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THE CONDUCTOMETRIC MEASUREMENT OF [ACDTT] AND [CTBCD] AT VARIOUS MOLAR CONCENTRATIONS

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ABSTRACT

The conductometric measurements of *(4S,4aS,5aS,6S,12As,Z)-2-[amino(hydroxy)-methylene]-7-chloro-4-(dimethylamino)-6,10,11,12a-tetrahydroxy-6-methyl-4a,5,5a,6-tetrahydrotetracene-1,3,12(2H,4H,12aH)-trione* ***[ACDTT]*** *and (2S, 6R)-7-chloro -2, 4, 6-trimethoxy-6'-methyl-3H, 4'H-spiro[1-benzofuran 2, 1'-] cyclohex-2-ene]-3,4'-dione[****CTBCD****]* were recently carried out at different molar concentrations of solute at constant temperature to investigate the solute-solvent, ion-solvent interactions as well as the effect of dilution was investigated. The conductance data in all cases have been analyzed by Shedlovsky method to obtain limiting molar conductance (λ_m) data and ion association constants (K_A) values. The thermodynamic parameters like change in enthalpy, entropy and free energy for the ion pair formation have been calculated from the value of ion association constant at constant temperature. The results have been discussed in terms of ion-ion, ion-solvent and solvent-solvent interactions and also the effects of various substituents(groups) were investigated. This investigation gave detail information regarding pharmokinetics and pharmodynamics of these drugs.

Keywords: Conductometric measurements, *(4S,4aS,5aS,6S,12As,Z)-2-[amino(hydroxy)-methylene]-7-chloro-4-(dimethylamino)-6,10,11,12a-tetrahydroxy-6-methyl-4a,5,5a,6-tetrahydrotetracene-1,3,12(2H,4H,12aH)-trione [ACDTT] and (2S, 6R)-7-chloro -2, 4, 6-tri- methoxy-6'-methyl-3H,4'H-spiro[1-benzofuran 2,1'-]cyclohex-2-ene]-3,4'-dione [CTBCD],* Thermodynamic parameters, Walden Product.

INTRODUCTION

To measure the conductance of electrolyte in the solution gives outstanding information about the solubility and permeability, which are the two key biopharmaceutical parameters responsible for the effective bioavailability and good in vivo and in vitro correlation [1]. One of the best methods of solubalisation is considered as hydrotropic solubilisation [2]. To enhance the solubility and dissolution rate and oral bioavailability of poor water soluble drugs are still the challenging aspects for the pharmaceutical technologists [3]. Aqueous solubilisation of insoluble drugs can be achieved by the addition of hydrotropic agents. Many work highlighted the effect of the solubility enhancers (hydrotropic agents) [4,5] and hence improved stability of the drug but no detailed explanation is available telling to the improvement phenomena. The split of electrolyte conductivities into the ionic components ideally requires transference numbers, the accurate measurements of which present serious experimental problems in many non-aqueous solvents. The conductance measurements provide valuable information regarding the ion-ion and ion-solvent interactions [6].

Izonfuo and Obunwo [7] and Roy et al [8] studied the conductance of alkali metal in different mixtures mixed solvents. The conductometric measurement of ionic association of divalent asymmetric electrolyte $Cu(NO_3)_2$ with Kryptofix-22 in mixed (MeOH-DMF) solvents at different temperatures were carried out by Gomaa and Al-Jahdalli [9]. The ion pair formation and thermodynamic parameters of Glycine Bis-1-amidino-O-methylurea cobalt(III) halides in water-methanol mixture at different temperatures were studied Singh et al [10]. The charge transfer complexes of vitamin K with several classes of antimicrobialswere studied by Dozal et al [11]. The thermo dynamic parameters and Walden products of

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different complexes were studied by few researcher and they also determined the comparison of transition metal complexes among the halide groups [12-16]. Solanki et al [17] studied conductuctance of nimesulide in aqueous solutions of hydrotropic agents at different temperatures. Alnajjar [18] studied simultaneous determination of o-floxacin and cefixime in their combined dosage form by using simple and sensitive CE method.

In the present investigation the study of conductometric properties, thermodynamic behaviour and Walden product of *(4S,4aS,5aS,6S,12As,Z)-2-[amino(hydroxy)-methylene]-7-chloro-4-(dimethylamino)-6,10,11,12a-tetrahydroxy-6-methyl-4a,5,5a,6-tetrahydrotetracene-1,3,12(2H,4H,12aH)-trione [ACDTT]* and (2S, 6R)-7-chloro -2, 4, 6-trimethoxy-6'-methyl-3H, 4'H-spiro[1-benzofuran 2, 1’-] cyclohex-2-ene]-3,4'-dione[CTBCD] in ethanol-water mixture at different concentration and at constant temperature i.e. 25^0C. The data were analyzed by Shedlovsky method [19]. The thermodynamic parameters like ΔH^0; ΔS^0 and ΔG^0 for the formation have been studied from the values of ion association constant at 25^0C temperatures. The calculated values have been used to discuss qualitatively the nature of different interactions.

EXPERIMENTAL

(4S,4aS,5aS,6S,12As,Z)-2- [amino(hydroxy)-methylene]- 7-chloro-4-(dimethylamino)-6,10,11,12a-tetrahydroxy-6-methyl-4a,5,5a, 6-tetrahydrotetracene-1,3,12(2H,4H,12aH)-trione [ACDTT] and (2S, 6R)-7-chloro -2, 4, 6-trimethoxy-6'-methyl-3H, 4'H-spiro[1-benzofuran 2, 1’-] cyclohex-2-ene]-3,4'-dione[CTBCD] are used as drug. The 0.1M solution of each drug was then diluted to 0.075M, 0.050M and 0.025M by serial dilution method in 100% water and ethanol-water mixture respectively. Similar solutions were prepared for 80% and 70% water-ethanol mixture. All the solutions of drug were always used a fresh in the present investigation. In 50 ml Borosil glass beaker drug solution was taken and it was kept inside the thermostat for 15-20 minutes to attain the thermal equilibrium (25^0C). After achieving the thermal equilibrium, the conductivity of that electrolyte was measured.

RESULTS AND DISCUSSION

During this investigation conductometric measurements of 100%, 80%, and 70% mixtures of water-ethanol were freshly prepared. In first set 0.1M solution of [ACDTT] was prepared in conductivity water and by serial dilution method 0.075M, 0.050M and 0.025M solutions were prepared. At 25^0C the conductance of each solution is measured by Conductivity Bridge. The results obtained are given in Table 1 to Table 2.

From the data observed conductance (G), specific conductance (k) and molar conductance (μ) were determined by known literature method.

From Table 1 to Table 2, it was observed that the observed conductance (G), specific conductance (k) and molar conductance (μ) were decreases from [ACDTT] to [CTBCD] continuously. The decrease in all conductances is due to number of -OH groups which is phenolic present in the individual molecule. In [ACDTT] electron donating groups are present in the molecule hence, the stability of carbanion increases which help to carry current easily in the solution. So, there is a increase in observed, specific and molar conductance in [ACDTT], such types of functional groups are not present in [CTBCD] so these conductance decreases in [CTBCD].

In [ACDTT] observed conductance continuously decreases from 0.1M concentration to 0.025M concentration continuously. This is due to the numbers of [CTBCD] present in these solutions were continuously decreases. Similar pattern was observed in percentage compositions of the mixture. It means that the absorption, transformation and metabolism of [ACDTT] is better than [CTBCD], so [ACDTT] possesses best drug activity and drug effect than [CTBCD].

Specific conductance of [ACDTT] decreases when the molar concentration and percentage composition of water decreases but the specific conductance increases at the same temperature. In [ACDTT] it was also observed that molar conductance increases from 0.1M concentration to 0.025M concentration as well as it increases in all percentage compositions. In 100% water molar conductance is highest while it will decreases from 100% to 70% water-ethanol percentage compositions. As molar conductance in 100% water is highest in all molar concentrations therefore, this drug is best drug which obey pharmokinetics and pharmodynamics of the standard drug. Same patterns of observed conductance, molar conductance and specific conductance were observed for [CTBCD].

The specific constant (Ksp), log (Ksp) and thermodynamics parameter viz. change in free energy (ΔG), change in entropy (ΔS) and change in enthalpy (ΔH) of [ACDTT] and [CTBCD] were determined by known literature methods at various molar concentration, percentage compositions and at same temperature. The results obtained were given inTable-3 to Table-8.

From Table 3 to Table 8 it was observed for all three drugs Ksp, log Ksp, ΔH and ΔS decreases continuously while ΔG increases when we go from 0.1M concentration solution to 0.025M concentration. Similar pattern was observed in percentage composition of the mixture viz. these thermodynamic parameters are highest in 100% water while least in 70% water-ethanol solvent. When the temperature increases in all system Ksp, log Ksp and ΔS decreases while ΔG increases. In [CTBCD] the values of all thermodynamic parameter as well as Ksp and log Ksp are the greatest than [ACDTT] possesses these thermodynamics values. From this study it is clear that various functional groups such as electron donating, electron withdrawing, acidic, basic and various functional groups present in the molecule directly affect conductance, specific conductance, molar conductance, Ksp, ΔH, ΔS and ΔG values of that drug. The structure of the drug as well as nature of that drug directly affects these parameters. The temperature, molar concentrations and percentage compositions are also responsible for changing the values of these parameters. The solute(drug)-solvent interactions, solvent-solvent interactions, solvent-solvent-solute interactions and –solute-solute-solvent interactions are another factors which directly hamper these parameters. The internal geometry as well as internal and intra hydrogen bonding affect these parameters. During this investigation it was observed that the molar conductance of [ACDTT] is highest than [CTBCD] which clearly indicates the drug effect of [ACDTT] is comparatively [CTBCD].

Table 1. Conductometric Measurements at Different Concentration of Drug [ACDTT]

Determination of G, k and μ at Different Concentrations and Temperature 25^0C				
% of solution (Water- ethanol)	**Concentration C (M)**	**Observed conductance (G)**	**Specific conductance (k)**	**Molar conductance (μ)**
100%	0.1 M	7.69X10-3	7.41287 X10-3	74.12953
	0.075 M	6.21 X10-3	6.01400 X10-3	80.18802
	0.050 M	4.50 X10-3	4.38676 X10-3	87.7365
	0.025 M	2.56 X10-3	2.54065 X10-3	101.6298
80%	0.1 M	4.55X10-3	4.43435 X10-3	44.3435
	0.075 M	3.87 X10-3	3.79676 X10-3	50.6240
	0.050 M	3.10 X10-3	3.06404 X10-3	61.2819
	0.025 M	2.01 X10-3	2.01728 X10-3	80.6945
70%	0.1 M	4.07 X10-3	3.97758 X10-3	39.7758
	0.075 M	3.76 X10-3	3.68258 X10-3	49.1014
	0.050 M	3.23 X10-3	3.17823 X10-3	63.5659
	0.025 M	2.15 X10-3	2.15050 X10-3	86.0235

Table 2. Conductometric Measurements at Different Concentration Of Drug [CTBCD]

Determination of G, k and μ at Different Concentrations and Temperature 25^0C				
% of solution	**Concentration C (M)**	**Observed conductance (G)**	**Specific conductance (k)**	**Molar conductance (μ)**
100%	0.1 M	0.19X10-3	0.20932 X10-3	2.09349
	0.075 M	0.14 X10-3	0.16174 X10-3	2.15693
	0.050 M	0.09 X10-3	0.11416X10-3	2.28381
	0.025 M	0.06 X10-3	0.07609X10-3	3.04509
80%	0.1 M	0.13X10-3	0.15222X10-3	1.52253
	0.075 M	0.12 X10-3	0.14271X10-3	1.90317
	0.050 M	0.09 X10-3	0.11416X10-3	2.28381
	0.025 M	0.06 X10-3	0.07609X10-3	3.04509
70%	0.1 M	0.12 X10-3	0.14271X10-3	1.42736
	0.075 M	0.10 X10-3	0.123705X10-3	1.64940
	0.050 M	0.08 X10-3	0.104673X10-3	2.09349
	0.025 M	0.05 X10-3	0.066609X10-3	2.66445

Table 3. Conductometric Measurements at Different Concentration Of Drug [ACDTT]

Determination of Ksp, log Ksp, λG, λH and λS at Different Concentrations and at Same Temperature						
System: Drug DMPMDC		**Medium - 100% Water**				
Temp T (°C)	**Conc. C (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
25	0.100	0.099774991	-1.000978282	5673.098512	-425066.5521	-1455.20148
	0.075	0.074831242	-1.125917020	6381.195560	-425066.5521	-1457.59369
	0.050	0.049887493	-1.302008282	7379.202301	-425066.5521	-1460.96534
	0.025	0.024943744	-1.60303826	9085.306119	-425066.5521	-1466.72921

Table 4. Conductometric Measurements at Different Concentration of Drug [ACDTT]

Determination of Ksp, log Ksp, ΔG, ΔH and ΔS at Different Concentrations and at Same Temperature						
System: Drug [DMPMDC]			Medium - 80% Water			
Temp T (°C)	**Conc. C (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
25	0.100	0.079819992	-1.097888294	6222.34121	-425066.5521	-1457.057070
	0.075	0.059864992	-1.222827038	6930.43832	-425066.5521	-1459.449290
	0.050	0.039909993	-1.398918301	7928.44504	-425066.5521	-1462.820934
	0.025	0.019954995	-1.699948308	9634.54890	-425066.5521	-1468.584799

Table 5. Conductometric Measurements at Different Concentration of Drug [ACDTT]

Determination of Ksp, log Ksp, ΔG,ΔH and ΔS at Different Concentrations and at Same Temperature						
System: Drug [DMPMDC]			Medium - 70% Water			
Temp T (°C)	**Conc. C (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
25	0.100	0.069842492	-1.155880244	6551.01372	-425066.5521	-1458.167450
	0.075	0.052381868	-1.280818981	7259.11080	-425066.5521	-1460.559670
	0.050	0.034921242	-1.456910254	8257.11759	-425066.55241	-1463.931313
	0.025	0.017460619	-1.757940261	9963.22143	-425066.5521	-1469.695179

Table 6. Conductometric Measurements at Different Concentration of Drug [CTBCD]

Determination of Ksp, log Ksp, ΔG, ΔH and ΔS AT Different Concentrations and at Same Temperature						
System: Drug [CTMBCD]			Medium - 100% Water			
Temp T (°C)	**Conc. C (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
25	0.100	3.925965084	0.593946430	-3366.223498	-425066.5521	-1424.663270
	0.075	2.944471813	0.469007693	-2658.126456	-425066.5521	-1427.055490
	0.050	1.962982541	0.292916434	-1660.119731	-425066.5521	-1430.427539
	0.025	0.981491268	-0.00811352	45.98402833	-425066.5521	-1436.199998

Table 7. Conductometric Measurements at Different Concentration of Drug [CTBCD]

Determination of Ksp, log Ksp, ΔG,ΔH and ΔS at Different Concentrations and at Same Temperature						
System: Drug [CTMBCD]			Medium - 80% Water			
Temp T (°C)	**Conc. C (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
25	0.100	3.14077204	0.497036417	-2816.980763	-425066.5521	-1426.518820
	0.075	2.35557902	0.372097680	-2108.883721	-425066.5521	-1428.914025
	0.050	1.57038601	0.196006421	-1110.876996	-425066.5521	-1432.024746
	0.025	0.78519301	-0.10502354	595.22676327	-425066.5521	-1434.024746

Table 8. Conductometric Measurements at Different Concentration of Drug [CTBCD]

Determination of Ksp, log Ksp, ΔG, ΔH and ΔS at Different Concentrations and at Same Temperature						
System: Drug [CTMBCD]			Medium - 70% Water			
Temp T (°C)	**Conc. C (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
25	0.100	2.748175558	0.439044470	-2488.308270	-425066.5521	-1427.629200
	0.075	2.061131668	0.314105733	-1780.211120	-425066.5521	-1430.021420
	0.050	1.374087778	0.138014474	-782.2045053	-425066.5521	-1433.393064
	0.025	0.687043886	-0.68704389	923.8992560	-425066.5521	-1439.156928

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