Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 44 No. 3 (2023)

Micellization of Ammonium Dodecyl Sulfate in Binary System in Presence of Azithromycin and Piroxicam

Sobika M[a], Anjali S[a], Bharathi Balasubramaniyan[a], and Sasmita Dash[a]*

[a]Department of Chemistry, Annamalai University, Chidambaram-608002, Tamilnadu, India.
*E-mail: mishra342sas@gmail.com

Abstract

The micellization properties of anionic surfactant Ammonium dodecyl sulfate (ADS) has been investigated in presence of three binary micellar mediums for two drugs. The micellar systems were ADS+ Pluronic L-35, ADS+Pluronic L-64 and ADS+Pluronic P-123. The two drugs used were Azithromycin (AZI) and Piroxicam (PYM). The investigations were carried out through UV- visible spectroscopy, FTIR Spectroscopy and Conductivity studies. There was greater binding of both the drugs in presence of ADS+P-123 as observed from UV spectroscopic measurements. This was because of probable high molecular weight and lower HLB compared to the other two binary pluronic combinations. The Gibbs free energy of micellization, ΔG_m was negative for all the six combinations of binary system and drugs predicting that the reactions are spontaneous in nature. The lowering of CMC of ADS in a gradually manner while proceeding from ADS, ADS+P-123, ADS+P-123+drug presumes that there is greater solubilization of drug in the mixed micellar system.

Keywords: Micellization, Pluronics, Azithromycin, Piroxicam, Ammonium dodecyl sulfate.

Introduction:

Micelles are self-assembled units which are generated from monomer units of amphiphiles. They are generally spherical, supra-molecular and nano-sized colloidal particles whose structures are divided into an internal hydrophobic core region and an external hydrophilic corona region (shell).[1,2] Micellization occurs above the critical micellar concentration (CMC) of any surfactant. It is an important characteristic of a surfactant. It is a dehydration process which leads to a large increase of the free water with respect to the bounded water. Any surfactant lowers the interfacial tension which helps the medium to spread better across a material or solubilize a substance with higher efficacy.[3,4]

In the group of amphiphiles, the anionic group consists of the ones consisting of organic molecules which when dissolved in water, readily create anions. Many of the anionic surfactants are used in in-vitro drug-release studies when new drug products are developed. Surfactants like sodium dodecyl sulphate (SDS) are generally used for their purpose.[5,6] Also, in addition, this amphiphile has bacteriostatic properties against gram-positive bacteria. But, its use is restricted due to the irritable nature. Another anionic surfactant, Ammonium dodecyl sulphate (ADS) is used on many occasions in pharmaceutical industry because of its inhibitory activity of enzyme protein synthesis and biological process. Its less damaging and less irrating nature compared to SDS extends its use in both pharmaceutical and cosmetic industry.[7,8]

Different types of polymeric single/mixed micelles are used for drug delivery and other applications because of their superior property compared to their individual amphiphilic ones.[9-14]

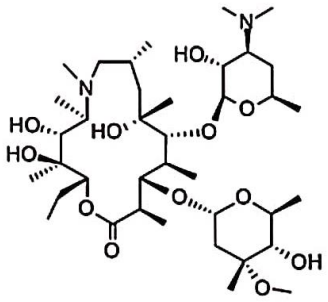
Micellar delivery system provides a promising method adopted widely for the enhancement of solubilization of hydrophobic drugs. In the recent past a good number of researchers have reported their findings in this field. This field is extensive because a sizable number of trial and error experiments are to be conducted to get a positive finding for a particular hydrophobic drug and a mixed micellar system. Sheng Feng et al have prepared polymeric mixed micelles through hot-melt extrusion method.[15] Another research group have formulated the polymeric mixed micelles using quercetin to be used for ovarian, breast and multidrug resistant tumors.[16] From a study on polymeric mixed micelles used as nanocarriers for hydrophobic antibiotic drugs has

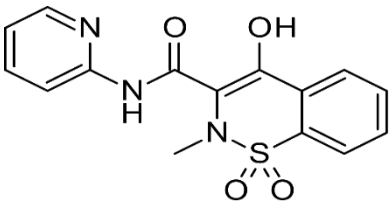
been reported.[17] In a study of novel mixed polymeric micellar system from biocompatible polymers to encapsulate gambogenic acid (GNA) was developed by Tong-Yuan Lin et al.[18] The preparation and evaluation of a novel mixed micellar system has been used in the form of nanocarriers for the drug propofol to be delivered intravenously.[19] The micellar drug delivery system used for various hydrophobic drugs are described by previous workers.[20] The solubilization of hydrophobic drugs in polymeric mixed micelles has been narrated by few workers where improved characterizations are observed compared to single micellar systems.[21-26] In many of these studies, the binary micellar system of the polymeric surfactant has superior properties compared to single micellar counter parts. One important property is reduction in micellar size. For any nanoparticle to encapsulate more drug molecules, the smaller size is preferred because of larger surface area. Hence, by achieving this it is possible to incorporate more drug into the micelle.

Azithromycin (AZI) is an antibiotic which has high degree of penetration in tissues. It is mainly used for treating infections occurring in ear, nose and chest. This belongs to an azalide subclass which has 15-memebered ring and methyl-substituted nitrogen. It has poor aqueous solubility and low bioavailability.

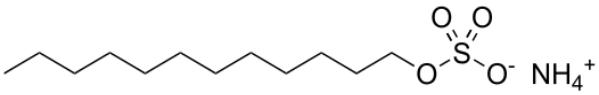
Piroxicam (PYM) in an anti-inflammatory and non-steroidal drug belonging to oxicam group. This is used to treat different types of arthritis. It can exist in anionic, neutral as well as zwitterionic forms in aqueous medium. Due to low aqueous solubility it displays poor bioavailability. Hence, different methods for improving the solubility are still under research.

(a) Azithromycin dihydrate

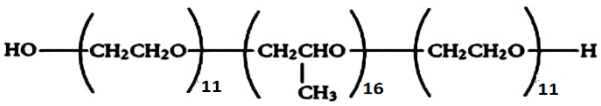




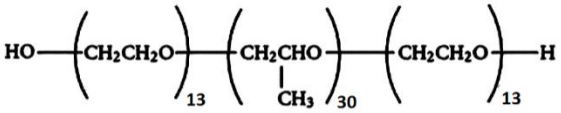
(b) Piroxicam



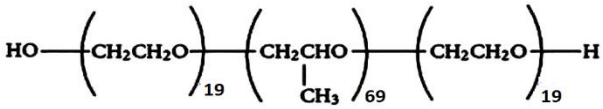
(c) Ammonium Dodecyl Sulfate



(d) Pluronic L-35



(e) Pluronic L-64



(f) Pluronic P-123

Fig.1. Structure of (a) Azithromycin dihydrate (AZI), (b) Piroxicam (PYM), (c) Ammonium Dodecyl Sulfate (ADS), (d) Pluronic L-35, (e) Pluronic P-123 and (f) Pluronic L-64.

In this study, therefore, we have tried to tune the anionic surfactant ADS by combining different polymeric surfactants and investigating their interaction on two drugs. The selected polymeric surfactants were Pluronic L-35, Pluronic L-64 and Pluronic P-123 which were of different molecular weights and hydrophilic lipophilic balance (HLB). They are presented in **Table 1**. Two drugs were taken for study. They are Azithromycin (AZI) and Piroxicam (PYM). The structure of all the surfactants and drugs are displayed in **Fig.1**

Table.1. Different molecular weights and hydrophilic lipophilic balance (HLB) of polymeric surfactants Pluronic L-35, Pluronic L-64 and Pluronic P-123.

Surfactant	Molecular weight	HLB	CMC
Pluronic L-35	1900	19	$5.3x10^{-3}$
Pluronic L-64	2900	15	$4.8x10^{-4}$
Pluronic P-123	5750	8	$4.4x10^{-6}$

Materials

Pluronic surfactants, Pluronic L-35, L-64, and P-123 and ADS were purchased from Sigma Aldrich and were used as such. The molecular weights are 1900 M^{-1}, 2900 M^{-1} and 5750 M^{-1} respectively. Drugs AZI and PYM were procured from Madras chemicals Ltd. as gift samples. Double distilled water was used for preparation of all solutions.

Methods

Preparation of drug solutions

Drug solution of AZI was prepared by weighing about 0.2 g of drug and dissolving in 20 ml methanol. After the solution became transparent, it was made up to 100 ml using buffer solution of pH 6.4. The clear drug solution was used for all the characterizations.

Piroxicam drug solution was prepared by weighing 0.0165 g quantity and dissolving in 15 ml ethanol. After complete dissolution it was made up to 100 ml using buffer pH 6.8 to yield a clear solution, which was used for the experiments. The stock solution was suitably diluted to get optimized OD.

Preparation of surfactant solutions

ADS Preparation

About 1.8 g of ADS was accurately weighed and solubilized in 100 ml of double distilled water. The stock solution prepared was suitably diluted to be used for different experiments.

Pluronic Surfactant Solutions

Pluronic L-35 was prepared for 100mM concentration by weighing appropriate quantity. The solution was kept in refrigerator for 24 hours to bring to transparent homogeneous solution. Pluronic L-64 was prepared for 6.89mM stock solution by taking the required amount and preparing in cold condition. And, Pluronic P-123 was prepared for 20mM stock solution by taking weight and preparing in cold condition as mentioned earlier. All the three Pluronic solutions were suitably diluted to get optimum concentration of O.D. Care was taken to keep the concentration above the CMC of each surfactant in every characterization.

In the next step, mixed micellar solutions were prepared by taking 6mM ADS with 100mM L-35, 6.89mM L-64 and 20mM P123. Then suitable amount of drug was added to each mixed micelle before characterization.

Characterizations

1. Fourier transforms infrared spectroscopy (FTIR)

The FTIR spectra of the two drugs AZI and PYM in presence of three mixed micellar systems were carried out using Cary-630 FTIR Agilent Technology in the range of 600 cm^{-1} and 3600 cm^{-1}. For each aliquot 1 ml each of the solution was taken, mixed thoroughly, dried and the spectra were recorded. For both the drugs two separate sets of readings are presented in **Fig.2** and **3** for AZI and PYM respectively along with pure drug and single surfactant spectra.

2. UV Spectrophotometry

UV Spectra of the drugs without and with single/mixed micelles were recorded using Shimadzu UV-1650 PC Spectrophotometer with 1 cm quartz cell. The stock solutions of each drug were used for calibration and then the required concentration was taken for each reading. Three different sets were measured for each drug, they are, AZI+L-35+ADS, AZI+L-64+ADS, AZI+P-123+ADS, and PYM+L-35+ADS, PYM+ L-64+ADS, PYM+P-123+ADS.

3. Conductivity Study

The specific conductance measurements of the ionic surfactant ADS and ADS as mixed micelle with both drug were carried out by using PICCO-180 conductivity meter which is provided with a platinum electrode. The measurements were done at 300 K. The specific conductance values plotted with concentration. The break in the points were identified as CMC. The slopes of pre and post micellar concentrations were S_1 and S_2 which were used for calculating the counter ion binding constant β, using the equation below.

$$\beta = 1 - \alpha, \qquad \alpha = \frac{S_1}{S_2}$$

From the counter ion binding constant β, the thermodynamic parameters ΔG_m^o, Gibbs free energy of micellization, were calculated using formula,

$$\Delta G_m^o = (2 - \beta) RT \ln X_{CMC}$$

Results and Discussion

FTIR Spectroscopy

For both the drug the IR spectra and their explanation are given separately. **Fig.2** presents the spectra for AZI group and **Fig.3** for PYM group.

In the AZI group, as shown in **Fig.2** and **Table.2** pristine AZI displays prominent bands at 3485 cm^{-1}, 2970 cm^{-1}, 1719 cm^{-1}, 1186 cm^{-1}, 1047cm^{-1} which represents OH stretching, C-H stretching, esteric bond and C=O stretching respectively. Pure ADS displayed bands at 3381 cm^{-1}, 2923 cm^{-1}, 1636 cm^{-1}, 1457 cm^{-1}, 1204 cm^{-1} which symbolize OH stretching, N-H stretching, C=C stretching, CH stretching and C-O stretching respectively **Fig.2(b)**. The spectra of three pluronic surfactants L-35, L-64 and P-123 have the similar structure of polyethylene oxide (PEO) and polypropylene oxide (PPO) groups for which the three spectra have resemblance, this is

presented by **Fig.2(c), (d)** and **(e)** respectively. The complex of AZI+L-35+ADS is presented by **2(f)** which shows bands at 3427 cm^{-1}, 2922 cm^{-1}, 1636 cm^{-1}, 1456 cm^{-1}, 1081 cm^{-1} and 945 cm^{-1}. Here, 3427 cm^{-1} stands for OH stretching which is shifted from 3485 cm^{-1} of AZI, a shift to a lower wave number **2(a)**. The 2922 cm^{-1} standing for N-H stretching has retained its position from 2923 cm^{-1} of ADS with change in intensity. The 1636 cm^{-1} of C=C stretching band from the three pluronics has occupied its place in the complex formation with reduced intensity in the complex. The 1081 cm^{-1} peak standing for C-O stretching has shifted from 1186 cm^{-1} of AZI **2(a)** this is another shifting to lower wave number.

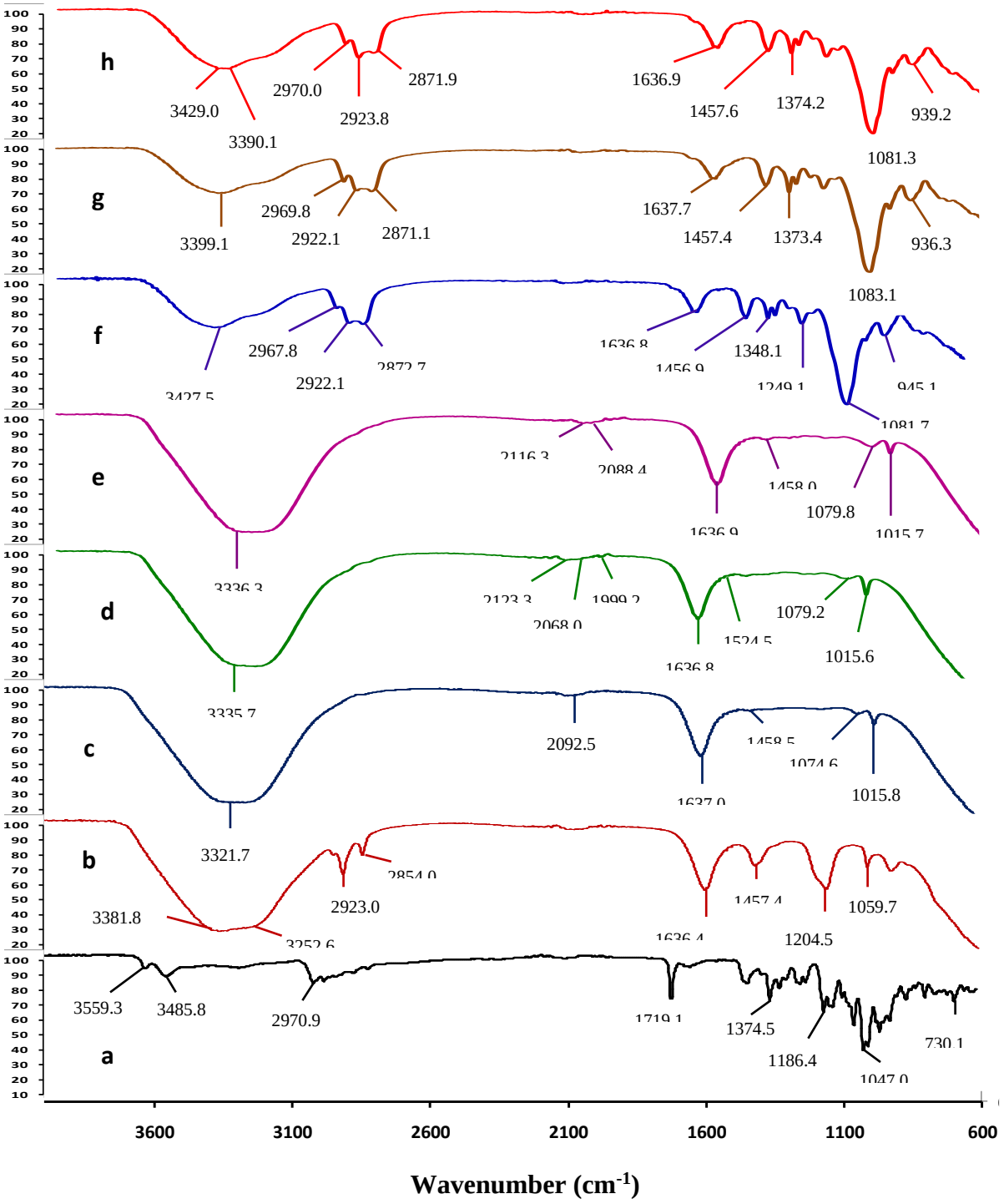


Fig.2. (a) AZI, (b) ADS, (c) L-35, (d) P-123, (e) L-64, (f) AZI+L-35+ADS, (g) AZI+

Table.2. Band assignments of IR Spectrum showing (a) AZI, (b) ADS, (c) L-35, (d) P-123, (e) L-64, (f) AZI+L-35+ADS, (g) AZI+P-123+ADS and (h) AZI+L-64+ADS

Assignments	Wavenumber (cm^{-1})							
	AZI	**ADS**	**L-35**	**P123**	**L-64**	**AZI+ L35+ ADS**	**AZI+ P123+ ADS**	**AZI+ L-64+ ADS**
O-H Stretching	3559, 3485	3381, 3252	3321, 2092	3335	3336	3427, 2967, 2922, 2872	3399, 2969, 2922	3429, 3390, 2970, 2923
N-H Stretching	2933, 2892	2923, 2854	-	-	-	-	2871	2871
C-H Stretching	2970, 2830	1457	-	-	-	1456	1457	1457
C≡C	-	-	-	-	2116	-	-	-
C=C Stretching	-	1636	1637, 1561	1636, 1560	1636, 1560	1636	1637	1636
C-N Stretching	1269	-	1074	-	1079	-	-	-
C-Br Stretching	-	-	-	-	-	-	-	-
C=O Stretching	-	-	-	-	-	-	-	-
C-O Stretching	1186, 1081	1204	-	-	-	1296, 1249, 1081	1296, 1249,	1295, 1248,
CO-O-CO Stretching	1047	-	-	-		-	-	-
C-H Bending	1654, 1375	-	1458	2025, 1999, 1458	1458	802	-	-
C=C Bending	990	974	-	-	-	945	936	939
O-H Bending	1341, 1317	-	-	-	-	-	1373, 1347	1348

Here, it can be observed that there is enhanced peak intensity of 1081 cm^{-1}. The 945 cm^{-1} is assigned for C=C bending vibration which gets shifted from 990 cm^{-1} of AZI **Fig.2(a)**. Hence, there are three shifting to lower wave number predicting short and strong bond formation in the complex which has higher molecular weight. In the other two AZI+ P-123+ADS and AZI+L-64+ADS also, same type of bonding and shifting takes place. This concludes that in all the three types of complexes there is strong binding between the mixed micelle of ADS with Pluronic L-35/P-123/L-64 surfactants and the drug AZI. The three complexes have very similar in structure due to the similarity of the pluronic surfactants taking part in the complex formation. IR studies on AZI with other chemicals have been reported before.[27-30]

Drug PYM displayed peaks at 3335 cm^{-1}, 2116 cm^{-1}, 1627 cm^{-1}, 1523 cm^{-1}, 1347 cm^{-1}, 1178 cm^{-1} and 770 cm^{-1}which represent for OH stretching, C=C stretching N-H stretching, C=O stretching, OH bending, CO stretching and C-H bending respectively which is shown in **Fig.3(a)**. The ADS and three pure pluronic surfactant band assignments have been described in the previous part. Hence, they are not repeated here. The complex of PYM+L-35+ADS displayed bands at 3427 cm^{-1}, 2870 cm^{-1}, 1085 cm^{-1}, 943 cm^{-1} which stand for OH stretching, NH stretching, CO stretching and CH bending respectively. Out of these, the peaks that are shifted are (i) 2870 cm^{-1}, which got shifted from 2923 cm^{-1} of ADS in **3(b)**, a shift to lower wavenumber (ii) The 1645 cm^{-1} got shifted from 1636 cm^{-1} of ADS **3(b)**, a higher wave number shifting. (iii) The 1085 cm^{-1} peak got shifted from 1178 cm^{-1} of PYM **3(a)**. And (iv) 943 cm^{-1} peak got shifted from 1015 cm^{-1} of **3(c)**, **(d)** and **(e)**, which is due to C-C stretching frequency. These shiftings mark the bonding between the mixed micelle of ADS+L-35 with PYM to form complexes. Owing to the structural similarity of L-35, P-123 and L-64, the three complexes have

more or less similar in structure, as observed from the infrared studies. IR studies on PYM has been reported before.[31-33]

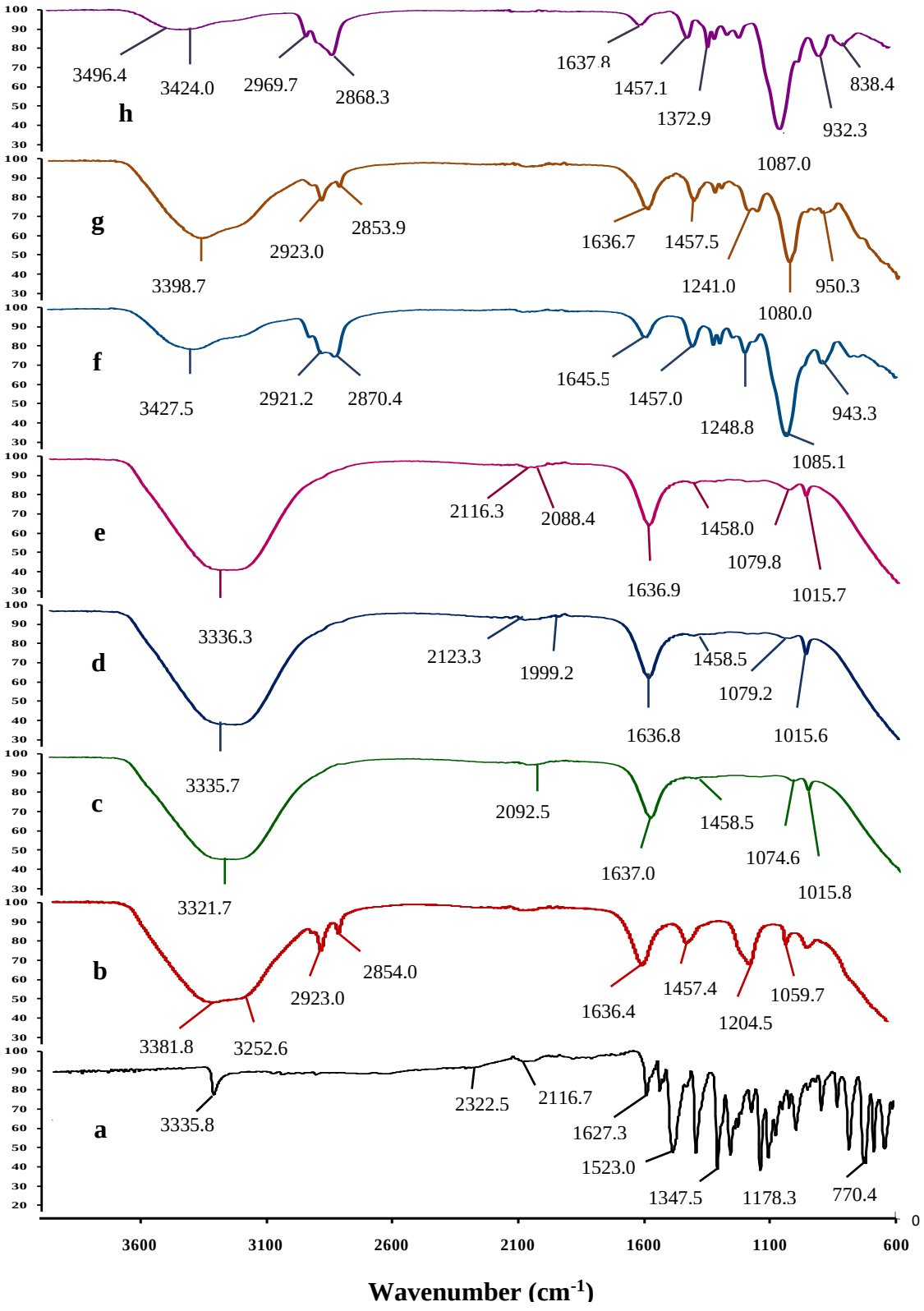


Fig.3. (a) PYM, (b) ADS, (c) L-35, (d) P-123, (e) L-64, (f) PYM+L-35+ADS, (g) PYM+ P-123+ADS , (h) PYM+L-64+ADS

Table.3. Band assignments showing vibration for (a) PYM, (b) ADS, (c) L-35, (d) P-123, (e)L-64, (f) PYM+L-35+ADS, (g) PYM+P-123+ADS , (h) PYM+L-64+ADS

Assignments	Wavenumber (cm^{-1})							
	PYM	**ADS**	**L-35**	**P123**	**L-64**	**PYM+ L35+ ADS**	**PYM+ P123+ ADS**	**PYM+ L-64+ ADS**
O-H Stretching	3335	3381, 3252	3321, 2092	3335	3336	3427, 2921	3398	3496, 3424, 2969, 2868
N-H Stretching	1627	2923, 2854	-	-	-	2870	2923, 2853	-
C=C Stretching	2116	-	-	-	2116	-	-	-
C=C Stretching	1627	1636	1637, 1561	1636, 1560	1636, 1560	-	-	1637
C=O Stretching	1523	-	-	-	-	-	-	-
C-O Stretching	1178	1204	-	-	-	1248, 1085	1208	1296, 1249, 1087
C=C Bending	730	974	-	-	-	-	950, 700	-
C-H Bending	770	1457	1458	2025, 1999, 1458	1458	1457	1457	1457
O-H Bending	1347	-	-	-	-	1373, 1348	1348	1372, 1347

UV Spectroscopic Analysis

The change of hydrophobic behavior of the single and binary surfactant system due to the presence of drugs AZI/PYM were observed through UV spectroscopic study. The possible complex formation are also assessed as reported earlier by previous authors.[34] The aqueous solution of AZI (0.75 mM in methanol-water system at pH 6.4) displayed λ_{max} at 227 nm. For clarity, we have presented the magnified image in the range of 200-250 nm. On adding Pluronic L-35, ADS, there was increase in absorbance with blue shift of 5 nm as shown in **Fig.4(a)**. In the next step, different concentrations of ADS (3.17 mM to 15.8 mM) were added to a fixed quantity of AZI and L-35. There was progressive increase of intensity of absorption. This implies that there is more drug encapsulated in the mixed micellar system at higher concentration. Also, there is occurrence of complex formation between AZI and ADS+L-35.

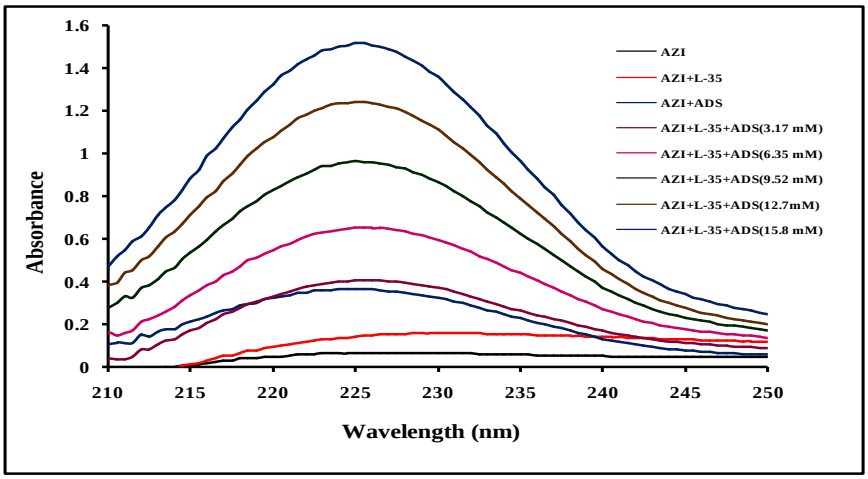


Fig.4(a). UV absorption spectrum of AZI in presence of single and mixed micellar concentrations with fixed L-35 and varied ADS concentrations.

With another mixed micellar system comprising of ADS+L-64, the drug AZI was used for interaction. Here, the drug solution displayed λ_{max} at 227 nm which showed an increase in absorbance with L-64 addition in the first step and further increase with ADS. On adding L-64+ADS, there was still increase of absorption compared to both single micellar systems. This shows that the mixed micelle has better efficiency than both the single micelles as far as interaction with AZI is concerned. In the next step, different concentration of ADS (from 3.17mM to 15.8mM) were added to fixed AZI and L-64 solution. This showed a linear increase in the intensity of absorption. This confirms the complex formation taking place between L-64+ADS and AZI. The binding constant values of the three mixed micellar systems with ADS are displayed in Table 4. This shows that in the AZI and three mixed micellar systems, there is lowest binding constant obtained for L-64+ADS and the maximum value 36.01 M^{-1} observed for P-123.

In another mixed micellar system, ADS+P-123, the drug AZI displayed similar behavior. Increase in absorbance followed by blue shift, which can be assigned for complex formation and change of hydrophobicity in the system **Fig.4(c)**. The incorporation of P-123, a hydrophilic surfactant, in the ADS system appeared to have more effect as absorbed from the binding constant values shown in **Table. 4.** For L-35 however, there was an intermediate value of 11.6 M^{-1}. This may be due to the hydrophilic nature of the pluronic surfactants which showed a difference in the affinity while binding with drug AZI.

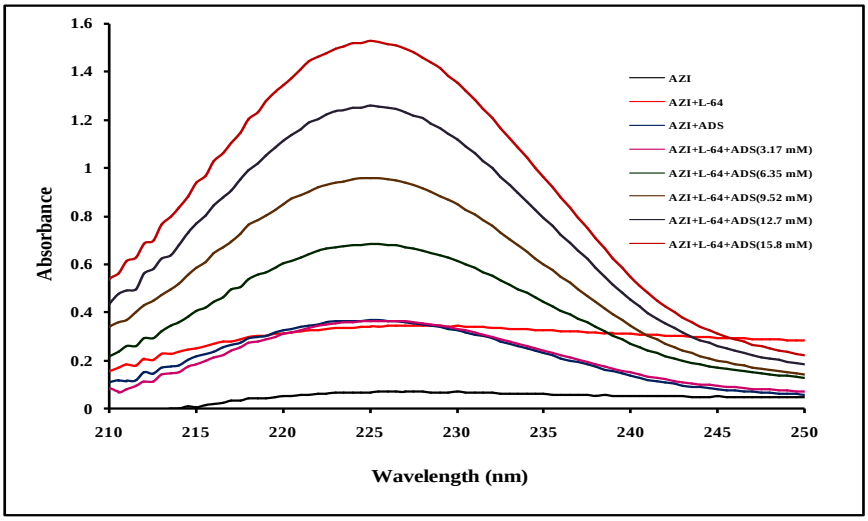


Fig.4(b). UV absorption spectrum of AZI in presence of single and mixed micellar concentrations with fixed L-64 and varied ADS concentrations

.

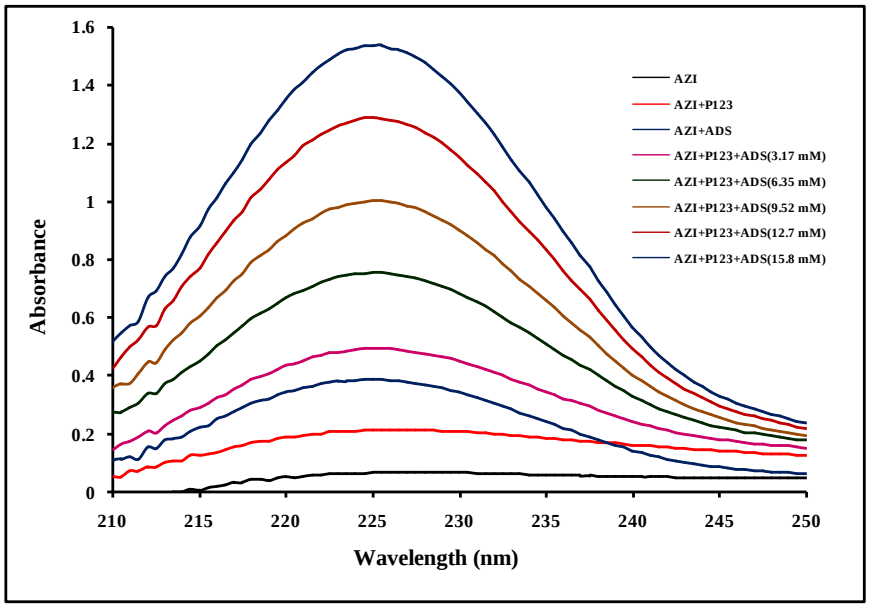


Fig.4(c). UV absorption spectrum of AZI in presence of single and mixed micellar concentrations with fixed P-123 and varied ADS concentrations.

The aqueous solution of PYM (0.02mM in 6.8pH) displayed λ_{max} of 354 nm. This value is in good agreement with literature value.[35-36] . For a better view, we have presented the spectra between 300-420 nm. On addition of L-35+ADS with fixed L-35 and varied ADS concentration to a PYM aqueous solution, there was increased absorption. This is a symbol with higher encapsulation of drug in the mixed micellar system of L-35+ADS. This is shown in **Fig.5(a)**. Another mixed micellar system of ADS+L-64 also displayed similar result as shown in **Fig.6(b)**. The third binary system with ADS+P-123 was observed with its interaction of PYM which showed increased absorbance like the previous two systems **Fig.6(c)**. Hence, in all the three systems, there was complex formation. The binding of PYM with three binary systems as calculated using B-H plot are shown in **Table 4**. This shows that the P-123+ADS system had the maximum binding with drug PYM. Their depends on the possible change of hydrophobicity created by the PYM, which has global neutral characteristic in different pH solutions. The affinity of the three pluronic surfactants also played a major role in the binding.

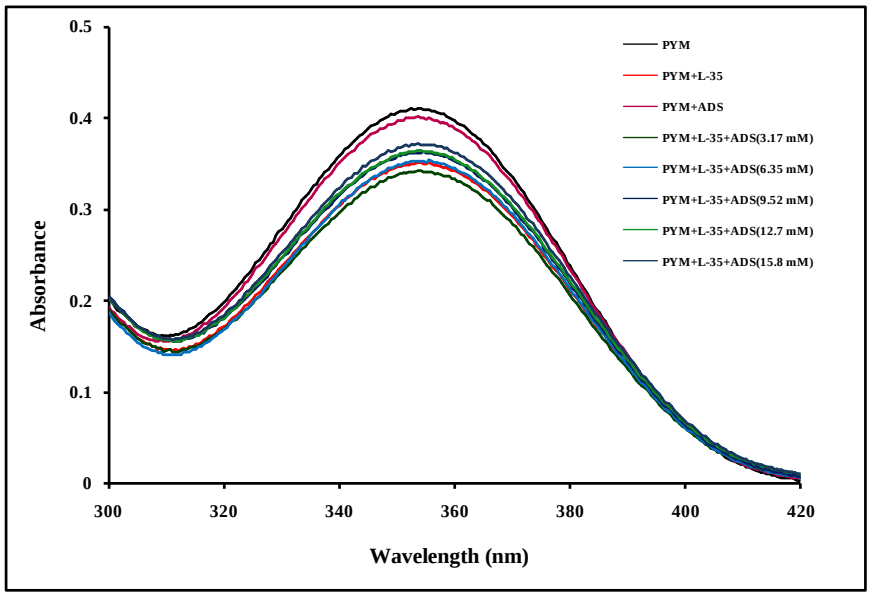


Fig.5(a). UV absorption spectrum of PYM in presence of single and mixed micellar concentrations with fixed L-35 and varied ADS concentrations.

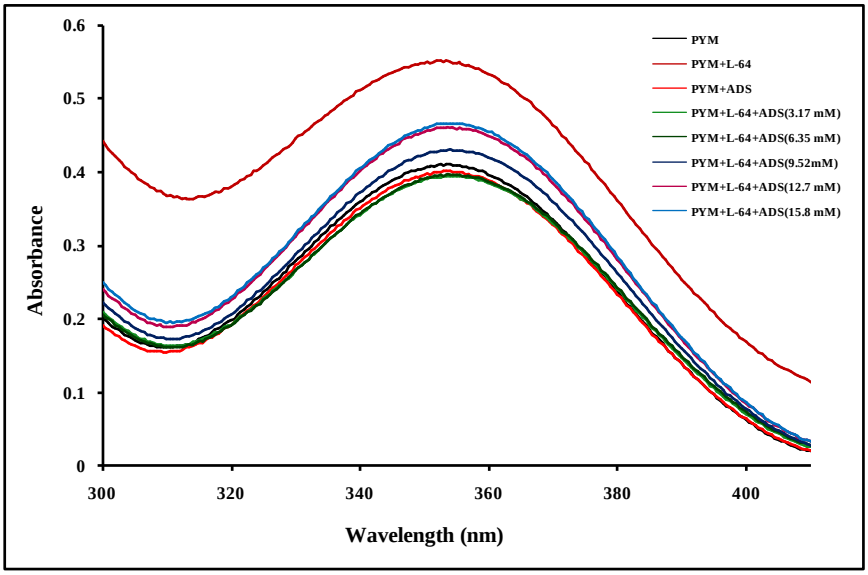


Fig.5(b). UV absorption spectrum of PYM in presence of single and mixed micellar concentrations with fixed L-64 and varied ADS concentrations.

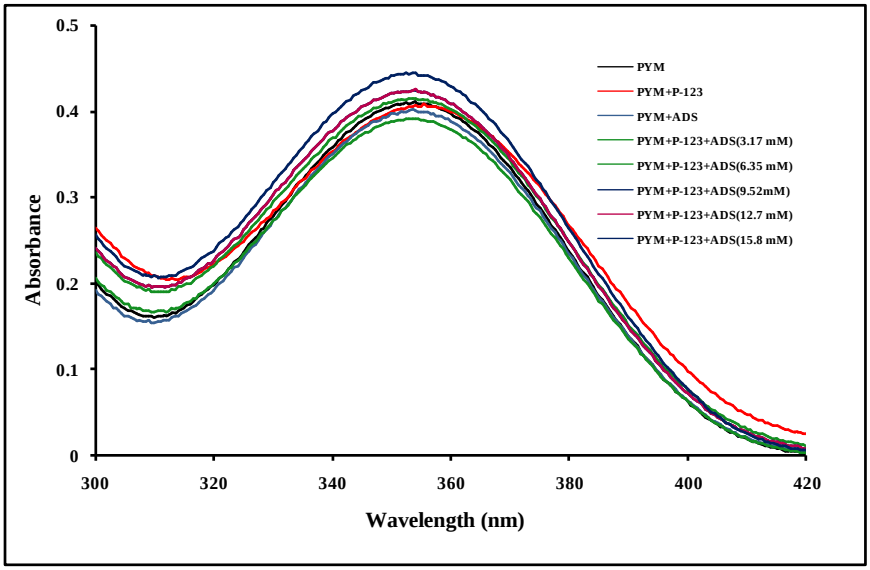


Fig.5(c). UV absorption spectrum of PYM in presence of single and mixed micellar concentrations with fixed P-123 and varied ADS concentrations.

Table.4. Binding constants calculated from various mixed micellar system for AZI/PYM using B-H plot.

S.No.	System	Binding constant (K)
1	AZI+ADS+L-35	11.6
2	AZI+ADS+L-64	1.5
3	AZI+ADS+P-123	36.01

S.No.	System	Binding constant (K)
1	PY+ADS+L-35	0.0408
2	PY+ADS+L-64	0.060
3	PY+ADS+P-123	0.0832

Conductivity

Conductivity is an important study in the pharmaceutical industry. Its analysis helps to know how well a drug solution conducts electricity which in turn indicates the amount of dissolved ions present. The change in conductivity and mobility of any drug solution gives an idea about the drug excipient interactions.[37] In this work we have used two drugs AZI and PYM with binary solution of ADS with L-35/L-64/P-123 surfactants. The specific conductivity (κ) is measured for different solutions without and with drugs. The two drugs have been analyzed separately.

AZI

Anionic surfactants behave like electrolytes in aqueous solution. The specific conductivity (κ) of ADS was measured at different concentrations. There was increase in conductivity value. The sharp change in the κ was taken as the CMC which was found to be 6mM. This is in good agreement with literature.[38, 39] On adding L-35 to ADS, there was a lowering of CMC to 5.4mM. On adding AZI in the next step there was no further change in CMC. It is shown in **Fig.6(a)** and **Table.5.** After identifying the CMC, the pre and post micellar slopes S_1 and S_2 were determined which were used for calculating ΔG_m^o, Gibb's free energy of micellization. The ΔG_m^o values were -11.48, -23.04 and -34.56 kJ mol^{-1} for ADS, ADS+L-35 and ADS+L-35+AZI respectively. All the three values are negative indicating spontaneity of the reactions. The higher negative value for the drug solubilized mixed micelle

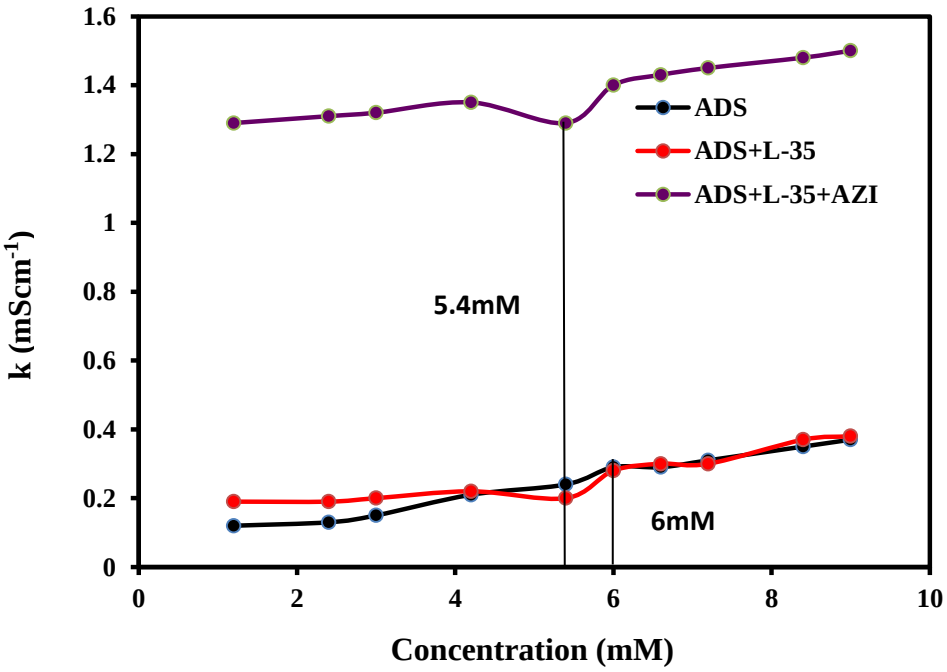


Fig.6(a). The specific conductance vs. Conc. plots of ADS, ADS+L-35, ADS+L-35+AZI

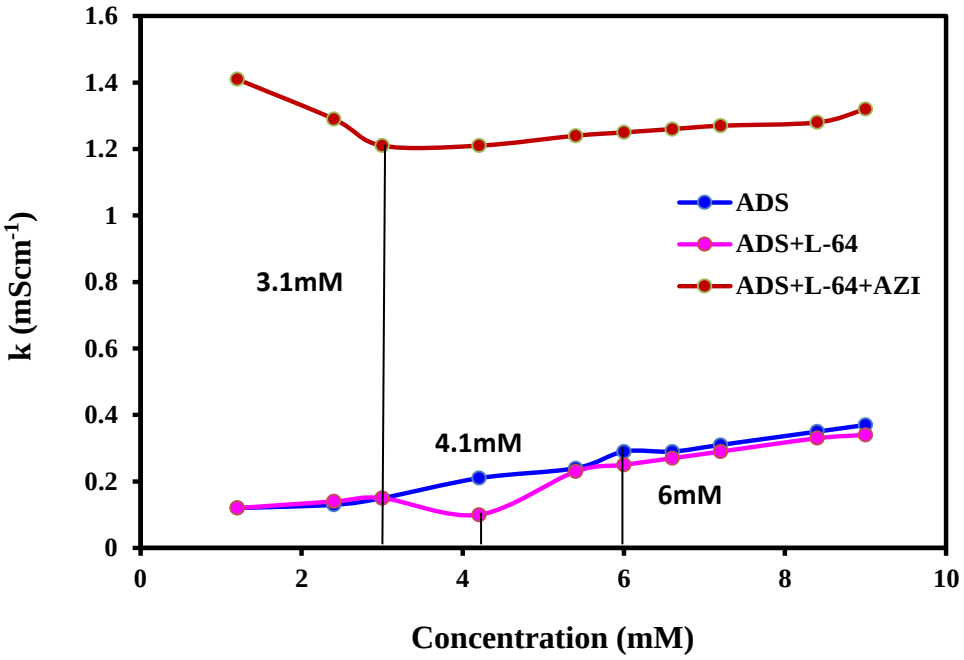


Fig.6(b). The specific conductance vs. Conc. plots of ADS, ADS+L-64, ADS+L-64+AZI

is an indication of greater spontaneity and stability of the system compared to ADS and ADS+L-35. In the next set the ADS+L-64 displayed a CMC of 4.2mM which got further reduced to 3mM for ADS+L-64+AZI. Here too, the ΔG_m^o values were -23.67 and -44.11 kJ mol^{-1} showing spontaneity of the reactions. It is displayed in **Fig.6(b)**. In the third set, the ADS+P-123 and ADS+P-123+AZI showed 4.2mM as CMC which got reduced from 6mM for pure ADS. And, the ΔG_m^o was -23.67 and -33.14 kJ mol^{-1} for both the sets. This is shown in **Fig.6(c)**. The reduction in CMC for all the three binary micellar mediums when solubilized AZI drug is an indication of greater solubility of the drug.

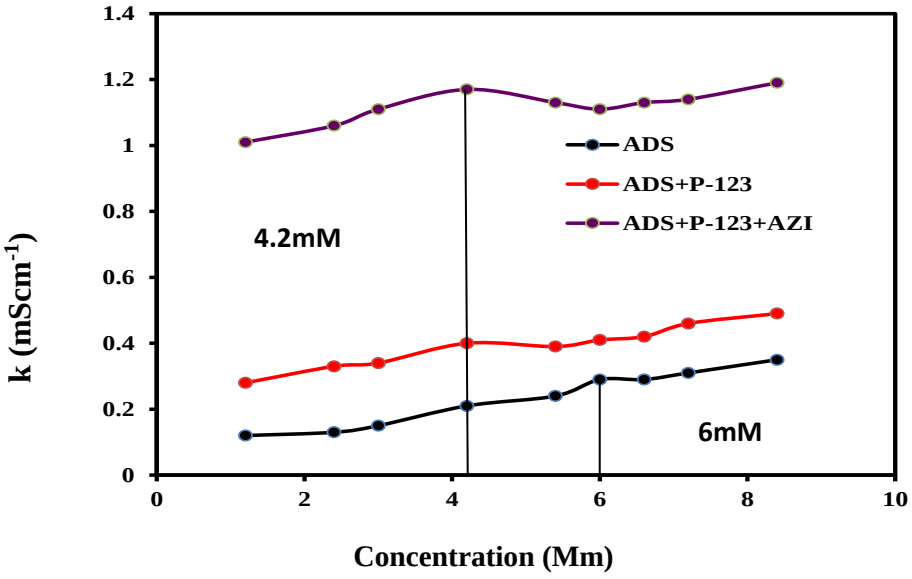


Fig.6(c). The specific conductance vs. Conc. plots of ADS, ADS+P-123, ADS+P-123+AZI

Table.5. The variation of CMC and ΔG_m^o of ADS in L-35/L-64/P-123 surfactants and AZI/PYM drugs at 300 K.

S.NO	System	CMC (mM)	ΔG_m^o (kJ mol^{-1})
1	ADS	6	-11.48
2	ADS+L-35	5.4	-23.04
3	ADS+L-64	4.2	-23.67
4	ADS+P-123	4.2	-23.67
5	ADS+L-35+AZI	5.4	-34.56
6	ADS+L-64+AZI	3	-44.11
7	ADS+P-123+AZI	4.2	-33.14
8	ADS+L-35+PY	3	-29.41
9	ADS+L-64+PY	3	-36.20
10	ADS+P-123+PY	3	-24.48

PYM

In the PYM set, the CMC of ADS got reduced from 6mM to 5.4mM for ADS+L-35 which further reduced to 3mM for ADS+L-35+PYM. The ΔG_m^o values were -11.48, -23.04 and -29.41 kJ mol^{-1} respectively showing greater spontaneity and stability of the drug in the mixed micellar system. It is shown in **Fig.7(a)** with L-64+ADS system, there was lowering from 6mM to 4.2mM and again lowered to 3mM on adding PYM. The lowering of free energy was followed in the order, -11.48, -23.67 and -36.2 kJ mol^{-1} for the three systems. It is displayed in **Fig.7(b)**. In the ADS+P-123 binary micellar system, the CMC was 4.2mM and ADS+P-123+PYM it was 3mM. The ΔG_m^o values were -11.48, -23.67 and -24.48 kJ mol^{-1} respectively **7(c)**. All the three systems have shown spontaneity of the systems with greater stability with drug PYM.

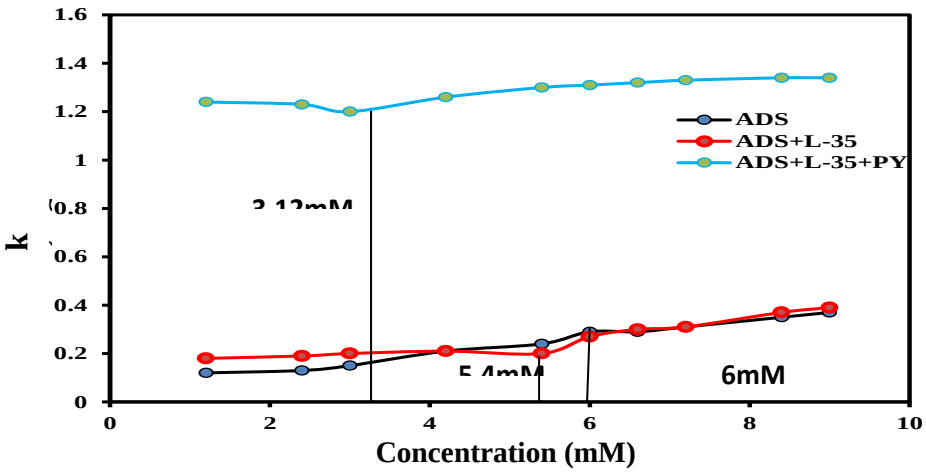


Fig.7(a). The specific conductance vs. Conc. plots of ADS, ADS+L-35, ADS+L-35+PYM

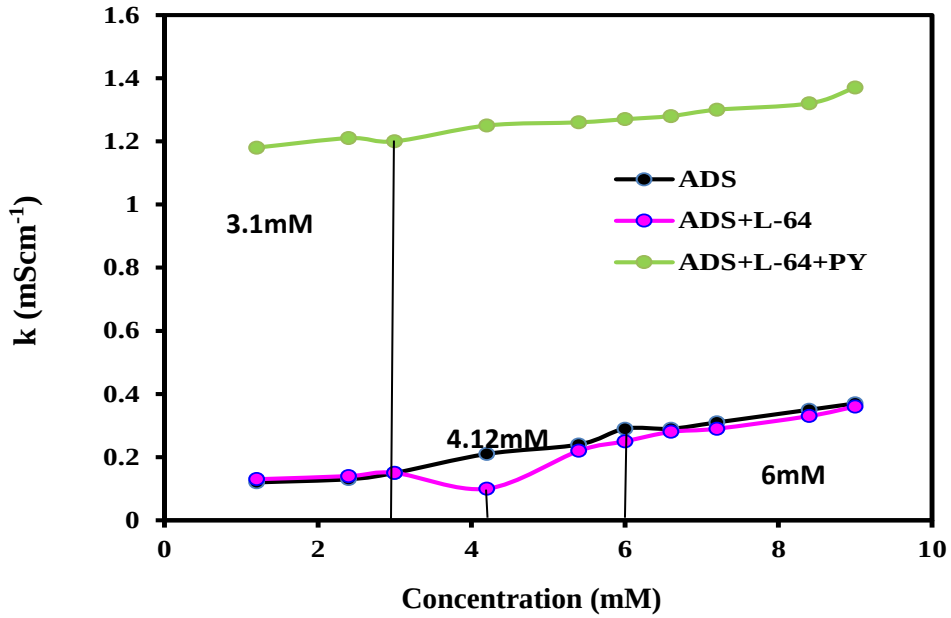


Fig.7(b). The specific conductance vs. Conc. plots of ADS, ADS+L-64, ADS+L-64+PYM

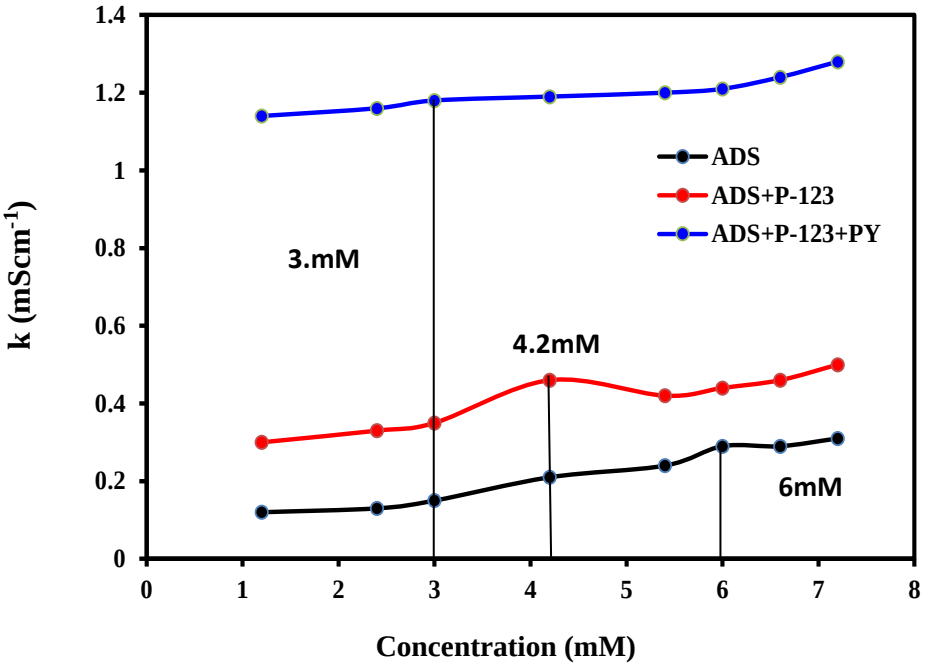


Fig.7(c). The specific conductance vs. Conc. plots of ADS, ADS+P-123, ADS+P-123+PYM

Conclusion

The micellization and interaction study of the anionic surfactant ADS in presence of three pluronic micellar systems with drugs AZI and PYM are carried out. There was spontaneous binding of drug to all the binary micellar systems. The system of ADS+P-123 is observed to bind more strongly to AZI and PYM compared to ADS+L-35 and ADS+L-64. This study offers three new binary systems for the hydrophobic drugs AZI and PYM with increased solubility and greater bioavailability.

References

1. Ramyasree Jwalapuram1 , Hindustan Abdul Ahad2*, Chinthaguinjala Haranath2, Reshma Thadipatri1 , Chenga Venkata Hima Varshitha1 and Yedire Bharath Kumar. Solubility Enhancement of Drugs with Aid of Surfactants: Research Done Since Last Two Decades. ijlpr 2020; doi 10.22376/ijpbs/lpr.2020.10.5.P11-16.

2. Dilli Ram Pokhrel, ad Manish Kumar Sah, b Bibaran Gautam, a Hriday Kumar Basak, cd Ajaya Bhattarai *be and Abhik Chatterjee, A recent overview of surfactant–drug interactions and their importance. RSC Adv., 2023, 13, 17685, DOI: 10.1039/d3ra02883f.

3. Nidhi Patel, Vaibhav Patel, Deep Sharma, Pradip Macwan, Sanjay Panjab, Effect of hydrocarbon surfactants on the properties of 1-dodecyl-1-methylpiperidinium chloride: synthesis, micellization, thermodynamics, and surface parameters, Colloid and Polymer Science (2022) 300:903-916. https://doi.org/10.1007/s00396-022-04996-w.

4. Bhat, P. A., Dar, A. A., & Rather, G. M. Solubilization Capabilities of Some Cationic, Anionic, and Nonionic Surfactants toward the Poorly Water-Soluble Antibiotic Drug Erythromycin. Journal of Chemical & Engineering Data, 53(6), (2008), 1271–1277. doi:10.1021/je700659g.

5. Madelung, P., Østergaard, J., Bertelsen, P., Jørgensen, E. V., Jacobsen, J., & Müllertz, A. (2014). Impact of sodium dodecyl sulphate on the dissolution of poorly soluble drug into biorelevant medium from drug-surfactant discs. International Journal of Pharmaceutics, 467(1-2), 1–8. doi:10.1016/j.ijpharm.2014.02.043.

6. Kawakami, K., Oda, N., Miyoshi, K., Funaki, T., & Ida, Y. (2006). Solubilization behavior of a poorly soluble drug under combined use of surfactants and cosolvents. European Journal of Pharmaceutical Sciences, 28(1-2), 7–14. doi:10.1016/j.ejps.2005.11.012.

7. Vigneshwari R., K. Sivakumar, G. Parinamachivayam, V. Ragavendran, Puspalata Rajesh, Sasmita Dash (2023). A proof of concept for the micellization of quercetin with anionic surfactants: Effect of counter ion, Journal of Molecular Liquids (IF 6) Pub DOI:10.1016/j.molliq.2023.122671.

8. Ghezzi, M., Pescina, S., Padula, C., Santi, P., Del Favero, E., Cantù, L., & Nicoli, S. (2021). Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. Journal of Controlled Release, 332, 312–336. doi:10.1016/j.jconrel.2021.02.031.

9. V.K. Mourya*, Nazma Inamdar, R.B. Nawale, S.S. Kulthe, Polymeric Micelles: General Considerations and their Applications, Ind J Pharm Edu Res, Apr-Jun, 2011/ Vol 45/ Issue 2.

10. R.P. Singh, A.S. Tomer, Romy Chaudhary, Effect of polymers on the micellization of surfactants by conductance measurements, July 2008**,** Asian Journal of Chemistry 20(6):4503-4510.

11. Singh, V., Khullar, P., Dave, P. N., & Kaur, N. (2013). Micelles, mixed micelles, and applications of polyoxypropylene (PPO)-polyoxyethylene (PEO)-polyoxypropylene (PPO) triblock polymers. International Journal of Industrial Chemistry, 4(1), 12. doi:10.1186/2228-5547-4-12.

12. Ahmad, Z., Shah, A., Siddiq, M., & Kraatz, H.-B. (2014). Polymeric micelles as drug delivery vehicles. RSC Adv., 4(33), 17028–17038. doi:10.1039/c3ra47370h.

13. Ronak Makhija2, Aarti Ganpat Jagtap2, Puthusserickal Abdul Rahiman Hassan3, Mangal Shailesh Nagarsenker1*, Soluplus Based Polymeric Micelles and Mixed Micelles of Lornoxicam: Design, Characterization and In vivo Efficacy Studies in Rats, Indian Journal of Pharmaceutical Education and Research | Vol 50 | Issue 2 | Apr-Jun, 2016.

14. Sheng Feng [1], Ziru Zhang [1], Ahmed Almotairy [2], Michael A Repka [3], Development and Evaluation of Polymeric Mixed Micelles Prepared using Hot-Melt Extrusion for Extended Delivery of Poorly Water-Soluble Drugs, J Pharm Sci. 2023 Jun 14;S0022-3549(23)00238-1.doi:10.1016/j.xphs.2023.06.007.

15. Vol.:(01234567Zhang, N., & Li, L. (2002). Ammonium Dodecyl Sulfate as an Alternative to Sodium Dodecyl Sulfate for Protein Sample Preparation with Improved Performance in MALDI Mass Spectrometry. Analytical Chemistry, 74(7), 1729–1736. doi:10.1021/ac015624h.
16. Patra, A., Satpathy, S., Shenoy, A., Bush, J., Kazi, M., & Hussain, M. D. (2018). Formulation and evaluation of mixed polymeric micelles of quercetin for treatment of breast, ovarian, and multidrug resistant cancers. International Journal of Nanomedicine, Volume 13, 2869–2881. doi:10.2147/ijn.s153094.

17. Tănase, M. A., Raducan, A., Oancea, P., Diţu, L. M., Stan, M., Petcu, C., … Cinteza, L. O. (2021). Mixed Pluronic—Cremophor Polymeric Micelles as Nanocarriers for Poorly Soluble Antibiotics—The Influence on the Antibacterial Activity. Pharmaceutics, 13(4), 435. doi:10.3390/pharmaceutics13040435

18. Lin, T., Zhu, T., Xun, Y., Tao, Y., Yang, Y., Xie, J., … Chen, W. (2019). A novel drug delivery system of mixed micelles based on poly(ethylene glycol)-poly(lactide) and poly(ethylene glycol)-poly(ε-caprolactone) for gambogenic acid. The Kaohsiung Journal of Medical Sciences. doi:10.1002/kjm2.12110.

19. Li, X., Zhang, Y., Fan, Y., Zhou, Y., Wang, X., Fan, C., … Zhang, Q. (2011). Preparation and evaluation of novel mixed micelles as nanocarriers for intravenous delivery of propofol. Nanoscale Research Letters, 6(1), 275. doi:10.1186/1556-276x-6-275.

20. Harshad S. Kapare*, Sarika R. Metkar, Micellar Drug Delivery System: A Review, Pharmaceutical Resonance 2020 Vol. 2 - Issue 2.

21. Senthilkumar, M., & Dash, S. (2019). Interaction of methylparaben and propylparaben with P123/F127 mixed polymeric micelles. Colloids and Surfaces B: Biointerfaces, 176, 140–149. doi:10.1016/j.colsurfb.2018.12.068.

22. Ezhilrani, V. C., Karunanithi, P., Sarangi, B., Joshi, R. G., & Dash, S. (2021). Hydrophilic-hydrophilic mixed micellar system: effect on solubilization of drug. SN Applied Sciences, 3(3). doi:10.1007/s42452-021-04250-y .

23. Prakash Karunanithi a , Vigneshwari R a , E Paul Raj a , Puspalata Rajesh b , Sivakumar Krishnamoorthy c , Sasmita Dash a, Pluronic based neutral-ionic binary micellar surfactant systems for solubilizing the cationic methylene blue dye, Chemical Physics Impact 5 (2022) 100092, https://doi.org/10.1016/j.chphi.2022.100092.

24. M. Sobika, E. Paul Raj, Sivakumar Krishnamoorthy, Sasmita Dash, Development and evaluation of azithromycin dihydrate in single and binary micellar mediums Chemical Physics Impact 6 (2023) 100229, https://doi.org/10.1016/j.chphi.2023.100229.

25. B. Sheelarani, E. Paul Raj, R. G. Joshi, Sasmita Dash, Efect of drug aceclofenac on physicochemical properties of mixed micellar systems, SN Applied Sciences (2022) 4:179, https://doi.org/10.1007/s42452-022-05055-3.

26. Raj, E.P., Karunanithi, P., Rajarajan, M. et al. Solubilization of ornidazole in single and mixed polymeric micellar medium of Pluronic F-127 and L-35. J Polym Res 30, 161 (2023). https://doi.org/10.1007/s10965-023-03552-6.

27. E. Adeli, Preparation and evaluation of azithromycin binary solid dispersions using various polyethylene glycols for the improvement of the drug solubility and dissolution rate, Braz. J. Pharm. Sci. 52 (2016) 1–13, https://doi.org/10.1590/ S1984-82502016000100002.

28. H.R. Pouretedal, Preparation and characterization of azithromycin nanodrug using solvent/antisolvent method, Int. Nano Lett. 4 (2014) 103, https://doi.org/ 10.1007/s40089-014-0103-x.

29. E. Adeli, The use of spray freeze drying for dissolution and oral bioavailability improvement of azithromycin, Powder Technol. 319 (2017) 323–331, https://doi. org/10.1016/j.powtec.2017.06.043.

30. W. Wei, S. Li, H. Xu, F. Zhou, Y. Wen, Z. Song, S. Feng, R. Feng, MPEG-PCL copolymeric micelles for encapsulation of azithromycin, AAPS PharmSciTech 19 (2018) 2041–2047, https://doi.org/10.1208/s12249-018-1009-0.

31. Trivedi MK, Patil S, Shettigar H, Bairwa K, Jana S (2015) Effect of Biofield Treatment on Spectral Properties of Paracetamol and Piroxicam. Chem Sci J 6: 98. doi:10.4172/2150-3494.100098.

32. Bertoluzza, A., Rossi, M., Taddei, P., Redenti, E., Zanol, M., & Ventura, P. (1999). FT-Raman and FT-IR studies of 1:2.5 piroxicam: β-cyclodextrin inclusion compound. Journal of Molecular Structure, 480-481, 535–539. doi:10.1016/s0022-2860(98)00734-0.

33. Bunaciu AA, Fleschin Ş, Aboul-Enein HY. A new method for a quantitative determination of piroxicam in pharmaceutical formulations using FT-IR spectrometry. Antiinflamm Antiallergy Agents Med Chem. 2012;11(3):262-6. doi: 10.2174/1871523011202030262. PMID: 23140406.

34. Bi, S., Song, D., Tian, Y., Zhou, X., Liu, Z., & Zhang, H. (2005). Molecular spectroscopic study on the interaction of tetracyclines with serum albumins. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 61(4), 629–636. doi:10.1016/j.saa.2004.05.028.

35. Toshikee Yadav, Deepti Tikariha, Jyotsna Lakra, Amit K. Tiwari, Subit K. Saha And Kallol K. Ghosh, Surface Properties of Amphiphilic Drugs in Presence of Cationic Surfactants, J. Surface Sci. Technol., Vol 30, No. 3-4, pp. 93-110, 2014.

36. Mostafa, G. A. E., Al-Dosseri, A. S., & Al-Badr, A. A. (2019). Piroxicam. Profiles of Drug Substances, Excipients and Related Methodology. doi:10.1016/bs.podrm.2019.10.007.

37. Fung, M. H., DeVault, M., Kuwata, K. T., & Suryanarayanan, R. (2018). Drug-Excipient Interactions: Effect on Molecular Mobility and Physical Stability of Ketoconazole–Organic Acid Coamorphous Systems. Molecular Pharmaceutics, 15(3), 1052–1061. doi:10.1021/acs.molpharmaceut.7b00932.

38. Kang, KH Kim, HU Lim, KH Jeong, NH, Mixed micellization of anionic ammonium dodecyl sulfate and cationic octadecyl trimethyl ammonium chloride, B KOR CHEM, 22(9), 2001, pp. 1009-1014.

39. Hong-Un Kim† and Kyung-Hee Lim, Sizes and Structures of Micelles of Cationic Octadecyl Trimethyl Ammonium Chloride and Anionic Ammonium Dodecyl Sulfate. Surfactants in Aqueous Solutions Bull. Korean Chem. Soc. 2004, Vol. 25, No. 3. DOI: 10.5012/bkcs.2004.25.3.382.