Oriental Journal of Chemistry Vol. **26**(4), 1491-1495 (2010)

Aggregation of cefprozil monohydrate

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(Received: October 19, 2010; Accepted: November 11, 2010)

ABSTRACT

Aggregation behaviour of cefprozil monohydrate ($C_{18}H_{19}N_3O_5S.H_2O$), an antibiotic, has been studied in presence of sodium dodecyl sulphate (SDS) and Cetyltrimethylammonium bromide (CTAB). Critical micelle concentration (CMC) of drug is determined to be 0.34 mM and is observed to decrease significantly at SDS < 2 mM. Above this concentration increase is less prominent and remains almost constant. However a regular decrease in CMC of Cepprozil monohydrate have been observed by increasing the concentration of CTAB. Variation in CMC values of SDS and CTAB have been studied at the premicellar region of Cefprozil monohydrate. A sharp decrease in the CMC of SDS and CTAB have been observed at low concentration of drug but at higher concentration variation in CMC of detergents is not significant. Effect of temperature on micellization of SDS and CTAB have been studied at 30°, 40° and 50°C with and without additive. Physicochemical parameters have been calculated utilizing pseudophaze model.

Keywords : Cefprozil monohydrate, critical micelle concentration, sodium dodecyl sulphate, Cetyltrimethylammonium bromide.

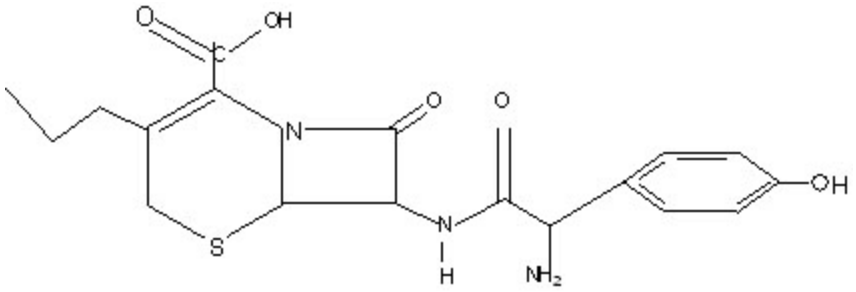
INTRODUCTION

The amphiphilic character of surfactants leads to the formation of various self-assembled aggregates in water. Surfactant molecules consists of a polar head group and one or more hydrocarbon chains. The polar head promotes dissolution in water, whereas hydrocarbon chains are hydrophobic and thus nearly insoluble. The insolubility is based on entropically unfavourable orientation of water molecules, which are highly ordered in the viscinity of hydrocarbon chains[1]. Already at low or moderate concentrations, surfactant molecules organise themselves into aggregate structures to shield their hydrocarbon chains from water. The aggregation is driven by a strong effective attraction between chain segments, which tends to minimize the unfavourable contacts between polar solvent and apolar solute molecules. This indirect force usually denoted as hydrophobic interaction is known to be several times stronger than the familiar van der Waals force between hydrocarbon chains.[2] In many cases, the amphiphilic molecules aggregate into spherical micelles.[3]

Drug molecules may possess amphiphilic or surface active characteristics and assemble at the oil / water interface. Knowledge of their surface activity is essential for understanding the physicochemical and biological properties of the drug. When the surface active drugs are delivered through hydrogeles or micelle drug carrier the diffusion and release rates of the drug molecules may be affected[4-6] because the absorption of amphiphilic drug molecules is located to certain sites at the drug carrier matrix. Also the free energies for the micellization of the surface – active drug molecules in solution are of the same magnitude as the free energy for absorption of drug molecules to the carrier matrix. Hence, the hydrophobic moieties of the drug interact and tend to stabilize a cluster – like structure at the matrix of the carrier, which means that cooperative binding phenomenon has the same energetics as the micellization.[7-8]

The aggregation behaviour of tricyclic antidepressant drugs have widely been investigated[9-11]. The effect of additives like

β-cyclodextrin on the aggregation behaviour of these amphiphilic antidepressants have also been evaluated by determining their apparent critical aggregation concentration.[12] However, very little attention has been drawn on some other amphiphilic drugs which may show similar aggregation as that of tricyclic antidepressants. The present research work has a specific intension to explore this possibility by selecting an amphiphilic antibiotic cefprozil monohydrate.



Cefprozil Monohydrate (CM)

Cefprozil monohydrate (CM) is an oral second generation cephalosporin antibiotic which works by inhibiting the synthesis of bacterial cell wall[13-16]. It is used especially in the treatment of respiratory and urinary tract infection. Its structure indicates more than one polar sites as well as appreciable hydrophobic part. The present investigation studies the aggregation behaviour of this drug and its interaction with the common surfactants like SDS and CTAB.

MATERIAL AND METHODS

The drug was found to be non-conducting. Hence, its CMC was determined by spectrophometric method. A sharp deviation in the slope was observed in the plot of absorbance Vs. concentration of CM. Similarly variation in the CMC of CM in presence of SDS and CTAB was dermined spectrophotometrically. Variation in the CMC of SDS and CTAB in presence of CM was determined by conductivity method. Both conductivity meter and UV-VIS spectrophotometer are of systronics Make. Double distilled water with specific conductance value less than 5 mS was used in all experimental purposes. All chemicals used here of AR grade. The drug cefprozil monohydrate has been procured as a gift from Lupin Limited, Mandideep, Raisen (M.P.).

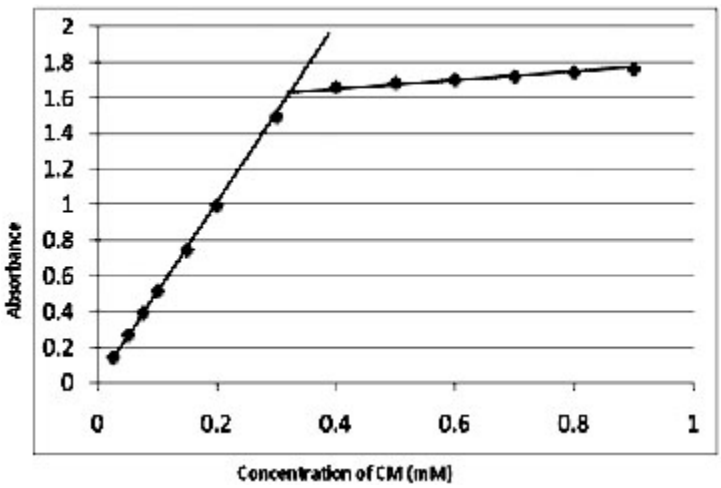


Fig. 1 : CMC of CM by spectrophotometric method

RESULTS AND DISCUSSION

The compound CM shows distinct λ_{max} at 243 nm. Due to non-conducting nature spectrophotometric technique seems to be best option to determine its CMC. The CMC value found by this technique is 0.34 mM. This value is in accordance with earlier expectations due to its appreciable solubility in water. The plot of absorbance vs concentration of CM (Fig. 1).

In order to study the contribution of SDS in the micellization of CM the CMC of CM was determined at a fixed concentration of SDS. The variation in CMC of CM has been determined in premicellar region of SDS and has been reported in Table 1.

Table 1 : CMC of CM in presence of SDS

Sr.No.	[SDS]/mM	CMC/mM
1.	0	0.340
2.	1	0.080
3.	2	0.256
4.	4	0.210
5.	5	0.225

The result shows that low concentration of SDS is more effective for aggregation of CM. After 2 mM of SDS the CMC of CM remains almost constant. This may be due to fact that micelle structure of CM has some limitations for accommodation of surfactant monomers. Secondly, this constancy may be due to repulsions among anions of surfactant monomers and - COO^- and $–O^-$ present in the drug moiety beyond a concentration limit. Similarly participation of CTAB in the aggregation of CM has been investigated by determining CMC of CM at varying concentration of CTAB. The result in presented in Table 2.

Table 2 : CMC of CM in presence of CTAB

Sr.No.	[CTAB]/mM	CMC/mM
1.	0	0.340
2.	0.1	0.225
3.	0.2	0.175
4.	0.3	0.150
5.	0.4	0.125
6.	0.5	0.100

Table 3 : CMC and β values of SDS and CTAB in presence of CM

Sr. No.	[Cefprozil]/ mM	CMC /cM for SDS	β for SDS micelles	CMC/mM for CTAB	β for CTAB micelles
1.	0	7.8	.67	0.86	0.25
2.	0.05	5.5	0.5		
3.	0.08	4.5	0.4	0.58	0.39
4.	0.1	4.0	0.5	0.5	0.3
5.	0.2	3.9	0.4	0.42	0.39
6.	0.3	4.0	0.45		

The results shows that there is a regular decrease of CMC by increasing the concentration of CTAB. This is in accordance with the established trend that the self-assembling characteristics of drug is favoured by the addition surfactants from outside[17]. This may be due to attraction between cationic head group of CTAB and anionic part of drug as a consequence of which the CTAB monomers are easily accommodated in the micelles of drug.

In the second part of study role of CM has been investigated in the micellization of SDS and CTAB. The CM remains again at the premiceller stage in all solutions. The counter – ion association β have also been determined for both SDS as well as CTAB micelles.

For this, the degree of dissociation α was determined from the specific conductance Vs. concentration of surfactant plot. Actually, α is the

ratio of the post micelles slope to the premicellar slope of these plots. The β of the micelles in equal to 1-α. The results for both SDS and CTAB micelles has been shown in Table 3.

It is evident from the above result that low concentration of drug is more effective for the formation of SDS micelles. Above 0.1 mM of CM CMC of SDS remains almost constant. Reason may be the same as given above. There may again be the limitation for the accommodation of drug molecules in the SDS micelles due to anion – anion repulsion. However, a regular decrease in the CMC of CTAB has been observed as expected. The driving force may again be cationic – anionic attraction. The counter-ion association values are not throughing any specific informations for such micellization. This is due to complex nature of interactions in such mixed, micellar systems.

Physicochemical parameters like in free energy of micellisation ΔG^{o}_{m} enthalpy of micellization ΔH^{o}_{m} and entropy of micellization ΔS^{o}_{m} have been calculated utilising pseudophase model for both SDS – CM and CTAB-CM 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 *l*n (CMC/288.4/55.6) Vs 1/T for SDS – CM mixed micelles and from the plot of *l*n (CMC/364.5/55.5) Vs. 1/T for CTAB-CM mixed micelle system. Here pure surfactant has been taken as the reference state[18]. ΔG^{o}_{m} has been calculated by the relation ΔG^{o}_{m} = RT ln (CMC/288.4/55.6) for SDS – CM system and ΔG^{o}_{m} = RT ln (CMC/364.5/55.6) for CTAB – CM mixed micellar system. ΔS^{o}_{m} has been calculated by the well known thermodynamic relation $\Delta G^{o}_{m} = \Delta H^{o}_{m} - T\Delta S^{o}_{m}$ for both SDS – CM and CTAB – CM mixed micellar system. These parameters are shown in Table 4.

Table 4: Thermodynamic parameters of SDS – CM and CTAB – CM mixed in micellar system

Temp.	ΔG^{o}_{m} (kJ/mol)	ΔH^{o}_{m} (kJ/mol)	ΔS^{o}_{m} (Jk^{-1}/mol^{-1})
A) SDS-0.1 mM CM			
303	-38.3		122.27
313	-39.0	- 1.125	120.92
323	-40.1		120.27
B) SDS-0.2 mM CM			
303	-38.4		123.40
313	-40.1	- 1.00	124.92
323	-40.2		121.36
C) SDS-0.3 mM CM			
303	-38.3		121.22
313	-38.8	- 1.57	118.94
323	-39.6		117.7
CTAB-0.2mM CM			
303	-	44.6	133.99
313	- 45.9	- 4.0	133.86
323	- 47.0		133.12

It is clear from above data that formation of mixed micelle is favoured by negative values of free energy. Further, positive value of entropy of micellization serve as driving force and main cause for mixed micelle formation.

CONCLUSION

Cefprozil monohydrate aggregates within a particular concentration range. Its aggregations is assisted by surfactants like SDS and CTAB.

However, in the bed of drug aggregates SDS monomers have accommodation limit above certain concentration range. The micelle formation of SDS and CTAB in also assisted by the addition of CM in its premicellar range. But, in this case also this assistance is not regular at higher of concentration of CM for SDS – CM mixed micellar system. Thermodynamic parameters are favourable for SDS-CM and CTAB –CM mixed micelle formation.

ACKNOWLEDGEMENTS

Authors are thankful to Principal, RIE, Bhopal for providing laboratory facilities. Lupin Limited, Mandideep is gratefully acknowledged for providing pure sample of CM.

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