Viscometric Measurement Of Substituted-Dioxo-Naphthacene-2-Carboxamide And Substituted-Spiro[1-Benzofuran2,1'-Cychlohex-2-Ene]-3,4'-Dione Drugs In Ethanol–Water Mixture At Various Percentage Compositions.

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ABSTRACT

*Recently in this laboratory the viscometric measurement of (4S,6S,12aS)-4-(dimethyl- amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- naphthacene -2-carboxamide**[DMPMDC]** and (2S, 6R)-7-chloro -2, 4, 6-trimethoxy-6'-methyl-3H, 4'H-spiro[1-benzofuran 2, 1'-] cychohex-2-ene]-3,4'-dione**[CTMBCD]** were carried out at different percentage compositions of solvent to investigate the solute-solvent interactions of drugs with solvent and the effect of dilution of the solvent. The effects of various substituents were also investigated. The results obtained during this investigation gave detail information about pharmokinetics and pharmodynamics of these drugs.*

KEYWORDS (4S,6S,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide **[DMPMDC]**, (2S, 6R)-7-chloro -2, 4, 6-trimethoxy-6'-methyl-3H, 4'H-spiro[1-benzofuran 2, 1'-] cychohex-2-ene]-3,4'-dione**[CTMBCD],** ethanol-water mixture, viscometric measurements, etc.

INTRODUCTION

Viscosity is the internal friction of the liquid molecules. Viscosity measurements play an important role in pharmaceutical, medicinal, agricultural and drug chemistry[1-3]. In drug chemistry viscometric studies provides useful and important information regarding solute-solute, solute-solvent and solvent-solvent interactions. The activities of the drug like absorption, transmission and its effect will directly related to viscosity measurements of the drugs and solvent interactions in the human anatomy.

The pharmaceutical and medicinal literature survey reveals that the drugs which are the best for particular diseases became non-active for that disease due to rapid evolutionary phenomenon in pathogens. Hence it becomes challenge to chemist and researcher to synthesized new type of drug for

such diseases. Carboxamide and spiro[1-benzofuran 2, 1'- cychohex-2-ene]-3,4'-dione nucleus containing drug create their own identity and importance in drug and pharmaceutical chemistry[4-10]. Hence, taking all these things into consideration it was thought interesting to carry out the viscometric measurements of (4S,6S,12aS)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide**[DMPMDC]**, (2S, 6R)-7-chloro -2, 4, 6-trimethoxy-6'-methyl-3H, 4'H-spiro[1-benzofuran 2, 1'-] cychohex-2-ene]-3,4'-dione**[CTMBCD]** at various compositions. This study is helpful to predict the potency of drugs.

EXPERIMENTAL

All the chemicals used of A.R. grade. Double distilled water was used throughout the work. Weighing was made on Mechaniki Zaktady Precyzyjnej Gdansk balance (Poland make [±0.001gm]). Densities were determined by bicapillary having an internal diameter of 1mm. The viscosities were measured by Ostwald's viscometer. It was kept in Elite thermostatic water bath and temperature variation was maintained at 23^0C (±0.1) for each measurements. Sufficient time was allowed to attain thermal equilibrium in between viscometer and water bath.

The present study deals with the viscosity investigation of **[DMPMDC]** and **[CTMBCD]** drugs at 0.1M concentration in 60%, 70% and 80% ethanol-water system separately at 23^0C (296.15K) temperature. All solutions of the drugs were always used freshly in the present study. The viscometric readings were taken as described in literature[11].

OBSERVATIONS AND CALCULATIONS

The data obtained in this study is used to compute molecular interactions in terms of β-coefficient of drugs. The result obtained was mentioned in **Table No. 1-6**. According to Jone's-Dole equation, $(\eta r-1)/\Gamma C = A+\beta\Gamma C$ at different concentration and different percentage. A and β-coefficient values calculated and are enlisted in **Table No.7-8**.

A] For Drug **[DMPMDC]**

TABLE – 1 - VISCOSITY MEASUREMENTS AT DIFFERENT CONCENTRATION OF DRUG

DETERMINATION OF RELATIVE AND SPECIFIC VISCOSITIES AT DIFFERENT CONCENTRATIONS AND TEMPERATURE

SYSTEM:DRUG [DMPMDC] | MEDIUM - 60% ETHANOL-WATER

Temp T (°C)	Conc. C (M)	√C	Time t (sec.)	Density ρx10^3 (kg.cm^{-3})	$\acute{\eta}_r$	$\acute{\eta}_{sp}=\acute{\eta}_r-1$	$(\acute{\eta}_r-1)/\sqrt{C}$ (pa s)
23	0.100	0.31613	451.91	1.0243	1.8462	0.8462	2.67680
	0.075	0.27376	428.19	1.0240	1.7488	0.7488	2.73530
	0.050	0.23653	407.00	1.0238	1.6902	0.6902	2.91787

	0.025	0.20483	398.08	1.0236	1.6252	0.6252	3.05210

TABLE – 2 - VISCOSITY MEASUREMENTS AT DIFFERENT CONCENTRATION OF LIGAND

DETERMINATION OF RELATIVE AND SPECIFIC VISCOSITIES AT DIFFERENT CONCENTRATIONS AND TEMPERATURE

SYSTEM:DRUG [DMPMDC] MEDIUM - 70% ETHANOL-WATER

Temp T (°C)	Conc. C (M)	√C	Time t (sec.)	Density $\rho x10^3$ ($kg.cm^{-3}$)	$\acute{\eta}_r$	$\acute{\eta}_{sp}=\acute{\eta}_r-1$	$(\acute{\eta}_r-1)/\sqrt{C}$ (pa^-s)
23	0.100	0.31617	515.37	1.0288	1.7212	0.7212	2.28155
	0.075	0.27379	490.13	1.0278	1.6353	0.6353	2.32085
	0.050	0.23657	470.30	1.0268	1.5676	0.5676	2.39979
	0.025	0.20487	452.42	1.0261	1.5070	0.5070	2.47534

TABLE – 3 - VISCOSITY MEASUREMENTS AT DIFFERENT CONCENTRATION OF LIGAND

DETERMINATION OF RELATIVE AND SPECIFIC VISCOSITIES AT DIFFERENT CONCENTRATIONS AND TEMPERATURE

SYSTEM:DRUG [DMPMDC] MEDIUM - 80% ETHANOL-WATER

Temp T (°C)	Conc. C (M)	√C	Time t (sec.)	Density $\rho x10^3$ ($kg.cm^-$	$\acute{\eta}_r$	$\acute{\eta}_{sp}=\acute{\eta}_r-1$	$(\acute{\eta}_r-1)/\sqrt{C}$ (pa^-s)
23	0.100	0.31620	483.30	1.0389	1.5478	0.5469	1.73035
	0.075	0.27383	484.41	1.0353	1.5453	0.5451	1.99147
	0.050	0.23661	467.38	1.0314	1.4863	0.4863	2.05621
	0.025	0.20491	457.62	1.0289	1.4506	0.4506	2.20012

TABLE 4- VISCOSITY MEASUREMENTS AT DIFFERENT CONCENTRATION OF LIGAND							
DETERMINATION OF RELATIVE AND SPECIFIC VISCOSITIES AT DIFFERENT CONCENTRATIONS AND TEMPERATURE							
SYSTEM:LIGAND [CTMBCD] MEDIUM - 60% ETHANOL-WATER							
Temp T (°C)	**Conc. C (M)**	**√C**	**Time t (sec.)**	**Density ρx10^3 (kg.cm^{-3})**	**$\acute{\eta}_r$**	**$\acute{\eta}_{sp}=\acute{\eta}_r-1$**	**$(\acute{\eta}_r-1)/\sqrt{C}$ (pa˙s)**
23	0.100	0.31617	527.36	1.03709	2.18097	1.18097	3.73462
	0.075	0.27379	510.06	1.03127	2.09762	1.09762	4.00802
	0.050	0.23657	485.22	1.02757	1.98832	0.98832	4.17651
	0.025	0.20487	462.83	1.02427	1.89048	0.89048	4.34521

TABLE 5 - VISCOSITY MEASUREMENTS AT DIFFERENT CONCENTRATION OF LIGAND							
DETERMINATION OF RELATIVE AND SPECIFIC VISCOSITIES AT DIFFERENT CONCENTRATIONS AND TEMPERATURE							
SYSTEM:LIGAND [CTMBCD] MEDIUM - 70% ETHANOL-WATER							
Temp T (°C)	**Conc. C (M)**	**√C**	**Time t (sec.)**	**Density ρx10^3 (kg.cm^{-3}))**	**$\acute{\eta}_r$**	**$\acute{\eta}_{sp}=\acute{\eta}_r-1$**	**$(\acute{\eta}_r-1)/\sqrt{C}$ (pa˙s)**
23	0.100	0.31617	532.13	1.03939	1.79520	0.79520	2.51471
	0.075	0.27379	509.59	1.03237	1.70757	0.70757	2.58376
	0.050	0.23657	486.11	1.02927	1.62398	0.62398	2.63689
	0.025	0.20487	478.63	1.02607	1.59402	0.59404	2.89873

TABLE 6 - VISCOSITY MEASUREMENTS AT DIFFERENT CONCENTRATION OF LIGAND							
DETERMINATION OF RELATIVE AND SPECIFIC VISCOSITIES AT DIFFERENT CONCENTRATIONS AND TEMPERATURE							
SYSTEM:LIGAND [CTMBCD] MEDIUM - 80% ETHANOL-WATER							
Temp T (°C)	**Conc. C (M)**	**√C**	**Time t (sec.)**	**Density ρx10^3 (kg.cm^{-3}))**	**$\acute{\eta}_r$**	**$\acute{\eta}_{sp}=\acute{\eta}_r-1$**	**$(\acute{\eta}_r-1)/\sqrt{C}$ (pa˙s)**
23	0.100	0.31617	536.51	1.04018	1.71897	0.71897	2.27365
	0.075	0.27379	515.77	1.03707	1.64757	0.64757	2.36467
	0.050	0.23657	497.51	1.03317	1.58327	0.58327	2.46486

	0.025	0.20487	479.68	1.02997	1.52179	0.52179	2.54619

A and β Co-Efficient Value from Graphs at Different Temperatures for 60%, 70% and 80% Ethanol-Water Mixture for drugs [DMPMDC].

TABLE – 7 - FOR [DMPMDC]			
W-E Mixture %	**Temp °C**	**Mean "A"**	**β (Slope "m")**
60	23	3.14	-3.1557
70	23	2.54	-2.2219
80	23	2.35	-7.6917

A and β Co-Efficient Value from Graphs at Different Temperatures for 60%, 70% and 80% Ethanol-Water Mixture for drugs [CTMBCD].

TABLE – 8 - FOR [CTMBCD]			
W-E Mixture %	**Temp °C**	**Mean "A"**	**β (Slope "m")**
60	23	4.53	-5.5199
70	23	2.73	-1.6299
80	23	2.63	-2.7797

Thus, the knowledge of viscosity and A and β coefficient of viscosity leads to determining the solute-solute, solvent-solvent and solute-solvent interactions. From the result given in **Table No. 1 to 9**, it is clear that, as the concentration of drugs decreases, the density and relative viscosity also decreases. This result is similar for drugs [DMPMDC] and [CTMBCD] at 23^0C temperature for 60%, 70% and 80% ethanol-water mixture. This may be due to the fact that, as the concentration decreases, number of solute molecule decreases and at same time number of solvent molecules increases and so the solvation effect increases. So along with the decrease in concentration i.e. number of moles per liter, solute solvent interactions also decreases. As the temperature of drugs increases the density and relative viscosity decreases. The similar trend is observed for drugs [DMPMDC] and [CTMBCD] at 0.1 M concentration for 60%, 70% and 80% ethanol-water mixture. For [DMPMDC] as the percentage of ethanol-water mixture as solvent increases, the relative viscosity decreases. As the concentration of drugs decreases and temperature goes on increases, the similar result is observed. This may be due to, as the percentage of

ethanol-water mixture goes on increasing from 60% to 80%, the solvation effect goes on decreasing and due to which molecular interactions become weak.

Similar result obtained for the [CTMBCD] for 60%, 70% and 80% ethanol-water mixture as solvent.

We have the result,

At 23°C for 60% ethanol-water mixture,

Drug	[DMPMDC]	[CTMBCD]
ηr	1.8465	2.1807
Substitution	$-C_6H_5$ group	$-CH_3$ group

At 23°C for 60% ethanol-water mixture, the relative viscosity (η_r) of [DMPMDC] was found to be 1.8465 and for [CTMBCD] 2.1810. Generally, it was observed that, when the molecules are aromatic the relative viscosity is always greater. This trend was observed in [DMPMDC]. Literature survey also reveals that, when there is a bulkier group, the relative viscosity is greater. But in this investigation, the value of relative viscosity of [CTMBCD] is greater than [DMPMDC]. It means that, only the bulkiness of the group as a substituent not only interfere the values of relative viscosity but the reactivity and stability and tautomeric properties also interfere the values of relative viscosities. It is clear from the result that, in [DMPMDC] there is resonance stabilization in the benzene rings substituted by hydroxyl groups while in the case of [CTMBCD] there are methoxy, chloro as well as quinone groups present.

Such type of greater interference of methyl will not involved in but when we compare, relative viscosity of **[**DMPMDC**]** and **[**CTMBCD**]** as per the general norms, the relative viscosity of bulkier group must be greater but in this investigation, the relative viscosity of **[**CTMBCD**]** is greater than that of **[**DMPMDC**]**, this may be due to the donating capacity of $-CH_3$ group to the **[**CTMBCD**]** molecule. As the oxygen atoms in **[**CTMBCD**]** molecule is electron rich species and $-CH_3$ group is also electron donating group, hence in **[**CTMBCD**]** molecule there occurs compactness in the bond which is greater than **[**DMPMDC**]** molecule. This will also interfere the change in relative viscosity (the normal trend is change due to this reason). From this discussion , it is clear that bulky substituent on the molecule is not only factor in trend of relative viscosity but electron donating nature, electron clouds, nature of hetero atom present in drugs and the compactness in the molecule will directly hampered results and trends in the relative viscosity.

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