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Surface and micellar properties of Clindamycine Phosphate in aqueous solution

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Abstract
This manuscript reports the solution and micellar behaviour of an antibiotic drug Clindamycine Phosphate (CLN) in aqueous media. Surface tension and specific conductivity were used to find the critical micelle concentration (CMC) and in this way its surface and thermodynamic parameters were calculated. The electrical conductivity was measured as a function of concentration at various temperatures and CMC was calculated in the temperature range of 20-50°C. Thermodynamic parameters i.e. standard free energy of micellization, ΔG_m^o standard enthalpy of micellization, ΔH_m^o and standard entropy of micellization, ΔS_m^o were calculated from CMC value using closed association model.
Keywords: Micellization, drug, surface tension, entropy, conductivity, free energy, enthalp.

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Introduction

The solution, thermodynamics and colloidal behavior of amphiphilic drugs largely depends on the nature of the aromatic ring system of their hydrophobic part, and they help to probe the relationship between molecular architecture and physicochemical properties. It is done by conducting study about the thermodynamics of their aggregation and the factors governing this process [1].

The objective of present study is to relate the physicochemical properties of drug with its molecular structure. The structural features of amphiphilic drugs influence their association pattern in aqueous solution. Drugs represent an interesting variety amphiphilic structure ranging from the ones which are easily recognized as typical surfactants, to more complex aromatic, heteroaromatic or fused ring structure. It is interesting to know that micellization is not only the way in which drug molecules form aggregates, albeit another one which amphiphilic molecules exhibit in solution. The typical surfactants have flexible hydrocarbon based hydrophobic group and clear separation of charges creating distinct polar and nonpolar regions. Their hydophobic parts easily intertwine to form aggregates. This type of association is called closed association or micellization. If this flexible hydrocarbon chain is replaced by rigid aromatic or heterocyclic rings, the way in which molecules are disposed within aggregates changes in such way that process of aggregation may no longer be regarded as micellization. A well-known illustration of this effect is association of cationic dyes and purines and pyramidines which associate by stacking process. Such association is generally known as continuous or open association and there is no equivalent to CMC. The amphiphilic drugs lie between these two extremes. Although their hydrophobic group is aromatic but they resemble pure surfactants because of having high degree of flexibility. The lack of flexibility of hydrophobic moiety is, although, a necessary criterion for continuous association, it is not the only structural requirement. Many drugs having rigid aromatic system show closed association or micellization because their charges are generally localized at a terminal group of relatively long side chain rather than delocalized in the ring system as is common in dyes. Drugs provide an opportunity to investigate factors which are responsible for type of association exhibited by amphiphilic molecules in solution. It is this respect of studies on colloidal properties of amphiphilic drug, Citalopram HBr, rather than any pharmacological consequence of colloidal behaviour, which are being emphasized in this paper [1-6].

We, in our previous work, have already studied solution and thermodynamic behaviour of anti allergic drug Certizine HCl [7], anti-depression drug Citalopram 2HBr [8] and antibiotic drugs Dexamethasone sodium phosphate [9], Chloroquine diphosphate [10] and Quinacrine 2HCl [11]. In this paper we have discussed how antibiotic drug Clindamycine Phosphate does behave in its aqueous solution. Fig. 1 displays structure of Clindamycine.

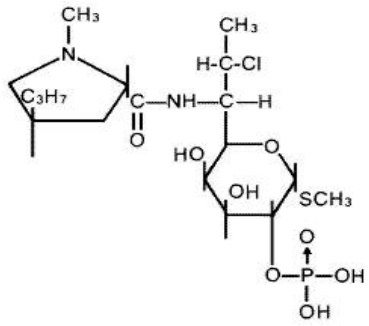

Fig. 1: Molecular structure of Clindamycine Phosphate.

Materials and Methods

Materials and preparation of solution

The antibiotic drug Clindamycine Phosphate (CLN) was obtained from Sigma Aldrich and used as received. Water was distilled using Water Still Apparatus Model IM-100 and then deionized by passing though Elga B114 deionizer. For measurement of surface tension and conductivity aqueous solution of each drug was prepared, in term of molality, in deionized water ranging from pre micellar to post micelle concentration.

Apparatus and methods

Surface Tension of aqueous solutions of drugs was determined using Torsion balance (White Elect. Inst. Co. Ltd) equipped with Platinum ring (4.0 cm circumference) along with water circulator (Irmeco I-1800) to control temperature at 30°C (303K). The instrument was kept free from vibrations. The torsion balance was checked for zero and calibrated with water. It is well known that critical concentration derived by surface tension is particularly sensitive to impurities. No minima were evidenced in this region of critical concentration which was proof of absence of surface active impurities [10].

Specific conductivities were measured with Jenway 4310. This instrument has auto ranging from 0.01 µS to 199.9 mS, conductivity control with accuracy of ± 0.5 % ± 2 digits and temperature control accuracy of 0.5°C. The electrode used has cell constant of 0.98 $cm^{-1}$and was coated with platinum black in order to avoid the polarization effect. The conductivities were measured at temperature range of 293-323K with increment of 10K. The temperature was controlled using water circulator (IRMECO I-2400 GmbH Germany). The electrode was calibrated using KCl over the appropriate concentration range.

Results and Discussion

Surface tension

For surface-active solute, the surface excess concentration can be considered to be actual surface concentration without significant error. For ionic surfactant Γ_2, can be determined by the application of Gibbs Adsorption Equation.

$$\Gamma_2 = -\frac{1}{2.303RTx}\left(\frac{d¥}{d\log m}\right)_T \qquad (1)$$

Where R is the gas constant, T the temperature in Kelvin. The variable x is introduced to allow for the simultaneous adsorption of cations and anions.

$$x = 1 + \left[\frac{m}{m + m_s}\right] \qquad (2)$$

Where m and m_s are concentrations of drug and added electrolyte, if any. The value of x is 2 in water and approaches to 1 in the presence of excess inert electrolyte. The area per molecule at interface (A) gives information about the degree of packing and orientation of adsorbed surfactant. Where $A = 1/N_A\Gamma_2$. The free energy of micellization (ΔG^o_{mic}) can be calculated by using the equation;

$$\Delta G_m^\circ = (1 + \sim)RT \ln X_{CMC} \qquad (3)$$

Where α is the counter ion binding , R is the gas constant having value 8.314 J $mol^{-1}K^{-1}$, T is the absolute temperature, X_{CMC} is CMC in term of mole fraction. The standard free energy of adsorption, ΔG^o_{ads} for pure surfactant solutions as well as mixed system can be calculated by using equation below.

$$\Delta G_{ads}^\circ = \Delta G_m^\circ - \frac{®_{CMC}}{\Gamma_m} \qquad (4)$$

Where $®_{CMC}$ is the surface pressure at critical concentration and is given by

$$®_{CMC} = ¥_\circ - ¥_{cmc} \qquad (5)$$

Here γ_o is surface tension of pure solvent and γ_{CMC} is that of surfactant solution at CMC.

A plot of surface Tension, γ, verses molal concentration (m) for CLN in water at 303K (Fig. 2) shows that surface tension remains constant below

inflection in plot signifying the formation of full Gibbs monolayer at air /solution interface.

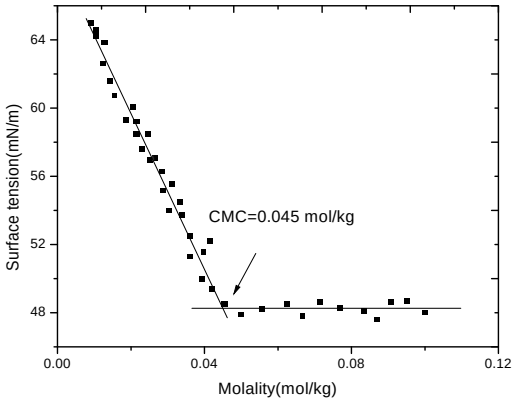

Fig. 2: Typical plot of Surface tension as a function of molality for aqueous solution of CLN at 303K.

The inflection in surface tension curve at 0.045 molkg^{-1} is in reasonable agreement with that detected by conductivity at 303K (0.0377 molkg^{-1}). It seems, in first glance, that both values are different but in actual practice it is accepted, by and large, that values of CMC vary to a certain extent according to what physical properties are considered to find the CMC. The slope of plot of γ against molal concentration below CMC concentration was used to compute an approximate value of minimum area per molecule in full surface monolayer, A, from the surface excess concentration, Γ. A value of minimum area of 2.24nm^2/molecule was calculated in this manner. Area per molecule at interface gives information about degree of packing and orientation of adsorbed amphiphilic molecule, when compared with the dimension of molecules obtained by molecular models. Table 1 shows the various parameters calculated from surface tension.

Table 1: Different parameters calculated from Surface Tension measurement of CLN at T=303K.

Surface Excess Concentration (Γ) ×10^7 mol/m^2	Minimum area per molecule (A) nm^2	Free Energy of Adsorption (ΔG_{ads}) kJ/mol	Free Energy of Micellization (ΔG_m) kJ/mol
7.43	2.24	-54.21	-22.52

The standard Gibbs free energy of adsorption (ΔG_{ads}) at 303K was calculated by equation 4 giving a value of –54.2 kJ/mol while value of free energy of micellization (ΔG_m) as calculated from equation (3) is -22.5 kJ/mol. The value of ΔG_{ads} is more negative than that of ΔG_m which indicates that process of adsorption is more spontaneous than micellization. Therefore surface adsorption takes place earlier than micellization [1-10].

Electrical Conductivity

Fig. 3 shows plots of electrical conductivity versus molality of CLN at different temperatures while typical plot of conductivity as a function of molality is visible in Fig. 4. The CMC values were determined from the intersection points.
Various parameters obtained from electrical conductivity of aqueous solution of CLN are given in Table 2 and discussed on following lines.

Table 2: Micellar and thermodynamic parameters calculated from Electrical conductivity of CLN at different temperatures.

$\frac{T}{K}$	$\frac{CMC}{molkg^{-1}}$	$\frac{\Delta H_m}{kJmol^{-1}}$	$\frac{\Delta G_m}{kJmol^{-1}}$	$\frac{\Delta S_m}{JK^{-1}mol^{-1}}$	α	β
298	0.0352	-34.52	-23.65	6.93	0.29	0.71
303	0.0377	-35.68	-23.66	3.55	0.29	0.71
308	0.0383	-36.87	-23.84	1.38	0.28	0.72
313	0.0411	-38.08	-23.92	-1.7	0.27	0.73

The values of CMC increase with temperature, which is due to greater degree of hydrophilic dehydration rather than hydrophobic dehydration. Hydrophilic ends, thus, get exposed to each other and repulsion between them increases which increases CMC. The negative value of ΔG_m and positive value of ΔS_m point toward the spontaneous nature of micellization. The negative value of ΔS_m at 323K show more organized behaviour of molecules in micellar form than in free state [11-14].

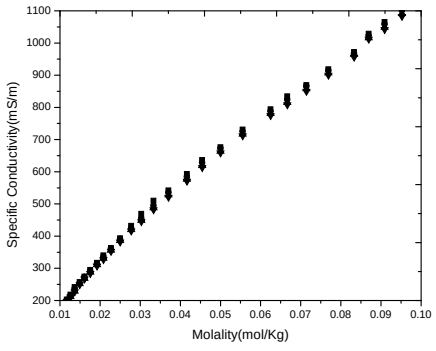

Fig. 3: Plots of Electrical Conductivity versus molality for aqueous solution of CLN at 293K (■), 303K (●), 313K (▲) and 323K (▼).

Positive value of ΔS_m is primarily responsible for spontaneous nature of micellization. The process of micellization is shown by the equilibrium $nS \leftrightarrow S_n$. At first glance

positive value of entropy looks unforeseen because above equilibrium shows that there is decrease in number of independent kinetic units during micellization. So value of ΔS_m should be negative. The problem is that actually we have ignored what happens to water structure during micelle formation. The reason behind this entropy increase is the extensive hydrogen bonding in water.

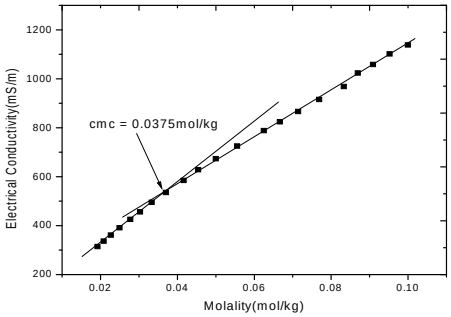

Fig. 4: Typical plot of Electrical Conductivity versus molality for aqueous solution of CLN at 303K.

Water molecules have tetrahedral structure with oxygen atom at center while two hydrogen atoms and two lone electron pairs are at corners of tetrahedron. A loose network is formed between water molecules due to hydrogen bonding between hydrogen atom of one molecule and lone pair of other. This network keeps on breaking and reforming at various points due to thermal fluctuation but at equilibrium a high average level of hydrogen bond prevails. When amphiphilic molecules are added in water no hydrogen bond develops between water molecules and hydrophobic part of amphiphile so it behaves as if it is embedded in water merely occupying a hole in water structure. During formation of holes or cavities hydrogen bonding between water molecules is broken and the molecules at the surface of cavities regenerate hydrogen bonding and, as a result, become more ordered around hydrophobic groups with decrease in entropy. On micelle formation hydrophobic groups are removed from water into micellar environment and cavities revert to the structure of pure water. The highly ordered water molecules at surface of so called cavity become disordered with an increase in entropy [10-14].

Conclusions

Surface and bulk properties of Clindamycine have been studied from surface tension and specific conductivity measurements. The clear inflection in physicochemical properties (Surface tension and conductivity) versus concentration plot, at CMC, is indicative of its amphiphilic behaviour having flexible hydrophobe and charges being localized at a terminal group. The value of CMC obtained by surface tension is 0.045mol kg^{-1} at 30°C while the conductivity data shows 0.038 mol kg^{-1} as CMC at the same temperature. The value of CMC increases with temperature because at high temperature the degree of hydrophilic dehydration is greater than hydrophobic dehydration which disfavors micellization and hence increase in CMC. The ΔG_m° values of drug are negative and become more negative at high temperature showing that the process of micellization becomes more spontaneous with temperature. The positive value of ΔS_m° and negative value of ΔH_m° indicates that micellization is both entropy as well as enthalpy driven and is equally supported by both hydrophobic and electrostatic interactions. The positive value of ΔS_m° is due to removal of hydrophobic parts of drugs from aqueous environment to micellar core which destroys ordered water structure around them and enables them to get rid of mobility constraints. The negative value of ΔH_m° displays that hydration of hydrophilic groups is more important than destruction of water structure around hydrophobic groups.

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