THERMODYNAMIC BEHAVIOUR OF BILE SALTS WITH DISPRINE

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***Abstract*-**The complex behavior of Bile salt -Sodium cholate (SC) and Sodium deoxycholate (SDC) has been studied in presence of disprine at temperature range 300K by conductivity method.
Critical micelle concentration (CMC), extent of counter ion binding (α), thermodynamic parameters (ΔG°, ΔH°, ΔS°) for micellization process have been reported and discussed and Menger and Portnoy's and Piszkiewicz models are also applied. In order to develop colloidal drug carriers with desired properties, it is important to determine physico-chemical characteristics of these systems. Bile salt mixed micelles are extensively studied as novel drug delivery systems.

***Keywords*-**Bile salt -Sodium cholate (SC) and Sodiumdeoxycholate (SDC), CMC, Disprine, conductivity method.

I. INTRODUCTION

Bile salts are essential for the dissolution of cholesterol. Sodium cholate and sodium deoxycholate are some important anionic type of surfactants, in other words it is also known as bile salt. It is a steroidal detergent, which together with lipids/ fats/ cholesterol forms mixed micelles in the intestine to enable fat digestion and absorption through the intestinal wall. They are bio-synthesized from cholesterol in the liver and stored in gall bladder. The role of the bile salt [Sodium choalte (NaC) and Sodium deoxycholate (NaDC)] as physiological surfactant is based on their micelle forming properties [1, 2]. The molecular structure of bile salts, having hydrophobicity due to the steroid ring system and hydrophilicity due to the hydroxy and carboxy groups, provides them aggregating ability. The aggregation behavior of bile salts is, however, different from that of conventional head-and-tail type surfactants. Bile salts form primary aggregates due to hydrophobic interactions in which the hydrophobic surfaces face each other and the hydrophilic groups point outward toward the aqueous phase. As the bile salt concentration increases, secondary aggregates are formed due to hydrogen bonding between the hydroxy groups [3]. This is a generally accepted model for bile salt aggregates and these aggregates are also called facial micelles. In the second model, a helical structure of bile salt micelles in polar solvents has been proposed, in which the hydrophobic surfaces of the bile salts are oriented outward toward the aqueous phase. Micellar systems can solubilize poorly soluble drugs and thus increase their bioavailability, they can stay in the body (blood) long enough to provide gradual accumulation in the required area, and their sizes permit them to accumulate in areas with leaky vasculature. An important property of micelles with particular significance in pharmacy is their ability to increase the solubility of poorly soluble drug in water, this increase their bioavailability. The micellar soulibilization is a powerful alternative for dissolving hydrophobic drugs in aqueous environments. In this work, the soulibilization of drug was studied in micellar solutions of surfactant, namely Sodium Cholate (SC). The solubility of various drugs increased linearly with increasing surfactant concentration, as a consequence of the association between the drug and the micelles. The oral administration is the most frequently used route for drug administration and usually intended for systemic effects resulting from drug absorption through the various mucosa of gastrointestinal tract. In current formulations, the oral dosage forms are tablets, must have disintegrate after contact with body fluid, and reach into the blood stream. Since a drug must normally be in solution before absorption can take place, drug gives via orally administered tablets must dissolve in the contents of the gastrointestinal tract before systemic absorption can occur. Often the rate of drug absorption is determined by the rate of dissolution from the tablet. [5]. Dissolution provides valuable information about bioavailability of the drug. It is considered to be one of the most important quality control tests performed on pharmaceutical dosage form.Critical micelle concentration of the Anionic bile salts SC in aqueous solution was determined by conductometric method. Purpose of the present work is to investigate the dissolution and complex behavior of various drugs in presence of bile salts.

In the present work, micellization of bile salt (SC and SDC) in pure and aquo-organic solvent mixture has been measured by surface tension and conductometric methods.

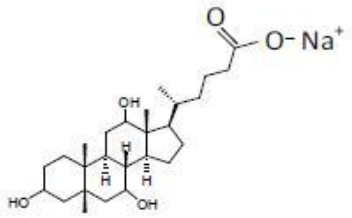


Fig.1 Sodium cholate

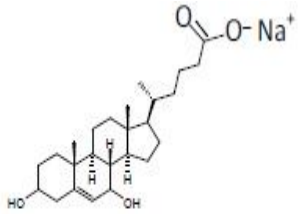


Fig.2 Sodium deoxycholate

As a part of programme dealing with the micellization of novel surfactants in presence of various drugs. [2,6,7], here we report the effect of various drugs like Disprine, Antideprassnt drugs at temperature range 300K and thermodynamic parameters of micellization (ΔG°, ΔH°, ΔS°), critical micelle concentration (CMC), extent of counter ion binding (α), were obtained by applying conductometric method. Our aim was to obtain basic knowledge about the importance of bile salt in dissolution of drugs by adsorption and micellization characteristics and since they behave differently from conventional surfactants due to formation of facial micelles.

2 Experimental

2.1 Materials-

The anionic bile surfactants sodium cholate was produced from LOBA Chemic. Drugs like Disprine. Solutions were prepared in triple distilled water.

2.2 Conductance measurement-

Step 1- Conductometric measurements were done with the help of Systronic direct reading conductivity meters (Model number 306). Appropriate temperature (± 0.01ºC) was maintained over the range of 300K. The errors in conductance measurement were within (± 0.5%). The conductometer was calibrated with KCl solutions of the appropriate concentration range. The conductance was measured after through mixing and temperature equilibrium at each dilution. The temperature setting remained undisturbed throughout whole investigation. Step 2- critical micelle concentration (CMC) and counter ion dissociation (α) determination- CMC of sodium cholate and sodium deoxycholate in aquo-organic solvents determined by graph plotting between specific conductivity versus surfactants concentration. The intersection point between the two straight lines gave the CMC and α is determined from the ratio of the post micellar and pre micellar slopes of the plot.

Step 3- Determination of thermodynamic parameters- The thermodynamic of micellization (ΔG°, ΔH°, ΔS°) were calculated using equation derived from the mass action model.

Fig 1.1

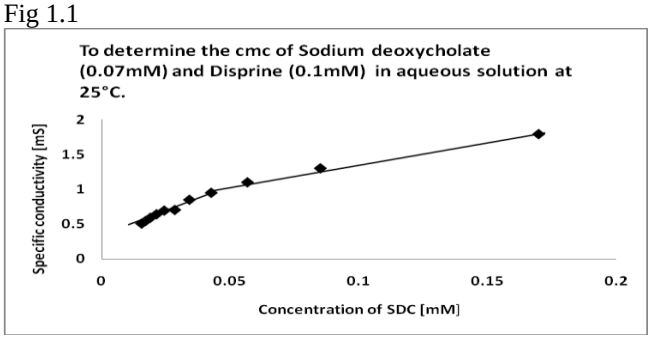


Fig 1.2

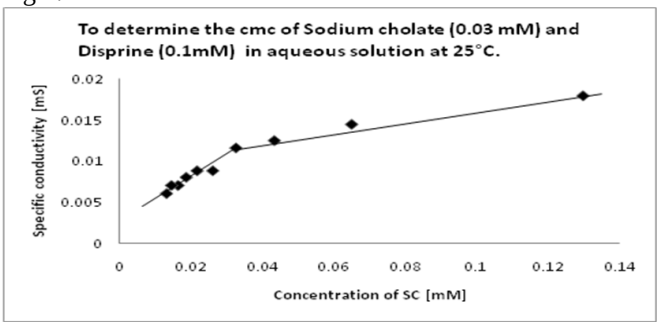
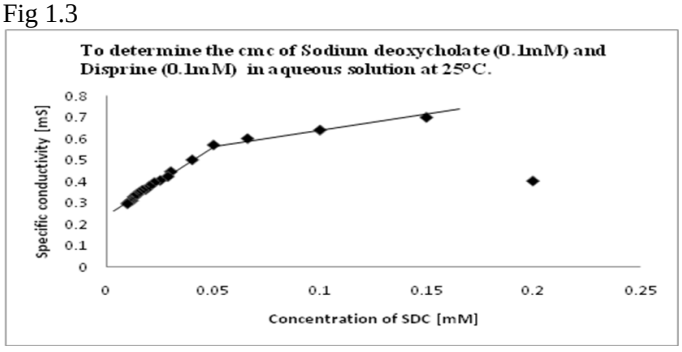


Fig 1.3

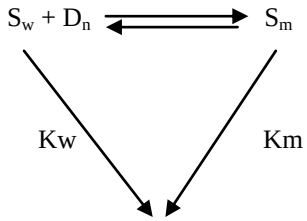


3 Result and discussion

The present study provides an insight into the mechanism of interaction of bile salts with various drugs like disprine. Based on the experimental findings it is possible to propose the concentration ranges involved with different stages of changes in the solubilisation of drugs by NaDC. The experiments showed that the concentration of a bile salt needed to bring about a certain change in the drugs is strongly dependent on the absolute concentrations of bile salt and not on their molar ratio. The bioavailability of orally administered drugs can be influenced by interactions with food components and by physico-chemical conditions in the upper gastrointestinal tract. Normally, bile salts enhance the transport of lipophilic drugs across mucosal membranes. Bile salts are able to form stable mixed micelles consisting of fatty acids and phospholipids. Conventional micellar systems are known to solubilize lipophilic drugs having a low bioavailability.

Table 1 indicated that the dissolution rate of the drug like Disprine tablets increased when the surfactant added in the de-ionized water. The dissolution rate of the drug was increased when anionic surface-active agent added in the de-ionized water. It shows that even presence small concentration of bile salts is very helpful for the dissolution of various drugs.

The data of variation of the observed rate constants k_Ψ, with concentration of surfactants were analyzed by Menger and Portnoy's [9] and Piszkiewicz models [10]. A standard kinetic scheme for micellar catalysis is shown below.



Scheme 1

The model lead to the relationship,

$$\frac{1}{kw - k\Psi} = \frac{1}{kw - km} + \frac{1}{(kw - km)\,Ks\,([D] - CMC)}$$

Where kw and km are observed first order rate constant outside and inside micellar phase, respectively, Dn represents the micellized surfactants whose concentration is given by the total surfactants concentration D less than CMC (the monomer concentration remaining in the solution) values of anionic surfactants were determined conductometrically in kinetic conditions at room temperature and values for Bile salt and Disprine. A plot of the left hand side eqn (1) versus 1/ ([D] - CMC) shows fairly linear correlation. From the slope and intercept km and ks values were computed (table 2). The decrease in rate for this bimolecular reaction has also been treated by Piszkiewicz model. For the relation is valid.

$\text{Log } [(k_\Psi - kw) / (km - k_\Psi)] = n \log [D] - \log K_D$

The values of co-operativity index, n and K_D derived there from are summarized in Table 2.

If a reaction favorably takes place in the bulk aqueous phase, the rate constant for the reaction in on micellar phase (km) is nearly zero. The 'n' values obtained in the present study range between 0.80-0.45 (Table 2) indicating negative cooperatively, i.e. the first molecule bound to micelle makes it more difficult for the next to bind. Once there is sufficient surfactant to take all the substrate into micelle, addition of more surfactant merely increases the counter ion concentration and this counter ion inhibits approach of ionic reagents [11].

The thermodynamics parameters for micellization like Gibbs free energy (ΔG°), enthalpy (ΔH°), and entropy (ΔS°) can be derived from the temperature dependence of the cmc. The trends of this parameter Table 3 can give valuable insight in to the principle which governs the formation of micelle.

The Gibbs free energy of micellization $\Delta G^o m$ was calculated by using equation, Where R is gas constant, T is temperature and is cmc in mole fraction unit. The free energy decrease with rising temperature, this value show that the micellization process is spontaneous in aqueous solution with Disprine Table 3.

$$\Delta G^\circ_m = (2 - \alpha)\, RT \ln X_{cmc}$$

The standard enthalpy of micelle formation ΔH°_m can be derived by the Von't Hoff equation.

$$\Delta H^\circ_m = -(2 - \alpha)\, RT^2 \left(\frac{d \ln X_{cmc}}{dT}\right)$$

The result also shows that standard enthalpy of micellization for drug and bile salt mixture is negative which indicates that the micellization process is exothermic.

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shows that standard enthalpy of micellization for bile salt and drug mixture in aqueous solution is negative which indicates that the micellization process is exothermic.

The standard entropy of micelle formation was calculated from the obtained values of and equation and well known relationship

$$\Delta S^{o}_{m} = (\Delta H^{o} - \Delta G^{o}_{m})/T$$

The ΔS^{o}_{m} values are positive in all case, indicating that the micellization process is entropy dominated. [16].

4 Conclusion -

The cmc and α value of sodium cholate (SC) and sodium deoxycholate (SDC) in aqua solvent mixtures were determined. It was observed that both values were depending on concentration of solvent and temperature. It was observed that micellization tendency of SDC decrease in the presence of solvents. The thermodynamic parameters of the process of micellization have been calculated for each system. $\Delta G^{o}m$ is negative and becomes less negative with increase in concentration of solvent. This suggest the micellization formation is becomes less spontaneous with increasing amount of solvents.The entropy of micellization is positive indicated that the micellization process is somewhat entropy dominated.

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Table 1 Critical micellization concentration of mixed solution of SC and Disprine.

concentration of SC (mM)	Concentration of Disprine (mM)	cmc (mM)
0.1	0.1	0.06
0.09	0.1	0.056
0.08	0.1	0.045
0.07	0.1	0.04
0.06	0.1	0.0314
0.05	0.1	0.03
0.04	0.1	0.035
0.03	0.1	0.0325
0.02	0.1	0.0183
0.01	0.1	0.0275

Table 2 Kinetic parameters for pseudophase and Piszkicwicz

Concentration of SC	CMC (mM)	Menger and Portnoy's			Piszkiewicz models			
		C	Ks	R	C	n	K_D	r
0.1	0.06	7	97.9	0.98	6	0.83	0.09	0.98
0.09	0.056	6	71.56	0.99	5	0.57	0.0632	0.99
0.08	0.045	5	66.2	0.971	4	0.58	0.046	0.995
0.07	0.04	5	75.4	0.97	5	0.53	0.066	0.99
0.06	0.0314	4	64.5	0.997	4	0.47	0.041	0.985
0.05	0.03	3	58	0.921	4	0.48	0.052	0.991
0.04	0.035	3	67	0.976	5	0.61	0.041	0.983
0.03	0.0325	4	65.4	0.975	5	0.46	0.061	0.989
0.02	0.0183	4	47.0	0.95	4	0.57	0.05	0.992
0.01	0.0275	3	45.8	0.967	5	0.55	0.051	0.995

Table 3 Thermodynamic parameters for the micellization of sodium deoxycholate (SC) and Disprine in aqueous solvents at 300 Kelvin temperature.

Concentration of SC	Concentration of Disprine	cmc	ΔG^o_m (kj/mol)	ΔH^o_m (kj/mol)	ΔS^o_m (kj/mol)
0.01	0.1	0.0275	-36.5	-9.5	46.6
0.02	0.1	0.0183	-37.8	-8.6	51.1
0.03	0.1	0.0325	-28.0	-9.1	43.6
0.04	0.1	0.035	-37	-8.5	54.8
0.05	0.1	0.03	-32.6	-10.1	46.8
0.06	0.1	0.0314	-31.6	-9.4	42.9
0.07	0.1	0.04	-29.9	-9.7	55.6
0.08	0.1	0.045	-30.4	-8.1	46.1
0.09	0.1	0.056	-31.2	-8.3	64.2
0.1	0.1	0.06	-32.6	-8.1	53.2

