensured. Densities of solutions were determined by using clean and dry single capillary pycnometer of (*Borosil*). Volume of pycnometer was determined at experimental temperature using double distilled water. It was immersed in specially designed constant temperature water bath for about 10 min to attain thermal equilibrium. Temperature of thermostat was checked from time to time. Weighing was done on electronic balance (Anamed, AA 2200; e=0.0001g). Pycnometer was rinsed with water and acetone and dried properly after every weighing. Viscosity was determined from flow time and density of drug solution and pure solvent. Flow times were measured using Ostwald's type viscometer. Refractive index was measured on thermostatically controlled Cyber LAB-Cyber Abbe Refractometer (*Amkette Analytics*, 1.3000 to 1.7000) by direct reading (±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, relative viscosity and refractive index are reported.

RESULTS AND DISCUSSION

Density, relative viscosity, η_r-$1/\sqrt{m}$ and refractive index data are presented in Table 1.

Table 1 Density (ρ), relative viscosity (η_r), Jones-Dole η_r-$1/\sqrt{c}$, and refractive index (n_D) data of aqueous-DMH solutions at different temperatures

m (mol · kg^{-1})	ρ (g · cm^{-3})	η_r	η_r-$1/\sqrt{m}$ (mol$^{-1/2}$ · kg$^{1/2}$)	n	R_M (cm^3 · mol^{-1})	α (cm^3)
			297.15 K			
0.01	0.9951	1.018	0.181	1.3312	3.716	1.474
0.02	0.9959	1.030	0.212	1.3315	3.727	1.478
0.04	0.9965	1.047	0.234	1.3323	3.753	1.488
0.06	0.9981	1.067	0.275	1.3335	3.781	1.499
0.08	1.0008	1.091	0.320	1.3348	3.805	1.509
0.10	1.0011	1.117	0.371	1.3355	3.832	1.520
			302.15 K			
0.01	0.9930	1.015	0.154	1.3295	3.707	1.470
0.02	0.9949	1.023	0.166	1.3301	3.716	1.474
0.04	0.9955	1.043	0.217	1.3311	3.745	1.485
0.06	0.9977	1.057	0.234	1.3325	3.772	1.496
0.08	1.0003	1.079	0.280	1.3338	3.796	1.505
0.10	1.0008	1.106	0.336	1.3349	3.827	1.518
			307.15 K			
0.01	0.9912	1.007	0.074	1.3280	3.698	1.466
0.02	0.9922	1.016	0.115	1.3285	3.710	1.471
0.04	0.9936	1.032	0.159	1.3295	3.736	1.481
0.06	0.9944	1.042	0.173	1.3303	3.762	1.492
0.08	0.9954	1.057	0.203	1.3312	3.788	1.502
0.10	0.9960	1.080	0.251	1.3326	3.821	1.515

It is seen that density and relative viscosity decreased with rise in temperature. Whereas at given temperature, density and relative viscosity increased with increase in concentration of drug which suggests existence strong drug-solvent interactions and structure modification. Refractive index increased with drug concentration and decreased with temperature. Concentration dependence of refractive index was studied using following Equation (1):

$$n = K \times m + n^0 \quad (1)$$

From the plot of n versus m, the refractive index at infinite dilution (n^0) was obtained as an intercept and constant K as slope (dn/dm). Graphical values of n^0 and constant K are reported in Table 2. The n^0 decreased with increase in temperature.

Table 2 Graphical parameters of plots from Equation (1) for aqueous-DMH solutions

T (K)	n^0	K ($dm^3 \cdot mol^{-1}$)	r^2
297.15	1.3305	0.0504	0.9901
302.15	1.3288	0.0608	0.9981
307.15	1.3275	0.0491	0.9927

Molar refractivity, R_M and polarizability of drug solution was calculated [15-16] from density and refractive index data using following Equations (2) and (3) and are reported in Table 2.

$$R_M = \frac{(n_D^{\ 2} - 1)}{(n_D^{\ 2} + 2)} \times \frac{\sum X_i M_i}{\rho} \quad (2)$$

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

Both n and R_M increased with drug concentration due to tighter packing of drug molecules because of strengthening of drug-solvent interactions and decreased with temperature due to reverse effect. R_M is directly proportional to molecular polarizability [17-18]; therefore, overall polarizability of solutions increases [19] and becomes stronger with increase in relative amount of drug due existence and modification of molecular interactions.

Relative viscosity ($\eta_r = \eta/\eta_0$) of aqueous drug solution was calculated using Equation (4):

$$\eta_r = t\rho / t_w \rho_w \quad (4)$$

The η_r values are reported in Table 1. It is seen that η_r increased with concentration of drug due to increasing association of drug in solution and strong drug-water intractions. The η_r decreased with temperature. The data was analyzed by Jones-Dole relation [20], equation (5).

$$\eta_r - 1/\sqrt{m} = A + B\sqrt{m} \quad (5)$$

Where, A and B are viscosity Jones-Dole constants determined as intercept and slope of plot of η_r-$1/\sqrt{c}$ against $\sqrt{m}$. Viscosity A and B coefficients are reported in Table 3.

Table 3 Viscosity coefficients and $\Delta B/\Delta T$ of aqueous drug solutions at different temperatures

T (K)	B ($dm^3 \cdot mol^{-1}$)	A ($dm^{3/2} \cdot mol^{-1/2}$)	$\Delta B/\Delta T$ ($dm^3 \cdot mol^{-1} \cdot K^{-1}$)
297.15	0.832	0.087	
302.15	0.806	0.059	-8.8×10^{-3}
307.15	0.744	0.003	

Viscosity B-coefficients reflects solute-solvent interactions, solvation of solute and effect of solute on structure of solvent in local vicinity of solute [21]. Large and positive value of viscosity B-coefficients at all

three temperatures indicates presence of strong drug-solvent interactions and structure making effects of drug [22]. The *B*-coefficient values decreased with rise in temperature which indicates decrease in solvation of drug, reduction in structural organization and deterioration of structure making effect of drug.

The *B*-coefficient were also fitted to polynomial of following type, Figure 2 yields Equation (6).

$$B = -0.0007T^2 + 0.033T - 0.4557 \quad (6)$$

First derivative d*B*/d*T* was determined from plot of *B*-coefficient against *T* (°C), Figure 2. The sign of d*B*/d*T* straightforwardly indicates structure-breaking (positive value) or structure-making (negative value) ability of solute on water [23]. The d*B*/d*T* value is found to be negative which indicates drug behave as a structure maker in aqueous solutions [24].

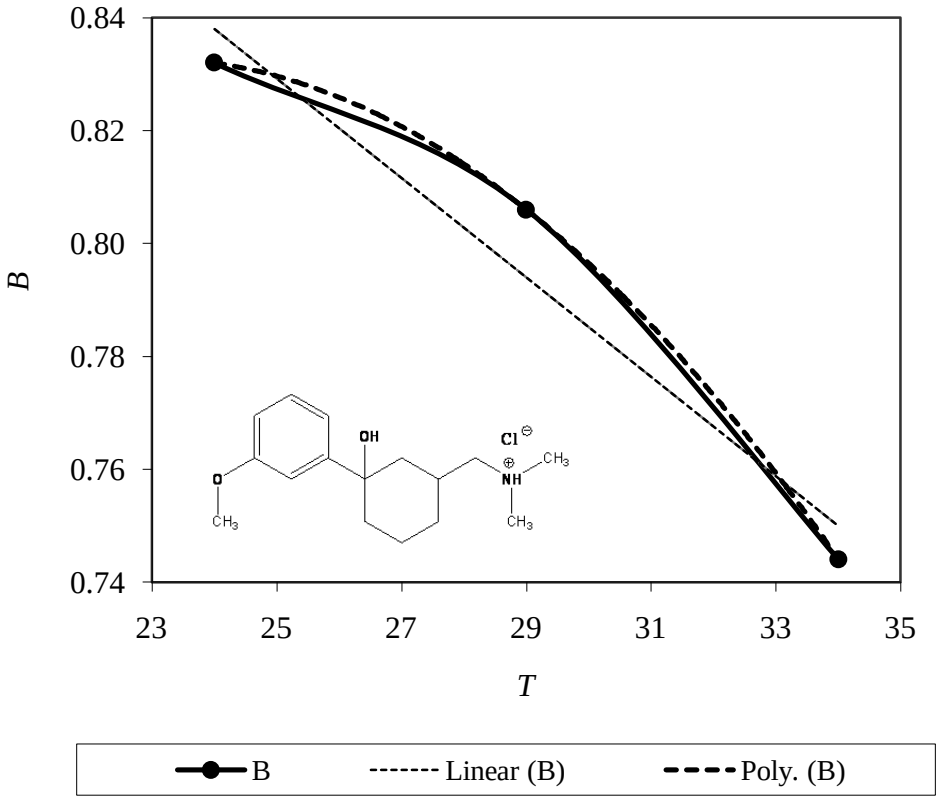
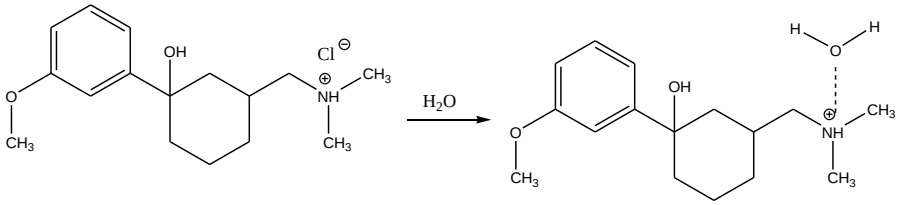


Fig. 2. Viscosity *B*-coefficient vs. T (°C), linear and polynomial fit

Positive but small values of *A*-coefficient (0.005-0.09 $dm^{3/2}$ $mol^{-1/2}$) indicate weak drug-drug interactions compared to drug-water interactions. The drug interacts with water through –OH group and protonated $–NH^+(Me)_2$ ionic part of the drug (Scheme I). These interactions are of dipole-dipole or ion-dipole type. Higher magnitude of *B*-coefficient over *A*-coefficient suggests the supremacy of drug-solvent interactions over drug-drug interactions [25].



Scheme I. Protonated amine-water interaction in aqueous-DMH solution

In ordered solvent like water, it is difficult to fit the complex structured drug molecules. But, at elevated temperatures, due to cavity formation, the better fit of the drug is observed. In aqueous media water molecules orients to form local cage like structure surrounding drug molecule through ion-dipole or dipole-dipole interactions. One of such representative interaction of drug with water is presented in Scheme I. The –OH group of the drug also interacts with water through hydrogen bonding interactions.

CONCLUSION

Temperature and concentration effects on molecular interactions and structural fittings in aqueous-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride solutions have been investigated through density, relative viscosity and refractive index measurements. Viscosity *B*-coefficients are found to be strongly dependent on concentration and temperature. Existence of strong drug-solvent interactions is conformed from *B*-coefficient values. Further, solvent structure making behaviour of present drug is conformed from temperature dependence of *B*-coefficient. Packing of drug molecule in solution become tighter with drug concentration and weakens with temperature. Enhancement in the overall polarizability occurs with increase in drug concentration.

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