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Binding of Procaine Hydrochloride to Hydrocarbon and Fluorocarbon Surfactants: The Role of Hydrophobicity

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Authors' contributions

This work was carried out in collaboration between both authors. Author SG designed the study, evaluated the data, wrote the protocol and the first draft of the manuscript. Author SB managed the experiments, analyses and the literature searches of the study. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: The interaction of procaine hydrochloride (PC·HCl) with sodium dodecyl sulfate (anionic hydrocarbon surfactant; SDS), Tween 20 (nonionic hydrocarbon surfactant), cetyltrimethyl ammonium bromide (cationic hydrocarbon surfactant; CTAB), lauryl sulphate betaine (amphoteric hydrocarbon surfactant; LSB) and Zonyl-FSN100 (non-ionic fluorocarbon surfactant; Zonyl FSN) has been aimed to study by UV-vis spectrophotometry.
Methodology: Interactions with a fixed concentration of PC·HCl in the wide concentration range of Tween 20, Zonyl FSN, SDS, CTAB and LSB were studied spectrophotometrically at 298 K. Binding constants of PC·HCl to micelles was determined by using the Benesi-Hildebrand Equation.
Results: Comparison of the binding constants (K_B) showed that the most binding tendency of PC·HCl to micelles in case of Zonyl FSN. Due to the electrostatic repulsion between cationic CTAB and cationic PC·HCl the binding constant could not be calculated. The effect of Zonyl FSN on the binding of PC·HCl to hydrocarbon micelles has been also studied in the presence of fixed micelle

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concentration of Zonyl FSN. The binding tendency has been found to be related to the hydrophobicity of the medium.
Conclusion: Interactions between different surfactants and amphiphilic drug PC·HCl showed that binding tendency of PC·HCl followed the order as; Zonyl FSN > Tween 20 > SDS > CTAB > LSB and presence of Zonyl FSN micelles increased incorporation of PC·HCl to all types of micelles.

Keywords: Procaine hydrochloride; zonyl FSN-100; surface active drugs; surfactants; micelle; interaction; binding constant.

1. INTRODUCTION

Surfactants are widely used not only in many industrial sectors such as paper, cement, mining, agriculture, textile but also in fields such as medicine, pharmaceuticals, nanotechnology and biotechnology related to the interface and solution properties resulting from amphiphilic structures. Especially, above the certain concentrations of surfactants, known as critical micelle concentrations (CMC), the aggregation properties are of great interest to be used as a wide range of potential carrier systems such as medicines, genterapi agents, food products, personal care products etc. As well as the microscopic environment formed by surfactant micelles, it is similar to phospholipid membranes, so they form a model for biological membrane systems in order to study interactions between drug and surfactant. What is essential and important in the interaction of drugs with biological tissues at the molecular level is their binding to membranes. Therefore, the data related to the binding of drugs to the different type of micelles are very important in terms of clarifying the mechanism of action of the drug. As compared to various other membrane models such as soluble polymers and liposomes, the micellar systems are considered to be more advantageous, because of their relative simplicity, low toxicity, narrow size distribution, the longer residence time in the system, and the enhanced bioavailability and stability of the drug through micelle incorporation [1-3]. Trends and recent applications of analytical methods such as spectrophotometry, fluorimetry, and potentiometric analysis have been used in investigation techniques to study on organized molecular assemblies formed by different surfactants. Among these techniques, spectrophotometry has been most widely used to study interactions between drugs and surfactants in solution. A large number of studies [4-13] have been dedicated to drug/conventional surfactant systems with mostly hydrocarbon chains using spectrophotometry, which is important for a thorough understanding of drug transport and receptor binding of these drugs at the molecular level. Recently, apart from these conventional surfactants, fluorinated amphiphilic compounds have also received great attention due to their properties which differ in many respects from their counter parts with hydrocarbon aliphatic chains and which are interesting for potential applications in medicine (oxygen delivery [14]) and technology (emulsifiers[15], hydrophobic surface layers [16,17]. Previously, an excellent review has been made on fluorocarbons and fluorinated amphiphiles in drug delivery and biomedical research by Marie Pierre Krafft (2001) [18]. Fluorinated surfactants are comprised of a polar head and a hydrophobic moiety that features partially or completely fluorinated chains [19]. Zonyl FSN-100, $F(CF_2CF_2)_{1-9}CH_2CH_2O(CH_2CH_2O)_{0-25}H$ is one of the nonionic fluorinated surfactant produced by DuPont which was the subject of a number of studies dealing with its applications as an emulsification of plasmid DNA delivery systems [20], stabilization of gold nanoparticles [21] or formation of superhydrophobic self-assembled monolayers on gold [16].

Many pharmacologically active compounds are amphiphilic, particularly those with local anaesthetic, tranquillising, antidepressant and antibiotic actions; exert their activity by interaction with biological membranes [22]. Surface active drugs of quite a different chemical structure are reported to self-associate and bind to membranes, causing disruption and solubilization, in a detergent-like manner. Classes of amphiphilic drugs include phenothiazine and benzodiazepine tranquillizers, analgesics, peptide and non-peptide antibiotics, tricyclic antidepressants antihistamines, anticholinergics, L-blockers, local anaesthetics, non-steroidal anti-inflammatory drugs, anticancer drugs. Many of these drugs contain one or more (condensed or not) aromatic nuclei, while others are of peptide nature (22,23). One of the local anaesthetic drugs, Procaine HCl (PC·HCl) is used in allopathic medicine and neural therapy

[24,25]. The molecular structure of PC·HCl is shown in Fig. 1.

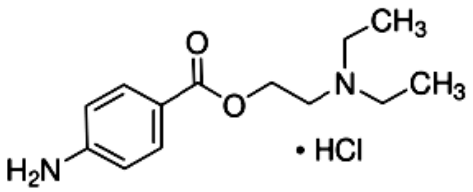

Fig. 1. Chemical structure of PC·HCl.

In recent years some studies have been published on the interactions of surface active drugs with different surfactants [11, 12, 26-35]. To the best of our knowledge, there are only a few papers reported related to interaction between PC·HCl and surfactants [36-39] as well as complexation with cyclodextrins [40-42]. PC·HCl has a great solubility in water and the solution thermodynamics in some ethanol+water cosolvent mixtures and aqueous media has been previously reported by Delgado et al (2010) [43]. According to our literature survey, there is not much work concern about binding properties of PC·HCl especially in the presence of nonionic fluorinated surfactants. However, no study has been published on the effect of hydrophobicity on micellar binding of PC·HCl by studying binary mixtures of different type of surfactants i.e. sodium dodecyl sulfate (anionic hydrocarbon surfactant; SDS), Tween 20 (nonionic hydrocarbon surfactant), cetyltrimethylammonium bromide (cationic hydrocarbon surfactant; CTAB), lauryl sulphate betaine (amphoteric hydrocarbon surfactant; LSB) and Zonyl-FSN100 (non-ionic fluorocarbon surfactant; Zonyl FSN). In the present study, we have also focused the study on how the binding tendency of PC·HCl is affected by the presence of fluorocarbon Zonyl FSN non-ionic micelles, to put light on the interaction between conventional hydrocarbon surfactants and PC·HCl. To evaluate the thermodynamic aspects of binding process of PC·HCl to micelles Gibbs energy was also determined.

2. MATERIALS AND METHODS

2.1 Materials

PC·HCl (2-(diethylamino)ethyl *p*-(amino)benzoate) (purity > 97%), sodium dodecyl sulfate (SDS) (purity > 99%), Tween 20 (purity > 97%), cetyltrimethylammonium bromide (CTAB) (purity > 99%), laurylsulfobetaine (LSB) (purity > 97%) and Zonyl FSN-100 (purity > 97%) were used as received and supplied from Sigma Chemical Company (Germany). All of the reagents were used directly without further purification. Triple distilled deionized water was used through all the experiments.

2.2 Methods

2.2.1 Spectrophotometric measurements

Visible absorption spectra were recorded with ultraviolet-visible (UV-VIS) spectrophotometer (UV-1601, Shimadzu, Japan) with a matched pair of cuvets of 1 cm optical length placed in a thermostated cell holder at 298K (±0.1) keeping the concentrations of drugs fixed (0.02 mM). The absorption spectra of PC·HCl solutions containing surfactant in the wide concentration range of surfactants were recorded and reproducibility for λ_{max} of the spectra was ±0.1 nm. All measurements were done at least in triplicate during the study.

2.2.2 CMC determination

The CMC values for each surfactant-PC·HCl system were determined spectrophotometrically based on the change in absorption spectrum of PC·HCl in the presence of surfactants which indicate the onset of micelle formation as described previously [44].

2.2.3 Determination of micellar binding constants of PC·HCl

The binding constants of PC·HCl to micelles can be quantitatively determined using the Benesi-Hildebrand Equation [44] in the following modified form [6, 45];

$$\frac{[D]l}{A-A_0} = \frac{1}{\Delta\varepsilon} + \frac{1}{K_b[C](\Delta\varepsilon)} \quad (1)$$

where [D] and [C] represent the concentrations of PC·HCl and micelles, respectively. In the case of all micelles C is micellized surfactant concentration i.e. [C] = (total surfactant concentration – CMC). *l* is the optical path length of the solution. A and A_0 are the absorbances of PC·HCl in the absence and presence of surfactants, respectively. ∆ε, is the difference in molar absorption coefficients between bound and free drug. The plot of *l* [D] /(∆A) against 1/[C] was found to be linear in all cases.

3. RESULTS AND DISCUSSION

PC·HCl having the molecular structure shown in Figure 1 is a basic drug with pKa 8.95 [46]. pH of the PC·HCl solution as a function of drug concentration has been reported previously [40] and determined the value of $5.0x10^{-10}$ at 298 K. In our experimental conditions PC·HCl exists as an ionized form in agreement with literature data. Binding of PC·HCl to ionic and nonionic surfactants has been studied by UV–Vis absorption spectroscopy in submicellar and micellar surfactant concentrations. The absorption spectra of PC·HCl solutions containing different concentrations of CTAB, LSB, Tween 20, Zonyl FSN and SDS are shown in Figure 2, respectively. In order to observe change in absorption characteristics of PC·HCl in the presence of different surfactants, the concentration of PC·HCl was held constant, at 0.02 mM while the surfactant concentration was varied. The wavelength of maximum absorption (λ_{max}) of PC·HCl in water appears at 220 and 290 (±1) nm.

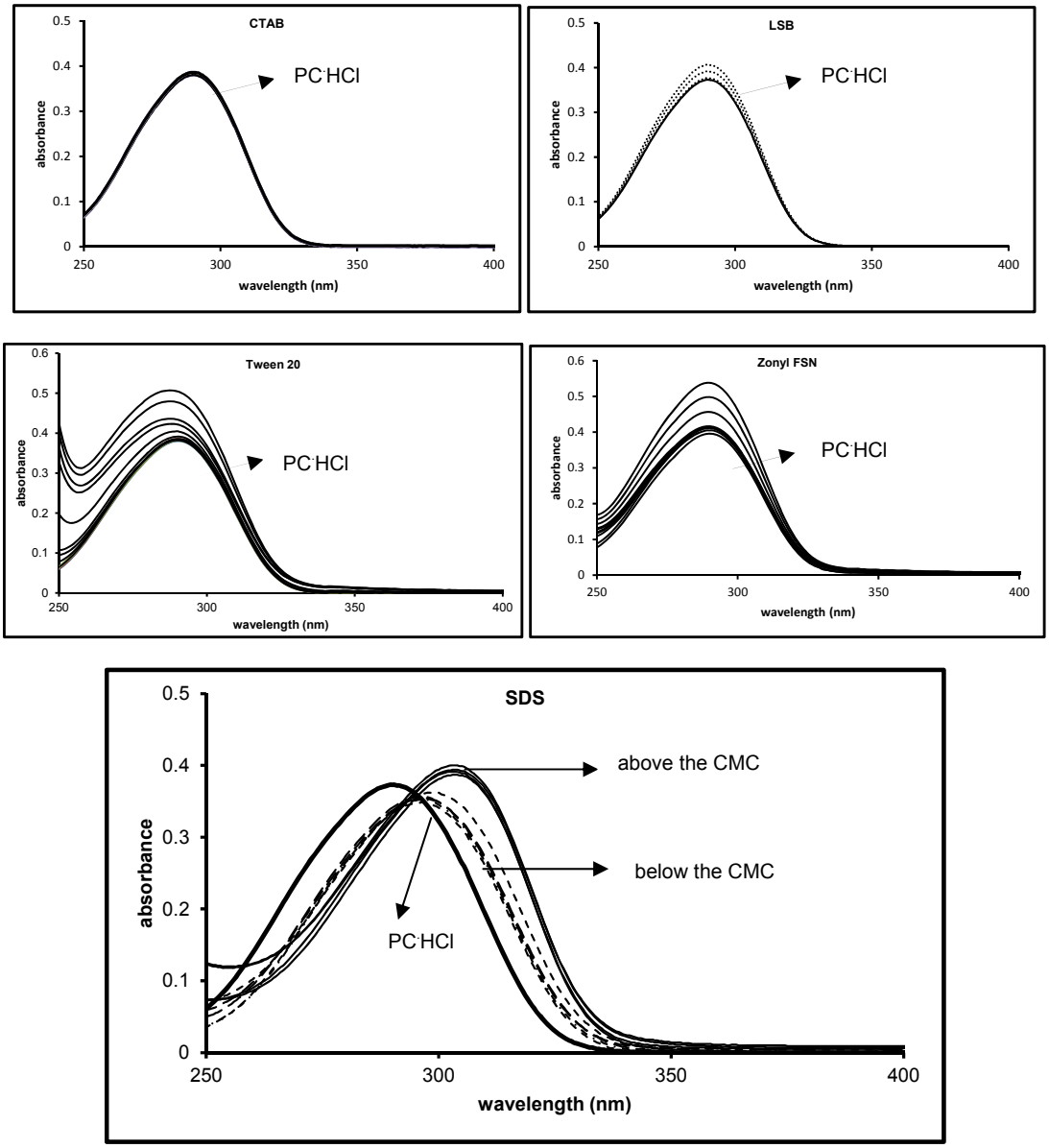

Fig. 2. UV–visible spectra of aqueous PC·HCl (0.02 mM) at various concentrations of CTAB, LSB, Tween 20, Zonyl FSN and SDS

The change in absorbance value at 290 nm have been used to study the interaction between PC·HCl and surfactants in this study. Based on the validity of Lambert-Beer Law, from the linear regression of the values of the absorbance at 290 nm as a function of PC·HCl concentration, the molar absorption coefficient (ε) were determined as 27583 ± 50 mol^{-1} L cm^{-1} at 298 K. The changes in absorbance of 0.02 mM PC·HCl in the presence of varying concentrations of surfactants is shown in Fig. 3. Among the studied surfactants, the presence of SDS showed a different effect on the absorption spectra of PC·HCl (Fig. 2). As seen in Fig. 3 for SDS concentrations up to 3.0 mM, absorbance of PC·HCl sharply decreased with a slight red shift. This decrease in absorbance indicates molecular complex formation between PC·HCl and SDS molecules. A progressive enhancement was observed in absorbance with a red shift at the surfactant concentrations above the CMC when SDS concentration reached the micellar region.

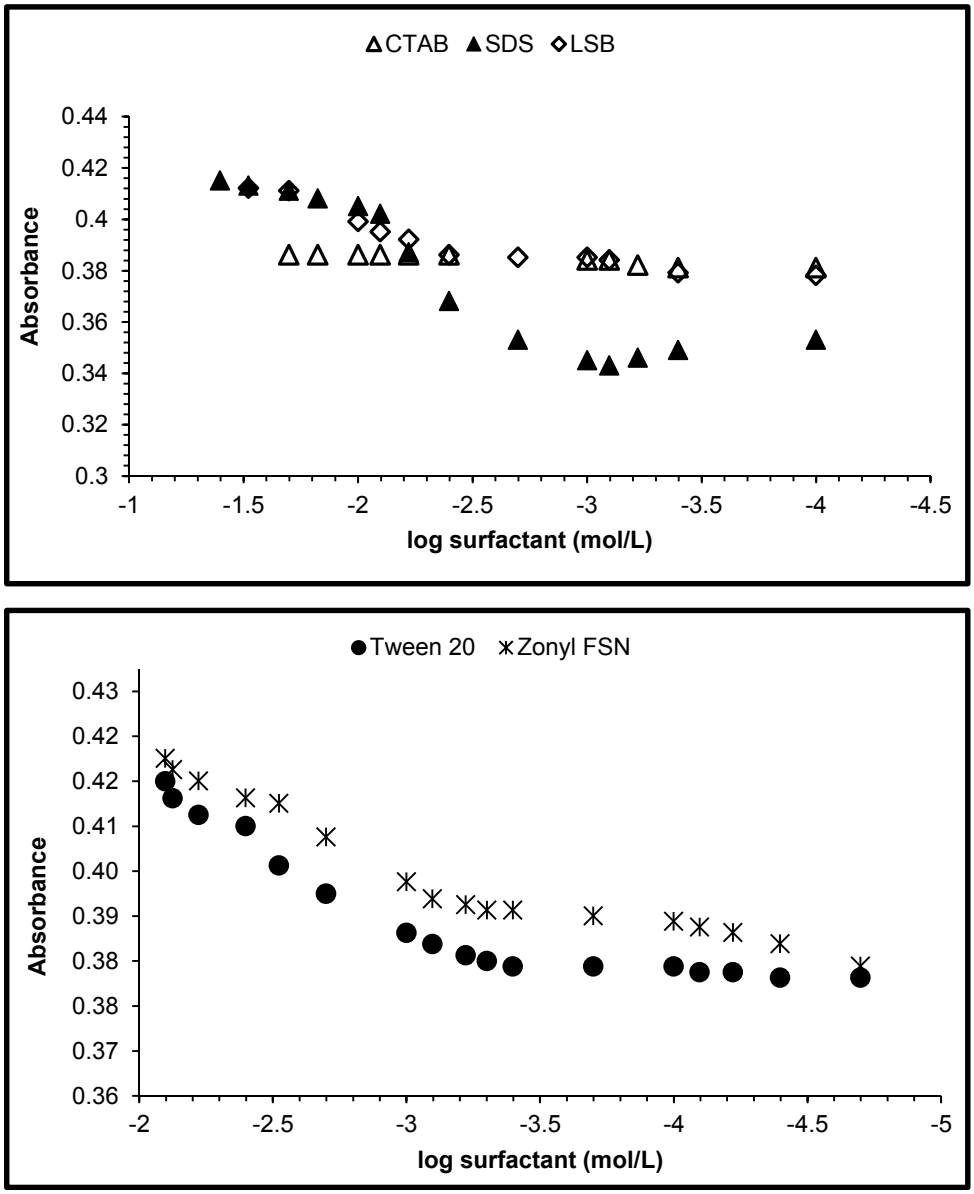

Fig. 3. Plots of absorbance of aqueous PC·HCl (0.02 mM) solutions as a function of the logarithm of the concentrations of ionic (CTAB, SDS and LSB) and nonionic (Tween 20 and Zonyl FSN) surfactants

The complex formation of PC·HCl and SDS is a consequence of mutual influences of electrostatic interactions since PC·HCl is a positive charged compound, which is opposite to the negative

charged SDS molecules, so PC·HCl could induce the screening of the electric repulsion between the head groups of SDS. Thus the absorbance and the CMC value of SDS reduced from 8.0 mM to 3.0 mM. This behaviour can also explain that no interaction was observed between PC·HCl and CTAB micelles due to electrostatic repulsion (Fig. 2). Whereas, at the concentrations of LSB, Tween 20 and Zonyl FSN below the CMC, the lack of change in absorbance of PC·HCl indicates absence of interaction between PC·HCl and molecules of nonionic and zwitterionic surfactants i.e. the absorbance of PC·HCl remained almost constant. Besides for all surfactants studied a similar behaviour, that is, a progressive enhancement in absorbance above the CMC was observed except CTAB which has no perturbation effect on the spectrum of PC·HCl including its postmicallar region. The increase in absorbance of PC·HCl above the CMC is attributed to the increase in the amount of solubilized PC·HCl in the micelles. The incorporation of PC·HCl to micelles can be provided quantitatively from determining binding constant using by Benesi- Hildebrand Equation. As seen in Fig. 4 linear plots between 1/ΔA and 1/C obtained (r>0.999) in all cases indicated binding affinity of PC·HCl to micelles. K_B values obtained from this equation by least-square analysis with their associated error limits and correlation coefficients were given in Table 1.

Computations of binding constants explain that binding degree of PC·HCl in the case of hydrogenated non-ionic Tween 20 and fluorinated non-ionic Zonyl FSN is stronger than that of anionic and zwitterionic. Combined electrostatic and hydrophobic forces take place in binding onto anionic micelles, while hydrophobic interaction plays the main role in binding onto nonionic. The lack of interaction between PC·HCl and CTAB support this expectation. The smaller binding constant obtained in case of LSB is related that beans act as cationic in solution so they interact with anions although they are formally neutral [47,48]. However, comparison between fluoro- and hydrocarbon nonionic surfactants studied, it can be seen that Zonyl FSN formed incorporation with PC·HCl more strongly than Tween 20.

Hydrophobicity is the main important force that affects the binding tendency of a molecule to micelles. The larger surface presented by the fluorinated chains the 'hydrophobic' effect of the chain is roughly proportional to its area in contact with water [49], in conjunction with the low polarizability of the fluorine atoms, results in enhanced hydrophobicity. Perfluorinated chains thus combine two characteristics that are usually considered to be antinomic: they are extremely hydrophobic, and lipophobic at the same time [15,18]. Fluorinated surfactants have also lower CMC since the smaller CMC plays a fundamental role in the hydrophobic interaction and could represent its degree of hydrophobicity. For this purpose, this study not only presents interaction of PC·HCl with different surfactants, but the importance of hydrophobicity on a binding process that is required to increase its sensitivity.

Table 1. Calculated binding constants for the interaction of 0.02 mM PC·HCl with surfactants in the absence and presence of Zonyl FSN micelles according to Benesi-Hildebrand Equation at 298 K. [a] *The correlation coefficients are >0.99 for each drug–surfactant system studied. Error limit in K_B is ±5%*

Surfactant	K_B[a] (M^{-1})	ΔG_B^0 (kJ/mol)
CTAB	-	-
LSB	82.270	-10.93
SDS	238.00	-13.60
Tween 20	593.85	-15.82
Zonyl FSN	10005.4	- 22.82
…… ……	…… …….	……
CTAB+Zonyl FSN	246.48	-13.66
LSB+Zonyl FSN	89.820	-11.14
SDS+Zonyl FSN	301.71	-14.15
Tween 20+Zonyl FSN	633.93	-15.98

The interaction of PC·HCl has been also studied in a combination of Zonyl FSN with SDS, Tween 20, LSB and CTAB micelles for observing the binding tendency of PC·HCl to micelles in order to understand the role of increasing on the hydrophobic character in a micellar environment. The addition of Zonyl FSN micelles did not influence the spectral characteristics of the fixed concentration of PC·HCl but increase the absorbance value of PC.HCl in the presence of SDS, Tween 20, LSB and CTAB micelles (Figure 5). Results obtained in the presence of ionic, zwitterionic and nonionic surfactants were correlated with the results obtained from the addition of fluorocarbon nonionic surfactant to increase the binding tendency of PC·HCl to all types of micelles including cationic CTAB micelles. As can be seen in Table 1 the binding affinity of PC·HCl to SDS, CTAB, LSB and Tween 20 significantly increased with the

addition of Zonyl FSN micelles i.e. a higher binding constant was determined in the case of Tween 20 micelles. According to the Benesi–Hildebrand equation plot of 1/ΔA vs 1/C for the interaction of 0.02 mM PCHCl with SDS, CTAB, LSB and Tween 20 micelles in the presence of a fixed concentration of Zonyl FSN micelles were given in Fig. 6.

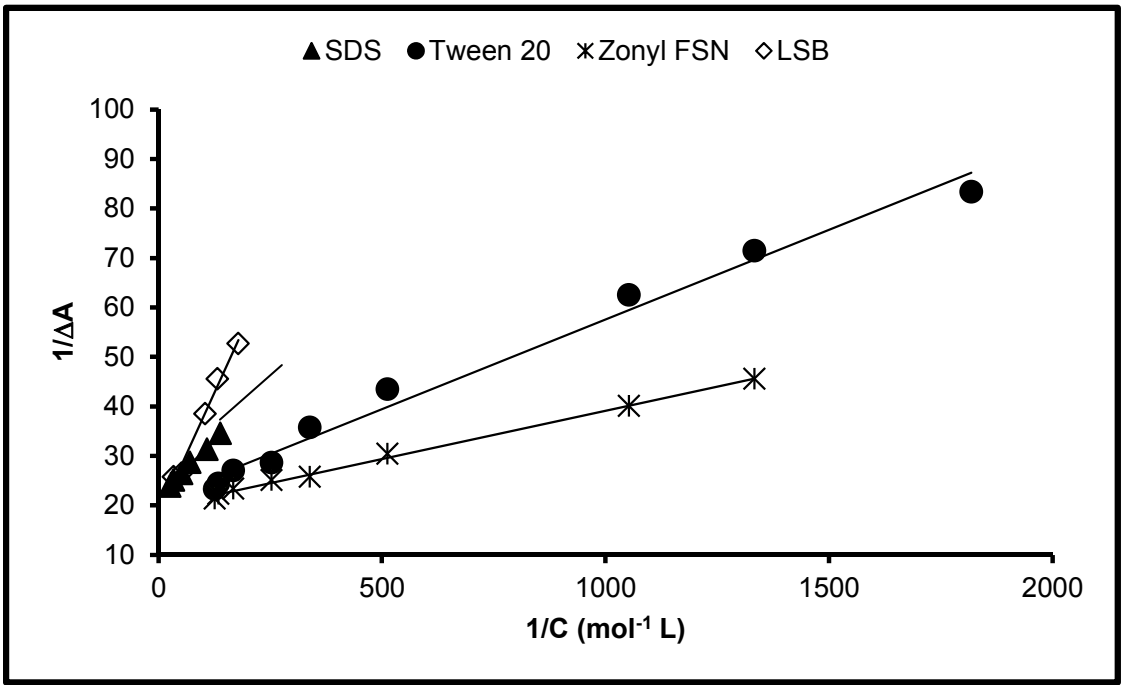

Fig. 4. The plot of 1/ΔA versus 1/C for the interaction of 0.02 mM PC.HCl with SDS, Tween 20, Zonyl FSN and LSB based on Benesi-Hildebrand equation at 298 K

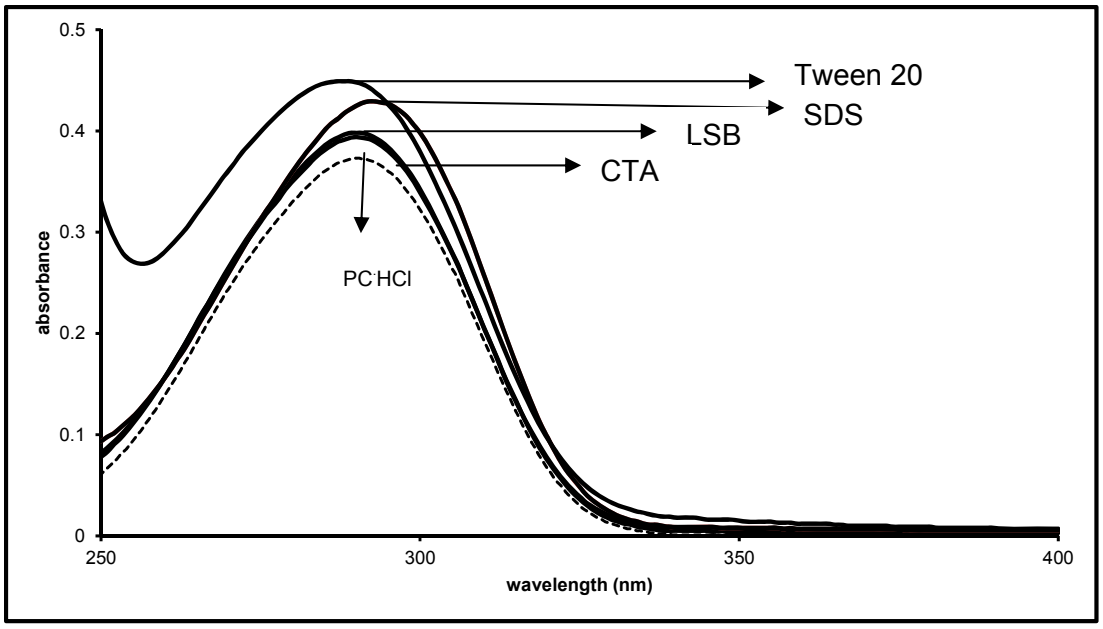

Fig. 5. Effect of Zonyl FSN micelles UV–visible spectra of aqueous PC·HCl (0.02 mM) in the presence of fixed concentrations of CTAB, LSB, Tween 20 and SDS micelles

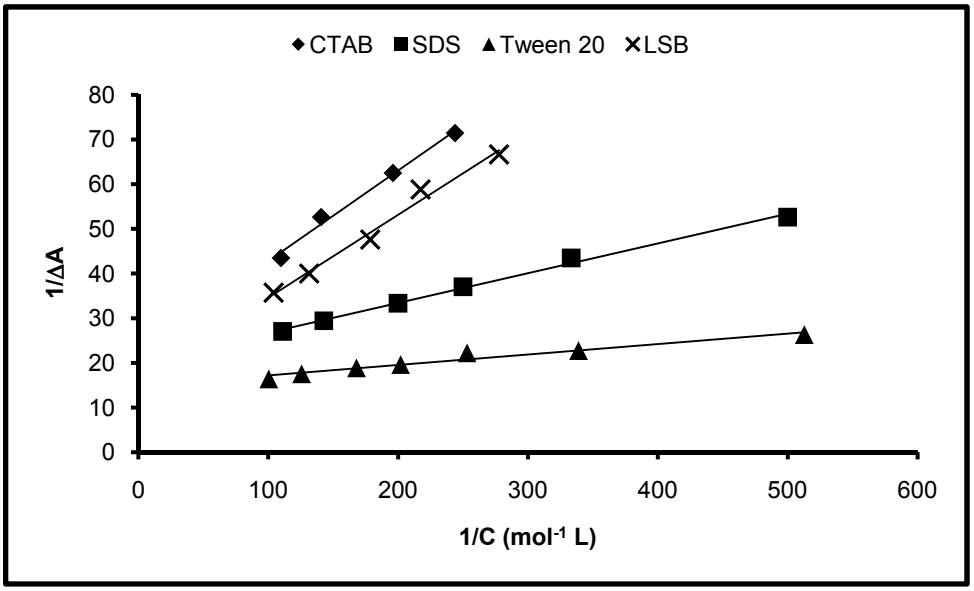

Fig. 6. The plot of 1/ΔA versus 1/C for the interaction of 0.02 mM PC·HCl with SDS, Tween 20, CTAB and LSB based on Benesi-Hildebrand equation at 298 K in the presence of 1.0 mM Zonyl FSN micelles

What is surprising in these mixtures system of Zonyl FSN increased apparently the binding affinity of PC·HCl to CTAB micelles and allowed to calculate binding constant as well when compared to single CTAB micelles which were observed a very weak interaction occurred between PC.HCl and CTAB micelles due to the electrostatic repulsion (Table 1). This behaviour confirms that there is a substantially hydrophobic interaction play an important role of the micellar binding process of PC·HCl. This indicates that electrostatic repulsion sufficiently decreased in the presence of Zonyl FSN, so hydrophobic forces were able to overcome electrostatic repulsion and K_B was calculated as 246.48 M^{-1} for the interaction of PC·HCl with CTAB micelles. As seen in Table 1, the binding affinity of PC.HCl to all types of micelles significantly increased with the addition of Zonyl FSN (Fig. 7).

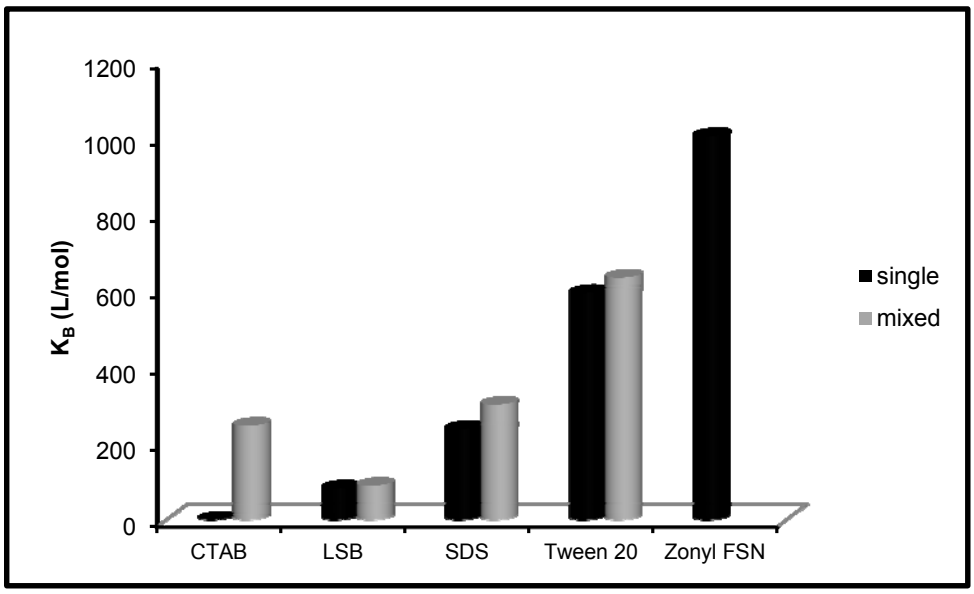

Fig. 7. A plot of K_B values in the absence (single) and presence of Zonyl FSN micelles (mixed)

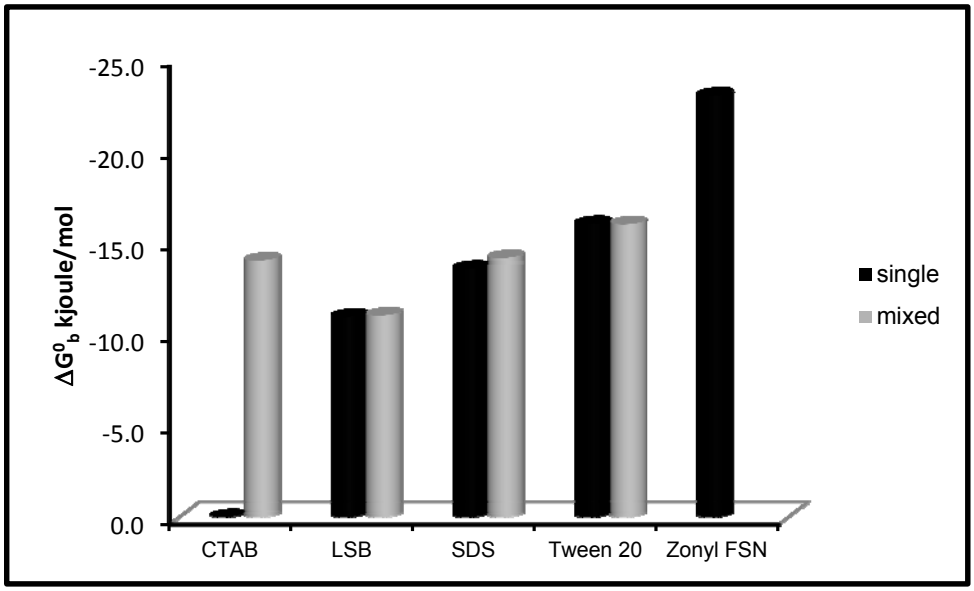

Fig. 8. A plot of ΔG_B^0 values in the absence (single) and presence of Zonyl FSN micelles (mixed)

Besides, absorbance-concentration dependence allows determining the related thermodynamic parameter which is the standard free energy change. It can also be calculated from the values of K_B for interactions of PC·HCl and surfactants, as follows [13,50,51]:

$$\Delta G_B^0 = - RT\ln K_B$$

ΔG_B^0 which is an indication of the tendency of the binding of PC·HCl to micelles shows that PC·HCl interacts with Zonyl FSN more easily and strongly than Tween 20, SDS, LSB and CTAB under the same conditions. As seen in Table 1 and Figure 8 ΔG_B^0 values increased with increasing hydrophobicity of surfactants. This increasing can also be seen clearly in the presence of Zonyl FSN micelles. In case of Zonyl FSN, ΔG_B^0 is high compared to that found in case of SDS, CTAB, Tween 20 and LSB. ΔG_B^0 shows also that PC·HCl interacts with CTAB more easily when compared to that found in the absence of Zonyl FSN.

4. CONCLUSION

This study reports the results based on change of absorbance values upon binding allowed obtaining the binding constants of PC·HCl to different type of micelles. Binding tendency of PC·HCl to single and the mixing of the hydrocarbon surfactants SDS, LSB, CTAB and Tween 20 with the fluorocarbon surfactant, Zonyl-FSN-100 is quantified, in particular, effect of hydrophobicity on binding process. Although electrostatic interaction plays the major role in binding of oppositely charged PC.HCl and SDS hydrophobic bonding should have a major importance. Computations of binding constants reveal that binding in the case of nonionic is stronger than ionic micelles. This also indicates that the interaction of PC·HCl with ionic micelles not only depends on the electrostatic attractions but also on hydrophobic association. The results obtained in case of fluorinated non-ionic Zonyl FSN showed that PC·HCl interacted with Zonyl FSN micelles more effectively than Tween 20 micelles. This high affinity mainly comes from micellar local polarity since the lower polarity leads to higher binding constant. The results obtained from in binary mixtures of fluorinated non-ionic Zonyl FSN has been correlated with the increase in binding tendency of positively charged drug PC·HCl to cationic surfactant CTAB. The presented results affirm that the higher binding constants of PC·HCl indicate that nonionic micelles especially Zonyl FSN provide a more hydrophobic environment to PC·HCl. As a conclusion, characteristics of each surfactant are often modulated in the mixture, based on the interactions between the various components present. Very different structurally and specifically found surfactants are used as model systems in biological investigations as well as in drug formulations for various purposes such as increasing or decreasing the solubility, activity and stability of drugs. Therefore, it is believed that this research will lead to the results of the

drug development as a model system, the tendency to binding to membranes and the related studies.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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