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Dilantin Sodium-Surfactant Interaction

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ABSTRACT

The mutual interaction between 5, 5-diphenyl hydantoin sodium salt ($C_{15}H_{11}N_2NaO_2$) also known as dilantin sodium (DS) and surfactants like sodium dodecyl sulphate (SDS) and cetyltrimethylammonium bromide (CTAB) has been studied by measuring the variation of their aggregation properties in pressence of each other. Critical micelle concentration (CMC) of DS determined by spectrophotometric and conductivity methods in found to be 0.15 mM and this value is seen to decrease significantly in presence of SDS and CTAB. The aggregation of SDS and CTAB are also highly catalysed in presence of DS. A threefold decrease in the CMC of SDS and CTAB have been observed on varying the concentration of DS in its premicellar region. Effect of temperature on micellization of SDS and CTAB have been studied at 30°, 40° and 50° C with and without DS. Physicochemical parameters has been calculated utilizing biphasic model.

Key words : Dilantin Sodium, Critical micelle concentration, Sodium dodecyle sulphate, Cetyltrimethylammonium bromide.

INTRODUCTION

The micellization of surfactants (amphiphiles) after a critical concentration (called the critical micellar concentration, CMC) is an important solution property which needs evaluation to know the existence of micelles in solutions as well as evaluating the thermodynamics of the process which is essential for characterisation and comparison in the light of spontaneity and stability. Several methods are available to determine CMC to realize the existence of micelles[1-2] and also the thermodynamics of micelle formation of ionic surfactants have widely been investigated[3-4]. Many pharmacological active compounds are amphiphilic molecules which may undergo different kinds of association and whose site of action in the organism frequently is the plasma membrane. These amphiphilic drugs bear an ionic or non-ionic polar head group and a hydrophobic portion. In aqueous medium they are able to organise themselves. The spatial separation between the polar and non-polar moieties, as well as the molecular shape and the hydrophobic-hydrophilic balance, determine their tendency to form aggregates[5]. In recent years the thermodynamics, aggregation and surface properties of several tricyelic antidepressants (TCA) were widely studied[6-8]. The aggregation behaviour of amphiphiles are significantly influenced by additives[9-11]. These additives may themselves self associate and many a times are capable to form mixed micelles with surfactants[12].

Mixed micelle formation has recently emerged as a new approach for the simple and

rapid quantitation of amphiphilic substances. The solubilization power as well as the viscosity of an aqueous solution of amphiphilic polymer bound micelle is higher than that of solutions of either pure surfactants or pure polymer[13]. These properties are very much appreciated in the formulation for paints and coating, cosmetic products and many other applications.

Hydantoin drugs are known for their antimicrobial anticonvulsant properties and are commonly used antiepileptical drugs[14]. Most drugs of the hydantoin category are still open for investigation. However, they have been used with much clinical success against all types of epileptic form seizures. Surface activity of such antiepileptic drugs can predict their ability to cross the blood-brain barrier and can be quantified by CMC and surface area requirement of the drug at the air / water interface. Identification of these properties will be leading to the molecular assembly and the transport kinetics of the drug component.

Although the different therapeutic and pharmacological effects of hydantoins were studied[14] the surface activity of these drugs are not widely investigated. Recently self-aggregation behaviour and drug-surfactant interaction of hydantoin and its tyrosine derivative have been reported[15-16]. The present study is the extension of above investigation with the hydantoin drug dilantin sodium (scheme-I)

Dilantin sodium is a commonly used antiepileptic and acts to suppress the abnormal brain activity, seen in seizures by inducing electrical conductance among brain cells by stabilizing the inactive state of voltage-gated sodium channels. Aside from seizures, it is an option in the treatment of trigeminal neuralgia in the event that carbamazepine or other first line treatment seems inappropriate.

MATERIALS AND METHODS

DS was found to be conducting in aqueous medium, hence its CMC was determined by conductivity and spectrophotometric methods. The variation in the CMC of DS in presence of fixed concentrations of SDS or CTAB was determined by conductivity method. Similarly variation in the CMC of SDS and CTAB in presence of DS was also measured conductometrically. Both conductivity meter and uv-visible spectrophotometer are of systronics MAKE. Double distilled water with specific conductance less than 5µS was used in all experiments. DS has been procured from sigma and was used as supplied. All other chemicals used are of AR grade.

RESULTS AND DISCUSSION

The compound DS, feebly soluble in water, shows appreciable conductivity in aqueous solution. Hence, both conductivity and spectrophotometric method were employed to determine its CMC. Absorbance value determined at λmax = 216 nm as well as conductivity values shows a distinct deviation in their slope when plotted against the increasing concentration of DS (Fig. 1 and Fig. 2).

CMC of DS is found to be 0.15 mM by both the methods. This decrease in CMC compared to 1.5 mM for hydantoin reported earlier[15] clearly indicates the major role played by the two phenyl groups in increasing hydrophobicity and micellization tendency.

SDS and CTAB monomers are expected to allign in the bed of DS enhancing its micellization process. In order to verify this behaviour CMC of DS was determined at various fixed concentrations of SDS and CTAB in their premicellar regions. The results are shown in Table 1.

The results shown above indicates that CMC of DS gradually decreases on increasing concentration of SDS upto 2.5 mM beyond which it attains constant value. This limitation in the accommodation of anionic surfactant SDS in the bed of drug with a negative charge on nitrogen may be due to repulsion among similar charges. Secondly, as the concentration of SDS increases the surfactant monomers may start aligning in the micellar shape supported by the drug molecules.

A regular decrease in the CMC of drug is observed at increasing concentration of CTAB. The attraction between positive charge on the surfactant

Table 1: CMC of DS in presence of SDS and CTAB

[SDS]/mM	CMC/mM	[CTAB]/mM	CMC/mM
0	0.15	0	0.15
1.0	0.1	0.08	0.13
2.5	0.08	0.1	0.1
5.0	0.08	0.20.3	0.080.075
		0.5	0.07

Table 2: CMC and Counter-on association b values of SDS and CTAB in presence of DS

S. No.	[DS]/mM	CMC/mM for SDS-DS mixed micelle	β for SDS-DS mixed micelle	CMC/mM for CTAB-DS mixed micelle	β for CTAB-DS mixed micelle
1.	0	7.8	0.67	0.86	0.25
2.	0.01	5.3	0.232	-	-
3.	0.03	4.0	0.262	0.6	0.214
4.	0.05	3.3	0.6	0.46	0.23
5.	0.08	2.1	0.49	0.42	0.24
6.	0.1	-	-	0.36	0.54

Table 3 : Thermodynamic parameters for SDS – DS and CTAB-DS mixed micellar systems.

	Temp./K	CMC/ mM	$\Delta G^{o}m$ (kJ/mol)	$\Delta H^{o}m$ (kJ/mol)	$\Delta S^{o}m$ (JK^{-1} mol^{-1})
A)	SDS- 0.03 mM DS				
	303	4	-38.3		+114.5
	313	6.4	-38.3	-3.6	+110.8
	323	7	-39.3		+110.5
B)	SDS- 0.05 mM DS				
	303	3.3	-38.8		+119.8
	313	3.9	-39.6	-2.5	+118.5
	323	5	-40.2		+116.7
A)	CTAB- 0.05 mM DS				
	303	0.46	-44.3		+137.9
	313	0.54	-45.4	-2.5	+137.4
	323	0.65	-46.3		+135.6
B)	CTAB- 0.1 mM DS				
	303	0.36	-44.9		+137.3
	313	0.5	-45.6	-3.3	+135.1
	323	0.64	-46.6		+133.4

and negative charge on the drug may be one of the region. But, in this case also micellization of DS is prominently assisted by the low concentration of CTAB.

The interaction of DS with surfactants like SDS and CTAB has been studied by determining CMC of SDS and CTAB at various fixed concentration of DS. The results of the measurement which is limited in the premicellar region of DS is shown in Table 2.

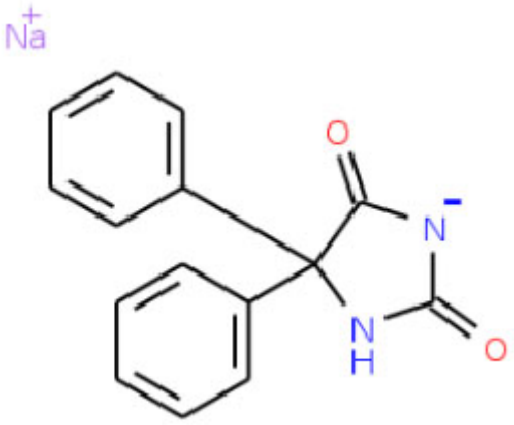
An encouraging result showing almost a threefold decrease in the CMC of both SDS and CTAB have been observed in presence of DS. This variation is in accordance with usual trend reported earlier[13,16]. Due to amphiphilic nature the hydrophobic part of the drug sufficiently interact with the long chain hydrocarbon of the surfactants whereas its polar part behave similar to that of surfactant head group. However, β values do not reflect any significant information. For determination of b, first degree of dissociation α was determined which is actually ratio of the post micellar slope to the premicellar slope. The counter-ion association β = 1 - α.

The β is abnormally low in case of SDS – DS mixed micellar system. This may be due to repulsion among sodium ions coming from drug and surfactants. On the other hand β values of CTAB – DS mixed micelles is comparable to CTAB micelles at low concentration of DS and increases at high concentration as expected. Here the counter ion Br of surfactants is expected to be stabilized due to presence of Na^+ from the drug. This attraction may serve as the driving force to bring the Br in the viscinity of micellar aggregates.

Physicochemical parameters like free energy of micellization $\Delta G^o m$, enthalpy of micellization $\Delta H^o m$ and entropy of micellization $DS^o m$ have been calculated utilizing biphasic model for SDS – DS and CTAB – DS mixed micellar systems at three temperatures 30°C, 40°C and 50°C. $\Delta H^o m$ has been estimated from the slope of the plot of ln (CMC/288.4/55.5) Vs. 1/T for SDS-DS mixed micelles and from the plot of ln (CMC / 364.5/55.5) Vs, 1/T for CTAB-DS mixed micelle system. In all such calculations pure surfactant has been taken as the reference state[3]. $\Delta S^o m$ have been calculated by the following two equations.

$$\Delta S^o m = RT \ln (CMC/288.4/55.5) \quad \ldots (1)$$

$$\Delta S^o m = (DH^o m - DG^o m)/T \quad \ldots (2)$$



Scheme I: Molecular structure of 5, 5-diphenylhydantoin sodium salt (DS)

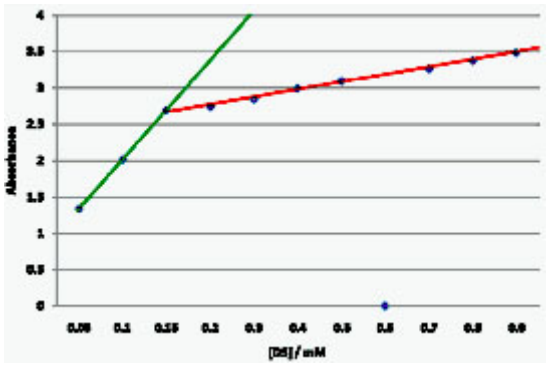


Fig. 2: CMC of DS by Spectrophotometric method

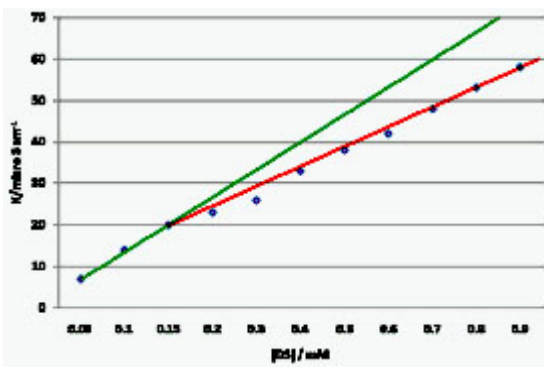


Fig. 1: CMC of DS by conductivity method

The results of this calculation is shown in Table 3.

$\Delta G^{o}m$ values for all systems are negative and take more negative value with increasing additive concentration. Moreover, these values are appreciably lesser compared to the $\Delta G^{o}m$ reported for pure surfactant – water system[16]. This indicates that the micellization is more spontaneous in presence of DS.

The high positive value of entropy change of micellization clearly indicates that the formation of micelle is an entropy driven process. When a surfactant is dissolved in water the hydrocarbon chain is surrounded by the solvation layer of water. Hence entropy of the system decreases remarkably. The clustering of amphiphilic drug into surfactant micelle within which hydrocarbon chains are located in the interior and molecules are anchored at the interface by the hydrophilic head groups, however, decreases the extent of solvation layer. This aggregation releases the mobility constraints on the water molecules and, therefore, results in a favourable increase in entropy.

CONCLUSION

Dilantin sodium forms micellar aggregates and its micellization is favored by the surfactants like SDS and CTAB. The incorporation of CTAB in the bed of drug is favored even at higher concentration of surfactants due to interaction among the opposite charges. The micellization of SDS and CTAB is also favored in presence of drug additives. The negative value of free energy of micellization advocates favorable interaction between drug and surfactants towards mixed micelle formation. The high positive value of entropy of micellization serves as the driving force towards the formation of mixed micellar aggregates.

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