Interfacial and antibacterial properties of imidazolium based ionic liquids having different counterions with ciprofloxacin

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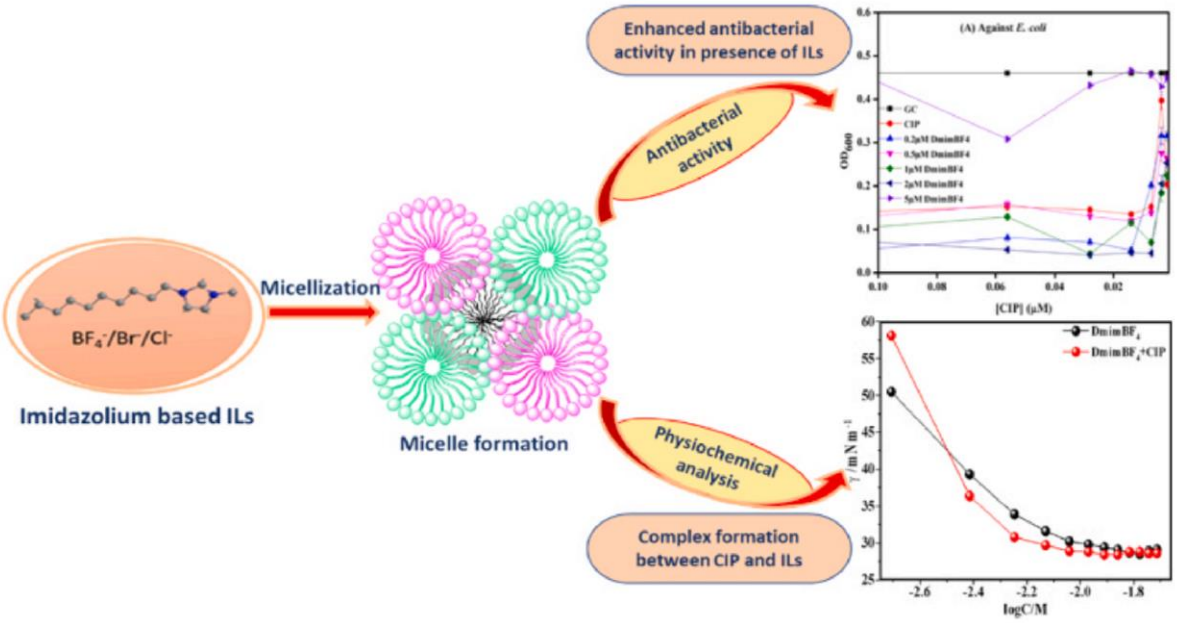
Abstract

The study of active pharmaceutical ingredients (API) with ionic liquids (ILs) becomes a significant research area for pharmaceutical industry. Thus, the present study aims to study the physicochemical and biological behaviour of ionic liquids having different counter ions in presence of an antibacterial drug, ciprofloxacin (CIP). The interaction of CIP with ILs, 1-decyl-3-methylimidazolium tetrafluoroborate [C10mim][BF4], 1-decyl-3-methylimidazolium bromide [C10mim][Br], and 1-decyl-3-methylimidazolium chloride [C10mim][Cl] has been studied by utilising surface tension, conductivity and DLS techniques. The various interfacial and thermodynamic properties of pure ILs and their complexes with CIP have been investigated from surface tension data. The thermodynamic data thus obtained suggested that the interaction between ILs and CIP was spontaneous. The dynamic light scattering (DLS) measurement showed that the aggregates size of ILs increases in presence of CIP. The complexation of ILs and drug was further confirmed by zeta potential measurement. The combined analysis suggested that the drug molecules is solubilized within the micellar core of ILs due to hydrophobic interaction, however, few molecules reside in the upper palisade layer of micelle-water interface. In addition, we have also investigated the antibacterial activity of individual

ILs and CIP against two clinically relevant microorganism, E. coli and S. aureus. The effect of ILs on antibacterial activity of CIP was determined against E. coli and S. aureus and results showed the remarkable improvement in the activity of CIP in the presence of imidazolium ILs. The maximum reduction in MIC was found in presence of [C10mim][BF4] was found as compared to [C10mim][Br]/ [C10min][Cl]. The results of the current study showed the importance of ILs in pharmaceutical industries.



Highlights

- The cmc values of ILs decreases in presence of CIP.
- The Gibbs free energy of micelle indicates the adsorption at air-water interface.
- The composition of CIP and ILs showed improved antibacterial activity as compared to CIP and IL alone against E. coli and S. aureus.

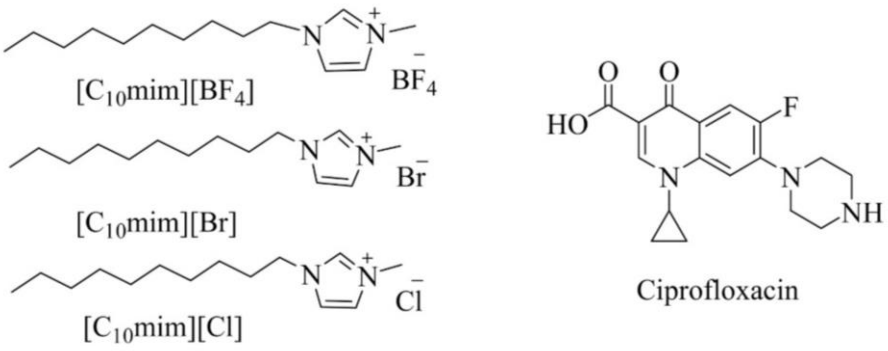
Introduction

The design of new drugs by pharmaceutical industries has met challenges because of drug stability, biocompatibility, and solubility [1, 2]. A lot of work has been done to improve the problem associated with stability and biocompatibility of poorly soluble drugs [3–8]. There have been a very few strategies developed for improving the solubility of poorly soluble drugs which include their complexation with other surface-active substances like conventional surfactants, gemini surfactants and ionic liquids [5,9–12]. To lower the hydrophobicity and increasing hydrophilicity of poorly soluble drugs, alternative solvents like ILs have been used. ILs not only have the tendency to act as alternate solvents but also have rendered themselves as drug delivery agents from more than a decade [9,13–17]. The ILs are tuned easily with simple modification of their existing cation and anion which is the fascinating property of the ILs. These exceptional properties of ILs gives wider choice in different fields of chemistry and pharmaceuticals. It has already been established that the micelle formation property of ILs in aqueous medium is explored to utilize them in drug delivery [18]. The micellar core can solubilize the sparingly soluble drug as well as mimic the bio-membranes which permits one to study the interactions of drug with ILs [19,20]. Therefore, complexes of drug with ILs enhances the binding affinity and can improve the transportation of drugs on the targeted site of action [21,22]. For the utilization of ILs in biomedical or any other fields, we need to understand the physicochemical, biocompatible, and biodegradable properties of the ILs [21,23,24]. In this regard, many research groups including our own group have utilized ILs actively to modify the drug and protein properties such as dissolution rate permeability, solubility, stability and biocompatibility [3,25–32]. Recently, Ali et al. reported the IL mediated microemulsion, a potential tool for drug delivery for the poorly water-soluble drug [33]. Santos et al. investigated the solubility and antimicrobial activities of sparingly soluble drug in the presence of ILs. They reported that IL-drug conjugate exhibited the high biological

activity and solubility than pure drug in aqueous medium [34]. Garcia et al. have studied the antimicrobial activity of different imidazolium based ILs and analysed the effect of alkyl chain on the growth of microorganism against several strains of bacteria and fungi. In addition, they have reported that the dependency of antimicrobial activity on the alkyl chain substituted to imidazolium cation [35,36]. Reid et al. studied the synthesis of cholinium based ILs and evaluate their antimicrobial activity. They revealed that antimicrobial activities enhances with increasing the chain attached to the cation [37]. Singh et al. investigated the interfacial behaviour of ILs having a different aromatic anion with common imidazolium cation through different techniques. They showed that bulkier organic counter ion as aromatic ring containing imidazolium cation ILs exhibited much superior surface activity than inorganic anions [38]. In the same way, Wang et al. describes the physiochemical behaviour of a series of imidazolium based ILs with a variety of aromatic anion in aqueous medium.

The effects of anion directly validate the various micellization behaviours, shape/size of micelles and physiochemical properties of ILs [39]. Most of the studies have designed and report the conjugation of non-steroidal anti-inflammatory drug (NSAID) with ILs in which physicochemical and biological activities of drugs has been enhanced [40–42]. The self assembly and aggregation behaviour of different ILs with variety of head groups and hydrophobic chain lengths have been reported. The effect of structural differences in the counter ion on the physicochemical behaviour have also been reported. The structure of head group cation and anion plays vital role in the self-assembly properties of IL and their mutual combining capacity and hydrophobicity of imidazolium IL have been explored [18]. All the studies illustrated the fact that molecular structure of ILs can have different effect on physicochemical properties. However, there is a lack of literature showing the effect of anions of imidazolium SAIL with the antibacterial drug. Hence, the significant efforts have been made to alter the physicochemical and antibacterial property of an antibacterial drug in presence of

ILs by altering the anions of ILs. Ciprofloxacin (CIP) is a second-generation fluoroquinolone and a broad-spectrum anti-bacterial drug. It is extensively used in the treatment of infections such as urinary, intra-abdominal and skin disease [43, 44]. The present work is an effort to enhance the solubility and biological activity of sparingly soluble drug with imidazolium based ILs. We have studied the interactions of three ILs, 1-decyl-3-methylimidazolium tetrafluoroborate [C10mim][BF4], 1-decyl-3-methyl-imidazolium bromide [C10mim][Br], and 1-decyl-3-methylimidazolium chloride [C10mim][Cl] with (CIP) in aqueous medium. The interaction studies compared the micellar behaviour and antimicrobial properties of imidazolium cationic head groups with different counter ions in the absence and presence of CIP.



Scheme 1. Schematic representation of the structures of ILs and ciprofloxacin.

2.2. Methods

2.2.1. Surface tension measurements The DeltaPi-4 surface tensiometer (Kibron) was employed to determine the surface tension of ILs and ILs–drug mixtures in an aqueous medium (precision of ± 0.01 mNm^{-1}). The tensiometer well plate and probe were cleaned properly with double distilled water followed by high temperature flame to remove the contamination after each experiment. The tensiometer was calibrated by measuring the surface tension of water (γ = 72.8 mNm^{-1}) [46]. Triplicate studies were performed for each experiment and the average value was reported at 298.15 K.

2.2.2. Conductivity measurements

Conductivities measurements of ILs solution were measured using JENWAY 4520 auto temperature digital conductivity meter equipped with a cell having 1.01 cm^{-1} cell constant. All the measurements were measured at a constant temperature 298.15 K. Before the measurements, the instrument cell was calibrated with KCl solution.

2.2.3. Dynamic light scattering (DLS) and zeta potential measurements

The hydrodynamic diameter (Dh) of ILs micelles and micelles loaded drug were determined by using Zeta sizer Nano-ZS (Malvern) with a He–Ne laser emitting polarised light (λ = 632 nm) at a scattering angle of 173°. The zeta potential (ζ) measurements were determined from the same instrument. All measuring sample were filtered through micro syringe (0.2 μm) to avoid interference of dust. For the measurements, bubble free sample of 2.5 ml was taken into a sample cell. All the results were analysed by Malvern Zeta sizer software. The collected scattering intensities of all the measurements were estimated to calculate the hydrodynamic diameter (Dh), according to the following Eq. (1) [47].

$$Dh = kBT\ 3\pi\eta D \quad (1)$$

where k_B = Boltzmann constant, T = temperature (K), η = viscosity and D = diffusion coefficient. The average size of triplicate measurement was taken into consideration of each study.

2.2.4. Antimicrobial activity

A couple of bacterial strains, *Escherichia coli* (E. coli) (MTCC 40) and *Staphylococcus aureus* (S. aureus) (MTCC 87) were purchased from Microbial type culture collection and gene bank (MTCC), CSIR-Institute of microbial technology, Chandigarh, India. The bacterial inoculum of E. coli and S. aureus were prepared in Luria Broth (LBB). The fresh culture of each strain

was prepared up to the logarithmic phase in LBB at 37 ˚C for 16–18 h. The quantitative growth of bacterial culture was determined by recording the optical density at 600 nm (OD600) using a UV–vis spectrophotometer. The recorded at optical density at 600 nm (OD600) for each culture was 0.5. The working concentration of inoculum was 105 -106 CFU/ml.

2.2.4.1. Dye preparation.

The resazurin sodium (dye) was purchased from Sigma-Aldrich USA. The stock solution of dye in an aqueous medium was prepared by dissolving 0.03 g in 4 ml distilled water and a homogenous mixture of dye was prepared by mixing the solution thoroughly using a vortex rotator. The solution was filtered through a micro syringe filter (0.22 µm) and stored at 4 ◦C for further uses.

2.2.4.2. Determination of minimum inhibition concentration (MIC). The antibacterial efficiency of all the tasted compound, CIP, [C10mim][BF4], [C10mim][Br], and [C10mim][Cl], was evaluated using a two-fold serial dilution method in 96-well plate. The activity was performed according to the Clinical and Laboratory Standards Institute guidelines (CLSI) protocol [48]. A two-fold serial dilution method was employed to determine the MIC of the tested compounds. The stock solution of samples was serially diluted row wise in 96 well plate. The stock solution of CIP was diluted to give the concentration ranges from 2.5 µM to 0.0005 µM whereas, the concentration range of [C10mim][BF4], was 0.25–0.0005 mM. Similarly, for the [C10mim][Br], and [C10mim][Cl], concentration ranges varied from 0.50 mM to 0.001 mM and 250–0.48 mM, respectively. The bacterial inoculum (10 µL) whose working concentration was kept 105 -106 CFU/ml was added to each well excluding sterile control. LBB with and without bacterial inoculum served as growth control [49], and sterile control, respectively. The 96-well plate was incubated for 16–18 h at 37 ◦C for the culture to grow. After incubation, the dye solution (10 µL) was added to each well in the plate including

GC and SC. The plate was again subjected to the incubation period of 2–4 h at 37 ◦C to observe the colour change. After complete incubation, well with no colour change (blue colour of resazurin remained unchanged) before a complete change of colour (blue colour of resazurin was changed to pink), was recorded as the MIC value of the corresponding compound. A triplicate experiment was performed for each sample and their average was considered as the MIC value.

2.2.4.3. Biological study to evaluate the effect of IL on CIP.

The testing procedure consists of a two-fold serial dilution of CIP vertically in a 96- well plate followed by the addition of [C10mim][BF4], (0.2, 0.5, 1.0, 2.0, 5.0 µM), [C10mim][Br], (2.0, 5.0, 10, 20, 50 µM,), and [C10mim][Cl], (5, 10, 20, 30, 50 µM). After preparing the plate, 10 µL bacterial culture whose working concentrations were adjusted to 105 -106 CFU/ml was added to each well, except sterile control (LBB without inoculum). The plate was incubated at 37 ◦C for 16–18 h. After incubation, optical density was recorded at 600 nm for each plate. All tested compounds were performed in triplicate for each experiment.

3. Results and discussion

3.1. Surface tension studies

Surface tension measurement is an important technique for investigating the interaction between ILs and drug at an air water interface. It gives vital information about the adsorption process. The surface tension of [C10mim][BF4], [C10mim][Br] and [C10mim][Cl] was measured in the absence and presence of CIP at the air-water interface. Fig. 1A-C shows the surface tension plot, γ versus logC of [C10mim][BF4], [C10mim][Br] and [C10mim][Cl] in the absence and presence of CIP at 298.15 K. The plots of surface tension revealed that the value of γ decreases with the increasing concentration of ILs followed by a sudden change in the plot has been obtained. Near at the plateau region γ value of ILs solutions remains constant,

such behaviour suggest the formation of micelles within the ILs. The plateau region of surface tension plot describes the critical micelle concentration (cmc) of ILs. The measured cmc value of pure [C10mim][BF4], [C10mim][Br] and [C10mim][Cl] calculated as 0.014 M, 0.052 M, and 0.048 M, respectively given in the Table S1. The measured cmc value of each ILs from surface tension measurements is found in close agreement with earlier study [26, 50–52]. The [C10mim][BF4] has lowest cmc suggests its high hydrophobicity. It may be due to the presence of bulky counter ion, which facilitate micelle aggregation at lower concentration [20]. Further, lower cmc of [C10mim][Cl] than [C10mim][Br] due to the high hydration of small Cl- than Br- , more efficiently decrease the electrostatic repulsion and in this way decrease the cmc. Further, surface tension of [C10mim] [BF4] and [C10mim][Br] were measured in the presence of CIP (20 μM) and revealed that the value of γ decreased more sharply than pure ILs as shown in the Fig. 1 A-B. On contrary, opposite trend was observed in case of [C10mim][Cl] as shown in Fig. 1C. As suggested by our conductivity results, weak interaction was observed between [C10mim] [Cl]-CIP complex which tends to collapse of ion-pair complex into the bulk leading to increase in the γ value after pre-micellar concentration [26]. Also, the cmc value of all the three IL with CIP was observed less than pure ILs shown in the Table S1. The decrease in cmc of ILs in the presence of CIP suggests the formation of surface-active complex between ILs and CIP at air-water interface. The drug CIP is slightly polar organic molecule that probably adsorb at the outer portion of the micelles. The adsorption of drug molecules at the interface decreases the energy required for micellization due to mutual repulsion of the head group in the micelles of ILs. The formation of the surface-active aggregate complex between $[C10mim]^+$ and CIP^- driven by electrostatic interaction among head group [C10mim]+ of [C10mim][BF4] and carboxylate ion (COO^-) of CIP through π-π interaction. These phenomena increased the entropy in the bulk that enhances the formation of surface active ILs-CIP complexes [53].

The surface tension plots of [C10mim][Br] and [C10mim][Cl] did not significantly decrease, it showed two break point with the increasing concentration. The first break point corresponding to pre-micelle (Cp), as shown in the Fig. 1B-C. It suggests that the energetically weak attraction between the hydrophobic part of ILs and water and this may be due to suppressed by the self-aggregation of ILs molecules in the bulk solution to form organized aggregates called pre-micelles. From the premicellar range, γ value increased up to a limit concentration and remained constant, that intersection point referred the critical micelles concentration [54]. The interfacial adsorption of ILs, reduces the free energy of a solution up to a concentration and after that no further adsorption occurs at the interface. The appearance of pre-micelles before micellar concentration in surface tension curve was also described for 1-dodecyl-3-methylimidazolium bromide [55]. The formation of pre-micelles before bulk aggregation has been attributed the energetically favourable contact between water and hydrophobic part of the ILs and resettlement of a surface monolayer. The variation in physicochemical property of 1-decyl-3-methylimidazolium cation in the present study suggests that counter ion attached with the head group is responsible for aforesaid changes.

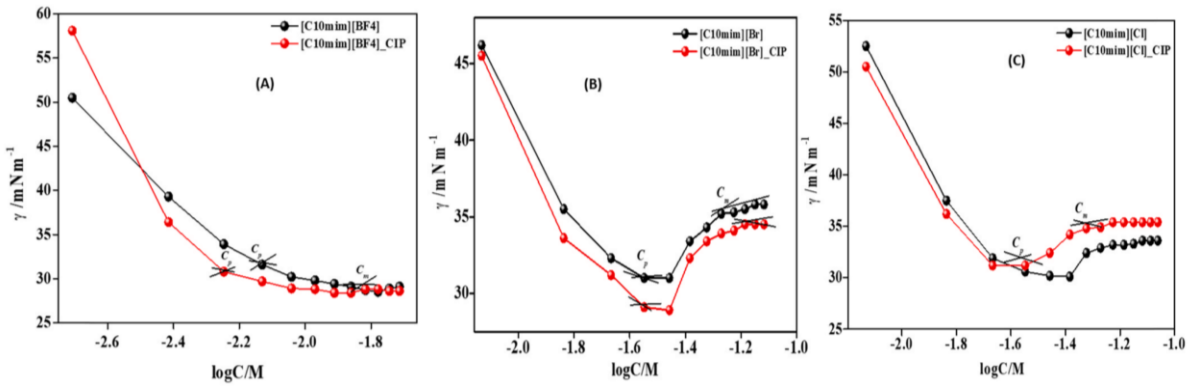


Fig. 1 Plots of variation of surface tension (γ) vs. logC of (A) [C10mim][BF4], (B) [C10mim][Br] and (C) [C10mim][Cl] in the absence and presence of CIP (20 µM).

The surface tension studies tell us about the adsorption of additives at air-water interface of surface-active molecules. Hence, various micellar and physiochemical properties of ILs in the presence of CIP were assessed to know the interaction through interfacial and thermodynamics parameters. The surface pressure (π_{cmc}), effectiveness of adsorption (pC20), surface excess concentration (rmax) and the minimum area occupied per molecules (A_{min}) for [C10mim][BF4]/[C10mim][Br]/ [C10mim][Cl] in the absence and presence of CIP at air - water interface has been estimated. The above-mentioned properties describe the significant features of adsorption of the additive at an interface.

The surface pressure, π_{cmc} is a degree of reduction in the surface tension to minimum in presence of IL in aqueous medium. It can estimate from the following

Eq. (2). $\pi cmc = \gamma_o - \gamma_{cmc}$ (2)

where, γ_o is the surface tension of pure solvent and γcmc is the surface tension of the solution at the cmc. The calculated value of πcmc for different ILs and ILs with CIP are given in the Table S1 which shows an overall decreased sequentially in the order [C10mim][BF4] > [C10mim] [Cl]> [C10mim][Br] as the bulkiness of counter ion decrease. However, π_{cmc} value of ILs increased in the presence of CIP caused by dissolution of drug molecules. The value of adsorption efficiency, pC20 elucidate the concentration of ILs required to reduce the γ value of solvent/water by 20 mNm^{-1} and measures the effectiveness of the adsorption that is related to the negative logarithm of C20 and determined by Eq. (3).

$pC20 = -\log C20$ (3)

The values of pC20 for ILs and ILs+CIP mixture are given in the Table S1. Based on the calculated value DmimBF4 have larger pC20 value than [C10mim][Br] and [C10mim][Cl]. The result thus obtained reveal that the ILs with imidazolium cation bearing same hydrocarbon chain length suggests the superior surface activity and greater adsorption tendency at the air

water interface. Another important interfacial parameters such as maximum excess concentration (Γ_{max}) and the minimum area occupied per molecules at the air-water interface [56] was estimated from the tensiometric profiles by using the Gibbs adsorption isotherm Eq. (4) [57].

$$\text{г}_{max} = -1/(2.303nRT)\cdot(\delta\gamma / \delta\log C) \quad (4)$$

where, ($\delta\gamma$ $\delta\log C$) is the slope for the of plot γ vs. logC, T is the temperature (K), R is the universal gas constant (8.314 JK^{-1} mol^{-1}), n is the number of ionic species (n = 2, for IL), and C is the concentration. The Γ_{max} value was further used in A_{min} calculation according to Eq. (5).

$$A_{min} = 10^{20}/ N_A\cdot\text{г}max \quad (5)$$

where, NA is the Avogadro number. All the values of Γ_{max} and A_{min} are summarized in Table S1 which revealed that the value of Γ_{max} increases and A_{min} decreased for all the three ILs in presence of CIP. The hydrophilic head group is important to determined A_{min}. Thus, a decrease in the value of A_{min} and increase in Γ_{max} was observed, indicates the dense packing arrangement of aggregate at an interface.

Further decrease in A_{min} values in the presence of drug (except [C10mim][Cl]+CIP mixture) indicates that denser arrangement may be due to the adsorption of drug molecules [58]. The lowest value of A_{min} was found in case of [C10mim] [BF4]+CIP may be due to the formation of compact mixed IL+drug monolayer at an interface because of attractive interactions and van der Waal forces between hydrophobic part of the CIP molecule and IL. In the case of [C10mim][Cl] the reverse trend was obtained, Γ_{max} decreased and A_{min} increase in the presence of drug suggest the looser packing arrangement of chlorine functionalized IL molecules at an interface. This is due to the less steric factor between CIP and alkyl chain of IL which enhances the minimum area per molecule. The change in adsorption parameters of ILs with the addition

of CIP indicated the easy solubilization of CIP with ILs and becoming a good solvent than water.

Further, the maximum changes in Γ_{max} and A_{min} in the presence of drug was found for DmimBF4, this could be attributed to the highest surface activity of tetrafluoro functionalized IL. The decrease in A_{min} value in the presence of CIP suggest the drug molecules are mainly localized in the hydrophobic core. The value of A_{min} was used to determine the packing parameter (p), which demonstrates the geometry of micelles and was calculated from

the following Eq. (6).

$$p = V_0 / lcA_{min} \quad (6)$$

where, V_0 and l c are the volume and length occupied by the hydrophobic portion of the alkyl chain length in micellar core, respectively which is calculated by the Tanford's formula [59].

$$Vo = [27.4 + 26.9(n_c - 1)]2 \ (Å^3)$$

$$lc = [1.54 + 1.26(n_c - 1)](Å)$$

In the given formula nc is the number of carbon atom in the hydrophobic chain, generally it considers one carbon less than total number of carbons in alkyl chain. Table S1 shows the values of p, that are higher than 0.50, suggesting that formation of lamellar shape of the aggregate (p = 0.5–1.0), it may be due to the concentration of ILs undergoing the process of self-aggregation [60,61]. The value of p for IL+CIP mixtures was found higher than pure ILs revealing that electrostatic interaction between ILs and CIP mixtures. This is due to the solubilization of drug on the inner portion of the aggregates.

3.2. Thermodynamic studies of ILs and ILs + CIP mixtures

By applying the surface tension profiles, we evaluated different thermodynamic parameters such as Gibbs free energy change of micellization (ΔG° mic) and free energy change of adsorption (ΔG° ad)) for ILs and ILs+CIP mixtures from the following equations.

$$\Delta G^{\circ} m = RT\ln X_{cmc} \quad (7)$$

$$\Delta G^{\circ} ad = \Delta G^{\circ} m - (\pi_{cmc}/ \Gamma_{max}) \quad (8)$$

where, R is the universal gas constant (8.314 JK^{-1} mol^{-1}), T is the temperature (K), and X_{cmc} is cmc in mole fraction unit. The thermodynamic values thus obtained for ILs and their mixture with CIP are given in the Table 1. The value of Gibbs free energy of micellization (ΔG°_{mic}) for all the system is negative, suggests the spontaneous formation of the aggregates and becomes more negative in the presence of CIP likely due to the involvement of more hydrophobic forces. The ΔG°_{mic} values for all the system are given in the Table 1. The ΔG°_{mic} of [C10mim][BF4]-CIP mixture is more negative than[C10mim][Br]/[C10mim][Cl], indicating that the micellization comes more easily with the $BF4^-$ counter ion than Br^- /Cl- . The presence of a $BF4^-$ to the alkyl imidazolium cation causes an increase in the electrostatic interactions between cation and anion enhances the inductive and dielectric polarization. Hence, the observed increase in ΔG°mic values with change in counter ion revealed that the micellization is driven by inductive, hydrophilic and hydrophobic/ cation-anion interactions. Another thermodynamic property was calculated for pure ILs and ILs+drug mixtures i.e., Gibb's adsorption isotherm (ΔG°_{ad}) which illustrate the maximum adsorption at the interface. The calculated values are given in the Table 1. The value of ΔG°_{ad} for pure ILs and their mixture with CIP was observed to be negative, which suggest that the adsorption at the air water interface is spontaneous in nature. The absolute value of free energy of adsorption, ΔG°_{ad} is significantly higher than free energy of micellization which indicates the adsorption at the interface is energetically more favourable than micellization process in the bulk. The highest value of ΔG°_{ad} for [C10mim][BF4] and [C10mim][BF4]+CIP mixtures suggests that the hydrophobicity of the

counterion, favour the molecules at interface more energetically. The differences in the ΔG values may be due to structural changes in the counter ion directly attached to the imidazolium ion which alters the values of both adsorption and micellization. The nature of tetrafluoroborate containing IL elucidated that the greater charge on the ILs by strongly bound counter ion consequently decrease the electrical repulsion between adsorbed ILs and ions at an interface. Further, the thermodynamic steadiness of the surfaces may be attributed by the Gibbs energy of surface at equilibrium (GS min) and calculated from the Eq. (9).

$$G^{S}_{min} = A_{min}\gamma_{cmc}N_{A} \quad (9)$$

G^{S}_{min} is an important thermodynamic parameter for surface active molecules [62]. The lower the value of G^{S}_{min} means more thermodynamically stable surface is formed. The value of G^{S}_{min} is given in the Table 2 and shows that ILs+CIP mixtures have lower G^{S}_{min} value than pure ILs except in the [C10mim][Cl]. The lower value of G^{S}_{min} suggests the greater surface activity and formation of more thermodynamically stable surface is attained [63].

3.3. Degree of counter ion binding (β) determination.

The conductivity of ILs in absence and presence of CIP was also measured. The values were set into straight lines with different slopes for pre- and post-aggregation regions (Fig. S1). The ratio of the conductivity slopes above and below cmc was used to calculate the binding of the counter ion (β) in micelles/aggregates. The adsorption of counter ion at an air-water interface decreases the electrostatic repulsion between the cationic head group, which permits the adsorption at an interface. The degree of counter binding (β) was calculated by using the following Eq. (10) [64].

$\beta = 1 - S_2/S_1$ (10) where, S2 and S1 are the slopes of the conductivity curve, above and below the cmc. The cmc values and β of [C_{10}mim][BF4], [C_{10}mim][Br] and [C_{10}mim][Cl] and their mixture with CIP are given in the Table S1. The value thus obtained was agreed with the

previously stated data, and progressively decrease in β values for IL in order of [C_{10}mim][BF4] > [C_{10}mim][Br] > [C_{10}mim][Cl] [65]. Further, in presence of CIP, the β values decreases suggesting the increase in counter ion binding in the aggregate. The maximum reduction in the β value was found in the case of [C10mim][BF4] which attributes to the structural change in the counter ion. Thus, lower the value of β arise due lower ability of bromide/chloride anion to micelles. It is likely due to decreased electrostatic repulsion between imidazolium head group. The lowest value of β revealed that lower binding ability of chloride ion and lower the electrostatic repulsion between imidazolium cation in aqueous medium [35].

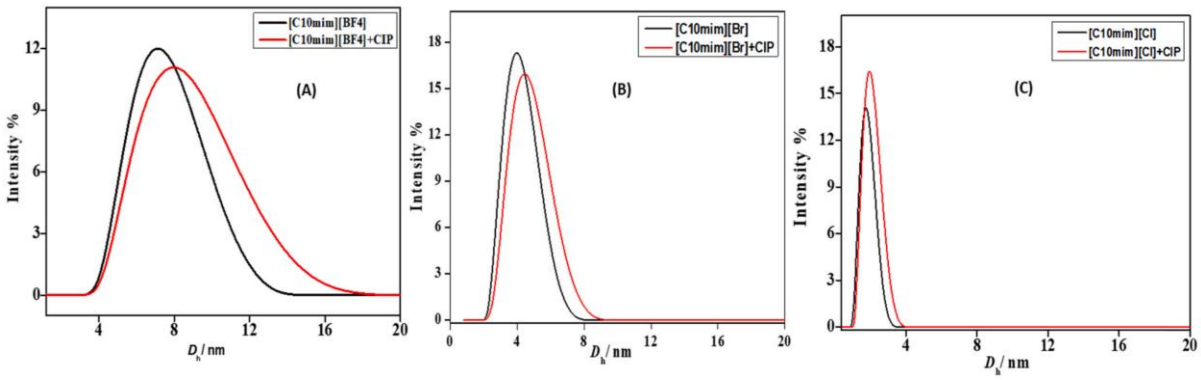


Fig. 2. Aggregate size distributions of [C10mim][BF4], (A), [C10mim][Br] (B), [C10mim][Cl] (C) in the absence and presence of CIP (20 μM).

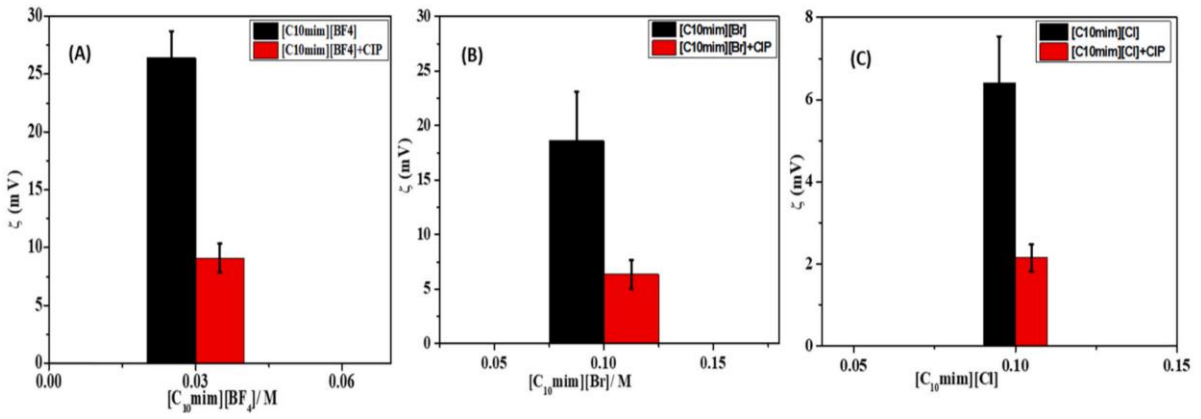


Fig. 3. Zeta potential plots for [C10mim][BF4], [C10mim][Br] and [C10mim][Cl] in the absence and presence of CIP.

3.4. Hydrodynamic size of ILs and ILs-CIP using DLS.

The size of aggregates in terms of hydrodynamic diameters (Dh) of imidazolium based ILs and their mixture with drug were investigated by DLS measurements in aqueous medium. The Dh of ILs-micelles and micelles loaded CIP were investigated at 2-fold higher concentrations than cmc value. The CONTIN plots, and corresponding Dh distribution for [C10mim][BF4], [C10mim][Br] and [C10mim][Cl] micelles and micelles loaded CIP are given in the Fig. 2. The average size of the [C10mim][BF4] (0.030 M), [C10mim][Br] (0.1 M) and [C10mim][Cl] (0.1 M) micelles was measured 7.0, 3.9 and 1.65 nm, respectively, at maximum scat tering intensity (%) as shown in Fig. 2 [66–68]. The value of Dh comes out to be different with different ILs in aqueous solution. Fig. 2 [66] revealed that the size of IL-micelles increased in the presence of drug, indicating the solubilization of CIP within ILs-aggregate. The Dh values obtained for ILs, and ILs-CIP mixture are given in the Table S2 (supporting information). The value given in Table S2 revealed that as the size of counter ion increases, the Dh value increases. Also, the Dh value of [C10mim][BF4] micelles increased from 7.0 to 8.2 nm in the presence of CIP. The maximum increased in Dh value of [C10mim][BF4] with the addition of drug suggests, the aggregates of larger size provided more solubilization space to CIP. Similar studies of drug solubilization within ILs micelles have been reported by Vashishat et al. [68].

3.5. Zeta Potential

Zeta (ζ) potential is an important parameter that controls the electrostatic interactions in the dispersed medium and give an idea about the stability of the aggregates in the terms of ζ values. It measures the potential difference between fixed and diffused layer of liquid related to the dispersion and micellar aggregates which stretches out from the surface of the particles due to thermal motion of colloidal molecules. To check the surface charge and stability of colloidal solution of ILs and IL incorporated CIP in terms of zeta (ζ) potential has been demonstrated in

aqueous medium. The zeta potential of ILs micelles, and micelles incorporated CIP are shown in the Fig. 3, and corresponding zeta values are given in the Table S2. The ζ potential of CIP (20 μM), [C10mim][BF4], [C10mim][Br] and [C10mim][Cl] was measured as - 19.22, + 26.4, + 18.6 and + 6.4 mV, respectively (ILs measured at twofold higher concentration from the cmc value). The value of ζ potential of [C10mim][BF4]/[C10mim][Br]/[C10mim][Cl] aggregate decreases in the presence of CIP as shown in the Fig. 3 [69]. This suggests that the CIP is effectively incorporated into the ILs micelles by electrostatic attraction due to opposite charged present in the solution. Analogous variation of ζ values between ILs and drug has been observed by Singh et al. [70]. The decrease in ζ value may attributed to complex formation by the combination of drug and ILs, which in turn reduces the micellar surface charge density. This fact indicated the incorporation of CIP into the ILs because the binding of CIP to the micelle and conformational change from extended to a shortened form.

3.6. Antibacterial activity study

3.6.1. Determination of MIC value

The antibacterial activity of the ILs and CIP was examined against clinically relevant couple of microorganisms, E. coli and S. aureus. The activity was determined in terms of MIC as per the CLSI guidelines [48]. The lowest concentration of antimicrobial agent where no visible growth of microorganism is seen refers to minimum inhibition concentration of the corresponding antimicrobial agent [71]. The mean MIC values are given in the Table 2. Table 2 shows the CIP and ILs responses towards microorganisms and reflects a good response in terms of bacterial inhibition against both E. coli and S. aureus. The obtained MIC value of each IL shows a relation to the substituted counter ions in imidazolium based ILs containing decyl chain length. IL containing BF4 as counter ion shows the maximum antibacterial activity amongst the three ILs selected. The action mechanism of IL is still unknown. However, it is

considered that cationic characteristic and hydrophobicity plays an important role in the antibacterial mechanism of ILs. The positive charge in ILs enable it to get attached to negatively charged bacterial cell membrane through electrostatic interactions [30]. Whereas, hydrophobic part in ILs further helps to get penetrated to the bacterial lipid membrane through hydrophobic-hydrophobic interaction leading to disruption of cell membrane and ultimately to cell death [72]. Antibacterial activity depends on various other physiochemical parameters such as adsorption, hydrophobicity, accumulation of the cell wall [35]. In the present study the antibacterial activity of imidazolium based ILs with varied counter ion was evaluated. The obtained mean MIC values are listed in Table 2. From Table 2, the order of antibacterial efficiency of ILs observed was [C10mim][BF4]> [C10mim][B] > [C10mim][Cl]. Further, the obtained trend of antibacterial activity of ILs was supported by our physicochemical results, where the value of free energy of adsorption gives the idea about the adsorption of ILs at the cell [73]. The calculated values of ΔG° ad are listed in Table 1. From Table 1, the highest value of $\Delta G \circ$ ad was seen for tetrafluoroborate functionalized ([C10mim][BF4]) IL revealing that it has a maximum efficiency to get adsorbed on the membrane as compared to [C10mim][BF4] and [C10mim][Cl] [31,36, 74]. 3.6.2. Effect of ILs on the antibacterial activity of CIP The effect of ILs was evaluated on the antibacterial property of drug, CIP. The effect of various concentration of [C10mim][BF4], [C10mim] [Br], and [C10mim][Cl] on the antibacterial properties of CIP was examined by monitoring the inactivation of E. coli and S. aureus. In-vitro study of CIP alone and in presence of [C10mim][BF4], [C10mim][Br], and [C10mim][Cl] were performed. The addition of ILs to CIP considerably improved antibacterial activity of CIP against E. Coli and S. aureus strains compared to CIP alone. The observed MIC of CIP was 0.015 µM against E. coli and 0.007 µM against S. aureus. The best response in terms of the reduction of bacterial burden was observed at a 105 -106 CFU/ml inoculum when susceptible E. coli and S. aureus strains were tested for 16–18 h. The obtained results in terms of reduced

MIC are listed in Table 3. The effect of selected ILs on the antibacterial efficacy of CIP is shown in the form of graph as shown in Figs. 4–6 (A-B). With the addition of 2 µM [C10mim][BF4] the MIC value of CIP reduced from 0.015 µM to 0.007 µM against E. coli as shown in Fig. 4(A) whereas, 0.2 µM of DmimBF4 reduced the MIC of CIP from 0.007 µM to 0.0014 µM against S. aureus as shown in Fig. 4(B). Similarly, in the presence of 10 µM [C10mim][Br] the MIC of CIP has reduced from 0.015 µM to 0.007 µM against E. coli as shown in Fig. 5(A) whereas, 2 µM [C10mim][Br] caused the decrease in MIC of CIP from 0.007 µM to 0.0014 µM against S. aureus as shown in Fig. 5(B). Further, in the presence of 50 µM [C10mim][Cl] the MIC of CIP has reduced from 0.015 µM to 0.007 µM against E. coli as shown in Fig. 6(A) whereas, 50 µM [C10mim][Cl] caused the decrease in MIC of CIP from 0.007 µM to 0.0014 µM against S. aureus as shown in Fig. 6(B). To conclude the results, the obtained data showed that much lower concentration of IL with maximum hydrophobicity [C10mim][BF4] caused the maximum reduction in the MIC value of CIP as compared to the ILs with least hydrophobicity ([C10mim][Br], [C10mim][Cl]). The observed results showed the remarkable improvement in the bacterial efficiency of CIP with ILs. Toxicity factor associated with ILs has always been a matter of concern for the scientist working in this filed. Therefore, we examined the toxicity profile of used ILs in the study by extensive literature survey where we found that the working concentration of the ILs in the antibacterial activity is safe against human cells [31,49,75,76] and might help in developing a new combination of drug for treating bacterial resistance and will exclude the toxicity factor.

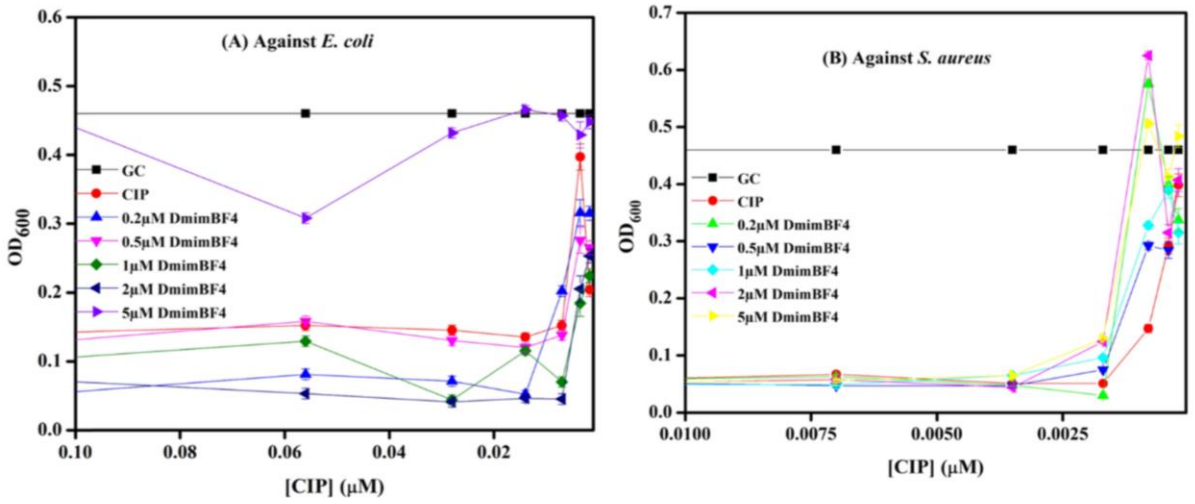


Fig. 4. Showing the effect of [C10mim][BF4], on the antibacterial activity of CIP against (A) *E. Coli* (B) *S. aureus*.

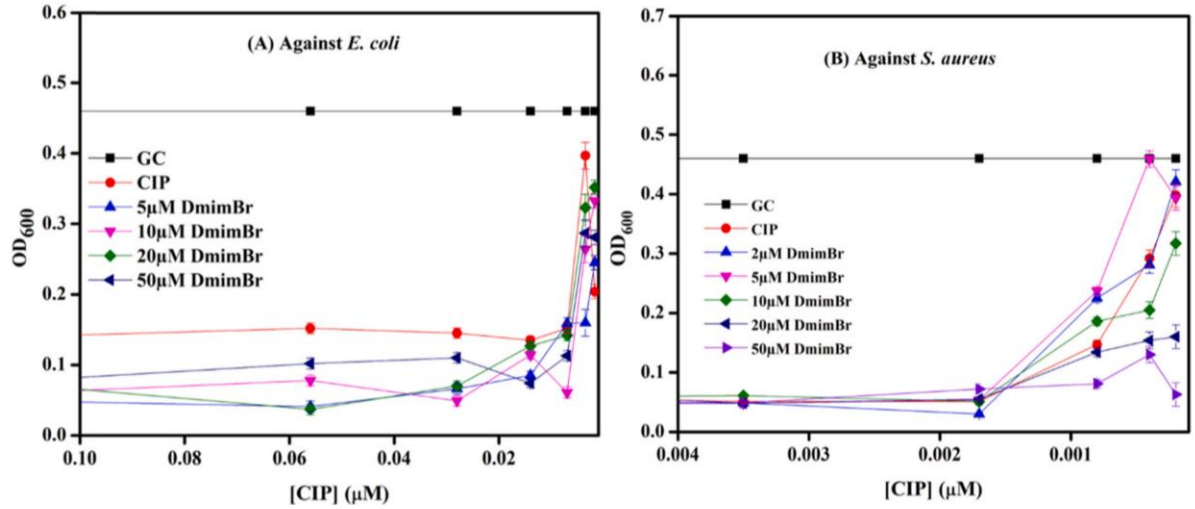


Fig. 5. Showing the effect of [C10mim][Br] on the antibacterial activity of CIP against (A) *E. Coli* (B) *S. aureus*.

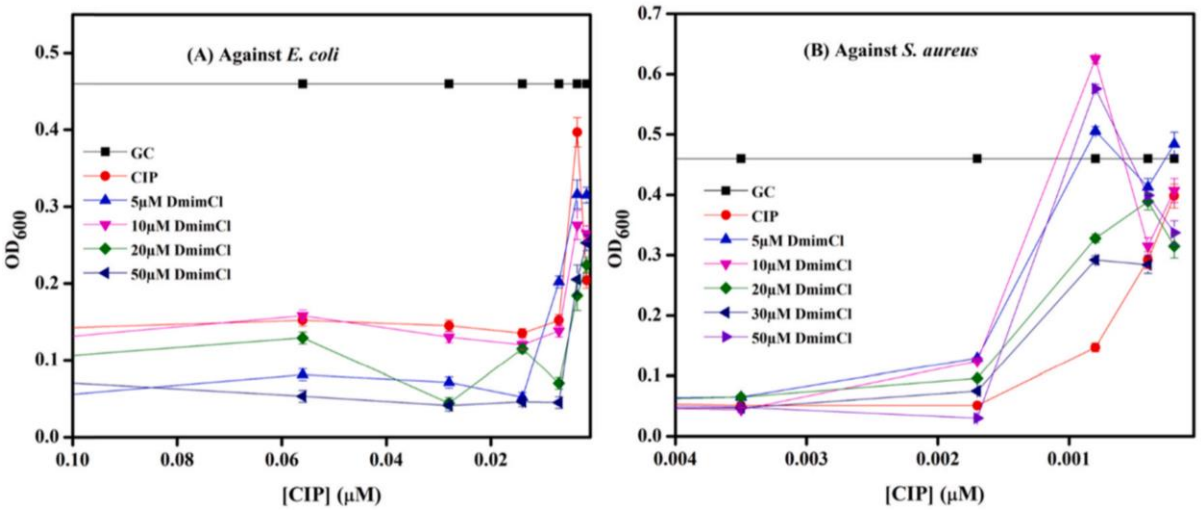


Fig. 6. Showing the effect of [C10mim][Cl] on the antibacterial activity of CIP against (A) *E. Coli* (B) *S. aureus*.

4. Conclusion

The interaction studies of imidazolium-based surface active ILs with CIP has been investigated by surface tension, DLS and zeta potential techniques to reveal the effect of drug on physicochemical properties of ILs. Various interfacial and thermodynamic parameters of ILs in the absence and presence of the drug have been investigated. The decrease in cmc of ILs in presence of CIP revealed the formation of the complex between ILs and CIP. The associated interfacial and thermodynamic parameters suggest the ILs+CIP complex formation is feasible, and enthalpy driven. The higher the value of ΔG◦ ad than ΔG˚mic indicates the adsorption at air water interface are energetically more favourable. The DLS studies indicated that Dh of ILs aggregate decreases in the presence of CIP which suggests the increase in the compactness of IL micelles with CIP. Further, the decrease in ζ values of ILs in presence of the drug indicates that CIP resides in ILs micelles. Also, the stability in the complexation attained through electrostatic forces due to the presence of two oppositely charged species in the solution. The antibacterial activity study against two bacterial strains, E. coli and S. aureus shows the remarkable improvement in the antibacterial activity of CIP in presence of ILs. The current

outcomes of the study demonstrate the use of ILs with drugs in various pharmacological applications.

Table 1 Thermodynamics parameters of [C10mim][BF4], [C10mim][Br] and [C10mim] [Cl] with CIP at 298.15 K.

System	ΔG°_{mic} (kJ mol^{-1})	ΔG° ad (kJ mol^{-1})	GS min (kJ mol− 1)
[C10mim][BF_4]	-20.53	-47.96	167.66
[C10mim][BF4]-CIP	-20.19	-53.46	137.05
[C10mim][Br]	-17.28	-43.63	685.86
[C10mim][Br]-CIP	-17.53	-51.89	651.96
[C10mim][Cl]	-17.48	-35.27	312.63
[C10mim][Cl]+ CIP	-17.81	-36.14	523.43

Table 2 Minimum inhibition concentration (MIC) of CIP, [C10mim][BF4], [C10mim][Br] and [C10mim][Cl] in μM.

S.no.	System	*E. coli* (μM)	*S. aureus* (μM)
1.	CIP	0.015	0.007
2.	[C10mim][BF4]	32	32
3.	[C10mim][Br]	36	18
4.	[C10mim][Cl]	62,500	15,620

Table 3 Minimum inhibition concentration (MIC) of CIP (μg/ml) in the absence and presence various concentration of [C10mim][BF4], [C10mim][Br] and [C10mim] [Cl].

Microorganisms	**Minimum Inhibition concentration**	
In presence of [C_{10}mim][BF_4]		
	CIP alone	Best combination
E. coli (MTCC 40)	0.015 μM	0.007 μM [C_{10}mim][BF_4] CIP+ 2 μM
S. aureus (MTCC 87)	0.007 μM	0.0014 μM [C_{10}mim][BF_4] CIP+ 0.2 μM
In presence of [C_{10}mim][Br]		
E. coli (MTCC 40)	0.015 μM	0.007 μM [C_{10}mim][Br] CIP+ 10 μM
S. aureus (MTCC 87)	0.007 μM	0.0014 μM [C_{10}mim][Br] CIP+ 2 μM
In presence of [C_{10}mim][Cl]		
E. coli (MTCC 40)	0.015 μM	0.007 μM [C_{10}mim][Cl] CIP+ 50 μM
S. aureus (MTCC 87)	0.007 μM	0.0014 μM [C_{10}mim][Cl] CIP+ 50 μM

CRediT authorship contribution statement A.S. and J.S. performed the research and wrote the paper. M.U.P. and F.A.W analysed the data. M.R.K., R.B. and B.S.K. help to revise the manuscript. R.P. designed and reviewed the manuscript. All authors had read and approved the final manuscript.

Declaration of Competing Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supporting Information

Interfacial and antibacterial properties of imidazolium based ionic liquids having different counterions with ciprofloxacin

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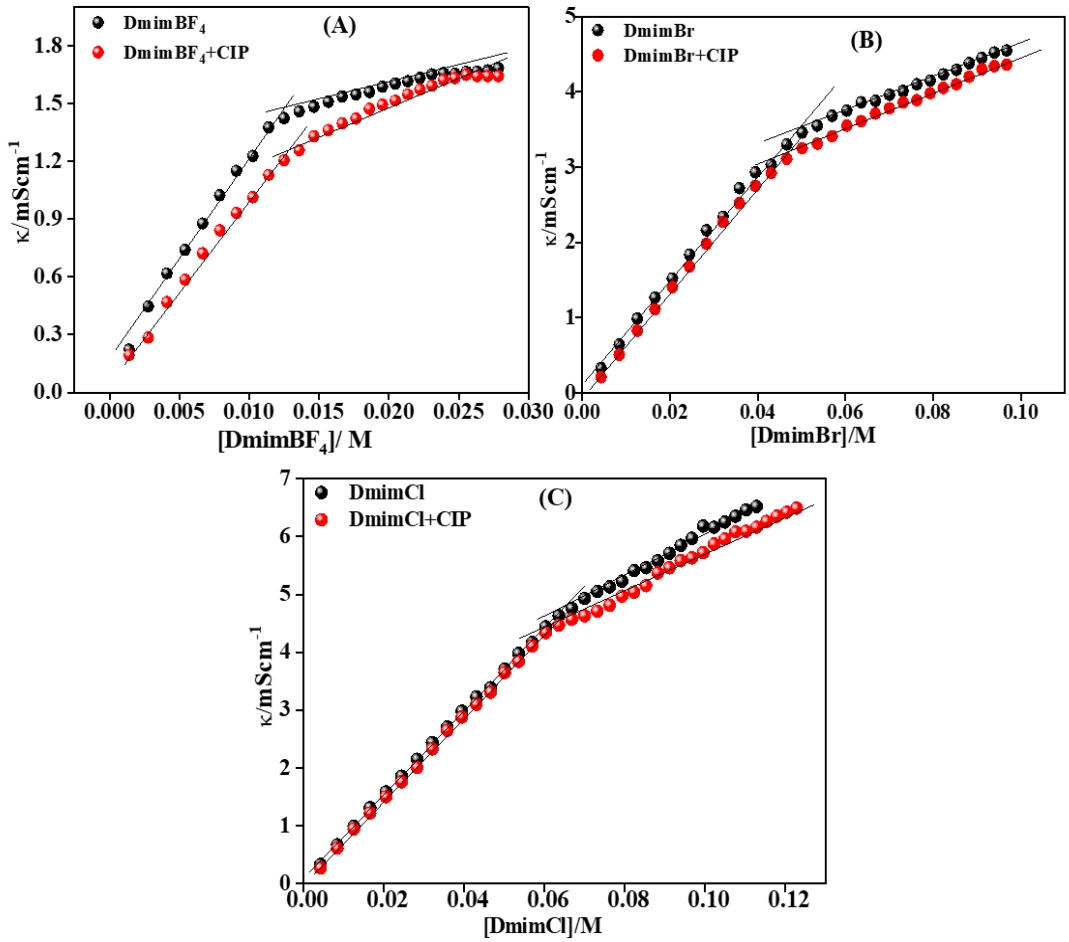

Figure S1. Plots of specific conductivity (κ) versus [Con.] for (A) DmimBF4, (B) DmimBr and (C) DmimCl in the absence and presence of CIP (20 μM) at 298.15 K.

Table S1. Various interfacial parameters of $[C_{10}mim][BF_4]$, $[C_{10}mim][Br]$ and $[C_{10}mim][Cl]$ with CIP at 298.15K

System	cmc (M)	*cmc (M)	γ_{cmc} mNm^{-1}	π_{cmc} mNm^{-1}	pC_{20}	Γ_{max} (10^{-6}) $mol\ m^{-2}$	A_{min} $(Å^2)$	P	β
$[C_{10}mim][BF_4]$	0.014	0.014	29.35	43.45	2.70	2.50	0.66	0.62	0.85
$[C_{10}mim][BF_4]$+CIP	0.012	0.013	28.29	44.51	2.70	3.39	0.48	0.85	0.72
$[C_{10}mim][Br]$	0.052	0.049	35.15	37.65	2.13	2.01	0.82	0.50	0.68
$[C_{10}mim][Br]$+ CIP	0.048	0.047	33.39	39.41	2.13	2.16	0.76	0.54	0.68
$[C_{10}mim][Cl]$	0.048	0.065	32.23	40.57	2.13	3.40	0.48	0.85	0.49
$[C_{10}mim][Cl]$+ CIP	0.042	0.062	34.67	38.13	2.13	3.04	0.54	0.76	0.49

***** *cmc* calculated from conductivity method.

Table S2. The hydrodynamic diameter (D_h) and Zeta potential (mV)value of $DmimBF_4$, DmimBr and DmimCl micelles and micelles loaded drug.

System	D_h (nm)	ζ (mV)(+)	PDI
$[C_{10}mim][BF_4]$	7.0	26.4	0.534
$[C_{10}mim][Br]$	3.9	18.6	0.639
$[C_{10}mim][Cl]$	1.65	6.4	0.649
$[C_{10}mim][BF_4]$+CIP	8.2	9.10	0.639
$[C_{10}mim][Br]$+CIP	4.7	6.35	0.262
$[C_{10}mim][Cl]$+CIP	2.1	0.73	0.340