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Solutions and thermodynamic properties of three pharmacologically important drugs in ethanol

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This manuscript reports the determination of critical micelle concentration of three pharmacologically important drugs at four temperatures within the range 288K-318K by using conductivity and refractive index measurements. These drugs included chlorpheniramine maleate, losartan potassium and sodium valporate. The effect of change in temperature on CMC of these drugs was also studied. The electrical conductivity measurements were used to find important thermodynamic parameters for the micellization process. These thermodynamic parameters include free energy of micellization, enthalpy of micellization and entropy of micellization. The results showed that the process of micellization is spontaneous, endothermic and leads to a decrease in entropy for all the drugs studied.

Keywords: Micellization, entropy of micellization, sodium valporate, conductometry.

INTRODUCTION

Most of the allopathic drugs are organic compounds and have amphiphilic character because they have both hydrophilic and hydrophobic parts in their molecules. These drugs also act as surfactants and have ability to form micelles in solution. The study of these drug micelles is important as these micelles may become accumulated in different parts of the body as a result of micellization when a drug is administered in a large amount in the body. The concentration of drug at which micelles just start to form is called critical micelle concentration (CMC). The size and shape of micelles depend on pH, temperature, concentration and ionic strength [1]. CMC of an amphiphile depends on temperature, pressure and presence and concentration of the added substance [1].

CMC can be determined by measuring specific physical properties as these properties undergo changes in different manner before and after CMC and so when these properties are plotted *versus* concentration straight lines of different slopes are obtained. The point of intersection of these straight lines gives the CMC of the drug. The micelles are structurally similar to biomembranes due to which they can be used as a model system to study drug membrane interaction *in vitro* [2-4].

In micelles the distribution of water molecules is anisotropic which results in solubilization of non-polar molecules in the micellar core and molecules of low polarity at intermediate position between core and surface of micelles so these micelles can increase the solubility of insoluble or less soluble substances [5].

Our present work is related with the determination of CMC and definite thermodynamic parameters of micellization of three pharmacologically important drugs. These drugs are chlorpheniramine maleate (CPAM), sodium valporate (SV) and losartan potassium (LP). Most workers select drugs which either have similar structures or similar mode of action but here we have chosen different drugs so that the properties of different drugs can be compared.

CPAM is a first-generation alkylamine antihistamin and is used to treat hay fever or other respiratory allergies. It is used to prevent symptoms of allergic conditions like urticaria and rhinitis and is also found to have anti-anxiety and anti-depressant effects [6]. Due to relatively weaker sedative effects it is advantageous over other antihistamin drugs [6].

SV is one of the series of fatty acids or carboxylic acids with antiseizure activity and is used for the treatment of panic attack, epilepsy, anxiety disorder, anorexia nervosa, post-traumatic stress disorder, migraine and bipolar disorder and to treat other psychiatric problems [7].

LP is mainly used for the treatment of hypertension [8] and also delays the progression of diabetic nephropathy [9]. In patients having type 2 diabetes, hypertension and microalbuminuria, it is used for reducing renal disease progression [8]. By maintaining blood pressure, it also has a beneficial effect on mitochondria by reversing age-related dysfunctions in cellular energy usage [10].

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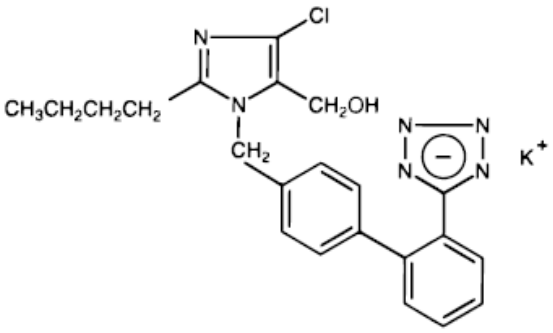
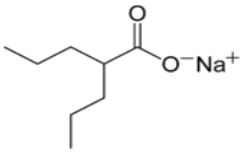
EXPERIMENTAL

Materials

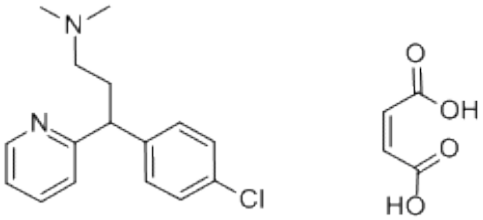
Sodium valporate (≥ 98% purity) was purchased from Sigma, CPAM (≥ 98.5% purity) from Fluka, LP (purity 99.5%) from TCI America and absolute ethanol from Merck. The structures of the drugs are shown in scheme 1. The solutions of drugs having different concentrations in terms of mol/kg were prepared at room temperature in dry absolute ethanol using a balance (Rice Lake TA-120) with precision of ±0.0001 g.



Losartan potassium



Sodium valporate



Chlorphinaramine maleate

Scheme 1. Structures of drugs used

Apparatus and methods

Specific conductivities were measured with digital conductivity meter (Model No. 103 Manufacturer: Jinco Electronics Ltd.) having accuracy of ± 0.5 % ± 2 digits and temperature control accuracy of ± 0.5°C. The measurements of electrical conductivity were taken in the temperature range of 288K-318K at 10K intervals.

The temperature was controlled by using a water circulator (IRMECO I-1800 GmbH, Germany). The conductivity meter was calibrated with a standard solution of KCl over the appropriate concentration range.

Refractive index measurements were taken at one temperature (room temperature) u-sing Abbe's refractometer (Model: ABBE 2WAJ Manufacturer: PCE Instruments) with accuracy of ±0.0002. The instrument was calibrated with distilled water.

RESULTS AND DISCUSSION

Critical micelle concentration

CMC can rapidly and accurately be determined by electrical conductivity measurements. For this purpose, the electrical conductivity measurements for solutions of drugs with different concentrations were plotted *versus* concentration to get straight lines in pre- and post-micellar regions and the point of intersection of these lines gave CMC (Figs. 1, 2, 3). Similarly, refractive index measurements can be used to find CMC (Figs. 4, 5, 6).

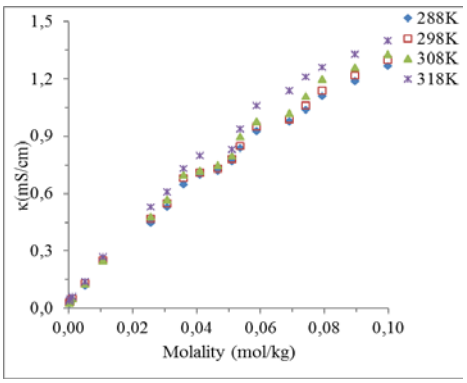


Figure 1. Electrical conductivity *versus* concentration plots for CPAM in ethanol at different temperatures.

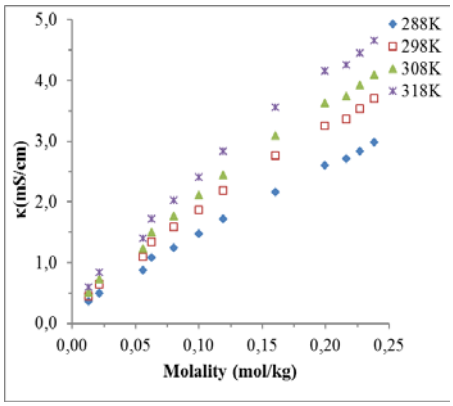


Figure 2. Electrical conductivity *versus* concentration plots for LP in ethanol at different temperatures.

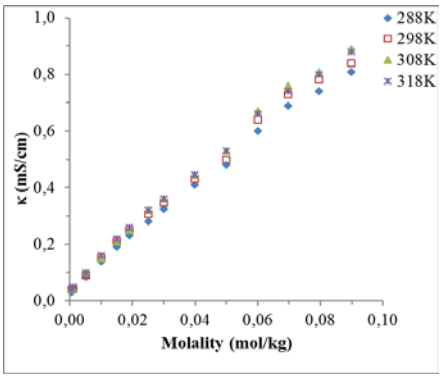


Figure 3. Electrical conductivity *versus* concentration plots for SV in ethanol at different temperatures.

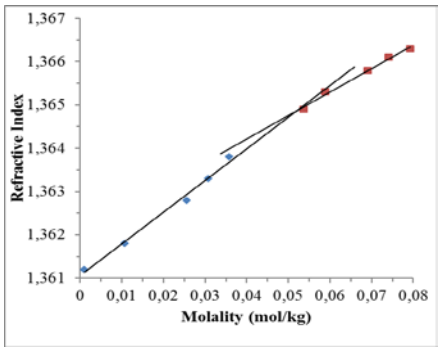


Figure 4. Refractive index *versus* concentration plots for CPAM in ethanol at 288K.

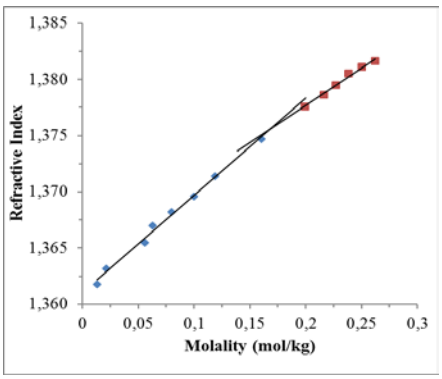


Figure 5. Refractive index *versus* concentration plot for LP in ethanol at 288K.

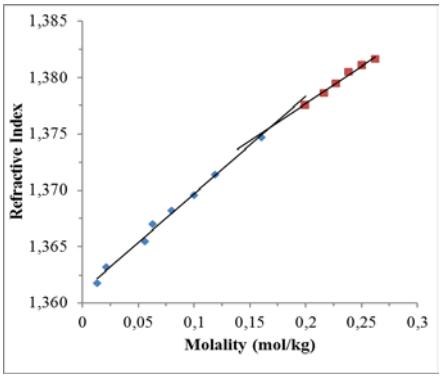


Figure 6. Refractive index *versus* concentration plot for SV in ethanol at 288K.

From the electrical conductivity measurements, we can also find some important parameters as follows:

The degree of ionization (β) of an electrolytic drug is the ratio of the slopes of post-micellar (S_2) to pre-micellar (S_1) regions of the conductivity-concentration plot and is calculated with the help of the following relation [11]:

$$\beta = \frac{S_2}{S_1} \qquad (1)$$

Free energy of micellization (ΔG°_m) can be calculated by the following equation [1]:

$$\Delta G^{\circ}_m = (2-\beta)RT \ln X_{CMC} \qquad (2)$$

Here, R is gas constant, T is temperature in Kelvin scale and X_{CMC} is CMC in mole fraction.

Enthalpy of micellization can be calculated by using equation (3) while entropy of micellization - by equation (4) [1]:

$$\Delta H^{\circ}_m = -(2-\beta)RT^2\left[\frac{\partial(\ln X_{cmc})}{\partial T}\right]_P \qquad (3)$$

$$\Delta S^{\circ}_m = \frac{\Delta H^{\circ}_m - \Delta G^{\circ}_m}{T} \qquad (4)$$

As apparent from table 1 CMC of CPAM at 288K is 0.0550 mol kg^{-1} as determined by the electrical conductivity method in ethanol, which is very close to that determined by refractive index measurements (0.054 mol kg^{-1}). The value of CMC first decreases with increase in temperature till 298K and then increases with increase in temperature. In ethanol CMC of LP (table 2) is found to be 0.168 mol kg^{-1} at 288K which is very close to that determined by refractive index measurements (0.166 mol kg^{-1}). This value also first decreases up to 298K and then increases. CMC of SV in ethanol is found to be 0.0345 mol kg^{-1} at 288K (table 3) as determined by a conductivity method which is very close to that determined by refractive index measurements (0.033 mol kg^{-1}).

The reason for such variation in CMC is due to two opposing processes which directly affect CMC of amphiphiles with temperature changes. Firstly, the temperature rise decreases lyophobic solvation which decreases CMC by favoring micellization. Secondly, the increase in temperature decreases lyophilic solvation which disfavors micellization due to the increase in repulsion between ionic heads which increases CMC by making micellization unfavorable [12]. Relative magnitude of these opposing processes decides about the change in CMC. In case of CPAM and LP lyophobic desolvation is dominant over lyophilic desolvation up to 298K. The effect of lyophilic desolvation

becomes dominant above this temperature, as a result CMC decreases up to 298K and then increases [12]. However, in case of SV the CMC of the drug decreases with temperature rise due to the dominance of lyophobic desolvation over lyophilic desolvation.

ΔG°_m is found to be negative for all the drugs under study and this negative value further increases with temperature rise which shows that the process of micellization is spontaneous and becomes more spontaneous at elevated temperatures [1]. ΔH°_m is positive for all drugs in ethanol solvent and its values become higher at higher temperatures showing that micellization is endothermic and becomes more heat-absorbing at higher temperatures [1].

ΔS^{o}_m is found to be positive representing that micellization results in a decrease in randomness [13,14]. The positive values of ΔS^{o}_m point to a transfer of solvophobic chains of SV from the bulk solution phase to the micelle core, which results in an increase in disorder of the system [12,15,16]. There exists strong hydrogen bonding between molecules of solvent in the immediate vicinity of solvophobic chains, which is different from normal interaction of a solvent with solute particles. The neighboring solvent molecules around solvophobic groups are more strongly attracted by nearby solvent molecules as there exists no attractive force between solvophobic drug molecules and solvent, which causes tightening of solvent structure around solvophobic chains.

Table 1. Thermodynamic and micellar parameters for CPAM in ethanol at different temperatures.

Temperature (K)	CMC (mol/kg)	CMC ($X\times10^4$)	β	α	ΔG°_m (kJ/mol)	ΔH°_m (kJ/mol)	ΔS°_m (J/K/mol)
288.0	0.0550	25.30	0.583	0.417	-20.29	10.01	105.20
298.0	0.0545	25.07	0.599	0.401	-20.79	10.75	105.84
308.0	0.0570	26.22	0.580	0.420	-21.61	11.36	107.07
318.0	0.0575	26.45	0.486	0.514	-23.76	11.97	112.36

Table 2. Thermodynamic and micellar parameters for LP in ethanol at different temperatures.

Temperature (K)	CMC (mol/kg)	CMC ($X\times10^4$)	β	α	ΔG°_m (kJ/mol)	ΔH°_m (kJ/mol)	ΔS°_m (J/K/mol)
288.0	0.168	77.28	0.732	0.268	-14.76	16.81	109.63
298.0	0.164	75.44	0.678	0.322	-16.01	18.04	114.26
308.0	0.166	76.36	0.617	0.383	-17.26	19.17	118.28
318.0	0.168	77.28	0.575	0.425	-18.32	20.34	121.57

Table 3. Thermodynamic and micellar parameters for SV in ethanol at different temperatures.

Temperature (K)	CMC (mol/kg)	CMC ($X\times10^4$)	β	α	ΔG°_m (kJ/mol)	ΔH°_m (kJ/mol)	ΔS°_m (J/K/mol)
288.0	0.0345	15.87	0.791	0.209	-18.67	5.86	85.14
298.0	0.0340	15.64	0.778	0.222	-19.56	6.29	86.77
308.0	0.0340	15.64	0.775	0.225	-20.27	6.73	87.65
318.0	0.0332	15.27	0.756	0.244	-21.33	7.22	89.76

As a result, internal torsional vibrations of chains of drug molecules become restricted in solution, leading to a decrease in entropy of the system. When the solvophobic groups are transferred from the bulk ethanolic medium to the micelles then this order is destroyed and

randomness increases making the process of micellization entropically favorable [17,18].

CONCLUSIONS

The CMCs of CPAM and LP were found to first decrease and then increase with temperature rise while that of SV was found to decrease with temperature rise. The ΔG°_{m} was negative, becoming more negative at elevated temperature, showing that the spontaneous nature of the process becomes more spontaneous at elevated temperatures for all the drugs. Positive ΔH°_{m} represented the endothermic nature of micellization while positive ΔS°_{m} showed that the process of micellization took place with a rise in randomness of the system due to transfer of hydrophobic chains from the bulk solution to the micellar phase. This transfer of lyophobic chains results in destruction of the ethanol structure because the presence of these chains results in lyophobic solvation which results in an increase in structure of solvent.

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