Research Article

Hydrophilic-hydrophilic mixed micellar system: effect on solubilization of drug

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Abstract

Mixed micellar systems have been tried with the aim of achieving higher solubility of drugs compared to single micellar systems. Hydrophobic-hydrophilic mixed micellar systems have been used for the above purpose for the drug ciprofloxacin in the past. In the present study, a hydrophilic-hydrophilic binary micellar system comprising of pluronic copolymers pluronic F127 and pluronic L64 has been studied for its effect on solubilization of the drug Ciprofloxacin. The solutions of the two individual pluronic and their mixed micellar system with drugs were subjected to characterizations viz. UV-spectrophotometry, fluorimetry, FT-IR, dynamic light scattering (DLS), rheology, and partition coefficient. The mixed pluronic–drug system displayed greater solubility of the drug compared with the neat pluronic-drug systems in most of the characterizations. New C–OH bond formation was evidenced by FT-IR spectra due to drug micelle interaction. The values of free energy changes of micellization were found to be −25 kJ mol^{-1} for pluronic F127, −74.5kJmol^{-1} for L-64, and −170.4 kJ mol^{-1} for the mixed pluronic. This is suggestive of spontaneous and stronger binding of drug ciprofloxacin with mixed pluronic in comparison with that in single micellar systems.

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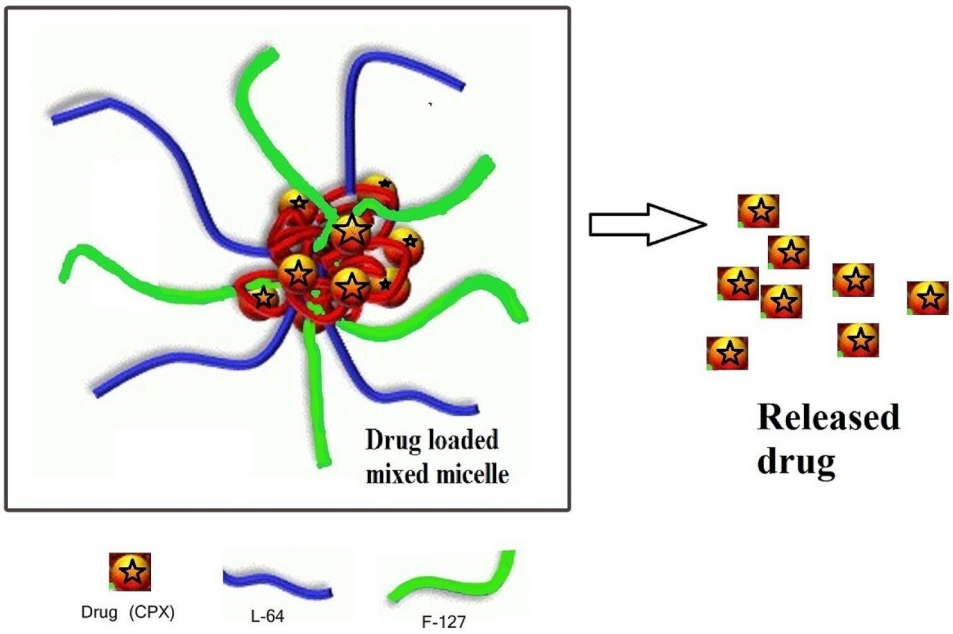
Graphic abstract



Keywords Micelles · Encapsulation · Surfactant · Uv/vis spectroscopy · Mixed micelles · hydrophilic

Abbreviations

CPX	Ciprofloxacin
PdI	Polydispersity
HLB	HydrophileLipophile Balance
PEO	(Hydrophilic) poly ethylene oxide
PPO	(Hydrophobic) poly propylene oxide

1 Introduction

Pluronic® block copolymers have a unique structural feature similar to amphiphiles. They encompass hydrophilic ethylene oxide (PEO) and hydrophobic propylene oxide (PPO) blocks arranged in the basic structure PPOmPPOn-PEOm. A broad range of pluronic is commercially available in various PO/EO ratios as well as molecular weights. They have many novel and interesting properties that are applicable in industries such as foaming, detergency, emulsification, dispersion, stabilization, and lubrication [1]. They have also attracted a sizeable number of researchers in the application of solubilization and delivery of many water-insoluble drugs [2–5].

Surfactants are amphiphilic subastances which have got numerous applications through formation of micelles [6, 7]. Micelles obtained from single pluronic copolymers were used extensively in drug delivery efforts for several decades. But, lately the mixed micellar systems are starting to harvest immense attraction due to their advantage over single micelles. The negative aspects of a single micellar system such as larger particle size, low drug loading capacity, low stability, etc. are overcome by the sagacious mixing of non-identical polymers to prepare mixed micellar systems [8]. For example, mixed micelles prepared by Gao et al. from pluronic P105 and d-α-Tocopheryl polyethylene glycol 1000 succinate provided a more efficient and stable solubilizing medium for camptothecin [10]. A mixed micellar system of pluronic P105 and L101 has been used for incorporating paclitaxel(PTX) which was used for multidrug resistance tumors [9]. Concerning pluronic micelles, the first formulation with micelles to get clinical trials was a doxorubicin-loaded mixed micellar system constituted from pluronic L61 and F127 [11]. The binary system comprising of F127 and P123 was developed which produced a stable nanosized system demonstrating several-fold higher loading efficiency compared to F127 single micelles. The mixed pluronic micelles have shown enhancement of in-vitro cytotoxicity in comparison with Taxol and also increased blood circulation time of PTX [12].

Ciprofloxacin (CPX) is an antibacterial agent. It is a fluoroquinolone that exhibits bactericidal action resulted from an inhibition of some enzymes (topoisomerase 2, topoisomerase 4). These enzymes are necessary for DNA replication, repair, and recombination. The antibacterial efficiency of the drug CPX results from the inhibition of two enzymes

which are connected with bacterial DNA synthesis resulting in rapid cell death in bacteria. CPX interaction with the bacterial pathogen occurs in peripheral tissues, not in the bloodstream. Hence, the microbial therapy to be effective requires the delivery of the adequate drug to the infection site [13]. The acidic pH of commercial CPX available in the market leads to the low bioavailability of the drug. Additionally CPX displays very low solubility in neutral pH. Single micelles from pluronic F-127 have been employed to improve the ocular delivery of CPX earlier [14]. In our previous study, we have used a mixed micellar system constituting of pluronic L81 (87% PPO, hydrophobic) and pluronic F108 (16% PPO, hydrophilic) surfactants for the solubilization of CPX [15]. Both pluronics have either very low or very high PPO composition in their polymeric matrix. The PPO percentage has importance in the solubilization of hydrophobic drugs. Hence, in this paper attempts have been made to use two hydrophilic pluronic (pluronic L64, 54% PPO, HLB 15; pluronic F127, 25% PPO, HLB 22) with closer percentages of PPO units and observe the change in solubility of the drug CPX with change in hydrophobicity. This is, probably, the first report on the effect of a hydrophilic-hydrophilic mixed micellar system on the solubilization of drugs.

2 Experimental section

2.1 Materials

Ciprofloxacin was obtained as a gift sample from MMC health care, Ltd. Chennai, and was used for characterization. Pluronic F127, pluronic L64, and pyrene were obtained from Sigma Aldrich chemicals Ltd. Sodium chloride salt was obtained from Merck Co. Triple distilled water was used for all the experiments.

2.2 Methods

2.2.1 Preparation of mixed micellar system

A stock solutions of pluronic F127 (5%w/v) and L64 (5%w/v) in distilled water were prepared and kept in the refrigerator at 5 °C for 24 h. To prepare mixed pluronic, required volumes of (10 ml each of 5% solution of F127 and L64) were mixed and kept at 5 °C for 12 h. This concentration of pluronic was well above their CMC. The samples were allowed to stand and stabilize at room temperature before the characterization to ensure complete formation of aggregated structures. 2 M sodium chloride solution was prepared.

2.2.2 Preparation of drug sample

CPX was prepared in an aqueous solution by the solvent evaporation method [15]. A stock solution of CPX with 0.102 g in 100 ml distilled water was prepared. Different concentrations of drug solutions were added to suitably diluted pluronic F127, L64, and 50/50 wt% mixed pluronic solutions. With this concentration of copolymer being well above the CMC of F127 and L64 it was presumed that micellization was completed. They were sonicated and then kept at room temperature. In this paper mixed pluronic term is used for the above composition of mixed pluronic solutions which was kept constant in this study. The structures of F127, L64, and CPX are shown in supplementary section S_1-S_3.

2.2.3 Ultraviolet spectroscopic measurement

A Shimadzu (UV-1650) PC spectrophotometer was obtained for determining the solubility of the drug. The amount of solubilized drug was measured from the absorbance at 270 nm. Ciprofloxacin stock solution (1000 µg ml-1) was prepared (0.102 g CPX in 100 ml water) by the solvent evaporation method. Calibration was done with a diluted solution of the drug ranging from 0 to 12 µg ml^{-1}. The solution of 5% pluronic F127, 5% pluronic L64 and mixed pluronic in 1000 µg ml-1 drugs were prepared and spectrophotometric measurements were done.

2.2.4 Fourier transformation infrared spectroscopy

From the stock solution, 2.5% neat and mixed pluronic were prepared. Equal volumes (2 ml each) of neat pluronic, ciprofloxacin, and mixed pluronic, ciprofloxacin were taken. The FT-IR studies of ciprofloxacin with and without neat and mixed pluronic at 298 K were recorded by using Cary-630 FT-IR Agilent Technology in the range 400–4000 cm^{-1}. The spectrum for OH stretching vibration arising due to water was common for all the solutions because of the aqueous medium, hence ignored.

2.2.5 Fluorescence spectroscopic measurement

Florescence measurements were taken for pyrene (5×10^{-6} M), pyrene added to three micellar solutions, F127, L64, and mixed pluronic. CPX was added in the following step. Fluorescence measurements were taken using instrument LS-55 Perkin Elmer. The spectroscopic measurements were taken using an excitation wavelength of 325 nm. The changes occurring in emission spectra due to the incorporation of drugs were recorded and

were compared with the blank (containing pluronic and pyrene).

2.2.6 DLS measurement

The particle size determination of micelles was done by dynamic light scattering measurement. It was carried out by using zeta sizer Nano ZS (Malvern instrument) at 25.0 ± 0.1 °C. The light source used was of a 4mw He–Ne laser (633 nm). The measurements were done at a scattering angle of 173° for all the aliquots.

2.2.7 Rheological measurements

Rheology measurements were performed by an MC R 301rheometer (Anton Paar, Germany -double gap cylindrical geometry) in strain-controlled mode with cone plate geometry (diameter 50 nm, angle 1°). The concentration of a solution prepared for rheological measurements was the same as used for FTIR studies. The measurements of mixed pluronic with drug and mixed pluronic with drug and sodium chloride salt were taken.

2.2.8 Partition co-efficient and thermodynamics of solubilization

The partition coefficient is determined by the ratio of the drug in two slightly immiscible liquids when the system has attained equilibrium at the interface between them. Here, the partition coefficient (p) between micellar and then the aqueous phase was determined using the Eq. 1.

$$P = Cm/Cw \quad (1)$$

where Cm and Cw represent the concentration of drug in micellar medium and water respectively which was determined from UV measurements.

The standard free energy of micellization was found out by using the Eq. 2.

$$\Delta G^0 = -RT\left[\ln P\right] \quad (2)$$

where R and T are the universal gas constant and absolute temperature respectively.

Solid CPX was added to 10 ml of water, two neat pluronic, and mixed pluronic till saturation. All four solutions were stirred for 24 h using a magnetic stirrer. Then they were filtered, suitably diluted to obtain optical density 1. The solubilized drug quantity in water, pluronic F127, pluronic L64, and mixed pluronic were determined and the partition coefficient was calculated.

3 Result and discussion

3.1 UV visible spectroscopy

When a drug is added to a particular surfactant, there are probable changes in the drug due to drug-surfactant interaction. The changes such as hydrophobicity and complexation are predicted by the UV visible spectroscopy. The drug ciprofloxacin displayed the maxima at 270 nm [16]. On the addition of pluronic F127, pluronic L64, and mixed pluronic solution to the drug ciprofloxacin there was no shift of λ_{max} but absorbance was seen to increase. Out of the three, the mixed pluronic–CPX spectra lay in between the spectra of two pure surfactant- CPX solutions (pluronic F-127 and L-64). Such findings have been described before. The CMC of the mixed pluronic system lay in between the CMC of single micelles [17]. The behavior of pluronic mixture with high HLB values (22 for F127 and 15 for L64) and their PPO percentages played an important role. Pluronic F127 although hydrophilic compared to pluronic L64, occupies a lower position compared to the mixed pluronic in the spectra. Thus the solubilization properties of pluronic F127 are enhanced on the addition of L64 to form the binary mixture. It is shown in (Fig. 1).

The calibration for CPX and the structure of pluronic surfactants are presented in the supplementary section (S_4). All the solubilization properties of two neat pluronics and their mixed micelle described above are subject to their interaction with ciprofloxacin drug. Following that, the mixed pluronic with different concentrations

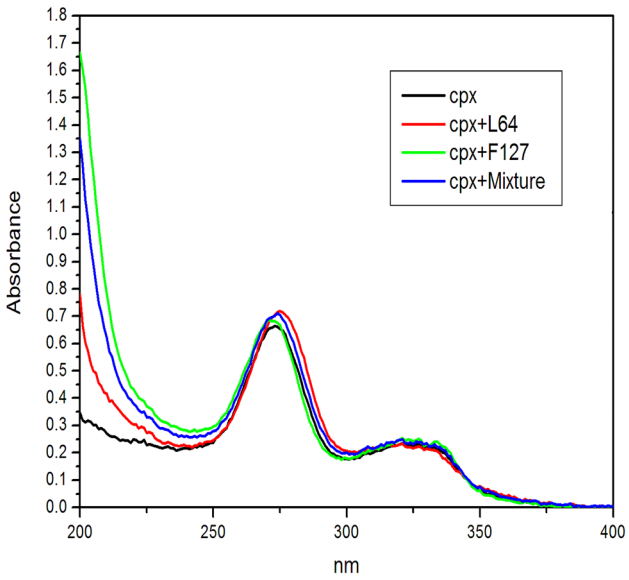


Fig. 1 Absorbance of ciprofloxacin in presence of pure and mixed pluronic solutions

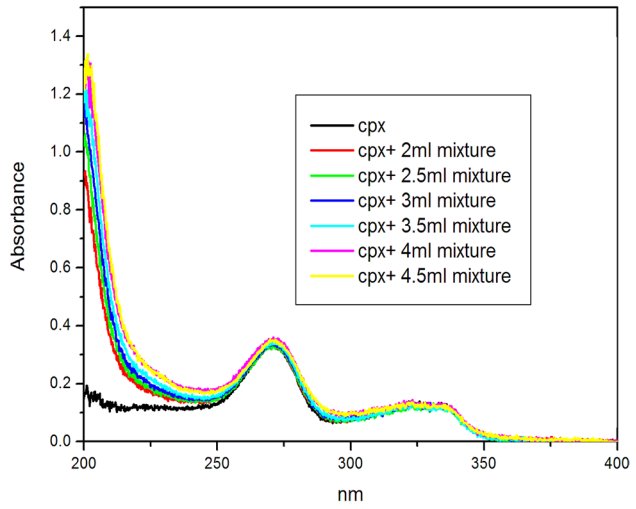


Fig. 2 Absorbance of different concentration of binary mixture of ciprofloxacin

were prepared and added to a fixed quantity of the drug. Absorbance increased progressively with an increase in mixed pluronic concentrations. This indicates that a greater number of ciprofloxacin molecules got encapsulated at a higher concentration of mixed pluronic. This is shown in (Fig. 2).

3.2 Fourier transforms infrared spectroscopy

FTIR studies help to identify different functional groups in the molecule [18]. The interaction between the mixed pluronic and ciprofloxacin was visualized from IR spectra. The peak of FT-IR is shown in (Fig. 3a–d) (Fig. 3a) presents the spectra for pure drug CPX. Fig. (B), (C) and (D) represent the drug combined with L64, F127, and mixed pluronic respectively. The main bands of the drug ciprofloxacin displayed –OH stretching vibration at 3287.6 cm^{-1} and carbonyl group of conjugated carboxylic acid at 1633.9 cm^{-1}.

On the addition of pluronic L64, pluronic F127, and mixed pluronic, the –OH stretching vibration bandwidth 3287.6 cm^{-1} was seen to shift to 3319.89 cm^{-1}, 3331.91 cm^{-1}, and 3306.87 cm^{-1} respectively. This is indicative of a change in the structure of drug molecules in drug–surfactant combinations due to hydrogen-bonded clusters and lowering of bond length in all three combinations. Hence, this is a possible binding site of the drug. Our previous study on hydrophobic-hydrophilic combination with pluronic F108 and Pluronic L81 system had displayed bands at lower wavenumbers compared to the present study [15]. The effect was more in the present study because of the hydrophilic-hydrophilic combination. The band at 1633 cm^{-1} which is generally assigned to the carbonyl group of conjugated carboxylic acid showed

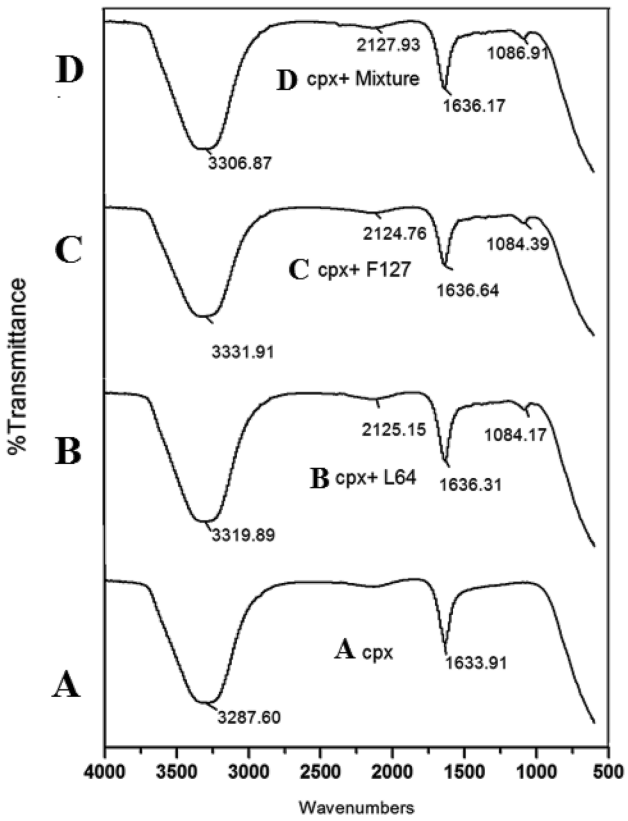


Fig. 3 FT-IR spectra of **a** Ciprofloxacin. **b** Ciprofloxacin + L-64. **c** Ciprofloxacin + F-127. **d** Ciprofloxacin + pluronic mixture

minimal change in all three cases pointing at the fact that there may not be any bonding possibility at this site. Even though no band is present at 1084 cm^{-1} for the pure drug spectra, it is visible for all the three surfactant–drug spectrum. This shows the probability of new bonds due to C–OH bond stretching vibration appearing in (B), (C), and (D), of the spectrum at 1084.17 cm^{-1}, 1084.39 cm^{-1}, and 1086.91 cm^{-1} respectively.

The IR analysis, therefore, suggests bond formation due to C–OH vibration and hydrogen bonding in the –OH stretching frequency area.

3.3 Fluorescence spectroscopic study

Fluorescence analysis is important in studying multimolecular aggregates like micellar membranes. Studies with pyrene as a fluorescence probe have received considerable attention. The aqueous solution of pyrene displayed the vibronic structure of the pyrene monomer at 384 nm [19]. On the addition of L64 and F127 and the mixed pluronic, there was an increase in intensity. The mixed pluronic band showed the highest intensity compared to the neat micelles of L64, F127 in presence of pyrene (Fig. 4). This suggests that maximum hydrophobicity

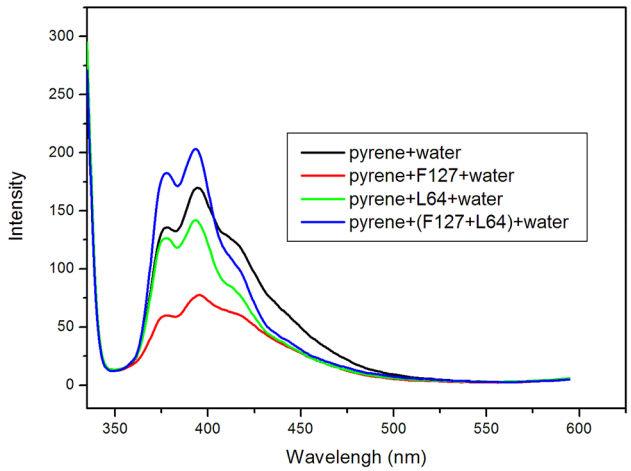


Fig. 4 Fluorescence spectra of ciprofloxacin with pure and mixed pluronic system in presence of pyrene

occurred for mixed micelle pyrene compared to single pluronic-pyrene combinations. In the next step different concentration of ciprofloxacin drug was added to a fixed concentration of pyrene and mixed pluronic. There was the progressive enhancement of intensity followed by broadening of peak. It has been shown in Fig. 5. Also, there was a redshift visible for all the concentrations of the drug. There may be a possibility of excimer formation arising from the combinatorial action of pyrene and drug ciprofloxacin in presence of mixed pluronic.

During the excimer formation, the pyrene molecule exists in two possible environments: (a) isolated monomer and (b) excimer. The isolated monomer is formed at lower drug concentration where as at high concentration, excimer formation takes place. In the latter case, due to proximity of drug molecule and probe there can be strong interaction in the ground state itself. Such findings have been earlier reported in the literature [20–22].

3.4 DLS measurements

The micellar particle size gave an idea about the structural changes occurring in pluronic micelles after the incorporation of the drug. Such observations have been reported by Bahadur et.al [23]. The dynamic light scattering measurements for 5% F127, pluronic mixture (F127, and L64), were taken. Following that the diameter of the drug-loaded F127, pluronic mixture were measured. Lastly, the effect due to the addition of 0.1 M NaCl at 25 °C was noted. The results have been presented in Table 1and Fig. 6.

The size distribution plots showed 27.11 nm as the hydrodynamic diameter of neat pluronic F127. This was obtained with PdI 0.39. Hence, the size distribution was in the low range. The observed size was 23 nm which is in agreement with the literature value [24]. upon addition of the drug the micellar size was seen to swell up to 50.28 nm. The mixed pluronic was seen to have a diameter of 25.97 nm with PdI 0.33. The addition of drugs increased the size to 70.32 nm with PdI 0.18. This clearly indicates that more amount of drug has been encapsulated in

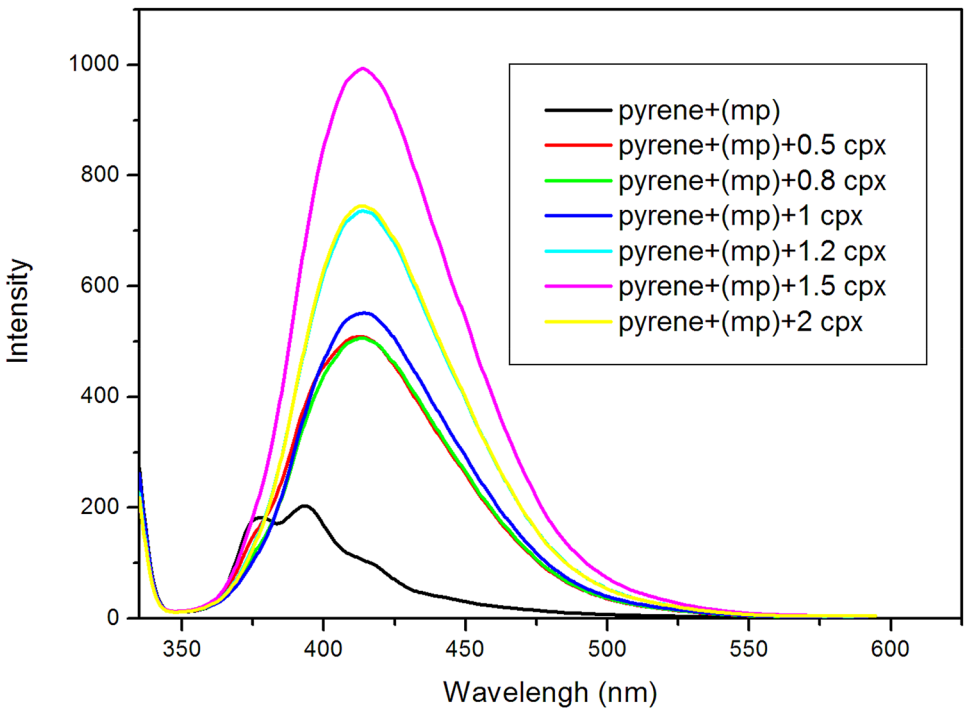


Fig. 5 Fluorescence spectra of ciprofloxacin in different concentrations with mixed pluronic system and pyrene

Table 1 The average size and polydispersity of 5% F127, mixed Pluronic, drugloaded pluronics, and drug loaded pluronic in 0.1 M NaCl

Pluronic	Z-Average(d nm)	pdI
F127	27.11	0.39
F127 + L64	25.97	0.33
F127 + Drug	50.28	0.24
(F127 + L64) + Drug	70.32	0.18
(F127 + L64) + Drug + NaCl	85.65	0.21

the mixed pluronic compared to pure micelle of F127. The drug encapsulation was higher in the present study because of the hydrophilic-hydrophilic combination of both copolymers compared to our previous study on CPX where there was only about 4 nm enhancement of size [15].

On the addition of NaCl to the pluronic mixture, the diameter of the drug-loaded mixed micelle got further enhanced to 85.65 nm. About 15.33 nm increase in diameter is suggestive of the fact that salt addition facilitates drug encapsulation.

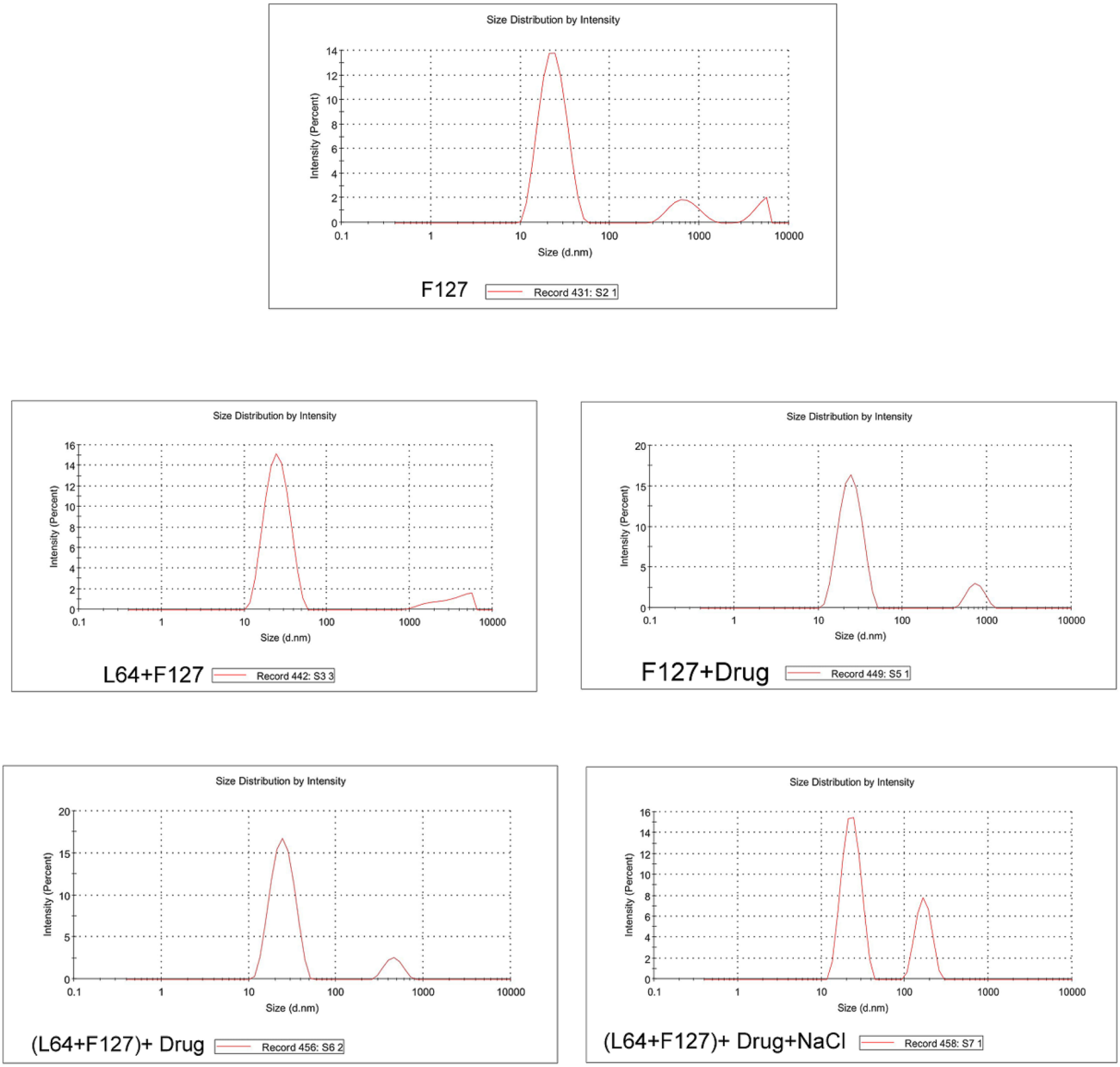


Fig. 6 DLS study

It can be inferred from the dynamic light scattering studies that the encapsulation efficiency of mixed pluronic with ciprofloxacin drug was higher in comparison with single pluronic F127. And that the addition of sodium chloride further enhanced its encapsulation efficiency.

3.5 Rheological studies

The behavior of pluronic mixture and water, pluronic mixture with drug ciprofloxacin, and pluronic mixture with drug and sodium chloride were studied by viscosity measurement at various shear rates. The pluronic mixture with drug ciprofloxacin displayed high viscosity compared to the pluronic mixture alone (Fig. 7). The difference in viscosity was more prominent at low shear rates and can be due to the extra bondings which have been formed as a result of encapsulation of drug ciprofloxacin into pluronic mixed micellar cavity [21]. The lowering of viscosity was observed to be maximum for the pluronic mixture, drug, and salt combination. In general the rate of solubilization of any drug is inversely proportional to the viscosity. Here, the maximum lowering of viscosity for pluronic mixture, drug, and salt combination at a low shear rate shows that it has the highest solubility among the four samples. Every system has a balance of all the forces of interaction within the micelle. When this is disturbed by the addition of foreign substances, the general physical properties like viscosity can change. All the four systems studied here showed non-Newtonian behavior viz. strong dependence of viscosity on shear rate. It is reported earlier that the increased shear rate tries to break apart the colloidal structure. Here a similar situation arises in which there is very little difference in the viscosity of all the four combinations when the shear rate is high [25, 26]. Here, the addition of sodium chloride to the pluronic mixture and drug combination shows reduced viscosity which indicates higher solubility.

3.6 Partition coefficient and thermodynamics of solubilization

The proportionality of drug concentration in the micellar layer and water is defined as the micelle-water partition coefficient [27, 28]. The concentration of the drug depends upon the molecular weight, type of polymers, and also environmental factors like temperature and pressure. This study was carried out at room temperature. The partition coefficient and free energy of micellization of single and mixed pluronic are presented in Table 2.

With the mixed pluronic, CPX solubility is higher compared to neat pluronic. The partition coefficient values

Table 2 The partition coefficient and free energy of micellization of single and mixed pluronic

Pluronic	Partition coefficient	$\triangle G^{o}$ kJ mol^{-1}
F127	0.9381	+160
L64	1.03	−74.5
Mixed pluronic (F127 + L64)	1.07	−170.4

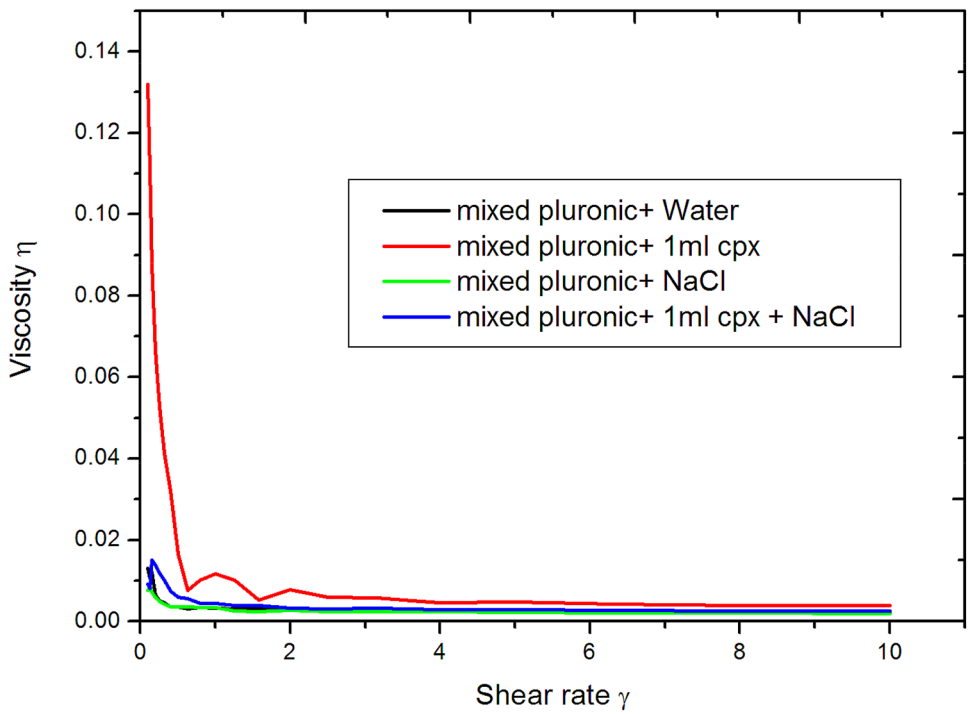


Fig. 7 The change in viscosity with shear rate for mixed pluronic, mixed pluronic with ciprofloxacin, mixed pluronic with sodium chloride and mixed pluronic with sodium chloride, ciprofloxacin

were calculated from the drug concentration present in neat and mixed pluronic. As observed from Table 2, the partition coefficient values for neat pluronic are 1.01 and 1.03 for the F127 and L64 respectively. The value was 1.07 for the mixed micelle and CPX which was comparatively higher.

The $\triangle G^0$ values showed $-170.4 kJmol^{-1}$ for the mixed pluronic compared to 25 $kJmol^{-1}$and -74.5 $kJmol^{-1}$ for F127 and L64 respectively. Our previous work on the solubilization of CPX in another mixed micellar system (pluronic L81 and F108) had displayed $\triangle G^0$ -7.9 kJ mol^{-1} for mixed pluronic [15]. This is indicative of better spontaneous binding of the drug CPX with hydrophilic-hydrophilic mixed pluronic (F127, L64) compared to the single micelles and also our previous system of hydrophobic-hydrophilic pluronics (L81, F108).

4 Conclusion

A hydrophilic-hydrophilic binary micellar system comprising of pluronic copolymers pluronic F127 and pluronic L64 displayed higher solubilization of and greater spontaneous binding with the drug Ciprofloxacin compared with the individual pluronic. Addition of salt facilitated drug encapsulation in the mixed micellar system. Also, this hydrophilic-hydrophilic system demonstrated higher solubility of the drug ciprofloxacin compared with the hydrophobic-hydrophilic mixed micellar system reported in the literature. This is, probably, the first report on the effect of a hydrophilic-hydrophilic mixed micellar system on the solubilization of drugs.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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