Aggregation Behavior of Antipsychotic Drug under the Influence of Bile Salt in Aqueous/Urea Solution

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Abstract: The self-assembly of pharmaceutical amphiphiles is an important area of research because of the involvement of these amphiphiles in physiological processes. The mixed micellization behavior of antipsychotic drug (chlorpromazine hydrochloride, CPZ) in the presence of bile salt (sodium cholate, SC) was studied by surface tension and fluorescence techniques in aqueous/urea solution. The output of the study has been analyzed by using different models (Clint, Rubingh, and Motomura) for mixed amphiphilic systems. The attractive or synergistic interactions between these two amphiphiles in water/urea were confirmed by the obtained data. Various thermodynamic parameters for the mixed micellization process have been computed and discussed.

Key words: anti-psychotic drug, bile salt, mixed micelle, synergism, urea

1 Introduction

The liver of vertebrate secreted a greenish-yellow color compound, known as bile or gall. The main compositions of bile are bile acid, cholesterol, phospholipids, water, and pigments. The physicochemical properties of these compounds have been broadly investigated and are still significant in scientific research1–3. The bile acids or bile salts are special classes of bio-surfactants that have scientific values such as solubilizer for cholesterol and lipids, emulsifier and dispersion agents in cosmetics, medicines, and chemicals. The bile stored in gallbladder after that it discharges into the duodenum through a biliary duct. The lipolysis occurs at the duodenum and simpler compounds formed in lipolysis. The solubilization of cholesterol and lipids are being done by bile salt and phospholipids make mixed micelle for utilization by mammal’s body4. The compounds like bilirubin, cholesterol, and lecithin have a narrow concentration in water. Though, the bile has high concentration due to solubilization by bile salts. The formation of gallstones is the result of precipitation of sterols in abnormal conditions. The aggregation of bile salt is different from conventional surfactants and is important because of its physicochemical properties. The ordinary surfactants have both hydrophobic and hydrophilic parts in the same body. On the other hand, bile salt has facial amphiphility. The polar side generally known as α side while non-polar face named as β side in a rigid steroid skeleton (Scheme 1).

When a bile salt is dissolved in water it makes micelle by hydrophobic interaction over their hydrophobic sides by the hydrogen bond formation. The micelles of bile salt solubilize poorly soluble molecules so these are used in pharmaceutical formulations5, 6. Bile salts interact with phospholipids in the cell membrane to increase drug penetration through various biological membranes and act as permeability enhancers7, 8. The ability of bile salt to achieve a specific goal depends on its hydrophobicity. The more hydrophobic micellar core has great capability to admit hydrophobic drug constituents. The solubilization capability of the micellar system can be increased by chemical alteration of the bile steroid skeleton. The other technique to develop the solubilization properties of the micellar system is to produce mixed micelles by combining individual amphiphiles with different physicochemical properties. In the scientific world, one of the capable schemes for drug delivery may be mixed micelles of bile salts.

The physicochemical properties of a mixed micelle of bile salts with amphiphilic drugs are a dynamic part of modern research. A large number of researches has been done on the aggregation behavior of bile salts alone or mixed with other amphiphiles9–12. Herein, we have investigated the mixed micellization behavior of bile salt, sodium cholate (SC) with an antipsychotic drug, chlorpromazine
also seen in mixed micelle of bile salt and CPZ. The endeavor of this effort is to give the improved information about the formation of bile CPZ/SC mixed micelle and to be aware of the actions of such coordination in pharmaceuticals to improve the relevance of mixed systems.

2 Experimental Section

2.1 Chemical reagents

The anti-psychotic drug (chlorpromazine hydrochloride, CPZ) and bile salt (sodium cholate, SC) both have opposite nature are used in the experiments and were the products of Sigma having purity ≥ 0.97. The de-ionized double-distilled water was used to make all solutions having specific conductivity 1 to 6 μS cm⁻¹. Microsoft Excel was used to compute all parameters and graphs were made by Origin 8.0 software.

2.2 Surface tension measurements

The surface tension of individual and mixed amphiphiles were determined by the attension tensiometer (Sigma 701, Germany). The ring detachment technique was followed for experiments. The ultrapure water having a surface tension value of around 70 at 298.15 is used to calibrate the instrument time to time earlier than any measurement was completed. The temperature of the examined solution keeps constant 298.15 K (error ± 0.1 K) by using a thermostat. Attension tensiometer works on Du Nouy’s principal given by French physicist Pierre Lecomte du Nouy. Ethanol flame was used to clean the ring after each set of experiments. The cmc was determined by the logarithm of surfactant concentration vs. measured surface tension graph (Fig. 1).

2.3 Fluorescence measurements

The steady-state fluorescence measurement was done by utilizing Hitachi F–7000 spectrometer having a 150W xenon lamp as an excite source. The CPZ emission spectrum was obtained in the range of 400 to 600 nm by choosing the excitation wavelength of 315 nm (Fig. 2). The 10 nm quartz cell was used for the experiments and emission and excitation slits were fixed at 5nm. The concentrations of the examined solution were prepared above than the value of cmc.

3 Results and Discussion

3.1 Critical micelle concentration (cmc)

The surface tension measurements were used to determine the cmc of individual and mixed amphiphiles. The surface tension of the solution (γ) was measured against the concentration of amphiphile as shown in Fig. 1. The
surface tension of water decreases in the addition of a surfactant solution until the interface is saturated with amphiphilic monomers. At this saturation point, the monomers try to aggregate and to ensure a hydrophilic periphery, hiding the hydrophobic tail within a cage to avoid water. Therefore, the surface tension values do not change after reaching a critical concentration known as critical micelle concentration (cmc). The cmc value of CPZ (14.5 mM) is higher than CTAB (1.0 mM) being both cationic in nature. The higher cmc value of CPZ is due to its structure. The hydrophobic portion of the CPZ molecule is short and rigid in comparison to CTAB. Therefore, CPZ aggregates at higher concentration. It is confirmed from SC structure (Scheme 1) that it behaves like an anionic surfactant. The molecular structure of SC differs from the other conventional anionic surfactants. Instead of the hydrophobic tail and hydrophilic head, bile salts have a rigid steroid group with four rings attached to a short and flexible tail and have higher cmc values. The hydrophilic character of bile salt comes from the presence of OH groups. The dissimilarity is owing to the manner of aggregation of two amphiphiles. The drug monomers aggregate in a normal way while the bile salt forms micelle in two steps. In the current study, the cmc values of CPZ, SC and CPZ + SC mixed system were computed by surface tension method in the absence and presence of urea. The values of cmcs in the absence and presence of urea are given in Table 1.

The values for individual amphiphiles are a good agreement with the previously reported values. In the presence of urea the cmc values for individual and mixed...
system increases. Similar behavior has been found in the literature\(^\text{19}\). The direct and indirect mechanism has been proposed to clarify the outcome of urea on the micelle properties of amphiphiles\(^\text{20, 21}\). According to Frank’s theory\(^\text{22}\), the water molecules around the hydrophobic solute make ice-like cages also known as icebergs, where water-water interactions are reinforced. The urea breaks the iceberg structure of water without altering the micellar structure so the cmc values increase in the presence of urea. Another mechanism of increasing the cmc values in the presence of urea is the direct binding of urea molecules with the hydrophobic solute. Out of the above two mechanisms, the first one is more acceptable.

It is apparent from Table 1 that the experimentally cmc values of mixed systems are lower than the CPZ and SC individually. The electrostatic repulsive interactions between ions of SC are minimized by the accumulation of the drug molecules through the electrostatic attractive interactions between \(-\text{COOH}\) group of SC and \((\text{CH}_3)_2\text{NH}\) group of CPZ molecules (Scheme 2).

As a result of this, the cmc values of the mixed amphiphilic system decreases and the association of monomers takes place at lower concentration. The data of Table 1 clearly indicate that the cmc values of mixed systems increase with the mole fraction of drug, the reason behind this is the attractive interactions between \((\text{CH}_3)_2\text{NH}\) group of drug and \(-\text{COOH}\) group of bile salt defeated by the overcome repulsive interactions between the same charged head groups of drug molecules\(^\text{18}\). The experimental cmc values of CPZ/SC mixture at all mole fractions of the CPZ

| α_{CPZ} | cmc (mmol · dm\(^{-3}\)) | cmc_{ideal} (mmol · dm\(^{-3}\)) | \(X_1\) | \(X_{1\text{ideal}}\) | \(-\beta\) | \(f_1\) | \(f_2\) |
|---------|------------------------|-------------------|------|-----------------|------|------|------|
|         | CPZ + SC               |                   |      |                 |      |      |      |
| 0       | 9.00                   |                   |      |                 |      |      |      |
| 0.10    | 2.20                   | 9.35              | 0.37 | 0.06            | 7.92 | 0.04 | 0.35 |
| 0.20    | 2.47                   | 9.74              | 0.39 | 0.13            | 6.63 | 0.09 | 0.36 |
| 0.80    | 2.82                   | 12.90             | 0.56 | 0.71            | 6.42 | 0.28 | 0.14 |
| 0.90    | 3.16                   | 13.70             | 0.60 | 0.85            | 6.85 | 0.33 | 0.09 |
| 1       | 14.50                  |                   |      |                 |      |      |      |
|         | CPZ + SC + 250 mM Urea |                   |      |                 |      |      |      |
| 0       | 11.10                  |                   |      |                 |      |      |      |
| 0.10    | 2.57                   | 11.15             | 0.37 | 0.07            | 8.04 | 0.04 | 0.33 |
| 0.20    | 2.70                   | 11.90             | 0.40 | 0.14            | 7.01 | 0.08 | 0.32 |
| 0.80    | 3.01                   | 15.20             | 0.56 | 0.73            | 6.84 | 0.25 | 0.12 |
| 0.90    | 3.39                   | 15.90             | 0.60 | 0.86            | 7.29 | 0.30 | 0.07 |
| 1       | 16.70                  |                   |      |                 |      |      |      |

Table 1 Physicochemical parameters for CPZ + SC mixed amphiphilic systems in the absence and presence of 250 mM urea at temperature \(T = 298.15\) K and pressure \(p = 0.1\) MPa.

Scheme 2 Schematic diagram showing the interaction between CPZ and SC.
drug concentration, the cmc value of mixtures increases means smaller size, as well as loose-packed micelles, are formed, therefore the availability of the hydrophobic portion of employed amphiphiles increases means more water molecules are present in the region of the hydrophobic portion of the amphiphiles. The effect of urea decreased with increases in the concentration of CPZ because of the binding ability of urea with the hydrophobic portion of the solutes mixtures was decreased to some extent due to the presence of more water in that province.

The cmc values of individual and mixed amphiphiles increase in the presence of urea. The urea act as a water structure breaker, therefore, the hydrophobic interaction decreases in the presence of urea. The urea molecules adsorbed on the charges amphiphile monomers ions as a result of this the repulsion between them increases and hydrophobic interaction decreases. These two factors are responsible for the outcomes in the presence of urea. In our case the amount of urea is sufficient to stabilize the amphiphiles monomer ions. As a result, the aggregation of amphiphiles monomers is delayed and cmc increases. Here the monomer stability outcomes are dominating over the solvation of the head groups. Similar behavior has been obtained by Kabir-ud-Din et al. (2021).

As already stated, the cmc values of CPZ + SC mixed systems are lower than the individual amphiphiles indicates that the two amphiphiles form mixed micelles. The Clint equation (23) can be used to differentiate the ideal and non-ideal behavior of the mixed system. The cmc values of the ideal mixtures can be computed by the proposed Clint’s equation:

\[
\frac{1}{\text{cmc}_{\text{ideal}}} = \frac{a_1}{\text{cmc}_1} + \frac{1-a_1}{\text{cmc}_2}
\]  

(1)

Where the \(a_1\) value is the mole fraction of component 1 (CPZ) and cmc1 and cmc2 are the experimentally obtained cmc of the individual component. The values of cmcideal are computed by considering that each constituent units of the mixed micelle behave as a separate pseudo phase and form micelle with the enthalpy of mixing equal to zero. The values cmcideal are given in Table 1. The deviation of cmc and cmcideal are depicted in Fig. 3.

Figure 3 clearly indicates a negative deviation and confirms the attractive interaction between CPZ/SC amphiphiles in the mixed micelle. The presence of a negatively charged head group of SC near the positively charged drug molecule reduces the repulsion among head groups of a drug. Therefore, micellization becomes facile and the experimental cmc values revealed to be lower than the ideal one (25, 26). The pH of the micellar solution is an important parameter for determining the stability of the system. Therefore, we examined the pH of the CPZ (pKa = 9.32) and in the presence of bile salt, SC (pKa = 5.13). It is observed that the pH for the individual and mixed amphiphiles was remain constant, nearly the pH value of water (~

7).

3.2 Drug–bile salt interactions in mixed micelles

The interaction parameter (\(\beta\)) can be computed to describe the nature and strength of the interaction between drug and bile salt. On the basis of phase separation model for mixed micellization, Rubingh (27) determined the relationship appeared in equation (2):

\[
\beta = \frac{\ln \left( \frac{a_1 \text{cmc}_1 X_1 \text{cmc}_1}{\text{cmc}_{\text{ideal}}} \right)}{(1-X_1)^2}
\]  

(2)

Where \(X_1\) is the mole fraction value of CPZ in the aqueous (\(\alpha\)) and urea \(\beta\) solution. Solid lines represent experimental data and dashed lines were calculated from Clint’s model.

![Figure 3](image)

The interaction parameter \(\beta\) can be computed by solving equation (3) iteratively:

\[
\frac{(X_1)^2 \ln \left( \frac{a_1 \text{cmc}_1 X_1 \text{cmc}_1}{\text{cmc}_{\text{ideal}}} \right)}{(1-X_1)^2 \ln \left( \frac{1-a_1}{1-a_2} \text{cmc}_1/\text{cmc}_{\text{ideal}} \right)} = 1
\]  

(3)

The values of \(X_1\) and \(\beta\) are given in Table 1. At the lower mole fraction of drug, values \(X_1\) are larger than the stoichiometric mole fraction of CPZ (\(a_1\)), confirm bile salt do not participate noteworthy as CPZ in the formation of mixed micelle. Table 1 also contains the parameter \(\beta\). The values of \(X_1^{\text{ideal}}\) reveals micellar mole fraction CPZ at the ideal state and can be computed by the following equation given by Motomura (28):

\[
X_1^{\text{ideal}} = \frac{a_1 \text{cmc}_2}{a_1 \text{cmc}_2 + a_2 \text{cmc}_1}
\]  

(4)

Table 1 illustrates the comparison of \(X_1^{\text{ideal}}\) and \(X_1\). It is interpreted from Table 1 data that the \(X_1\) values are more than \(X_1^{\text{ideal}}\) at lower drug mole fractions, indicating that the mixed micelle formed by the drug and bile salt enclose extra involvement of CPZ molecules than its ideal mixing state and the lower number of bile salt molecules are transferred from the solution to micellar phase. While at
higher mole fraction of drug we get the opposite trend. The more transfer of bile salt from solution to the mixed micellar phase might be due to the fact that more concentration of bulky drug molecules causes steric hindrance among drug molecules thus their transfer to mixed micelles lessen.

The values of interaction parameter ($\beta$) judge the favorable or unfavorable interaction between two components in the mixed micelle. In binary mixture, according to Rubingh’s, a positive (antagonism) and negative (synergism) values of the interaction parameter indicates the repulsive, attractive interaction between the two components in a mixed micelle. Table 1 indicates that there are attractive interactions between two amphiphiles at all mole fraction of CPZ. On increasing the mole fraction of CPZ the negative values of $\beta$ decrease.

The $\beta$ values are associated with the activity coefficients in the micelles of drug and bile salt by the following equation:

$$f_1 = \exp[\beta(1 - X_i)^2]$$  \hspace{1cm} (5)

$$f_2 = \exp[\beta X_i]^2$$  \hspace{1cm} (6)

The $f_1$ and $f_2$ values of the current CPZ/SC mixed system in the absence and presence of urea are less than unity (Table 1) reveals non-ideal performance.

### 3.3 Synergism in CPZ/SC mixed system

It is confirmed form the above discussion that the present mixed systems have lower cmc values than the individual components. The presence of synergism in a mixed system depends on the strength of the interaction as well as the significant characteristics of pure amphiphiles of the mixed system. The conditions of synergism between two amphiphiles in the bulk are the following:

(i) $\beta$ should be negative

(ii) $\beta > \ln \frac{\text{cmc}_1}{\text{cmc}_2}$

It is confirmed from the data (Table 2) obtained that the present drug–bile salt mixtures exhibit synergism in the

### Table 2 Various physic-chemical parameters to judge the synergism between CPZ + SC.

|                | CPZ + SC             | CPZ + SC + 250 mM Urea |
|----------------|----------------------|------------------------|
| $-\beta_{av}$  | 6.95                 | 7.30                   |
| $\ln \frac{\text{cmc}_1}{\text{cmc}_2}$ | 0.48                 | 0.41                   |

nonattendance and attendance of urea. The phenomena of adsorption and mixed micellization can be quantified with the help of various thermodynamic parameters.

### 3.4 Thermodynamic parameters for CPZ/SC mixed system

The standard free energy of micellization ($\Delta G_m^\circ$) is calculated by applying the phase separation model from the following equation:

$$\Delta G_m^\circ = RT \ln X_{\text{cmc}}$$  \hspace{1cm} (7)

Where $X_{\text{cmc}}$ is the cmc in the mole fraction scale. The values of $\Delta G_m^\circ$ calculated by equation (7) are listed in Table 3.

The values $\Delta G_m^\circ$ for the mixture are more negative than individual amphiphiles indicates more spontaneity drug–bile salt system in attendance and nonattendance of urea. As the content of drug increases, the configuration of micelles turns out to be less favorable. In the presence of urea, the negative values of $\Delta G_m^\circ$ slightly decrease. The decrease or increases in the $\Delta G_m^\circ$ depends upon the contributions of enthalpic and entropic factors. The entropy of the system increases due to the breakdown of the ordered water structure and it is the main driving force for the micelle formation. Thus $\Delta G_m^\circ$ values decrease with the increasing concentration of urea in the micellar system.

The excess Gibbs energy ($\Delta G_{ex}$) can be obtained from

### Table 3 Thermodynamic properties for CPZ + SC mixed amphiphilic systems in the absence and presence of 250 mM urea at temperature $T = 298.15$ K and pressure $p = 0.1$ MPa.

| $\alpha_{CPZ}$ | CPZ + SC | CPZ + SC + 250 mM Urea |
|----------------|----------|------------------------|
| $-\Delta G_m^\circ$ (kj $\cdot$ mol$^{-1}$) | $-\Delta G_m^\circ$ (kj $\cdot$ mol$^{-1}$) | $-\Delta G_m^\circ$ (kj $\cdot$ mol$^{-1}$) | $-\Delta G_m^\circ$ (kj $\cdot$ mol$^{-1}$) |
| 0              | 21.62    | 21.09                  |
| 0.10           | 25.11    | 24.72                  | 4.65 |
| 0.20           | 24.82    | 24.60                  | 4.17 |
| 0.80           | 24.49    | 24.33                  | 4.19 |
| 0.90           | 24.21    | 24.04                  | 4.35 |
| 1              | 20.44    | 20.09                  |
\[ \Delta G_{\text{ex}} = [X_1 \ln f_1 + (1 - X_1) \ln f_2]RT \] (8)

The \( \Delta G_{\text{ex}} \) be a sign of the stability of the micelles. The values of \( \Delta G_{\text{ex}} \) basically mirrored the other parameters and the amphiphile molecules enclose the directional arrangement of the micelles. The directional arrangement of amphiphiles makes micelle. The hydrophilic groups of amphiphiles adjust superficially, while the hydrophobic groups adjust internally. The solubilizates can place in the middle of the micelles to form micelles together. The stability of the micelle depends on the \( \Delta G_{\text{ex}} \) values, more negatives its values (Table 3), the more stable will be the mixed micelles.

4 Spectroscopic Studies

The interactions of an antipsychotic drug with bile salt have further been investigated by steady-state fluorescence. The aromatic ring of CPZ is responsible for the fluorescence properties of CPZ, which vary with the local environment. The emission spectra of CPZ consist of broadband with maxima around 490 nm. This absorption larger than 270 nm is generally owing to the \( n \) to \( \pi^* \) transitions. When the fluorophore is excited from the ground state to the first state the electron density is transferred from sulfur atom to the benzene rings that have a greater \( \pi \) character in the excited state. Due to this charge transfer torsion angle decreases and the dipole moment of the excited state increases. With the increase in dipole moment on excitation, the polar solvent stabilizes the first state (S1) and decreases its energy relative to the ground state in the same solvent. This decreasing the energy is associated with the increase in the wavelength in fluorescence measurements of CPZ. It can be seen from Fig. 2 that the gradual addition of SC to the CPZ solution is connected with the increase in fluorescence intensity and blue shift in the emission maximum. Therefore, it is concluded that the surroundings in the region of the CPZ get disturbed in the presence of SC. The blue shift in the presence and absence of urea is approximately 11 nm (Fig. 2). The lower polarity of the surrounding is associated with the blue shift in the emission maxima.

5 Conclusion

This work reports the mixed micellization behavior of antipsychotic drug, CPZ and bile salt, SC in aqueous and urea solution using tensiometry and fluorescence.

1. In the presence of urea the cmc values for individual and mixed systems increases. The direct and indirect mechanism has been proposed to clarify the outcome of urea on the micelle properties of amphiphiles. The urea breaks the iceberg structure of water without altering the micellar structure so the cmc values increase in the presence of urea. Another mechanism of increasing the cmc values in the presence of urea is the direct binding of urea molecules with the hydrophobic solute. Out of the above two mechanisms, the first one is more acceptable.

2. The cmc values of mixed systems increase with the mole fraction of drug and the values fall in between the values of individual amphiphiles confirm the attractive interaction between two components.

3. The non-ideal behavior is confirmed by the negative deviation between the experimental cmc and ideal cmc values.

4. The present mixed systems follow all conditions for synergism in the absence and presence of urea.

5. The higher negative values of \( \Delta G_{\text{ex}} \) for mixtures indicate more spontaneity for the mixed system. In the presence of urea spontaneity of the mixed system decreases.

6. The addition of SC to the CPZ solution is connected with the increase in fluorescence intensity and blue shift in the emission maximum. The CPZ surrounding gets disturbed in the presence of SC.

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