

Effects of Polymeric Surfactant on the Self-Assembly of Bile salts

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The synergistic interactions between bile salts (BS) and the Pluronic block copolymer (P123) in aqueous solution at various mole fractions were investigated using the surface tension technique to explore the appropriate sequestrant (Pluronic P123) for bile salt. The interaction parameters in the bulk and surface were evaluated using ideal mixing and regular solution models. The synergistic effects operating in these amphiphile mixtures were confirmed by the negative values of the interaction parameter and reduction in critical micelle concentration (*cmc*) values. Energetic parameters computed for bile salts and block copolymer mixtures were also discussed in detail.

Keywords: Bile salts, Pluronic, mixed micelle, synergism

1. INTRODUCTION

Mixed systems containing amphiphilic compounds and a biodegradable polymer are preferred over single component systems in several industrial formulations because of their better performance [1–4]. Copolymer and surfactant mixtures are used in many household and industrial products[5–7]. Pluronics or triblock copolymers have been extensively used in biomedical applications[8–10]. Due to their versatile molecular structure (Fig. 1) and non-toxicity, Pluronics have several applications, such as encapsulation and drug delivery. The main body of a Pluronic is composed of three units: the central hydrophobic part (polyoxypropylene, PPO) linked to the hydrophilic (polyoxyethylene, PEO) end parts. Because of their structure, they are amphiphilic molecules and their applications are based on self-assembly; in aqueous solutions, they can aggregate to form micelles.

Bile salts (BS) are natural, self-associating molecules found in the bile of vertebrates[11–13]. BS have a specific chemical structure composed of a concave hydrophilic (OH groups present) α -phase and convex hydrophobic β -phase (Fig. 2).

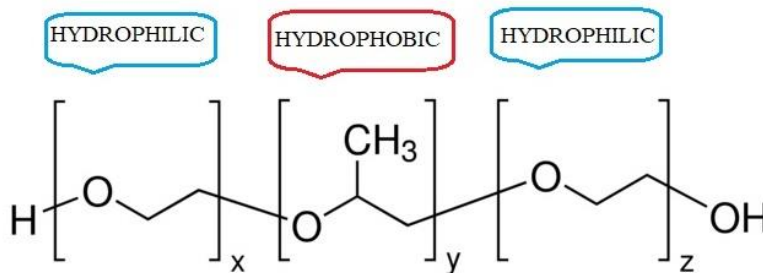


Figure 1. Chemical structure of Pluronic, P123 (x=20, y=70 and z=20).

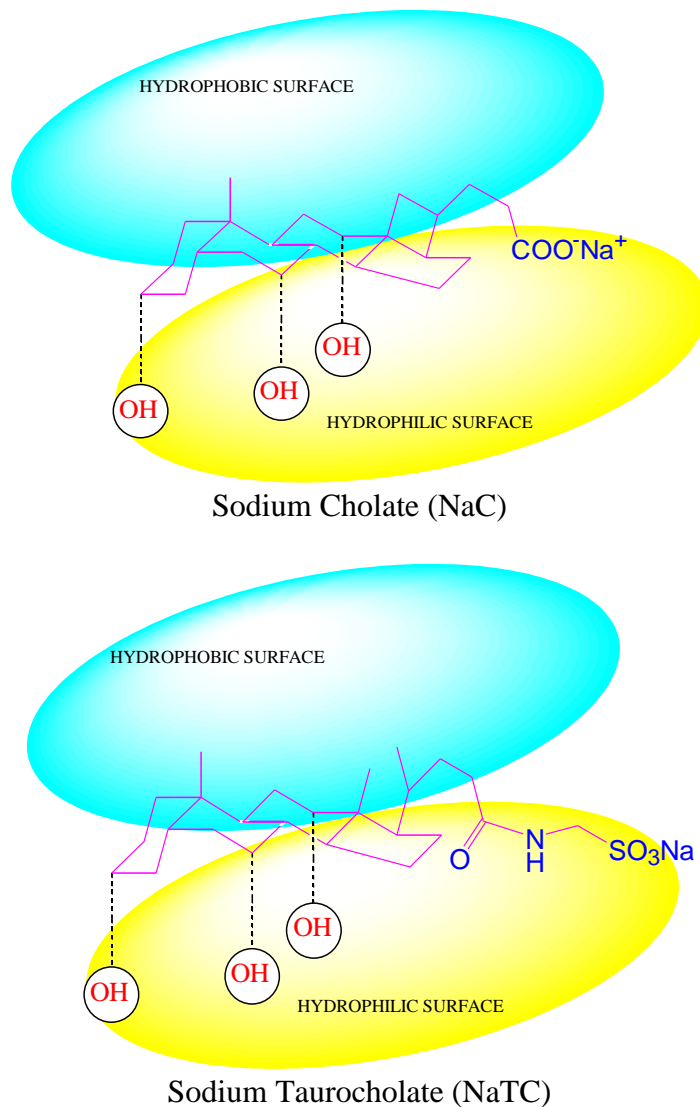


Figure 2. Chemical structure of bile salts.

This dual characteristic of BS is responsible for its surface activity, interfacial properties, and micelle formation. In aqueous solution, they are oriented such that the OH groups interact with the water molecules. The length and radius of a BS molecule are approximately 20 and 3.5 Å, respectively. Bile is synthesized from cholesterol and stored in the gallbladder. It is secreted into the duodenum to emulsify and solubilize fats from the food we eat. Then, 95% of the BSs are taken back into the bloodstream and

are prepared for a new cycle; this process is known as enterohepatic circulation (EHC). When EHC is interrupted, the situation stimulates BS production (bile acid diarrhea or bile acid malabsorption) and the excess BS passes into the large intestine. In contrast, when the cholesterol level is excessively high, a large amount of bile is required. Under both conditions, bile acid sequestrant could be used as a BS binding agent. In this context, we studied the physicochemical properties of BSs in the presence of a Pluronic (P123) copolymer to find a new potential sequestrant.

BS-polymer hybrid nano systems have garnered considerable attention, from an academic perspective as well as for industrial, biomedical, and pharmaceutical applications[14–16]. Reports of interactions between various types of Pluronic and different amphiphiles are available in the literature[17–19]. The mechanism of association of Pluronic micelles upon addition of conventional surfactants has been thoroughly explored by different techniques[17–22]. However, only a few studies have focused on the interaction between Pluronic and BSs. Herein, we aim to study the formation of new copolymer and BS amphiphilic nano systems capable of self-aggregation. These nanomaterials may be tested for potential drug delivery systems in the form of physical mixtures or in conjugation with a drug.

2. EXPERIMENTAL PROCEDURE

2.1. Materials and chemicals

The BS (sodium cholate, NaC and sodium taurocholate, NaTC) and Pluronic (P123) used in these experiments were the products of Sigma-Aldrich having purity ≥ 0.97 . No further purifications were involved, and all chemicals were used as received. We utilized ultra-pure de-ionized double-distilled water for all experiments. We crisscrossed the purity of water (specific conductivity 1 to 6 μScm^{-1}) by the conductivity. The software Origin (2018 version) is used to plot the graphs and Microsoft Excel was used to calculate the parameters.

2.2. Surface Tension Measurements

The surface tension experiments were carried out on an Attension automated force tensiometer (Sigma 701, Germany) followed by ring detachment. The instrument was calibrated at regular intervals using ultrapure water with a surface tension value of ~ 70 at 298.15 K. The temperature of the examined solution was maintained using a thermostat connected to the instrument. A tensiometer works on the Du Nouy principle proposed by the French physicist Pierre Lecomte du Nouy[23]. The surface tension measurement ring was cleaned in an ethanol flame before starting the experiment. A plot of the surface tension (γ) vs. logarithm of the amphiphile concentration was used to determine the *cmc* values of single and mixed amphiphilic systems (Fig. 3).

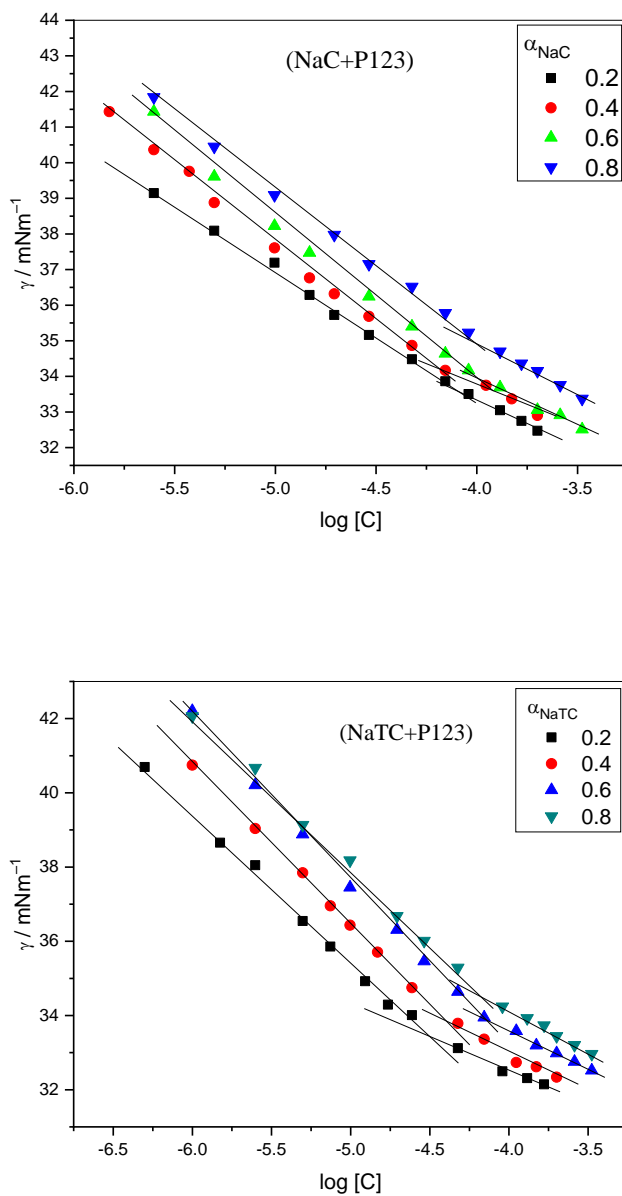


Figure 3. Plots of surface tension (γ) vs. log molar concentration of BS+Pluronic ($\log [C]$) mixed systems at different mole fractions of BS at 298.15 K.

2.3 Conductometry Measurement

The *cmc* values for bile salts were also determined by conductometry at 298.15 K. An Equiptronic system (EQ 661, India) with a temperature probe was used in these studies. The solutions were prepared in ultra-pure de-ionized double-distilled water. The electrode was washed with water after each reading. The plot of specific conductivity (κ) vs. molar concentration of BSs was used to obtain the *cmc* values (Fig. 4).

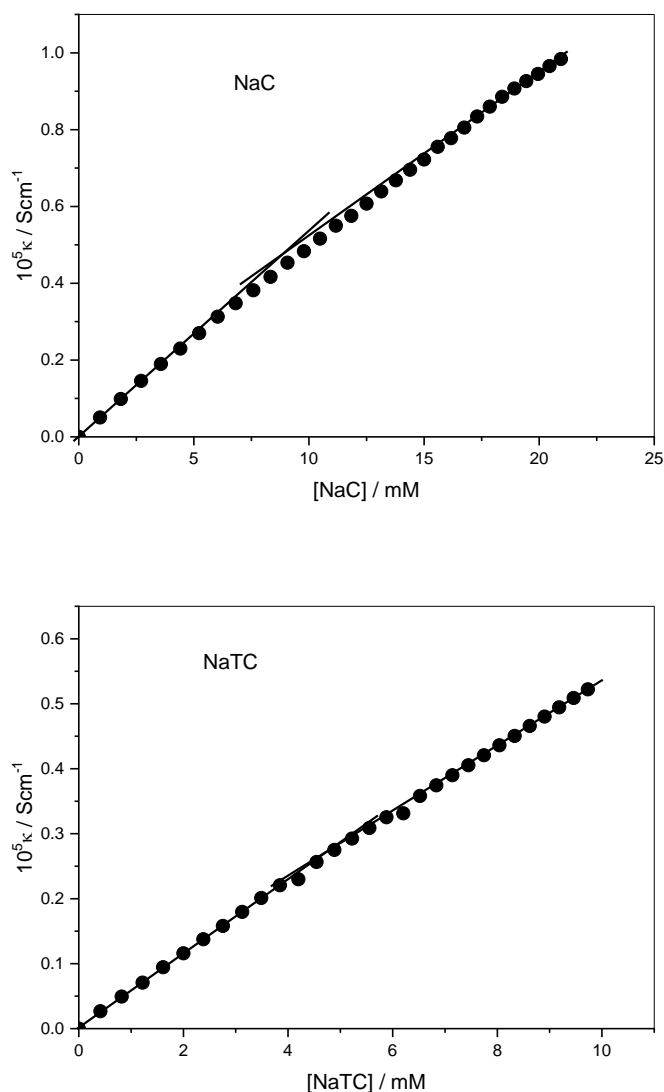


Figure 4. Plots of specific conductivity (κ) vs. molar concentration of bile salts at 298.15 K.

3. RESULTS AND DISCUSSION

3.1 Bile Salts – Pluronic Interactions in Mixed Micelles

The measurement of electrical quantities (potential, current, and charge) of a liquid solution in electrochemical analysis, provide the information about reaction kinetics of components and composition of the solution. Conductometry, potentiometry, voltammetry and coulometry are the main traditional techniques for electrochemical analysis. Out of these techniques, conductometry is the most important nonfaradic method depends on electric conductance of electrolyte solution (+ve and –ve charged species in solution). Conductometry is used where high purity of water is required due to the high sensitivity of the procedure. It is used to control the pollution of rivers and lakes and in oceanography to control the salinity of seawater. It is also used in oscillometry (high-frequency titration) and sensing (conductometric

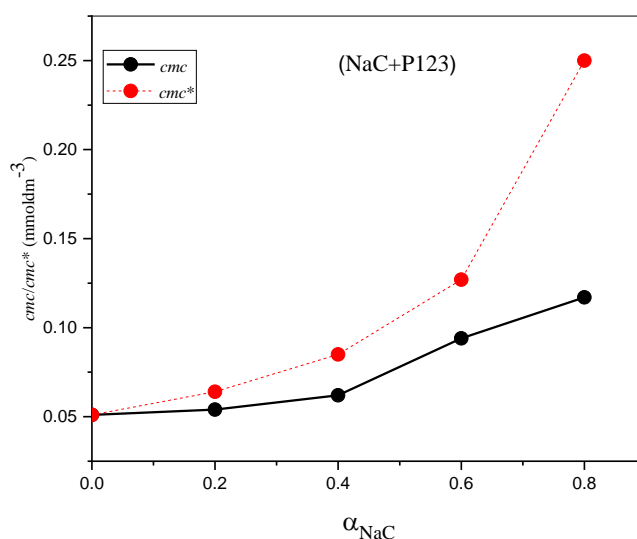
gas sensing and conductometric chemiresistors). The *cmc* values of NaC and NaTC were determined via conductometry. The computed *cmc* values were found to be 8.87 and 4.5 mM, respectively[24,25]. The conductivity measurements in case of Pluronic (P123) is not feasible because of nonionic nature. The *cmc* values of BSs, Pluronic, and their mixed systems were also determined via surface tension measurements. The surface tension values decreased linearly with the concentration of the amphiphile up to a certain point, following which there were no changes in the surface tension vs. concentration profile. At this point, the monomer aggregated, and the hydrophobic part of the molecule enclosed itself in a cage to avoid contact with water. Therefore, beyond this critical point (*cmc*), the surface tension values did not change. Both the BS's (NaC and NaTC) have higher *cmc* values than the Pluronic (P123) due to their complex structure. All the obtained *cmc* values are in good agreement with previously reported values[26–28]. The BSs formed mixed micelles in the presence of the Pluronic copolymer. The *cmc* values of the pure amphiphiles is related to the *cmc* values of the mixed systems by the following expression:

$$\frac{1}{cmc^*} = \frac{\alpha_i}{f_i cmc_i} \tag{1}$$

where f_i and α_i denote the activity coefficient and mole fraction, respectively. Assuming that the mixed micelles formed by two (or more) amphiphiles behave ideally, binary mixed system is described by the Clint equation [29,30]:

$$\frac{1}{cmc^*} = \frac{\alpha_1}{cmc_1} + \frac{\alpha_2}{cmc_2} \tag{2}$$

As the above equation was applicable for ideal mixed systems, the obtained *cmc* values (*cmc**) are reflected as ideal *cmc* values.



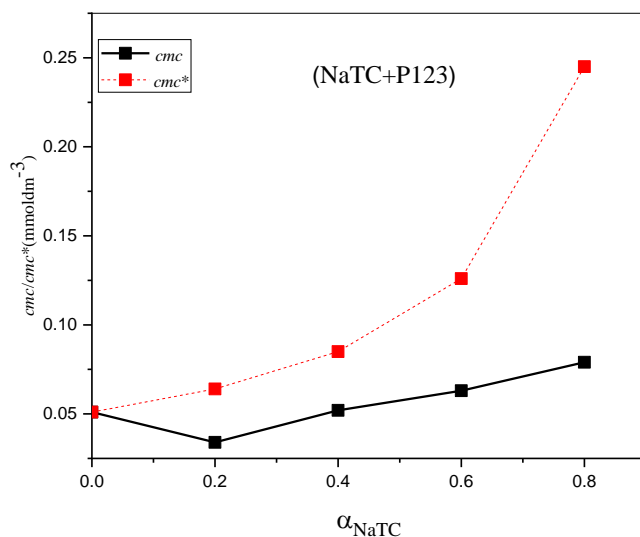


Figure 5. Plots of experimental cmc and ideal cmc (cmc^*) of BS+Pluronic mixed systems vs. mole fraction of BS.

The experimental cmc and ideal cmc values (cmc^*) are plotted against the mole fraction in Fig. 5. The ideal cmc values are evidently greater than the experimental values, confirming synergism in the mixed components. To understand the synergism or non-ideality between the mixed components, we applied the Rubingh model[31,32], according to which, non-ideality in the mixed system is a consequence of the attractive interaction among the monomers of the amphiphiles. The interaction parameter (β) can be calculated by the following equation:

$$\beta = \frac{\ln(\alpha_1 cmc / X_1 cmc_1)}{(1-X_1)^2} \tag{3}$$

where X_1 is the micellar mole fraction of component 1 (NaC/NaTC). The value of X_1 can be computed iteratively as

$$\frac{(X_1)^2 \ln(\alpha_1 cmc / X_1 cmc_1)}{(1-X_1)^2 \ln[(1-\alpha_1) cmc / (1-X_1) cmc_2]} = 1 \tag{4}$$

The ideal values of the micellar mole fraction can be computed using the Motomura theory[33,34]:

$$X_1^{ideal} = \frac{\alpha_1 cmc_2}{\alpha_1 cmc_2 + \alpha_2 cmc_1} \tag{5}$$

The values of β , X_1 , and X_1^{ideal} are listed in Table 1.

Table 1. Micellar parameters: experimental critical micelle concentration (*cmc*), ideal critical micelle concentration (*cmc**), micellar mole fraction (X_1), ideal micellar mole fraction (X_{ideal}), interaction parameter (β) and activity coefficients bile salts and P123 mixed systems at temperature $T = 298.15$ K.

α_{BS}	<i>cmc</i> (mmol · dm ⁻³)	<i>cmc*</i> (mmol · dm ⁻³)	X_1	X_{ideal}	$-\beta$	f_1	f_2
NaC + P123							
0	0.051						
0.2	0.054	0.064	0.106	0.001	5.614	0.011	0.939
0.4	0.062	0.085	0.160	0.004	5.761	0.017	0.863
0.6	0.094	0.127	0.165	0.008	4.688	0.038	0.880
0.8	0.117	0.250	0.274	0.022	6.208	0.038	0.627
1	9.000						
NaTC + P123							
0	0.051						
0.2	0.034	0.064	0.218	0.003	8.207	0.006	0.677
0.4	0.052	0.085	0.210	0.007	6.195	0.021	0.761
0.6	0.063	0.126	0.260	0.016	6.357	0.031	0.651
0.8	0.079	0.245	0.330	0.042	7.117	0.041	0.461
1	4.700						

The extent of interaction between the two mixed components is governed by β . Positive, negative, and zero values of β represent antagonism, synergism, and absence of interactions, respectively, between the two amphiphiles. The data (Table 1) show strong attractive interactions for both mixed systems, which are greater in the case of the NaTC + P123 mixed systems. The clear deviation in the values of X_1^{ideal} from X_1 also indicates synergism between the components of the current mixed systems. On increasing the concentration of NaC/NaTC, a large number of BS molecules take part in the formation of mixed micelles; thus, X_1 increases upon increasing the stoichiometric mole fraction of BS. The values of X_1 and X_1^{ideal} in Table 1 show that $X_1 > X_1^{ideal}$, which confirms that the BS contribute more toward the mixed micelles than in its ideal mixing state, while a smaller number of Pluronic molecules transfer from the solution to the micellar phase.

The activity coefficients of the mixed systems can be computed as[35–37]

$$f_1 = \exp[\beta(1 - X_1)^2] \quad (6)$$

$$f_2 = \exp[\beta(X_1)^2] \quad (7)$$

For the current mixed systems, the values of activity coefficients are less than 1 (Table 1), confirming that mixed micelles are formed at lower concentrations with high propensity.

3.2 Bile Salts – Pluronic Interactions at Surface

When surfactants or amphiphiles are dissolved in water, the hydrophilic part of the molecules is located in the aqueous phase while the hydrophobic hydrocarbon chains escape from the aqueous phase. The monomers of an amphiphile try to migrate toward an energetically favorable situation. The strong adsorption of monomers at the surface in the form of an oriented monolayer is known as a surface activity. It is a dynamic phenomenon where a balance is maintained between the expansion of the surface (due to the packing of the molecules) and contraction due to the surface tension.

Table 2. Surface parameters: molar concentrations (C^S), micellar mole fraction at surface (X_1^S), interaction parameter at surface (β^S), surface excess (Γ_{max}), minimum area per molecule (A_{min}), minimum area per molecule at ideal conditions (A_{ideal}), surface tension at cmc (γ_{cmc}), and surface pressure at the cmc (π_{cmc}) of bile salts and P123 mixed systems at temperature $T = 298.15$.

α_{BS}	$10^5 C^S$ (mmol · dm ⁻³)	X_1^S	$-\beta^S$	$10^6 \Gamma_{max}$ (mol · m ⁻²)	A_{min} (nm ²)	A_{ideal} (nm ²)	γ_{cmc} (mN · m ⁻¹)	π_{cmc} (mN · m ⁻¹)
NaC + P123								
0	0.141			0.680	2.442		34.32	35.68
0.2	0.012	0.354	28.404	0.453	3.669	2.092	33.58	36.42
0.4	0.042	0.320	21.129	0.515	3.223	2.126	34.23	35.77
0.6	0.069	0.320	19.156	0.561	2.959	2.126	33.97	36.03
0.8	0.091	0.360	20.536	0.502	3.305	2.086	34.98	35.02
1	912			1.138	1.458		45.37	24.63
NaTC + P123								
0	0.141			0.680	2.441		34.32	35.68
0.2	0.071	0.580	58.275	0.478	3.476	1.997	33.29	36.71
0.4	0.148	0.595	54.109	0.528	3.141	2.040	33.53	36.47
0.6	0.269	0.610	51.913	0.552	3.009	2.040	33.94	36.06
0.8	0.339	0.630	54.129	0.518	3.205	1.99	34.30	35.696
1	490			1.396	1.189		40.47	29.527

Thus, the surface pressure at the cmc can be calculated by the following relation:

$$\pi_{cmc} = \gamma_0 - \gamma_{cmc} \quad (8)$$

where π_{cmc} , γ_0 , and γ_{cmc} are the surface pressure, surface tension of water, and surface tension at the *cmc* value, respectively. The π_{cmc} values for the pure and mixed systems are given in Table 2.

It is evident that the BS + P123 mixture has higher π_{cmc} values than pure BS; this is because the mixed system causes a larger decrease in the surface tension values and is favorably adsorbed at the air/water interface. NaTC is slightly more surface active than NaC, but in the mixed micelles, both salts have the same tendency to lower the surface tension of water.

The extent of adsorption of amphiphiles at the surface is expressed in terms of surface excess concentration. This is the quantity of amphiphiles adsorbed per unit area of the surface at the *cmc*. The maximum surface excess values, Γ_{max} , related to the surface tension values in the Gibbs equation may be expressed as [7,10,38,39].

$$\Gamma_{max} = -\frac{1}{2.303nRT} \left(\frac{d\gamma}{d\log(c)} \right)_T \quad (9)$$

where R is the universal gas constant, T is the temperature in Kelvin, $\left(\frac{d\gamma}{d\log(c)} \right)$ is the slope of the surface tension vs. log concentration plot near the *cmc*, and n is the number of ionic species at the surface. The value of n is 1 for P123 since the Pluronic behaves as a nonionic surfactant. However, for BS, the value of n is 2. For mixtures, n is calculated using the equation $n = n_1X_1^S + n_2X_2^S$, where n_1 and n_2 are the numbers of species of two pure amphiphiles, and X_1^S and X_2^S are the molar fractions of BS and P123 amphiphiles in the mixed adsorbed mono layers at the surface, respectively. The values of X^S can be obtained by solving the following equation iteratively [13,40]:

$$\frac{(X_1^S)^2 \ln(\alpha_1 C_{exp}^S / X_1^S C_1^S)}{(1-X_1^S)^2 \ln[(1-\alpha_1) C_{exp}^S / (1-X_1^S) C_2^S]} = 1 \quad (10)$$

In the above equation, C_1^S , C_2^S , and C_{exp}^S are the molar concentrations of BS, P123, and the mixture, respectively. In all cases, the surface excess values are positive, indicating that the amphiphiles are favorably adsorbed at surface. The mixed systems studied herein formed a less compact monolayer owing to the lower surface excess values for mixtures than the pure amphiphiles. The average area occupied by an amphiphile at the surface may be calculated from Γ_{max} as [41,42]:

$$A_{min} = \frac{10^{18}}{N_A \Gamma_{max}} \quad (11)$$

where N_A is Avogadro's number (6.022×10^{23}). The values of A_{min} (Table 2) for the mixtures are larger than that for single components, contributing to the dissimilarity, such as the interaction between hydrophobic and hydrophilic groups in the mixed adsorbed layer. Similar results have been reported [41,43] for mixtures of cationic and nonionic surfactants. The minimum area per molecule under ideal conditions (A_{ideal}) can be evaluated by the following equation:

$$A_{ideal} = X_1^S A_1 + X_2^S A_2 \tag{12}$$

Table 2 confirms that the current mixed system has a higher A_{min} at most mole fractions than A_{ideal} . The reason for this enlargement is the weak positive charge on the oxyethylene chains in the presence of an anionic amphiphile. Zhou and Rosen[44] also reported similar results for ionic and nonionic mixed micelles.

Similar to the interaction parameter in the bulk, the interaction parameter at the surface can be evaluated by the equation

$$\beta^S = \frac{\ln(\alpha_1 c_{exp}^S / X_1^S c_1^S)}{(1 - X_1^S)^2} \tag{13}$$

The values of the interaction parameter (β^S) along with micellar mole fraction (X_1^S) at the surface are reported in Table 2. The increase in values of X_1^S with the mole fraction of BS confirms that a greater number of bile salt molecules are present in the mixed monolayer. The negative values of β^S confirm the synergistic interactions in the mixed monolayer. The β^S values are higher than β , confirming that the synergism at the surface is greater than that of the solution.

3.3 Thermodynamic Properties of Bile Salt–Pluronic Mixtures

To obtain more information related to BS-Pluronic interactions, the thermodynamic parameters were computed and examined. The standard Gibbs free energy of micelle formation can be calculated based on the pseudo-phase model[36,44,45]

$$\Delta G_m^o = RT \ln X_{cmc} \tag{14}$$

where the cmc is expressed in mole fraction unit, R is the gas constant, and T is the temperature in Kelvin. The obtained values are listed in Table 3.

Table 3. Thermodynamic parameters: free energy of micellization (ΔG_m^o), excess Gibbs energy of mixing (ΔG_{ex}), free energy of adsorption (ΔG_{ads}), and minimum free energy of a surface (G_{min}) of bile salts and P123 mixed systems at temperature $T = 298.15$ K.

α_{BS}	$-\Delta G_m^o$ (kj · mol ⁻¹)	$-\Delta G_{ex}$ (kj · mol ⁻¹)	$-\Delta G_{ads}$ (kj · mol ⁻¹)	G_{min} (kj · mol ⁻¹)
NaC + P123				
0	34.431		86.901	50.470
0.2	34.311	1.318	114.794	74.207
0.4	33.962	1.918	103.397	66.446
0.6	32.918	1.603	97.132	60.542
0.8	32.238	3.059	102.099	69.636
1	21.621		43.263	39.866

NaTC + P123				
0	34.431		86.901	50.470
0.2	35.452	3.466	112.311	69.698
0.4	34.407	2.546	103.423	63.451
0.6	33.928	3.030	99.278	61.507
0.8	33.3407	3.898	102.246	66.218
1	23.231		44.374	28.980

The ΔG_m^o values for the mixed system are more negative than that for the single components, confirming that the formation of the mixed micelle is favorable. Alternatively, ΔG_m^o can be translated into the standard free energy of adsorption (ΔG_{ad}^o) at the surface using the equation

$$\Delta G_{ad}^o = \Delta G_m^o - \frac{\pi_{cmc}}{\Gamma_{max}} \tag{15}$$

where the surface pressure at *cmc* is represented by π_{cmc} . Moreover, the ΔG_{ad}^o values indicate the transfer of hydrophobic chains in the molecules toward air from water and the modification in the degree of hydration of the hydrophilic part. The privileged adsorption of a molecule is governed by the higher and negative values of ΔG_{ad}^o . Thus, at the mixed adsorbed monolayer, there is no phase separation. In addition, the higher negative values of ΔG_{ad}^o than ΔG_m^o indicate that the interaction between amphiphiles at the surface is greater than that in the bulk. The ΔG_{ad}^o values for single amphiphiles are lower than that for the mixture, implying that the mixed systems are more favorable. A thermodynamic parameter, G_{min} , can be calculated to estimate the synergism in the mixed system[46,47]:

$$G_{min} = A_{min} \gamma_{cmc} N_A \tag{16}$$

G_{min} represents the work required to build a surface or the change in free energy related to the movement of monomers from the bulk phase to the surface in a solution. The low values of G_{min} are associated with the formation of a surface that is thermodynamically stable. The values also help to estimate the synergism in the mixed systems. The values of G_{min} listed in Table 3 validated the creation of energetically stable surfaces with synergistic interactions.

The excess Gibbs energy is given by[48,49]

$$\Delta G_{ex} = [X_1 \ln f_1 + (1 - X_1) \ln f_2] RT \tag{17}$$

The stability of a micelle can be monitored by a thermodynamic parameter, the excess Gibbs energy (ΔG_{ex}). The ΔG_{ex} values reflect the other parameters and the directional arrangement of the micelles. The higher the negative values of ΔG_{ex} , the more stable the mixed micelle. The NaTC/P123 mixed system had higher negative values of ΔG_{ex} than the NaC/P123 mixture, confirming the higher stability (Table 3).

4. CONCLUSION

The mixed system composed of BSs and Pluronic amphiphiles has garnered considerable attention from an academic point of view as well as for industrial, biomedical, and pharmaceutical applications. In order to understand their mixing behavior, we investigated the mixed micellization in the bulk as well as the surface. The following conclusions can be drawn:

1. The complex structure of BSs resulted in higher *cmc* values than those obtained for Pluronic (P123).
2. The ideal *cmc* values for the mixed system are higher than the experimental *cmc* values.
3. The interaction parameter values in bulk (β) and at the surface (β^S) are negative, suggesting a synergistic interaction. The β values are less negative than the β^S values.
4. $X_1 > X_1^{\text{ideal}}$, confirming that a smaller number of Pluronic molecules transfer from the solution to the micellar phase. However, in comparison with the ideal mixing state, the contribution of BS molecules in the creation of mixed micelles is greater.
5. The negative ΔG_m^o values are higher for the mixed system, implying that the formation of mixed micelles is favored.
6. The ΔG_{ad}^o values for individual amphiphiles are less than that of the mixture, which makes the mixture suitable for this process.
7. The formation of energetically stable surfaces exhibiting synergism was confirmed by the values of G_{min} .

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