International Journal of Material and Mechanical Engineering, 2012, 1: 66-70
Published Online July 2012

www.ijm-me.org

Acoustical Studies of Drug Combiflam in Aqueous Alcoholic Mixtures

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(Abstract) Ultrasonic velocity and density measurements have been measured for drug Combiflam in binary aqueous alcoholic (Methanol and Ethanol) mixtures at 25^0C. The velocity and density data of solvent/solvent mixtures/ drug solutions have been employed to calculate various desired acoustical parameters e.g. specific acoustic impedence (Z), relative association (R.A.), adiabatic compressibility (β), intermolecular free length (L_f), molar volume (V_m) and molar sound velocity (R_m) The results of the desired parameters have been discussed as a function of solvent mixtures, concentration of drug and nature of alcohol. However, these acoustical parameters are examined in terms of drug-drug, drug-solvent and drug-surfactant interactions resulting from various electrostatic and hydrophobic interactions.

Keywords: Ultrasonic Velocity; Density; Combiflam; acoustical parameters.

1. INTRODUCTION

Physicochemical properties of drugs are of great interest to understand 'drug action' at the molecular level. The pharmadynamics and pharmakinetics [1] i.e., what a drug does to the body and what the body does to the drug, must be regarded as the ultimate consequence of physicochemical interactions [2] between the drug and functionally important molecules in the living organism. Most drugs are organic molecules with both hydrophilic and hydrophobic groups due to which these molecules show specific as well as electrostatic interactions [3]. Thus, knowledge of the physicochemical properties of drugs plays an important role to understand their physiological actions which is highly dependent upon the solution behavior [4].

As a part of a long-term objective to investigate thermodynamic aspects of biochemical processes involving such drug-molecular interactions, acoustical studies of drug combifam were carried out .

It is evident from a detailed survey of literature that no systematic work has been reported in respect of the transport properties [5] of the drug in aqueous-alcoholic solvent systems. However, a good deal of understanding can be obtained from studies of such properties especially as regard to the interactions of drug molecules with the solvent medium. Further, interest in this regard can be observed to center around the effect of structural consequences of intermolecular on drug-solvent interactions. In other words, transport studies of drug solutions are of great help in characterizing the physico-chemical [6] behaviour of drug solutions, which forms a part of biological system of animals and human beings.

Drug molecules, are characterized by the presence of polar, non-polar and hydrophobic groups and are generally administered in the form of salt. In consequence, transport properties of drug molecules are governed by forces, like hydrophobic, electrovalent or hydrogen bonding etc. In view of the point that these various kinds of interactions, and their subsequent effect on the transport properties of solute species can be well established from transport properties such as ultrasonic velocity. So, it is proposed to carry out such studies on the drug, in aqueous mixtures of alcohols ; MeOH, and EtOH. Thus an understanding of physico-chemical behaviour of the drug can be of great interest from academic as well as physiological [7] point of view.

2. EXPERIMENTAL DETAILS

The solvents methanol and ethanol (AR grade obtained from S.D. fine chemicals Ltd) were used as such. All the measurements were carried out in an automatic digital temperature controller high precision water thermostat supplied by Harco & Co, Ambala, maintained at temperature of 25.00 ± 0.01^0C.

Density measurements were carried out with a precision of ± 0.01% by using sealable pyknometer of capacity 25 cm^3. Ultrasonic velocity measurements were carried out at frequency 1 MHz using interferometer (Mittal enterprises, New Delhi). Solvent system having 100 to 0 mol% of water with methanol (MeOH) and ethanol (EtOH) at 10 mol% intervals have been prepared and investigated. Solutions containing a

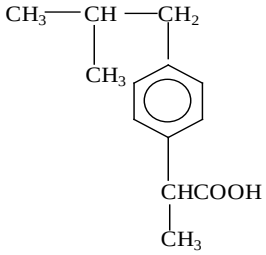
fixed amount of drug (0.250 g in 40 ml of a solvent/solvent system) have also been prepared and studied.

The studied drug Combiflam (Cm) (Aventis Pharma Ltd., G.I.D.C. Estate, Ankleshwar-393 002) was used as received. However, this drug was kept overnight in the vacuum oven. The drug Cm is composed of Ibuprofen (400 mg) and Paracetamol (325 mg). This drug is taken in form of tablets which selectively relieve pain by acting as anti-inflammatery [8] analgesic drug.

The chemical structures [9] of the drug are as follows:

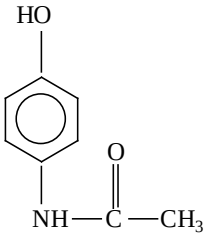
Combiflam (Cm) : mol. wt. 177.26, consists of two components.

i). Ibuprofen (400 mg) [$C_{13}H_{18}O_2$] mol. wt. 206.



(±)- p-Isobutylhydratropic Acid

ii). Paracetamol (325 mg) [$C_8H_{99}NO_2$] mol. wt. 151



N-(4-hydroxyphenyl) acetamide.

3. RESULTS AND DISCUSSIONS

The experimental values of ultrasonic velocity and density for MeOH-water, EtOH-water and PrOH-water with and without drug are presented in Tables 1 - 4. From these tables, it is evident that the density values decrease with an increase of the alcohol content for all the studied solvent systems. Density increases with the addition of drug in all studied systems. Similar behavior has been reported for methanol-water and ethanol-water by Lahiri [10] et. al. The plot of density vs. mole% of methanol in absence as well as presence of drug is shown in figure 1.

The Ultrasonic velocity data for studied solvent systems have been presented in tables (1-4). From the perusal of tables and figure 2, it is evident that ultrasonic velocity values increases with the addition of methanol in methanol-water mixtures up to 20 mol% of methanol and then decreases with the further addition of methanol. However for ethanol maxima for velocity value are obtained at 10 mole% of ethanol.

The increase of velocity of sound with the increase of organic solvent well up to about 16 wt.% methanol and 25 wt.% ethanol respectively in alcohol-water mixtures and beyond which decrease of velocity with the further addition of organic component has been reported in the literature [10]. The addition of drug increase with the value of ultrasonic velocity but general behavior remains the same as for all studied pure solvent systems.

This increase and decrease of ultrasonic velocity of water with the addition of organic solvent component can be explained on the basis of fact that the interstitial spaces of water molecules are filled by the organic solvent molecule but beyond a certain limit, there can not be further accommodation of alcohol molecules.

However, some following acoustical parameters [11-13] viz: specific acoustic impedence (Z), relative association (R.A.), adiabatic compressibility (β),intermolecular free length (L_f), Molar volume (V_m) and Molar sound velocity (R_m) have been calculated as given below and are reported in Tables 1-8, in order to gain an insight into the drug-solvent interactions viz-a-viz structural consequences of intermolecular interactions.

Adiabatic compressibility (β) $= 1/U^2\rho$ --1)

Specific acoustic impedance (Z) $= U\rho$ --2)

Intermolecular free length (L_f) $= K\sqrt{\beta}$ --3)

Relative association (R_A) $= [\rho/\rho_o][U_o/U]^{1/3}$ --4)

Molar sound velocity (Rm) $= \left[\frac{\overline{M}}{\rho}\right]U^{1/3}$ --5)

Molar volume (V_m) = M/ρ (in case of pure solvent)

$= \overline{M}/\rho$ (where $\overline{M} = x_1M_1 + x_2M_2$) (in case of solvent mixture) –6)

where u_o, ρ_o, β_o refer to the velocity, density and adiabatic compressibility of pure solvent-solvent mixtures respectively and u, ρ, β, those of solution. K is the temperature dependent constant [14] and is given as : $K = [(93.875+0.375)\,T \times 10^{-8}]$, T is the absolute temperature. M = Molecular weight of the drug taken. $\overline{M} = \overline{M}_{12}$ and $\overline{M}_{123}$ are the molecular weight of the solution as given by the relation: $\overline{M}_{12} = x_1\overline{M}_1 + x_2\overline{M}_2$ where $\overline{M}_1$ and $\overline{M}_2$ are the molecular weights of solvents respectively. $\overline{M}_{123} = \overline{M}_{12}$ + weight of drug.

The ratio of the acoustic impedence in a medium to the associated particle velocity is defined as the specific acoustic impedence (Z) of the medium. The values of Z are presented in tables (1-4). From the perusal of tables and figure 3, it is evident that its value goes on increasing with the addition of methanol up to 20 mole % and then decreases with further addition of alcohol. Similar behavior has been obtained with drug. However, for ethanol + water mixtures, maxima is obtained at 10 mole % of ethanol. This trend is similar to our earlier study [15] for drug Parvon Spas in different aqueous-alcoholic mixtures. Also with different alcohols, Z-values increase in the order:

Water-MeOH < Water-EtOH

Calculated values of relative association (R.A.) for studied drugs have been presented in Tables (1-4). From the perusal of Tables, it is evident that these values remain unaffected with presence as well as absence of drug at all compositions of solvent mixtures. Further, the R. A. values do not change as alcohol content in these mixtures is increased. For sympathomimetic drugs [16] in water and for drug Parvon Spas

in aqueous – alcoholic solvent systems [15] also, no change in R. A. values has been reported.

Adiabatic compressibility (β) have been presented in tables (1-4) and in figure 4 for different solvent mixtures. It is clear from the tables that the β- values first decrease at 20 mole % of methanol and then increase with further addition of methanol in methanol + water system. In ethanol + water solvent mixture, a minimum in β- values has been obtained at 10 mole % of ethanol.

This shows that two components to water-alcohol mixture i.e methanol and ethanol are alcoholic in nature but due to change in chain length of alcohol molecule, some difference in molecular volume as well as dielectric constant of different alcohols.

The variation of Intermolecular free length (L_f) values is in accordance with the variation of β-values with respect to presence of drug (Figure 5) as well as alcohol content (tables 1-4). Further, in order to determine the variation of ultrasonic velocity in solutions, Eyring and Kinkaid [17] have proposed L_f to be a predominating factor. The change in free length indicates that there is significant interaction between the solute and solvent molecules due to which structural arrangement is also affected [18].

Molar volume (V_m) of drug solutions system in a particular solvent system decreases with the presence of drug concentration but increases with increase of alcohol content indicating its dependence upon the molecular mass and density of solvent mixtures. Its variation with different alcohols is as follows (Figure- 6):

Water-MeOH ≈ Water-EtOH

The calculated values of molar sound velocity (R_m) of studied drug in binary mixtures of alcohol + water show a slight increase with the presence of drug. Also, the R_m values increase with increase of alcohol content in water + alcohol mixtures showing that R_m depends upon the nature of solvent mixture.

4. CONCLUSIONS

Thus, the inference drawn from all the studies is that the studied drug Combiflam when added to aqueous alcoholic mixtures act as structure promoter for the solvent system. As the systems are characterized by hydrogen bond, the solute-solvent can be interpreted in terms of structural changes due to hydrogen bond interactions between various components of the solvent and solution systems. Various acoustical parameters also support the existence of drug – solvent interactions. The results obtained from these studies can thus be helpful for pharmacological application of drugs.

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Table 1:- Density (ρ), ultrasonic velocity (U), specific acoustic impedence (Z), relative association (R. A.), Adiabatic compressibility (β), intermolecular free length (L_f), molar volume (V_m) and molar sound velocity (R_m) for MeOH + water solvent system.

Mole % of MeOH	ρ x 10^{-3} (kg m^{-3})	U (ms^{-1})	Z x 10^{-6} (Kg $m^{-2}s^{-1}$)	R.A.	β x 10^{5} (atm^{-1})	L_f x10^{11} (m)	V_m x10^{5} (mol cm^{-3})	R_m x 10^{4} (ms^{-1})
0	0.9970	1501	1.496	1.0000	4.51	4.34	1.80	2.067
10	0.9700	1522	1.488	0.9723	4.46	4.22	1.99	2.291
20	0.9510	1540	1.474	0.9445	4.44	4.32	2.19	2.529
30	0.9270	1535	1.423	0.9232	4.64	4.40	2.39	2.761
40	0.9050	1463	1.324	0.9157	5.23	4.67	2.61	2.959
50	0.8810	1402	1.235	0.9043	5.85	4.94	2.84	3.174
60	0.8610	1330	1.145	0.8992	6.65	5.27	3.06	3.371
70	0.8410	1264	1.063	0.8937	7.53	5.61	3.30	3.572
80	0.8040	1205	0.981	0.8793	8.56	5.98	3.58	3.813
90	0.8045	1154	0.924	0.8810	9.45	6.28	3.80	3.988
100	0.7848	1107	0.868	0.8712	10.1	6.63	4.08	4.218

Table 2:- Density (ρ), ultrasonic velocity (U), specific acoustic impedence (Z), relative association (R. A.) Adiabatic compressibility (β), intermolecular free length (L_f), molar volume (V_m) and molar sound velocity (R_m) for drug Combiflam in MeOH + water solvent system.

Mole % of MeOH	ρ x 10^{-3} (kg m^{-3})	U (ms^{-1})	Z x 10^{-6} (Kg $m^{-2}s^{-1}$)	R.A.	β x 10^{5} (atm^{-1})	L_f x10^{11} (m)	V x10^{5} (mol cm^{-3})	R_m x 10^{4} (ms^{-1})
0	0.997	1503	1.499	1.000	4.50	4.33	1.80	2.067
10	0.9836	1542	1.516	0.977	4.33	4.25	1.97	2.278
20	0.9710	1570	1.524	0.959	4.23	4.20	2.14	2.489
30	0.9472	1567	1.484	0.936	4.36	4.26	2.34	2.722
40	0.9432	1553	1.464	0.935	4.45	4.31	2.50	2.897
50	0.9251	1528	1.413	0.922	4.69	4.42	2.70	3.112
60	0.9036	1467	1.325	0.913	5.21	4.66	2.92	3.319
70	0.8810	1393	1.227	0.905	5.93	4.97	3.13	3.524
80	0.8488	1290	1.095	0.895	7.17	5.47	3.44	3.744
90	0.8239	1223	1.007	0.884	8.22	5.86	3.71	3.971
100	0.7898	1119	0.837	0.873	10.0	6.54	4.05	4.206

Table 3:- Density (ρ), ultrasonic velocity (U), specific acoustic impedence (Z), relative association (R. A.), Adiabatic compressibility (β), intermolecular free length (L_f), molar volume (V_m) and molar sound velocity (R_m) for EtOH + water solvent system.

Mole % of EtOH	ρ x 10^{-3} (kg m^{-3})	U (ms^{-1})	Z x 10^{-6} (Kg $m^{-2}s^{-1}$)	R.A.	β x 10^{5} (atm^{-1})	L_f x10^{11} (m)	V_m x10^{5} (mol cm^{-3})	R_m x 10^{4} (ms^{-1})
0	0.997	1501	1.496	1.000	4.50	4.34	1.81	2.06
10	0.9655	1626	1.569	0.942	3.97	4.07	2.15	2.52
20	0.9372	1549	1.451	0.930	4.50	4.34	2.52	2.91
30	0.9078	1460	1.325	0.918	5.24	4.67	2.91	3.29
40	0.8838	1400	1.237	0.907	5.89	4.94	3.30	3.69
50	0.8635	1344	1.160	0.898	6.49	5.21	3.71	4.08
60	0.8442	1304	1.100	0.887	7.06	5.43	4.12	4.50
70	0.8310	1261	1.047	0.883	7.67	5.66	4.52	4.88
80	0.8161	1229	1.003	0.874	8.22	5.86	4.95	5.30
90	0.8033	1198	0.962	0.868	8.79	6.06	5.38	5.70
100	0.7909	1157	0.915	0.865	9.57	6.32	5.82	6.10

Table 4:- Density (ρ), ultrasonic velocity (U), specific acoustic impedence (Z), relative association (R. A.), Adiabatic compressibility (β), intermolecular free length (L_f), molar volume (V_m) and molar sound velocity (R_m) for drug Combiflam in EtOH + water solvent system.

Mole % of EtOH	ρ x 10^{-3} (kg m^{-3})	U (ms^{-1})	Z x 10^{-6} (Kg $m^{-2}s^{-1}$)	R.A.	β x 10^{5} (atm^{-1})	L_f x10^{11} (m)	V_m x10^{5} (mol cm^{-3})	R_m x 10^{4} (ms^{-1})
0	0.9970	1503	1.499	1.000	4.50	4.33	1.80	2.067
10	0.9656	1629	1.573	0.942	3.95	4.06	2.15	2.534
20	0.9374	1564	1.466	0.927	4.42	4.29	2.52	2.922
30	0.9071	1470	1.333	0.916	5.17	4.64	2.91	3.309
40	0.8861	1402	1.242	0.909	5.82	4.93	3.30	3.688
50	0.8639	1351	1.167	0.897	6.42	5.18	3.70	4.094
60	0.8485	1309	1.110	0.890	6.97	5.39	4.10	4.486
70	0.8317	1264	1.051	0.883	7.62	5.64	4.52	4.888
80	0.8188	1232	1.008	0.877	8.15	5.83	4.93	5.289
90	0.8064	1206	0.972	0.870	8.64	6.00	5.35	5.702
100	0.7934	1169	0.927	0.864	9.34	6.24	5.80	6.107

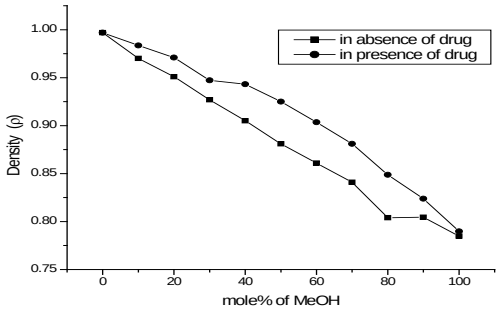

Figure 1:- Plot of Density versus mole% of MeOH in absence as well as in presence of drug in various aqueous-alcoholic mixtures.

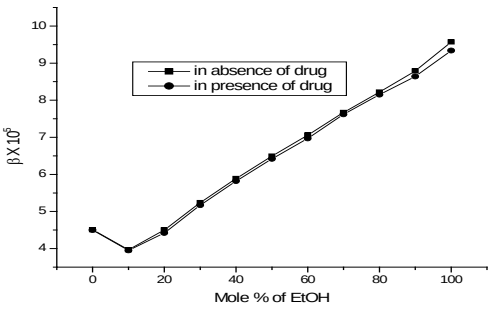

Figure 4:- Plot of β X 105 versus mole% of EtOH in absence as well as in presence of drug in various aqueous-alcoholic mixtures.

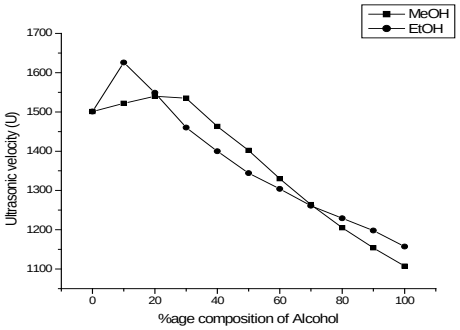

Figure 2:- Plot of Ultrasonic velocity (U) versus %age composition of alcohol in various aqueous-alcoholic mixtures.

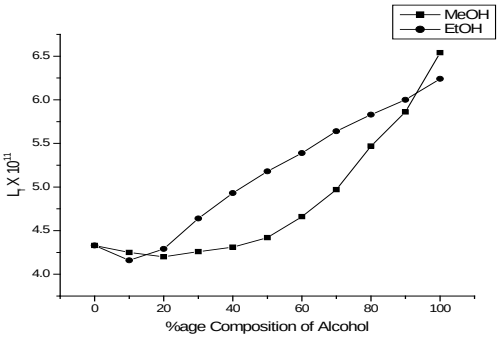

Figure 5:- Plot of Lf X 1011 versus %age composition of alcohol in various aqueous- alcoholic mixtures.

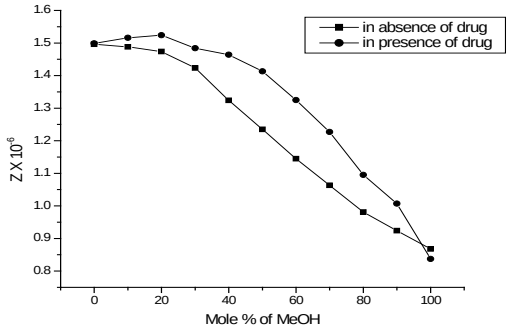

Figure 3:- Plot of Z X 10-6 versus mole% of MeOH in absence as well as in presence of drug in various aqueous- alcoholic mixtures.

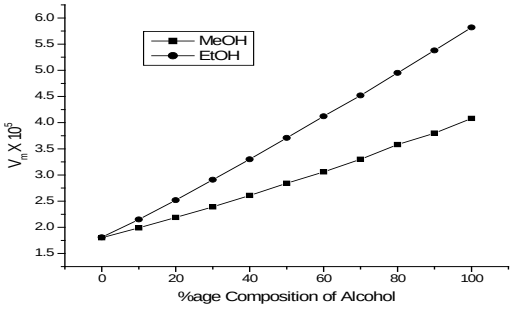

Figure 6:- Plot of Vm X 105 versus % age composition of alcohol in various aqueous- alcoholic mixtures.