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Research Article

2-Methylpyridinium Based Surfactants: Synthesis, Characterization and Potential Application as Drug Carrier Systems

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Abstract: New cationic surfactants i.e., n-hexyl-2-methylpyridium bromide (**a6**), n-heptyl-2-methylpyridium bromide (**a7**) and n-octyl-2-methylpyridium bromide (**a8**) have been synthesized and characterized by multinuclear (^{1}H, ^{13}C) Nuclear magnetic resonance (NMR) and Fourier-transform infrared spectroscopy (FTIR) spectroscopy. Critical micelle concentration (CMC) values of these compounds were studied in ethanol using conductometric and UV-Visible spectroscopic methods. Dependence of CMC of synthesized surfactants on temperature was used as a parameter to determine the thermodynamic parameters (ΔG, ΔH and ΔS) of micellization process. The negative values of ΔG and positive values of ΔH indicated the spontaneous and endothermic nature of micellization process, respectively. Bioactivity tests of these surfactants showed them as significant biological active compounds. The interaction of drugs (Flurbiprofen and Ketoprofen) with these compounds has been studied by employing UV-Visible spectroscopic method. The binding constant (K_b) and number of drug molecules incorporated per micelle (n) gives evidence of strong interaction of selected drugs with these synthesized surfactants. Negative value of Gibb's free energy calculated from (K_b) showed the spontaneous nature of drug surfactant interaction.

Keywords: Micelle, Critical micelle concentration, Cationic surfactant, Drug carriers, Binding constant.

1. INTRODUCTION

Over the past few years, trend of synthesizing new surfactants having tailored and targeted properties has grown rapidly [1]. Surfactants play important role in every walk of life, ranging from agriculture sprays to oil recovery including areas such as catalysis, coating, dispersion, electronics, flotation of minerals, lubrication and retardation of evaporation from lakes and reservoirs [1–2].

Surfactants are amphiphilic compounds having both long chain hydrocarbons with a nonpolar tail and ionic or polar head groups. Surfactants are classified into four kinds on the basis of their chemical structure; namely cationic, anionic, nonionic and ampholytic (zwitterionic) [3]. The polar portion possesses strong affinity for polar solvents, particularly water, and therefore called its hydrophilic or solvophilic part. On the other hand, its nonpolar part is called hydrophobic or solvopohobic part. Due to the twin affinity of a surfactant molecule towards solvent, it does not stay comfortable in solution unless it adopts one of several supramolecular arrangements in solution, such as circular aggregates called micelles. Micelles

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are formed when the surfactant concentration reaches a certain value, termed as the critical micelle concentration (CMC), and are arranged with the hydrophobic tails oriented inward and the hydrophilic heads oriented towards the aqueous solution [4]. In solution chemistry, the CMC is considered as one of the important parameters used for the evaluation /comparison of efficiency of surfactants for their desired applications. Various methods such as conductometry, UV-Vis spectroscopy, viscometry etc. are used for the estimation of CMC. These methods rely on changes in the nature of functional dependence of some physical properties with concentration on account of micelle formation by a surfactant in its solution [5]. The thermodynamics of the micellization process can be investigated based on the CMC value of the surfactant, as its value measures the stability of the surfactant in micellar form.

Recently, surfactants are being explored heavily for their potential as drug carrier due to their dual nature and capability to interact with different drugs and ability to cross the membranes [6-9]. There are numerous reports where cationic micelles are employed to evaluate their role as model drug carriers [10, 11]. Comparing with other drug carrier models, surfactants have some profound pharmaceutical benefits: (a) they are able to solubilize poorly soluble drugs hence enhancing drug bioavailability; (b) micelles are capable of residing in the human being extended sufficient as long as steady gathering in the involved part; and (c) these are reproducible systems [12]. Therefore, studying drug-surfactant interaction is a matter of biological interest and the system will eventually help to design controllable and efficient drug delivery systems [13, 14].

The drug-surfactant interaction can be assessed by determining the association between charge on drug and the surface area of surfactant molecules. Drug-surfactant binding constant and micelle-solvent partition coefficient are valuable parameters for the numerical calculation of the micellar effect on the properties of pharmaceutical drugs [15, 16], which helps in understanding the drug structure-activity relationships and its interaction with the biological membranes [17].

In the present work, three new n-alkyl-2-methylpyridinium bromides are synthesized and characterized by NMR (^{1}H and ^{13}C NMR) and FT-IR spectroscopic techniques. Their CMC values and thermodynamic parameters are reported. Moreover, their biological activities, interaction with selected drugs (Flurbiprofen and Ketoprofen, Fig. S1) and mechanism of action in drug delivery systems are discussed. Although a number of studies on the interaction of surfactants with different solute molecules including drugs are reported in the literature [18-22] to the best of our knowledge, the interaction of 2-methylpryridinium based surfactants with Ketoprofen and Flurbiprofen is not known.

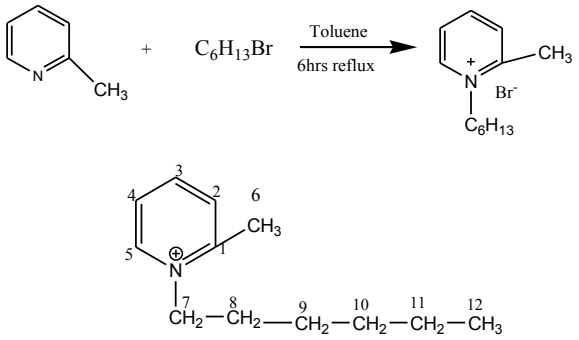
2. MATERIALS AND METHODS

The chemicals and reagents used were obtained from Sigma-Aldrich, USA, and used as received. Analytical grade toluene was used as solvent and was dried before using it in experiments. Bruker 300MHz NMR spectrometer (Switzerland) was used for recording the ^{1}H and ^{13}C NMR of the synthesised compounds. The Bruker Tensor II FT-IR Spectrophotometer was used for recording infrared spectra (4000-400 cm-1). Conductivity measurements were carried out by Conductometer Inolab Cond-720. Shimadzu double beam spectrophotometer UV-1601 was used for determining the CMC values and for studying the interaction of the synthesised surfactants with the selected drugs.

The synthesized three compounds are coded as **a6**, **a7** and **a8** for n-hexyl-2-methyl pyridinium bromide, n-heptyl-2-methyl pyridinium bromide, and n-octyl-2-methyl pyridinium bromide, respectively.

2.1 Synthesis of n-Hexyl-2-Methylpyridinium Bromide (a6)

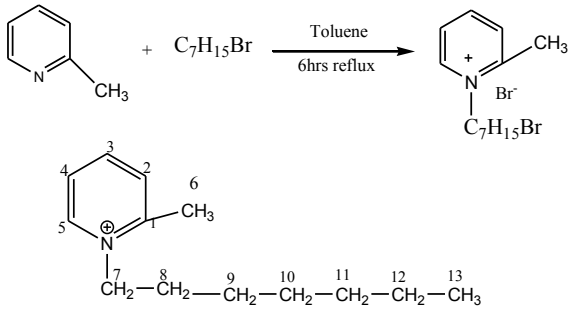
For the synthesis of compound **a6** , 25 mL dry toluene was taken in 100 mL round bottom flask and then 2 mL of bromohexane (0.01M) and 4 mL of 2-methylpyridine(0.01M) were added. The reaction mixture was refluxed for 6 hrs. The resultant product was filtered off and the filterate was rotary evaporated. The compound obtained was a brownish oily product.



^{1}H-NMR (300 MHz, $CDCl_3$, δ-ppm): 8.4 (1H, H^2, d,), 9.45 (1H, H^3, t,^3J [^{1}H, ^{1}H]=7.5Hz), 8.3 (1H, H^4, t, ^3J [^{1}H,^{1}H]=6.0Hz), 9.43 (IH, H^5 , d, ^3J [^{1}H,^{1}H]=6.0Hz), 2.68 (3H, H^6, s), 4.75 (2H, H^7, t, ^3J [^{1}H,^{1}H] =5.7 Hz), 1.1-1.3 (8H, H^{8-11}, m), 0.83 (3H, H^{12}, t, ^3J [^{1}H, ^{1}H]=6.6Hz). ^{13}C-NMR (75.5 MHz $CDCl_3$, δ -ppm): 154.2 (C1), 126.4 (C2), 146.3 (C3), 128.2 (C4), 145.3 (C5), 20.74 (C6), 58.4 (C7), 22.34-31.15 (C8-C11), 13.9 (C12). FT-IR (υ, cm^{-1}); 1300 (C-N), 1634 (C=N), 1570 (C=C), 1462 ($-CH_2$), 3019 (CH-Aromatic), 1154 ($-CH_3$)

2.2 Synthesis of n-Heptyl-2-Methylpyridinium Bromide (a7)

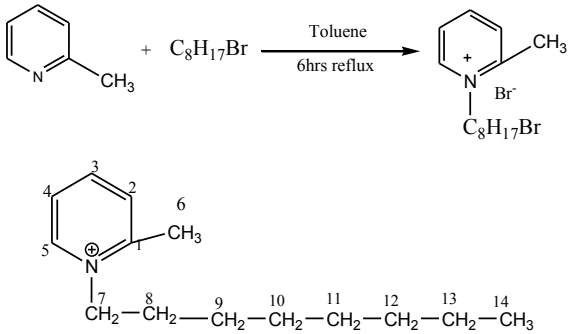
For the synthesis of compound **a7**, 25 mL dry toluene was taken in 100 mL round bottom flask and then 3 mL of bromoheptane and 6 mL of 2 methylpyridine was added to it. The reaction was carried out under the reflux conditions for 6 hrs. The reaction mixture was filtered off and the filterate was rotary evaporated. The compound was obtained as a yellowish brown oily product.



^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 8.02 (1H, H^2, d), 7.99 (1H, H^3, t, ^3J [^{1}H, ^{1}H] =7.5Hz), 8.3 (1H, H^4, t, ^3J [^{1}H,^{1}H] =6.0Hz), 9.40 (IH, H5, d, 3J [^{1}H,^{1}H] =6.0Hz), 2.94 (3H, H^6, s), 4.75(2H, H^7, t, ^3J [^{1}H,^{1}H]=5.7 Hz), 1.2-1.4 (10H, H^{8-12}, m), 0.84 (3H, H^{13}, t, ^3J [^{1}H, ^{1}H]=6.6Hz). **^{13}C-NMR** (75.5 MHz, $CDCl_3$, δ ppm): 154.2 (C1), 126.4 (C2), 146.3 (C3), 130.4 (C4), 145.3 (C5), 20.7 (C6), 58.4 (C7), 22.4-31.4 (C8-C12) 14.0 (C13). **FTIR** (υ, cm^{-1}); 1202 (C-N), 1634 (C=N), 1570 (C=C), 1462 ($-CH_2$), 3019 (CH-Aromatic), 1154 ($-CH_3$).

2.3 Synthesis of n-Octyl-2-Methylpyridinium Bromide (a8)

For the synthesis of compound **a8**, 25 mL dry toluene was taken in 100 mL round bottom flask and then 2 mL of bromooctane and 5 mL of 2-methylpyridine was added to it. The reaction was carried out under the reflux conditions for 6 hrs. The resultant product was filtered off and the filterate was rotary evaporated. The compound was obtained as a yellowish brown oily product.



^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 8.42 (1H, H^2 ,d), 7.91 (1H, H^3, t, ^3J [^{1}H, ^{1}H]=7.5Hz), 8.36 (^{1}H, H^4, t, 3J [^{1}H,^{1}H] =6.0Hz), 9.34 (IH, H^5, d, ^3J [^{1}H,^{1}H]=6.0Hz), 2.94 (3H, H^6, s), 4.70 (2H, H^7, t, ^3J [^{1}H, ^{1}H]=5.7 Hz), 1.1-1.87 (12H, H^{8-13}, m), 0.79 (3H, H^{14}, t, ^3J [1H, 1H]=6.6Hz). **^{13}C-NMR** (75.5 MHz $CDCl_3$, δ -ppm): 154.2 (C1), 126.4 (C2), 146.1 (C3), 130.4 (C4), 147.3(C5), 20.6 (C6), 58.3(C7), 22.4-31.5 (C8-C13) 13.9 (C14). FT-IR (υ cm^{-1}); 1300 (C-N), 1630 (C=N), 1575 (C=C), 1464 (-CH2), 3039 (CH-Aromatic), 1141 ($-CH_3$).

2.4 Procedure for Antibacterial Activity

The agar well-diffusion method was used for the determination of antibacterial activity [17]. The synthesized surfactants were tested against six bacterial strains; three Gram-Positive *Micrococcus luteus* (ATCC10240), *Bacillus subtilis* (23857) and *Staphylococcus aureus* (ATCC6538)) and three Gram-negative (*Escherichia coli* (ATCC15224), *Klebsiella pneumonia* (ATCC11296) and (*Enterobacter aerogenes* (ATCC13048)). Broth culture (0.75 mL) containing ca. 106 colony forming units (CFU) per mL of the test strain was added to 75 mL of nutrient agar medium at 45° C, mixed well, and then poured into a 14 cm sterilized

petri-plate. The media was allowed to solidify, and 8 mm wells were dug with a sterilized metallic borer. Then a DMSO solution of the test sample (100 µL) of 1 mg/mL was added to the respective wells. DMSO served as a negative control, and the standard antibacterial drug Streptomycin sulphate (1 mg/mL) were used as positive controls. Triplicate plates of each bacterial strain were prepared, which were incubated aerobically at 37±1°C for 24 h. The activity was determined by measuring the diameter of the zone showing complete inhibition (mm).

2.5 Antifungal Activity

To assess the anti-fungal activity of these compounds against different fungal strains, three fungal strains, *Aspergillus niger*, *Aspergillus flavus*, and *Aspergillus fumigatus* were selected to study. Sabouraud's dextrose agar was used as media for antifungal assay. The fungal strains were inoculated separately in Sabouraud's dextrose broth for 6 hours and the suspensions were established to give approximately 105 CFU/mL. The agar well diffusion method was adopted to assess antifungal activity [23]. Sabouraud's dextrose agar (SDA) was used for fungal cultures. The culture medium was inoculated with the fungal strains separately suspended in Sabouraud's dextrose broth. Eight mm diameter wells were perforated into the agar and filled with compounds and solvent blanks (hydro alcohol, and n-hexane). Standard antibiotic (Terbinafine concentration 1 mg/mL) was used as positive control and fungal plates were incubated at 37 °C for 3 days. Diameters of the observed inhibition zone were measured.

2.6 Antioxidant Activity

The antioxidant activity of the compounds was evaluated by the β-carotene method, following the procedure as reported [24, 25] with minor adjustments. An aliquot (50 µL) of the β-carotene chloroform solution (20 mg/mL) was transferred into to a flask containing 40 µL of linoleic acid, 1.0 mL of chloroform, and 530 µL of Tween 40 and then mixed. The chloroform was evaporated. After the evaporation, oxygenated distilled water (approximately 100 mL) was added to obtain an absorbance of 0.65 ± 0.5 units at 470 nm. An aliquot (0.4 mL) of Trolox solution (200 mg/L) or diluted fruit extract (200 mg/L) was added to 5 mL of the β-carotene solution and incubated in a water bath at 40 °C. The absorbance measurements were made after 2 min and 120 min at 470 nm using a spectrophotometer. The antioxidant activity was calculated as the percent inhibition relative to the control.

3. RESULTS AND DISCUSSION

3.1 Synthesis of Compounds

FTIR, ^{1}H- and ^{13}C-NMR spectroscopic data (see experimental section) confirmed the synthesis and purity of surfactants. In FTIR spectra, the presence of vibrational bands of all reacting species i.e. 1634 cm^{-1} (C=N), 1570 cm^{-1} (C=C), 1462 cm^{-1} (–CH2), 3019–3039 cm^{-1} (CH-Aromatic), 1141–1154 cm^{-1} (–CH3) and appearance of 1202–1300 cm^{-1} (C–N), confirmed the formation of all **a6-a8** compounds. Furthermore, the downfield shift of ^{1}H- and ^{13}C-NMR signals for C-7 confirmed the formation of compounds (**a6–a8**). The signals are shifted to 4.75 ppm (**a6**), 4.75 ppm (**a7**), and 4.70 ppm (a8), value for H^{7} and 58.4 ppm (**a6**), 58.4 ppm (a7) and 58.3 ppm (a8) value for C (7) from 3.39 ppm and 33.71 ppm, respectively.

3.2 CMC determination by Conductometry and UV-Vis Spectroscopy

Critical Micelle Concentration (CMC) is the most important indicator to be evaluated for a surfactant. The CMC value is the direct measure of efficiency of a surfactant. It shows the amount of surfactant required to reach maximum surface tension reduction. The lower the CMC value, the less amount of surfactant is required to effectively emulsify, solubilize and disperse at the surface. Lower CMC values will give rise to outstanding wetting and detergency performance [26]. Low CMC values of surfactants are significant for drug solubilization because they provide high stability of their micelles in solutions upon dilution in the blood [27-30].

The critical micelle concentration (CMC) of the synthesized compounds in ethanol and the effect of temperature on CMC has been determined by electrical conductivity and UV-Visible spectroscopic methods. The CMC values obtained by both methods are in closed agreement with

each other. CMC value is obtained by taking the point of junction or break point of the lines in the conductivity verses concentration plot (Fig. 1) and absorbance vs concentration graph (Fig. 2) [31]. The obtained CMC values for the compounds (**a6, a7** and **a8**) were 0.42, 0.41 and 0.40 mM respectively.

CMC value is plotted against temperature for all three compounds, where it can be seen that by increasing the temperature of system, the CMC value first goes down and then rises providing a U-shaped CMC vs temperature graph (Fig. S2). Such behavior has also been observed by other compounds of this type in literature [32-33].

This fluctuation in CMC values with temperature is the result of orientation of solvent molecules around the solvophilic and solvophobic parts of the amphiphiles in monomeric and micelles formed. Initial value of CMC is due to interaction between head group of surfactants and solvent molecules. An increase in temperature has affected the CMC in two conflicting manners. Initially CMC has decreased because higher temperature reduces interaction between polar head group of surfactants and solvent molecules, where the process of aggregate formation is favored and hence, micellization occurs at low concentration. Secondly, elevation in the value of CMC at further higher temperature is because of more unrest in solvent molecules, where the solvent molecules around micelles change their position more rapidly which leads to collapse of micelles. So, to form a stable micelle, comparatively larger number of amphiphile molecules are required leading to higher CMC value. Another observation is that CMC value declines by increasing the chain length of compound from C_6 to C_8. Increasing the length of hydrocarbon chain has the tendency of lowering the concentration at which aggregation is initiated owing to enhanced hydrophobic interaction between counter ion and micellar core [21]. So due to increase of hydrophobic character by lengthening the chain, decrease in the CMC value is clearly seen in these compounds. CMC values of all three compounds were also determined at different temperatures, (298 K, 303 K, 308 K, 313 K, and 318K), the results obtained are shown in the form graphs in Figures (S3-S5).

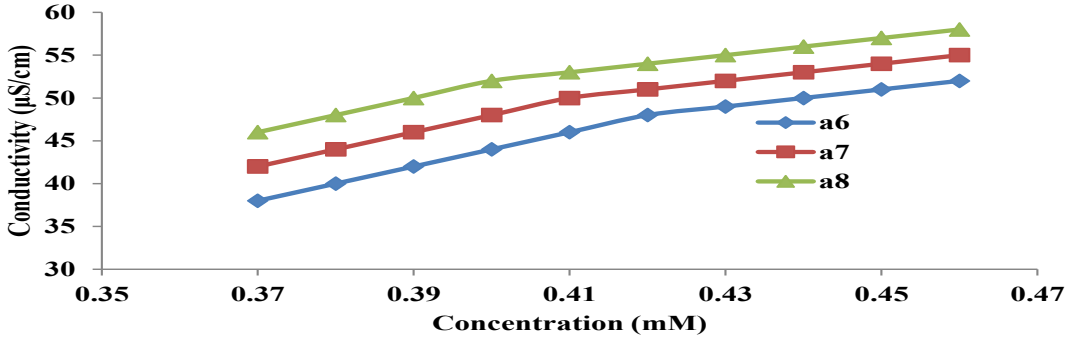


Fig. 1. Conductance vs. Concentration plots of compounds **a6-a8**

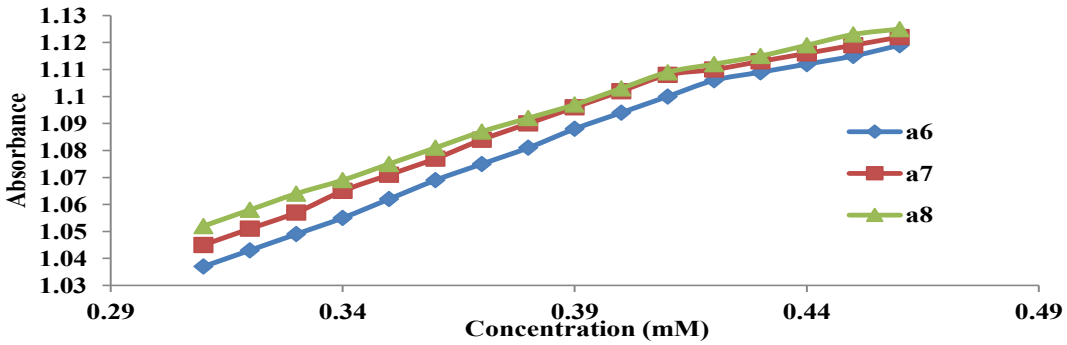


Fig. 2. Absorbance vs. Concentration plot of compounds **a6-a8**

3.2.1 Thermodynamics of the Micellization Process

From the CMC values at different temperatures, the thermodynamic parameters (ΔG, ΔH and ΔS) are calculated, using equations 1-4. Equation (1) gives the values of Gibbs free energy ΔG.

$$\Delta G = (2 - \beta)\, RT \ln X_{CMC} \quad (1)$$

where
β= Degree of dissociation.
R = Gas constant (8.314 J/mol K).
T = Absolute temperature.
X_{CMC} = CMC in terms of mole fraction.

"β" is calculated from the ratio of slopes of post-micellar and pre-micellar regions of conductivity concentration plots (Fig. S3-S5 for compounds **a6-a8**) respectively using following equation.

$$\beta = S_2 / S_1 \quad (2)$$

In equation (2) S_2 and S_1 show the slopes of straight lines in the post-micellar and pre-micellar regions, respectively. The enthalpy of micelle formation, "ΔH", was calculated according to equation 3.

$$\Delta H = -(\partial(\Delta G/T)/\partial T)\, T^2 \quad (3)$$

where
$\partial(\Delta G/T)/\partial T$ is obtained from the slope of plot between ΔG/T and T. The entropy of micellization was calculated by using equation 4.

$$\Delta S = (\Delta H - \Delta G)/T \quad (4)$$

The thermodynamic parameters obtained for micelle formation at different temperatures are represented in Table S1. The negative value of ΔG for all the three compounds shows that the micellization process is spontaneous in nature. The increase in the numerical value of ΔG with the rise of temperature indicates that the micellization process is favorable at the elevated temperatures. The positive value of ΔH for all compounds indicates that process of micellization is endothermic. Whereas the positive value of entropy shows that the process is entropy driven process. It follows the flickering cluster model of solvent, where the ice berg formation of solvent molecules around surfactant molecules, increases the order of solvent system. But the micellization process removes the surfactant molecules from solvent medium to micelles which make the entropy of system positive due to rupture of iceberg.

3.3 Antibacterial Activities

Antibacterial activities of these compounds were experienced against six bacterial strains (Table 1). The standard antibiotic used was Streptomycin sulphate. The zone of inhibition above 20 mm is regarded as significant, 18-20 mm as good; 15–17 mm is low and below 11-14 mm is considered as insignificant [22]. In this study, efficacy of all three compounds was good against all the bacterial strains, when compared with the standard drug Streptomycin sulphate. The main factors which account for antimicrobial activities of pyridinium surfactants are hydrophobicity of alkyl chain, surface activity and electron density of pyridinium nitrogen atom. The studied compounds have hydrophilic nitrogen atom and hydrophobic chain in the same molecule which could be responsible for the antimicrobial activities [34]. All these factors collectively contribute towards the antimicrobial nature of such compounds. From the present data, no clear trend could be made regarding the antimicrobial activity in relation to carbon chain length of the studied n-alkyl-2-methylpyridinium bromides.

Comparing the antimicrobial activity of these compounds with N-alkylimidazolium bromides with equal chain length, like n-Hexyl-3-methyl imidazolium bromide and n-octyl-3-methyl imidazolium bromide [35], it was found that all three pyridinium surfactants are better antibiotics as compared to imidazolium ionic liquids.

3.4 Antifungal Activity

Cationic surfactants can also act as efficient fungicides. Thus, the anti-fungal activity of synthesized surfactants was tested against three different fungal-strains; i-e, *Aspergillus niger*, *Aspergillus flavus*, and *Aspergillus fumigatus*. Terbinafine was used as a standard anti-fungal agent. Anti-fungal activity was measured in terms of percent inhibition in the linear growth of strain and

Table 1. Antibacterial activity of compounds **a6-a8.**

		Average Zone of Inhibition in mm ± SD					
S. No.	**Compounds**	***Enterobacte-aerogenes* (-)**	***Escherich-ia coli* (-)**	***Klebsiella pneumo-nia*(-)**	***Bacillus subtilis* (+)**	***Micrococcus leutus*(+)**	***Staphylococcus aureus* (+)**
1	**a6**	4.00	5.5	11.5	9.00	2.5	13.5
2	**a7**	7.00	4.9	12	7.00	1.8	11.25
3	**a8**	2.00	7.25	16	3.00	7.00	14.78
	Streptomycin Sulfate	12	13	23	10	19.00	10

Table 2. Antifungal activity of compounds **a6-a8.**

		Antifungal activity (% inhibition in linear growth)		
S. No.	**Sample code**	***Aspergillus niger***	***Aspergillus flavus***	***Aspergillus fumigatus***
1	**a6**	28.5±2.50	52.0±1.00	62.5±4.50
2	**a7**	25.3 ±1.00	57.0±2.15	64.7±2.81
3	**a8**	31.7±1.09	53.01±1.99	61.92±1.88
	Terbinafine	96.5±0.75	89.5±0.75	94.0±.0.00

is shown in Table 2. All the synthesized surfactants were highly active against fungal strains being tested and showed good results. Surfactants have a potential to work as antifungal agents, because they target the extra cytoplasmic region and thus does not need to enter the cells, thereby avoiding most cellular pump-based resistance mechanisms [36]. Hydrophilic part of the surfactant binds with an intermolecular hydrogen bond like a hook by attaching itself to the hydrophilic portion of the membrane surface. It is the first step of surfactant as an antifungal agent and length of the alkyl chain plays also an important role in eliciting the activity. The role of hydrophobic alkyl portion is still not well understood.

3.5 Antioxidant Activity

All three compounds have shown the excellent antioxidant activity which is presented in Table 3. Ascorbic acid was used as standard antibiotic and activity is shown in terms of percent inhibition. Our results of antioxidant activity reveal that an antioxidant with notable surface-active properties would possess better ability to inhibit lipid oxidation in emulsions because it would concentrate at the oil-water interface. Therefore, the antioxidant would act as a shield for the oil placed in the interior of the micelle [37].

Moreover, lipophilic antioxidants are more active in systems of high surface area, such as emulsions, micelles and membranes [38, 39]. That's why lipophilic antioxidants would have more affinity for the oil-water interface, therefore, would inhibit lipid oxidation more efficiently. The results open up potential new applications for these surfactant antioxidants in the food, pharmaceutical, or personal-care industries.

3.6 Surfactant as Drug Carrier

Micelles play a role in drug delivery as they provide system for high drug loading, control drug release, enhanced plasma circulation time and slow in vivo clearance. Drug molecules can be entrapped physically in these micellar assemblies via passive diffusion or in situ loading during formation. On addition of various concentration of surfactant molecules, change in absorption pattern of drug was used as a basic parameter to study the extent of drug-surfactant interactions. The interaction of compound **a6** with Ketoprofen as drug is shown in Fig. 3. In pre-miceller concentration of surfactants, maximum absorptions of Ketoprofen has decreased with red-shift (Fig. 3). This decrease in absorption maxima is because of increase in the local concentration of the chromophore that indicates binding of drug molecules to the polar heads of

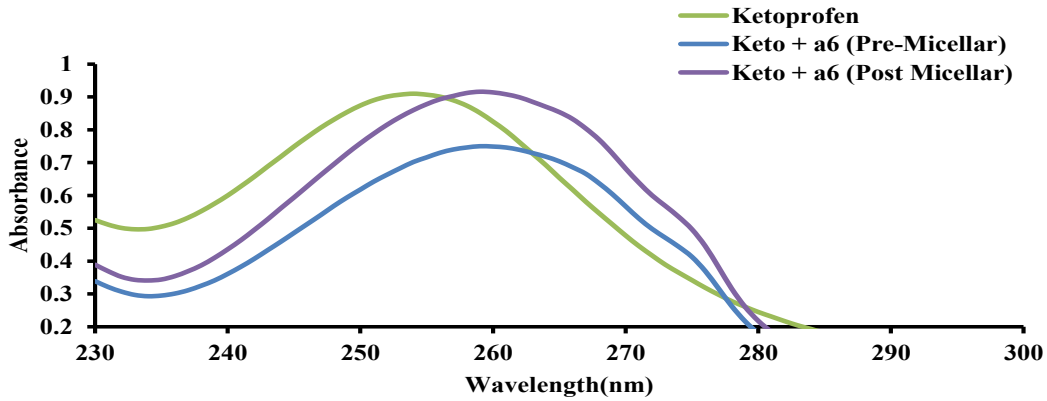


Fig. 3. Absorption spectra of Ketoprofen in the absence and presence of pre-micellar and post-micellar concentration of compound **a6**.

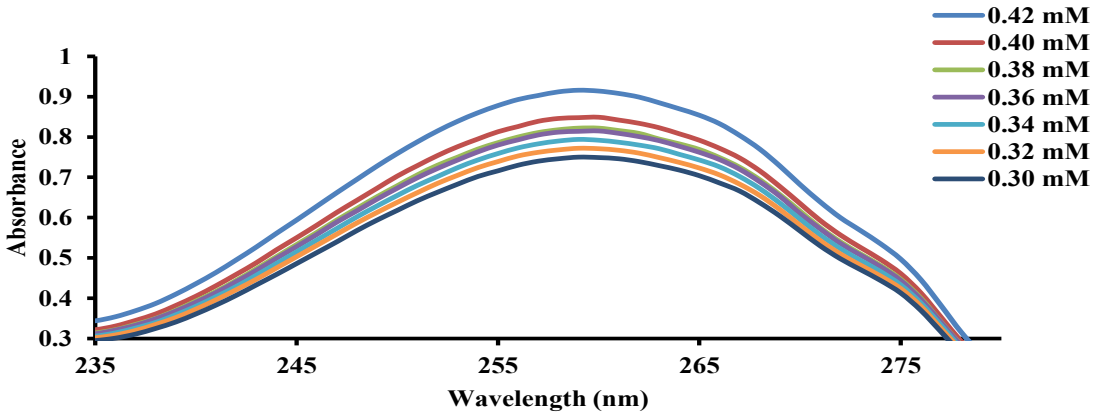


Fig. 4. Absorption spectra of Ketoprofen in the presence of varying concentration of compound **a6**.

amphiphiles. The negetively charged portion of ketoprofen is oriented towards the positively charged head group of the surfactant molecule leading to formation of a drug-surfactant complex. Moreover, it was observed that absorption of the system rises from 0.30 mM to 0.42 mM) by varying the concentration of **a6** while keeping the concentration of ketoprofen constant (Fig. 4). As the concentration of surfactant is gradually increased, hydrophobic interaction of alkyl chain group with polar solvent start to escalate. This condition forces alkyl chains of the surfsctnts to bind with the aromatic groups of ketoprofen. As the alkyl chains start to combine with aryl groups of the drug, negetively charged groups of the drug become free which causes an increase in the absorption [40-43]. Similar observations were reported for the interaction of Ketoprofen with compound **a7** and **a8** (Fig. S6-S9).

The UV-Visible spectroscopic studies of the interaction of Flurbiprofen with the varying concentration (0.30-0.42 mM) of compound a6 has been shown in Fig. 5, and 6, which depict that the absorption decreases with the increase in concentration of a6 along with bathochromic shift, indicating the encapsulation of drug in the micelles. Similar observations were observed for the interaction of Flurbiprofen with compounds **a7** and **a8** (Fig. S11-S13).

3.6.1 Binding constant (Kb) and Gibb's free energy (ΔG)

The Kawamura equation was used to study the partitioning of the drug molecules in solvent micellar system (Kawamura et al., 1989) given as equation 5.

$$1/\Delta A = 1 / K_b \Delta A_\infty (C_a + Cs^{mo}) + 1/\Delta A \qquad (5)$$

where

$\Delta A = A - A^o$

A = absorbance of drug in the presence of surfactant

A^o = absorbance of drug in the absence of surfactant

C_a = drug concentration

$Cs^{mo} = Cs\text{-}CMC^o$.

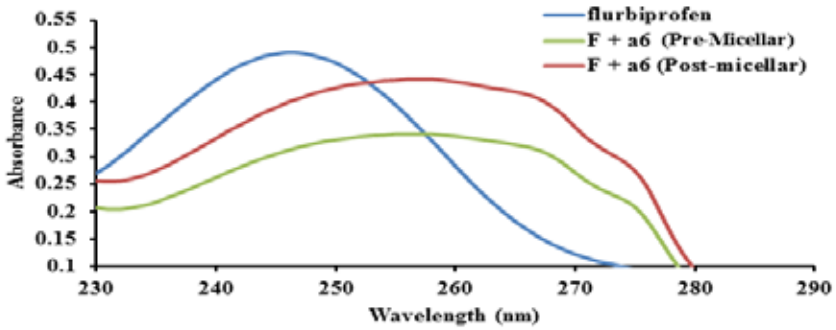


Fig. 5. Absorption spectra of Flurbiprofen in the absence and presence of pre-micellar and post-micellar concentrations of compound **a6**.

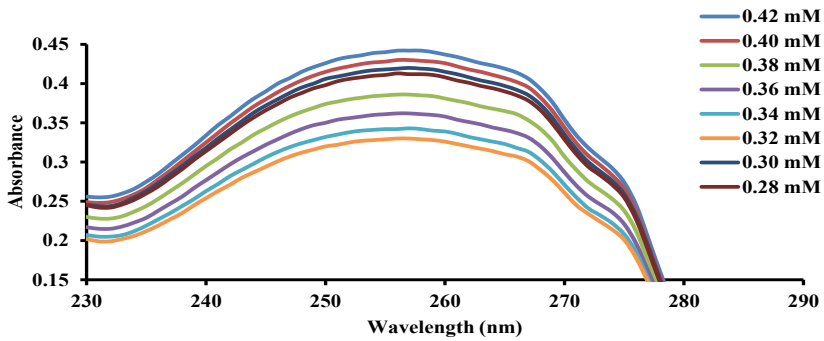


Fig. 6. Absorption spectra of Flurbiprofen in the presence of varying concentrations of compound **a6**.

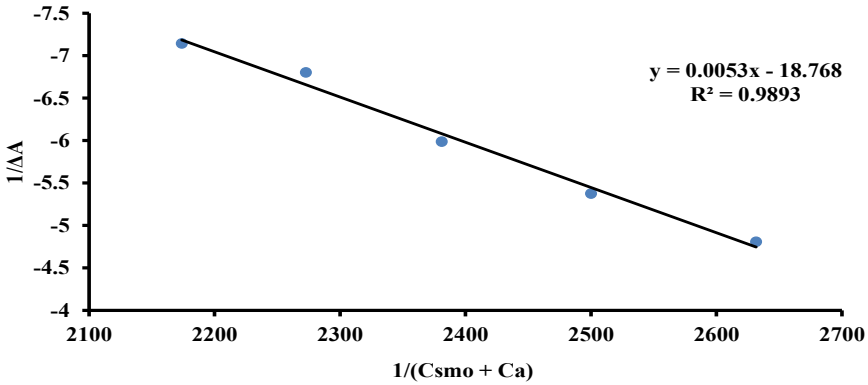


Fig. 7. Plot of 1/(Csmo + Ca) vs.1/ΔA for **a6** with Ketoprofen.

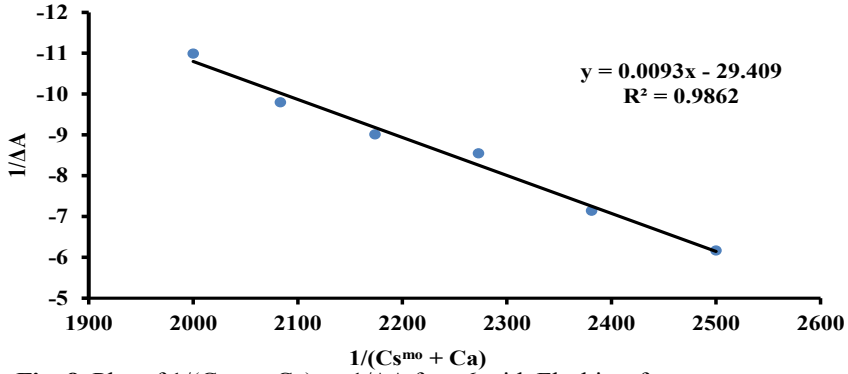


Fig. 8. Plot of 1/(Cs^{mo} + Ca) vs.1/ΔA for **a6** with Flurbiprofen.

Table 3. Antioxidant activity of compounds **a6-a8.**

Antioxidant activity (% inhibition)						
S. No.	**Sample code**	**5 mg/10 ml**	**4mg/10 ml**	**3mg/10 ml**	**2mg/10 ml**	**1mg/10 ml**
1	**a6**	56.5±1.50	32±1.00	13.5±2.50	10±1.00	7.5±0.50
2	**a7**	42±0.99	21.25±1	16±0.98	11.43±1.7	9.23±0.35
3	**a8**	39.04±1.21	27± 0.75	13±0.51	11.98±1.2	11.20±0.72
	Ascorbic acid	80.5±2.00	70.5±3.50	58±3.00	49.5±0.50	42.5±3.50

Table 4. : Parameters calculated from Kawamura equation for drug surfactant interaction of compounds **a6-a8** with Ketoprofen

S. No.	**Cs**	**(CMC) 10-3**	**(Cs-CMC) 10-3**	**(Ca) 10-3**	**(Csmo+Ca) 10-3**	**1/ Csmo + Ca**	**ΔA**	**1/ΔA**
				a6				
1	0.42	0.42	0	0.5	0.5	2000	-0.05	-20
2	0.4	0.42	-0.02	0.5	0.48	2083.33	-0.115	-8.696
3	0.38	0.42	-0.04	0.5	0.46	2173.91	-0.14	-7.143
4	0.36	0.42	-0.06	0.5	0.44	2272.72	-0.147	-6.803
5	0.34	0.42	-0.08	0.5	0.42	2380.95	-0.167	-5.988
6	0.32	0.42	-0.1	0.5	0.4	2500	-0.186	-5.376
7	0.3	0.42	-0.12	0.5	0.38	2631.58	-0.208	-4.808
				a7				
1	0.42	0.41	0.01	0.5	0.51	1960.78	-0.245	-4.082
2	0.4	0.41	-0.01	0.5	0.49	2040.82	-0.263	-3.802
3	0.38	0.41	-0.03	0.5	0.47	2127.66	-0.283	-3.534
4	0.36	0.41	-0.05	0.5	0.45	2222.22	-0.298	-3.356
5	0.34	0.41	-0.07	0.5	0.43	2325.58	-0.342	-2.294
6	0.32	0.41	-0.09	0.5	0.41	2439.02	-0.376	-2.66
7	0.3	0.41	-0.11	0.5	0.39	2564.1	-0.4	-2.5
8	0.28	0.41	-0.13	0.5	0.37	2702.7	-0.42	-2.381
				a8				
1	0.42	0.40	0.02	0.5	0.52	1923.08	-0.22	-4.55
2	0.4	0.40	0	0.5	0.5	2000	-0.228	-4.39
3	0.38	0.40	-0.02	0.5	0.48	2083.33	-0.241	-4.15
4	0.36	0.40	-0.04	0.5	0.46	2173.91	-0.245	-4.08
5	0.34	0.40	-0.06	0.5	0.44	2272.73	-0.257	-3.89
6	0.32	0.40	-0.08	0.5	0.42	2380.95	-0.26	-3.84
7	0.3	0.40	-0.1	0.5	0.4	2500	-0.282	-3.55

Table 5. Parameters calculated from drug interaction studies**.**

Compound+Ketoprofen	**A**	**Am**	**A◦**	**E◦**	**Em**	**Cm**	**M**	**n**
a6	0.497	0.677	0.653	1.92	1.35	2.73	3.3	0.7
a7	1.223	1.396	1.405	3.69	3.32	4.86	2.6	0.9
a8	1.345	1.678	1.456	3.56	3.34	4.78	2.6	1.7

CMC^o= CMC of surfactant in solvent
C_s = total surfactant concentration.
$\Delta A\infty = A_b - A^o$.
A_b = absorbance of surfactant bound drug

By plot of $1/(Cs^{mo} + Ca)$ Vs $1/\Delta A$, it is possible to calculate binding constant (K_b) from slope of the straight line obtained. Gibb^{o}s free energy (ΔG) can be calculated from equation 6.

$$\Delta G = - RT \ln K_b \quad (6)$$

The plot $1/(Cs^{mo} + Ca)$ Vs $1/\Delta A$ for the interaction of Ketoprofen and Flurbiprofen with compound **a6**.have been shown in Fig. 7 and 8. Similar observations are found for compounds **a7** and **a8** with both drugs. Fig. S14-S17. The calculated parameters from Kawamura equation for the interaction of compounds **a6-a8** with Ketoprofen are shown in Table 4 and of Flurbiprofen are shown in Table S2.

3.6.2 Number of Drug Molecules Attached per Micelle (n)

Number of drug molecules attached per micelle can be determined by using following equations;

$$n = Cm/M \quad (7)$$
$$M = Cs\text{-}CMC / N \quad (8)$$
$$Cm = A^\circ\text{-}A \,/\, E^\circ\text{-}Em \quad (9)$$

where
E^o is calculated from A^o and E_m from
n = number of drug molecules per micelle
C_m= concentration of drug solubilized in micelle in mol/dm3
M= micelle concentration
C_s= concentration of surfactant in mol/dm3
N = aggregation number of surfactant
A^o is the absorbance of drug in the absence of surfactant while A is the absorbance of drug at same wavelength in the presence of surfactant. E^o and E_m are absorptivities at A^o and A_m respectively.
A_m = the value of absorbance where it becomes almost constant.

Number of drug molecules per micelle (n) calculated from the equation 6-8 shows the stronger interaction of the selected drugs with the synthesised compounds. Parameters calculated from equations are shown in Table 5 and S3.

4. CONCLUSIONS

In the present study, three new cationic surfactants were synthesized, characterized and evaluated for their micellization behavior, antibacterial, antifungal and antioxidant activities. The CMC values obtained via aggregation studies i.e. conductometry and UV-Vis spectroscopy for the compounds **a6**, **a8** and **a9** were 0.42 mM, 0.41mM and 0.40 mM, respectively. The UV-Visible spectroscopic technique was further employed to study drugs-surfactant interaction and their partitioning behavior between aqueous and micellar phase. The data obtained from UV-Visible spectra is utilized for determining partition characteristics of anionic drug with cationic surfactant. The drug-surfactants interaction study revealed that the structure of additive molecule and the charge present on surfactant molecules contributes largely towards the phenomenon of solubilization. The drug surfactant interaction parameters calculated has shown that the drugs (Ketoprofen and Flurbiprofen) have high binding constant with surfactant micelles due to the electrostatic interaction. The electrostatic force prevents the drug from entering in to the inner core of micelle and drug molecule remain attach to the periphery of surfactant micelle. The Gibb's free energy value has shown the spontaneity of interaction process whereas value of n i.e. number of drug molecules attached per micelles also support the interaction of drugs with the synthesized compounds.

5. ACKNOWLEDGMENTS

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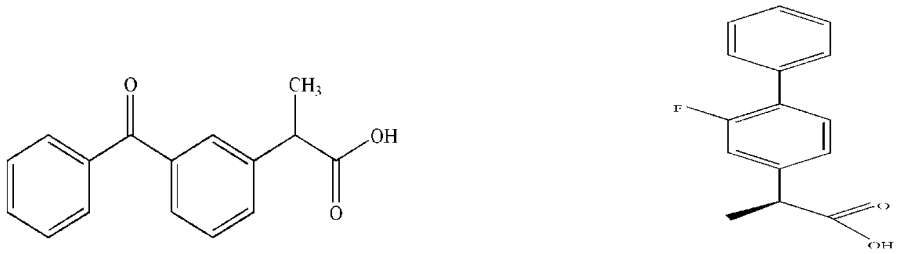
Supplementary Material



Ketoprofen. Flurbiprofen.

Fig. S1. Chemical structures of drugs used.

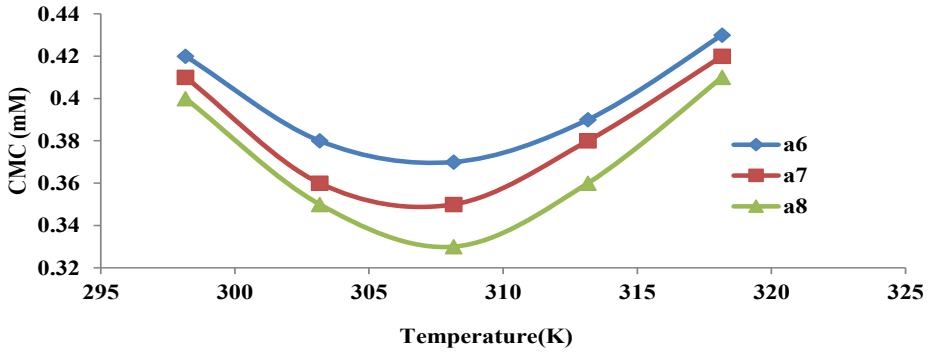


Fig. S2. CMC vs. Temperature plot for compounds (**a6-a8**).

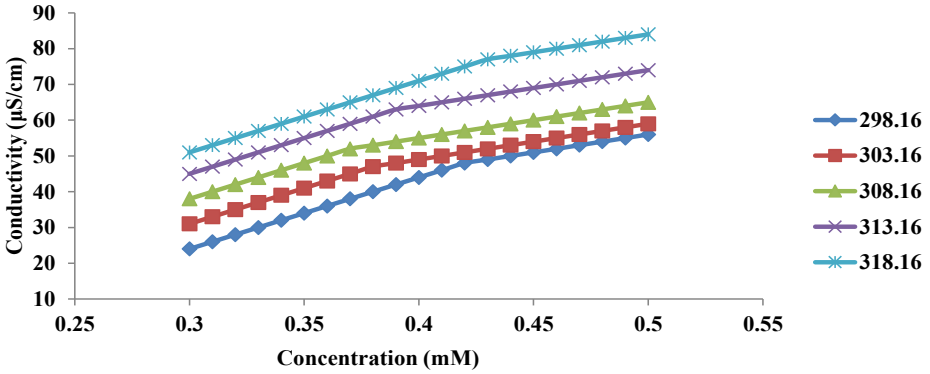


Fig. S3. Conductance vs. Concentration plot compound **a6** at different temperatures.

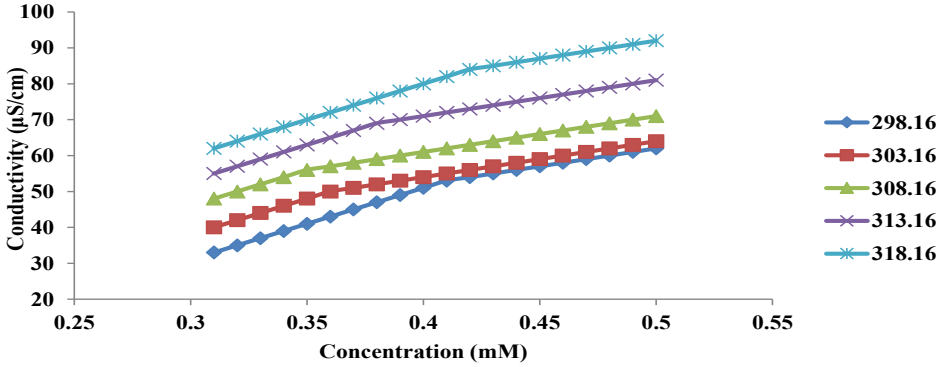


Fig. S4. Conductance vs. Concentration plot of compound **a7** at different temperatures.

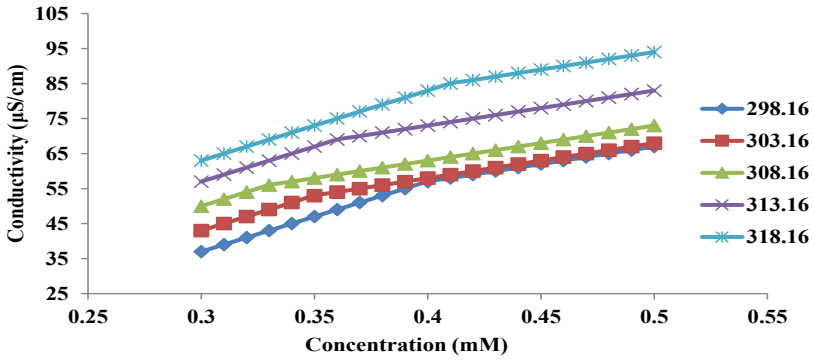


Fig. S5. Conductance vs. Concentration plot of compound **a8** at different temperatures.

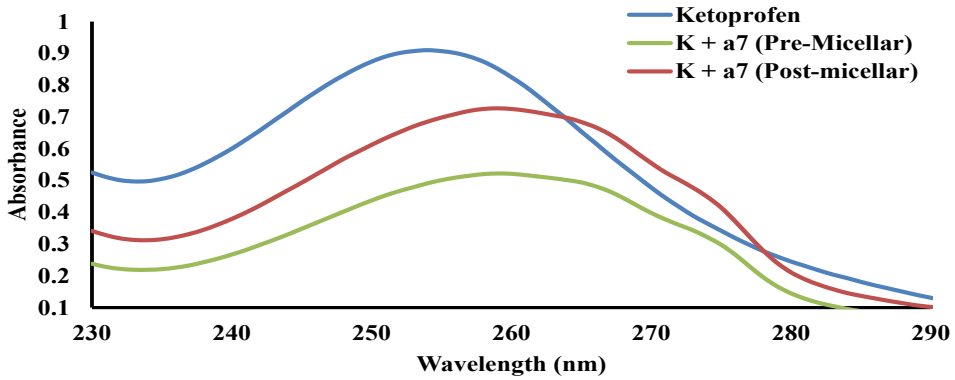


Fig. S6. Absorption spectra of Ketoprofen in the absence and presence of pre-micellar and post-micellar concentration of compound **a7**.

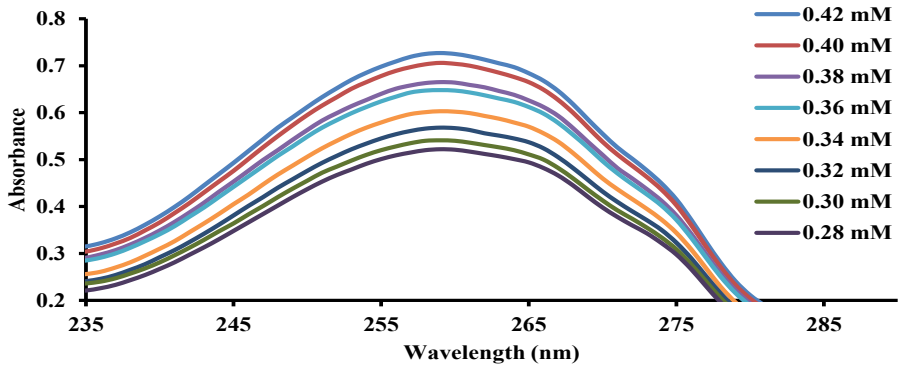


Fig. S7. Absorption spectra of Ketoprofen in the presence of varying concentrations of compound **a7**.

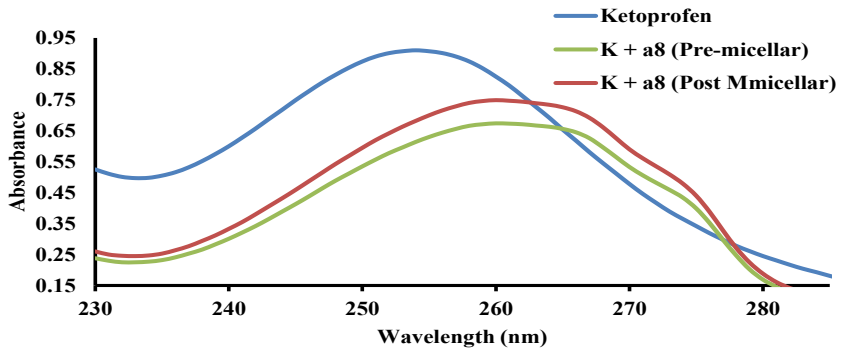


Fig. S8. Absorption spectra of Ketoprofen in the absence and presence of pre-micellar and post-micellar concentrations of compound **a8**.

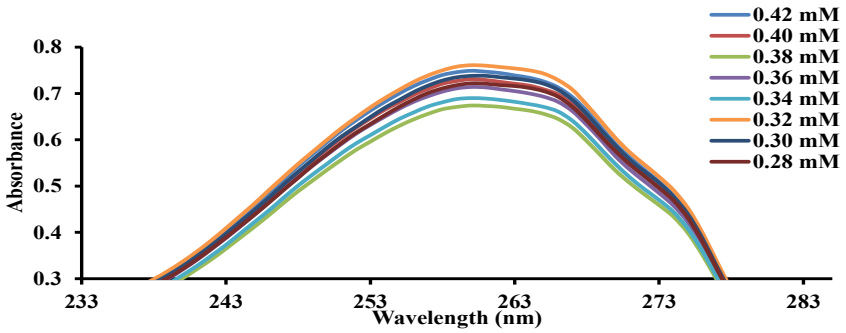


Fig. S9. Absorption spectra of Ketoprofen in the presence of varying concentration of compound **a8**.

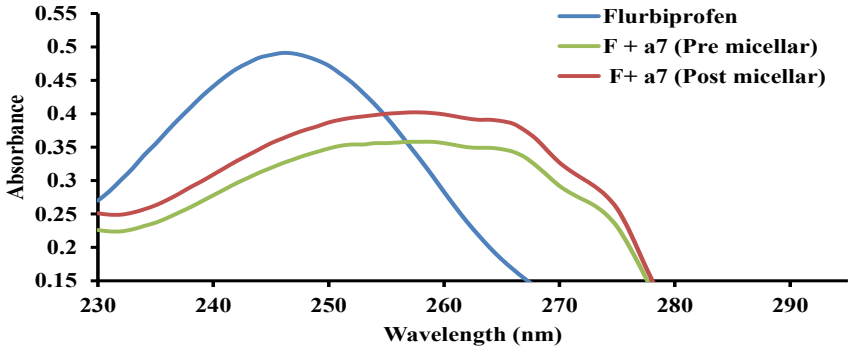


Fig. S10. Absorption spectra of Flurbiprofen in the absence and presence of pre-micellar and post-micellar concentrations of compound **a7**.

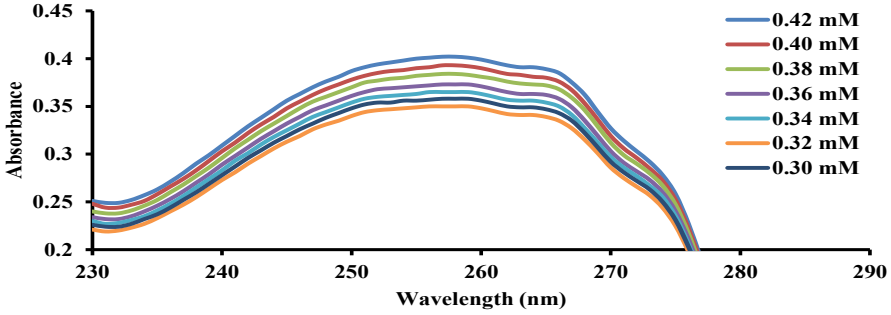


Fig. S11. Absorption spectra of Flurbiprofen in the presence of varying concentrations of compound **a7**.

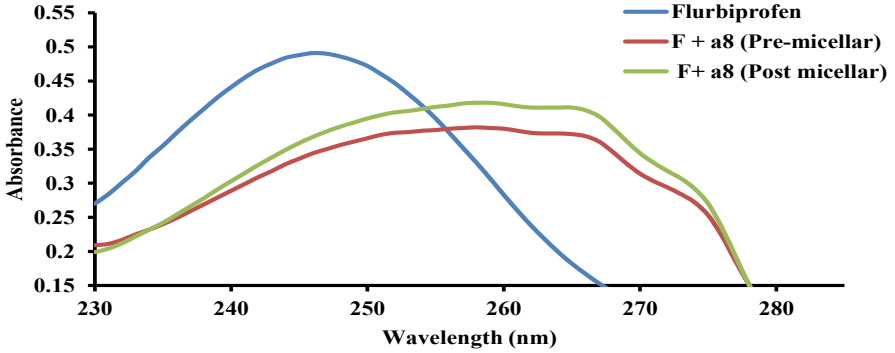


Fig. S12. Absorption spectra of Flurbiprofen in the absence and presence of pre-micellar and post-micellar concentrations of compound **a8**.

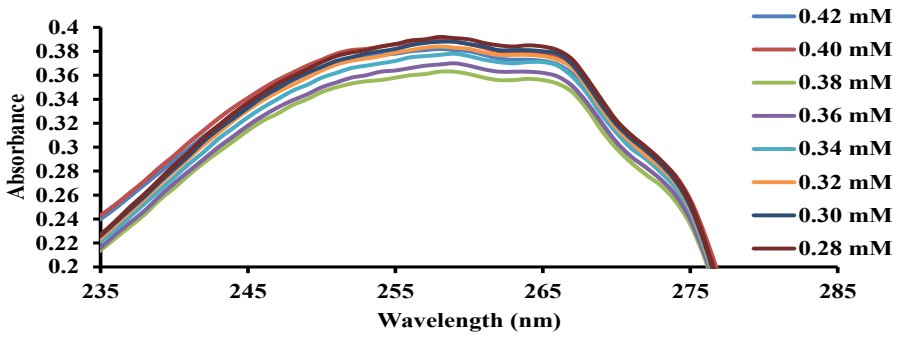


Fig. S13. Absorption spectra of Flurbiprofen in the presence of varying concentrations of compound **a8**.

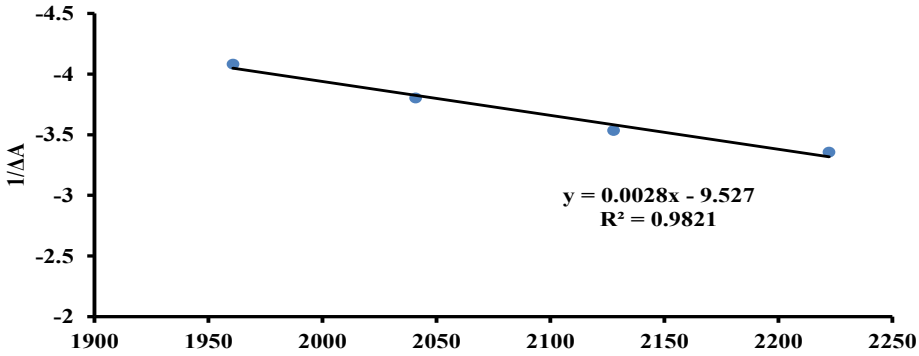


Fig. S14. Plot of 1/(Cs^{mo} + Ca) vs.1/ΔA for **a7** with Ketoprofen.

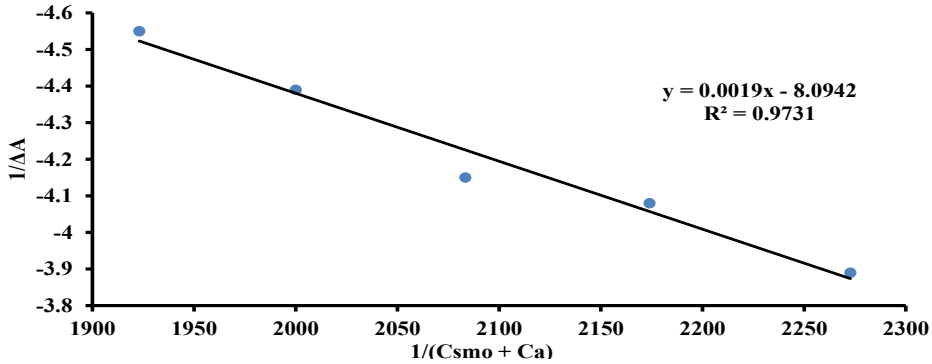


Fig. S15. Plot of 1/(Cs^{mo} + Ca) vs.1/ΔA for **a8** with Ketoprofen

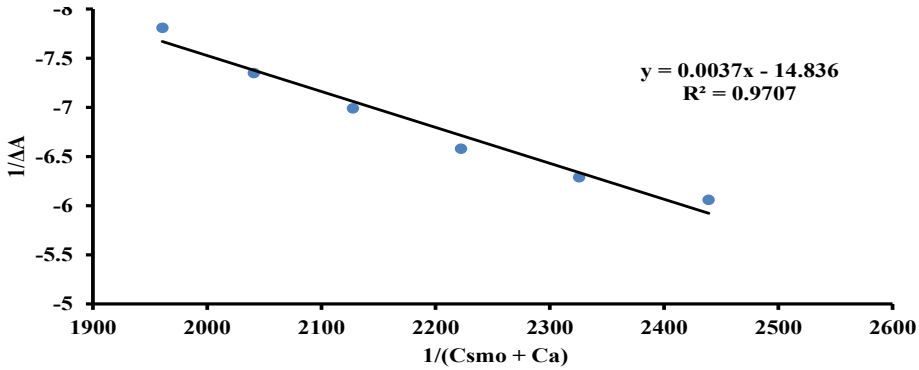


Fig. S16. Plot of 1/(Cs^{mo} + Ca) vs.1/ΔA for **a7** with Flurbiprofen.

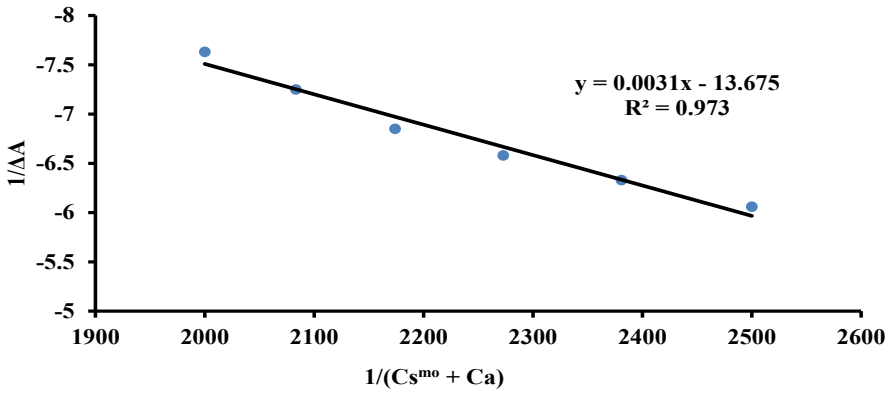


Fig. S17. Plot of $1/(Cs^{mo} + Ca)$ vs.$1/\Delta A$ for **a8** with Flurbiprofen

Table S1. Thermodynamic parameters of **a6-a8** at different temperatures

S. No.	Temperature (K)	CMC (mM)	XCMC	LnXCMC	ΔG(J/mol)	ΔH(J/mol)	ΔS(J/mol.K)
				a6			
1	298.16	0.42	0.0000244	-10.6174	-39479.29	102945.92	477.67
2	303.16	0.38	0.0000194	-10.8471	-41009.79	106427.13	486.33
3	308.16	0.37	0.0000215	-10.7441	-41290.49	109871.71	490.53
4	313.16	0.39	0.0000227	-10.6915	-41754.84	113466.04	495.66
5	318.16	0.43	0.0000250	-10.5938	-42034.12	117118.23	533.78
				a7			
1	298.16	0.41	0.0000239	-10.6415	-39568.88	157351.19	185.48
2	303.16	0.36	0.0000209	-10.7715	-40724.12	16267.359	187.49
3	308.16	0.35	0.0000204	-10.7997	-41504.04	16808.377	189.27
4	313.16	0.38	0.0000221	-10.7174	-41856.29	17358.240	189.08
5	318.16	0.42	0.0000244	-10.6174	-42127.48	17916.961	188.72
				a8			
1	298.16	0.40	0.0000233	-10.6661	-39660.69	21246.95	204.27
2	303.16	0.35	0.0000204	-11.7997	-40830.63	21965.53	207.13
3	308.16	0.33	0.0000192	-11.8585	-41727.44	22696.05	209.05
4	313.16	0.36	0.0000209	-11.7715	-42067.44	23438.53	209.17
5	318.16	0.41	0.0000239	-10.6415	-42223.08	24192.96	215.03

Table S2. Parameters calculated from Kawamura equation for drug surfactant interaction of compounds **a6-a8** with Flurbiprofen.

S. No.	Cs	(CMC) 10^{-3}	(Cs-CMC) 10^{-3}	(Ca) 10^{-3}	(Cs^{mo}+Ca) 10^{-3}	1/ Cs^{mo} + Ca	ΔA	1/ΔA
				a6				
1	0.42	0.42	0	0.5	0.5	2000	-0.091	-10.99
2	0.4	0.42	-0.02	0.5	0.48	2083.33	-0.102	-9.8
3	0.38	0.42	-0.04	0.5	0.46	2173.91	-0.111	-9.01
4	0.36	0.42	-0.06	0.5	0.44	2272.72	-0.117	-8.55
5	0.34	0.42	-0.08	0.5	0.42	2380.95	-0.14	-7.14
6	0.32	0.42	-0.1	0.5	0.4	2500	-0.162	-6.17
7	0.3	0.42	-0.12	0.5	0.38	2631.58	-0.178	-5.62
				a7				
1	0.42	0.41	0.01	0.5	0.51	1960.78	-0.128	-7.81
2	0.4	0.41	-0.01	0.5	0.49	2040.82	-0.136	-7.35
3	0.38	0.41	-0.03	0.5	0.47	2127.66	-0.143	-6.99
4	0.36	0.41	-0.05	0.5	0.45	2222.22	-0.152	-6.58
5	0.34	0.41	-0.07	0.5	0.43	2325.58	-0.159	-6.29
6	0.32	0.41	-0.09	0.5	0.41	2439.02	-0.165	-6.06
7	0.3	0.41	-0.11	0.5	0.39	2564.1	-0.172	-5.81
8	0.28	0.41	-0.13	0.5	0.37	2702.7	-0.128	-7.81
				a8				
1	0.42	0.40	0.02	0.5	0.52	1923.08	-0.123	-8.13
2	0.4	0.40	0	0.5	0.5	2000	-0.131	-7.63
3	0.38	0.40	-0.02	0.5	0.48	2083.33	-0.138	-7.25
4	0.36	0.40	-0.04	0.5	0.46	2173.91	-0.146	-6.85
5	0.34	0.40	-0.06	0.5	0.44	2272.73	-0.152	-6.58
6	0.32	0.40	-0.08	0.5	0.42	2380.95	-0.158	-6.33
7	0.3	0.40	-0.1	0.5	0.4	2500	-0.165	-6.06
8	0.28	0.40	-0.12	0.5	0.38	2631.58	-0.169	-5.92

Table S3. Parameters calculated from drug interaction studies

Compound+Flurbiprofen	A	Am	A◦	E◦	Em	Cm	M	n
a6	0.789	0.678	0.879	2.45	2.89	2.27	3.4	0.73
a7	0.987	0.698	0.879	2.35	1.98	2.87	3.5	0.43
a8	0.678	0.712	0.879	3.45	1.67	2.98	3.9	0.63