FINAL PROGRESS REPORT
[UGC PROJECT]
(1.11.15 To 31.06.18)

MICELLAR, INTERFACIAL AND SPECTROSCOPIC
STUDIES OF ANTIDEPRESSANT-DRUG-
SURFACTANT SYSTEMS

UGC SANCTION LETTER NO. 43-183/2014(SR) Dated 30.10.15

Submitted by
Principal Investigator
Prof. Kallol K. Ghosh
School of Studies in Chemistry,
Pt. Ravishankar Shukla University, Raipur, (C.G.) 492010
Final Report of the work done on the Major Research Project

1. Project report No. 1st/ 2nd / 3rd and Final: Final

2. UGC Reference: F. No. 43-183/2014(SR) Dated 30.10.15

3. Period of report: from 30/10/2015 to 31/10/2018

4. Title of research project: MICELLAR, INTERFACIAL AND SPECTROSCOPIC STUDIES OF ANTIDEPRESSANT-DRUG-SURFACTANT SYSTEMS

5. (a) Name of the Principal Investigator: Prof. Kallol K Ghosh
   (b) Deptt.: School of Studies in Chemistry
   (c) University/College where work has progressed: Pt. Ravishankar Shukla University, Raipur

6. Effective date of starting of the project: 1/11/2015

7. Grant approved and expenditure incurred during the period of the report:
   a. Total amount approved: Rs. 10,20,600=00
   b. Total expenditure: Rs. 7,51,105=00
   c. Report of the work done: Please see Encl. 1

   Brief objective of the project:

Antidepressant drugs are widely used in treating psychiatric and neurologic disorder. Over the year many classes of antidepressants have been used in Chhattisgarh region. The excess amount of drugs can cause overstimulation, psychotic illness and other disorders. So the targeted drug delivery in body organs with surfactants and other system is necessary. In order to use these systems as drug carrier, a detailed study of drug-surfactant interaction as well as the effect of microenvironment is prerequisite. This field is very much important for biochemical application and drug delivery system and as this field is still in the infancy, needs proper examination.

The project seeks to understand in detail the nature of interactions between antidepressant drugs and novel surfactants.
ii. Work done so far and results achieved and publications, if any, resulting from the work (Give details of the papers and names of the journals in which it has been published or accepted for publication: Please see Encl. 2)

iii. Has the progress been according to original plan of work and towards achieving the objectives. If not, state reasons: Yes

iv. Please indicate the difficulties, if any, experienced in implementing the project: NIL

v. If project has not been completed, please indicate the approximate time by which it is likely to be completed. A summary of the work done for the period (Annual basis) may please be sent to the Commission on a separate sheet: Completed

vi. If the project has been completed, please enclose a summary of the findings of the study. One bound copy of the final report of work done may also be sent to University Grants Commission: Please see Encl. 3

vii. Any other information which would help in evaluation of work done on the project. At the completion of the project, the first report should indicate the output, such as

(a) Manpower trained: 3

(b) Ph. D. Awarded: Toshikee Yadav, Date: 24.11.2017

   Title: Studies on Antidepressant Drug-Surfactant Systems and Hydrophobic Organic Compound Surfactant Interaction

(c) Publication of results: 2 (Please see Encl. 2)

(d) Other impact, if any: NIL
1. TITLE OF THE PROJECT: Micellar, Interfacial and Spectroscopic Studies of Antidepressant-Drug-Surfactant Systems

2. NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR: Prof. Kallol K Ghosh
   School of Studies in Chemistry
   Pt. Ravishankar Shukla University,
   Raipur, 492010 (CG)

3. NAME AND ADDRESS OF THE INSTITUTION: Pt. Ravishankar Shukla University,
   Amanaka, GE Road,
   Raipur, 492010 (CG)

4. UGC APPROVAL LETTER NO. AND DATE: F. No. 43-183/2014(SR) MRP-MAJOR-CHEM-2013-14435 Dated 30.10.15

5. DATE OF IMPLEMENTATION: 30/10/2015

6. TENURE OF THE PROJECT: 30/10/2015 to 31/10/2018

7. TOTAL GRANT ALLOCATED: Rs. 14,58,600=00

8. TOTAL GRANT RECEIVED: Rs. 10,20,600=00

9. FINAL EXPENDITURE: Rs.

10. TITLE OF THE PROJECT: MICELLAR, INTERFACIAL AND SPECTROSCOPIC STUDIES OF ANTIDEPRESSANT-DRUG-SURFACTANT SYSTEMS

11. OBJECTIVES OF THE PROJECT:

Most of the drugs are used in combination with additives specially surfactants. Therefore, it is necessary to have knowledge of the additive effect on the cmc of amphiphilic drugs. The micellar and interfacial properties are very useful for the development of new drugs as well as
drug-delivery system. This project seeks to understand the nature of interactions between some antidepressant drugs and novel surfactants. The objectives of the project are as follows:

I. To study the surface and micellar properties of some amphiphilic antidepressant drugs by conductometric, tensiometric and fluorimetric methods.

II. To determine the interaction parameter of amphiphilic drugs in the presence of single and mixed surfactants.

III. To characterize the solubilization of drugs in the presence of surfactants.

IV. To study the micellar growth and surfactant as drug-surfactant interaction.

12. WHETHER OBJECTIVES WERE ACHIEVED: Yes

(a) The surface and micellar properties of some amphiphilic antidepressant drugs have been determined by conductometric, tensiometric and fluorimetric methods.

(b) Various interaction parameters of amphiphilic drugs in the presence of single and mixed surfactants have been examined.

(c) Solubilizations of poorly soluble antidepressants drugs have been done using UV-visible spectrophotometer.

(d) Study of the micellar growth has been done as drug-surfactant interaction using dynamic light scattering.

13. ACHIEVEMENTS FROM THE PROJECT:

(i) We have determined the appropriate surfactant systems to increase the activity of antidepressant drugs.

(ii) We obtained the appropriate results for the antidepressant drug-surfactant systems which enhance the bioavailability of amphiphilic antidepressant drugs.

(iii) We have found the increasing solubility of poorly soluble antidepressant drugs by surfactant systems.

14. SUMMARY OF THE FINDINGS: Please see Encl. 3
15. CONTRIBUTION TO THE SOCIETY:

Depression is a major problem in our society. Antidepressants drugs have proved useful for the treatment of depression. They are also used for the treatment of other depressive disorders like obsessive compulsive disorder, anxiety disorders, migraine, dysthymia, chronic pain, dysmenorrhoea, snoring, addiction, neuropathic pain, attention-deficit hyperactivity disorder (ADHD) and sleep disorders. But they have some side effects and we can decrease their side effects using surfactants. Several problems arise in the formulation of hydrophobic drugs and major inconvenience is their solubilization in body fluids and interaction with biological membrane.

Surfactants have wide application in various fields such as environmental, biomedical, pharmaceuticals, industrial, detergency, cosmetics and nano-science. They play a key role in the pharmaceutical field because they have numerous unique properties like low viscosity, small aggregation size, long shelf life, simple preparation, narrow size distribution and bioactivity. Owing to these properties they have increase the bioavailability and solubilization of slightly soluble substances in aqueous medium. Micelles are used as vehicles for the sparingly water-soluble drugs.

Thus, the study of physicochemical properties of surfactants and the interaction of drugs with surfactants can provide valuable information for the development of novel drug molecules. These important studies are useful to enhance the solubility of drugs and to increase the bioavailability and prevent from side effects. Drug-Surfactant interaction remains an important research to improve the drug delivery systems.

16. WHETHER ANY PhD ENROLLED/ PRODUCED OUT OF THE PROJECT : Yes
PhD Awarded : 01, PhD Enrolled :

17. NO. OF PUBLICATIONS OUT OF THE PROJECT : 02

SIGNATURE OF THE PRINCIPAL INVESTIGATOR

REGISTRAR/ PRINCIPAL (SEAL)
REPORT OF THE MAJOR RESEARCH PROJECT

MICELLAR, INTERFACIAL AND SPECTRO-SCOPIC STUDIES OF ANTIDEPRESSANT-DRUG-SURFACTANT SYSTEMS

Submitted to the

University Grants Commission, New Delhi

(UGC Ref. No. 43-183/2014(SR) Dated 30.10.15)
MRP ID : MRP-MAJOR-CHEM-2013-14435

By

Prof. Kallol K Ghosh
Principal Investigator
School of Studies in Chemistry
Pt. Ravishankar Shukla University
Raipur- 492010 CG
MICELLAR, INTERFACIAL AND SPECTROSCOPIC STUDIES OF ANTIDEPRESSANT-DRUG-SURFACTANT SYSTEMS

The project aims to study the physicochemical aspects of interaction of drug to surfactant which is very important factor in drug-delivery systems. Various methods have been used to study the antidepressant-drug surfactant systems:

METHODOLOGY USED FOR THE STUDY

Surface Tension Measurement

The tensions (γ) at the air/solution interface of the drug/surfactant solutions were measured with a calibrated Jencon tensiometer (Kolkata, India) by the du Nouy ring detachment method. The surface properties viz. critical micelle concentration (CMC), maximum surface excess concentration at the air/water interface (Γ_{max}), minimum area per surfactant molecule at the air-water interface (A_{min}) and the surface pressure at the CMC (π_{CMC}) have been determined.

Conductivity Method

Conductance measurements will be taken by direct reading conductivity meter using cell constant of unity. The critical micelle concentration (CMC) and degree of counter ion binding will be measured.

Solubilization Experiment

The solubilization experiments were performed by spectroscopic measurement on Varian Cary-50, UV-visible spectrophotometer. Quantification of solubilization capacity were undertaken in terms of the molar solubilization ratio (MSR), the micellar water partition coefficient (lnK_m) and Gibb’s free energy of solubilization (ΔG°_s) by employing spectrophotometric method.
Fluorimetric Method

The fluorescence measurements were performed on a Cary Eclipse Fluorescence Spectrophotometer. 1-Pyrene carboxaldehyde was used as a probe. Critical Micelle Concentration (cmc), binding constant and Stern-Volmer (Ksv) constant have been measured in mixed miceller system.

Absorption Measurements

The absorption measurements were performed on Varian Cary-50, UV-visible spectrophotometer. The titrations were performed by successive additions of 0.01 M stock solutions of surfactants directly into the cuvette containing 3 mL of 0.33 mM drug solution.

(a) Study on surface and micellar properties of some amphiphilic antidepressant drugs by conductometric, tensiometric and fluorimetric methods:

The micellar and surface properties of some antidepressants (amitriptyline hydrochloride (AMT), imipramine hydrochloride (IMP) and chlorpromazine hydrochloride (CPZ)) (Scheme 1) have been studied by surface tension and fluorescence methods in aqueous solution at 300 K.

Scheme 1. Structures of Antidepressant Drugs.
Determination critical micelle concentration (CMC) of antidepressant drugs:

The CMC values for some antidepressants were determined by surface tension and fluorescence measurements. A representative plot of the surface tension versus log molar concentration of drugs AMT, IMP and CPZ in aqueous solution is shown in Fig. 1, 2 and 3 respectively. Fluorescence spectra for the determination of CMC of CPZ have shown in Fig. 4, in which 1-pyrenecarboxaldehyde is used as a probe. Fig. 5 is showing the plot of intensity ($I_1$) vs concentration of drug (CPZ). The CMC values and other parameters (surface tension at cmc ($\gamma_{cmc}$), surface excess concentration ($\Gamma_{max}$), minimum area per molecule ($A_{min}$)) of antidepressants obtained from both the techniques are given in Table 1.

![Fig. 1. Plot of log C versus Surface Tension for Amitriptyline hydrochloride](image1)

![Fig. 2. Plot of log C versus Surface Tension for Imipramine hydrochloride](image2)
**Fig. 3.** Plot of log C versus Surface tension for Chlorpromazine hydrochloride

**Fig. 4.** Fluorescence spectra of chlorpromazine hydrochloride for the determination of CMC

**Fig. 5.** Plot of intensity ($I_1$) vs concentration of drug Chlorpromazine hydrochloride
Surface Properties

From the surface tension measurements, several interfacial parameters can be determined such as the surface excess concentration ($\Gamma_{\text{max}}$) and minimum area per molecule at the air-water interface ($A_{\text{min}}$), using following eqs.:

$$\Gamma_{\text{max}} = -\frac{1}{2.303 nRT} \left[ \frac{d\gamma}{d\log C} \right]_{T,P}$$

$$A_{\text{min}} = \frac{1}{N\Gamma_{\text{max}}}$$

where, $R$ is the ideal gas constant (8.314 Jmol$^{-1}$K$^{-1}$), $T$ is the absolute temperature in Kelvin, $C$ is the surfactant concentration, $(d\gamma/d\log C)$ is the slope of the surface tension versus log $C$ plot taken below the CMC, and $N$ is Avagadro’s number ($6.022 \times 10^{23}$ mol$^{-1}$).

The value of $\Gamma_{\text{max}}$ generally decreases and that of $A_{\text{min}}$ increases with increasing amounts of drug (shown in Table 1). The value of the surface pressure at the CMC ($\pi_{\text{CMC}}$) was obtained from this eq.,

$$\pi_{\text{CMC}} = \gamma_0 - \gamma_{\text{CMC}}$$

where, $\gamma_0$ is the surface tension of solvent and $\gamma_{\text{CMC}}$ is the surface tension at the CMC. The values of the $\pi_{\text{CMC}}$ of drug solutions are listed in Table 1. This parameter indicates the maximum reduction of surface tension caused by the dissolution of drug molecules; hence, it becomes a measure of effectiveness of the surface tension reduction, and the greater the $\pi_{\text{CMC}}$ values, the higher the effectiveness of the drugs.

Table 1: Interfacial Parameters: surface tension at cmc ($\gamma_{\text{cmc}}$), surface excess ($\Gamma_{\text{max}}$), minimum area per molecule ($A_{\text{min}}$) of antidepressants AMT, IMP and CPZ

<table>
<thead>
<tr>
<th>Antidepressant Drugs</th>
<th>CMC x $10^{-4}$ mol dm$^{-6}$</th>
<th>$\gamma_{\text{cmc}}$</th>
<th>$\Gamma_{\text{max}}$ x $10^6$ mol.m$^{-2}$</th>
<th>$A_{\text{min}}$ x $10^{20}$ m$^2$</th>
<th>$\pi_{\text{cmc}}$ mNm$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. T.</td>
<td>S. T.</td>
<td>Fluo</td>
<td>S. T.</td>
<td>Fluo</td>
<td>S. T.</td>
</tr>
<tr>
<td>AMT</td>
<td>33.0</td>
<td>35.0</td>
<td>58.0</td>
<td>0.81</td>
<td>203</td>
</tr>
<tr>
<td>IMP</td>
<td>41.0</td>
<td>42.0</td>
<td>58.5</td>
<td>0.71</td>
<td>233</td>
</tr>
<tr>
<td>CPZ</td>
<td>16.0</td>
<td>20.0</td>
<td>42.0</td>
<td>0.30</td>
<td>546</td>
</tr>
</tbody>
</table>

S.T.- Surface Tension, Fluo- Fluorescence Method
(b) Determination of various interaction parameters of amphiphilic drugs in the presence of single and mixed surfactants

Determination of interfacial parameter of antidepressants in the presence of surfactants:

Surface tension measurement

Surface tension measurements were carried out using ring detachment method on Jencon Surface tensiometer (Kolkata) at room temperature. Adsorption of amphiphiles at the air-water interface changes the surface properties of solutions. For the determination of amount of adsorbed surfactants at air/water interface, Gibb’s adsorption equations are applied. Critical micelle concentration (cmc), surface tension at cmc ($\gamma_{\text{cmc}}$), Surface excess concentration ($\Gamma_{\text{max}}$), minimum area per molecule ($A_{\text{min}}$) and surface pressure at cmc ($\pi_{\text{cmc}}$) have been determined and given by the following relations:

**Surface excess concentration ($\Gamma_{\text{max}}$)**

$$\Gamma_{\text{max}} = -\frac{1}{2.303 nRT} \left[ \frac{d\gamma}{d\log C} \right]_{T,P}$$

**Minimum area per molecule ($A_{\text{min}}$)**

$$A_{\text{min}} = 1/N\Gamma_{\text{max}}$$

where, $R$ is the ideal gas constant (8.314 Jmol$^{-1}$ K$^{-1}$), $T$ is the absolute temperature in Kelvin, $C$ is the surfactant concentration, ($d\gamma/d\log C$) is the slope of the surface tension versus log C plot taken below the CMC, and $N$ is Avagadro’s number (6.022 X 10$^{23}$ mol$^{-1}$).

**Surface pressure at cmc ($\pi_{\text{cmc}}$)**

$$\pi_{\text{cmc}} = \gamma_{0} - \gamma_{\text{CMC}}$$

where $\gamma_{0}$ and $\gamma_{\text{CMC}}$ refers to the surface tension of solvent and the surfactant solution at the CMC, respectively. This parameter indicates the maximum reduction of surface tension caused by the dissolution of surfactant molecules; hence, it becomes a measure of effectiveness of the surface tension reduction, and the greater the $\pi_{\text{CMC}}$ values, the higher the effectiveness of the surfactants. $\pi_{\text{CMC}}$ value of pure surfactants are lower than pure drug and mixed systems in all cases. $\pi_{\text{CMC}}$ values decrease with an increasing mole fraction of gemini surfactants.
Thermodynamic quantity for the evaluation of synergism in mixing, i.e., the free energy of the given air/water interface $G_{\text{min}}$ which is defined as follows:

$$G_{\text{min}} = A_{\text{min}} \cdot \gamma_{\text{CMC}} \cdot N_A$$

$G_{\text{min}}$ is regarded as the work needed to make an interface per mole or the free energy change accompanied by the transition from the bulk phase to the surface phase of the solution components. In other words, the lower the values of $G_{\text{min}}$, the more thermodynamically stable surface is found. The $G_{\text{min}}$ values are decreased with increasing the additive concentration/mole fraction.

A representative plot of the surface tension versus log molar concentration of drugs AMT and CPZ with gemini surfactants i.e. alkanediyl-$\alpha,\omega$-bis(dimethylhexadecylammonium bromide) ($C_{16-10-C_{16},2Br}$, $C_{16-12-C_{16},2Br}$) are shown in Fig. 6, 7, 8 and 9 respectively. The surface tension ($\gamma$) of solutions was measured for a range of concentrations above and below the critical micelle concentration (CMC). A linear decrease in the surface tension was observed with increase in concentrations for all the surfactants above the CMC value. The values of all interfacial parameters are listed in Table 2. The CMC values of drugs decrease with an increasing mole fraction of gemini surfactant.

![Fig. 6. Plot of log C versus Surface Tension for Chlorpromazine hydrochloride in the presence of 16-10-16](image1)

![Fig. 7. Plot of log C versus Surface Tension for Chlorpromazine hydrochloride in the presence of 16-12-16](image2)
Table 2: Interfacial parameters: surface pressure ($\pi_{\text{cmc}}$), surface excess ($\Gamma_{\text{max}}$), minimum area per molecule ($A_{\text{min}}$) and free energy at air/water interface ($G_{\text{min}}^s$) of drugs (AMT/CPZ) in presence of surfactants.

<table>
<thead>
<tr>
<th>Systems</th>
<th>$\text{cmc} \times 10^{-4}$ mol dm$^{-3}$</th>
<th>$a_{\text{Surf.}}$</th>
<th>$\text{cmc}$</th>
<th>$\gamma_{\text{cmc}}$ mNm$^{-1}$</th>
<th>$\Gamma_{\text{max}}$ $10^6$ mol m$^{-2}$</th>
<th>$A_{\text{min}}$ $10^{20}$ m$^{-2}$</th>
<th>$\pi_{\text{cmc}}$ mNm$^{-1}$</th>
<th>$\Delta G_{\text{min}}^{(b)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPZ+16-10-16</td>
<td>0.000</td>
<td>19.0</td>
<td>42.0</td>
<td>1.89</td>
<td>87.49</td>
<td>28.0</td>
<td>22.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td>18.0</td>
<td>50.0</td>
<td>1.12</td>
<td>148.16</td>
<td>20.0</td>
<td>89.23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>16.0</td>
<td>48.7</td>
<td>1.10</td>
<td>150.43</td>
<td>21.3</td>
<td>45.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>15.0</td>
<td>47.0</td>
<td>1.03</td>
<td>160.15</td>
<td>23.0</td>
<td>45.30</td>
<td></td>
</tr>
<tr>
<td>CPZ+16-12-16</td>
<td>0.000</td>
<td>19.0</td>
<td>42.0</td>
<td>1.89</td>
<td>87.49</td>
<td>36.0</td>
<td>18.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td>16.5</td>
<td>48.1</td>
<td>0.99</td>
<td>167.01</td>
<td>24.1</td>
<td>48.38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>14.0</td>
<td>52.0</td>
<td>1.18</td>
<td>140.15</td>
<td>20.2</td>
<td>43.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>12.0</td>
<td>58.0</td>
<td>1.38</td>
<td>120.07</td>
<td>14.2</td>
<td>41.94</td>
<td></td>
</tr>
<tr>
<td>AMT+16-10-16</td>
<td>0.000</td>
<td>33.0</td>
<td>56.5</td>
<td>0.81</td>
<td>203.96</td>
<td>13.5</td>
<td>69.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td>31.0</td>
<td>49.4</td>
<td>1.11</td>
<td>149.37</td>
<td>20.6</td>
<td>44.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>25.0</td>
<td>47.5</td>
<td>1.10</td>
<td>150.82</td>
<td>22.5</td>
<td>43.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>23.0</td>
<td>45.8</td>
<td>1.09</td>
<td>152.14</td>
<td>24.2</td>
<td>41.96</td>
<td></td>
</tr>
<tr>
<td>AMT+16-12-16</td>
<td>0.000</td>
<td>33.0</td>
<td>56.5</td>
<td>0.81</td>
<td>203.96</td>
<td>13.5</td>
<td>69.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td>28.0</td>
<td>45.0</td>
<td>1.15</td>
<td>143.46</td>
<td>25.0</td>
<td>38.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>23.0</td>
<td>43.2</td>
<td>1.27</td>
<td>129.92</td>
<td>26.8</td>
<td>33.80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>20.0</td>
<td>41.0</td>
<td>1.26</td>
<td>131.63</td>
<td>29.0</td>
<td>32.50</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 8: Plot of log C versus Surface Tension for Amitriptyline hydrochloride in the presence of 16-10-16

Fig. 9: Plot of log C versus Surface Tension for Amitriptyline hydrochloride in the presence of 16-12-16
The interactions of antidepressant drugs chlorpromazine hydrochloride (CPZ) and desipramine hydrochloride (DSP) with bile salts (Sodium cholate (NaC) and sodium deoxycholate (NaDC)) (Scheme 2) have been investigated by employing the UV-visible spectroscopy and steady state fluorescence. The aromatic rings of these drugs are responsible for their significant absorption and fluorescence properties, which vary with its local environment.

Absorption measurements

This technique is useful for studying the interaction between drug and surfactants. The titrations were performed by successive additions of 0.01 M stock solutions of surfactants (NaC and NaDC) directly into the cuvette containing 3 mL of 0.33 mM drug solution. The absorption spectra of CPZ and DSP in aqueous solutions with varying concentrations of NaC and NaDC are shown in Figs. 10 and 11. The spectra of CPZ presented two characteristic peaks at 245 nm and 305 nm wavelengths. In which the shorter wavelength band is due to π-π* transition and longer wavelength is due to n- π* transition and also the presence of lone pair of electron on sulfur atom in tricyclic region of antidepressant drug CPZ. In the case of absorption spectra of DSP it appears at 250 nm. On the addition of surfactants the absorption intensity of antidepressants increases (red shift). It is also observed from the Figs. 10 [(a), (b)] CPZ shows spectral shift of 5 nm at λ_{max} 245 nm but the second spectra at 305 nm not shows spectral shift after addition of bile salts. Similarly from Figs. 11 [(a), (b)] DSP shows the spectral shift of 5 nm at λ_{max} 250 nm. These spectral shifts show the interaction of drug and bile salts which further indicate the new complex formation between antidepressants and bile salts. Binding of bile salts with drug molecules calculated by Benesi–Hildebrand equation:

\[
\frac{1}{A-A_0} = \frac{1}{K(A_{max}-A_0)} \frac{1}{[\text{Bile Salt}]} + \frac{1}{A_{max}-A_0}
\]
Where, $A_0 =$ absorbance in the absence of bile salts  
$A =$ absorbance at intermediate concentration of bile salts  
$A_{\text{max}} =$ absorbance at infinite concentration of bile salts  
$K =$ binding constant

![Absorption spectra of CPZ with increasing concentration of (a) NaC and (b) NaDC.](image)

![Absorbance spectra of DSP with increasing concentration of (a) NaC and (b) NaDC.](image)

**Fig. 10** Absorption spectra of CPZ with increasing concentration of (a) NaC and (b) NaDC.

**Fig. 11** Absorbance spectra of DSP with increasing concentration of (a) NaC and (b) NaDC.

When we plot the graph between $1/(A-A_0)$ and $1/[$Surfactant$, it gives a straight line shown in Fig. 12, which reveals that antidepressants (CPZ, DSP) and surfactants (NaC, NaDC) formed the 1:1 complex between them. The binding constants $K$ were calculated from the ratio of intercept and slope of Benesi–Hildebrand plot are $0.063 \times 10^{-3}$ mol dm$^{-1}$, $0.883 \times 10^{-3}$ mol dm$^{-1}$, $0.027 \times 10^{-3}$ mol dm$^{-1}$ and $0.040 \times 10^{-3}$ mol dm$^{-1}$ for CPZ+ NaC, CPZ+NaDC, DSP+NaC and DSP+ NaDC.
respectively. The values of binding constant tell that NaDC shows more binding affinity towards the antidepressants drugs.

**Fig 12** Benesi–Hildebrand plot using changes in absorption spectra of (a) CPZ, (b) DSP for NaC and NaDC

**Fluorometric Measurements**

To understand the interaction between antidepressants and bile salts the spectroscopic techniques such as steady state fluorescence have been employed. The fluorescence emission spectra (Fig 13 and Fig 14) of CPZ and DSP show the addition of bile salts quenched the spectra of CPZ and DSP at 474 nm which shows the new complex formation between antidepressants and bile salts. The addition of constant volume of quencher (i.e. .001 mL of 10 mM bio-surfactant solutions) to the drug solution avoids complications due to dilution effects within titration type experiments. Process of fluorescence quenching is explained by Stern–Volmer equation.

$$\frac{I_0}{I} = 1 + K_{sv} [Q]$$

where, $I_0$ = fluorescence intensity of CPZ and DSP without quencher
$I$ = fluorescence intensity of CPZ and DSP with quencher
$K_{sv}$ = Stern-Volmer constant
$[Q]$ = concentration of quencher

Figs 15 (a) and 16 (a) show the plot of $I_0 / I$ versus $[Q]$) and give the value of Stern-Volmer constant shown in Table 3. By applying the following equation we can calculate the value of binding constant $K_a$ and binding sites $n$, 

$$\frac{1}{I} = \frac{1}{I_0} + \frac{1}{I_0 K_a n [Q]}$$
\[ \log \left( \frac{(I_0 - I)}{I} \right) = \log K_a + n \log [\text{Surfactant}] \]

here, \( K_a \) = binding constant

\( n \) = binding sites

The values \( K_a \) and \( n \) are given in Table 3.

All systems show the value of binding capacity (\( n \)) is greater than unity. CPZ + NaDC system shows higher binding capacity while other systems (CPZ + NaC, DSP + NaDC and DSP + NaC) show less binding capacity indicating that they do not show significant binding to each other.

Using the value of \( K_a \) the Gibb’s free energy changes for binding obtained for this process from following equation,

\[ \Delta G_{\text{Binding}} = -RT \ln K_a \]
Fig. 13 Fluorescence spectra of CPZ with increasing concentration of (a) NaC and (b) NaDC.

Fig. 14 Fluorescence spectra of DSP with increasing concentration of (a) NaC and (b) NaDC.

The negative value of Gibb’s free energy changes for binding ($\Delta G_{\text{Binding}}$) assure that the binding process is spontaneous and it is helpful for studying the interaction of drugs with biosurfactants. The NaDC shows higher value of $K_a$ for both antidepressants than NaC due to hydrophobicity which leads to their different binding abilities. It is also examined that between CPZ + NaC and DSP + NaC systems, the binding is stronger for former case showing higher binding affinity which also explains about the more hydrophobic nature of CPZ than DSP. In the case of CPZ + NaDC and DSP + NaDC, the previous one shows higher binding affinity. CPZ contains phenothiazine ring and positively charged group shows a better binding with negatively charged bile salt. NaDC possesses more hydrophobic nature which promotes the absorption as compare to NaC. The binding constants ($K_a$) showed a considerable hydrophobic contribution modulated by electrostatic interactions of the positively charged drug with the head group of biosurfactants. Fig 17 shows the schematic representation of drug-surfactant interaction.
Fig. 15 (a) Stern-Volmer plot of fluorescence quenching of DSP by NaC
   (a) A plot of \( \log \left( \frac{I_0 - I}{I} \right) \) vs. log [Surfactant] for NaC

Fig. 16 (a) Stern-Volmer plot of fluorescence quenching of CPZ by NaDC
   (b) A plot of \( \log \left( \frac{I_0 - I}{I} \right) \) vs. log [Surfactant] for NaDC
Table 3 Stern–Volmer quenching constants ($K_{sv}$), binding constants ($K$), number of binding sites ($n$), free energy change for binding ($\Delta G_{\text{Binding}}$) for the drug-bile salt complexation of CPZ + NaC/NaDC and DSP + NaC/NaDC using fluorescence technique

<table>
<thead>
<tr>
<th>Drug-bile salts complex</th>
<th>$K \times 10^{-3}$ (mol dm$^{-1}$)</th>
<th>$K_{sv} \times 10^{-3}$ (mol dm$^{-1}$)</th>
<th>$n$</th>
<th>$\Delta G_{\text{Binding}}$ (kJ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPZ + NaC</td>
<td>2.221±0.04</td>
<td>0.0591±0.003</td>
<td>1.68</td>
<td>-19.76±0.7</td>
</tr>
<tr>
<td>CPZ+ NaDC</td>
<td>5.543±0.05</td>
<td>0.1647±0.002</td>
<td>2.02</td>
<td>-42.42±0.4</td>
</tr>
<tr>
<td>DSP + NaC</td>
<td>1.343±0.08</td>
<td>0.0710±0.002</td>
<td>1.65</td>
<td>-7.30±0.2</td>
</tr>
<tr>
<td>DSP + NaDC</td>
<td>2.228±0.06</td>
<td>0.4746±0.003</td>
<td>1.71</td>
<td>-19.84±0.7</td>
</tr>
</tbody>
</table>
Mixed Micellization of Gemini Surfactant with Pluronic Block Copolymer and Their Interaction with Tricyclic Antidepressants

Pluronics are amphiphilic tri block co-polymers. These are water soluble nonionic macromolecular surfactants plays an important role for solubilizing the poorly soluble drugs and as a drug carrier in drug delivery system. Gemini surfactants possess strong self-assembly ability. Interaction of polymeric micelles with gemini surfactants have gained paramount significance in pharmaceutical field. This study involves the mixed micellization of pluronic F-127 and gemini surfactant C_{12-4}(OH)_{2}-C_{12}2Br^- (Scheme 3) and their interaction with antidepressant drugs chlorpromazine hydrochloride (CPZ) and desipramine hydrochloride (DSP) using surface tension, fluorescence spectroscopy and dynamic light scattering studies at 300 K.

![Scheme 3](image)

Pluronic F-127 [EO_{97}PO_{69}EO_{97}] 1-4 bis (dodecyl-N,N-dimethylammonium bromide)-2,3-butanediol (C_{12-4}(OH)_{2}-C_{12}2Br^-)


Mixed Micellization of Gemini Surfactant with Pluronic Block Copolymer

The study of copolymer-surfactant interaction is very essential due to their importance in industrial, biomedical and pharmaceutical applications. The surface tension values were measured for mixed system C_{12-4}(OH)_{2}-C_{12}2Br^- + F-127 at various mole fraction (0.2-0.8) at 300 K. The values of critical micelle concentration (CMC) are listed in Table 4.

Fig 18 shows the plots of surface tension versus log [surfactants] for binary mixture of C_{12-4}(OH)_{2}-C_{12}2Br^- + F-127. With the increasing mole fraction of gemini surfactant the value of surface tension decreases. The CMC values obtained for binary systems increases by increasing the mole fraction of gemini surfactant shown in Table 4 The experimental CMC values of binary systems were found to be less than the ideal CMC values calculated using Clint equation, which indicates negative deviation from ideal behaviour for mixed micelle formation.

\[
\frac{1}{cmc_{ideal}} = \frac{\alpha_1}{cmc_1} + \frac{1 - \alpha_1}{cmc_2}
\]
Various interfacial parameters such as maximum surface excess concentration ($\Gamma_{\text{max}}$), minimum area per molecule at the interface ($A_{\text{min}}$), effectiveness of the surface tension reduction measured by the surface tension at the CMC ($\gamma_{\text{CMC}}$) have been evaluated using following eqs. respectively,

$$\Gamma_{\text{max}} = -\frac{1}{2.303nRT} \left[ \frac{d\gamma}{d\log C} \right]_{T,P}$$

where $R$ is the gas constant (8.314 Jmol$^{-1}$ K$^{-1}$), $T$ is the absolute temperature, $C$ is the surfactant concentration, and $(d\gamma / d \log C)$ is the slope of the $\gamma$ versus log $C$ plot taken at the CMC.

$$A_{\text{min}} = 1 / N \Gamma_{\text{max}}$$

where $N$ is Avogadro’s number

$$\gamma_{\text{CMC}} = \gamma_o - \gamma_{\text{CMC}}$$

where $\gamma_o$ and $\gamma_{\text{CMC}}$ refers to the surface tension of solvent and the surfactant solution at the CMC, respectively.

**Fig. 18** Plots of surface tension vs log C of C$_{12}$-4(OH)$_2$-C$_{12}$,2Br$^-$ + F-127 binary system.

Interaction parameters ($\beta$) for mixed systems of C$_{12}$-4(OH)$_2$-C$_{12}$,2Br$^-$ + F-127 have been calculated by applying the Rosen model. Activity coefficient ($f_{1}^{\sigma}$ and $f_{2}^{\sigma}$) have been evaluated by using the equation given below. All the interaction parameters are listed in Table 4. The negative value of interaction parameter ($\beta^{\sigma}$) indicates the deviation from ideality which indicates the degree of interaction between two surfactants in mixed micelle.
\[
\left( X^\alpha \right)^2 \ln \left( \frac{\alpha_1 C_{\text{mix}}}{X^\alpha C_1^0} \right) = \left( 1 - X^\alpha \right)^2 \ln \left( \frac{(1 - \alpha_1) C_{\text{mix}}}{(1 - X^\alpha) C_2^0} \right) = 1
\]

where \( C_{\text{mix}} \), \( C_1^0 \) and \( C_2^0 \) are the concentrations of the mixture, pure surfactant 1 and 2 respectively at a fixed \( \gamma \) value, \( \alpha_i \) is the stoichiometric mole fraction of surfactant 1 in solution.

\[
\beta^\sigma = \frac{\ln \left( \frac{\alpha_1 C_{\text{mix}}}{X^\alpha C_1^0} \right)}{(1 - X^\alpha)^2}
\]

Interaction parameter \( \beta^\sigma \) indicates the degree of interaction between the two components as well as the deviation from ideality.

\[
f_1^\sigma = \exp \left[ \beta^\sigma \cdot (1 - X^\sigma)^2 \right]
\]

\[
f_2^\sigma = \exp \left( \beta^\sigma X^\sigma \right)^2
\]

The excess free energy of mixing has calculated from using eq. given below. The negative value of \( \Delta G_{\text{ex}} \) indicates more attractive interaction between molecules in mixed micelles.

\[
\Delta G_{\text{ex}} = RT \left[ X_1 \cdot \ln f_1 + (1-X_1) \cdot \ln f_2 \right]
\]
Table 4 Critical micelle concentration ($C_{\text{exp}}$, $C_{\text{ideal}}$), maximum surface excess concentration ($\Gamma_{\text{max}}$), minimum area per molecule at the interface ($A_{\text{min}}$), the surface tension at the CMC ($\gamma_{\text{CMC}}$), micellar mole fraction ($X_1$ and $X_{\text{ideal}}$), interaction parameter ($\beta^\sigma$), activity coefficients ($f_1^\sigma$ and $f_2^\sigma$) and excess Gibbs free energy ($\Delta G^F$) for binary mixture ($\text{C}_{12}-4(\text{OH})_2-\text{C}_{12}\text{Br}^- + \text{F}^{-}$) system at 300 K.

<table>
<thead>
<tr>
<th>$\alpha_{\text{gemini}}$</th>
<th>$C_{\text{exp}}$ (mM)</th>
<th>$C_{\text{ideal}}$ (mM)</th>
<th>$\Gamma_{\text{max}}$ $10^6$ mol.m$^{-2}$</th>
<th>$A_{\text{min}}$ $10^{20}$ m$^{-2}$</th>
<th>$\pi_{\text{cmc}}$ mN.m$^{-1}$</th>
<th>$X_{\text{ideal}}$</th>
<th>$X_1^\sigma$</th>
<th>$\beta^\sigma$</th>
<th>$f_1^\sigma$</th>
<th>$f_2^\sigma$</th>
<th>$\Delta G_{\text{exp}}$ kJ/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.043</td>
<td></td>
<td>303</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-678.4</td>
</tr>
<tr>
<td>0.2</td>
<td>0.048</td>
<td>0.053</td>
<td>0.096</td>
<td>302</td>
<td>0.011</td>
<td>0.11</td>
<td>-2.78</td>
<td>0.111</td>
<td>0.967</td>
<td>-1114.9</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>0.062</td>
<td>0.081</td>
<td>0.204</td>
<td>307</td>
<td>0.041</td>
<td>0.21</td>
<td>-2.70</td>
<td>0.185</td>
<td>0.888</td>
<td>-2673.8</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>0.069</td>
<td>0.176</td>
<td>0.386</td>
<td>316</td>
<td>0.048</td>
<td>0.39</td>
<td>-4.50</td>
<td>0.187</td>
<td>0.504</td>
<td>-2673.8</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>0.780</td>
<td></td>
<td>173</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-2673.8</td>
</tr>
</tbody>
</table>
The fluorescence spectroscopic technique have been applied to study the interaction between CPZ and DSP with mixed system of $12-4(OH)_{12}+F^{-}$-127. Figs 19 to 24 show that the addition of binary surfactant system ($C_{12}-4(OH)_{2}-C_{12}2Br^{-}+F-127$) quenched the fluorescence emission spectra of antidepressant drugs (CPZ and DSP) at 474 nm when excited at 368 nm at different mole fractions (0.2, 0.5 and 0.8). Figs 25 and 26 show the Stern-Volmer plots of fluorescence quenching of CPZ and DSP by $C_{12}-4(OH)_{2}-C_{12}2Br^{-}+F-127$ system respectively at various mole fractions (0.2 to 0.8), explains the quenching of antidepressant drugs by binary surfactant system Fig 27 shows the plots of $\log \left( (I_0-I)/I \right)$ vs. $\log$ [Surfactant] for CPZ.

The Stern-Volmer constants of studied system have been calculated. Binding constants have also been calculated. All the parameters are listed in Table 5. The higher values of binding constant have been found at 0.8 mole fraction for both of the antidepressant drugs. With the increasing mole fraction the interaction between drugs and mixed surfactant system have increase.

![Diagram](image_url)

**Fig. 19** Fluorescence spectra of CPZ at increasing concentration of binary system $C_{12}-4(OH)_{2}-C_{12}2Br^{-}+F-127$ ($\alpha_{\text{gemini}} = 0.2$)
Fig. 20 Fluorescence spectra of CPZ at increasing concentration of binary system C12-4(OH)2-C12,2Br- + F-127 ($\alpha_{\text{gemini}} = 0.5$)

Fig. 21 Fluorescence spectra of CPZ at increasing concentration of binary system C12-4(OH)2-C12,2Br- + F-127 ($\alpha_{\text{gemini}} = 0.8$)
Fig. 22 Fluorescence spectra of DSP at increasing concentration of binary system C12-4(OH)2-C12,2Br- + F-127 (αgemini = 0.2)

Fig. 23 Fluorescence spectra of DSP at increasing concentration of binary system C12-4(OH)2-C12,2Br- + F-127 (αgemini = 0.5)
Fig. 24 Fluorescence spectra of DSP at increasing concentration of binary system C_{12-4}(OH)_2-C_{12,2}Br^- + F-127 (a_{gemini} = 0.8)

Fig. 25 Stern-Volmer plots of fluorescence quenching of CPZ by C_{12-4}(OH)_2-C_{12,2}Br^- + F-127 systems
Fig. 26 Stern-Volmer plots of fluorescence quenching of DSP by C$_{12}$-4(OH)$_2$-C$_{12}$-2Br$^-$ + F-127 systems

Fig. 27 Plots of log [(I$_0$-I) / I] vs. log [Surfactant] for CPZ
Table 5 Stern–Volmer quenching constants ($K_{sv}$), binding constants (K), correlation coefficient (R) and free energy change of binding ($\Delta G_{\text{Binding}}$) for antidepressant drug – mixed surfactant systems at 300 K using fluorescence technique.

<table>
<thead>
<tr>
<th>$\alpha_{\text{gemi}}$</th>
<th>Chlorpromazine hydrochloride (CPZ)</th>
<th>Desipramine hydrochloride (DSP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$K \times 10^4$ (mol dm$^{-1}$)</td>
<td>$K_{sv} \times 10^4$ (mol dm$^{-1}$)</td>
</tr>
<tr>
<td>0.0</td>
<td>0.20</td>
<td>1.17</td>
</tr>
<tr>
<td>0.2</td>
<td>0.51</td>
<td>0.94</td>
</tr>
<tr>
<td>0.5</td>
<td>0.76</td>
<td>1.18</td>
</tr>
<tr>
<td>0.8</td>
<td>1.59</td>
<td>1.29</td>
</tr>
<tr>
<td>1.0</td>
<td>0.96</td>
<td>1.77</td>
</tr>
</tbody>
</table>

(c) Solubilization of antidepressant drugs in the presence of surfactants

Solubilization of poorly soluble drugs using surface active agents is a very useful technique in pharmaceutical science. This study reports the solubilization of phenothiazone (Scheme 4). Phenothiazines are the drugs possessing a hydrophobic tricyclic ring system and hydrophilic side chain. These drugs are generally employed as antihistamines, antipsychotics and neuroleptics.

![Scheme 4. Phenothiazone](image.png)

1-4 bis (dodecyl-N,N-dimethylammonium bromide) butane (C$_{12}$-4-C$_{12}$, 2Br$^-$) 1-4 bis (dodecyl-N,N-dimethylammonium bromide)-2-butanol (C$_{12}$-4(OH)-C$_{12}$2Br$^-$)
Solubilization of antipsychotic drug phenothiazine by single system of cationic gemini surfactant using cationic gemini surfactants (C\textsubscript{12}-4-C\textsubscript{12}, 2Br'), 1,4 bis(dodecyl-N,N-dimethylammonium bromide)-2-butanol (C\textsubscript{12}-4(OH)-C\textsubscript{12},2Br'), 1,4 bis(dodecyl-N,N-dimethylammonium bromide)-2,3-butanediol (C\textsubscript{12}-4(OH)\textsubscript{2}-C\textsubscript{12},2Br') (Scheme 5) were evaluated and compared. The absorbance of the solubilizate of specified concentration was determined by measuring the molar extinction coefficient ($\varepsilon$) in micellar solutions. Straight line was obtained by plotting the absorbance versus the solubilizates concentrations. The solubility of phenothiazine were greatly enhanced increased by all surfactant systems where solubility increased with increasing surfactant concentrations above the CMC. A molar solubilization ratio (MSR) is given to quantify the effectiveness of a surfactant in solubilizing a given solubilizate. It can be defined as the number of compound solubilized per moles of surfactant added to the solution and can be calculated as per eq.

$$\text{MSR} = \frac{(S - S_{\text{CMC}})}{(C_s - \text{CMC})}$$

where, $S$ = Apparent solubility of organic compound at surfactant concentration C\textsubscript{s} (C\textsubscript{s} > CMC) and $S_{\text{CMC}}$ = Apparent solubility of organic compound at CMC.

In addition to MSR, the effectiveness of solubilization can also be expressed in terms of the partition coefficient, $K_m$, of the compound between micelles and the aqueous phase. The value of $K_m$ is a function of temperature and the nature of surfactant and solubilizate. The partition coefficient can be written as

$$K_m = \frac{X_m}{X_a}$$

where $X_m$ and $X_a$ are the mole fractions of solute in micelles and the aqueous phase, respectively. The value of $X_m$ can be calculated as $X_m = \frac{\text{MSR}}{1 + \text{MSR}}$, and $X_a$ can be expressed as $X_a = S_{\text{CMC}}V_w$, where $V_w = 0.01805$ L/mol is the molar volume of water. Consequently, eq can be rearranged to yield

$$K_m = \frac{\text{MSR}}{S_{\text{CMC}} V_w (1 + \text{MSR})}$$
The MSR and $K_m$ values for the all the surfactants are listed in Table 6. The slopes of the curve of solubility of phenothiazine versus surfactant concentration, expressed in molar concentration, represent the MSR, which was determined using least-squares linear regression.

The order of solubilizing strength for gemini surfactants of C$_{12}$ series is found to be: C$_{12}$-4-C$_{12}$, 2Br$^-$ < C$_{12}$-4(OH)-C$_{12}$, 2Br$^-$ < C$_{12}$-4(OH)$_2$-C$_{12}$, 2Br$^-$ for phenothiazine. The CMC value of gemini surfactants decreases with substitutional hydroxyl group on spacer of same chain length. The substituted spacer group could form hydrogen bond with water more readily and reduce the unfavourable hydrocarbon-water contact. So the C$_{12}$-4(OH)$_2$-C$_{12}$, 2Br$^-$ having two hydroxyl group on spacer reflects greater solubilization as compared to others.

![Fig 28 Absorption spectra of Phenothiazine at different concentration of 12-4(OH)$_2$-12](image)

![Fig 29 Variation of solubility of Phenothiazine with Gemini Surfactants](image)

**Thermodynamics of Solubilization**

The knowledge of the thermodynamic parameters controlling solubilization is helpful for better understanding of the mechanism involved in the process. From the thermodynamic point of view, solubilization can be considered as normal partitioning of the drug between micellar and aqueous phases and the Gibb’s free energy of solubilization, $\Delta G^\circ$, can be represented by the expression

$$\Delta G^\circ = -RT \ln K_m$$

The $\Delta G^\circ$ values thus calculated are presented in Table 6. For all the systems, the $\Delta G^\circ$ values appear to be negative showing spontaneity of the solubilization process.
Table 6  Molar solubilization ratio (MSR), $\ln K_m$ and the Gibb’s free energy of solubilization ($\Delta G^\circ_s$) of Phenothiazine in cationic gemini surfactant systems at 300 K.

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>CMC (mM)</th>
<th>Phenothiazine</th>
<th>$\Delta G^\circ_s$ (kJ/mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{C}<em>{12}-\text{C}</em>{12}2\text{Br}^-$</td>
<td>1.17</td>
<td>0.164</td>
<td>11.4</td>
</tr>
<tr>
<td>$\text{C}<em>{12}-4(\text{OH})-\text{C}</em>{12}2\text{Br}^-$</td>
<td>0.94</td>
<td>0.235</td>
<td>11.6</td>
</tr>
<tr>
<td>$\text{C}_{12}-(\text{OH})<em>2-\text{C}</em>{12}2\text{Br}^-$</td>
<td>0.87</td>
<td>0.663</td>
<td>13.9</td>
</tr>
</tbody>
</table>

(d) Study of the micellar growth of drug and surfactant mixture using dynamic light scattering

The hydrodynamic radii ($R_h$), polydispersity index (PDI) and zeta potential values of pure and mixed systems of antidepressant drugs CPZ and DSP with ($\text{C}_{12}-4(\text{OH})_2-\text{C}_{12}2\text{Br}^- + \text{F}-127$) have been determined by dynamic light scattering measurements at 300 K. CONTIN software has been used to analyze the polydispersity. All the values are shown in Table 7. Hydrodynamic radii of pure and mixed system in aqueous solution were calculated from the diffusion coefficients, $D_0$, using the Stokes–Einstein equation,

$$R_h = \frac{k_B T}{6\pi \eta D_0}$$

where, $k_B$ is the Boltzmann constant, $T$ is the absolute temperature, and $\eta$ is the viscosity of water. Figs 30 to 35 show the size distribution graph of DLS spectra of all studied systems as a function of hydrodynamic radii.

The hydrodynamic radii of drug-surfactant mixed systems increase with the increasing mole fraction of mixed surfactant. The mixture of CPZ / DSP- ($\text{C}_{12}-4(\text{OH})_2-\text{C}_{12}2\text{Br}^- + \text{F}-127$) makes larger aggregates. However, up to 0.5 mole fraction, aggregation is mild and only mixed micelle are formed. With increasing mile fraction of mixed system increases the micellar radii, indicates the formation of larger aggregates. But at higher mole fraction of mixed system (0.8), due to repulsive interaction (dispersion force) the mixed surfactant micelles dissociate and form micelle with smaller size.
**Fig. 30** Size distribution graph of DLS spectra of pluronic F-127

**Fig. 31** Size distribution graph of DLS spectra of $\text{C}_{12}\text{-4(OH)}_{2}\text{-C}_{12,2\text{Br}}$

**Fig. 32** Size distribution graph of DLS spectra of chlorpromazine hydrochloride (CPZ)
Fig 33 Size distribution graph of DLS spectra of desipramine hydrochloride (DSP)

Fig 34 Size distribution graph of DLS spectra of F-127 + CPZ

Fig 35 Size distribution graph of DLS spectra of F-127 + DSP
Table 7 Hydrodynamic radii values ($R_h$), polydispersity index (PDI) and zeta potential values of pure and mixed systems of antidepressant drugs + (C$_{12}$-4(OH)$_2$-C$_{12}$,2Br + F-127) at 300 K

<table>
<thead>
<tr>
<th>Systems</th>
<th>CPZ</th>
<th>DSP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R_h$ (nm)</td>
<td>PDI</td>
</tr>
<tr>
<td>0.0</td>
<td>30.4 (42)$^a$</td>
<td>0.36</td>
</tr>
<tr>
<td>0.2</td>
<td>124.7</td>
<td>0.27</td>
</tr>
<tr>
<td>0.5</td>
<td>159.8</td>
<td>0.64</td>
</tr>
<tr>
<td>0.8</td>
<td>84.1</td>
<td>0.33</td>
</tr>
<tr>
<td>1.0</td>
<td>239.4</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Principal Investigator
Prof. Kallol K Ghosh
School of Studies in Chemistry
Pt. Ravishankar Shukla University
Raipur- 492010 CG
## PUBLICATIONS

**Paper Communicated /Accepted in National /International Journal**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Title</th>
<th>Journal Name</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Biophysical studies on the interactions between antidepressant drugs and bile salts</td>
<td>Journal of Molecular Liquids</td>
<td>T. Yadav, D. Tikariha, S. Sinha, K. K. Ghosh</td>
</tr>
<tr>
<td></td>
<td></td>
<td>201 (2017) 216-221</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>199 (2018) 376-386</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Antidepressant drug -protein interactions studied by spectroscopic methods based on fluorescent carbon quantum dots</td>
<td>Colloids and Surfaces B: Biointerfaces (Communicated)</td>
<td>, Reshma, Srishti Sinha and Toshikee Yadav, Kallol K. Ghosh</td>
</tr>
</tbody>
</table>

**Papers Accepted/Presented in Conferences**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Title of the Paper</th>
<th>Name of the Conference</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interaction between tricyclic antidepressant drugs and human serum albumin : Spectroscopic and molecular docking approach</td>
<td>22nd CRSI National Symposium in Chemistry, Pt. Ravishankar Shukla University, Raipur (CG)</td>
<td>Kallol K. Ghosh, Reshma, Srishti Sinha and Toshikee Yadav</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

**Principal Investigator**
Prof. Kallol K Ghosh
School of Studies in Chemistry
Pt. Ravishankar Shukla University
Raipur- 492010 CG
EXECUTIVE SUMMARY OF MAJOR RESEARCH PROJECT

MICELLAR, INTERFACIAL AND SPECTRO-SCOPIC STUDIES OF ANTIDEPRESSANT-DRUG-SURFACTANT SYSTEMS

Submitted to the

University Grants Commission, New Delhi

(UGC Ref. No. 43-183/2014(SR) Dated 30.10.15)
MRP ID : MRP-MAJOR-CHEM-2013-14435

By
Prof. Kallol K Ghosh
Principal Investigator
School of Studies in Chemistry
Pt. Ravishankar Shukla University
Raipur- 492010 CG
EXECUTIVE SUMMARY OF MAJOR RESEARCH PROJECT  
(UGC Ref. No. 43-183/2014(SR) Dated 30.10.15)

Most of the drugs are used in combination with additives specially surfactants. Therefore, it is necessary to have knowledge of the additive effect on the CMC of amphiphilic drugs. This project gives emphasis the micellar and interfacial properties of drug-surfactant systems which are very useful for the development of new drugs as well as drug-delivery system.

The studies of micelles in drug delivery yield the necessary information to minimize drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability. The use of micelle in pharmacy is an important tool that finds numerous applications. Special emphasis is given to the more recent use of polymeric micelles.

So this project gives the following information about antidepressant drug-surfactant systems:

(a) The physicochemical behavior and solubilization of tricyclic antidepressant drugs viz. amitriptyline hydrochloride (AMT) and Imipramine hydrochloride (IMP) with cationic surfactants i.e. alkyltriphenylphosphonium bromide (R = 14, 16) and alkyl-diethylethanolammonium bromide (R = 14, 16) have been investigated by surface tension. The surface properties viz. CMC, maximum surface excess concentration at the air/water interface ($\Gamma_{\text{max}}$), minimum area per surfactant molecule at the air/water interface ($A_{\text{min}}$) surface pressure at the CMC ($\pi_{\text{CMC}}$) have been evaluated. The mixtures of drugs with cationic surfactants show non-ideal behaviour. The mixture of drug and surfactants are more stable compared to pure drug and pure surfactants.

(b) This study deals with the spectroscopic investigation of interaction between antidepressants and bile salts which give the valuable and plentiful information about uses of bile salts in pharmaceutics. The spectroscopic techniques such as UV-visible and fluorescence have been employed for the determination of binding constant ($K, K_a$), Stern – Volmer constant ($K_v$), binding sites (n) and free energy changes for binding ($\Delta G_{\text{binding}}$). The value of binding constant ($K, K_a$) is found to be maximum for CPZ + NaDC mixtures from both the spectroscopic methods. More hydrophobic nature of NaDC is responsible
for better interaction with antidepressants drugs. The negative values of Gibb’s free energy changes reveal the spontaneity of all the systems. The order of Gibb’s free energy changes of the studied systems is found to be: CPZ + NaDC (−42.42) < DSP + NaDC (−19.84) < CPZ + NaC (−19.76) < DSP + NaC (−7.30).

(C) Interaction of antidepressant drugs with binary system (C_{12-4}(OH)_2-C_{12}2Br^- + F-127) have also been studied by fluorescence technique. The more binding affinities have been found at higher mole fraction of mixed surfactant system for both of the drugs. Size distribution, polydispersity and zeta potential values have also been evaluated by dynamic light scattering (DLS) studies.

Principal Investigator
Prof. Kallol K Ghosh
School of Studies in Chemistry
Pt. Ravishankar Shukla University
Raipur- 492010 CG