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Synergistic Interaction and Binding Efficiency of Tetracaine Hydrochloride (Anesthetic Drug) with Anionic Surfactants in the Presence of NaCl Solution Using Surface Tension and UV–Visible Spectroscopic Methods

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Abstract: Surfactants are ubiquitous materials that are used in diverse formulations of various products. For instance, they improve the formulation of gel by improving its wetting and rheological properties. Here, we describe the effects of anionic surfactants on an anesthetic drug, tetracaine hydrochloride (TCH), in NaCl solution with tensiometry and UV–visible techniques. Various micellar, interfacial, and thermodynamic parameters were estimated. The outputs were examined by using different theoretical models to attain a profound knowledge of drug–surfactant mixtures. The presence of attractive interactions among drug and surfactant monomers (synergism) in mixed micelle was inferred. However, it was found that sodium dodecyl sulfate (SDS) showed greater interactions with the drug in comparison to sodium lauryl sarcosine (SLS). The binding of the drug with surfactants was monitored with a spectroscopic technique (UV–visible spectra). The results of this study could help optimize the compositions of these mixed aggregates and find the synergism between monomers of different used amphiphiles.

Keywords: tetracaine hydrochloride; sodium dodecyl sulfate; sodium lauroyl sarcosine; drug–surfactant mixed micelle; synergistic interaction

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1. Introduction

It is often observed that the surfactant mixtures (e.g., surfactant–co-polymer, surfactant–drug, and surfactant–surfactant) exhibit better performance than single surfactants [1–6]. It is also common to use mixtures of surfactants and polymers to formulate gels that are used in drug-dosage forms to improve their properties or to improve their physical stability [7]. The anionic surfactant used in this study, sodium dodecyl sulfate, has been used to synthesize nanogels [8]. SDS has shown better activity in the formation of microgels based on poly(N-isopropylacrylamide) [8]. The synergistic or antagonistic effects of binary mixtures are produced by attraction or repulsion between surfactant monomers. Synergism is observed when the molecular interaction between the monomers of a mixture is greater than before mixing. The strength of synergism between different types of surfactants follows the order of anionic–cationic > nonionic–ionic > ionic–ionic > nonionic–nonionic. The interaction between oppositely charged head groups and the hydrophobic interaction between chains of amphiphiles are the two main factors that are responsible for strong synergistic effects inside cationic–anionic mixtures [9–11]. Ionic–anionic mixtures become turbid (precipitation) at some mole fractions, producing lamellar phases and rod-like morphologies.

A lesser water solubility and the dissolution characteristics of a drug usually limit its bioavailability and therapeutic efficacy. The poor water-solubility of drugs may also

lead to disappointing and inconstant ingesting, which aggravates the complications of bioavailability and scarcity in the delivery of drugs. In addition, excessive dosages of drugs cause side effects such as vomiting, nausea, dizziness, and fatigue [12,13]. The development of increasing water solubility and improvements in encapsulation efficiency can enhance absorption, enhance bioavailability, and lower the required therapeutic dose [1,14,15]. Researchers have often studied different ways to increase solubilities, such as using small drug carriers, preparing nanoparticles, and using self-emulsifying formulations or amorphous formulations based on water-soluble polymers. A surfactant is a most-capable drug transporter in biomedical applications since it can be easily fabricated into different formulations such as micelles, hydrogels, and nanoparticles to enclose bioactive agents at several points of hydrophobicity [16–19]. Surfactants are polar molecules and contain both hydrophilic and hydrophobic components orientated at the surface to diminish the surface tension of water [20–22]. A micelle will only form when the concentration of the amphiphile is higher than a specific concentration (called the critical micelle concentration or cmc) that can be determined using diverse methods (surface tension, conductometry, fluorometry, UV–visible spectroscopy, cyclic voltammetry, and isothermal calorimetry) [23–26]. A valuable feature of these molecules is their cmc value. The cmc value depends on various aspects such as ionic strength, temperature, and the existence of additional compounds in the solution. Most chemical industries utilize surfactants, e.g., as pharmaceuticals, corrosion inhibitors, detergents, paints, and cosmetics [27–31].

Certain types of drugs, such as antidepressants, anticholinergics, antihistamines, and local anesthetics, are amphiphilic; they have surfactant-like properties and form micelles [32–35]. Invariably, their therapeutic activity is determined by how they interact with surfactants. Depending on their interactions in solution, any drug can be made more active. The mixed systems of many amphiphilic drugs have also been researched by our group using different techniques with different amphiphiles [36–45]. Tetracaine hydrochloride, TCH (Figure 1), is an amphiphilic compound that also possesses colloidal properties and is one of the most used local anesthetic drugs. It is used for stopping pain during surgery and eye infections. Since tetracaine is a poorly water-soluble compound, it is usually formulated as tetracaine hydrochloride. It has been hypothesized that the +ve charge on the drug, which is the functional component, interacts with the Na^+ channels on neuronal membranes and stops the transmission of the pain sensation along the nerve [46,47]. Furthermore, the cationic form provides an amphiphilic structure to such a drug, so it can be classified as a cationic tension-active molecule. Therefore, a TCH-like cationic surfactant undergoes an abrupt change above a critical concentration (cmc) and the Krafft temperature. The aqueous dissolution of tetracaine follows the same principle as all ionic surfactants (in that it is governed by both solubility and micellization). As a result, the nature of the surfactant, its counter ions, concentration, and temperature all affect the process. As the use of high concentrations of local anesthetic in spinal anesthesia is known to occasionally result in the sudden death of patients, it is important to understand how the micellization process occurs and what its phase diagram looks like.

In this work, surface tension and UV–visible measurements were carried out to examine the effects of anionic surfactants on a cationic drug. To the best of our knowledge, the mixed micellization of tetracaine hydrochloride (TCH) with sodium lauroyl sarcosine (SLS) and sodium dodecyl sulfate (SDS) in the presence of sodium chloride (NaCl) has not been previously described. Different theoretical approaches of mixed micellization (such as those by Clint, Rubingh, Rodenas, Rosen, and Motomura) were utilized to investigate the interactions of TCH + SDS/SLS mixtures. Various interfacial, micellization, and energetic parameters were analyzed. The output of this work can support the search for a surfactant-based carrier for drug delivery.

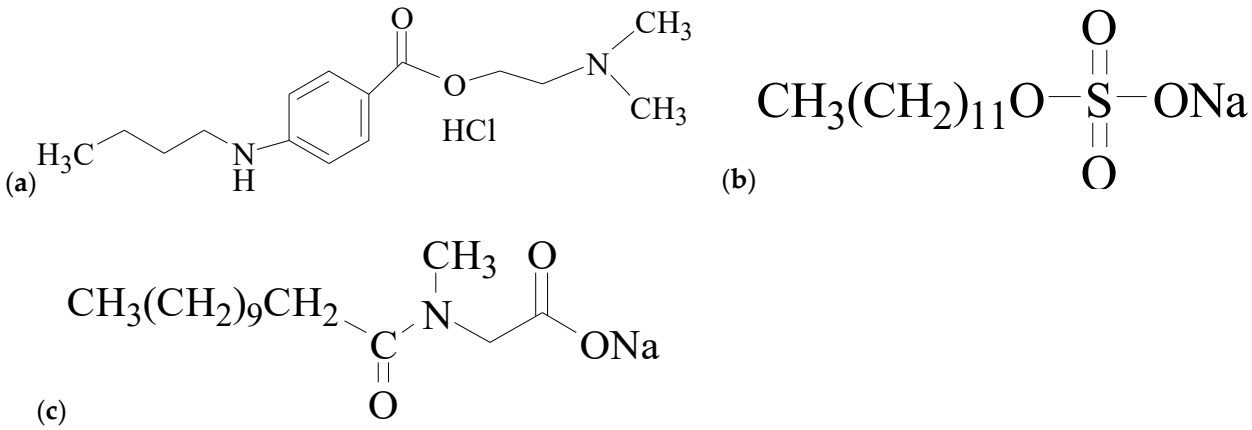


Figure 1. Chemical structures of (**a**) tetracaine hydrochloride (TCH), (**b**) sodium dodecyl sulfate (SDS), and (**c**) sodium lauryl sarcosine (SLS).

2. Result and Discussion

The stock solutions of numerous mole fractions (α_1) of component 1 (SDS/SLS) from 0 to 1 were prepared. As shown in Figure 2, the solution was turbid at some mole fractions (which barred the experiment), and we selected the mole fractions where no turbidity was observed. The surface tension (ST) measurements were used to estimate the cmc values of pure and binary mixtures of drugs and surfactants. Measurements of surface tension are widely used to provide authentic cmc values for all types of surfactants (cationic, anionic, and non-ionic). Illustrative ST graphs for the mixtures at different mole fractions of SLS in the presence of 100 mM NaCl at 298.15 K are displayed in Figure 3. The cmc values acquired via surface tension are listed in Table 1. As the surfactant molecules were mixed, a complex, which was more deeply adsorbed at the surface than single amphiphiles, was formed, thus suggesting an enhanced surface activity. The cmc values of single and mixed amphiphiles could be evaluated by the intersection of the linear fitting of the points (Figure 3). The cmc value of TCH was found to be 79.43 mM, which was lower than the values published by Miller et al. [48], who reported a value of nearly 100 mM without any salt. The cmc values of both employed surfactants in the existence of salt were also found to be less than those with a lack of salt. The values of cmc for currently employed surfactants in the presence of NaCl were in good agreement with the literature [49,50]. The obtained value of cmc for SDS in the presence of 100 mM NaCl was much lower than the cmc value computed by Thapa et al. [51] in an aqueous solution. When NaCl was added to the drug solution, the electrical atmosphere changed. The charge between the head group in the cationic drug became neutralized. Micelles could be formed at much lower concentrations in pure water because of the reduced electrostatic repulsion among the polar head groups. The cmc values for all mixtures unified in the center of two single amphiphiles, suggesting that the micellization of a drug was preferred in the company of surfactants. The observed decline in the cmc values of the mixture was due to the enrichment in the hydrophobic interaction among drugs and surfactants.

The whole study can be divided into two parts: (A) interactions of drugs with surfactants in the solution and (B) interactions of drugs with surfactants at the surface.

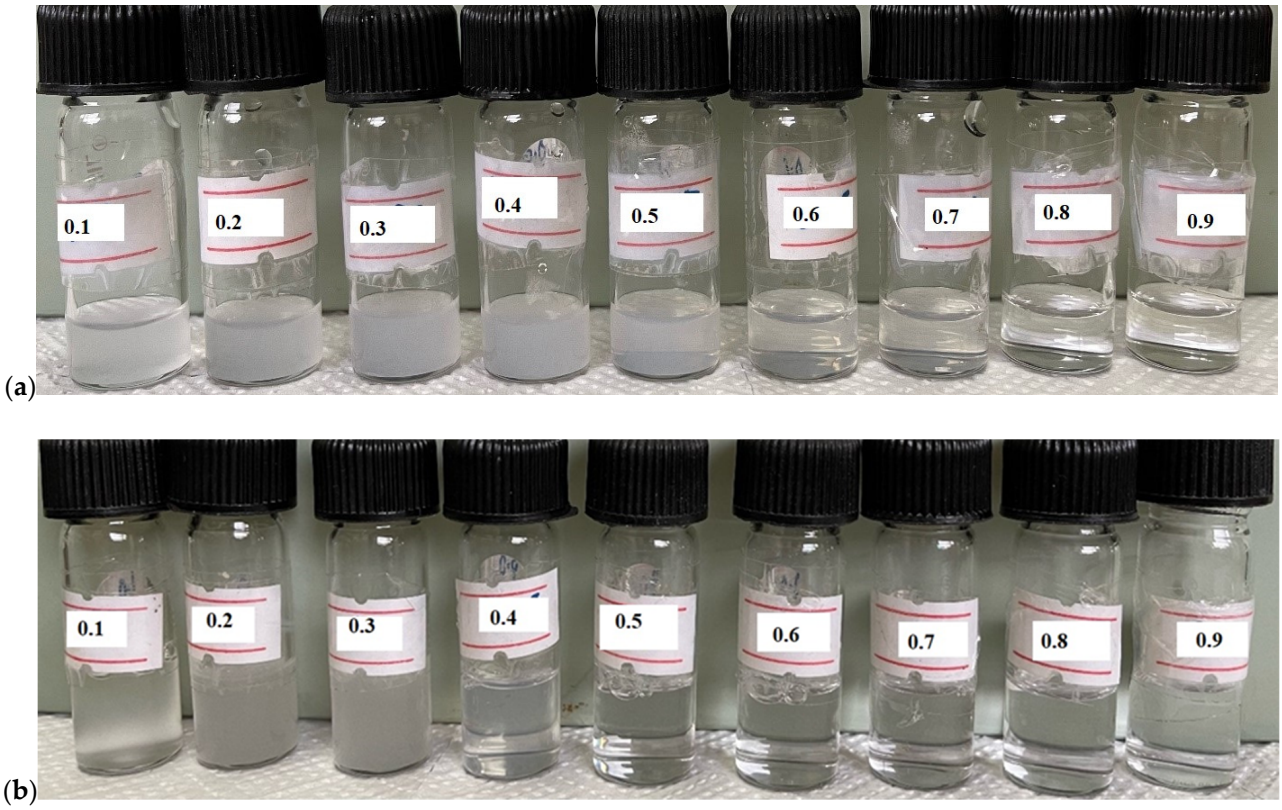


Figure 2. The physical appearance of TCH + SDS/SLS mixtures at different compositions: (**a**) SDS + TCH and (**b**) SLS + TCH.

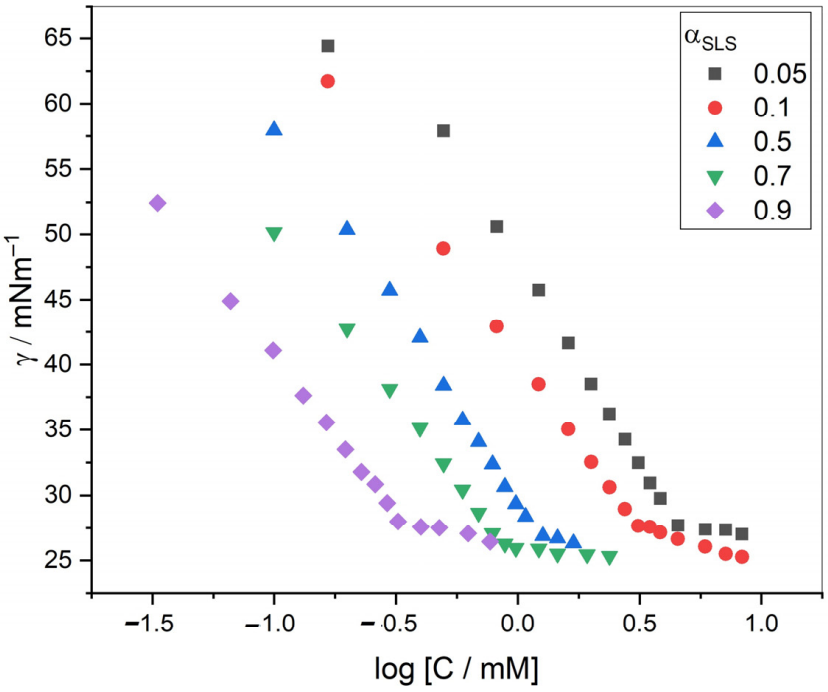


Figure 3. Graph of surface tension versus log molar concentration for SLS + TCH mixed systems.

Table 1. Physical parameters of TCH + SDS/SLS mixed systems in aqueous NaCl.

	cmc **(mM)**	***cmc**** **(mM)**	X_1^{Rub}	X_1^{ideal}	$-\beta^{Rub}$	f_1^{Rub}	f_2^{Rub}
			SDS + TCH				
0.0	79.43	-	-	-	-	-	-
0.05	0.37	16.42	0.54	0.80	16.04	0.033	0.0095
0.1	0.31	9.16	0.56	0.90	15.20	0.055	0.0081
0.7	0.13	1.45	0.65	0.99	15.72	0.139	0.0014
0.8	0.15	1.27	0.66	0.99	15.44	0.174	0.0011
0.9	0.12	1.13	0.67	0.99	17.11	0.156	0.0004
1.0	1.02	-	-	-	-	-	-
			SLS + TCH				
0.0	79.43	-	-	-	-	-	-
0.05	4.49	41.24	0.50	0.51	8.86	0.110	0.1078
0.1	3.05	27.85	0.53	0.68	9.09	0.139	0.0742
0.5	1.24	7.74	0.62	0.95	9.96	0.243	0.0207
0.7	0.79	5.68	0.64	0.98	11.81	0.212	0.0082
0.9	0.33	4.49	0.64	0.99	16.53	0.115	0.0012
1.0	4.07	-	-	-	-	-	-

Relative standard uncertainties (u_r) are $u_r(cmc/cmc^*)$ = 0.03, u_r (X_1^{Rub}/X_1^{ideal}) = 0.02, u_r (β^{Ru}) = 0.03, and u_r (f_1^{Rub}/ f_2^{Rub}) = 0.04.

2.1. Interactions of Drug with the Surfactants in the Mixed Micelle

Using Rubingh's regular solution theory (RST) for mixtures of amphiphiles [52], the cmc of a mixed system (*cmc**) can be calculated via Equation (1):

$$\frac{1}{cmc^*} = \frac{\alpha_1}{f_1 cmc_1} + \frac{\alpha_2}{f_2 cmc_2} \quad (1)$$

where f_1 and f_2 are the activity coefficients of the surfactant (SDS/SLS) and drug in mixed micelles, respectively, and α_1 represents the mole fraction of surfactant (SDS/SLS) in the total mixed solution. The cmc values of surfactants and drugs are cmc_1 and cmc_2, respectively. $f_1 = f_2 = 1$ if we assume ideal behavior, so Equation (1) becomes:

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

Equation (2) was proposed by Clint [53]. Using the Clint equation, we could judge the ideality or non-ideality of a mixed system. Figure 4 displays a plot of *cmc* (experimentally determined)/*cmc** (calculated with Equation (2)) vs. α_1 (SDS/SLS). The *cmc* values of both mixtures were decreased with increases in the α_1. According to one possible explanation, the mixture was more favorable than expected under an ideal condition because of the interactions among hydrophobic chains of amphiphiles.

In contrast, for non-ideal mixtures, a new theory has been established and is referred to as the Rubingh model [52]. The Rubingh model uses RST to relate the activity coefficients of components with micellar mole fractions of component 1 as follows:

$$f_1^{Rub} = exp\left[\beta^{Rub}\left(1 - X_1^{Rub}\right)^2\right] \quad (3)$$

$$f_2^{Rub} = exp\left[\beta^{Rub}\left(X_1^{Rub}\right)^2\right] \quad (4)$$

where β^{Rub} and X_1^{Rub} are the interaction parameter and micellar mole fraction, respectively of component 1. If two variables have values of less than 1, the mixing components are not ideal. When computing the β^{Rub} values (parameter based on the *cmc* values of each amphiphile and their mixtures), the nature and strength of the interactions between the two

surfactants are determined. Rubingh [52] derived the relationship shown in Equation (5) by considering the phase separation model for micellization.

$$\beta^{Rub} = \frac{\ln\left(\alpha_1 cmc / X_1^{Rub} cmc_1\right)}{\left(1 - X_1^{Rub}\right)^2} \quad (5)$$

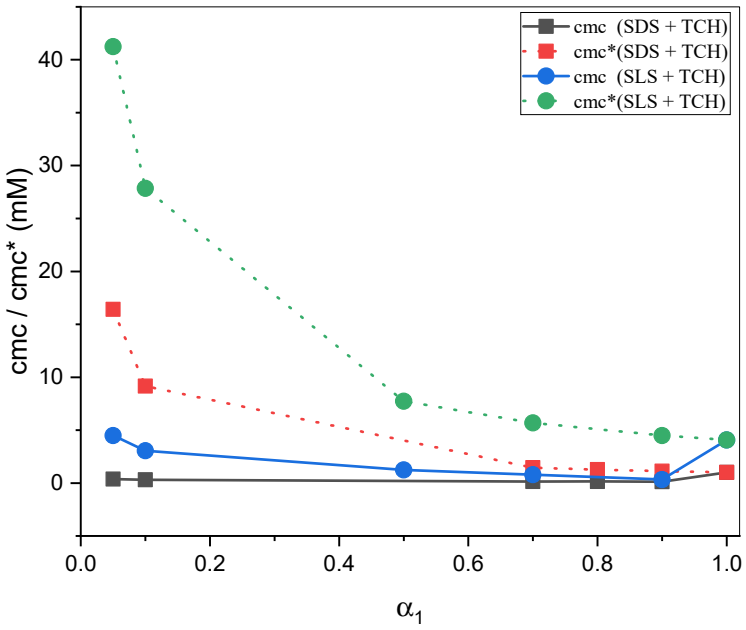


Figure 4. Experimentally determined critical micelle concentration (*cmc*) and ideal critical micelle concentration (*cmc**) against mole fraction of surfactants (SDS/SLS) in mixed systems at 298.15 K.

The micellar mole fraction of component 1 is represented by X_1^{Rub}, which is calculated by iteratively solving Equation (6):

$$\frac{\left(X_1^{Rub}\right)^2 \ln\left(\alpha_1 cmc / X_1^{Rub} cmc_1\right)}{\left(1 - X_1^{Rub}\right)^2 \ln\left[(1 - \alpha_1) cmc / \left(1 - X_1^{Rub}\right) cmc_2\right]} = 1 \quad (6)$$

It is commonly believed that the deviation from zero of the interaction parameters (β^{Rub}) is due to interactions among the amphiphile head groups. Positive divergence from zero indicates antagonistic behavior, and negative deviation indicates synergistic interactions between two components. Free energy subsidies associated with amphiphile head groups have been found to be the main sources of mutual interaction. When positively and negatively charged amphiphiles are assorted in water, the most noteworthy feature of this mixture is its unusually huge drop in cmc values. A mixture of anionic and non-ionic surfactants usually yields a nonconformity from ideal behavior (less negative β^{Rub}) and synergistic effects in the mixed micelles of two non-ionic amphiphiles are even to a lesser extent. In most cases, experimentally computed values of β^{Rub} for mixtures of positively and negatively charged amphiphiles are higher. According to Table 1, there were considerable interactions (synergism) between the current mixed systems. The synergism was detected because of the electrostatic interaction among +ve and –ve charged head groups. The β^{Rub} average values were – 15.90 and – 11.25 for SDS + TCH and SLS + TCH, respectively. The positive and negatively charged amphiphiles were found to be firmly tied to one another through electrostatic and hydrophobic forces, consequently leading to ultimate attraction that promoted the growth of micellar aggregates. The synergism between two amphiphiles depends not only on the strength of the interaction but also on

the individual amphiphile properties. The higher the hydrophobicity of an amphiphile, the easier it is to make micelles.

In a mixed system, the ideal micellar mole fraction of component 1 is represented by Equation (7) [54]

$$X_1^{ideal} = \frac{\alpha_1 cmc_2}{\alpha_1 cmc_2 + \alpha_2 cmc_1} \quad (7)$$

The values of X_1^{ideal} are given in Table 1. The values of X_1^{ideal} display nonconformity from the values of X_1^{Rub}, signifying non-ideality. The higher values of X_1^{ideal} for both binary mixtures at all mole fractions confirmed that added drug molecules replace some of the surfactant molecules from the mixed micelles, so the contribution of drug molecules is greater in mixed micelles than it should be in ideally mixed systems.

Thermodynamic Parameters for Drug–Surfactant Mixtures in the Mixed Micelle

Using RST, it is feasible to evaluate the free energy change for micellization in the following way [55–59]:

$$\Delta G_{mix} = RT[X_1^{Rub} ln(X_1^{Rub} f_1^{Rub}) + X_2^{Rub} ln\left(X_2^{Rub} f_2^{Rub}\right)] \quad (8)$$

If the values of activity coefficients (f_1^{Rub} and f_2^{Rub}) for an ideal mixed system are equal to unity, then Equation (8) becomes:

$$\Delta G_{mix}^{ideal} = RT[X_1^{Rub} lnX_1^{Rub} + X_2^{Rub} lnX_2^{Rub}] \quad (9)$$

where ΔG_{mix}^{ideal} is the free energy change for an ideal mixed system. Interestingly, the data (Table 2) show that the values were negative, implying that the micelles were spontaneously formed and were stable. If the values of ΔG_{mix}^{ideal} deviate from the values of ΔG_{mix}, rather than forming an ideal micelle, it then forms a real one. The literature confirms that previous investigators have observed the same behavior [60,61].

Table 2. Energetic constraints of TCH + SDS/SLS mixtures in aqueous NaCl [a].

α_1	$-G_{mix}^E/-\Delta H_m$ (kJmol^{-1})	$-\Delta G_{mix}$ (kJmol^{-1})	$-\Delta G_{mix}^{ideal}$ (kJmol^{-1})	$T\Delta S_m$ (kJmol^{-1})	$\lvert \frac{T\Delta S_m}{\Delta G_{mix}} \rvert$	$-\Delta G_m^o$ (kJmol^{-1})
			SDS + TCH			
0.0	-	-	-	-	-	16.23
0.05	9.87	11.78	1.71	6.40	0.54	29.48
0.1	9.27	11.15	1.69	6.32	0.57	29.93
0.7	8.90	10.69	1.61	6.01	0.56	32.08
0.8	8.54	10.29	1.58	5.88	0.57	31.79
0.9	9.36	11.12	1.57	5.89	0.53	32.34
1.0	-	-	-	-	-	27.01
			SLS + TCH			
0.0	-	-	-	-	-	16.23
0.05	5.49	7.33	1.72	6.17	0.84	23.34
0.1	5.60	7.44	1.71	6.16	0.82	24.30
0.5	5.79	7.56	1.64	5.93	0.78	26.54
0.7	6.76	8.52	1.62	5.92	0.69	27.66
0.9	9.45	11.26	1.62	6.07	0.54	29.77
1.0	-	-	-	-	-	23.59

[a] Relative standard uncertainties (u_r) are $u_r(G_{mix}^E/\Delta H_m) = 0.03$, $u_r(\Delta G_{mix}/\Delta G_{mix}^{ideal}) = 0.03$, $u_r(\Delta S_m) = 0.03$, and $u_r(\Delta G_m^o) = 0.03$.

An excess thermodynamic function is a variation among the energetic function of the mixer for a non-ideal solution and the subsequent values for an ideal solution at a similar pressure and temperature [54]. The excess free energy of mixed micellization G_{mix}^E for a

two-amphiphile mixtures can be computed with the help of equations 8 and 9 in form of Equation (10).

$$G^E_{mix} = \Delta H_m = RT[X_1^{Rub} ln f_1^{Rub} + X_2^{Rub} ln f_2^{Rub}] \quad (10)$$

From Table 2, we can observe that the values of G^E_{mix} were negative over the entire mole fraction range, confirming observations that the creation of the mixed micelles was thermodynamically more stable than the ideal state.

For the mixed system, Equations (9) and (10) were also used to calculate the entropy change as Equation (11):

$$\Delta S_m = \frac{\Delta H_m - \Delta G_m}{T} = -R\left[X_1^{Rub} ln X_1^{Rub} + X_2^{Rub} ln X_2^{Rub}\right] \quad (11)$$

Moreover, both binary and mixed micellization were found to be constrained by positive entropy values, which confirmed that entropy contribution drives mixed micellization. In the literature, the same results have previously been reported [55]. When we consider SDS + TCH mixed systems, the contributions to entropy were more significant at initial fractions. It was found to be an entropically favorable process when mixed micelles were formed, as the entropy/free energy change in this process was greater than 0.

Equation (12) was utilized to compute standard Gibbs free energy per mole of micellization using the mass-action model without considering counterion binding [58]:

$$\Delta G^o_m = RT ln X_{CMC} \quad (12)$$

In the above equation, X_{CMC} is the cmc value at mole fraction unit while R and T have their basic scientific meaning. The values of ΔG^o_m listed in Table 2 are negative for single and mixed amphiphiles. The negative values show that the micellization spontaneously occurred in the aqueous NaCl solution. The ΔG^o_m values of the drug were less than the single surfactants (SDS or SLS) and mixtures, confirming that mixed micelle formation of a drug with surfactants is more spontaneous compared to a drug alone. It is interesting to note here that the β^{Rub} values and ΔG^o_m values were directly proportional with respect to α_1, confirming that the higher interactions between amphiphile monomers cause more spontaneity in the process; the same results were reported by Bagheri et al. [54].

2.2. Interfacial Properties of TCH + SDS/SLS Mixed System

When amphiphiles are dissolved in water, the amphiphile monomers are adsorbed at the surface and the surface tension of water decreases, mainly due to the hydrophobic effects. The thermal motion and dynamic equilibrium determine the adsorption or desorption of monomers. Electrostatic interactions, hydrogen bonding, van der Waals interactions, and solvation/desolvation are factors that are less responsible for adsorption. Gibb's adsorption equation can be used to quantify the amount of amphiphiles adsorbed per unit area of the interface (surface excess, Γ_{max}) [62]:

$$\Gamma_{\max} = -\frac{1}{2.303nRT}\left(\frac{d\gamma}{dlogC}\right) \quad (13)$$

In Equation (13), $\frac{d\gamma}{dlogC}$ is the maximum slope, T is the absolute temperature in K, and R = 8.314 J mol^{-1} K^{-1}. Based on literature, the value of n was taken as 2 for pure amphiphiles and was calculated for mixtures with the following expression [62,63]

$$n = X_1^s n_1 X_2^s n_2 \quad (14)$$

The $\Gamma_{\max}$ values can be used to calculate the values of minimum area per molecule (A_{min}) with Equation (15) [64]

$$A_{min} = \frac{10^{20}}{N_A \Gamma_{\max}} \quad (15)$$

where N_A = 6.02214 × 10^{23} (Avogadro's number). The minimum area per molecule of an amphiphile suggests the packing (loose or close) and orientation of the amphiphile molecule at the surface. The low A_{min} (high Γ_{max}) values of the mixture at all mole fractions confirmed strong electrostatic interactions between cationic drugs and anionic surfactants (Table 3). This fact was also reflected in the negative interaction parameter values for the mixture. If there is no interaction between two amphiphiles in a mixed adsorbed film at the surface, the minimum area per molecule can be calculated with the following equation [62]:

$$A_{ideal} = \alpha_1 A_{min,\,1} + \alpha_2 A_{min,\,2} \quad (16)$$

Table 3. Interfacial and packing data of TCH + SDS/SLS mixed system in aqueous NaCl [a].

α_1	$10^6\ \Gamma_{max}$ (molm^{-2})	A_{min} (Å^2)	A_{ideal} (Å^2)	C_{20}	γ_{cmc} (mNm^{-1})	π_{cmc} (mNm^{-1})
			SDS + TCH			
0.0	1.64	1.01	-	19.36	39.57	31.43
0.05	1.77	0.94	1.01	0.03	27.79	43.21
0.1	2.44	0.68	1.01	0.05	28.55	42.45
0.7	3.10	0.53	0.99	0.03	29.88	41.12
0.8	3.39	0.49	0.98	0.04	30.17	40.83
0.9	3.28	0.51	0.97	0.03	30.68	40.32
1.0	1.71	0.97	-	0.09	30.60	40.40
			SLS + TCH			
0.0	1.64	1.01	-	19.36	39.57	31.43
0.05	2.73	0.61	1.01	0.80	27.88	43.11
0.1	2.28	0.73	1.01	0.41	27.72	43.28
0.5	2.57	0.65	1.03	0.19	26.89	44.11
0.7	2.14	0.77	1.04	0.09	27.11	43.89
0.9	2.01	0.83	1.05	0.04	28.04	42.96
1.0	1.57	1.05	-	0.18	23.80	47.20

[a] Relative standard uncertainties (u_r) are $u_r(\Gamma_{max})$ = 0.05, $u_r(A_{min}/A_{ideal})$ = 0.03, $u_r(C_{20})$ = 0.03, and $u_r(\gamma_{cmc}/\pi_{cmc})$ = 0.02.

The observed values (A_{min}) were lower than ideal values (A_{ideal}), indicating significant attractive interactions between the two components (Table 3). Water became 84–99% saturated following the adsorption of amphiphiles, which reduced its surface tension by approximately 20 dyn/cm. Adding an amphiphile to the water decreased the surface tension of H_2O by 20 mNm^{-1}, indicating the efficiency of its adsorption. Hence, it has the lowest concentration required to achieve saturation adsorption. By using Equation (17), we could calculate the adsorption efficiency (pC_{20}) as:

$$pC_{20} = -logC_{20} \quad (17)$$

where C_{20} is a measure of the adsorption efficiency of surfactants at the interface. The values of C_{20} are also listed in Table 3. It was concluded that the C_{20} values of SDS decreased with the addition of TCH. Decreasing C_{20} values of SDS with TCH were also shown by an earlier study [51]. In the case of SLS, the values of C_{20} only decreased at higher mole fractions. The C_{20} value of SDS in the presence NaCl has been found to be lower than in its absence [51], confirming that the surface activity of SDS is enhanced in the presence of NaCl.

Rosen and Hua modified Equations (5) and (6) for amphiphile adsorption to calculate the X_1^S and β^s with the following equations [64]

$$\frac{(X_1^s)^2 \ln(\alpha_1 C_{mix}/X_1^s C_1)}{(1-X_1^S)^2 \ln[(1-\alpha_1)C_{mix}/(1-X_1^S)C_2]} = 1 \quad (18)$$

$$\beta^s = \frac{ln(\alpha_1 C_{mix}/X_1^S C_1)}{(1-X_1^S)^2} \quad (19)$$

The interpretation of interaction parameter at the surface (β^s) is the same as in the case of bulk (β^{Rub}), with negative and positive β^s values that suggest synergism and antagonism, respectively. Here, the values of X_1^s were increased with the stoichiometric mole fraction (Table 4) and were always greater than X_1^{Rub}, showing amphiphiles contributed more to mixed monolayer formation than in the mixed micelle. Additionally, the contribution of SDS was greater than SLS in the mixed monolayer formation with the TCH. The β^s values were negative for both mixed systems, suggesting attractive interaction. The activity coefficients at the surface could be calculated by the following equations

$$lnf_1^S = \beta^s (X_2^S)^2 \quad (20)$$

$$lnf_2^S = \beta^s (X_1^S)^2 \quad (21)$$

Table 4. Thermodynamic and interfacial properties of TCH + SDS/SLS mixtures in aqueous NaCl [a].

α_1	X_1^s	$-\beta^s$	f_1^s	f_2^s	$-G_{ex}^s$ (kJmol^{-1})	$-\Delta G_{ads}$ (kJmol^{-1})	G_{min} (kJmol^{-1})
				SDS + TCH			
0.0	-	-	-	-	-	35.34	24.07
0.05	0.56	17.66	0.033	0.004	10.77	53.89	15.69
0.1	0.59	14.60	0.091	0.006	8.71	47.35	11.71
0.7	0.71	12.28	0.370	0.002	6.19	45.33	9.62
0.8	0.74	11.40	0.486	0.002	5.32	43.82	8.88
0.9	0.75	12.83	0.454	0.001	5.92	44.61	9.34
1.0	-	-	-	-	-	50.74	17.97
				SLS + TCH			
0.0	-	-	-	-	-	34.83	24.07
0.05	0.54	19.05	0.018	0.004	11.71	39.16	10.22
0.1	0.57	16.09	0.051	0.005	9.77	43.27	12.14
0.5	0.64	14.52	0.157	0.002	8.25	43.71	10.47
0.7	0.67	13.48	0.251	0.001	7.26	48.17	12.67
0.9	0.70	15.10	0.261	0.001	7.83	51.15	13.94
1.0		-	-	-	-	53.58	15.12

[a] Relative standard uncertainties (u_r) are $u_r(X_1^S)$ = 0.02, $u_r(\beta^s)$ = 0.03, $u_r(f_1^s/f_2^s)$ = 0.04, $u_r(G_{ex}^s)$ = 0.03, $u_r(\Delta G_{ads})$ = 0.03, and $u_r(G_{min})$ = 0.03.

The values of f_1^S and f_2^S are listed in Table 4 and were found to be less than unity, thus indicating non-ideality at the surface.

Thermodynamic Parameters for Drug–Surfactant Mixtures at the Surface

The standard free energy of interfacial adsorption (ΔG_{add}^o) can be computed by using the following relation [58]:

$$\Delta G_{add}^o = \Delta G_m^o - \left(\frac{\pi_{CMC}}{\Gamma_{max}}\right) \quad (22)$$

At the cmc, surface pressure is measured with the term π_{CMC}. Here in Equation (22), G_m^o is the standard Gibbs free energy previously computed with Equation (12). It was observed that the accomplished upsides of ΔG_{add}^o were –ve, similar to those of ΔG_m^o;

nonetheless, the extent was much more noteworthy, showing that adsorption was further unconstrained for this situation. f_1^S and f_2^S can be utilized to ascertain excess free energy (G_{exc}^s) at surface:

$$G_{exc}^s = RT\left[X_1^S ln f_1^S + \left(1 - X_1^S\right) ln f_2^S\right] \quad (23)$$

With negative values of G_{exc}^s, stability can be attained by the stable mixing at the surface, which is possible with the monolayer of surfactants or drugs alone. Negative G_{exc}^s values (Table 4) also indicate synergism at the surface. The degree of synergism for a mixed system can also be quantified by an energy parameter [65],

$$G_{min}^s = A_{min}\gamma_{CMC}N_A \quad (24)$$

The energy parameters that define the work required to create an interface per mole of the solution by transferring monomers from bulk to interface can be determined by the above-described energy parameters (G_{min}^s). According to Table 4, a lower value of G_{min}^s indicates a more stable surface, and this in turn results in increased surface activity.

3. UV–Visible Spectroscopic Study

The interaction of TCH with SDS and SLS was monitored with UV–visible absorption spectroscopy. The absorption spectrum of TCH (0.05 mM) in a 100 mM NaCl solution showed two absorption peaks at 226 and 310 nm due to the attendance of the aminobenzoate group. π–π* and *n*–π* transitions were involved in the first and second ones, respectively. When increasing concentrations of SDS and SLS were added to the TCH solution, the absorbance increased but the maximum absorbance at 310 nm was not changed (Figure 5). This spectral behavior indicates the electrostatic interactions between the positive charge of TCH molecules and the negative charge of surfactant monomers.

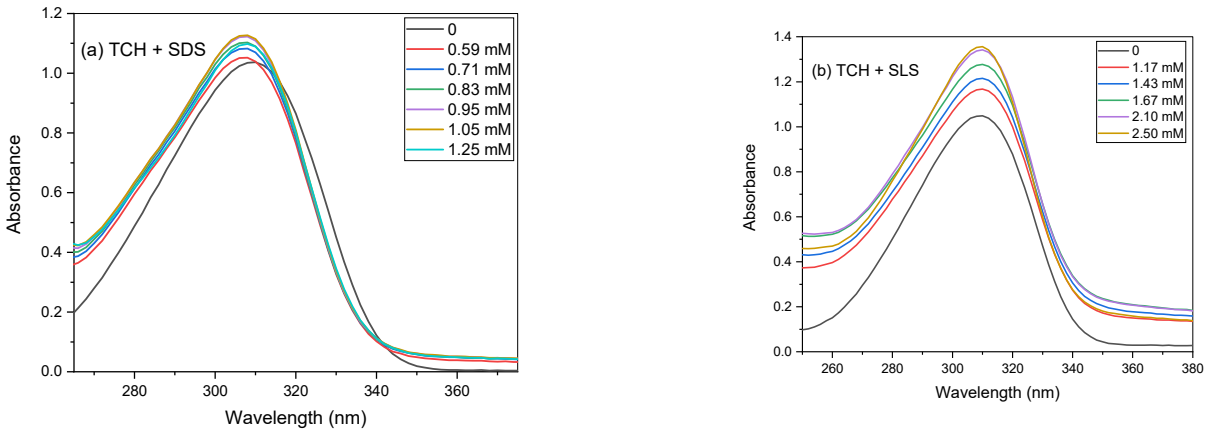


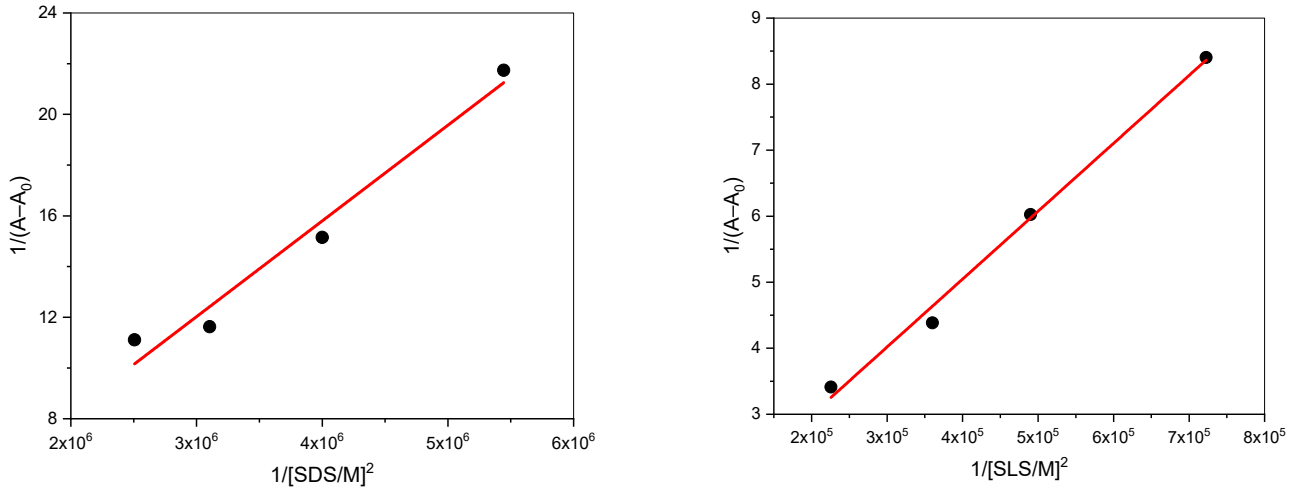
Figure 5. Absorption spectra of tetracaine hydrochloride in the presence of increased concentrations of (**a**) TCH + SDS and (**b**) TCH + SLS.

The binding constant and stoichiometric ratio were estimated with the differential absorbance method represented by the Benesi–Hildebrand equation [66]:

$$\frac{1}{A - A_0} = \frac{1}{K(A_{max} - A_0)[S]^n} + \frac{1}{A_{max} - A_0} \quad (25)$$

where the concentration of SDS/SLS is represented by [S], while A, A_0, and $A_{\max}$ represent values of absorbance due to the presence of surfactants, the absence of surfactants, and resulting absorbance due to the drug–surfactant complex, respectively. When plotting $1/(A - A_0)$ against $1/[\text{SDS/SLS}]^2$, a straight line is obtained (Figure 6), specifying the creation of the 1:2 complex. For an SDS + TCH mixed system without the addition of

salt, Thapa et. al. reported a 1:1 complex [51]. However, for our system, a curvilinear fit was obtained, so the SDS + TCH complex was mainly 1:2. Using the Benesi–Hildebrand equation, the binding constant could be calculated (intercept/slope). We found values of K of 1.86×10^5 ($\pm$ 0.04) and 9.09×10^4 ($\pm$ 0.04) mol^{-1} dm^3 for the SDS + TCH and SLS + TCH mixed systems, respectively. The SLS + TCH mixed system had lesser binding constant values than the SDS + TCH system. In comparison, SDS has one functional group and SLS has two functional groups. The localized positive charge on the nitrogen atom on the TCH interacts with the negative charge on the sulphonic group, thus enhancing the electrostatic attraction between the guest and host. SLS, however, has methylated amide nitrogen, so the amide bond cannot be a hydrogen bond donor, which inhibits intermolecular attraction between SLS and TCH at the palisade layer. Furthermore, the steric hindrance of the N-methyl group of SLS may make it difficult to tightly align the amphiphiles. All these behaviors of SLS are responsible for its lesser binding constant compared to SDS.



(**a**) (**b**)

Figure 6. Benesi–Hildebrand plots for the interaction of TCH (**a**) SDS and (**b**) SLS.

By using binding constant (K) values, free energy change of binding could be attained with Equation (26):

$$\Delta G_K = -RTlnK \quad (26)$$

The binding free energies were –30.08 ($\pm$ 0.2) $Jmol^{-1}$ for SDS + TCH and – 28.30($\pm$ 0.2) $kJmol^{-1}$ for SLS + TCH. In both mixed systems, the G values were negative, indicating that the binding process was spontaneous.

4. Conclusions

The synergistic interaction of TCH (+ve charged head group) with SDS and SLS (–ve charged head group) surfactants in the presence of salt (100 mM NaCl) was analyzed with both tensiometry and UV–visible spectroscopic techniques. The following conclusions can be derived:

1. The negative deviation of experimentally determined cmc values with hypothetical values confirms the nonideality of current mixtures.
2. The interaction parameter at the interface and in solution was determined to be – ve, thus validating synergism between monomers of two species at the surface and in bulk.
3. The higher values of the ideal mole fraction of component 1 (X_1^{ideal}) for both binary mixtures at all mole fractions indicate the strong ability of the drug to form of mixed micelles.

4. Energetics parameters confirm the spontaneity, stability, and entropic favorability of drug–surfactant mixtures.
5. The TCH with SLS had smaller binding constant values than SDS, possibly because SLS has a methylated amide nitrogen so the amide bond cannot be a hydrogen bond donor, which inhibits the intermolecular attraction between SLS and TCH at the palisade layer. Furthermore, the steric hindrance of the N-methyl group of SLS may make it difficult to tightly align the amphiphiles. All these behaviors of SLS are responsible for its smaller binding constant in comparison to SDS.

5. Experimental

5.1. Materials

Tetracaine hydrochloride (TCH, 99%), an anesthetic amphiphilic drug, and sodium lauroyl sarcosine (SLS, >95%) were supplied by Molecules On (Switzerland) and used as received. Sodium chloride (NaCl, 99%) and sodium dodecyl sulfate (SDS, 98.5%) were acquired from Sigma-Aldrich (St. Louis, MO, USA). At 298.15 K, all experiments were performed using ultra-pure, double-distilled de-ionized water with a conductivity between 1 and 2 μScm^{-1}. To prepare standard solutions for experiments, amphiphiles (both pure and mixed) were dissolved and accurately weighed in a 100 mM NaCl solution. The stock solutions for both techniques (surface tension and UV–vis spectrophotometer measurements) were prepared in aqueous 100 mM NaCl solutions.

5.2. Methods

5.2.1. Surface Tension Measurements

The surface tension experiments were conducted with a digital tensiometer (Sigma 700, Attention, Darmstadt, Germany) by using a platinum ring. The instrument was occasionally calibrated with ultra-pure distilled water. In tensiometric titration, an amphiphile stock solution was titrated into a static volume of H_2O. Throughout all experiments, water was circulated from a thermostatically controlled water bath through the outer jacket to keep the temperature at 298.15 K.

5.2.2. UV–Vis Spectrophotometer Measurements

We measured the spectra of the aqueous solutions of the drug and the drug–surfactant binary mixtures to determine the level of the binding of the drug with surfactants. As a first step, TCH in water was prepared as a stock solution in a volumetric flask. The desired concentration of surfactant solution was prepared from the aqueous TCH solution. Finally, a suitable volume of surfactant solution was added to the H_2O solution of TCH in a quartz cell. We measured the absorption spectra of TCH solutions with surfactants and plotted them against the wavelengths. For the measurement of the absorption spectrum of TCH solutions over the range of 200–400 nm, an Evolution 300 spectrophotometer from Thermo Scientific, Tokyo, Japan was used to record UV–visible spectra (Figure 2).

Author Contributions: N.A., M.A.R. & A.K. were involved in experimental planning, interpreting data and writing the manuscript; M.M.A., A.M.A. reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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